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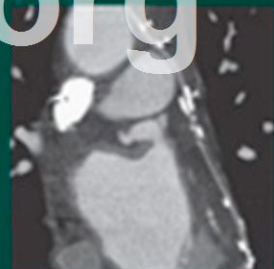
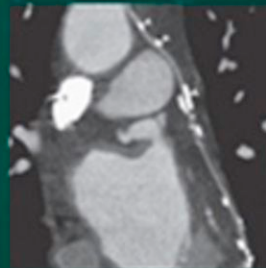
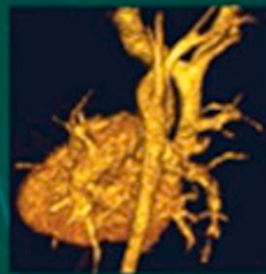
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EDITION 9

SABISTON & SPENCER

SURGERY *of the* CHEST

Frank W. Sellke
Pedro J. del Nido
Scott J. Swanson



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SURGERY *of the* CHEST

Frank W. Sellke, MD

Karl Karlson & Gloria Karlson Professor and Chief of Cardiothoracic Surgery
Warren Alpert Medical School of Brown University and Rhode Island Hospital
Director, Lifespan Cardiovascular Institute
Providence, Rhode Island

Pedro J. del Nido, MD

William E. Ladd Professor of Surgery
Harvard Medical School
Chairman, Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Scott J. Swanson, MD

Director, Minimally Invasive Thoracic Surgery
Brigham and Women's Hospital
Vice Chair, Cancer Affairs
Department of Surgery, Brigham and Women's Hospital
Chief Surgical Officer
Dana-Farber Cancer Institute
Professor of Surgery
Harvard Medical School
Boston, Massachusetts

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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*To my wife, Amy, who gives me love, inspiration,
and unwavering support and to our children,
Michelle, Eric, Nicholas, and Amanda.
They provide us with unlimited pleasure.*

FWS

*To Martha, my loving wife, and to my children,
Alexander and his wife Erika, to Sara, Daniel,
Elizabeth, and to my grandson Matthew who keeps
reminding us of the important things in life.
Thank you.*

PJD

*To my mother, Anne Parkhurst, and my wife,
Donna, and our children, Whit, Kate, and Maggie:
I am very appreciative and grateful for the guidance,
love, and support; gives meaning to all of what I do.
To my patients: the inspiration to work hard and do
better every day.*

SJS

CONTRIBUTORS

Brian G. Abbott, MD

Associate Professor of Medicine
Cardiovascular Institute
Warren Alpert Medical School of Brown University
Providence, Rhode Island

J. Dawn Abbott, MD

Associate Professor of Medicine
Director, Interventional Cardiology
Fellowship Training Program
Warren Alpert Medical School of Brown University
Interventional Cardiologist
Rhode Island Hospital
Providence, Rhode Island

David H. Adams, MD

Professor and Chairman
Department of Cardiovascular Surgery
The Mount Sinai Medical Center
New York, New York

Talal Al-Atassi, MD, CM, MPH

Chief Resident
Division of Cardiac Surgery
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Ali Al-Dameh, MD

Clinical Fellow in Thoracic Surgery
Brigham and Women's Hospital
Boston, Massachusetts

Mark S. Allen, MD

Professor of Surgery
Thoracic Surgery
Mayo Clinic
Rochester, Minnesota

Nasser K. Altorki, MB, BCh

Professor of Cardiothoracic Surgery
Weill Cornell Medical College
Chief, Division of Thoracic Surgery
Cardiothoracic Surgery
New York Presbyterian Hospital/Weill Cornell
Medical College
New York, New York

Jatin Anand, MD

Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Cardiovascular Research
Center for Cardiac Support
Texas Heart Institute
Houston, Texas

Robert H. Anderson, BSc, MD, FRC Path

Emeritus Professor
Institute of Child Health
University College
London, United Kingdom;
Visiting Professor
Division of Pediatric Cardiology
Medical University of South Carolina
Charleston, South Carolina;
Visiting Professor
Institute of Human Genetics
Newcastle University
Newcastle Upon Tyne, United Kingdom

Masaki Anraku, MD, MSc

Assistant Professor
Department of Thoracic Surgery
Graduate School of Medicine
The University of Tokyo
Tokyo, Japan

Anelechi C. Anyanwu, MD

Professor and Vice Chairman
Department of Cardiovascular Surgery
The Mount Sinai Medical Center
New York, New York

Amit Arora, MD

Department of Cardiovascular Surgery
The Mount Sinai Medical Center
New York, New York

Erle H. Austin, III, MD

Professor and Vice Chairman
Department of Cardiovascular and Thoracic Surgery
University of Louisville
Chief, Cardiothoracic Surgery
Kosair Children's Hospital
Louisville, Kentucky

Eric H. Awtry, MD

Associate Professor of Medicine
 Boston University School of Medicine
 Vice Chair for Clinical Affairs
 Division of Cardiology
 Boston Medical Center
 Boston, Massachusetts

Emile A. Bacha, MD, FACS

Chief, Division of Cardiothoracic and Vascular Surgery
 Department of Surgery
 Columbia University Medical Center
 New York Presbyterian Hospital
 New York, New York

Leah M. Backhus, MD

Assistant Professor
 Division of Cardiothoracic Surgery
 University of Washington
 Seattle, Washington

Jayant Bagai, MD

Assistant Professor of Medicine
 Division of Cardiovascular Medicine
 Vanderbilt University Medical Center
 Nashville, Tennessee

Richard Baillot, MD, FRCSC

Institut Universitaire de Cardiologie et de
 Pneumologie de Québec
 Québec City, Québec, Canada

Christopher W. Baird, MD

Assistant Professor of Surgery
 Harvard Medical School
 Associate in Cardiac Surgery
 Boston Children's Hospital
 Boston, Massachusetts

David J. Barron, MD, FRCP, FRCS(CT)

Consultant Cardiac Surgeon
 Birmingham Children's Hospital
 NHS Foundation Trust
 Birmingham, United Kingdom

Joseph E. Bavaria, MD

Brooke Roberts/William Maul Measey Professor of
 Surgery
 Vice Chair, Division of Cardiovascular Surgery
 Director, Thoracic Aortic Surgery
 Department of Surgery
 Division of Cardiovascular Surgery
 University of Pennsylvania
 Hospital of University of Pennsylvania
 Philadelphia, Pennsylvania

Jose M. Bernal, MD, PhD

Consultant and Professor of Surgery
 Department of Cardiovascular Surgery
 Hospital Valdecilla
 University of Cantabria
 Santander, Spain

Valentino J. Bianco, DO, MPH

Research Fellow, Thoracic Surgery
 Department of Cardiothoracic Surgery
 University of Pittsburgh School of Medicine
 University of Pittsburgh Medical Center
 Pittsburgh, Pennsylvania

David P. Bichell, MD

Cornelius Vanderbilt Chair in Surgery
 Professor of Surgery
 Cardiac Surgery
 Vanderbilt University School of Medicine
 Nashville, Tennessee

Sigurbjorn Birgisson, MD

Department of Gastroenterology
 Digestive Disease Institute
 Cleveland Clinic
 Cleveland, Ohio

Nick J.R. Blackburn, BSc

Division of Cardiac Surgery
 University of Ottawa Heart Institute
 Department of Cellular and Molecular Medicine
 University of Ottawa
 Ottawa, Ontario, Canada

Johannes Bonatti, MD

Chairman, Department of Cardiothoracic Surgery
 Cleveland Clinic Abu Dhabi
 Abu Dhabi, United Arab Emirates

Munir Boodhwani, MD, MMSc

Associate Professor
 Division of Cardiac Surgery
 University of Ottawa Heart Institute
 Ottawa, Ontario, Canada

Edward L. Bove, MD

Helen F. and Marvin M. Kirsh Professor of Cardiac
 Surgery
 Chair, Department of Cardiac Surgery
 Professor of Cardiac Surgery
 Professor of Pediatrics and Communicable Disease
 University of Michigan
 Ann Arbor, Michigan

William J. Brawn, CBE, FRCS, FRACS

Consultant Cardiac Surgeon
 Birmingham Children's Hospital
 NHS Foundation Trust
 Birmingham, United Kingdom

Christian P. Brizard, MD

Associate Professor
 University of Melbourne Faculty of Medicine,
 Dentistry
 Health Sciences School of Medicine
 Cardiac Surgery Unit
 Royal Children's Hospital
 Melbourne, Victoria, Australia

Julie A. Brothers, MD

Assistant Professor of Pediatrics
Perelman School of Medicine
University of Pennsylvania
Attending Physician, Cardiology
Medical Director, Coronary Anomaly Management
Program
Medical Director, Lipid Heart Clinic
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Lisa M. Brown, MD, MAS

Cardiothoracic Surgery Fellow
Division of Cardiothoracic Surgery
Washington University
St. Louis, Missouri

Ayesha S. Bryant, MD

Assistant Professor of Surgery
Division of Cardiothoracic Surgery
University of Alabama at Birmingham
Birmingham, Alabama

Harold M. Burkhart, MD

Professor of Surgery
Section of Cardiothoracic Surgery
The University of Oklahoma Health Sciences School of
Medicine
Director of Pediatric Cardiovascular Surgery
Medical Director of Pediatric Cardiovascular Surgical
Services
The Children's Hospital
Oklahoma City, Oklahoma

Christopher A. Caldarone, MD, FRCSC

Cardiovascular Surgery
The Hospital for Sick Children
Toronto, Ontario, Canada

Jeremy W. Cannon, MD, SM, FACS

Lieutenant Colonel, U.S. Air Force
Chief, Trauma and Critical Care
San Antonio Military Medical Center
San Antonio, Texas
Associate Professor of Surgery
Uniformed Services University of the Health Sciences
Bethesda, Maryland

Justine M. Carr, MD

Chief Medical Officer
Steward Health Care System
Senior Director, Department of Clinical Resource
Management
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Serenella Castelvechio, MD

Department of Cardiac Surgery
IRCCS Policlinico San Donato
Milan, Italy

Javier G. Castillo, MD

Department of Cardiovascular Surgery
The Mount Sinai Medical Center
New York, New York

Frank Cecchin, MD

Professor of Pediatrics
Pediatric Cardiology
New York University
New York, New York

Robert J. Cerfolio, MD

Chief of Thoracic Surgery
Professor of Cardiothoracic Surgery
University of Alabama at Birmingham
Birmingham, Alabama

A. Alfred Chahine, MD

Associate Professor of Surgery and Pediatrics
George Washington University School of Medicine
Attending Surgeon
Children's National Medical Center
Chief of Pediatric Surgery
MedStar Georgetown University Hospital
Washington, DC

Elliot L. Chaikof, MD, PhD

Johnson and Johnson Professor of Surgery
Chairman, Roberta and Stephen R. Weiner
Department of Surgery
Harvard Medical School
Surgeon-in-Chief
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Vincent Chan, MD, MPH

Assistant Professor
Division of Cardiac Surgery
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Sunit-Preet Chaudhry, MD

Cardiovascular Institute
Warren Alpert Medical School of Brown University
Providence, Rhode Island

Frederick Y. Chen, MD, PhD

Associate Professor of Cardiac Surgery
Harvard Medical School
Department of Surgery
Division of Cardiac Surgery
Brigham and Women's Hospital
Boston, Massachusetts

Stuart H. Chen, MD

Clinical Fellow in Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Aaron M. Cheng, MD

Assistant Professor
Division of Cardiothoracic Surgery
University of Washington
Seattle, Washington

Victor Chien, MD

Research Fellow in Surgery
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Alvin J. Chin, MD

Professor of Pediatrics, Emeritus
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Cynthia S. Chin, MD

Director of the Women's Cancer Program Services
Thoracic Surgery
White Plains Hospital
White Plains, New York

Peter Chiu, MD

Resident, Department of Cardiothoracic Surgery
Stanford University School of Medicine
Stanford, California

Joseph C. Cleveland, Jr., MD

Professor of Cardiothoracic Surgery
Surgical Director, Cardiac Transplantation and MCS
University of Colorado Anschutz Medical Center
Aurora, Colorado

Lawrence H. Cohn, MD

Hubbard Professor of Cardiac Surgery
Harvard Medical School
Department of Surgery
Division of Cardiac Surgery
Brigham and Women's Hospital
Boston, Massachusetts

William E. Cohn, MD

Professor of Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Director, Center for Technology and Innovation
Director, Cullen Cardiovascular Research Laboratory
Texas Heart Institute
Houston, Texas

Yolonda L. Colson, MD, PhD

Professor
Department of Surgery
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

Wilson S. Colucci, MD

Thomas J. Ryan Professor of Medicine
Professor of Physiology
Boston University School of Medicine
Chief, Section of Cardiovascular Medicine
Co-Director, Cardiovascular Center
Boston Medical Center
Boston, Massachusetts

Andrew C. Cook, PhD

Senior Lecturer
Cardiac Unit
UCL Institute of Cardiovascular Science
Great Ormond Street Hospital
NHS Foundation Trust
London, United Kingdom

Joseph S. Coselli, MD

Professor and Chief
Division of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Chief, Section of Adult Cardiac Surgery
The Texas Heart Institute
Houston, Texas

Todd C. Crawford, MD

Division of Thoracic Surgery
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Melissa Culligan, BSN, RN

Department of Thoracic Surgery
University of Pennsylvania Health System—Presbyterian
Philadelphia, Pennsylvania

François Dagenais, MD, FRCSC

Institut Universitaire de Cardiologie et de Pneumologie
de Québec
Québec City, Québec, Canada

Ralph J. Damiano, Jr., MD

Evarts A. Graham Professor of Surgery
Chief, Division of Cardiothoracic Surgery
Washington University School of Medicine
Barnes-Jewish Hospital
St. Louis, Missouri

Thomas A. D'Amico, MD

Gary Hock Endowed Professor and Vice Chair of
Surgery
Duke University School of Medicine
Chief, Section of General Thoracic Surgery
Program Director, Thoracic Surgery
Duke University Medical Center
Durham, North Carolina

Philippe G. Dartevelle, MD

Head, Service de Chirurgie Thoracique, Vasculaire et
Transplantation Cardiopulmonaire
Hôpital Marie Lannelongue
Le Plessis Robinson, France

Tirone E. David, MD

Professor of Surgery
University of Toronto
Attending Surgeon
Peter Munk Cardiac Centre
Toronto General Hospital
Toronto, Ontario, Canada

Jonathan D'Cunha, MD, PhD

Associate Professor of Surgery
Vice Chairman, Academic Affairs and Education
Surgical Director, Lung Transplantation
Associate Program Director, Thoracic Surgery
Department of Cardiothoracic Surgery
University of Pittsburgh
Pittsburgh, Pennsylvania

Kim I. de la Cruz, MD

Assistant Professor of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Clinical Staff
The Texas Heart Institute
Houston, Texas

Joseph A. Dearani, MD

Professor of Surgery
Chair, Cardiac Surgery
Division of Cardiovascular Surgery
Mayo Clinic
Rochester, Minnesota

Daniel T. DeArmond, MD

Cardiothoracic Surgery
University of Texas Health Science Center
San Antonio, Texas

Pedro J. del Nido, MD

William E. Ladd Professor of Surgery
Harvard Medical School
Chairman, Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Tom R. DeMeester, MD

Professor and Chairman, Emeritus
Department of Surgery
University of Southern California
Los Angeles, California

Philippe Demers, MD, MSC, FRCSC

Associate Professor of Surgery
Cardiac Surgery
University of Montreal
Cardiovascular Surgeon
Montreal Heart Institute
Montreal, Quebec, Canada

Todd L. Demmy, MD

Chairman, Department of Thoracic Surgery
Roswell Park Cancer Institute
Buffalo, New York

Elisabeth U. Dexter, MD

Assistant Professor of Oncology
Department of Thoracic Surgery
Roswell Park Cancer Institute
Assistant Professor of Surgery
SUNY University at Buffalo
Buffalo, New York

Rajeev Dhupar, MD

Assistant Professor of Surgery
Department of Cardiothoracic Surgery
Division of Thoracic and Foregut Surgery
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

James A. DiNardo, MD

Professor of Anesthesia
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Thomas P. Doyle, MD

Associate Professor of Pediatrics
Division of Cardiology
Vanderbilt University School of Medicine
Nashville, Tennessee

Afshin Ehsan, MD

Assistant Professor of Surgery
Brown Alpert Medical School
Rhode Island Hospital
Providence, Rhode Island

Gebrine El Khoury, MD, PhD

Professor
Department of Cardiovascular and Thoracic Surgery
Cliniques Universitaires Saint-Luc
Brussels, Belgium

Ethan R. Ellis, MD

Harvard-Thorndike Electrophysiology Institute
Cardiovascular Division
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Nassrene Y. Elmadhun, MD

Research Fellow
Cardiovascular Research Center
Warren Alpert Medical School
Brown University
Providence, Rhode Island
Surgical Resident
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Sitaram M. Emani, MD

Assistant Professor in Surgery
 Harvard Medical School
 Assistant in Cardiac Surgery
 Surgical Director, Adult Congenital Heart Program
 Director, Complex Biventricular Repair Program
 Surgical Director, Division of Cardiovascular Critical
 Care
 Boston Children's Hospital
 Boston, Massachusetts

Jeremy J. Erasmus, MD

Professor
 Department of Diagnostic Imaging
 The University of Texas MD Anderson Cancer Center
 Houston, Texas

Dario O. Fauza, MD

Associate Professor of Surgery
 Harvard Medical School
 Associate in Surgery
 Boston Children's Hospital
 Boston, Massachusetts

Adam S. Fein, MD

Cardiac Services
 Beth Israel Deaconess Medical Center
 Boston, Massachusetts

Amy G. Fiedler, MD

Clinical Fellow in Surgery
 Department of Surgery
 Division of Cardiac Surgery
 Brigham and Women's Hospital
 Boston, Massachusetts

Murilo Foppa, MD, DSc

Department of Medicine
 Cardiovascular Division
 Harvard-Thorndike Laboratory
 Harvard Medical School
 Beth Israel Deaconess Medical Center
 Boston, Massachusetts;
 Division of Cardiology
 Hospital de Clinicas de Porto Alegre
 Federal University of Rio Grande do Sul
 Brazil

Rosario V. Freeman, MD, MS

Medical Director, Echocardiography
 Program Director, Cardiology Fellowship Programs
 University of Washington
 Seattle, Washington

Joseph Friedberg, MD, FACS

Chief of Thoracic Surgery
 University of Pennsylvania Health System–Presbyterian
 Philadelphia, Pennsylvania

Michael Friscia, MD

Associate, Thoracic and Cardiac Surgery
 Geisinger Health System
 Danville, Pennsylvania

Francis Fynn-Thompson, MD

Assistant Professor of Surgery
 Surgical Director, Heart and Lung Transplantation
 Surgical Director, Mechanical Circulatory Support
 Program
 Program Director, Congenital Cardiac Surgery
 Residency/Fellowship
 Department of Cardiac Surgery
 Boston Children's Hospital
 Harvard Medical School
 Boston, Massachusetts

J. William Gaynor, MD

Professor of Surgery
 Perelman School of Medicine
 University of Pennsylvania
 Attending Surgeon
 Director, Fetal Neuroprotection and Neuroplasticity
 Program
 Daniel M. Tabas Endowed Chair, Pediatric
 Cardiothoracic Surgery
 The Children's Hospital of Philadelphia
 Philadelphia, Pennsylvania

Liang Ge, PhD

Assistant Professor of Surgery
 Department of Surgery
 University of California, San Francisco School of
 Medicine
 Department of Surgery
 San Francisco VA Medical Center
 San Francisco, California

Tal Geva, MD

Professor of Pediatrics
 Harvard Medical School
 Chief, Division of Noninvasive Cardiac Imaging
 Senior Associate, Department of Cardiology
 Boston Children's Hospital
 Boston, Massachusetts

Neil M. Gheewala, MD

Cardiovascular Institute
 Warren Alpert Medical School of Brown University
 Providence, Rhode Island

A. Marc Gillinov, MD

The Judith Dion Pyle Chair in Heart Valve Research
 Department of Thoracic and Cardiovascular Surgery
 Cleveland Clinic
 Cleveland, Ohio

Donald D. Glower, MD

Professor of Surgery
Department of Surgery
Division of Cardiovascular and Thoracic Surgery
Duke University School of Medicine
Durham, North Carolina

Andrew B. Goldstone, MD

Postdoctoral Research Fellow
Department of Cardiothoracic Surgery
Stanford University School of Medicine
Stanford, California

Shawn S. Groth, MD, MS

Assistant Professor of Surgery
Division of General Thoracic Surgery
Baylor College of Medicine
Houston, Texas

Frederick L. Grover, MD

Professor of Cardiothoracic Surgery
University of Colorado Anschutz Medical Center
Aurora, Colorado

Julius Guccione, PhD

Professor of Surgery
Department of Surgery
University of California, San Francisco School of
Medicine
Associate Professor of Surgery
San Francisco VA Medical Center
San Francisco, California

Richard Ha, MD

Clinical Assistant Professor
Surgical Director, Mechanical Circulatory Support
Program
Department of Cardiothoracic Surgery
Stanford University School of Medicine
Stanford, California

John W. Hammon, MD

Wake Forest University Baptist Medical Center
Winston-Salem, North Carolina

Jennifer M. Hanna, MD

Resident, General Surgery
Duke University School of Medicine
Durham, North Carolina

David G. Harrison, MD

Betty and Jack Bailey Professor of Medicine and
Pharmacology
Director, Division of Clinical Pharmacology
Director, Center for Vascular Biology
Vanderbilt University Medical Center
Nashville, Tennessee

Thomas H. Hauser, MD, MMSc, MPH

Department of Medicine
Cardiovascular Division
Harvard-Thorndike Laboratory
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Matthew C. Henn, MD

Resident, Division of Cardiothoracic Surgery
Washington University School of Medicine
Barnes-Jewish Hospital
St. Louis, Missouri

Jennifer C. Hirsch-Romano, MD

Assistant Professor of Cardiac Surgery
University of Michigan
Ann Arbor, Michigan

Chuong D. Hoang, MD

Assistant Professor
Department of Cardiothoracic Surgery
Division of Thoracic Surgery
Stanford University School of Medicine
Stanford, California

Wayne L. Hofstetter, MD

Professor of Surgery
Director of Esophageal Surgery
Department of Thoracic and Cardiovascular Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Osami Honjo, MD, PhD

Cardiovascular Surgery
The Hospital for Sick Children
Toronto, Ontario, Canada

Tam T. Huynh, MD

Professor
Department of Thoracic and Cardiovascular Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Carlos E. Bravo Iñiguez, MD

Postdoctoral Fellow
Division of Thoracic Surgery
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Sebastian Iturra, MD

Structural Heart and Valve Center
Division of Cardiothoracic Surgery
Joseph B. Whitehead Department of Surgery
Emory University School of Medicine
Atlanta, Georgia

Jeffrey P. Jacobs, MD, FACS, FACC, FCCP

Professor of Surgery
 Division of Cardiac Surgery
 Department of Surgery
 Johns Hopkins University
 Baltimore, Maryland;
 Chief, Division of Cardiovascular Surgery
 Director, Andrews/Daicoff Cardiovascular Program
 Surgical Director of Heart Transplantation and
 Extracorporeal Life Support Programs
 Johns Hopkins All Children's Heart Institute
 All Children's Hospital and Florida Hospital for
 Children
 Saint Petersburg, Tampa, and Orlando, Florida

Marshall L. Jacobs, MD

Division of Cardiac Surgery
 Department of Surgery
 Johns Hopkins University
 Baltimore, Maryland

Michael T. Jaklitsch, MD

Associate Professor
 Surgeon, Division of Thoracic Surgery
 Brigham & Women's Hospital
 Harvard Medical School
 Boston, Massachusetts

Stuart W. Jamieson, MB, FRCS

Distinguished Professor of Surgery
 Endowed Chair, Division of Cardiothoracic Surgery
 University of California, San Diego
 San Diego, California

Doraid Jarrar, MD

Thoracic Surgeon
 Einstein Healthcare
 East Norriton, Pennsylvania

Craig M. Jarrett, MD

Department of Thoracic and Cardiovascular Surgery
 Cleveland Clinic
 Cleveland, Ohio

David R. Jones, MD

Professor and Chief of Thoracic Surgery
 Memorial Sloan-Kettering Cancer Center
 New York, New York

Mark E. Josephson, MD

Harvard-Thorndike Electrophysiology Institute,
 Cardiovascular Division
 Harvard Medical School
 Beth Israel Deaconess Medical Center
 Boston, Massachusetts

Lilian P. Joventino, MD

Wentworth Health Partners Cardiovascular Group
 Dover, New Hampshire

Amy L. Juraszek, MD

Associate Professor
 Departments of Pediatrics and Pathology
 University of Texas Southwestern Medical Center
 Dallas, Texas

Stefan S. Kachala, MD

Department of Thoracic and Cardiovascular Surgery
 Cleveland Clinic
 Cleveland, Ohio

Larry R. Kaiser, MD

Dean and Professor of Surgery
 Temple University School of Medicine
 President and CEO
 Temple University Health System
 Sr. Executive Vice President for the Health Sciences
 Temple University
 Philadelphia, Pennsylvania

Kirk R. Kanter, MD

Professor of Surgery
 Pediatric Cardiac Surgery
 Emory University School of Medicine
 Atlanta, Georgia

John M. Karamichalis, MD

Clinical Instructor in Surgery
 Department of Surgery
 Division of Pediatric Cardiothoracic Surgery
 University of California, San Francisco
 San Francisco, California

Aditya K. Kaza, MD

Assistant Professor of Surgery
 Harvard Medical School
 Associate in Cardiac Surgery
 Department of Cardiac Surgery
 Boston Children's Hospital
 Boston, Massachusetts

Clinton D. Kemp, MD

Division of Thoracic Surgery
 The Johns Hopkins Medical Institutions
 Baltimore, Maryland

Kemp H. Kernstine, Sr., MD, PhD

Professor and Chief, Division of Thoracic Surgery
 Department of Cardiovascular & Thoracic Surgery
 University of Texas Southwestern Medical Center
 Dallas, Texas

Suresh Keshavamurthy, MD

Cleveland Clinic
 Cleveland, Ohio

Shaf Keshavjee, MD, MSc, FRCS, FACS

Surgeon-in-Chief, University Health Network
 James Wallace McCutcheon Chair in Surgery
 Professor, Division of Thoracic Surgery
 University of Toronto
 Toronto, Ontario, Canada

Deborah J. Kozik, DO

Assistant Professor of Surgery
Department of Cardiovascular and Thoracic Surgery
University of Louisville
Cardiothoracic Surgery
Kosair Children's Hospital
Louisville, Kentucky

Roger J. Laham, MD

Associate Professor of Medicine
Harvard Medical School
Research Investigator
CardioVascular Institute
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Michael J. Landzberg, MD

Director, Boston Adult Congenital Heart (BACH) and
Pulmonary Hypertension Program
Department of Cardiology
Brigham and Women's Hospital and Boston Children's
Hospital
Boston, Massachusetts

Christopher P. Lawrance, MD

Resident, Division of Cardiothoracic Surgery
Washington University School of Medicine
Barnes-Jewish Hospital
St. Louis, Missouri

Lawrence S. Lee, MD

Clinical Fellow in Surgery
Harvard Medical School
Department of Surgery
Division of Cardiac Surgery
Brigham and Women's Hospital
Boston, Massachusetts

Scott A. LeMaire, MD

Professor and Vice Chair for Research
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Professional Staff, Department of Cardiovascular
Surgery
The Texas Heart Institute
Houston, Texas

Sidney Levitsky, MD

David W. and David Cheever Professor of Surgery
Harvard Medical School
Director, Cardiothoracic Surgery Care Group
Senior Vice Chairman, Department of Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Jerrold H. Levy, MD, FAHA, FCCM

Professor of Anesthesiology
Associate Professor of Surgery
Departments of Anesthesiology, Surgery, and Critical
Care
Co-Director, Cardiothoracic ICU
Duke University School of Medicine
Duke University Medical Center
Durham, North Carolina

Philip A. Linden, MD

Associate Professor of Surgery
Case Western Reserve School of Medicine
Chief, Division of Thoracic and Esophageal Surgery
University Hospitals Case Medical Center
Cleveland, Ohio

Michael J. Liptay, MD

The Mary and John Bent Professor and Chairperson
Department of Cardiovascular and Thoracic Surgery
Rush University Medical Center
Chicago, Illinois

Virginia R. Litle, MD, FACS

Associate Professor of Surgery
Department of Surgery
Division of Thoracic Surgery
Boston University School of Medicine
Boston, Massachusetts

Mauro Lo Rito, MD

Cardiovascular Surgery
The Hospital for Sick Children
Toronto, Ontario, Canada

James D. Luketich, MD

Henry T. Bahnson Professor and Chairman
Department of Cardiothoracic Surgery
Chief, Division of Thoracic and Foregut Surgery
University of Pittsburgh School of Medicine
Director, Thoracic Surgical Oncology
Co-Director, Lung Cancer Center
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Bruce W. Lytle, MD

Chairman, Strategic Development and Planning
for Cardiovascular Medicine and Surgery
The Heart Hospital Baylor Plano
Plano, Texas

Michael Madani, MD

Professor of Surgery
Chief, Division of Cardiothoracic Surgery
University of California, San Diego
San Diego, California

Feroze Mahmood, MD

Associate Professor of Anaesthesiology
Harvard Medical School
Director, Vascular Anesthesia/Perioperative
Echocardiography
Beth Israel Deaconess Medical Center
Harvard Medical Faculty Physicians at Beth Israel
Deaconess Medical Center
Boston, Massachusetts

Hari R. Mallidi, MD

Associate Professor of Surgery
Chief, Division of Transplant & Assist Devices
Lester and Sue Smith Endowed Chair in Surgery
Baylor College of Medicine
Houston, Texas

Abeel A. Mangi, MD

Associate Professor of Surgery, Section of Cardiac
Surgery
Surgical Director, Center for Advanced Heart Failure,
Mechanical Circulatory Support and Heart
Transplantation
Surgical Director, Trans-Catheter Therapies
Yale University
New Haven, Connecticut

Warren J. Manning, MD

Departments of Medicine and Radiology
Cardiovascular Division
Harvard-Thorndike Laboratory
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Edith M. Marom, MD

Professor
Department of Diagnostic Imaging
The University of Texas MD Anderson Cancer Center
Houston, Texas

Audrey C. Marshall, MD

Chief, Invasive Cardiology
Boston Children's Hospital
Boston, Massachusetts

Mauricio Perez Martinez, MD

Division of Thoracic Surgery
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Christopher E. Mascio, MD

Assistant Professor of Clinical Medicine
Perelman School of Medicine
University of Pennsylvania
Pediatric Cardiothoracic Surgeon
Division of Cardiothoracic Surgery
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

David P. Mason, MD

Chief, Thoracic Surgery and Lung Transplantation
Department of Thoracic Surgery
Baylor University Medical Center
Dallas, Texas

Douglas J. Mathisen, MD

Chief of Thoracic Surgery
Massachusetts General Hospital
Boston, Massachusetts

Kenneth L. Mattox, MD, FACS

Professor of Surgery
Division of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Houston, Texas

Robina Matyal, MD

Associate Professor of Anaesthesiology
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

James D. McCully, PhD

Associate Professor of Surgery
Harvard Medical School
Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Robert J. McKenna, Jr., MD

Director, Thoracic Surgery
Surgery
Cedars-Sinai Medical Center
Los Angeles, California

Ciaran McNamee, MD

Instructor in Surgery
Harvard Medical School
Associate Surgeon
Brigham and Women's Hospital
Boston, Massachusetts

Jeffrey D. McNeil, MD

Colonel, U.S. Air Force
Chief, Cardiothoracic Surgery Service
San Antonio Military Medical Center
San Antonio, Texas
Clinical Assistant Professor, Cardiothoracic Surgery
University of Texas Health Science Center, San
Antonio
San Antonio, Texas

Lorenzo Menicanti, MD

Chief of Cardiac Surgery
IRCCS Policlinico San Donato
Milan, Italy

Carlos A. Mestres, MD, PhD, FETCS

Senior Consultant
Department of Cardiovascular Surgery
Hospital Clinico
University of Barcelona
Barcelona, Spain;
Cardiothoracic and Vascular Surgery
Heart and Vascular Institute
Cleveland Clinic Abu Dhabi
Abu Dhabi, United Arab Emirates

Bret A. Mettler, MD

Assistant Professor
Division of Pediatric Cardiac Surgery
Vanderbilt University School of Medicine
Department of Cardiac Surgery
Vanderbilt University Medical Center
Nashville, Tennessee

Bryan Fitch Meyers, MD, MPH

Patrick and Joy Williamson Professor of Surgery
Chief, Thoracic Surgery
Washington University School of Medicine
St. Louis, Missouri

Stephanie Mick, MD

Cardiovascular Surgeon
Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Tomislav Mihaljevic, MD

Chief of Staff and Chairman of the Heart and Vascular
Institute
Cleveland Clinic Abu Dhabi
Abu Dhabi, United Arab Emirates;
Attending Surgeon
Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Professor of Surgery
Cleveland Clinic Lerner College of Medicine at Case
Western University
Cleveland, Ohio

Carmelo A. Milano, MD

Professor of Surgery
Cardiovascular and Thoracic Surgery
Duke University
Durham, North Carolina

D. Craig Miller, MD

Thelma and Henry Doelger Professor of
Cardiovascular Surgery
Department of Cardiovascular Surgery
Stanford University School of Medicine
Department of Cardiothoracic Surgery
Stanford University Medical Center
Stanford, California

Daniel L. Miller, MD, FACS

Clinical Professor of Surgery
Georgia Regents University
Chief, General Thoracic Surgery
WellStar Health System
Mayo Clinic Care Network
Marietta, Georgia

Meagan M. Miller, RN, BSN

Vanderbilt University Medical Center
Nashville, Tennessee

John D. Mitchell, MD

Courtenay C. and Lucy Patten Davis Endowed Chair
in Thoracic Surgery
Professor and Chief, Section of General Thoracic
Surgery
Division of Cardiothoracic Surgery
University of Colorado School of Medicine
Aurora, Colorado

Mario Montealegre-Gallegos, MD

Department of Anaesthesia
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Neal G. Moores, MD

Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Charles E. Murphy, MD

Assistant Professor of Surgery
Division of Cardiovascular and Thoracic Surgery
Duke University School of Medicine
Duke University Medical Center
Durham, North Carolina

Raghav A. Murthy, MD

Department of Cardiovascular & Thoracic Surgery
University of Texas Southwestern Medical Center
Dallas, Texas

Sudish C. Murthy, MD, PhD

Section Head, General Thoracic Surgery
Surgical Director, Center for Major Airway Disease
Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Sacha Mussot, MD

Hôpital Marie Lannelongue
Service de Chirurgie Thoracique, Vasculaire et
Transplantation Cardiopulmonaire
Le Plessis Robinson, France

Yoshifumi Naka, MD, PhD

Professor of Surgery
Columbia University College of Physicians and Surgeons
Attending Surgeon
New York–Presbyterian Hospital
New York, New York

Meena Nathan, MD, FRCS

Instructor in Surgery
Harvard Medical School
Staff Cardiac Surgeon
Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Kurt D. Newman, MD

President and Chief Executive Officer
Children's National Medical Center
Washington, DC

Chukwumere Nwogu, MD

Associate Professor
Department of Thoracic Surgery
Roswell Park Cancer Institute
Buffalo, New York

Kirsten C. Odegard, MD

Associate Professor
Department of Anesthesiology, Perioperative and Pain Medicine
Boston Children's Hospital
Boston, Massachusetts

Daniel S. Oh, MD

Assistant Professor of Surgery
Division of Thoracic Surgery
University of Southern California
Los Angeles, California

Richard G. Ohye, MD

Professor of Cardiac Surgery
University of Michigan
Ann Arbor, Michigan

Mark W. Onaitis, MD

Associate Professor of Surgery
Department of Surgery
Division of Cardiovascular and Thoracic Surgery
Duke University School of Medicine
Duke University Medical Center
Durham, North Carolina

Aleksandra Ostojic, MSc

Division of Cardiac Surgery
University of Ottawa Heart Institute
Department of Cellular and Molecular Medicine
University of Ottawa
Ottawa, Ontario, Canada

Harald C. Ott, MD

Division of Thoracic Surgery
Massachusetts General Hospital
Boston, Massachusetts

Maral Ouzounian, MD, PhD

Assistant Professor of Surgery
University of Toronto
Cardiovascular Surgeon
Division of Cardiovascular Surgery
University Health Network
Toronto General Hospital
Toronto, Ontario, Canada

Khurram Owais, MD

Department of Anaesthesia
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Massimo Padalino, MD, PhD

Department of Cardio Thoracic and Vascular Sciences
University Hospital
Padova, Italy

Konstantinos Papadakis, MD

Instructor in Surgery
Harvard Medical School
Department of Surgery
Boston Children's Hospital
Boston, Massachusetts

G. A. Patterson, MD

Evarts A. Graham Professor of Surgery
Chief, Division of Cardiothoracic Surgery
Washington University
St. Louis, Missouri

Edward F. Patz, Jr., MD

Professor
Department of Radiology
Duke University
Durham, North Carolina

Subroto Paul, MD

Associate Professor
Department of Cardiothoracic Surgery
Weill Cornell Medical College
New York, New York

Arjun Pennathur, MD

Sampson Family Endowed Chair in Thoracic Surgical Oncology
Associate Professor of Cardiothoracic Surgery
Department of Cardiothoracic Surgery
University of Pittsburgh School of Medicine
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Yaron Perry, MD

Clinical Associate Professor of Surgery
Case Western Reserve University School of Medicine
Director, Minimally Invasive Esophageal Surgery
University Hospitals Case Medical Center
Cleveland, Ohio

Robert N. Piana, MD

Professor of Medicine
Division of Cardiovascular Medicine
Director, Adult Congenital Interventional Program
Vanderbilt University Medical Center
Nashville, Tennessee

Frank A. Pigula, MD

Associate Professor of Surgery
Harvard Medical School
Senior Associate in Cardiac Surgery
Clinical Director, Cardiac Surgery Program
Director, Neonatal Cardiac Surgery Program
Boston Children's Hospital
Boston, Massachusetts

Duane S. Pinto, MD, MPH

Associate Professor of Medicine
Harvard Medical School
Associate Director, Cardiac Catheterization Laboratory
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Jose L. Pomar, MD, PhD, FETCS

Senior Consultant and Professor of Surgery
Department of Cardiovascular Surgery
Hospital Clinico
University of Barcelona
Barcelona, Spain

Ourania Preventza, MD

Assistant Professor of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Clinical Staff
The Texas Heart Institute
Houston, Texas

Bradley Pua, MD

Assistant Professor of Radiology
Weill Cornell Medical College
Program Director, Interventional Radiology Fellowship
Director, Lung Cancer Screening Program
New York Presbyterian Hospital/Weill Cornell Medical Center
New York, New York

Varun Puri, MD

Assistant Professor of Surgery
Division of Cardiothoracic Surgery
Washington University
St. Louis, Missouri

Luis Quinonez, MD

Instructor in Surgery
Harvard Medical School
Assistant in Cardiac Surgery
Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Siva Raja, MD, PhD

Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Mark Ratcliffe, MD

Professor of Surgery
Department of Surgery
University of California, San Francisco
Chief Surgical Consultant
Sierra Pacific VA Network
San Francisco, California

Michael J. Reardon, MD

Professor of Cardiothoracic Surgery
Allison Family Distinguished Chair of Cardiovascular Research
Houston Methodist DeBakey Heart & Vascular Center
Houston, Texas

John J. Reilly, Jr., MD

Dean
University of Colorado School of Medicine
Vice Chancellor for Health Affairs
University of Colorado
Aurora, Colorado

Karl G. Reyes, MD

Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Thomas W. Rice, MD

Head, Section of General Thoracic Surgery
Department of Thoracic and Cardiovascular Surgery
Heart and Vascular Institute
Cleveland Clinic
Cleveland, Ohio

Robert C. Robbins, MD

President and Chief Executive Officer
Texas Medical Center
Houston, Texas;
Consulting Professor
Stanford Cardiovascular Institute
Stanford, California

Gaetano Rocco, MD, FRCS(Ed), FECTS

Director, Department of Thoracic Surgery and Oncology
National Cancer Institute, Pascale Foundation
Naples, Italy

Fraser D. Rubens, MD, MSc, FACS, FRCSC

Professor of Surgery
Division of Cardiac Surgery
Residency Program Director
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Marc Ruel, MD, MPH

Professor and Chair
Division of Cardiac Surgery
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Valerie W. Rusch, MD

Attending Surgeon, Thoracic Service
Vice Chair for Clinical Research
Miner Family Chair in Intrathoracic Cancers
Department of Surgery
Memorial Sloan-Kettering Cancer Center
New York, New York

Ashraf A. Sabe, MD

Clinical Teaching Fellow, General Surgery
Harvard Medical School
Resident, General Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts;
Research Fellow, Cardiothoracic Surgery
Warren Alpert Medical School of Brown University
Providence, Rhode Island

Sameh M. Said, MD

Senior Associate Consultant
Division of Cardiovascular Surgery
Mayo Clinic
Rochester, Minnesota

Pamela P. Samson, MD, MPH

Resident, Department of Surgery
Washington University and Barnes-Jewish Hospital
St. Louis, Missouri

Stephen P. Sanders, MD

Professor of Pediatrics
Harvard Medical School
Director, Cardiac Registry
Departments of Cardiology, Pathology, Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Eric L. Sarin, MD

Assistant Professor of Surgery
Structural Heart and Valve Center
Division of Cardiothoracic Surgery
Joseph B. Whitehead Department of Surgery
Emory University School of Medicine
Atlanta, Georgia

Hartzell V. Schaff, MD

Professor of Surgery
Mayo Clinic
Rochester, Minnesota

Lara W. Schaheen, MD

Resident, Department of Cardiothoracic Surgery
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Christopher W. Seder, MD

Assistant Professor of Thoracic and Cardiac Surgery
Rush University Medical Center
Chicago, Illinois

Frank W. Sellke, MD

Karl Karlson & Gloria Karlson Professor and Chief of
Cardiothoracic Surgery
Warren Alpert Medical School of Brown University
and Rhode Island Hospital
Director, Lifespan Cardiovascular Institute
Providence, Rhode Island

Boris Sepesi, MD

Assistant Professor
Department of Thoracic and Cardiovascular Surgery
Division of Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Rohit Shahani, MD

Cardiothoracic Surgery
Hudson Cardiothoracic Surgeons
Poughkeepsie, New York

Robert C. Shamberger, MD

Robert E. Gross Professor of Surgery
Harvard Medical School
Chief of Surgery
Boston Children's Hospital
Boston, Massachusetts

Oz M. Shapira, MD

Professor and Chairman
Department of Cardiothoracic Surgery
Hebrew University
Hadassah Medical Center
Jerusalem, Israel

Steven S. Shay, MD

Department of Gastroenterology
Digestive Disease Institute
Cleveland Clinic
Cleveland, Ohio

Joseph B. Shrager, MD

Professor, Department of Cardiothoracic Surgery
Chief, Division of Thoracic Surgery
Stanford University School of Medicine
Stanford, California

Ming-Sing Si, MD

Assistant Professor of Cardiac Surgery
University of Michigan
Ann Arbor, Michigan

Steve K. Singh, MD, MSc, FRCSC

Assistant Professor of Surgery
Division of Transplant & Assist Devices
Baylor College of Medicine
Houston, Texas

Peter K. Smith, MD

Professor and Chief, Thoracic Surgery
Duke University
Durham, North Carolina

Neel R. Sodha, MD

Assistant Professor of Surgery
Cardiothoracic Surgery
Warren Alpert Medical School of Brown University
Providence, Rhode Island

R. John Solaro, PhD

Distinguished University Professor and Head
Department of Physiology and Biophysics
University of Illinois at Chicago College of Medicine
Chicago, Illinois

Harmik J. Soukiasian, MD

Associate Director, Thoracic Surgery
Cedars-Sinai Medical Center
Los Angeles, California

David Spurlock, MD

Junior Fellow, Cardiac Surgery
University of Michigan
Ann Arbor, Michigan

Giovanni Stellin, MD

Director of Pediatric and Congenital Cardiac Surgery
Department of Cardio Thoracic and Vascular Sciences
University Hospital
Padova, Italy

Brendon M. Stiles, MD

Associate Professor of Cardiothoracic Surgery
Weill Cornell Medical College
Cardiothoracic Surgery
New York Presbyterian Hospital/Weill Cornell Medical
College
New York, New York

Michaela Straznicka, MD

Thoracic Surgeon
Sutter Health Medical Center
Walnut Creek, California

David A. Stump, PhD

Wake Forest University Baptist Medical Center
Winston-Salem, North Carolina

David J. Sugarbaker, MD

Director, The Lung Institute
Chief, Division of Thoracic Surgery
The Olga Keith Wiess Chair of Surgery
Baylor College of Medicine
Houston, Texas

Erik J. Suuronen, PhD

Division of Cardiac Surgery
University of Ottawa Heart Institute
Department of Cellular and Molecular Medicine
University of Ottawa
Ottawa, Ontario, Canada

Lars G. Svensson, MD, PhD

Professor of Surgery, Thoracic and Cardiovascular
Surgery
Chairman, Heart and Vascular Institute
Cleveland Clinic
Cleveland, Ohio

Scott J. Swanson, MD

Director, Minimally Invasive Thoracic Surgery
Brigham and Women's Hospital
Vice Chair, Cancer Affairs
Department of Surgery, Brigham and Women's
Hospital
Chief Surgical Officer
Dana-Farber Cancer Institute
Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Wilson Y. Szeto, MD

Associate Professor of Surgery
Division of Cardiovascular Surgery
Department of Surgery
University of Pennsylvania
Philadelphia, Pennsylvania

Sharven Taghavi, MD

Resident, Department of Surgery
Temple University
Philadelphia, Pennsylvania

Hiroo Takayama, MD, PhD

Assistant Professor of Surgery
Columbia University College of Physicians and
Surgeons
Attending Surgeon
New York-Presbyterian Hospital
New York, New York

Koji Takeda, MD, PhD

Assistant Professor of Surgery
Columbia University College of Physicians and
Surgeons
Attending Surgeon
New York-Presbyterian Hospital
New York, New York

Ravi R. Thiagarajan, MBBS, MPH

Senior Associate in Cardiology
Associate Professor of Pediatrics
Boston Children's Hospital
Boston, Massachusetts

Patricia A. Thistlethwaite, MD, PhD

Professor of Surgery
Program Director, Division of Cardiothoracic Surgery
University of California, San Diego
San Diego, California

Vinod H. Thourani, MD

Professor of Surgery
Structural Heart and Valve Center
Division of Cardiothoracic Surgery
Joseph B. Whitehead Department of Surgery
Emory University School of Medicine
Atlanta, Georgia

Hadi D. Toeg, MD, MSc

Surgical Resident
Division of Cardiac Surgery
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Michael Z. Tong, MD, MBA

Associate Staff, Thoracic and Cardiovascular Surgery
Heart and Vascular Institute
Cleveland Clinic
Cleveland, Ohio

Alexander G. Truesdell, MD

Cardiac and Vascular Interventionalist
PinnacleHealth CardioVascular Institute
Harrisburg, Pennsylvania

Peter I. Tsai, MD, FACS

Assistant Professor of Surgery
Division of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Houston, Texas

Harold C. Urschel, Jr., MD[†]

Professor of Cardiovascular and Thoracic Surgery
University of Texas Southwestern Medical School
Chair, Cardiovascular and Thoracic Surgical Research,
Education, and Clinical Excellence
Department of Cardiovascular and Thoracic Surgery
Baylor University Medical Center
Dallas, Texas

[†]Deceased.

Anne Marie Valente, MD

Associate Professor of Pediatrics and Internal Medicine
Harvard Medical School
Outpatient Director, Boston Adult Congenital Heart
Disease and Pulmonary Hypertension Program
Department of Cardiology
Boston Children's Hospital
Department of Medicine
Division of Cardiology
Brigham and Women's Hospital
Boston, Massachusetts

Prashanth Vallabhajosyula, MD, MS

Assistant Professor of Surgery
Division of Cardiovascular Surgery
Department of Surgery
University of Pennsylvania
Philadelphia, Pennsylvania

Jeffrey B. Velotta, MD

Thoracic Surgery
Oakland Medical Center
Oakland, California

Vladimiro Vida, MD, PhD

Department of Cardio Thoracic and Vascular Sciences
University Hospital
Padova, Italy

Gus J. Vlahakes, MD

Professor of Surgery
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Pierre Voisine, MD, FRCSC

Department of Cardiac Surgery
Institut Universitaire de Cardiologie et de Pneumologie
de Québec
Québec City, Québec, Canada

Matthew J. Wall, Jr., MD, FACS

Professor of Surgery
Division of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Houston, Texas

Garrett L. Walsh, MD

Professor of Surgery
Department of Thoracic and Cardiovascular Surgery
Division of Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Dustin M. Walters, MD

Division of Cardiothoracic Surgery
University of Washington Medical Center
Seattle, Washington

Benjamin Wei, MD

Assistant Professor of Surgery
Division of Cardiothoracic Surgery
University of Alabama at Birmingham
Birmingham, Alabama

Ian J. Welsby, MB BS

Associate Professor of Anesthesiology
Departments of Anesthesiology, Surgery, and Critical
Care
Duke University School of Medicine
Durham, North Carolina

Margaret V. Westfall, PhD

Associate Professor
Department of Cardiac Surgery
University of Michigan School of Medicine
Ann Arbor, Michigan

Daniel C. Wiener, MD

Assistant Professor of Surgery
Harvard Medical School
Thoracic Surgeon
Brigham and Women's Hospital
Boston, Massachusetts

Benson R. Wilcox, MD[†]

Professor of Surgery
Department of Cardiothoracic Surgery
University of North Carolina at Chapel Hill
University of North Carolina Hospital
Chapel Hill, North Carolina

Judson B. Williams, MD, MHS

Resident, Cardiothoracic Surgery
Duke University
Durham, North Carolina

Jay M. Wilson, MD

Associate Professor of Surgery
Harvard Medical School
Senior Associate in Surgery
Boston Children's Hospital
Boston, Massachusetts

Y. Joseph Woo, MD

Norman E. Shumway Professor and Chair
Department of Cardiothoracic Surgery
Stanford University School of Medicine
Professor, by courtesy, Department of Bioengineering
Stanford University
Stanford, California

Douglas E. Wood, MD

Professor and Chief, Endowed Chair in Lung Cancer
Research
Division of Cardiothoracic Surgery
University of Washington
Seattle, Washington

John V. Wylie, Jr., MD

Tufts University School of Medicine
St. Elizabeth's Medical Center
Boston, Massachusetts

Stephen C. Yang, MD

Professor of Surgery
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Sai Yendamuri, MD

Associate Professor
Department of Thoracic Surgery
Roswell Park Cancer Institute
Buffalo, New York

Susan B. Yeon, MD, JD

Department of Medicine
Cardiovascular Division
Harvard-Thorndike Laboratory
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts;
Deputy Editor
UpToDate
Wolters Kluwer Health
Waltham, Massachusetts

Peter J. Zimetbaum, MD

Associate Professor of Medicine
Harvard Medical School
Cardiac Services
Beth Israel Deaconess Medical Center
Boston, Massachusetts

[†]Deceased.

PREFACE

Since its beginning as a specialty to treat tuberculosis and empyema, thoracic surgery has undergone constant change. Indeed, much has evolved in the fields of adult and pediatric cardiovascular and thoracic surgery even since our last edition. Our new ninth edition contains the latest information on the diagnosis and treatment of disease of the thorax. Especially in such areas as repair of aortic and mitral valvular disease, intervention for congenital heart disease, minimally invasive thoracic and cardiac surgery, surgical treatment of arrhythmias, and endovascular treatment of aortic disease, the field has markedly transformed. As with the previous editions, many of the same authors were asked to update their chapters, but some chapters have been added or eliminated and many others have been completely rewritten. Often new authors were chosen not based on poorly written previous chapters but to provide a novel perspective. We hope that the ninth edition will be received with the same enthusiasm as the last.

Several years ago, we lost one of the former editors of this textbook and a giant in the field of surgery, Dr. David Sabiston. We are fortunate to still have with us another editor, Dr. Frank Spencer. Dr. Spencer is not only one of the true pioneers in our specialty but a great mentor to many in our field. We are all indebted to both Dr. Sabiston and Dr. Spencer for their innumerable contributions to the field of surgery.

Finally, we would like to thank our families for providing immeasurable support not only for this textbook but for our entire careers.

Frank W. Sellke
Pedro J. del Nido
Scott J. Swanson

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¹From Coselli JS, LeMaire SA: Extent II repair of thoracoabdominal aortic aneurysm secondary to chronic dissection. *Ann Cardiothorac Surg* 1(3):394–397, 2012.

²Courtesy Ralph Chitwood, MD, Karen A. Gersch, MD, Michael W. Chu, MD, L. W. Nifong, MD, and Jerome Fuller, MD.

³From *Sabiston & Spencer Surgery of the Chest*, ed 8.

⁴From Vassiliades TA: Endoscopic and traditional minimally invasive direct coronary artery bypass. In Sellke FW, editor: *Atlas of cardiac surgical techniques*, Philadelphia, 2009, Elsevier.

⁵Courtesy Keith Horvath, MD.

⁶From Frazier OH: Implantation of the Heart Mate II. In Sellke FW, editor: *Atlas of cardiac surgical techniques*, Philadelphia, 2009, Elsevier.

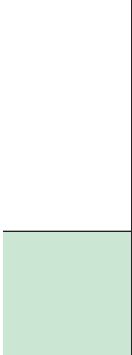
⁷From Reitz BA, Baumgartner WA, Borkon AM, the American College of Surgeons Video-Based Education Collection.

⁸Courtesy Lorenzo Menicanti, MD, and Marisa Di Donato, MD.

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SABISTON & SPENCER

SURGERY *of the* CHEST



SECTION 1

THORACIC SURGERY

SECTION OUTLINE

PART A EVALUATION AND CARE
PART B ENDOSCOPY
PART C TRAUMA
PART D TRACHEA
PART E BENIGN LUNG DISEASE
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PART I PLEURA
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PART A

EVALUATION AND CARE

PART OUTLINE

- | | |
|--|---|
| 1 ANATOMY OF THE THORAX | 3 PREOPERATIVE EVALUATION OF PATIENTS UNDERGOING THORACIC SURGERY |
| 2 RADIOLOGIC IMAGING OF THORACIC ABNORMALITIES | 4 PERIOPERATIVE CARE OF THE THORACIC SURGICAL PATIENT |

ANATOMY OF THE THORAX

Cynthia S. Chin • Rohit Shahani

CHAPTER OUTLINE

THORACIC CAGE

Thoracic Inlet
 Cervicoaxillary Canal
 Diaphragm
 Bony Thoracic Cage
 Sternum
 Ribs

MUSCLES OF THE THORAX

Intercostal Muscles
 Anatomy of Breathing

SURFACE ANATOMY**MEDIASTINUM****TRACHEOBRONCHIAL TREE****LUNGS****ESOPHAGUS****VESSELS OF THE THORAX**

Descending Thoracic Aorta
 Azygos Vein
 Thoracic Duct

NERVES OF THE THORAX

Vagus and Recurrent Laryngeal Nerves
 Thoracic Sympathetic Chain
 Phrenic Nerves

The thorax is the upper part of the trunk, bounded by the diaphragm inferiorly, the thoracic inlet superiorly, and the thoracic cage between. Vital organs, such as the heart and lungs, reside completely within the thoracic cavity, and other, equally vital organs, such as the aorta and esophagus, extend into the abdominal cavity. The thorax can be divided into a right and left hemithorax, separated by the mediastinum. This chapter gives an overview of the anatomy of the thoracic cavity and its contents.

THORACIC CAGE

The cylindrical thoracic cage has two main purposes: it provides protection for the underlying organs, and the dynamic interactions of the bony and muscular components of the chest wall allow changes in respiratory volumes.

The bony thorax has two apertures, or openings: the superior thoracic aperture, often referred to as the thoracic inlet or cervicothoracic junction, and the inferior thoracic aperture (Fig. 1-14).

Thoracic Inlet

The thoracic inlet is limited by the body of the first thoracic vertebra posteriorly, the first pair of ribs and their costal cartilages anterolaterally, and the superior border of the manubrium anteriorly. Many important structures

travel through the cervicothoracic junction. Resection of malignancies (e.g., Pancoast tumor) or repair of thoracic outlet syndrome requires intimate knowledge of the anatomic relationships in this area. In this kidney-shaped inlet, the trachea is midline and behind the great vessels, and the esophagus is posterior and slightly to its left. The innominate artery arises from the aortic arch and passes posterior to the manubrium and anterior to the trachea as it travels cephalad. The right and left internal jugular and subclavian veins join behind their respective sternoclavicular joints to form the left and right brachiocephalic veins. The left brachiocephalic vein travels right to join its counterpart to form the superior vena cava. The main muscles of this region are the sternocleidomastoid and scalene muscles, and the main nerves form the brachial plexus, but the phrenic and vagus nerves also pass through this aperture.

As the margin of the aperture slopes inferoanteriorly, the apex of each lung and its covering pleura (pleural cupola) project superiorly through the lateral parts of the thoracic inlet and are covered by a piece of cervical fascia, the suprapleural membrane (Sibson fascia).

Cervicoaxillary Canal

The cervicoaxillary canal is bounded by the first rib inferiorly, the clavicle superiorly, and the costoclavicular ligament medially (Fig. 1-2). The structures that pass through this space include the subclavian vein and artery and the brachial plexus.

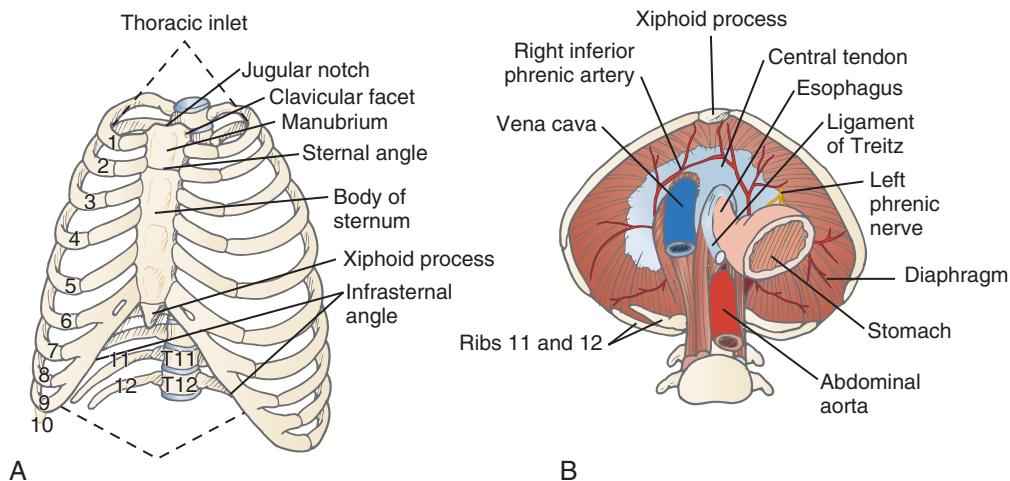


FIGURE 1-1 ■ **A**, Bony thorax. **B**, Inferior thoracic aperture. The vena cava enters the right hemithorax through the most cranial diaphragmatic opening, located at the level of the eighth thoracic vertebra (T8). The esophagus and vagus nerves enter the abdomen at the level of the T10 vertebra. The hiatus at T12 allows the aorta, azygos vein, and thoracic duct to pass in their respective directions.

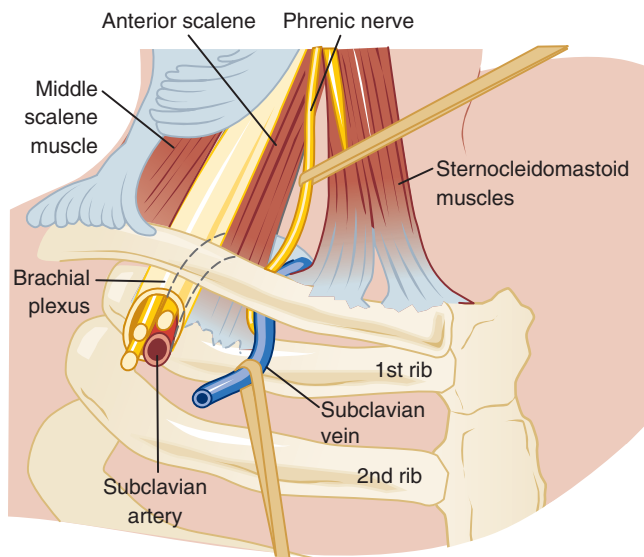


FIGURE 1-2 ■ Cervicoaxillary canal and the structures that traverse this opening.

The subclavian artery passes over the first rib and goes between the scalenus anterior and scalenus middle muscles. Before passing over the first rib on its way out of the cervicoaxillary canal, the subclavian artery gives off branches, including the thyrocervical, internal mammary, and vertebral arteries. It becomes the axillary artery after it exits from behind the pectoralis minor muscle. Compression of this artery can lead to poststenotic dilation, stenosis, aneurysmal formation, or occlusion.

The subclavian vein travels from the arm and goes behind the pectoralis minor muscle before going between the first rib and clavicle. This space is bounded medially by the costoclavicular ligament and laterally by the scalenus anterior muscles as it inserts onto the first rib.

Compression of the vein occurs in this area and can lead to stenosis and occlusion.

The brachial plexus is composed of nerve roots from the C5 through the T1 vertebral foramina. These nerve roots join to form the superior trunk (C5 and C6), the middle trunk (C7), and the inferior trunk (C8 and T1). These trunks separate into anterior and posterior divisions that fuse again to form lateral, medial, and posterior cords of the brachial plexus. The plexus travels through the tunnel formed by the anterior and middle scalene muscles. It travels between the first rib and the clavicle and finally under the pectoralis minor muscle to gain access to the arm.

In the normal anatomy, there is ample room for each of these structures. There are four major areas in which the vessels or nerves can be compressed ([Table 1-1](#)). This topic will be discussed in detail in [Chapter 26](#).

Diaphragm

The diaphragm, at the inferior thoracic aperture, separates the thoracic cavity from the abdominal cavity. The inferior thoracic aperture, which slopes inferoposteriorly, is limited by the 12th thoracic vertebra posteriorly, the 12th pair of ribs and costal margins anterolaterally, and the xiphisternal joint anteriorly.

The diaphragm is a curved, musculotendinous sheet that is mainly convex toward the thoracic cavity. It is a continuous sheet of muscle with low posterior and lateral attachments and high anterior attachments. The central tendon is a thin but strong aponeurosis. The domes of the diaphragm descend 2 cm during quiet respiration and can travel as much as 10 cm during heightened respiratory requirements. During expiration, the right diaphragm can rise as high as the level of the nipple, whereas the left rises to a level one rib space lower. With maximal inspiration, the diaphragm flattens against the abdominal contents. The right diaphragm can flatten to the level of the 11th rib, whereas the left can flatten to the level of

TABLE 1-1 Sites and Structures Compressed in Thoracic Outlet Syndrome

Site	Description	Abnormalities	Structures Compressed
Sternal-costovertebral circle	This aperture can be narrowed by bony variations	Cervical first rib First rib Long transverse process	Subclavian artery Subclavian vein Brachial plexus
Scalene muscle triangle	The scalenus anterior and middle muscle insert on the first rib, creating a tunnel	Scalenus anterior and middle	Subclavian artery Brachial plexus
First rib, clavicular space	The neurovascular structures lie above the rib and below the clavicle	Costoclavicular ligament Clavicle First rib	Subclavian vein Subclavian artery Brachial plexus
Behind the pectoralis minor muscle	The neurovascular structures travel to and from the arm behind this muscle	Pectoralis minor Costocoracoid ligament	Subclavian vein Subclavian artery Brachial plexus

the 12th rib. The right diaphragm has to work against the liver, whereas the left needs to push only against the stomach and spleen; therefore, the right diaphragm has significantly stronger fibers than the left.

The costal diaphragm receives its blood supply from the lower five intercostal and subcostal arteries, and the central portion is supplied by the phrenic arteries. The phrenic arteries can arise directly from the aorta, above the celiac axis, as a common trunk or individually. Occasionally, they arise from the celiac or renal arteries. The sole motor supply to the diaphragm is the phrenic nerve. It also supplies sensory fibers to the parietal and peritoneal pleura overlying the diaphragm; this accounts for the diaphragmatic irritation that is sometimes interpreted as ipsilateral shoulder pain.

The diaphragm has several openings through which structures can transverse from one cavity to another (see Fig. 1-1B). The inferior vena cava hiatus lies anteriorly and to the right of the midline, at the level of vertebra T8. The right phrenic nerve travels through this hiatus, and the left phrenic nerve penetrates laterally through its own opening at the same level. The esophageal aperture is at the level of the T10 vertebra, and the right and left vagal trunks that adhere to it enter the abdomen along with the esophagus.

The aortic aperture, at the T12 vertebral level, is formed by the interdigitating fibers (median arcuate ligament) of the right and left diaphragmatic crura. The azygos and hemiazygos veins and the thoracic duct also pass through this opening.

The greater and lesser splanchnic nerves gain access to the abdominal cavity via two small apertures in each of the crura, and musculophrenic branches of the internal mammary artery penetrate the diaphragm through small apertures near its connection with the costal cartilages of ribs seven to nine.

Diaphragmatic hernias can develop through known openings, such as a hiatal hernia through the esophageal hiatus, or through congenital defects. The most common congenital abnormality is a Bochdalek hernia, in which abdominal contents go through a posterolateral defect. This abnormality is seen more commonly on the left side. A Morgagni hernia, however, occurs with a defect in the anterior aspect of the diaphragm just lateral to the xiphoid.

Bony Thoracic Cage

Sternum

The sternum or breastbone is made of cancellous bone and filled with hemopoietic marrow throughout life. The main parts, the manubrium and body, are connected by a secondary cartilaginous joint that normally never ossifies and contributes to movement of the ribs.

Up to puberty, the six segments, or sternebrae, are held together by hyaline cartilage. The central four segments fuse to form the body of the sternum between 14 and 21 years of age. The manubrium sterni (superiorly) and the xiphoid process (inferiorly) remain separate.

The manubrium receives the sternal ends of the clavicles in a shallow concave facet. The widest portion of the manubrium has bilateral costal incisurae that articulate with the first costal cartilage to form a primary cartilaginous joint. The second costal cartilage articulates with both the lower lateral ends of the manubrium and the body of the sternum, forming separate synovial joints. The muscular attachments of the manubrium include the sternocleidomastoid muscle, the sternohyoid and the sternothyroid superiorly, and the pectoralis major muscle anterolaterally. Most of the posterior surface is bare bone, which can be in contact with the brachiocephalic vein unless thymic remnants lie between.

The gladiolus, or body of the sternum, is slanted at a steeper angle than the manubrium; its articulation with that bone forms the sternal angle. Ossification of this joint, synchondrosis, in adult life can limit normal movement at this joint. The articular facets for ribs two to seven lie along the lateral border of the body of the sternum. These make single synovial joints with the costal cartilages. The facets for the sixth and seventh costal cartilages can coalesce, especially in females. The lateral border gives attachment to the anterior intercostal membrane and the internal intercostal muscles, and the pectoralis major arises anteriorly. Weak sternopericardial ligaments pass into the fibrous pericardium.

The cartilaginous xiphoid may be bifid or perforated, is of variable length, and usually ossifies in the fourth decade of life. The costoxiphoid ligaments prevent its displacement during diaphragmatic contractions.

Ribs

The 12 pairs of ribs are divided into the upper seven, which are called *true ribs* or *vertebrosternal ribs* because they form complete loops between the vertebrae and the sternum, and the lower five ribs, which fail to reach the sternum and are considered false ribs. The 8th, 9th, and 10th ribs are called *vertebrocostal* because each of their costal cartilages articulates with the adjacent rib cartilage. Ribs 11 and 12 are free-floating or *vertebral ribs* because their only articulation is with their vertebrae.

Ribs three to nine are classified as typical ribs and have a head, neck, and a shaft. The head has an upper and a lower articular facet divided by a crest for articulation with two adjacent vertebrae in synovial costovertebral joints, the lower facet articulating with the upper border of its own vertebra. The neck is flattened, with the upper border curling up into a prominent ridge—the crest. A tubercle projects posteriorly from the end of the neck and marks the junction of the neck and the body (Fig. 1-3).

MUSCLES OF THE THORAX

The muscles of the chest wall serve to protect the contents of the thoracic cavity, and they assist the movements of the thorax and upper extremities (Fig. 1-4). The 17 muscles of the chest wall are not discussed in detail here, but Table 1-2 lists them with their innervations and sites of attachments. This section focuses on muscle groups that are used in chest wall reconstruction. The latissimus dorsi, pectoralis major, serratus anterior, trapezius, rectus abdominis, and external oblique are the six major muscles that are available for reconstruction (Table 1-3).

The latissimus dorsi is the largest muscle of the thorax. It originates from the lower six thoracic spinous processes and from the lumbodorsal fiber, which is attached to the lumbar and sacral vertebrae. It also has fibers originating from the iliac crest. The muscle narrows and then inserts on the intertubercular groove of the humerus. It is sup-

plied by the thoracodorsal artery, a branch of the subscapular artery. The subscapular artery arises from the axillary artery and gives a branch to the serratus anterior muscle before supplying the latissimus dorsi. The artery can be found on the undersurface of the latissimus dorsi. The mobile arterial supply and excellent musculocutaneous collaterals allow this muscle to be moved with or without its overlying skin.

The pectoralis major muscle arises from the sternum, clavicle, and first seven ribs. It inserts on the bicipital humeral groove. It receives arterial supply from a pectoral branch of the thoracoacromial artery arising midclavicularly. It also receives some blood supply from the internal mammary, lateral intercostals, and lateral thoracic perforators. This flap is most frequently used for sternal defects.

Located between the latissimus dorsi and pectoralis major muscles is the serratus anterior muscle. This small muscle originates from the superior borders of the eighth through tenth ribs. It inserts on the tip of the scapula. Its blood supply is from a branch of the thoracodorsal artery and from the long thoracic artery. It can be used for intrathoracic purposes such as bronchial stump coverage or muscle interposition between the trachea and esophagus after a tracheoesophageal fistula repair.

The trapezius muscle arises from the occipital bone and from the spinous process of the seventh cervical vertebra and all the thoracic vertebrae. It inserts on the lateral aspect of the clavicle, the acromion process, and the spine of the scapula. It receives its blood supply from the transverse cervical artery. Although the trapezius is a large muscle, its use is limited to reconstruction of the upper thoracic cavity.

Arising from the inferior borders of the 4th through 12th ribs and inserting on the iliac crest is the external oblique muscle. It accepts blood supply from the lower thoracic intercostal arteries. Unlike the trapezius muscle, uses of the external oblique muscle are limited to the thoracic cavity below the inframammary crease.

The rectus abdominis muscle spans the entire anterior abdominal wall. It originates at the pubic crest and rises superiorly to insert on the fifth through seventh rib cartilages and xiphoid process. The superior and inferior epigastric arteries supply this vast muscle. It has been used for reconstruction of the anterior thoracic cavity, most notably after breast surgery.

Intercostal Muscles

Fibers of the intercostalis externi muscle arise from the sharp lower border of the rib above and course inferomedially (i.e., in the direction of the fingers when the hands are put into the front pockets of trousers) to the smooth upper border of the rib below. Anteriorly, it is replaced by the anterior intercostal membrane. Between the bony ribs is muscle; between the costal cartilages is membrane. In the lower spaces, the muscle interdigitates with the fibers of the external oblique (Fig. 1-5).

The intercostalis interni muscle runs from the lower costal groove of ribs 1 to 11, to the upper surfaces of ribs 2 to 12 downward and backward. Anteriorly, the muscle extends up to the sternum, but posteriorly only up to the

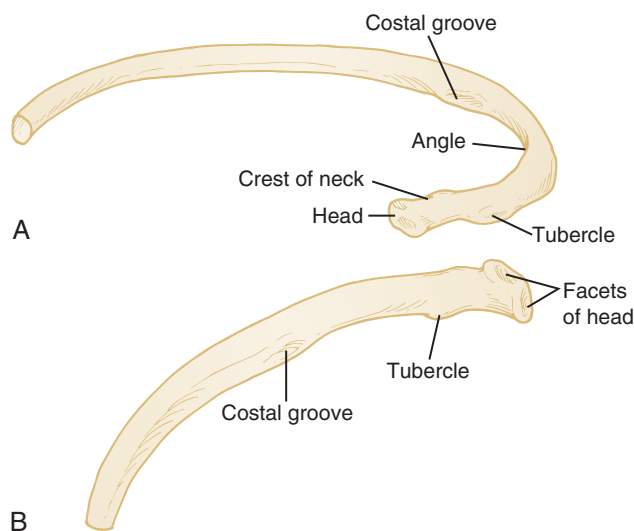


FIGURE 1-3 ■ Typical rib.

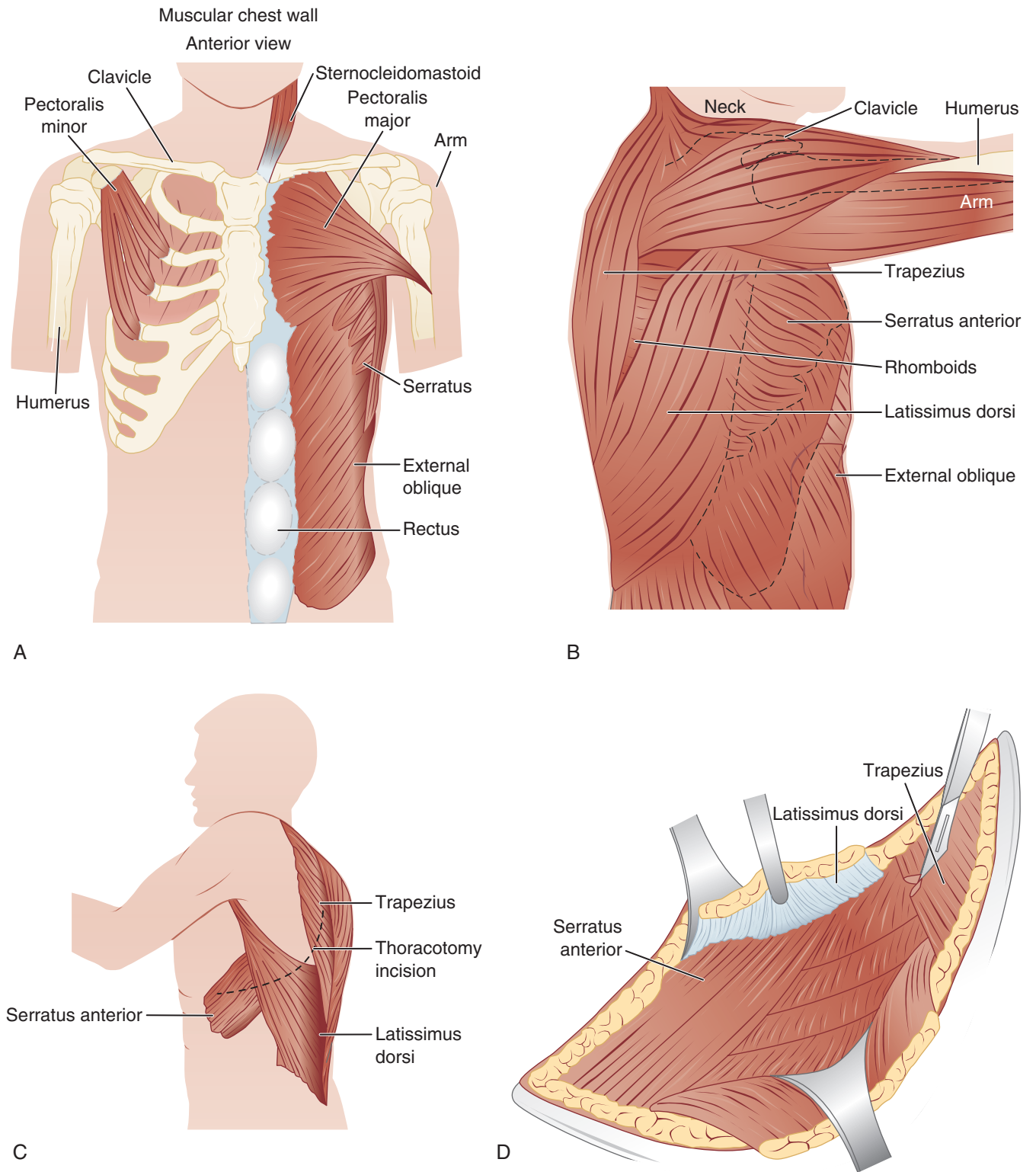


FIGURE 1-4 ■ **A**, Anterior view of major muscles of the chest wall. **B**, Lateral view of the muscles of right hemithorax. **C**, Dotted line indicates placement of a standard posterolateral thoracotomy. **D**, Incisional view of muscles encountered during a posterolateral thoracotomy.

TABLE 1-2 Attachments and Innervation of the Muscles of the Thoracic Wall

Muscle	Proximal Attachments	Distal Attachments	Innervation
Pectoralis major sternocostal head	Half of sternum, costal cartilages 1 to 6, aponeurosis of external obliquus muscle	Lateral lip of intertubercular sulcus of humerus	Medial pectoral nerve (C8-T1)
Pectoralis major clavicular head	Medial half of clavicle	Lateral lip of intertubercular sulcus of humerus	Lateral pectoral nerve (C5, 6, 7)
Pectoralis minor	Ribs 3 to 5	Coracoid process of scapula	Medial pectoral nerve
Subclavius	First rib	Medial clavicle	Nerve to subclavius (C5-6)
Deltoid	Lateral third of clavicle, acromion, and spine of scapula	Deltoid tuberosity of humerus	Axillary nerve (C5-6)
Serratus anterior	Angles of superior 10 ribs	Medial border of scapula	Long thoracic muscle nerve (C5, 6, 7)
Supraspinatus	Supraspinous fossa of the scapula, fascia of trapezius	Greater tubercle of the humerus	Suprascapular nerve (C5)
Infraspinatus	Infraspinous fossa	Greater tubercle of the humerus	Suprascapular nerve
Subscapularis	Costal surface of the scapula	Lesser tubercle of the humerus and its crest	Upper (C5-6) and lower (C5, 6, 7) subscapular nerve
Latissimus dorsi	Spinous processes of T7-12, L1-5, S1-3 vertebrae, posterior part of iliac crest, lower three to four ribs	Crest of the lesser tubercle and floor of the intertubercular groove of the humerus	Thoracodorsal nerve (C6-7)
Serratus posterior inferior	Spine of C6-T2 vertebrae	Angles of ribs 2 to 5	Segmental intercostal nerves
Serratus posterior superior	Spine of T11-L2 vertebrae	Lower border of ribs 9 to 12	Segmental intercostal nerves
Trapezius	Ligamentum nuchae, external occipital protuberance, thoracic vertebral spinous processes	Lateral one third of clavicle, acromion process along spine of scapula	Spinal accessory nerve
Levator scapulae	Transverse process of C1, C2, C3, C4 (cervical vertebrae)	Medial border of scapula, superior angle to base of scapular spine	Dorsal scapular nerve (C5)
Rhomboid major and minor	Spinous processes of C7-T5 and supraspinous ligaments	Medial border of scapula up to the inferior angle	Dorsal scapular nerve (C5)
Teres major	Lower lateral border of the scapula	Crest of the lesser tubercle of the humerus	Lower subscapular nerve (C5, 6, 7)
Teres minor	Mid to upper lateral border of the scapula	Greater tubercle of the humerus	Axillary nerve (C5-6)

TABLE 1-3 Arterial Supply of Muscles Used in Chest Wall Reconstruction

Muscle	Arterial Supply
Latissimus dorsi	Thoracodorsal artery
Pectoralis major	Thoracoacromial, lateral thoracic perforators, internal mammary artery, lateral intercostal artery
Serratus anterior	Thoracodorsal artery, long thoracic artery
Trapezius	Transverse cervical artery
External oblique	Lower thoracic intercostal arteries
Rectus abdominis	Superior and inferior epigastric arteries

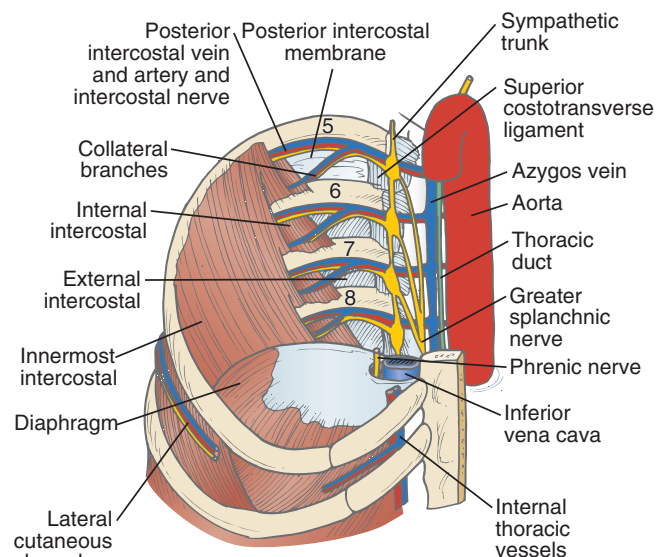


FIGURE 1-5 ■ Spatial organization of the thoracic wall on the right side.

angles of the rib. Beyond that, it is replaced by the internal intercostal membrane, which attaches to the tubercle of each rib and vertebra.

The innermost or transversus layer is divided into three groups: the innermost intercostals (anterolateral), subcostal (posterior), and transversus thoracis (anteromedial) muscles. The fibers run downward and backward, as in the internal intercostal muscles. The subcostal muscles lie in the paravertebral gutter, are better developed inferiorly, and cross more than one space. The transversus thoracis was formerly called the *sternocostalis*, a more appropriate name. Digitations arise from the sternum bilaterally to the costal cartilages of ribs two to six.

The intercostalis intimi muscles also traverse more than one space and are better developed in the lower lateral spaces. The neurovascular bundle runs in the plane between the innermost and outer two layers. From above downward, the order is vein, artery, and nerve (mnemonic: VAN). Beyond the angle of the rib posteriorly, they are protected by the downward projection of the lower border of the rib. For a thoracotomy, the periosteum is stripped off the upper half of the rib, avoiding the lower border and the neurovascular bundle (Fig. 1-6).

As in the rest of the body, the mixed spinal nerve is formed from a dorsal and a ventral root, the dorsal root being sensory and the ventral root containing somatic motor neurons. As it emerges from the intervertebral foramina, it branches into a dorsal and a ventral ramus. The dorsal ramus of the thoracic spinal nerve supplies the paravertebral back muscles and skin of the back. The ventral ramus communicates with the sympathetic chains via white rami communicantes (postganglionic fibers). Beyond this point, the true intercostal nerve lies just superficial to the parietal pleura in the endothoracic fascia. It gains the costal groove between the innermost intercostal and the internal intercostal muscles near the angle of the rib, where a collateral branch is given off. This small branch supplies the muscles of the space, the

parietal pleura, and the periosteum of the rib. The main nerve itself has muscular branches, a lateral cutaneous branch, and a terminal anterior cutaneous branch. The lateral cutaneous branch given off along the midaxillary line gives off anterior and posterior branches to supply the skin over that space. Just lateral to the sternal margin, the terminal anterior cutaneous branches of the upper six nerves pierce the internal intercostal muscles, the external intercostal membrane, and the pectoralis major to reach skin. The lower five intercostal nerves slope downward behind the costal margin into the neurovascular plane of the abdominal wall. The subcostal or 12th thoracic nerve leaves the thorax by passing behind the lateral arcuate ligament and the subcostal artery and vein (Fig. 1-7). The cutaneous branches of each dermatome tend to overlap considerably; hence anesthesia after thoracic incisions is quite rare unless multiple intercostal nerves have been damaged. The first intercostal nerve is very small and supplies no skin, lacking both lateral and anterior cutaneous branches.

Two sets of intercostal arteries, the posterior and the anterior, are responsible for supplying the intercostal spaces. Their course and branching patterns closely conform to those of the intercostal nerves. The posterior intercostal arteries are branches of the descending thoracic aorta except in the first two spaces, where they are branches of the supreme intercostal artery, given off by the costocervical trunk of the second part of the subclavian artery. The aortic branches lie on the left side of the mediastinum; consequently, the right posterior intercostal arteries are longer, can be easily dissected in the left chest, and are seen best while operating on descending thoracic aortic aneurysms.

The anterior intercostal arteries are branches of the internal thoracic arteries from the first part of the subclavian artery. The internal thoracic artery runs anterior to the transversus thoracis and on the internal surface of the costal cartilages and the internal intercostal muscles. Approximately one fingerbreadth from the border of the sternum running vertically downward, the artery gives off two anterior intercostal arteries in each space. At the costal margin, below the sixth costal cartilage, the artery divides into the superior epigastric and musculophrenic arteries. The anterior intercostal arteries are smaller than the posterior intercostal arteries with which they anastomose and run predominantly along the lower border of each costal cartilage in the same fascial neurovascular plane. In the lower spaces, they are branches of the musculophrenic artery. There are no true anterior intercostal arteries in the last two spaces.

The internal thoracic arteries also give branches to the mediastinum, the thymus, the pericardium, and the sternum, and especially large perforating branches in the second to fourth space, the predominant supply to the lactating breast in females.

In each space, there are one posterior and two anterior intercostal veins, designated by names identical to the arteries that they accompany. The veins lie above the artery and the nerve throughout their course (i.e., VAN) in the intercostal space. The anterior veins drain into the musculophrenic and internal thoracic veins. The vein of the first space or the supreme intercostal vein, posteriorly,

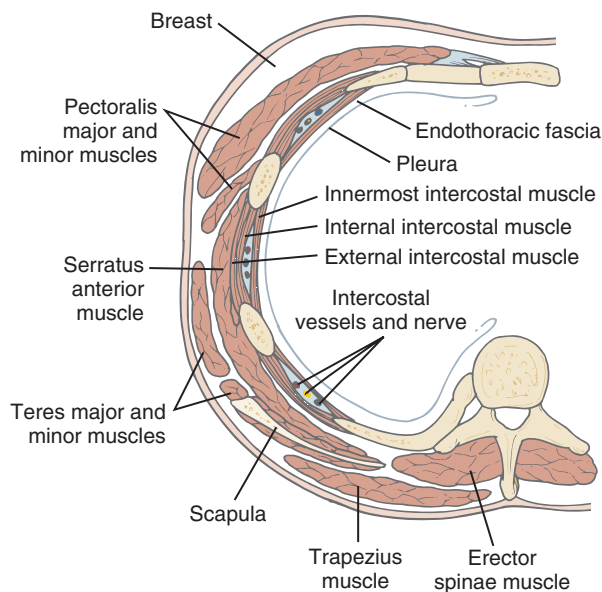


FIGURE 1-6 ■ Layers of the chest wall.

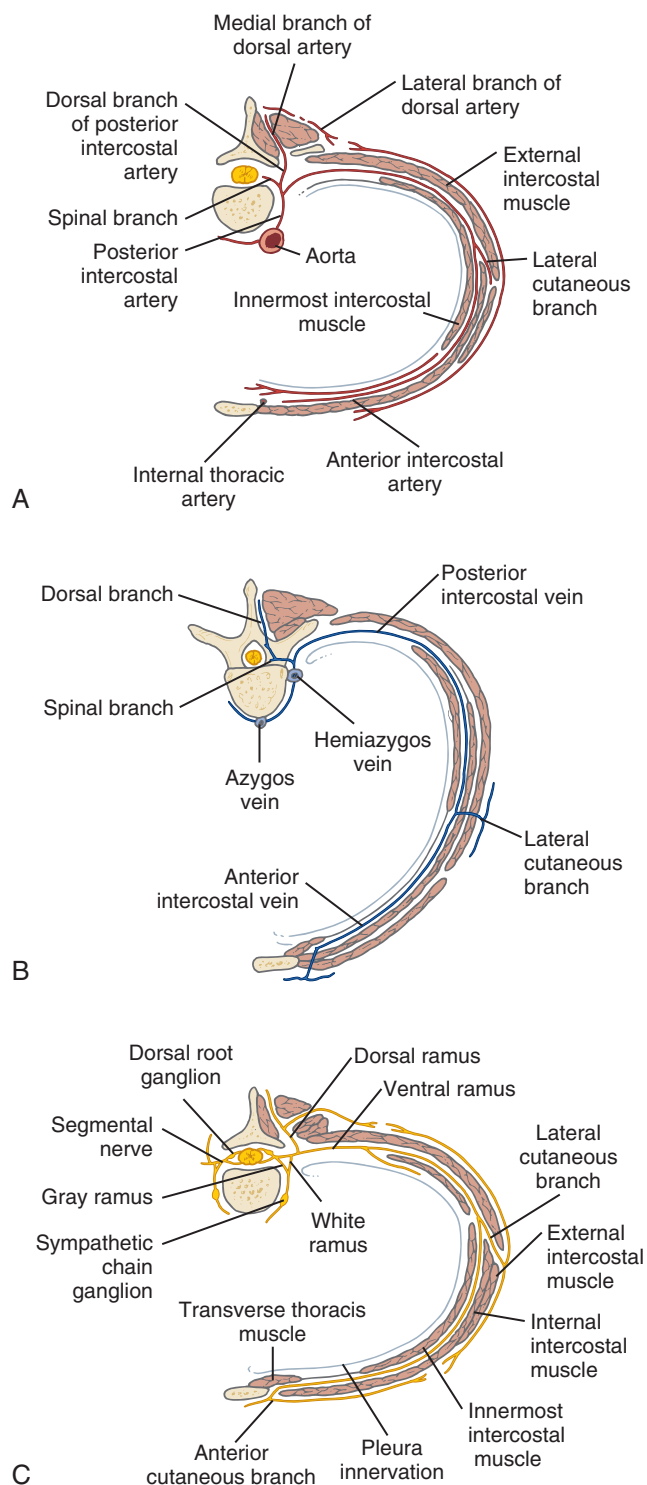


FIGURE 1-7 ■ Organization of the intercostal space and the relationship of the arteries (A), veins (B), and nerves (C) to the muscle layers.

may be a tributary of the brachiocephalic, vertebral, or superior intercostal vein. The superior intercostal vein is formed by the posterior intercostal veins of the second, third, and sometimes the fourth spaces. This vein drains into the azygos vein on the right side, and on the left side it arches over the aorta, superficial to the vagus

and deep to the phrenic to open into the left brachiocephalic veins. Subcostal veins join the ascending lumbar veins and ascend on the left side as the hemiazygos and on the right side as the azygos vein draining the lower eight spaces. The blood in the hemiazygos vein drains across the midline, through median anastomoses into the azygos vein.

The internal thoracic vessels are part of the anastomotic chain that links the subclavian artery and brachiocephalic veins to the external iliac vessels. The intercostal vessels in turn connect to the descending aorta and azygos system of veins. In the presence of obstruction to flow, these anastomoses provide alternative channels for arterial and venous blood flow.

Anatomy of Breathing

Simple respiratory effort is attained mostly by diaphragmatic motion. The bony and muscular components of the thorax remain a stable cavity while the diaphragm acts as a piston. It flattens during inspiration to create negative intrathoracic pressure, resulting in expansion of the lungs. Once inspiration is complete, the diaphragm relaxes and the lung recoils to its original position. The intercostal muscles are important to prevent paradoxical motion during inspiration.

The thoracic cavity can change to meet increased respiratory needs. The accessory muscles of the chest wall help to increase intrathoracic volume during inspiration and decrease volume during expiration. In addition to the piston action of the diaphragm, the accessory muscles elevate the sternal body and xiphoid process anteriorly and superiorly. The lower ribs attached to the sternum follow this movement and therefore increase the diameter of the lower chest cavity. The manubrium of the sternum is relatively fixed, and the chest cavity at this level does not contribute significantly to increased respiratory needs. This dynamic response of the chest cavity helps to meet increasing demands for oxygenation and ventilation.

SURFACE ANATOMY

An understanding of surface anatomy enables identification of bony and prominent structures and hence the position of deeply related structures (Fig. 1-8 and Table 1-4). The chest radiograph (Fig. 1-9) is an extension of the routine physical examination.

The suprasternal notch on the superior aspect of the manubrium is palpable between the prominent medial ends of the clavicle, and it lies at the level of the lower border of the body of the second thoracic vertebra. At the lower sternal border, the palpable xiphisternum is covered by the rectus abdominis muscles. The xiphisternal joint lies opposite the body of the ninth thoracic vertebra. The sternal angle of Louis (the junction of the manubrium with the body of the sternum) is an important landmark for the description of structures inside the chest. At this level, the second costal cartilage joins the lateral margin of the sternum. The sternal angle lies opposite the lower border of the fourth thoracic vertebral

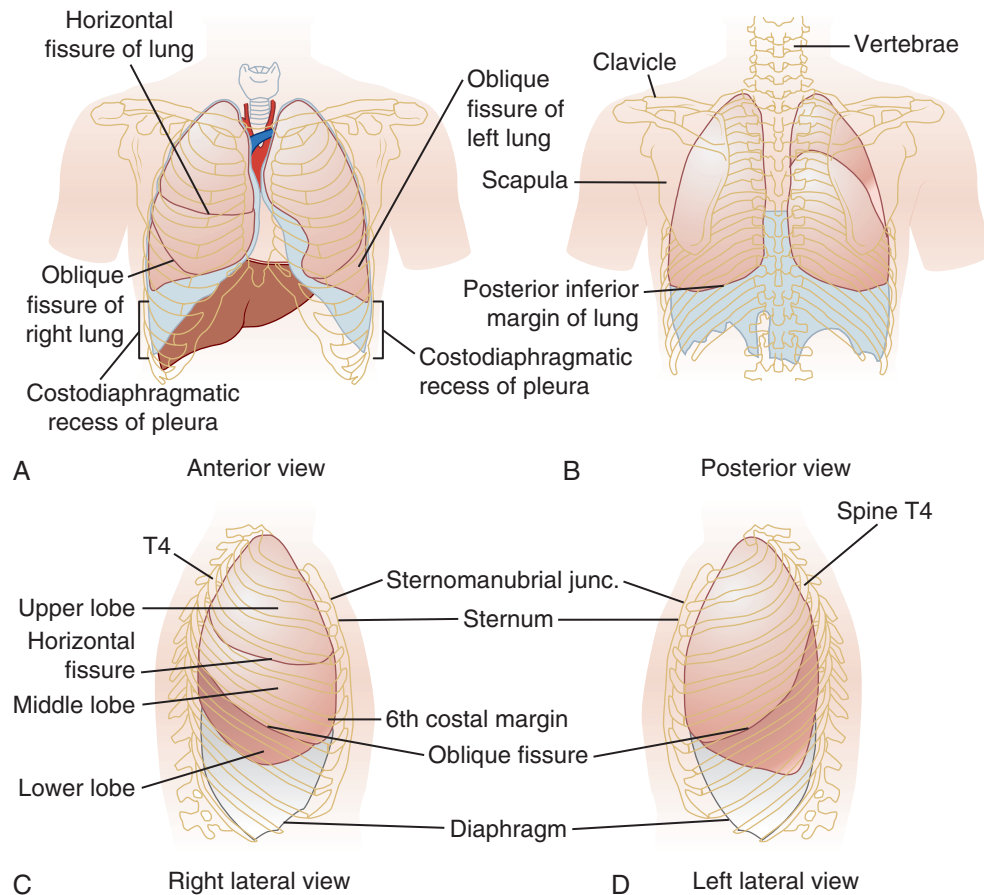
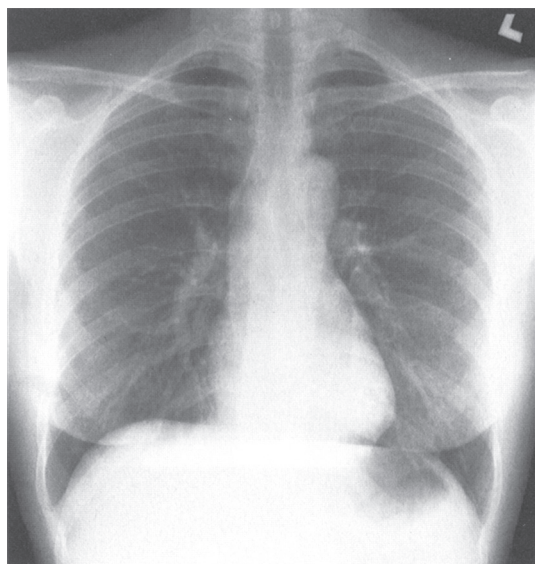


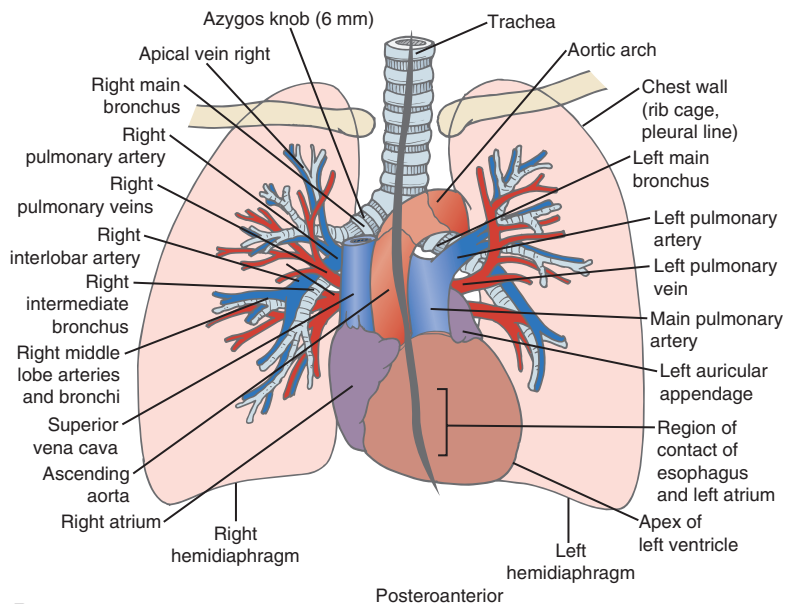
FIGURE 1-8 ■ Correlation of lungs and overlying bony structures. **A**, Anterior view. **B**, Posterior view. **C**, Right lateral view. **D**, Left lateral view. The right oblique fissure courses anteriorly at the level of the fifth rib, ending near the level of the sixth rib. The posteriorly left oblique fissure is more variable, starting at a level between the third and fifth ribs. Anteriorly, it ends consistently at the level of the fifth rib. The horizontal fissure starts anteriorly at the fourth costal cartilage and joins the oblique fissure at the level of the fifth rib.

TABLE 1-4 Surface Landmarks and Correlating Intrathoracic Structures

Landmark	Underlying Structures
Sternocleidomastoid muscle (SCM)	Internal jugular vein, cupola of pleura Internal mammary artery originates between sternal and clavicular heads of the SCM and runs 2 cm from sternal edge until the sixth costal cartilage
Right manubrial border	Right brachiocephalic vein, origin of superior vena cava, brachiocephalic artery
Manubrium	Aortic arch and origin of great vessels, left brachiocephalic vein
Left manubrial border	Left common carotid and left subclavian vessels
Angle of Louis	Trachea bifurcation Level of the fourth vertebral body
Body of sternum and third to sixth costal cartilages	Heart
At the level of the angle of Louis in the right hemithorax	Azygos vein joins superior vena cava Thoracic duct crosses midline
At the level of the angle of Louis in the left hemithorax	Aortic pulmonary window
Left third costal cartilage	Origin of aorta and pulmonary artery
Right third costal cartilage	Superior vena cava empties into right atrium
Sixth costal cartilage	Level of the eighth vertebral body Inferior vena cava and right phrenic nerve pass through the diaphragm
Left seventh costal cartilage	Tenth vertebral body Esophagus and vagal trunks pass through the diaphragm
Tip of the scapula	Seventh intercostal space



A



B

FIGURE 1-9 ■ **A**, Posteroanterior radiograph of the chest in a normal male adult. **B**, Schematic representation of the surface projection of intrathoracic structures seen on a normal chest radiograph. (From Butler P, Mitchell AWM, Ellis H: *Applied radiological anatomy*. Cambridge, 1999, Cambridge University Press.)

body. All other ribs are counted from this point, as the first rib is not palpable. The angle of Louis is a useful reference point for counting ribs on a computed tomography scan, and for localizing structures in the thoracic cavity. For example, the sternomanubrial joint is an important level for many structures. At this level, the azygous crosses midline to join the superior vena cava, the thoracic duct crosses from the right hemithorax to the left hemithorax on its ascent to the left neck, the trachea bifurcates into right and left main-stem bronchus, and the aorta and pulmonary artery form the aortic pulmonary window.

The clavicle articulates with the acromion process of the scapula laterally and the sternum medially. Just below the medial joint lies the fusion of the first ribs with the lateral margin of the sternum. The costal margin is the lower boundary of the bony thorax and is formed by the cartilages of the 7th, 8th, 9th, and 10th ribs and the ends of the 11th and 12th cartilages. The lowest part of the margin is the 10th rib, and it lies at the level of the third lumbar vertebra. The lower border of the pectoralis major muscle forms the anterior axillary fold. The tendon of the latissimus dorsi forms the posterior axillary fold as it passes around the lower border of the teres major muscle.

Posteriorly, the thoracic cage is covered by muscles (trapezius, latissimus dorsi, and erector spinae) and is obscured by the scapula, but there are a few useful landmarks to the rib levels. The superior angle of the scapula lies opposite the spine of the second thoracic vertebra. The transversely running spine of the scapula is easily felt and lies at the level of the third thoracic vertebra. The lower angle of the scapula overlies the seventh rib.

The first prominent spinous process in the low midline of the neck posteriorly is that of the seventh cervical vertebra, the vertebra prominens. The tip of a spinous

process of a thoracic vertebra lies posterior to the body of the next vertebra below.

The apex of the pleura extends approximately 3 cm above the medial third of the clavicle and behind the sternocleidomastoid muscle. It passes downward and medially behind the sternoclavicular joints. The left pleura, at the level of the fourth costal cartilage, deviates laterally for a variable distance from the cardiac notch. Both pleurae lie at the level of the 8th rib in the midclavicular line, at the level of the 10th rib in the midaxillary line, and at the level of the 12th rib at the paravertebral level posteriorly.

The more constant right oblique fissure of the lung follows the course of the fifth rib from the midline posteriorly, more toward its lower border. Anteriorly it ends at the costochondral junction at the level of the sixth rib. The left oblique fissure has a more variable origin from the third to the fifth rib level, but anteriorly it follows a more predictable course along the fifth rib.

The transverse or horizontal fissure (present only on the right side) is marked by a horizontal line that runs backward from the fourth costal cartilage to reach the oblique fissure at the midaxillary line at the level of the fifth rib.

The pulmonary hilum lies laterally to the sternum behind the second to fourth costal cartilages and in front of the fourth to sixth vertebral bodies. The pulmonary trunk starts behind the left costal cartilage, and it ascends to the level of the second costal cartilage before it bifurcates. The aorta also arises from the heart at the level of the left third costal cartilage. It travels superiorly to the right side of the angle of Louis before arching leftward.

The great vessels arise from the aortic arch behind the sternomanubrial joint. The brachiocephalic artery travels under the manubrium toward the right sternoclavicular joint. The left common carotid artery makes a similar

ascent under the manubrium but travels toward the left sternomanubrial joint before entering the neck. The left subclavian artery travels just left of the common carotid artery. The use of surface anatomy to guide incisions and approaches for various thoracic and cardiac procedures will be discussed in later chapters.

Transcribing a chest radiograph and a computed tomographic scan to a physical location on a patient is vital for any thoracic surgical procedure, but it is particularly important for video-assisted thoracic surgery (VATS). Often, small nodules are hard to palpate thoracoscopically unless a more localized area is identified. Anatomic landmarks can help to divide and further subdivide the lung to help localize these nodules (Fig. 1-10).

MEDIASTINUM

The mediastinum is centrally located in the thoracic cavity. A pleural cavity bounds each side of the mediastinum, and its inferior and superior borders are defined by the diaphragm and the thoracic inlet, respectively. In classic descriptions, the mediastinum is divided into a superior and inferior mediastinum. The superior mediastinum lies above the plane from the sternomanubrial joint to the fourth thoracic vertebra. In the superior compartment lies the upper part of the thymus, the lower ends of the strap muscles, and the upper half of the superior vena cava, trachea, thoracic duct, and esophagus. The inferior compartment is further subdivided into anterior, middle, and posterior.

In 2000, Shields recategorized the mediastinum into three compartments: anterior, middle, and posterior. The diaphragm and bilateral pleural cavities remain the inferior and lateral borders for each of these compartments. The superior border now extends to the thoracic inlet for each compartment. The anterior compartment lies

between the sternum and pericardium and the great vessels. The posterior compartment lies behind the pericardium, great vessels, and tracheal bifurcation and extends to the vertebral column. The middle mediastinum is between the anterior and posterior compartments and includes the entire thoracic inlet (Table 1-5). Disease entities of the mediastinum are discussed in later chapters.

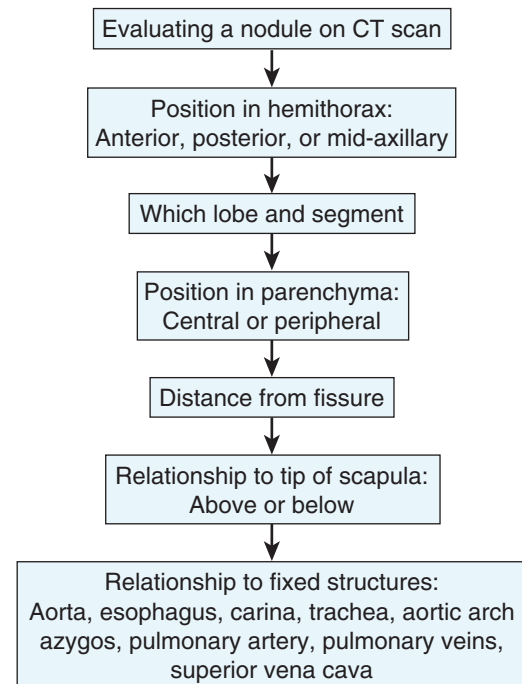


FIGURE 1-10 ■ Algorithm for correlating a pulmonary nodule on a computed tomographic (CT) scan for the patient during the operation.

TABLE 1-5 Structures in the Mediastinum

Compartment	Structures or Tissues	Pathologic Entities
Anterior	Thymus Internal mammary artery Fat Internal thoracic and prevascular lymph nodes Connective tissue Ectopic parathyroid Substernal thyroid	Thymic disease Teratoma Substernal thyroid Disease of lymph nodes Parathyroid disease Bronchogenic cysts
Middle	Heart Great vessels Trachea Proximal bronchi Vagus and phrenic nerves Esophagus Thoracic duct Proximal azygos vein Descending aorta Paratracheal lymph nodes	Lymph node disease (malignant and benign) Esophageal disease Tracheal disease Bronchogenic, pericardial, and esophageal cysts Morgagni hernia Angiomas
Posterior	Sympathetic chain Distal azygos vein Posterior paraesophageal lymph nodes	Neurogenic tumors Spinal lesions

TRACHEOBRONCHIAL TREE

The trachea is a continuation of the larynx at the infra-cricoid level. Its average length is 11.8 cm. It has approximately 17 to 21 incomplete cartilaginous rings (4 mm wide and 1 mm thick) that maintain its elliptical shape in adults, but the shape is more circular in children. The coronal dimensions in men and women are 13 to 25 mm and 10 to 21 mm, respectively. The sagittal dimensions also differ between the sexes: 13 to 27 mm in men and 10 to 23 mm in women. With flexion of the neck, the trachea becomes almost completely an intrathoracic organ, coursing backward and downward from a subcutaneous position to rest ultimately on the esophagus and vertebral column at the level of the carina. Bearing a common embryologic origin with the esophagus, these two structures remain in intimate contact with one another, with the posterior muscular membranous wall of the trachea resting on the esophagus. The thyroid is anterior to the trachea in the neck and in the mediastinum, the thymus and parts of some of the great vessels lay anterior to the distal trachea.

The isthmus of the thyroid crosses the trachea at the second ring. The innominate artery crosses the mid trachea obliquely from right to left, and the arch of the aorta indents the esophagus slightly and appears to shift the trachea toward the right, away from its midline position. Lateral structures on the right side are predominantly venous and include the superior vena cava, azygos,

and right brachiocephalic veins; lateral arterial structures on the left side include the arch of the aorta and the left common carotid artery. Both right and left vagi, along with their recurrent laryngeal nerves and the right and left sympathetic trunks, are also laterally related to the trachea. These intimate relationships of the trachea with surrounding organs are of important concern when performing cervical mediastinoscopy with lymph node biopsy.

Segmental blood supply to the trachea is from the inferior thyroid, subclavian, supreme intercostals, internal thoracic, innominate, and superior and middle bronchial arteries. This blood supply is shared with the esophagus and the main bronchi. Anastomotic arcades develop on the lateral tracheal wall and feed transverse vessels that travel between cartilaginous rings. For this reason, the trachea should not be devascularized circumferentially for a distance greater than 1 to 2 cm. The lateral arcades allow safe pretracheal dissections. Lymph drains to the posterior inferior group of deep cervical nodes and to paratracheal nodes.

The trachea bifurcates into the right and left principal bronchi (Fig. 1-11). The right principal bronchus arises in a more direct line with the trachea at an angle of approximately 25 degrees and passes behind the superior vena cava to reach the hilum of the lung. The left principal bronchus is slightly smaller, leaves the trachea more obliquely at an angle of approximately 45 degrees, passes below the arch of the aorta and the left pulmonary artery, and is almost twice as long as the right main bronchus

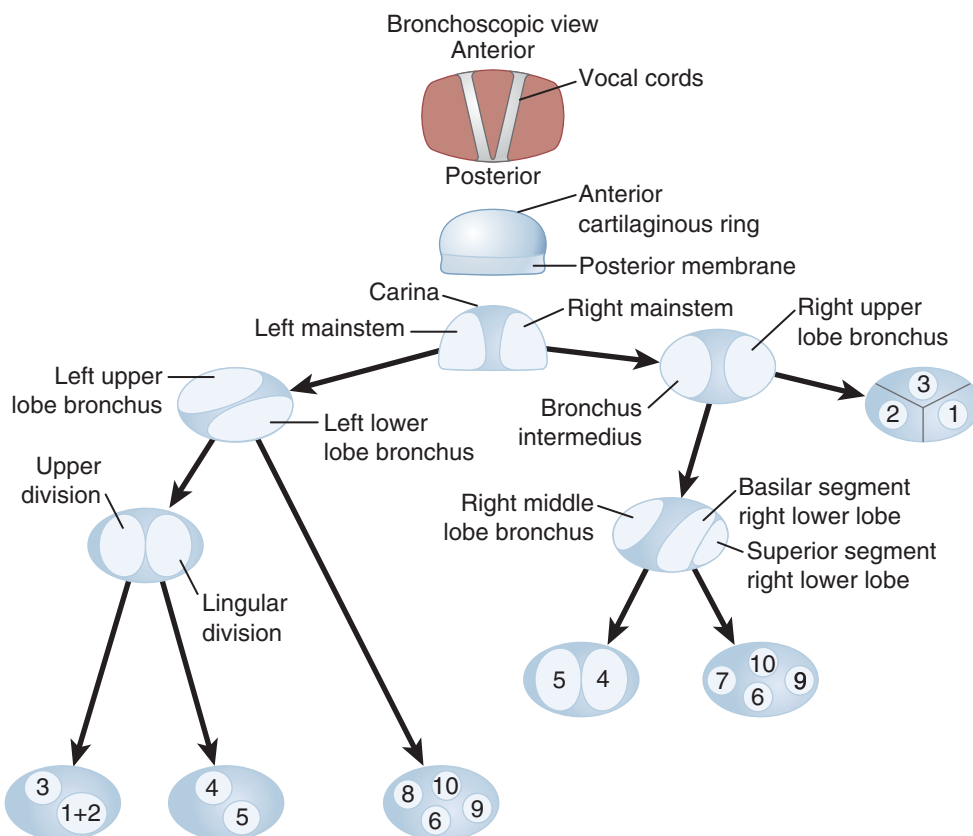


FIGURE 1-11 ■ Bronchoscopic view of the tracheobronchial tree. See Figure 1-12 for names of the numbered segments.

(4 to 6 cm). The carinal angle can be wider in women and obese people. It can also be wider in patients with bulky subcarinal nodal disease.

The right upper lobe bronchus, also known as the *eparterial bronchus*, branches from the lateral wall of the right principal bronchus approximately 1.2 cm distal to the trachea. The upper lobe bronchus, approximately 1 cm in length, gives off three segmental bronchi as it makes almost a 90-degree angle with the right main bronchus and the bronchus intermedius. After a distance of approximately 1.5 to 2 cm, the middle lobe bronchus arises from the anterior surface of the bronchus intermedius. The middle lobe bronchus is 1.5 to 2.2 cm long and bifurcates into lateral and medial branches. The superior segmental bronchus to the lower lobe arises from the posterior wall of the bronchus intermedius as it terminates into the basal-stem bronchus that sends off segmental bronchi to the medial, anterior, lateral, and posterior basal segments. The medial basal segment arises antero-medially, whereas the lateral basal and posterior basal segments most often arise as a common stem.

The longer left principal bronchus bifurcates into the upper lobe bronchus that travels anterolaterally and the lower lobe bronchus that continues posteromedially. The left upper lobe bronchus divides into the superior and inferior divisions that supply the upper lobe and lingula, respectively. The superior division branches into an apical posterior segmental bronchus and an anterior segmental bronchus. The inferior or lingual bronchus, which is the equivalent of a middle lobe bronchus on the right, is 1 to 2 cm long and divides into the superior and inferior divisions. The lower lobe bronchus on the right side gives off the superior segmental bronchus as its first branch before the basal trunk continues for about 1.5 cm as a single trunk; this then bifurcates into an anteromedial basal segmental bronchus and a common bronchial stem for the remaining basal segments.

Anatomic variations usually involve segmental bronchi arising as a common stem. Occasionally, additional bronchi arise from the main stem and distribute to a segment that has its own bronchus. A right upper lobe bronchus originating from the trachea (a porcine tracheobronchial tree) occurs in 3% of the population. Recognizing aberrant tracheobronchial anatomy is important for placement of the double-lumen endotracheal tube and for performing the ensuing surgical procedure.

LUNGS

To conserve healthy tissue and to perform operations safely on the lung, the thoracic surgeon must have a thorough knowledge of the segmental bronchopulmonary anatomy. Developing as outpouchings of the foregut, the ventral lung buds undergo repeated branching to yield approximately 20 generations from the principal bronchi to the terminal alveolar sacs. With the bronchus at the center, each bronchopulmonary segment functions as an individual unit with its own pulmonary arterial and venous supply. Importantly, the pulmonary veins run in the intersegmental plane and do not accompany the bronchus and the pulmonary artery to each unit.

The lungs are free of the pleural cavity except for attachments to the heart, trachea, and inferior pulmonary ligaments. The larger right lung has three lobes—upper, middle, and lower—and is composed of 10 bronchopulmonary segments. The left lung has two lobes—upper and lower—and eight segments (Fig. 1-12). The lingula on the left side is the anatomic equivalent of the middle lobe and is incorporated into the upper lobe. The terminology proposed by Jackson and Huber for the pulmonary segments and the branches supplying them has been universally adopted. The apparent discrepancy of there being only eight segments on the left side is explained by the fact that the apical and posterior segmental bronchi of the left upper lobe and the anterior and medial segmental bronchi of the left lower lobe originate from a common stem bronchus (Fig. 1-13 and Table 1-6).

The oblique fissure on each side separates the lower lobe from the rest of the lung. Anomalous fissures of varying depth may be seen along any of the segments, but they are most commonly seen separating the superior

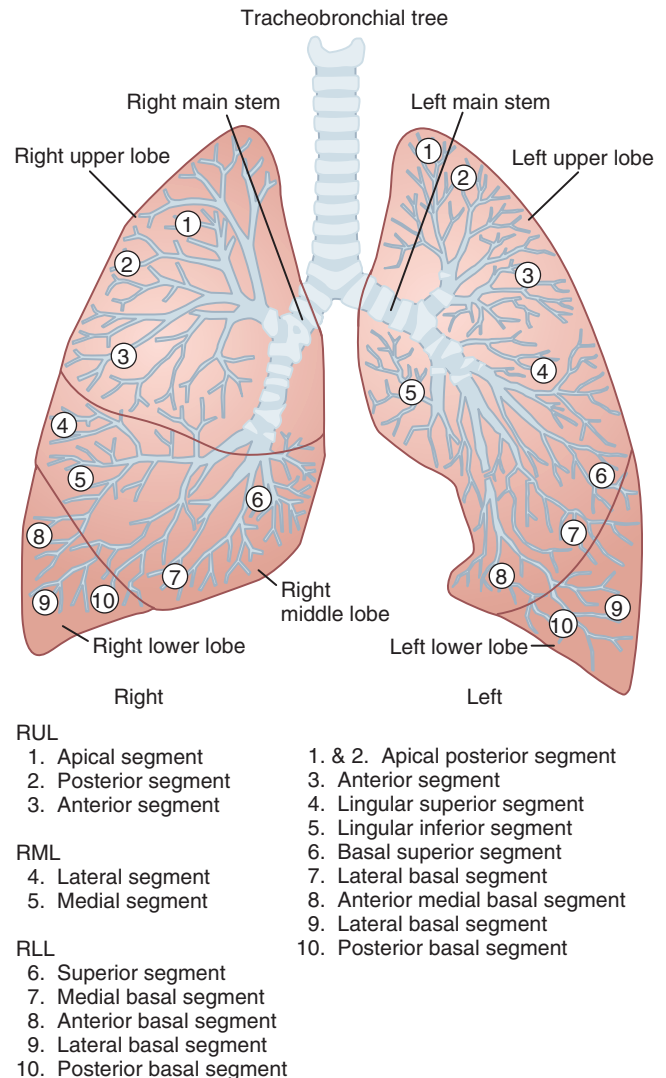


FIGURE 1-12 ■ Segments of the right and left lung. *RLL*, Right lower lobe; *RML*, right middle lobe; *RUL*, right upper lobe.

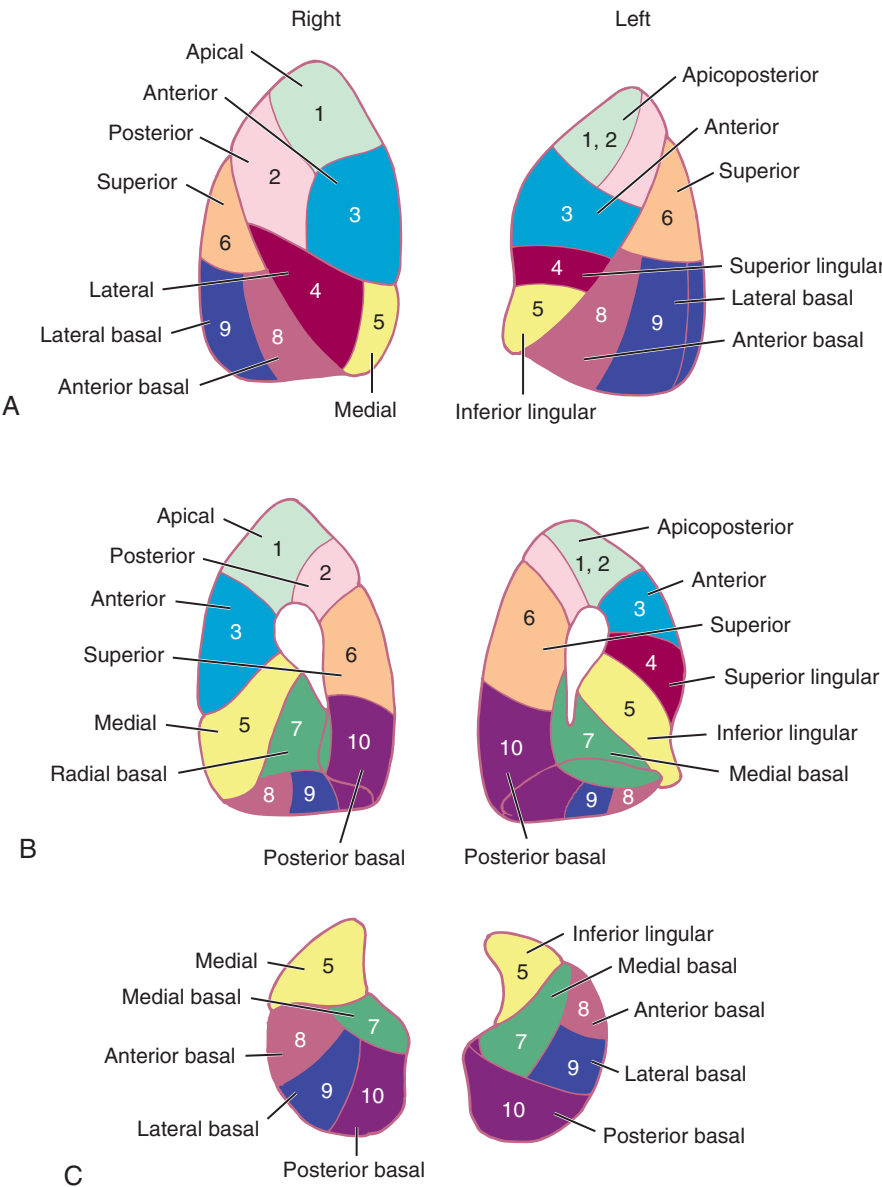


FIGURE 1-13 ■ Bronchopulmonary segments. **A**, Lateral surface. **B**, Medial surface. **C**, Diaphragmatic surface.

TABLE 1-6 Pulmonary Segmental Classification	
Right	Left
Upper Lobe	Upper Lobe
1. Apical	1. Apical posterior
2. Posterior	2. Apical posterior
3. Anterior	3. Anterior
Middle Lobe	Lingula
4. Lateral	4. Superior lingula
5. Medial	5. Inferior lingula
Lower Lobe	Lower Lobe
6. Superior	6. Superior
7. Medial basal	7. Anteromedial basal
8. Anterior basal	8. Anteromedial basal
9. Lateral basal	9. Lateral basal
10. Posterior basal	10. Posterior basal

segment of the lower lobe. Rarely, the apical segment of the right upper lobe may be a true tracheal lobe, with its bronchus arising directly from the trachea. The azygos lobe is not a true segment, but is formed by the azygos vein cutting into the pleura and apex of the lung. Medlar evaluated 1200 lungs and found an incidence of incomplete oblique fissure on the left and right of 18% and 30%, respectively. Of these patients, 63% had an incomplete horizontal fissure.

The right and left hila have different characteristics (Table 1-7). The right hilum exits the mediastinum below the confluence of the azygos and superior vena cava, and behind the superior vena cava and right atrial juncture. The left hilum lies below the aortic arch. The position of the pulmonary artery is somewhat different on the two sides. On the left (Fig. 1-14), the artery lies anterior and superior to the bronchus and runs in a slightly posterior

TABLE 1-7 Characteristics of Left and Right Lung and Their Lobes

Side or Lobe	Characteristics
Right lung	Hilum enters behind the superior vena cava or the right atrial juncture below the azygos nerve Ten segments Three lobes with a horizontal and oblique fissure The most superior and posterior structure in the right hilum is the right main-stem bronchus The right pulmonary artery is superior and slightly posterior to the right superior pulmonary vein The right pulmonary artery is inferior and anterior to the right main-stem bronchus Pulmonary veins most often enter heart separately
Left lung	Hilum courses under aortic arch Eight segments Two lobes with an oblique fissure Left pulmonary artery lies anterior and superior to the left main-stem bronchus The left superior vein is anterior and inferior to the left pulmonary artery Greatest variation in number and location of pulmonary artery branches Superior and inferior veins form common trunk before entering left atrium in 25% of the population
Right upper lobe	Arterial supply from truncus anterior branch coming off right main pulmonary artery at apex of hilum and from posterior ascending artery, found posterior to superior pulmonary vein or in fissure as ongoing pulmonary artery exits lung parenchyma Venous drainage into upper division of superior pulmonary vein Right upper lobe bronchus posterior in hilum Three segments
Right middle lobe	Arterial supply from one (45%) or two (48%) middle lobe arteries found from the right pulmonary artery at the confluences of the horizontal and oblique fissures Middle lobe vein drains most often into superior pulmonary vein and occasionally into inferior pulmonary vein Middle lobe bronchus from bronchus intermedius Two segments
Right lower lobe	From anterior to posterior: middle lobe vein, bronchus, artery Superior segmental artery and basilar artery are terminal branches of right pulmonary artery in the fissure Inferior pulmonary vein Right lower lobe bronchus Five segments
Left upper lobe	From anterior to posterior: inferior pulmonary vein, pulmonary artery, bronchus Two to eight arterial branches First branch of the pulmonary artery comes off behind superior pulmonary vein Varying number of posterior ascending arteries are given off after first branch as the pulmonary artery courses over and behind the left main-stem bronchus Lingular artery: most anterior branch in fissure going to upper lobe Superior pulmonary vein with upper division and lingular veins Four segments
Left lower lobe	Left upper lobe bronchus posterior to vein Superior segmental artery and basilar artery are terminal branches of right pulmonary artery in the fissure Inferior pulmonary vein Left lower lobe bronchus Four segments
Segments	From anterior to posterior: inferior pulmonary vein, pulmonary artery, bronchus Triangular parenchyma with apex toward center Bronchus runs in middle of segment Segmental artery on posterior surface of bronchus Veins in intersegmental planes Veins vary more than arteries, which vary more than bronchus Lingular and superior segmentectomies are easiest Basilar and apical segmentectomies harder Anterior segmentectomy hardest

direction before curving around and behind the left upper lobe bronchus. The right main-stem bronchus is the most superior and posterior of the right hilar structures, and the artery, though slightly anterior, is inferior to the bronchus (Fig. 1-15). The superior pulmonary veins are inferior and anterior to the pulmonary arteries, and the inferior pulmonary veins are even more inferior and posterior to the superior veins.

The main pulmonary artery arises to the left of the aorta and passes superiorly and to the left, anterior to the

left main-stem bronchus, where it divides into the right and left main pulmonary arteries. The right pulmonary artery passes to the right behind the ascending aorta and forms the superior border of the transverse sinus. It then passes posterior to the superior vena cava and forms the superior border of the postcaval recess of Allison, whereas the right superior pulmonary vein forms the inferior border of the recess. The first branch is the truncus anterior (rarely intrapericardial); it arises superolaterally and supplies the upper lobe before the pulmonary artery

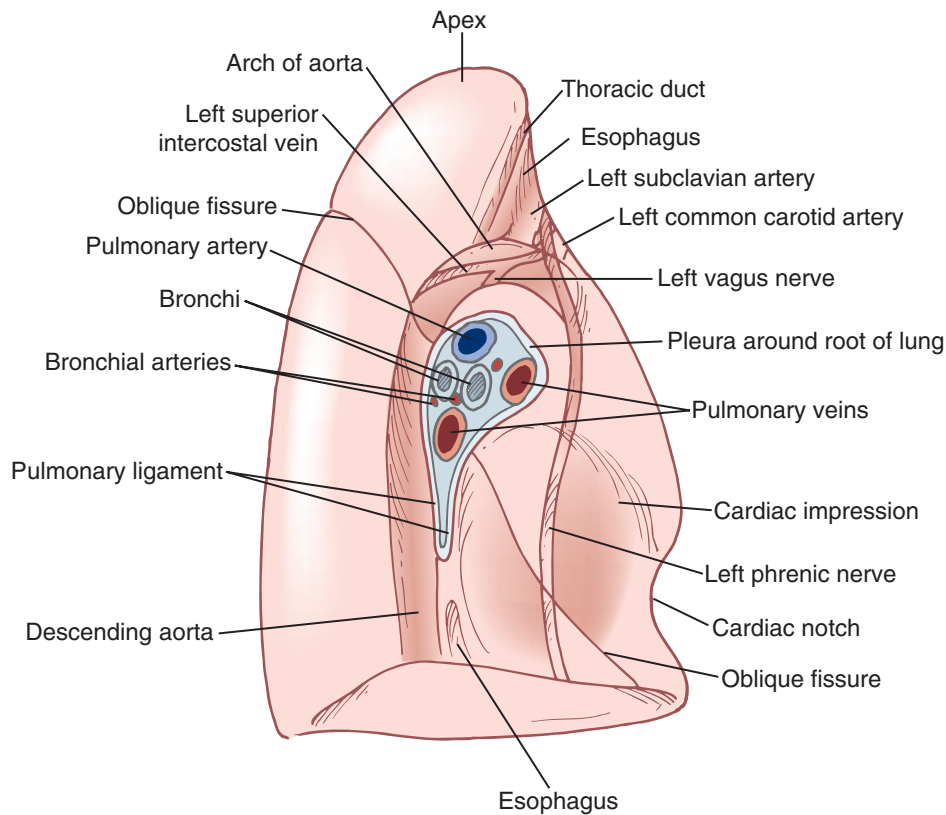


FIGURE 1-14 ■ The medial surface of the left lung.

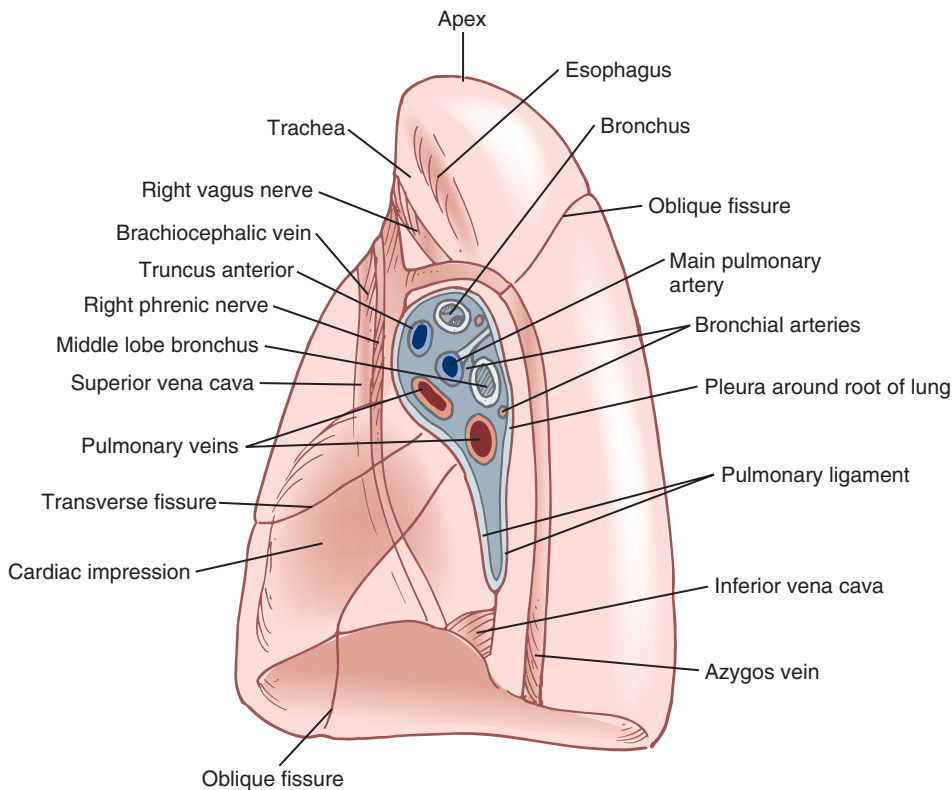


FIGURE 1-15 ■ The medial surface of the right lung.

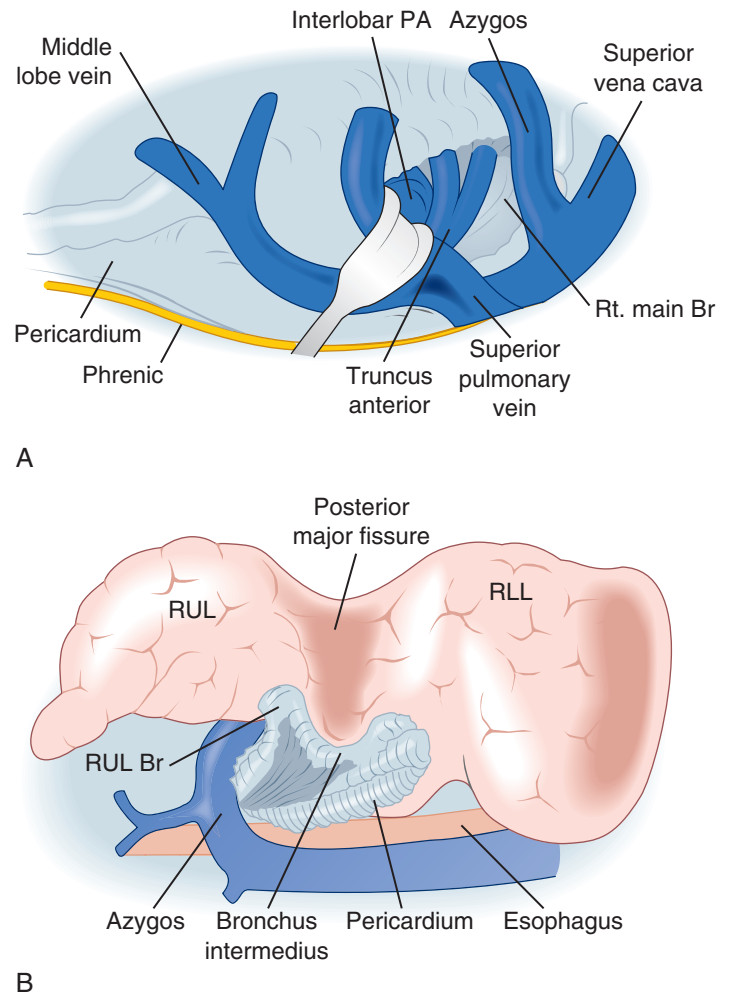


FIGURE 1-16 ■ Hilum of the right lung. **A**, Anterior view. **B**, Posterior view. *Br*, Branch; *PA*, pulmonary artery; *RLL*, right lower lobe; *RUL*, right upper lobe.

enters the lung hilum (Fig. 1-16). The interlobar pulmonary artery goes between the bronchus intermedius (posterior) and superior pulmonary vein (anteriorly) and gives off the posterior ascending artery to the posterior segment of the upper lobe (Fig. 1-17). The ongoing pulmonary artery then runs behind the middle lobe bronchus. Opposite the posterior ascending artery, the middle lobe artery arises anteromedially, usually at the junction of the horizontal and oblique fissures. The arterial branch to the superior segment of the lower lobe arises posteriorly and opposite the middle lobe artery at the same level or slightly distal to it. Beyond the superior segmental artery, the common basal trunk continues in the fissure to give rise to the medial basal segmental artery, occasionally as a common branch with the anterior basal branch. The terminal branches supply the lateral and posterior basal segments.

The left pulmonary artery passes more posteriorly and superiorly than the right and is longer before giving off its first branch. Commonly, there are four branches to the left upper lobe, but the number varies from two to seven. The first branch arises from the anterior portion of the artery and is quite short, and often its branches

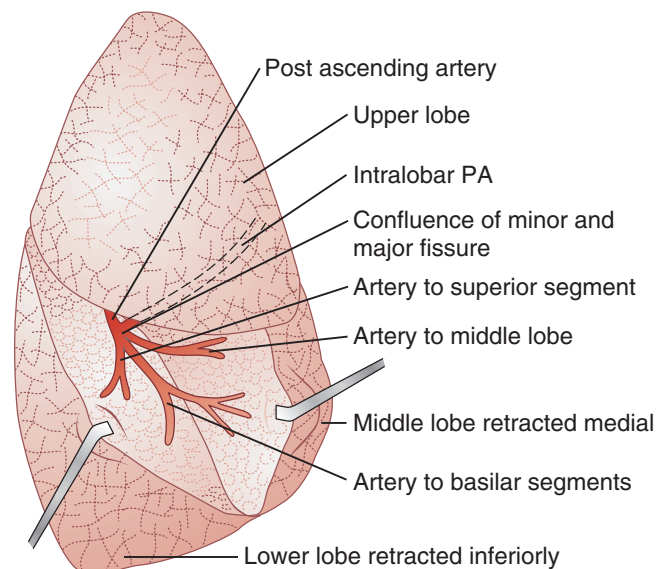


FIGURE 1-17 ■ Pulmonary artery as it exits the parenchyma of the right upper lobe into the confluence of the major and minor fissures. *PA*, Pulmonary artery.

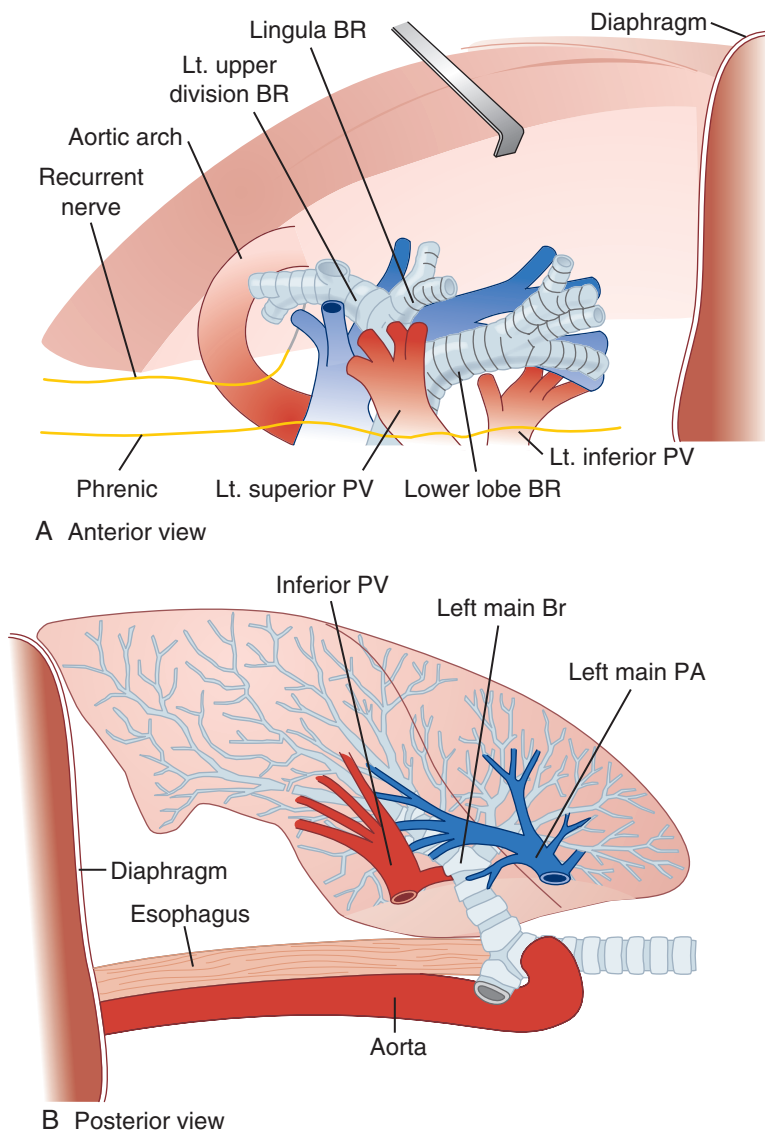


FIGURE 1-18 ■ Hilum of the left lung. **A**, Anterior view. **B**, Posterior view. BR, Branch; Lt., left; PA, pulmonary artery; PV, pulmonary vein.

appear as separate vessels arising from the main artery. The second branch usually arises posterosuperiorly as the main artery passes over the left upper lobe bronchus and into the interlobar fissure, where more ascending upper lobe branches may originate (Fig. 1-18). As it enters the interlobar fissure, it gives off a branch to the superior segment of the left lower lobe and the lingular artery. Beyond the lingular branch, the common basal trunk divides into two major branches. The anterior branch supplies the anteromedial basal segments and the posterior branch supplies the lateral basal segments.

Among the common variations of the pulmonary arterial supply, the first anterior trunk on the left may be the major supply to the lingular segments. This should be suspected if a small lingular artery is found in the anterior fissure. The right side may have two major arteries that arise from the truncus anterior, which are designated the truncus anterior superior and the truncus anterior inferior.

The left superior pulmonary vein receives all the tributaries from the left upper lobe. It is closely applied to the

anteroinferior portion of the pulmonary artery and makes dissection of the anterior branches quite hazardous. Its three main tributaries are apical posterior, anterior, and lingular. Occasionally, the superior and inferior lingular veins are separate. A common anomaly is drainage of the inferior lingular vein into the inferior pulmonary vein. The inferior pulmonary vein, lying more posteriorly and inferiorly, drains the entire lower lobe via two principal tributaries, the superior segmental and common basal veins. The right superior pulmonary vein is usually made up of four branches: the apical anterior, anterior-inferior, and posterior branches, which drain the upper lobe, and the inferior branch, which drains the middle lobe. Occasionally, the middle lobe vein drains into the atrium as a separate vessel and very rarely it becomes a tributary of the inferior pulmonary vein.

The right inferior pulmonary vein is similar to the one on the left and is composed of two trunks. The common basal vein is composed of the superior basal and inferior basal tributaries, and the superior segmental vein drains the superior segment of the lower lobe. The superior and

inferior pulmonary veins on the right most often enter the left atrium separately. In contrast, on the left, the two veins form a common trunk in more than 25% of the population.

The segmental branches of the pulmonary arteries usually lie on the superior or lateral surface of the segmental bronchus that they accompany and with which they branch. The venous tributaries occupy an intersegmental position, do not bear as close a relationship to the segmental bronchi, and tend to lie on their medial or inferior surfaces. Variations from the usual pattern are common. As a general rule, veins vary more than arteries, and arteries vary more than bronchi.

The systemic circulation of the lung tissues is derived from the bronchial arteries that supply the bronchi from the carina to their terminal bronchioles and that also nourish the connective tissue and visceral pleura. A single right bronchial artery usually branches from the third posterior intercostal artery, and two left bronchial arteries usually branch from the dorsal aorta, one near vertebra T5 and one inferior to the left principal bronchus. Although variations are known, most bronchial arteries arise from the anterolateral aspect of the aorta or its branches within 2 to 3 cm of the origin of the left subclavian artery and come to lie on the membranous portion of the principal bronchi. The bronchial arteries usually give off branches to the esophagus and then follow the bronchi into the lung, also giving off branches along the interalveolar connective tissue septae to the visceral pleura. There is a rich anastomosis with the pulmonary arterial supply, which is important after pulmonary transplantation.

The bronchial veins have a superficial system, with two bronchial veins on each side draining from the hilar region and visceral pleura into the azygos vein on the right and the accessory hemiazygos vein on the left. Most of the venous drainage from the deeper lung substance drains into the pulmonary venous system, accounting for the less than 100% saturation of the blood in the left atrium.

Lymphatic drainage channels run toward the hilum from subpleural vessels along the bronchi and pulmonary arteries. This flow is interrupted by multiple lymph nodes along the way, mostly situated at forking points of the bronchi. Each nodal station has a number assigned to it and is the basis of the most recent staging system for primary bronchogenic carcinoma, as proposed by [Moun-tain and Dressler in 1997](#).

The most peripheral pulmonary nodes include subsegmental lymph nodes (level 14) and segmental (level 13), lobar (level 12), and interlobar (level 11) nodes in the fissures, and they are reliably removed during a lobectomy. The hilar lymph nodes (level 10), also known as *bronchopulmonary nodes*, are at the root of the lung and can be accessed using thoracoscopy or thoracotomy. The inferior pulmonary ligament nodes (level 9) lie in the inferior pulmonary ligament on the left and the right, and the parasophageal nodes (level 8) lie dorsal to the posterior wall of the trachea and inferior to the carina, to the right or left of the midline esophagus ([Fig. 1-19](#)). From then onward, drainage is to the central mediastinal and tracheobronchial nodes and upward via mediastinal lymph trunks to the brachiocephalic veins (see [Fig. 1-19A](#)).

The right and left paratracheal lymph nodes (levels 2R and 2L), and the lower paratracheal lymph nodes at the tracheobronchial angle (levels 4R and 4L), and the subcarinal (level 7) lymph nodes can be identified and sampled via a standard cervical mediastinoscopy. During a right VATS or right thoracotomy, lymph nodes at levels 4R, 7, 8, and 9 can be sampled (see [Fig. 1-19C and E](#)). The Chamberlain procedure or the left VATS procedure can give access to the subaortic (level 5) and para-aortic (level 6) lymph nodes. Left VATS can also provide access to lymph nodes at levels 7, 8, and 9 (see [Fig. 1-19B and D](#)). The Delphian lymph node (the highest mediastinal, pretracheal lymph node) is classified as level 1.

Thus, levels 1 through 9 are considered mediastinal lymph nodes, and metastases are classified as N2 if ipsilateral and as N3 if contralateral spread of cancer is present in these lymph node stations. Anomalies of this ipsilateral, centrally directed drainage pattern are common and are more likely on the left side, especially with lower lobe tumors. Up to 50% of left lower lobe tumors and 35% of left upper lobe tumors have positive contralateral (N3) mediastinal nodes, whereas contralateral metastasis is found in only 42% of right lower lobe tumors and 18% of right upper lobe tumors when N2 lymph nodes are negative for tumor. Instead of draining to hilar nodes, the left upper lobe tumors follow an alternative path to the subaortic, periaortic, and anterior mediastinal nodes in up to one third of patients.

The vagus nerve and the sympathetic plexus contribute to the poorly developed anterior pulmonary plexus around the main pulmonary arteries, and to the well-developed posterior plexus of nerves around the bronchi. The vagus nerve carries all the afferent innervation from the bronchial mucosa, sensing stretch in the alveoli and pleura, pressure in the pulmonary veins, and mediating pain. Efferent fibers in the vagus constrict the bronchi, and the sympathetic efferents are vasoconstricting to the pulmonary vessels and secretomotor to the bronchial plexus.

The left and right hemithoraces each contain a variety of other vital organs in addition to the lungs. The thoracic duct, esophagus, aorta, and azygos vein can be visualized in the right hemithorax, whereas the aortic arch, descending aorta, and distal esophagus may be seen in the left hemithorax.

ESOPHAGUS

The esophagus is a muscular tube that starts at the upper esophageal sphincter (the cricopharyngeus) and travels approximately 25 cm to the lower esophageal sphincter at the gastroesophageal junction. The cricopharyngeus is 15 cm from the incisor teeth. With endoscopy, the gastroesophageal junction is measured to be 38 to 40 cm from the incisors in men, and generally 2 cm shorter in women. The cervical esophagus is slightly left of midline as it enters the thoracic inlet in front of the body of the T1 vertebra and posterior to the trachea. After it passes the aortic arch, it inclines forward and passes in front of the descending thoracic aorta to obtain a position left of midline as it travels through the esophageal hiatus

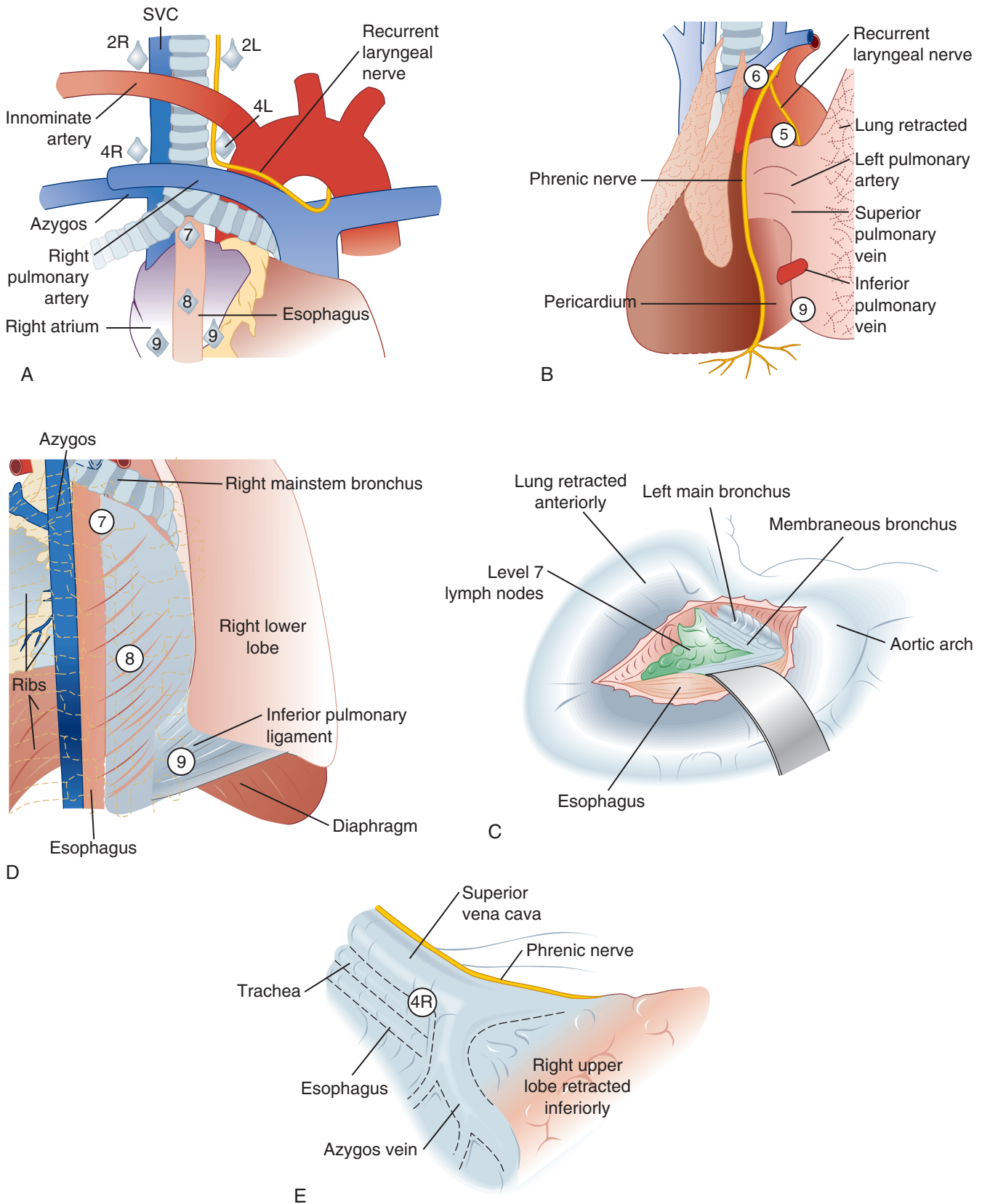


FIGURE 1-19 ■ Mediastinal lymph nodes. **A**, Anterior view. **B**, Left lung retracted posteriorly to expose lymph nodes at levels 5, 6, and 9. **C**, Anterior retraction of the left lung to expose lymph nodes at level 7. **D**, Anterior retraction of right lung to expose lymph nodes at levels 7, 8, and 9. **E**, Inferior and posterior retraction of right lung to expose lymph nodes at level 4R. SVC, Superior vena cava.

opposite the body of the 10th thoracic vertebra. At the level of the T8 vertebra, the left lateral wall of the esophagus that was covered by the aorta is in contact with the parietal pleura as the aorta goes directly behind it. This is a common site of perforation in patients with Boerhaave syndrome. The right lateral surface of the esophagus is completely covered by parietal pleura except where the azygos vein crosses it at the level of the T4 vertebra. When choosing the side for a thoracotomy, avoiding interference from the aortic arch is the primary concern. Access to the proximal esophagus is difficult from the left hemithorax because of the overlying aortic arch.

Endoscopic examination of the esophagus reveals several constrictions on the esophageal lumen in addition to the narrowing at the upper and lower esophageal sphincters. The additional constrictions are seen endoscopically where the esophagus crosses the aortic arch at 22 to 25 cm from the incisors, and where it is crossed by the left main-stem bronchi at 27.5 cm from the incisors. These anatomic relationships may also be seen radiographically. A notch indentation is often seen in its left lateral wall on a barium swallow radiograph as the esophagus passes to the right of the aorta at the level of the tracheal bifurcation. The left main-stem bronchus may indent it slightly as it passes over the esophagus.

The blood supply of the cervical esophagus is from branches of the inferior thyroid artery. The thoracic esophagus is supplied by the esophageal branches of the aorta and the bronchial arteries. Most individuals have one right-sided and one or two left-sided bronchial arterial branches. The upper aortic esophageal branch is usually shorter and originates at the T6 or T7 vertebral level, and the lower larger branch originates at the level of the eighth or ninth thoracic vertebra. Finally, the abdominal esophagus receives its supply from branches of the left gastric and inferior phrenic arteries. In the wall of the esophagus, there is an extensive longitudinal anastomotic network in the muscular and submucosal layers, a basis for portasystemic anastomoses. The venous drainage follows the arterial supply. A submucosal plexus drains into a periesophageal venous plexus, from which the veins originate and empty into the inferior thyroid, bronchial, azygos, and left gastric veins.

Two large interconnecting networks that course longitudinally form the lymphatic network of the esophagus. The mucosal network extends into the submucosal network, and flow is predominantly (6:1) longitudinal rather than segmental. These pierce the muscular wall, and ultimately lymph channels follow the arterial supply. The cervical esophagus drains into the deep cervical nodes alongside the inferior thyroid vessels, whereas the abdominal portion drains to the preaortic group of the celiac nodes along the left gastric artery. The thoracic esophagus drains into the tracheobronchial nodes superiorly and the subcarinal and paraesophageal nodes inferiorly.

After giving off their recurrent laryngeal branches, which supply the cricopharyngeal sphincter and cervical esophagus, the vagus nerves descend onto the anterior wall of the esophagus and form a complex vagal esophageal plexus, a network of interconnecting fibers that forms the preganglionic parasympathetic supply to the esophagus. These fibers connect to the enteric ganglia in

the myenteric and submucosal plexuses that are located in the wall of the esophagus. Just above the diaphragm, the plexus usually gives rise to two nerve trunks: the anterior and posterior vagal. The anterior trunk contains predominantly left vagal fibers and the posterior contains mainly right, with considerable contribution from one another.

Cervical and thoracic sympathetic ganglia contribute visceral branches to the esophagus, and a few branches from the splanchnic nerves reach the esophagus. Their effect on the esophageal muscle is unknown. The vagus nerve is the motor supply to the esophageal muscle, and the secretomotor nerve supplies the esophageal glands. Afferent pain fibers appear to run in both the vagal and vasomotor sympathetic supply; hence, esophageal pain can be referred to the neck, arm, and thoracic wall.

The mucosal lining of the esophagus is composed of nonkeratinized, stratified squamous epithelium supported by a lamina propria and a thick muscularis mucosa. The mucous membrane is thick and in the collapsed state is thrown into longitudinal folds. Mucosal glands in the submucosa are mainly found at the upper and lower ends of the esophagus. The muscular wall consists of an inner circular and an outer longitudinal layer that are visceral smooth muscle in the lower two thirds and skeletal striated muscle in the upper third. Except for the short intra-abdominal segment, the lack of a serosa in the rest of the esophagus accounts for the difficulty in suturing the esophagus.

VESSELS OF THE THORAX

Descending Thoracic Aorta

The descending thoracic aorta starts at the level of the fourth thoracic vertebra. It is a posterior mediastinal structure that arises just left of the vertebral column and travels toward the midline as it descends toward the diaphragm. When it goes through the aortic hiatus at the level of the 12th thoracic vertebra, it is anterior to the vertebral column. In the left hemithorax, anterior to the descending aorta, are the left pulmonary hilum, the pericardium, and the esophagus, and posteriorly is the vertebral column. In the right hemithorax, the esophagus is lateral to the aorta until it takes up a position anterior to the aorta near the diaphragm. The thoracic duct and azygos vein are lateral to the aorta in the right hemithorax. Branches of the descending thoracic aorta include pericardial, bronchial, mediastinal, phrenic, and posterior intercostal and subcostal arteries. The descending aorta is fixed at the origin of the left subclavian artery, which is therefore a common site for transection of the aorta during motor vehicle accidents.

Azygos Vein

The origin of the azygos vein is not constant. It typically starts from the posterior aspect of the inferior vena cava, but it may originate from a lumbar azygos vein or from the confluence of the subcostal and ascending lumbar vein. It ascends through the aortic hiatus in the

diaphragm. It rises in the right hemithorax in the posterior mediastinum until the fourth vertebral body, and then it turns medially over the right pulmonary hilum to join the superior vena cava.

Thoracic Duct

The thoracic duct carries chylous material, which is rich in lipids, proteins, and lymphocytes. It begins at the confluence of the abdominal lymphatic trunks known as the cisterna chyl. From its origin at the level of the 12th thoracic vertebra, the thoracic duct travels through the aortic hiatus and ascends in the right hemithorax between the descending thoracic aorta (medial) and the azygos vein (lateral) and posterior to the esophagus, until it crosses medially at the level of the fifth thoracic vertebral body. Once in the left hemithorax, it continues its ascent on the left side of the esophagus. It crosses the aortic arch anteriorly and then travels posterior to the left subclavian artery. It travels out of the thoracic inlet for 3 to 4 cm before arching and descending anterior to the medial border of the scalenus anterior and finally joining the venous system near the confluence of the left subclavian and internal jugular veins.

NERVES OF THE THORAX

Vagus and Recurrent Laryngeal Nerves

The vagus nerve passes inferiorly from the base of the skull to the thoracic inlet in the carotid sheath. On the right side, the right vagus travels behind the internal jugular vein and dives behind the sternoclavicular joint to give off the right recurrent laryngeal nerve. The right recurrent laryngeal nerve recurs on the ipsilateral subclavian artery and then ascends in the tracheoesophageal groove. The left recurrent laryngeal nerve recurs on the aortic arch and then rises in the tracheoesophageal groove. Both recurrent laryngeal nerves enter the larynx with the laryngeal branch of the inferior thyroid artery.

The right vagus continues to descend into the thoracic cavity behind the right brachiocephalic vein and then lateral to the trachea. It travels posteriorly and lies predominantly posterior to the right pulmonary hilum, where several bronchial branches are given off. The remaining vagal fibers join fibers from the left to form the posterior vagal trunk.

The left vagus enters the thorax between the common carotid and the subclavian arteries behind the left brachiocephalic vein. It crosses the left side of the aortic arch and gives off the left recurrent laryngeal nerve before descending behind the left pulmonary hilum. It also gives off bronchial branches at this level. Fibers from the left and right vagi form the anterior and posterior vagal trunks, which enter the abdomen through the esophageal hiatus.

Thoracic Sympathetic Chain

The thoracic sympathetic chain is formed by ganglia of the autonomic nervous system. The first thoracic

ganglia, in the majority of patients, fuses with the inferior cervical ganglia. The thoracic sympathetic chain predominantly lies on the costal head under the pleura. The nerves interact with corresponding spinal nerves with white and gray rami. Ligation of sympathetic ganglia is performed to treat hyperhidrosis, facial blushing, Raynaud disease, and reflex sympathetic dystrophy. When collateral nerve fibers bypass the sympathetic trunk, sympathectomy results in failure. These fibers can reach the brachial plexus without passing through the sympathetic ganglia. The nerve of Kuntz is the most described collateral nerve. Although in clinical literature, the nerve of Kuntz is reported in 10% of cases, it is reported 80% of the time in anatomic descriptions. Techniques for ligation of ganglia from T1 to T3 are discussed in later chapters.

Phrenic Nerves

The right and left phrenic nerves arise from the third, fourth, and fifth cervical rami and course inferiorly in an oblique manner on the respective anterior surfaces of the scalenus anterior muscle. At the thoracic inlet, the nerve is on the medial border of the scalenus anterior muscle, just 3 to 4 cm from the sternoclavicular joint. It then enters the thoracic inlet posterior to the subclavian vein and anterior to the internal mammary artery. Injury to the phrenic nerve may occur during surgical procedures such as a scalene node biopsy or Pancoast tumor resection. When dissecting a pre-scalene node, which is often done for lung cancer staging or confirmation of sarcoidosis, caution should be used to avoid entering the scalenus anterior sheath in which the phrenic nerve lies. Pancoast tumor resections require division of the first rib. The scalenus anterior muscle should be divided as close to the first rib as possible to avoid injury to the overlying phrenic nerve.

After entering the thoracic cavity, the right phrenic nerve travels inferiorly, just lateral to the brachiocephalic vein and the superior vena cava. It continues its descent over the pericardium and the underlying right atrium and inferior vena cava. Just as it goes through the diaphragm, it divides into three branches: the anterior, posterior, and anterolateral.

The left phrenic nerve at the root of the neck may pass anterior to the first part of the subclavian artery and behind the thoracic duct, or it may follow the same course as the right phrenic nerve. It then crosses anterior to the internal mammary artery and travels in the groove between the left common carotid and subclavian arteries. The nerve crosses anteromedial to the aortic arch and travels over the pericardium toward the diaphragm. In the same manner as its right-sided counterpart, the nerve divides as it travels through the diaphragm to give off branches on the abdominal surface. The branches travel from its central position in the diaphragm to supply the sternal, crural, and posterior aspects of the diaphragm. Radial incisions in the diaphragm from the costal edge to the esophagus will lead to damage of the phrenic nerve. Peripheral circumferential incisions in the diaphragm are safest with regard to the phrenic nerve. Similar incisions in the central tendon are also safe.

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RADIOLOGIC IMAGING OF THORACIC ABNORMALITIES

Jeremy J. Erasmus • Edith M. Marom • Tam T. Huynh • Edward F. Patz, Jr.

CHAPTER OUTLINE

MEDIASTINAL ABNORMALITIES

Aorta
Aortic Dissection
Aortic Trauma
Trauma: Airways and Esophagus
Evaluation of Airways: Nontrauma
Mediastinal Tumors

LUNG ABNORMALITIES

Solitary Pulmonary Opacities
Staging Lung Cancer

Interstitial Lung Disease and Pulmonary Abscesses

PLEURAL AND CHEST WALL ABNORMALITIES

Malignant Pleural Mesothelioma
Pleural Collections
Chest Wall Disease

POSTOPERATIVE IMAGING

Pulmonary Embolism

SUMMARY

Since the late 1990s advances in imaging technology, including digital subtraction chest radiographs, multi-detector spiral computed tomography (MDCT), dual-energy computed tomography (CT) techniques, electrocardiograph (ECG)-gated CT, positron emission tomography (PET) with CT, and magnetic resonance imaging (MRI), have improved diagnostic accuracy and management of patients with thoracic abnormalities. The electronic distribution of these studies as digital images via a picture archiving and communication system, has also expedited information transfer and interpretation.

This chapter is a general overview of the advances in thoracic imaging, with a focus on imaging modalities used for the evaluation of the surgical patient. Topics reviewed include a spectrum of mediastinal, lung, pleural, and chest wall abnormalities commonly encountered by thoracic surgeons in which imaging is important in the diagnosis and management of patients.

MEDIASTINAL ABNORMALITIES

Mediastinal abnormalities have a variety of causes, including congenital malformations, infections, trauma, and neoplasms. Clinical history and prior radiographs are often sufficient to determine the cause and the necessity for further evaluation. In the absence of prior imaging studies, chest radiographs, CT, or MRI are most commonly used to establish a diagnosis or to provide a differential diagnosis.

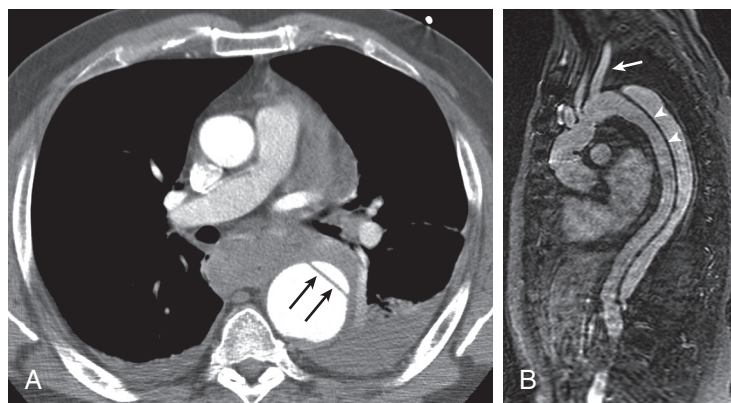
Aorta

Multidetector computed tomography, dual-energy CT, and ECG-gated CT together with sophisticated post-processing methods have transformed imaging of the thoracic aorta. More recently, rapidly acquired (single breath-hold) non-ECG-gated CT imaging has become available and is being used as the initial diagnostic imaging modality to evaluate patients with suspected acute aortic dissection. Furthermore, because single-acquisition dual-source CT with the availability of low- and high-kVp data acquired from the same volume eliminates aortic precontrast imaging, reduces radiation exposure, and uniquely characterizes aortic pathology, it is being recommended in the initial evaluation of the aorta.

Aortic Dissection

Acute aortic syndrome is the term currently used to refer to a group of potentially life-threatening disorders of the thoracic aorta including aortic dissection, intramural hematoma (IMH), and penetrating atheromatous ulcer (PAU).¹ The most common presenting complaint in patients with acute aortic syndrome is acute onset of severe chest pain, but symptoms can be nonspecific and variable.^{1,2} Aortic dissection is the most common acute aortic disorder, and IMH and PAU account for 10% to 20% of acute aortic syndrome cases.^{2,3} Two different mechanisms leading to the characteristic intimal tear in aortic dissection have been proposed and remain

FIGURE 2-1 ■ Type B aortic dissection. **A**, Axial contrast-enhanced chest computed tomography shows a dilated descending aorta and an intimal flap (*arrows*). There are small pleural effusions and increased attenuation of mediastinal adipose tissue raising the possibility of hemorrhage within the mediastinum. **B**, Sagittal oblique magnetic resonance imaging of the aorta shows an intimal flap (*arrowheads*) arising distal to the left subclavian artery (*arrow*).



debatable: primary disruption of the intima versus secondary rupture of a hematoma arising from the vasa vasorum.^{4,5}

MDCT with intravenous contrast is the imaging modality of choice when an aortic dissection is suspected, and it can determine the type and extent of the dissection for management decisions. The DeBakey and Stanford classifications are widely recognized and both based on the origin of the intimal tear and the extent of the aortic involvement. Stanford Type A dissection involves the ascending aorta and originates just above the aortic valve plane; it is usually considered for surgical repair. Stanford Type B dissection originates just below the level of the ligamentum arteriosum, and it is generally managed medically. Endovascular or surgical interventions are indicated for patients who develop complications from Stanford Type B dissections (Fig. 2-1).

The primary diagnostic finding on CT is an intimal flap separating the true from the false lumen. The sensitivity and specificity approaches 100%, with an accuracy that is superior to that of angiography.⁶⁻⁸ Images are usually viewed as two-dimensional orthogonal axial sections, combined with volume-rendering and multiplanar reconstruction images. However, these techniques are unable to depict the dissection wall as a whole. To overcome this limitation, an automatic segmentation and three-dimensional visualization of the dissection wall has been proposed to isolate the dissection (or flap) from the rest of the vascular structures and improve diagnosis and characterization of the dissection.⁹ When iodinated contrast agents are contraindicated, MRI or transesophageal echocardiography can be used to diagnose and determine the type of dissection.¹⁰ Although these imaging modalities are accurate, both have limitations in large patients, and the ability to perform these studies in the acute setting is not optimal.

Aortic Trauma

Patients with thoracic trauma usually require imaging evaluation, and the type of study depends on the mechanism of injury and the structures potentially involved. From an imaging perspective, the chest radiograph is typically the first study performed and often dictates whether additional imaging is warranted. The radio-

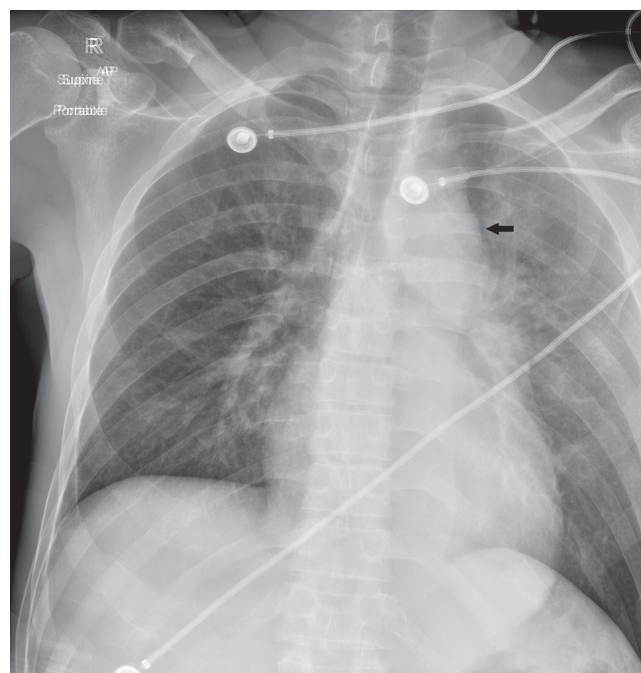


FIGURE 2-2 ■ Traumatic aortic injury. Portable chest radiograph shows widening of the superior mediastinum, lobular contour abnormality of the transverse aorta (*arrow*), indistinct descending aorta, and opacities in the left lung consistent with pulmonary contusion/hemorrhage.

graphic findings suggestive of traumatic aortic injury (TAI) are an indistinct aortic arch or descending aorta, a left apical cap, tracheal displacement to the right, displacement of the nasogastric tube to the right of the T4 spinous process, mediastinal widening, and inferior displacement of the left main-stem bronchus (Fig. 2-2).¹¹⁻¹³ Less specific findings include a left pleural effusion and widening of the paravertebral stripe. These features, however, are only suggestive, not indicative, of an aortic injury. In contrast, the negative predictive value of a normal chest radiograph for an aortic injury is 94% to 96%.^{14,15} If there is a chest radiographic abnormality, MDCT is the primary imaging method for the diagnosis of TAI. The sensitivity for this technique is 100%, and the specificity ranges from 83% to 99.7% (Fig. 2-3).¹⁶⁻²⁰ In fact, MDCT has superseded aortography in the



FIGURE 2-3 ■ Traumatic aortic injury after motor vehicle accident. **A**, Axial contrast-enhanced chest computed tomography (CT) shows focal contained collection of contrast (*asterisks*) located external to the descending aorta, consistent with a pseudoaneurysm. Note mediastinal widening due to hemorrhage and moderate pleural effusion. **B**, Sagittal reconstructed CT shows pseudoaneurysm arising from the thoracic aorta immediately distal to the transverse arch (*asterisk*). (Courtesy Page H. McAdams, Duke University, Durham, N.C.)

diagnosis of TAI and vascular injuries and selective aortography is now reserved for therapeutic catheter-based endovascular interventions. Direct signs for TAI include a linear intraluminal filling defect, pseudoaneurysm formation, an abrupt caliber change, and contrast extravasation. Indirect signs of TAI, most notably a periaortic hematoma, are found in 91% of patients with surgically proven TAI.¹⁷ The absence of a periaortic abnormality and a normal-appearing aorta on MDCT has a negative predictive value of 100%.^{19,20} Additional nonvascular thoracic injuries can be found in 7% of patients who do not have an aortic transection on MDCT. Such abnormalities are usually a combination of pneumothoraces, multiple rib fractures, and pulmonary contusions.^{17,21}

Trauma: Airways and Esophagus

Tracheal and esophageal injuries are uncommon but are typically found after intubation, a motor vehicle crash, or penetrating trauma (Fig. 2-4). Many of these injuries are not recognized initially because of subtle or nonspecific clinical and radiologic findings. Delayed or missed

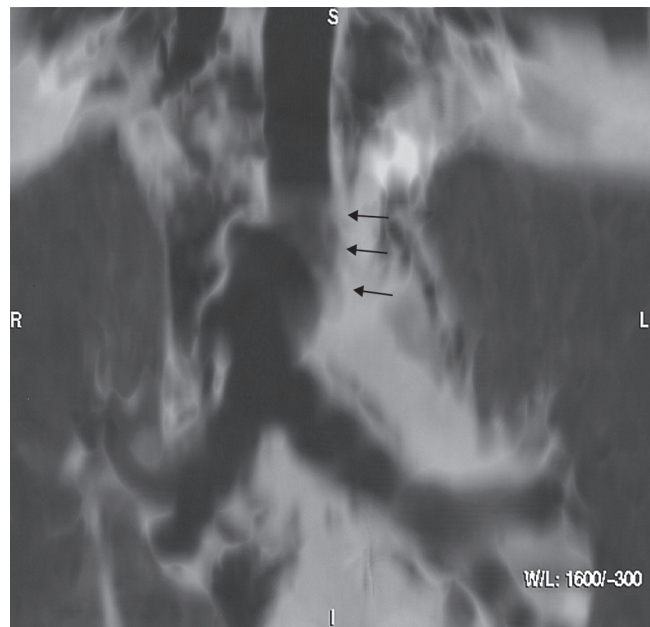


FIGURE 2-4 ■ Tracheal rupture after a motor vehicle crash in a patient with no respiratory symptoms and a chest radiograph demonstrating pneumomediastinum. Coronal reformations of computed tomography (2.5-mm collimation) show pneumomediastinum and discontinuation of the trachea (*arrows*).

diagnosis can result in death or severe complications, such as ventilatory failure, mediastinitis, sepsis, airway stenosis, bronchiectasis, recurrent pulmonary infections, and permanent pulmonary function impairment.

Injuries to the trachea or bronchi can be difficult to diagnose, because patients can have no clinical findings and the radiograph can be normal in up to 10%.^{22,23} In addition, the radiographic findings of tracheobronchial and esophageal injury are nonspecific and can include pneumomediastinum, pneumothorax, and progressive subcutaneous emphysema. However, diagnosis of these injuries is important because there is a high association with esophageal and major vascular injuries.^{22,23} MDCT with multiplanar reconstructions is the imaging modality of choice for visualization of the airways. MDCT has a sensitivity of 85% for the detection of tracheal injuries.^{22,23} Patients with tracheal rupture characteristically have an abnormal air collection in the thorax, and air can occasionally be demonstrated in the soft tissues of the neck.²² Success in visualizing the tracheal injury ranges from 71% to 94%, and multiplanar reconstructions can be useful in localizing and defining the extent of injury.^{22,24} MDCT also provides information about the esophagus, although if pneumomediastinum, with or without mediastinal fluid is present on chest radiographs or CT after trauma, fluoroscopic esophagography or endoscopy is usually warranted to exclude an esophageal tear. However, recently it has been reported that the high sensitivity and negative predictive value of CT in patients with pneumomediastinum being evaluated for esophageal perforation after trauma negates performing fluoroscopic esophagography.²⁵

Evaluation of Airways: Nontrauma

Focal or diffuse lesions of the central airways are produced by a variety of diseases, including infection, malignancy, trauma, aspiration, collagen vascular disease, and idiopathic entities such as sarcoidosis or amyloidosis. Although patients might have significant symptoms, airway abnormalities are frequently not apparent or are overlooked on the chest radiograph. If there is a clinical suspicion of a tracheobronchial abnormality, further evaluation by CT is warranted. MDCT using thin slices (1 to 3 mm) is preferred, as it produces excellent axial and multiplanar images, including virtual bronchoscopy, that allow complex tracheobronchial anatomy to be visualized, depicting even weblike stenosis that can easily be missed or underestimated with thicker sections (Fig. 2-5).²⁶ MDCT performed during dynamic exhalation is also useful in demonstrating the excessive tracheal collapse that can occur because of either weakness of the supporting tracheal cartilaginous structures (tracheomalacia) or from excessive anterior bulging of the posterior membranous wall of the trachea (excessive dynamic airway collapse).^{27,28} These related disorders are a potentially underdiagnosed cause of chronic respiratory symptoms.

Mediastinal Tumors

Mediastinal tumors, a large, diverse group of neoplasms, have historically been described radiographically according to their location in the anterior, middle, or posterior

compartments. This description facilitates differential diagnosis and can aid in treatment planning.

Tumors that occur primarily in the anterior mediastinum include hemangiomas, lymphatic malformations, thymic lesions (e.g., cysts, thymolipoma, thymoma, thymic carcinoma), parathyroid adenomas, germ cell tumors, and lymphoma (Fig. 2-6). CT and MRI are particularly useful for showing local soft tissue and vascular invasion of thymomas, local invasion, and early dissemination to regional lymph nodes of thymic carcinomas and, because of the varying composition of soft tissue, fat, calcium, and hemorrhage in teratomas, can occasionally differentiate these tumors from thymomas and lymphomas.

Tumors that occur primarily in the middle mediastinum are foregut malformations, pericardial cysts, and neoplasms arising from the esophagus and trachea. Bronchogenic cysts are the most common mediastinal foregut cysts and are typically located in the subcarinal or right paratracheal region. They appear on CT as round or spherical masses of water attenuation, although many have increased attenuation from proteinaceous debris or blood.²⁹ Esophageal tumors can manifest as middle mediastinal masses, although esophageal carcinoma more frequently manifests as diffuse thickening of the esophagus. Endoscopy and endoscopic-directed ultrasound biopsy are usually used to evaluate locoregional extent and nodal metastases. CT is useful in showing the extent of involvement of adjacent structures such as the airways, aorta, pericardium, and spine, and in revealing nodal (e.g., celiac, gastrophatic ligament) and systemic metastases.

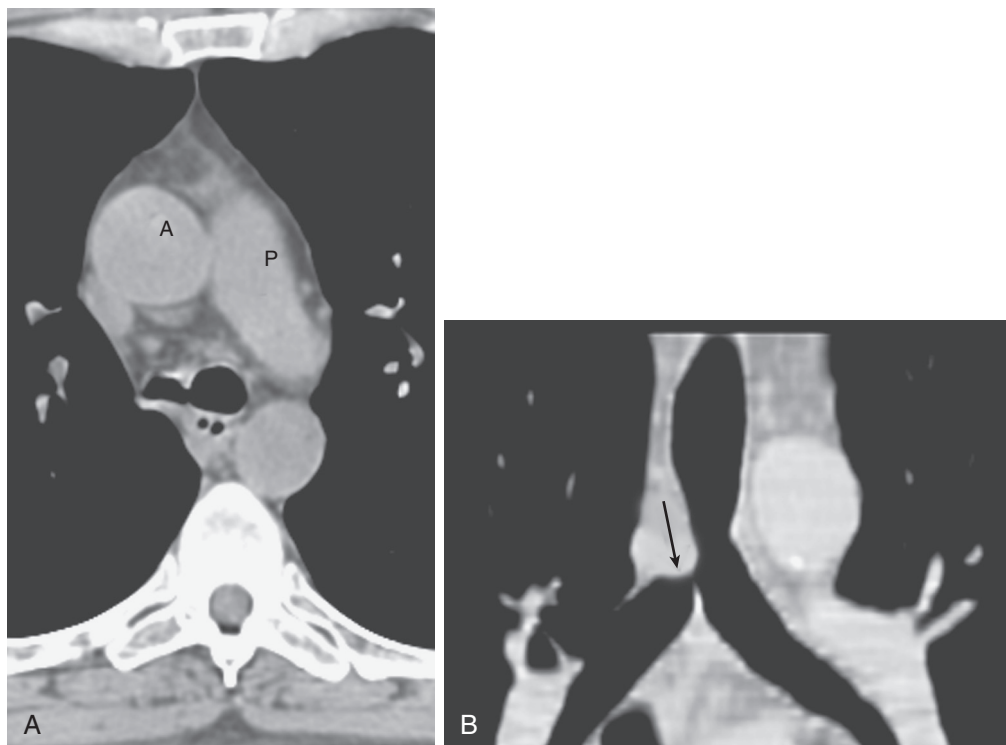


FIGURE 2-5 ■ Focal stenosis of the right main-stem bronchus from invasive aspergillosis. **A**, Axial computed tomography shows normal caliber of left main bronchus and marked concentric narrowing of right main bronchus. **B**, Coronal reconstruction shows that the right main bronchus stenosis involves a short focal segment (arrow). A, Ascending aorta; P, pulmonary artery.

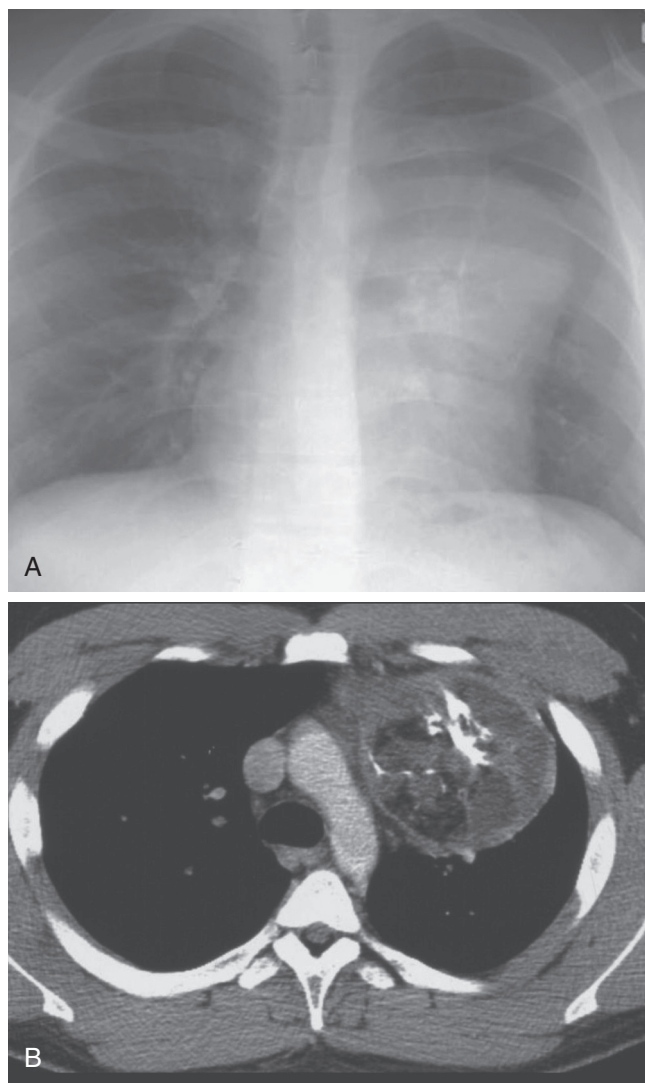


FIGURE 2-6 ■ Anterior mediastinal mass. **A**, Posteroanterior chest radiograph demonstrates a smoothly margined, left-sided anterior mediastinal mass. **B**, Axial computed tomographic image confirms the mass, with mixed heterogeneous components, including fat, soft tissue, fluid, and calcification. These findings are diagnostic of a teratoma.

Tumors that occur primarily in the posterior compartment are neurogenic tumors. In fact, 20% of all adult and 35% of all pediatric mediastinal neoplasms are neurogenic tumors, and most are located in the posterior mediastinum.³⁰ Neurogenic tumors are classified as tumors of peripheral nerves (neurofibromas, schwannomas, malignant tumors of nerve sheath origin) or sympathetic ganglia (ganglioneuromas, ganglioneuroblastomas, neuroblastomas) and are optimally assessed by MRI. MRI is the preferred modality for evaluating neurogenic tumors, because it can simultaneously assess intraspinal extension, spinal cord abnormalities, longitudinal extent of tumor, and extradural extension.

LUNG ABNORMALITIES

Thoracic imaging is essential in the workup of pulmonary abnormalities, including lung nodules and focal opacities,

intrathoracic malignancies, diffuse interstitial lung disease, and infection. Low-dose CT (LDCT) is being used as a screening tool for lung cancer and the National Lung Screening Trial, a randomized study comparing the effectiveness of LDCT to chest radiography in more than 50,000 participants, has reported significant reductions in lung cancer (20%) and all-cause mortality (6.7%).³¹

Solitary Pulmonary Opacities

Solitary pulmonary opacities are a common radiologic finding and are usually benign, but because of concern about lung cancer, further evaluation is often suggested. The goal is to differentiate malignant and benign lesions so that patients who require surgery are identified correctly. Although morphologic features can suggest whether a nodule is benign or malignant, there is considerable overlap, and at least 20% of malignant nodules have a benign appearance.^{32,33} Specific patterns of calcification and stability in size for 2 years have historically been the only reliable findings useful in determining benignity. More recently, the ability to distinguish between benign and malignant opacities has improved with the assessment of perfusion using contrast-enhanced CT and the assessment of metabolism using PET imaging with fluorodeoxyglucose labeled with radioactive fluoride (¹⁸F; FDG).

Contrast-enhanced CT can be used to differentiate benign and malignant nodules because the intensity of enhancement is directly related to the vascularity of the nodule and to the likelihood of malignancy.^{34,35} Typically, malignant nodules enhance greater than 20 Hounsfield units (HU), whereas benign nodules enhance less than 15 HU.³⁶ Although nodule-enhancement CT has a high negative predictive value, it is performed infrequently because of the general availability of FDG PET-CT.³⁷

FDG PET allows differentiation of malignant and benign nodules that are indeterminate after conventional imaging (Fig. 2-7). A metaanalysis of 40 studies on the accuracy of FDG-PET reports a sensitivity of 97% and a specificity of 78% when used in the evaluation of 10-mm or larger nodules.³⁸ However, a recent prospective integrated PET-CT evaluation of 585 patients (496 malignant, 89 benign nodules) showed that although a high standardized uptake value (SUV > 4.1) was associated with a 96% likelihood of malignancy, the likelihood of malignancy was still 25% when the SUV was 0 to 2.5.³⁹ Furthermore, in malignant nodules that are smaller than 1 cm in diameter or have ground-glass or partially solid morphology, FDG uptake is variable and unreliable in differentiating benign from malignant nodular opacities (Fig. 2-8).⁴⁰

Staging Lung Cancer

Staging—the assessment of the anatomic extent of non-small cell lung cancer (NSCLC)—usually determines treatment and prognosis. Clinical staging typically includes CT and, more recently, PET-CT. CT is typically used to determine the size, location, and presence of locoregional invasion of the primary tumor (T), the presence and location of nodal (N) metastasis, and intrathoracic and distant systemic metastasis (M1a, M1b).^{41,42}

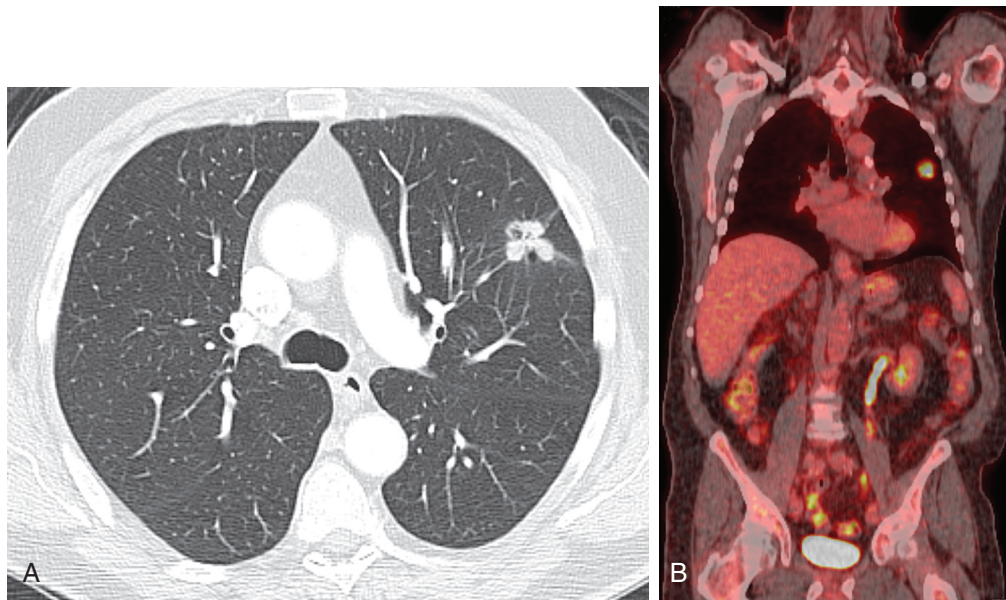


FIGURE 2-7 ■ Non-small-cell lung cancer. **A**, Axial computed tomography shows a lobular left upper lobe nodule. **B**, Fused coronal positron emission tomography–computed tomography shows small nodule in the upper lobe with increased uptake of [^{18}F] fluorodeoxyglucose, consistent with malignancy. Note the absence of nodal and distant metastases.

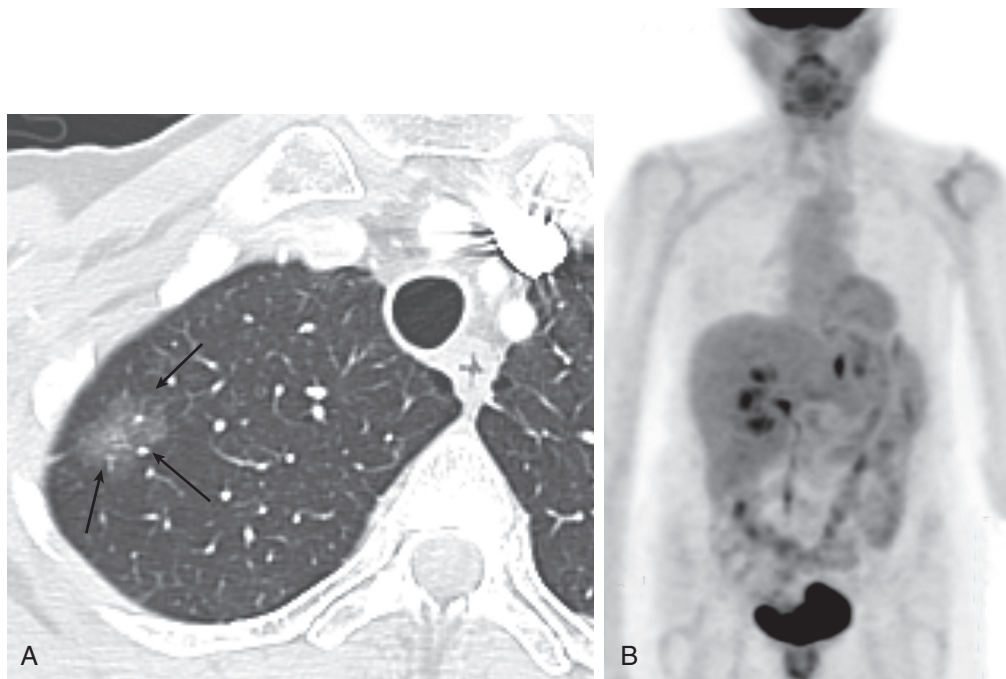


FIGURE 2-8 ■ Non-small-cell lung cancer. **A**, Axial computed tomography shows a ground glass right upper lobe lung nodule (arrows). **B**, Whole body maximum intensity PET shows no uptake of [^{18}F] fluorodeoxyglucose (FDG) in the nodule. Note that FDG uptake is variable and unreliable in nodules with ground glass morphology and is not useful in differentiating benign from malignant nodules.

CT is also usually used to define chest wall or mediastinal invasion but is inaccurate in differentiating between anatomic contiguity and subtle invasion. MRI has better soft-tissue contrast resolution than CT and is useful in the evaluation of superior sulcus tumors and the brachial plexus (Fig. 2-9).^{43,44}

The presence of nodal metastases and their locations are important for determining management and prognosis (Fig. 2-10).^{41,42} CT is most commonly used to assess the size of nodes, and a short-axis diameter greater than

1.0 cm is the criterion typically used to diagnose nodal metastases. However, a limitation is the overlap in the size of malignant and benign lymph nodes. In this regard, a metaanalysis (20 studies, 3438 patients) evaluating CT for staging of the mediastinum yielded a pooled sensitivity of 57% and specificity of 82%.⁴⁵ PET imaging improves the accuracy of nodal staging. In a metaanalysis of 17 studies comprising 833 patients, the overall sensitivity of PET for detecting nodal metastases was 83% and the specificity was 92%, whereas the sensitivity

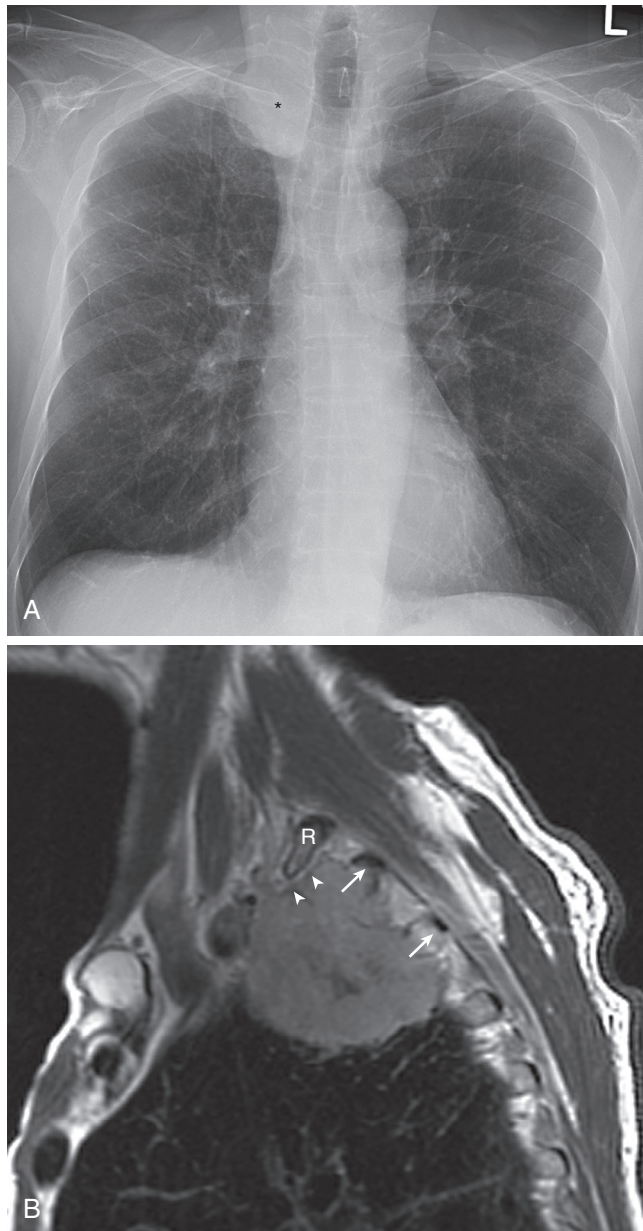


FIGURE 2-9 ■ Non-small-cell lung cancer superior sulcus tumor. **A**, Posteroanterior chest radiograph shows a right upper lobe mass (asterisk). **B**, Sagittal magnetic resonance imaging shows a mass invading the second and third ribs (arrows). Preservation of adjacent soft tissue planes (arrowheads) adjacent to the first rib (*R*) indicates that the C8 nerve root of the brachial plexus located superior to the rib is not involved by tumor and the patient is potentially a surgical candidate.

and specificity of chest CT were 59% and 78%, respectively.⁴⁶ Interestingly, in the presence of enlarged lymph nodes, PET and PET-CT become less specific and less accurate, but more sensitive in detecting nodal metastases.^{47,48}

The adrenal glands, liver, brain, bones, and lymph nodes are the most common sites of metastatic disease at presentation. However, the role of imaging these areas at presentation is not clearly defined. Routine imaging of the upper abdomen is performed as part of the initial chest CT evaluation in most patients with NSCLC.

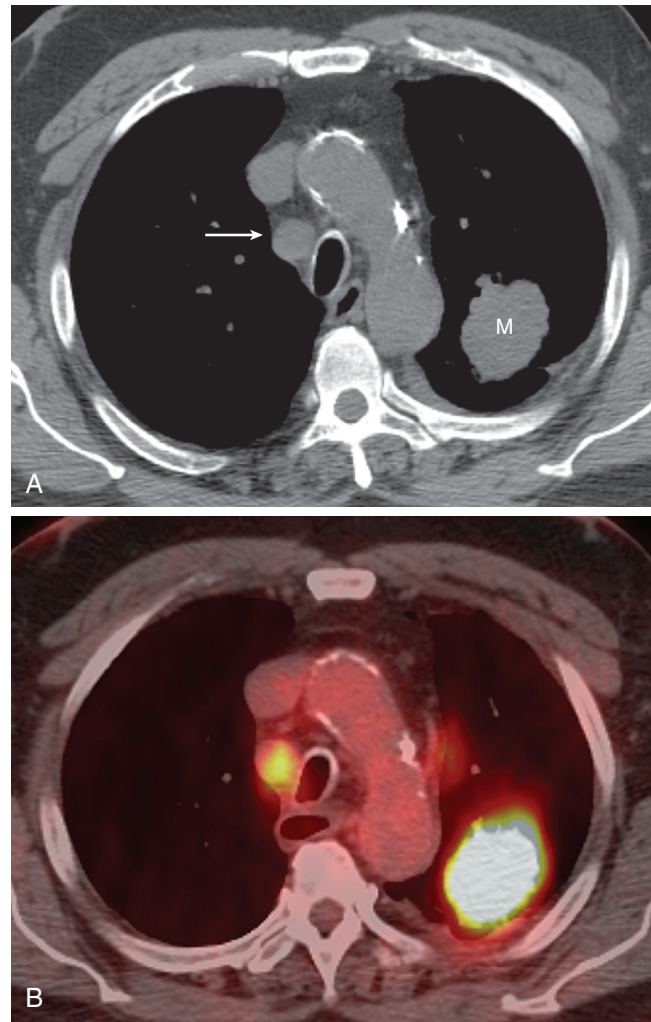


FIGURE 2-10 ■ Non-small-cell lung cancer. **A**, Axial computed tomography shows left upper lobe lung malignancy (*M*) and enlarged right paratracheal node (arrow). **B**, Axial fused positron emission tomography–computed tomography shows increased uptake of [¹⁸F] fluorodeoxyglucose within the mass and right paratracheal lymph node consistent with a malignancy. Biopsy confirmed N3 nodal metastasis.

However, because clinical staging of NSCLC with CT and MRI is often inaccurate, whole-body imaging with PET-CT can be performed to improve accuracy. PET has a higher sensitivity and specificity than CT does in detecting metastases to the adrenal glands, bones, and extrathoracic lymph nodes. Whole-body PET imaging stages intrathoracic and extrathoracic disease in a single study, detects occult extrathoracic metastases in up to 24% of patients selected for curative resection, and is cost effective (Fig. 2-11).⁴⁹⁻⁵³

Metastases to the adrenal glands are detected in up to 20% of patients with NSCLC at presentation. If an adrenal mass contains fat or has an attenuation value of less than 10 HU on a noncontrast CT scan, the mass can be considered benign.⁵⁴ Lesions with attenuation values of greater than 10 HU can be further evaluated with MRI using chemical shift analysis and dynamic gadolinium enhancement to determine whether they are malignant or benign.⁵⁴ FDG-PET has a specificity of 80% to 90%;

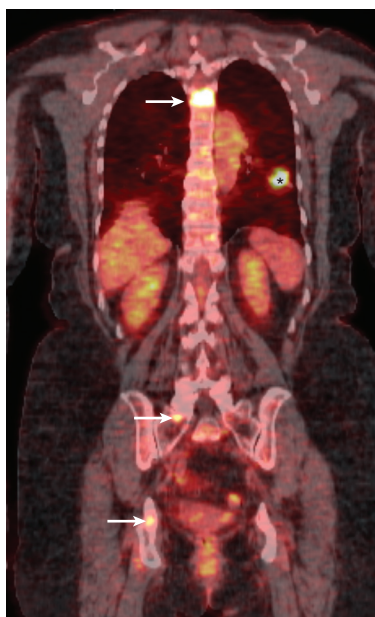


FIGURE 2-11 ■ Non-small-cell lung cancer. Fused coronal positron emission tomography–computed tomography shows left upper lobe lung nodule (*asterisk*) with increased [^{18}F] fluorodeoxyglucose (FDG). Note focal increased FDG uptake in thoracic spine and pelvis due to metastases (*arrows*).

it is useful in distinguishing benign from malignant adrenal masses detected on CT and is particularly advocated when the adrenal mass is small.⁵⁵⁻⁵⁷

Routine CT or MRI of the central nervous system has been advocated because up to 18% of patients with NSCLC have brain metastases at presentation, and 10% of these patients have no associated neurologic symptoms. However, routine CT or MRI of the central nervous system remains controversial, as the yield is low for asymptomatic patients with early disease. The prevailing clinical practice is to perform CT or MRI for patients who have neurologic signs or symptoms, as well as for asymptomatic patients with stage III disease who are being considered for aggressive local therapy such as thoracotomy or radiation.^{58,59}

PET-CT has high specificity, sensitivity, negative predictive value, positive predictive value, and accuracy in the assessment of bone metastases. PET-CT has to a large extent replaced $^{99\text{mTc}}$ -labeled methylene diphosphonate bone scintigraphy in the evaluation of bone metastases in patients with NSCLC.^{60,61} Because routine imaging rarely reveals occult skeletal metastases in an asymptomatic patient, MRI is generally performed only if the patient has focal bone pain or an elevated alkaline phosphatase level.

Interstitial Lung Disease and Pulmonary Abscesses

Imaging studies are essential for determining the diagnosis in patients with pulmonary symptoms and focal or diffuse lung disease. If the diagnosis is uncertain after clinical and imaging evaluations, surgical biopsies can be requested before therapy is initiated. Radiologic studies are often useful in determining the optimal site to biopsy,



FIGURE 2-12 ■ Usual interstitial pneumonitis (UIP). Axial high-resolution computed tomographic image through the bases demonstrates diffuse lung disease with area of predominantly peripheral ground-glass opacities, architectural distortion, and cystic spaces consistent with pulmonary fibrosis. Lung biopsy confirmed UIP.

as well as the biopsy method (i.e., transbronchial or wedge biopsy; Fig. 2-12). Lung abscesses, usually caused by aspiration of anaerobic bacteria, typically occur in patients with altered levels of consciousness, gastroesophageal dysmotility, and poor dental hygiene. Medical therapy (systemic antibiotics, postural drainage) is the initial treatment of choice and is curative in most patients. However, lung abscesses in children younger than 7 years typically do not drain spontaneously and are less likely to respond to medical management. Surgical or percutaneous drainage is required in the 11% to 21% of patients with lung abscesses who fail to respond to medical therapy. Drainage of an abscess is recommended when (1) the patient has persistent sepsis 5 to 7 days after initiation of antibiotic therapy, (2) the abscess is larger than 4 cm, or (3) the abscess increases in size while the patient is on medical therapy.

Percutaneous CT-guided catheter drainage has less morbidity and mortality than surgical resection does, and in most cases clinical and radiologic improvement occurs rapidly after catheter drainage. Although the mean time to abscess resolution is 10 to 15 days, marked improvement of sepsis (fever, leukocytosis) usually occurs within 48 hours of drainage. Failure of percutaneous drainage can occur when the abscess (1) contains viscous, organized tissue, (2) is multiloculated, or (3) has a thick, non-collapsible wall. Potential complications of lung abscesses drainage with a percutaneous tube include bleeding, bronchopleural fistula, and empyema.

PLEURAL AND CHEST WALL ABNORMALITIES

Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is an uncommon tumor that arises from mesothelial cells of the

pleura and less commonly of the pericardium or peritoneum. In the United States, it is estimated that there will be 2500 to 3000 cases per year, predominantly in older men, and the majority are associated with prior asbestos exposure.^{62,63}

Imaging is important not only in the diagnosis of MPM, but also in staging and monitoring of response to therapy.^{64,65} In an attempt to identify patients who are potentially resectable, the current staging for MPM emphasizes criteria used to determine local tumor extension and regional lymph nodes status in a traditional tumor node metastasis (TNM) system. The TNM staging system effectively distinguishes the T and N categories, but there are areas for potential revision. In this regard, by multivariable analyses, significant differences in overall survival were seen for: T4 versus T3 and T3 versus T2 but not T2 versus T1; N0 versus N1 and N2 but not N1 versus N2; stages III and IV versus I but not II versus I.⁶⁶⁻⁶⁸ Treatment options depend on the stage at presentation, with surgical resection sometimes performed in limited disease. Although the role of surgery (extrapleural pneumonectomy, extended pleurectomy/decortication) remains controversial, the presence of advanced locoregional primary tumor (T4), N2-3 disease (mediastinal, internal mammary, and supraclavicular lymph nodes), or M1 disease precludes resection.

MRI has historically been considered superior to CT in the staging of MPM. However, in a study comparing the accuracy of MRI and nonspiral CT in evaluation of MPM,⁶⁹ MRI and CT were found to have nearly equivalent diagnostic accuracies (50% to 65%) in overall staging. The only significant differences were in two categories: invasion of the diaphragm (CT accuracy, 55%; MRI accuracy, 82%; $P = 0.01$) and invasion of endothoracic fascia or a single chest wall focus (CT accuracy, 46%; MRI accuracy, 69%; $P = 0.05$). PET-CT is being used to evaluate patients with MPM (Fig. 2-13). PET-CT has improved the accuracy of tumor staging, and a sensitivity of 67% has been reported for T4 disease.⁷⁰ The sensitivity of PET-CT for detecting nodal metastatic disease is poor (i.e., 11% for PET alone and 38% for integrated PET-CT).^{70,71} PET-CT imaging is useful in detecting distant metastatic disease and has been reported to detect extrathoracic metastases that were not detected by clinical and morphologic imaging in 24% of patients with MPM.⁷⁰⁻⁷²

Pleural Collections

Fluid collections in the pleural space are caused by a variety of diseases, including infection, trauma, inflammation, and neoplasm. Although some patients can be managed conservatively, interventional procedures such as pleural fluid aspiration, with or without placement of a drainage catheter, or pleural biopsies are frequently performed for either diagnostic or therapeutic purposes. The type of intervention depends on a spectrum of clinical and imaging features, including symptoms, extent of disease, and etiology of the pleural abnormality. Imaging studies, most frequently with CT, can delineate the extent and complexity of the pleural collection.

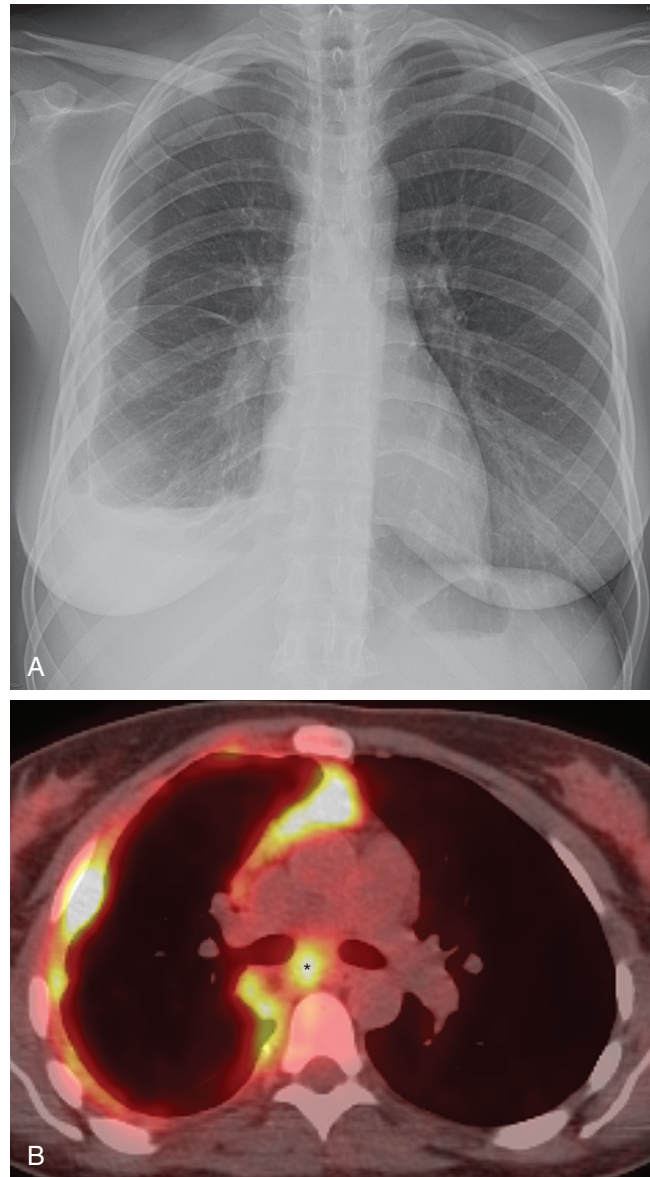


FIGURE 2-13 ■ Malignant pleural mesothelioma. **A**, Posteroanterior chest radiograph shows moderate right pleural effusion and lobularity of the pleura. **B**, Axial fused positron emission tomography-computed tomography shows increased [¹⁸F] fluorodeoxyglucose uptake in pleural masses and focal uptake in subcarinal node (*asterisk*). Biopsy of subcarinal node revealed metastatic pleural mesothelioma, precluding extrapleural pneumonectomy.

Chest Wall Disease

Abnormalities of the chest wall are unusual and are most commonly the result of soft tissue tumors, metastatic disease, infections, iatrogenic causes, trauma, and congenital lesions. The choice of imaging modality for this spectrum of diseases often depends on the suspected etiology, but CT is usually the initial study for evaluation. Although CT can provide the requisite diagnostic information and has superb multiplanar capabilities for surgical planning, MRI is typically also performed; its superior soft tissue contrast resolution can be useful in accurately

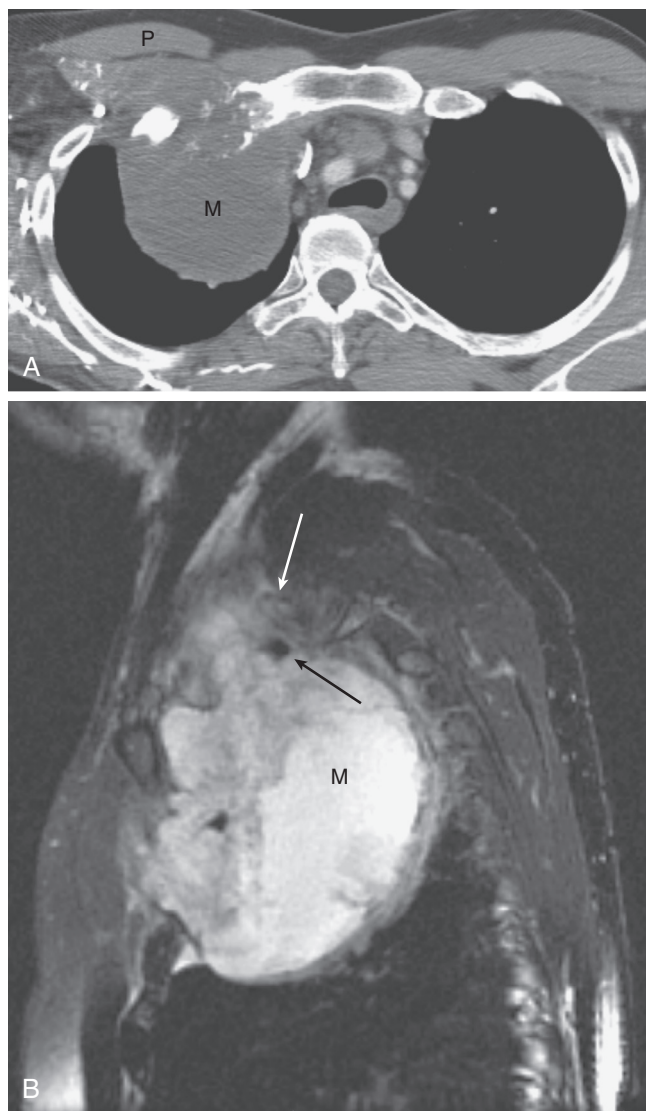


FIGURE 2-14 ■ A 60-year-old man with newly diagnosed chondrosarcoma of the first rib presented with right shoulder pain. **A**, Contrast-enhanced axial chest computed tomography shows a large mass (M) arising from the right first rib. Note that the density of the mass is similar to that of muscle, as compared with the right pectoralis major muscle (P). The brachial plexus cannot be visualized. **B**, T2-weighted sagittal magnetic resonance imaging distinguishes the intensity of the mass (M) from that of surrounding soft tissues and muscles. This enables direct visualization of the right subclavian artery (black arrow) and brachial plexus (two black dots abutting tip of white arrow), which are surrounded by the tumor.

delineating the extent of involvement of the chest wall (Fig. 2-14).

POSTOPERATIVE IMAGING

Early awareness of surgical complications is important, as timely management is associated with a decrease in mortality. Chest radiographs commonly demonstrate abnormalities in patients after cardiothoracic procedures. An increase in heart size can be caused by perioperative

myocardial infarction or hypervolemia, although most frequently it is the result of fluid in the pericardial sac or mediastinal fat. In some cases, the mediastinal contours appear normal on chest radiographs even though a significant amount of bleeding has occurred. In other cases, the normal mediastinum may appear enlarged because of magnification effects on the supine, expiratory radiograph. CT can be used to evaluate mediastinal widening and air collections in patients after sternotomy, and it can be useful in suggesting the diagnosis of mediastinitis.⁷³

Pulmonary Embolism

Clinical signs and symptoms of pulmonary embolism (PE) are neither sensitive nor specific, because patients can have chest pain, shortness of breath, or oxygen desaturation. Initial imaging with chest radiographs is useful to search for other causes that can clinically mimic PE, such as pleural effusions, pneumothorax, pneumonia, or congestive heart failure. The chest radiographic findings in patients with PE are nonspecific and include consolidation, atelectasis, pleural effusion, peripheral wedge-shaped opacities, enlargement of a pulmonary artery, and focal oligemia. However, 80% of patients with PE have a normal chest radiograph.⁷⁴

If a diagnosis of PE is suggested, and the chest radiograph does not suggest a reasonable alternative diagnosis, other imaging modalities can be used for further evaluation. Multidetector CT angiography (CTA) is the method of choice for imaging the pulmonary vasculature when PE is suspected. In the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) study, pulmonary CTA had a sensitivity of 83% and specificity of 96% for the diagnosis of PE.⁷⁵ Additional advantages of using multidetector CTA to diagnose PE include the detection of alternative abnormalities that explain the patient's clinical presentation, the ability to quantify the obstruction to the pulmonary arterial bed,⁷⁶⁻⁷⁹ and the ability to predict 30-day mortality after acute pulmonary embolism by assessing cardiac strain as seen by an increase in right-left ventricular diameter ratios (Fig. 2-15).⁸⁰⁻⁸³ Pulmonary CTA is commonly acquired with low-pitch helical modes and without use of ECG synchronization (standard pulmonary CTA). More recently, a high-pitch helical CT technique with prospective ECG triggering has been reported to facilitate high-quality imaging with a decrease in radiation dose compared with standard CTA.⁸⁴

Evaluation of PE can also be performed with other imaging modalities such as conventional angiography, MRI, or ventilation-perfusion (V/Q) scans. Currently, because of the high sensitivity and specificity of CTA in detecting PE, as well as the ability to suggest alternative diagnoses, these modalities are infrequently used in the evaluation of patients with suspected PE. V/Q scans still have a role in the evaluation of PE disease in patients who are allergic to iodinated contrast agents or who have impaired renal function. In patients with a normal chest radiograph and a normal V/Q scan, there is a very low probability of pulmonary embolus, and no further evaluation for PE is required. Patients with a high pretest

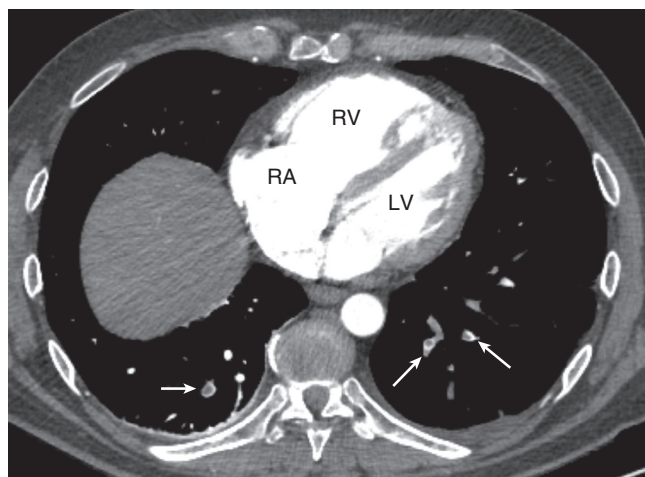


FIGURE 2-15 ■ Pulmonary embolism and right ventricular strain. Contrast-enhanced axial multidetector computed tomography shows multiple filling defects in the segmental pulmonary arteries of the lower lobes (arrows). Note dilation of the right ventricle (RV) and right atrium (RA). The right ventricle is larger than the left ventricle (LV), and there is straightening of the interventricular septum. These findings are consistent with right heart strain.

probability of PE and a high-probability scan are likely to have pulmonary embolism, and treatment is often initiated. Single positron emission computed tomography (SPECT) V/Q can be used to improve the diagnosis of PE compared with planar V/Q. A prospective study reported a sensitivity of 100% and a specificity of 87% for SPECT V/Q, whereas planar V/Q scintigraphy had a sensitivity of 64% and a specificity of 72%.⁸⁵ Although magnetic resonance angiography (MRA) has been reported to have a similar negative predictive value compared with CTA-PE when used for the primary diagnosis of pulmonary embolism in symptomatic patients,⁸⁶ MRA has two main limitations that restrict acceptance as a second-line diagnostic test for PE diagnosis in patients with a contraindication to CTA: the limited sensitivity in detecting segmental and smaller emboli and the large proportion of technically inadequate studies.^{87,88} In this regard, 25% of the studies in the PIOPE III study evaluating contrast-enhanced MRA for PE diagnosis were technically inadequate for interpretation and sensitivity was 78%.⁸⁹ A further limitation of MRI is that the study can be technically challenging to perform, especially in the acute setting, in the postoperative patient, or in the patient in the intensive care unit. In addition, the use of MRI contrast agents is contraindicated in patients with impaired renal function, because of an association between gadolinium-based contrast agents and the development of nephrogenic systemic fibrosis.^{90,91} However, a recent study reported that whereas contrast-enhanced angiographic MRI sequences showed the highest sensitivity (82.9% to 89.7%) and specificity (98.5% to 100%), unenhanced angiographic sequences, although less sensitive overall (68.7% to 76.4%), were sensitive for the detection of proximal PE (92.7% to 100%) and showed high specificity (96.1% to 99.1%).⁹²

SUMMARY

Imaging plays an important role in the diagnosis and follow-up of patients with pulmonary diseases. Recent advances in imaging technologies have revolutionized evaluation of thoracic disease, with improvements in patient management. Careful selection of the appropriate imaging studies improves diagnostic accuracy, limits the number of tests performed, and decreases unnecessary surgery. It is anticipated that further improvement of existing modalities and continued development of novel imaging technologies will improve diagnostic imaging strategies and patient outcomes in the future.

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PREOPERATIVE EVALUATION OF PATIENTS UNDERGOING THORACIC SURGERY

John J. Reilly, Jr.

CHAPTER OUTLINE	
PHYSIOLOGIC EFFECTS OF THORACIC SURGERY	IMAGING STUDIES
PATIENT POPULATION UNDERGOING THORACIC SURGERY	PULMONARY FUNCTION TESTING
COMMON COMPLICATIONS AFTER THORACIC SURGERY	PREDICTION OF POSTOPERATIVE LUNG FUNCTION
EFFECT OF SURGICAL APPROACH ON PERIOPERATIVE COMPLICATIONS	CARDIAC ASSESSMENT OF PATIENTS UNDER CONSIDERATION FOR THORACIC SURGICAL PROCEDURES
GOALS OF THE PREOPERATIVE EVALUATION	ASSESSMENT OF FUNCTIONAL CAPACITY
HISTORY AND PHYSICAL EXAMINATION	Arterial Blood Gas Measurements
History	Pulmonary Hemodynamics
Physical Examination	Age
Laboratory Studies	EVALUATION AND RISK STRATIFICATION

The decision to proceed with any surgical procedure involves a careful consideration of the anticipated benefits of surgery and an assessment of the risks associated with the surgical procedure. An important component of estimating the benefit of surgery is knowledge of the natural history of the condition in question in the absence of surgery.

A popular, and inaccurate, conception of preoperative evaluation is that the evaluating physician “clears” the patient for surgery. Implicit in this terminology is the assumption that a cleared patient has a low risk for perioperative morbidity. As will be discussed in this chapter, it is more accurate to view the role of preoperative evaluation as meeting two goals: defining the morbidity and risks of surgery, both short and long term, and identifying specific factors or conditions in patients that can be addressed to modify the patient’s risk of morbidity. The formulation of an approach to accomplish these goals requires knowledge of the effects of thoracic surgery on patients.

PHYSIOLOGIC EFFECTS OF THORACIC SURGERY

Surgical procedures and the anesthesia administered to allow such procedures have significant effects on

respiratory physiology that contribute to the development of postoperative pulmonary complications. Given that the incidence of pulmonary complications is directly related to the proximity of the planned procedure to the diaphragm, patients undergoing pulmonary, esophageal, or other thoracic surgical procedures fall into the category of patients at high risk for postoperative respiratory complication.¹

The intraoperative use of inhaled volatile agents can affect gas exchange by altering diaphragmatic and chest wall function. These changes occur without corresponding alterations in blood flow, which creates low ventilation-perfusion areas, resulting in widening of the alveolar-arterial oxygen gradient.

In the postoperative period, a variety of factors contribute to the development of complications; these include an alteration in breathing pattern to one of rapid shallow breaths with the absence of periodic deep breaths (sighs) and abnormal diaphragmatic function. These complications result both from pain and from diaphragmatic dysfunction resulting from splanchnic efferent neural impulses arising from the manipulation of abdominal contents. This has the effect of reducing the functional residual capacity (FRC)—the resting volume of the respiratory system. The FRC declines by an average of 35% after thoracotomy and lung resection and by

approximately 30% after upper abdominal operations.²⁻⁴ If the FRC declines sufficiently to approach closing volume, the volume at which small airway closure begins to occur, patients develop atelectasis and are predisposed to infectious complications. Closing volume is elevated in patients with underlying lung disease.

The alterations in lung volumes that occur result in a reduction in both the inspiratory capacity (the maximal inhalation volume attained starting from a given lung volume) and the expiratory reserve volume (the maximal exhalation volume from a given lung volume), contribute to a decline in the effectiveness of cough, and result in increased difficulty in clearing of pulmonary secretions.

PATIENT POPULATION UNDERGOING THORACIC SURGERY

Many patients undergoing a noncardiac thoracic surgical procedure do so because of known or suspected lung or esophageal cancer. These diseases share the common risk factor of a significant and prolonged exposure to cigarette smoking. The combination of age and prolonged cigarette smoking results in a patient population with a significant incidence of comorbid factors in addition to the primary diagnosis. Several reports use the Charlson Comorbidity Index as an indicator of comorbid conditions and predictor of postoperative complications. This index generates a score based on the presence of comorbid conditions; it has been demonstrated to stratify risk of postoperative complications in thoracic surgery patients.^{5,6}

In one study, the mean age of patients undergoing esophagectomy was 58.1 years; 45% of patients were older than 60 years.⁷ In another Japanese study, the median age was 62.3 years; 88% were male.⁸ In a study comparing transhiatal esophagectomy with transthoracic esophagectomy, the mean ages of the patients were 69 years and 64 years, with patients up to the age of 79 years being included in the study.⁹ In a review, 28% to 32% of patients undergoing esophagectomy in the United States were older than 75 years, and 40% had a Charlson score above 3.¹⁰

Similarly, patients with lung cancer tend to be older and have comorbid conditions. In a series of 344 patients, 36% were older than 70 years and 95% had a significant smoking history.¹¹ A review of Medicare patients undergoing thoracic surgery in the United States showed that of patients undergoing lobectomy, 32% to 35% were older than 75 years (44% women), and 32% had a Charlson score greater than 3.¹⁰ In the same series, 21% to 26% of patients undergoing pneumonectomy were older than 75 years (28% women), and 56% had a Charlson score above 3.

A significant source of comorbidity in the population of patients with lung cancer is chronic obstructive pulmonary disease (COPD). The diagnosis of COPD is an independent risk factor, controlling for cigarette smoke exposure, for the development of lung cancer.

Thus, the patient population presenting for major thoracic surgical procedures tends to be older, has a high incidence of comorbid conditions, and contains a

disproportionate number of patients with obstructive lung disease. The combination of these factors, plus the magnitude of the surgical procedures, presents a challenge to the clinicians evaluating such patients. The potential for perioperative morbidity and mortality is substantial, but at the same time, the lack of effective alternative therapy for the patient's malignant disease means that the consequence of not being a surgical candidate is almost certain mortality. This quandary has led Gass and Olsen¹² to ask: What is an acceptable surgical mortality in a disease with 100% mortality?

COMMON COMPLICATIONS AFTER THORACIC SURGERY

These are discussed in more detail elsewhere in this book (see [Chapter 4](#)). In general, the most frequent complications after major thoracic procedures fall into the categories of respiratory and cardiovascular. Although the exact frequency varies by series, pneumonia, atelectasis, arrhythmias (particularly atrial fibrillation), and congestive heart failure are the most common. Myocardial infarction, prolonged air leak, empyema, and bronchopleural fistula also occur at a significant frequency.^{11,13,14} It follows, therefore, that particular attention to pulmonary and cardiac reserve and risk factors should be a major component of the preoperative evaluation.

EFFECT OF SURGICAL APPROACH ON PERIOPERATIVE COMPLICATIONS

Two developments in thoracic surgical practice have had particular impact on the assessment of marginal candidates for thoracic surgical procedures. The first is the rise in the prevalence of "minimally invasive" approaches, including video-assisted thoracoscopic approaches, for both pulmonary parenchymal resections and esophageal surgery. The reported data suggest a lower rate of pulmonary complications after the use of thoracoscopic resection as compared with conventional thoracotomy, likely because of reduction in pain and improved chest wall mechanics.¹⁵ The second is the reemergence of lung volume reduction surgery and the recognition that a subset of patients with COPD have nonhomogeneous distribution of emphysema with an upper-lobe predominance, which is also the most common site of non-small-cell lung cancer, and that upper lobe resection in such individuals produces less deleterious impact on measured pulmonary function and in some instances can result in improvement in measured lung function after resection.¹⁶

GOALS OF THE PREOPERATIVE EVALUATION

The clinicians evaluating a patient for a major thoracic surgical procedure have several goals for the evaluation process. The most obvious of these goals is to provide all parties with an assessment of the risks, both short and

long term, of morbidity and mortality from the procedure in a given patient and simultaneously to identify factors that can be addressed to reduce the possibility of adverse events. Less obvious is that the comprehensive evaluation of a patient as part of the preoperative assessment allows the identification of risk factors and health issues independent of the planned surgery and facilitates the institution of interventions indicated regardless of plans for surgery.

HISTORY AND PHYSICAL EXAMINATION

Although the field of thoracic surgery has been dramatically altered by the development of new technologies in both imaging and therapeutics, the history and physical examination remain the most important components of the preoperative evaluation. There is no substitute for a careful history and examination by an experienced clinician.

History

Box 3-1 highlights the important components of the patient's history. Whereas many of the elements of the history are self-explanatory, several benefit from further exposition. A critical component of the preoperative evaluation is the assessment of a patient's functional status. Functional status is an important component of the decision algorithm for both the pulmonary and cardiac elements of the preoperative evaluation. A variety of approaches have been taken to determine functional capacity. These include questionnaires; tests of locomotion, such as the 6-minute walk or stair climbing; and cardiopulmonary exercise testing (discussed later). One convenient approach to use is the Duke Activity Status Index (DASI; [Table 3-1](#)), a questionnaire that can be administered during an interview or be self-administered.¹⁷

There is a rough correlation between the score on the DASI, which ranges from 0 to 58.2, and maximal oxygen uptake. In addition, the answers to this questionnaire can be used to estimate the functional capacity of the patient in metabolic equivalents (METs), a common frame of reference used in structuring the approach to

preoperative cardiac evaluation (discussed later). Four METs is the energy expenditure required to climb a flight of stairs, to walk up a hill or briskly on level ground, or to run a short distance (items 3 to 5 on the DASI); 1 to 4 METs are required to perform self-care, to ambulate on level ground within a residence, and to perform light housework (items 1, 2, 3, and 6 on the DASI). More than 10 METs are required to participate in strenuous sports such as singles tennis, bicycling, or basketball (item 12 on the DASI).

In addition to these considerations, patients should be asked about signs or symptoms suggesting the presence of metastatic disease, such as new headaches, focal neurologic signs or symptoms, new-onset seizure disorder, bone pain, and recent fractures. Patients should also be questioned about symptoms related to paraneoplastic syndromes. These can range from the relatively subtle symptoms of hypercalcemia to more dramatic neurologic symptoms.

Physical Examination

The examination of the patient includes an assessment of general overall appearance, including signs of wasting. Respiratory rate and the use of accessory muscles of

BOX 3-1 Important Components of History in Preoperative Evaluation

- Presenting symptoms and circumstances of diagnosis
- Prior diagnosis of pulmonary or cardiac disease
- Comorbid conditions: diabetes mellitus, liver disease, renal disease
- Prior experiences with general anesthesia and surgery
- Cigarette smoking: never, current, ex-smoker (if ex-smoker, when did patient stop?)
- Inventory of functional capacity of patient (e.g., Duke Activity Status Index)
- Medications and allergies
- Alcohol use, including prior history of withdrawal syndromes

TABLE 3-1 Duke Activity Status Index

Question	Activity: Can You	Yes	No
1	Take care of yourself, that is, eating, dressing, bathing, or using the toilet?	2.75	0
2	Walk indoors, such as around your house?	1.75	0
3	Walk a block or two on level ground?	2.75	0
4	Climb a flight of stairs or walk up a hill?	5.50	0
5	Run a short distance?	8.00	0
6	Do light work around the house like dusting or washing dishes?	2.70	0
7	Do moderate work around the house like vacuuming, sweeping floors, or carrying in groceries?	3.50	0
8	Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	8.00	0
9	Do yard work like raking leaves, weeding, or pushing a power mower?	4.50	0
10	Have sexual relations?	5.25	0
11	Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?	6.00	0
12	Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?	7.50	0

From Hlatky MA, Boineau RE, Higginbotham MB, et al: A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 64:651–654, 1989.

respiration are noted. Examination of the head and neck includes assessment of adenopathy and focal neurologic deficits or signs, particularly Horner syndrome in patients with a lung mass. The pulmonary examination includes an assessment of diaphragmatic motion (by percussion) and notes any paradoxical respiratory pattern in the recumbent position. The relative duration of exhalation and the presence or absence of wheezing should be noted. The presence of rales should raise the possibility of pneumonia, heart failure, or pulmonary fibrosis. The cardiac examination includes assessment of a third heart sound to suggest left ventricular failure, murmurs to suggest valvular lesions, and an accentuated pulmonic component of the second heart sound suggestive of pulmonary hypertension. The heart rhythm and the absence or presence of any irregular heart beats are noted. The abdominal examination notes liver size, presence or absence of palpable masses or adenopathy, and any tenderness. The examination of extremities notes any edema, cyanosis, or clubbing. Clubbing should not be attributed to COPD and raises the possibilities of intrathoracic malignant disease or congenital heart disease. The patient's gait should be observed, both as an assessment of neurologic function and to confirm the patient's ability to participate in postoperative mobilization.

Laboratory Studies

It is reasonable practice to check electrolyte values, renal function, and clotting parameters and to obtain a complete blood count as part of the preoperative assessment. In patients with known or suspected malignant disease, liver function and serum calcium concentration should also be checked.

IMAGING STUDIES

This issue is covered in detail elsewhere in this text. For patients undergoing pulmonary parenchymal resection, a review of images is essential to estimate the amount of lung that will be removed in surgery. In this setting, patients usually have a computed tomographic (CT) scan of the chest. In addition to the pathologic process for which the patient has been referred, the scan should be reviewed for signs of emphysema or pulmonary fibrosis. As noted earlier, the distribution of emphysema (if present) may significantly affect postoperative lung function. In general, review of images is an important component of surgical planning and determination of the extent of resection, which in turn influences the process of evaluation of the patient.

PULMONARY FUNCTION TESTING

The utility of preoperative pulmonary function testing in part depends on the type of operative procedure being planned. For patients undergoing mediastinoscopy, drainage of pleural effusions, or pleural biopsy or esophageal surgery and who have no prior history of lung disease or unexplained dyspnea, preoperative pulmonary

function testing is unlikely to contribute to the preoperative evaluation.

For patients being considered for pulmonary parenchymal resection, preoperative pulmonary function testing should be performed. Although a variety of pulmonary function tests have been examined in this setting, the two that have emerged as being predictive of postoperative complications are the *forced expiratory volume in 1 second* (FEV₁) measured during spirometry and the *diffusing capacity for carbon monoxide* (DL_{CO}). The diffusing capacity is also referred to as the *transfer factor*. Both of these values can be used to provide a rough estimate of the risk of operative morbidity and mortality. In addition, they are used to calculate the *predicted postoperative* values for FEV₁ and DL_{CO} (ppo-FEV₁ and ppo-DL_{CO}, respectively).

PREDICTION OF POSTOPERATIVE LUNG FUNCTION

Predicted postoperative lung function has been demonstrated to be an important predictor of operative risk. In general, the available methods for calculation of postoperative lung function result in an underestimate of actual measured lung function once the patient has recovered from surgery. Two approaches are commonly used for calculation of postoperative lung function: simple calculation and the regional assessment of lung function.

Simple calculation is based on the assumption of homogeneously distributed lung function, and it requires knowledge of the number of segments to be resected and the preoperative value. For FEV₁, the formula is $\text{ppo-FEV}_1 = \text{FEV}_1 [1 - (\text{Number of segments resected} \times 0.0526)]$. A similar calculation is done for DL_{CO}. For the majority of patients, this approach to calculation is sufficient and, as mentioned before, it results in a postoperative predicted value that is somewhat less than what is measured after recovery.

In certain situations, simple calculation is inaccurate in predicting postoperative lung function. The clinical situations in which regional assessment of lung function is indicated are summarized in [Box 3-2](#). A variety of approaches have been used to attempt to assess the regional distribution of lung function, including lateral position testing, bronchosprometry, quantitative radionuclide ventilation-perfusion scanning, and quantitative

BOX 3-2

Indications for Preoperative Assessment of the Regional Distribution of Lung Function

- Significant air flow obstruction on spirometry (FEV₁ < 80% predicted and FEV₁/FVC < 0.70)
- Significant pleural disease
- Known or suspected endobronchial obstruction
- Central lung mass
- History of prior lung resection

FEV₁, Forced expiratory volume in 1 second; FVC, forced vital capacity.

CT scanning. The test that is used most frequently is radionuclide scanning. Typically, the data from quantitative radionuclide ventilation-perfusion scans are reported as the percentage of function contributed by six lung regions: upper third, middle third, and lower third of each hemithorax. These data, combined with the knowledge of the preoperative lung function value and the location and planned extent of resection, allow the calculation of a predicted postoperative value. An alternative approach is the use of quantitative CT scanning, which categorizes lung tissue with an attenuation between -910 and -500 Hounsfield units as “functional lung tissue,” and in a manner analogous to that used for radionuclide scanning, an estimate of remaining functional lung tissue can be made on the basis of knowledge of the extent of planned resection.¹⁸ Comparison with radionuclide scanning suggests that quantitative CT scanning correlates with measured postoperative function as well as or better than radionuclide scanning does.¹⁹ This approach also allows prediction of postoperative oxygen saturation, which in turn has a correlation with postoperative complications and recovery time.²⁰ Similar to other methods of predicting postoperative lung function, it may underestimate residual function in patients with COPD.²¹ Despite these data and the potential advantages of using the CT scan for both anatomic definition and functional calculations, eliminating the need for the additional time and expense of a radionuclide perfusion scan, it has not been widely adopted (see [Box 3-2](#)).

CARDIAC ASSESSMENT OF PATIENTS UNDER CONSIDERATION FOR THORACIC SURGICAL PROCEDURES

The basic philosophy of cardiac assessment for surgical procedures has changed in recent years, as reflected in the recently released Clinical Practice Guideline: 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery.²² The preoperative evaluation is now viewed as an opportunity to perform a general cardiac assessment and to initiate risk factor modification or management rather than a specific intervention centered on surgery. The practice is to institute medical management as indicated by the patient's condition, rather than specific preoperative recommendations. In keeping with this approach, current concepts are that coronary revascularization, by either catheter approach or bypass grafting, is rarely indicated solely to reduce operative risk in a particular patient.

The preoperative cardiac evaluation incorporates both the cardiac risks associated with the operation under consideration and the specific risk factors of the particular patient under consideration. In general, thoracic surgical procedures fall into the risk categories of high (cardiac risk $> 5\%$, operations with an anticipated long procedure time, major fluid shifts, or blood loss) and intermediate (cardiac risk $1\%-5\%$, intrathoracic surgery). Given this and the above-referenced demographic and risk factors of the population of patients undergoing thoracic

surgery, a 12-lead ECG should be a routine part of the preoperative evaluation.

As with the evaluation in general, the cornerstone of preoperative cardiac evaluation is a careful history and physical examination. In addition to inquiries directed at cardiac risk factors such as family history, smoking history, history of hypercholesterolemia, history of diabetes mellitus or hypertension, and history of prior cardiac disease, special attention is directed to questions to assess the patient's functional capacity, as discussed previously. The combination of the classification of clinical predictors, the patient's functional capacity, and the risk of surgery then determines the approach to preoperative evaluation. Since the prior edition of this text, several instruments to predict the risk of perioperative major adverse cardiac events have been developed and are widely available. Two of the more commonly used instruments have been developed by the American College of Surgeons: <http://www.surgicalriskcalculator.com/miocardiacarrest> and <http://www.riskcalculator.facs.org>.^{23,24} The latter also provides risk estimates for noncardiac complications and outcomes, but requires more data for its calculations.

Current guidelines recommend a stepwise approach to the evaluation after a comprehensive history, physical examination, and review of the electrocardiogram. If a patient has had coronary revascularization within the past 5 years and has not had a clinical change since then, or if the patient has had a cardiac evaluation within the past 2 years that did not demonstrate the patient to be at high risk, further testing is usually not indicated. If neither of these considerations applies, the next step is to classify patients according to their clinical predictors.

For patients with a history of myocardial infarction within 30 days, unstable coronary syndromes, decompensated congestive heart failure, significant arrhythmias, or severe valvular disease, delay of the procedure should be considered for all but emergency procedures. Such patients should have medical risk factor management and modification initiated, and consideration should be given to performing coronary angiography.

Patients with good functional capacity (defined as ≥ 4 METs) and no cardiac symptoms should proceed with the planned surgery. Patients with unknown functional status or other medical conditions, such as orthopedic or neurologic issues that affect functional status, should be considered for pharmacologic stress testing. In individuals with unexplained dyspnea or with a history of congestive heart failure and a recent increase in dyspnea or reduction in exercise capacity, evaluation of left ventricular function with echocardiography should be considered.²² Although recent data suggest that beta blockers can be used safely in acutely ill patients with COPD, the role of beta blockers in perioperative management is unclear.²⁵ Current recommendations are that individuals using beta blockers long term have these agents continued during the perioperative period. The data supporting the initiation of beta blockers for reducing perioperative complications is more complicated and do not clearly establish the benefit of a policy of prescribing them routinely.²² The approach to preoperative cardiac evaluation is summarized in [Figure 3-1](#).

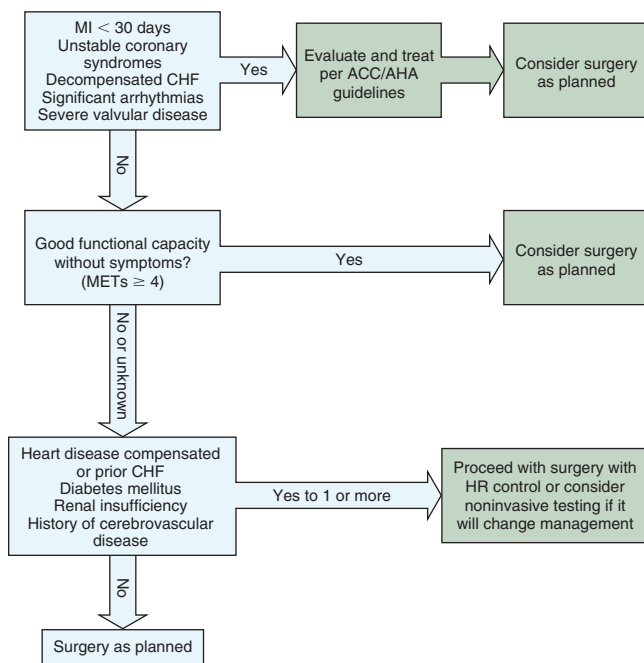


FIGURE 3-1 ■ Cardiac evaluation algorithm. ACC, American College of Cardiology; AHA, American Heart Association; CHF, chronic heart failure; HR, heart rate; METs, metabolic equivalents; MI, myocardial infarction. (Modified from Fleisher LA, Fleischmann KE, Auerbach AD, et al: 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *J Am Coll Cardiol* 64[22]:e77–e137, 2014.)

For all patients, any long-term issues meriting consideration of risk factor modification or therapy should be addressed in the postoperative period. Appropriate therapy is instituted when the patient is stable enough to tolerate it.

ASSESSMENT OF FUNCTIONAL CAPACITY

For patients undergoing pulmonary resection, functional capacity is an important predictor of postoperative morbidity and mortality. In addition to the role of functional capacity in determining the appropriate cardiac evaluation before surgery (see Fig. 3-1), functional capacity has predictive value for postoperative complications independent of that derived from pulmonary function testing.

In clinical practice, in addition to patient-reported functional status (described previously), there are two common approaches to objective assessment of functional capacity: (1) symptom-limited maximal cardiopulmonary exercise testing with expired gas analysis, and (2) threshold testing, which requires patients to attain a certain functional goal. Among the latter, the most commonly used test is stair climbing. Published data on stair climb testing suggest that patients who can climb more than three flights (54 steps) are at acceptable risk for lobectomy and that patients who can climb more than 4.6 to 5 flights are at acceptable risk for pneumonectomy. Conversely, patients unable to climb more than 12 m on

a symptom-limited stair-climbing test are at high risk for perioperative morbidity and mortality.^{11,26-33} An alternative to stair climbing is the shuttle walk, in which subjects walk back and forth (“shuttle”) on a 10-m course at a pace cued by an audio signal, increasing in speed every minute until the subject is too breathless to maintain the target pace. A result of less than 25 shuttles has been reported to correlate with maximal oxygen uptake (see later) of less than 10 mL/kg/min and, by inference, with prohibitive operative risk.³⁴

Maximal symptom-limited cardiopulmonary testing has been studied as a mode of assessment of functional capacity. The most commonly reported result of such testing is the maximal oxygen uptake ($\dot{V}O_2$) normalized for body mass, expressed as milliliters per kilogram per minute. Alternatively, the data are reported as a percentage of predicted value. There is good agreement that patients with an $\dot{V}O_2$ of more than 15 to 20 mL/kg/min are at low or “acceptable” risk for perioperative complications and mortality.³⁵⁻³⁷ Conversely, patients with an $\dot{V}O_2$ of less than 10 to 12 mL/kg/min are at high risk for thoracic surgery.^{33,38-40} In addition to these applications, the preoperative $\dot{V}O_2$ can also be used in concert with a regional assessment of lung function to calculate a predicted postoperative $\dot{V}O_2$ (ppo- $\dot{V}O_2$), in a manner analogous to that described for lung function parameters.³⁹ The ppo- $\dot{V}O_2$ can then be used to stratify perioperative risk.

Currently available data suggest that patients with a predicted postoperative FEV₁ or DL_{CO} of less than 40% should have additional risk stratification with a test of functional capacity. An alternative sequence of evaluation has been assessed by Bolliger and Perruchoud,⁴¹ who advocate functional assessment in all patients with an FEV₁ or DL_{CO} less than 80% predicted and reserve regional assessment of lung function for patients with a maximal oxygen uptake of 10 to 20 mL/kg/min or 40% to 75% of predicted. A synthesis of current recommendations for preoperative evaluation for pulmonary resection is presented in Figure 3-2.⁴²

Arterial Blood Gas Measurements

Commonly measured preoperatively, arterial blood gases have been used to attempt to stratify the risk of perioperative complications. Reports on the utility of arterial oxygen saturation in preoperative evaluation are contradictory; some suggest that resting hypoxemia or exertional desaturation identifies patients at higher risk, but others fail to confirm this association.^{43,44} This has led to the recommendation that patients with resting SaO₂ less than 90% undergo further physiologic evaluation.⁴² Patients with a resting PCO₂ greater than 45 mm Hg are at increased risk.^{35,45} Several studies, however, have demonstrated that resection can be undertaken safely in patients with resting hypercarbia in the absence of other contraindications to surgery.^{14,35,46}

Pulmonary Hemodynamics

Measurements of resting pulmonary hemodynamics, pulmonary artery occlusion, or exercise hemodynamics have

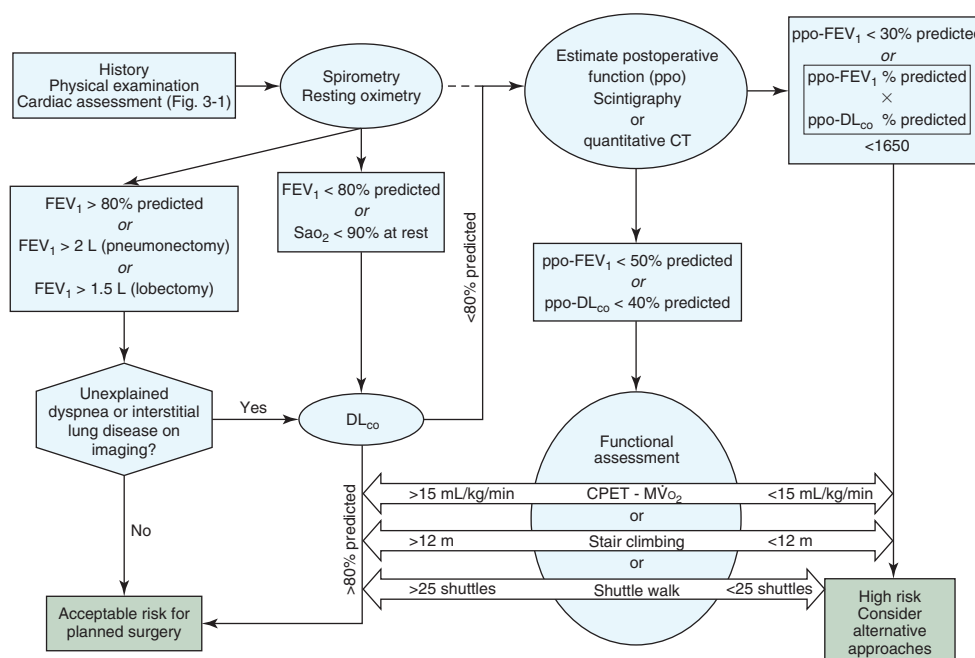


FIGURE 3-2 ■ Preoperative evaluation algorithm. CPET, Cardiopulmonary exercise testing; CT, computed tomography; DL_{CO} , diffusing capacity for carbon monoxide; FEV_1 , forced expiratory volume in 1 second; $M\dot{V}O_2$, maximal oxygen uptake; ppo, predicted postoperative; SaO_2 , arterial oxygen saturation.

been studied as preoperative assessments. The data generated are contradictory and generally do not add substantially to information obtained from functional assessment and pulmonary function testing.³⁰

Age

Although age has been confirmed in many series as a risk factor for perioperative complications, much of the additional risk from age results from comorbid factors. When studies control for comorbidities, patients are at mildly (approximately twofold) increased risk because of age.⁴⁷ Current consensus is that age alone, particularly in the presence of a good functional capacity, is not a contraindication to surgery.^{32,42}

EVALUATION AND RISK STRATIFICATION

Table 3-2 presents parameters that identify patients at higher and lower risk for complications after pulmonary surgery. Building on these parameters, various authors have attempted to create a multifactor risk assessment tool that incorporates a variety of these parameters.⁴⁸ A recommended approach to the preoperative evaluation, based on recent published consensus guidelines, is presented in Figure 3-2.⁴² Patients who fall into the conventional category of high or prohibitive risk and who are candidates for lung volume reduction surgery by virtue of having severe air flow obstruction and upper lobe-predominant emphysema may be candidates for parenchymal resection if the lesion requiring resection falls within the tissue that would be resected as part of lung

TABLE 3-2 Risk Assessment for Pulmonary Surgery

Higher Risk	Lower Risk
Age > 70 years	FEV_1 : >2 L for pneumectomy; >1.5 L for lobectomy; >0.6 L for segmentectomy
Higher extent of resection (pneumectomy, lobectomy, wedge resection)	Predicted postoperative FEV_1 > 30%-40%
Poor exercise performance	Stair climbing: >5 flights for pneumectomy; 3 flights for lobectomy
Low predicted postoperative FEV_1	Cycle ergometry > 83 watts
Low predicted postoperative DL_{CO}	Predicted postoperative DL_{CO} > 40%
Prolonged operative time	Maximal oxygen uptake > 15-20 mL/kg/min

DL_{CO} , Diffusing capacity for carbon monoxide; FEV_1 , forced expiratory volume in 1 second.

volume reduction. In this case, the predicted postoperative FEV_1 would actually be higher than that measured preoperatively, and standard prediction algorithms would not apply (see Table 3-2 and Fig. 3-2).⁴⁹⁻⁵²

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PERIOPERATIVE CARE OF THE THORACIC SURGICAL PATIENT

Elisabeth U. Dexter

CHAPTER OUTLINE

PREOPERATIVE PREPARATION

PROPHYLAXIS

Atrial Fibrillation
Deep Venous Thrombosis
Stress Ulceration and Gastritis
Infection
Anticoagulation
Miscellaneous

INTRAOPERATIVE CARE

Ventilation
Monitoring
Body Temperature
Positioning
Fluid Administration
Drainage
Specimen Management

POSTOPERATIVE CARE

Fluid Management
Blood Administration
Medications
Analgesia
Nutrition

Respiratory Therapy

Wound Care
Management of Drainage Tubes
Physical Therapy

MANAGEMENT OF COMPLICATIONS

Early Complications

Respiratory Complications
Cardiac Complications
Bleeding

Late Complications

Pulmonary Complications

Complications after Esophageal Surgery

Dysphagia
Anastomotic Leak
Stricture
Conduit Ischemia
Recurrent Laryngeal Nerve Damage
Chylothorax
Functional Problems
Reflux

Miscellaneous

DISCHARGE PLANNING

Patients who are undergoing thoracic surgery require careful attention in the perioperative period. These patients are often older and have baseline abnormalities of lung function, decreased nutritional status, and other comorbid diseases. Postoperatively, factors that influence patient recovery include removal of all or a portion of a lung, the esophagus, or the chest wall, painful incisions, retention of secretions, change in the shape and mechanics of the thoracic cage, and reconfiguration of gastrointestinal continuity, which result in suboptimal pulmonary function, decreased appetite, decreased mobility and strength, and increased risk of aspiration.

Perioperative care of the thoracic surgical patient requires a team approach. The surgeon is uniquely qualified to be the captain of the team, because he or she is aware of the patient's functional status preoperatively,

the operative findings and events, and the postoperative anatomy that will dictate each patient's needs and restrictions. Members of the team include the surgeon, anesthesiologist, pain management specialist, nurse, respiratory therapist, physical therapist, pharmacist, occupational therapist, speech pathologist, dietician, and social worker.

By the year 2030, an estimated 70 million people will be older than 65 years. A Surveillance, Epidemiology, and End Results study of lung cancer in older patients found that 14% and 33% of lung cancer patients were older than 80 years and 70-79 years, respectively.¹ In addition to evaluating the medical benefit of thoracic surgical procedures in the elderly, the effects on baseline functioning, living situation, and quality of life need to be assessed. Multiple different assessment tools predict the risk of

mortality or morbidity for these patients. Although no tool is perfectly accurate or reliable, they can be helpful for deciding whether to perform surgery, the extent of surgery, surgical approach, and hospital discharge planning and disposition.²⁻⁴

For palliative procedures, a discussion of the patient's expected outcome from the operation—symptomatically, medically, and functionally—is prudent to ensure that the patient and family understand the benefit/risk balance of each procedure and want to move forward. Knowledge of advanced directives and Do Not Resuscitate or Do Not Intubate status before the operation is recommended.⁵

In recent years, there has been increased focus on patient safety, quality of patient care, and cost savings. As care becomes more specialized, duty hours are restricted, and more practitioners become involved in each patient's care, communication between team members and hand-offs will be critical for safe patient care. Clinical pathways, protocols for patient updates and practitioner shift changes, and checklists are tools that have been developed and implemented. Some protocols have been assessed, whereas others need further study to ensure that they address the need for cost-effective, high-quality, standardized, and error-free patient care.⁶⁻⁸

PREOPERATIVE PREPARATION

An in-depth review of preoperative assessment is covered in [Chapter 3](#). Medical optimization for thoracotomy or thoracoscopy patients includes adjustment of medications for chronic obstructive pulmonary disease, including administration of bronchodilators and steroids and treatment of acute bronchitis or pneumonia.⁹ Total resolution might not be possible if the pneumonia is caused by a postobstructive process secondary to lung mass or chronic aspiration from gastroesophageal reflux disease.

Patients with borderline pulmonary function can benefit from pulmonary rehabilitation that increases their exercise tolerance and respiratory muscular strength before the resection.¹⁰⁻¹³ Preoperative pulmonary rehabilitation should be a routine component for all patients undergoing lung volume reduction surgery.^{10,14,15} Smoking cessation not only affects overall health; it also decreases postoperative morbidity and mortality of thoracic surgery.¹⁶ Support groups, counseling, nicotine replacement therapy, and pharmacologic treatment are available and successful.¹⁷ If there is no smoking cessation program associated with the provider's hospital, programs can be located by calling the local American Lung Association. Timing of smoking cessation before the operation remains debatable. Because of the number of conflicting studies, space does not allow review of this issue. Our current recommendation is that all smokers requiring lung resection should be encouraged to quit smoking, and assisted to do so, at any time before surgery.¹⁸⁻²²

Additional comorbid diseases that need to be managed include coronary artery disease, diabetes mellitus, and myasthenia gravis. The American Heart Association and the American College of Cardiology classify thoracic surgical procedures as medium risk. When there is no

clinical history of risk factors for cardiac disease, no further workup is necessary if a preoperative 12-lead electrocardiogram (ECG) is normal.^{23,24} If a patient has risk factors for cardiac disease, further testing should be done to assess the presence and degree of disease. However, revascularization for significant coronary stenosis simply to decrease risk of perioperative ischemic event has not been proved beneficial to overall survival.²⁵ Medical optimization with therapy such as β -blocker, statin, and after-load reduction and continuance of aspirin given for coronary disease is recommended.²⁶

Diabetic patients should have their cardiac, renal/intravascular volume, and glucose status checked before elective surgery, although there is controversy regarding rapid adjustment of chronic hyperglycemia in patients with diabetes. Electrolytes should be checked preoperatively, and abnormalities should be treated. Baseline creatinine measurement is helpful. Acute elevation in creatinine needs to be investigated before elective thoracic surgery. Orthostatic vital signs should be also performed.^{27,28}

Diabetic patients optimally should have good glycemic control preoperatively. Some guidelines recommend checking HbA1c and adjusting medications for better glucose control before the operation if time permits in patients with diabetes. However, other studies have shown no improvement in outcome and some adverse reactions from rapid glucose control in the weeks to months preceding elective noncardiac surgery.²⁹ Long-acting sulfonylureas and thiazolidinediones should be discontinued 24 to 48 hours before elective surgery. Shorter-acting sulfonylureas, secretagogues such as metformin, or GLP-1 agonists can be stopped 12 hours before surgery. DPP-4 inhibitors can be continued preoperatively. Long-acting insulin can be continued until the day of surgery if control has been good. If there is glucose level fluctuation, long-acting insulin should be stopped 24 to 48 hours before surgery, and sliding-scale insulin should be used with frequent glucose checks.^{27,28}

Another challenge is the patient who is not aware that they have diabetes mellitus. Perioperative complications can be decreased, and long term well-being will be affected with discovery and treatment of undiagnosed diabetes. Therefore, we recommend that patients having thoracic surgery be evaluated for diabetes preoperatively if they are older than 45 years or are younger and overweight with 1 or more of the risk factors shown in [Box 4-1](#) by testing a fasting glucose level or HbA1c.^{23,29}

For patients with myasthenia gravis, the goal of preoperative preparation is to reduce the risk of myasthenic crisis, which is acute respiratory muscle malfunction leading to respiratory failure. Medication and treatment adjustments may be needed to maintain adequate function for daily living until the time of surgery. Doses of steroids and anticholinesterase medication should be tailored to the patient's symptoms. More aggressive and rapid therapies include infusion of intravenous immune globulin and plasmapheresis, and they have effects lasting weeks to months.³⁰ Plasmapheresis usually requires multiple exchanges, and it is recommended for patients with a vital capacity of less than 2.0 L.

BOX 4-1**Criteria Used to Screen for Diabetes Mellitus: ADA and USPSTF****AMERICAN DIABETES ASSOCIATION***

1. Testing should be considered in all adults who are overweight (BMI ≥ 25 kg/m²) and have additional risk factors:
 - Physical inactivity
 - First-degree relative with diabetes
 - Members of high-risk ethnic populations
 - Women who delivered a baby weighing greater than 9 pounds or were diagnosed with GDM
 - Hypertension
 - HDL cholesterol <35 mg/dl or triglycerides >250 mg/dl
 - Women with PCOS
 - IGT or IFG on prior testing
 - Other clinical conditions associated with insulin resistance
 - History of cardiovascular disease
2. In the absence of aforementioned criteria, testing for diabetes and prediabetes should begin at age 45 years.
3. If the results are normal, testing should be repeated at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

U.S. PREVENTIVE SERVICES TASK FORCE

- Screen is recommended for asymptomatic adults with sustained blood pressure greater than 135/80 mm Hg.
- No recommendation for asymptomatic adults with blood pressure less than 135/80 mm Hg.

*American Diabetes Association. Standards of Medical Care in Diabetes 2011. Diabetes Care 2011; 34:S11. Copyright © 2011 American Diabetes Association.

BMI, Body mass index; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PCOS, polycystic ovarian syndrome.

From Sheehy AM, Gabbay RA: An overview of preoperative glucose evaluation, management, and perioperative impact. *J Diabetes Sci Technol* 3:1261–1269, 2009.

PROPHYLAXIS**Atrial Fibrillation**

The incidence of postoperative atrial fibrillation ranges between 3% and 30% in thoracic surgical patients. It increases the risk of stroke and prolongs postoperative length of stay, thus increasing hospital cost.³¹ Multiple risk factors are associated with development of atrial fibrillation after thoracic surgery including patient factors such as age, male sex, history of congestive heart failure, and previous history of atrial fibrillation. Procedural risk factors include length of procedure and dissection near the atria or pericardium.³² A retrospective review of more than 2900 patients revealed increased relative risks of atrial fibrillation of 3.89, 7.16, 8.91, and 2.95 for lobectomy, bi-lobectomy, pneumonectomy, and esophagectomy, respectively, compared with a single wedge resection.³¹ Numerous studies on the prevention and treatment of postoperative atrial fibrillation have been performed, but the majority were for cardiac surgical

patients. The Society of Thoracic Surgeons released guidelines regarding prophylaxis and treatment of atrial fibrillation in association with general thoracic surgery.³² Prophylaxis recommendations include resuming β -blockade if the patient was taking a β -blocker beforehand, or the use of diltiazem, amiodarone, or a β -blocker if the patient was not taking preoperative β -blockers for lobectomy patients. The use of amiodarone for prophylaxis is not recommended for patients undergoing pneumonectomy. Magnesium supplementation has been shown to be helpful for atrial fibrillation prophylaxis.

For atrial fibrillation with rapid ventricular response, rate control is the main priority. Conversion back to normal sinus rhythm is a secondary, but not an immediate goal unless there is hemodynamic instability.

Deep Venous Thrombosis

Postoperatively, a majority of thoracic surgery patients are slow to move because of pain, respiratory distress, and age. Venous thromboembolism (VTE) includes deep venous thrombosis and pulmonary embolism and causes an estimated 300,000 deaths annually in the United States. VTE prophylaxis could prevent 100,000 of these deaths.³³ The current recommendations for deep venous thrombosis prophylaxis from the American College of Chest Physicians vary depending on patient risk. A useful risk stratification model is the Caprini scoring system, which has been validated for general, vascular, urologic, and plastic and reconstructive surgery (Table 4-1).³⁴ The risk of VTE is even greater in patients undergoing treatment for cancer.^{33,35} VTE prophylaxis is not recommended for outpatients undergoing thoracic surgery (Box 4-2).³⁵

Stress Ulceration and Gastritis

Stress ulceration prophylaxis is recommended in critically ill patients with coagulopathy, expected mechanical ventilation for longer than 48 hours, on antiplatelet or anticoagulant medications, a history of gastrointestinal bleeding or gastric ulceration in the past year, and at least two of the following: sepsis, intensive care unit stay longer than 1 week, high-dose steroid administration, or occult bleeding lasting 6 or more days.³⁶ The incidence of clinically significant bleeding remains low with the use of pharmacologic agents for prophylaxis in these high-risk patients. The risk of gastritis and stress ulceration in patients without risk factors is low; therefore, routine prophylaxis is not recommended. Multiple studies have evaluated the use of proton pump inhibitors (PPIs) compared with histamine 2 receptor blockers (H₂ blockers) with respect to incidence of bleeding and incidence of nosocomial pneumonia. The data are not strong, and the use of either PPI or H₂ blockers for high-risk patients is recommended for the duration of their time in intensive care, but may not be necessary when patients are no longer critically ill or are discharged from the hospital. In addition, PPI may be associated with a higher rate of nosocomial pneumonia, whereas H₂ blockers can interfere with other medications metabolized by the P450 cytochrome pathway.^{36–39}

TABLE 4-1 Caprini Risk Assessment Model

1 Point	2 Points	3 Points	5 Points
41-60 yr old Minor surgery BMI > 25 kg/m ² Swollen legs Varicose veins Pregnancy or postpartum History of unexplained or recurrent spontaneous abortion Oral contraceptives or hormone replacement Sepsis (<1 mo) Serious lung disease, including pneumonia (<1 mo) Abnormal pulmonary function Acute myocardial infarction Congestive heart failure (<1 mo) History of inflammatory bowel disease Medical patient at bed rest	61-74 yr old Arthroscopic surgery Major open surgery (>45 min) Laparoscopic surgery (>45 min) Malignancy Confined to bed (>72 h) Immobilizing plaster cast Central venous access	≥75 yr old History of VTE Family history of VTE Factor V Leiden Prothrombin 20210A Lupus anticoagulant Anticardiolipin antibodies Elevated serum homocysteine Heparin-induced thrombocytopenia Other congenital or acquired thrombophilia	Stroke (<1 mo) Elective arthroplasty Hip, pelvis, or leg fracture Acute spinal cord injury (<1 mo)

BMI, Body mass index; VTE, venous thromboembolism.

From Gould MK, Garcia DA, Wren SM, et al: Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, ed 9: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 141(Suppl 2):e227S–277S, 2012.

BOX 4-2 ASCO Guideline: Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer

INTERVENTIONS

- Pharmacologic anticoagulation

TARGET AUDIENCE

- Medical oncologists, surgical oncologists, hospitalists, oncology nurses

KEY RECOMMENDATIONS

- Most hospitalized patients with cancer require thromboprophylaxis throughout hospitalization.
- Thromboprophylaxis is not routinely recommended for ambulatory patients with cancer; it may be considered for select high-risk patients.
- Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy or dexamethasone should receive prophylaxis with either LMWH or low-dose aspirin to prevent VTE.
- Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days.

- Extending postoperative prophylaxis up to 4 weeks should be considered in those with high-risk features.
- LMWH is recommended for the initial 5 to 10 days of treatment for patients with established deep vein thrombosis and pulmonary embolism, as well as for long-term (6 months) secondary prophylaxis.
- Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE.
- Anticoagulation should not be used to extend survival in patients with cancer in the absence of other indications.
- Patients with cancer should be assessed periodically for VTE risk.
- Oncology professionals should provide patient education about the signs and symptoms of VTE.

METHODS

- An expert panel was convened to develop clinical practice guideline recommendations based on a review of evidence provided by a systematic review of the medical literature.

ASCO, American Society of Clinical Oncology; LMWH, Low-molecular-weight heparin; VTE, venous thromboembolism.

© 2013 by American Society of Clinical Oncology. Published in Lyman GH, Khorana AA, Kuderer NM, et al: Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 31:2189–2204, 2013. The Data Supplement, including evidence tables, and clinical tools and resources, can be found at www.asco.org/guidelines/vte.

Infection

A properly timed dose of intravenous first-generation cephalosporin is efficacious in preventing wound infections from skin pathogens. For patients with β -lactam allergy, vancomycin or intravenous clindamycin are the substitutes of choice.⁴⁰ Vancomycin administration must be started early enough to ensure that the dose is completely infused before the first incision. There are

insufficient data to support the administration of more than one dose of prophylactic antibiotic for elective non-transplant thoracic surgical procedures. If the prophylactic antibiotic is continued beyond the preoperative dose, no data have supported the use of antibiotic beyond 24 hours for wound prophylaxis (Table 4-2).⁴⁰

Prophylaxis for pneumonia and empyema in patients undergoing lung resection or esophageal resection is an attractive concept, because these prophylaxes involve

TABLE 4-2 Perioperative Antimicrobial Recommendations for Thoracic Surgery

Procedure	Common Pathogens	Antibiotic Regimen
Pulmonary resections	<i>Staphylococcus aureus</i> Coagulase-negative staphylococci <i>Streptococcus pneumoniae</i>	Cefazolin 1 g IV preoperatively, with a total of 1-3 doses every 8 hours If penicillin allergic, vancomycin 1 g IV preoperatively, with a total of 1-3 doses every 12 hours
Esophageal surgeries	Gram-negative bacilli Enteric gram-negative bacilli Streptococci Oropharyngeal anaerobes	Cefazolin 1 g IV preoperatively, with a total of 1-3 doses every 8 hours If penicillin allergic, vancomycin 1 g IV preoperatively, with a total of 1-3 doses every 12 hours If high anaerobic burden likely, cefepime 1 g IV preoperatively, with a total of 1-3 doses every 12 hours
Lung transplantation	<i>Pseudomonas</i> spp. <i>Burkholderia cepacia</i> Gram-negative bacilli Methicillin-resistant <i>Staphylococcus aureus</i> Cytomegalovirus <i>Candida</i> spp. <i>Aspergillus</i> spp. <i>Pneumocystis carinii</i>	Cefepime 1 g IV preoperatively, with a 7-10 day course* For cystic fibrosis patients, sensitivities are sent and for multidrug-resistant <i>Pseudomonas</i> spp., inhaled colistin should be added perioperatively Vancomycin 1 g IV preoperatively, with a 7-10 day course* For seropositive recipients, valganciclovir 900 mg PO daily or ganciclovir 5 mg IV 5 times per week while CMV PCR positive* For seronegative recipients with seropositive donors, valganciclovir 900 mg PO daily for 6 months* or ganciclovir 5 mg IV 5 times per week or 1 g PO tid for 6 months Amphotericin B, itraconazole, or voriconazole for 1 year Trimethoprim-sulfamethoxazole prophylaxis 3 times per week For sulfa allergies, dapsone and inhaled pentamidine can be used
Empyema	<i>Staphylococcus aureus</i> <i>Streptococcus milleri</i> <i>Escherichia coli</i> <i>Pseudomonas</i> spp. <i>Haemophilus influenzae</i> <i>Klebsiella</i> spp. Anaerobes	Antibiotics should be based on culture and sensitivity from empyema; if not available, the following regimens are appropriate for 3 weeks Community acquired (all are acceptable periop abx) Cefuroxime 500 mg IV tid plus metronidazole 500 mg PO or 400 mg IV tid Penicillin 1 g qid plus metronidazole 500 mg PO or 400 mg IV tid Meropenem 1g tid plus metronidazole 500 mg PO or 400 mg IV tid Augmentin 875/125 mg PO tid Amoxicillin 1g PO tid plus metronidazole 400 mg PO tid Clindamycin 300 mg PO qid Hospital acquired (all are acceptable periop abx) Piperacillin-tazobactam 4.5g IV qid Ceftazidime 2 g IV tid Meropenem 1 g IV tid ± metronidazole 500 mg IV tid or 400 mg PO tid

*Based on empiric evidence gathered at Washington University in St. Louis, Mo.

abx, Antibiotics; CMV, cytomegalovirus; IV, intravenous; PCR, polymerase chain reaction; periop, perioperative; PO, by mouth; preop, preoperative; qid, four times per day; tid, three times per day.

From Chang SH, Krupnick AS: Perioperative antibiotics in thoracic surgery. *Thorac Surg Clin* 22:35-45, 2012.

clean-contaminated operative fields. Postoperative pneumonia was found in approximately 25% of patients undergoing lung resection in two different studies.⁴¹⁻⁴³ Radu and colleagues demonstrated that only 18% of the pathogens postoperatively isolated from patients with pneumonia were susceptible to first-generation cephalosporin.³ They recommend consideration of use of prophylactic antibiotics to cover gram-positive and gram-negative organisms.

Unfortunately, no clear data support this practice. The Surgical Care Improvement Project is a national program

sponsored by the Center for Medicare and Medicaid Services along with other health organizations (e.g., American Hospital Association, Centers for Disease Control and Prevention) to decrease the number of surgical complications.⁴⁴ Randomized trials showing an improved outcome with the use of antibiotics effective on gram-negative organisms are needed for surgeons in the United States to justify their practice. Surgical Care Improvement Project participation delineates the timing of prophylactic antibiotic administration (within 1 hour of surgical incision), the type of antibiotic (first-generation

cephalosporin with exceptions for allergies), and the duration of prophylactic antibiotic administration (limited to 24 hours or less for all surgeries except cardiac surgery; for cardiac surgery, 48 hours). If a patient is receiving antibiotics for a therapeutic reason, prophylactic antibiotic use does not apply.

Anticoagulation

Management of anticoagulation before thoracic surgery varies depending on the reason for anticoagulation, patient risk factors for bleeding or thrombosis, the urgency of the procedure, and which anticoagulant the patient is being given.⁴⁵⁻⁴⁸

For patients who are taking anticoagulation because of the risk of a thromboembolic event, risk stratification helps to guide management (Table 4-3).⁴⁸ When bridging with unfractionated or low-molecular-weight heparin (LMWH) or when continuing anticoagulation is the recommended strategy, assessment of the risk of bleeding perioperatively should be done.^{45,46} Some of the newer anticoagulants have a short half-life and do not require bridging. For patients taking anticoagulation for drug-eluting coronary artery stents, a period of 12 months before interrupting anticoagulation for elective surgery is recommended to prevent in-stent stenosis, which can have a mortality of 50%. For bare metal stents, a 6-week period of uninterrupted anticoagulation is recommended. If surgery is urgent or emergent, the risks of operation on anticoagulation versus in-stent stenosis should be weighed. If the risk of bleeding is thought to be such that anticoagulation needs to be stopped, treatment with antiplatelet medications with a short half-life such as tirofiban, cangrelor, or eptifibatide until several hours before surgery can be considered. If double antiplatelet treatment with aspirin and another antiplatelet medication such as clopidogrel is being used, continuation of the aspirin perioperatively is recommended.⁴⁸ More extensive discussion about managing the different types of target specific anticoagulants is not possible in this generalized

chapter. The references are helpful in describing specific patient situations.

Miscellaneous

Blood products are reserved for patients who have anemia preoperatively or a chance of significant blood loss during the surgical procedure. There are no studies that identify an unequivocal hemoglobin threshold for patient transfusion before or during surgery, but multiple studies have found that even critically ill patients will tolerate a hemoglobin of 7 mg/dL. An exception may be if the patient has acute ischemic cardiac disease.^{49,50} Previously, patients having elective major thoracic surgery were thought to be good candidates for the benefits of autologous blood donation, including decreased risk of infection, transfusion reaction, and immune modulation. However, the acceptance of lower patient hemoglobin levels, techniques leading to decreased intraoperative blood loss, and lack of cost effectiveness because of the processing and administration decreases the recommendation for autologous blood donation. The use of erythropoietic agents has been effective in eliminating or decreasing the amount of anemia in patients with cancer who have received chemotherapy or radiation therapy. Although preoperative or postoperative use of erythropoietin or darbepoetin is an attractive idea for thoracic oncology patients, increased mortality was found in patients who had not had neoadjuvant therapy.^{51,52} In addition, there are reports of increased risk of deep venous thrombosis in oncology patients who are given erythropoietic agents for anemia.⁵²

In the past, bowel preparation before esophageal resection was justified when colon interposition was planned.⁵³ Some surgeons also used bowel preparation for all patients undergoing esophagectomy, with gastric pull-up as a precaution should the stomach be found to be unusable during operation. Bowel preparation for colon resection has been studied by multiple randomized controlled trials and meta-analyses.⁵⁴ Evidence shows no

TABLE 4-3 Risk Stratification of Anticoagulated Patients for Further Thromboembolic Events

Risk Stratum	Indication for Anticoagulation		
	Atrial Fibrillation	Mechanical Heart Value	Venous Thromboembolic Disease
High >10% risk per annum	CHADS2 ≥ 5 Stroke or TIA within last 3 months Rheumatic valvular heart disease	Any mitral valve prosthesis Aortic valve prosthesis with tilting disc or caged ball Stroke or TIA in last 6 months	VTE within last 3 months Severe thrombophilia (deficiency in antithrombin, protein C or S)
Moderate 5-10% risk per annum	CHADS2 score of 3 or 4	Bileaflet aortic valve prosthesis with other stroke risk factors	Clot within last 3-12 months Recurrent VTE Active cancer
Low <5% risk per annum	CHADS2 score 2 or less and no previous stroke	Bileaflet aortic valve prosthesis	VTE > 12 months ago

CHADS2, 1 point each allocated for congestive heart failure, hypertension, age greater than 75 years, and diabetes mellitus, and 2 points for previous stroke; TIA, transient ischemic attack; VTE, venous thromboembolic disease.

From McKenzie JL, Douglas G, Bazargan A: Perioperative management of anticoagulation in elective surgery. *ANZ J Surg* 83:814-820, 2013.

benefit with mechanical bowel preparation regarding anastomotic leak or superficial surgical site infection for colon resection. Whether there is increased risk of anastomotic leak, deep or superficial surgical site infection for colon interposition after esophagectomy without bowel preparation has not been studied systematically. Histologic changes in colon mucosa were of a greater degree in patients who underwent mechanical bowel preparation, but it is not known whether these changes are clinically relevant.⁵⁵ Electrolyte and intravascular volume changes with bowel preparation may be magnified in esophageal surgery patients who have challenges with oral intake and hydration.

Surgery should never be delayed because of the unavailability of equipment. Hospitals often have equipment (laparoscopes, thoroscopes, video equipment, operative microscopes, lasers, vessel sealing and energy devices, ultrasonic devices, radiofrequency devices, cryoablation equipment, robots, specialized retractors) that is used by several different services. Such equipment should be reserved before the surgery to ensure that it is available and functioning properly. Perioperative management software allows for procedure scheduling, inventory maintenance, automatic supply reordering, and equipment conflict checking.

INTRAOPERATIVE CARE

Good communication with the anesthesiologist or anesthesiologist is essential. Airway management should be discussed beforehand if there are special circumstances. The entire operative team should know the plan of the operation including (1) anticipated anatomic outcome of the procedure, (2) position and planned position changes, (3) instrument, equipment, and medication needs (e.g., fluoroscopy devices, drainage tubes, local anesthetic), (4) general length of the operation, (5) possible unanticipated occurrences and treatment (e.g., bleeding), and (6) postoperative disposition (e.g., extubation versus postoperative ventilation, ward versus intensive care).

Ventilation

Single-lung ventilation during thoracotomy or thoracoscopy is accomplished by placing a double-lumen tube, bronchial blocker, endotracheal tube with in-line bronchial blocker, intermittent ventilation (for procedures of short duration) or, as a last resort, a single-lumen tube down the desired main-stem bronchus.^{56,57} Because of improvements in care, patients are living longer and selective lobar ventilation techniques may be necessary if previous lobectomy or pneumonectomy has been performed.⁵⁸ The use of lower intraoperative tidal volumes during single-lung ventilation has been shown to decrease the incidence of respiratory failure in lung resection patients.^{59,60} Increased peak inspiratory pressure, decreased oxygen saturation, and increased end-tidal CO₂ during the procedure without a known etiology from the surgical field lead to a differential diagnosis of retained secretions or blood, dislodgement of the endotracheal tube or blocker, or contralateral pneumothorax.

Stabilization may require reinflation of the operative-side lung if increased fraction of inspired O₂ (FiO₂) administration and oxygen flow and gentle bagging by the anesthesiologist do not improve the situation. Investigations and treatments include suctioning of obstructing blood or mucus, bronchoscopy and repositioning of single-lung ventilation equipment, or decompression of the contralateral pleural space of air.^{61,62}

Monitoring

Different operations require different levels of monitoring. ECG monitoring and continuous pulse oximetry measurements are necessary in all cases. An arterial line is placed if there is a need for multiple blood samples. Continuous arterial pressure monitoring is useful during procedures involving mediastinal dissection, such as transhiatal esophagectomy, to gauge cardiac or great vessel compression. Temperature monitoring by bladder temperature probe or esophageal temperature probe is necessary for major procedures (see [Body Temperature](#)).

Intravenous access should be appropriate for the invasiveness and potential blood loss of the procedure. Anticipated blood loss is rarely sufficient to justify the need for large-bore central lines. However, adequate access is necessary before the procedure starts, because the arms, chest, and groin are often inaccessible for line placement during an operation with a patient in the decubitus or prone position. In an emergency, a large-bore line can be placed in the operative field via the subclavian vein, superior vena cava, inferior vena cava, or azygous vein.

Body Temperature

Mild hypothermia has been shown to increase wound infection, blood loss and transfusion requirements, and cardiac events including ventricular tachycardia, cardiac arrest, and myocardial infarction.⁶³ Heat loss through thoracotomy, sternotomy, and laparotomy incisions can be lessened by keeping the room temperature greater than 21° C, using airway heating and humidification devices, covering portions of the patient not in the operative field, and using forced-air warming blankets. Warm saline lavage intrapleurally and intraperitoneally can also be performed. Intravenous fluid warmers are rarely necessary.⁶⁴

Positioning

Careful positioning of the patient is of utmost importance in the operating room. The surgeon needs to ensure adequate access for the planned operation and any potential counterincisions or chest wall resection. The use of muscle flaps often requires planning ahead to protect the vascular supply and to leave adequate skin coverage. Padding to prevent neuropathy includes the use of an axillary roll and head support to maintain neck alignment in the lateral decubitus position. Padding of all pressure points includes between the legs, the greater trochanter, fibular head, and lateral malleolus of the lower extremities. The dependent arm is supported on a padded board, the nondependent arm is slightly abducted,

and the shoulder and elbow are slightly flexed and rested on pillows or an arm support. Stability of the patient during the operation can be achieved using a deflatable beanbag, sand bags, laminectomy rolls, padded supports and posts, and security straps or tapes. The lithotomy position also requires careful positioning to prevent postoperative neuropathy, musculoskeletal strain to the lower spine, and skin and muscle ischemia.⁶⁵

Fluid Administration

Fluid administration during pulmonary resection is kept to a minimum. If pneumonectomy is planned, administration of 1 L of fluid during the intraoperative course has been advocated. During esophagectomy, additional fluid administration may be needed because of increased blood loss and third space fluid distribution. Clear communication between surgeon and anesthesiologist regarding blood loss, hemodynamic trends, and pressor and fluid administration during the operation is crucial.

Drainage

If the planned operation is scheduled to take longer than 3 hours or if an epidural catheter is used, a bladder catheter should be placed. Orogastric or nasogastric tube drainage is important for decompression during esophageal and gastric operations. The semirigid tube can be helpful for localization during reoperation or within radiated fields with abundant scar tissue or fibrous reaction.

The viscosity of the substance being drained dictates the size and shape necessary for adequate drainage of the pleural space. Smaller anterior tubes are used to drain air. Larger posterior tubes, including preformed 90-degree-angle tubes, are useful for dependent drainage of blood, pus, chyle, or exudative fluid along the diaphragm. One pleural tube is adequate for drainage after routine lobar resection if it is positioned posteriorly and to the apex of the pleural cavity to drain both fluid and air. If significant disruption of lung parenchyma is known or suggested, the use of more than one pleural drainage tube is prudent to prevent formation of subcutaneous emphysema and to improve the chance of pleural opposition. Additional chest tubes are used for empyema, hemothorax, or fistula drainage.⁶⁶⁻⁶⁸

The use of a drainage tube after pneumonectomy is controversial. Reasons cited for leaving a chest tube after pneumonectomy include the ability to monitor bleeding, to manipulate intrapleural pressure, and to adjust mediastinal shifting by instilling or removing air. The chest tube is removed intraoperatively after the patient is placed supine, in the recovery room, or on the first postoperative day. Many surgeons leave no drainage tube after pneumonectomy and encounter no increased morbidity.

A gastrostomy tube is useful if prolonged stomach drainage is needed. This can decrease the risk of aspiration that is theoretically present from having a tube traversing and stenting the upper esophagus open. A gastrostomy tube is more comfortable for the patient than an indwelling nasogastric tube. A jejunostomy tube is placed as access for nutrition and medicine administration if failure to thrive or a prolonged period of receiving

nothing by mouth (NPO) status is anticipated and intragastric feeding is not feasible.

If flaps are created, drains to prevent seroma formation are placed. If there is a possibility of leakage of the gastrointestinal tract, bronchopleural fistula, empyema, or chylothorax, good drainage can prevent systemic infection and can allow time for nutritional support and healing.

Specimen Management

The surgeon must also ensure that sample and specimen collection is performed properly. Careful labeling and delivery of frozen sections are of paramount importance in determining resection margins, resectability, and staging. Confirmation of adequate tissue sampling for diagnostic testing including immunohistologic and mutation testing is necessary as personalized medicine options increase. Intraoperative communication with the pathologist performing frozen section may be necessary before proceeding with the next portion of an operation. If possible, orienting the specimen and viewing the frozen section with the pathologist are recommended. A recent retrospective subset analysis of the data from the American College of Surgeons Oncology Group Z0060 trial of esophageal resection revealed that more accurate accounting and assignment of lymph node station occurs when surgeons separate and label lymph nodes for analysis than when the pathologist dissects, counts, and labels the nodes.⁶⁹ More lymph nodes were harvested during lung resection in a study that provided prelabeled containers for mediastinal and hilar lymph nodes.⁷⁰ Cultures for bacterial, fungal, viral, and acid-fast organisms need to be processed and collected in the correct specimen containers and mediums.

POSTOPERATIVE CARE

As in many other specialties, clinical pathways serve to improve the quality of care, and they have the added benefit of reducing cost.^{7,8,71,72} Almost all thoracic surgical patients can be transferred from the recovery room to a stepdown unit or surgical ward instead of to an intensive care unit. For thymectomy, segmentectomy, lobectomy, pneumonectomy, lung volume reduction, and esophagectomy patients, telemetry and continuous pulse oximetry measurements are recommended. The arterial line placed during surgery is transduced until the day after surgery.

Fluid Management

Fluid administration for lung resection patients must be determined on an individual basis. Controversies that have been studied without strong conclusion include (1) the use of goal-directed fluid therapy versus conventional fluid administration protocols, (2) liberal versus restricted fluid resuscitation, and (3) colloid versus crystalloid administration.⁷³⁻⁷⁶ The balance between providing enough fluid in the circulatory system for perfusion of end organs and microvasculature and overwhelming the

capillary filtration capacity leading to acute lung injury is not clear cut. A literature review of goal-directed fluid therapy by Wilms and colleagues revealed few studies with high or moderate quality evidence.⁷⁶ For patients not receiving mechanical ventilation, the high-quality study used central venous lactate levels to direct fluid resuscitation compared with a restrictive fluid strategy in patients having major gastrointestinal surgery for cancer. Patients with goal-directed therapy had fewer postoperative complications.⁷⁷ In patients receiving mechanical ventilation, goal-directed therapy included fluid administration or pressor and inotropic support to achieve a cardiac index of 2.5 as measured by a pulse contour arterial waveform monitor. This group had a shorter length of stay and a lower incidence of complications compared with patients receiving a conventional fluid administration protocol.⁷⁸ Restrictive fluid protocols are meant to decrease the incidence of acute lung injury, but they can contribute to acute kidney injury. There is also an increased incidence of acute kidney injury in patients who receive colloids intraoperatively, but this association has not been studied in depth. Chau and Slinger have published guidelines for fluid management perioperatively for lung and esophageal surgery⁷⁹:

1. Total positive fluid balance in the first 24 hours postoperatively should not exceed 20 mL/kg.
2. Crystalloid administration should be limited to less than 2 L intraoperatively and less than 3 L in the first 24 hours postoperatively.
3. Colloids should be used only to replace an equivalent volume of blood loss if blood is not required (maintain hemoglobin > 80 g); Maximum colloid volume = 1 L for an adult.
4. There is no third space loss.
5. Urine output greater than 0.5 mL/kg/h is unnecessary in the early postoperative period, unless the patient is at high risk of developing acute kidney injury
6. If increased tissue perfusion is needed postoperatively, appropriate invasive hemodynamic monitoring should be initiated to guide treatment with vasopressors, inotropes, or fluid administration.

Blood Administration

No hemoglobin level or hematocrit has been documented as being a threshold for recommending transfusion. Current clinical guidelines state that blood transfusion may be beneficial for patients with a hemoglobin less than or equal to 7 g/dL.⁴⁹ Although intuition argues that a higher hemoglobin level provides better oxygen delivery, the increased oxygen extraction by most organs and tissues when stressed negates the need for a higher hemoglobin level. This is not true for the heart, which extracts most of the oxygen delivered under nonstressed physiologic conditions and requires increases in blood flow to increase oxygen delivery with physiologic stress. For older patients with acute myocardial infarction and a hematocrit less than or equal to 30, decreased mortality was found with blood transfusion.⁸⁰

Perioperative blood transfusions have been shown to be associated with decreased survival after resection for

lung cancer.^{81,82} There have also been multiple retrospective series of decreased survival associated with perioperative blood transfusion after esophageal cancer resection.⁸³⁻⁸⁶

Medications

Each patient's preoperative medications should be reviewed before restarting them postoperatively. Often, antihypertensive medications need to be held for several doses until fluid shifting and intravascular volume equilibrium are attained to prevent continued hypotension. We recommend restarting β -blocker therapy as soon as possible after the operation to prevent rebound tachycardia from withdrawal. This therapy also decreases the occurrence of atrial fibrillation and of rapid ventricular response if postoperative atrial fibrillation occurs. Inadvertent discontinuation of home medications was shown for hospitalized patients, but especially for patients admitted to the intensive care unit.⁸⁷

Prolonged postoperative antibiotic administration to prevent surgical site infection has not been shown to be beneficial in multiple studies for pulmonary and esophageal resection.⁴⁰ The Surgical Care Improvement Project implemented in 2003 requires that prophylactic antibiotics for thoracic procedures be discontinued within 24 hours.⁴⁴ The use of a first-generation cephalosporin is recommended unless there is a concern for a high anaerobic burden in esophageal resection. In addition, prophylactic coverage for lung transplantation has specific recommendations because of the patient's immunosuppressed state (see [Table 4-2](#)).⁴⁰ Many patients suffer from nausea after general anesthesia or from postoperative pain medications. Antiemetics such as metoclopramide, ondansetron, promethazine, trimethobenzamide, and prochlorperazine can help. Stress ulcer prophylaxis is recommended for high-risk surgical patients only (see [Stress Ulceration and Gastritis](#), earlier).³⁶ Esophagectomy patients have a high risk of reflux.⁸⁸ H_2 -receptor blockers or proton pump inhibitors should be continued in patients who demonstrate reflux on barium swallow tests postoperatively, have symptoms of heartburn, or have a history of Barrett's disease.^{88,89} Some patients may have a bile reflux or a combination of bile and acid reflux and should be treated accordingly.⁹⁰ Vagotomized patients can benefit from the prokinetic effects of erythromycin or metoclopramide; however, erythromycin can cause gastrointestinal upset and metoclopramide can produce extrapyramidal symptoms.⁹¹

The use of low-molecular-weight heparin, low-dose unfractionated heparin, or sequential compression devices continues until the patient is reliably walking at least four times per day for patients with a low risk for deep venous thrombosis. For higher-risk patients, a combination of pharmacologic and mechanical prophylaxis should be used until the same ambulatory criteria are met. The use of LMWH for 4 weeks after hospital discharge in patients undergoing major abdominal, pelvic cancer surgery or with other high risk factors for VTE can reduce the incidence of asymptomatic deep venous thrombosis. There is no clear recommendation of whether extended prophylaxis should be applied to thoracic surgery patients

with cancer, but the American Society of Clinical Oncology supports a consideration of coverage for 4 weeks postoperatively (see [Box 4-2](#)).³⁵

Analgesia

Pain control is one of the most important aspects of postoperative care for thoracic surgery patients, and the amount of literature on this subject is beyond the scope of this chapter. Studies have shown the benefit of multimodal treatment for both acute and chronic pain after both thoracotomy and thoracoscopy. Recent articles by authors at Duke University review different classes of analgesics, how they are administered, and algorithms for decision making for postoperative pain control for thoracic surgery ([Figs. 4-1, 4-2, and 4-3](#) and [Table 4-4](#)).^{92,93}

Nutrition

Adequate nutrition is of paramount importance in the postoperative period. After lung resection, most patients can start consuming clear liquids or a regular diet the evening of surgery. A more cautious approach may be necessary if there is concern about a difficult airway, higher risk of respiratory failure, or aspiration. Nausea and vomiting are common after general anesthesia, and narcotic medications can magnify the problem. If liquids are tolerated, the patient's diet can be advanced starting

the day after surgery. After uneventful laparoscopic fundoplication, clear liquids can be given the evening of surgery. If a Collis gastroplasty or repair of inadvertent esophagotomy or gastrostomy was performed, NPO status and nasogastric tube aspiration may be desired for several days to prevent pressure on suture lines. These patients need to be counseled preoperatively and postoperatively about taking most of their fluid between meals, eating smaller portions more frequently during the day, and avoiding foods such as dry bread, raw vegetables, large chunks of meat, and foods and fluids that increase gas production in the immediate postoperative period. Providing patients at discharge with a list of eating tips and foods to avoid is recommended. Dysphagia caused by swelling of a complete fundoplication can occur after the operation; this can lead to an inability to advance the diet beyond liquids for several days or weeks.⁹⁴ If dysphagia persists past several weeks and the patient is losing weight, the need for dilation or investigation for a complication such as a slipped wrap, stricture, or previously undiagnosed motility disorder must be considered.^{94,95}

Oral intake after esophagectomy is usually started after a confirmatory test for leakage and blockage, such as a barium swallow test or grape juice test, is passed. Most surgeons wait 4 to 7 days postoperatively.^{71,96} Surgeon preference, problems encountered during the operation, and neoadjuvant therapy influence when oral intake is started. If the test results are favorable, clear liquids are started and the diet is advanced as tolerated.

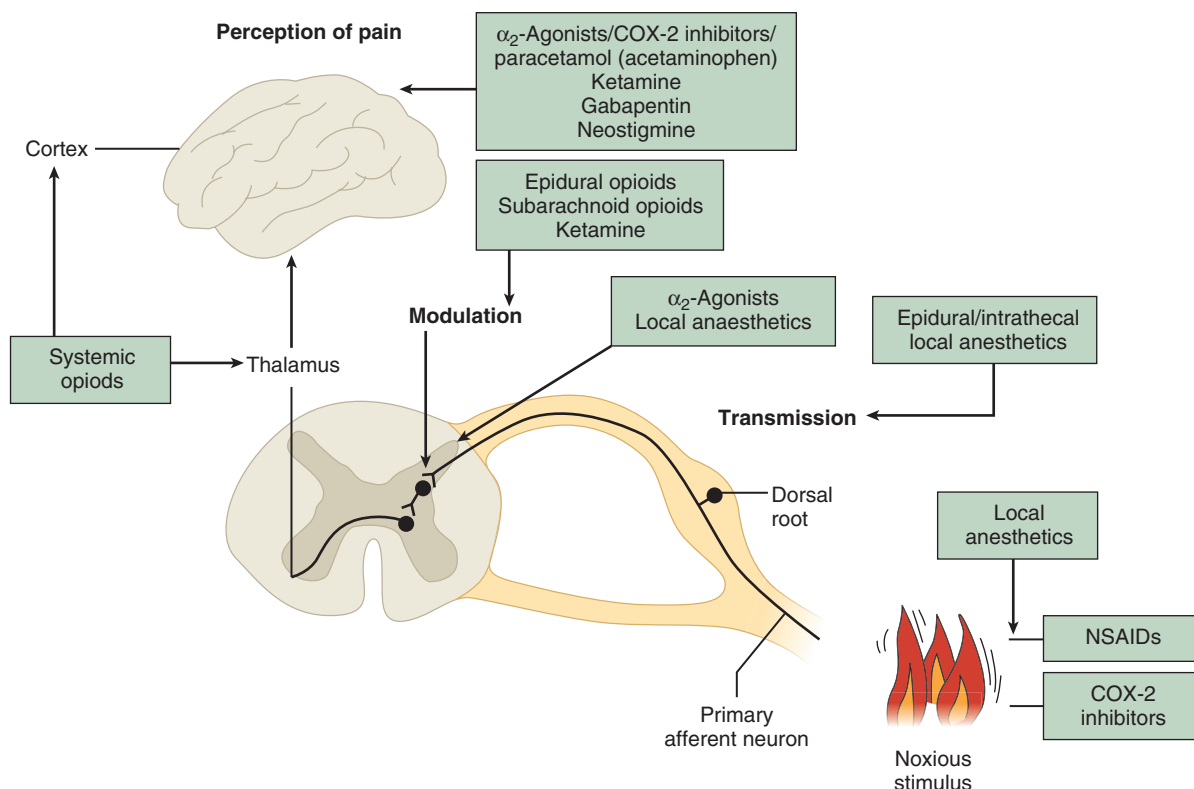


FIGURE 4-1 ■ Perception of pain along the afferent signalling pathway with pharmacologic targets and associated agents. NSAID, Nonsteroidal anti-inflammatory drug. (From Bottiger BA, Esper SA, Stafford-Smith M: Pain management strategies for thoracotomy and thoracic pain syndromes. *Semin Cardiothorac Vasc Anesth* 18:45–56, 2014.)

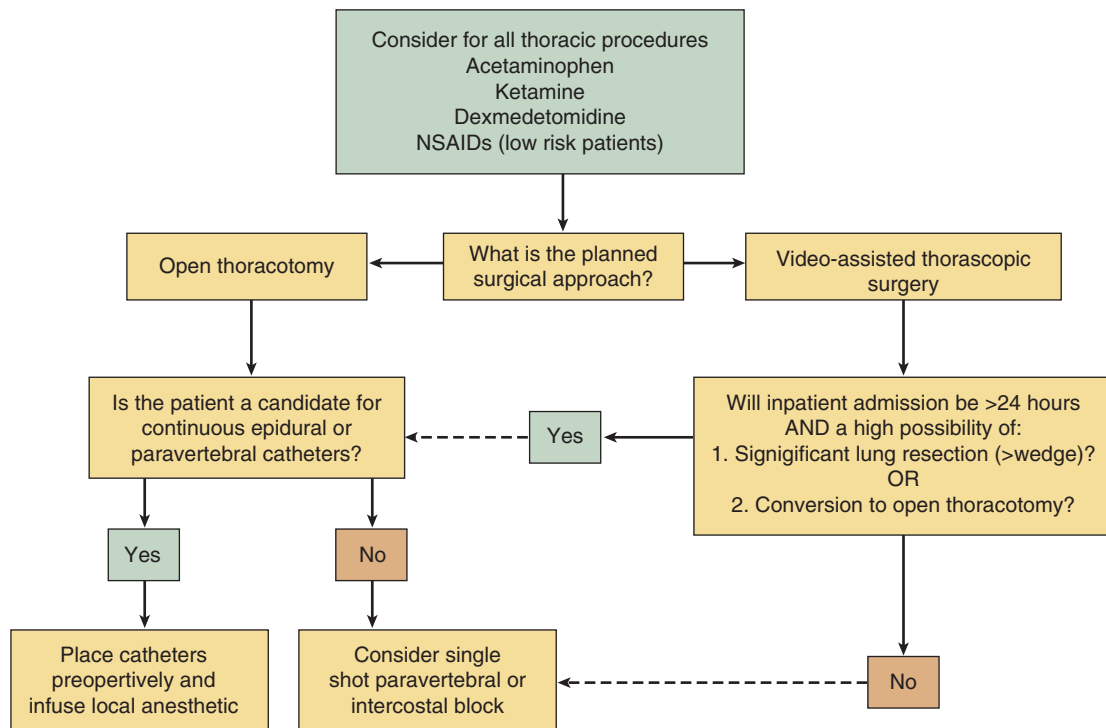


FIGURE 4-2 ■ Suggested algorithm for multimodal strategy for pain management of patients undergoing thoracic surgery. *NSAID*, Nonsteroidal anti-inflammatory drug. (From Bottiger BA, Esper SA, Stafford-Smith M: Pain management strategies for thoracotomy and thoracic pain syndromes. *Semin Cardiothorac Vasc Anesth* 18:45–56, 2014.)

The patient is counseled about expected changes in eating habits, dietary intake, jejunostomy tube feeding, and weight stabilization. Placement of a jejunostomy tube during esophagectomy allows enteral feedings to start 24 to 48 hours after operation. Tube feedings are generally started at a low rate, such as 20 mL/h, and advanced to a goal rate to provide total caloric and protein needs over the next 48 hours.⁷¹ If a jejunostomy tube is not placed, total parenteral nutrition administration until oral intake is tolerated can be considered.

Respiratory Therapy

The most common complications after thoracic surgery are related to the pulmonary system. Vigilant postoperative pulmonary care decreases the incidence of complications.^{97,98} Incentive spirometry and chest physiotherapy, including clapping, postural drainage, and vibratory therapy, aid in mobilizing mucous secretions and allowing patients to clear their own secretions.^{99,100} Cough can be stimulated and secretions can be suctioned by placing a soft suction catheter through the nose and into the trachea. Studies have advocated placement of a mini tracheostomy in high-risk patients and have shown favorable results in facilitating suctioning. There was no definitive evidence for decreased length of stay or mortality. Mini tracheostomy was associated with complications from placement, but most of these were minor and needed no further intervention.^{101,102} Ambulation is an excellent method of decreasing atelectasis. Nebulized albuterol is helpful in curtailing or preventing bronchospastic episodes. If a patient has had multiple

manipulations of the upper airway and there is concern about edema and stridor, intravenous and aerosolized steroids and aerosolized racemic epinephrine are effective in reducing edema.

Wound Care

Incision care is usually routine if the skin is closed. Open wounds historically are packed with gauze moistened with saline, dilute antibiotic solution, sodium hypochlorite (Dakin's) solution, acetic acid solution, or dilute Betadine solution. Newer dressings, including silicone-impregnated dressings, thin polyurethane films and foams, hydrocolloids, alginates, and hydrogels, are available, although there are no strong data to recommend the use of one over the other or gauze.¹⁰³ Vacuum dressings can be placed in clean or contaminated wounds and can speed the healing process.^{104–107} Open chests for bronchopleural fistula are packed with moistened gauze or negative pressure dressing to stimulate granulation and possible closure. If muscle or skin flaps are raised and there is the potential for seroma formation, drains can be left and binders or ace bandages can be considered. Depending on the muscle rotation used and the tautness of the closure, restriction of range of motion may be required for several days to prevent tension and dislodgement or compromise of flap vascular supply.

For wounds that are difficult to heal, such as those in previous radiation fields, hyperbaric oxygen therapy can be considered.¹⁰⁸ No randomized, blinded studies have shown definite benefit of hyperbaric oxygen therapy for wound healing except for osteoradionecrosis.

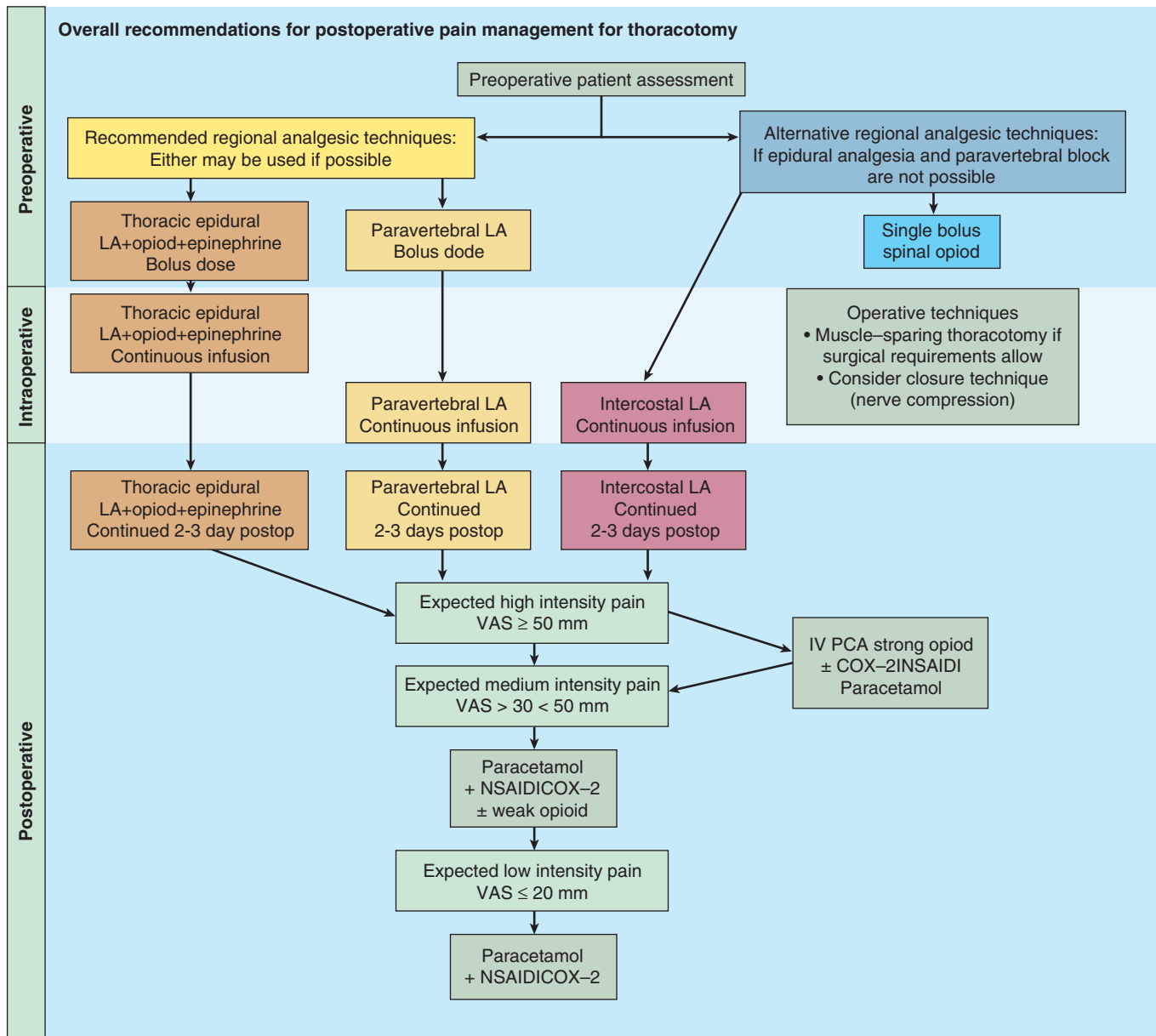


FIGURE 4-3 ■ Suggested algorithm for pain management following thoracotomy. COX-2, Cyclooxygenase; IV, intravenous; LA, local anesthetic; NSAID, nonsteroidal anti-inflammatory drug; PCA, patient controlled analgesia; postop, postoperatively; VAS, visual analog scale. (From Maxwell C, Nicoara A: New developments in the treatment of acute pain after thoracic surgery. *Curr Opin Anaesthesiol* 27:6–11, 2014.)

Management of Drainage Tubes

Placement and removal of chest tubes should be standardized by protocol after lung resection. Tubes are left in as long as any air leak remains, but recent studies indicate that earlier transition from water suction to water seal is not harmful and promotes quicker resolution of parenchymal air leakage. Fluid drainage of 300 to 400 mL or less per 24 hours is acceptable for chest tube removal after lung resection.^{66,71,109} Chest tube removal after pleurodesis for malignant pleural effusion has a stricter volume requirement, as these patients are known to have problems absorbing pleural fluid normally. Chest tube removal after drainage of chylothorax or empyema must be tailored to the particular patient's course. When

there is any concern about anastomotic leak in the chest or mediastinum after esophageal resection or tracheal reconstruction, tubes should be left until resolution of the leakage. Mediastinal tubes are left after median sternotomy is performed for removal of bilateral lung tumors, lung reduction surgery, or mediastinal mass resection.

Most surgeons leave a nasogastric tube after esophagectomy and for complicated benign esophageal operations. The tube is removed when drainage from the gastrointestinal tract is less than 300 to 500 mL per 24 hours and there is no concern of anastomotic leak.

Bladder catheters are placed for drainage and as a measure of adequate end-organ perfusion in patients having operations longer than 3 hours. Patients, especially older men, who have an epidural catheter often

TABLE 4-4 Consideration in Developing a Perioperative Pain Management Strategy*

Neuraxial Blockade or Continuous Paravertebral or Epidural Catheter	Intravenous Strategies or Single-Shot Peripheral Nerve Block
Medical conditions preclude the use of narcotics or predispose the patient to respiratory depression.	Clear contraindications to neuraxial blockade exist (e.g., allergy, patient refusal, infection, sepsis, recent thoracic spine surgery).
Anticoagulation is appropriately held or there is no predisposition for coagulopathy, or both.	Anticoagulation or coagulopathy is ongoing or highly likely.
The patient will have prolonged thoracotomy tubes and remain hospitalized for >24 hours.	Discharge will likely occur within 24 hours.
The patient will not be able to take oral pain medications for a few days.	The patient will be transitioned to oral pain medications quickly.
The patient has a chronic pain condition.	There is a minimal risk of conversion to open thoracotomy.
There is possible substantial lung resection, with a risk of conversion to open thoracotomy.	There is very little or no lung resection planned.

*The medical condition of the patient, surgical plan, and postoperative plan contribute to appropriate decision making when contemplating a comprehensive pain management strategy.

From Bottiger BA, Esper SA, Stafford-Smith M: Pain management strategies for thoracotomy and thoracic pain syndromes. *Semin Cardiothorac Vasc Anesth* 18:45–56, 2014.

have difficulty voiding and usually require the indwelling bladder catheter until the epidural is discontinued.

Physical Therapy

Exercise therapy after lung resection benefits patients by decreasing pulmonary complications, restoring mobility and independence, and decreasing the potential for deep venous thrombosis. Pulmonary rehabilitation is designed specifically to help patients clear secretions, strengthen respiratory muscles, and provide cardiopulmonary exercise.^{110,111} A patient who requires continuous chest tube suction can exercise on a stationary bicycle in the hospital room.

MANAGEMENT OF COMPLICATIONS

Early Complications

Respiratory Complications

Atelectasis and Pneumonia. The most common complication after a thoracic operation is respiratory failure. When complications are the result of atelectasis and retained secretions, treatment with aggressive pulmonary

toilet, postural drainage, incentive spirometry, nasotracheal suction, ambulation, and nebulized expectorant will help to clear the secretions. If pneumonia is suggested (fever, elevated and rising white blood cell count, purulent sputum production, no other source of infection), empiric treatment with a second-generation cephalosporin is justified, as radiographic changes of pneumonia may lag temporally.¹¹² The U.S. Food and Drug Administration (FDA) and the Infectious Disease Society of America advocate using bronchoscopy with lavage or protected brush for diagnosis of hospital acquired or ventilator associated pneumonia.¹¹³ Antibiotic therapy can be adjusted after culture results return. The worsening spiral of need for intubation can sometimes be avoided with bronchoscopy to remove thick tenacious secretions or retained blood clot from surgery. The benefits of mini tracheostomy have already been mentioned.^{101,102}

Prolonged Air Leak. A prolonged air leak is defined as one that lasts longer than 5 postoperative days. A useful review of different treatments for prolonged air leaks was recently published by Mueller and Marzluf.⁶⁸ If the patient has an emphysematous lung and the leak is small, several manipulations can be performed to encourage the leak to stop. If a pneumothorax or residual space still exists, placing the chest tube on higher suction can be tried, either by raising the water level in the suction chamber or by closing the air vent to the suction chamber and controlling the amount of suction pressure from the wall source. Pressures greater than 40 to 60 mm Hg are not recommended. Placement of another chest tube can help to fully reexpand the lung if the air leak is substantial. If the air leak and pleural space persist, pneumoperitoneum to raise the diaphragm and obliterate or lessen the space can be tried.¹¹⁴ Filling the space with viable tissue, such as muscle flaps or omentum, can be considered but is more invasive. If no residual space exists, placement of the chest tube to water seal or on a Heimlich valve can encourage the leak to seal. A blood patch can be attempted by injecting approximately 50 to 100 mL of the patient's own blood through the chest tube. This has been shown to be effective in both partially and fully expanded lungs, but it may need to be repeated several times and may increase the risk of empyema.¹¹⁴ Intrabronchial valves are approved by the FDA for prolonged air leak after lung resection and studies have shown improvement or resolution of leak in 45% to 50% of patients.^{115,116} Talc sclerosis through the chest tube can be performed, although this will cause pleural fusion, making it difficult to reenter the chest cavity in the future. If none of these methods work, the patient may need to be taken back to the operating room for leak closure. Air leak from the lung parenchyma can be troublesome because of friable lung tissue. Direct suturing with or without pledgets, use of fibrin sealants and glue,¹¹⁷⁻¹¹⁹ and stapling of a leak with pericardial or polytetrafluoroethylene strips can be attempted.

Pulmonary Edema. Pulmonary edema in lobectomy patients is serious but can usually be treated with diuresis. Postpneumonectomy pulmonary edema can be fatal. Aggressive respiratory care including intubation may

be necessary to manage a patient with postpneumonectomy pulmonary edema, which has a mortality rate of greater than 50%. Postpneumonectomy pulmonary edema should always be considered, and avoidance of excessive fluid administration is critical.^{75,79} Other maneuvers during surgery that have been recommended to avoid postpneumonectomy pulmonary edema include using tidal volumes of only 5 to 6 mL/kg to avoid barotrauma or volutrauma to the inflated lung,⁵⁹ avoidance of transfusion, and administration of steroids, although data are mainly from single-institution case series and retrospective studies.^{60,120} Although disruption of the lymphatic drainage resulting from lymphadenectomy has previously been implicated as a causative factor, data from the American College of Surgeons Oncology Group Z0030 trial did not support this finding.¹²¹ Controversy still exists regarding whether the laterality of the pneumonectomy affects the risk of postpneumonectomy pulmonary edema, and whether induction chemotherapy or chemoradiotherapy increases that risk.¹²²⁻¹²⁴

Urine output should be accepted at 0.5 mL/kg/h the night of surgery, and excess fluid administration should be avoided. Measures to keep pulmonary artery pressures low should be instituted. The patient should be given adequate FiO₂. Hypercarbia, pain that causes splinting, and atelectasis should be avoided. Routine administration of diuretic starting in the recovery room can be considered.

Acute Respiratory Distress Syndrome. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are rare but potentially fatal complications after thoracic surgery. The reported frequency of each is 2% to 16%.⁷⁹ Aggressive support with reintubation if necessary and administration of positive end-expiratory pressure and adequate FiO₂ to support the patient while the lung recovers is important. No medication has been shown to improve the outcome of ARDS. Steroids can be tried for a short course.^{125,126} Prone position, nitric oxide, and high-frequency oscillating ventilation improve arterial oxygenation, but no randomized controlled studies have shown increased survival with these treatments.^{127,128} Other therapies reported include prostaglandins, extracorporeal membrane oxygenation, and liquid ventilation. Treatment of underlying pneumonia is necessary. Careful attention to other organ systems and nutritional support give the patient's lungs time to recover. The mortality rate for ARDS with no other organ system affected remains at 50% to 64%. If a patient displays signs of hypoxia and the etiologies just mentioned are not the cause, then pulmonary embolism, myocardial ischemia, arrhythmia, and heart failure need to be investigated.

Cardiac Complications

Myocardial Infarction. Myocardial infarction should be managed expediently with oxygen therapy, ECG monitoring, morphine, statins, and aspirin if bleeding is not a great concern.¹²⁹⁻¹³¹ Inotropic or pressor support may be needed in the immediate postoperative period. If the patient's blood pressure cannot be supported adequately

with medications, intra-aortic balloon pump placement should be considered. Patients with continuing ischemia and hemodynamic instability should be taken for cardiac catheterization to delineate significant stenosis and should undergo catheter-based therapy if indicated. Anti-coagulants such as heparin, ADP receptor antagonists (ticlopidine, clopidogrel, or prasugrel) or GIIb/IIIa platelet inhibitors (abciximab, eptifibatide, or tirofiban), or both, are recommended for unstable angina,¹³² but recent surgery and risk of bleeding may preclude their use. Adesanya and colleagues have recommended algorithms for both non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction (Figs. 4-4 and 4-5).¹³¹ The surgeon must exercise judgment regarding the risks and benefits of these drug interventions after surgery. Arrhythmias should be treated according to advanced cardiac life support protocol if the patient is hemodynamically unstable.

Atrial Fibrillation. The Society of Thoracic Surgeons published recommendations regarding prophylaxis and treatment of atrial fibrillation in general thoracic surgery patients in 2011.³² Electric cardioversion is the initial treatment of atrial fibrillation with hemodynamic compromise. Chemical cardioversion is the initial treatment for hemodynamically stable atrial fibrillation with intolerable symptoms. Recommended treatment of postoperative atrial fibrillation without hypotension is rate control for 24 hours. If conversion to sinus rhythm does not occur or paroxysmal atrial fibrillation continues past 24 hours, then chemical cardioversion is then tried. Anticoagulation is recommended based on a patient's risk of stroke if atrial fibrillation occurs for longer than 48 hours (Fig. 4-6).

Bleeding

Postoperative bleeding is monitored by chest tube output. Sudden occurrence of large-volume, bloody drainage requires immediate re-exploration to find and stop the source of bleeding. Less rapid bleeding of more than 100 mL/h for 2 consecutive hours is also excessive after thoracic surgery. If the patient has been taking aspirin or other antiplatelet agents such as clopidogrel, prasugrel, or ticagrelor, and if surgery was emergent or required before the known washout period (5 to 10 days depending on the medication), then platelet dysfunction must be considered.¹³² Unfortunately, there is no reversal agent or antidote for the newer antiplatelet drugs. Platelet transfusion is ineffective if therapeutic levels of the active metabolite of the medication are present. Patients who are treated with newer anticoagulants to prevent or treat thrombovascular disease, including dabigatran, rivaroxaban, and apixaban, will have elevated prothrombin time and partial thromboplastin time, but there is no good correlation between test results and amount of drug activity. In life-threatening bleeding, prothrombin complex concentrate in combination with activated factor VII can be given to attempt to reverse the effects of these medications, but the risk of thromboembolic events will be increased.^{133,134} If a coagulopathy exists, goal directed expeditious administration of lysine analogs,

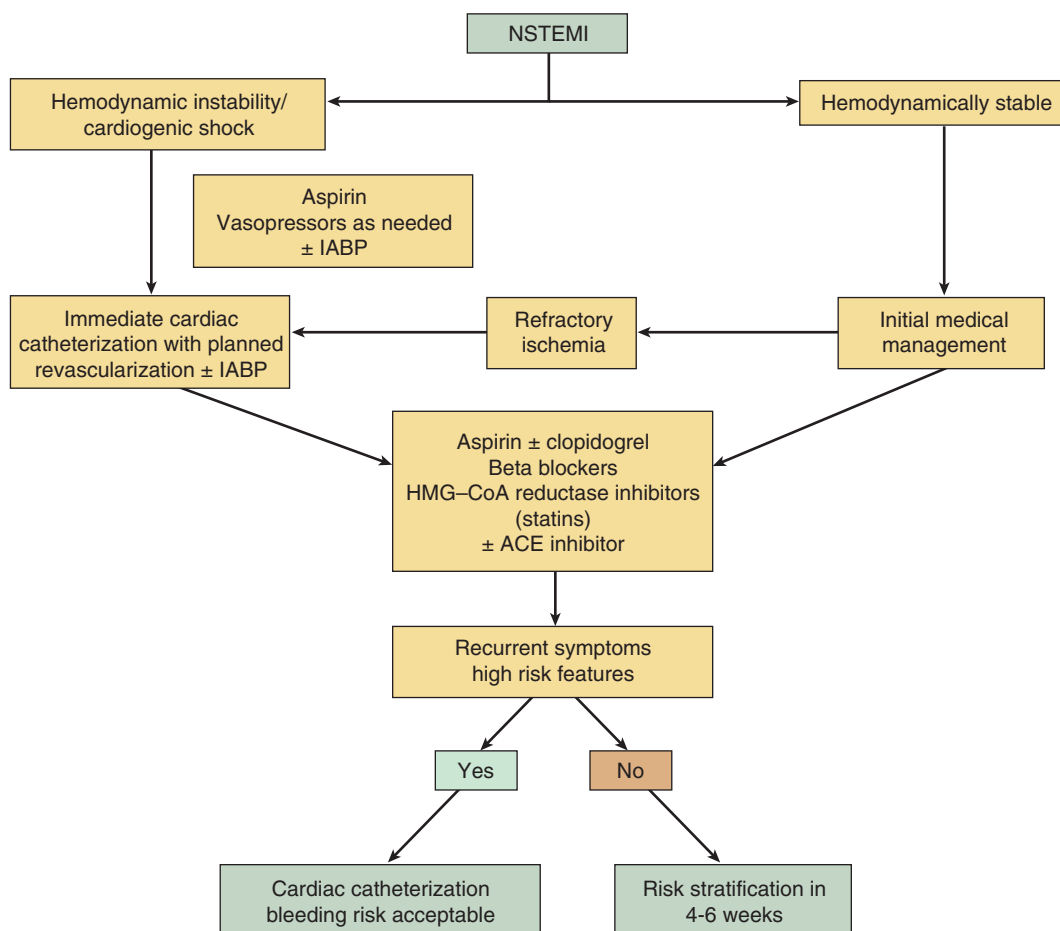


FIGURE 4-4 ■ Suggested algorithm for management of perioperative non-ST-segment elevation myocardial infarction. *ACE*, Angiotensin-converting enzyme; *HMG-CoA*, 3-hydroxy-3-methylglutaryl-coenzyme A; *IABP*, intra-aortic balloon pump; *NSTEMI*, non-ST-segment elevation myocardial infarction. (From Adesanya AO, de Lemos JA, Greilich NB, et al: Management of perioperative myocardial infarction in noncardiac surgical patients. *Chest* 130:584–596, 2006.)

prothrombin, DDAVP, cryoprecipitate, activated factor VII, and prothrombin complex concentrate, fresh frozen plasma¹³⁵ and keeping the patient normothermic⁶³ may help slow or stop bleeding. If bleeding persists after correction of deficient factors, exploration for a bleeding source should be performed. If coagulopathy and bleeding have been controlled but hematoma causes significant mediastinal or lung compression, then re-exploration is necessary. Transfusion of packed red blood cells should be considered, depending on the patient's hemoglobin level and hemodynamic condition.

Late Complications

Pulmonary Complications

Bronchopleural Fistula. If air is leaking from the bronchial stump, adequate chest tube drainage to prevent or drain empyema is necessary. Bronchoscopy should be performed to examine the stump and to identify the area of leak. If the hole cannot be visualized, slow administration of saline via the bronchoscope into the stump can reveal bubbles or drainage of the saline through a small hole. If the stump is not the area of leak, sequential bronchial examination and occlusion with balloon tipped

catheters within the lumen of segmental or lobar bronchi can be performed. By visualizing decreased air leakage from the chest tube with occlusion of certain airways, gross localization can be performed. Multidetector computed tomographic scanning with intravenous contrast using thin slice (1.25–5 mm) acquisition allows (1) visualization of air bubbles adjacent to the leaking bronchus or parenchymal rent if present, (2) coronal and sagittal views in addition to the usual axial cuts to allow better three-dimensional localization of bronchopleural fistula, and (3) construction of virtual bronchoscopy images.¹³⁶ Treatment can consist of operative closure or endobronchial closure. Multiple biological glues, adhesives, irritants, stents, vascular plugs or occluders, and coils have been reported to seal small bronchopleural fistulas successfully in case reports.¹³⁶ Special catheters and deployment devices are necessary to administer the treatments through the bronchoscope to the site of the leak. Reoperation for closure of the leaking bronchial stump may be needed. The standard approach of Zaheer and colleagues includes trimming a long bronchial stump or debriding a poorly vascularized stump and then covering the stump with an extraskelatal muscle flap (e.g., the serratus anterior or latissimus dorsi).¹³⁷ If vascularized tissue is inadequate to close a bronchopleural fistula, the extraskelatal muscle is

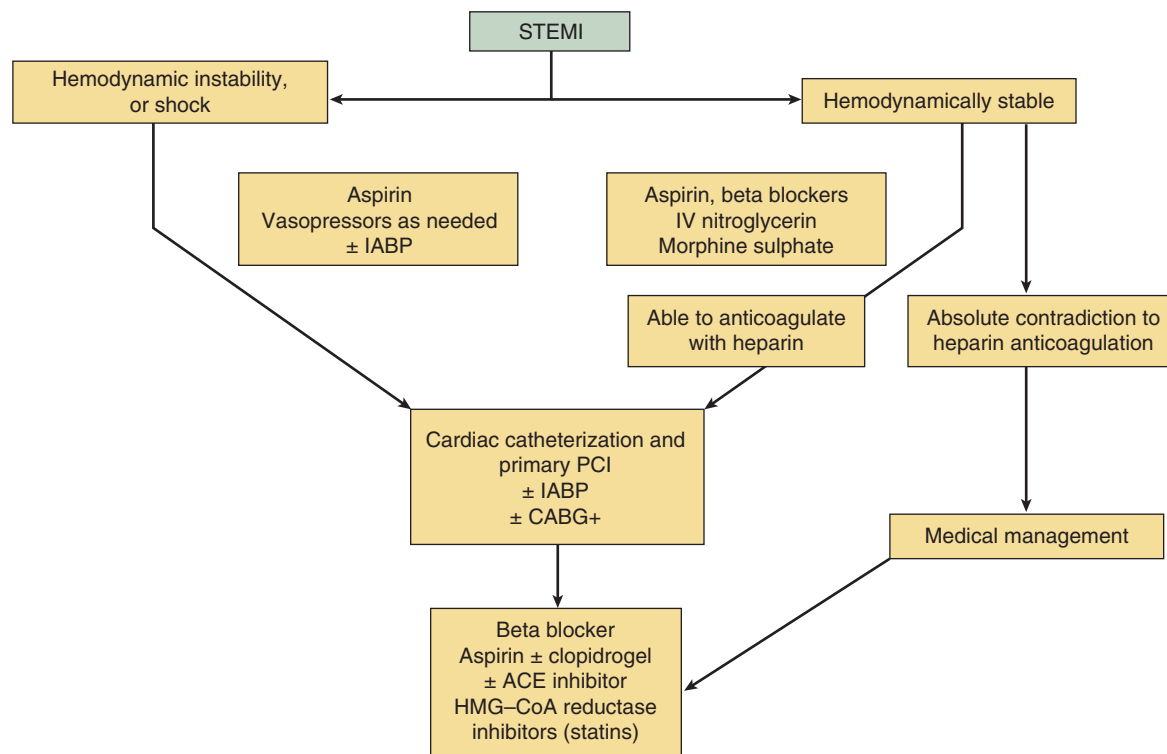


FIGURE 4-5 ■ Suggested algorithm for management of perioperative ST-segment elevation myocardial infarction (STEMI). CABG, Coronary artery bypass grafting; IABP, intra-aortic balloon pump; IV, intravenous; PCI, percutaneous coronary intervention. (From Adesanya AO, de Lemos JA, Greilich NB, et al: Management of perioperative myocardial infarction in noncardiac surgical patients. *Chest* 130:584–596, 2006.)

sewn circumferentially to the stump for closure. Wide drainage to prevent unilateral empyema and contralateral soiling should be performed; this can include thoracotomy and performing open packing in the operating room every several days or under conscious sedation in the patient's room for several days to weeks until the cavity is clean. An Eloesser flap can be performed to facilitate open packing. Once clean, dilute antibiotic solution is instilled, and airtight chest closure is performed. Mobilization of the remaining chest wall musculature and additional rib resection may be necessary to allow chest wall closure without tension; this alleviates a lifetime of packing an open chest, which predisposes to failure to thrive and recurrent bronchitis and pneumonia, and limits the patient's daily activities and lifestyle. If the chest wall is too contracted or rigid to allow airtight closure, an Eloesser flap can be used with packing or vacuum assist dressing to allow cleansing and possible granulation and closure of bronchopleural fistula.^{106,138} An alternative approach involves pleural irrigation with antibiotic solution, intravenous antibiotics, and nutritional support. Gharagozloo and colleagues recommend an antibiotic solution composed of gentamicin (80 mg/L), neomycin (500 mg/L), and polymyxin B (100 mg/L), and an airtight thoracotomy closure without drainage should be instituted when pleural cultures are negative.¹³⁹ Ng and coworkers used antibiotic irrigation for 2 weeks, tailored to the organism grown in pleural culture.¹⁴⁰

A persistent pleural space after lung resection can be prevented with a pleural tent if it is anticipated at the time of surgery. The apical portion of the parietal pleura is

dissected from the chest wall and tacked to a lower intercostal muscle. The chest tube(s) are placed within the pleural tent. The pleura adhere to the surface of the remaining lung and help seal over any leaking areas, and they decrease the volume of space that the remaining lung needs to fill. Either the space on top of the pleural tent in the apex fills with serous fluid, as it does after a pneumonectomy, or the lung expands to fill the whole space. This change is also aided by elevation of the hemidiaphragm. Encouraging the diaphragm to rise can be accomplished with pneumoperitoneum. Air can be instilled across the diaphragm with a needle during thoracoscopy/thoracotomy or periumbilically at a later time. Care must be taken not to damage the liver, spleen, or stomach.⁶⁸ Injection of the phrenic nerve with local anesthetic causes a temporary paralysis that also encourages the hemidiaphragm to rise. No respiratory compromise resulting from this practice has been reported. Filling of a residual space with healthy living tissue such as muscle or omentum can also be performed, although this is generally not done during resection because such extreme measures are unlikely to be needed. Lastly, thoracoplasty can be performed but is rarely used.¹⁴¹

Bronchovascular Fistula. Bronchovascular fistula is a rare complication that needs to be considered after bronchoplastic procedures are performed for lung cancer or lung transplantation.¹⁴²⁻¹⁴⁴ Fistulas sometimes first appear with a herald bleed, followed by massive hemoptysis. Salvage after a major bleed is rare, and the best treatment is to decrease the chance of fistula formation by placing

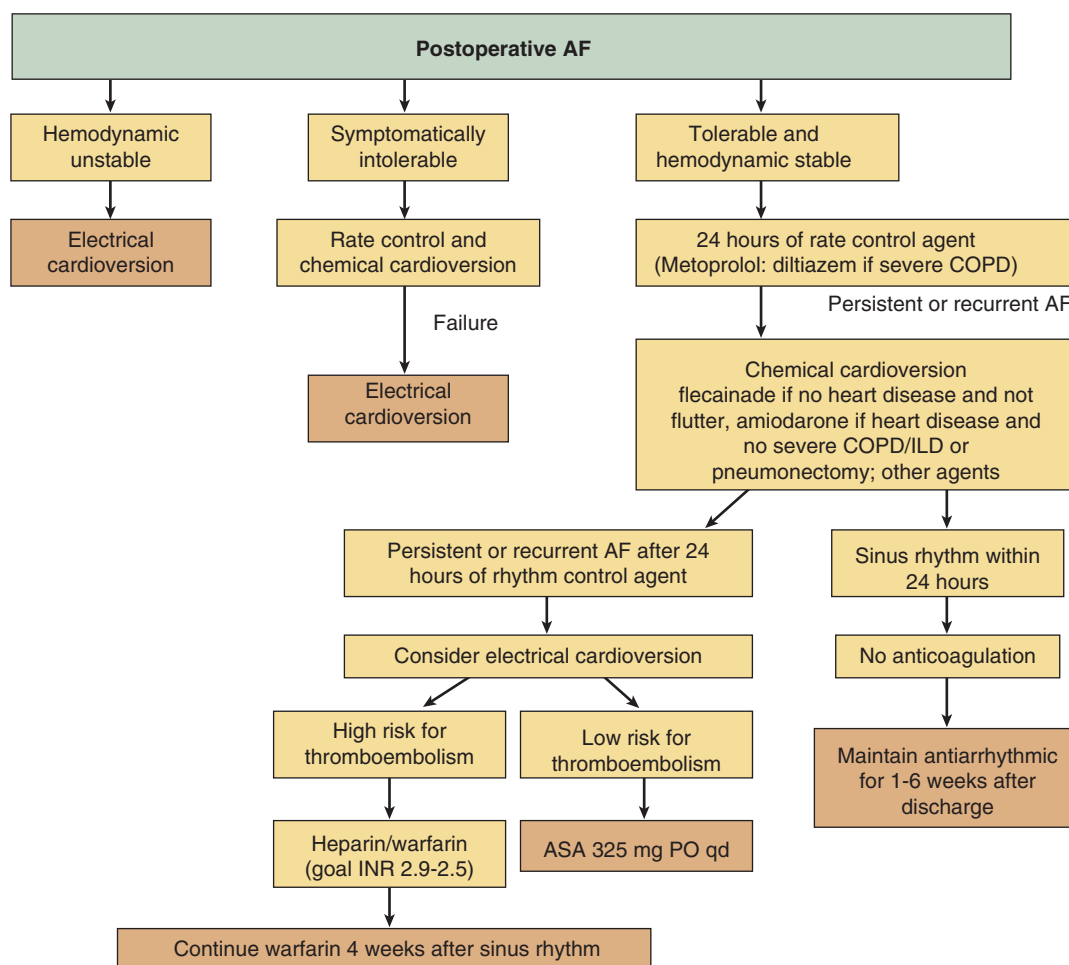


FIGURE 4-6 ■ Suggested algorithm for management of postoperative atrial fibrillation. AF, Atrial fibrillation; ASA, acetylsalicylic acid (aspirin); COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; INR, international normalized ratio; PO, by mouth. (From Fernando HC, Jaklitsch MT, Walsh GL, et al: The society of thoracic surgeons practice guideline on the prophylaxis and management of atrial fibrillation associated with general thoracic surgery: executive summary. *Ann Thorac Surg* 92:1144–1152, 2011.)

vascularized tissue, such as intercostal or extraskelatal muscle, pleura, pericardium, or omentum, between the pulmonary artery and the sutured bronchus. If massive hemoptysis occurs, an attempt at placing a double-lumen tube to isolate the nonaffected lung from blood spillage may allow enough time for the chest to be opened and the bleeding controlled. Unfortunately, salvage is rare and the patient dies of suffocation more often than exsanguination.

Postpneumonectomy Syndrome. Postpneumonectomy syndrome is torsion or compression of the trachea, bronchus, esophagus, or pulmonary vasculature caused by mediastinal shift after pneumonectomy. Placement of a tissue expander or a saline breast prosthesis into the post-pneumonectomy space is reported to reverse some of the mediastinal shift and its consequences.^{145,146}

Wound Infection and Empyema. Wound infection after chest surgery is rare. The wound should be opened to allow adequate drainage. If the patient also has an empyema, tube drainage of the pleural cavity through a separate site can be attempted along with opening of the wound. If the infection extends into the pleural space, it

is better to take the patient back to the operating room for a thorough drainage, irrigation, débridement, and decortication if the space is not well drained by chest tube. Strong consideration should be given to leaving the skin open. Wound vacuum dressings have been successful in pleural spaces even with remaining lung parenchyma and gross soilage.¹⁰⁶ If the cause of empyema is a bronchopleural fistula, the infection should be cleared, and then definitive treatment of the bronchopleural fistula is undertaken as mentioned earlier.

Post-thoracotomy Pain. Chronic post-thoracotomy pain syndrome remains a devastating and debilitating result after thoracotomy.^{92,93} It is pain that occurs along a thoracotomy scar at least 2 months after surgery, and its incidence is 44% to 67%. Minimally invasive thoracic surgery continues to increase and although it has been shown to cause less pain than thoracotomy, some patients still suffer from chronic pain.¹⁴⁷⁻¹⁴⁹ Treatment can involve several modalities, including medications, behavioral techniques, and procedures. Combinations of medication include nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, anticonvulsants such as gabapentin, opioids, and lidocaine patches. Behavioral techniques

such as biofeedback, hypnosis, and relaxation techniques may be offered. Procedural treatments include intercostal nerve block, paravertebral block, intrapleural local anesthetic, radiofrequency ablation, cryoablation, and transcutaneous electrical nerve stimulation. Referral to a pain specialty clinic with a team consisting of anesthesiologist, nutritionist, physical therapist, psychiatrist or psychologist, occupational therapist, and pharmacist is recommended for comprehensive care.

Complications after Esophageal Surgery

Many of the complications encountered after lung resection, particularly the respiratory complications, also occur after esophageal surgery. A recent meta-analysis compared perioperative outcomes of minimally invasive esophagectomy to hybrid minimally invasive esophagectomy and open esophagectomy.¹⁵⁰ Minimally invasive esophagectomy showed decreased overall morbidity, blood loss, hospital length of stay, and pulmonary complications. There was no difference on overall mortality and anastomotic leak. The mortality of esophagectomy has declined since 1999, but it continues to be higher than of other cancer resections, including lung resection, pancreatectomy, and cystectomy indicating continuing need for improvement in patient selection, preoperative optimization, intraoperative technique, and postoperative care whether performed by minimally invasive or open technique.¹⁵¹ The incidence of pulmonary complications after esophagectomy ranges from 11% to 32%.¹⁵² Patients are at high risk of aspiration after esophagectomy, especially if they have recurrent laryngeal nerve injury.¹⁵³ Aspiration precautions including elevation of the head of the bed at all times, the chin tuck maneuver, eating and drinking only out of bed and sitting at 90 degrees, smaller but more frequent meals, with the last meal being several hours before sleep, and education by speech pathologists and nutritionists about food choices, mechanics of eating, and concentration during eating are of paramount importance.

Dysphagia

Difficulty swallowing is one of the most frequent complications after any esophageal surgery. At times, it is self-limited and is caused by recent surgery.^{94,95,153-155} However, persistent dysphagia after fundoplication, myotomy, or esophageal resection should be investigated. Workup usually includes barium swallow, motility studies, esophagogastroduodenoscopy, or a combination of these. Anatomic or functional abnormalities such as too tight a fundoplication, slipped fundoplication, recurrent herniation, motility disorder, and ulceration may be found. Treatment depends on the cause of the dysphagia and ranges from simple observation to dilation, medical treatment, or reoperation.⁹¹

Anastomotic Leak

Anastomotic leak or perforation occurs because of multiple factors including ischemia, inflammation, distention of conduit and pressure at suture lines, poor nutrition,

anastomotic tension, or technical problems.^{156,157} The location and size of the leak determine the treatment. If a neck anastomosis is leaking, the neck wound is opened to allow drainage and healing over time. Stricture can form and require dilation, but it is usually not incapacitating. Some surgeons advocate NPO status during that time to reduce the amount of pressure and fluid draining past the hole, whereas others believe that oral intake serves to dilute bacterial rich saliva and allow dilation of the lumen, which promotes passage down the true lumen for cervical anastomotic leaks that are easily drained from the neck incision without mediastinitis. Antibiotics are not necessary if the leak is adequately drained. If the leak is more than a quarter of the circumference of the anastomosis, debriding unhealthy tissue and primary reclosure of the anastomosis should be considered.

If the anastomosis is within the chest, a leak may be contained in the space around the conduit, into the pleural cavity, or into the mediastinum. A leak into the pleural cavity should be drained with chest tubes. The patient is placed on NPO status. Intravenous antibiotics are administered unless the patient has no fever or leukocytosis and there is a well-formed drainage tract to the tube. Drainage into the mediastinum can be fatal if it is not evacuated. If the patient is toxic, reoperation for adequate drainage should be performed to prevent mediastinitis and sepsis. If there is adequate healthy tissue after débridement and the patient is not toxic at that time, reanastomosis can be considered. If ischemia or soiling with unhealthy tissue exists, wide débridement with esophageal diversion may be needed. If a significant amount of the stomach needs to be resected, the hiatus should be closed to prevent herniation. For small, persistent anastomotic leaks, both removable polyester-silicone stents and expandable covered metallic stents have been successful in excluding the leak and allowing tissues time to heal without continued soiling.¹⁵⁷

Stricture

Stricture after esophageal surgery can occur at an anastomosis; at the diaphragmatic hiatus; above, below, or within a fundoplication; at the pylorus; or at the site of previous myotomy. Stricture can be secondary to technical problems, ischemia, leak, ulceration, or reflux, and it can be multifactorial.¹⁵⁶ Most strictures that occur after recent esophageal surgery can be treated with either balloon or bougie dilation.¹⁵⁷ Multiple dilations may be necessary in the early period after surgery. With the passage of time, the frequency of dilation for each patient decreases until it is no longer necessary. If the anastomosis was performed for esophageal cancer, biopsy to exclude persistent or recurrent cancer should be performed.¹⁵⁶ A few patients need repeated dilation on a long-term basis, and some are able to dilate themselves at home after being taught. If a stricture remains refractory, temporary stenting may be beneficial.^{91,153,154}

Conduit Ischemia

Continuous knowledge of the position of the gastroepiploic arteries as the greater curvature dissection is

performed prevents inadvertent ligation or damage to the main vascular pedicle used during gastric pull-up. Leaving the right gastric artery intact provides a dual blood supply to ensure adequate blood flow to the stomach as it is transposed into the chest or neck. Careful handling of the gastric tube during passage into the chest or neck and prevention of twisting, torqueing, or folding is of paramount importance. The distal tip of the conduit should be pink when positioned and before anastomosis. Bleeding at the gastrostomy site created for stapler insertion or hand-sewn anastomosis and healthy-appearing mucosa should be seen. Conduit ischemia of colon interposition can be avoided by assessment of the blood supply before surgery if the patient has had previous gastric or colonic operations. An angiogram of the mesenteric arteries may be desired before the colon is used as a conduit to ensure patency of the marginal artery. Supercharging has also been used to provide increased perfusion to colonic or jejunal conduits when used as primary conduit or for reconstruction after esophageal diversion.^{158,159} Conduit ischemia can be difficult to diagnose postoperatively, but symptoms and signs of infection or an inflammatory response without a known source should raise the level of suspicion. Unless diagnosed and treated early, conduit ischemia leads to further morbidity or mortality. If a significant portion of the conduit is ischemic or the surrounding tissues are unhealthy from inflammation, takedown of the anastomosis, creation of an esophagostomy, and return of the gastric remnant to the peritoneal cavity with closure of the hiatus is recommended.^{153,160}

Recurrent Laryngeal Nerve Damage

Damage to the recurrent laryngeal nerve is more common after transhiatal resection or three-hole resection because of the dissection and retraction in the neck where the recurrent nerves are exposed in the tracheoesophageal groove. Recurrent laryngeal nerve damage not only causes hoarseness; it also compounds discoordination of swallowing and increased risk of aspiration in patients already at risk for these problems because of absence of the lower esophageal sphincter and decreased motility due to division of the vagus nerves. The incidence of this complication can be lowered by careful avoidance of metal retractors deep in the neck wound and visualization of the nerve. If vocal cord paralysis is evident after esophagectomy, assessment for aspiration by modified barium swallow or fiberoptic endoscopic evaluation, or both, by a speech pathologist is recommended before oral intake. If aspiration is present, the patient may need to be kept on NPO status with nutrition maintained by tube feeding until vocal cord medialization is performed to decrease the risk of aspiration and to increase the ability of the patient to make an effective cough.^{153,160}

Chylothorax

The incidence of chylothorax is 0.4% to 0.8% after esophagectomy. It usually manifests several days after the operation when tube feeding or oral intake is started.

Drainage of moderate to large volumes of milky whitish fluid from the chest tube or with thoracentesis is usually diagnostic. Analysis of the fluid for lipids with a triglyceride-to-cholesterol ratio of greater than 1 or a triglyceride level greater than 110 g/dL confirms the diagnosis. The thoracic duct may be injured while mobilizing the lower thoracic esophagus, and leakage is usually into the right chest. Conservative measures such as a low-fat or medium-chain triglyceride diet can be tried, but if the drainage does not decrease after several days, full NPO status and total parenteral nutrition should be instituted. Chyle contains abundant proteins, and patients can become nutritionally depleted quickly. Octreotide infusion or subcutaneous administration has been successful in treating chylothorax in case reports.^{153,160} Percutaneous embolization of the thoracic duct or cisterna chyli also has good results.¹⁶¹ Some surgeons prefer not to wait more than 5 days before taking the patient back to the operating room for thoracic duct ligation just above the right hemidiaphragm. This can be done thoracoscopically or with a thoracotomy. Lymphangiography is generally not helpful in localizing the leak, and most radiologists are not trained in this method anymore. Feeding the patient cream or a fat-laden food several hours before surgery can elucidate the leaking portion of the duct. The leaking point is ligated and the duct is ligated at multiple other points just above the diaphragm. Chest tube output should decrease drastically, and the patient can be fed again.

Functional Problems

Dumping syndrome occurs because of high osmotic load from the stomach into the small bowel because of a lack of antral control after the vagus nerves are divided and pyloromyotomy or pyloroplasty is performed.^{91,160} This can occur approximately 20 minutes or several hours after a meal. Dietary adjustments such as decreasing the intake of foods with refined sugars and eating smaller, more frequent meals without a large amount of fluid are helpful in improving symptoms. Fiber intake and acarbose, which interferes with carbohydrate absorption, may help. More severe symptoms can be treated by subcutaneous octreotide.¹⁶² Delayed gastric emptying also occurs after esophagectomy because of division of the vagus nerves and decreased stomach motility. Although in the past most surgeons performed a drainage procedure at the pylorus to prevent gastric outlet obstruction, there is no conclusive evidence that this is necessary.^{163,164} Some surgeons are now adopting balloon dilation, botulinum toxin injection, or no intervention of the pylorus. At times, dilation of the pylorus or the anastomosis will need to be performed.

Gas-bloat syndrome can occur after fundoplication. Patients complain of feeling full of gas and being unable to belch for relief. Dietary changes to decrease the amount of gas-producing foods, avoidance of carbonated beverages, eating slower to decrease air swallowing, prokinetic drugs, and the passage of time usually relieve the symptoms of this syndrome. There is some suggestion that a partial fundoplication leads to less gas-bloat syndrome than total fundoplication.¹⁵⁵

Reflux

Gastroesophageal reflux is common after esophagectomy and gastric pull-up. The lower portion of the stomach remains subjected to positive intraperitoneal pressure while negative intrathoracic pressure exerts an influence on the upper portion of the stomach without a lower esophageal sphincter. Patients with a history of Barrett's esophagus or symptoms or findings of esophagitis after gastric pull-up should receive antireflux medication. Patients should be counseled to eat and drink in the upright position and remain upright for at least 2 hours after eating. The head of the bed should be elevated 30 degrees, or they should sleep on a foam wedge to avoid nighttime reflux and aspiration. Avoiding damage to the recurrent laryngeal nerves helps to diminish the risk of aspiration when reflux occurs.^{91,155}

Miscellaneous

Myasthenic crisis is respiratory muscle weakness causing respiratory failure after thymectomy for myasthenia gravis. Positive-pressure mask breathing or ventilation should be used to support the patient through the acute crisis. Pyridostigmine is usually not effective during crisis. If steroids and intravenous immune globulin do not provide enough symptom relief, plasmapheresis may be needed to clear the circulating antibodies.¹⁶⁵ Cholinergic crisis results from overtreatment with anticholinesterase medications. The patient may have symptoms related to muscarinic receptor activity (e.g., excessive salivation, sweating, abdominal cramping, urinary urgency, bradycardia). Nicotinic receptor symptoms include fasciculations and muscle weakness. Cholinergic crisis does not respond to neostigmine. Treatment includes respiratory support, atropine, and cessation of anticholinesterase medications.¹⁶⁶

Cerebrospinal fluid leak is a rare complication seen when tumor is resected near the spine. The assistance of a neurosurgeon is recommended, and primary closure should be done if possible. Coverage with fat or pleura can also be used to help seal the leak. Other treatments involve placing lumbar drains to decrease the amount of cerebrospinal fluid pressure to allow the leak to seal on its own. The symptoms include leakage of clear fluid and development of intractable headache after resection close to the spine or involving the vertebrae.¹⁶⁷

DISCHARGE PLANNING

Discharge needs should be assessed preoperatively or soon after the surgery. The surgeon can often predict what services will be needed, based on the patient's preoperative health and family support network. A recent study used American College of Surgeons National Surgical Quality Improvement Program (NSQIP) data to develop a short tool to estimate the likelihood of discharge to another facility instead of to home.¹⁶⁸ The patient and family are made active participants in plans for timely discharge. Team meetings with social workers, nurses, physical therapists, and respiratory therapists

about each patient's needs are helpful for planning. Occupational therapists and physical medicine physicians can indicate what level of rehabilitation patients will need after discharge. A list of medications for home use, their purpose, and dosage is reviewed with the patient and the caregivers before discharge, including the changes from preoperative medications. Activity level and home-going exercises should be reviewed, and patients should demonstrate them to the therapist before leaving to ensure that they are being performed correctly. Driving of motor vehicles is limited while the patient is taking narcotic medications. If thoracoscopy for lung resection is performed, there are no limitations of activity save for those that affect intrathoracic pressure such as scuba diving. Patients who had minimally invasive foregut surgery involving the esophageal hiatus should limit heavy lifting to allow healing and prevent suture rupture from strong Valsalva. There is no prohibition for showering or stair climbing.

Outpatient pulmonary rehabilitation or physical therapy programs should be contacted and established before discharge. The goal is to return the patient to a normal lifestyle as soon as possible. Visiting nurses can be invaluable in helping patients once home, for vital sign checks, administration of antibiotics or blood draws, tube care, and wound care. They allow patients to be discharged who need help for only several minutes a day. The follow-up appointment and any laboratory studies or radiology studies that need to be obtained before the appointment should be arranged before the patient's discharge. Appropriate contact telephone numbers should be provided should the patient have difficulty after discharge.

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ENDOSCOPY

PART OUTLINE

5 ENDOSCOPIC DIAGNOSIS OF THORACIC DISEASE

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ENDOSCOPIC DIAGNOSIS OF THORACIC DISEASE

Leah M. Backhus • Aaron M. Cheng • Douglas E. Wood

CHAPTER OUTLINE

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Endoscopy, especially fiberoptic endoscopy, has revolutionized nearly all theaters of medicine in terms of diagnosis and therapeutic intervention.¹ This revolution is particularly true for thoracic surgery, where bronchoscopy and esophagoscopy are essential modalities in the diagnosis, approach, and treatment of tracheal, bronchial, and alimentary tract pathology. As the technology of optics, endoscope instrumentation, and appurtenances such as endoscopic ultrasound and yttrium-aluminum-garnet (YAG) laser have evolved, so have the indications and capabilities of the skilled endoscopist. Although many clinicians may perform endoscopy, thoracic surgeons in particular should be adept and pioneering with these procedures, because new endoscopic technology will continue to enable all aspects of minimally invasive thoracic surgery.

ESOPHAGOSCOPY

In 1868, Kussmaul intubated a sword swallower's stomach via the esophagus with a 13-mm hollow metal tube. This maneuver proved that the oral cavity, esophagus, and stomach could be simultaneously intubated with one rigid instrument. Mikulicz added one crucial aspect to the tube—a distal light to illuminate the esophagus and stomach—and he was able to visualize gastric motility and view probable malignancies. The fiberoptic endoscope was introduced in 1958. This instrument allowed more patient comfort as well as greater therapeutic possibilities in the distal stomach and proximal small

intestine. Although the scope itself has not changed greatly, the adjunctive instruments have dramatically changed the way many disease states can be treated.²

Indications

For the thoracic surgeon, dysphasia and odynophagia are two of the most common indications for esophageal endoscopy (Box 5-1). Others include reflux, an abnormal esophagogram, trauma, screening, or staging of gastrointestinal or adjacent masses including tracheoesophageal fistulas. Upper gastrointestinal bleeding is another common indication for endoscopy, which has become the first line in management of this clinical scenario. Likewise, esophagoscopy can be a useful tool in evaluating and treating patients with known or suspected complications following surgery of the foregut.

Dysphagia can arise from a number of pathologic processes. Many causes can be distinguished with a careful history that records the duration and persistence of symptoms and accompanying constitutional complaints. Endoscopy allows the surgeon to distinguish between malignant and benign causes of dysphagia with direct endoscopic visualization and pathologic sampling, thereby guiding therapy.

Reflux is another indication for upper endoscopy. The thoracic surgeon searches for any long-term sequelae associated with chronic gastroesophageal reflux disease, such as Barrett esophagus. Esophagoscopy is crucial in the surveillance of known Barrett esophagus because of the link with the development of adenocarcinoma. Many

BOX 5-1 Indications for Upper Endoscopy

- Persistent nausea and vomiting
- Upper abdominal pain, heartburn, or acid reflux symptoms (i.e., an acid or burning sensation in the throat or chest)
- Gastrointestinal bleeding (vomiting blood or blood found in the stool)
- Difficulty swallowing; food or liquids get stuck in the esophagus
- Abnormal or unclear findings on an upper gastrointestinal radiograph
- Removal of a foreign body
- Follow-up on previously found polyps (growths), tumors, or ulcers

From the American Society for Gastrointestinal Endoscopy: Appropriate use of gastrointestinal endoscopy. Gastrointest Endosc 52:831–837, 2000.

support recommendations for surveillance at 3- to 5-year intervals, but its efficacy in reducing death from esophageal cancer has not been firmly established.^{3,4}

Upper gastrointestinal bleeding is another indication for endoscopy, and the procedure is often used therapeutically, as with bleeding esophageal varices—a difficult problem that can be palliated endoscopically with banding or sclerotherapy.

The most common reason for a thoracic surgeon to perform upper endoscopy is to visualize and biopsy esophageal and proximal stomach masses. Biopsy has a sensitivity of 66% to 96% in esophageal cancers.^{5,6} Seven to 10 biopsies are usually taken throughout the area of the lesion, or randomly in the setting of Barrett esophagitis. For lesions with a tight stricture, the surgeon can use a small-diameter scope, and brushings have been shown to increase the yield of tissue in such cases.^{6,7} After foregut surgery, endoscopy is also useful in the management of postoperative complications for both therapeutic and diagnostic purposes. The role of endoscopic ultrasound in the diagnosis and staging of esophageal disease will be discussed later.

Upper endoscopy can also play a role in the assessment of other mediastinal masses and malignancies that cause esophageal obstructive symptoms. Endoscopy can reveal whether the lesion is causing mass effect or actual erosion through the wall of the esophagus, possibly resulting in a fistula.

Upper endoscopy is also important for investigating trauma—blunt, penetrating, or caustic—and for foreign body retrieval. When using endoscopy to remove foreign bodies lodged in the esophagus, the surgeon should be alert to the potential for intraesophageal lesions, which may be responsible for the failure of material to pass through. The thoracic surgeon is frequently asked to document and manage iatrogenic trauma to the esophagus via instrumentation. Although the esophagogram is the mainstay for the diagnosis of perforation, the usefulness of endoscopy for the diagnosis and documentation of the extent of injury should not be underestimated. Cases of esophageal perforation have been reportedly managed with endoscopic techniques—primarily stenting. Most experience comes from extreme cases when

patients either are too acutely ill for attempts at repair or have minimal systemic derangement. In these highly select cases, outcomes have been favorable.⁸

Corrosive ingestion is another indication for early (within 36 hours) endoscopic inspection, which can help to identify transmural involvement and subsequent development of strictures.⁹

Preprocedure

Most endoscopies can be performed on an outpatient basis with conscious sedation. Patients should receive nothing by mouth (NPO) after midnight for a morning examination, and those with obstructive symptoms should be administered a clear liquid diet for 24 to 48 hours before the examination. When the patient arrives, a peripheral intravenous line and electrocardiograph (ECG) leads should be placed. Because the sedatives can cause respiratory depression, continuous ECG and pulse oximetry monitoring is performed, and blood pressure measurements are obtained frequently during the procedure. Once the monitors are in place, sedation is given to ensure that the patient is comfortable and cooperative. Local anesthesia minimizes the degree of conscious sedation required.

Flexible Esophagoscopy

Technique

The most common position for examination of the outpatient is the left lateral decubitus, with the head flexed. A bite block is placed into the mouth to protect the endoscope from the teeth, and the endoscope is introduced under direct vision. The epiglottis and larynx should be seen and advanced over until the piriform sinuses become apparent. If the vocal cords are visualized, any abnormalities should be documented. Gentle pressure is applied against the upper esophageal sphincter at the cricopharyngeus, and the patient is instructed to swallow, which usually results in successful and atraumatic esophageal intubation.

The four normal endoluminal landmarks in the esophagus are as follows: (1) the upper esophageal sphincter at the cricopharyngeus, 15 to 18 cm from the incisors; (2) the aortic arch, usually evident as an indentation on the left anterolateral wall; (3) the left atrium, seen in the distal esophagus as wavelike pulsations of the anterior wall of the esophagus; and (4) the lower esophageal sphincter, which in reality is just a physiologic sphincter and which can be demonstrated by asking the patient to perform a Valsalva maneuver and noting the pinching off of the lumen. The esophagus is generally easy to assess, and very little air insufflation is required to view its entire course.

Once the gastroesophageal junction has been passed, it is easy to advance into the stomach. The stomach should be insufflated with enough air to flatten out the rugae and allow visualization of the entire mucosal surface. The pylorus is visualized, and the scope can be advanced beyond the sphincter when it is relaxed. The duodenum should be inspected to the third portion.

Once this has been performed satisfactorily, the scope should be withdrawn slowly to see any potentially missed pathology. In the stomach, retroflexion of the scope allows visualization of the body and cardia of the stomach as well as evaluation of the distal extent of disease for lesions at the level of the gastroesophageal junction. Insufflated air should be suctioned before leaving the confines of the stomach. During the withdrawal, the scope should be pulled back slowly to assess the esophagus carefully. Next, the endoscope is removed and monitoring of the patient continues.

Complications

Complications are rare after flexible upper endoscopy. Morbidity rates of 0.13% to 0.092% include cardiovascular reactions to premedication, perforation, and bleeding. Most complications occur within the setting of instrumentation and risk must be placed in context of the underlying pathology or indications for the procedure. Mortality rates are exceedingly rare, quoted at 0.018% to 0.004%.^{10,11}

Rigid Esophagoscopy

Rigid esophagoscopy is a rarely used modality, usually reserved for three instances: trauma, removal of impacted food, and removal of foreign bodies. Rigid esophagoscopes can accommodate larger graspers than the working channel of a standard flexible esophagoscope and do not require insufflation. The scope is held in the examiner's right hand while the left hand keeps the mouth open with the left thumb protecting the upper dentition. During the insertion of the scope, the head is initially held forward, in the "sniffing position" used for tracheal intubation. Once the cricopharyngeus is passed, the head is extended to eliminate the angle of the mouth and the pharynx. The scope can then be advanced carefully throughout the length of the esophagus and proximal stomach. Manipulating the head and cervical spine at the areas of narrowing allows less traumatic passage.

ENDOSCOPIC ULTRASOUND

Endoscopic ultrasound (EUS), for which a small ultrasonic transducer is attached to the end of the endoscope, is a relatively new adjunctive procedure that has expanded the examination of the esophagus and the periesophageal tissues. It is never an initial procedure, but it is indicated when a previous esophagoscopy has been performed and pathology has been located and evaluated. Indications for esophageal ultrasound range from benign to malignant esophageal disease and include evaluation of periesophageal pathology, usually bronchogenic carcinoma (Box 5-2). The most common indication for EUS is the evaluation of esophageal malignancy. The stage of the lesion, as defined by the depth of invasion and nodal involvement, is the best predictor of surgical resection and therefore possible cure.

The normal esophagus has five distinct layers of alternating echogenicity. The first layer, which is the most

BOX 5-2 Indications for Endoscopic Ultrasound

ESOPHAGUS

- Staging esophageal cancer
- Evaluating esophageal submucosal lesions
- Evaluation of high-grade dysplasia arising in Barrett esophagus
- Evaluation of response of esophageal cancer after chemotherapy
- Differentiating achalasia from pseudoachalasia
- Evaluation for periesophageal varices

MEDIASTINUM

- Nodal staging of lung cancer
- Evaluation of selected mediastinal masses
- Evaluating posterior mediastinal lymphadenopathy

hyperechoic (white), is the epithelium and lamina propria. The second layer, which is hypoechoic (black), is the muscularis mucosa. The third layer, which is again hyperechoic, is the submucosa. The fourth hypoechoic layer is the muscularis propria. The last layer, the paraesophageal tissue, is thick and hyperechoic. Tumor (T) stage is determined by which layers are invaded. Accumulating data suggest that EUS is the most accurate imaging modality for staging esophageal malignancies. When EUS results are compared with surgical pathology specimens, EUS demonstrates a preoperative sensitivity of 80% to 92%.¹² The main advantage of EUS over conventional radiology (computed tomography [CT]) is the differentiation of the T stage, especially between the T3 and T4 stages, which can influence the decision to offer the option of surgery to the patient.¹³ The accuracy of EUS for staging of regional lymph node metastasis has been in the range of 70% to 80%, which is better than that of CT or magnetic resonance imaging.¹³ The regional lymph nodes (N) stage and distant metastasis (M) stage are determined in part by biopsy results, which depend on their being seen on examination. Accurate staging is now achieved by fine-needle aspiration biopsy, which can be performed on nodal tissue or organ tissues in direct contact with the esophageal wall. After examination of the three different TNM tissues, the patient can be preoperatively staged. EUS is becoming the standard of care in the evaluation of esophageal malignancies. It can also be a useful adjunct for access to the lower mediastinal lymph node stations for staging for primary lung cancer and other malignancies with concern for mediastinal involvement.

TRACHEOBRONCHOSCOPY

Gustav Killian, a German laryngologist, is credited with first use of bronchoscopy in 1897. He used a rigid scope to remove a foreign body (bone) from the right mainstem bronchus of a patient. The modern era of flexible bronchoscopy arrived at about the same time as esophagoscopy, once the problem of flexible fiber orientation was solved. Ikeda was the first to report the use of a flexible fiberoptic bronchoscope in a patient.¹⁴ New

modalities such as ultrasound, cautery, fine-needle biopsy, YAG laser, and autofluorescence techniques have been coupled with more elegant instrumentation and digital optics to produce the scopes of today. Some of these new modalities have yet to find their particular niche in the modern paradigm.

Tracheobronchoscopy can be performed with a flexible or a rigid instrument, or a combination of the two, depending on the indication and the disease encountered. Flexible bronchoscopy allows the thoracic surgeon not only to diagnose, stage, plan surgical approach, and monitor therapy, but also to palliate, temporize, and alleviate a myriad of thoracic pathologies. Rigid bronchoscopy is used less, and it requires more care, but it is nonetheless indispensable in certain situations. Endobronchial ultrasound (EBUS) is a relatively new modality with growing applications in the diagnosis and staging of primary lung cancer.

Indications

Flexible bronchoscopy can be used for definitive diagnosis of infectious, malignant, and traumatic tracheobronchial diseases (Box 5-3). Pulmonary toilet, endoluminal débridement, endotracheal intubation and extubation, percutaneous tracheostomy placement, and treatment of atelectasis are also elegantly accomplished with the flexible bronchoscope. Perhaps the most important use for the thoracic surgeon, however, is in the staging and assessment of disease before surgery, and in particular, the surgical staging of a primary lung malignancy. After preliminary evaluations with CT and positron emission tomography suggest a resectable lesion, the surgeon surveys the tracheobronchial tree for evidence and extent of endoluminal disease before proceeding with mediastinoscopy and ultimately formal resection. Not only is this evaluation essential from a surgical oncologic perspective, but it is also invaluable in terms of defining anatomy and planning resection. If a video-assisted thoracoscopic approach is to be used for resection, the ability to recognize abnormal bronchial anatomy by endoscopy allows resection to be conducted more safely and can influence anesthetic decisions regarding lung isolation strategies. Furthermore, assessing the cancer's endoluminal involvement can help to determine whether lobectomy, sleeve lobectomy, pneumonectomy, or carinal resection should be used.

Direct forceps biopsy, fine-needle aspiration (FNA), endoluminal brush biopsy, and washings are all methods of obtaining tissue that can be performed with flexible bronchoscopy. Mediastinal lymph nodes can be sampled by ultrasound-guided FNA. Although this is inferior, in terms of sensitivity and specificity, to mediastinoscopy as a staging modality, it is often a useful adjunct to cancer staging.

For patients with acute pneumonia in the intensive care setting, flexible bronchoscopy is indispensable for acquiring samples to culture for microbial speciation and antibiotic sensitivities. Routine washings are performed by administering sterile saline through the irrigation port of the bronchoscope, usually in 10-mL volumes. This fluid is then aspirated into a sterile specimen and sent to

BOX 5-3

Indications for Flexible Bronchoscopy

DIAGNOSTIC

- Lung cancer
- Positive sputum cytology
- Paralyzed vocal cord
- Localized wheeze
- Unexplained pleural effusion
- Hemoptysis
- Cough
- Diffuse interstitial infiltrates
- Immunocompromised state
- Ventilator-associated pneumonia
- Endotracheal tube position or patency
- Atelectasis
- Tracheoesophageal fistula
- Acute inhalation injury
- Bronchography

THERAPEUTIC

- Mucous plug
- Acute lobar collapse
- Difficult intubation
- Foreign body removal
- Hemoptysis
- Brachytherapy
- Laser ablation
- Electrocautery
- Stent placement with pulmonary infiltrates
- Balloon dilation

the laboratory for cytology and culturing. The washing may also be performed by bronchoalveolar lavage (BAL), in which larger volumes of saline are used to reach more terminal bronchioles. The advantage of BAL is that more cellular and noncellular material is retrieved for examination. After the flexible scope is wedged into the fourth or fifth terminal bronchioles, sterile saline is instilled in increments of 50 mL, aiming for a total of 150 to 200 mL, and then aspirated into a specimen trap. The first aspirations contain mostly airway cells, whereas later aspirations can contain alveolar samples. The specimens are handled in the same manner as routine washings, but the absolute cell counts obtained can be useful in the workup of inflammatory, allergic, and autoimmune lung disease. Certain infections, such as atypical tuberculosis, histoplasmosis, and those caused by *Mycobacterium tuberculosis*, *Pneumocystis carinii*, and *Mycoplasma* spp., are readily diagnosed by BAL.¹⁵

In intubated patients with copious secretions, endoluminal stents, mucous plugs or clots, and purulent pneumonias, regular bronchoscopy can assist with pulmonary toilet and diagnosis. Toilet bronchoscopy is often particularly helpful for patients with impaired mucus clearance, such as active smokers, those with chronic obstructive pulmonary disease or cystic fibrosis, and those who have undergone pulmonary resection or lung transplantation.

Bronchopleural fistula and traumatic tracheobronchial injury are also readily diagnosed by flexible bronchoscopy. Suspicion of either entity should prompt evaluation

by endoscopy to definitively and expeditiously rule out such a contingency.

In addition to being used for diagnosis, the flexible bronchoscope is also invaluable for intubation and extubation in precarious airway situations. Small-caliber fiberoptic scopes can be used to define obscure or complex oropharyngeal anatomy, intubate the trachea, and serve as a guide wire over which an endotracheal tube can be passed securely. In these patients, the scope can also aid in withdrawal of the endotracheal tube and then a temporary trial of extubation, providing the ability for a rapid and secure reintubation should the extubation fail.

Percutaneous tracheostomy, the technique of choice for tracheostomy placement in many intensive care units, is considerably safer with the use of flexible bronchoscopy to ensure proper needle, guidewire, dilator, and finally tracheostomy tube placement.

Endobronchial Ultrasound

EBUS uses a small ultrasound probe fitted through a flexible bronchoscope port, and it enhances visualization of the soft tissue of the mediastinum adjacent to the bronchial lumen. Both radial probes, which provide a 360-degree image of the airway and surrounding structures, and convex probes, which provide a 90-degree image, can be used. Soft tissue characteristics of pulmonary nodules, lymph nodes, and tumors can be delineated. This imaging can effectively guide transbronchial FNA to sample pulmonary nodules, tumors, or lymph nodes with greater safety and accuracy. Although primarily used for determining the N staging component of the non-small cell type of lung cancer, EBUS can also help to define the T component if the tumor is adjacent to or approaching the tracheal or bronchial lumen. EBUS allows access to superior and anterior mediastinal lymph nodes, and it can be combined with EUS access of inferior and posterior mediastinal lymph nodes to allow a more comprehensive sampling of the mediastinum. An advantage of EBUS is that it is a minimally invasive office procedure. Disadvantages include the need for several passes of the needle for increased diagnostic accuracy, limited availability, and access to rapid on-site cytologic examination. In terms of pathologic assessment for metastasis, FNA can be performed only with a 22-gauge needle; therefore, comprehensive staging is subject to sampling error. In the setting of highly suggestive mediastinal lymph nodes (enlargement on CT or increased metabolic activity on positron emission tomography), EBUS with FNA has reported sensitivities of 82% to 88%.^{16,17} The negative predictive value is low (60%); therefore, a negative EBUS examination result for mediastinal lymph node staging should always be followed by surgical mediastinoscopy, which remains the gold standard for N staging in lung cancer.^{18,19}

Navigational Bronchoscopy

By coupling high-resolution CT imaging with electromagnetic guidance of bronchoscope-delivered biopsy instruments, investigators have sampled more peripheral lung lesions that are inaccessible to conventional

methods.^{20,21} Lesions that are beyond tertiary bronchioles, and some beyond secondary, are too small to accommodate even small biopsy bronchoscopes. Guiding brushes or biopsy forceps into the distal bronchial tree is assisted somewhat with fluoroscopy, but this is still an almost blind procedure. Real-time, three-dimensional CT has been coupled to an electromagnetic navigational system (the superDimension bronchus system, superDimension, Herzliya, Israel)²⁰ that can virtually guide the bronchoscopist in sampling peripheral lung lesions. The procedure is a two-stage process with preprocedure planning and the procedure itself. The patient is placed on an electromagnetic board that can define the biopsy probe location in three dimensions and in real time. The probe's location is then coupled with its anatomic location in a three-dimensional, superimposed CT scan map of the patient. The biopsy device is then virtually guided to the sample site. Thus far, only feasibility studies¹⁵ have been performed; they show promise for this new technique as a means to sample peripheral lung lesions heretofore accessible only by surgery or CT-guided biopsy. Barriers to more widespread use include cost, specialized imaging, technical training required, and lack of direct comparison studies between navigational bronchoscopy and transthoracic CT-guided biopsy techniques.

Flexible Bronchoscopy

Technique

Most diagnostic bronchoscopy procedures should be performed with an awake patient and with topical anesthesia. When the patient is already intubated or needs general anesthesia for a combined procedure, local anesthesia is not needed. In the outpatient setting, the room should be equipped with monitors for pulse, blood pressure, and continuous pulse oximetry readings.

The size and caliber of the bronchoscope usually depends on the size of the patient and the need for larger working channels if endobronchial intervention is anticipated. The field of vision is generally 80 degrees, and the angle of deflection is usually 160 to 180 degrees. The light source is connected with a flexible cord, and the transmission of light and the resultant resolution are based on the number of flexible fiberoptic bundles. More light, however, results in higher-caliber scopes.

Essential equipment consists of the bronchoscope, a light source, a camera, biopsy tools, suction and irrigation, and a sputum trap. After informed consent has been obtained, the patient is positioned in a seated position so that topical anesthesia (gargled and spray lidocaine solution) and gentle sedation (intravenous midazolam) can be administered. Either a transnasal or a transoral approach can be used in the awake patient, with the latter being better tolerated. The transnasal approach in the awake patient has the advantage of allowing visualization of the nasal and upper airway and better stabilization of the scope.²² Manipulation of the scope begins with the user holding the handle of the scope in the dominant hand, controlling the shaft with the nondominant hand, and viewing with an eyepiece or a video screen. By manipulating the thumb lever at the scope handle and rotating a

taut scope shaft, the tip of the scope can be pointed in all directions. After insertion, the trachea is examined, searching for luminal irregularities. The first landmark is the carina, which should be a sharp bifurcation; any fullness in this area should alert the operator to subcarinal adenopathy or mass involvement of the proximal airway. Orientation is maintained by noting that the membranous trachea is always posterior. The operator then systematically examines all airways to the segmental and subsegmental bronchus level. Digital photography and video are both superb for documenting any disease encountered. This documentation is a useful reference for monitoring disease progression at subsequent procedures or when planning a surgical resection. All pathology should be documented with detailed written descriptions or pictures of the actual findings. Depending on the findings, the surgeon can investigate further with washings, lavage, brushings, and biopsy. Once extracted, the bronchoscope should be irrigated with sterile solution and sent for disinfection.

Complications

In experienced hands, flexible bronchoscopy is safe. The complication rate reflects the patient's preexisting disease and degree of intervention and therapy. Injudicious suctioning can cause damage to the endobronchial lumen and bleeding, and careless advancement of the scope can disrupt anastomoses and bronchial stump staple lines, dislodge broncholiths or clots, and even cause perforation,²³ all with disastrous consequences. Patients with a history of asthma or bronchospasm should be approached with particular caution, and with appropriate medications at hand. Intubated patients in extremis who manifest refractory hypoxia, elevated airway pressure, or cardiac arrhythmias should undergo bronchoscopy with extreme prejudice only.

Most large series on flexible bronchoscopy cite morbidity rates of 0.05% to 0.1% and a mortality rate of approximately 0.01%.²⁴ Morbidity is generally defined as respiratory compromise, symptomatic bradycardia, hypotension, syncope, or arrhythmias. Although manipulation of the instrument may be responsible for some of these manifestations, morbidity is usually related to the administration of and reactivity to the premedication and local anesthesia. Transbronchial FNA, with ultrasound guidance, has a pneumothorax rate of approximately 5% in most series; this is minor in most cases. Significant hemorrhage is also a risk with FNA, because major vessels (e.g., the pulmonary artery) can be punctured inadvertently, but the risk is greatly reduced by Doppler ultrasound.

Rigid Bronchoscopy

Rigid bronchoscopy should be mastered by all thoracic surgeons because it can be lifesaving in dire situations; it is a diagnostic and therapeutic intervention availed by our specialty alone. Massive hemoptysis, foreign body removal, tracheobronchial obstruction by benign or malignant stricture, airway stenting and dilation, and laser therapy are best approached with the rigid

bronchoscope. This procedure is performed less often than flexible bronchoscopy, because general anesthesia is required, and because it is difficult to become facile with the instrument. However, despite its greater technical difficulty, the rigid scope has several distinct advantages over the flexible scope. First, the rigid scope allows accurate definition of central airway lesions; with it, the surgeon can palliate these lesions. Second, the rigid scope allows ventilation through its lumen, providing direct control of the airway in the setting of airway disease. Third, the instruments, including suctioning tools, that can be used with the rigid scope are larger and thus more effective than the small instruments developed for use with the flexible scope. Therefore, the rigid scope is more helpful in managing hemoptysis and in foreign body removal.

Massive hemoptysis, defined as 600 mL of blood over 24 hours, mandates urgent rigid bronchoscopy. Once bronchoscopy is introduced, the airway is controlled. The point of bleeding is then investigated, and intervention is planned and attempted. The use of a proximal eyepiece allows visualization without compromising ventilation. Rigid bronchoscopy does not obviate the use of the flexible scope; flexible bronchoscopy can be performed through the lumen of the rigid scope to further the examination and possible intervention of the airway disease.

Foreign body extraction is usually technically easier through the rigid scope because of the large caliber of the instrument. Again, airway control is established, and the foreign body can be extracted with forceps, or on some occasions with a balloon catheter should the offending mass be lodged in the airway. Rigid bronchoscopy is also a critical evaluation tool in the management of patients with malignant airway obstruction. In this setting, it provides not only diagnostic information in terms of anatomy and pathologic sampling for consideration of surgical resection, but it also provides excellent palliation of symptoms in the setting of unresectable disease.

Shortcomings of the rigid method include poor visualization of the terminal bronchi, the inability to perform instrumentation and suction with excellent vision, and the need for general anesthesia.

Technique

Elective rigid bronchoscopy is performed on an intubated, paralyzed, and sedated patient. Often, a laryngeal mask airway is used to secure the airway before the intubation. Communication with the anesthesia team concerning the plan and expectations of the procedure is essential to ensuring smooth transition between the rigid scope and the endotracheal tube and laryngeal mask airway. Adequate sedation and paralysis and optimal oxygenation via the rigid scope are essential. A shoulder roll is placed under the patient to allow maximal extension of the neck. The rigid scope is introduced with the thumb of the surgeon's nondominant hand braced on the upper incisors and, as when positioning a laryngoscope blade, the scope is advanced around the tongue until the arytenoids and cords are visible. The scope is then delicately insinuated between the cords, a maneuver that is

facilitated by the appropriate angle of insertion and by rotating the scope 90 degrees as it is passed between the cords. Once beyond the cords, the scope is rotated back so that its longer lip is placed posteriorly. The side port attachment is then fitted to allow oxygenation via the scope throughout the procedure. At this point, biopsy, foreign body removal, balloon tamponade, YAG laser, and stenting procedures can be executed. A myriad of specialized endobronchial instruments accompany most rigid bronchoscope sets. Should the need arise, modern laparoscopic instruments can be useful for difficult foreign body or biopsy extractions. Passage of the flexible bronchoscope, or videoscope, down the rigid scope provides more magnified viewing of the trachea and bronchi. Measurements for stenting and dilation procedures, as well as for tracheal resection, can be performed accurately with the dual scope configuration. The scope is then withdrawn carefully under direct vision. It is of utmost importance that the scope be stabilized by the operator at all times.

Complications

Although rare, complications of bronchoscopy do occur. Preprocedure steps include workup of any comorbid cardiac disease or coagulopathy, and careful consideration of the underlying pathology and the possible consequences of bronchoscopic intervention. An essential step to any procedure is the informed consent, which entails educating the patient about the possible complications and the probable effects on the patient.

The risks of rigid bronchoscopy are much more significant than those of flexible bronchoscopy, with the largest series quoting a morbidity of 5.1% and with 1.1% being construed as major.²⁵ The main reason for the increased risk encountered with rigid bronchoscopy is the greater likelihood that patients selected for this procedure have more complex pathologies and thus require more complex interventional procedures. The increased morbidity also reflects the increased use of the rigid scope for palliative procedures, and the increased risk of subsequent complications.

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ENDOSCOPIC THERAPIES FOR THORACIC DISEASES

Lara W. Schaheen • James D. Luketich

CHAPTER OUTLINE	
PHOTODYNAMIC THERAPY Definition and Mechanism of Action Technique Contraindications Lung Cancer Curative Intent Palliative Intent Barrett Esophagus and Esophageal Cancer Curative Intent Palliative Intent LASER ABLATION OF ENDOLUMINAL TUMORS Airway Esophagus BRACHYTHERAPY STENTS Expandable Metal Stents Silicone-Based Stents Technique Expandable Metal Stents Silicone-Based Stents	 Indications Benign Airway Strictures Malignant Airway Strictures Benign Esophageal Strictures Malignant Esophageal Strictures COMPARISON OF PALLIATIVE ENDOSCOPIC THERAPIES EVOLVING ENDOSCOPIC TREATMENT MODALITIES FOR BENIGN ESOPHAGEAL DISEASES Achalasia Zenker Diverticulum Open Approaches to Zenker Diverticulum Transoral Endoscopic Stapling Gastroesophageal Reflux Radiofrequency Therapy to the Lower Esophageal Sphincter Injection of Biopolymers at the Gastroesophageal Junction Endoscopic Plication of the Gastroesophageal Junction

The first recorded bronchoscopic intervention is attributed to Gustav Killian, who in 1897 used an esophagoscope to remove a piece of pork bone from a patient’s right mainstem bronchus.¹ A few decades later, Chevalier Jackson, now known as the father of endoscopy, became instrumental in the advancement of the field of rigid endoscopy of both the airway and esophagus.¹ Advancements in endoscopic technology have led to safer and more effective alternatives to surgery in non-operative candidates. This chapter focuses on endoscopic bronchial and esophageal interventions, including photodynamic therapy, radiofrequency ablation, laser ablation, brachytherapy, and stenting. Evolving endoscopic procedures for benign esophageal diseases (achalasia, Zenker diverticulum, and gastroesophageal reflux) are also discussed.

PHOTODYNAMIC THERAPY

Definition and Mechanism of Action

The principle of photodynamic therapy (PDT) lies in the preferential accumulation and subsequent activation of a photosensitizing agent in target cells, that when activated by light of a specific spectrum, results in selective tissue destruction. Photosensitizers used in thoracic surgery include the most commonly used purified hematoporphyrin derivatives (porfimer sodium [Photofrin]), chlorines (temoporphin or *m*-tetrahydroxyphenyl chlorin [*m*-THPC]), and 5-aminolevulinic acid (5-ALA). Each molecule is activated at an optimal wavelength of light absorption (630 nm for porfimer sodium and 5-ALA and 652 nm for *m*-THPC).

Although photosensitizers accumulate in all cells of the body, higher concentrations are retained within neoplastic cells and their interstitium within 1 to 4 days. Although the mechanism remains unclear, increased cellular proliferation, altered lymphatic drainage, and neovascularization are hypothesized to be responsible for the increased accumulation seen in neoplastic tissues. When laser light of the appropriate wavelength is delivered to neoplastic cells harboring the photosensitizer, it triggers a series of events culminating in cell destruction. The individual cells are bombarded with photons of a wavelength specific to the photosensitizer being used. The absorbed energy then acts as a catalyst in the formation of highly reactive oxygen species (e.g., superoxide anions, peroxide anions, singlet oxygen) whose primary cellular targets of photodamage include cellular membranes, amino acids, and nucleosides. It is important to remember that all cells will absorb some of the currently available photosensitizers; thus, surrounding normal tissue will be damaged to some degree and can limit the effectiveness of phototherapy.

Technique

The first step in PDT is the administration of the photosensitizer. Porfimer sodium (1.5 to 2.0 mg/kg) and *m*-THPC (0.075 mg/kg) are injected intravenously; 5-ALA (30–60 mg/kg) is given orally. Despite the benefit of being able to administer orally, increased tumor specificity and shorter duration of skin photosensitivity, 5-ALA has yet to gain widespread clinical acceptance.^{2,3} At the current oral dose, 5-ALA PDT accumulates preferentially in the mucosa and results in a more shallow tissue injury with necrosis only to a depth of 1 mm. Higher 5-ALA doses are avoided because of its increased side effects (e.g., malaise, nausea, vomiting, alopecia, transient elevation of liver enzymes). On the other hand, *m*-THPC is 100 times more photoactive than porfimer sodium, and it has a shorter elimination half-life; this results in deeper penetration and necrosis. As a result, *m*-THPC is typically reserved for use in malignant lesions that penetrate into submucosa or deeper.

The most commonly used photosensitizer is porfimer sodium, which has a depth of penetration of approximately 5 mm. It can be given in the outpatient setting, 1 to 4 days before endoscopic light application. It is most commonly used for endoluminal tumors of the airway and the esophagus, but other applications include anorectal, dermatologic, gastric, and hepatobiliary. Its short-term side effects include chest pain, odynophagia, and fever. Education of the patient is essential to minimize complications related to photosensitivity. Patients are instructed to avoid all sunlight and bright indoor light exposure for 30 days. Patients remain photosensitive for a period of 4 to 8 weeks, after which they can be gradually reexposed to sunlight.

Our preference has been to use conscious sedation and flexible endoscopy in most cases. A cylindrical diffuser fiber is used to deliver light therapy to the tumor. The sizes used are 1, 2.5, and 5 cm (Fig. 6-1). Choice of fiber length is based on technical ability to expose the tumor maximally to the light and to minimize the surrounding normal tissue

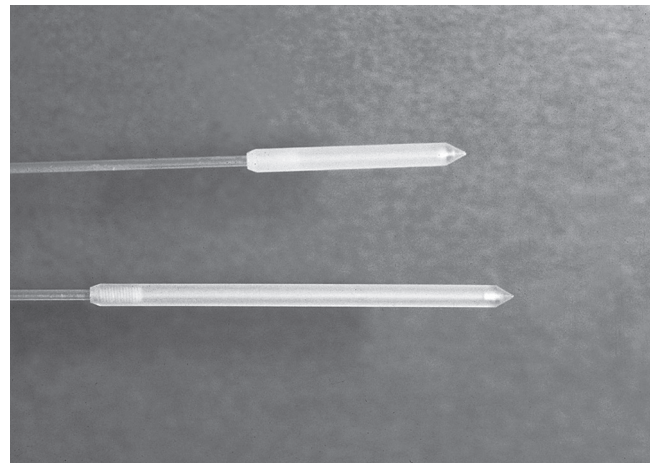


FIGURE 6-1 ■ Photodynamic therapy diffuser fibers: 2.5 and 5 cm.

exposure. The diffuser fiber is placed alongside the tumor. If this is not possible because of occlusion of the lumen, the tumor can be impaled with the probe. Caution should be exercised if impalement of the tumor is attempted, because without viewing and defining the length of tumor obstruction and determining where and whether patent distal lumen begins it can be somewhat risky. Multiple light illumination cycles may be needed, depending on the length of the tumor relative to the length of the probe. The diffuser must be positioned to minimize light delivery to normal tissues. Endoscopy is repeated at 48 hours and sometimes a third time after an additional 48 hours. During the repeated endoscopic procedures, necrotic debris is removed by irrigation and suction. Usually, further light treatments are delivered to the tumor at the time of repeated endoscopy.

In many cases, PDT can be performed in the outpatient setting; however, caution should be exercised in treating nearly obstructing lesions of the esophagus or central airways, because perioperative edema and necrotic tissue can temporarily worsen obstruction, leading to dyspnea or, in the case of esophageal obstruction, initial worsening of the dysphagia.

Contraindications

Contraindications to PDT are few. Patients suffering from porphyria or those who are allergic to porphyrins cannot receive porfimer sodium. PDT is contraindicated in the presence of an esophagorespiratory fistula or in tumors eroding into a major blood vessel. PDT is not recommended for the treatment of obstruction caused by extraluminal compression, since the effectiveness is limited because of an inability to expose the tumor to the light activation. Caution should be used in treating patients with underlying renal or hepatic dysfunction.

Lung Cancer

Curative Intent

Photodynamic therapy has been used in an investigational setting for the treatment of lung cancer since 1980.

It is currently approved as a treatment option for centrally located early stage 0 (TisN0M0) and stage 1 (T1N0M0) lung cancer. These small central tumors are rare, although some centers with active early screening programs, such as sputum cytology or light-induced fluorescence bronchoscopy, encounter these tumors more frequently.⁴ The results of PDT for these small lesions should be compared with the results of surgical resection. The central location of these tumors may necessitate complex airway reconstructions. PDT may be a suitable alternative to resection in patients who are not surgical candidates or as an adjunct in decreasing tumor burden prior to surgical resection. There are few central airway tumors that are discovered at a curable stage, because most of these early-stage, centrally located endobronchial lesions often go undetected by radiologic studies. In addition, only about 10% of all non-small cell lung cancer tumors occur in a central location. Superficially spreading tumors (<3 cm²) and small endobronchial tumors (<1 cm²) are reasonable targets for PDT. Initial complete response can be expected in 65% (<3 cm²) to 85% (<1 cm²) of superficial cancers and in 30% (>0.5 cm nodule) to 92% (<0.5 cm nodule) of nodular cancers.^{5,6} Long-term response rates (i.e., >1 year) vary between 30% and 80%.^{5,9} At 5 years of follow-up, complete response rates of up to 29% to 66% have been reported depending upon the exact size, location, and stage of the lesion.^{5,7}

In a study of 21 operative candidates treated initially with two courses of PDT, 52% (11 of 21) were free of tumor at 1 year.⁷ Curative PDT failed in the remaining 48% (10 of 21), and they were offered surgery; 8 consented. Of the 11 responders, 9 (9 of 21; 43%) did not require surgery (mean follow-up, 68 months), and 2 were operated on for a second primary lung cancer. It is noteworthy that of the patients who eventually underwent resection, 30% were found to have N1 disease, supporting the role of resection when possible. Our policy has been to reserve curative PDT for patients with significant comorbid factors or those who refuse pulmonary resection. In this group of patients, PDT is an excellent option, with an expected 1-year survival of up to 80%.¹⁰ In our initial experience of treating 10 superficial cancers, a complete response was seen in 70% at a follow-up of 30 months.⁸ In other prospective series, 80% to 93% of nonsurgical candidates were alive at 5 years of follow-up.^{5,11}

Palliative Intent

Resection should continue to be the main therapy for early-stage non-small cell lung cancer, because only a relatively small number of patients will have curable central tumors that are suitable for PDT with curative intent. A much larger group of patients with advanced, inoperable, or obstructive central lung cancers may benefit from palliative PDT. In this situation, the therapeutic goal should be symptomatic relief and preservation of quality of life and functional status. Patients most notably find improvement in obstructive symptoms, such as dyspnea or hemoptysis, yet the need for strict photosensitivity precautions should be considered in patients with limited survival.

A cohort of 175 patients with endobronchial non-small cell lung cancer treated with PDT was observed prospectively for a period of 14 years.¹¹ Most patients had squamous cell carcinoma (89.3%), and treatment by conventional modalities, including chemotherapy, radiotherapy, laser ablation, and surgery, had failed in 73.1%. The mean number of treatments was 2.8 per patient. After multivariate analysis, stage was found to have the most significant effect on survival. Poor performance status (i.e., Karnofsky performance status < 50) negatively affected outcome in advanced-stage tumors (IIIA-IV). However, patients with a low Karnofsky performance status (<50) secondary to pulmonary symptoms still derived benefit from PDT. Prolonged survival (12 to 37 months) was observed in 66% of stage IIIA-IV patients with poor performance. The median survival for the entire group was 7 months. Of the 44 patients with stage IV disease, 21% survived 12 months or longer.

Our initial experience with palliative PDT involved 44 patients with lung cancer and symptoms related to obstruction and hemoptysis.¹⁰ Thirteen patients required a second treatment course at a mean of 2.3 months for recurrent symptoms. There were no fatalities, and 82% of treatments were performed without complications. Hemoptysis was effectively palliated in 90% of treatment courses. Obstruction was successfully palliated in 59% of treatments. Median survival was 2.3 months. PDT has also been shown to be effective in palliating hemoptysis and dyspnea in patients with endobronchial metastases from malignant neoplasms of nonpulmonary etiology.¹² An example of a patient who was treated for a complete lobar obstruction is demonstrated in [Figures 6-2 through 6-6](#). In general, we have not used PDT for massive hemoptysis for practical reasons; those best suited have subacute but persistent hemoptysis of low volume and have visible endoluminal granular tumor with a bleeding surface area.

In a randomized prospective study, PDT was compared with standard laser techniques for inoperable non-small cell lung cancer.¹³ The bronchoscopic response rate (PDT, 38.5%; laser, 23.5%) and symptomatic improvement at 1 month were equivalent in each group. PDT

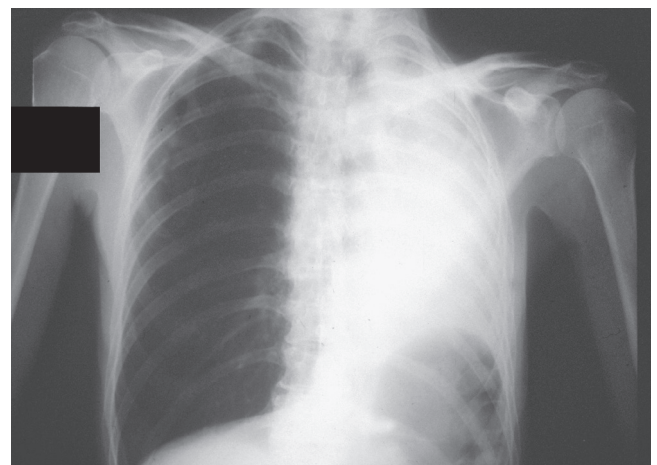


FIGURE 6-2 ■ Radiographic picture of lung cancer obstructing the left mainstem bronchus before photodynamic therapy.

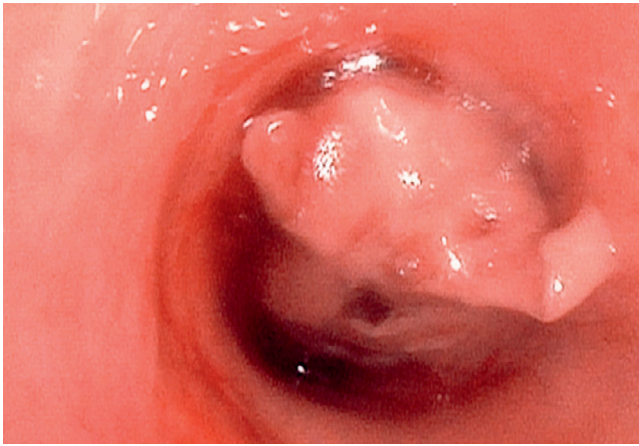


FIGURE 6-3 ■ Bronchoscopic picture before photodynamic therapy.

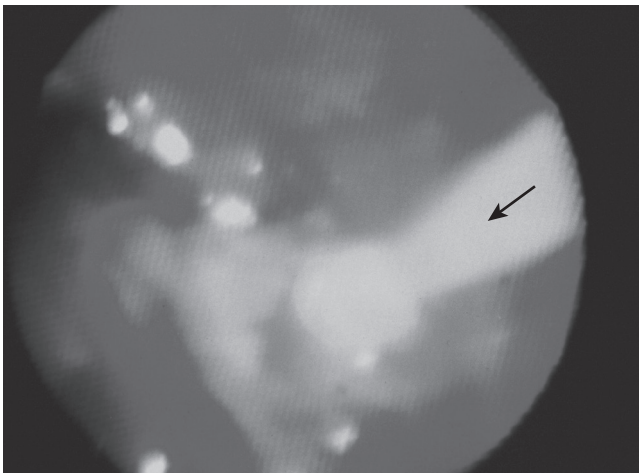


FIGURE 6-4 ■ Bronchoscopic picture during photodynamic therapy. Probe impaled into tumor during treatment (arrow).

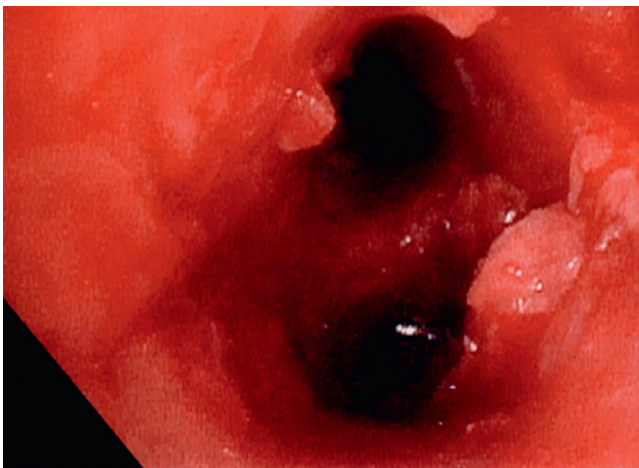


FIGURE 6-5 ■ Bronchoscopic picture after photodynamic therapy.

provided significantly longer-lasting relief (50 days vs. 38 days) and improved median survival (265 days vs. 95 days) compared with laser resection. However, this finding may be explained in part by the lower proportion of advanced-stage tumors seen in the PDT group.



FIGURE 6-6 ■ Radiographic picture after photodynamic therapy.

In general, PDT is well tolerated with minimal morbidity. All bright light and direct sunlight exposure must be avoided initially. Patients remain photosensitive for 4 to 8 weeks, after which they can be gradually reexposed to sunlight.^{14,15} Inadvertent direct sunlight exposure has been reported to cause first- and second-degree burns in up to 10% of patients.¹⁶ The restrictions imposed by photosensitivity and their potential impact on quality of life should be considered before treatment. Immediate postprocedure mortality for lung and esophageal PDT (30-day) ranges from 2.6% to 7.1%, but in large part is due to the comorbidities and advanced stage of many of the patients in these series.^{11,13-15}

Barrett Esophagus and Esophageal Cancer

Curative Intent

The management of high-grade dysplasia associated with Barrett esophagus is controversial. In the recent past, most surgeons advocated esophagectomy because of the associated risks of occult malignant disease and lymph node metastases.¹⁷ On the other hand, concerns related to the morbidity and mortality of esophagectomy have led some clinicians to advocate alternative approaches, such as surveillance, endoscopic mucosal resection, or mucosal ablation.¹⁸ In our experience, we have reported good results and a mortality of approximately 1% with a minimally invasive esophageal resection for patients with Barrett esophagus and high-grade dysplasia.^{19,20} Currently available mucosal ablative methods include

endoscopic mucosal resection, PDT, laser ablation, argon plasma coagulation, and radiofrequency ablation.²¹⁻²⁴ All these techniques attempt to resect or eradicate Barrett epithelium with the hope that it will be replaced by squamous epithelium. Unfortunately, in some instances, islands of columnar epithelium may recur under a normal-appearing squamous epithelial layer leading to difficult detection.²⁵ This problem is addressed by other endoscopic techniques, such as initial endoscopic mucosal resection or endoscopic submucosal dissection, whereby the esophageal mucosa is actually resected piecemeal. An in-depth discussion of endoscopic resection techniques is beyond the scope of this chapter, but it should be noted that this approach has become the standard of care in many centers for properly selected patients.

PDT is arguably the most established of these ablative techniques. In a large single-institution study, PDT was combined with the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser to treat 73 patients with high-grade dysplasia and 14 patients with low-grade dysplasia.²⁶ All patients were observed endoscopically for 12 months. Regression to low-grade dysplasia or no dysplasia was observed in 88% of high-grade dysplasia cases and in 93% of low-grade dysplasia cases. Complete eradication of Barrett epithelium occurred in only 9% of patients after PDT alone. In focusing on the PDT-treated area, a 49% eradication rate was reported. The addition of laser ablation to residual areas of Barrett epithelium increased the eradication rate to 87%. In a 5-year prospective randomized multicenter international trial, PDT with Photofrin plus omeprazole was compared with omeprazole only for the treatment of Barrett esophagus with high-grade dysplasia.^{27,28} Complete ablation of high-grade dysplasia was observed significantly more often in the Photofrin group compared with controls (77% vs. 39%). Progression to esophageal cancer was significantly decreased in the Photofrin group (13% vs. 28%). Treatment-related side-effects were more common in the Photofrin group (94% vs. 13%). Strictures developed in 36% of patients, with 98% resolving after dilation. Notably, the benefits on dysplasia resolution and cancer progression persisted at 5-year follow-up. At 5 years, the study demonstrated that the addition of PDT with Photofrin to proton pump inhibitor therapy resulted in a 38% increase in eradication of Barrett esophagus with high-grade dysplasia, a 14% decrease in the incidence of invasive carcinoma, and a longer time to progression to cancer.²⁹

PDT can also be used to treat early-stage esophageal tumors (T1-T2) in patients who are not candidates for surgical resection. In a group of patients that included mostly T1 tumors (12 of 13), regression to Barrett esophagus with low-grade dysplasia or without dysplasia was observed in 77% of patients (10 of 13).²⁶ At our center, PDT with curative intent is reserved for patients with prohibitively high operative risk. All others undergo minimally invasive esophagectomy.¹⁹ We have reviewed our institutional experience, from 1997 to 2005, using PDT for patients with high-grade dysplasia or superficial esophageal cancer.²⁸ A total of 50 patients, who either refused or were unfit for surgery, had PDT with curative intent. The majority of patients (70%) had high-grade dysplasia or small ($\leq$ T1) tumors. At a median follow-up

of 28 months, 32% of patients were alive without recurrence, 30% were alive with recurrent disease, and 38% were deceased from cancer or other causes. The patients with recurrences were retreated with PDT. There was no procedure-related mortality, and the stricture rate was 42%, which were generally easily dilated. Although these results are clearly inferior to esophageal resection, endoscopic ablation appears to be a suitable treatment option for nonsurgical candidates. In another cohort of 28 patients with high-grade dysplasia treated with minimally invasive esophagectomy, 96% remained free of recurrence at 13 months.¹⁹ These results were corroborated by other investigators who have observed excellent long-term survival (100%) after esophagectomy for high-grade dysplasia.²⁹

In the treatment of Barrett esophagus with high-grade dysplasia, PDT is well tolerated with usually transient side effects, such as nausea, regurgitation, constipation, odynophagia, dysphagia, weight loss (average of 6 kg), and noncardiac chest pain.^{30,31} Other complications include stricture, tumor growth below the PDT-induced scarring, and Barrett esophagus and tumor recurrence.³² In our experience, approximately 30% of patients with high-grade dysplasia undergoing PDT will develop an esophageal stricture.²⁸ Stricture is minimized by decreasing the intensity of light therapy compared with doses used for larger tumors.

Another endoscopic treatment modality for patients with Barrett esophagus is radiofrequency (RF) ablation. The components of the system include a sizing balloon (18 to 34 mm), a 3-cm balloon-based bipolar RF electrode, and a dedicated RF generator. The sizing balloon is used to ensure proper contact between the balloon electrode and the esophageal mucosa. The RF mucosal ablation is achieved by using a power of 300 W to deliver 10 to 12 J/cm². The coagulum is then removed from the esophageal surface by irrigation and suction. The maximum ablation depth is 1 mm, which translates to a depth of injury that is superficial to the muscularis mucosa.³³ The depth of injury is highly reproducible and has been confirmed in the human esophagus. In addition to the circumferential balloon electrode, the approval of an RF ablation device that can be attached to the end of a flexible esophagoscope can be used to ablate focal areas of esophageal mucosa. Encouraging results have been published showing complete eradication of Barrett mucosa and intramucosal carcinoma when RF ablation was used in combination with endoscopic mucosal resection.³⁴

With further analysis, it seems that patients with high-grade dysplasia without visible raised or nodular lesions are the optimal candidates for endoscopic management with RFA. The presence of visible lesions requires the addition of a mucosal resection technique to allow for adequate staging and treatment.

Visible lesions containing high-grade dysplasia or intramucosal carcinoma can be treated successfully with RFA, but only as an adjunct to a mucosal resectional technique such as endoscopic mucosal resection.

The Surveillance vs. Radiofrequency Ablation (SURF) trial was a randomized multicenter trial conducted in Europe that randomized patients with a confirmed histologic diagnosis of Barrett esophagus with low-grade dysplasia to treatment with either RFA or standard

endoscopic surveillance (at 6, 12, 24, and 36 months). RFA was demonstrated to significantly reduce the risk of progression to high-grade dysplasia or esophageal adenocarcinoma compared with standard endoscopic surveillance (1.5% vs. 27%) while also reducing the risk of progression to esophageal adenocarcinoma (1.5% vs. 8.8%).

Palliative Intent

Stenting of the esophagus is often the most commonly used modality to palliate dysphagia³⁵; however, PDT offers some advantages in certain clinical situations. In addition to relieving obstruction, PDT can often be used to control or prevent tumor bleeding. It can also prevent the globus sensation associated with stents in the proximal esophagus and the reflux symptoms observed with stents bridging the gastroesophageal junction. PDT is a potential alternative to stenting for endoluminal cancers in both of these locations.

PDT has been compared with laser ablation in a randomized trial. PDT was equivalent to laser ablation for malignant dysphagia and was associated with a lower rate of perforation (PDT, 1%; laser, 7%).³⁶ We reviewed our experience with PDT in 215 patients suffering from obstructing esophageal cancer.³⁷ The most common pathologic process was adenocarcinoma (83%). The distal esophagus was involved in 71% of cases. Dysphagia improved in 85% of patients, and bleeding was successfully controlled in 90%. Stenting was subsequently required in 24% of patients. As expected, median survival was poor at 4.9 months; however, effective palliation lasting 3 to 4 months was provided to many of these unfortunate patients. In another prospective series of 77 patients for whom conventional therapy had failed or who were deemed unfit for surgery, investigators reported a median survival of 6.3 months after PDT.¹⁴ The only significant predictor of mortality was clinical stage. Photosensitivity appears to be an acceptable tradeoff in these patients. In one study using satisfaction questionnaires, patients reported that the ability to swallow food was more important than the limitations of photosensitivity.²⁹ In most cases, the potential benefits of PDT far outweigh the risk of complications.

In patients with obstructing aerodigestive tumors, PDT can result in adverse events. Esophageal strictures (4.8% to 5.2%), perforation (0% to 9.1%), and esophagorespiratory fistulas (0% to 5.2%) are among the most serious PDT-related complications.^{7,14,38-40} Esophageal perforation and fistula are probably best treated by esophageal stenting. Other factors contributing to the mortality rate and risk of esophageal perforation include the generally poor performance status of this particular group of patients with advanced tumors and the fact that some patients with obstructing tumors receive concurrent radiation therapy and chemotherapy.

LASER ABLATION OF ENDOLUMINAL TUMORS

Although several types of lasers including carbon dioxide, argon, potassium titanyl phosphate, and diode are

available throughout medicine, the most commonly used endoscopic laser in thoracic surgery is the Nd:YAG laser. The Nd:YAG laser energy can be delivered through a small-caliber fiberoptic conduit, thus making it ideal for use with the flexible bronchoscope or esophagoscope. Adjustments in power level allow either photocoagulation (low power) or thermal necrosis (high power) of tissue. Depending on the energy level selected, the laser can penetrate tissue depths ranging from millimeters to several centimeters in depth. Airway and esophageal Nd:YAG laser procedures can be performed safely with sedation alone. During the past 25 years, experience with laser photoresection has led to the emergence of clinical safety guidelines and the characterization of lesions ideally suited to laser therapy. Communication among the surgeon, the anesthesiologist, and the rest of the operating team is essential to minimize risks to the patient and staff during laser procedures. The fractional inspired oxygen (FiO₂) should be set to the lowest possible level required to maintain adequate oxygenation, and it should never exceed 40% because of the risk of airway fire. Experienced centers have published a set of simple rules to increase the safety of lasers in the airway (Box 6-1).⁴¹ These rules, often referred to as the “Ten Commandments,” are also applicable to the esophagus. Other investigators have contributed an excellent mnemonic, “The

BOX 6-1 Adaptation of Dumon's 10 Commandments of Pulmonary Laser Photoresection

1. Know the anatomy. The aortic arch, the pulmonary artery, and the esophagus are danger zones.
2. Have a well-prepared laser team that includes an anesthesiologist specialized in conscious sedation and two assistants equipped with emergency response procedures.
3. Any endoluminal growth is amenable to lasering, but purely external compression is a contraindication.
4. Use the rigid bronchoscope with two suction catheters for high-grade obstruction, especially if a malignant neoplasm is involved.
5. Monitor blood gases and cardiac performance. At the least sign of hypoxemia, interrupt treatment long enough to oxygenate the patient, if necessary under closed-circuit conditions.
6. Fire parallel to the wall of the airway. Never aim directly into it.
7. Coagulate at will but avoid using the laser at high-power settings; mechanical resection after laser coagulation is preferable to laser resection alone whenever possible.
8. Control hemorrhage. Even slow bleeding will lead to hypoxemia if it is left unattended.
9. Terminate each procedure with a thorough laser irradiation of the resected area and a tracheobronchial toilet to remove all secretions or debris.
10. Observe and monitor the patient in the recovery room for a reasonable time.

Adapted from Dumon JF, Reboud E, Garbe L, et al: Treatment of tracheobronchial lesions by laser photoresection. Chest 81:278-284, 1982.

BOX 6-2 “Rule of Fours” for Optimal Outcome from Endobronchial Nd:YAG Lasering

LESION

- Length of lesion $\leq$ 4 cm
- Duration of collapse $<$ 4 weeks

INITIAL SETTINGS

- Power: 40 watts
- Pulse duration: 0.4 second

DISTANCES

- Endotracheal tube to lesion $>$ 4 cm
- Fiber tip to lesion: 4 mm
- Flexible bronchoscope to tip: 4 mm

TECHNIQUE

- FiO₂ $<$ 40%
- Number of pulses between cleaning $<$ 40
- Procedure time $<$ 4 hours
- Total number of treatments $<$ 4
- Life expectancy $>$ 4 weeks
- Laser team: 4 persons

Nd:YAG, Neodymium:yttrium-aluminum-garnet.

Adapted from Lee P, Kupeli E, Mehta AC: *Therapeutic bronchoscopy in lung cancer: laser therapy, electrocautery, brachytherapy, stents, and photodynamic therapy*. *Clin Chest Med* 23:241–256, 2002.

Rule of Fours,” to remember favorable lesion characteristics, power and pulse settings, and techniques to optimize the results of airway lasering (Box 6-2).⁴² Lesions of the central airways less than 4 cm in length, localized to one wall, and protruding through the lumen (e.g., exophytic, pedunculated) without complete obstruction are ideal for laser ablation.⁴²

Airway

Symptomatic relief from cough, dyspnea, hemoptysis, and postobstructive pneumonia and accelerated weaning from mechanical ventilation can be achieved in approximately 80% of patients with malignant airway obstruction who are treated with laser therapy.⁴² In a series of more than 1800 patients treated with Nd:YAG laser, 93% had improvement in symptoms and quality of life.⁴³ Even in patients with advanced tumors for whom radiotherapy and chemotherapy have failed, 64% may experience symptomatic relief after laser ablation.⁴⁴ Nd:YAG lasering is successful in controlling hemoptysis in 60% of patients; however, recurrence should be expected within 30 days of treatment.⁴⁵ At least 50% of patients can be extubated immediately after laser treatment.⁴² There is no difference in response between primary and metastatic airway lesions. Success rate decreases from 90% to 60% in patients with central airway tumors.⁴⁶

The overall complication rate of laser ablation varies between 0% and 2.2%.⁴² Serious complications include perforation of vascular structures and endobronchial fire, which usually involves the endotracheal tube, the flexible bronchoscope sheath, or suction catheters. As stated

before, fires can be avoided by keeping the FiO₂ below 40%, using nonflammable anesthetic agents, and keeping the scope and field as clean as possible. Hemorrhage from the tumor, pneumothorax, and pneumomediastinum are other recognized complications of airway lasering.

Esophagus

Malignant tumors of the esophagus are also amenable to treatment by Nd:YAG laser. Depending on the size of the tumor, several weekly treatments may be necessary to provide significant relief from obstruction. Lasering can also be used to recanalize a tumor in preparation for stenting. The best candidates for laser therapy are patients with small ($<$ 5 cm) exophytic tumors located in the middle esophagus, at the site of a previous esophagogastric anastomosis, or above a stent. The incidence of laser-related esophageal perforation varies between 0% and 6%.^{47,48} Recurrence of dysphagia can be expected within 4 to 6 weeks of treatment. The combination of laser ablation with radiotherapy has prolonged the dysphagia-free interval in patients with malignant obstruction.⁴⁹

BRACHYTHERAPY

Brachytherapy can be defined as the placement of interstitial or intracavitary radioactive sources to facilitate the safe delivery of high radiation doses with relative sparing of normal surrounding tissues. High-dose-rate brachytherapy allows the delivery of high doses of radiation to the airway during a short period with minimal effect to surrounding tissue. Typically, bronchoscopy is performed with sedation and local anesthesia. A blind-ended 6-French afterloading catheter is passed through the working channel of a bronchoscope, and dummy seeds are placed within the catheter to confirm its position by fluoroscopy. The catheter is taped securely, and the patient is transferred to the radiation suite. Radiation seeds (¹⁹²Ir) are then placed in the afterloading catheter. Typically, a few treatments will be required over 2 to 3 weeks, each session requiring only 10 to 15 minutes of radiation exposure. An advantage of brachytherapy over Nd:YAG laser therapy is the greater depth of penetration (0.5 to 2 cm) compared with laser therapy, making it more suitable for tumors with a predominantly extraluminal component. A disadvantage is that symptomatic improvement will be slower to occur than with PDT or Nd:YAG laser therapy. On longer follow-up, bronchitis with stricture (9% to 13%) or hemoptysis (7%) can develop as a result of brachytherapy^{42,50}; these two complications are more commonly encountered with high radiation doses to the central airways. Symptomatic improvement after brachytherapy occurs in 72% to 94% of cases, depending on the symptom.^{42,51} Endobronchial tumor regression may be observed in 54% to 94% of patients.⁴² Complete histologic response has been documented in up to 72% of early-stage lung cancers.⁵² Finally, there are prospective randomized data suggesting that the combination of brachytherapy and external beam radiation leads to further improvement in symptom-free interval and quality of life.⁵³

STENTS

Malignant endoluminal obstruction and extraluminal compression by enlarged lymph nodes or tumor are common indications for stenting of the airway or esophagus. The two major types of stents used in thoracic surgery are expandable metal stents and silicone-based stents.

Expandable Metal Stents

Expandable metal stents are constructed with cobalt alloys (Wallstent, Schneider), stainless steel (Gianturco, Cook), or a nickel-titanium alloy referred to as *nitinol* (Esophacoil [Medtronic] or Ultraflex [Microvasive]). These materials are resistant to corrosion and are biologically inert, even in patients who are allergic to nickel. The wire stents can be woven (Wallstent), knitted (Ultraflex), or bent into a zigzag (Gianturco) or coil (Esophacoil) configuration. The stent design influences its retraction properties (i.e., shortening). Retraction percentage is highest with the coil configuration and lowest with the zigzag configuration. The shape memory characteristics of the materials allow the stent to reexpand to its original tubular shape, even when it is compressed into a delivery system. The available systems can deploy the stent from the proximal end, the center, or the distal end. Proximal delivery is better suited for proximal strictures, and distal delivery is best for strictures of the gastroesophageal junction. Expandable metal stents can also be partially covered with polyurethane or silicone (e.g., Alimaxx-E, Alveolus; Polyflex, Microvasive; Ultraflex). Covered designs help to reduce tumor ingrowth but have a propensity for migration.⁵⁴ The wide range of available diameters and lengths allows expandable metal stents to fit most upper aerodigestive strictures. More recently, endoluminal clips that are easy to deploy have been used successfully to secure the upper border of the stent to the esophageal mucosa to minimize migration.

Silicone-Based Stents

Silicone-based stents are made of silicone rubber (Silastic, Dow Corning), a ubiquitous component of industrial, household, and medical equipment. Celestin esophageal tubes have fallen out of favor because of the need for an open gastrotomy for anchoring and the higher complication rate in comparison with expandable metal stents.⁵⁵

Flanged (Hood, Hood Laboratories, Pembroke, MA) or studded (Dumon, Bryan Corp., Woburn, MA) cylindrical silicone stents are used in the trachea or bronchi. T-, Y-, and T-Y-shaped silicone stents are also available to treat tracheal and proximal tracheobronchial strictures. If a silicone stent has to be shortened to fit the patient's airway, the manufacturer can provide a customized replacement on request. Silicon stents play an important role in problem areas at or near the cricopharynx. In this location, the funnel-like proximal end may sit above the cricopharynx for intervals of up to several weeks to allow a complex injury or fistula to heal. We also have used these with great success in proximal

tracheal strictures in the shape of a T-tube for proximal airway injuries or a T-Y for extension into the distal airway near the carina.

Technique

Expandable Metal Stents

The procedure can be performed with either conscious sedation or general anesthesia. The stricture is identified endoscopically and measured. Esophageal stents are available in a wide range of lengths (60 to 150 mm), but in contrast to airway stents, most have a similar maximal internal diameter (17 to 23 mm). If the opening of the stricture is too small to accept the endoscope, the lumen may require dilation and laser ablation before length can be assessed accurately. Fluoroscopy is then used to mark the location of the stricture on the patient's skin. This is done with two radiopaque markers (e.g., small stylets, paper clips) that are aligned with the tip of the endoscope when the endoscope is positioned at the proximal and distal edges of the stricture. Alternatively, some clinicians prefer to inject the submucosa at the proximal and distal ends of the tumor with a radiopaque liquid (Conray). Once the measurement of the tumor length is completed, the proper stent is selected. In general, we use an 18- to 23-mm-diameter stent that is 1 to 2 cm longer than the stricture to avoid crimping and infolding of the ends. A guidewire is passed through the stricture, and the endoscope is withdrawn. Under fluoroscopic control, the delivery system is inserted over the guidewire through the stricture and aligned with the skin or mucosal markers. The stent is deployed and expands within the lumen. Proper positioning and deployment are confirmed fluoroscopically and endoscopically. A postprocedure chest radiograph (in all cases) and barium esophagogram (in esophageal cases) are obtained. Expandable metal stents are popular because they are easier to insert and do not require expertise in rigid bronchoscopy. Silicone stents are more challenging to place but may be less problematic in the long term for specific applications. We prefer these stents for patients with benign strictures of the proximal airway or esophagus.

Silicone-Based Stents

Unless the patient has a tracheal stoma, rigid bronchoscopy is needed to insert a silicone-based stent. A chest tube and the stent are passed over a rigid scope in sequence. The chest tube serves as a pusher to deliver the stent over the rigid scope. For Y-shaped stents, the right mainstem bronchus limb is invaginated, and the rigid scope is passed through the left mainstem bronchus limb. After it is positioned, the scope is pulled back within the tracheal limb, and biopsy forceps are used to push out the right-sided limb. An alternative technique is to guide the right-sided limb into the right mainstem bronchus with a Fogarty catheter while positioning the proximal portion of the stent endoscopically. A complete technical description of rigid endoscopic stent insertion has already been published.⁵⁶ Table 6-1 compares some of the features of silicone and metal stents.

TABLE 6-1 Characteristics of Silicone and Expandable Metal Stents

Stent Type	Description	Method of Insertion	Pros	Cons
Silicone Based				
Internal	Made of Silastic rubber Straight or Y shaped Studded (Dumon) Flanged (Hood) Silicone mesh with outer polyester coating (Polyflex)	Rigid endoscopy	Resistance to lateral compression Prevents ingrowth Easier to remove	Eliminates mucociliary clearance (airway) Propensity for mucus plugging (airway) Propensity for dislodgment (airway and esophagus)
External	T or T-Y shaped	Rigid bronchoscopy or per tracheal stoma	Maintains tracheal stoma Tracheal port allows suction Prolonged relief of dyspnea in nonoperative candidates Custom-fitted	Cosmesis Regular maintenance (irrigation, suction)
Expandable Metal				
Internal, partially or fully covered or noncovered	Nickel-titanium (Ultraflex) Cobalt-steel (Wallstent) Steel (Gianturco) Fully covered (Alimaxx-E, Aero)	Flexible endoscopy	Easy to insert Adapt to irregularly shaped stricture Potentially removable (fully covered)	Weaker expansile force Granulation Allow ingrowth of tumor (noncovered) Nonremovable (noncovered)

Indications

The recommended definitive treatment of focal benign airway strictures is surgical resection. Stenting is indicated for strictured or malacic airways that are not amenable to resection or in nonsurgical candidates in whom dilation or laser resection has failed. Stenting can also be used as a bridge to surgery in patients needing time for their general condition to improve or for the scar to mature. It should be clear that stenting of benign strictures as definitive treatment is suboptimal therapy, as 40% of patients will need reintervention.⁵⁷

Malignant airway strictures, especially those caused by extrinsic tumor compression, can be managed with stenting. In the esophagus, stents are indicated for obstruction or esophagorespiratory fistula associated with malignant disease.

Benign Airway Strictures

Stenting of benign airway strictures should be regarded as second-line therapy, reserved for situations in which surgical resection is not possible. In comparison with the shorter survival expected with malignant strictures, patients with benign strictures live longer and require further intervention over time. For this reason, silicone stents are recommended. Previous experience with silicone stents for benign strictures in nonoperative candidates has been relatively good.^{58,59} Of 112 patients with T stents, only 5 (4.5%) required removal for obstructive problems, and 85% were managed successfully for periods of 3 months to more than 5 years.⁵⁹ In another case series, 94% of patients with benign strictures had successful palliation of obstruction.⁵⁷ Only 3 of 54 silicone stents (5.6%) needed removal or replacement for migration or compression, and the mortality rate was 12.5% at 4 years

of follow-up. Other studies involving smaller numbers of patients (6 to 22) reported symptomatic and spirometric improvement after stenting.⁶⁰⁻⁶² In one report, it was acknowledged that granulation tissue is a common finding (up to 80% of patients), which may lead to removal in 20% of cases.⁶²

Our experience supports the use of silicone-based stents over expandable metal stents for benign strictures. In a cohort of 36 patients, reintervention was necessary in 61% of patients at a mean of 6 months. Nd:YAG laser was required to ablate granulation in a significantly higher number of patients with metal stents compared with silicone stents. One in five expandable metal stents had to be removed for complications. Extirpation of uncovered metal stents required thoracotomy in 33% of cases. Despite their relative ease of insertion, uncovered expandable metal stents should probably be avoided in nonsurgical candidates with benign airway strictures. A newer silicone-based stent (Polyflex) may be a reasonable temporizing measure. It may be useful in benign strictures associated with inflammation, in which case luminal patency can be maintained while airway remodeling and fibrosis take place. Although the stent is made of silicone, the outside polyester mesh coating can render removal difficult.

Malignant Airway Strictures

Because most patients with malignant airway obstruction usually have a limited survival from the time of stenting, the emphasis should be placed on preserving quality of life more than on the particular type of stent used. Surgeons familiar with silicone stents have achieved relief of dyspnea in 87% to 94% of patients.^{57,63} Complications, including migration and occlusion, occurred in 12.5% to 23.1% of stents placed. Mortality was 68.7%, at a mean

interval of 7.6 months.⁶³ Polyurethane-covered expandable metal stents can also provide significant improvement in dyspnea and Karnofsky score; however, up to 55.6% of patients experience complications, including stent migration in 22.2%.⁶⁴ Although covered stents prevent tumor ingrowth, they have a propensity for dislodgment.

In malignant airway obstruction, stenting is part of a multidisciplinary approach to palliation. In the majority of the studies discussed before, patients received chemotherapy or radiation therapy in addition to stenting. The importance of adjuvant therapy has been highlighted in a prospective trial.⁶⁵ In 22 patients with tracheobronchial strictures treated by stenting, 50% eventually had the stent removed after appropriate radiation therapy and chemotherapy regimens.

We recently reviewed 53 cases in which expandable stents were used to treat tracheobronchial obstruction.⁶⁶ Concurrent interventions included balloon dilation (29%), Nd:YAG laser (29%), PDT (23%), rigid bronchoscopy with débridement (15%), and brachytherapy (2%). Bronchoscopic patency was achieved in 92% of patients. Radiographic improvement was noted in 46% of patients with lung collapse. Reintervention was required in 19 patients (36%) for obstruction by mucous plugging or granulation tissue. The median post-stenting survival was relatively short, at 41 days.

Benign Esophageal Strictures

In benign esophageal strictures, routine use of stents cannot be recommended in light of a 41% rate of stent-induced restenosis and almost uniform (91%) recurrence of dysphagia.^{67,68} In some selected cases when an anastomotic stricture is recalcitrant to repeated endoscopic dilations, insertion of an esophageal stent that is potentially removable (e.g., Alimaxx-E, Polyflex) may be an acceptable option. It has even been suggested that this approach may be as effective clinically and less costly than repeated endoscopic dilations.⁶⁹ We have reported our initial experience with removable esophageal stents (Polyflex) to manage at least 25 patients with benign esophageal strictures, including those associated with an anastomotic leak after esophagectomy.⁷⁰ Although dysphagia was significantly improved after stenting, distal migration was a significant problem that occurred in more than two thirds of the patients. Stenting failed to seal anastomotic leaks and malignant tracheoesophageal fistula in 38%. It is hoped that future changes in removable esophageal stent design will address the significant problem of migration. The recent introduction of endoscopically placed clips has allowed us to fix the upper border of the stent to the esophageal wall with good short-term success in preventing migration.

Malignant Esophageal Strictures

Depending on the referral pattern, up to 80% of malignant esophageal tumors will be inoperable at the time of diagnosis. Endoscopic palliation with laser or stents assumes a preponderant role in providing relief from dysphagia to many of these patients. During the past

decade, advances in expandable stent technology have led to smaller, more flexible delivery systems that are easier to manipulate than their silicone counterpart. These attributes often allow successful stent deployment with minimal or no endoscopic dilation, thereby minimizing the risk of perforation.

Both silicone-based and mesh wire stents are susceptible to tumor overgrowth above and below the stent, leading to recurrence of esophageal obstruction. In addition, ingrowth of tumor through noncovered mesh wire interstices can occur. In the absence of an esophagorespiratory fistula, the decision to use a covered stent is influenced by the potential for recurrent obstruction by tumor ingrowth and the likelihood of stent migration. When tumor overgrowth or ingrowth occurs, therapeutic modalities including PDT, laser, and further stenting (i.e., placement of a stent within a stent) may be of additional palliative benefit.¹⁶

Few studies have compared silicone and expandable metal stents in a prospective randomized fashion.^{55,71} In comparable groups of patients, technical success (95% to 100%), improvement in dysphagia (91% to 100%), and the need for reintervention were similar regardless of stent type. However, the use of silicone stents was associated with a higher rate of complications (43% to 47% for silicone stents vs. 0% to 16% for metal stents) and a longer hospital stay (silicone, 6 to 12 days; metal, 4 to 5 days). Although 30-day mortality was not significantly different (silicone, 29%; metal, 14%), death resulting from stent insertion occurred only in the silicone stent group.⁵⁵ Despite a higher purchase price, expandable metal stents were found to be more cost-effective because of shorter hospitalization and lower complication rates.⁴¹

At the University of Pittsburgh, a review of 100 stented patients demonstrated relief of dysphagia in 85%, with a low probability of perforation (0.8%) and no short-term fatalities.¹⁶ Reasons for initial stent failure were inability to resume oral diet, intractable reflux and pain, bulky tumors resulting in inadequate stent expansion, and inadequate stent position. Sixteen stents were placed in patients undergoing neoadjuvant therapy before esophagectomy. Supplemental enteral or intravenous nutrition was not necessary in 88% ($n = 14$) of those patients. At the time of esophagectomy, dissection of the periesophageal planes was more difficult, but no postoperative complications could be attributed directly to preoperative stenting. Patients receiving chemotherapy or radiation therapy at the time of stenting may be prone to perforation or fistulization and local abscess formation.^{16,72,73} Although this has not been evaluated in controlled trials, alternatives to stenting should be considered in this subgroup of patients. Fully covered esophageal stents may be a better choice in this situation. These stents can be used for temporary relief of dysphagia and can provide the necessary time window for chemotherapy or radiation therapy to take effect and then proceed with stent removal when a tumor response has been obtained making the stent unnecessary. In other large series of patients undergoing stenting (≥ 100 patients), placement was successful, and improvement of dysphagia was observed in 90% to 100%.⁷⁴⁻⁷⁸ Patients were stented with a mortality of 0% to 2.5% and a complication rate of 20%

to 41%. These findings lend additional support to the use of stents as a relatively safe and effective method of palliation for obstructing esophageal cancer.

COMPARISON OF PALLIATIVE ENDOSCOPIC THERAPIES

We have described a number of different approaches to palliate obstruction or bleeding from endoluminal tumors. Because most of these patients have a shortened life expectancy, the goals of therapy should be to improve symptoms and quality of life and to minimize morbidity and hospital stay. No randomized trials are available to compare these modalities. The perception among physicians that palliative treatment modalities are complementary rather than alternative has caused difficulties in patient accrual for randomized trials.⁷⁹ Typically, a center will favor one approach over another. It is our opinion that the thoracic surgeon should be familiar with all these modalities, as many clinical scenarios will require the combination of various treatment modalities. An example

is given of our approach to palliation of obstructing lung cancer (Fig. 6-7). The relative merits of each treatment modality are summarized in Table 6-2.

EVOLVING ENDOSCOPIC TREATMENT MODALITIES FOR BENIGN ESOPHAGEAL DISEASES

Achalasia

Historically, the management of achalasia has included a collection of medical, endoscopic, and surgical treatments aimed at symptom palliation and targeted at the incomplete relaxation of the lower esophageal sphincter. Medical treatment with nitrate and calcium antagonists assist in smooth muscle relaxation, often improving the symptom of chest pain, but they are limited by their poor efficacy and side effects.⁸⁰⁻⁸² Until recently, the only available endoscopic treatments included Botox injections and pneumatic dilation. Although initially successful in 90% of patients, Botox injections at the gastroesophageal

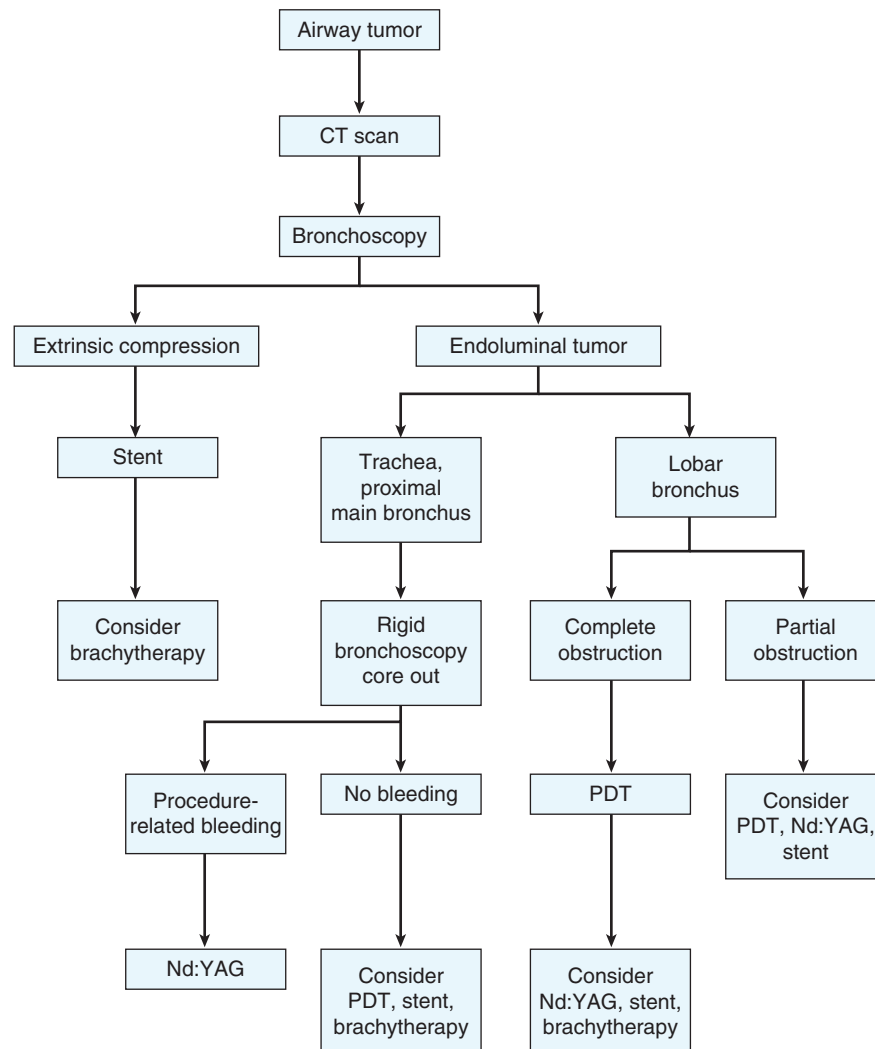


FIGURE 6-7 ■ Approach to malignant obstruction of the airway. CT, Computed tomography; Nd:YAG, neodymium:yttrium-aluminum-garnet; PDT, photodynamic therapy.

TABLE 6-2 Relative Attributes of Endoscopic Therapies for Palliation of Endoluminal Obstruction

	Photodynamic Therapy	Stent	Nd:YAG Laser	Brachytherapy
Local anesthesia	Yes	Yes	Yes	Yes
Effective for intraluminal tumor	Yes	Yes	Yes	Yes
Effective for extrinsic compression	No	Yes	No	Yes
Effective for complete obstruction	Yes	No	Occasionally	No
Effective for bleeding	Yes	No	Yes	Yes (not acutely)
Depth of penetration	0.5-1 cm	N/A	N/A	0.5-2 cm
Use in lobar and segmental airways	Yes	No	Yes	Yes
Onset of effect	Rapid	Immediate	Rapid	Slow
Photosensitivity	Yes	No	No	No
Late hemoptysis (non-tumor-related)	No	No	No	Yes
Late stricture or dysphagia (non-tumor-related)	Yes (if normal tissue treated)	Yes (migration)	No	Yes (radiation bronchitis)

Nd:YAG, Neodymium:yttrium-aluminum-garnet.

junction last typically less than 6 to 9 months and are therefore reserved for older patients or nonoperative candidates.⁸³ Pneumatic dilation was originally shown to offer short-term success rates similar to those seen with a laparoscopic Heller myotomy with Dor fundoplication.⁸⁴ A recent multicenter randomized study demonstrated equivalent clinical success between the two approaches at 2-year follow-up,⁸⁵ but on further long-term evaluation pneumatic dilation was noted to have a failure rate of 50% to 60%. To date, laparoscopic Heller myotomy with Dor fundoplication remains the treatment of choice in young or otherwise healthy patients.⁸⁴

In 2008, the first human cases of per-oral endoscopic myotomy were published. Since then, per-oral endoscopic myotomy has been gaining traction as a developing endoscopic treatment for achalasia that combines the surgical element of a controlled myotomy with the low impact of an endoscopic approach.

Key steps of the procedure include: (1) marking of the distal end of the dissection 2 cm distal from the gastroesophageal junction on the short curvature; (2) creation of the submucosal lift using a saline injection; (3) opening of the submucosal channel using sharp dissection with a cautery knife; (4) injection of lifting solution through the balloon allows correct delineation of the submucosal plane; (5) sharp dissection of the circular muscle fibers; (6) intraoperative retroflexed view confirming 2 cm extension of myotomy onto stomach wall; and (7) multiple clip closure of the mucosal defect. This technique requires advanced endoscopic skills and a learning curve of at least 20 cases.

Per-oral endoscopic myotomy is highly successful with intermediate-term clinical results demonstrating an average dysphagia relief of 98%. The most common long-term complication is gastroesophageal reflux (GER) with an estimated incidence of 35%, similar to the incidence of GER after laparoscopic Heller myotomy with fundoplication. GER symptoms are present in 0% to 44% of patients, with a reported anti-acid use of 0% to 50% after per-oral endoscopic myotomy. Endoscopic evidence of erosive esophagitis is present in 0% to 43% of patients, and positive pH studies is present in 0% to 38% of patients. Although these numbers reflect a high incidence of postoperative GER, they are in fact similar to the 21% to 42% of abnormal pH studies after laparoscopic Heller and partial fundoplication.^{86,87}

Patients are often discharged home on the morning of the first postoperative day and return to work an average of 3 days after the intervention. Although per-oral endoscopic myotomy represents a paradigm shift in the treatment of achalasia, additional long-term data are needed to further define its role in the treatment algorithm of achalasia and possible role in other esophageal pathologies, such as diffuse esophageal spasm, nonrelaxing hypertensive lower esophageal sphincter (LES), and nutcracker esophagus. We have been impressed that in experienced hands, there has been a low incidence of serious complications such as clinical perforations or abscesses with good initial relief of dysphagia. However, we stress the importance of a careful approach to this procedure using animal models to gain an understanding of the procedure and then a prolonged series of cases with an experienced proctor present. In our opinion, this procedure should only be considered by surgeons with significant experience in laparoscopic, thoracoscopic, and open esophageal surgical experience with the treatment of achalasia.

Zenker Diverticulum

The pharyngoesophageal diverticulum was first described by Ludlow⁸⁸ in 1764 but was methodically characterized by Zenker in 1867.⁸⁹ Killian elegantly described the anatomic relationship of the diverticulum and Killian triangle, where it arises.⁹⁰ For many years this finding has been referred to as a condition that occurs for unknown reasons as the upper sphincter seemingly for no reason, fails to open with the initiation of the pressures of swallowing to propel the food bolus beyond the cricopharyngeus, leading to an outpouching through the Killian triangle. In our clinical experience and that of a few other centers, there is an increasing awareness of the correlation of a Zenker diverticulum and the globus sensation that precedes this, with the coexistent finding of longstanding GER disease (GERD) and initial failure of the LES. It is our opinion that this abnormally tight and unrelaxing upper esophageal sphincter is not an aberrant freak of nature but is more likely a triggered neurogenic response of the upper sphincter to maintain a tighter than normal tone to contain the refluxate coming up from an incompetent lower esophageal sphincter from coming up

through a lax upper sphincter. In fact, on careful examination, we have seen small to moderate hiatal hernias and preceding GERD symptoms in the majority of patients with a Zenker diverticulum. Regardless of the etiology, surgical treatment is indicated to treat symptoms of dysphagia, regurgitation, and aspiration pneumonia. Surgical options include open cricopharyngeal myotomy alone, diverticulectomy and myotomy, and diverticulopexy and myotomy. In 1993, Collard first published a small case series of patients treated with the transoral stapling approach.⁹¹ Each technique is briefly reviewed; the transoral technique is described in detail.

Open Approaches to Zenker Diverticulum

Cricopharyngeal myotomy is an attractive option in the surgical treatment of Zenker diverticula, because the risks of complications are low and the underlying cause of the problem is addressed. Belsey⁹² noted that small diverticula disappeared when a myotomy alone was performed. However, when the pouch is large, myotomy alone does not yield satisfactory results.⁹³ In our opinion, myotomy alone should probably be reserved for the treatment of small (≤ 2 cm), symptomatic diverticula.

The combination of a myotomy with a diverticulectomy became popular in the 1960s, and several groups reported lower morbidity and lower recurrence rates when the two procedures were done simultaneously.⁹³⁻⁹⁶ Lerut⁹⁵ reported a significant decrease in morbidity from 21% to 11% when a myotomy was performed at the time of diverticulum resection.

Suspension of the diverticulum to the retropharyngeal fascia or to the anterior spinal ligament combined with a myotomy is another acceptable surgical option that we prefer for the management of symptomatic Zenker diverticulum. This approach avoids the potential morbidity of a leak at the site of diverticulum resection. Konowitz reported no morbidity in patients undergoing diverticulopexy and myotomy versus 20% morbidity for those undergoing diverticulectomy and myotomy.⁹⁷ Additional literature to support the routine use of this technique over diverticulectomy and myotomy is lacking.^{93,98,99} With very large diverticula, we prefer to resect these at the time of myotomy because they can be difficult to pexy if they are larger than 6 to 8 cm.

Transoral Endoscopic Stapling

Transoral stapling of the common septum between the diverticulum and the esophagus gained popularity after the first series by Collard, published in 1993.⁹¹ The procedure can result in shorter anesthetic time, decreased hospital stay, and reduced complication rates compared with open procedures. In a recent review of series of transoral stapling published between 1993 and 2002, 541 of 576 (94%) attempted staplings were completed successfully, and 96% of the patients had a satisfactory outcome. The incidence of major complications was 3%, and 2.6% of the patients had a perforation or leak.¹⁰⁰

In our own experience, we have performed more than 100 transoral staplings and have found this to be an ideal approach if the following are present⁹⁰: (1) minimum

diverticulum size of 2 cm, (2) edentulous patient, (3) ability to fully extend the neck without restriction and absence of cervical spine abnormalities, (4) low Mallampati classification (I-II), (5) absence of a receding lower jaw, (6) classified as an easy intubation with traditional anesthetic criteria, and (7) desire by the patient to avoid open surgery.

Patient Positioning. The first step to a successful endoscopic stapling is patient selection. Ideal patient characteristics are ability to fully extend the neck without restriction, low Mallampati classification (I-II), edentulous mouth, and adequate diverticulum size (>2 cm).¹⁰¹ The procedure is performed under general anesthesia with a single-lumen endotracheal tube. The patient is supine with a small pillow placed for back support and to allow extension of the neck. The surgeon is behind the patient's head.

Endoscopy. All patients should undergo flexible endoscopy, and the esophagus should be carefully inspected for any associated pathologic process (e.g., hiatal hernia, Barrett esophagus). Care must be taken to find the true esophageal lumen. We have found that leaving a guide-wire in place temporarily can confirm the true esophageal lumen. After a thorough flexible endoscopy, the Weerda rigid endoscope (Karl Storz, Tuttlingen, Germany) is inserted into the patient's mouth (Fig. 6-8). A 5-mm straight or 30-degree thoracoscope connected to a video camera is used to improve visualization through the rigid endoscope or just lateral to it. The blades of the Weerda scope are opened gently to demonstrate both the true esophageal lumen and the lumen of the diverticulum. If needed, the diverticulum is cleaned of any residual contents with the help of suction and saline irrigation. The septum between the diverticulum and true esophageal lumen should be well demonstrated.



FIGURE 6-8 ■ The Weerda rigid endoscope. One blade is placed in the esophagus and the other in the diverticulum. (From Morse CR, Fernando HC, Ferson PF, et al: Preliminary experience by a thoracic service with endoscopic transoral stapling of cervical [Zenker's] diverticulum. *J Gastrointest Surg* 11:1091-1094, 2007. Used with permission, Springer Verlag.)

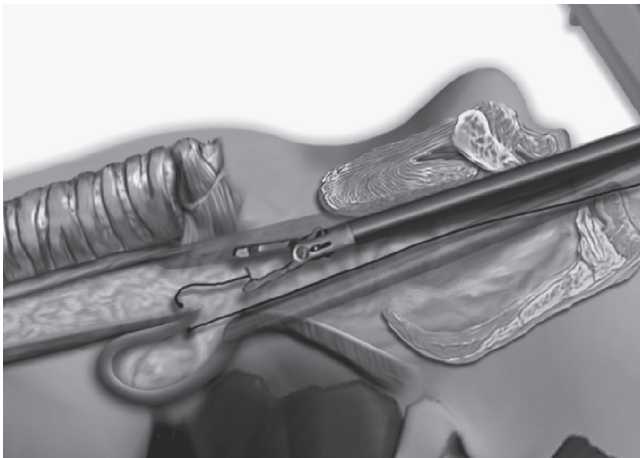


FIGURE 6-9 ■ Traction stitch placed in the septum with use of 2-0 Ethibond on an Endo Stitch device (U.S. Surgical Corp., Norwalk, CT). This prevents the septum from being “squeezed” out of the stapler jaws. (From Morse CR, Fernando HC, Ferson PF, et al: Preliminary experience by a thoracic service with endoscopic transoral stapling of cervical [Zenker’s] diverticulum. *J Gastrointest Surg* 11:1091–1094, 2007. Used with permission, Springer Verlag.)



FIGURE 6-11 ■ Endoscopic transoral stapling of Zenker diverticulum. (From Morse CR, Fernando HC, Ferson PF, et al: Preliminary experience by a thoracic service with endoscopic transoral stapling of cervical [Zenker’s] diverticulum. *J Gastrointest Surg* 11:1091–1094, 2007. Used with permission, Springer Verlag.)

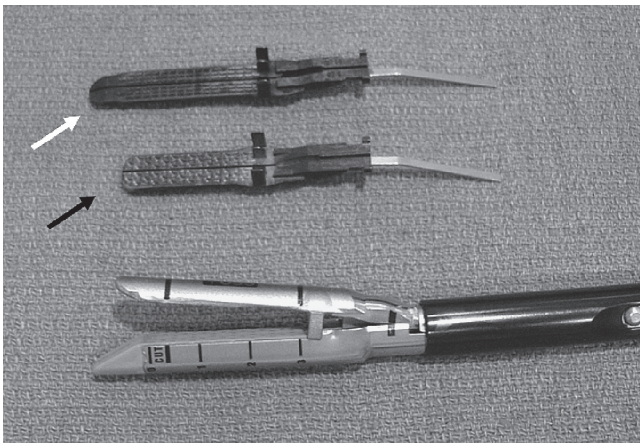


FIGURE 6-10 ■ The modified Endo GIA 30 stapler (U.S. Surgical Corp., Norwalk, CT). The anvil is modified by shortening the tip to allow the staple to go to the base of the septum. The *white arrow* indicates an unmodified anvil. The *black arrow* indicates an anvil modified by removal of the tapered end. (From Morse CR, Fernando HC, Ferson PF, et al: Preliminary experience by a thoracic service with endoscopic transoral stapling of cervical [Zenker’s] diverticulum. *J Gastrointest Surg* 11:1091–1094, 2007. Used with permission, Springer Verlag.)

Stapling. To facilitate the insertion of the stapling device, a traction suture is placed on the septum, separating the true lumen of the esophagus and the diverticulum, by use of the Endo Stitch device (Covidien, Dublin, Ireland; Fig. 6-9). An Endo GIA 30-mm with Tri-staple technology (Covidien) is used for stapling. We prefer the smaller stapler height so that the staple line can reach the base of the septum and still allow visualization (Fig. 6-10). The stapler is inserted through the rigid endoscope, and the jaws are placed across the septum, in the midline (Fig. 6-11). The suture provides countertraction on the septum during placement and firing of the endostapler.

Results. The two largest series on transoral stapling of Zenker diverticula come from Italy.^{102,103} Peracchia and colleagues¹⁰³ reported experience with 95 attempted transoral staplings of Zenker diverticula. Ninety-two patients (97%) had successful stapling. Two patients had limited neck extension, and one patient had a mucosal tear during the procedure. All three patients had an open procedure without complications. The author reported that the three unsuccessful attempts occurred in the early years of the series. Satisfactory outcome was achieved in 94% of the patients, and 5% had recurrence or persistence of the diverticula. Narne and colleagues¹⁰² described 102 patients, of whom 98 (96%) had successful stapling. A satisfactory outcome was achieved in 96% of patients, with a 4% recurrence rate and no major morbidity.

We presented our results with transoral stapling in 24 patients.¹⁰⁴ Of the 28 patients enrolled, the procedure was completed in 24 patients (85%). Four patients had conversion to an open procedure because of unfavorable anatomy (two patients), perforation of the diverticula (one patient), and a diverticulum smaller than 2 cm (one patient). There were no other significant complications, and the length of stay was 2.2 days. Time to oral intake was 1.38 days, and dysphagia scores improved remarkably after the procedure (2.78 to 1.1).

In experienced hands, transoral stapling is a safe, rapid, and effective way to treat Zenker diverticula. Surgeons contemplating the use of this approach should be familiar with rigid esophagoscopy and open surgical management of Zenker diverticula.

Gastroesophageal Reflux

Gastroesophageal reflux disease (GERD) is defined as the presence of symptoms, such as heartburn or regurgitation, or the presence of esophageal mucosal damage secondary to acid reflux. Up to 44% of the population will experience heartburn at least once a month, and 17.8% will at least once per week,¹⁰⁵ making GERD the third

most common gastrointestinal disorder in the United States. It is responsible for 96,000 hospitalizations per year, at a cost of almost \$10 billion.¹⁰⁶ GERD significantly impairs quality of life and may have a worse impact on patients than angina pectoris and congestive heart failure. After initial medical therapy, only 10% to 25% of patients will remain symptom free 6 months after stopping medications; the rest require long-term medical therapy.¹⁰⁷ Up to 20% of GERD patients receiving proton pump inhibitors (PPIs) will experience breakthrough symptoms.¹⁰⁸ The daily dependence on medications, the high associated costs, and the suboptimal symptom control have spurred interest in minimally invasive endoscopic approaches to GERD.

For historical completeness, endoscopic procedures for GERD can be classified into three major groups: RF therapy to the lower esophageal sphincter (Stretta, Curon Medical, Fremont, CA), injection of biopolymers at the gastroesophageal junction (Enteryx, Boston Scientific, Natick, MA), and endoscopic plication of the gastroesophageal junction. These treatment modalities are mentioned for completeness, as they are no longer commercially available. Endoscopic plicators (e.g., Esophyxx, EndoCinch) are currently approved for use in the United States.

Radiofrequency Therapy to the Lower Esophageal Sphincter

Curon Medical, the manufacturer of the Stretta system, stopped making the device after filing for bankruptcy in November 2006. The devices delivered low-power RF energy to the gastroesophageal junction. The procedure involved the delivery of RF energy to the esophageal tissue from 1 cm above the gastroesophageal junction to a level immediately below the squamous-columnar junction. The proposed mechanisms of action for the Stretta procedure include mechanical alteration of the gastroesophageal junction and neural modulation of the lower esophageal sphincter, resulting in decreased relaxation and acid exposure.^{109,110}

The short-term results (6 to 12 months) of a prospective study of 118 patients showed significant improvement in DeMeester score, lower esophageal sphincter pressure, heartburn score, GERD health-related quality of life (GERD-HRQL) score, and Short Form 36 (SF-36) questionnaire score.¹¹¹ At baseline, 88% of patients required daily PPIs compared with 30% at 12 months. An ad hoc analysis of the results concluded that symptomatic improvement after the Stretta procedure correlated with decreased lower esophageal sphincter acid exposure, linking symptomatic improvement with proximal and distal esophageal acid control.¹¹²

Corley¹¹³ conducted a blinded, randomized, controlled trial in 64 patients with GERD. At 6 months, treated patients showed a significantly improved heartburn score, GERD-HRQL score, and general quality of life. There was no difference between the groups in daily medication use, median 24-hour pH score, and lower esophageal sphincter pressure or esophageal mucosal erosions. This trial showed that the Stretta procedure was effective in improving symptoms and quality of life but failed to

improve acid exposure or healing of mucosal lesions. The authors could not explain the findings. In the largest published study, Wolfsen¹¹⁴ evaluated GERD symptoms, patient satisfaction, and medication use in 558 patients treated in 33 centers. Mean follow-up was 8 months, ranging from 2 to 33 months. Satisfaction of patients improved from 23.2% to 86.5%, symptom control improved from 50% to 90%, and 77% of patients reported absent or mild GERD after the Stretta procedure compared with 26.3% at baseline. Subset analysis showed that improvement persisted beyond 1 year after the procedure, and most patients did not require antacid medication.

In summary, the Stretta procedure appears to be effective in controlling GERD symptoms in a select group of patients. However, questions about the precise mechanism of action and the long-term effects are likely to remain unanswered and have led our group to use other approaches.

Injection of Biopolymers at the Gastroesophageal Junction

Enteryx is a biocompatible polymer in the form of a nonviscous liquid that solidifies rapidly when it is injected into tissue, becoming an inert spongy mass. The procedure was usually performed under fluoroscopic guidance, and most treatment sessions placed 1-mm blebs circumferentially around the gastroesophageal junction. Enteryx injections can be repeated if symptoms are not fully controlled; however, it is not reversible.¹¹⁵ The proposed mechanism of action of Enteryx injection to the lower esophageal sphincter is the prevention of lower esophageal sphincter unfolding or relaxation in response to gastric distention in an effort to prevent reflux and improve lower esophageal sphincter tone.¹¹⁶

A prospective, multicenter international trial of Enteryx implantation for GERD was conducted, and 12- and 24-month follow-up data are available.^{117,118} Results were reported for 85 patients for 12 months and for 144 patients for 24 months. Patients entered the trial if their symptoms were well controlled and symptom scores were normalized with PPIs and returned to abnormal levels after withdrawal of PPIs. At 12 months, 84% of the patients had a reduction in use of PPIs of more than 50%, and 73% of the patients stopped using PPIs completely. This effect was maintained at 24 months; 72% of patients had a reduction in use of PPIs of more than 50%, and 67% had complete cessation of PPIs. GERD-HRQL score improved in 78% of the patients at 12 months and in 80% at 24 months. Median heartburn score improved in 71% at 12 months and in 80% at 24 months. Regurgitation score improved in 77% at 12 months and 88% at 24 months. The median score of the physical component of the Short Form-36 questionnaire improved by 12%, but the mental component did not change significantly. Esophageal manometry was not significantly changed at 12 months. Esophageal acid exposure declined significantly at 12 months. Median supine, upright, and total acid exposure times were decreased by 42%, 28%, and 31%, respectively. Thirty-seven percent of patients had acid exposure normalized 12 months after the

procedure. At 12 months, esophagitis was unchanged in 59 patients (55%), decreased in 14 patients (13%), and increased in 34 patients (32%). Of the 34 patients with an increase in esophagitis, 19 had increased by one level and 14 by two levels. One patient had an increase in esophagitis from 0 to III. Adverse effects in the trial were relatively minor, with retrosternal chest pain being the most frequent. One patient had a paraesophageal fluid collection, which was treated conservatively. Outside the trial, serious adverse events were reported. One patient died of gastrointestinal bleeding from an aorto-esophageal fistula and was found on autopsy to have Enteryx material embedded in the aorta. Another patient developed severe flank pain and was noted to have embolization of Enteryx to his aorta and renal arteries.¹¹⁹ The U.S. Food and Drug Administration ordered a recall of the product in 2005. Although the international trial demonstrated good symptomatic relief in patients with GERD controlled with PPIs, 30% worsening in esophagitis and reports of fatalities preclude us from recommending this treatment option.

Endoscopic Plication of the Gastroesophageal Junction

Esophyx. The transoral incisionless fundoplication procedure attempts to restore the angle of His and improve the antireflux mechanism by creating an omega-shaped valve, 3 to 5 cm in length and 200 to 300 degrees in circumference, through the use of transorally inserted full-thickness endoscopic fasteners. The Esophyx device is essentially an overtube with a channel for the esophagoscope and a flexible section that retroflexes and compresses the tissue at the angle of His.¹⁰⁴ Clinical details are limited. A canine model did not show any adverse effects, and the fasteners were effective in creating a stable serosa-to-serosa fusion at 1 year.¹²⁰ Animals with a circumferential valve demonstrated a significant and lasting increase in the lower esophageal sphincter pressure, decreased esophageal acid exposure, and decreased DeMeester score. Cadiere and colleagues¹²¹ published a series of 17 patients treated with the Esophyx device. One year after surgery, GERD-HRQL score improved by 67%, 82% of patients discontinued PPIs, and more than 80% were either satisfied or very satisfied with the procedure. Endoscopy at 1 year revealed that 81% of the valves maintained their tightness, median circumference, and length. Grade A and B esophagitis was observed in 13 patients, and hiatal hernias remained reduced in 8 of 13 patients. Long-term results have not been substantiated; this combined with technical difficulty of performing the procedure and the inability to yield a consistent valve have led our group and most others to abandon this approach.

EndoCinch. The EndoCinch (Bard Medical, Covington, GA) requires an overtube and two endoscopes, one for the suturing and the other for suction and visualization. The procedure entails plication of a fold of mucosa just below the squamous-columnar junction. Three sutures are placed below the gastroesophageal junction in a circumferential, linear, or helical pattern.¹²²

Sham-controlled trials of the EndoCinch have had remarkably different results. Rothstein and colleagues,¹²³ in a single-blinded trial, compared 78 patients undergoing the EndoCinch procedure with 81 patients undergoing a sham procedure. At 3 months, more than 50% of patients undergoing the EndoCinch procedure had an improvement in the GERD-HRQL score, as opposed to only 18% in the sham group. In addition, patients treated with EndoCinch had a significant improvement in pH acid exposure and a higher rate of discontinuation of PPI therapy (50% vs. 24%). There were no significant complications in the treated patients.

In contrast, Montgomery and coworkers¹²⁴ randomized 46 patients to the EndoCinch procedure or sham endoscopy. At 12 months, the investigators could not demonstrate differences between groups regarding GERD-HRQL score, PPI use, acid exposure, or esophageal manometric findings. At 12 months, 33% of the EndoCinch sutures were not visible, leading the investigators to conclude that the detachment of the sutures led to failure of the procedure. Both sham and EndoCinch subjects had significant improvements in GERD symptoms and PPI use after 12 months. The procedure was performed without major complications. In another sham-controlled trial, Schwartz and colleagues¹²⁵ randomized 60 patients to EndoCinch therapy, sham procedure, or observation alone. Heartburn symptoms and the use of PPIs were significantly decreased after EndoCinch compared with sham or control. Quality of life was also significantly improved in treated patients compared with sham patients. Esophageal acid exposure did not significantly differ between the treatment and the sham groups, although both groups experienced a reduction in overall acid exposure after 3 months.

Results of a North American multicenter trial were published in 2005. Eighty-five patients were enrolled and observed for 24 months.¹²⁶ Patients had a significant improvement in heartburn symptoms, and 77% reported no or minimal heartburn and no or minimal regurgitation in 2 years. Forty percent of patients reported complete cessation of use of PPIs at 24 months, and the annualized per patient medication costs decreased from \$1564 at baseline to \$183 at 2 years. Esophageal acid exposure was also significantly decreased at 6 months. One patient experienced severe dysphagia requiring removal of the fundoplication sutures 10 days after the procedure.

NDO Plicator. The NDO Plicator (NDO Surgical, Mansfield, MA) was designed to create a full-thickness plication of the gastroesophageal junction by delivery of a suture-based implant. This is accomplished by direct visualization of the gastroesophageal junction in a retroflexed fashion with a pediatric endoscope inserted through a dedicated channel of the plicator device. The plication is done 1.0 to 1.5 cm below the Z line, and either one or two plications are performed. Unfortunately, because of insufficient demand for the device, the company filed for bankruptcy in 2008.

In the North American open-label multicenter trial, 64 patients were treated with one plication with the NDO Plicator.¹²⁷ At 12 months of follow-up, the

GERD-HRQL score improved from 19 to 7 ($P < 0.0001$). The proportion of patients receiving daily PPI therapy decreased from 93% to 32% at 12 months. At 6 months, there was significant improvement in acid exposure at the distal esophagus, with both the number of episodes and the total acid exposure time showing significant improvement. In a randomized, sham-controlled trial of 159 patients, 56% of plicator patients versus 18.5% of sham patients had an improvement of more than 50% in the GERD-HRQL score at 3 months.¹²³ Discontinuation of PPI therapy occurred in 50% of the treated patients and 24% of the sham patients at 3 months. Most adverse effects included mild chest and epigastric pain. One patient underwent laparoscopy for persistent epigastric pain and was found to have adhesions between the stomach and the diaphragm. In another study of 33 patients observed for 5 years, there was a significant improvement of the GERD-HRQL score, and 33% had completely discontinued PPI therapy.¹²⁸ Adverse effects included sore throat (45%), abdominal pain (41%), chest pain (24%), and transient dysphagia not requiring dilations (21%).

In summary, endoscopic fundoplication is a procedure in evolution that has demonstrated short-term effectiveness in controlling symptoms of GERD. In general, patients with dysphagia, severe esophagitis, Barrett metaplasia, previous esophageal or gastric surgery, or a type I hiatal hernia larger than 2 cm were excluded from these trials. Most of the trials were also industry sponsored. Overall, it appears that patients with a very small hiatal hernia and a good response to PPIs may be the best candidates for endoluminal therapy. At this time, this treatment modality should probably be reserved for non-surgical candidates or those who refuse surgery. The role of endoluminal fundoplication in the management of GERD will be further delineated once more complete long-term follow-up data become available.

With technological advancement, these minimally invasive techniques may improve and become even more attractive to patients. It is important for thoracic surgeons to remain aware of further developments and to continue to critically evaluate new therapeutic modalities as they are introduced into clinical practice.

First-line therapy for GERD includes medical management with acid suppressing proton pump inhibitors, often providing incomplete control of reflux symptoms in nearly half of patients. As the pathologic cause of GERD lies in the incompetence of the lower esophageal sphincter, it has been demonstrated that sphincter augmentation may improve barrier function without altering the hiatal and gastric anatomy or interfering with swallowing, belching, or vomiting. A newly introduced sphincter augmentation therapy includes the LINX Reflux Management System by Torax Medical, Inc.

The LINX device is a small band of titanium beads with magnetic cores placed around the LES, the magnetic attraction allows for resistance to gastric distention while allowing for opening during the presence of esophageal swallowing forces thus preventing reflux and improving the natural barrier of the LES.

The magnetic attraction between the beads is intended to help the LES resist opening to gastric pressures,

preventing reflux from the stomach into the esophagus (see Fig. 6-1). LINX is designed so that swallowing forces temporarily break the magnetic bond, allowing food and liquid to pass normally into the stomach (see Fig. 6-2). Magnetic attraction of the device is designed to close the LES immediately after swallowing, restoring the body's natural barrier to reflux. A prospective assessment of 100 GERD patients who underwent sphincter augmentation with the LINX device demonstrated decreased esophageal acid exposure, symptomatic improvement, and reduction in use of PPI therapy. Outcomes at 3 and 5 years were reported. Normalization of esophageal acid exposure or a 50% or greater reduction in exposure at 1 year was achieved in 64% of patients. Improvement in quality of life related to gastroesophageal reflux disease and a reduction in the use of proton-pump inhibitors at 1 year occurred in 93% of patients. The most frequent adverse event was dysphagia (68% of patients postoperatively, 11% at 1 year, and in 4% at 3 years). Serious adverse events occurred in six patients, and six patients requested to have the device removed.¹²⁹

The median time needed to implant the device laparoscopically was 36 minutes (range, 7 to 125 minutes). All patients were discharged within 1 day after surgery, with an unrestricted diet. As the field of thoracic surgery continues to change and evolve, it is important for thoracic surgeons to continue to expand their armamentarium of available therapies.

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PART C

TRAUMA

PART OUTLINE

7 THORACIC TRAUMA

THORACIC TRAUMA

Todd C. Crawford • Clinton D. Kemp • Stephen C. Yang

CHAPTER OUTLINE

PRIMARY SURVEY

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EMERGENCY DEPARTMENT THORACOTOMY

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Great Vessels
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Diaphragm

Esophagus

PENETRATING TRAUMA

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COMPLICATIONS OF THORACIC TRAUMA

Acute Lung Injury and Respiratory Distress Syndrome
Pneumonia
Pleural Space Problems
Bronchopleural Fistula
Great Vessel Fistula

The earliest recorded reference to thoracic trauma is found in *The Edwin Smith Surgical Papyrus*, written around 3000 BC.¹ In this report of 58 cases, three were related to the chest: a penetrating injury to the cervical esophagus, a stab wound to the sternum, and blunt trauma resulting in rib fractures. Homer reported on many thoracic injuries during the Trojan War in his *Iliad*, perhaps the most famous of which occurred when King Agamemnon slayed Odius during the Battle of Troy with a well-placed spear through his chest.² At the start of the common era, there are descriptions of fatal thoracic injuries suffered by the ancient Olympians in their often more violent version of the familiar games, as well as those suffered by the gladiators and depicted by Galen.^{3,4} Many of these injuries were the focus of art in the ancient world (Fig. 7-1).⁵ More recent was the well-known assassination attempt of President Ronald Reagan by John Hinckley on March 30, 1981, whose bullet struck the president in his left chest, causing a nonfatal hemothorax (Fig. 7-2).^{6,7} In the most recent conflicts in Afghanistan and the Middle East, Operation Enduring Freedom and

Operation Iraqi Freedom, respectively, thoracic trauma was observed in 8.6% of all casualties, carrying an almost 10% associated mortality rate. Penetrating trauma was the most common mechanism of injury (61.5%). Changes in warfare have borne out with explosive devices now representing the most common cause of thoracic injury.⁸

Through the eras of Hippocrates and Galen, open packing and local treatment with common ingredients (red meat, honey, lint) was the mainstay of treatment, until the thirteenth century when wound débridement and closure was advocated. However, wound closure became a topic of great debate somewhat clarified by Paré in 1514. He advocated immediate closure of wounds without blood or a small amount in the chest, enlargement of small wounds if better drainage of blood was required, and delay of wound closure until blood drainage had ceased (usually 2-4 days).⁹ During the next century, various cannulas were developed to irrigate infected wounds and empyemas; these cannulas eventually evolved into the closed drainage systems during World War II.

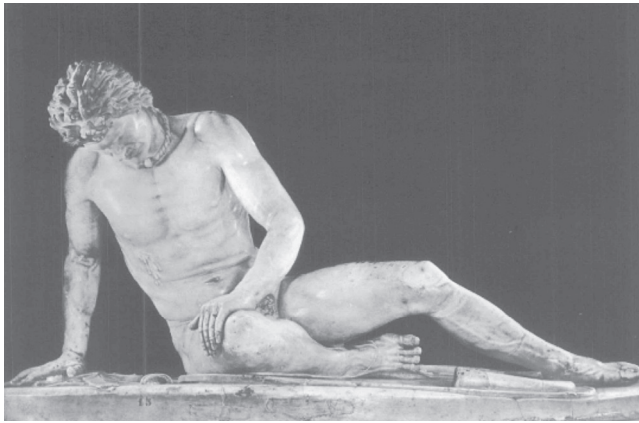


FIGURE 7-1 ■ *The Dying Gaul*, from the first or second century BC, the Capitoline Museum of Rome. Note the penetrating trauma to the right hemithorax. (From Churchill ED: Chest wounds in ancient sculpture. *J Hist Med Allied Sci* 26:304–305, 1971.)



FIGURE 7-2 ■ Chest radiograph following the assassination attempt of President Ronald Reagan on March 30, 1981. Note the presence of a left-sided chest tube and a bullet fragment near the left border of the heart. (From Rockoff SD, Aaron BL: The shooting of President Reagan: a radiologic chronology of his medical care. *Radiographics* 15:407–418, 1995.)

Also during this conflict, thoracotomy became commonplace not only as the most effective means in draining retained blood and infected debris, but also to remove the peel that formed over the lung from the hemothorax. As thoracic surgical principles developed, so too came advances in endotracheal intubation, mechanical ventilators, and thoracic pain control that became pivotal in the management of most thoracic injuries over the next several decades.

As a result, mortality from chest wounds had progressively decreased from a wartime high of 80% to 90% as reported by Billings during the American Civil War¹⁰ to 8.3% in a 10-year review of Operation Enduring Freedom and Operation Iraqi Freedom⁸ to 4% to 7% in

recent civilian experience. Nevertheless, thoracic trauma accounts for 25% of all trauma deaths, representing approximately 160,000 deaths annually.¹¹ More than 70% of thoracic injuries result from blunt trauma, most of which are due to automobile accidents. One in four cases with cardiothoracic trauma regardless of etiology requires hospital admission.

Age of the patient plays an important role in the severity of injuries. In the pediatric patient where the immature chest wall is elastic and flexible, fractures are rare, but intrathoracic injuries are more significant. In older patients, the fragile bony thorax is highly susceptible to even low-impact forces, and it offers poor protection for the underlying viscera. Mortality is high, even with minor injuries.

Penetrating injuries are uncommon on either extreme of age groups, but they remain one of the most common causes of death from trauma up to the age of 40 years. Low-velocity handguns, seen primarily in the civilian population, transmit little damage to surrounding tissues. Conversely, much more damage and energy is conducted along the path of high-velocity missiles, usually associated with the military, but now often seen in community violence.

PRIMARY SURVEY

The standard resuscitation of the trauma patient has been outlined by the American College of Surgeons in the *Advanced Trauma Life Support* (ATLS) guidelines.¹² Upon the patient's arrival in the trauma bay, it is crucial to rapidly perform a primary survey with attention to the airway, breathing, and circulation (the ABCs) so that potentially life-threatening injuries can be recognized immediately before they become lethal. Following this algorithm, first the airway must be controlled; second, breathing is assessed and immediately assisted with mechanical ventilation if necessary. Next, circulation must be supported through the rapid establishment of reliable, large-bore venous access and the initiation of fluid resuscitation. Finally, the patient's neurologic disabilities are assessed, and the entire body is exposed to identify any significant deformities or penetrating injuries that might have been overlooked. The goal of the primary survey is to identify immediate, life-threatening injuries that could account for ventilatory or hemodynamic compromise, which if left uncorrected could cause death.¹³

Injuries to the thoracic cavity or its contents comprise the majority of this group, and generally speaking they require urgent intervention as a life-saving measure. These life-threatening injuries and preferred treatment measures are listed in [Table 7-1](#). These problems should always be kept in mind during the resuscitation of every trauma patient. The mechanism of injury should also influence the index of suspicion for these injuries, as some are more likely to be sequelae of blunt trauma (aortic rupture, diaphragmatic hernia, cardiac tamponade), penetrating trauma (cardiac tamponade, massive intrathoracic hemorrhage), or common to both (pneumothorax).

TABLE 7-1 Potentially Acutely Lethal Injuries of the Chest and Their Management

Injury	Management
Tension pneumothorax	Tube thoracostomy
Massive intrathoracic hemorrhage	Tube thoracostomy, operative repair
Cardiac tamponade	Pericardiocentesis, operative repair
Deceleration aortic injury	Operative repair
Massive flail chest with pulmonary contusion	Intubation, pain control, fluid restriction
Upper/lower airway obstruction	Intubation, airway, bronchoscopy
Tracheobronchial rupture	Bronchoscopy, operative repair
Diaphragmatic rupture with visceral herniation	Operative repair
Esophageal perforation	Operative repair

DIAGNOSTIC TESTS

Approximately one third of all deaths from thoracic trauma occur immediately or shortly thereafter when transported to a treatment facility. Diagnostic and emergency management modalities are essential to evaluate these injuries fully and to direct care toward the proper therapeutic interventions.¹⁴

Chest Radiography

The chest radiograph remains paramount in every trauma victim and should be the central focus from which potential life-threatening thoracic problems are suspected. Chest radiographs can be obtained rapidly upon arrival to the trauma bay with the patient still on the transportation backboard. A systematic review of the film should reveal suspected and unsuspected injuries, and the presence of any foreign bodies. Fractures of the bony thorax, including the ribs, clavicles, spine, and scapulae, should be excluded. Fractures of the thoracic cage indicate significant energy transfer to the patient; those of the upper ribs are associated with trauma to the great vessels, and those of the clavicle are associated with pulmonary or cardiac contusions. The lung fields should be examined for pneumothorax, hemothorax, or pulmonary contusion. Along the mediastinum, widening, pneumomediastinum, or shifting are highly suggestive of aortic transection, tracheobronchial or esophageal injuries, or tension pneumothorax or hemothorax. The soft tissues may reveal subtle subcutaneous air or foreign bodies. Finally, the width of the cardiac silhouette may raise the suggestion of tamponade.

Computed tomography (CT) is not essential for every patient with chest trauma and should not be performed in the severely hemodynamically unstable patient or in the presence of obvious life-threatening injuries; however, it can be done with rapidity, and may reveal injuries not seen clearly on plain radiographs: aortic disruption, pneumothorax, pneumomediastinum, hemothorax, or pulmonary contusions. It may be useful to screen all patients with blunt trauma and to evaluate unusual or

abnormal findings on an initial chest radiograph (e.g., diaphragmatic injuries).

CT of the chest has been shown to be more sensitive at detecting thoracic injuries such as pulmonary contusions, hemothorax, and pneumothorax.^{15,16} Up to 75% of trauma patients with a normal physical examination and chest radiograph will have an occult injury diagnosed on chest CT, and 5% of these patients will need intervention for their injuries.^{17,18} Even when evidence of thoracic trauma is seen on a physical examination and plain radiography, the addition of chest CT leads to altered management and therapeutic decisions in up to one third of all patients with thoracic injuries.^{16,17} In addition, chest CT can be used to exclude diagnoses made by the less sensitive chest radiograph, which can happen in up to 15% of patients.¹⁷ More recently, the routine use of CT in the evaluation of thoracic trauma has been scrutinized because of the cost and time associated with performing and interpreting this test. The NEXUS Chest decision instrument is one model that has arisen to potentially mitigate these unnecessary expenses. In using seven clinical criteria to predict thoracic injury seen on chest imaging with major clinical significance and as indicators to proceed with CT, the NEXUS Chest instrument yielded a sensitivity of 99.7% and a negative predictive value of 99.9%.¹⁹

Ultrasonography

Ultrasonography has become fairly routine in the early evaluation of the abdomen and pericardium.²⁰ Termed the *focused assessment for the sonographic evaluation of the trauma patient* (FAST) examination, four standard viewing ports are used to quickly assess for abnormal fluid collection: right upper quadrant, left upper quadrant, pelvis and subxiphoid. In addition, the E-FAST, or extended-FAST, that uses an extension of the right and left upper quadrant views to include the right and left hemithoraces—right and left longitudinal thoracic views, respectively—can aid in the diagnosis of hemothorax or pneumothorax (Fig. 7-3).^{21,22} Recent meta-analyses have demonstrated that ultrasound is more sensitive in detecting traumatic pneumothoraces than conventional supine chest radiography is; however, supine anteroposterior radiographs remain superior in regard to specificity.²³ Although not as precise as an ultrasound performed by a board-certified radiologist or cardiologist, this examination is able to detect fluid collections that might influence the need for urgent operative intervention. Of the four views, the subxiphoid view is the most accurate in the hands of surgeons in detecting abnormalities in the trauma setting.²⁰ It has the advantages of being safe, expeditious, repeatable, and effective even in the hands of surgeons from different specialties,²⁴ and it can be useful to identify injuries to the heart and fluid in the pericardium.

Echocardiography

There has been a major shift in the diagnosis of aortic and great vessel injuries in recent times.²⁵ In the 1990s and earlier, these injuries were diagnosed almost exclusively with aortic angiography and/or transesophageal

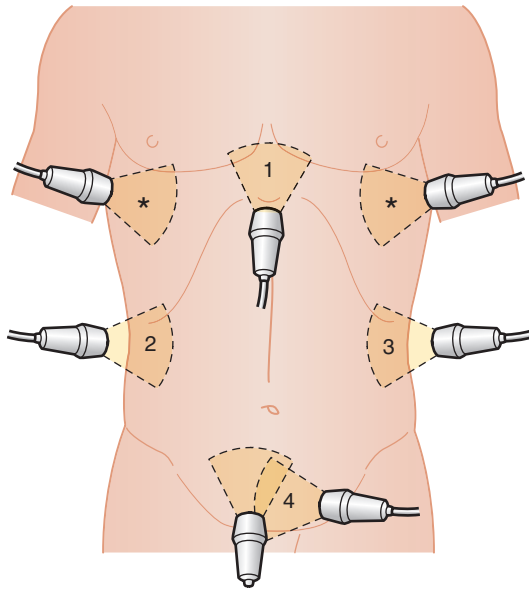


FIGURE 7-3 ■ The extended focused assessment for the sonographic evaluation of the trauma patient, or E-FAST, examination using four standard viewing ports (numbered): right upper quadrant, left upper quadrant, pelvis, subxiphoid, and the extended views of the left and right hemithoraces (*asterisks*). (From Körner M, Krötz MM, Degenhart C, et al: Current role of emergency US in patients with major trauma. *Radiographics* 28:225–242, 2008.)

echocardiography (TEE). Over the past decade there has been a major shift toward CT angiography as the most prevalent diagnostic modality in this patient population, with only a small percentage of patients undergoing conventional angiography or TEE. In two large trauma center reviews, CT angiography was found to be 90% to 95% sensitive and to have a 99% to 100% negative predictive value, making it useful as a screening modality.^{26,27} Meta-analyses of smaller case series from the literature over the past two decades appear to support these conclusions with sensitivity and negative predictive values approaching 100%.²⁶

Cited reasons for the shift in diagnostic modalities include technical improvements in the quality of CT angiograms with the addition of multi-row detector CT techniques to the standard helical CT, the relative ease of performing the test, reliable interpretations of rapidly obtained results, cheaper cost to perform the test, ability to perform real-time three-dimensional (3D) reconstructions, and the ubiquitous nature of CT machines in emergency departments across the nation. This examination can be performed at the same time as the common whole-body CT scan that many trauma patients undergo as part of their routine workup. Furthermore, the level of detail achieved with CT aortography far exceeds that from conventional aortography, allowing the radiologist and the surgeon to identify even the most subtle of aortic injuries that may have been missed on conventional aortography. Cardiac gating, an emerging technique, is used to limit motion artifact and has rendered questionable arterial lesions on routine CT amenable to better characterization. Large case series have identified CT aortography as



FIGURE 7-4 ■ Conventional angiogram demonstrating aortic transection injury just distal to the left subclavian artery.

an appropriate medium for screening, diagnosing, and planning operative repair of aortic injuries.²⁷

In addition, unlike CT angiograms, results and interpretation from TEE are extremely user-dependent, and the expertise requires an understanding of the anatomic structures and of the sensitivity levels of the machine. The new role for TEE may be reserved for its ability to detect and follow small intimal tears not seen on angiography and intraoperative imaging before and after a repair.

Angiography

Conventional angiography was once the gold standard in the diagnosis of aortic transection or injuries to the great vessels (Fig. 7-4).²⁸ In aortic transection, the classic aortographic image displays a pseudoaneurysm near the site of the isthmus. Partial or complete interruption of the aortic contour may be seen when the aortic wall has retracted, or if debris of the wall prolapses into the lumen. Occasionally, a ductus diverticulum (i.e., Kommerell diverticulum), a normal finding at the site of the ligamentum arteriosum, may be mistaken for aortic injury.²⁹

The role of conventional arteriography is unclear at the present time, as many centers currently use highly detailed, 3D aortic reconstructions alone for diagnosis and operative planning (Fig. 7-5). Others will obtain a conventional aortogram if the results of the CT angiogram are equivocal or if the study was technically inadequate. Still others will routinely get conventional arteriograms to confirm the presence of an aortic injury before surgical intervention.³⁰ When performed, a retrograde femoral arteriogram is the preferred study. Generally agreed upon indications for aortography in these patients either by conventional methods or CT angiography are listed in Box 7-1.

In fact, the use of conventional aortography for further evaluation of patients whose CT angiography has been read as indeterminate is unlikely to diagnose any aortic

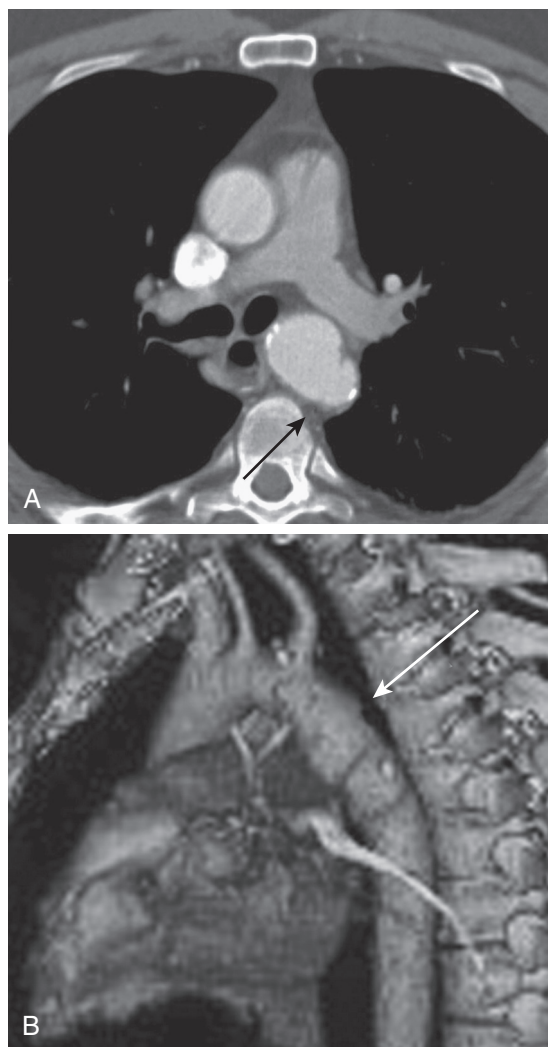


FIGURE 7-5 ■ Aortic injury with saccular aneurysm (arrows) following chest trauma as seen by CT angiogram (A) and three-dimensional reconstruction (B). (From Steenburg SD, Ravenel JG, Ikonomidis JS, et al: Acute traumatic aortic injury: imaging evaluation and management. *Radiology* 248:748–762, 2008.)

or other great vessel injuries, and thus may no longer be part of the evaluation of these patients.³¹ Thus, some have argued that the role of conventional angiography is limited to centers without adequate multidetector CT scanners with software for 3D reconstruction and an available radiologist for interpretation, for cases in which artifact from air or metallic objects preclude adequate imaging, or when angiography is used to direct therapy (e.g., embolization of smaller arteries).¹⁴

The presence of a mediastinal hematoma is often the first manifestation of an aortic injury seen on CT angiography (CTA).³² It is important, however, to note the exact location of this hematoma, as hematoma outside of the aortic walls with preservation of the fat plane around the aorta does not represent an aortic injury, but rather usually damage to surrounding periaortic mediastinal vasculature. A hematoma extending from a point adjacent to the aortic wall can be suggestive of a true aortic injury, and careful examination of the remainder of the thoracic CTA is important. Rarely will one see active extravasation

BOX 7-1

Indications for Angiographic Studies for Potential Thoracic Injuries

- High-speed deceleration injuries
- Chest radiography findings:
 - Widened mediastinum
 - Loss of aortic knob shadow
 - Tracheal or esophageal deviation to the right
 - Widening of paraspinal stripe or apical capping
 - Downward displacement of left mainstem bronchus
 - Obliteration of the aortopulmonary window
 - Fractured first rib, sternum, or scapula
 - Multiple rib fractures or flail chest
 - Massive hemothorax
- Upper extremity hypertension
- Unexplained hypotension
- Pulse deficits or asymmetry
- Systolic murmur

of contrast into the mediastinum or thorax, as this type of injury is almost always uniformly fatal.

There are several radiographic signs on CTA that are diagnostic of traumatic aortic injury and should lead to immediate repair without further diagnostic evaluation, especially in patients in unstable condition. These signs include intraluminal thrombi, clear evidence of mural dissection or an intimal flap, and changes to the diameter or contour of the aorta itself. Delay of definitive repair in these patients can lead to increased mortality among this patient population.

EMERGENCY DEPARTMENT THORACOTOMY

The indications for emergency department (ED) thoracotomy have been widely debated.³³ ED thoracotomy clearly plays a role in penetrating thoracic trauma, particularly in the setting of trauma patients with cardiac tamponade from penetrating chest injuries.³⁴ The role of ED thoracotomy for patients with blunt traumatic injuries is heavily debated and appears to be limited. The Western Trauma Association recently published the results of a prospective study involving 18 trauma centers and concluded that resuscitative ED thoracotomy may be considered futile when prehospital cardiopulmonary resuscitation (CPR) for blunt trauma exceeds 10 minutes with no response.³⁵

Thoracotomy allows relief of cardiac tamponade, the ability to perform open cardiac massage, and control of ongoing intrathoracic hemorrhage. In addition, by applying a crossclamp to the thoracic aorta, one can limit intra-abdominal bleeding and improve cerebral and coronary perfusion in the setting of exsanguinating hemorrhage. Patients with penetrating cardiac stab wounds are the most likely population to survive resuscitation with ED thoracotomy; the same is true for other penetrating cardiac injuries. The likelihood of patient survival depends on patient down time, the patient's age and

BOX 7-2 Indications and Contraindications for Emergency Room Thoracotomy

ACCEPTED INDICATIONS

- Unresponsive hypotension (SBP < 60 mm Hg)
- Rapid exsanguination from indwelling chest tube (<1500 ml)
- Traumatic arrest with previously witnessed cardiac activity (pre- or in-hospital) following penetrating thoracic injuries
- Persistent hypotension (SBP < 60 mm Hg) with diagnosed cardiac tamponade, air embolism

RELATIVE INDICATIONS

- Traumatic arrest with previous witnessed cardiac activity (pre- or in-hospital) following blunt trauma
- Traumatic arrest without previously witnessed cardiac activity (pre- or in-hospital) following penetrating chest injuries
- Prehospital cardiopulmonary resuscitation less than 10 minutes in intubated patient, 5 minutes in non-intubated patient

CONTRAINDICATIONS

- Blunt thoracic injuries with no previously witnessed cardiac activity
- Multiple blunt trauma
- Severe head injury

SBP, Systolic blood pressure.

comorbidities, and signs of life on arrival in the ED. General guidelines have been recommended for ED thoracotomies by the American College of Surgeons' Committee on Trauma in the setting of thoracic trauma (Box 7-2).³⁶

Although these general guidelines have been debated, most agree that the best results occur in patients with penetrating cardiac trauma and in whom there is a good likelihood for preservation of cerebral activity. Even with an experienced team and established protocols, results are still poor. The length of time of prehospital CPR has become one of the determinants whether to perform ED thoracotomy. In one report, there were no survivors from ED thoracotomy when prehospital CPR had been in progress in an intubated patient for more than 10 minutes, or more than 5 minutes in a nonintubated patient.³⁷ Another relatively poor marker of outcome is refractory metabolic acidosis monitored during the initial resuscitation efforts, with pH of less than 6.8 or severe base deficits restraining the use of ED thoracotomy. However, signs of life upon presentation to a trauma center nearly quadruple the probability of survival.³⁸

The surgical approach is a left fourth interspace anterolateral thoracotomy. This can be performed with the patient prone or preferably with a few folded blankets placed under the patient's left side to elevate it and to allow the incision to be opened more posteriorly if necessary. The incision can also be carried across the sternum into the right chest if necessary to improve exposure or to evaluate the right side for injury. The pectoralis muscle is divided with a large scalpel, and the intercostal muscles are divided widely using curved Mayo scissors. The

sternum is transected with an oscillating saw, Lebsche knife, Gigli saw and even (if nothing else is available) a good pair of trauma shears. The mammary vessels are divided as they are crossed, and they are ligated once the patient's condition is more stable. The pericardium is opened widely in a cranial, caudal direction, staying anterior to avoid the phrenic nerve. A large pericardiotomy allows easier evacuation of clot, visualization of the heart, and ability to perform more efficient open heart massage. Cross-clamping the descending aorta requires opening the overlying parietal pleura, taking down the inferior pulmonary ligament or retracting the inferior lobe in a superior fashion, and then freeing the aorta from the esophagus bluntly via digital dissection. Care should be taken not to avulse any intercostal vessels. At this point a vascular aortic cross-clamp can be placed across the aorta. Aortic cross-clamp time should be kept to the minimal amount of time (less than 30 minutes) required to resuscitate the patient to avoid the sequelae of spinal cord ischemia and lactic acidosis caused by distal hypoperfusion. When the patient's condition is sufficiently stable, he should be taken immediately to the operating room to definitively manage any injuries and to provide a sterile chest washout with antibiotic irrigation and formal closure of the thoracotomy with wide chest tube drainage.

Even with these extraordinary ED efforts on the part of the trauma team, the results from ED thoracotomy are dismal, with overall survival rates of 1.8% to 27.5%.³³ Although the survival rates of patients who undergo ED thoracotomy vary substantially among case series in the literature, mechanism of injury is the most important factor affecting mortality as patients suffering penetrating injuries are more likely to benefit from this procedure, with mean survival rates of 13% (range, 2.7%–38.9%) compared with a mean of 1% (range, 0%–12%) of patients with blunt injuries. Even among those who survive their injuries after ED thoracotomy, up to half of these patients will have some neurologic deficit, although some authors have reported more than 90% of patients regaining neurological function in their series.³⁸

BLUNT TRAUMA

As mentioned previously, blunt trauma to the chest in the United States is far more common than penetrating injury. A 2002 report by the National Safety Council reported that of all blunt trauma deaths, 25% were due to thoracic trauma. The high-speed deceleration and crush injuries involved in automobile accidents have become increasingly prevalent since the 1950s, and they account for the majority of blunt thoracic trauma. Falls, sports mishaps, assaults, and blast injuries follow. The damage from a powerful blast can be particularly severe as the blast pressure wave imparts a large amount of kinetic energy to a small area. Blast kinetic energy especially affects gas-containing organs, such as the lung, resulting in pulmonary hemorrhage, hypoxia, and shock. In addition, because of the mechanisms that provide the amount of energy needed to produce significant blunt thoracic trauma, many of these patients will have

associated head, abdominal, or extremity injuries along with those of the thorax that are presented here.³⁹ Nevertheless, even among this multiply injured population, the thoracic injuries are responsible for the majority of mortality among these patients.⁴⁰

Chest Wall

Optimal mechanical properties of the chest wall are important determinants for effective functioning of the entire respiratory system. Blunt trauma to the chest wall can disrupt respiratory mechanics and perturb intrathoracic pressure gradients, leading to poor pulmonary toilet and significant morbidity. Chest wall trauma alone occurs in only 16% of cases,⁴¹ and it is often a marker of more ominous visceral injury inside the thoracic cage or below the diaphragm. Since the chest wall, composed of the ribs, sternum, clavicles, and scapulae, provides a protective bony skeleton around the vital organs of the chest, the effect of fracturing each of these bones will be considered.

Rib Fractures

Fracture of the ribs is the most common blunt thoracic injury, occurring in an estimated 300,000 people in the United States during the year 2000, or 39% of patients admitted to major trauma centers.^{42,43} It is important to realize that rib fractures represent an important indicator of trauma severity. The greater the number of ribs fractured, the higher the patient's morbidity and mortality, even from nonpulmonary causes, especially if six or more ribs are broken.⁴³⁻⁴⁵ The number of ribs fractured has been significantly correlated with the presence of hemothorax or pneumothorax, with 81% of patients having either condition if two or more ribs were fractured.⁴⁶ Fractures of the fourth through the ninth ribs are associated with injuries to the lung, bronchus, pleura, and heart, whereas fractures below the ninth rib are indicative of spleen, hepatic, or renal injuries.

The main symptoms include pain, exquisite point tenderness, and possibly crepitus. As the initial examination, an upright chest radiograph should be obtained as a routine part of the trauma series if possible; otherwise, a supine chest radiograph will suffice. In the event that special documentation of a crime, such as child abuse, is needed, rib detail films are performed. Chest radiography alone fails to diagnose rib fractures in more than half of trauma patients with fractures; thus, the addition of CT to the trauma evaluation improves the sensitivity of the diagnosis of rib fractures.⁴⁷ Careless dismissal of a simple rib fracture and underestimating its pathophysiologic potential, especially in older patients, is a common management pitfall. After adjusting for severity of injury, comorbidity, and the presence of multiple rib fractures, older patients (≥ 65 years old) with simple rib fractures still were five times more likely to die compared with patients younger than 65 years.⁴⁸ First rib fracture has particular significance because of the great force required for it to occur and the likelihood that intrathoracic visceral injury has also taken place. The two most common sites of first rib fracture are at the subclavian sulcus and

in the neck of the first rib posteriorly. Subclavian artery and/or aortic arch angiography (conventional or CTA) is indicated if the first rib fracture is displaced posteriorly, the subclavian groove is fractured anteriorly, there is widened mediastinum on chest radiography, or there is an upper-extremity pulse deficit, a concomitant brachial plexus injury, or an expanding hematoma.⁴⁹ In the pediatric population, a chest radiograph can have predictive value in assessing for associated intrathoracic vascular trauma in children with first rib fractures. A normal mediastinum on CXR in the setting of a first rib fracture carried a 100% negative predictive value in a study done at a level 1 pediatric trauma center.⁵⁰

Although binders, cumbersome rib belts, and taping were advocated in the past, the modern approach to treatment emphasizes relief of pain, prevention of atelectasis, and optimization of pulmonary toilet. The importance of adequate analgesia to proper pulmonary toilet is evident by studies showing decreased mortality among patients with rib fractures who received epidural anesthesia.⁴⁵ A prospective case series at a level 1 trauma center found that patients with isolated, simple rib fractures suffered an average over 50 days of disability and lost work and usual activity because of pain.⁴⁴ Interventions favored for short-term pain relief include epidural analgesia, intercostal rib blocks, intrapleural instillation of anesthesia, and intravenously giving opiates and oral nonsteroidal anti-inflammatory drugs.^{42,51-53} More recently, continuous intercostal nerve blockade has been explored as an analgesic adjunct at multiple institutions. Patients with three or more unilateral rib fractures, managed with continuous intercostal nerve blockade through an extrathoracic, paravertebral approach, demonstrated significant improvement in numeric pain scale scores and sustained maximal inspiration lung volumes.⁵⁴ Chronic pain control is invariably required usually with oral narcotics, nonsteroidal anti-inflammatory drugs, and transdermal patches. Patients must be reminded to practice adequate pulmonary toilet after discharge by using an incentive spirometer, deep breathing, coughing, and ambulation. Patients should be counseled that their pain will likely continue for weeks and that sustained need for oral analgesics during this time is not uncommon. In addition to chronic pain, other long-term sequelae include chest wall deformities, persistent dyspnea, and neurologic deficits. A relatively uncommon but potential long-term complication of severe blunt chest wall trauma is a thoracic lung hernia. These entities should be repaired, because they pose a constant threat of incarceration, pneumothorax, or strangulation.⁵⁵

Flail Chest

During the primary survey of a patient who has suffered blunt trauma, careful observation for the presence of a flail chest is imperative because of the associated pathophysiologic derangements that accompany this finding.⁵⁶ This injury usually results from the fracture of four or more ribs at two sites either unilaterally or bilaterally (multiple contiguous rib fractures with multiple fractures of each rib), promoting enough instability that the thoracic cage exhibits paradoxical motion locally as evidenced

by thoracic wall collapse with inspiration. This instability impairs respiratory mechanics resulting in hypoventilation, poor pulmonary drainage, and atelectasis. Patients with flail chest are distinct from those with multiple rib fractures since they are at a higher risk of respiratory compromise and often require early intubation.⁵⁷ Endotracheal intubation is required in more than two thirds of patients with flail chest, and it is indicated for a respiratory rate greater than 40 breaths/minute, or a PO_2 of less than 60 mm Hg despite 60% face-mask oxygen. Relative indications for intubation include shallow respirations, depressed consciousness, pre-existing chronic lung disease, or the presence of associated injuries. In fact, in the presence of multiple injuries, intubation of the patient with a flail chest is almost unavoidable, and early controlled intervention is often preferred to obviate sudden respiratory decompensation and its subsequent morbidity.⁵⁷

A flail chest invariably occurs because of high kinetic energy absorption by the thoracic cage; therefore, it is an important marker for significant intrathoracic injury in patients with blunt trauma. Flail chest is highly associated with pulmonary contusion, which occurs in approximately 45% of patients.⁵⁸ Pneumothorax and hemothorax are common acute sequelae, while acute respiratory distress syndrome occurs in as many as one third of patients, resulting in mortality rates as high as 33%.⁵⁸

Conservative therapy with emphasis on pain relief with thoracic epidural analgesia is the mainstay of therapy in most centers. In a minority of cases, however, patients require chest wall stabilization (Fig. 7-6).^{59,60} These commonly are intubated patients with no possibility of being weaned from the ventilator because of a large unstable flail segment of chest wall. However, recent meta-analyses suggest that chest wall stabilization of flail segments may have significant effects on both morbidity and mortality. Patients who underwent operative management for flail chest were noted to have significantly decreased duration of mechanical ventilation, length of ICU stay, risk for pneumonia, need for tracheostomy, and mortality.^{61,62} A recent prospective randomized trial corroborated a significantly decreased length of ICU stay in patients undergoing chest wall stabilization for flail chest.⁶³

Sternal Fractures

Current estimates suggest traumatic sternal fractures occur in 3-8% of blunt trauma.⁶⁴ Isolated fractures of the sternum are seen with increasing frequency in motor vehicle crashes, particularly since the passing of the mandatory seatbelt legislation because of the rapid deceleration that occurs from this mechanism of injury, especially in vehicles with absent or malfunctioning airbags.⁶⁵ Point tenderness, edema, and obvious deformity are occasionally detected on physical examination, but lateral chest radiography is diagnostic in the majority of patients.

Mortality from isolated sternal fractures remains low (3.5%), and surgical repair is uncommon (<2%).⁶⁶ Some have suggested that patients with isolated sternal fractures, a normal echocardiogram, and no elevation of cardiac enzymes in the early hours of injury will have a benign course. They advocate discharging these patients

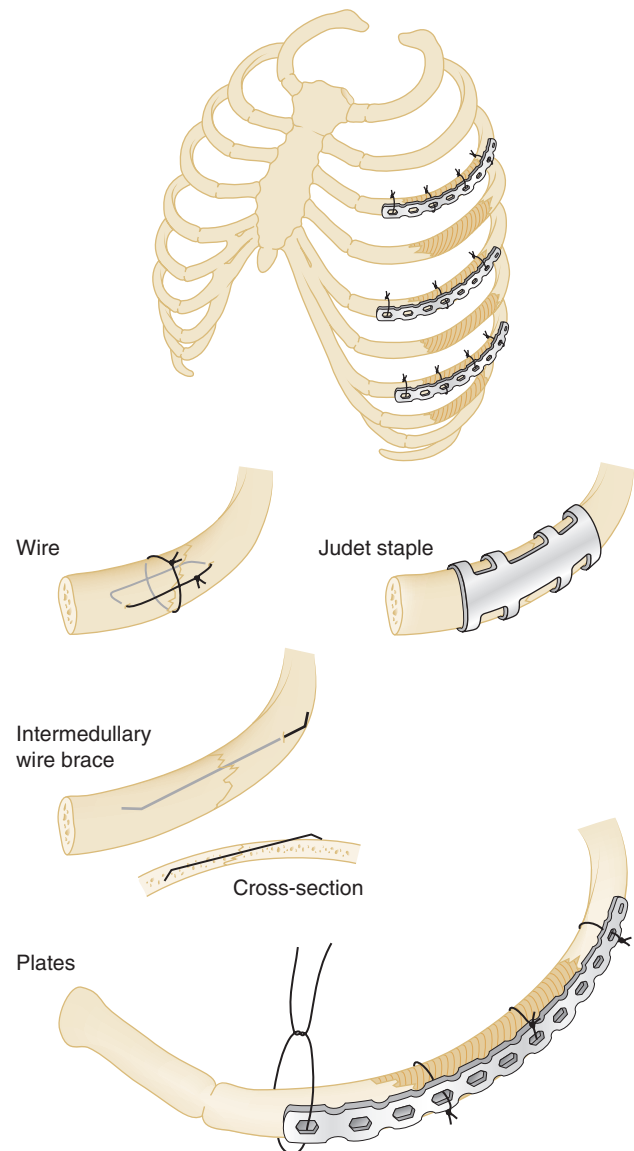


FIGURE 7-6 ■ Stabilization of flail segments with wire, Judet staple, intermedullary wire brace and periosteal plates. (From Trunkey DD: Chest wall injuries. In Blaisdel FW, Trunkey DD, editors: *Cervicothoracic trauma*, ed 2, New York, 1994, Thieme Medical Publishers.)

home within 24 hours of arrival in the ED.⁶⁷ Others support selective repair for those with severe deformities or associated chest wall fractures, because this procedure can be performed with low mortality and morbidity with good outcomes.⁶⁸ Surgical management options include metal plates with or without autologous bone grafts.^{69,70} Although an isolated sternal fracture carries a favorable prognosis, other life-threatening concomitant injuries occur in up to one third of patients necessitating careful evaluation and clinical vigilance.

Clavicular Fractures

Management of traumatic clavicular fractures often depends on location. As the clavicles are thin and exposed, the middle third of the clavicle is the most frequently

fractured region of the clavicle, occurring in three fourths of patients with clavicular fractures.⁷¹ The remaining one fourth of clavicular fractures is found in the acromial region and is classified according to the location and integrity of the surrounding ligaments. Type I fractures are found distal to the coracoclavicular ligaments, and the acromioclavicular joint remains intact with minimal displacement of the fracture segments. Type IIa fractures are found medial to the conoid ligament, whereas IIb fractures are found within the coracoclavicular ligaments and involve disruption of the conoid ligament. Type III fractures are again observed distal to the coracoclavicular ligaments, extending into the acromioclavicular joint. Type IV fractures are reserved for the pediatric population and are evidenced by disruption of the epiphyseal plate.

In a type V fracture, a small fragment of clavicle remains attached to the coracoclavicular ligaments with separation from the remaining clavicle.⁷² Fractures of the medial one third of the clavicle are rare. Right and left clavicles tend to be fractured with equal frequency. Clinical examination reveals tenderness, deformity, crepitus, and less commonly upper extremity neurovascular injury. Routine chest radiographs are often sufficient for diagnosis.

Conservative treatment is the preferred practice for medial and middle clavicular fractures, using closed reduction and figure-of-eight slings. This results in normal healing in 95% of patients. Operative intervention is typically reserved for displaced fractures, comminution, or neurologic deficits associated with the fracture. Surgical techniques include placement of steel reconstruction plates and cannulated bone screws. A recent meta-analysis of prospective studies comparing operative (plating or elastic intramedullary nailing) versus nonoperative (sling or bandage fixation) management demonstrated a significantly reduced rate of non-union, malunion, and neurologic complications when surgical intervention is used.⁷³ Late sequelae of clavicular fractures include painful non-unions, altered shoulder mechanics, neurogenic thoracic outlet syndrome, vascular abnormalities, and brachial plexus injuries. Contributing factors to non-union include severe initial trauma, open fracture, marked initial displacement and shortening, soft tissue interposition, primary open reduction and internal fixation, refracture, multiple trauma, and inadequate initial mobilization.⁷⁴

Scapular Fractures

Since the scapula is thick and well protected, scapula fractures are relatively rare and occur usually only after high-kinetic-energy impacts. In fact, many patients with scapular fractures will have other serious injuries to other anatomic sites because of the large transfer of energy needed to produce this type of injury.⁷⁵ Still, they should always be in the differential diagnosis in any patient who complains of shoulder pain or violent muscular contractions about the shoulder after blunt trauma. Most fractures occur in the neck and body, with glenoid, acromion, and coracoid process injuries being less frequent. As is the case with other thoracic cage trauma caused by severe

blunt trauma, associated pulmonary contusions and rib fractures are common. Diagnosis is often difficult on physical examination, occasionally identified by localized tenderness, swelling, and hematoma formation over the fracture site. Scapular fractures are often overlooked on supine chest radiographs, and the three-view trauma series of the shoulder is often necessary to reveal the fracture. Chest CT scans are not recommended.

Immobilization in a sling with pain relief and early range-of-motion exercises is usually all that is needed for recovery of good glenohumeral function. Open surgical reduction is rare. Brachial plexus injuries sustained are often chronic, leading to long-term disability including loss of shoulder mobility. In these patients, a severely debilitated and insensate extremity may occasionally require amputation.

Traumatic Asphyxia

Traumatic asphyxia, or Perthes syndrome, is an uncommon clinical syndrome usually occurring after a severe crushing or compression-related injury to the chest preceded by deep inspiration. Symptoms and associated physical findings include subconjunctival hemorrhage, cervicofacial cyanosis resulting in a purple-blue neck and face discoloration, facial edema, vascular engorgement of the head, mucosal petechiae, and multiple ecchymotic hemorrhages of the face, neck, and upper chest. Cerebral hypoxia owing to hypoventilation is a life-threatening complication that can result in varying degrees of cerebral dysfunction. Sore throat, hoarseness, dizziness, numbness, and headaches are common. Pitting lower-extremity edema, hemoptysis, hemotympanum, hematuria, rectal bleeding, and transient visual loss can also be evident.⁷⁶ The diagnosis is made primarily from the history and physical examination, with chest radiographs being largely normal.

Prompt assessment of airway, breathing, and circulation—the overarching principles of trauma management—is critical, with special attention paid to re-establishing oxygenation and perfusion to ensure a successful outcome. Head elevation should be maintained at 30 degrees. If a patient survives the initial insult, the prognosis is excellent. Skin discoloration resolves within 3 weeks, but complete resolution of subconjunctival hemorrhage can take up to 1 month.

Pulmonary Contusion

The lung parenchyma fills a large portion of the chest cavity and lies close to the bony thorax, making it vulnerable to contusion. In fact, pulmonary contusion is the most common injury in blunt chest trauma.⁵⁶ The mechanism of injury usually involves a sudden deceleration injury, such as in a motor vehicle crash with the chest hitting the steering wheel, or in a blast injury or a fall from a great height. Although pulmonary contusions are generally associated with concomitant thoracic cage damage and other visceral injuries, they can occur isolated without evidence of rib fracture. Wagner and colleagues⁷⁷ have suggested that the pathophysiology of a pulmonary contusion is based on hemorrhage into

adjacent alveolar spaces rather than injury to the alveolar capillary wall itself.

Classic symptoms include dyspnea, tachypnea, hemoptysis, cyanosis, and hypotension. Physical examination can demonstrate inspiratory rales, and decreased breath sounds on the affected side. CT scan is the study of choice; it is more sensitive than radiography in detecting a pulmonary contusion. All patients with a pulmonary contusion should be observed on supplementary oxygen in a hospital setting, because of a tendency of their ventilatory status to deteriorate rapidly. By standard ATLS protocol, patients with significant hypoxia with PaO₂ less than 65 mm Hg and SaO₂ less than 90% despite oxygen supplementation should be intubated and undergo ventilation within 1 hour after injury. A conservative fluid management strategy should be undertaken; however, if large volumes of fluid are necessary for resuscitation of associated extrathoracic injuries, a pulmonary artery catheter should be placed.

As mentioned previously, patients with pulmonary contusions are at a high risk of respiratory insufficiency and secondary pneumonia because of the parenchymal damage and large systemic inflammatory response that accompanies this injury. The formation of a pulmonary contusion along with an Injury Severity Score greater than 65 have been identified as risk factors that have the greatest contribution to the development of acute respiratory distress syndrome.⁷⁸ The mortality rate from an isolated pulmonary contusion is low, but when combined with other severe injuries, it rises to as high as 50%.⁷⁹ Clinical factors predisposing to mortality after a pulmonary contusion include patient age, resuscitation volume, and severity of the pulmonary parenchymal injury as measured by PaO₂/FiO₂ (P/F ratio) at 24 and 48 hours after injury.⁸⁰ For patients requiring mechanical ventilation, little literature exists in predicting successful extubation. Reintubation after extubation occurs not infrequently, and it is associated with significant morbidity and mortality. A recent retrospective study identified both a P/F ratio of less than 190 or an Alveolar-arterial (A-a) oxygen gradient greater than 100 mm Hg as independent predictors of failed extubation after pulmonary contusion.⁸¹

Laryngeal Injuries

The larynx enjoys a position of relative protection in the neck shielded laterally by the sternocleidomastoid, posteriorly by the cervical spine, and from the front and above by the mandible. Blunt trauma to the larynx is therefore rare, but has a mortality rate reaching as high as 40%, with most patients dying at the trauma scene because of the nature of the injury.⁸² Death is due primarily to asphyxia from laryngospasm, hemorrhage from an associated major vascular laceration, or laryngeal concussion. Laryngeal trauma is suspected after motor vehicle crashes, hanging attempts, sporting blows such as in karate or soccer, and severe falls.

Signs and symptoms after laryngeal blunt trauma include hoarseness, pain, skin contusions, cervical emphysema, cervical neck crepitus, dysphagia, and upper airway obstruction. Subtle signs of dysphonia including easy fatigue during phonation, marked difficulty with

high-pitched and singing voice, and decreased phonation time can also occur. Diagnosis requires a high index of suspicion because many patients remain asymptomatic at an early stage of injury and minor symptoms may belie serious abnormalities. Furthermore, patients may be unable to supply critical aspects of the history and physical examination because of aphonia or intubation. Early diagnosis and appropriate therapy have a significant effect on the patient's condition later, especially regarding scar formation, ease of breathing, and voice quality.

After securing a patent and stable airway, transnasal flexible laryngoscopy is used for definitive diagnosis. Because the risk for laryngospasm and sudden airway obstruction is increased in the presence of a laryngeal lesion, preparations for emergency intubation or tracheostomy should be readied before performing endoscopy. Flexible laryngoscopy involves inspection for vocal cord mobility, mucosal edema, hematomas, tears, and arytenoid cartilage subluxation. CT scan is a sensitive diagnostic test for laryngotracheal injury, and it may be indicated despite normal flexible laryngoscopy. The status of the laryngeal skeleton can be determined more precisely with high-resolution CT scanning.

The decision to repair or observe laryngeal trauma is primarily based on the patient's respiratory distress and associated injuries. The presence of laryngeal fractures, air in the soft tissues, and extravasation of contrast material in the neck are helpful in assessing the extent of the injuries before surgical intervention. Immediate initial surgery is aimed at stabilizing the cartilaginous framework of the larynx and repairing the mucosa. For minor lacerations and abrasions of the larynx, observation is sufficient; however, for larger injuries, primary closure via a thyrotomy is the preferred management. Early and low tracheostomy is recommended for patients with endoluminal disruption of the larynx. Suboptimal results are found in patients with bilateral vocal cord paralysis, displaced cricoid fracture, and arytenoid subluxation.

Tracheobronchial Injuries

Tracheobronchial injuries are uncommon, but they usually occur after a high-energy impact and are associated with trauma to other vital organs.⁸³ According to an extensive review of all published tracheobronchial injuries since 1873, 59% of these injuries are due to motor vehicle crashes, 76% occur within 2 cm of the main carina, and 43% are located within 2 cm of the right main bronchus.⁸⁴ As the carina is in a relatively fixed position in the chest, it is more susceptible to shear forces from rapid acceleration and deceleration. Three potential mechanisms of blunt tracheobronchial disruption have been identified. The first and most common is due to a forceful anteroposterior compression of the thoracic cage, the so-called dashboard injury in which an unrestrained automobile occupant hyperextends and strikes their neck on the dashboard or steering wheel, producing a crushing injury of the cervical trachea. The second mechanism is a consequence of high airway pressures, whereas the third is due to rapid deceleration.

Typical clinical features include respiratory distress, dyspnea, and air leak. Hoarseness or dysphonia is also

common, occurring in up to 45% in some series. In patients with central airway injuries contained in the mediastinum, subcutaneous emphysema may be evidenced by crepitus. Injuries to the tracheobronchial tree that are in communication with the pleural space may progress to tension pneumothorax. If tube thoracostomy is required, an air leak is commonly observed with these injuries. A massive air-leak may be indicative of severe injury, and significant ventilatory volume loss can result when tube thoracostomy is maintained at high amounts of negative pressure. Persistence of an undiagnosed air leak is life threatening and can progress to respiratory insufficiency. On physical examination, the most common diagnostic signs are subcutaneous emphysema (35%-85%), pneumothorax (20%-50%), and hemoptysis (14%-25%).

The definitive diagnostic study of choice is flexible bronchoscopy. A careful bronchoscopic examination includes an inspection of the tracheobronchial tree documenting the site and extent of injury, including a withdrawal of the endotracheal tube in an intubated patient to diagnose proximal tracheal tears. A high level of suspicion is imperative for diagnosis because patients with tracheobronchial injuries occasionally exhibit normal clinical appearance and negative endoscopic findings. In fact, diagnoses of tracheobronchial injuries are often delayed, with the repair performed months and even years after the initial injury.⁸⁴ No statistically significant association was found between delay in treatment and successful repair of the injury, with 90% of patients undergoing successful surgical reconstruction more than 1 year after initial injury. Effective airway management consists of bypassing the lesion with endobronchial intubation to the healthy bronchus using a single-lumen or double-lumen endotracheal tube. Primary surgical repair of the injured airway is often necessary, with the decision to intervene based on the size of the lesion and the respiratory status of the patient. Simple, clean lacerations without much devitalized tissue can be repaired with simple, interrupted 4-0 Vicryl sutures (Ethicon, Cincinnati, OH). More severe injury may require lobectomy or pneumonectomy. The proximal one half to two thirds of the trachea is best seen using a low cervical collar incision, whereas the distal third of the trachea, the carina, and both the proximal right and left mainstem bronchi should be approached through a right thoracotomy. Prompt diagnosis and treatment generally lead to good functional recovery, but if tracheobronchial injuries remain undetected and untreated, late complications such as bronchial stenosis, recurrent pneumonia, and bronchiectasis can develop.

Great Vessels

The thoracic great vessels consist of the aorta and its major intrathoracic branches, the pulmonary arteries and veins, the vena cavae, and the azygous vein. By far the most lethal of these is the descending aortic injury, which accounts for as much as 40% of fatalities after blunt thoracic trauma with the majority of deaths occurring at the trauma scene.⁸⁵ Approximately 8000 people die annually in the United States from blunt thoracic aortic injury, and

it is second only to traumatic brain injury in terms of its overall mortality rate. Most of these deaths are due to free intrapleural aortic rupture. The site of injury is usually the isthmus, an area of the medial descending aorta near the ligamentum arteriosum where shear forces from rapid deceleration cause a tear at this point of fixation of the vasculature. Blunt thoracic aortic trauma is graded based on severity of injury. Type I injury involves an intimal tear, type II injury is seen as an intramural hematoma, type III injury involves pseudoaneurysm of the aorta, and type IV injury is evidenced by free rupture.⁸⁶ Again, a high index of suspicion in a patient who has suffered a high speed collision is critical because approximately half of the patients with contained aortic rupture have no external signs of trauma.⁸⁷

A plain chest radiograph has a 95% negative predictive value for identifying blunt traumatic aortic lesions, and thus represents an adequate diagnostic screening study.⁸⁸ The classic signs on plain chest radiograph (Fig. 7-7) as described by Kirsh and Sloan^{88a} include a widened mediastinum (>10 cm), loss of aortic knob contour, shift of the endotracheal tube and the trachea to the right, elevation of the left main stem bronchus, depression of the right main stem bronchus, shift of the nasogastric tube to the left, apical capping, first rib fracture, acute left-sided hemothorax, and a retrocardiac density. Of these, the finding that most reliably correlates with an aortic tear is loss of aortic knob contour. Still, traumatic aortic intimal injuries or pseudoaneurysms can evade plain radiographic detection. Spiral-CT scanning with angiography, which has 96.2% sensitivity and 99.8% specificity for blunt traumatic aortic abnormalities, has become the preferred confirmatory study in the algorithm of blunt aortic injury for hemodynamically stable trauma patients, and it is widely available. Conventional biplane contrast aortography should be considered despite previous negative studies if the clinical suspicion remains high, as 2% of patients with great vessel injuries are detected with this modality.⁸⁹ Those patients with an obviously widened mediastinum on radiography along with hypotension and

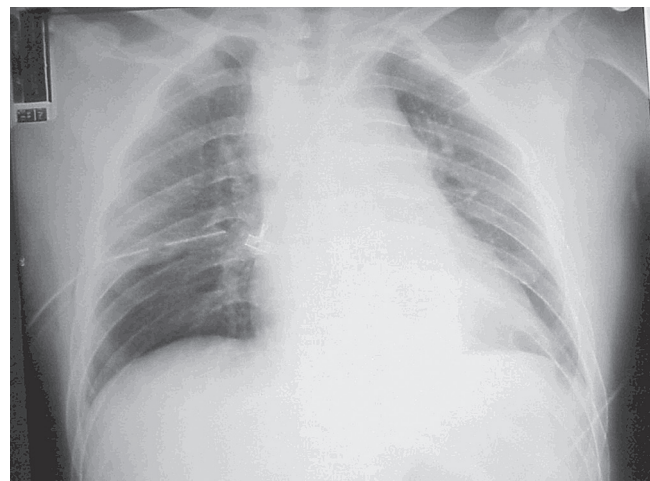


FIGURE 7-7 ■ Typical chest radiograph with widened mediastinum suggestive of aortic transection from decelerating blunt chest injury.

hemothorax are at high risk for imminent rupture of a contained aortic injury and can be taken to the operating room without further delay in obtaining confirmatory studies.⁹⁰

Once a contained aortic rupture is diagnosed, urgent management is required. Specifically, invasive monitoring and careful blood pressure and heart rate control with intravenous beta blockade followed by afterload reduction are indicated as a first step. A thorough neurologic examination to document any preoperative deficits is vital. If other life-threatening injuries, such as intra-abdominal bleeding, are detected in the primary or secondary survey, these are repaired first before the thoracic aortic injuries are addressed. If there is little time for preoperative studies, a TEE can even be performed during laparotomy to identify signs of blunt traumatic aortic injury. In the last decade or so, the four most dramatic changes in management of these patients have been nonoperative management, delay to definitive treatment, use of endovascular stenting for repair, and the increasing use of left heart bypass via centrifugal pumps in the operating room.⁸⁹

A subset of patients with contained aortic rupture including those with severe central nervous system injury, extensive burns, hemodynamic instability from other traumatic injuries, respiratory failure or those with small intimal defects are appropriately managed either nonoperatively or with a delayed operation.⁹¹ Mean arterial pressure should be maintained near 60 to 70 mm Hg in a manner similar to patients who have suffered an acute dissection of the descending thoracic aorta.⁸⁹ Although the length of time necessary for rigorous antihypertensive therapy is unknown, reports in a small series of patients followed serially by TEE have shown that complete resolution of small injuries (<20 mm) occurs in approximately 9 days (range, 3–19 days).⁹²

Since 1991, when the first endovascular stenting of the aorta was performed for an abdominal aortic aneurysm, interest in stent grafting as an alternative to traditional aortic surgery has surged. Preliminary experience is now accumulating from percutaneous positioning of endovascular stent grafts under angiographic guidance for blunt traumatic aortic lesions.^{93–96} An analysis of the available data has demonstrated this to be a safe and effective procedure.⁹⁶ This procedure has excellent technical success rates, averaging 96.3% with endoleak rates of 5.1% while maintaining low rates of complication, including overall and graft-related mortalities of 7.7% and 2%, respectively, and rates of paraplegia of 1.1%. More recent analyses including the RESCUE trial, a multicenter prospective trial, have demonstrated similar outcomes with an overall 30-day mortality of 8% and aortic-related mortality of 4%.⁹⁷ Coverage of the left subclavian artery with the endograft is reported in 39% to 48% of cases.^{86,97,98} Similar analyses of open repairs have demonstrated worse outcomes, with mean mortality of 14.7% and a rate of paraplegia of 3.3%. A meta-analysis from 2008 involving 17 retrospective studies comparing endovascular stent grafting to open repair demonstrated significantly lower 30-day mortality rates and postoperative paraplegia in those who underwent stent grafting.⁹⁹ In addition, length of hospital stay, transfusion requirement,

and need for additional surgical procedures have been shown to be lower among patients who undergo percutaneous stenting compared with open repair of traumatic aortic injuries.¹⁰⁰ As the technology progresses and the grafts and their delivery systems become easier to use, long-term studies, including randomized, prospective trials evaluating the durability and efficacy of this approach, will be warranted.

The open surgical approach uses a fourth interspace left posterolateral thoracotomy. Proximal and distal control is obtained, with care taken to avoid injury of the recurrent laryngeal and vagus nerves and the thoracic duct. There has been considerable controversy over more than two decades between proponents of the use of clamp-and-sew techniques versus unloading the heart proximally and shunting the blood distally. Traditional arguments against the use of left heart bypass with passive shunts included the need to heparinize a trauma patient with associated injuries and the lack of data demonstrating decreased neurologic injury with passive shunting. Convincing evidence is accumulating, however, demonstrating the benefits of left atrial to femoral shunting via a centrifugal pump. Many of these systems do not require heparin, and there is a growing body of literature demonstrating low rates of paraplegia and mortality.^{101–103} Although prolonged clamp times and the increasing complexity of the repair are associated with rising paraplegia rates, another important predictor of paraplegia has been the occurrence of upper body hypotension during surgery. Left atrial-to-femoral shunting during and immediately after clamping of the aorta allows strict control of upper body blood pressure. In fact, results from a review of a 30-year experience of blunt traumatic aortic rupture remarked on the gradual evolution in clinical surgical technique from “clamp-and-sew” to “passive shunt” to “heparin-less partial bypass.”¹⁰³

Blunt Cardiac Injuries

For decades, the term *cardiac contusion* has been used to describe a wide clinical spectrum of conditions thought to be associated with blunt injury, ranging from elevation of cardiac enzymes to complex intracardiac defects or rupture. This term should now be omitted entirely because of its inconsistent clinical descriptions, and because it offers little in terms of its ability to dictate therapy or predict outcomes.¹⁰⁴ In keeping with the system of assigning trauma scores in the acutely injured patient, a new classification for blunt cardiac injury has been developed and is currently in use at major trauma centers (Table 7-2).¹⁰⁵

Although frequently highlighted in the literature, only a few patients require intervention for blunt cardiac injuries. These injuries are usually a result of high-speed motor vehicle crashes, falls from heights, crush and blast injuries, or direct violent assaults. Most motor vehicle-related deaths, however, are related to blunt injuries of the heart and great vessels. Mechanisms of decelerating cardiac trauma include compression by the sternum, impingement between the sternum and vertebral bodies, and increased venous return from crushing lower extremities injuries resulting in rupture of the cardiac chambers

TABLE 7-2 Blunt Cardiac Injury Terminology and Scoring System

Blunt Cardiac Injury	Trauma Score
No ECG, physiologic, or anatomic abnormality	1
Minor ECG abnormality	1
Major ECG abnormality	1
Cardiac enzyme elevation	1
Free wall hematoma	2
Septal hematoma	2
Septal defect	2
Valvular insufficiency	4
Free wall rupture	5
Cardiac herniation	5
Coronary artery injury	5

ECG, Electrocardiogram.

from overdistention. Although it was once thought that sternal fractures were associated with a high incidence of blunt cardiac injuries, ironically, there has been no proven association between the two. The incidence of these injuries, however, ranges from 10% to 70%, depending on the diagnostic modality and criteria used.

Clinically, there are few signs and symptoms that are specific for blunt cardiac injuries. Chest wall abnormalities may or may not be present. Chest pain is common and is usually related to external injuries, and occasionally patients will describe anginal-type pain, unrelieved with nitrates. One relies on the mechanism of injury, external chest trauma, and a high index of suspicion to determine whether a more aggressive workup of cardiac trauma is warranted. With more significant blunt injuries, hemo-pericardium can develop. Progression to cardiac tamponade is life threatening and may be signified by Beck's triad, consisting of decreased heart sounds, hypotension, and elevated central venous pressure as evidenced by jugular venous distention. In addition to decreased cardiac sounds, auscultation may reveal a murmur stemming from septal or valvular defects.

To date, there is no diagnostic gold standard for blunt cardiac injury. Although no direct correlation exists, one should have a heightened suspicion of blunt cardiac injury when a sternal fracture is present. An electrocardiogram (ECG) should be performed on all patients in whom blunt cardiac injury is suggested, but practically all trauma victims eventually undergo electrocardiography on admission. New-onset tachyarrhythmias, especially sinus tachycardia, are the most common findings on admission ECG, and this initial ECG is the best indicator of blunt cardiac injury.^{106,107} Otherwise, the ECG is unreliable unless ST elevation is present.

Levels of creatinine kinase-myocardial bands and troponin have become part of the standard laboratory evaluation tests, but like the ECG are limited by the lack of a precise threshold for the diagnosis of a blunt cardiac injury. In the patient with musculoskeletal trauma, the significance of the creatinine kinase-myocardial band level remains questionable. Recently, cardiac troponin I and T levels were found to be highly sensitive for myocardial injury and useful in the stratification of patients

at risk for complications.¹⁰⁸ Alternatively, in a single institution study of the diagnostic utility of troponin I and troponin T, the specificities of elevated troponin I and T levels for myocardial contusion were found to be 97% and 100%, respectively, whereas the sensitivities of troponin I and T were 23% and 12%, respectively.¹⁰⁹ Thus, debate still exists regarding the utility of an abnormal ECG, echocardiogram, and cardiac enzyme levels in predicting myocardial injury, and how these affect therapy, decision making, and outcomes.¹⁰⁵

Echocardiography remains the best diagnostic tool for detecting injuries, wall motion abnormalities, effusions, valvular or septal defects, and particularly chamber rupture.¹¹⁰ This should be performed in all patients with an abnormal ECG or who are hemodynamically unstable. An attempt at transthoracic imaging should be made first, but if insufficient data are rendered, the transesophageal route should be undertaken. Because of their anterior location, the right atrium and ventricle are the most frequent chambers injured, followed by the left atrium and left ventricle. Mortality from one chamber rupture is 60%, and universally fatal if two are involved.

Radionucleotide imaging can be helpful in documenting cardiac defects and predicting complications; however, it might not be practical in the acutely injured patient, and it cannot differentiate new injuries from chronic pre-existing disease. Furthermore, in the presence of a normal echocardiogram, this test is of little utility because it offers little direction in terms of management. Multiple gated acquisition scans are recommended, however, if the ECG is abnormal and there is evidence of ventricular failure.¹¹¹

The recommended observation and treatment options depend on the suggestion of blunt cardiac injury and any associated diagnostic test abnormalities. As stated previously, the presence of a sternal fracture does not predict blunt cardiac injury, and monitoring is not necessarily indicated. Patients with an abnormal ECG (e.g., arrhythmia, ST changes, ischemic changes, heart block) should be admitted for continuous ECG monitoring for at least 48 hours. Conversely, a prolonged hospital stay with cardiac monitoring is no longer required if the initial ECG and echocardiogram are normal, and most patients are discharged after 12 hours. The younger patient rarely develops cardiac complications even when there are mild ECG, echocardiogram, and enzyme abnormalities. However, in older patients with known cardiac disease, appropriate cardiac monitoring is necessary when injury is associated with hemodynamic instability, multisystem trauma, or ECG changes or when the patient is to undergo general anesthesia. In addition, in the hemodynamically unstable patient with concern for myocardial injury, and with multiple potential reasons for instability, consideration should be given to pulmonary artery catheter placement.

Operative intervention is required in 5% to 10% of patients with nonpenetrating cardiac injuries. Chamber ruptures are usually isolated events. Repair is typically done with simple cardiorrhaphy and a running suture, usually 4-0 polypropylene. Pledgets are required for right and left ventricular repairs. Valvular injuries have been reported in the aortic, mitral, and pulmonary positions.

Cardiopulmonary bypass is required for left-sided repairs. Occasionally, valve resuspension or chordae reattachment can be done, but most injuries require valvular replacement. Ventricular septal defects can present either acutely or after several days of progressively worsening congestive heart failure. Operative repair is required for larger defects and for those associated with a left ventricular aneurysm. Pericardial tears with associated cardiac herniation are uncommon and have been described in the left, right, and midline diaphragmatic locations. With small tears and complete herniation, death is almost immediate. Larger tears manifest as intermittent positional hypotension, and they are usually found at the time of exploration for other injuries. Direct suture closure is required. Patch closure is rarely needed. Finally, arteriovenous fistula or thrombosis is an uncommon complication involving the coronary vessels. The diagnosis is usually made after the appearance of long-term sequelae, including left ventricular pseudoaneurysm, cardiac failure, embolism, or arrhythmias. Surgery is directed at the specific complication.

Diaphragm

With the advent of modern high-speed transportation, traumatic diaphragmatic injury appears to be a disease in evolution. Injury to or rupture of the diaphragm because of blunt torso trauma is seen with increasing frequency. In North American series, the prevalence of diaphragmatic rupture among blunt trauma victims ranges from 0.8% to 8%, with a slight predisposition for the left side.¹¹² Because of greater awareness, routine use of chest roentgenograms in the initial evaluation of trauma patients, availability of minimally invasive techniques, and improved access to modern trauma care systems, surgeons are increasingly facing the diagnosis and management of diaphragmatic injuries. Despite these advances, persons with traumatic diaphragmatic injury suffer a higher mortality rate in comparison with blunt trauma patients without this injury.

Diaphragmatic injuries can be classified according to the mechanism of injury, side involved, unilateral or bilateral location, clinical sequelae following the onset of injury, and severity of the anatomic disruption. The latter has an important practical application in predicting outcome and associated visceral injury, because these patients with diaphragmatic injuries are at risk for severe multisystem trauma. Blunt diaphragmatic rupture occurs mainly from high-speed motor vehicle crashes when the rapid deceleration results in a nonuniform pressure load on the inflexible central tendon. In particular, lateral impact to the torso is three times more likely to rupture the diaphragm than from a frontal direction. Because the diaphragm is buffered by the liver on the right, a larger percentage of injuries occur on the left; bilateral injuries occur in less than 3% of all cases. Compared with the left side, patients with right hemidiaphragm ruptures tend to have worse increased multiorgan involvement, more hypovolemic shock, lower Glasgow Coma Scale score, and higher mortality. Bilateral ruptures, including those involving the pericardium, are rare in patients who reach the hospital alive.

Diaphragmatic injury or rupture can also be classified by the time of presentation. Three clinical phases follow the onset of traumatic diaphragmatic injury: acute, latent, and obstructive phases.¹¹² The acute phase begins with the original trauma and ends with the apparent recovery from other injuries, and thus may mask the diaphragm injury. Most patients (60%) have nonspecific pain in the left upper quadrant or lower thoracic or shoulder pain. Others have severe acute symptoms of dyspnea, hypotension, or cyanosis owing to compression of the lung and mediastinal shift from the herniated organs.

In the latent or interval phase, symptoms are variable and nonspecific as the patient compensates for having intrathoracic abdominal contents. The symptoms may mimic other disorders such as peptic ulcer disease, biliary colic, partial bowel obstruction, and chronic obstructive pulmonary disease. Symptoms of intermittent bowel obstruction aggravated by eating or lying on the left side are relieved by belching, vomiting, or flatus.

Finally, the obstructive phase can occur at any time when bowel obstruction occurs following incarceration of herniated viscera. This can lead to necrosis if diagnosis and treatment is further delayed. In one series, the onset of the obstructive phase ranged from 20 days to 28 years, but 90% usually present with strangulation within 3 years. These patients exhibit symptoms consistent with slow progressive herniation of stomach and bowel contents into the chest cavity. These include nausea, vomiting, abdominal pain, and obstipation, and they can ultimately lead to respiratory distress, shock, obstruction, strangulation, and signs of viscus perforation.

The diagnosis of acute diaphragm injury or rupture is a clinical challenge, especially in patients who do not have obvious indications for emergent exploration. Because diaphragmatic defects do not heal and can eventually lead to a latent visceral herniation, delayed diagnosis can be catastrophic. With previous blunt trauma, intermittent bowel obstruction without a previous abdominal incision should raise the possibility of diaphragm disruption. Findings on physical examination such as paradoxical motion of the left upper abdominal quadrant, decreased intercostal retraction, decreased breath sounds, or shifting of cardiac sounds should raise suspicion. Diagnosis in the latent phase can be also difficult, particularly with right-sided injuries, because of vague symptoms. Often, patients might not recall any previous history of trauma, and physical examination may reveal bowel sounds over the chest.

Plain chest films are the initial screening test of choice, but up to 75% of them will be non-diagnostic. Findings suggestive of a diaphragm defect include an indistinct costophrenic angle, elevated or indistinct hemidiaphragm, air fluid levels in the chest, and abnormal pleural densities (Fig. 7-8). Right diaphragm injuries are rarely detected. CT and ultrasonography are often positive when there is frank visceral protrusion into the chest. The development of high-resolution CT has improved the sensitivity of this diagnostic modality.

For left-sided ruptures, the diagnosis is usually made if a nasogastric tube passed into the stomach is seen in the hemithorax, or if an upper gastrointestinal contrast series reveals a narrowing of the obstructed stomach or



FIGURE 7-8 ■ Chest radiograph following blunt thoracic trauma suggestive of left diaphragmatic rupture.

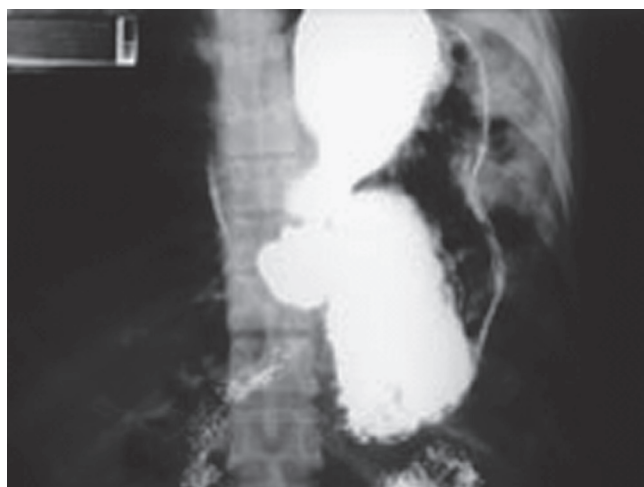


FIGURE 7-9 ■ Upper gastrointestinal barium study delineating stomach and small bowel contents years after blunt decelerating injury.

bowel segment above the diaphragm (Fig. 7-9). If an aortogram is performed for other reasons, the splenic or gastric vessels may be seen above the diaphragm. Although radionuclide scanning, fluoroscopy, and magnetic resonance imaging are highly accurate in the diagnosis of blunt diaphragmatic rupture, the use of these modalities in multiply injured, unstable patients is impractical.¹¹³ Right-sided ruptures may show a total or partial (“mushroom” projection) liver herniation with or without associated bowel contents.

Minimally invasive surgery for the evaluation of the diaphragm and other structures can be performed effectively while avoiding the morbidity of an open procedure. Routine laparoscopy is recommended to evaluate occult diaphragmatic injuries in stable patients with left thoracoabdominal penetrating injuries who otherwise have no indications for an open operation. Among these patients, up to one quarter will have diaphragmatic injuries that were missed during the trauma radiographic workup.¹¹⁴ These diaphragmatic injuries can be repaired at the time

of diagnosis during laparoscopy. In patients with previous abdominal surgery, a video-assisted thoracic surgical approach may be preferred to evaluate and repair the diaphragm once intra-abdominal injuries have been ruled out.

The surgical approach to repair acute diaphragmatic injury or rupture depends on the mechanism of injury, condition of the patient, and time of presentation. Shock should be corrected, and a nasogastric tube should be placed to decompress the stomach. After immediate life-threatening injuries are addressed, the diaphragm can be inspected thoroughly for defects. Even the smallest defects should be closed. Laparotomy can be performed first to explore the abdomen for other injuries, but diaphragmatic defects can be repaired from either the abdomen or chest. When both cavities need to be explored, separate incisions are favored over a continuous one because of the higher morbidity.

In patients who require emergent laparotomy for suspected intra-abdominal injuries, thorough inspection of both hemidiaphragms is mandatory, regardless of the direction of the blunt impact. Diaphragmatic rupture resulting from blunt trauma should be approached through a laparotomy because of the high incidence of simultaneous intra-abdominal solid organ injuries. Similarly, hemodynamically stable patients with diaphragmatic injury confirmed with noninvasive imaging or by laparoscopy should undergo laparotomy to rule out occult intra-abdominal injuries.

In contrast to the acute presentation, many surgeons prefer a thoracotomy approach for injuries and hernias that manifest in a delayed fashion. Although this approach provides excellent exposure to divide the adhesions between the trapped viscera and lung parenchyma, a transabdominal approach may be preferable for left hemidiaphragmatic hernias in which segments of small or large bowel may have to be resected and anastomosed. However, a thoracotomy approach should be used for all right-sided diaphragmatic defects, regardless of the timing following initial injury.

The herniated viscera is first carefully reduced and returned to the abdominal cavity. The preferred method of closure of the diaphragmatic defect is by interrupted full-thickness nonabsorbable 0 or no. 1 sutures. Adhesions are taken down, the lung is decorticated, and if necessary, the diaphragm is loosened from the lower rib to take tension off the repair. For the chronic rupture, a splenectomy may need to be performed, followed by enlargement of the defect in order to facilitate repair. Finally, on the rare occasion in which the tissue loss is extensive, closure of the defect can be achieved with fascia lata, biologic material such as bovine pericardium, or synthetic material.

Mortality and morbidity in patients with acute diaphragmatic injuries differ considerably from those with a delayed presentation.¹¹⁵ In the former, multiorgan trauma is usually present, and thus irreversible shock and head injury are most often cited as the causes of early death approaching 40%. With strangulated bowel, the rate goes to 80%. When these injuries are isolated and repaired adequately, complications are rare, and usually pulmonary in nature. With the chronic type, sepsis and

multisystem organ failure are the usual causes of mortality. In the presence of bowel strangulation and gangrene, a much higher postoperative mortality (66%) and morbidity (80%) is encountered compared with patients with an uncomplicated operative approach.

Esophagus

Blunt and penetrating trauma to the esophagus are both rare because of the relatively protected location of the thoracic esophagus in the posterior mediastinum.¹¹⁶ Blunt esophageal trauma is much rarer compared with penetrating injuries, but when it occurs, it is more commonly the result of a direct blow to the cervical region, such as hitting the steering wheel during decelerating motor vehicle crashes or from padded objects such as boxing gloves. Simultaneous rupture of the esophageal wall and adjacent membranous trachea wall can occur if both are compressed between the sternum and vertebral body, resulting in fistula formation. It is estimated that one third of all tracheoesophageal fistula have this etiology, second only to iatrogenic causes. Other blunt force injuries include manual compression during cardiopulmonary resuscitation (up to 12% incidence found during autopsy) and the Heimlich maneuver.

A Boerhaave-like rupture injury can occur from increased intraluminal pressure with a closed glottis and increased intra-abdominal pressure. This usually occurs just above the esophagogastric junction, with rupture into the left pleural space where there is less protection by the pleural lining. Mortality is high, not because of the severity of the injury but because of the delayed diagnosis and ensuing complications. Other etiologies of barotraumas include blast injuries and introduction of high pressure gases (e.g., fire extinguisher discharges, eruption of carbonated drinks, and gas ingestions from biting of inner tubes). Finally, localized wall or long segment necrosis has been described despite its rich blood supply, as the arterial inflow is torn away from severe blunt trauma.

Blunt esophageal injuries are often difficult to diagnose early, because of the multisystem trauma issues and lack of recognition. Patients may exhibit signs and symptoms of esophageal leak: subcutaneous air, pneumomediastinum, aspiration (from fistula formation), mediastinitis, hypotension, tachycardia, and sepsis in the more advanced cases. Diagnosis can be made from a contrast swallow study, but in the compromised trauma patient, this usually cannot be performed. A CT scan in some cases may detect small leaks into the neck or mediastinum not seen on contrast esophagography. Esophagoscopy is helpful, and it has been reported to have higher sensitivity than contrast studies.¹¹⁷

With free perforation or fistula formation, early surgical repair is advocated. Conservative medical therapy (broad-spectrum antibiotics, close observation, parenteral nutritional support) is chosen only in selected patients when the leak is minimal and contained and the patient's condition is clinically stable. Approaches are dictated by the level of involvement. Cervical incisions usually suffice for defects in the neck, but may require exposure with an upper sternal split for the thoracic inlet.

A right thoracotomy may be required for the upper thoracic third of the esophagus, whereas the left side is preferred for those just above the esophagogastric junction. The surgical principles are like those of other benign perforations of the esophagus. The edges are trimmed of devitalized tissue and closed in multiple layers. A tissue flap is added to buttress the repair. When a fistula is taken down, the esophageal and tracheal openings are closed primarily, and the suture lines must be separated by a tissue flap to prevent reformation. These flaps include intercostal muscles, strap muscles, mediastinal thymic fat, pericardium, and diaphragm. A tracheostomy has been advocated to help protect the tracheal suture line. For patients with delayed diagnosis and in those who remain in hemodynamically unstable condition, esophageal diversion rather than primary repair may be required.

Extensive necrosis of the esophagus is associated with a much higher mortality rate. When suggested, the diagnosis is made with endoscopy noting the mucosal ischemic changes. In these circumstances, emergency esophagectomy and proximal diverting esophagostomy is required, with reconstruction of gastrointestinal continuity performed at a later date.

PENETRATING TRAUMA

Stab Wounds versus Firearm Injuries

The evaluation and management of penetrating trauma to the thorax is best broken down by anatomic distribution.¹¹⁸ This includes the chest wall, the great vessels and other major vascular structures, the trachea and major bronchi, the lung parenchyma, the heart, the esophagus, and the diaphragm. Each of these structures can be injured individually and in combination with other intrathoracic or extrathoracic structures. The evaluation of thoracic injury requires a systematic approach founded on anatomy to rapidly identify injury and initiate therapy. Penetrating injuries to the chest can be both subtle and dramatic in presentation. Paramount in the management is a rapid assessment and evaluation of the patient's severity of injury. Patients who appear "stable" can deteriorate rapidly and can become acutely moribund through tension pneumothorax or pericardial tamponade as well as massive intrathoracic hemorrhage.

Once the initial primary survey has been performed, the patient's disability should be evaluated, specifically with determination of the location and mechanism of penetrating injury. Puncture wounds can be small and easily missed. The patient must be rolled and completely exposed with close inspection of critical areas, such as the axilla. Central wounds and peripheral wounds have different implications. Lower thoracic versus upper thoracic wounds suggest potential injuries to neck structures and abdominal structures, respectively, in addition to a thoracic injury. Stab wounds differ from gunshot wounds in their potential depth of penetration and degree of damage to surrounding organs. Knife wounds are limited to the direct tract of the blade and impart only the kinetic energy transfer to surrounding tissue that is manually produced. Gunshot wounds, however, impart kinetic

energy to the surrounding tissue produced by the mass and velocity of the bullet (Kinetic energy = $\frac{1}{2} \times \text{Mass} \times \text{Velocity}^2$). In addition to injury along the direct wound path, radial injury is produced by the kinetic energy transferred to the surrounding tissue. Wounds can be classified as “low energy transfer” or “high energy transfer.”¹¹⁹ In general, handgun wounds produce low-energy-transfer injuries, and high-velocity rifles produce high-energy-transfer injuries. These issues should be evaluated rapidly and considered in the primary survey.

Chest Wall Injury

The chest wall provides a rigid support and protection to the contents of the chest. Injuries that are limited to the chest wall itself rarely require surgical intervention. These injuries include intercostal vascular injuries that can produce hemothorax and injuries to the internal mammary artery. These injuries are usually managed easily with ligation or electrocautery. Blast injuries caused by high-velocity missiles or shotgun injuries can result in major tissue loss of the chest wall, including soft tissue and the bony thorax. These injuries can be initially covered with adhesive sterile drapes or a soft Esmarch covering with placements of chest tubes inside the thorax to achieve lung inflation and control any air leak. Definitive coverage of the defect using rotational flaps or free flaps of latissimus muscle, pectoralis major, serratus anterior, or omentum can be performed at a later time.

Tracheal and Bronchial Penetrating Injuries

Although penetrating injuries to the trachea and major bronchi are rare, encompassing 1% to 2% of thoracic trauma admissions, the nature of these injuries is serious, and these patients often present with respiratory distress.¹²⁰ Following the principles of ATLS, airway management and control of breathing with endotracheal intubation for adequate ventilation is the first role in management. Although a vast majority of blunt injuries to the trachea occur with 2.5 cm of the carina, almost three quarters of penetrating tracheobronchial injuries involve the cervical trachea.¹²¹ The need to establish a surgical airway in more proximal laryngotracheal injuries should be anticipated and performed without hesitation should oral endotracheal intubation prove difficult or impossible. In one series, almost half of these injuries required surgical airway.¹²² Cricothyroidotomy or tracheostomy is unlikely to provide any advantage over endotracheal intubation in more distal tracheal or bronchial injuries. Gunshot wounds are the most common cause of central airway injury although stab wounds are also possible. Stab wounds that injure the airway are more likely to be in the neck.^{123,124}

Signs of airway injury include subcutaneous emphysema, hemoptysis, pneumothorax, and air leak upon chest tube insertion. Plain films may reveal pneumothorax, pneumomediastinum, atelectasis in an underinflated lung or lobe, or the “falling lung sign of Kumpe” if the lung has collapsed away outward and downward (rather than inward and upward) from the hilum.¹²⁵ Adequate

ventilation may prove challenging in the setting of a tracheal or hilar injury. Intrapleural injuries produce pneumothorax and should be treated with immediate chest tube insertion. Massive air leak should raise the suspicion of a major bronchial injury but lack of air leak in the chest tube drainage system does not rule out the presence of injury. Bronchial edges may be approximated to seal a leak. A clot obstructing the bronchus may prevent air egress from the area of injury. Intubation and bronchoscopy are the first steps in managing a suspected bronchial injury. Extrapleural or mediastinal injury might not manifest as pneumothorax, but instead as massive mediastinal air or subcutaneous emphysema.

Flexible bronchoscopy should be performed and the complete tracheobronchial tree examined, as this remains the gold standard for diagnosis. If a proximal tracheal injury is suggested, the patient can be intubated over a bronchoscope to inspect the airway fully. Fiberoptic intubation can be performed with the patient awake, and sedation and paralysis are initiated after the airway has been established. Proximal tracheal injuries are best managed initially with intubation distal to the area of injury and control of the air leak. Injuries to the mainstem bronchi can be more challenging to manage initially. Bronchial blockers or Fogarty catheters are used to occlude the side of the injury, to control massive air leak, and to prevent inadequate ventilation. Double lumen endotracheal tubes should be used if possible for selective ventilation of the lung on the side of the uninjured airway. Injuries to the airway can result in significant amounts of blood in the tracheobronchial tree and can contribute to problems with ventilation. Aggressive toilet bronchoscopy must be performed with lavage of the airway until clear.

Surgical management of tracheal or bronchial injuries follows the same principles of tracheobronchial resection and repair used for neoplasms (Fig. 7-10). Proximal tracheal injuries can be managed through a cervical collar incision or an upper sternal split. More distal tracheal injuries are best approached through a right posterolateral thoracotomy incision. Bronchial injuries are best

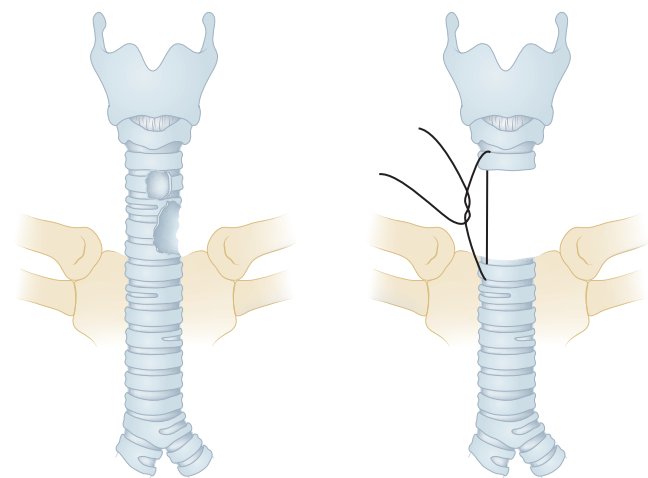


FIGURE 7-10 ■ Resection and repair after gunshot wound to the cervical trachea. (From Lee RB: Traumatic injury of the cervicotracheal trachea and bronchi. *Chest Surg Clin N Am* 7:300, 1997.)

approached through posterolateral thoracotomy to the side of the injury; the exception is that for proximal left mainstem bronchial injuries and carinal injuries, the right side is the optimal approach. On initial entry, control of the hilum with isolation of the pulmonary artery and veins is the initial goal. Unsuspected vascular injury may be present, and proximal control of these vessels is critical. Umbilical tape can be used, and tourniquets can be draped loosely around the vessels to control bleeding rapidly and to mitigate the potential for air embolus. The airway is then dissected out, débrided, and repaired using interrupted absorbable sutures in the standard manner of sleeve resection or bronchoplasty. Tension-free technique of airway repair should be performed. Mobilization of the airway should be adequate to decrease tension but not compromise blood supply, which usually runs along the membranocartilaginous junction. Large defects in the airway may require lung resection, although lung sparing techniques should be attempted. Injury to a lobar bronchus might be best treated with standard or sleeve lobectomy. Pneumonectomy should be avoided at all costs given the extremely poor outcomes of patients requiring pneumonectomy for trauma.^{126,127} Postoperative care should include aggressive pulmonary toilet and attempts to wean from positive pressure ventilation as soon as possible. Aggressive bronchoscopy should be performed to keep the airway clear of secretions and prevent atelectasis. As in all thoracic surgery, early ambulation is critical.

Pulmonary Injuries and Hemothorax

Pulmonary injuries secondary to penetrating trauma can vary from small pleural or parenchymal lacerations from a stab wound to massive pulmonary injury secondary to a gunshot wound. The initial evaluation in addition to the ABCs should include a routine chest radiograph in the stable patient. Physical exam to detect hemothorax and hemopneumothorax can be unreliable, particularly in a patient who is stable with minimal symptoms. Asymptomatic patients with a normal chest x-ray can be safely observed and discharged after an appropriate time interval.¹²⁸ This time interval is a subject of debate although a serial chest radiograph at 6 hours seems to be a reasonable time period to pick up a delayed hemothorax or pneumothorax. In fact, of all thoracic trauma patients, less than one fifth will have injuries that necessitate placement of a chest tube to manage their injuries.¹²⁹

Local wound exploration and tractotomy of thoracic wounds is not recommended due to the potential to cause a pneumothorax and contaminate the pleural space. Tube thoracostomy should be performed in all patients with a pneumothorax or findings of pleural fluid resulting from penetrating trauma. We recommend this even if the pneumothorax is small or the fluid appears minimal. Tube thoracostomy allows monitoring of bleeding and any potential need for thoracotomy should the bleeding prove to be significant. In addition, it prevents accumulation of clot that might later prove difficult to drain and require decortication. Patients with minimal chest tube output and no air leak can have the chest tube removed on the first hospital day and be discharged. Persistent bleeding mandates thoracotomy or video-assisted tho-

racic surgery (VATS). Massive bleeding on chest tube insertion should be treated with emergent thoracotomy with no attempt to use thoroscopic techniques.

Most pulmonary lacerations do not require surgery and can be treated with tube thoracostomy. In fact, in a series of 755 penetrating injuries to the chest, more than half of which were gunshot wounds, only 8% required thoracotomy.¹³⁰ Drainage of the pleural space with reestablishment of pleural apposition can tamponade what is generally low pressure venous bleeding and serves to seal an air leak. Even high-velocity war-related injuries usually respond to conservative measures of chest tube drainage, antimicrobial therapy, and wound care.¹³¹ Large air leaks on chest tube insertion should raise the concern for bronchial injury and require further evaluation with prompt bronchoscopy and possible thoracotomy.

If thoracotomy is necessary, the general rule is to spare as much lung as possible and to avoid anatomic resection. A posterolateral thoracotomy is performed to gain access to the hilum of the lung. Lung isolation is obtained expeditiously with a double lumen tube or bronchial blocker. This isolation serves to induce atelectasis in the damaged lung so as to perform a tension-free repair or resection of the lung and to help prevent air embolus. As in all thoracotomies for penetrating thoracic trauma, the hilum and pulmonary vessels are controlled early with umbilical tapes or vessel loops to allow rapid vascular control should an unsuspected central injury be present that was previously unnoticed. Nonanatomic resections are performed whenever possible. Stapling devices allow for a generous margin around the area of injury during resection of damaged tissue. Hematomas should be treated with a broad margin and vascular load to the stapler to achieve hemostasis. Staple lines can be oversewn to reinforce the region and to support hemostasis if the staple line was not adequate to stop bleeding. Persistent bleeding from deep missile injuries can be opened and exposed by inserting the anvil of the linear stapler into the tract and firing the device to perform a "tractotomy." If there is extensive tissue loss, anatomic resection of an injured lobe may be necessary. The literature shows that mortality is directly correlated to the extensiveness of the procedure, ranging from 13% with tractotomy to 50% with pneumonectomy in one series.^{132,133} Multiple studies have identified extent of resection and blunt injury mechanism as independent predictors of mortality.^{133,134} Pneumonectomy is to be avoided and performed only if all other measures to salvage the lung have been exhausted. Anatomic resections require some form of bronchial stump coverage given the contamination of the pleural space and risk for subsequent infection and bronchopleural fistula.

The timing of thoracotomy for thoracic hemorrhage after trauma has been widely discussed. Recommendations have been made to perform thoracotomy if there is an initial chest tube output greater than 1500 mL or if there is greater than 250 mL/hr chest tube output for 3 consecutive hours after its placement.¹³⁵ Slightly differing amounts of chest tube outputs have been used as guidelines for operative intervention for ongoing bleeding. However, one recent multicenter trial showed that mortality linearly increased as the total amount of chest tube

output increased and used 1500 mL total chest tube output within the first 24 hours after injury as a recommendation to intervene surgically.¹³³

Cardiac Injuries

Penetrating injuries to the heart are a significant challenge to manage.¹³⁶ They are one of the leading causes of death in urban trauma, accounting for a high rate of prehospital death and in-hospital mortality. Most patients who sustain cardiac injuries die before reaching the hospital, and almost two thirds of patients with penetrating cardiac injuries have no vital signs upon arrival to the trauma bay. Reported mortality for these injuries varies from one series to another. What is clear is that the mechanism of injury clearly influences survival. In general, these injuries are one of two types: stab or gunshot wounds. Penetrating cardiac injuries secondary to blunt trauma that produces fragments of fractured rib or sternum are rare. Gunshot wounds carry higher mortality than knife wounds do because stab wounds will often seal themselves quickly, and the resulting cardiac tamponade can allow these patients time for definitive management. Ballistic trauma, however, produces much larger, irregularly contoured wounds that result in hemorrhage without tamponade because the pericardial sac is no longer intact. The management of patients in extremis or near extremis with penetrating injuries to the heart consists of airway management with endotracheal intubation, the establishment of intravenous access capable of massive volume resuscitation, and immediate thoracotomy through a left anterolateral approach. This approach allows rapid exposure of the heart and the ability to relieve tamponade from hemorrhage. In addition, it allows the surgeon the ability to perform open cardiac massage, control cardiac injuries, cross clamp the descending aorta to preferentially perfuse the brain and coronaries, and allow volume resuscitation in the setting of exsanguination and shock.

The patient's physiologic condition at the time of presentation significantly affects outcome. The clinical features of a patient with a penetrating cardiac injury depend on the degree of pericardial tamponade and the amount of blood loss. Coronary artery injuries are rare but can cause ischemia resulting in hemodynamic instability from myocardial dysfunction. One prospective study of 105 patients with penetrating cardiac injury showed that patients in physiologic collapse on presentation that required emergent ED thoracotomy had a mortality rate of 86%, whereas those who were stable enough to be transported to the operating room for thoracotomy had a 26% mortality.¹³⁷ The need for aortic cross-clamping was a significant predictor of poor outcome (89% mortality), which was likely due to the poor physiologic condition of these patients on presentation. Survival from stab wounds (65%) in this study was significantly higher than for gunshot wounds (16%). More recent studies have identified ambulance transportation, stab wound versus gunshot wound, sinus tachycardia, and the presence of vital signs upon arrival to the trauma bay as predictors of survival following ED thoracotomy following penetrating cardiac trauma.¹³⁸

All penetrating cardiac injuries have the potential for mortality, and it is not clear that the particular area of the heart that is wounded carries a worse prognosis. More than one third of all penetrating cardiac trauma results in isolated right ventricular injury, whereas one quarter of patients will have isolated left ventricular injury.¹⁰¹ In addition, 30% of patients will have multichamber injuries. Ventricular injuries, particularly right ventricular injuries, seem to be more common given its more anterior location. The left and right atrium are less commonly injured given their smaller size and more protected location. Intrapericardial great vessel injuries also are unusual. Although it is not possible to say that one anatomic location of injury portends a worse outcome, it does appear that multichamber and complex cardiac wounds have a worse prognosis than a single chamber injury does.

Although many cardiac injuries are obvious on presentation, such as a patient in hemodynamically unstable condition with a penetrating injury in proximity to the heart, diagnostic evaluation is necessary for other patients that are in stable condition and may harbor occult cardiac injury. These injuries must be identified. Even small knife wounds to the heart are unlikely to seal spontaneously and will eventually result in tamponade. The hole in the pericardium produced by the knife or projectile will frequently seal with clot or pericardial fat. Blood from the heart will accumulate and impinge on the filling of the atrium and ventricle. The incidence of occult injury has been reported to be as high as 20% in asymptomatic patients with penetrating stab wounds to the chest.¹³⁹ A workup is indicated in patients with penetrating precordial, right- or left-sided chest wounds as well as thoracoabdominal and abdominal wounds. Tachycardia is usually the earliest sign of decreased preload and impending tamponade. As the pericardium fills with blood, elevated filling pressures become necessary to overcome the compressive effects of accumulating pericardial pressure and to maintain delivery of blood to the right and subsequently left heart. This results in the clinical findings of distended neck veins and pulsus paradoxus (decrease in systolic pressure with inspiration). These signs can be subtle and difficult to detect in a noisy ED or in a hypolemic patient.

Several modalities can be used to evaluate occult cardiac injuries. In the hemodynamically unstable patient, the FAST can be carried out expeditiously. Echocardiography is sensitive in detecting pericardial fluid, and specific signs of tamponade can be demonstrated by echocardiogram before they become clinically evident, such as diastolic collapse of the atrium or ventricle. Cardiac ultrasound and echocardiography have been used with good reliability to evaluate penetrating intrapericardial injury.¹⁴⁰ Echocardiography was found to be 97% specific and 90% sensitive in stable patients with precordial wounds.¹⁴¹

All patients with penetrating thoracic trauma and echocardiograms or FAST scan pericardial views that demonstrate free pericardial fluid or that suggest clotted lacerations should be explored surgically. This is based on poor outcomes in patients who are initially managed nonoperatively. One study showed that two of three

patients in clinically stable condition and with ultrasound suggesting clotted laceration subsequently became unstable, and only one of these patients survived.¹⁴² Patients with echocardiographic evidence of even small amounts of pericardial effusion were found to have major intrapericardial injury at exploration.¹⁴³

CT scan is another noninvasive modality to evaluate cardiac injury, although it might also fail to pick up subtle injuries or small amounts of pericardial fluid. While not sensitive for small amounts of fluid, it is an excellent means of identifying and localizing intrapericardial or intracardiac foreign bodies, such as bullets and gunshot pellets. These foreign bodies should be removed in most circumstances to prevent embolization and infection. Because of a lack of sensitivity in imaging modalities, a high degree of clinical suspicion needs to be exercised when hemodynamic instability suggests cardiac injury despite a normal echocardiogram, and more invasive measures must be taken. All patients suffering penetrating trauma with sonographic evidence of intrapericardial fluid should undergo pericardiotomy, preferentially through a subxiphoid approach.¹⁴⁴ Minimally invasive evaluation has been recommended in select, stable patients using a subxiphoid pericardial window (Fig. 7-11).¹³⁹ Pericardial windows have also been performed using laparoscopic and VATS approaches.¹⁴⁵⁻¹⁴⁷ Upon performing pericardiotomy, if persistent hemorrhage is appreciated, formal exploration should use a median sternotomy to gain better exposure to the heart and great vessels.

Successful repair of penetrating cardiac trauma was first described in 1896 when Dr. Ludwig Rehn, a surgeon in Frankfurt, Germany, primarily repaired a stab wound to the right ventricle in a 22-year-old man in hemorrhagic shock with silk suture using a left thoracotomy incision.¹⁴⁸ Today, management of penetrating injuries to the heart follows standard principles of cardiac

surgery. If cardiac injury is suspected and time allows, transfer to the operating room with median sternotomy is performed. Otherwise, left anterolateral thoracotomy using a fourth interspace incision with extension across the sternum to the right chest if necessary is performed. Minimally invasive procedures are not advocated in the setting of hemodynamic compromise and suspected cardiac injury. Unilateral VATS or laparoscopy is an option in patients in stable condition in whom diagnosis is unclear. Management of ventricular stab wounds should be repaired using mattress sutures with large, full-thickness bites across the injury. A 2-0 large needle with Ethibond suture and Teflon pledgets is used to prevent tearing of the myocardium. Bleeding should be controlled using manual pressure or a sponge stick until sutures can be applied. In general, insufflation of a Foley balloon to tamponade a ventricular or atrial defect is not advocated, given the possible interference with the valvular apparatus of the tricuspid or mitral valve or obstruction of either the right or left ventricular outflow tract. Finally, the use of a Foley catheter increases the likelihood of pulmonary air embolus or stroke.

Repair of atrial injuries with 4-0 polypropylene suture is recommended. Pledgets can be used depending on the quality of the atrial tissue and size of the defect. Autologous pericardium can be used to reconstruct larger defects. Hemorrhage can be extraordinary, necessitating massive transfusion of blood products. An intraoperative cell salvage system should be used whenever possible should a perfusionist be available. Coronary injuries present a particularly challenging injury and carry a high mortality; this is due to blood loss, early tamponade, and the resultant myocardial ischemia that can produce hemodynamic instability secondary to myocardial failure. Mattress sutures beneath the coronary artery that control bleeding but do not completely obstruct coronary flow should be attempted whenever possible (Fig. 7-12).

Left main and anterior descending artery injuries likely produce the most catastrophic outcomes given the large territory of myocardium that the vessel supplies. Hemorrhage from coronary injuries can be temporarily controlled using a small gauze on the end of a hemostat to compress the artery both proximal and distal to the injury. Direct repair or off-pump coronary bypass is likely to be impractical but might be considered if a cardiac surgeon with the equipment and experience is available. Ligation or oversewing of a major coronary artery should be undertaken only as a last option. If the hemodynamic instability is encountered after ligation, institution of cardiopulmonary bypass and performance of coronary artery bypass grafting distal to the area of ligation should be considered.

Intrapericardial great vessel injuries are unusual because of their short segments, but they carry a high mortality. Intrapericardial aortic injuries were uniformly fatal in one series.¹⁴⁹ Lacerations to the intrapericardial aorta can be repaired using basic vascular technique, a side-biting vascular clamp, and oversewing with 3-0 prolene suture. Temporary inflow occlusion of the inferior vena cava (IVC) and superior vena cava (SVC) can be used to try to minimize hemorrhage while performing the repair. Gunshot injuries producing a significant aortic

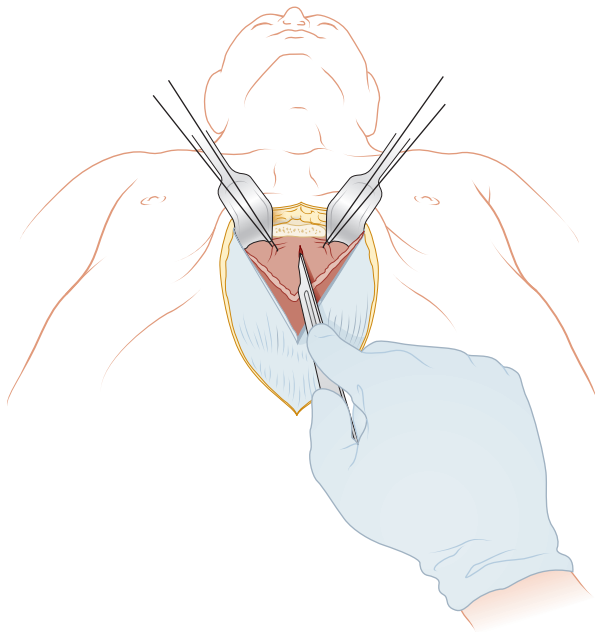


FIGURE 7-11 ■ Subxiphoid approach for pericardial window. (From Brown J, Grover FL: Trauma to the heart. *Chest Surg Clin N Am* 7:325, 1997.)

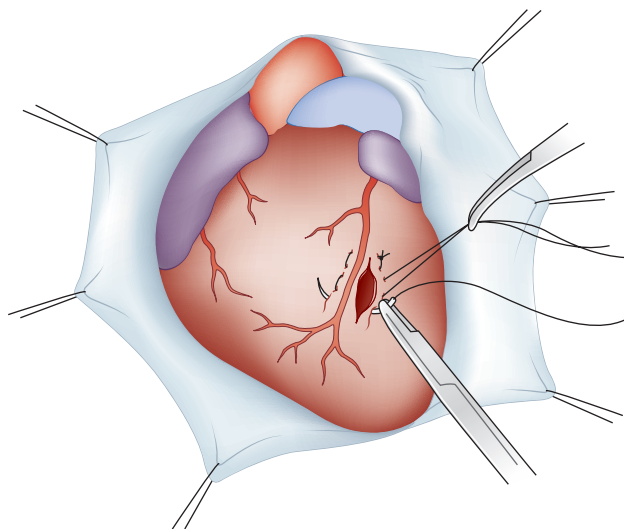


FIGURE 7-12 ■ Suture repair of ventricular injuries positioned next to the coronary vessels. (From Blaisdel FW, Trunkey DD, editors: *Cervicothoracic trauma*, ed 2, New York, 1994, Thieme Medical Publishers.)

disruption are usually fatal; however, if cardiopulmonary bypass is available, aortic cross-clamping for repair and grafting is optimal.

SVC and IVC injuries are also difficult to control. Lifting or pulling on the heart to expose these injuries usually results in hemodynamic instability in the hypovolemic patient; therefore, volume loading is critical. Side-biting vascular clamps can be used to control smaller, tangential injuries, but they can result in iatrogenic injury if not placed with care on fragile tissue. Shunts such as chest tubes and endotracheal tubes have been recommended to control hemorrhage but can be cumbersome to use. Care must be taken not to worsen the original injury. Cardiopulmonary bypass can be used for SVC or IVC drainage; it allows more controlled repairs of complex injuries. Circumstances that might necessitate cardiopulmonary bypass include exsanguination uncontrolled by other measures, injury to a coronary artery, valvular injuries, intracardiac septal defects, and retained intracardiac foreign bodies.¹⁴⁸ Cardiopulmonary bypass, while uncommon for use in emergency penetrating injuries to the heart, has been used with success if applied in a timely manner.^{150,151} Outcomes for patients with penetrating wounds to the heart show that gunshot wounds have lower survival than stab wounds do. Multiple chamber injuries or penetrating injuries to intrapericardial great vessels were found to have a reduction in survival rate to nearly one fourth of survival rates for single-chamber injuries. Patients with lower physiologic status had lower survival than did those with higher physiologic status.¹⁴⁹

Air Embolism and Bullet Embolism

Bullets and other missiles are not routinely removed from the chest if associated injuries are excluded. Foreign body embolism to the heart is rare. It occurs when missiles migrate intravascularly from sites of more peripheral injuries. Diagnosis is made with chest radiography, CT

scan, echocardiography, or fluoroscopy. The management of intracardiac foreign bodies in asymptomatic patients has been debated, ranging from a philosophy of removing all intracardiac foreign bodies to expectant management. Most surgeons recommend selective management.

The presence of an intracardiac foreign body must first be determined to be embolic and not from direct thoracic injury. Direct injury resulting in an intracardiac foreign body clearly mandates sternotomy to evaluate a penetrating cardiac injury. However, if there is no thoracic injury, intracardiac missiles can be assumed to be embolic. Workup should include a chest CT scan and two-dimensional echocardiogram.¹⁵² CT scan helps to localize the foreign body. Echocardiography confirms its presence and determines the exact location of the embolus in relation to other cardiac structures and whether there is any valvular dysfunction or septal defect. In addition, echocardiography can determine whether the missile is fixed or whether it is mobile. Because of their embolic nature, these missiles are generally on the right side of the heart. If these right-sided missiles appear stable and without tumbling movement on echocardiography and appear lodged in a chamber or ventricular wall, they can be followed expectantly.^{153,154} Some authors recommend intervention on larger missiles (greater than 5 mm), irregularly shaped missiles, missiles proximal to an artery, and left-sided intracavitary or partially embedded missiles.¹⁵⁵

In general, intracardiac embolic missiles should be removed if they are left sided, mobile, large, or symptomatic with valvular incompetence. Anticoagulation or prophylactic antibiotics are not recommended for expectant management, but follow-up echocardiogram at 3 months, 6 months, and 1 year is recommended.

Systemic air embolus is a relatively uncommon but frequently unrecognized cause of death in patients with penetrating lung injury. This generally occurs in the setting of patients with a central lung injury. A missile or stab wound creates a fistula from the bronchus to the pulmonary veins, producing an air embolus in patients when placed on positive-pressure ventilation. This is believed to occur more often in the setting of high airway pressures. Cardiovascular collapse occurs when air enters the coronary arteries, causing myocardial ischemia resulting in ventricular fibrillation or asystole. The hallmark of an air embolus is hemoptysis and bloody, frothy air leak from a lung injury. This can then be confirmed intraoperatively by visualizing air in the coronaries.¹⁵⁶

If air embolus is suspected, immediate thoracotomy should be performed to the side of the injury. The hilum of the lung should be clamped to prevent further sources of embolus. The patient should be placed with his or her head down to prevent cerebral embolus. Removal of a massive air embolus can then be performed using a large-gauge needle and syringe through the left ventricular apex or through the roof of the left atrium as open cardiac massage is performed. Coronary air emboli can also be removed using a syringe and small gauge needle. Outcomes for massive air embolus are poor, with only 3 of 9 patients surviving in a small series by Estera and colleagues.¹⁵⁶ Prevention of this problem is paramount and should include lung isolation to prevent positive

pressure on an injured lung until repair or resection is performed.¹⁵⁷ Management has also been described using prompt institution of cardiopulmonary bypass to restore circulation while lung resection and cardiac de-airing are performed.¹⁵⁸

Great Vessels

More than 90% of patients with great vessel injuries have penetrating thoracic trauma.¹⁵⁹ The thoracic great vessels include the ascending aorta, aortic arch and descending aorta, the innominate artery and veins, the subclavian artery and veins, pulmonary artery, and pulmonary veins. Injuries to the great vessels are challenging to manage. Most patients die before reaching the hospital. Of those who reach the hospital, most require immediate thoracotomy in the ED.^{160,161} Workup for major thoracic vascular injuries is frequently limited given the instability of these patients and their need for immediate surgical intervention. However, plain chest radiography may reveal hemothorax, hemopneumothorax, or mediastinal hematoma.

Further workup in the patient in stable condition should include a FAST scan focusing specifically on the pericardial view and chest CT with intravenous contrast or aortography. This is particularly pertinent in patients with a transmediastinal gunshot wound.^{162,163} Given the improved sensitivity of the new generation of CT scanners and the increased speed with which a CT scan can be performed, CT angiograms are replacing angiography as the diagnostic modality for these injuries. In addition, CT scan allows the identification of other thoracic injuries. Angiography can still be useful as a diagnostic tool in centers without adequate CT scanners or dedicated trauma radiologists, as well as a therapeutic, interventional modality to address selective injuries.

The initial management of major vascular thoracic penetrating injuries is prompt thoracotomy and manual tamponade of the injury or control with a vascular clamp. Subclavian injuries can be difficult to tamponade because of their location behind the clavicle. Foley balloon insertion into a neck wound and application of traction to tamponade the bleeding has been recommended until more definitive control can be achieved.¹⁶⁴

Definitive management of thoracic vascular injuries follows the principles of vascular repair. Aortic injuries are frequently lethal. Rapid exposure of these injuries to establish control is critical, and the appropriate choice of incision cannot be overemphasized. Ascending aortic and aortic arch injuries are best approached through a median sternotomy. Manual pressure or control with side-biting vascular clamps can allow for a primary repair. Cross-clamping the ascending aorta is not possible without cardiopulmonary bypass, because cessation of perfusion to the brain is not tolerated in a normothermic patient. Repair of complex vascular injuries has been described using cardiopulmonary bypass and deep hypothermic circulatory arrest.¹⁶⁵ Descending thoracic aortic injuries should be approached through a left thoracotomy. The descending aorta can be cross-clamped to achieve proximal and distal control and to perform a primary repair or interposition graft.

Pulmonary artery or vein injuries are best approached through a posterolateral thoracotomy. Proximal control of the pulmonary artery should be achieved as a first step and can be achieved with a tourniquet placed and cinched down to decrease blood loss and to allow better visualization for vascular repair. Similar control can be achieved on the pulmonary veins. Primary repair should be attempted. Pneumonectomy should be avoided because of the aforementioned increase in morbidity and mortality associated with procedure.

Vena caval and innominate vein injuries are also repaired using standard vascular techniques. The intrapericardial SVC and IVC can be difficult to expose and repair. They can be approached through a right thoracotomy or median sternotomy. Ligation of the SVC or IVC without shunting is not compatible with survival. Innominate vein injuries are best repaired through a sternotomy. The innominate vein can be ligated if repair is not possible given the existence of adequate collateral venous drainage.

Subclavian injuries are the most frequently injured thoracic great vessel, particularly given their exposure and vulnerability with penetrating neck injury.¹⁶¹ Surgical exposure for control of bleeding makes these injuries challenging. Many approaches have been recommended for control of the subclavian vessels. This includes a clavicular incision, clavicular incision combined with sternotomy (Fig. 7-13), "trapdoor" or upper sternotomy combined with fourth interspace anterior thoracotomy (Fig. 7-14), or a high anterior thoracotomy using a second or third interspace incision (Fig. 7-15). Each of these techniques has its advantages, and the choice of incision should be based on the surgeon's familiarity with the approach and whether the vascular injury is left or right sided or more proximal or distal. Left-sided subclavian injuries can be difficult to control through a sternotomy. In general, these injuries can be repaired primarily or if necessary with an interposition graft of autologous vein or prosthetic graft.¹⁶⁶

Currently, the role of endovascular stent grafts for nonaortic great vessel injury is being addressed.⁹⁶ Successful stenting for nontraumatic carotid and subclavian arterial pathologies has been well reported, but the application to traumatic injuries less so. It has been estimated that well over one third of all nonaortic great vessel injury would be amenable to stent graft placement, but higher risks of endoleak associated with injuries proximal to arterial origins and multiple branch points with risk of occlusion and distal ischemia are several cited reasons for the lack of progress in this area. Limited case series to date have reported endovascular stenting to be safe and efficacious in selected cases, with up to a 95% success rate at excluding the traumatic lesion. Rates of early graft failure owing to stenosis or thrombosis as well as late failure owing to intimal hyperplasia have been observed in the range of 5% to 10%.⁹⁶

Diaphragmatic Injuries

Diaphragmatic injuries in penetrating trauma can be difficult to diagnose although once the diagnosis is made, their management is straightforward. Any penetrating

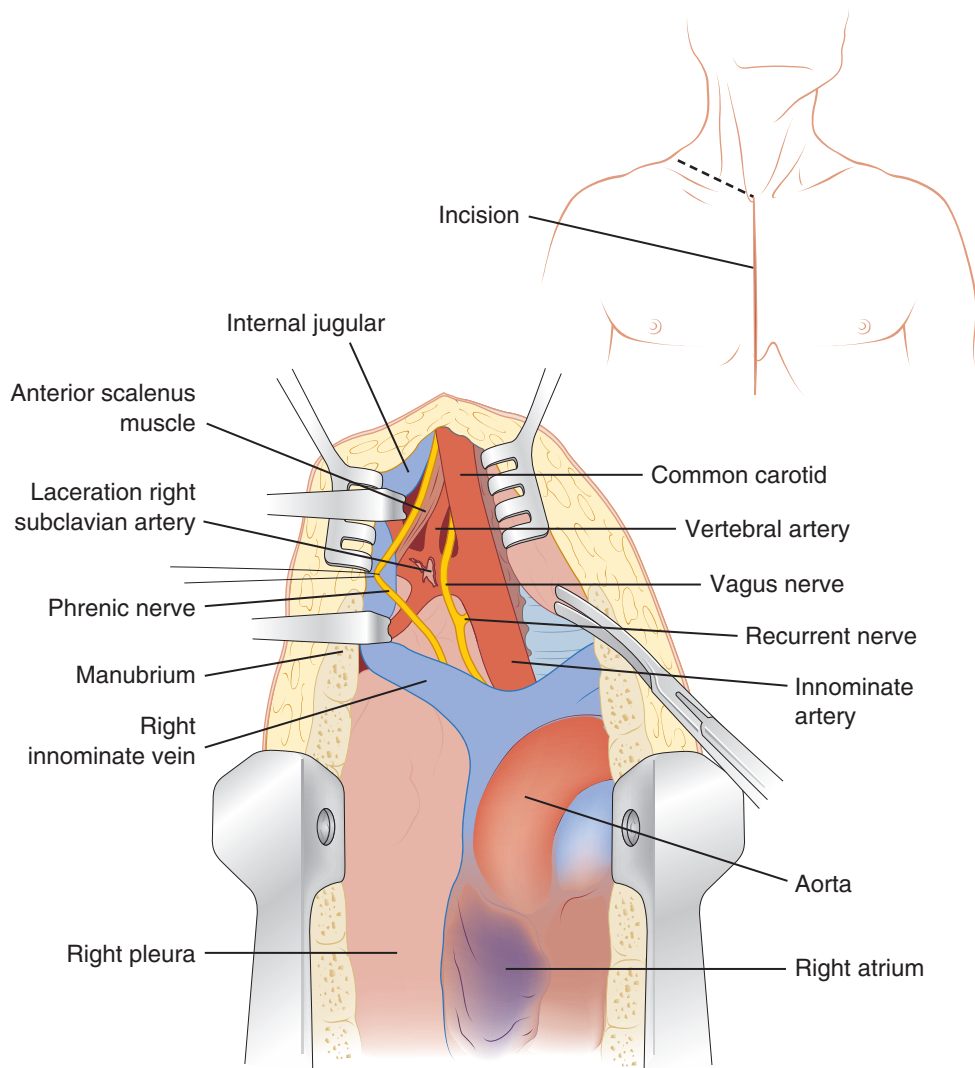


FIGURE 7-13 ■ Clavicular incision and median sternotomy for exposure and control of the proximal innominate and right subclavian artery. (From Ravitch MR, Steichen FM, Schlossberg L: *Atlas of general thoracic surgery*, Philadelphia, 1988, WB Saunders, p 147.)

injury at the nipple line or below should be considered to have the potential for both abdominal and thoracic injury and traversal of the diaphragm. The dilemma in management is how to diagnose the injury and to inspect both the chest and diaphragm for injury. Injuries to the diaphragm may be small, but repair is indicated because of the potential for associated abdominal injuries and the long-term sequelae of chronic diaphragmatic hernia with the potential for bowel incarceration. Non-invasive methods used to diagnose diaphragmatic injury are chest radiograph and chest CT scan. However, these methods can be unreliable for the diagnosis of diaphragmatic injury, with accuracy rates of only 50%.¹⁶⁷ Other more invasive methods for diagnosing penetrating diaphragmatic injury are diagnostic peritoneal lavage (DPL), but this can also miss diaphragmatic injury. Therefore, some have recommended exploratory laparotomy in patients with penetrating wounds inferior to the fourth intercostal space anteriorly, sixth interspace laterally, or eighth interspace posteriorly because of the contour and insertions of the diaphragm.¹⁶⁸ Laparos-

copy and VATS have been used to improve diagnostic sensitivity in evaluating the diaphragm without resorting to laparotomy. VATS has proved to be a safe and reliable method of evaluating the diaphragm and diagnosing and treating a variety of thoracic trauma. Current recommendations incorporate concepts from these series (Box 7-3).^{146,147,169}

Clearly, anyone with indication for thoracotomy or laparotomy should have the diaphragm inspected at the time of surgery. For patients without hard signs for surgery, VATS is a reasonable approach in the setting of an abnormal chest radiograph with an entry wound in the zone of insertion of the diaphragm and in the setting of a high velocity injury in the proximity of the diaphragm. Clearly, a high degree of suspicion is warranted for diaphragmatic injury. Because the procedure is fast and simple with minimal morbidity, VATS should be used liberally when diagnosis is uncertain. Repair of the diaphragm can be performed using VATS coupled with standard suturing techniques and a running or interrupted method of repair. The diaphragm can be repaired

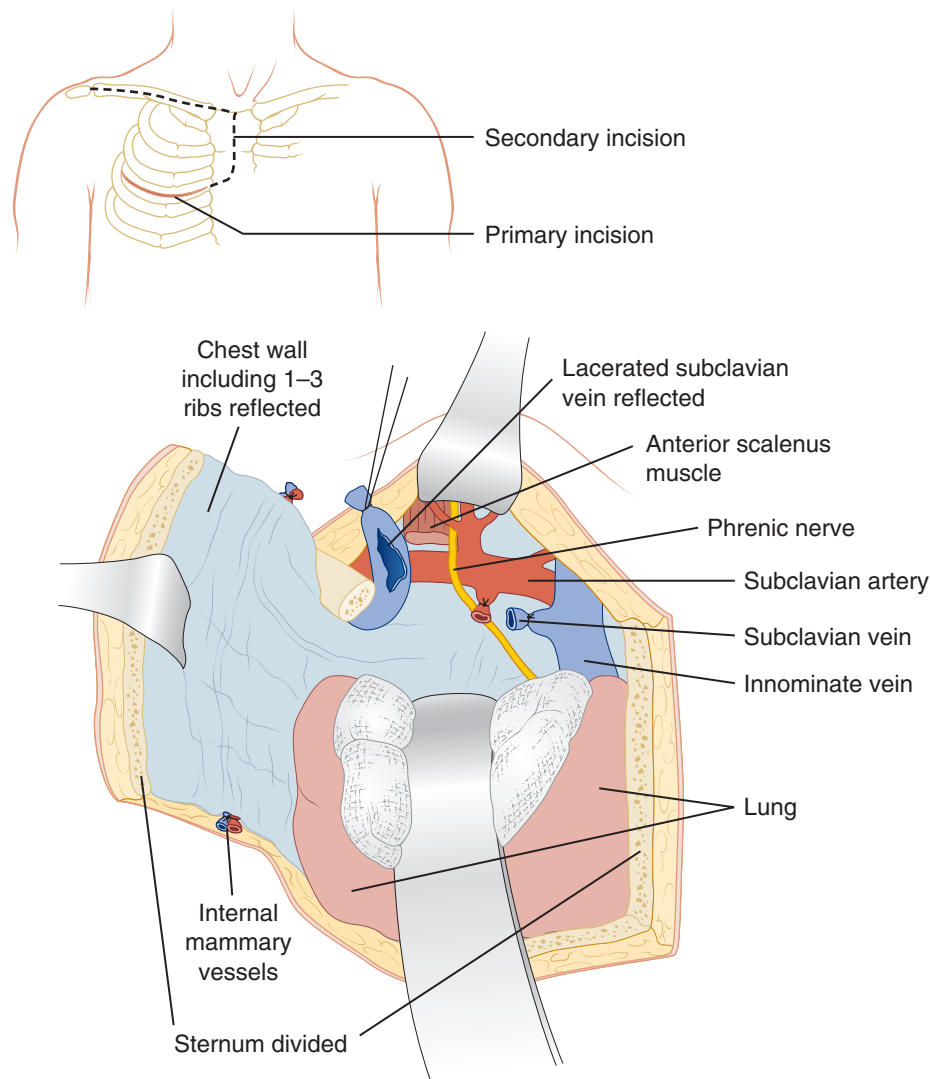


FIGURE 7-14 ■ “Trapdoor” incision for exposure and control of the distal right subclavian artery injuries, which can be used for the left as well. (From Ravitch MR, Steichen FM, Schlossberg L: *Atlas of general thoracic surgery*, Philadelphia, 1988, WB Saunders, p 155.)

transabdominally should laparotomy be required. An interrupted repair (of polypropylene) rather than a continuous suture of the diaphragm should be used.

In one series of 171 patients with penetrating chest trauma, an algorithm was proposed to identify occult diaphragmatic injury. An initial chest radiograph was obtained, followed by chest tube placement should a pneumothorax or hemothorax be present. In addition, a DPL or abdominal CT was performed to assess abdominal injuries. Should the DPL or abdominal CT scan suggest abdominal injury or if the hemothorax was significant, the patient was taken to the operating room and the diaphragm was evaluated using laparotomy or thoracotomy. In patients in stable condition with findings that did not mandate thoracotomy or laparotomy, VATS inspection of the diaphragm was recommended when two or more of the following findings were present: abnormal chest radiograph, associated abdominal injury, high-velocity injury, injury inferior to the nipple, or a right-sided wound.¹⁷⁰

Esophageal Injuries

Injuries to the intrathoracic esophagus owing to penetrating injury are rare. The esophagus is more commonly injured in the neck, where it is most exposed; however, thoracic esophageal injuries carry a high morbidity and mortality. In a multicenter cross-sectional study, thoracic trauma with an associated esophageal injury was associated with a nearly threefold increase in the need for operative intervention and almost a twentyfold increase in mortality rate.¹⁷¹ The reasons are multiple. Given its central location in the chest, associated injuries are extremely common (98%) in one series.^{172,173} In addition, these injuries can be missed unless specifically investigated. Finally, repair of the esophagus can be technically difficult and associated with morbid complications. A multicenter study of penetrating esophageal injuries showed that preoperative workup of esophageal injuries resulted in delay in surgery and poorer outcomes.¹⁷⁴ They concluded that if selective evaluation and management of

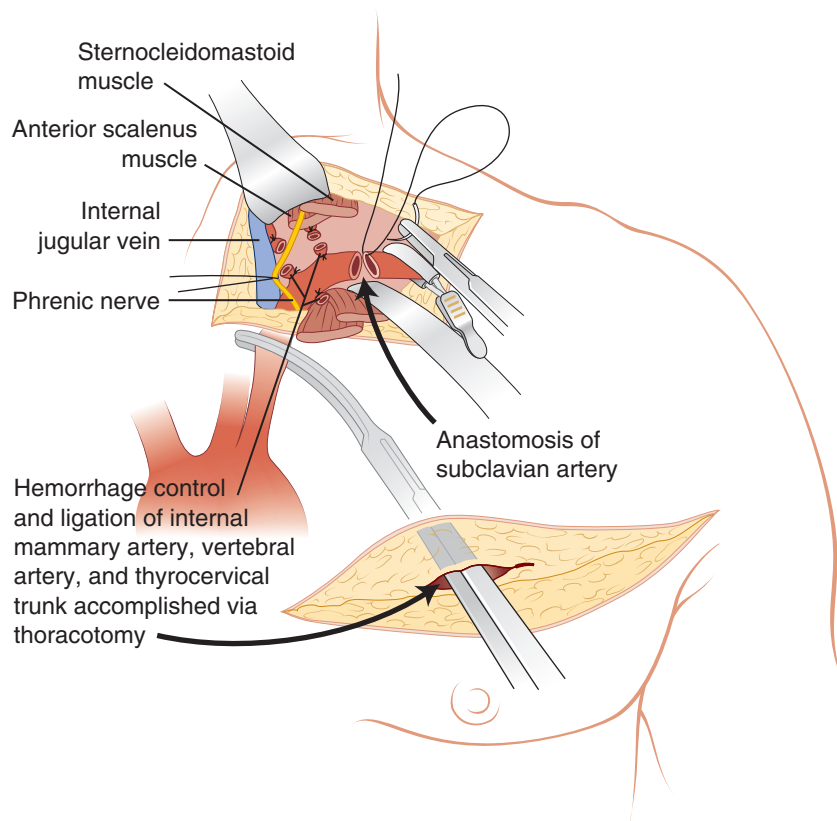


FIGURE 7-15 ■ Clavicular incision for exposure and control of distal left subclavian artery injuries, and separate upper anterior thoracotomy for proximal control. (From Ravitch MR, Steichen FM, Schlossberg L: *Atlas of general thoracic surgery*, Philadelphia, 1988, WB Saunders, p 150.)

BOX 7-3 Role of Video-Assisted Thoracic Surgery in Thoracic Trauma

INDICATIONS

- Treatment for ongoing thoracic hemorrhage
- Treatment of retained hemothorax
- Treatment of persistent pneumothorax
- Diagnosis and treatment of diaphragmatic injuries
- Pericardial window for relief of cardiac tamponade
- Management of thoracic duct injuries
- Treatment of posttraumatic empyema
- Removal of foreign bodies

RELATIVE CONTRAINDICATIONS

- Coagulopathy
- Prior thoracotomy

ABSOLUTE CONTRAINDICATIONS

- Hemodynamic instability
- Suspected cardiac injury
- Suspected great vessel injury
- Inability to tolerate single lung ventilation
- Inability to tolerate lateral decubitus position

injuries is to be performed, it should be done rapidly with the plan of expeditious transfer to the operating room. If this is not possible, they recommend proceeding to prompt surgical exploration.

Investigation for esophageal injuries depends on the stability of the patient. If the patient's condition is stable with a mediastinal or transmediastinal gunshot wound, CT scan of the chest should be performed immediately

with intravenous contrast and injection of Gastrografin contrast through a nasogastric tube. This can help to delineate associated injuries and the course of the bullet and help to choose a surgical approach. If the patient's condition is not sufficiently stable to undergo CT scan and emergent operative exploration is necessary, then intraoperative flexible bronchoscopy and esophagoscopy should be performed first, followed by thoracotomy on the side in which major associated injury is suspected. Thoracotomy should be performed to the left side if the injury is uncertain, to have access to the descending aorta for cross-clamping should this prove necessary. Lung isolation through a double lumen endotracheal tube or bronchial blocker is preferable to provide atelectasis for better visualization and to optimize repair of injuries. Flexible endoscopy for the diagnosis of esophageal trauma has been shown to be an excellent diagnostic tool (100% sensitivity, 96% specificity with 97% accuracy in one study).¹⁷⁵ Intraoperative insufflation of air through the esophagoscope with the chest filled with saline can help to identify a small injury. More proximal injuries are best explored through the right chest through the fifth intercostal space, particularly if associated airway injury is suggested. Bronchoscopy is mandatory to examine both the trachea and the more distal airway for injury. Distal esophageal injuries around the esophagogastric junction are best explored through a sixth interspace left thoracotomy.

Thoracic esophageal injuries should be repaired using primary closure with wide drainage. Prompt recognition of esophageal injury is critical, and the injury must be repaired. Missed diagnosis allows mediastinal soilage

with ensuing sepsis in a patient who has already undergone one physiologic insult. Nonoperative chest tube drainage alone has no place in the management of penetrating esophageal injuries. One series had a 50% mortality in this setting.¹⁷⁶

The injured esophagus should be débrided back to clean, viable tissue. Like other esophageal repairs, a two-layer closure is done with attention to a watertight mucosal closure using absorbable suture with an overlying second layer of nonabsorbable suture to close the muscular layer. The repair should be covered with an intercostal muscle flap or the fundus of the stomach if the injury is close to the gastroesophageal junction. Multiple chest tubes should be used to ensure complete drainage of the hemithorax and complete reexpansion of the lung to seal the pleura against the closure. In addition to chest tubes, soft, closed suction drains (e.g., Jackson-Pratt or Blake drains) should be left close to the area of injury. Therefore, should the repair prove to leak postoperatively, the chest tubes can be removed slowly, and the patient can eventually be discharged from the hospital with the Jackson-Pratt drain in controlling the leak until it seals. Gastric and jejunal feeding tubes should be considered and placed operatively either at the time of initial surgery or at a second operation to provide access for long-term feeding should a postoperative leak preclude oral intake. Esophageal repairs are evaluated for leak with a barium esophagram on postoperative day 7.

COMPLICATIONS OF THORACIC TRAUMA

A complete discussion of complications following thoracic trauma is beyond the scope of this chapter, but the more common problems are listed in Box 7-4. Many complications and their therapies are similar to their counterparts found in nontrauma settings, and the reader is referred to those specific sections in this textbook; however, several issues specific to thoracic injuries are important to note.¹⁷⁷

Acute Lung Injury and Respiratory Distress Syndrome

Up to 20% of cases of acute respiratory distress syndrome (ARDS) in the United States are caused by thoracic trauma. Whether a direct injury to the lung parenchyma was incurred or was a sequela of the critically injured patient, mortality from ARDS remains approximately 50%. Differentiation from acute lung injury may be difficult, and it is sometimes included in the spectrum of diseases; both reflect the concept of acutely occurring nonhydrostatic pulmonary edema, infiltrates on chest radiography, and hypoxemia, which are generally worse in ARDS.¹⁷⁸ With alterations in immune competence and production of proinflammatory cytokines, the systemic inflammatory response can develop and can progress to septic shock and ARDS with a proven infection source.¹⁷⁹ Regardless of the etiology, the development of ARDS is difficult to predict, but there are several factors that increase the risk of ARDS in these patients (Box 7-5).

BOX 7-4 Complications of Thoracic Trauma

PULMONARY

- Atelectasis
- Acute respiratory distress syndrome
- Acute lung injury
- Pneumonia
- Infarction
- Lung abscess
- Arteriovenous fistula
- Bronchial stenosis
- Tracheoesophageal fistula

PLEURAL SPACE

- Empyema
- Bronchopleural fistula
- Organized hemothorax
- Chylothorax
- Fibrothorax
- Diaphragmatic hernias

VASCULAR

- Thromboembolism
- Air embolism
- Pseudoaneurysm
- Great vessel fistula

CHEST WALL

- Hernias
- Persistent pain

MEDIASTINUM

- Mediastinitis
- Pericarditis

BOX 7-5 Acute Respiratory Distress Syndrome Risk Factors

- Pneumonia with aspiration
- Pulmonary contusion with penetrating injury
- Closed head injuries
- Orthopedic injuries
- Sepsis or infections
- Multiple transfusions
- Pancreatitis
- Coagulopathies
- Inhalation injury
- Burns

Therapy for ALI and ARDS is mainly supportive and is directed at correcting the possible underlying etiology that precipitated the pulmonary problem.^{180,181} Other therapies include mechanical ventilatory support with or without oscillation, adequate nutritional status, minimization of fluid requirements, permissive hypercapnia to minimize barotrauma, and constant rotation of position to redistribute pulmonary edema. Pharmacologic therapy includes inhaled nitric oxide, exogenous or aerosolized surfactant, corticosteroids, and the use of mediator-directed therapy such as nonsteroidal anti-inflammatory drugs and monoclonal antibodies directed against endotoxin. In addition, extracorporeal membrane oxygenation

has been used to support these patients. Although most mediators have not shown vast improvement in a prospective fashion, these nonconventional therapies still hold great promise.

Pneumonia

Pneumonia remains the most common infectious complication after any polytrauma, particularly those involving the thorax. The incidence increases with the duration of endotracheal intubation, and it is associated with up to 50% of deaths following trauma. The etiology of nosocomially acquired pneumonias can be complex and related to a number of factors: underlying pulmonary conditions, associated injuries, multiple antibiotic therapies, colonization of the upper airway, aspiration at the time of initial injury, impairment of local defenses, and depression of the immune response.

Diagnosis is often difficult, with only half presenting classically with fever, leukocytosis, respiratory distress, and an abnormal chest radiograph. Sputum sampling is essential; however, in the intubated patient, invasive testing is required, such as transtracheal or bronchoscopic aspiration with bronchoalveolar lavage. Pleural effusions can occur and are seen in 50% of patients with *Haemophilus influenzae* pneumonia.

Broad-spectrum antibiotic therapy is used initially, but it is narrowed once the offending organism and antibiotic sensitivities return. Other principles in therapy include good pulmonary care and toilet, and the maintenance of nutritional function. Prophylaxis is paramount, to include effective infection control and prophylactic antibiotic and gastric bleeding measures.

Pleural Space Problems

The incidence of posttraumatic empyemas ranges from 2% to 6%, which rises to 26% of patients developing pleural space infections after chest tube insertion.¹⁸² The management of these empyemas is the same as that resulting from parapneumonic processes, with goals of controlling infection, evacuation of pus, obliteration of the pleural space, and restoring complete lung expansion. However, it is postulated that these empyemas differ from their parapneumonic counterparts in several aspects. Posttraumatic empyemas usually include, in addition to gram-positive organisms, a gram-negative component, which is a frequent consequence of retained hemothorax. In addition, these infections have an effusion that is often thick and of little volume, is not in the early or exudative phase, and requires open thoracotomy, drainage, and aggressive decortication.¹⁸³

Bronchopleural Fistula

Persistent bronchopleural fistula is a common problem following significant penetrating trauma to the lung parenchyma. Massive air leaks, identified with a loss of 30% to 50% of the tidal volume, are usually due to main-stem bronchial injuries, and they require immediate surgery. Fistula persisting more than 7 to 10 days is an indication for operative intervention. The use of

sclerosing agents has been reported, but failure rates are high. If surgery is performed in the persistent parenchymal fistula, careful dissection and closure is advised because of the friability and fragility of the tissues, sometime in the presence of ARDS inflammatory changes. The internal parenchymal injury should be exposed, and major bronchioles are oversewn. The parenchyma is closed in layers, and the visceral pleural lining is oversewn with a running suture to minimize air leaks. If the parenchyma is not properly closed in layers, a parenchymal cavity will persist and act as a nidus for a lung abscess. Anatomic resection is rarely needed; if it is required, wedge resection usually suffices.

Great Vessel Fistula

Nearly all traumatic arteriovenous fistulas result from penetrating injuries. Although a majority occur in the cervicomedial region, approximately 30% are found in the intrathoracic great vessels.¹⁸⁴ A thrill is heard in only 20% of patients 1 week following the injury, and increases to 100% at 2 weeks. At 12 weeks, 85% will have some type of significant clinical presentation.

Surgery is recommended once the fistula is demonstrated radiographically, usually by angiography. There is no role for fistula "maturation," as venous hypertension can cause bleeding complications during and after the repair. Autogenous vein patch is suggested for peripheral vessels, whereas prosthetic grafts are reserved for the great vessels, aorta, and main pulmonary artery. Endovascular stenting and embolization have been reported; however, selective use of these methods is suggested for smaller vessels.

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PART D

TRACHEA

PART OUTLINE

8 TRACHEAL LESIONS

TRACHEAL LESIONS

Harald C. Ott • Douglas J. Mathisen

CHAPTER OUTLINE

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SUMMARY

A variety of benign and malignant lesions can develop in the trachea and lead to airway obstruction. The infrequent occurrence of tracheal pathology and its frequently insidious nature can lead to a delayed diagnosis for patients in whom these conditions exist. Advances in surgical and anesthetic techniques have enabled safe and effective resection with primary reconstruction for many of these lesions. For obstructive lesions whose extent precludes primary tracheal resection and reconstruction, there is still no universally definitive treatment, but several palliative measures exist to provide patients with a satisfactory airway. Most recently, several reports of tracheal replacements using tissue-engineered grafts have generated hope for these patients.

This chapter focuses on surgically correctable lesions of the trachea, including those that involve the subglottic larynx. Pathology and treatment of carinal lesions will be discussed in a separate chapter. Historical perspective, along with preoperative assessment, operative strategies, and postoperative care for patients with obstructive pathology of the trachea will be discussed in detail.

HISTORICAL PERSPECTIVE

When the field of tracheal surgery was young, it was widely accepted that only four tracheal rings, or approximately 2 cm, of trachea could be resected safely with immediate reconstruction. It was the work of Dr. Hermes Grillo, widely considered the father of modern tracheal surgery, that led to the surgical practices used today.

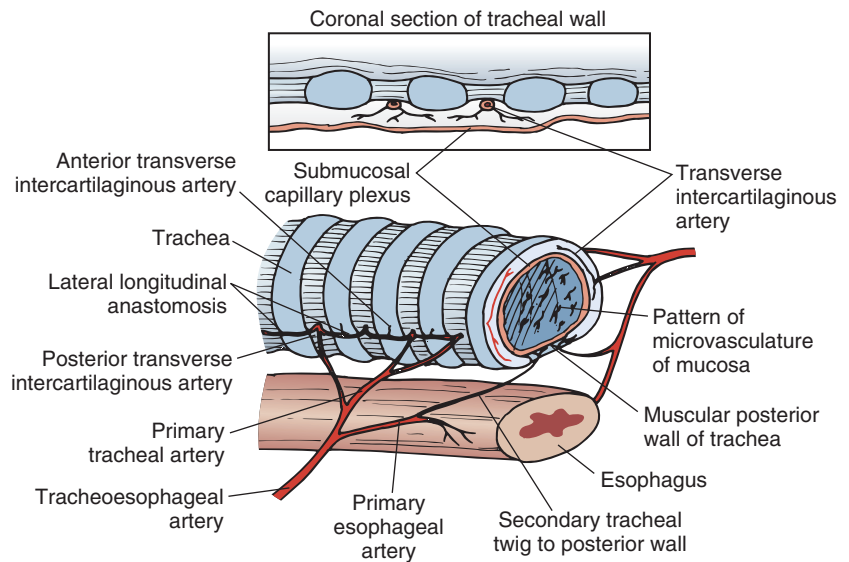
Grillo et al¹⁻³ systematically investigated the limits of resection of the trachea to permit reconstruction without excessive anastomotic tension. Among other findings, these studies demonstrated that the tracheal blood supply entered in its lateral pedicles, and that safe mobilization of the trachea could be accomplished only with anterior and posterior dissection. Dedo and Fishman⁴ described laryngeal release maneuvers to minimize tension on lengthier tracheal resections. These contributions led to the realization that, in extreme cases, up to 50% of the human trachea could be resected and reconstructed without detrimental tension.

ANATOMY

The trachea averages 11 cm in length from the lower border of the cricoid cartilage to the carinal spur, with an additional 1.5 to 2 cm of subglottic laryngeal airway. The structural support comes from 18 to 22 cartilaginous C-shaped rings, with about two rings per centimeter. The cricoid cartilage is the only complete cartilaginous ring in the normal airway. Most of the trachea lies within the thoracic inlet and the chest. Cervical hyperextension delivers up to half of the trachea into the neck, and flexion devolves most of the trachea into the mediastinum.

The blood supply to the trachea is provided by many segmental end arteries. The upper trachea is supplied principally by branches of the inferior thyroid artery, and the lower trachea by branches of the bronchial arteries.

FIGURE 8-1 ■ Microscopic blood supply of the trachea. Transverse intercartilaginous arteries derived from the lateral longitudinal anastomosis penetrate the soft tissues between the cartilaginous rings to supply a rich vascular network beneath the endotracheal mucosa. (From Salassa JR, Pearson BW, Payne WS: Gross and microscopical blood supply of the trachea. *Ann Thorac Surg* 24:100–107, 1977. Reprinted with permission from the Society of Thoracic Surgeons.)



These vessels enter the trachea via very fine lateral pedicles and lack intersegmental collateralization (Fig. 8-1).⁵ The pretracheal plane and the plane between the esophagus and the trachea are avascular. The recurrent laryngeal nerves ascend in the tracheoesophageal grooves bilaterally and pass medially to the inferior cornua of the thyroid cartilage to enter the larynx. The nerve on the left is present along the entire length of the trachea, whereas the right recurrent laryngeal nerve is present in the tracheoesophageal groove for only the proximal cervical trachea.

TRACHEAL PATHOLOGY

A wide spectrum of pathology can afflict the trachea, ranging from benign conditions to malignant ones. Most conditions lead to central airway obstruction with subsequent respiratory insufficiency. Others, such as fistulas between the trachea and innominate artery or esophagus, can also occur and be equally deleterious. Direct external trauma, blunt or penetrating, can result in a tear or complete disruption of the trachea at any level. Inhalational burn injuries are usually maximal in the proximal subglottic region and diminish in the more distal airway. In most cases, the tracheal rings are not destroyed.⁶ Idiopathic laryngotracheal stenosis appears to be a distinct disease entity, which leads to an inflammatory process in the subglottic region. This is an unusual problem almost exclusively occurring in white women most commonly in the third to fifth decade of life.⁷

Postintubation Injuries

Iatrogenic injuries resulting from tracheal intubation have long been the most common lesion afflicting the airway. Postintubation injuries include granulomas, strictures, malacia, and tracheoesophageal and tracheoinnominate fistulas (Fig. 8-2).

Postintubation tracheal stenosis represents the most common iatrogenic injury of the trachea. It occurs after

intubation and develops principally at the level of the endotracheal tube (ETT) or tracheostomy tube cuffs. The radial pressure exerted from the cuff causes circumferential pressure necrosis, which results in cicatricial scarring stenosis (Fig. 8-3).^{8,9} The route of entry of the ventilatory tube does not affect the occurrence of cuff injury, only its level. These lesions are seen in patients who have had only oral endotracheal intubation and in those with previous tracheostomy. The development of the large-volume, low-pressure cuff for tracheostomy and ETTs for ventilation has greatly lowered the incidence of cuff-related stenoses. However, overinflation of these cuffs can still result in local airway damage and subsequent scar formation, and it contributes to the continued incidence of these lesions. Stenosis in the subglottic region can occur because of prolonged intubation with ETTs, after cricothyroidotomy, or after high placement of a tracheostomy where the neck of the tube erodes through the cricoid cartilage.¹⁰

Stomal stenosis results from the gradual enlargement of a tracheal stoma and its eventual healing by contraction. This pulls the sides of the defect together, distorting the tracheal lumen to a triangular configuration, with the base of the triangle located posteriorly and consisting of the uninjured membranous wall (Fig. 8-4). The large stoma can result from overzealous excision of anterior tracheal cartilage at the time of the initial tracheostomy, from erosive infection around the margins of the stoma, or, most commonly, from erosion resulting from leverage by equipment attached to the tracheostomy tube during ventilation. The stenotic process can extend into the subglottic larynx if the previous tracheostomy was placed inappropriately high in the trachea.

Prolonged endotracheal intubation combined with a nasogastric tube can lead to a tracheoesophageal fistula (Fig. 8-5). This fistula results from pressure necrosis generated by a ventilating cuff in the trachea and a nasogastric feeding tube in the esophagus. Consequently, these fistulas occur in the shared location between the membranous tracheal wall and the anterior wall of the esophagus. Anterior injuries of the trachea can lead to the

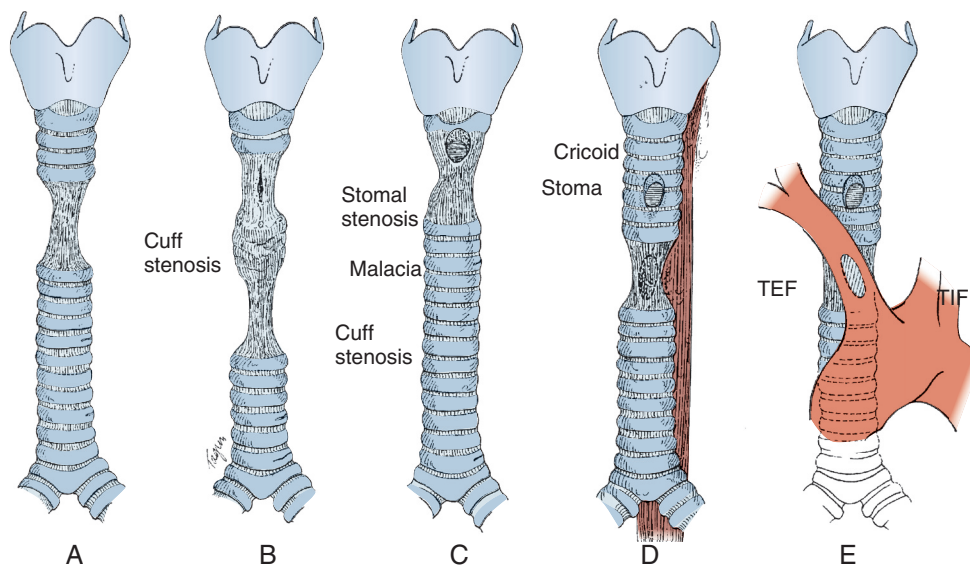


FIGURE 8-2 ■ Diagrams of principal postintubation tracheal lesions. **A**, Cuff stenosis from the cuff of an endotracheal tube. **B**, Cuff stenosis from the cuff of a tracheostomy tube, usually lower in the trachea than that from an endotracheal tube. Stoma stenosis also occurs at the site of the tracheostomy itself. Malacia can occur either at the level of the cuff or in the segment between the stoma and the cuff stenosis. **C**, Cuff stenosis at the site of a high tracheostomy stoma, which has eroded into the lower margin of the cricoid cartilage. In older patients, this can erode back further into the subglottic larynx, producing a laryngotracheal stenosis. **D**, Tracheoesophageal fistula (TEF) produced by pressure of the cuff against the membranous wall, often abetted by an indwelling, firm, nasogastric tube. **E**, One type of tracheoinnominate fistula (TIF) is the result of a high-pressure cuff erosion. The more common type, but also rare, is that seen with a low-placed tracheostomy stoma, which rests against the innominate artery itself. Not shown here are the lesions that occur in the larynx as the result of endotracheal tubes. (From Grillo HC: Surgical management of postintubation tracheal injuries. *J Thorac Cardiovasc Surg* 78:860, 1979.)

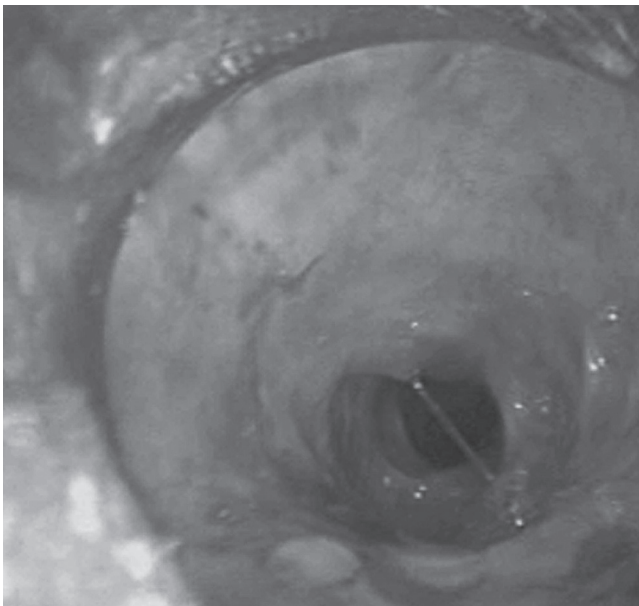


FIGURE 8-3 ■ Cuff-level stenosis. The stenosis here is circumferential, and the remaining lumen is round.

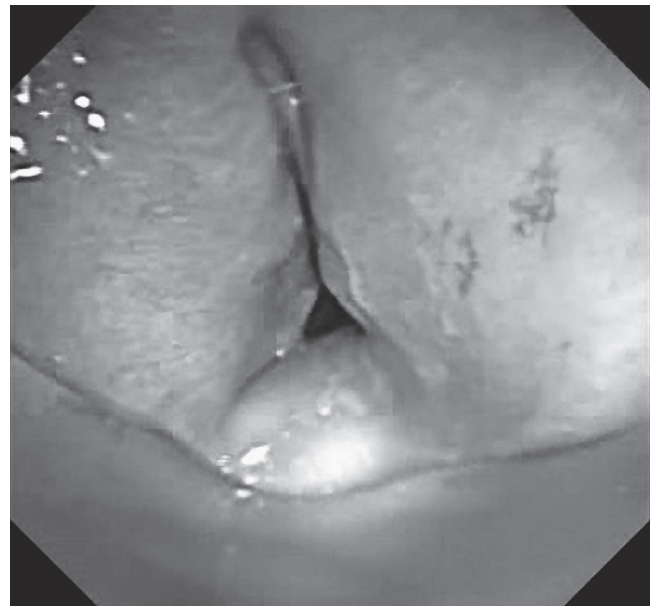


FIGURE 8-4 ■ Tracheostomy stomal site stenosis. The characteristic A-shaped lumen is evident and results from a primarily anterior and lateral cicatricial process.

development of a tracheoinnominate artery fistula. These most often result from direct erosion of the inner elbow of the tracheostomy tube in an inferiorly placed stoma, and they can arise either from a tracheostomy tube placed too low in the trachea or from an innominate artery lying high, near the sternal notch.

Idiopathic Laryngotracheal Stenosis

Rarely, a patient has stenosis of the airway without history of trauma, infection, inhalation injury, or airway intubation. Idiopathic laryngotracheal stenosis is a diagnosis of exclusion, characterized by an inflammatory cicatricial

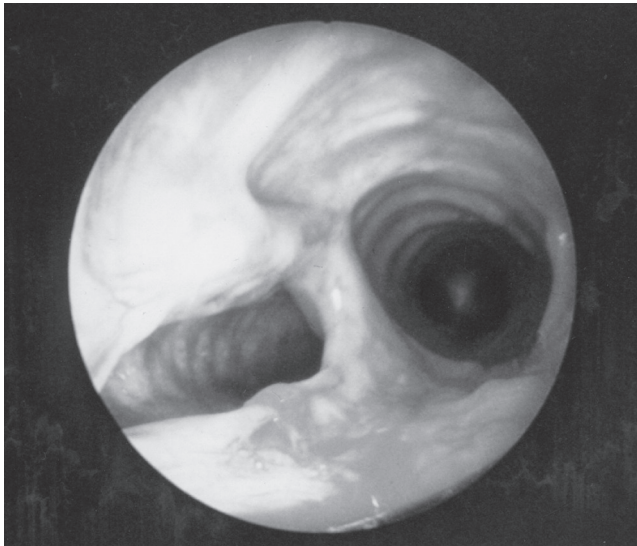


FIGURE 8-5 ■ Endoscopic view of a tracheoesophageal fistula.

stenosis at the level of the subglottic larynx, cricoid, and upper trachea.⁷ Causes such as gastroesophageal reflux with silent aspiration, Wegener granulomatosis, and connective tissue disorders must be excluded. As part of the routine preoperative workup, all patients undergo serologic screening (antinuclear antibody [ANA], antineutrophil cytoplasmic antibody [ANCA]) for these conditions. Over 95% of patients with idiopathic laryngotracheal stenosis are female between the third and fifth decade of life, and they typically exhibit signs and symptoms of upper airway obstruction. Pharyngeal and laryngeal anatomy and vocal cord function are usually normal, whereas the inflammatory process leading to luminal narrowing is confined intrinsically to the wall of the airway and the immediately surrounding connective tissue of a short (<2.5 cm) segment at the level of the cricoid cartilage.

The biggest clinical challenge in the surgical management of idiopathic laryngotracheal stenosis lies in the unpredictability and variability of the future clinical course. When airway obstruction becomes severe and dilation does not provide sustained relief of symptoms, surgery may be entertained, with, however, the clear caveat that the disease may progress. Most patients are best treated with definitive laryngotracheal resection and primary reconstruction.^{11,12} Timing of resection and reconstruction is central and must be done when inflammation is minimal. Bridging the time to definitive operation may require repeated bronchoscopic dilation. We prefer dilation to be performed in the operating room with rigid bronchoscopes starting with pediatric sizes increasing to adult bronchoscopes.

Tracheobronchomalacia

Airway malacia may be a consequence of a postintubation injury; however, in patients with chronic obstructive pulmonary disease, malacia can develop in the lower trachea, main bronchi, and sometimes the more distal bronchi, even in the absence of prior intubation.¹³ When the patient attempts a deep expiration or a cough, the mem-

branous wall approximates to the anterior, softened cartilaginous wall, causing nearly total obstruction. Subsequently, the posterior membranous wall elongates and becomes redundant. Afflicted patients may have dyspnea, cough, and secretion retention. It is possible to address the deformity surgically by pulling the ends of the cartilages toward one another posteriorly, restoring a more circular shape to the airway. The redundant membranous wall must be tacked to a posterior splinting material to prevent it from falling forward into the lumen. Various materials have been used for splinting, but none with complete success. These have included fascia lata, pericardium, lyophilized bone, polytetrafluoroethylene, and rigid plastic splints. Biomesh and cryopreserved aortic allografts can be useful biologic alternatives to synthetic tissues, especially when tissue quality or comorbidities are a factor, and airway erosion is of concern. To obtain maximum long-term relief, we currently use sheets of nonabsorbable polypropylene mesh to plicate the membranous wall as described by Rainer and colleagues.¹⁴

Tracheal Tumors

Primary tracheal tumors are rare, with an estimated incidence of 2.7 cases per million people per year.¹⁵ Approximately two thirds of primary tracheal tumors are either squamous cell carcinomas (SCCs) or adenoid cystic carcinomas (ACCs). These two types occur with equal frequency. The remaining third of the tumors are widely distributed in a heterogeneous group of tumors, both malignant and benign. Secondary tumors that involve the trachea include carcinomas of the larynx, thyroid, lung, and esophagus. Rarely, tumors metastasize to the submucosa of the trachea or to the mediastinum, with secondary invasion of the trachea.

Squamous cell carcinomas can be either exophytic (Fig. 8-6) or ulcerative. The tumor can metastasize to the regional lymph nodes, and, in its more aggressive and late forms, it invades mediastinal structures. In general, its progress appears to be relatively rapid in comparison with that of adenoid cystic carcinoma. A number of affected patients develop synchronous or metachronous second SCC primary cancers of the lung or oropharynx. Squamous cell carcinoma occurs predominantly in men who are cigarette smokers.¹⁶

ACC often has a prolonged course of clinical symptoms, sometimes extending for years. After resection, many years can pass before a recurrence is noted. ACC can extend submucosally over long distances in the airways and along perineural tissue. It can spread to regional lymph nodes, although this is less characteristic than in SCC. Although it can invade the thyroid or the muscular coats of the esophagus by contiguity, ACC that has not been surgically interfered with frequently displaces mediastinal structures before actually invading them. Metastases to the lungs, bone, and other organs can occur. These metastases can grow slowly over a period of many years and remain asymptomatic until they become large. In contrast to patients with tracheal SCC, the male-to-female ratio of patients with ACC is essentially equal, and any smoking history of these patients appears to be incidental.¹⁶

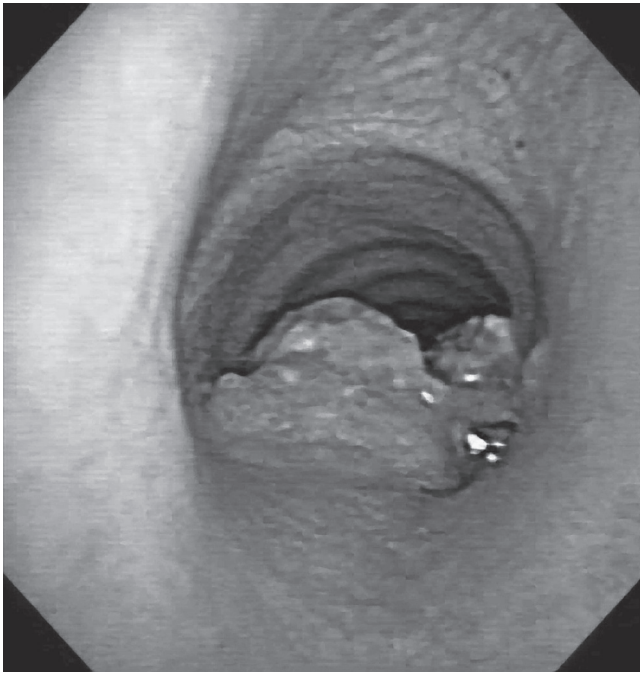


FIGURE 8-6 ■ An exophytic squamous cell carcinoma of the trachea.

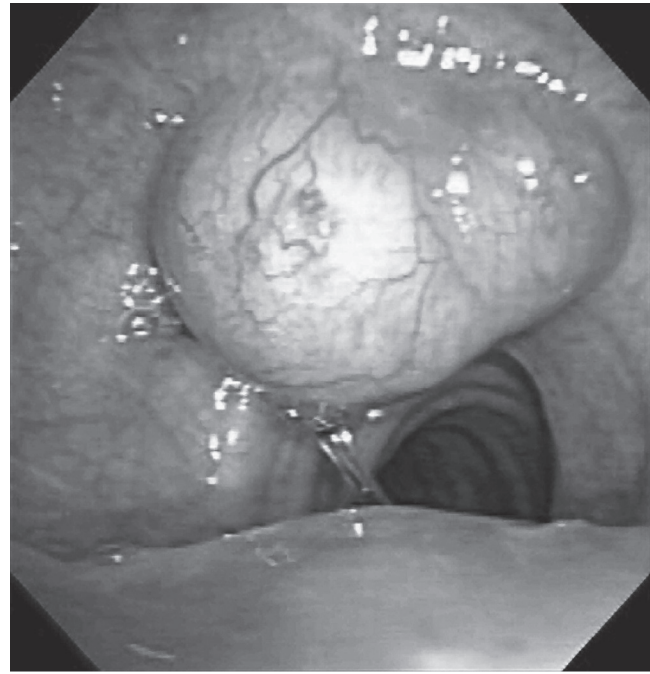


FIGURE 8-7 ■ Bronchoscopic view of a papillary thyroid carcinoma with tracheal invasion.

The third group of primary tracheal tumors is composed of a multitude of tumor types and varying degrees of malignancy, including both epithelial and mesenchymal neoplasms. The list includes pleomorphic adenomas, leiomyomas, chondromas, carcinoid tumors, mucoepidermoid tumors, and sarcomas.

Secondary neoplasms can involve the trachea through direct extension. Thyroid carcinomas typically invade the trachea at the second and third rings, where the thyroid isthmus is adherent to the trachea (Fig. 8-7).¹⁷ More commonly, invasion is seen after thyroidectomy for carcinoma, when the surgeon was aware of shaving off the tumor from the trachea. In such cases, concurrent or early resection of the involved trachea should be considered. Both bronchogenic and esophageal carcinomas can erode into the trachea from local extension.

CLINICAL PRESENTATION

Patients with pathologic lesions of the trachea usually exhibit signs and symptoms of upper airway obstruction: dyspnea on exertion, wheezing, or stridor. Unfortunately, this presentation is frequently misinterpreted as adult-onset asthma, and it is not uncommon for patients to undergo treatment with corticosteroids for months to years before the correct diagnosis is finally made. Any patient with obstructive airway and a history of tracheal intubation must be considered to have airway stenosis until proven otherwise.

Tumors of the trachea often present insidiously. Their most common signs and symptoms are cough (37%), hemoptysis (41%), and the signs of progressive airway obstruction, including shortness of breath on exertion

(54%), wheezing and stridor (35%) and, less commonly, dysphagia or hoarseness (7%).¹⁵ Signs and symptoms can vary with the histology of the tumor. Hemoptysis is prominent in patients with SCC, usually leading to a prompt diagnosis. Patients with ACC more commonly exhibit wheezing or stridor as the predominant symptom, which often leads to a delay in diagnosis. In one study, the mean duration of symptoms before diagnosis in patients with SCC of the trachea was only 4 months, whereas in those with ACC it was 18 months.¹⁸

A tracheoesophageal fistula frequently appears as an increase in tracheal secretions and the appearance of orally ingested material in the airway. If the patient is using a mechanical ventilator, gastric distention can develop. Tracheoinnominate arterial fistulas may be heralded by a premonitory hemorrhage. In evaluating a patient with bleeding from a tracheostomy tube, it is important to determine whether the source is from erosion of tracheal granulation tissue or mucosal trauma, as opposed to the more deleterious arterial fistula.

RADIOGRAPHIC IMAGING

A standard posteroanterior chest radiograph, centered high on the trachea, may reveal some tracheal pathology. Detailed information about the location of the lesion, its longitudinal extent, and the amount of normal trachea available for reconstruction can be demonstrated by computerized axial tomography scans. These are particularly useful in evaluating tracheal tumors, as they characterize extraluminal extension and any mediastinal lymphadenopathy. Recently, the use of high-speed helical computed tomographic scanners to acquire images, combined



FIGURE 8-8 ■ **A**, Reformatted computed tomographic (CT) two-dimensional (2D) image of post-tracheostomy stenosis. **B**, A 2D image of an adenoid cystic carcinoma of the carina. **C**, Three-dimensional (3D) image of a tracheal airway column showing the endobronchial component of the same carinal mass. **D**, The same carinal mass as viewed endobronchially by a 3D image via virtual CT bronchoscopy.

with powerful three-dimensional-image software, has created impressive two- and three-dimensional airway reconstructions (Fig. 8-8).

BRONCHOSCOPY

Bronchoscopic evaluation is necessary to confirm a diagnosis, design an operative strategy, and ameliorate impending airway obstruction. Measurements taken with a rigid bronchoscope determine the amount of normal trachea that is available, both proximal and distal to the pathology, for reconstruction. Factors such as age, body habitus, prior surgery, and lesion location influence the amount of trachea that can be safely resected. With benign strictures, special attention must be given to evaluating the condition of the tracheal mucosa. Indwelling tracheostomy or tracheal T-tubes must be removed and

the mucosa assessed. If extensive mucosal inflammation or ulceration exists, definitive repair should be delayed until mucosal healing occurs. This may require a short period of decannulation or a change to a smaller T-tube. Often, patients with idiopathic laryngotracheal stenosis have active inflammation extending into the immediate subglottis. These patients should undergo dilation of their stenosis, and the operation should be delayed until the inflammatory state of the airway mucosa subsides. Patients taking corticosteroids should be weaned from them completely at least 1 month before an operative repair is undertaken. This is done to minimize the adverse wound-healing effects of these medications.

Expertise with the techniques of interventional bronchoscopy is essential to dilate a benign stenosis safely or “core out” an obstructing airway tumor. Coring out the tumor allows evaluation of the distal airway, safe passage of an ETT, or temporary creation of a patent airway to

allow delay in operation. Dilating a narrow, fibrotic stricture is challenging and can result in airway rupture, complete obstruction, or excessive destruction of tracheal mucosa. Progressively larger Jackson dilators passed through a rigid bronchoscope can be used to dilate the stenosis. An assortment of pediatric and adult rigid bronchoscopes can then be used, increasing the sizes and using a gentle corkscrew motion.¹⁹ Balloon dilators placed through the working channel of a flexible bronchoscope permit effective airway dilation, but we prefer rigid bronchoscopic dilation because of better control and visualization.

Obstructing tracheal tumors are managed first by core-out techniques using the rigid bronchoscope, forceps, and suction.²⁰ Using the tip of the bronchoscope in a corkscrew motion, most tumors can be débrided from the tracheal wall, and a forceps can then be used to remove dislodged tumor fragments. If bleeding ensues, the bronchoscope is advanced distal to the lesion and is used to tamponade the bleeding. Direct application of epinephrine-soaked pledgets can assist in achieving hemostasis.

Patients with critical airway stenosis should be assessed in the operating room where rigid bronchoscopy, biopsy forceps, and instruments required to perform emergent tracheotomy are available. Placement of a tracheostomy tube may be necessary in some patients as the only means to secure an airway. When possible, these tubes should be placed through the stenosis, preserving the uninvolved trachea for future reconstruction.¹⁹

ANESTHESIA

Anesthesia for airway surgery is challenging for both surgeon and anesthesiologist because of the underlying compromised airway and the necessity to share the airway during resection and reconstruction while maintaining respiration.²¹ Continuous close communication between the surgical and anesthesia teams is required throughout the case, particularly during the open airway phase of the operation. Clinical examination and history during preoperative evaluation, with special attention to exertion dyspnea and dyspnea at rest, the pattern of dyspnea, and the patient's ability to breathe comfortably in supine position, help to plan induction and airway management. In preparation for induction, an assortment of small-diameter ETTs (from 4.0 to 6.5), a sterile, spiral steel-enforced ETT (for ventilation across the surgical field), and a pediatric bronchoscope (in case the ETT needs to be checked, or in case of inadvertent extubation) should be immediately available. One or two midsize peripheral intravenous catheters and placement of an arterial line should be considered, whereas placement of a central venous line is usually not necessary. In patients with compromised airway, especially when there is a high degree of airway obstruction, usual intravenous induction is an acceptable choice (e.g., propofol, 2 mg/kg; fentanyl, 2 µg/kg; and cisatracurium, 0.15 mg/kg) to provide satisfactory anesthesia and muscle relaxation for rigid bronchoscopy and intubation. In selected cases, slow inhalative patient induction maintaining spontaneous ventilation

may be a valid alternative if there is a high degree of airway obstruction.²² This method can be safer than the administration of muscle relaxants, which paralyze respiration with a consequently urgent need to establish an airway.

The surgeon should have available an array of rigid bronchoscopes from pediatric to adult sizes as the induction commences. The residual airway through which the patient is breathing may be as narrow as 2 or 3 mm in diameter. In most cases, tumors are not circumferential. After bronchoscopy, a small ETT can often be insinuated past a highly obstructive lesion. Although not ideal, an ETT can be secured above the obstructive pathology.

At the time of tracheal division, the ETT is pulled back under direct vision, after a flexible red rubber catheter has been sutured to the Murphy eye of the ETT. The red rubber catheter serves as a guide for blind re-advancement of the ETT during the later phase of reconstruction. To maintain ventilation, a sterile, cuffed, and armored ETT is inserted into the distal airway across the operative field. Sterile connecting tubing is passed to the anesthesiologist to allow ventilation of the patient. This armored tube is removed whenever necessary for suctioning or placement of sutures. Toward the completion of the operation, the original ETT is advanced into the distal airway and the anastomotic sutures are tied. High-frequency ventilation has been used with equal success intraoperatively, but we have been quite satisfied with the technique described here. High-frequency ventilation is especially useful in certain complex carinal reconstructions.

Anesthesia is maintained with total intravenous anesthesia using short-acting agents such as propofol and agents blunting airway reflexes such as remifentanyl. This allows for quick emergence and immediate extubation at the completion of the procedure and maintains continuous anesthesia during periods when inhalational agents are interrupted by the procedure. Both teams have to be at the bedside during emergence and extubation, because most severe complications such as anastomotic disruption can occur during this critical stage of the operation. Tools for airway rescue such as laryngoscopes, bronchoscopes, ETTs, and laryngeal mask airways have to be immediately available. In general, the patient should be extubated and be able to breathe spontaneously at the conclusion of the procedure. Particularly when the trachea has been greatly shortened, it is desirable not to have even a low-pressure cuff lying in contact with the anastomosis. To optimize the immediate postoperative period, we routinely use techniques to keep the upper airway clear, including good oropharyngeal suctioning, antiemetics, and elevation of the head of bed. If swelling is anticipated, nebulized epinephrine can be a useful tool, while we try to avoid corticosteroids in the immediate postoperative setting. To prevent disruption caused by inadvertent movements during emergence, after extubation, and during patient transfer, one member of the team should be designated to ensure that the patient's neck remains flexed at all times. The use of cardiopulmonary bypass is rarely necessary in adult tracheal surgery, but it may be required in some complex carinal reconstructions²³; however, it may be requisite in repairing congenital airway lesions in the

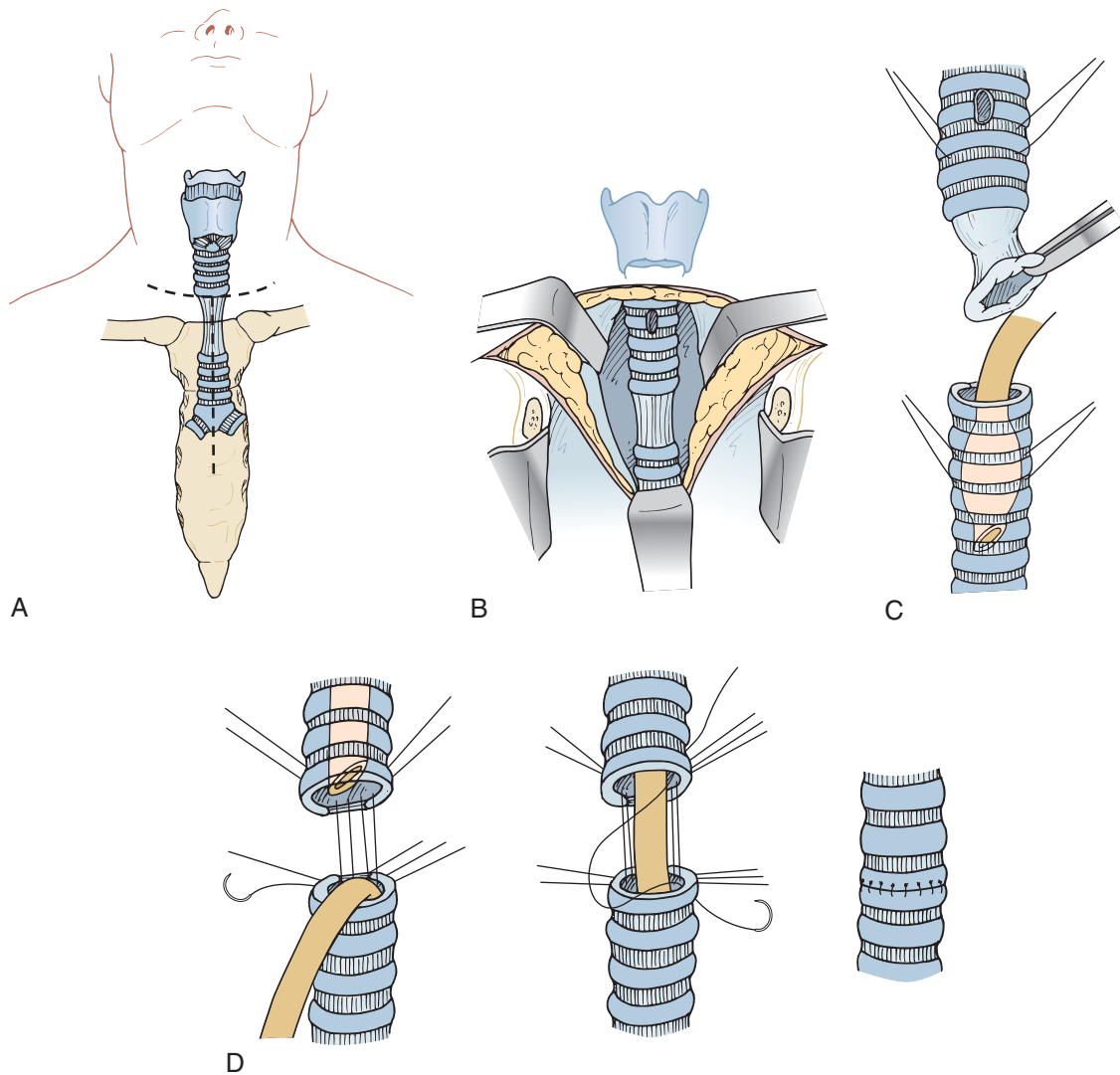


FIGURE 8-9 ■ Resection of a midtracheal airway stenosis. See text for description of **A** to **D**. (From Grillo HC: Surgery of the trachea: current problems in surgery. *Ann Thorac Surg* 7:3–59, 1970. Reprinted with permission from Mosby, Inc.)

pediatric population, especially in the presence and correction of cardiac anomalies.²⁴

TRACHEAL RESECTION

For uncomplicated resections of the middle and upper trachea, the patient is positioned supine with neck extended using an inflatable airbag beneath the shoulders. The inflatable bag facilitates exposure by extending the neck during dissection, and when deflated, it allows cervical flexion just before the anastomotic sutures are tied. The head is supported in a foam ring, and the arms are tucked at the sides. Care must be taken not to over-extend the neck to avoid compression injury of cervical nerve roots. In patients with limited cervical mobility, testing the range of motion and the limits of comfortable extension before induction can be highly informative.

A low collar cervical incision is adequate for most tracheal resections that involve the upper trachea. When the lesion involves the middle to lower trachea, vertical

extension with a partial sternal split facilitates exposure (**Fig. 8-9A**). Dissection is carried through the platysma, and subplatysmal flaps are elevated superiorly to the level of the thyroid cartilage and inferiorly to the level of the sternal notch. The strap muscles are separated in the midline, and a plane of dissection is established very close to the tracheal wall to avoid injury to the recurrent laryngeal nerves (see **Fig. 8-9B**). The pretracheal plane is dissected to the level of the carina. The investing fascia of the innominate artery and the adjacent mediastinal fat are left intact to guard against postoperative tracheoinnominate fistulization. Retraction on the innominate artery is kept to a minimum to avoid impeding cerebral blood flow. Compression can be monitored by a right radial arterial line.

The area of involved trachea is transilluminated with a flexible bronchoscope through the oral ETT, allowing the assistant to mark the distal extent of resection. The balloon of the ETT is deflated. The trachea is sharply dissected circumferentially at the most distal aspect of the lesion, with the dissection plane maintained on the

tracheal wall. The oral ETT is withdrawn into the upper trachea and sutured to a red rubber catheter as described earlier. The trachea is partially divided at the most distal extent of the lesion, and bilateral 2-0 Vicryl traction sutures are placed. These sutures are placed in the midlateral aspect of the tracheal wall 1 cm below the anticipated level of transection. Distal tracheal division is completed, and circumferential dissection of the residual distal trachea is limited to 1 cm to protect the segmental tracheal blood supply. A cuffed, wire-wound ETT is promptly passed into the distal tracheal segment and attached to sterile connecting tubing, and cross-table ventilation is instituted (see Fig. 8-9C). The diseased segment of trachea is sharply dissected from the esophagus and amputated at the most proximal extent of the lesion. Proximal 2-0 Vicryl traction sutures are then placed.

The patient's neck is then flexed and the anastomosis tested for tension by crossing the traction sutures. If the limits of flexion and safe dissection have been reached and anastomotic tension exists, then one can proceed with release procedures. When the surgeon is satisfied that the anastomosis will not be under tension, interrupted, 4-0 Vicryl anastomotic sutures are placed so that the knots will be on the outside, beginning posteriorly in the midline and proceeding around either side to the front (see Fig. 8-9D). The sutures are placed 5 to 6 mm from the cut edge of the trachea and 4 mm apart. They should encircle a tracheal ring on either side of the anastomosis to help prevent dehiscence. Frequently, the cross-field ETT must be withdrawn for short periods to allow accurate placement of the more difficult sutures or for suctioning blood from the distal airway. After placing the anterior sutures, the cross-field ETT is removed from the distal tracheal segment, and the oral ETT is advanced carefully beyond the anastomosis.

Before tying down the anastomotic sutures, the inflatable airbag beneath the shoulders is deflated, the 2-0 traction sutures are tied, and any last few degrees of neck flexion that may be required are instituted. The anastomotic sutures are then tied from anterior to posterior—the reverse order to that in which they were placed. After all knots are tied, we test patency of the airway by deflating the cuff and pressurizing the airway with 20 to 40 cm H₂O to listen for an air leak around the tube. The integrity of the suture line is tested under saline immersion with the cuff deflated. We inflate to 20, 30, and 40 cm H₂O. During this maneuver, it is necessary to occlude mouth and nose manually. The bilateral sternohyoid muscles are mobilized from their surrounding attachments and sutured to the anterior trachea, above and below the anastomosis, to serve as a vascularized tissue buttress. A closed suction drain is left in the pretracheal space.

A chin-to-chest suture is placed with the neck in moderate flexion to prevent cervical hyperextension. This suture is tied without slack to prevent neck extension for the first 5 to 7 postoperative days. Patients are extubated in the operating room. When postoperative intubation is thought to be necessary, a small ETT is left in place, and a stitch is placed at least two rings below the anastomosis to mark the site for possible future tracheostomy. This allows limited dissection and accurate placement in a

reoperative field. It is best to wait a few days before placing a tracheostomy to allow skin flaps and other tissue layers to seal before exposing them to airway secretions. This also allows postsurgical airway edema to resolve, possibly obviating the need for a tracheostomy. Extubation should be attempted in the operating room, where bronchoscopic evaluation and placement of a small tracheostomy tube can be performed if necessary. Careful positioning and fixation of sternothyroid and sternohyoid muscle flaps during the initial operation help to keep a possible tracheostomy separate from the resection wound bed. For tracheal tumors, the approach is slightly modified. Considerable experience is required to judge whether a tumor can be safely resected with sufficient tissue to provide a clear margin and yet allow successful primary reconstruction of the airway. This decision can be particularly difficult in patients with adenoid cystic carcinoma, because frozen sections may show microscopic tumor at grossly clear resection margins. The plane of tissue dissection in tumor cases must be kept away from the involved portion of trachea to ensure an adequate radial margin. By dissecting further away from the trachea, it endangers the recurrent laryngeal nerves more than during resections for benign disease. If one recurrent laryngeal nerve is involved by tumor, the nerve should be sacrificed. Adjacent paratracheal lymph nodes are resected en bloc with the specimen, but, to minimize devascularization of the airway involved in the tracheal anastomosis, extensive lymph node dissection should not be performed. Postoperative radiation therapy is often recommended in cases of bronchogenic or adenoid cystic carcinoma, unless it is contraindicated by performance status or anastomotic complications.¹⁵

The transthoracic approach, using a posterolateral thoracotomy through the fourth intercostal space, is used for tumors of the lower trachea and carina and for a few inflammatory lesions. An extra-long, single-lumen ETT with sufficient diameter is used to intubate the left main-stem bronchus for selective ventilation.

Dissection of the thoracic trachea is performed in a fashion similar to that for more proximal pathology. In cases of malignancy, effort is made to resect surrounding tissues with the tumor. Eventually, the trachea is dissected circumferentially below the tumor, and sometimes above it, although the upper portion of the dissection may be completed after division of the trachea below. Traction sutures are placed in the midlateral tracheal wall distal to the tumor. If the transection is close to the carina, the sutures are placed in the lateral walls of the right and left main bronchi. Again, anesthesia tubing brought across the field is joined to a flexible armored tube placed in the distal trachea or, preferably, the left main bronchus, to allow collapse of the right lung for better exposure while performing the anastomosis. If this results in significant intrapulmonary shunting, the right pulmonary artery may be gently clamped.

Flexion of the neck, even with the patient in the lateral thoracotomy position, delivers the proximal trachea into the thorax. Dissection anterior to the trachea and both main bronchi will provide additional mobility. These are important maneuvers for obtaining a tension-free anastomosis. In the resection of a malignant tracheal

tumor, paratracheal and subcarinal lymph nodes that are not in proximity to the mass should not be radically resected for fear of devascularization of the airway. The technique of anastomosis is similar for that used in the upper trachea.

LARYNGOTRACHEAL RESECTION

When an upper tracheal lesion involves the cricoid cartilage, a laryngotracheal resection will be necessary (Fig. 8-10). The operative procedure must be tailored to address the particular anatomic involvement encountered. The recurrent laryngeal nerves are protected by beveling off the cricoid anteriorly and laterally while preserving the posterior cricoid plate.^{25,26} The extent of anterior cricoid resection ranges from complete, with a line of transection through the cricothyroid membrane, to

none at all, depending on the extent of involvement. In patients with significant subglottic side-to-side narrowing, tailored partial resection of the lateral cricoid cartilage with subsequent resurfacing provides a technique to achieve a larger ventricle.²⁷ Tracheal resection depends on the distal extent of the lesion (Fig. 8-11A and B). The trachea is appropriately tailored so that the proximal trachea approximates well with the cut edge of the larynx (see Fig. 8-11C and D). Vicryl traction sutures are placed in the mid-lateral position both proximally and distally. Interrupted 4-0 Vicryl sutures are used to fashion the anastomosis. The traction sutures are crossed and tied, followed by the individual 4-0 Vicryl anastomotic sutures (see Fig. 8-11E and F).

When the lesion involves the posterior subglottic larynx, a line of mucosal division is performed high on the posterior cricoid plate to excise involved mucosa and submucosa. The posterior cartilage is not resected. Mucosal resection should not extend proximally beyond the superior border of the cricoid plate. A posterior broad-based flap of membranous wall is created and advanced to resurface the posterior cricoid plate (Fig. 8-12). Four to five sutures are placed through the cartilaginous portion of the inferior margin of the cricoid plate and the outer portion of the membranous wall of the trachea below the proximal edge of the flap in order to fix the membranous wall to the inferior edge of the cricoid plate.^{25,26} These base of flap sutures are vertical mattress sutures to allow the knots to be tied on the outside of the airway. The posterior portion of the anastomosis is made with interrupted 5-0 Vicryl sutures placed only through the full thickness of mucosa and submucosa of the posterior wall of the larynx, and then through the full thickness of the membranous wall of the trachea. For ease of tying, the knots can be on the inside of the anastomosis.

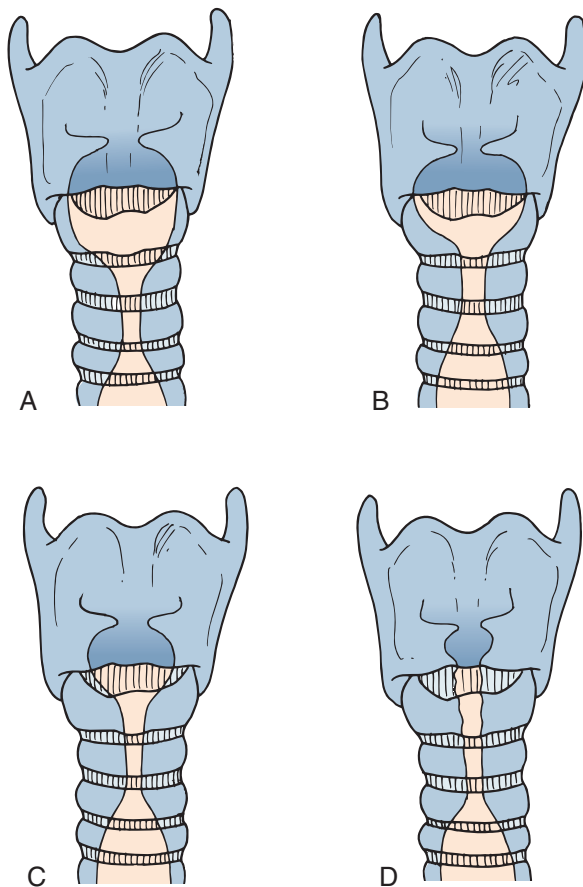


FIGURE 8-10 ■ Upper airway stenosis. **A**, High tracheal stenosis, easily treated by segmental resection and tracheotracheal anastomosis. **B**, Stenosis that reaches to the lower border of the cricoid cartilage. **C**, Stenosis of the lower subglottic larynx and upper trachea. The extent of the lesion anteriorly is so great that correction requires removal of the anterior portion of the cricoid cartilage. **D**, Stenosis that reaches to the glottis. There is no subglottic space to which an effective anastomosis can be made. (From Grillo HC: Primary reconstruction of airway after resection of subglottic laryngeal and upper tracheal stenosis. *Ann Thorac Surg* 33:3-18, 1982. Reprinted with permission from the Society of Thoracic Surgeons.)

RELEASE PROCEDURES

Dissection of the pretracheal plane combined with cervical flexion produces sufficient airway mobility to allow tracheal resection and primary reconstruction in most patients. When extensive resections are performed, further mobilization with certain maneuvers may be required to enable a tension-free anastomosis. This has been shown to be necessary in 8.3% of patients undergoing resections for postintubation stenoses and in 15% of patients undergoing resections for tumors.¹⁹ The location of the lesion is an important factor in determining which procedures will be of benefit.

Certain release maneuvers are more effective for achieving additional mobility of the cervical trachea, whereas others are more effective for freeing the intrathoracic trachea. When an upper trachea resection is performed, an additional 1.5 cm of length may be gained by releasing the larynx with a Montgomery suprahyoid release.²⁸ This is accomplished by dividing the muscles that insert on the superior aspect of the central part of the hyoid bone. The hyoid itself is then divided just lateral to its lesser cornua on both sides, and the stylohyoid tendons are divided (Fig. 8-13). Laryngeal release

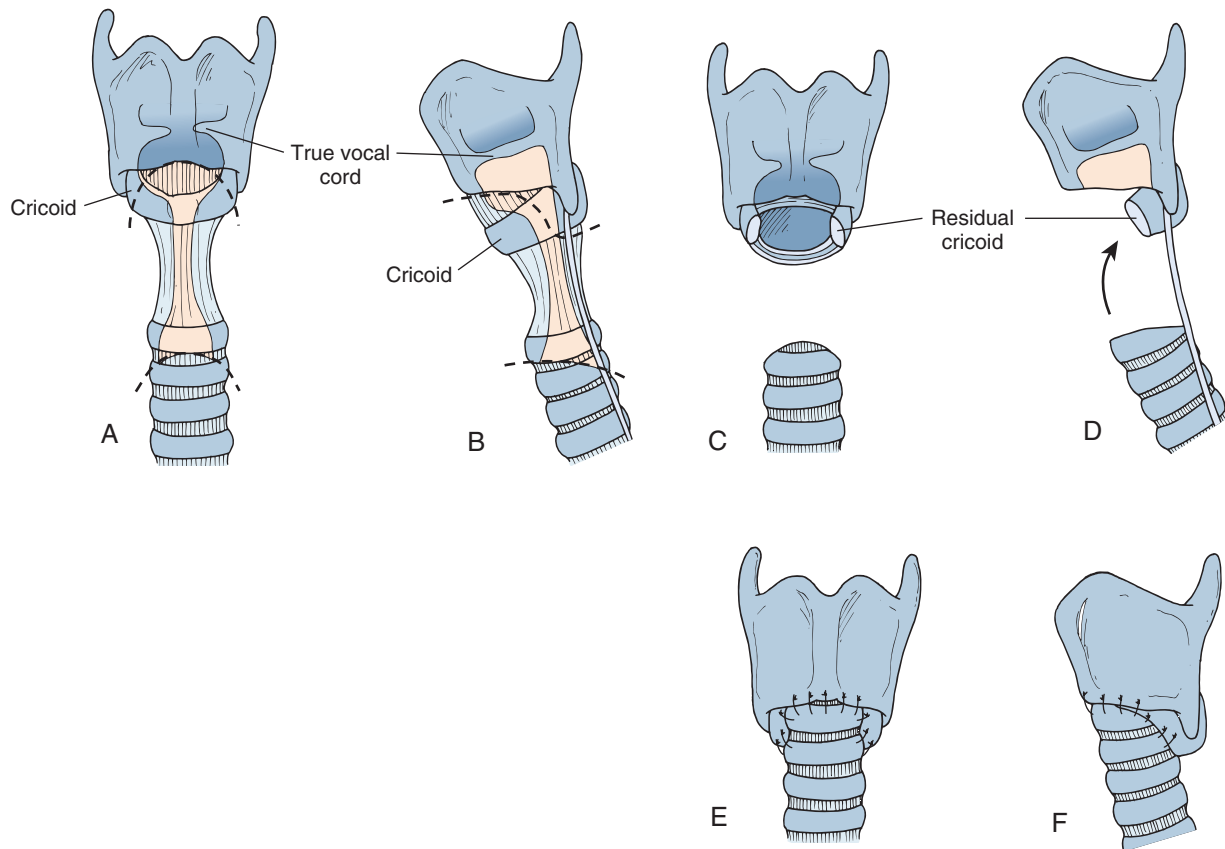


FIGURE 8-11 ■ Operative repair of anterolateral stenosis of the subglottic larynx and upper trachea. **A**, Anteroposterior view. **B**, Lateral view, showing the extent of disease involvement and the ultimate lines of transection. **C** and **D**, Larynx and trachea after removal of the specimen. Recurrent nerves have been left intact. Mucous membrane of the larynx has been transected sharply at the same level of division as cartilage. Anteroposterior (**E**) and lateral (**F**) views of reconstruction. (From Grillo HC: Primary reconstruction of airway after resection of subglottic laryngeal and upper tracheal stenosis. *Ann Thorac Surg* 33:3–18, 1982. Reprinted with permission from the Society of Thoracic Surgeons.)

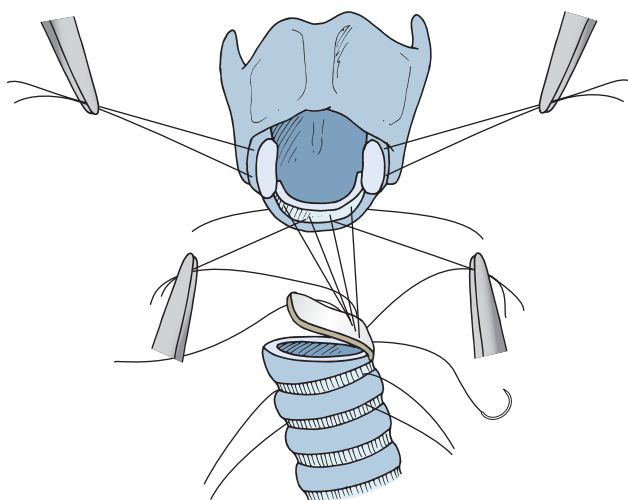


FIGURE 8-12 ■ Technique of posterior membranous tracheal wall flap with cricoid resurfacing. (From Grillo HC: Primary reconstruction of airway after resection of subglottic laryngeal and upper tracheal stenosis. *Ann Thorac Surg* 33:3–18, 1982. Reprinted with permission from the Society of Thoracic Surgeons.)

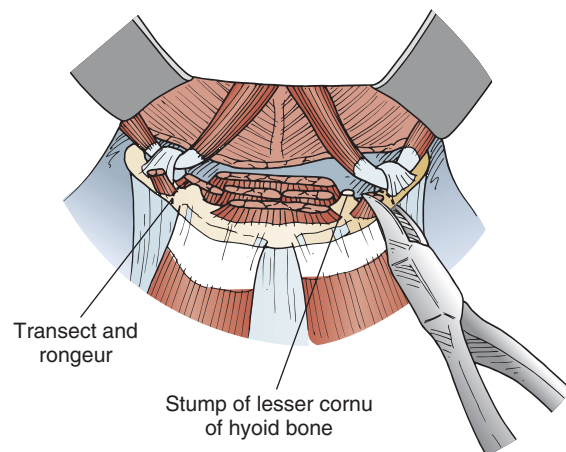


FIGURE 8-13 ■ The dotted lines indicate the point where the hyoid bone is divided, separating its body from the greater horn on each side. (From Montgomery WW: Suprahyoid release for tracheal anastomosis. *Arch Otolaryngol* 99:255–260, 1974. Reprinted with permission from the American Medical Association.)

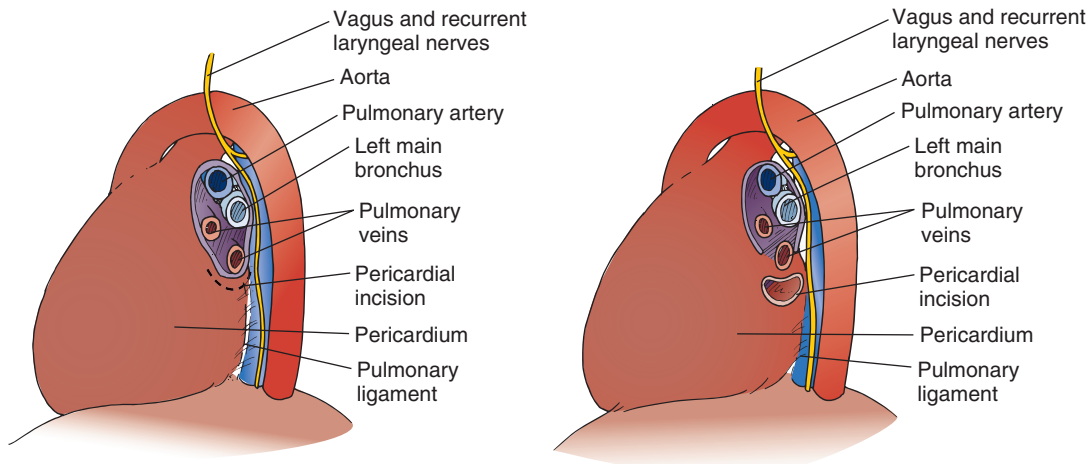


FIGURE 8-14 ■ The left-sided intrapericardial hilar release technique demonstrates the U-shaped pericardial incision allowing 1 to 2 cm of upward hilar mobility to facilitate the creation of a tension-free anastomosis. (From Newton JR, Grillo HC, Mathisen DJ: Main bronchial sleeve resection with pulmonary conservation. *Ann Thorac Surg* 52:1272–1280, 1991. Reprinted with permission from the Society of Thoracic Surgeons.)

maneuvers may predispose patients to postoperative aspiration, but in time this problem resolves in most patients.

For transthoracic tracheal resections, additional length is best achieved by hilar release.²⁹ Mobilization of the right hilum should be approached first, along with division of the inferior pulmonary ligament. A U-shaped incision is then made in the pericardium below the inferior pulmonary vein. The pericardium can be incised 360 degrees around the hilum for additional mobility. In this event, the vascular and lymphatic pedicle to the main-stem bronchus is left preserved behind the pericardium. If further mobility is needed, the left hilum may be similarly mobilized (Fig. 8-14); this can be accomplished through a median sternotomy by opening the pericardium, by bilateral thoracotomies or an extended clamshell incision. As with most airway surgery, neck flexion is helpful; however, laryngeal release has not been shown to produce meaningful mobility at the level of the carina.³⁰

REPAIR OF TRACHEOINNOMINATE AND TRACHEOESOPHAGEAL FISTULAS

Tracheoinnominate fistulas appear as either massive airway bleeding or episodic hemoptysis. Significant bleeding from around or through a tracheostomy should be evaluated in the controlled environment of the operating room. The surgeon should be prepared to manage massive airway bleeding before removing the tracheostomy cannula. The patient is then decannulated and a bronchoscopy performed. In the event of massive hemorrhage, control can usually be obtained by finger compression through the stoma, pushing anteriorly against the sternum at the site of bleeding. A small oral ETT is advanced into the airway beyond the finger and the cuff firmly inflated to ventilate and protect the lungs from aspiration of blood. If the fistula lies beyond reach, hemorrhage can be controlled by placing an inflated ETT cuff over the bleeding vessel.

Exposure is obtained through a collar incision at the level of the stoma, along with a vertical extension for sternotomy. With finger compression maintaining hemostasis, the vessel is dissected to obtain proximal and distal vascular control. The involved segment of artery is resected, and the proximal and distal ends are oversewn. The stumps are covered with surrounding, well-vascularized tissue. Innominate division usually does not result in neurologic sequelae. Depending on the degree of airway destruction, a concomitant tracheal resection may be necessary. A new tracheal stoma is created at a higher level, and a tracheostomy tube long enough to pass beyond the previous stoma is used. Local strap muscle flaps are sutured over the original stoma to hasten its healing. In contaminated fields, transfer of omentum can be a useful backup source of well-vascularized tissue that can be mobilized with a midline extension of a median sternotomy incision.

Acquired, nonmalignant tracheoesophageal fistulas often appear while the patient remains ventilator-dependent. The fistula develops at the level of the cuff and is usually associated with a circumferential tracheal injury.³¹ Temporizing measures are taken to allow weaning from the ventilator before repair is undertaken. A tracheostomy tube should be positioned with the occluding cuff located below the fistula to prevent contamination of the tracheobronchial tree. Gastrostomy and jejunostomy tubes should be placed for drainage and feeding, respectively. The esophagus is kept free of tubes, and cuff overinflation is assiduously avoided. Before successful surgical repair can be attempted, pulmonary sepsis has to be controlled with adequate, tailored antibiotic coverage and aggressive pulmonary toilet. Ideally, the patient should be weaned or ready to be weaned from ventilator support before undergoing surgery, to minimize the need for mechanical ventilation, and prolonged intubation in the immediate postoperative period.

A collar incision is performed that encompasses the stoma (Fig. 8-15). As described previously, the trachea is dissected and divided distal to the fistula. As the posterior

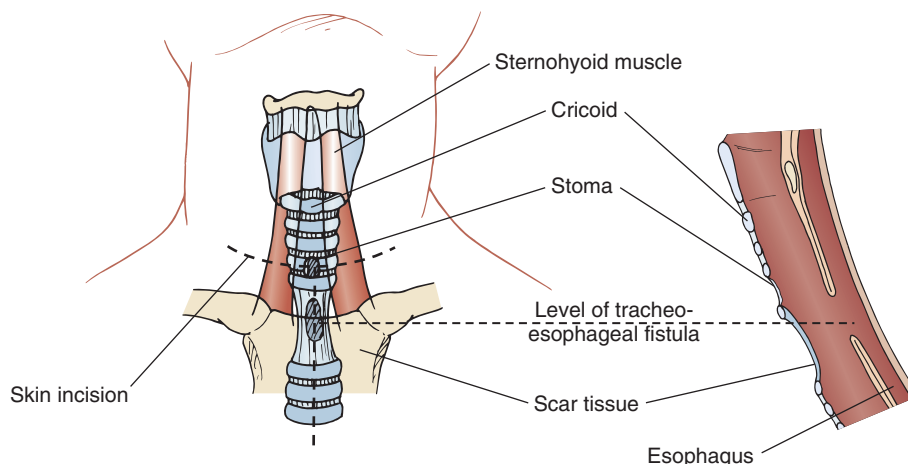


FIGURE 8-15 ■ Exposure for most tracheoesophageal fistulas is through a low collar incision. Occasionally, a partial upper sternotomy is required for more distal exposure of the trachea. (From Mathisen DJ, Grillo HC, Wain JC, et al: Management of acquired nonmalignant tracheoesophageal fistula. *Ann Thorac Surg* 52:759–765, 1991. Reprinted with permission from the Society of Thoracic Surgeons.)

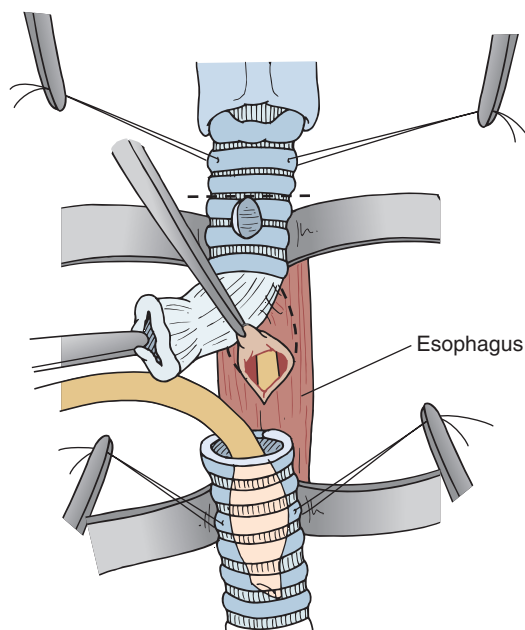


FIGURE 8-16 ■ Circumferential dissection above and below the fistula is performed in close proximity to the trachea to avoid injury to the recurrent laryngeal nerve. Division of the damaged trachea gives excellent exposure of the esophageal defect. (From Mathisen DJ, Grillo HC, Wain JC, et al: Management of acquired nonmalignant tracheoesophageal fistula. *Ann Thorac Surg* 52:759–765, 1991. Reprinted with permission from the Society of Thoracic Surgeons.)

wall of the trachea is dissected from inferior to superior, the fistulous connection is isolated circumferentially and detached from the esophagus with a small rim of normal esophageal tissue (Fig. 8-16). After removal of the specimen, the esophagus is closed longitudinally with two layers of 4-0 silk (Fig. 8-17). A strap muscle is used to buttress the esophageal closure and as a flap of vascularized tissue interposed between the esophageal and tracheal suture lines (Fig. 8-18). An end-to-end tracheal anastomosis is then performed. It may be necessary to repair the defect partially in the posterior membranous wall with a vertical suture line to limit the amount of

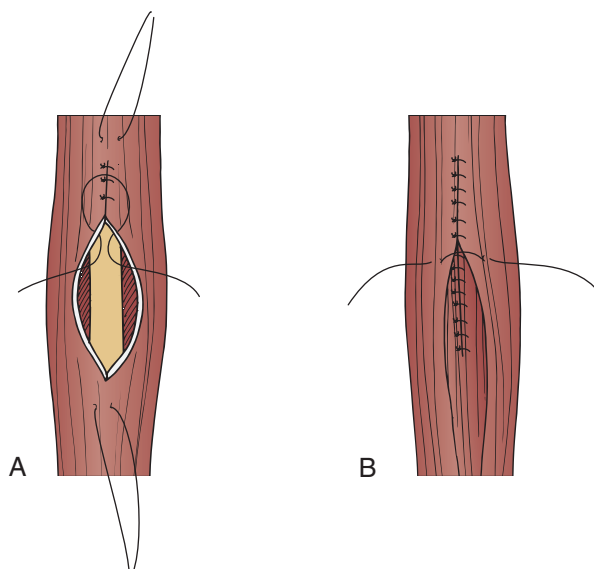


FIGURE 8-17 ■ The esophageal defect is closed in layers. **A**, The first layer closes the esophageal mucosa. **B**, The esophageal muscle is closed over the first layer. (From Mathisen DJ, Grillo HC, Wain JC, et al: Management of acquired nonmalignant tracheoesophageal fistula. *Ann Thorac Surg* 52:759–765, 1991. Reprinted with permission from the Society of Thoracic Surgeons.)

tracheal resection needed to treat a large fistula. In cases of extensive tracheal destruction, when end-to-end anastomosis may not be feasible, closure of the airway over a T-tube may be a valid alternative. Occasionally, there may be only insignificant damage to the trachea; a simple esophageal and tracheal repair with a muscle buttress would then be performed.

AIRWAY REPLACEMENT

When assessing surgical resectability of any tracheal lesions no clear guidelines of maximum tumor dimensions allowing for safe reconstruction via direct end-to-end anastomosis exist. Multiple parameters including tumor

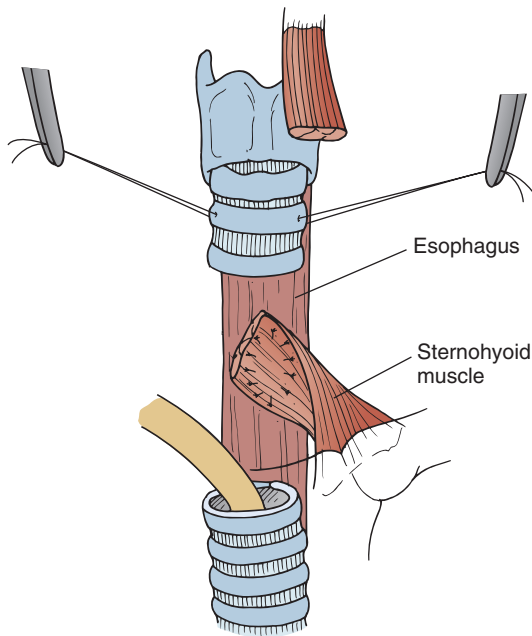


FIGURE 8-18 ■ A local strap muscle is used to buttress the esophageal closure and separate it from the suture line. (From Mathisen DJ, Grillo HC, Wain JC, et al: Management of acquired nonmalignant tracheoesophageal fistula. *Ann Thorac Surg* 52:759–765, 1991. Reprinted with permission from the Society of Thoracic Surgeons.)

extent, body habitus, age, and surgeon experience have to factor in the decision to proceed with an attempted resection. In our experience, in patients treated for adenoid cystic carcinoma (ACC) or squamous cell carcinoma (SCC), complete resection is associated with higher survival compared with incomplete or no resection.³² A multicenter retrospective study confirmed that patients who had complete resection had a higher 5-year survival (55%) compared with incomplete resection (25%).³³ Radiation treatment may delay disease progression for up to 2 years in SCC or 5 to 7 years in ACC, but recurrence inevitably occurs.³⁴ While resection with curative intent is the optimal treatment, a subgroup of patients has to be treated nonoperatively because of the length of airway involvement. In our experience, 25% of patients with ACC and 33% of patients with SCC were deemed unresectable on preoperative evaluation.

Tracheal replacement grafts could offer a surgical option for patients in whom end-to-end anastomosis cannot be performed safely. Several strategies have been explored, including allotransplantation, synthetic materials, and tissue-engineered grafts. Although successful allotransplantation has been reported, the need for chronic immunosuppression to prevent graft rejection and graft failure limits its therapeutic potential in an oncologic patient population.³⁵ Successful two-stage tracheal allotransplantation after indirect revascularization in heterotopic location and subsequent withdrawal of immunosuppression has been reported in one case.³⁶ In a follow-up study by the same group, withdrawal of immunosuppression led to graft rejection and necrosis in four subsequent patients, indicating that transplanted allogeneic airway remains immunogenic and requires

chronic immunosuppressive treatment to maintain graft viability and integrity.³⁷

Cryopreserved aortic homografts were examined extensively in large animal models of tracheal replacement and have reached clinical application in several cases.^{38,39,40} However, short- and long-term mechanical stability of cadaveric aorta was not sufficient, and stenting was required to maintain airway patency. In two reported cases, anastomotic dehiscence and subsequent mediastinitis led to a poor outcome. To address mechanical stability and need for immediate perfusion, especially in the setting of a tissue graft exposed to the nonsterile tracheobronchial tree, experimental models of composite tissue grafts featuring cartilage reinforcement and tissue wrapping have been reported.⁴¹ We recently reported our experience with laryngeal reconstruction for airway reconstruction after partial laryngectomy with cryopreserved aortic homografts.⁴² In this series, 15 patients underwent single-stage wide-field transcervical partial laryngectomy with subsequent cryopreserved aortic homograft reconstruction, thereby avoiding total laryngectomy. In this approach, the reconstructed field was in the neck rather than the chest, well-vascularized tissue was available to support rapid revascularization, and covered defects were partial rather than circumferential. At follow-up, all patients were decannulated successfully and had laryngeal phonation.

Recent reports of tissue engineered tracheal grafts have fueled the enthusiasm for personalized, regenerated tissue grafts for tracheal replacement. Based on the concept of combining a biologic or synthetic scaffold material with viable, patient-derived cells and growth factors, various grafts have been generated and reached the stage of investigational clinical application. Several case reports describe the use of decellularized trachea and synthetic scaffold materials that were repopulated with patient derived cells and used successfully to replace circumferential airway defects.^{43,44,45} Similar to aortic homografts, these engineered tissues struggle with short and long-term mechanical stability, and the lack of immediate perfusion, but on long-term follow-up appear to incorporate and achieve acceptable airway stability and patency. Systematic evaluation of various scaffold materials, cell seeding and culture strategies, and surgical implantation technique will be required to generate clinical protocols for broader use of tissue engineered tracheal replacement grafts.

All tracheal replacement grafts face similar challenges. Immediately after implantation, any graft tissue is in direct contact with the outside world, creating risk for epithelial damage (in the case for viable grafts), infection, and subsequent anastomotic failure. In addition, short- and long-term mechanical integrity of the implanted graft has to be maintained to allow early weaning from mechanical support and extubation, prevent airway collapse, and avoid the need for airway stenting.

PERIOPERATIVE MANAGEMENT

The goals of both intraoperative and postoperative care are the promotion of anastomotic healing and the

maintenance of good pulmonary toilet. Ideally, patients are extubated in the operating room. The need for postoperative ventilation is a contraindication to tracheal resection. Patients with marginal lung function need careful management during the operation to help avoid the need for postoperative mechanical ventilation. During the procedure, secretions and blood are kept from contaminating the distal tracheobronchial tree, and volume overload is avoided. Rarely, an especially high laryngotracheal resection will cause enough laryngeal edema to necessitate 24 hours of steroids to avoid impending reintubation and tracheostomy. In these cases, it is recommended to give 10 mg of dexamethasone (Decadron) intravenously, then 4 mg every 6 hours. Heliox, with its low viscosity, is sometimes useful in these circumstances, as it can occasionally assist in gaining enough time for the other maneuvers to take effect. The patient is cautioned against unnecessary speech during this period, because it can contribute to the laryngeal edema. Diuresis and elevation of the head of the bed are important to diminish edema. Postoperatively, patients are supplied with humidity through a face mask to facilitate clearance of secretions. Most patients are able to clear their airway by coughing. Frequently, therapeutic flexible bronchoscopy is performed to suction secretions under direct vision. Cervical flexion is maintained with the chin-to-chest suture for 5 to 7 days, after which the patient is advised not to extend the neck for another week. Before removing the chin-to-chest suture, we routinely examine the anastomosis with a flexible bronchoscope to ensure normal healing. Oral alimentation is begun cautiously in the first few postoperative days.

RESULTS

Postintubation tracheal injuries remain the most common indication for tracheal resection and reconstruction, despite definition of the etiology of these lesions and development of techniques to avoid them. In 1995, we reported 503 patients who underwent tracheal resection and reconstruction for postintubation lesions.⁴⁶ The balloon cuff of an endotracheal or tracheostomy tube accounted for 251 lesions, 178 lesions were at the site of a tracheostomy, and 38 patients had evidence of both lesions. In 36 patients, the exact site was uncertain, often because of prior attempts at treatment, including multiple tracheostomies. Of the 503 patients, 441 had lesions that were isolated to the trachea, and 62 had concomitant involvement of the subglottic larynx.

Many patients had undergone prior attempts at surgical treatment before referral. These attempts included resection ($n = 53$), tracheal operations such as wedge resection, splinting, or fissure ($n = 31$), and laryngeal procedures such as stenting, grafting, or fissure ($n = 20$). Sixty had had T-tubes placed, and at least 45 had suffered laser treatment. Eight patients had prior repairs of tracheoesophageal fistulas, three of which had failed.

The initial procedure was performed through a cervical incision in 350 patients. In 145 patients, a partial upper sternal division through the sternal angle was used, and two more patients required the addition of right

anterior thoracotomy to this approach. Six patients underwent repair via a high posterolateral thoracotomy. The amount of trachea resected ranged from 1.0 to 7.5 cm and was usually 2 to 4 cm.

Of the 503 initial patients, 324 underwent a trachea-to-trachea anastomosis, and in 117 patients the reconstruction involved partial resection of the cricoid cartilage with laryngotracheal anastomosis. In the total series of 503 patients, 9.7% underwent laryngeal release procedures. However, only 8% of the 450 patients who had not undergone previous tracheal resection and reconstruction required a laryngeal release, in comparison with 24.5% of the 53 who had prior resection and reconstruction. Many in the former group represent our earlier experience in tracheal surgery. Only one patient required intrapericardial hilar release.

The results have been classified as good, satisfactory, failure, and death. The result is described as *good* if the patient is functionally able to perform usual activities and if postoperative roentgenograms or bronchoscopic examinations show an anatomically good airway. Patients are placed in the *satisfactory* category if they can perform normal activities, but are stressed on exercise; this is also applied, in the absence of symptoms, to those with abnormalities involving the vocal cords or those with significant airway narrowing evident on either endoscopic or roentgenologic examination. *Failure* indicated the need for a permanent tracheostomy or T-tube. The average length of follow-up was 3 years. The results were good in 440 patients, satisfactory in 31 patients, and there were 20 failures and 12 deaths. Failure was treated with tracheostomy ($n = 11$), T-tube ($n = 7$), or dilations ($n = 2$).

In experienced hands, laryngotracheal resection and reconstruction is associated with excellent results and minor complications. The results of single-staged laryngotracheal resection for idiopathic laryngotracheal stenosis were initially reported by Grillo and colleagues⁴⁷ and have been updated to include a series of 73 patients.⁴⁸ The majority of these patients were women (71/73), with a mean age of 46 years (range, 13 to 74 years). Twenty-eight patients (38%) had undergone a previous laser, dilation, laryngeal, or tracheostomy procedure. After laryngotracheal resection, the majority of patients (67/73) were extubated in the operating room, and 7 required temporary tracheostomies, with only 1 in the last 30 cases. All patients were successfully decannulated. There was no perioperative mortality. The principal morbidity was alteration in voice quality, which improved with time. Sixty-seven (91%) required no further intervention for idiopathic laryngotracheal stenosis. Six patients required at least one bronchoscopy for granulation tissue or dilation (or both), and progression of disease was observed in only one patient. In our current experience, none of the last 100 patients required tracheostomy. In a subgroup of patients with idiopathic subglottic laryngotracheal stenosis, side-to-side narrowing poses a challenge for successful reconstruction.²⁷ In 2009, we reported a series of 18 patients in whom the standard technique of anterior cricoid resection was modified to specifically address the small ventricle. By performing a tailored cricoplasty in addition to resecting the anterior portion of the cricoid—that is, resecting and resurfacing the inner

third to half of the lateral cricoid cartilage—we achieved horizontal enlargement of 3 to 5 mm and thereby increased the side-to-side dimensions of the resulting subglottic airway. Functional postoperative outcome was excellent with overall satisfaction at follow-up of resting and exertional dyspnea at 9.7 and 9.5, respectively, on a 10-point scale.

The results from the repair of tracheoesophageal fistulas (TEFs) were reported in a series of 38 patients in whom 41 operations were performed.³¹ Simple division and closure of the fistula were performed in nine patients. Tracheal resection and reconstruction were combined with esophageal repair in the remainder. The esophageal defect was closed in two layers, and a viable strap muscle was interposed between the airway and esophageal suture lines in all cases. There were four deaths (10.9%); three of these occurred after attempted transthoracic repair of distal tracheoesophageal fistulas. Three patients developed recurrent fistulas and one patient suffered a delayed tracheal stenosis. All were successfully treated with reoperation. Of the 34 survivors, 33 can swallow normally and 32 breathe without the need for a tracheal appliance. We recently updated this series with an additional 36 patients undergoing surgical repair from 1992 to 2010.⁴⁹ The incidence of complex TEF after esophagectomy and laryngectomy has increased, while postintubation TEF has become less prevalent. Correspondingly, airway resection and reconstructions were performed in fewer patients (54%) than in the earlier series (75%). Despite the technical challenges of TEF repairs after anastomotic leak, airway ischemia, or prior failed attempts of repair, the surgical principles involved in their closure remain the same. Interposition of robust vascular tissue and separation of suture lines are even more important in reoperations.

For the oncologic results of primary tumors of the trachea, 208 patients were evaluated in a retrospective multicenter study.⁵⁰ Histologic types included 94 squamous cell carcinomas, 4 adenocarcinomas, 65 adenoid cystic carcinomas, and 45 miscellaneous tumors. The procedures performed consisted of 19 laryngotracheal, 165 tracheal, and 24 carinal resections. Operative mortality was 10.5%. As expected, long-term survival was significantly better for ACC than for SCC, with 73% versus 47% at 5 years, and 57% versus 36% at 10 years, respectively.

Gaissert and coworkers⁵¹ published the 40-year cumulative Massachusetts General Hospital experience of treating primary adenoid cystic and squamous cell carcinomas of the trachea. During this period, 270 patients were evaluated, with histologic distribution equally distributed between ACCs and SCCs. Resection was performed in 191 patients (71%), with an operative mortality of 7.3% (14/191). Importantly, both rates of resection and hospital mortality have improved each decade. As this center's experience has grown, operative mortality has decreased from 21% in the 1960s to 3% in the decade preceding the report.

Resection was not performed in 79 patients—34 patients with ACC (25%) and 45 patients with SCC (33%). Contraindications to resection included tumor length (67%) and locoregional extent (24%) in the vast

majority of cases, with distant metastases only rarely present (7%). The determination of unresectability was made during operative exploration in 17 of 208 patients (8%). ACC lesions tended to be longer and to be associated with more significant locoregional extension. This explains the more frequent observation of ACC resections having positive microscopic tracheal and radial margins (59%) when compared with SCC (18%).

The overall survival for all patients with primary tracheal carcinoma was 84% at 1 year, 45% at 5 years, and 25% at 10 years. Mean survival was 38 months for resected SCC, 8.8 months for unresectable SCC, 69 months for resected ACC, and 41 months for unresectable ACC. Notably, survival in patients with ACC after incomplete resection was still 14.5% at 15 years. Multivariate analysis identified ACC and complete resection to be associated with 5-year survival, and ACC, complete resection, and age to be associated with 10-year survival. Tumor length, lymph node status, or type of resection did not influence long-term survival.

The presence of tumor at the resection margins of ACC, even by frozen section during operation, has particular importance in airway reconstruction. The surgeon must often compromise complete resection for safety, and the data just cited indicate that a small, though not statistically significant, survival benefit exists in these patients. All these patients now receive postoperative irradiation. Suture line recurrence thus far has been rare, and late recurrence has been related to distant disease. In contrast, irradiation of unresected tumor is all but uniformly characterized by local recurrence in 3 to 5 years despite early good response.

Secondary cancers arising in the thyroid and invading the trachea have also been resected with good results. Of 27 patients undergoing resection and reconstruction of the trachea for thyroid cancer invading the airway, including patients with both simple and complex laryngotracheal reconstructions, two died in the postoperative period, one had a short segment of tracheal necrosis requiring reoperation, and all others were provided with an adequate airway by their initial operation. Only two patients experienced an airway recurrence.¹⁷ This series was recently updated to include 82 patients treated at the Massachusetts General Hospital.⁵² There were no additional operative mortalities in this expanded series. With mean follow-up at greater than 6 years, mean survival was 9.4 years and 10-year survival was 40%.

COMPLICATIONS

Complications after tracheal surgery are similar regardless of the problem for which resection and reconstruction is performed. In 2004, Wright and colleagues⁵³ presented the most complete analysis of anastomotic complications after tracheal resection. This review of 901 patients identifies relevant risk factors for the development of these problems and further describes their management. Anastomotic complications include granulations at the suture line, stenosis, and tracheal separation.

A significant reduction in suture granuloma formation has been seen since the conversion to absorbable suture

material used for the anastomosis. In fact, the use of absorbable Vicryl sutures since 1978 has all but eliminated suture-related granulations. These granulations can be successfully managed with bronchoscopic suture removal and local steroid injection. Extensive processes may require reoperation for resection or placement of a T-tube or tracheostomy.

Several predictors of anastomotic complications were demonstrated: reoperation, diabetes, lengthy (>4 cm) resections, laryngotracheal resections, age less than 17 years, and need for a tracheostomy before operation. The frequency of anastomotic complications was higher in patients undergoing operations for tracheoesophageal fistula than in those with tracheal tumors, postintubation stenoses, and idiopathic laryngotracheal stenoses. Of note, corticosteroid use was not associated with an increased complication rate, probably because of the management strategy used for this group, which is to defer tracheal operations in the presence of high-dose steroids until they can be effectively tapered.

Overall, 81 patients experienced anastomotic complications in this series. Thirty-seven patients had separation of the suture line, 37 patients developed anastomotic stenosis, and 7 patients had airway obstruction from granulation tissue formation. Complications were treated with multiple dilations ($n = 2$), temporary tracheostomy ($n = 7$) or tracheal T-tube ($n = 16$), permanent tracheostomy ($n = 14$) or T-tube ($n = 20$), and reoperation ($n = 16$). The mortality of patients who had anastomotic complications was 7.4% (6/81), compared with 0.06% (5/820) in those without anastomotic complications. In this series, no patient has died since 1988. This success can be attributed to the routine use of postoperative bronchoscopy, and the early recognition and subsequent definitive management of anastomotic complications.

We have had experience with four patients who developed anastomotic complications with varying degrees of ischemic cartilage necrosis. Presentation ranged from subcutaneous emphysema, cellulitis, to bronchoscopic evidence of partial cartilaginous loss. All patients had strap muscles carefully sutured to the anastomosis at the time of reconstruction. All patients were assessed for airway integrity and deemed stable. Patients were treated with intravenous antibiotics, inhaled tobramycin nebulizers, and inhaled heliox if any shortness of breath was experienced. All four patients underwent treatment with hyperbaric oxygen to increase tissue partial oxygen pressure and to improve wound healing. Patients generally received 20 treatments of hyperbaric oxygen administered twice daily. All patients healed without the need for tracheostomy or T-tubes. All patients remained asymptomatic with only minor narrowing seen on radiographs. Consideration for this approach should be given if evidence of tissue necrosis is seen on postoperative bronchoscopy, and airway stability can be assured.⁵⁴

SUMMARY

Some of the most challenging problems facing thoracic surgeons include benign strictures arising from postintubation stenosis or idiopathic laryngotracheal stenosis,

fistulas from the trachea to the esophagus or innominate artery, and primary or secondary tumors of the trachea. Bronchoscopic evaluation is essential to ascertain the diagnosis and in preoperative planning. If critical airway stenosis is suspected, flexible bronchoscopy should be performed only in an operative suite where a rigid bronchoscope is available in case the airway needs to be reestablished. An anesthesia team familiar with the techniques of cross-table ventilation and capable of an interactive team approach is essential.

All patients with tracheal lesions, from benign strictures to malignant tumors, deserve serious consideration for definitive resection. Nonsurgical methods such as dilation, ablation, or stenting are palliative and should be used only as temporizing maneuvers or in poor surgical candidates. Deciding whether a lesion is resectable requires mature surgical judgment. Postoperative radiation should be given to all patients with resected squamous cell or adenoid cystic carcinomas. Patients with thyroid cancer secondarily invading the trachea should be considered for tracheal resection, even with advanced disease, to avoid fatal loss of the airway. With an experienced team, most patients can be treated successfully with a single-stage tracheal resection with low morbidity and mortality and excellent long-term results.

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PART E

BENIGN LUNG DISEASE

PART OUTLINE

9	CONGENITAL LUNG DISEASES	12	INFECTIOUS LUNG DISEASES
10	BENIGN LESIONS OF THE LUNG	13	SURGERY FOR EMPHYSEMA
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CONGENITAL LUNG DISEASES

Raghav A. Murthy • Kemp H. Kernstine • Harold M. Burkhardt • Daniel T. DeArmond

CHAPTER OUTLINE

HISTORY

EMBRYOLOGY

TRACHEAL ABNORMALITIES

Tracheal Agensis and Atresia
Congenital Tracheal Stenosis
Tracheomalacia

BRONCHIAL BRANCHING ABNORMALITIES

Bronchial Atresia
Congenital Bronchiectasis
Tracheobronchomegaly (Mounier-Kuhn Syndrome)
Laryngotracheoesophageal Cleft
Tracheobronchial-Esophageal Fistula
Bronchobiliary Fistula
Bronchopulmonary Foregut Malformations
Sequestrations
Azygos Lobe
Horseshoe Lung
Bronchogenic Cysts

LUNG BUD ANOMALIES

Pulmonary Agenesis, Aplasia, and Hypoplasia

Congenital Lobar Emphysema

Congenital Parenchymal Cysts

Congenital Cystic Adenomatoid Malformation

Infantile Pulmonary Emphysema

Polyalveolar Lobe

Pulmonary Lymphangiectasia

VASCULAR ABNORMALITIES

Unilateral Absence of a Main Pulmonary Artery

Idiopathic, Hyperlucent Lung Syndrome (Swyer-James or Macleod Syndrome)

Pulmonary Artery Sling

Isolated Pulmonary Artery Aneurysm

Dysphagia Lusoria

Pulmonary Vein Abnormalities

Pulmonary Varix

Pulmonary Arteriovenous Malformations

CONCLUSION

Various congenital abnormalities involve the pulmonary system. Some of these result in arrested development and stillbirth. Some infants survive delivery only to die shortly thereafter. Neonates with severe anomalies typically display dyspnea and cyanosis at birth. Older children with less critical anomalies may have feeding problems, respiratory infections, developmental delays, or activity limitations. For neonates who are in respiratory distress, speed of diagnosis and early treatment are critical. Intubation may be life-saving. Examination of the naso-oropharynx, neck, and chest along with an emergent radiograph allows rapid diagnosis in most cases. Quality computed tomography (CT) may be necessary to delineate the anomaly. Other important adjuncts that may enhance diagnostic speed and accuracy are echocardiography, magnetic resonance imaging (MRI), and endoscopy.

During the past decade, improvements in prenatal diagnosis¹ have allowed intrauterine repair of some defects.² With non-life-sustaining defects such as anencephaly and renal agenesis, parents may opt for pregnancy termination. For potentially correctable lesions,

the pregnant mother can be transferred to a tertiary medical center. Advanced supportive and surgical techniques have led to improved survival in these infants.

HISTORY

The first report of a congenital lung defect was by Fontanus in 1639,³ describing an infant with a lung cyst. In 1777, Huber⁴ described an infant with an intralobar sequestration, with blood supply from the thoracic aorta. In the mid-1800s, an extralobar (Rokitansky lobe) sequestration was reported. The neonatal prevalence of lung infections in the 1900s was so high that it was difficult to formulate concepts of congenital lung disease, and the technology was not sufficiently advanced to correct such defects. In 1917, Gladstone and Cockayne theorized how sequestrations occurred, and in 1925, Koontz reviewed congenital pulmonary cystic diseases. The first surgical correction of a congenital lung anomaly was performed by Rienhoff⁵ in 1933, that being local lung cyst excision

in a 3-year-old boy.⁶ Gross and Lewis⁷ performed the first pediatric lobectomy in a child with congenital lobar emphysema. Cystic disease in the right upper and right middle lobes was resected by lobectomy in 1943.⁸ In 1946, Gross⁹ performed a pneumonectomy in a 3-year-old with cystic lung disease. Potts performed the first neonatal lobectomy in 1949. Lewis later reported the death of a child on whom a lobectomy was being performed for intralobar sequestration, citing exsanguination after lost control of the systemic feeding artery. With development of advanced supportive, anesthetic, vascular, and bypass techniques, the mortality rate for children at high risk for congenital lesions has significantly decreased.

EMBRYOLOGY

Lung development occurs both prenatally and postnatally and continues into adulthood. Intrauterine pulmonary development is divided into four phases: embryonic, weeks 1 to 5; pseudoglandular, weeks 5 to 16; canalicular, weeks 16 to 26; and terminal sac, weeks 26 to birth.¹⁰⁻¹²

During the embryonic phase, the foregut begins to develop from the embryonic endoderm beginning on day 9, and the median pharyngeal groove develops from the foregut on day 22. At approximately 4 weeks of gestational age, the respiratory diverticulum, or lung bud, emerges as a 3-mm outpouching from the ventral wall of the embryonic foregut. The respiratory diverticulum at this stage is surrounded by splanchnic mesenchyme that later gives rise to the visceral pleura. Concurrently, the lateral mesoderm grows to form the tracheoesophageal septum, effectively separating the tissues that will become the lung from those that will become the esophagus. The lung bud initially forms the trachea, followed by two bronchial buds that enlarge to form the right and left main bronchi by the start of the fifth week. The individual five lobes become evident during the next few weeks.

In the pseudoglandular stage (weeks 5 to 16), the bronchial tree develops, including the cuboidal and columnar epithelial layers and cartilaginous rings. Repetitive branching of the bronchial tree during this stage gives rise to all the conducting airways. The pulmonary vasculature develops in tandem with the airways; however, the airways and pulmonary arterial branches remain separated by mesenchyme. By the 16th week, the bronchial tree and the pulmonary arteries are fully formed, and the common pulmonary vein drains into the sinoatrial region of the heart.

In the canalicular phase (weeks 16 to 26), respiratory bronchioles divide to form alveolar ducts, and the mesenchymal separation of the airways from pulmonary arterial branches begins to recede, allowing the first appearance of the air-blood barrier. By the 25th week, the pulmonary venous drainage has completely developed.

The terminal sac period (weeks 26 to 40) is marked by continued extension of the air-blood barrier. The primitive alveoli proliferate and become intimately involved with the surrounding capillaries as the mesenchyme

separating them thins out. Terminal sac formation from the terminal lung buds occurs in a coordinated interaction between promoter factors, such as fibroblast growth factor 10, and inhibitory factors, such as Sonic hedgehog and transforming growth factor β .¹³⁻¹⁵ Mechanical fluid pressure on the terminal lung bud also appears to play a critical role.^{11,16,17} The adult form of alveoli has developed by the 30th to the 36th week, and the airways are almost fully developed before term. Type II pneumocytes produce surfactant in preparation for delivery.

Lung development continues postnatally with alveolar multiplication that results from progressive septation within the terminal sacs. Septation is driven by transcription factors, growth factors, and extracellular matrix molecules and is closely tied to sprouting angiogenesis (under the influence of vascular endothelial growth factor), followed by the splitting and remodeling of alveolar capillaries. Immediately after birth, alveoli are fairly thick walled and number approximately 20 million, less than 10% of their eventual number. Acinar development continues to the eighth year of life, but the rate of development diminishes after the second to fourth years. By the end of the eighth year, there are approximately 300 million acini, and after the tenth year of life, alveoli enlarge rather than increase in number. The lung-environmental interface increases from 3 to 4 m² at birth to 75 m² in adults. From birth to the age of 5 years, airway diameter increases; after the age of 5 years, the proximal airway grows at a faster rate than the more distal airways. The trachea is initially funnel-like but becomes more cylindrical by the age of 4 years. Pulmonary vessel length and diameter rapidly increase until 18 months of age.

Normal airway and vascular development depends on a variety of factors. These include cell-to-cell interactions, local and systemic hormones and growth factors, central and peripheral neural influences, and chest wall effects. The latter involve contact influences of the bony and muscular structures. Alterations in normal development may result from defects in any of these factors. Viral infection, hypoxia, starvation, and teratogens also may disrupt normal lung development. In utero airway obstruction may produce a variety of lesions.¹⁸ Of these patients, 84% have additional nonpulmonary anomalies.¹⁹

Three major hypotheses have been formulated to explain the pathogenesis of anomalous tracheobronchial development.^{20,21}

1. The *reduction theory* postulates that the final anatomy is the result of shrinkage and finally suppression of portions of a primitive pattern encompassing all the components of the extant mammalian bronchial distribution.
2. The *migration theory* considers that bronchial outgrowths have the potential of migrating from their initial locus to new points of origin of a bronchus or the trachea.
3. The *selection theory* advocates local disturbances in the development during budding of the bronchial buds under the influence of bronchial mesenchyme.²²

Lung resection in neonates and children is fairly well tolerated. Anatomy is easily defined because there is less

mediastinal and hilar fat, adenopathy, and scarring from chronic disease compared with adults. Outcomes after pediatric lung resection are good. Children younger than 5 years develop new alveoli after resection. In those older than 5 to 10 years, the alveoli enlarge, although they no longer increase in number. In an infant pneumonectomy model, lung function returns to normal within 9 to 12 months.²³⁻²⁵ Emphysematous changes do occur, as in adults. After lung resection in children in whom the remaining lung is normal, the child appears to grow, develop, and perform normally with maximal exercise.^{24,25} The diffusion capacity for carbon monoxide is reduced and pulmonary artery pressure increases with exercise, but pulmonary vascular resistance is normal after resection.²⁶

TRACHEAL ABNORMALITIES

Tracheal Agenesis and Atresia

Payne²⁷ first described congenital absence of the trachea in 1900. Fewer than 150 cases have been reported.²⁸ It represents a partial or complete absence of the trachea below the level of the normal larynx. This abnormality is incompatible with life if there is no connection of trachea or bronchi to the esophagus.²⁹ Floyd and others^{30,31} classified three distinct types of tracheal agenesis (Fig. 9-1). In type I, the trachea originates from the esophagus, and the distal trachea, including the carina, is fairly normal. Type I represents 10% to 13% of the total number of tracheal agenesis cases. In type II, the trachea and carina

are fused to the esophagus, and there is no residual trachea. Type II represents 59% to 62% of the total. In type III, the left and right mainstem bronchi originate from the esophagus, and there is no carina. Type III represents 22% to 31% of the total. Male incidence predominates in a 2:1 ratio. In 90% of the cases, there are other congenital lesions.³² Tracheal agenesis may be associated with VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, and limb patterns of congenital anomalies)³³ or with complex congenital heart defects as well as with upper extremity defects and duodenal atresia (referred to as TACRD).³⁴ It is believed that tracheal agenesis is the result of developmental failure of the laryngeal tracheal bud at the third to sixth week of development. The tracheoesophageal septum fails to develop normally.³⁵ Antenatal diagnosis of tracheal agenesis offers the best chance of early treatment. The usual findings include polyhydramnios, fluid-filled and dilated esophagus, distended lungs, an inverted diaphragm, and fetal hydrops. Many of these features are similar to those found in congenital high airway obstruction syndrome (CHAOS), thus suggesting that these abnormalities may be components of the same spectrum and differing only in severity and extent. It is important to differentiate between tracheal agenesis/atresia and CHAOS because ex utero intrapartum treatment (EXIT) may be life-saving for CHAOS but has not been described for tracheal atresia.^{36,37}

Neonates usually present with a triad of severe respiratory distress, the inability to cry, and the inability to be intubated.³⁷ Survival is unlikely, although there are a few cases of survival reported in the literature.^{38,39} Those who are successfully managed are endoesophageally intubated,⁴⁰ with a nasogastric tube alongside the endotracheal tube for gastric decompression. Urgent bronchoscopy or tracheostomy can assist in diagnosis.^{41,42} CT scan is the procedure of choice for delineating the anatomy in a newborn.⁴³ A survivor is described who had a type II defect and underwent esophageal intubation, gastrostomy, and distal esophageal banding.³⁸ The patient is reported to have survived to 4 years, undergoing a colonic interposition at 3 years of age. A second patient is described with a type I defect who survived to 6 years of age.³⁹ Extracorporeal membrane oxygenation (ECMO) may temporize these patients until a more definitive solution can be achieved.⁴⁴ If the patients can be stabilized, they should be examined for other life-threatening defects, such as neural and cardiac anomalies, that may require correction. The gastroesophageal continuity can be corrected with colonic interposition or gastric conduit, but there have been no attempts to reconstruct the trachea. Perhaps, for the future, to reconstruct the incompletely developed airway, tracheal allografts⁴⁵ or tissue-engineered replacements⁴⁶ may be used for long-term success.

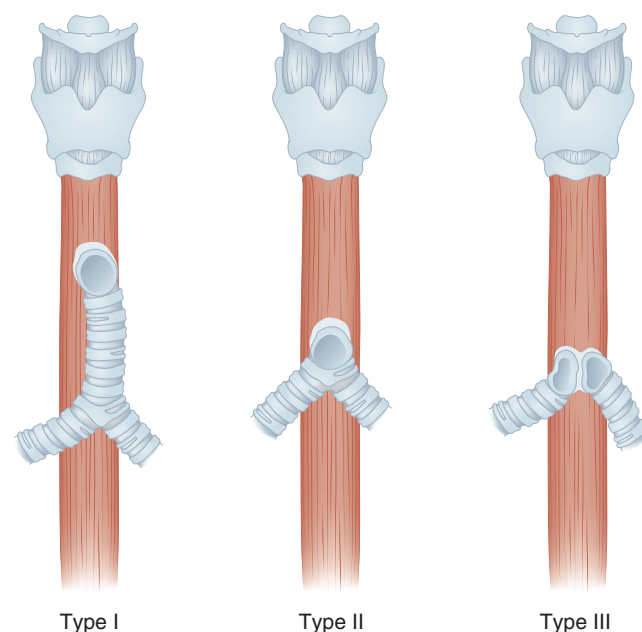


FIGURE 9-1 ■ Tracheal agenesis classification. There are three types of tracheal agenesis: type I, the trachea originates from the esophagus rather than from the larynx; type II, no trachea is present and the carina originates from the esophagus; and type III, each mainstem bronchus originates from the esophagus. (Modified from Haben CM, Rappaport JM, Clarke KD: Tracheal agenesis. *J Am Coll Surg* 194:217-222, 2002.)

Congenital Tracheal Stenosis

Congenital tracheal stenosis (Fig. 9-2) is rare. Cantrell and Guild⁴⁷ described three forms of stenosis. Type I is stenosis of the full length of the trachea. Type II is a funnel-shaped stenosis of the upper, lower, or entire

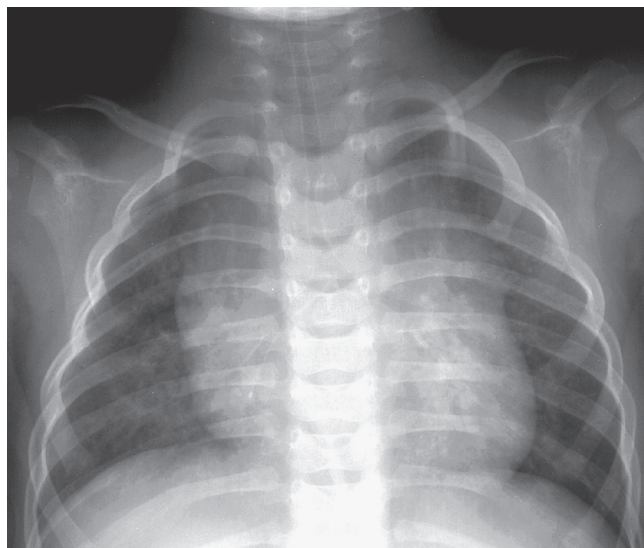


FIGURE 9-2 ■ Tracheal stenosis (stovepipe trachea) in a 20-month-old boy with stridor since birth. Frontal chest radiograph shows a diffusely narrowed trachea faintly outlined by water-soluble contrast medium. (Courtesy Simon C. Kao, MD, Iowa City, IA.)

trachea. Type III is a segmental stenosis of the lower trachea. This classification assists in identifying patients who are more likely to have associated anomalies and in planning treatment. Stenotic regions have complete cartilaginous rings, the number of which is variable, anywhere from 2 to 18. This rare anomaly is associated with pulmonary vascular sling or vascular ring in 50% of cases.⁴⁸ A functional classification system has been proposed to assist in selection of the operative candidate.^{49,50}

These patients usually have exertional wheezing or stridor after birth. The type II and type III abnormalities are associated with anomalous location of one or more bronchi, most likely a left pulmonary artery sling. All three types are associated with pulmonary agenesis. A new morphologic classification has been proposed and is based on the bronchial arborization pattern, thus introducing the term *congenital tracheobronchial stenosis*.⁵¹ Symptoms vary according to the degree of stenosis. Patients presenting during the neonatal period or infancy with severe stridor, cyanosis, and recurrent stridor have the highest mortality rate. Many of these patients have associated congenital malformations and infections. Their prognosis, even after surgical correction, is variable.⁴⁹ Older children presenting at 1 year of age or soon thereafter have a surgical mortality rate of 10% to 20%.⁵² Some children, late in childhood or early teens, may present for an evaluation for asthma with varying degrees of exertional dyspnea. Typically, these children have a better prognosis. CT, especially multidetector CT, works better than flexible bronchoscopy⁵³ because it provides enough detail to not only assess the tracheobronchial abnormality with a sensitivity of 90% but also to assess any associated anomalies. Bronchoscopy aids in diagnosis, treatment planning, and evaluation of the surgical repair intraoperatively and postoperatively. Echocardiography is helpful to assess for cardiac and vascular

anomalies. Patients should be aggressively treated because, without surgical correction, they are at high risk for sudden death.⁵⁴ Partial tracheal resection is the most frequently performed operation. The neonatal trachea does not tolerate tension as well as the adult trachea.⁵⁵ Up to 50% of the infant trachea can be resected with primary reanastomosis. The repair is much more difficult if more than 50% of the trachea or the carina is involved.

In 1964, the first repair, a primary resection and end-to-end anastomosis, was reported by Cantrell and Guild.⁴⁷ Reconstruction has been performed with pericardium,⁵⁶ aortic homograft,⁵⁷ costochondral graft,⁵⁸ slide tracheoplasty (Fig. 9-3),^{59,60} and tracheal autograft.⁶¹ Complete repair of the tracheal stenosis and any vascular ring or sling requires cardiopulmonary bypass and potential circulatory arrest. Backer and coworkers⁶² reviewed their 18-year experience in 50 patients, comparing four tracheal stenosis repair techniques¹: pericardial patch,² primary resection,³ tracheal autograft, and slide tracheoplasty.⁴ They concluded that when eight or fewer rings are involved, primary resection is preferable. For stenosis longer than eight rings, an autograft is better. Vascular endothelial growth factor application has the potential of improving the results of tracheal autograft.⁶³ In contrast, Muraji and coworkers⁶⁴ demonstrated that the slide tracheoplasty technique allowed early extubation and an excellent long-term result in one case. Currently, slide tracheoplasty is the operation of choice for long-segment tracheal stenosis.⁵¹ ECMO may be necessary to support the neonate postoperatively.^{44,58} Long-term outcome after resection appears to result in normal growth and development.⁶⁵ For patients who are considered surgically uncorrectable, palliative maneuvers include balloon dilation and split posterior tracheoplasty,⁶⁶⁻⁶⁸ stenting, local steroid injection, electroresection, and cryotherapy.^{49,50}

Tracheomalacia

In tracheomalacia, weakened cartilage collapses on expiration. With inspiration, there is sufficient suspension of the tracheal wall to maintain patency. The most common pathologic finding is oval rather than round cartilaginous rings. There are both congenital and acquired forms of tracheomalacia. The congenital form can be diffuse and both proximal and distal, involving the mainstem bronchi; it is associated with tracheoesophageal fistula.^{69,70} The more common, acquired form results from degeneration of the cartilaginous support, usually by vascular compression such as from a vascular ring or sling, adjacent inflammatory process, tumor, or chest wall deformity (e.g., pectus excavatum).

Tracheomalacia is not usually manifested at birth. It worsens as the child grows, usually after several weeks of life. Coughing, respiratory distress, severe dyspnea, stridor, and cyanosis can occur. Acute apnea, referred to as “dying spells,” is the most severe presentation. Dyspnea worsens with agitation or respiratory tract infections. These severe symptoms should prompt further investigation.

One fourth of all patients with esophageal atresia have tracheomalacia. Tracheoscopy, bronchoscopy,

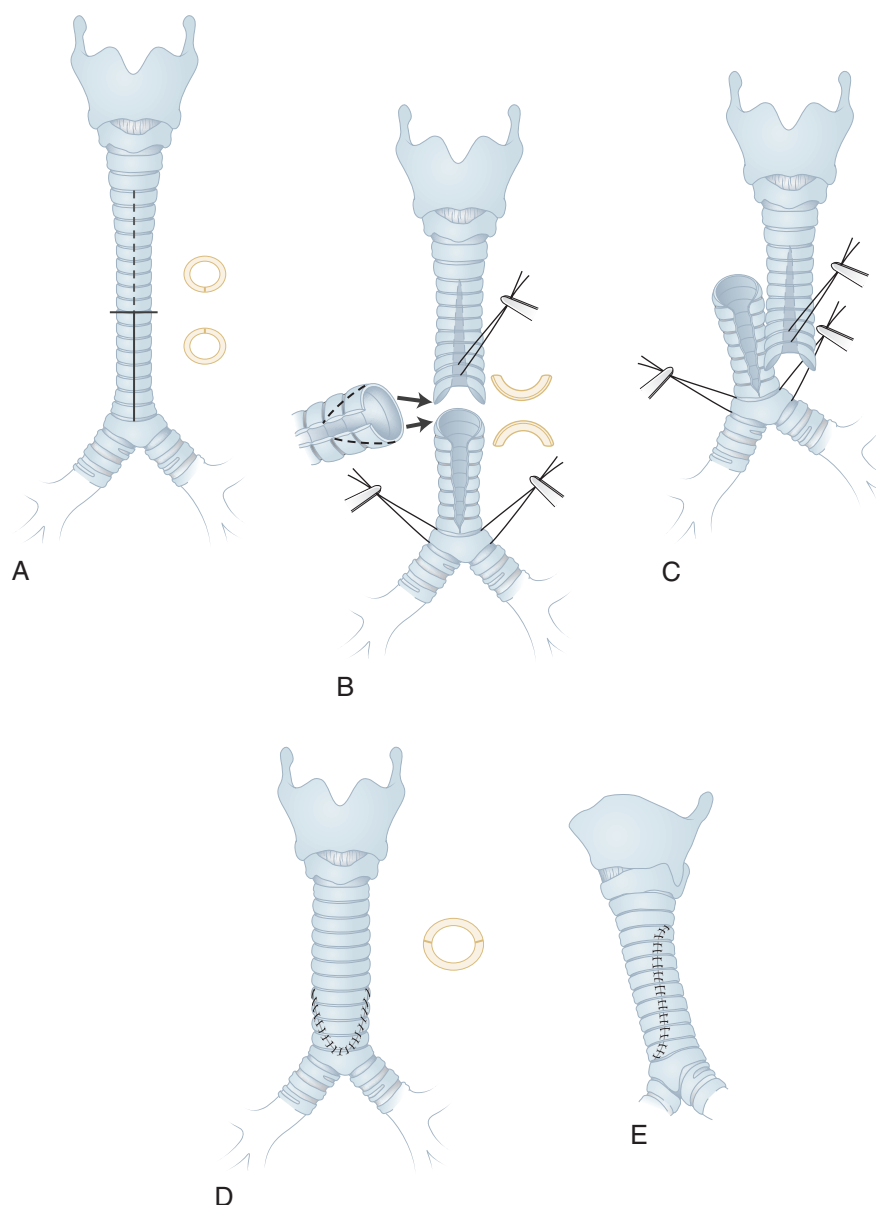


FIGURE 9-3 ■ Congenital tracheal stenosis. **A**, After identification of the area of stenosis, the midportion of the stenosis is transected, leaving two halves of the trachea disconnected. **B**, A longitudinal tracheal incision is then made in each half, the full length of the stenosis, posterior in the upper half and anterior in the lower half. The corners are trimmed to allow an even, uncrimped anastomosis. **C**, Stay sutures help in retraction and alignment. **D** and **E**, The anastomosis results in an oblique suture line. The resultant cross-sectional area is quadrupled. (Modified from the Society of Thoracic Surgeons. Grillo HC: Slide tracheoplasty for long-segment congenital tracheal stenosis. *Ann Thorac Surg* 58(3):613–619, discussion 619–621, 1994.)

esophagoscopy, and esophagography may be necessary for complete evaluation. CT and MRI provide additional information. The differential diagnosis includes normal pulsatile collapse, bronchial webs, and tracheal tumors. Many patients suspected of having tracheomalacia may instead have gastroesophageal reflux disease or reflux disease in addition to tracheomalacia. This may warrant either a trial of a proton pump inhibitor and prokinetic agent or a formal evaluation for reflux.⁷¹

Tracheomalacia improves with age in most cases. Dying spells (acute life-threatening events), inability to be weaned from the ventilator, and failure to thrive are indications for more aggressive therapy. If tracheomalacia is mild, the infant should be supported and observed because infants usually outgrow their tracheomalacia

within the next 2 years. In more severe forms, the mortality rate is as high as 80% with conservative management. Stents have been used with varying success to allow cartilage maturation; this usually takes several months.^{72,73} Tracheostomy also has been used but is associated with some complications.⁷⁴ Aortopexy (Fig. 9-4), by itself or with tracheal resection or stenting, has been performed by a left submammary thoracotomy through the third interspace or through a median sternotomy. The thymus is preserved. After exposure of the ascending aorta, three or four nonabsorbable sutures are placed through the aortic adventitia above and below the innominate artery takeoff. These sutures are attached to the periosteum. Finally, the endotracheal result is visualized by intraoperative bronchoscopy. By 4 weeks, 80% of the patients

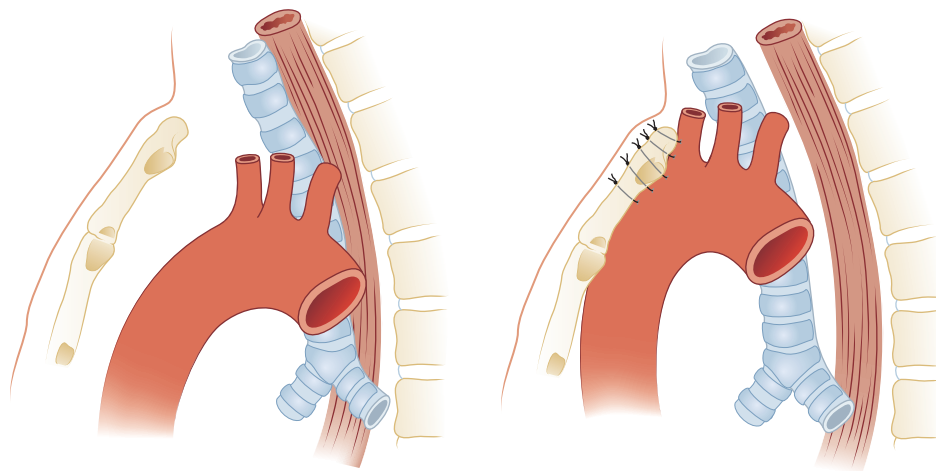


FIGURE 9-4 ■ Tracheomalacia and aortopexy. In patients with severe tracheomalacia and aortopexy, suturing of the proximal transverse-ascending aorta to the anterior chest wall or sternum may significantly improve the obstructive symptoms. (Modified from Weber TR, Keller MS, Fiore A: Aortic suspension [aortopexy] for severe tracheomalacia in infants and children. *Am J Surg* 184:573–577, 2002.)

are extubated, and the long-term results are good.⁷⁵ The acquired form is treated similarly to the congenital form. Longer segment lesions without vascular compression often require tracheostomy and mechanical ventilation for a time. Bronchomalacia may require both aortopexy and pulmonary artery pexy.⁷⁶ The failure rate after aortopexy ranges between 10% and 15%.⁷⁷ Direct anterior tracheal suspension is gaining popularity. This is performed through a median sternotomy, and the space between the superior vena cava and the aorta is developed. Sutures are passed into the tracheal wall, brought out through the sternal tables, and tied under direct bronchoscopic visualization. Mitchell and colleagues report on 21 such procedures performed with excellent results.⁷⁷

BRONCHIAL BRANCHING ABNORMALITIES

Bronchial branching abnormalities are rarely symptomatic. Accessory bronchi can originate off the trachea or mainstem bronchi and may be attached to rudimentary lung. They are usually incidental findings at autopsy. Cervical diverticula present in utero may regress before birth. There are case reports of bronchi crossing the mediastinum to supply the opposite lung.^{22,78} Tracheal bronchus, or *bronchus suis*, is a congenital branching anomaly in which the bronchus arises directly from the trachea above the carina (Fig. 9-5). The most frequent tracheal bronchus is to the right upper lobe. These abnormalities may be isolated or associated with other tracheopulmonary anomalies. They can be associated with wheezing, stridor, pneumonia, bronchiectasis, and hemoptysis. Accessory bronchi and associated abnormal pulmonary tissue should be resected if symptomatic.⁷⁹ Chest radiography and high-resolution CT are helpful in defining the anomaly.^{80,81} Fiberoptic bronchoscopy, bronchoalveolar lavage, and biopsy have been used to evaluate the abnormality. Endobronchial aspiration,

lung resection, and transplantation have all been methods of treatment.²²

The following are anomalies that are more frequently symptomatic, potentially life-threatening, and possibly treatable.

Bronchial Atresia

Bronchial atresia, first described by Ramsay and Byron in 1953,⁸² is the second most common abnormality of the airway after tracheoesophageal fistula. A lobar or segmental bronchus ends blindly in the lung tissue. Lung tissue distal to the bronchial atresia expands and becomes emphysematous as a result of air entering through the intra-alveolar pores of Kohn and bronchoalveolar channels of Lambert.⁸³ Beyond the atretic segment but proximal to the hyperinflated lung, the terminal airway is filled with mucus. It is believed that the bronchial bud somehow separates distally from the proximal bronchial bud and continues to develop. Another potential explanation is that there is a vascular insult of the airway in the atretic segment. In either case, the distal airway continues to develop normally.

Infants usually develop respiratory distress 4 or 5 days to several weeks after birth. They may have wheezing, stridor, and repeated pulmonary infections. The most common location is in the left upper lobe, then the left lower lobe, followed by the right upper lobe. A segmental bronchus rather than a lobar bronchus is atretic, most frequently presenting as a lung mass on the first chest radiograph of the newborn. Fetal lung fluid is slowly absorbed, becoming a localized translucency with an opaque circular or oval density at the hilum. Patients rarely mature to adulthood without investigation.

For better assessment of this abnormality, a CT scan should be performed.^{84,85} Prenatal diagnosis by ultrasonography has been reported.⁸⁶ The differential diagnosis includes acquired bronchial stenosis (which may result from long-term intubation), bronchial adenoma, sequestration, mucoid impaction, vascular

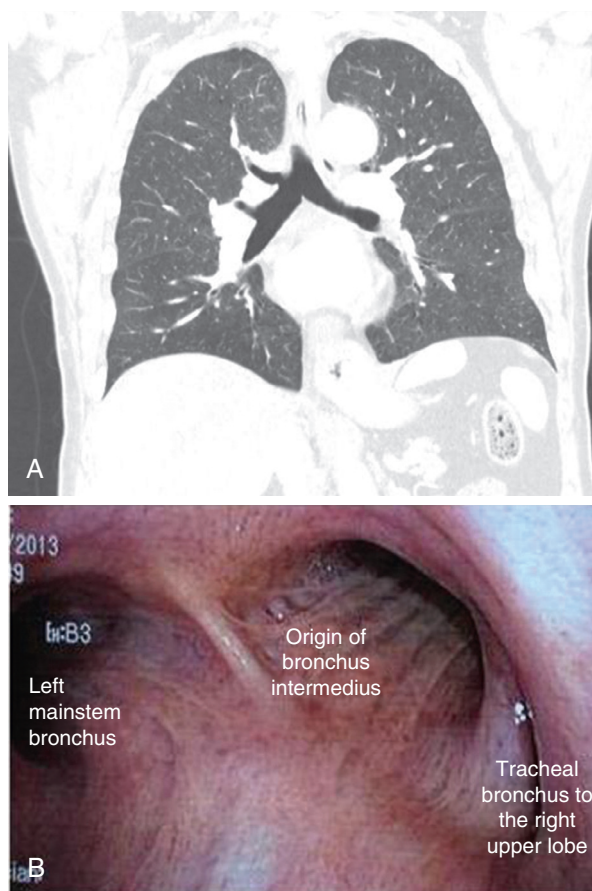


FIGURE 9-5 ■ **A**, Coronal view of a computed tomography scan showing a tracheal bronchus. **B**, Bronchoscopic view of the origin of the right upper lobe bronchus from the trachea.

compression syndrome, Swyer-James syndrome, and atypical bronchogenic cyst.

Indications for resection in bronchial atresia include a recurrent and possibly serious pulmonary infection, respiratory distress, and increasing size of the translucent lung.⁸⁷ Some surgeons resect the abnormal tissue to prevent infection. Segmentectomy is possible, but lobectomy is usually required.

Congenital Bronchiectasis

Bronchiectasis is an abnormal dilation of the bronchi or bronchioles. It is thought to be secondary to failure of the mesenchyme to differentiate into cartilage and muscle.⁸⁸ It is not a specific disease entity per se, but the common end stage of a variety of pathophysiological processes. Cystic fibrosis, primary ciliary dyskinesia, Young syndrome, Williams-Campbell syndrome, α_1 -antitrypsin deficiency, and certain primary immune deficiency syndromes are associated with bronchiectasis. It results in a chronic, mildly productive cough with recurrent pneumonia. CT usually confirms the diagnosis,⁸⁹ and bronchoscopy typically is unnecessary. Bronchography is rarely necessary, given the detail provided by high-resolution CT. Treatment and prognosis depend on the number of segments or lobes involved. Patients are provided with humidity, chest physiotherapy, and oxygen, as

necessary. Therapeutic bronchoscopy is performed for suspected mucoid obstruction or bleeding. Bleeding is initially controlled by embolization, topical epinephrine, or intravenous pitressin. Oral, intravenous, and nebulized antibiotics may be helpful in controlling symptoms.⁹⁰ Patients who have localized congenital symptomatic bronchiectasis may require a segmentectomy, lobectomy, or possibly pneumonectomy. The success of surgical intervention is related to the ability to resect all the diseased lung.⁹¹

Tracheobronchomegaly (Mounier-Kuhn Syndrome)

Tracheobronchomegaly was first described in 1932 by Mounier-Kuhn.⁹² It is characterized by excessive dilation of the trachea and main bronchi (Fig. 9-6).⁹³ This dilation is the result of atrophy of the elastic tissue and smooth muscle of the trachea and mainstem airways.⁹⁴ Airway dilation continues to third-order subdivisions. During the course of the disease, mucosal herniations develop between tracheal rings, creating a diverticulosis pattern. Associated conditions include cutis laxa, Ehlers-Danlos syndrome, Marfan syndrome, Kenny-Caffey syndrome, ataxia-telangiectasia, ankylosing spondylitis, Brachmann-de Lange syndrome, and light chain deposition disease. When an isolated process occurs, there is recessive

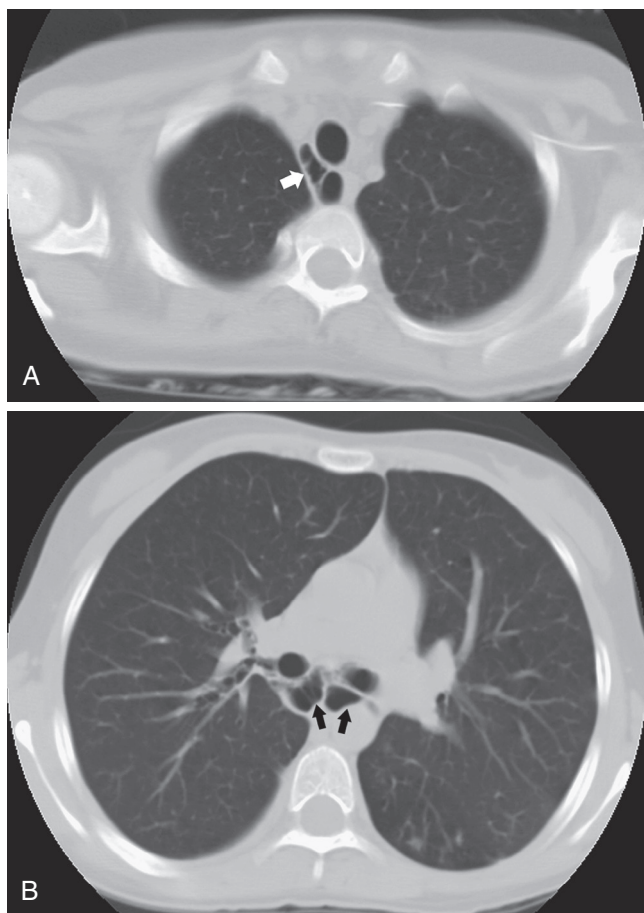


FIGURE 9-6 ■ Tracheobronchomegaly (Mounier-Kuhn syndrome) in a 13-year-old girl with chronic cough and bronchiectasis. Computed tomography scan at the level of the trachea (**A**) and mainstem bronchi (**B**) shows air-filled sacculi (arrows) around the airway from chronic inflammation destroying the normal elastic properties of the tracheobronchial tree and its smooth muscles. (Courtesy Simon C. Kao, MD, Iowa City, IA.)

inheritance.⁹⁵ Tracheobronchomegaly also may result from severe pulmonary fibrosis with increased traction on the tracheal wall.^{96,97} As these diverticula develop, mucus retention occurs with resultant development of bronchiectasis and fibrosis. Patients eventually are unable to clear secretions, and they succumb to chronic infection and respiratory failure.

The patients are usually men in their third to fourth decades of life.⁹⁸ Fifty percent of patients with tracheobronchomegaly have no symptoms until their third decade. They usually have recurrent lower respiratory tract infections. Asymptomatic patients may be identified in that the trachea is three standard deviations larger than normal; for adults, it exceeds 3 cm.⁹⁹ Patients with tracheobronchomegaly frequently have recurrent respiratory tract infections and persistent cough. Plain chest radiography demonstrates an enlarged trachea and mainstem airways that may be ectatic. CT more clearly demonstrates changes, and tracheal dimensions for adults¹⁰⁰ and children¹⁰¹ are helpful in making the diagnosis. Bronchography may be necessary to differentiate it from acquired bronchiectasis. Bronchoscopy generally is

unrewarding because of inadequate visualization of the airway lumen as a result of multiple tracheal wall diverticula.

In general, there is no surgical role in the treatment of tracheobronchomegaly. Management of secretions helps minimize the symptoms. Stenting and T tubes^{102,103} may provide significant palliation. Tracheobronchoplasty may have a role. Recently, a successful double-lung transplantation with bilateral bronchial stents performed to treat tracheobronchomegaly was reported.^{98,104}

Laryngotracheoesophageal Cleft

Laryngotracheoesophageal cleft is a rare congenital abnormality resulting from failure of the esophagus to separate from the laryngotrachea.¹⁰⁵ Infants with this abnormality have a toneless cry and choke with feeding. On an attempt to pass a nasogastric tube, a communication with the airway is seen. A barium study or endoscopy can demonstrate the fistula. Rigid bronchoscopy is necessary to make the diagnosis and to define the extent of the lesion. One half to more than three fourths of patients survive.^{106,107} With late detection, the mortality rate is high. Patients are first treated with a gastrostomy. Then, through a cervical approach, the fistula is divided, the esophagus and larynx are repaired, and a muscle flap is placed between them to reduce likelihood of recurrence. A nasogastric stent is left in place for a time. For large defects, a combined cervical and thoracic approach may be necessary.¹⁰⁸

Tracheobronchial-Esophageal Fistula

Tracheobronchial-esophageal fistula (TEF) is the most common abnormality of the trachea, occurring in 2.4 out of 10,000 births.¹⁰⁹ The most commonly used anatomic classification system for TEF is the one proposed by Gross¹¹⁰: type A, esophageal atresia without TEF; type B, esophageal atresia with proximal TEF; type C, atresia with distal TEF; type D, atresia with both proximal and distal TEF; and type E, TEF without esophageal atresia (H-type). Type C is the most common, accounting for 87% of the anomalies, followed by type A (8%), type E (4%), type B (1%), and type D (1%). Associated congenital defects are common¹⁰⁹; cardiovascular anomalies lead the list, with concomitant occurrence in 35% of TEF cases. In approximately 20% of cases, TEF occurs as part of the VACTERL constellation of defects.

Patients present with feeding difficulties and excessive salivation. Intermittent cyanosis and tracheobronchial infections are seen as well. Diagnosis of the most common form (type C) is suspected when a large amount of air is seen in the esophagus, stomach, and small bowel. Failure of nasogastric tube passage and its position on plain radiography or contrast fluoroscopy confirm the condition. Haight is credited with the first successful pediatric TEF repair.¹¹¹ Although it was initially accomplished through left thoracotomy, Haight came to prefer right extrapleural thoracotomy for division of the fistula and esophageal anastomosis. Esophageal anastomotic leak is seen in approximately 15% of cases, but with a functioning chest tube in proximity, 95% of leaks heal spontaneously.¹¹²

Subsequent stricture formation is common, but it generally responds well to dilation. Major, life-threatening leaks occasionally occur. In this situation or in the case of so-called long-gap atresia, wherein esophageal continuity cannot be established despite a variety of elongation techniques, esophageal replacement by colonic interposition or gastric transposition may be necessary. Even in critically ill neonates with a substantial esophageal anastomotic leak, gastric pull-up has been successfully applied as an alternative to temporizing with wide drainage alone.¹¹³ Long-term outcome after surgery for TEF has been the subject of several reviews.¹¹⁴⁻¹¹⁷

For ligation of the H-type fistula, a right neck incision is made, allowing avoidance of the thoracic duct. The sternocleidomastoid muscle and carotid sheath contents are retracted laterally. The recurrent laryngeal nerve is identified and protected, and the fistula is divided and oversewn. An interposition muscle flap reduces the likelihood of recurrence. TEF recurrence has been successfully managed with a minimally invasive technique. In one pediatric series, the fistula tracts were de-epithelialized by fulgurating diathermy under endoscopic guidance with successful track obliteration by way of fibrin glue application.¹¹⁸ For the lower-lying H-type fistula not accessible through a cervical incision, thoracoscopic ligation has been successful.^{119,120} Early postoperative complications include anastomotic stricture, recurrence of fistula, and gastroesophageal reflux.

Not surprisingly, minimally invasive techniques have been increasingly applied not only to management of fistula obliteration but to esophageal reconstruction as well.¹²¹⁻¹²³ Thoracoscopic repair has been accomplished through an extrapleural approach,¹²⁴ and even long-gap esophageal atresia has been amenable to the thoracoscopic approach. The latter consists of initial thoracoscopically mediated esophageal traction followed by staged thoracoscopic creation of the esophageal anastomosis.¹²⁵ Nuances of anesthetic and intensive management of neonates undergoing thoracoscopy and laparoscopy are becoming better appreciated.^{126,127} Meticulous anesthetic management has allowed successful TEF repair in a neonate with single-ventricle physiology (unpalliated tricuspid atresia).¹²⁸ In a recent survey of 217 surgeons from 31 countries, the thoracoscopic approach to repair is used by more than 50% of the surgeons. Thoracoscopic repairs are now performed intrapleurally in 96% of cases compared with 89% performed extrapleurally with the open approach.¹²⁹

Preservation of the azygos vein, previously divided with impunity during repairs of esophageal atresia and TEF, has been advanced as desirable. The theory is that postoperative mediastinal edema may be avoided, thereby minimizing esophageal anastomotic complications.^{130,131} Clinical significance of this concept awaits further evaluation.

Bronchobiliary Fistula

Bronchobiliary fistula (Fig. 9-7) is a very rare congenital abnormality with perhaps fewer than 50 cases reported.¹³² The embryologic basis for this lesion is either that the tract represents a duplication of upper gastrointestinal

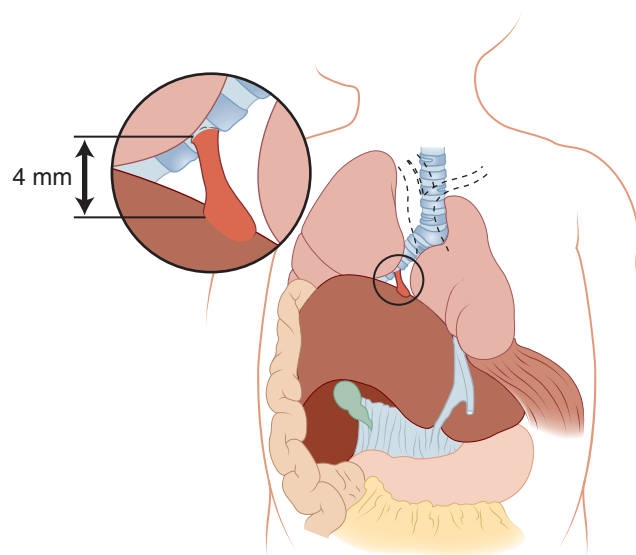


FIGURE 9-7 ■ Bronchobiliary fistula. In this child with bilious sputum and a congenital diaphragmatic defect, a fistula was found between the right mainstem bronchus and the biliary tree. (Modified from DiFiore JW, Alexander F: Congenital bronchobiliary fistula in association with right-sided congenital diaphragmatic hernia. *J Pediatr Surg* 37:1208-1209, 2002.)

tract for the distance of the gut between the laryngotracheal outgrowth and the hepatic diverticulum or that the tract results from the union of an anomalous bronchial bud with an anomalous bile duct.¹³³ It has generally been reported in infants and children, but a number of cases have been diagnosed in adulthood.¹³⁴⁻¹³⁶ The fistula track is composed of bronchial and biliary-type tissue from its origin in the airway to the liver. Patients produce green sputum and develop dyspnea and chronic cough. Infants may present with respiratory distress¹³⁷; girls are more commonly affected. The right middle lobe and right mainstem airways are most frequently involved and usually drain to the left hepatic ductal system. Associated anomalies, although not the rule, include esophageal atresia and TEF,¹³⁸ biliary atresia,¹³⁹ and right-sided diaphragmatic hernia.¹³²

Diagnosis is made by bronchoscopy, during which a catheter may be passed into the fistula for administration of contrast material and concomitant radiography.¹⁴⁰ This represents a more modern form of bronchography. Diagnosis also has been achieved with a nuclear biliary scan (^{99m}Tc-HIDA cholescintigraphy)^{141,142}; this is useful for postoperative surveillance as well. Finally, MRI for neonatal diagnosis has been reported, emphasizing the usefulness of T1-weighted gradient-echo sequences.¹⁴³

Patients with a confirmed bronchobiliary fistula are treated by ligation and division of the fistula, transecting it as close to the airway as possible. Pulmonary resection has been necessary on occasion.¹³⁵ Access is by way of transpleural or extrapleural right thoracotomy. Cholecystography is used selectively to verify biliary drainage into the duodenum.¹⁴² For those with impaired prograde biliary drainage or biliary sepsis, hepatic lobectomy (generally left-sided) or Roux-en-Y hepaticojejunostomy may be necessary.¹⁴⁴

Bronchopulmonary Foregut Malformations

Bronchopulmonary foregut malformations represent another category of congenital lung diseases. The classification includes sequestrations (intralobar and extralobar), bronchogenic cysts, and other, less common entities.

Bronchopulmonary foregut malformations are an abnormal communication between normal lung and esophagus or stomach and represent the second most frequent abnormal communication between the airway and intestinal tract, tracheoesophageal fistula being the most common. Abnormal ventral foregut budding is the embryologic basis for bronchopulmonary foregut malformations.¹⁴⁵ Right and left lower lobes are equally and most commonly affected. The fistula rarely involves the gastric fundus or mid-esophagus, almost always tracking to the lower esophagus. It is associated with extralobar sequestrations, more often on the left side. Diagnosis is usually made in the first few months of life up to 18 years of age. The most useful diagnostic test is esophagography. These malformations are associated with other anomalies, such as diaphragmatic hernia and cardiac, gastrointestinal, or vertebral anomalies. Because of chronic infection, lobectomy is usually necessary, and the fistulous communication must be divided and the esophageal defect repaired. If there is no evidence of infection, lung tissue may be preserved. Hybrid lesions refer to the overlap between congenital cystic adenomatoid malformation and sequestration.

Sequestrations

Sequestrations are lung parenchymal defects that have systematic arterial blood supply and lack continuity with the upper respiratory tract.¹⁴⁶ They are divided into intralobar and extralobar types. They are invariably located in the base of the lung, with males more frequently affected than females by a 3:1 ratio. Intralobar sequestrations (Fig. 9-8) are cystic abnormalities within the visceral pleural covering of the lung, whereas extralobar sequestrations (Rokitansky lobe; Fig. 9-9) are mass lesions that have their own separate visceral covering.¹⁴⁶ Intralobar sequestrations represent 75% of all sequestrations. As a group, intralobar sequestrations receive vascular blood supply from the thoracic aorta in 74% of cases, from the abdominal aorta in 19% of cases, from the intercostals in 3% of cases, and from multiple sources in 20% of cases. The aberrant blood supply most commonly enters the anomalous lung away from the hilum. The venous drainage of sequestrations is usually through pulmonary veins, but it may be through systemic veins. Intralobar sequestration is most frequently found within the posterior segment of the left lower lobe.

Extralobar sequestrations are rounded, smooth, soft masses that usually lie just above the dome of the diaphragm; 90% occur at the base of the left lung. The venous drainage of extralobar sequestrations occurs most frequently through the systemic circulation, to either azygos or hemiazygos systems; only 20% of cases

demonstrate venous drainage into the pulmonary veins. On microscopic examination, all lung structures are present in extralobar sequestrations, including alveoli, bronchi, and cartilage.

Intralobar and extralobar sequestrations are derived from foregut tissue and thus may possess an esophageal fistula. Intralobar sequestrations may present in utero as polyhydramnios or may become symptomatic in adolescents or young adults. Repeated bouts of pulmonary infection and hemoptysis are the most common symptoms. Intralobar sequestration is rarely associated with other congenital anomalies; extralobar sequestration is sometimes associated with other anomalies, especially congenital diaphragmatic hernias. Extralobar sequestrations may be found within either the pericardium or the diaphragm or beneath the diaphragm retroperitoneally. Malignant neoplasms have been reported within extralobar sequestrations, and a simultaneous discovery of congenital cystic adenomatoid malformation has been reported, as have other anomalies such as pericardial cysts, esophageal achalasia, and cardiac defects. In the absence of malignant disease, patients with both intralobar and extralobar sequestrations may demonstrate marked serum elevations of the tumor markers CEA and CA19-9.¹⁴⁷

CT is sensitive and specific for identification of either intralobar or extralobar sequestrations.¹⁴⁸ MRI may be helpful.¹⁴⁹ Bronchography and bronchoscopy are less likely to provide additional information. Barium esophagography may be necessary to demonstrate an esophageal communication. Angiography is seldom necessary, because noninvasive studies generally demonstrate the feeding systemic vessels.

Many lesions are discovered prenatally, and careful follow-up is recommended. If hydropic changes are noted, delivery is indicated.^{150,151} In infants, cysts that are large or cause hemodynamic compromise can be temporarily drained by needle aspiration or tube thoracostomy to allow adequate induction of anesthesia. If no infection is involved, the cyst alone, or possibly a segment, can be removed. In most cases, however, lobectomy is required. Early identification of the aberrant arterial blood supply is critical and helps avoid disastrous bleeding. Most of the arteries are less than 1 mm in diameter, but some have been reported to be as large as 2.5 mm. Atherosclerotic changes in the systemic artery may make it difficult to manipulate during surgery. A communication with the gastrointestinal tract should be thoroughly searched for at the time of surgery. Venous drainage also may be aberrant, and it should be ascertained before resection, if possible. Both intralobar and extralobar sequestrations may be amenable to resection by minimally invasive techniques. The outcomes after resection are excellent.^{152,153} The use of Amplatzer vascular plugs has been described for the control of hemoptysis in these patients.¹⁵⁴

Azygos Lobe

An azygos lobe (Fig. 9-10) is present on 0.5% of routine chest radiographs. It is found as an abnormal lobation where the azygos vein creates an additional sulcus separating two portions of the upper lobe and the azygos vein

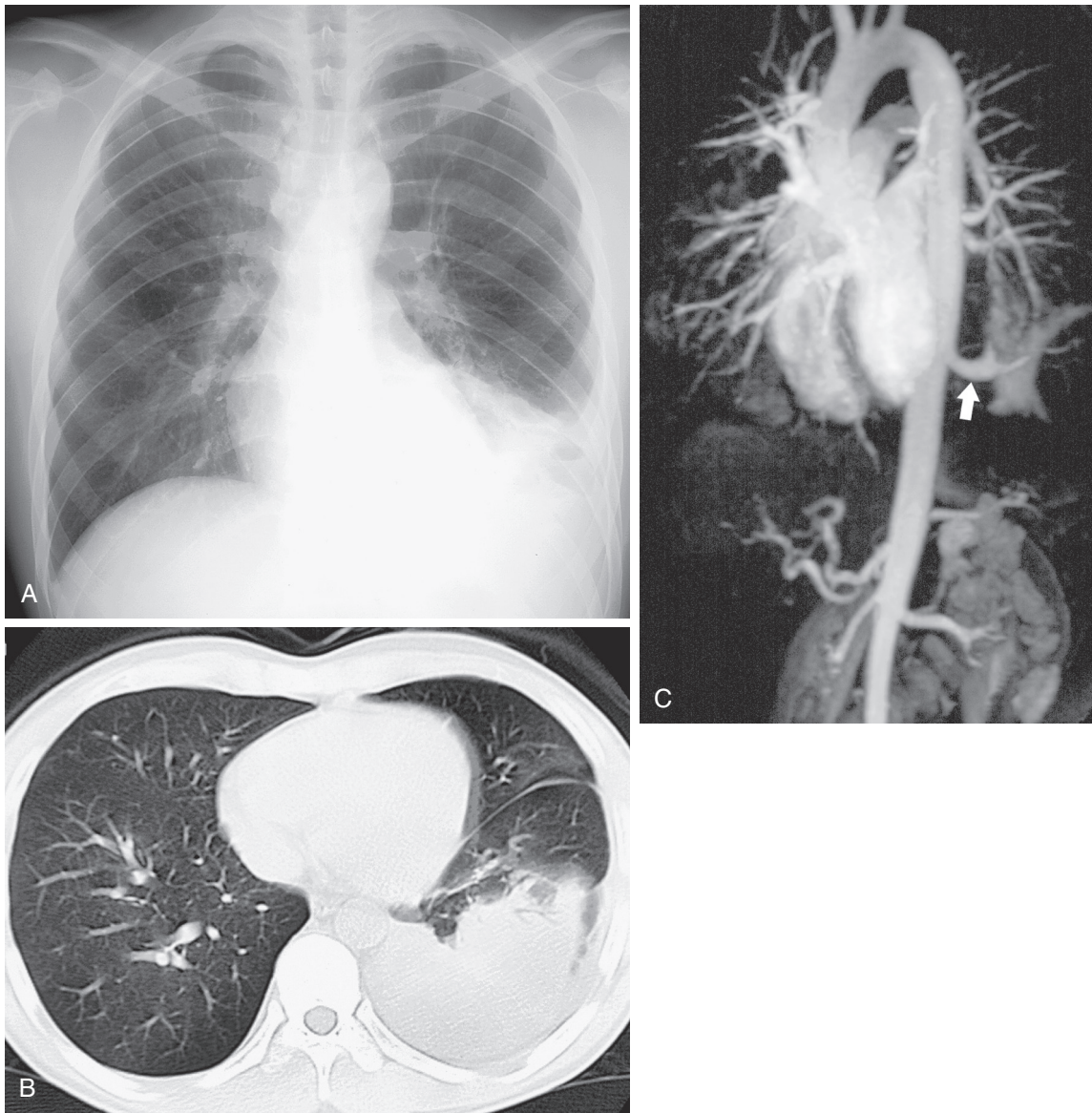


FIGURE 9-8 ■ Intralobar pulmonary sequestration. A, Frontal chest radiograph shows consolidation of the left lower lobe. **B,** Computed tomography image of lung base shows opacification of the left posterior lower lobe. **C,** Contrast-enhanced magnetic resonance angiogram shows that a large arterial branch (*arrow*) arising from the low thoracic aorta supplies this region. (Courtesy Koji Takahashi, MD, Asahikawa Medical College, Asahikawa, Japan.)

lies within the substance of the right lung. The term *azygos lobe* is somewhat of a misnomer. This entity does not represent a true anatomic lobe because there is no separate segmental bronchus. Other regions of unusual, separate lobations may be found, particularly in the lingula or in the right and left superior segments. These abnormal lobations are not associated with any other congenital anomaly, nor do they increase the likelihood for any future pathologic or developmental abnormality. They require no treatment.

Horseshoe Lung

In this rare, recently reviewed pulmonary anomaly,¹⁵⁵ right and left lung bases are fused by common tissue extending through the posterior mediastinum anterior to the aorta but posterior to the heart and esophagus. The

clinical relevance lies in its association with recurrent pulmonary infections and pulmonary hypertension. Scimitar syndrome accompanies horseshoe lung in up to 80% of cases.^{156,157} Horseshoe lung also should be suspected in patients with the VACTERL constellation and in patients with other bronchopulmonary foregut anomalies.¹⁵⁵

Bronchogenic Cysts

Bronchogenic cysts result from abnormal budding from the perimeter of the trachea after it has differentiated from the foregut. They are the most frequent cysts of the mediastinum, accounting for approximately 60% of these lesions. Men are more frequently affected than are women. The usual location of the cysts is along the right paratracheal area, but they may also be attached to the

carina, frequently anterior to the esophagus. They may be hilar, attached to a lobar bronchus, and occasionally they are intrapulmonary. They may also be situated below the diaphragm or in the parasternal subcutaneous tissue, skin, or pericardium. The cyst's inner lining is composed of ciliated pseudostratified respiratory epithelium interspersed with goblet cells. Bronchial communication is rare.¹⁵⁸ The cysts are unilocular and usually measure 2 to 10 cm. They may contain normal bronchial elements, including cartilage and smooth muscle, which helps

differentiate a bronchogenic cyst from an enteric cyst. Noninfected cysts may contain mucus, blood, or milky material. Symptoms may relate to pulmonary artery compression and possibly paroxysmal atrial fibrillation.^{159,160} Bronchogenic cysts most commonly are an incidental finding on chest radiography, usually an air-filled cyst with or without an air-fluid level (Fig. 9-11). Serial radiographs may demonstrate rapid expansion. Intraparenchymal bronchogenic cysts more frequently present with symptoms of infection (90%) compared with mediastinal cysts (36%).¹⁶¹

The differential diagnosis of bronchogenic cyst includes lymphadenopathy, pulmonary sequestrations, teratoma, hemangioma, lipoma, hamartoma, neurogenic tumors, foregut and pericardial cysts, and lung abscesses. CT is helpful, and a low Hounsfield unit (<20) is characteristic. MRI may provide additional information. Differentiation of bronchogenic cysts from enteric cysts may be made on the basis of location: enteric cysts usually develop in the posterior mediastinum in close association with the esophagus. Also in the differential diagnosis of bronchogenic cysts, bronchopulmonary foregut malformations are usually multilocular and are more frequently associated with recurrent cough, pneumonia, and hemoptysis. Endoscopic ultrasonography may be beneficial, but endoscopic ultrasonography-directed fine-needle aspiration may be hazardous.¹⁶²

Bronchogenic cysts should be excised completely, if possible, with repair of any associated communication.¹⁶³ Needle aspiration alone is likely to result in recurrence. Mediastinoscopic unroofing has been performed and has been diagnostic. Asymptomatic cysts should be removed for diagnosis and to prevent complications associated with the natural history of these cysts, including perforation, hemorrhage, enlargement, infection, and malignant degeneration. In children, the airways are pliable and much more susceptible to life-threatening compression by an enlarging cyst.¹⁶⁴ Malignant degeneration has been reported,¹⁶⁵⁻¹⁶⁷ including an adenocarcinoma in an 8½-year-old girl.¹⁵⁸ Typically, the bronchogenic cyst can be enucleated from the mediastinum. If there is a stalk, it is ligated, and the bronchial defect is repaired. Long-term results are excellent. Video-assisted and robot-assisted removal has become increasingly popular,^{163,168} but pericystic adhesions, tracheal or bronchial communications,

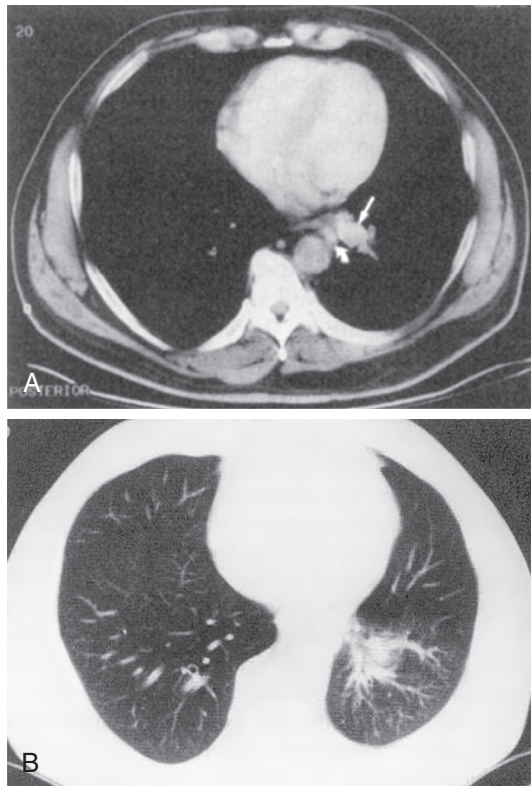


FIGURE 9-9 ■ Extralobar sequestration. Extralobar sequestration is most frequently found in the lower left chest with its own pleural investment and systemic venous drainage. Computed tomography scan is beneficial in better identifying the anatomic details of the defect. (From Singh SP, Nath H: A 53-year-old man with hemoptysis. *Chest* 120:298-301, 2001.)

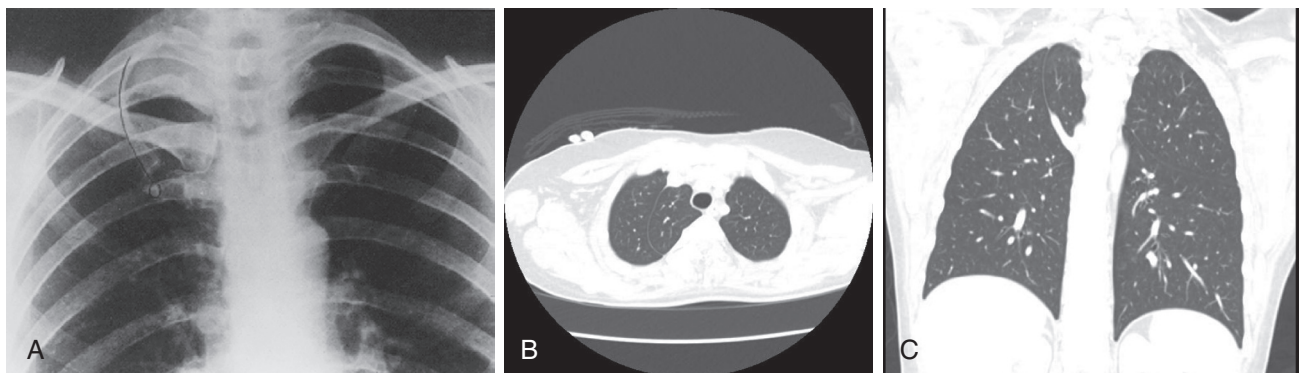


FIGURE 9-10 ■ Azygos lobe. **A**, An additional fissure is found in this chest radiograph. The azygos vein creates a separate division within the right upper lobe. **B**, Axial cut on computed tomography (CT) scan showing the azygos lobe. **C**, Coronal view on CT scan showing a part of the azygos vein and the azygos lobe.

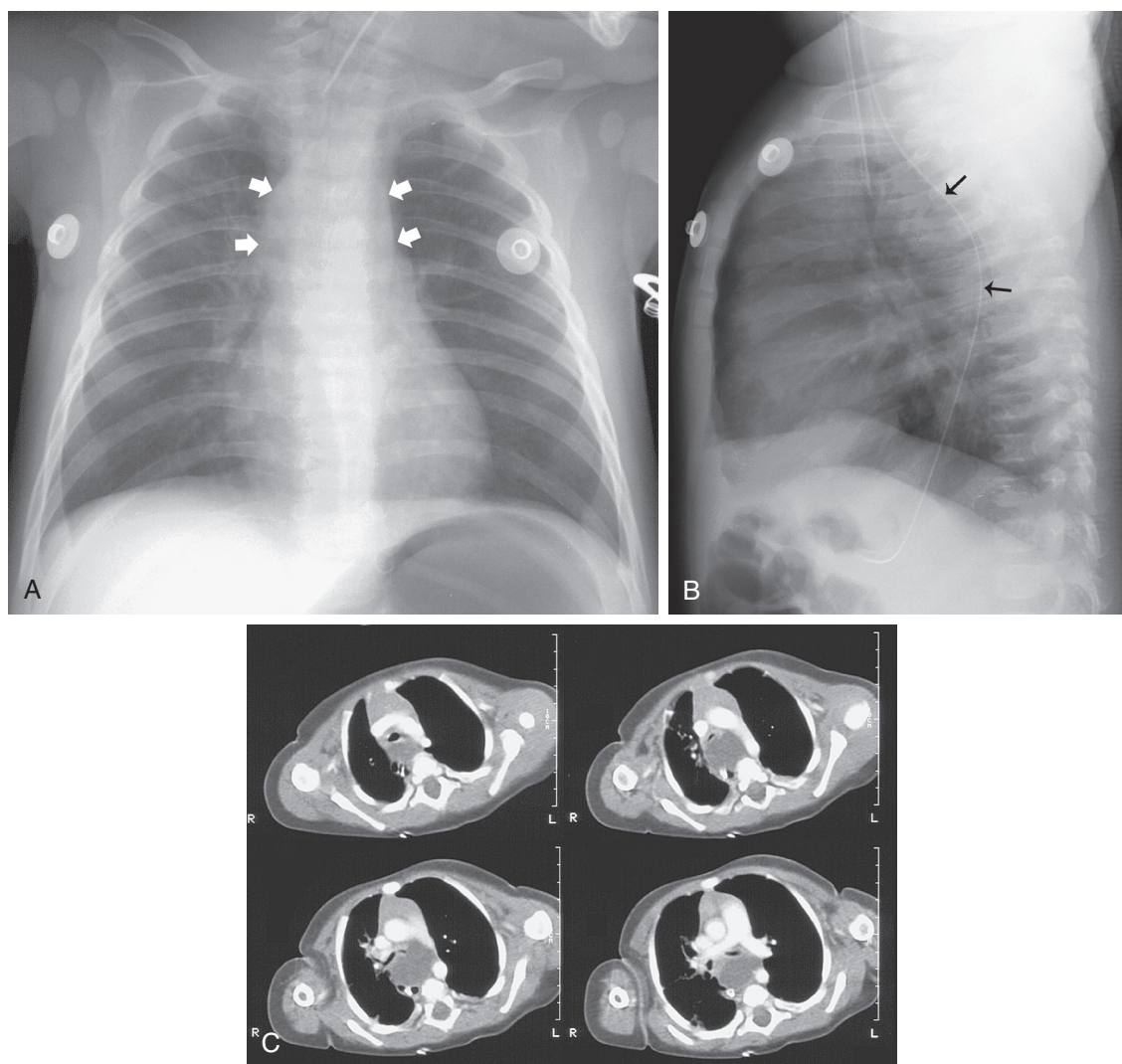


FIGURE 9-11 ■ Bronchogenic cyst in a 4-month-old boy with cough. Anteroposterior (A) and lateral (B) chest radiographs show a central mediastinal mass (*white arrows*) displacing the esophagus (outlined by nasogastric tube, *black arrows*) posteriorly. C, Four contiguous axial computed tomography images of the chest show a retrotracheal and subcarinal mass with low-density contents. Excision of the mass and pathologic examination showed bronchogenic cyst. (Courtesy Simon C. Kao, MD, Iowa City, IA.)

and the possibility of malignant transformation should be considered relative indications for thoracotomy.

LUNG BUD ANOMALIES

Pulmonary Agenesis, Aplasia, and Hypoplasia

Pulmonary agenesis is the complete absence of the carina as well as the mainstem bronchus, the lung, and the pulmonary vasculature on the affected side. First described by Morgagni, fewer than 20 cases have been reported. Cardiac anomalies are usually associated when pulmonary agenesis is bilateral. Unilateral cases have cardiac anomalies in 50% and are more frequently associated with right-sided agenesis.¹⁶⁹ The sex distribution is roughly equal. Right and left agenesis is also equally distributed. There is some evidence of a chromosomal abnormality.¹⁷⁰ Left-sided pulmonary agenesis has been

reported as part of a syndrome with ipsilateral facial, radial ray, and renal agenesis in a series of three patients.¹⁷¹ In these three infants, pulmonary artery dilation caused marked bronchial compression. Associated gastroesophageal reflux exacerbated respiratory distress. Other factors associated with impaired intrauterine lung growth include intrathoracic or extrathoracic compression, diminished fetal respiratory movements, and decreased amniotic fluid volume.¹⁷² Abnormal pulmonary development can be detected on fetal ultrasound examination.¹⁷³

When the carina and bronchus are present but the vessels and parenchyma are absent, the defect is referred to as pulmonary aplasia. There is a rudimentary bronchial stump, and the carina appears to be normal. Aplasia may be present in a single lobe or in a combination of lobes. It is most frequently unilobar. The right upper and right middle lobes are the most commonly involved.

Agenesis or aplasia may be symptomatic when it is unilateral or even when a single lobe is involved. Patients may have tachypnea, dyspnea, or cyanosis. Older patients

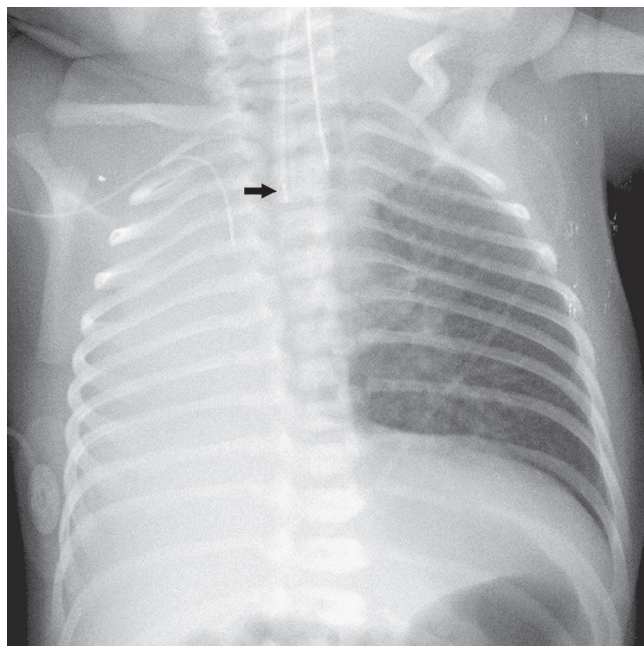


FIGURE 9-12 ■ Right pulmonary agenesis. Frontal chest radiograph in a newborn with respiratory distress. Note complete opacification of the right hemithorax with mediastinal shift toward the same side. The patient also has esophageal atresia (nasogastric tube lodged in the dilated proximal esophageal pouch, arrow) with distal tracheoesophageal fistula (note air in the stomach). (Courtesy Simon C. Kao, MD, Iowa City, IA.)

may present with wheezing. Boys are more commonly affected than girls are. When congenital cardiac anomalies are present, cyanosis and respiratory distress are generally evident at birth.

Chest radiography shows a shift in the mediastinum toward the area of agenesis or aplasia (Fig. 9-12). Pulmonary angiography shows absence of the ipsilateral pulmonary artery. Bronchoscopy may be helpful to evaluate bronchial stump presence, length, and character in patients with aplasia. CT and esophagography are helpful elements of the evaluation to differentiate agenesis or aplasia from sequestration and atelectasis.

Bilateral agenesis is incompatible with life. Survival periods of up to 6 years in right-sided lesions and up to 16 years in left-sided lesions have been reported.¹⁷⁴ Of those surviving the neonatal period, 30% die within the first year and 50% succumb within the first 5 years of life.¹⁷⁵

In pulmonary hypoplasia, the bronchus and the bronchial tissue are poorly formed, and there is a reduced number of alveoli. Lung weight is at least one standard deviation below the mean.¹⁷⁶ Most cases of hypoplasia are the result of another defect that prevents normal lung development, such as a diaphragmatic hernia, chest wall defect, bone dysplasia, or even muscular dystrophy. Primary pulmonary hypoplasia is rare and is frequently associated with Down syndrome.¹⁷⁷ It is often fatal and is the result of hypertrophy of the pulmonary artery smooth muscle and resultant pulmonary artery hypertension. Associated congenital abnormalities also reduce the life expectancy of these patients.

In pulmonary aplasia, removal of the rudimentary stump may be necessary if it is recurrently infected. There is no specific surgical therapy for pulmonary hypoplasia, except to treat the cardiac anomalies or to ameliorate the chest wall anomalies. The severity of the pulmonary artery hypertrophy may result in persistent fetal circulation. At delivery, the affected infant may be hypoxemic, acidotic, and hypercarbic. Such patients are treated with sedation, paralysis, high-frequency ventilation, vasodilators, respiratory alkalosis, and, if necessary, ECMO. Survival has improved with ECMO.¹⁷⁸⁻¹⁸⁰ Another means to treat these patients is with high-frequency oscillatory ventilation.¹⁸¹ One half of the infants with congenital diaphragmatic hernias require ECMO, and 70% of those patients survive. In patients with a congenital diaphragmatic hernia, it is unnecessary to resect the underdeveloped lung at the time of diaphragmatic repair. There should be no attempt to aggressively inflate the lung. Bilateral lung transplantation has been performed in extreme circumstances.¹⁸² Antenatal surgical therapy has been directed at relief of lung compression, but efficacy is equivocal.¹⁸¹ Surgical options have recently been reviewed,¹⁸³⁻¹⁸⁵ although the absence of large randomized trials precludes robust quantification of risks and benefits of antenatal surgery vis-à-vis postnatal therapy. A review of the literature shows 53 reported cases of cardiac surgery being performed in patients with unilateral pulmonary agenesis or atresia with a reported 7.7% mortality.¹⁸⁶

Congenital Lobar Emphysema

Congenital lobar emphysema represents 50% of all congenital lung anomalies. It is a postnatal overdistention of histologically normal and mature lung parenchyma resulting from a disorder of the bronchial patency, of either internal or external causes.¹⁸⁷ It is the result of obstruction of a lobar bronchus, usually an upper airway, resulting in overexpansion of alveolar airspaces but lacking parenchymal destruction, in contradistinction to the adult form. The vasculature to the affected lobe is normal. A subtype, congenital segmental emphysema, has recently been described.¹⁸⁸

Expanded lung frequently compresses adjacent lung and, in some cases, shifts the mediastinum away from the emphysematous lobe. Other descriptive terms include infantile lobar emphysema, congenital segmental bronchomalacia, congenital lobar overinflation, and emphysema of infancy or childhood. A cartilaginous defect obstructs the lobar bronchus in 25% of cases.¹⁸⁹⁻¹⁹¹ Other potential causes of intrinsic obstruction include mucus plugging and intraluminal granulation tissue. Extrinsic obstruction may result from cardiac or vascular anomalies such as tetralogy of Fallot, pulmonary stenosis, anomalies of pulmonary venous return, adenopathy, mediastinal tumors, and bronchogenic or enteric duplication cysts.¹⁹² In more than one half of the cases, there is no identifiable causative factor.¹⁹³

Patients with congenital lobar emphysema are symptomatic at birth. Within several days, they can develop wheezing, dyspnea, or cough.⁵⁴ The left upper lobe is most frequently involved, followed by the right upper

lobe, then the right middle lobe, and finally the lower lobes.¹⁹⁴ When it develops bilaterally, it is usually the left upper lobe and the right middle lobe that are affected. There is a 3:1 male-to-female ratio of involvement. Of those affected, 80% are symptomatic by 6 months of age. Fourteen percent of patients have an associated cardiac malformation. Rib and thoracic cage abnormalities also are common. If congenital lobar emphysema is symptomatic but left untreated, the mortality is 50% within the first week, and an additional 30% to 40% of patients will die during the next month.

In the newborn with severe respiratory distress, a chest radiograph usually suffices for diagnosis (Fig. 9-13A). The combination of an enlarged, hyperlucent lobe with fairly normal vasculature coupled with compression of

adjacent lung tissue and contralateral mediastinal deviation is diagnostic. For mild to moderate symptoms, a CT scan (see Fig. 9-13B) may be necessary to rule out mediastinal masses or vascular anomalies. In older children, bronchoscopy can be helpful to assess for mucus plugs or foreign bodies. Bronchography is unlikely to be helpful and is rarely used now. The ventilation-perfusion scan has yielded useful information in some cases.¹⁹⁵ Respiratory distress in the newborn must be differentiated from other lung abnormalities, such as pneumothorax, congenital diaphragmatic hernia, parenchymal lung cysts with a ball-valve mechanism, cystic adenomatoid malformation, and extralobar sequestration.

Acquired lobar emphysema is yet a different disease entity, a complication of respiratory distress syndrome and long-term mechanical ventilation and usually develops in the right upper lobe. In acquired childhood emphysema, lung scans demonstrate low flow to the affected lung, in contrast to normal flow in the congenital form.¹⁹⁶ For the congenital form, echocardiography and additional tests (e.g., magnetic resonance angiography) may be required to evaluate for associated cardiac or vascular anomalies. There is no surgical indication for asymptomatic or mildly symptomatic patients. Pulmonary function is likely to remain stable. One half of the patients will normalize during infancy. For patients who are symptomatic, all emphysematous tissue should be resected. Lobectomy is frequently required. Segmental resection when possible is also appropriate management.¹⁸⁷ Operative mortality is as high as 7% in some series. The greatest risk appears to be at the time of anesthesia induction. Selective intubation has been used to prevent overinflation of the emphysematous lobe, with resulting cardiovascular collapse.¹⁹⁷ High-frequency ventilation also has been used to prevent mediastinal shift and hemodynamic compromise.¹⁹⁸ Needle aspiration has been performed as necessary.¹⁹⁹ In addition, flexible fiberoptic bronchoscopy has been used in the neonate to decompress an emphysematous lobe.²⁰⁰ The surgeon should be prepared for immediate thoracotomy soon after induction. Once the chest is open, the emphysematous lobe may spontaneously project out of the chest. Typically, it remains inflated even after the lobe has been removed. The hilar anatomy is usually normal, and the goal should be to resect all of the emphysematous tissue, preserving the adjacent normal lung. Lung function is compromised after resection,^{193,201} but the child's development is normal.²⁰² Long-term follow-up has been reported.²⁰³ In contrast to patients with congenital lobar emphysema, those with acquired lobar emphysema progress to further respiratory difficulties after lung resection.²⁰⁴ Balloon dilation of the airway stenosis has been used successfully.²⁰⁵

Management of coexisting congenital lobar emphysema and congenital heart disease has been described in detail.²⁰⁶ Presence or absence of pulmonary hypertension is a key factor in the development of an operative strategy. On occasion, the emphysema may be caused by vascular compression of a bronchus, such as in the case of a large ductus arteriosus. The emphysematous changes may resolve after surgical correction of the vascular anomaly.

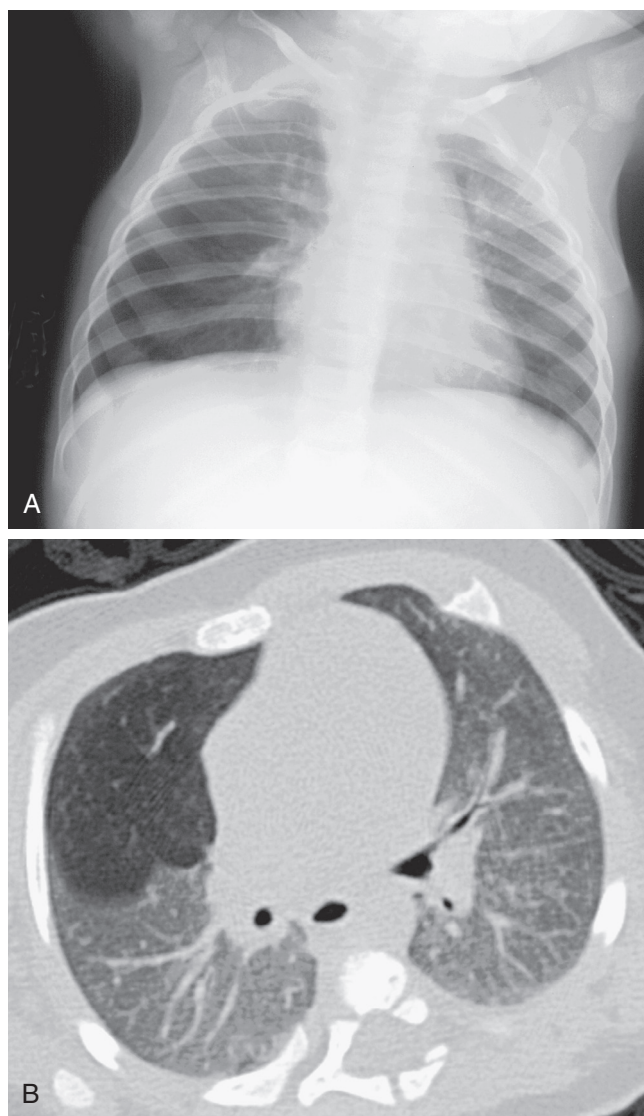


FIGURE 9-13 ■ Congenital lobar emphysema. **A**, Chest radiograph of a 1-month-old boy shows hyperlucency in the right lower lung field. **B**, Computed tomography image of the lungs just below the carinal bifurcation shows right middle lobe emphysema with paucity of blood vessels and decreased attenuation. (Courtesy Simon C. Kao, MD, Iowa City, IA.)

Congenital Parenchymal Cysts

Congenital parenchymal cysts are rare and may develop as a unilocular entity within the parenchyma, most commonly in the left lower lobe. An aberrant systemic artery often supplies the cyst region. Such cysts are lined with mucus-secreting pseudostratified columnar epithelium. The cyst usually communicates with a bronchus. This condition may represent a variant of cystic adenomatoid malformation. It may also result from entrapped lung blood, with subsequent air trapping after the blood has been resorbed. Affected infants show symptoms ranging from a chronic cough to frank sepsis. Congenital parenchymal cysts are frequently associated with other anomalies. This disease category includes intraparenchymal bronchogenic cysts.²⁰⁷ Parenchymal cysts are associated with subtype B Niemann-Pick disease.²⁰⁸

Respiratory distress is common within the first few days of life, and the cyst often becomes infected by the first few weeks of age. Air trapping may shift the mediastinum.

It may be difficult to differentiate a cyst from an intraparenchymal abscess. The presence of a systemic artery feeding the cyst is diagnostic. Failure of the cyst to completely collapse with tube drainage also is helpful in making the diagnosis. Other anomalies that appear similar include congenital diaphragmatic hernia and postpneumonic staphylococcal pneumatoceles.

Once discovered, congenital parenchymal cysts can be observed unless they become infected, expand, or are otherwise symptomatic. If present for more than a year, they are unlikely to resolve. As noted before, malignant transformation of a pulmonary cyst is a concern.²⁰⁹ For infected cysts, preliminary antibiotic treatment is followed by resection once sepsis subsides. Lobectomy is usually necessary, although cyst resection can suffice, for example, by right S3 segmentectomy.²⁰⁷ Pneumonectomy occasionally may be necessary for definitive treatment. Management of congenital parenchymal lung cysts has been grouped with that of congenital cystic adenomatoid malformation, congenital lobar emphysema, and sequestrations to compare and contrast the fine points of each entity.²¹⁰ Perioperatively, a combination of one-lung high-frequency ventilation and low-rate intermittent mandatory ventilation has been described for the management of the symptomatic neonatal lung cyst.²¹¹

Congenital Cystic Adenomatoid Malformation

Congenital cystic adenomatoid malformation (CCAM) was first described in 1949.²¹² Also referred to as congenital pulmonary airway malformation (CPAM),²¹³ CCAM is a mass consisting of excessive proliferation of bronchi but without normal alveolar development. Composed of cartilage, smooth muscle, and bronchial glands containing columnar and cuboidal epithelial cells, CCAM represents 25% of all congenital lung anomalies (second only to congenital lobar emphysema). There is normal vascular development, and the affected area communicates with the normal airway. Usually only one lobe is affected, and that lobe generally has a solitary lesion.

The abnormality may be identified in the fetus whose mother develops polyhydramnios by the 23rd week of gestation. Up to one third of those identified in utero resolve before birth.¹⁸⁹⁻¹⁹¹ In most cases, CCAM manifests as neonatal acute respiratory distress with or without associated lung infection. CCAM must be differentiated from congenital diaphragmatic hernia because both entities show multiple air-fluid levels within the affected hemithorax. The initial chest radiograph shows a solid mass. Over time, the fetal fluid is resorbed and the cysts become filled with air (Fig. 9-14). A CT scan may be helpful in achieving a diagnosis. The most commonly associated anomaly is pectus excavatum, and cardiac and pulmonary vessel malformations can be present as well. The Stocker classification assists in treatment planning, categorizing presentations into types I, II and III.²¹⁴ Type I lesions are large, widely spaced, and irregular cystic structures that exceed 1 cm. Affected patients usually reach term but occasionally are stillborn. It is rare to have polyhydramnios or other anomalies associated with a

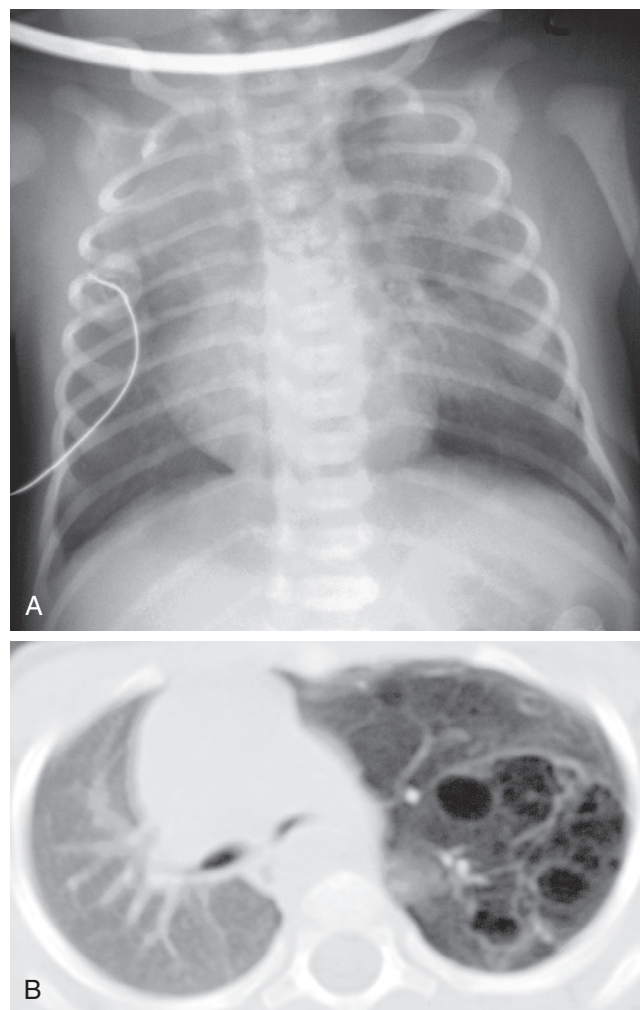


FIGURE 9-14 ■ Cystic adenomatoid malformation. **A**, Chest radiograph of a newborn with ill-defined lesions in the mid-left lung field. **B**, Computed tomography image of the chest shows multicystic lesions in the same region. Excision and histologic examination showed cystic adenomatoid malformation. (Courtesy Simon C. Kao, MD, Iowa City, IA.)

type I lesion. Of these patients, 75% have mediastinal shifting with some associated cyanosis and grunting. The prognosis is generally good. One half of the patients develop pneumonia in infancy and early childhood. In type II CCAM (40% of cases), the cysts are smaller than 1 cm and have an appearance of dilated bronchioles. The patients are more frequently premature or stillborn. Mediastinal shift is less often seen, and there appears to be more bronchiolar proliferation. Type III lesions are very small cysts, less than 0.5 cm. They represent 10% of all cases. The mass is much firmer, appearing to surround the entire affected lobe, most often the lower lobe. Prognosis is very poor, and patients usually expire within a few hours of birth. The new Stocker pathologic classification of CCAMs has five subtypes based on origin.²¹³

Asymptomatic CCAM patients may be observed for the first 4 to 6 months. Repeated CT at 6 months is performed to assess for CCAM enlargement or malignant degeneration (a consideration but a poorly defined phenomenon in this condition). Delayed intervention allows the child to mature, reducing the operative morbidity. Lesion shrinkage or disappearance, compensatory hypertrophy of normal lung, and unlikely occurrence of later malignant neoplasia all support a conservative approach in asymptomatic patients.²¹⁵ Only approximately 10% of untreated asymptomatic lesions eventually become clinically significant.²¹⁶ Any lesion that decreases in size but has not completely regressed should be observed until it has completely resolved. Many surgeons still favor resection of cystic lung lesions in asymptomatic neonates, citing persistent risk of infection or malignant transformation.^{217,218} Of the total number of primary pulmonary rhabdomyosarcomas and malignant mesenchymomas of lung reported in children, approximately 50% have antecedent lung cysts.²⁰⁹ Symptomatic lesions after birth certainly should be resected, and lobectomy has been considered the standard operation. Remaining unaffected lung tissue should be preserved. There is evidence that segmentectomy and wedge resection, when feasible, are just as efficacious as lobectomy, with the obvious advantage of maximizing pulmonary reserve, provided prolonged pulmonary air leaks are avoided.²¹⁹ By extension, with ipsilateral multilobar involvement, segmentectomies allow avoidance of pneumonectomy. After *complete* CCAM resection, prognosis is generally excellent.

Antenatal diagnosis suggests the possibility of in utero surgical therapy, but efficacy remains controversial. Crombleholme proposed using the ratio of lesion mass to the head circumference, the CCAM volume ratio (CVR), for follow-up and/or to predict fetal demise.²²⁰ For most cases, normal delivery with postnatal evaluation is sufficient. Only few CCAMs cause fetal problems, with fetal hydrops being the best predictor of death. When the CVR is higher than 1.6, the risk for hydrops ranges between 15% and 75%.²²⁰ Successful serial cyst aspiration has been demonstrated in fetal CCAM.²²¹ Other fetal procedures to be considered include placement of a thoracoamniotic shunt, prenatal steroids, open resection of large lesions, or EXIT.^{213,222} However, in one study, only 8 of 20 infants who had a prenatal diagnosis of CCAM were symptomatic in the neonatal period.²²³ Minimally

invasive techniques and parenchyma-sparing techniques are increasingly used, with good success for the management of these lesions in infancy and early childhood.²²⁴

Infantile Pulmonary Emphysema

Infantile pulmonary emphysema is uncommon, accounting for approximately 2% of congenital anomalies. Its morphologic spectrum has been described in detail in a series of 33 cases accessioned to the Armed Forces Institute of Pathology in Washington, DC, during an approximate 30-year period.²²⁵ An entity different from congenital lobar emphysema, infantile pulmonary emphysema does appear most prominently in the upper lobes and is multilobar in approximately 20% of cases. Associated anomalies are common. The condition presents as gas surrounding the bronchovascular structures and may evolve to pneumomediastinum or pneumothorax. It occurs in approximately 20% of patients with respiratory distress syndrome and 40% of patients who require positive end-expiratory pressure. Infantile pulmonary emphysema can appear as diffuse multicystic abnormalities within all lobes.²²⁶ It must be differentiated from CCAM and congenital diaphragmatic hernia. Once the diagnosis is made, less than 2% of patients require surgical resection; most improve with supportive measures alone. Atelectasis, ventilator dependence, and recurrent or persistent infections are indications for surgery. Thoracentesis or thoracostomy is necessary to treat pneumothorax and respiratory embarrassment. Resection of affected tissues with preservation of relatively healthy parenchyma is the objective of surgical intervention.

Polyalveolar Lobe

Polyalveolar lobe is a significant increase in the number of alveoli compared with the bronchi. It was first described in 1970 and was thought to be congenital lobar emphysema.²²⁷ Polyalveolar lobe is differentiated from lobar emphysema in that there is little trapped air and no true emphysematous changes. Radiographic translucency in this condition is the result of a reduction in vasculature to amount of lung, unlike congenital lobar emphysema.^{227,228} There appears to be retention of fetal lung liquid in these patients, an occurrence not primarily associated with congenital lobar emphysema.²²⁹ However, polyalveolar lobe may at times give rise to congenital lobar emphysema.¹⁹³ There may also be a relationship between polyalveolar lobe and type II CCAM²³⁰ and with infantile pulmonary emphysema.²²⁵ In older children, bronchoscopy should be performed to differentiate obstructive emphysema from foreign bodies or bronchial obstructive inflammation. Diagnosis is usually made by high-resolution CT. Resection is performed as necessary for symptomatic patients.

Pulmonary Lymphangiectasia

Pulmonary lymphangiectasia (Fig. 9-15) was first described by Virchow as diffuse cystic lymphatic duct dilation in infancy.²³¹ There are primary and secondary forms. The primary form involves dilated lymphatic

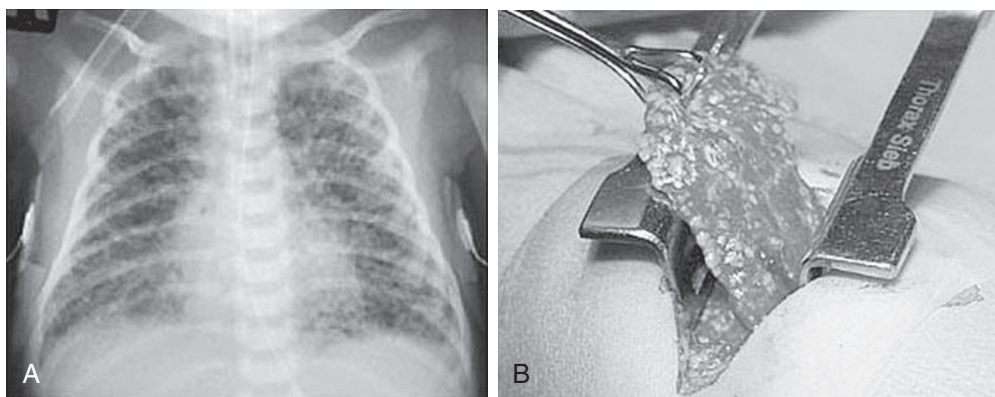


FIGURE 9-15 ■ Pulmonary lymphangiectasia. **A**, The chest radiograph demonstrates the bilateral “soap bubble” appearance of lymphangiectasia. **B**, Gross findings at surgery demonstrated the cystic nature of the disease.

channels within the lung, and the secondary form results from pulmonary venous obstruction. Both forms are symptomatic in neonates, with respiratory distress and cyanosis. One half of these patients have associated cardiac anomalies, usually involving venous return. Their chest radiographs demonstrate a “soap bubble” appearance with ground-glass opacification. CT is more specific in making the diagnosis, but even with current techniques, it may be radiographically difficult to distinguish pulmonary lymphangiectasia from congenital lobar emphysema.²³² Lymphoscintigraphy is a helpful adjunct to CT in distinguishing lymphangiectasia from lobar emphysema.²³³ Almost exclusively diagnosed in infants, it has been seen in adults, with histologic verification after thoracoscopic pulmonary resection.²³⁴

Lymphatic obstruction may be secondary to venous obstruction. Congenital chylothorax may result. Thus, venous impairment may indirectly produce nonimmune hydrops fetalis and the concept of a congenital pulmonary lymphangiectasia–congenital chylothorax–hydrops fetalis continuum has been proposed.²³³ Patients with pulmonary lymphangiectasia may also have extrapulmonary organ involvement, especially in the alimentary canal and solid organs of the abdomen. Prognosis correlates best with the degree of pulmonary involvement, and outcome is worse when pulmonary involvement is extensive.²³⁵ Prognosis is particularly poor if pulmonary lymphangiectasia is present bilaterally. Survival beyond infancy is unusual, but overall outcome may be better than once believed.^{236–238}

To effect survival, immediate postnatal ventilator support and pleural drainage are almost always required. Progress in neonatal intensive care has improved the outlook for these severely ill infants. Surviving patients have a course similar to that of others with major chronic lung disease. Home oxygen therapy, symptomatic treatment of wheezing and cough, and intermittent pleural drainage are generally necessary.²³⁹ Successful pleurodesis using autologous blood instillation and Betadine have been reported.²⁴⁰ Ethiodized oil (Lipiodol, Roissy–Charles de Gaulle Cedex, France) is an oil-based contrast agent used for lymphangiography and can be both diagnostic and therapeutic. Because of its high viscosity, Lipiodol results in mechanical occlusion of the lymphatic vessels.²⁴¹

Whereas most cases of pulmonary lymphangiectasia occur sporadically, the condition has been seen in siblings.²⁴² Candidate gene mutations include vascular endothelial growth factor receptor 3 (VEGFR3)²⁴³ and *FOXC2* in families with Milroy and lymphedema-distichiasis syndromes, respectively. According to the same research team, a correlating animal model of fatal chylothorax may be that of α_9 -deficient mice. Postmortem examination of one infant who died of pulmonary lymphangiectasis revealed marked upregulation of endothelial nitric oxide synthase in that disorder.²⁴⁴ From an immunohistochemical standpoint, key antibody markers useful in confirming the diagnosis of lymphangiectasis include CD31, CD34, desmin, smooth muscle actin, and D2-40.²⁴⁵

VASCULAR ABNORMALITIES

Unilateral Absence of a Main Pulmonary Artery

Absence of a main pulmonary artery is exceedingly rare and is commonly associated with other cardiac anomalies. It was first described by Frentzel in 1868.²⁴⁶ The pulmonary vein to the affected lung is normal, but the arterial supply derives from a systemic artery that is usually adjacent to the trachea. Patients develop recurrent respiratory infections and dyspnea in later childhood. Hemoptysis is the most serious complication and may be associated with bronchiectasis. Pulmonary infection warrants surgical resection. Of the 352 cases reported in the literature, 237 were associated with congenital cardiac defects.²⁴⁶ The presence of good intraparenchymal pulmonary arteries warrants surgically establishing a connection to the main pulmonary artery or the creation of a systemic to pulmonary shunt. Pulmonary hypertension is a severe complication of this disease process.²⁴⁶

Idiopathic, Hyperlucent Lung Syndrome (Swyer-James or Macleod Syndrome)

Hyperlucent lung syndrome is defined as a small or normal-sized lung with few pulmonary vessels and associated air trapping. A very rare anomaly with a prevalence of 0.01% in routine chest radiographs, it was first

described by Swyer and James²⁴⁷ and later by Macleod.²⁴⁸ It is thought to result from chronic childhood lower respiratory tract infections, potentially caused by bronchiolitis obliterans, that lead to pulmonary vascular changes and bronchiectasis.

Radiographically this syndrome is characterized by hyperlucency of a lobe or the entire lung with decreased vascular markings with no bronchial obstruction. Areas of bronchiectasis may be present. Patients are usually asymptomatic. A small or normal-sized lobe that is hyperlucent is incidentally discovered by chest radiography. Infants with the condition may have a mildly productive cough or dyspnea. CT and bronchoscopy are helpful in evaluating these patients. Agenesis or hypoplasia of the pulmonary artery can be associated with hyperlucent lung, but air trapping is absent, an important finding in this syndrome. A dynamic inspiratory and expiratory CT scan is performed to assess for trapping. The pulmonary vessels are markedly diminished. Hyperlucent lung usually requires no treatment, although surgical resection as a means of lung volume reduction has been reported.²⁴⁹

Pulmonary Artery Sling

Pulmonary artery sling relates to an anomalous origin of the left pulmonary artery. It arises from the right pulmonary artery anteriorly and then passes over the right mainstem bronchus behind the trachea and in front of the esophagus. Prevalence is reported as 59 per million school-age children based on a large two-dimensional echocardiographic study. It may be associated with tracheal stenosis secondary to complete cartilage tracheal rings. Symptoms include respiratory distress, choking, cyanosis, and stridor. The chest radiograph demonstrates hyperinflation. Bronchoscopy should be performed to rule out complete tracheal rings.²⁵⁰ Esophagography and CT (Fig. 9-16) may help assess the anatomy.

To correct the anomaly, the pulmonary artery is transected through a median sternotomy with the use of cardiopulmonary bypass. The left pulmonary artery is transected and reanastomosed to the main pulmonary

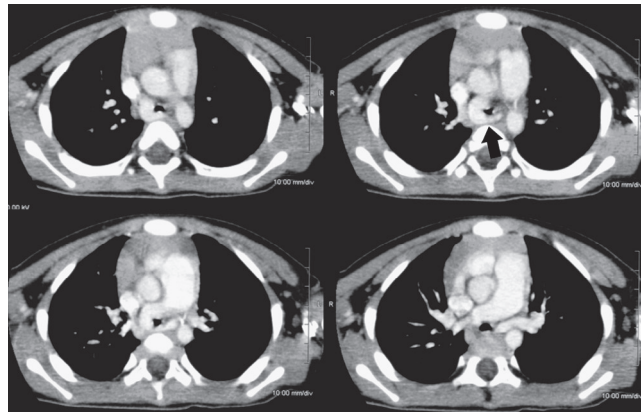


FIGURE 9-16 ■ Pulmonary sling (aberrant left pulmonary artery). Four contiguous enhanced computed tomography images at the level of the aortopulmonary window show that the left pulmonary artery (arrow) arises from the right pulmonary artery. (Courtesy Koji Takahashi, MD, Asahikawa Medical College, Asahikawa, Japan.)

artery anterior to the trachea. If tracheal stenosis is present, it may be treated at the same time. Others have reported an alternative procedure in which the trachea is divided and the left pulmonary artery is moved anterior to the trachea before the trachea repair is performed.^{251,252} Backer and Holinger²⁵⁰ reported on 34 patients who underwent repair of pulmonary artery sling through a median sternotomy with no early mortality and four late deaths. Complete tracheal rings were addressed at the same index operation. Slide tracheoplasty is the current procedure of choice for long-segment tracheal stenosis, and resection with reanastomosis is preferred for short-segment stenosis.

Isolated Pulmonary Artery Aneurysm

Pulmonary artery aneurysm (Fig. 9-17) is a rare vascular anomaly first described in 1947 by Deterling and Clagett.²⁵³ Approximately 40% to 50% of isolated pulmonary artery aneurysms are congenital, and a familial pattern has been described.²⁵⁴ Sporadic causes include penetrating trauma, prior chest tube placement, and pulmonary artery catheter-related injury. Pulmonary artery aneurysms have also been associated with infection from syphilis, tuberculosis (Rasmussen aneurysms), or, more frequently, fungus.²⁵⁵ Isolated aneurysms may also be associated with pulmonary arterial vasculitis in giant cell arteritis or Behçet syndrome. Behçet syndrome, which usually presents with oral and genital ulcers and uveitis, is a widespread vasculitis in which 5% of patients have pulmonary artery aneurysms from inflammatory destruction of the pulmonary arterial vasa vasorum. Hughes-Stovin syndrome may represent a subset of Behçet syndrome without the oral or genital ulcers but with associated peripheral venous thrombosis.

Pulmonary artery aneurysms may occur in a main pulmonary artery or in a lobar or segmental artery and are

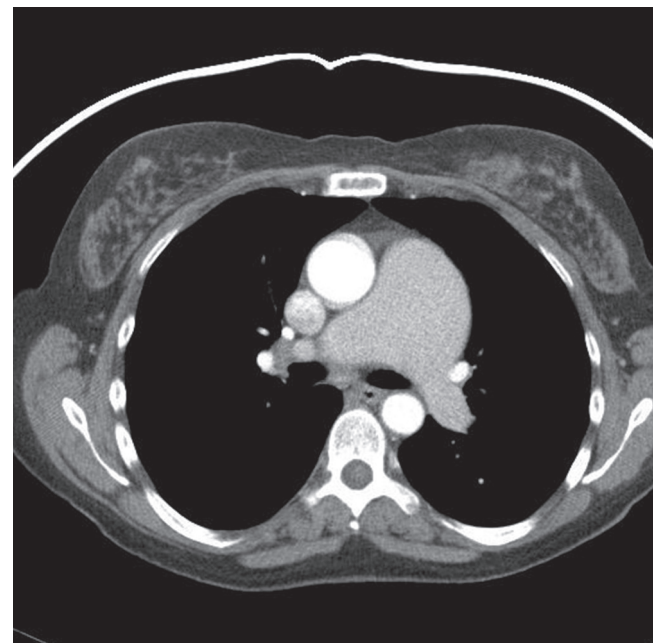


FIGURE 9-17 ■ Isolated pulmonary artery aneurysm.

either fusiform or saccular. Patients with isolated pulmonary artery aneurysms are usually asymptomatic, with lesions only recognized as a mass on chest radiography. Further evaluation is obtained with high-resolution CT, magnetic resonance angiography, or, classically, pulmonary artery angiography. Transesophageal echocardiography may be helpful for assessment of any associated thrombosis.

Rupture of a pulmonary artery aneurysm generally results in overwhelming hemoptysis or hemothorax, and aneurysms that are enlarging or symptomatic should be treated.²⁵⁶ If the lesions are fairly peripheral, embolization may be performed.²⁵⁷ In patients who have Behçet syndrome or Hughes-Stovin syndrome, immunosuppressive agents may be helpful in reducing the associated symptoms. Anticoagulation is used cautiously. Resection of the lung, primary resection of the pulmonary artery with reanastomosis, patch repair, and graft replacement have been performed.²⁵⁸ In the case of vasculitis, there is a 25% recurrence rate,²⁵⁹ which may be mitigated by perioperative medical treatment with steroids and immunosuppressive medications.

Dysphagia Lusoria

Dysphagia secondary to compression of the esophagus by a vascular structure is known as dysphagia lusoria. The most common vascular abnormality causing this is an aberrant right subclavian artery²⁶⁰ (Fig. 9-18). Management depends on defining the vascular abnormality causing the compression and correcting it surgically. With an aberrant right subclavian artery, it is often reimplanted into the carotid artery.

Pulmonary Vein Abnormalities

Congenital anomalies of the pulmonary veins, which cause their dilation, include scimitar syndrome, partial

anomalous pulmonary venous return (PAPVR), pseudo-scimitar syndrome, and pulmonary vein varix. The number of pulmonary veins draining into the left atrium can vary from one to five.²⁶¹ The presence of a single pulmonary vein (Fig. 9-19) either on the left or the right side has an incidence of 23.9%.^{261,262} An additional right middle pulmonary vein occurs in 1.6% of cases.²⁶¹ These abnormalities have implications for lung resection and lung transplantation.

Pulmonary Varix

Pulmonary varix is an aneurysmal dilation of a pulmonary vein. It may be seen in any area of the lung, and it is a very rare anomaly; as of 1988, only 71 cases had been reported.²⁶³ It is believed that varying combinations of two processes may be important for the development of a varix: pulmonary venous hypertension and inflammatory changes in the area of the affected pulmonary vein. Congenital pulmonary vein varices result from dilation of embryologic venous drainage channels.²⁶⁴ It has been described with bronchiectasis, tuberculosis, mitral valve disease, and congenital cardiac anomalies. Single lesions are usually asymptomatic; when symptoms are present, they are generally attributable to the associated cardiopulmonary condition. The age range at presentation is between 7 and 82 years, and most symptomatic patients present in their fourth to seventh decades of life. There is an equal gender distribution.

Pulmonary varix has been described as a surprise discovery at cervical mediastinoscopy.²⁶⁵ It may also present with symptoms of cerebral embolism or hemoptysis from spontaneous rupture into a bronchus. In patients who have a varix from mitral valve disease, it is more frequently found in the right lung. When a pulmonary varix is identified incidentally, an evaluation for cardiac disease should ensue. On pulmonary angiography, a Müller maneuver (inspiratory effort against a closed glottis after

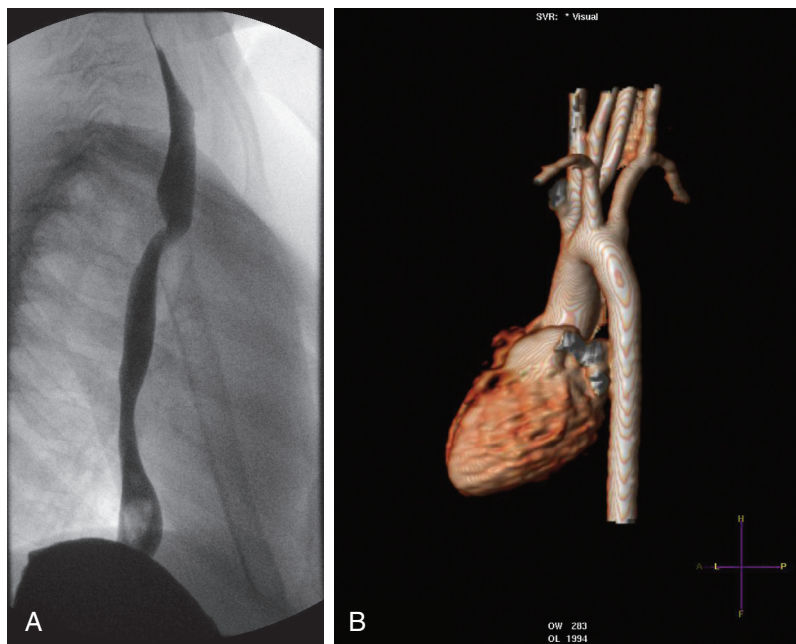


FIGURE 9-18 ■ **A**, Esophagogram showing posterior indentation of the esophagus secondary to vascular compression. **B**, Three-dimensional magnetic resonance imaging reconstruction revealing an aberrant right subclavian artery in the same patient.

expiration) increases the size of the varix, whereas a Valsalva maneuver decreases its size. CT or dynamic CT may be helpful. Three anatomic forms are recognized: saccular, tortuous, and confluent. The confluent form designates a dilation of the confluence of veins and is

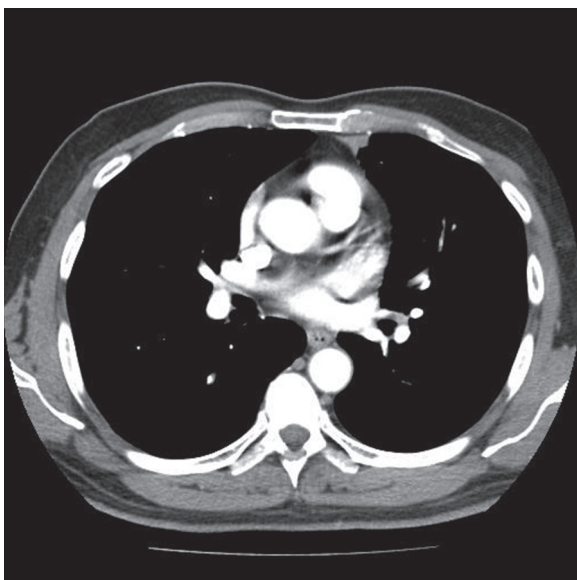


FIGURE 9-19 ■ Axial computed tomography scan showing a single pulmonary vein trunk on the left side draining into the left atrium.

more frequently associated with mitral and left-sided heart disease.²⁶³ Patients with asymptomatic pulmonary varices and without cardiac or infectious disease may be observed with a good prognosis.²⁶⁶ If a cardiac anomaly is present, it should be repaired; this will frequently result in regression of the varix. Hemoptysis associated with noncardiac cases warrant resection.²⁶⁴

Pulmonary Arteriovenous Malformations

As the name implies, pulmonary arteriovenous malformations involve a direct connection between branches of a pulmonary artery and vein. They may be acquired lesions from trauma, schistosomiasis, cancer, or actinomycosis and have been associated with the physiologic and hormonal changes of pregnancy. One third of patients have hereditary hemorrhagic telangiectasia (HHT, also known as Osler-Weber-Rendu syndrome). Sixty-five percent of patients with pulmonary arteriovenous malformations have single lesions, of which more than 50% are less than 1 cm in size, and lesions are rarely larger than 5 cm. They are frequently subpleural in location. Patients may present with hemoptysis, chest pain, epistaxis, and palpitations; complications also include cerebral thrombosis, brain abscesses, and pneumothorax. Children are more likely to have diffuse lesions associated with cyanosis and congestive failure.

The chest radiograph may demonstrate a noncalcified mass, and dynamic CT and pulmonary angiography may be helpful in achieving a diagnosis (Fig. 9-20). Patients

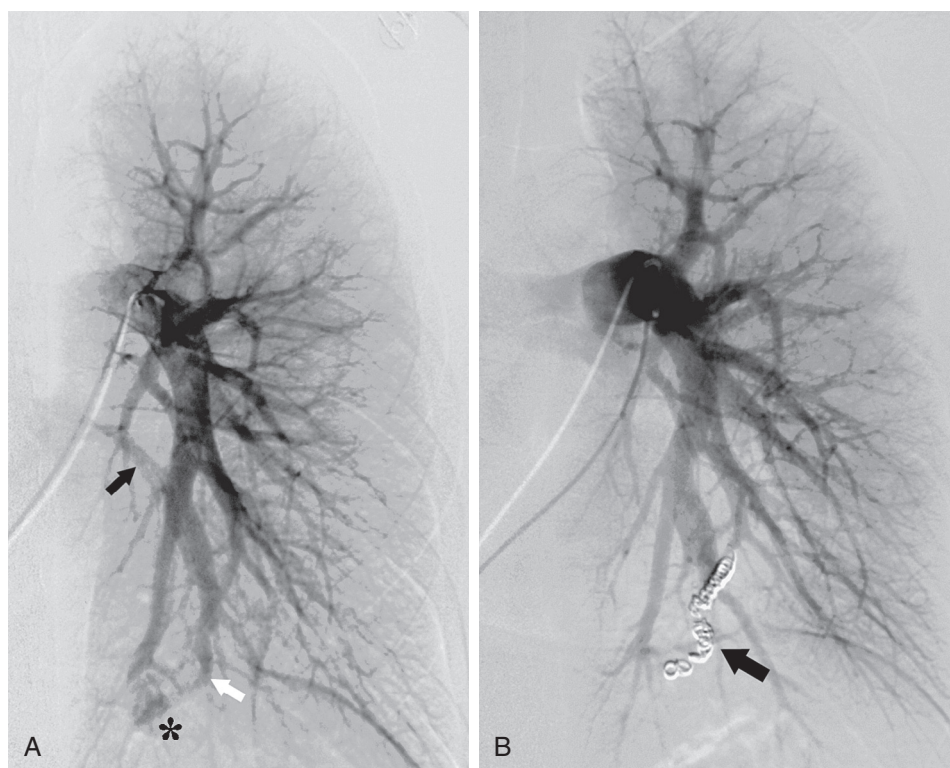


FIGURE 9-20 ■ Pulmonary arteriovenous malformation. Selective left pulmonary arteriography and coil embolization in a 14-year-old girl. **A**, Left pulmonary arteriogram shows a tangle of vessels (asterisk) at left lung base with arterial supply (white arrow) from a basal branch of left lower lobe artery and early pulmonary venous opacification (black arrow). **B**, After embolization of coils (arrow) by superselective catheterization, the malformation is occluded. (Courtesy Simon C. Kao, MD, Iowa City, IA.)

with suggestive radiographic findings should be evaluated for recurrent epistaxis, skin lesions, or hematuria (HHT), as well as a family history of similar complaints. HHT is a rare autosomal dominant abnormality that is associated with mucocutaneous and visceral telangiectasias. Between 7% and 15% of patients with HHT have pulmonary

arteriovenous malformations; when pulmonary arteriovenous malformations are present, patients have an increased likelihood for complications such as hemoptysis, polycythemia, epistaxis, cerebral bleeding, and brain abscesses.²⁶⁷ Contrast-enhanced transthoracic echocardiography has been helpful in assessing patients with

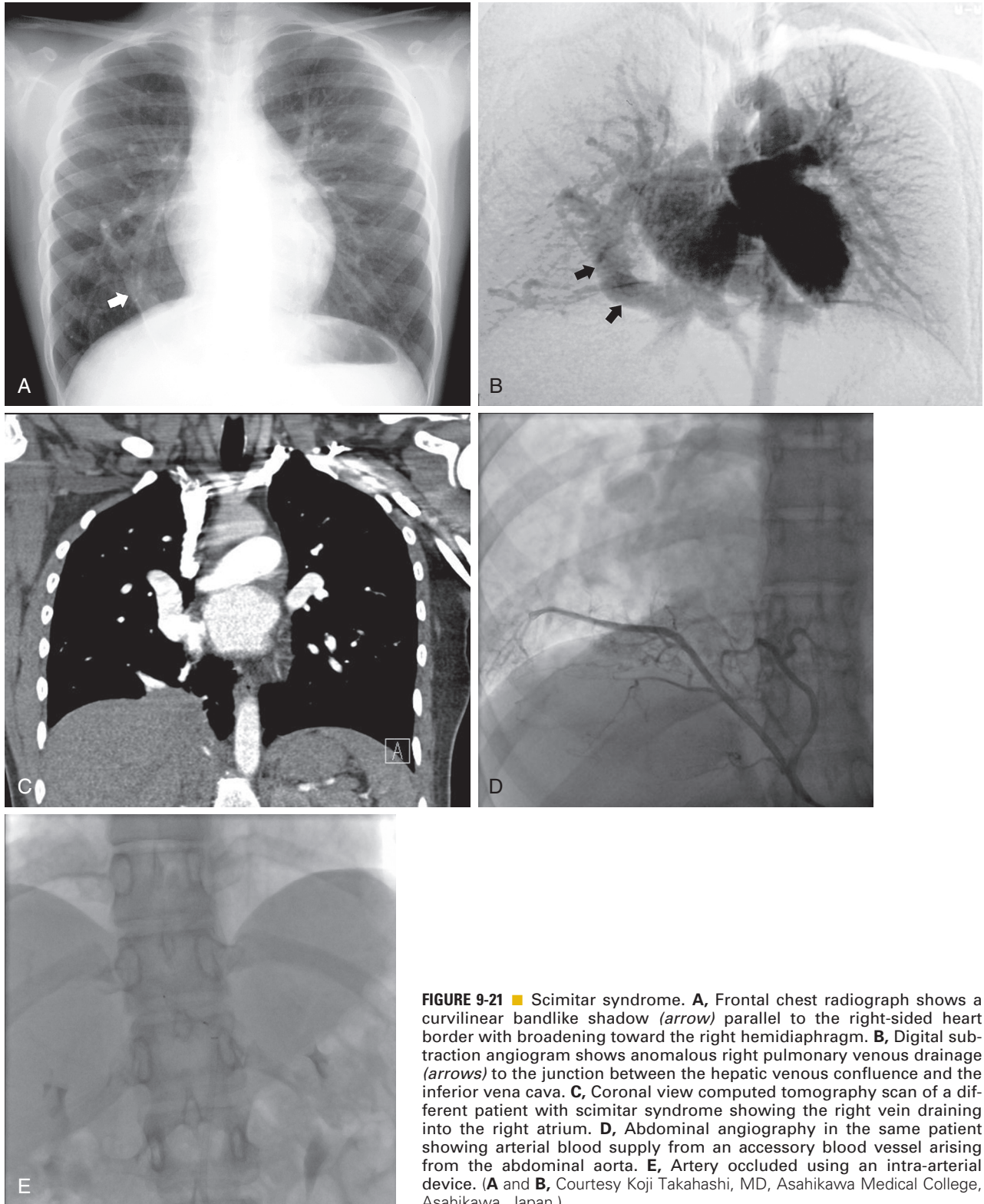


FIGURE 9-21 ■ Scimitar syndrome. **A**, Frontal chest radiograph shows a curvilinear bandlike shadow (*arrow*) parallel to the right-sided heart border with broadening toward the right hemidiaphragm. **B**, Digital subtraction angiogram shows anomalous right pulmonary venous drainage (*arrows*) to the junction between the hepatic venous confluence and the inferior vena cava. **C**, Coronal view computed tomography scan of a different patient with scimitar syndrome showing the right vein draining into the right atrium. **D**, Abdominal angiography in the same patient showing arterial blood supply from an accessory blood vessel arising from the abdominal aorta. **E**, Artery occluded using an intra-arterial device. (**A** and **B**, Courtesy Koji Takahashi, MD, Asahikawa Medical College, Asahikawa, Japan.)

pulmonary arteriovenous malformations, with a sensitivity of 94%.

If the patient has HHT or is symptomatic, if the lesion is large, or if the diagnosis is questionable, surgical resection may be necessary. In the case of HHT, one half of patients left untreated progress to brain abscess and stroke.^{268,269} If the lesion is resected, proximal vessel control is advisable. When telangiectasias are found, only symptomatic or enlarging lesions should be treated. When telangiectasias are present on the lung surface, it is unnecessary to resect them unless they are unusually large.

One other congenital anomaly of note is scimitar syndrome (hypogenetic lung syndrome)²⁷⁰ (Fig. 9-21). In this condition, the venous drainage from either part of the right lung or the entire right lung enters the inferior vena cava rather than the left atrium. Right lung arterial supply also may be anomalous with associated pulmonary sequestration or pulmonary hypertension. Left-to-right shunting may be so significant, akin to an atrial septal defect, that surgical repair may be necessary. Surgical options have recently been reviewed.²⁷¹

CONCLUSION

This chapter reviews the wide range of congenital lung diseases. Abnormalities may involve the tracheobronchial tree, lung parenchyma, or pulmonary vasculature. Defects may be so severe as to result in stillbirth or profound neonatal respiratory distress. Other manifestations assume a more insidious course. Knowledge of pulmonary embryology and historical contributions relating to these disorders allows a logical diagnostic and therapeutic approach in most cases. Advances in technology, neonatal surgery, and antenatal diagnosis and treatment have led to a markedly improved outlook for patients with congenital lung diseases.

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BENIGN LESIONS OF THE LUNG

Doraid Jarrar • Benjamin Wei • Ayesha S. Bryant • Robert J. Cerfolio

CHAPTER OUTLINE

DEFINITION AND INCIDENCE

EVALUATION FOR AN INDETERMINATE PULMONARY NODULE

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MUCOUS GLAND ADENOMA

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INTRAPULMONARY FIBROUS TUMOR

BENIGN ENDOBRONCHIAL FIBROUS HISTIOCYTOMA

GRANULAR CELL TUMOR

INFLAMMATORY PSEUDOTUMOR

PAPILLOMAS

NODULAR AMYLOID LESION

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MYOEPITHELIOMA

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ALVEOLAR ADENOMA

LEIOMYOMA

LYMPHANGIOLEIOMYOMATOSIS

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PRIMARY PULMONARY THYMOMA

CONCLUSION

DEFINITION AND INCIDENCE

Benign lesions of the lung are rare. A benign lung nodule is difficult to define and classify because some lesions that are called *benign* have malignant properties. However, the best definition of a benign lesion is one in the pulmonary parenchyma that does not metastasize and does not penetrate through surrounding tissue planes. When it is completely resected, a benign tumor should not recur.¹

Benign lung tumors can be classified pathologically, but a clinically useful classification would combine location (i.e., endobronchial or parenchymal) and information about whether the lesions are single or multiple. Benign lung tumors can also be classified by their presumed origin. Those classifications include unknown (hamartoma, clear cell, teratoma), epithelial (papilloma, polyps), mesodermal (fibroma, lipoma, leiomyoma, chondroma, granular cell tumor, sclerosing hemangioma), and other (myofibroblastic tumor, xanthoma, amyloid, mucosa-associated lymphoid tumor).

The controversy arises because some tumors are often labeled *benign*, such as pulmonary blastomas, but have the potential to exhibit malignant properties, and thus clear-cut boundaries between malignant and benign often are blurred. Benign tumors of the lung can arise from all of the various cell types that are present in the lung. [Box 10-1](#) lists the most common benign tumors based on their cells of origin.

Most times, benign nodules are resected because of the inability to differentiate them from a malignant process. For this reason, a benign lesion is identified after resection. The typical evaluation of a patient with an indeterminate pulmonary nodule is described next.

EVALUATION FOR AN INDETERMINATE PULMONARY NODULE

The single most important test for a patient who arrives at the office with an indeterminate pulmonary nodule is the review of old chest radiographs and computed tomographic (CT) scans. The radiograph should be interpreted in the context of the patient's medical history. Important factors include a history of a previous solid organ cancer and history of smoking. The physical examination is typically unremarkable, without any cervical lymphadenopathy. If the nodule is new or if the patient did not have a previous chest radiograph, chest computed tomography with contrast enhancement and possibly integrated positron emission tomography-computed tomography (PET/CT) are performed. If the nodule lacks calcification on the chest CT scan, it is indeterminate.^{2,3}

Positron emission tomography (PET) and integrated PET/CT scanning have recently become important adjuncts in the armamentarium of general thoracic surgeons. PET/CT has helped physicians investigate an

BOX 10-1 Common Benign Tumors of the Lung Based on Cells of Origin

TUMORS OF EPITHELIAL ORIGIN

- Mucous gland adenoma
- Clara cell adenoma
- Mucous cystadenoma
- Pleomorphic adenoma

TUMORS OF MESENCHYMAL ORIGIN

- Hamartoma
- Inflammatory pseudotumor
- Chondroma
- Fibroma
- Benign endobronchial fibrous histiocytoma
- Leiomyoma
- Lipoma
- Lymphatic lesions

TUMORS OF MISCELLANEOUS ORIGIN

- Nodular pulmonary amyloidosis
- Clear cell tumor (sugar tumor)
- Thymoma
- Granular cell tumor
- Teratoma
- Pulmonary paraganglioma

indeterminate pulmonary nodule that is larger than 8 mm (smaller nodules that are malignant can be missed by PET/CT). If the nodule has glucose avidity and a maximum standard unit value (maxSUV) of 2.5 or greater, it has a significant chance (>90% in our series) of being malignant.⁴ In a study by Bryant and Cerfolio⁵ of 585 patients, 496 patients had a malignant nodule, and their median maxSUV was 8.5. Eighty-nine patients had a benign nodule, and the median maxSUV was 4.9 ($P < 0.001$). They observed that if the maxSUV was between 0 and 2.5, the chance that the nodule was malignant was 24%; between 2.6 and 4.0, it was 80%; and for 4.1 or greater, it was 96%. False-negative results occurred from bronchoalveolar carcinoma in 11 patients, carcinoid in 4 patients, and renal cell in 2 patients. False-positives included fungal infections in 16 patients.⁵ Similarly, enlarged mediastinal lymph nodes with a maxSUV of greater than 2.5 are likely to be malignant; we have shown that a lymph node with a maxSUV of 5.3 or greater has a 92% chance of being malignant.⁶ Patients with lymphadenopathy on CT scans or uptake on PET/CT scans should have mediastinoscopy, endoscopic ultrasound fine-needle aspiration, or endoscopic bronchial ultrasound examination to obtain tissue diagnosis before a surgical resection. If the CT and PET scan results are equivocal or abnormal, resection is usually best in patients who are good candidates for surgery.

Needle biopsy, by either a transthoracic route or a transbronchial route, rarely changes the management of this type of nodule, especially if there is no lymphadenopathy. Definitive diagnosis is really achieved only with excisional biopsy, which can be performed by a video-assisted approach, an open technique, or by robotic assisted thoracoscopy, depending on many variables that

are discussed elsewhere in this text. Navigational bronchoscopy can be a helpful adjunct in the workup of these lesions, especially if the lesion is small and deep in the tissue. It allows the surgeon to biopsy the nodule (which may or may not change the need for resection) and to mark deeper lesions that are not palpable during minimally invasive surgery. In addition, biomarker panels may one day be helpful in determining whether solitary pulmonary nodules represent cancer, as opposed to a benign lesion.⁷

In this chapter, we discuss the most common benign tumors of the lung (adenomas and hamartomas constitute the largest group of benign lung tumors) and highlight the important clinical factors associated with each one. Each section is organized in the following fashion to help the reader: definition, incidence, special history or physical examination findings, unique radiologic characteristics, intraoperative tips for resection if indicated, pathologic characteristics, and special postoperative care or follow-up care, including the risk of recurrence. Box 10-2 lists the radiographic characteristics typical of benign lesions.

HAMARTOMA

Hamartomas are the most common benign lung lesions and account for more than 70% of all nonmalignant tumors of the lung.⁸ They are mesenchymal tumors with a peak incidence in the sixth decade of life, and approximately 90% are asymptomatic. Men are affected twice as often as women are. Ninety percent of these tumors appear as solitary peripheral nodules and account for approximately 4% of all solitary pulmonary nodules (Fig. 10-1). The 8% to 10% of hamartomas with presenting symptoms such as cough, hemoptysis, and recurrent pulmonary infections are usually endobronchial lesions. Resection of these lesions is usually needed, even when a definitive biopsy has been performed on them and they are proved to be benign because they cause local problems from airway obstruction. These problems include recurrent pneumonia, parapneumonic empyema, hemoptysis, and cough. Laser ablation can be used to help open the airway, but complete resection is preferred.

Cartilage is present in most lesions and is diagnostic of a hamartoma. There are usually nests of cartilage surrounded by cellular fibrotic tissue. Mature fat cells are a frequent component, and their presence on CT scan (low Hounsfield units) is strong evidence for the diagnosis of a hamartoma.⁹ Rarely, bone, vessels, bronchioles, and smooth muscle are found. On gross examination, the bosselated appearance is typical for a hamartoma. The usual size is 1 to 3 cm, with the lesion being round and firm. They are easily shelled out from the surrounding lung tissue (Fig. 10-2). As with any indeterminate pulmonary nodule, lung-preserving techniques are best if possible.

On radiographic examination (Fig. 10-3), hamartomas are peripheral lesions that are most often located in the lower lung fields and are well circumscribed. The majority are less than 4 cm in diameter, and calcifications can be appreciated on radiographs in 10% to 30% of cases

BOX 10-2 Radiographic Characteristics of Benign Nodules

- Nodular lesions with “tails” toward the hilum include rounded atelectasis (usually has thickening of the associated pleura as well), arteriovenous malformations, and occasional bronchogenic cysts.
- Lesions that are connected to blood vessels include nodular pulmonary infarcts, occasional solitary metastatic lesions, arteriovenous malformations, and bronchopulmonary sequestrations.
- Multiple peripheral triangular or rounded lesions with cavitation and with pulmonary artery branches leading up to them suggest septic embolization.
- In cavitating nodules, wall thickness provides diagnostic information. Thin-walled (<1 mm) cavities are uniformly benign, and 90% of cavitated nodules with wall thickness of 1 to 4 mm are benign. In contrast, cavitated nodules with a wall thickness greater than 16 mm are nearly always malignant.
- Nodules surrounded by a halo may be noted in the setting of angioinvasive aspergillosis, zygomycosis (mucormycosis), lymphoma, bronchioloalveolar carcinoma, coccidioidomycosis, and (rarely) bacterial infections.
- Nodules composed predominantly of ground-glass opacification (nonsolid nodules) can be seen in bronchioloalveolar carcinoma.
- Eighty percent of nodules smaller than 2 cm are benign; 90% of those larger than 3 cm are malignant, yet 40% of malignant nodules are smaller than 2 cm.
- Nodules surrounded by small satellite lesions are benign 90% of the time.
- Nodules with a doubling time of less than 30 days or greater than 480 days are usually benign. Bronchioloalveolar carcinoma is an exception to this rule and may have a radiographic doubling time of more than 700 days. Epstein-Barr virus-associated lymphoma or lung cancer in HIV-positive patients can have fast doubling times.

Data from Henschke CI, Yankelevitz DF, Mirtcheva R, et al: CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 178:1053–1057, 2002; and Tsubamoto M, Kuriyama K, Kido S, et al: Detection of lung cancer on chest radiographs: analysis on the basis of size and extent of ground-glass opacity at thin-section CT. Radiology 224:139–144, 2002.

(Fig. 10-4). Calcifications are described as being “popcorn-like” or “diffuse.” Hamartomas display a slow growth rate (≈ 3 mm/yr) and are rarely multiple. Although it is identifiable in only half of the cases, fat density as identified with CT scan (low Hounsfield units) is strongly suggestive of a benign hamartoma.^{10,11} Endobronchial lesions are not identifiable with radiographic examination unless distal parenchymal changes have occurred (e.g., pneumonia or atelectasis).

Although percutaneous transthoracic needle aspiration yields a definitive diagnosis in up to 85% of cases, only a positive and specific result negates the need for excisional biopsy. Depending on the location, lesions might be amenable to resection by video-assisted thoracoscopic surgery (VATS). For hilar or central tumors that would necessitate a greater resection, such as pneumonectomy, endobronchial ultrasound guided

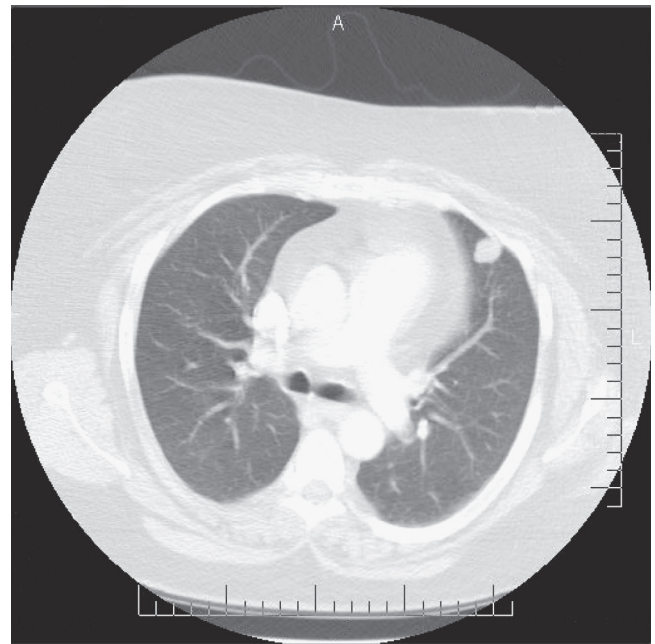


FIGURE 10-1 ■ CT scan of the chest showing a chondroid hamartoma measuring 1.4×1.7 cm in the inferior lingula of the left lung. The patient was a 49-year-old woman with a normal PET scan. Because her clinical presentation was suggestive of malignant disease, a left upper lobe wedge resection was performed. Ninety percent of hamartomas are located in the periphery, and they account for about 4% of all solitary lung nodules.

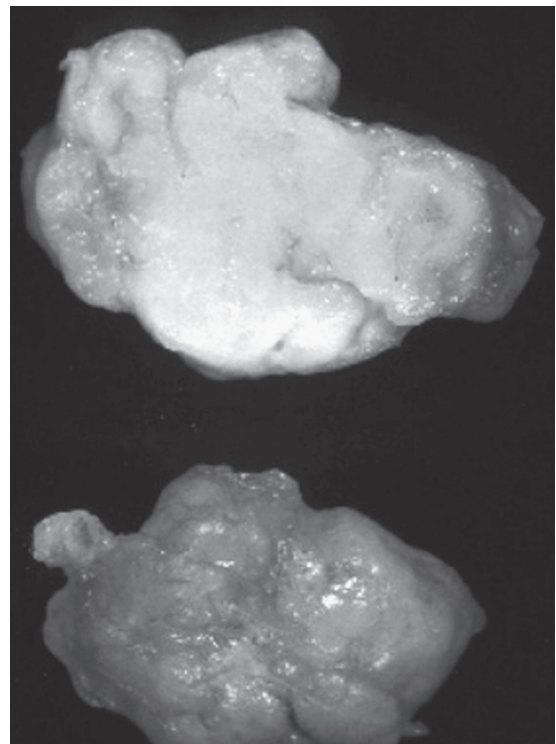


FIGURE 10-2 ■ Cut surface of a resected hamartoma.

fine-needle aspiration may be helpful in establishing a benign diagnosis of hamartoma and avoiding resection. Unlike cartilaginous tissue in normal bronchi, the cartilage in hamartomas tends to show irregular size, shape, and arrangement of chondrocytes and prominent empty

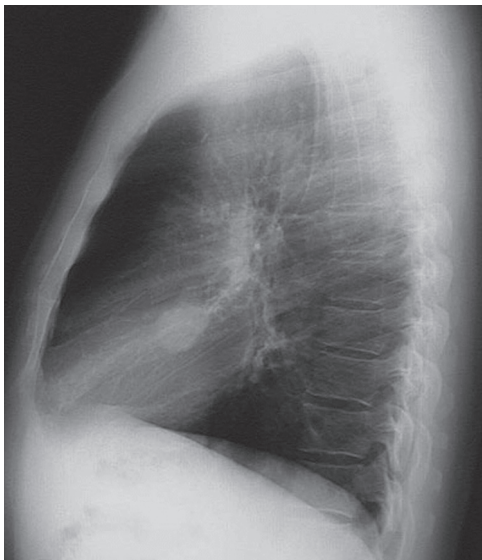


FIGURE 10-3 ■ Lateral chest radiograph showing a round lesion consistent with a hamartoma.

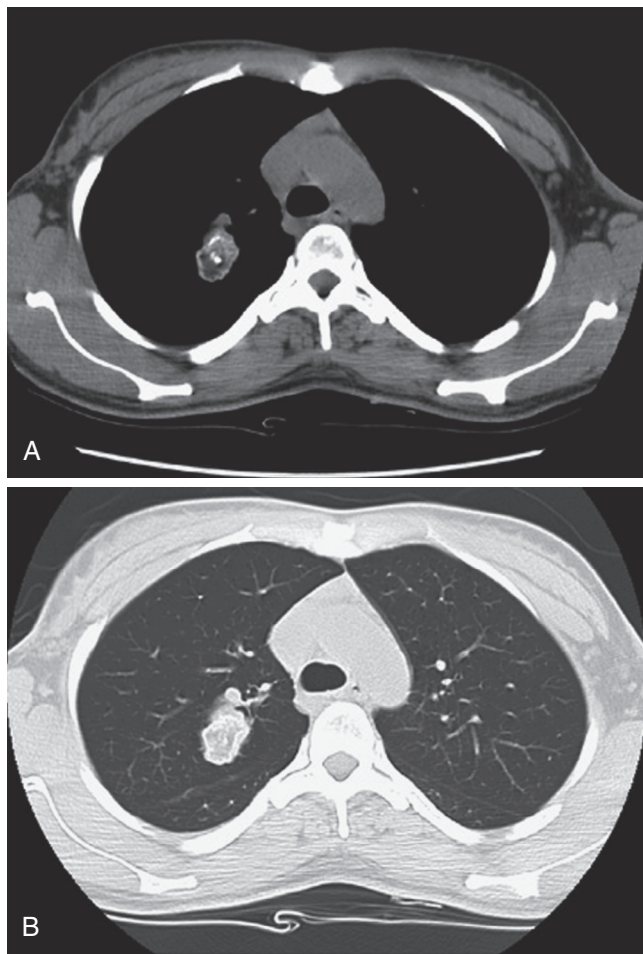


FIGURE 10-4 ■ **A**, Right lung hamartoma. The lesion was resected, and a benign process was confirmed. Lesions are most often located in the lower lung fields and are well circumscribed. **B**, The majority are less than 4 cm in diameter, and calcifications can be appreciated on radiographs in 10% to 30% of cases.

lacunae.¹² Given the potential for malignant transformation, continued observation of these lesions is warranted. Endobronchial lesions obstructing the airway may be amenable to bronchoscopic resection with either a snare or neodymium-yttrium-aluminum garnet laser resection, although long-term follow-up data on recurrence risk are not available.¹³ Historically, most of these patients have undergone sleeve resection.

Carney triad is found infrequently and consists of a gastric epithelioid leiomyosarcoma, a functioning extra-adrenal paraganglioma, and a pulmonary hamartoma.^{11,14} Most commonly, the gastric lesion is the first lesion identified, followed by the extra-adrenal paraganglioma.

Although hamartomas are benign per se, several cases of malignant transformation arising at the resection site have been reported.¹⁴ However, it appears that these synchronous or metachronous carcinomas are coincidental because the frequency is less than 7%. The etiology of these malignant neoplasms and their relationship to the hamartoma remain unknown.

MUCOUS GLAND ADENOMA

Mucous gland adenoma is a rare, benign tumor arising from the mucous glands of the bronchus; it is also known as *bronchial cystadenoma* and *mucous cell adenoma*. The exact incidence of these tumors is unknown, although several small series of case reports have been published. To be classified as a mucous gland adenoma, a tumor must contain cystic glands that are superficial to the cartilaginous plate, be in the bronchus, and contain features of normal bronchial seromucous glands. On histologic examination, numerous small mucus-filled cysts lined by well-differentiated epithelium are observed (Fig. 10-5).¹⁰

These benign lesions are typically exophytic in nature and cause bronchial obstruction; therefore, they usually appear because of hemoptysis, recurrent pneumonia, and persistent cough. Because of their nonspecific symptomatology, mucous gland adenomas may go undiagnosed for a prolonged period of time.¹⁵ The lesion itself does not have distinguishing radiographic features, but the chest radiograph may show obstructive pneumonitis. CT scan may demonstrate an intraluminal mass, while bronchoscopy reveals a firm, smooth, shiny, and well-defined mass that may be pedunculated.¹⁶ These noninvasive tumors are evenly distributed between the left and right lungs, with the major bronchi of the lower lobes being affected more often. The lesions are soft, spherical, and polypoid with an average diameter of 18 mm; however, lesions greater than 6 cm in size have been reported.^{11,16} Although the lesions rarely have a stalk, stalks can be completely removed endoscopically by curettage, cryotherapy, or laser ablation. Surgical resection is indicated only if the distal lung tissue is destroyed or chronically infected.

INFECTIOUS GRANULOMATOSIS

Infectious granulomas cause approximately 80% of benign nodules.^{14,17} Endemic fungi (e.g., histoplasmosis,

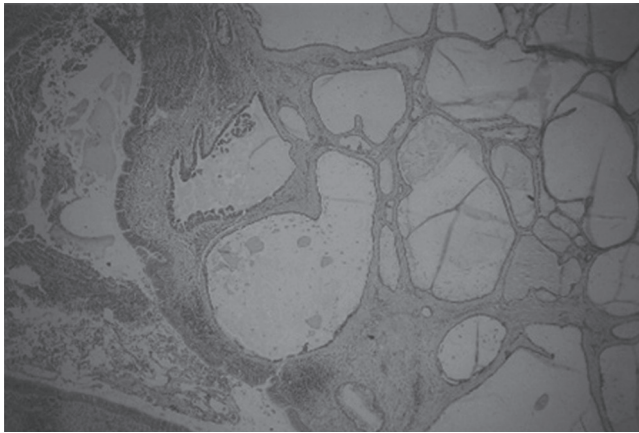


FIGURE 10-5 ■ Photomicrograph of a mucous gland adenoma.

coccidioidomycosis) and mycobacteria (either tuberculous or nontuberculous mycobacterial disease) are the most frequently recognized causes of infectious granulomas presenting as a solitary peripheral nodule. Especially in regions where granulomatous fungal disease is endemic (e.g., coccidioidomycosis in the Southwest and histoplasmosis in the Mississippi, Ohio, and lower Missouri River Valleys), the chances of an FDG-avid pulmonary nodule being lung cancer may be diminished. Working in an area where histoplasmosis is prevalent, Deppen and colleagues¹⁸ found that the specificity of PET scan for lung cancer was only 40% for lesions with a maxSUV greater than 2.5, compared with a recent meta-analysis that estimated it at 83%.¹⁸ When nontuberculous mycobacterial disease manifests as a solitary peripheral nodule, the cause of the nodule is typically unrecognized until the lesion is resected as a presumed primary lung cancer. In patients with acquired immunodeficiency syndrome, *Pneumocystis jiroveci* (previously called *Pneumocystis carinii*) infection can manifest as a solitary peripheral nodule and may cavitate.

INTRAPULMONARY FIBROUS TUMOR

Intrapulmonary fibrous tumors are contiguous with the visceral pleura and are identical to localized fibrous tumors of the pleura. Terms such as intraparenchymal localized fibrous mesotheliomas, intrapulmonary fibrous mesotheliomas, localized fibrous tumor of the pleura, and inverted fibrous tumor of the pleura have been used and are essentially interchangeable. The visceral pleura is the most common location of these tumors, but they also have been found in the retroperitoneum, mediastinum, and parietal surfaces of the intra-abdominal viscera. The tumors are round to oval and contain a smooth cover of visceral pleura (Fig. 10-6). Most lesions are less than 10 cm in diameter, and histologic examinations show spindle cells with oval nuclei, diffuse fine chromatin, and positive staining for vimentin and the surface receptor CD34.¹⁹ In most cases, the tissue of origin is the mesenchymal layer of the visceral pleura. No distinctive radiographic features are known for these lesions, although the radiologist often includes a malignant mesothelioma in

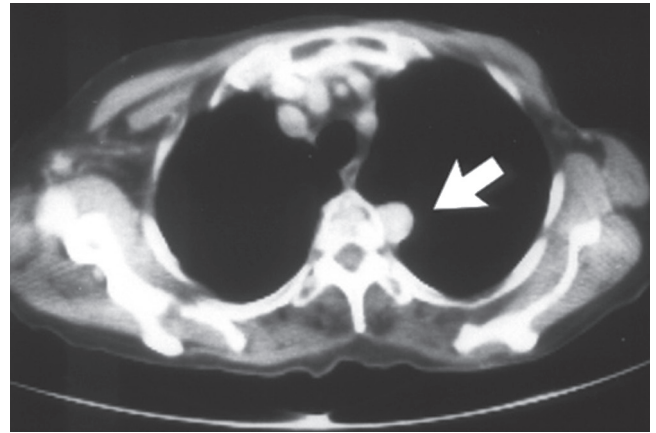


FIGURE 10-6 ■ The arrow indicates an intrapulmonary fibrous tumor. Lesions are contiguous with the visceral pleura. Tumors are round to oval and are usually less than 10 cm in diameter.

the differential diagnosis. The obtuse angle that these tumors make with the chest wall strongly suggests that the tumor is arising from the pleura and not from the lung. Unlike diffuse mesotheliomas, intrapulmonary fibrous tumors are not related to asbestos exposure. Surgical resection is usually performed by VATS. Solitary fibrous tumors, whether intrapulmonary, polypoid, or sessile, are usually benign, but up to 10% are malignant. The morphologic appearance of the tumor cannot be used to differentiate between benign and malignant tumors. The recurrence risk for patients with completely resected benign solitary fibrous tumors is very low, but not zero; however, patients with a malignant solitary fibrous tumor have a significantly higher risk of recurrence, and a 5-year survival that approaches 50%, as opposed to 90% in patients with benign solitary fibrous tumors.²⁰

BENIGN ENDOBRONCHIAL FIBROUS HISTIOCYTOMA

A fibrous histiocytoma is a benign lung tumor that is composed of collagen and inflammatory and mesenchymal cells. These lesions are rare endobronchial lesions that occur most often in either children or young adults. Because they are so rare, their exact incidence is unknown. No specific radiographic findings distinguish these lesions from others. Depending on the location or the extent of bronchial involvement, surgical therapy might entail a lobectomy or sleeve lobectomy. Bueno and coworkers²¹ described bronchoplastic resections of five endobronchial fibrous histiocytomas.

GRANULAR CELL TUMOR

Granular cell tumors, also called *granular cell myoblastomas*, are another type of rare, benign tumor. These tumors initially were thought to derive from skeletal muscle; however, evidence now suggests that these lesions originate from Schwann cells, as Deavers and associates²² described in 20 cases. In half of the patients, the lesion

was an incidental finding. In the other half, symptoms were caused by obstruction, including postobstructive pneumonia and atelectasis. The lesions were solitary in 75% of the cases. Chest radiographs showed lobar infiltrates, coin lesions, and atelectasis. Tumors usually are located in a large bronchus and can protrude into the bronchial lumen, but they also can be found in the pulmonary parenchyma. Tumors usually are circumscribed but not encapsulated and range in size from 0.3 to 5.0 cm. Nearly all granular cell tumors stain positive for S-100; unlike melanoma, which also stains positive for S-100, granular cell tumors are negative for HMB-45.²³ Complete resection is curative, although recurrences have been described.²² Epstein and Mohsenifar²⁴ reported the use of neodymium-yttrium-aluminum garnet laser to treat obstructing lesions.

INFLAMMATORY PSEUDOTUMOR

Inflammatory pseudotumors are usually asymptomatic solitary nodules that are found on routine chest radiography or CT scan.²⁵ They can be large or be primarily of the airway (Fig. 10-7). Because these tumors go by many other names, such as plasma cell granuloma–histiocytoma complex, plasma cell granuloma, histiocytoma, xanthofibroma, and xanthoma, there is often confusion. Inflammatory pseudotumors usually are well-circumscribed, nonencapsulated, firm, white or yellow masses. They can occur at any age and they are found equally in men and women. Two major groups have been identified: fibrohistiocytic and plasma cell granulomas. In both groups, the histologic examinations reveal a mixture of inflammatory cells, including plasma cells, lymphocytes, and macrophages. Some reports have shown that there may be two types of inflammatory pseudotumors.²⁵ Fibrohistiocytic inflammatory pseudotumors are

invasive, large, and more difficult to resect as opposed to plasma cell granuloma inflammatory pseudotumors, which are characterized by a small, easily wedged mass without evidence of local tissue invasion. The mechanism for these two types is unclear, although it appears microscopically to depend on the degree of inflammatory cells present. A clinicopathologic series from the Massachusetts General Hospital provided evidence that organizing pneumonia may be the nidus for the formation of inflammatory pseudotumors. *Cryptococcus*, *Histoplasma*, and *Actinomyces* spp. infections have been associated with the development of inflammatory pseudotumors.^{26,27} Excision of these lesions is usually both diagnostic and curative. The 10-year survival rate of patients following resection for inflammatory pseudotumors approaches 90%.²⁸ However, the clinical behavior of inflammatory pseudotumors is variable; they can exhibit aggressive local growth and the capacity to metastasize.^{29,30} In patients with multiple lesions not amenable to excision, radiation therapy and corticosteroid therapy are other options.

Although primary lung tumors are infrequent in childhood, plasma cell granuloma is the most common lung lesion in the preadolescent age category. Serial chest radiographs usually show the nodule to be unchanged in size, and it may even shrink without treatment in some patients. Slow growth occurs in less than 10% of cases.³¹ On CT scans, these lesions appear as a well-margined, lobulated mass with some heterogeneous attenuation.

PAPILLOMAS

Papillomas are classified as squamous, glandular, or mixed, and typically present as endobronchial lesions. Squamous papilloma is a benign epithelial neoplasm formed by squamous epithelium. Papillomas of the endobronchial tree have been classified into two main groups: multiple squamous papillomas and solitary papillomas. Drennan and coworkers³² also distinguished a third class, inflammatory polyps.

Multiple squamous papillomas are usually seen in children with laryngeal papillomatosis, usually caused by human papillomavirus. Children can become infected during vaginal childbirth because their oropharynxes and respiratory systems are exposed during the delivery. Serotypes 16 and 18 can act as promoters in carcinogenesis. On gross examination, the papillomas can be exophytic and may have a component outside the bronchial wall and endophytic and obstruct part of the airway. There may be distal bronchiectasis with atelectasis or consolidation of the surrounding lung. Papillomas have a connective tissue stroma that often is heavily infiltrated with lymphocytes and covered completely with cuboidal or squamous epithelium.

Solitary squamous papillomas are rare and affect middle-aged men who are smokers. Productive cough, hemoptysis, wheezing, and dyspnea are common complaints resulting from obstruction by the lesion. On histologic examination, they have a thin central fibrovascular core that is covered by stratified squamous epithelium, and they form multiple papillary fronds. Chest

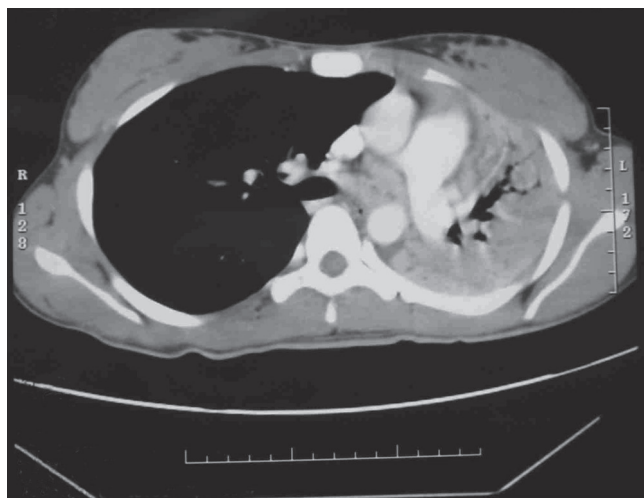


FIGURE 10-7 ■ Inflammatory pseudotumor of the left main-stem bronchus involving the carina. The patient was treated successfully in the past with steroids; however, she has recently become afflicted with multiple pneumonias, and radiographic studies suggest that she has obstruction of the main-stem bronchus. The patient underwent left main-stem bronchial sleeve resection.

radiography may show a lesion or atelectasis. The papillomas usually are located in segmental or more proximal bronchi. The human papillomavirus is the most common cause of these lesions. Squamous papilloma can be associated with dysplasia, carcinoma in situ, or foci of invasive squamous cell carcinoma. Close surveillance and repeated biopsies are sometimes necessary in observing these patients.

Glandular and mixed papillomas are found equally in men and women in an older population than patients with solitary squamous papillomas. These papillomas are not linked with smoking.

Fibrous polyps are another type of endobronchial lesion and can be found solitary or in multiple locations. These polyps usually arise from the bronchial mucosa and have a fibrous stalk. They are covered by ciliated columnar epithelium. The stalk usually is composed of loose connective tissue with an infiltrate of plasma cells, lymphocytes, and eosinophils. These polyps are always benign and may be secondary to chronic inflammatory processes.

Photodynamic therapy and laser or endoscopic removal are some of the options available to treat these lesions. Bronchotomy or sleeve resection usually is not needed.

NODULAR AMYLOID LESION

Nodular amyloid lesions represent a focal collection of amyloid deposition in the lung; they are most frequently found in the lower lobes. They are sometimes referred to as *amyloidomas*. They can occur as solitary or multiple nodules. The following three types have been described: tracheobronchial, nodular pulmonary, and diffuse pulmonary. Although nodular amyloid lesions are not associated with primary systemic amyloidosis, multiple myeloma should be ruled out. Patients are usually asymptomatic, and lesions are discovered incidentally on chest radiography. Patients should be followed up long term because of the association with macroglobulinemia and malignant lymphoma. Surgical resection is usually curative.

CHONDROMA

Chondromas are defined as benign cartilaginous tissue that can occur in the lung parenchyma or in the cartilaginous airways. Endobronchial lesions can cause obstructive symptoms, whereas parenchymal tumors are asymptomatic. Histologic examination of chondromas shows benign cartilaginous tissue. Some patients with this unusual lesion may have Carney triad, which is composed of pulmonary chondroma, multiple gastric smooth muscle tumors, and extra-adrenal paragangliomas.¹¹ The lesions may contain metaplastic bone, mature cartilage, and myxoid stroma. Single lesions are most commonly resected for diagnosis and have an excellent prognosis. When patients have multiple lesions, a tissue sample, often obtained by a minimally invasive approach with a needle biopsy, usually is sufficient to make the diagnosis.

MYOEPITHELIOMA

Myoepitheliomas are rare, benign tumors arising from myoepithelial cells that lie between the epithelial cells of a gland and the basement membrane. Although these lesions are more commonly found in salivary glands and the breast, rare cases have been reported in the lung parenchyma. Strickler and associates³³ described two patients in whom these lesions were found. Both patients had a mass on the chest radiograph. Immunostaining for S-100 was positive, which is consistent with the diagnosis of a myoepithelioma. Surgery appears to be curative. Because these lesions are so rare, pathognomonic radiographic and clinical signs have not been described. Rare cases of the malignant version of this tumor—primary myoepithelial carcinoma of the lung—have also been reported.³⁴

MUCINOUS CYSTADENOMA

Mucinous cystadenoma is a unilocular cystic lesion whose fibrous wall is lined by well-differentiated, benign columnar mucinous epithelium.³⁵ These lesions occur usually in the fifth and sixth decades of life in patients who smoke; however, the exact incidence is unknown. Most patients with this tumor are asymptomatic, and it represents an incidental finding on chest radiography. The lesions usually are located toward the periphery. Once the tumor is excised, the lesion appears as a unilocular cyst filled with gelatinous material. Sometimes the mucin extravasates into the surrounding lung parenchyma. Because these cysts may harbor adenocarcinoma, they should be completely excised. On microscopic examination, these lesions may look similar to a bronchogenic cyst and what was formerly known as *bronchioloalveolar carcinoma*.

ALVEOLAR ADENOMA

Alveolar adenomas are rare tumors characterized by the proliferation of cuboidal alveolar epithelial cells surrounded by a myxoid and collagenous interstitium.³⁶ These lesions are slow growing, well demarcated, and multicystic, and they can resemble normal lung on non-surgical biopsy specimens.³⁷ Yousem and Hochholzer³⁸ reported one of the largest series with six patients, most of them women. Other smaller reports also have been published.⁴ Lesions usually were identified on routine chest radiographs as an indeterminate nodule in the middle lung field. Excision appears to be curative.

LEIOMYOMA

Leiomyomas are benign lesions of the lung that can occur in the trachea, bronchus, pleura, or pulmonary parenchyma itself. Leiomyoma accounts for approximately 2% of all benign lung lesions. Vera-Roman and coworkers³⁹ reviewed the literature and found a female-to-male ratio of 1.5:1 (Fig. 10-8). There are no discrete

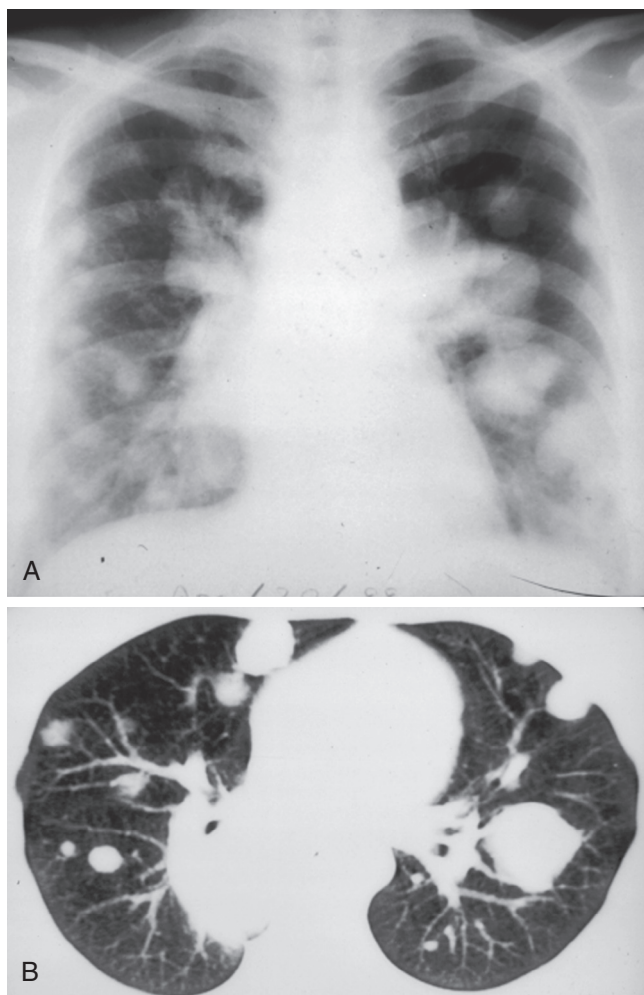


FIGURE 10-8 ■ Benign metastasizing leiomyoma. These lesions occur in young women and are associated with leiomyomas of the uterus. **A**, Anteroposterior chest radiograph demonstrating multiple leiomyomas. **B**, The corresponding chest CT scan.

findings on physical examination. Some patients have hemoptysis if an endobronchial component is present; in others, the tumor is an incidental finding on chest radiography. It appears that the distribution between tracheobronchial and parenchymal location is equal. On histologic examination, smooth muscle differentiation is found. Immunohistochemistry can confirm the mesenchymal origin of the tumor, which stains positive for desmin, muscle-specific actin, and vimentin. Some of these lesions stain positively for estrogen and progesterone receptors and can depend on a certain hormonal milieu, which explains why some of these lesions occasionally disappear during pregnancy, the postpartum period, and menopause.⁴⁰ Surgical treatment consists of excision and is the therapy of choice. Endobronchial lesions can occasionally be treated with laser ablation. Otherwise, sleeve bronchoplasty is needed. Benign metastasizing leiomyomas occur in young women and are associated with leiomyomas of the uterus.⁴¹ Treatment for this condition is not standardized, although certain concepts exist. Performing hysterectomy can remove the

source of the metastases. Hormonal manipulation with either pharmacologic means or bilateral oophorectomy, by decreasing levels of estrogen and progesterone, can lead to regression or stabilization of tumor growth. Surgery may be indicated if the lesions are growing in size in spite of therapy, or if diagnostic uncertainty exists.⁴² Although labeled a benign condition, these lesions can metastasize and cause death.

LYMPHANGIOLEIOMYOMATOSIS

Lymphangioleiomyomatosis (LAM) is a rare disease primarily found in women of childbearing age; it was first described in the medical literature by von Stossel in 1937.⁴³ It can be either sporadic or associated with tuberous sclerosis. LAM causes the progressive decline of pulmonary function through cystic degeneration of the parenchyma, and can lead to recurrent chylous pleural effusions and spontaneous pneumothoraces. Morphologically, LAM is characterized by progressive proliferation of spindle cells, resembling immature smooth muscle in the lung parenchyma and along lymphatic vessels in the chest and abdomen. The proliferation of spindle cells along the bronchioles leads to air trapping and eventually to the development of thin-walled cysts, which cause pneumothorax when they rupture. The proliferation of spindle cells impairs lymphatic drainage leading to chylous pleural effusions. Main symptoms stem from either a chylous pleural effusion (up to 80%) or a pneumothorax (30% to 50%). In both cases, dyspnea is the lead symptom.⁴⁴

Radiographic presentation of lymphangioleiomyomatosis includes reticular, reticulonodular, miliary, and honeycomb patterns on plain radiography. The CT scan usually shows multiple thin-walled lung cysts within normal lung parenchyma. The usual diameter of these cysts is between 0.2 and 5 cm. The disease pattern does not spare any lung zones and is distributed diffusely throughout the lungs. Hilar and mediastinal adenopathy are not uncommon. Diagnostic workup includes plain radiography, chest CT scan, and lung biopsy. Biopsy specimens can be obtained by either thoracoscopy or transbronchial biopsy.

The role of the thoracic surgeon for patients with LAM, besides to obtain a diagnostic biopsy, typically revolves around the management of chylothorax and pneumothorax and in some cases lung transplantation. Lung transplantation is the established option for LAM patients who develop end-stage lung failure. Fortunately, research into the mechanism behind LAM has recently led to some therapeutic insights. The smooth muscle cells in patients with LAM possess mutations in the tuberous sclerosis complex gene that result in constitutive activation of the mammalian target of rapamycin (mTOR) signaling pathway. Sirolimus, an inhibitor of the mTOR pathway, has been shown to stabilize the progressive decline in FEV1 typically experienced by patients with LAM.⁴⁵ LAM cells are also known to express the growth factors VEGF-C and VEGF-D, although therapies targeting this cellular growth pathway do not currently exist. Historically, anti-estrogen therapy with either

medications such as tamoxifen or bilateral oophorectomy was used for LAM, but data supporting the efficacy of this treatment strategy are lacking.

CLEAR CELL TUMOR (SUGAR TUMOR)

A clear cell tumor is a benign lesion of the lung of unknown tissue origin. Recent evidence suggests that it originates from either Clara cells (nonciliated bronchiolar epithelium) or epithelial serous cells. Detailed examination of these tumors showed some neuroendocrine differentiation and positive staining for human melanin black or melanosome-associated protein and S-100. On radiographic examination, the lesions are often peripheral and range in size from 1.5 to 3 cm.^{46,47} Excision is curative. The differential diagnosis includes clear cell, carcinoid, and renal cell carcinoma.

PRIMARY PULMONARY THYMOMA

A primary pulmonary thymoma is a thymoma that is present in the lung in a patient with a normal mediastinal thymus gland. Pulmonary thymomas are rare, and their exact incidence is unknown; they can occur peripherally or centrally. By definition, the tumor must be contained within the visceral pleura because ectopic mediastinal thymic tissue can be found in the aortopulmonary window and in the aortocaval groove. No distinctive radiologic features are known. Studies have used immunohistochemistry to confirm the diagnosis. Thymic T lymphocytes must be differentiated from lymphoepithelial-like carcinoma of the lung and from primary lymphomas. Surgical resection usually is curative. In rare cases, when the tumor is extensive and complete resection is difficult, neoadjuvant therapy with radiation has been described (Fig. 10-9).⁴⁸

CONCLUSION

Benign lesions of the lung are rare and often are diagnosed only after complete surgical resection. If a nodule remains indeterminate after a thorough evaluation as described in the preceding sections, resection is best if the patient's risk is acceptable. If surgery is not chosen, careful follow-up is needed to ensure that a malignant neoplasm is not missed. The solitary pulmonary nodule is a common radiologic finding that can require an extensive evaluation to establish a benign or malignant diagnosis. Morphologic evaluation of the size, margins, and contour with conventional imaging techniques alone often is not satisfactory. PET/CT scan has augmented the noninvasive armamentarium available to the general thoracic surgeon; however, careful interpretation of study results is needed. No test supplants tissue biopsy or, in some cases, complete excision. A normal finding on needle biopsy does not exclude a malignant process. The advent of minimally invasive techniques, such as VATS and robotics, may decrease the threshold to intervene on patients with lesions of uncertain significance due to the

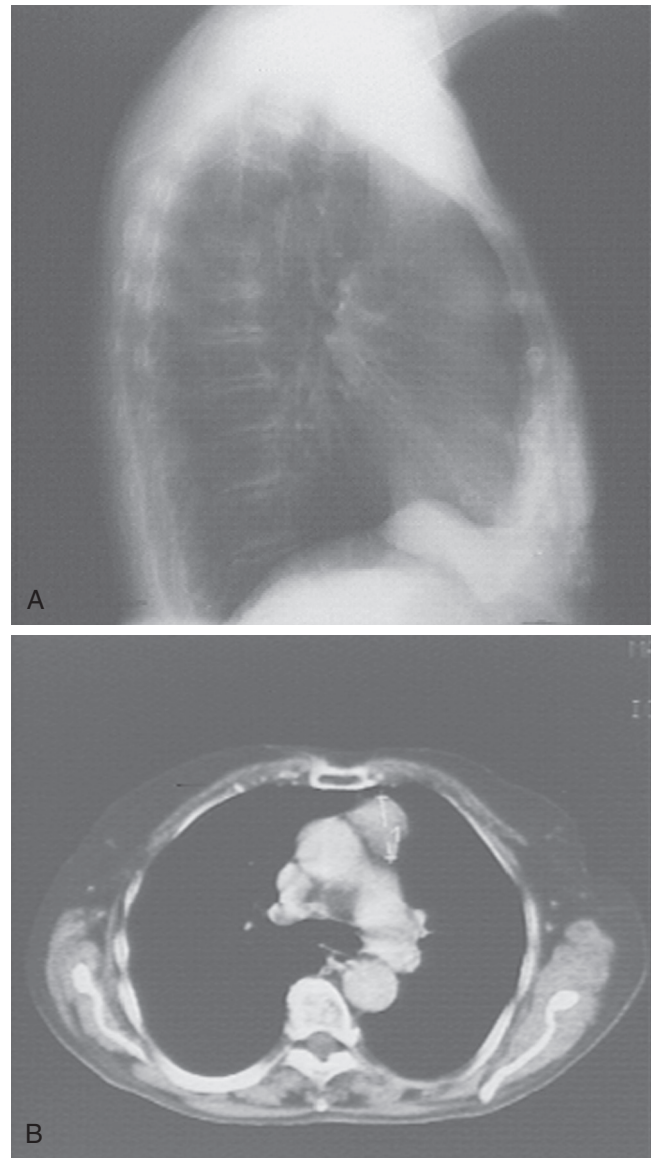


FIGURE 10-9 ■ Primary pulmonary thymoma. In rare cases, when the tumor is extensive, radiation therapy may be a good alternative. **A**, Lateral chest radiograph of a pulmonary thymoma. **B**, The corresponding CT scan image.

decreased morbidity of these procedures compared to lung resection via thoracotomy. Even if the nodule is benign, excisional resection offers peace of mind to the patient and obviates the need for repeated, expensive, time-consuming radiologic tests. For patients with symptoms related to airway obstruction or involvement such as recurrent pneumonia, hemoptysis, and atelectasis, the decision to intervene is more obvious. Selected patients are candidates for endobronchial intervention, whereas others may be better served with parenchyma-sparing resection, such as sleeve lobectomy. Although they are rare, the general thoracic surgeon should be familiar with the different types of benign lesions to counsel his or her patients and to provide a differential diagnosis. The surgeon must be able to interpret the radiographs and also the disease, which often are equivocal in these lesions.

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INTERSTITIAL LUNG DISEASES

Subroto Paul • Yolonda L. Colson

CHAPTER OUTLINE

GRANULOMATOUS PATTERNS OF INTERSTITIAL LUNG DISEASE

Foreign Bodies and Inorganic Dust
Hypersensitivity Pneumonitis
Infections
Sarcoidosis
Granulomatous Vasculitides: Granulomatosis with Polyangiitis and Churg-Strauss Syndrome
Eosinophilic Pneumonias
Pulmonary Langerhans Cell Histiocytosis

ALVEOLITIC PATTERNS OF INTERSTITIAL LUNG DISEASE

Drug-Associated Injury
Goodpasture Syndrome
Idiopathic Interstitial Pneumonia
Familial Forms of Idiopathic Interstitial Pneumonia

Idiopathic Pulmonary Fibrosis
Desquamative Interstitial Pneumonia
Idiopathic Nonspecific Interstitial Pneumonia
Acute Interstitial Pneumonitis
Respiratory Bronchiolitis–Associated Interstitial Lung Disease
Cryptogenic Organizing Pneumonia
Lymphocytic Interstitial Pneumonia
Idiopathic Pleuroparenchymal Fibroelastosis
Unclassifiable Idiopathic Interstitial Pneumonias
Interstitial Lung Disease Associated with Connective Tissue Diseases
Diffuse Alveolar Hemorrhage Syndrome
Lymphangioleiomyomatosis

PATIENT EVALUATION

TREATMENT

Interstitial lung disease (ILD) is a group of more than 200 clinical entities that manifest with chronic, progressive, diffuse inflammation of the pulmonary interstitium. This inflammatory process can result from a primary pulmonary process, or it can be the result of a systemic illness such as a connective tissue disease. ILD does not include inflammatory responses secondary to known malignant or infectious etiologies, and for the purposes of this chapter, it will not include adult respiratory distress syndrome. However, these entities can demonstrate highly similar clinical and radiographic findings, and they are certainly included in the clinical differential diagnosis of immunologic disease of the lung.

The interstitium includes the alveoli, the epithelial and capillary cells within the alveolar wall, the septal tissues, and the connective tissues that surround the vascular, bronchial, and lymphatic structures within the lung parenchyma. An inflammatory response can involve any or all of these structures with varying clinical and radiographic presentations. The pathologic response to the resulting immunologic insult permits a clinically useful, although not strict, categorization of ILD into those entities characterized by alveolitic and diffuse interstitial inflammation and those that result in a predominantly granulomatous pattern of disease (Box 11-1).

Either pathologic response can progress from injury to fibrosis; therefore, all these entities manifest clinically as progressive dyspnea on exertion, a persistent nonproductive, typically paroxysmal, cough in the setting of radiographic interstitial opacities, or as both. Symptoms are usually chronic, progressing over years; however, presentation can be acute, as in allergic responses seen with hypersensitivity pneumonitis, eosinophilic pneumonia, drug-induced alveolitis, or acute interstitial pneumonia, or subacute, as with sarcoidosis, alveolar hemorrhage syndromes, cryptogenic organizing pneumonia, and some of the connective tissue diseases.

Fatigue and weight loss are common. Wheezing, hemoptysis, or pleuritic chest pain can be present, but are relatively rare at presentation. In fact, sudden onset or increased chest pain in the setting of these diseases is more suggestive of spontaneous pneumothorax, particularly in histiocytosis X (pulmonary Langerhans cell histiocytosis), tuberous sclerosis, lymphangioleiomyomatosis, and neurofibromatosis. Hemoptysis is associated with diffuse alveolar hemorrhage syndromes and the granulomatous vasculitides. Disease manifestation in other organ systems is helpful in the diagnosis of granulomatosis with polyangiitis (formerly called *Wegener granulomatosis*) and Goodpasture syndrome. Age, sex,

medical, family, and smoking histories and occupational and environmental exposure all figure prominently in the development of a differential diagnosis for a particular patient. Physical examination usually reveals bibasilar end-inspiratory “Velcro” crackles, but this is less common in the granulomatous diseases. Baseline tachycardia is common. Cyanosis and clubbing can occur with advanced disease.

GRANULOMATOUS PATTERNS OF INTERSTITIAL LUNG DISEASE

Granulomas consist of activated immune cells, typically macrophages, encircling particles that are generally not recognized by the antigen-specific, or adaptive, immune

system. The particle can be a foreign body or an intrinsic protein antigen that activates the innate immune system. Innate immunity is a non-antigen-specific means by which the body provides a first line of defense against foreign pathogens, including inhaled irritants. The innate immune system activates macrophages directly, without any need for prior exposure or antigen processing as is required for an adaptive T and B cell-dependent response. Activated macrophages mature to form epithelioid cells around the foreign material and thereby form a granuloma.¹

Macrophage activation and granuloma formation are also influenced by specific immune signals generated by other cells of the immune system, including signals triggered in an antigen-specific manner by the foreign particle or protein (Fig. 11-1). Fragments of foreign proteins processed by antigen-presenting cells, such as dendritic cells, are displayed on the cell surface in the context of the host major histocompatibility complex (MHC). Through this indirect pathway, antigen-specific CD4⁺ helper T cells are activated in the context of class II MHC presentation; whereas CD8⁺ effector T cells traditionally require the class I MHC complex. These activated T cells produce various cytokines that trigger several antigen-specific and nonspecific cellular subsets. For example, the activated T_H1 subsets of CD4⁺ helper T cells and natural killer cells produce interferon-gamma (IFN-γ), leading to primarily macrophage activation. On the other hand, the T_H2 subset produces interleukin (IL)-4 and IL-5 and results in eosinophil production and activation.¹⁻³ Other T cell subsets, such as CD8⁺ effector cells, are also recruited to help clear the protein antigen and thus help regulate the immune system. Once activated, this inflammatory process results in the recruitment of other immune cells, complement, and growth factors to form discrete granulomas, or the process may spread to the alveolar spaces and walls, leading to alveolitic changes (described later). Tumor necrosis factor (TNF), a potent

BOX 11-1 Categories of Interstitial Lung Disease

GRANULOMATOUS

- Foreign body, inorganic dust
- Hypersensitivity pneumonitis
- Sarcoidosis
- Granulomatous vasculitides
- Wegener granulomatosis
- Churg-Strauss syndrome
- Eosinophilic pneumonias
- Histiocytosis X

ALVEOLITIC

- Drug-associated injury
- Goodpasture syndrome
- Idiopathic interstitial pneumonia
- Interstitial lung disease associated with connective tissue diseases
- Diffuse alveolar hemorrhage syndrome

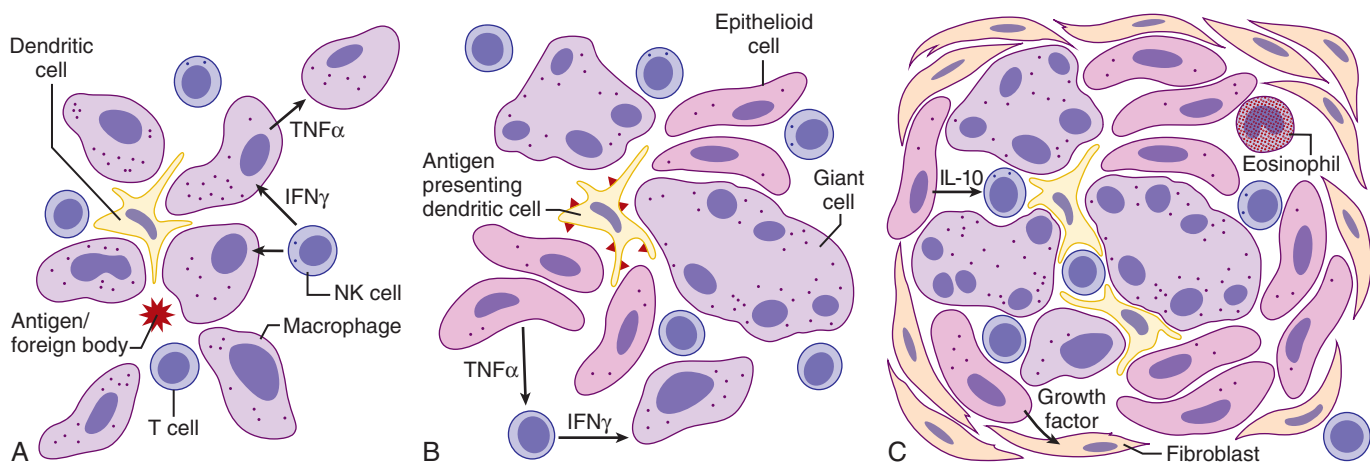


FIGURE 11-1 ■ Granuloma formation and maturation. **A**, Early accumulation of macrophages around antigen or foreign body. Release of proinflammatory cytokines tumor necrosis factor alpha (TNFα) and interferon-gamma (IFNγ), and chemokines such as macrophage inflammatory protein 1α results in activation of macrophages and recruitment of other immune cells. **B**, Antigen presentation by dendritic cells and macrophages to incoming T cells results in further activation, with development of epithelioid and giant cells. It is at this stage that fibroblasts become activated, resulting in focal areas of fibrosis. **C**, As the granuloma matures, the structure becomes more compact, with giant cells and T cells at the core. The initial helper T cell 1 (T_H1) response leads to the release of T_H2 cytokines as well, with interleukin (IL)-5 recruitment of eosinophils. NK, Natural killer.

inflammatory cytokine, has been implicated in initiating and driving the inflammatory process in many of these pathologic states. Newer targeted therapies for many inflammatory ILDs involve anti-TNF therapies.^{4,5} Granulomatous mechanisms are involved in a variety of pulmonary diseases, yet they all share this fundamental pathophysiologic mechanism. The clinical presentations and findings of these disease entities are described later.

Foreign Bodies and Inorganic Dust

Patients who have inhaled foreign bodies are typically asymptomatic at the time of initial exposure unless the particle is large enough to occlude the tracheobronchial tree. In such cases, as often seen in children, the diagnosis is made by history, confirmed by chest radiography, and, if needed, diagnosed as well as treated via bronchoscopy. However, prolonged exposure to smaller foreign particles, whether organic or inorganic, can lead to a spectrum of pulmonary disease processes. Chronic exposure to metal dusts, such as beryllium, aluminum, and zirconium—foreign particles that cannot be cleared by the mucociliary system or broken down by the pulmonary macrophages—is associated with a marked interstitial granulomatous disease pattern.⁶ Continuous exposure to small organic particles in susceptible individuals can also lead to hypersensitivity pneumonitis, with both alveolitic and granulomatous responses. The effect of a one-time massive exposure to inorganic fine particulate matter is less clear. A large subset of the pedestrians and workers exposed to smoke, dust, and particulate matter after the World Trade Center attacks in 2001 presented with a variety of nonspecific respiratory ailments, often with documented nonspecific histologic changes on lung biopsy. However, their long-term outcomes are not yet known; although recent reports suggest that many have developed a distinct restrictive type of respiratory dysfunction.⁷⁻¹¹

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis, also known as *extrinsic alveolitis*, describes a pulmonary disease process characterized by immunologically induced injury of the lung parenchyma with granuloma formation, alveolitis, and an antibody response, as the result of repeated exposure to inhaled protein antigen.¹²⁻¹⁴ Numerous antigens have been implicated, from *Aspergillus* spp. and fish meal dust to male rat urine, leading to various interesting, occupation-associated disease names (Table 11-1). Initial exposure to the antigen induces neutrophil and macrophage extravasation to the distal bronchioles and alveoli, thus leading to early alveolitis. Patients may present acutely with cough, fever, and chills several hours after exposure. With continued antigen exposure, patients develop a persistent cough with worsening dyspnea secondary to granuloma formation within the pulmonary parenchyma, and progressive interstitial disease.^{12,14}

Diagnosis relies on careful history taking, with particular emphasis on occupational and recreational exposures. Chest radiographs have no specific diagnostic pattern, although a reticular nodular pattern consistent

TABLE 11-1 Selected Hypersensitivity Pneumonitis Syndromes

Syndrome	Antigen
Bagassosis	<i>Actinomyces</i> species from sugar cane
Cheese washer's lung	<i>Penicillium casei</i> from moldy cheese
Compost lung	<i>Aspergillus</i> species from compost
Furrier's lung	Animal fur dust
Hot tub lung	Mold on ceilings
Laboratory worker's lung	Rat urine
Fish meal worker's lung	Fish meal dust
Woodworker's lung	Wood dust

with interstitial lung disease may be present. Chest computed tomography (CT) is typically nondiagnostic as well.^{13,14} Bronchoalveolar lavage (BAL) may be helpful, showing an increase in CD4⁺ T cells acutely and CD8⁺ T cells chronically. However, this only marginally narrows the spectrum because this finding is characteristic of nearly all granulomatous disease processes. Serum tests for antibodies to the suspected antigen are often required to make a diagnosis. Lung biopsy, either transbronchial or using video-assisted thoracoscopic surgery (VATS) or open thoracotomy, may be necessary to make a diagnosis in patients for whom other evidence is lacking. Even this aggressive approach, however, may be nondiagnostic in late stages when the acute granulomatous and alveolitic changes are replaced by interstitial fibrosis.

Treatment consists of removing exposure to the suspected antigen, and steroids for patients with the severe acute form of the disease or with chronic persistent fibrosis.¹³⁻¹⁶ Histologic evidence of fibrosis in lung biopsy specimens is correlated with a worse prognosis.¹⁵ Radiologic evidence of fibrosis seen on high-resolution CTs may serve as a surrogate for histologic findings once the diagnosis has been made, and this may correlate with long-term survival and response to therapy.¹⁶

Infections

Pulmonary infection with *Mycobacterium tuberculosis* is probably the most common cause of granulomatous lung disease worldwide.^{2,17} Local and disseminated miliary disease lead to granuloma formation in the infected field. Other infectious organisms, such as *Aspergillus* spp. and certain helminths, can also lead to pulmonary granulomatous disease.² Radiologic assessment alone is often inadequate to make a diagnosis, and the clinical context must be taken into account. The clinical pathogenesis, presentation, course, and treatment of pulmonary infections are discussed elsewhere in this book and are not included in this discussion of ILD.

Sarcoidosis

Sarcoidosis is a chronic systemic disorder that, although common, is still poorly understood. Various organ systems of these patients are often affected by granulomatous disease, and some individuals do not manifest

pulmonary involvement.¹⁸⁻²⁰ The incidence of sarcoidosis varies with the population studied. In Western populations, the incidence is estimated to be 10 to 20 per 100,000 population, with a higher rate in women and those of African American ancestry.²¹ Sarcoidosis is uncommon in Asian populations. Although the disease can manifest at any age, most patients present between the ages of 20 and 40 years.^{18,19,22,23}

The etiology of sarcoidosis is unknown. Environmental, infectious, hereditary, and immunologic factors have been postulated, with variable evidence to support each hypothesis.²³ The interstitial granulomatous disease that results from inhalation of metal dusts is pathologically identical to sarcoidosis, suggesting that an unknown environmental exposure may be responsible.^{6,24,25} Supporters of an infectious etiology argue that the causative agent must be inhaled, because 80% of affected individuals have pulmonary and mediastinal lymph node involvement. In fact, BAL of individuals with extrapulmonary sarcoid contains inflammatory cells even without evidence of pulmonary disease. The causative agent is suggested by some to be *Mycobacterium tuberculosis* or a nontuberculous mycobacterium. Genetic analyses of affected tissue by polymerase chain reaction as well as antibody analysis of afflicted individuals have been inconclusive. Other agents implicated have been *Yersinia enterocolitica* and *Borrelia burgdorferi*, but the evidence linking these agents to sarcoidosis is even less well established. There is familial clustering of the disease, and sarcoidosis has been linked to human leukocyte antigens (HLA) A1 and B8 in whites, suggesting that hereditary and genetic factors play an important role in this disease. Putative genes involved in the pathogenesis of the disease include butyrophilin-like 2 (BTNL2), a T cell costimulatory molecule, annexin A11, as well as polymorphisms in several cytokines and chemokines.²⁶⁻²⁸ Non-MHC immunologic factors are probably also involved, as patients with sarcoidosis have numerous abnormalities of the immune system, including altered T cell ratios, poorly responsive CD4⁺ T cell subsets, hyperactive B cell lines, and altered production of the inflammatory cytokines IFN- γ and RANTES by macrophages.²⁹⁻³³

Symptoms of sarcoidosis are variable and fluctuate with time. Most patients in whom the disease is identified by routine chest radiography are asymptomatic. Others may exhibit the acute onset of constitutional symptoms such as fever, chills, fatigue, and weight loss. Afflicted individuals often have an associated connective tissue disorder, such as rheumatoid arthritis, systemic lupus erythematosus, or progressive systemic sclerosis. Pulmonary symptoms commonly include dyspnea and a dry cough.²² Diagnosis is typically made radiographically, with chest radiographs showing bilateral hilar and mediastinal lymph node enlargement with or without an accompanying reticulonodular pulmonary pattern indicative of interstitial disease (Fig. 11-2). Consolidation and a ground-glass parenchymal pattern may also be evident, particularly on chest CT. Fibrosis is seen in later stages of the disease. Serum abnormalities can include an increase in levels of angiotensin-converting enzyme, presumably produced by the activated macrophages in the granulomas. A preponderance of lymphocytes in



FIGURE 11-2 ■ Computed tomography of the chest from a patient found to have noncaseating, non-necrotizing granulomata in the mediastinal lymph nodes on cervical mediastinoscopy. These findings are consistent with the diagnosis of sarcoidosis. **A**, Lung window. **B**, Mediastinal window.

the BAL suggests an alveolitic process with granulomatous changes. Diagnosis, however, is most often made by mediastinal lymph node biopsy if adenopathy is present.^{22,34,35} In rare cases, transbronchial or VATS biopsy may be needed to establish the diagnosis. Histologic findings of affected pulmonary tissue show noncaseating granulomas with high tissue angiotensin-converting enzyme levels.

Treatment consists primarily of steroids in symptomatic patients.²² Second-line agents such as hydroxychloroquine, methotrexate, leflunomide, azathioprine, and mycophenolate mofetil have also been used for refractory cases. Recent studies have suggested a benefit to tumor necrosis factor inhibitors such as infliximab or adalimumab in patients with poor responses to standard immunosuppressive regimens.^{27,36-41} These therapies are potentially toxic, and patients should be monitored carefully.

Granulomatous Vasculitides: Granulomatosis with Polyangiitis and Churg-Strauss Syndrome

Like sarcoidosis, granulomatosis with polyangiitis (GPA; formerly referred to as *Wegener granulomatosis*) is a systemic disorder characterized by granuloma formation within multiple organ systems. GPA is a rare disease with an incidence of 1 to 3 in 100,000. Affected individuals typically present between the ages of 40 and 60 years.⁴²

In its most extreme form, GPA is characterized by necrotizing granulomatous involvement of the pulmonary parenchyma and both pulmonary and renal vasculature.^{2,25,42-46} Disease expression is variable and may be limited to the pulmonary system. Numerous etiologies have been suggested, including infectious organisms such as parvovirus B19 and other respiratory agents, inhaled environmental agents such as silica, and genetic factors linked to the HLA alleles DR1, DR2, and DR12. Although all these possible etiologies are supported by some evidence, no explanation is conclusive. The sera of individuals afflicted with the disease contain antibodies to antineutrophil cytoplasmic antibodies (ANCA). Specifically, 90% of patients with GPA have C-ANCA, which chiefly binds to the PR3 plasma serine proteinase in neutrophils, as opposed to P-ANCA, which are antibodies to a perinuclear myeloperoxidase enzyme.^{25,43,44} The exact role of C-ANCA in the pathogenesis of GPA is unclear and, unfortunately, ANCAs are also found in other disease states, such as systemic lupus erythematosus, in which ILD may develop.^{25,43-47}

Individuals with GPA may present with fulminant disease, with massive hemoptysis and renal failure secondary to extensive necrotizing granulomatous lesions, or with more subtle findings of fever, malaise, weight loss, and progressive dyspnea, with hemoptysis appearing only as the disease progresses. Neurologic or ocular symptoms may also be present. Diagnosis relies not only on the history, but also on laboratory studies such as C-ANCA serologies and other associated systemic abnormalities.^{25,43,46} Chest imaging shows a reticulonodular pattern consistent with interstitial disease or discrete nodules in only 50% of affected individuals. Central necrosis in these nodules can give the appearance of cavitary lesions (Fig. 11-3). BAL fluid from patients with GPA contains

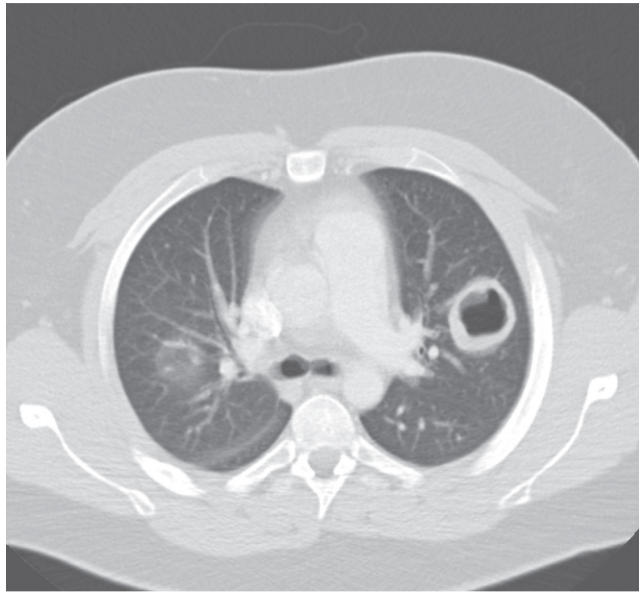


FIGURE 11-3 ■ Computed tomography of the chest from a young man with Wegener granulomatosis. Central necrosis in a granulomatous lesion has the appearance of a cavitary lesion. Many other such lesions were present throughout the lung parenchyma.

neutrophils and eosinophils. Biopsy of pulmonary or renal lesions may be necessary to establish or confirm the diagnosis. Pathologic analysis typically shows granulomas with neutrophils, macrophages, and eosinophils. Treatment options vary with the severity of the disease and include steroids and immunosuppressive agents, such as cyclophosphamide and methotrexate.⁴⁶ Rituximab, an anti-CD20 monoclonal antibody that targets B cells, has been used in some cases refractory to cyclophosphamide or methotrexate.^{48,49}

Churg-Strauss syndrome is a rare systemic disorder characterized by eosinophilia, vasculitis, and pulmonary parenchymal granuloma formation. Many view this disease as part of a spectrum of disease that includes GPA and other connective tissue diseases.^{25,44,45} The true incidence is unknown because of the difficulty of establishing a diagnosis, but it is estimated at 1 to 2 per 1 million people, and it affects individuals between the ages of 20 and 50 years.^{25,50} As in GPA and sarcoidosis, multiple etiologies have been suggested, including pigeon exposure, helminth infection, and cocaine use. Churg-Strauss syndrome has been associated with the weaning of steroids in asthma patients placed on leukotriene antagonists.^{25,45,51,52}

Affected individuals typically have a history of asthma or allergic symptoms and present with fever, cough, and occasionally hemoptysis. Gastrointestinal bleeding or neuropathy may also be present. Diagnosis rests on clinical suspicion and the combination of symptoms, laboratory studies, and pathologic findings. Chest radiographs typically reveal patchy consolidation throughout the lung fields. Levels of immunoglobulin E and P-ANCA may be elevated. The BAL fluid shows large numbers of eosinophils.^{34,35} A lung biopsy specimen, usually required for diagnosis, demonstrates vasculitis and parenchymal granulomas with eosinophils. Treatment consists of steroid therapy and other immunosuppressive agents such as cyclophosphamide, methotrexate, azathioprine, or mycophenolate mofetil. Intravenous anti-TNF, interferon- α therapy, gammaglobulin, and plasma exchange has also been investigated with some success in refractory cases.^{48,49,53,54} Prognosis for those diagnosed with the syndrome is poor, with a mortality of 50% to 60% at 5 years.^{44,45}

Eosinophilic Pneumonias

Eosinophilic pneumonia belongs to a spectrum of pulmonary processes that are distinguished by the accumulation of eosinophils in parenchymal tissue. Eosinophilic pulmonary diseases with known etiologies include those caused by helminth infections, such as *Strongyloides stercoralis* and *Ancylostoma duodenale*, and drug allergies, which cause peripheral blood eosinophilia and can have systemic effects, as well as those conditions associated with the granulomatous vasculitides (discussed earlier) in which the etiology is unclear.^{55,56} All these disease states can have pulmonary involvement. Diagnosis is made by history, blood eosinophil counts, blood serologies, and occasionally lung biopsy.

Idiopathic eosinophilic pneumonias can be divided into simple, acute, and chronic forms. Simple eosinophilic

pneumonia, also known as *Löffler syndrome*, is rare and characterized pathologically by interstitial edema with abundant eosinophils. Patients typically exhibit few or no symptoms. Chest radiographs show patchy parenchymal consolidation, and the diagnosis rests on the demonstration of peripheral blood eosinophilia in patients with a history of asthma or atopy. The disease usually resolves spontaneously; therefore, biopsy or BAL is rarely required to make a diagnosis. Patients with symptoms, even when symptoms are prolonged, may benefit from steroid therapy.^{55,56}

Acute eosinophilic pneumonia is a rare disorder that manifests as an acute illness with severe respiratory distress that may require ventilatory assistance. The etiology is unclear, but it is thought to be secondary to an eosinophil-mediated immune response to an unknown allergen. Patients present with severe shortness of breath and pleuritic symptoms. Chest radiography shows reticular opacities similar to the pattern found with interstitial pulmonary edema. The disease is characterized by a high number of eosinophils, up to 80%, in the BAL. Steroids are the mainstay of treatment, but a high relapse rate is associated with this disease.^{55,56}

Chronic eosinophilic pneumonia has a similar histologic and, in most cases, radiographic appearance. Again, diagnosis relies on the demonstration of peripheral blood eosinophilia in patients with a history of asthma or atopy. However, affected patients have chronic symptoms that do not resolve over time; therefore, eosinophilia on BAL fluid, tissue biopsy specimen, or both are often needed to make the diagnosis.^{55,56} Steroid treatments usually result in rapid disease regression.^{55,56}

Pulmonary Langerhans Cell Histiocytosis

Histiocytosis X, also known as *eosinophilic granuloma*, *pulmonary Langerhans cell histiocytosis*, or *Langerhans cell granulomatosis*, is a rare disorder characterized by the peribronchial accumulation of specialized antigen-presenting cells known as *Langerhans cells*. Letterer-Siwe and Hand-Schüller-Christian diseases are variants typically found in children and may not have pulmonary involvement.^{57,58} The adult form—eosinophilic granuloma—is characterized by pulmonary and skeletal system involvement. Although rare, histiocytosis X predominantly occurs in whites and in women. Viral infection with Epstein-Barr virus or other members of the herpesvirus family has been suggested as a possible etiology for this disease.^{57,58} Recent reports find that the clonal population of cells involved in this disease have short telomeres, much like those in other malignancies.⁵³ Telomerase activity has also been correlated with the degree of disease expression.⁵⁹ Chest radiographs in the early stages of the disease show bilateral nodular opacities. With progression of disease, a reticulonodular pattern is noted (Fig. 11-4). Patients are typically asymptomatic at the time of diagnosis in young adulthood. Diagnosis is commonly made by routine chest radiography. Symptomatic patients have a dry cough and shortness of breath. BAL can be useful, as Langerhans cell are abundant in the fluid.^{34,35,58} Lung biopsy can confirm

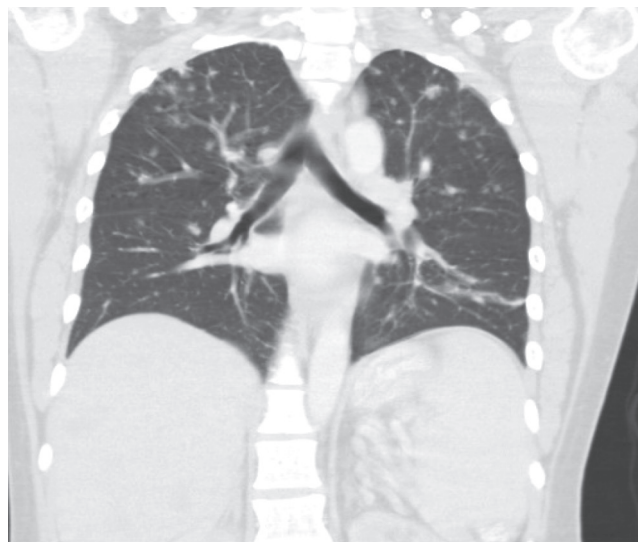


FIGURE 11-4 ■ Computed tomography of the chest from a patient with pulmonary Langerhans cell histiocytosis.

clinical suspicions in unclear cases, because the demonstration of Langerhans cells infiltrating the pulmonary bronchioles is pathognomonic of this disease. Despite the disease name, granulomas are not formed in the strict sense, because the chief cellular component in these lesions is Langerhans cells and not macrophages. Long-standing disease leads to interstitial fibrosis. Remission can occur spontaneously, and it can often be aided with steroid therapy.⁶⁰

ALVEOLITIC PATTERNS OF INTERSTITIAL LUNG DISEASE

When immunologic injury is directed primarily toward the alveolar epithelial surface, inflammation of the alveolar wall and airspaces results in a histopathologic pattern of alveolitis. Both cellular and humoral components of the immune system are involved in these alveolitic changes in the lung. Alveolitic mechanisms are involved in a variety of pulmonary diseases (see Box 11-1).⁶¹

Activated macrophages, T cells, and inflammatory cytokines can lead to B cell activation and antibody production. These antibodies form complexes with the antigen and are deposited within the lung parenchyma, leading to the activation of complement. Although the formation of the membrane attack complex is an attempt to destroy the antigen, injury to the surrounding lung tissue may be significant if this inflammatory reaction is not regulated. A basic diagram of this cascade is shown in Figure 11-5.⁶¹

Chemotactic peptides produced by the complement pathways, such as C5a and C3b, recruit other components of the cellular immune system. Neutrophils and macrophages thus destroy the pathogen and cause further parenchymal destruction. Activated macrophages and other immune cells produce additional cytokines, such as TNF and IL-1, which, together with immune complex deposition and complement activation, lead to direct

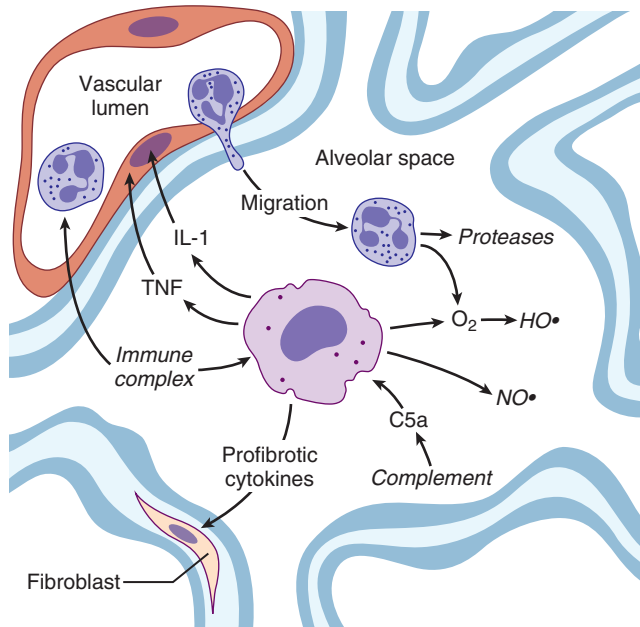


FIGURE 11-5 ■ Pathogenesis of alveolitic injury. Activation of alveolar macrophages and polymorphonuclear leukocytes by complement, immune complex deposition, and subsequent cytokine/chemokine release trigger a cascade of responses that result in acute lung injury to the surrounding alveolar membrane and interstitium. *IL*, Interleukin; *TNF*, tumor necrosis factor.

injury to the lung parenchyma and the surrounding vasculature. Numerous other cytokines and inflammatory modulators, such as prostaglandins, can also play important roles in the pathophysiology of ILDs. If the immune process continues unmitigated, the acute inflammatory response present in the lung parenchyma in the early phase of the disease is replaced by increasing degrees of fibrosis as more and more fibroblasts are recruited into the area of injury to repair the damage. Fibrosis is the final common pathway for both the alveolitic and granulomatous immune responses, often making it impossible to differentiate between these two disease processes in the late stages of ILD. Irreversible scarring and fibrosis of the alveolar–endothelial interface and surrounding parenchyma results in significant impairment in gas exchange and is consistent with end-stage ILD. Current investigational treatments focus on mitigating or abrogating the inflammatory response with targeted therapies directed at many of the cytokines involved in the immune response before the development of fibrosis.

Drug-Associated Injury

Whether resulting from direct toxic or immune mediated damage, drug-associated injury to the lung results in an alveolitic pattern of damage. Chronic concomitant damage often leads to irreversible fibrosis. Numerous drugs have been implicated in pulmonary injury, but only amiodarone and its mechanisms are discussed here. Direct toxic effects can result from radiation, bleomycin, nitrofurantoin, and prolonged exposure to high oxygen concentrations.⁶² Injury in these cases is principally the

result of free oxygen radical production. Acute changes are predominantly alveolitic, followed by progressive fibrosis as the lungs recover from the initial insult. BAL specimens from patients during the acute phase contain numerous neutrophils or eosinophils.^{34,35}

Amiodarone, a potent antiarrhythmic agent, has the ability to induce direct and immune-mediated injury. Direct amiodarone toxicity most likely results from the generation of free oxygen radical species. However, the large number of lymphocytes or foamy macrophages indicative of pulmonary phospholipidosis in the BAL suggests that immune-mediated mechanisms are also involved.^{62,63} Pulmonary toxicity has been correlated with patient age and duration of therapy.⁶⁴ However, a fulminant form of amiodarone pulmonary toxicity has been described, especially in patients undergoing lung surgery, and it is thought to be an idiosyncratic immune response.⁶³ Chest radiographs in drug-associated ILD demonstrate an interstitial disease pattern. As fibrosis intervenes, the BAL specimen becomes acellular and the chest radiograph shows a more prominent reticulonodular pattern.^{34,35} Diagnosis rests on the recognition of prior drug exposure. Lung biopsy, if done in late stages, may show only fibrotic change. Treatment of amiodarone pulmonary toxicity consists of prompt cessation of drug use and management of symptoms.

Other common drugs that can cause acute lung injury include statins, which are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase.⁶⁵⁻⁶⁷ These are uncommon but potentially fatal. Similar to patients with amiodarone toxicity, lymphocytes or foamy macrophages in the BAL is also found in patients with statin induced lung injury. Treatment consists of cessation of statin treatment and symptomatic management.

Goodpasture Syndrome

Goodpasture syndrome is characterized by the presence of pulmonary hemorrhage and glomerulonephritis. Its incidence is rare, it predominantly affects males 15 to 25 years old, and it is linked to the HLA-DR2 MHC allele. Other immunologic and hereditary factors, and an association with free-base cocaine use, have been implicated.⁶⁸ The pathogenesis of alveolitis, pulmonary hemorrhage, and glomerulonephritis results from the presence of antibodies directed against a collagen protein in the alveolar and glomerular membranes. Because of complement activation and cell-mediated injury, these antibodies produce immune complex-mediated injury to lung and renal parenchyma.^{31,69,70}

In most cases, patients present with hemoptysis and occasionally hematuria. Diagnosis is based on clinical symptoms and the characteristic linear staining of the basement membrane with anti-IgG antibodies present on renal biopsy.^{25,31} Chest radiographs demonstrate patchy consolidation secondary to hemorrhage. BAL is nondiagnostic and lung biopsy is rarely needed to make a diagnosis.^{34,35} Therapy consists of plasmapheresis to remove the antibodies, and immunosuppressive therapy.

Idiopathic pulmonary hemorrhage is similar to Goodpasture syndrome in terms of its pulmonary

manifestations. However, this disease predominantly affects children younger than 10 years, and it does not have any renal involvement. Patients exhibit hemoptysis and weakness secondary to iron deficiency. Radiographic appearance is similar to that in Goodpasture syndrome, but the absence of anti-basement membrane antibodies in lung and renal biopsy specimens differentiates between the two. Prognosis is variable, and treatment consists of plasmapheresis and immunosuppressive therapy.³¹

Idiopathic Interstitial Pneumonia

Idiopathic interstitial pneumonias (IIPs) are a spectrum of pulmonary disorders characterized by the infiltration of immune cells into the pulmonary interstitium, and the resultant alveolitic changes. Unabated inflammation leads to fibrosis of the lung parenchyma. Because many terms have been given to the various forms of this disease (Hamman-Rich disease, idiopathic pulmonary fibrosis, usual interstitial pneumonitis, diffuse pulmonary alveolar fibrosis), there has been much confusion in diagnosing this disease entity. A useful subclassification scheme based on pathology has been proposed by Averill Liebow.⁸⁰ An updated modification of this scheme formulated by the American Thoracic Society and European Respiratory Society is presented in Box 11-2.⁷¹ Both societies emphasize a multidisciplinary approach to classifying IIPs incorporating clinical, radiologic, and pathologic findings where warranted. Clinical information such as presentation, exposures, smoking status, associated diseases, and laboratory findings are combined with radiologic findings to make a diagnosis. A lung biopsy is then considered when diagnosis is not possible based on high-resolution chest CT and clinical presentation. Before proceeding with a diagnosis of IIP, all other potential causes such as drug and environmental exposures leading to hypersensitivity syndromes, infectious etiologies, and collagen vascular diseases should be excluded.⁷¹

It has been suggested by some that this classification scheme is arbitrary, with diseases being categorized by distinct names when they may merely be different manifestations of the same disease.⁷²⁻⁷⁴ Nevertheless, as these distinct entities are defined by distinct clinical, radiologic,

and pathologic criteria, they do appear to have their own prognostic indicators and treatment; therefore, it is often useful to distinguish between them whenever possible. We will highlight some of these entities below along with the histologic findings common to these diseases (Table 11-2).

TABLE 11-2 Summary of Histologic Findings for Immunologic Lung Diseases

Disease	Histology
Granulomatous	
Foreign body, inorganic dust	Simple granuloma
Hypersensitivity pneumonitis	Granulomas with CD4 ⁺ /CD8 ⁺ T cells; interstitial edema; fibrosis in later stages
Infections	
Tuberculosis	Caseating granulomas
Sarcoidosis	Noncaseating granulomas
Granulomatous Vasculitides	
Wegener granulomatosis	Necrotizing granulomas involving vasculature
Churg-Strauss syndrome	Necrotizing granulomas involving vasculature
Eosinophilic pneumonias	Granulomas with eosinophilic predominance; interstitial edema
Histiocytosis X	Granulomas with Langerhans cells
Alveolitic	
Drug-associated injury	Interstitial edema with inflammatory cells
Goodpasture syndrome	Linear staining of basement membrane with anti-IgG antibodies typically seen on renal biopsy; interstitial edema with inflammatory cells
Idiopathic Interstitial Pneumonias	
Idiopathic pulmonary fibrosis (IPF)	Interstitial edema and/or fibrosis with inflammatory cells; patchy fibrotic change
Desquamative interstitial pneumonia (DIP)	Interstitial edema with sparse inflammatory cells; mild diffuse fibrotic change
Idiopathic nonspecific interstitial pneumonia (NIP)	Thickened interstitium with inflammatory cells; some patchy fibrosis
Acute interstitial pneumonia (AIP)	Diffuse alveolar damage with thickened fibrotic interstitium; proliferating fibroblasts
Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD)	Macrophages infiltrating distal bronchioles
Cryptogenic organizing pneumonia (COP)	Chronically inflamed alveoli with granulation tissue in bronchioles and macrophages in alveoli
Lymphocytic interstitial pneumonia (LIP)	Diffuse lymphocytic and plasma cell infiltration; minimal alveolar injury
Idiopathic pleuroparenchymal fibroelastosis	Diffuse alveolar damage with fibrosis

BOX 11-2 Idiopathic Interstitial Pneumonias

MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS

- Idiopathic pulmonary fibrosis
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis–interstitial lung disease
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonia

RARE IDIOPATHIC INTERSTITIAL PNEUMONIAS

- Idiopathic lymphoid interstitial pneumonia
- Idiopathic pleuroparenchymal fibroelastosis

UNCLASSIFIABLE IDIOPATHIC INTERSTITIAL PNEUMONIAS

Familial Forms of Idiopathic Interstitial Pneumonia

There have been reports of IIPs occurring in related family members in 5% to 20% of cases.^{71,75-80} These cases are classified on the basis of their clinical, radiologic, and pathologic presentation despite genetic linkage to disease. Mutations have been found in lung surfactant proteins (SFTPC, SFTPA2) and telomerase proteins (TERT, TERC) in patients with familial forms of IIPs.^{71,75-80} These mutations account for at most 20% of familial forms of IIPs.^{71,75-80} Genetic transmission suggests an autosomal dominant mechanism. Familial IIPs cannot be distinguished from non-familial cases on HRCT and lung biopsy. They are suspected only by obtaining family history of lung disorders. Their treatment is dependent on their classification based on clinical, radiologic, and histologic criteria if needed.

Idiopathic Pulmonary Fibrosis

The typical pathologic finding of idiopathic pulmonary fibrosis (IPF) is thickened fibrotic alveolar interstitium infiltrated by inflammatory cells, such as lymphocytes and plasma cells, termed *usual interstitial pneumonia* (UIP). Histologic analysis in the acute phase of the disease demonstrates alveolitis, with an interstitium overrun with inflammatory cells and areas of patchy fibrotic changes.⁷² Patients who demonstrate interstitial lung disease on chest radiography and pathologic evidence of fibrosis on lung biopsy are given this clinical diagnosis when other causes of interstitial disease (e.g., sarcoidosis, hypersensitivity pneumonitis, histiocytosis X, infection) have been excluded.^{71,72,81-85}

IPF occurs with an estimated incidence of 5 to 20 per 100,000 persons, with a slight male predominance.^{50,81,86} The etiology of IPF is unknown. Exposure to heavy metal dusts, solvents, and Epstein-Barr and hepatitis C viruses have all been named as possible mediators of the initial lung injury in susceptible individuals, but there has been no definitive proof for any of these theories.³⁵ Cigarette smoking has been implicated in some case-control studies. IPF has been linked to HLA-B15, HLA-B8, and HLA-B12 loci, and a familial form of IPF has been described, suggesting a hereditary or immunologic component to this disease.^{87,88} Further evidence for an immunologic basis is that individuals afflicted with pulmonary disease related to rheumatoid arthritis, systemic lupus erythematosus, and progressive systemic sclerosis have a high incidence of interstitial inflammation and fibrosis that is clinically and pathologically indistinguishable from IPF. Recent studies have implicated matrix metalloproteinases (MMPs) in the pathogenesis of IPF based on microarray analysis and the results of MMP knockout mice. The diagnostic and therapeutic implications of these findings have not been determined.^{89,90}

Individuals with IPF have progressive shortness of breath, weight loss, and a nonproductive cough. In 80% of individuals, the chest radiograph reveals linear opacities in a diffuse reticulonodular pattern. The lower lung zones may be preferentially involved. High-resolution chest CT can further demonstrate a reticular pattern,



FIGURE 11-6 ■ Computed tomography of the chest in a patient with idiopathic pulmonary fibrosis. Note the reticular interstitial pattern and honeycombing at the lung bases. The patient subsequently underwent a single-lung transplant.

with honeycombing, cysts, and ground-glass opacities (Fig. 11-6).^{91,92} Mediastinal lymph node enlargement is common. BAL typically shows large numbers of neutrophils, eosinophils, or lymphocytes.^{34,35,81} Patients with high levels of lymphocytes in their BAL fluid have been shown to have a better response to steroid therapy and an improved prognosis in some studies.^{93,94} The diagnosis of IPF requires the exclusion of other known causes of interstitial lung disease, the presence of a UIP pattern on high resolution chest CT, and the presence of UIP pattern on surgical lung biopsy specimens that are consistent with high resolution chest CT findings. Hence, the principal role for lung biopsy is to exclude other etiologies of interstitial lung disease, which may alter the therapeutic plan or prognosis. Typically, a VATS or open biopsy is required because transbronchial biopsy yields inadequate tissue to make a diagnosis of IPF.^{81,95}

The mainstay of treatment for IPF is steroids or other immunosuppressive and anti-inflammatory therapies, or both, including azathioprine, methotrexate, penicillamine, colchicine, *N*-acetylcysteine (NAC), and cyclosporine. Combination therapy using prednisone, azathioprine, NAC had been recommended by international consensus committees as treatment for IPF; however, a recent randomized trial has compared the efficacy of combination therapy in patients with mild to moderate IPF to NAC alone or placebo.⁹⁶⁻⁹⁹ The combination arm of the study was prematurely terminated when interim analysis revealed combination therapy to be associated more with serious adverse events than the other arms of the trial. The NAC arm of the trial is still ongoing, but combination therapy can no longer be recommended.⁹⁶⁻⁹⁹ Novel

agents, such as pirfenidone, have also been developed to downregulate the fibrosis associated with inflammatory disorders. A recent randomized clinical trial in patients with idiopathic pulmonary fibrosis demonstrated that pirfenidone resulted in significant clinical benefit for these patients, indicating that this agent will be a mainstay of therapy in the future.^{58,59} Another phase II placebo-controlled, randomized trial examined the role of the tyrosine kinase inhibitor, nintedanib, on the progression of IPF as measured by declines in forced vital capacity (FVC), and secondary end-points of quality of life as measured by the St. George's respiratory questionnaire.^{26,100} Nintedanib is oral tyrosine kinase inhibitor that targets multiple factors including platelet-derived growth factor receptors, vascular endothelial growth factor receptors, and fibroblast growth factor receptors. These molecular pathways are involved in the development of fibrosis in animal as well as human models. The trial showed that those patients on nintedanib had a slower rate of decline in FVC and improved quality of life. As a result, two larger phase III trials evaluating nintedanib are now being conducted. Further investigation is needed to evaluate the safety and efficacy of these agents in the treatment of IPF.^{26,100}

Other medical therapies for IPF have focused on the modulating the coagulation cascade. Several animal studies have implicated the coagulation cascade in a causal role in the development of pulmonary fibrosis, and a prior clinical trial suggested a benefit to anticoagulation in patients with IPF.¹⁰⁰⁻¹⁰² However, a recent randomized trial of warfarin versus placebo in 145 patients with IPF (progressive disease) was terminated early when interim analysis demonstrated that patients taking warfarin had a worse mortality compared with placebo.¹⁰⁰⁻¹⁰² Accordingly, anticoagulation is currently not recommended.

Surgical therapies for IPF include antireflux surgery and lung transplantation. Gastrointestinal reflux disease has been shown to occur with greater frequency in those with chronic lung disease, particularly IPF.¹⁰³⁻¹⁰⁵ Consideration of antireflux surgery in this cohort is appropriate, particularly if significant reflux is detected by esophageal pH monitoring and symptom analysis despite medical therapy, because it has been suggested that surgery can improve exercise capacity, decrease oxygen requirements, and potentially delay disease progression. Patients with IPF who are undergoing antireflux surgery have variable response rates.¹⁰³⁻¹⁰⁵

Lung transplant is indicated for those patients who deteriorate despite best medical therapy.^{106,107} In general, lung transplantation is the procedure of choice for patients with IPF or other end-stage ILDs that fail medical management.^{72,108-111} The basic criteria for lung transplantation in this setting are (1) progressive dyspnea or hypoxia despite best medical therapy, (2) a predicted vital capacity of 60% to 70% or less or a predicted diffusing capacity of 50% to 60% or less, and (3) patient age of 60 years or less for double-lung transplant, or 65 years for single-lung transplant.^{112,113} Diagnosis and treatment of pulmonary fibrosis associated with connective tissue disease is similar to that for IPF.¹⁰⁸⁻¹¹⁰ However, pulmonary symptoms typically wax and wane with the disease

and often respond to treatment of the primary disease.⁸¹ Lung transplantation is indicated in those patients with stable connective tissue disease and progressive pulmonary symptoms refractory to medical therapy.¹¹³ The 5-year survival rate is only 50% to 70% after transplantation for IPF, but this is a significant improvement over the 28-month median survival reported for medically treated IPF.^{112,114,115}

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia (DIP) tends to have a more uniform histologic appearance than IPF, and the interstitium is only mildly thickened, with a sparse infiltrate of inflammatory cells and mild fibrosis. The incidence of DIP is low, and it affects smokers usually at age 40 to 50.*

Patients exhibit dyspnea and fatigue, and the chest radiograph reveals characteristic bilateral ground-glass opacities, which may be linear depending on the degree of fibrosis. Chest CT further highlights these ground-glass abnormalities. BAL specimens typically have fewer inflammatory cells than do those from patients with IPD but relative eosinophilia.^{34,35,81,116-118} Lung biopsy, as for IPF, may be indicated to exclude other etiologies of ILD. However, the diffuse changes present throughout the lung in DIP may be seen focally in IPF, making it difficult to distinguish IPF from DIP by this means. The presence of eosinophils in the BAL fluid may aid in the diagnosis.^{117,118} DIP typically occurs in smokers, but a form of DIP in nonsmokers has also been recognized. In these patients, it may represent an extension of genetic disease with mutations in surfactant proteins as seen in the childhood form. Patients may respond to steroid therapy, but the disease is typically progressive. Ten-year survival is in the range of 60% to 70%. Lung transplantation is indicated in end-stage disease.¹¹⁶

Idiopathic Nonspecific Interstitial Pneumonia

Lung biopsy specimens from patients with idiopathic nonspecific interstitial pneumonia (NSIP) reveal a mildly thickened interstitium with an infiltrate of inflammatory cells and some fibrosis.^{71,72,74,81,119} The incidence of NSIP is rare with no sex predominance, unlike for IPF. Clinical presentation and some radiologic features of the disease are similar to those of IPF. The most common chest CT abnormalities seen in NSIP are ground-glass opacities, reticular nodularities, and traction bronchiectasis similar to other IIPs. An NSIP pathologic pattern with fibrosis and interstitial inflammation from lung biopsy specimens can occur in other settings including from drug toxicity, hypersensitivity exposures, and collagen vascular disease. It is essential to rule out these clinical scenarios prior to concluding that the disease is idiopathic. The prognosis for NSIP is variable. However, NSIP has a much better clinical response to steroid and immunosuppressive therapy and is associated with improved overall survival.^{74,81,119}

*References 50, 71, 72, 81, 86, 116.

Acute Interstitial Pneumonitis

Acute interstitial pneumonia (AIP) is rapidly progressive and clinically similar to acute lung injury and acute respiratory distress syndrome (ARDS), with the exception that there is no preceding trauma, sepsis, or known source of injury. The clinical presentation involves rapid onset with progressive dyspnea, respiratory failure, and death usually within a year. Pathologic examination of lung biopsy tissue consists of diffuse alveolar damage with a thickened fibrotic interstitium infiltrated by proliferating fibroblasts.^{72,81} In acute fulminant cases, the fibrosis can be replaced with an exudative interstitial edema similar to that found in diffuse alveolar damage, suggesting that AIP is a point on the spectrum of disease between IPF and diffuse alveolar damage. Radiologically, AIP is similar to ARDS in that chest radiographs and chest CT demonstrate characteristic bilateral patchy airspace disease and ground-glass opacities. Prognosis for those afflicted with AIP, as for those with ARDS, is poor, with a fatality rate of 70% and most patients dying within 2 weeks of diagnosis.^{81,120}

Respiratory Bronchiolitis–Associated Interstitial Lung Disease

Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) is pathologically distinct in that it is characterized by the infiltration of macrophages surrounding the distal bronchioles.¹²¹ The incidence of RB-ILD is rare, and it chiefly affects men aged 40 to 50 years. RB-ILD is strongly correlated with a history of recent or current smoking.^{81,121,122} Chest radiographs demonstrate a diffuse reticulonodular pattern. BAL fluid samples are characteristic, with abundant macrophages.^{34,35} Biopsy specimens are used essentially to distinguish the disease from eosinophilic granuloma and histiocytosis X.¹²¹ Treatment consists of steroid therapy and smoking cessation. The disease course is variable with a significant number of patients demonstrating progressive disease during treatment.

Cryptogenic Organizing Pneumonia

Cryptogenic organizing pneumonitis (COP), or idiopathic bronchiolitis obliterans organizing pneumonia, is an alveolitic pulmonary disease characterized by chronic inflammation of the alveoli, the production of granulation tissue in the bronchioles and alveoli, and the accumulation of macrophages within the alveoli.^{30,71,121,123–125} The incidence and etiology of COP is unknown, although an association with antibodies to nuclear proteins suggests an immune etiology.¹²⁶ Patients with this rare disorder have weight loss and a nonproductive cough. Chest radiographs often demonstrate bilateral diffuse opacities. Chest CT shows airspace disease with ground-glass opacities, as seen in other peribronchial processes such as RB-ILD and histiocytosis X.^{91,92} BAL fluid analysis reveals high levels of immune cells, including lymphocytes, eosinophils, macrophages, and neutrophils. However, the definitive diagnosis is dependent on lung biopsy.^{30,121,123–125} Treatment consists of steroid therapy,

with a typically rapid response and resolution of the disease. Relapses occur more often in those who have secondary forms of bronchiolitis obliterans organizing pneumonia from infection, drugs, or connective tissue disease. Relapses are also treated with steroids or other immunosuppressive regimens for longer periods, and there are reports of a minority of patients that do not respond and can progress to interstitial fibrosis.¹²⁷

Lymphocytic Interstitial Pneumonia

Lymphocytic interstitial pneumonia (LIP) is a lymphoproliferative disorder characterized by the infiltration of lymphocytes and plasma cells into the lung parenchyma.^{87,128} There is minimal to no alveolar injury. It is included, however, in the differential diagnosis of interstitial lung disease, and a lung biopsy may be required to exclude this disorder in some patients. LIP is a rare disorder seen predominantly in children, immunosuppressed patients, and women between the ages of 40 and 80 years. As with the vast majority of the ILDs discussed here, the etiology is unknown. Afflicted individuals present with the nonspecific symptoms of fever, fatigue, and weight loss. Chest radiography and chest CT illustrate a reticulonodular pattern and sporadic ground-glass opacities with some progressing to parenchymal cyst formation. BAL fluid shows a large number of lymphocytes, but lung biopsy is usually required to make the diagnosis in susceptible patient populations.^{34,35} Progression to lymphoma has been documented, but initial treatment of LIP consists of steroid therapy.^{128,129}

Idiopathic Pleuroparenchymal Fibroelastosis

Idiopathic pleuroparenchymal fibroelastosis is an extremely rare condition in which there is fibrosis of the pleura and subpleural lung tissue. Patients typically present in the fifth decade of life with recurrent infections. Pneumothorax is common given the degree of subpleural fibrosis. The disease is often progressive with a case fatality rate of 40%.^{71,130}

Unclassifiable Idiopathic Interstitial Pneumonias

In many instances, the IIP cannot be classified. In these cases, there may be inadequate or discordant clinical, radiologic, or pathologic evidence. Patients may have had prior therapies that now make identification of the underlying disease impossible. Patients should then be treated based on the most likely diagnosis.⁵⁶

Interstitial Lung Disease Associated with Connective Tissue Diseases

Connective tissue diseases (CTDs) frequently involve the lungs. CTDs such as systemic sclerosis, polymyositis/dermatomyositis, and rheumatoid arthritis most frequently have lung involvement. The majority of patients with ILD and CTD have limited or stable disease, but a significant proportion develops progressive and severe disease. Lung involvement often is an indicator of disease

severity.^{56,96} Histologic patterns seen in lung tissue biopsied include NSIP, UIP, and LIP. NSIP is the most common pattern seen in CTDs except in rheumatoid arthritis where UIP can be seen. Treatment is geared at the underlying CTD typically with immunosuppressive or immunomodulating therapy, including steroids, mycophenolate, and rituximab.^{96,131,132}

Diffuse Alveolar Hemorrhage Syndrome

Diffuse alveolar hemorrhage is a life-threatening condition that is characterized by hemoptysis from bleeding that originates from the pulmonary vasculature. Patients develop diffuse parenchymal infiltrates and hypoxemia.¹³³ The condition can be progressive and is associated with a high morbidity and mortality rate. Histologically, there is diffuse alveolar damage similar to that seen in AIP and ARDS with evidence of a pulmonary capillary leak with interstitial edema and inflammation. Diffuse alveolar hemorrhage can occur from certain medications such as amiodarone, crack cocaine, propylthiouracil, and sirolimus.¹³³⁻¹³⁵ It is also associated with various connective tissue disorders, systemic vasculitis, as well as after bone marrow transplantation. Treatment is mainly supportive with steroids and directed toward the underlying disease and hemorrhage.¹³³⁻¹³⁵ Other immunosuppressive drugs such as azathioprine or cyclophosphamide have been used with varying degrees of success in patients unresponsive to steroids.¹³³⁻¹³⁵

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare progressive cystic disease of the lung that predominantly affects women. The disease is caused by the disorderly proliferation of smooth muscle cells throughout the lungs. Although LAM is not caused by an immune mechanism, it is listed in this section as patients with LAM have interstitial, predominantly cystic changes on their chest CT scans. Clinical features of LAM include the development of a pneumothorax, dyspnea, and cough resulting from the unrelenting cystic changes of the lung. Hence, LAM is characterized by a progressive clinical course leading to death typically within 10 to 15 years of diagnosis.¹³⁶⁻¹³⁸ Lung biopsy is required for diagnosis.

Currently, there is no standard effective medical therapy for LAM. Most therapies are supportive. New treatments are based on the discovery that individuals with LAM, much like tuberous sclerosis, have mutations in the *TSC1* and *TSC2* genes—mutations also found in tuberous sclerosis complex.^{136,139-141} The functional products of the *TSC1* and *TSC2* genes are hamartin and tuberin, respectively, which function as a cell surface associated complex regulating signal transduction through mammalian target of rapamycin (mTOR)—the target of rapamycin, the modulation of estrogen receptors, MMPs, and angiogenic factors such as vascular endothelial growth factor as well as other pathways, which are discussed further in several good reviews.^{136,140} This forms the basis of recent randomized clinical trials evaluating rapamycin as a treatment for LAM. Rapamycin targets and inhibits mTOR, which is known to be

inhibited by the hamartin-tuberin complex and whose regulation is lost in LAM.^{136,140} Doxycycline has been shown to be an inhibitor of MMPs in experimental in vitro and in vivo models, and it can be used to treat LAM.^{136,142,143} Progesterone has been used in the past with varying degrees of success to treat LAM disease progression based on the disease's predilection for women, the discovery of estrogen receptors in LAM cells, and its antiproliferative effect on LAM cells in vitro.^{144,145} Antiestrogen therapies such as tamoxifen may be useful in treating younger women.¹⁴⁶ Lung transplantation is an option for those unresponsive to therapy.

PATIENT EVALUATION

In approaching patients with suspected ILD, a thorough history and physical examination are critical (Fig. 11-7). The diagnosis may be suggested by a history of environmental or occupational exposure, connective tissue disease, or genetic disease. A similar clinical picture can be seen when intraparenchymal lymphatics are involved by malignant disease, so a history or evidence of malignancy must be sought.¹⁴⁷ Laboratory studies are performed for antibodies that suggest a connective tissue disease, for serum precipitins, or for elevated angiotensin-converting enzyme.

Pulmonary function tests are used to measure the extent of pulmonary dysfunction. ILDs are usually characterized by restrictive pulmonary physiology with a reduced total lung capacity, functional residual capacity, and residual volume. The forced expiratory volume in 1 second (FEV₁) and FVC are often decreased because of the decrease in total lung capacity. The lung's diffusing capacity for carbon

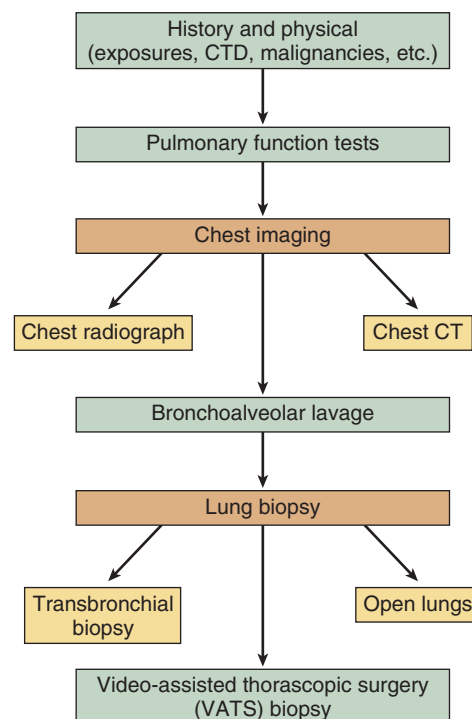


FIGURE 11-7 ■ Algorithm for the approach to a patient with interstitial lung disease. CTD, Connective tissue disease.

monoxide (DL_{CO}) is impaired because of the reduced compliance of the lung parenchyma and thus reflects the degree of resulting $\dot{V}/\dot{Q}$ mismatch more than the stage of disease. Arterial blood gases may be normal, but can reveal hypoxemia caused by significant $\dot{V}/\dot{Q}$ mismatch, particularly during exercise or sleep. Hypercarbia is usually indicative of end-stage disease. Chest imaging by plain film radiography and high-resolution chest CT is helpful in separating interstitial disease patterns from consolidative patterns and their associated diseases.¹⁴⁸ Findings on chest radiograph are often nonspecific, with bibasilar reticular markings, and may include nodular opacities, particularly in the upper lung fields in sarcoidosis, hypersensitivity pneumonitis, silicosis, berylliosis, and some of the connective tissue diseases. High-resolution chest CT provides information as to the extent and distribution of disease and is particularly useful in the investigation of early disease, when the chest radiograph may appear normal, and in the evaluation of coexisting adenopathy, malignancy, or emphysema, which have an impact on subsequent treatment. In general, the radiographic appearance may not directly correlate with the histopathologic stage of the disease or the degree of clinical impairment. However, the presence of classic radiographic findings on chest CT may be sufficient for diagnosis and thus obviate the need for tissue diagnosis in some cases.

BAL can be useful in the identification of diseases with a large inflammatory component, such as in GPA, or in the detection of a particular cellular subset, as seen in eosinophilic pneumonias or histiocytosis X (Langerhans cells), but it is nonspecific in most forms of ILD.^{34,35} Therefore, in many cases, lung biopsy by transbronchial, open, or VATS is required to make a definitive diagnosis.⁸⁴ Transbronchial biopsy is usually attempted first, particularly if sarcoidosis, Goodpasture syndrome, or eosinophilic pneumonia is a likely diagnosis, or to rule out lymphangitic carcinomatosis (Fig. 11-8) or an infectious origin. If definitive diagnosis is not possible, then surgical biopsy of two distinct disease sites, preferably on two different lobes, is warranted to provide the most effective means of establishing a diagnosis and prognosis. However, some clinicians argue that a single lung biopsy specimen from the lingual or right middle lobe has a diagnostic yield equivalent to two separate biopsies.¹⁴⁹ If adequate-size representative biopsies are obtained early in the disease course before treatment, avoiding areas of honeycombing (which reveals only nonspecific fibrosis), then the diagnostic accuracy approaches 90%.¹⁵⁰ Biopsy might not be beneficial if the clinical status or radiographic finding (e.g., extensive honeycombing) suggests that the patient is at high operative risk or that there is little benefit given the extent or prognosis of the disease.

VATS biopsy has proven to be as diagnostically accurate as open lung biopsy through a mini-thoracotomy.^{95,151} However, the patient must be able to tolerate single-lung ventilation and to remain in the full lateral decubitus position. Those who are acutely ill or are in a late stage of the disease have decreased pulmonary compliance and decreased DL_{CO} and thus a limited ability to tolerate general anesthesia, particularly with single-lung ventilation. These patients require an open lung biopsy through a mini-thoracotomy. Ideally, lung biopsies should be

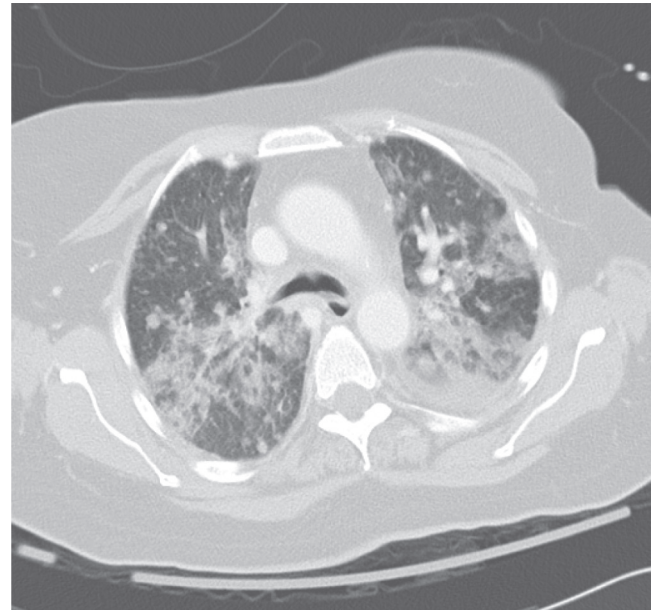


FIGURE 11-8 ■ Computed tomography of the chest in a patient with a history of breast cancer and rapidly progressive bilateral ground-glass opacities. Lung biopsy revealed metastatic adenocarcinoma. There was a desmoplastic reaction around sites of tumor leading to focal areas of interstitial fibrosis as well.

attempted in patients whose disease stage is early, before diffuse fibrosis has set in, making both diagnosis and intraoperative management increasingly difficult and VATS implausible. Ideal candidates for VATS are ILD patients who are symptomatic but ambulatory with relatively preserved lung function.

More recently, there has been considerable interest in determining biomarkers for IIPs, particularly IPF. Putative serum biomarkers identified have included epithelial and macrophage proteins such as metalloproteinases such as MMP-7 or chemokine ligands (CCL-18).^{26,96,152} The goals of biomarker research are to be able to distinguish IPF from non-IPF in IIP patients as well for prognostication. It is likely that biomarkers will augment current clinical, radiologic, and histologic data for classification of IIPs in the future.

TREATMENT

Treatment is directed at the underlying condition and symptomatic relief. Hypoxemia is treated with supplemental oxygen. Unless a causative agent is identified that can be removed or specifically treated, success is low. Glucocorticoids are the cornerstone of medical therapy, and they are recommended for all symptomatic patients diagnosed with idiopathic, interstitial, eosinophilic, or cryptogenic organizing pneumonias; connective tissue disease; sarcoidosis; or ILDs. A slow taper over several months is attempted if symptoms improve, because a rapid wean can be associated with recurrent disease. Although newer therapies are being investigated, the only currently available treatment option for the significant number of patients that are medical failures is that of lung transplantation.^{73,153}

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INFECTIOUS LUNG DISEASES

John D. Mitchell

CHAPTER OUTLINE

BACTERIAL LUNG INFECTIONS

Community-Acquired Pneumonia

Clinical Presentation of Community-Acquired Pneumonia

Determination of Community-Acquired Pneumonia Severity

Treatment of Community-Acquired Pneumonia

Hospital-Acquired (Nosocomial) Pneumonia

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Aspiration Pneumonia

BRONCHIECTASIS

LUNG ABSCESS

PULMONARY MYCOBACTERIAL DISEASE

MAJOR PULMONARY MYCOTIC INFECTIONS

Histoplasmosis

Coccidioidomycosis

Blastomycosis

Aspergillosis

Aspergilloma

Invasive Aspergillosis

Allergic Bronchopulmonary Aspergillosis

Cryptococcosis

Mucormycosis

The development of techniques to treat complications of infectious lung disease formed the cornerstone of modern thoracic surgery, dominating the specialty until approximately 1960. Although advances in critical care, antibiotic therapy, and other alternative treatments have lessened the impact of many lung infections in the practice of today's cardiothoracic surgeons, current evidence suggests other categories of pulmonary infection are on the rise. There are several reasons for this change: the use of broad-spectrum antimicrobial agents, selecting out resistant organisms; the emergence of new, opportunistic organisms, freshly minted as human pathogens; the widespread application of transplant techniques, accompanied by the ubiquitous immunosuppression protocols; and importantly, the failure of preventive medicine and public hygiene measures to reduce the rate of community-acquired infection. If anything, the infectious challenges facing cardiothoracic surgeons today are more daunting than they were 40 years ago. This chapter reviews the more common causes of pulmonary infection and their treatment.

BACTERIAL LUNG INFECTIONS

Community-Acquired Pneumonia

The term *pneumonia* refers to infection of the lower respiratory tract, involving the respiratory bronchioles to the

distal alveoli. These illnesses have been subclassified based on the mode and timing of presentation and on the existing comorbidities of the affected patient. These distinctions are often useful when considering empiric antibiotic therapy. The terms *typical* and *atypical pneumonias*, which refer to the causative organism, are outdated but still occasionally useful when considering this subject. Pneumonias caused by so-called atypical organisms (including *Mycoplasma pneumoniae*, *Legionella* species, and *Chlamydia pneumoniae*) can comprise up to 40% of cases but are rarely distinguishable from typical bacterial pneumonias at clinical presentation.¹ Thus, the initial therapy chosen should consider both typical and atypical pathogens.

Community-acquired pneumonia (CAP) describes an acute bacterial or viral respiratory infection, contracted outside the confines of the hospital or long-term care facility setting.²⁻⁴ It remains a common illness, with an estimated incidence of between 5 and 6 million cases resulting in more than 1 million hospitalizations annually.^{5,6} Because CAP is not a reportable illness, these figures likely underestimate the actual magnitude of the problem. The aggregate cost for treating these patients approaches \$9 billion a year, most of which is spent on inpatient management.⁶ The length of hospitalization has been shown to be the key factor in determining the cost of treatment.⁷ Pneumonia remains the eighth leading cause of death in the United States.⁸ The mortality rate associated with the development of pneumonia ranges

TABLE 12-1 Community-Acquired Pneumonia: Likely Pathogens

Outpatients without Comorbidities*	Outpatients with Comorbidities	Hospitalized Patients without Comorbidities	Hospitalized Patients Requiring ICU Admission
<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>
<i>M. pneumoniae</i>	<i>M. pneumoniae</i>	<i>H. influenzae</i>	<i>Legionella</i> spp.
<i>C. pneumoniae</i>	<i>C. pneumoniae</i>	<i>M. pneumoniae</i>	<i>H. influenzae</i>
<i>H. influenzae</i>	Mixed infection [†]	<i>C. pneumoniae</i>	Enteric gram-negative bacilli
Respiratory viruses	<i>H. influenzae</i>	Mixed infection	<i>S. aureus</i>
<i>Legionella</i> spp.	Enteric gram-negative bacilli	Enteric gram-negative bacilli	<i>M. pneumoniae</i>
<i>M. tuberculosis</i>	Respiratory viruses	Aspiration (anaerobes)	<i>Legionella</i> spp.
Endemic fungi	<i>M. catarrhalis</i>	Respiratory viruses	Respiratory viruses
	<i>Legionella</i> spp.	<i>Legionella</i> spp.	<i>C. pneumoniae</i>
	Aspiration (Anaerobes)	<i>M. tuberculosis</i>	<i>M. pneumoniae</i>
	<i>M. tuberculosis</i>	Endemic fungi	Endemic fungi
	Endemic fungi	<i>P. carinii</i>	<i>P. aeruginosa</i>

*Chronic obstructive pulmonary disease, congestive heart disease, diabetes mellitus.

[†]Often a polymicrobial infection of typical and atypical organisms.

Modified from Niederman MS, Mandell LA, Anzueto A, et al: Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 163:1730–1754, 2001.

from 1% to 5% for ambulatory patients without comorbidities, to 23% in those hospitalized, and to up to 40% for those requiring intensive care unit (ICU) admission.^{8,9}

The most common pathogens responsible for CAP are listed in Table 12-1. *Streptococcus pneumoniae* has remained the most commonly identified organism, followed by *Haemophilus influenzae*, *Staphylococcus aureus*, enteric gram-negative bacilli, *Legionella* species, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and respiratory viruses.^{3,5,9} In up to 50% of cases, a causative organism is not identified. The likelihood of finding a particular pathogen often depends on the population studied (see Table 12-1) and the diagnostic tests used. For example, the use of sputum culture favors pneumococcus as the most frequently identified organism, whereas *M. pneumoniae* is seen more commonly when serologic tests are used. The presence of a “mixed” infection involving atypical and typical organisms can approach 40%,¹⁰ although it is uncertain whether the atypical organisms, when present, represent an actual coinfection, a preceding infection, or simple colonization. However, empiric antibiotic regimens that cover both typical and atypical organisms have been associated with improved survival and shorter hospitalizations in several large retrospective studies.^{11–13}

Certain risk factors may predispose patients to infection with particular organisms. For example, pneumonia caused by drug-resistant pneumococcus has been associated with advanced age (>65 years), alcoholism, immune-suppressive illness or therapy, recent β -lactam therapy, and other significant comorbidities. Enteric gram-negative infections are seen more frequently in nursing home patients; patients with significant other medical conditions, including cardiopulmonary disease; and patients who have recently undergone antibiotic therapy. Pseudomonal infections are more likely to arise in those with structural lung disease, malnutrition, or in the presence of immune-suppressive or broad-spectrum antibiotic therapy.⁵ *H. influenzae* infections occur more frequently in smokers than in nonsmokers.

Clinical Presentation of Community-Acquired Pneumonia

Patients with CAP typically present with cough (90%), dyspnea (66%), sputum production (66%), and pleuritic chest pain (50%). Nonrespiratory symptoms such as malaise, headache, nausea, myalgias, arthralgias, abdominal pain, and mental confusion are seen in 10% to 30% of patients. Older adult patients often have fewer or less severe symptoms than younger patients. Presenting signs on physical exam include fever (80%), tachypnea, tachycardia, and a generalized toxic state. Crackles on auscultation are common (80%), with indications of consolidation in up to 30% of patients.¹⁴

Evaluation with chest radiography should be undertaken in all patients who have symptoms and signs suggestive of pneumonia.¹⁵ Standard posteroanterior and lateral films classically reveal a segmental (Fig. 12-1) or lobar infiltrate, often with evidence of a parapneumonic effusion. Chest films also help distinguish pneumonia from other disorders that may display similar symptoms and can help assess the severity (e.g., multilobar involvement) of the illness. Contributing or causative factors such as bronchial obstruction, lung abscess, or tuberculosis can also be seen. The addition of computed tomography may occasionally be helpful in difficult cases, but few data are available to support its routine use in the initial evaluation of patients with CAP.

Routine collection of laboratory studies in ambulatory patients is rarely necessary but may occasionally steer clinicians toward hospital admission in equivocal cases. Laboratory studies in hospitalized patients should include complete blood count, electrolytes and glucose, renal and liver function tests, and assessment of oxygen saturation. Patients aged 15 to 54 should undergo human immunodeficiency virus (HIV) testing with informed consent.¹⁵ Tests used to identify a causative agent (including blood cultures and sputum Gram stain and culture) should be performed in all patients admitted with pneumonia, although some have questioned the usefulness of blood cultures in low-risk patients.¹⁶ Viral cultures have not

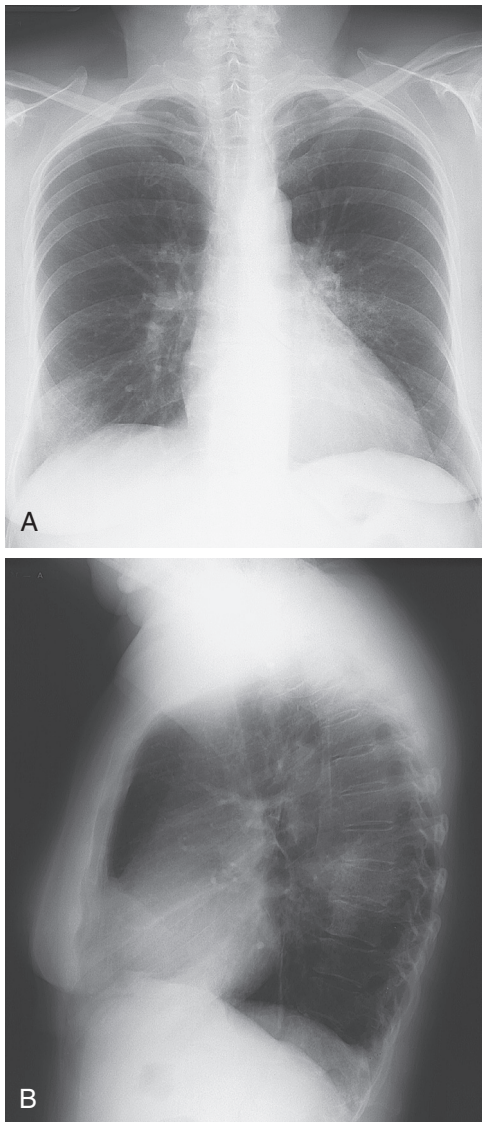


FIGURE 12-1 ■ Posteroanterior (A) and lateral (B) chest radiographs demonstrating segmental pneumonia involving the superior segment of the left lower lobe.

been shown to be useful in the initial evaluation of patients with CAP and should not be routinely performed,¹⁷ although clear improvement in the diagnostic yield has been demonstrated with the use of real-time polymerase chain reaction (PCR) analysis.¹⁸⁻²¹ Every attempt should be made to obtain these cultures before initiating therapy but not at the expense of unnecessary delays in treatment. Culture data should be correlated with the Gram stain result before narrowing antibiotic therapy. Significant pleural effusions should be tapped and sent for laboratory and culture studies. Routine serologic and cold agglutinin testing is generally not recommended in the initial evaluation of patients with CAP³ but may prove useful in select cases. This recommendation is based on the low failure rate seen with empiric therapy for patients treated in the outpatient setting. A pneumococcal urinary antigen assay approved by the U.S. Food and Drug Administration can be used to

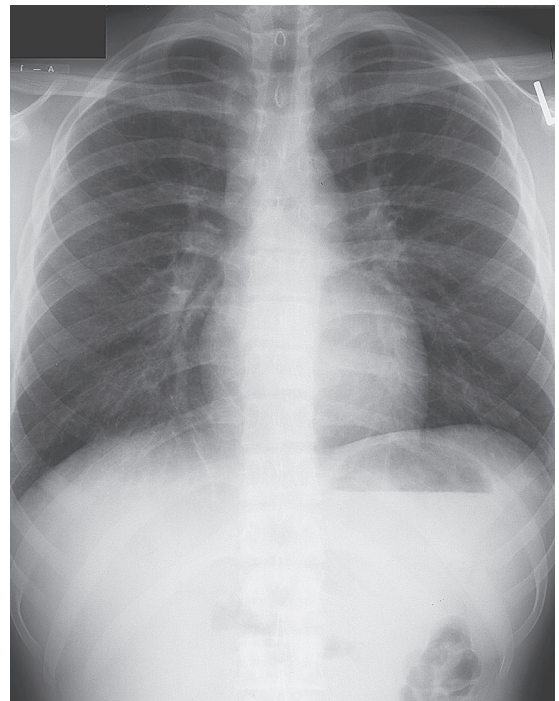


FIGURE 12-2 ■ Posteroanterior chest radiograph demonstrating a fine interstitial pattern indicative of *Mycoplasma pneumoniae*.

augment the standard diagnostic methods,²²⁻²⁴ with the advantage of rapid results similar to the Gram stain. Sensitivity and specificity rates of 80% to 90% have been reported. Use of similar technology to detect pneumococcal antigen in sputum has also been reported.²⁵

Patients with pneumonia caused by *Mycoplasma* species often show signs and symptoms reminiscent of a mild viral illness, with a more gradual onset and less intense nature. These infections, as with other “atypical” infections, occur more frequently in younger patients. Headache, malaise, sore throat, low-grade fever, and rhinorrhea are common. Cough, when present, is frequently non-productive and spasmodic in character. Extrapulmonary manifestations may predominate, with rash, arthralgias, and neurologic abnormalities present. The physical exam of the chest may yield minimal findings, although a wheeze and crackles can sometimes be appreciated. Radiologic findings include nodular or peribronchial infiltrates, an interstitial pattern of disease (Fig. 12-2), and occasional consolidation. Pleural effusions occur frequently. Although the white cell count is often normal, anemia can be seen as a result of hemolytic anemia associated with a positive Coomb test result. Serologic diagnosis can be obtained through measurement of immunoglobulin M (IgM) or immunoglobulin G (IgG) titer using a complement fixation test.

Pneumonia caused by *Legionella* (*Legionella pneumophila*) remains problematic since the initial recognized outbreak of the disease at an American Legion convention in Philadelphia in 1976. The organism is identified in 1% to 5% of patients hospitalized with pneumonia, with considerable variation in detection as a result of geographic

patterns and difficulties in accurate diagnosis. Culture may still be the best way of identifying *Legionella*, along with a urinary antigen assay.²⁶ However, the latter test can remain positive months after the acute infection. Symptoms suggestive of pneumonia predominate (high fever, chills, dyspnea, cough), but extrapulmonary manifestations (gastrointestinal complaints, malaise, myalgias) are not uncommon. Radiographs usually reveal patchy or diffuse interstitial infiltrates and occasionally consolidation (Fig. 12-3).

Pulmonary infection with *Chlamydia* organisms such as *C. pneumoniae* present in similar fashion to other atypical pneumonias. Infection with this organism has also been associated with chronic diseases such as atherosclerotic coronary disease. Diagnostic tests used to identify this organism include direct tissue culture (sputum smear and culture are not helpful) and display of a fourfold increase in IgG titer or a IgM titer of 1:16 or higher using a microimmunofluorescence test.

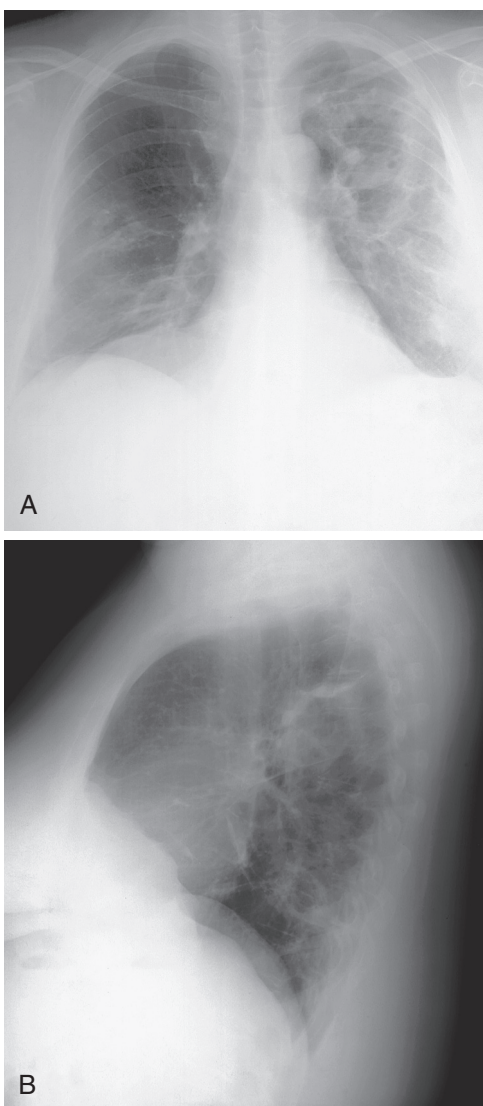


FIGURE 12-3 ■ Posteroanterior (A) and lateral (B) chest radiographs demonstrating diffuse infiltrates with cavitation, radiographic features of *Legionella* infection.

Determination of Community-Acquired Pneumonia Severity

One of the key decisions made in the initial evaluation of CAP, beyond establishing a presumptive diagnosis, pertains to the need for inpatient therapy. Many of the patients afflicted with CAP are older adults with significant comorbidities for whom the progressive pulmonary infection is clearly life-threatening. On the other hand, improper admission for CAP therapy taxes the health care system billions of dollars annually. In the United States, less than 20% of patients with CAP are admitted for inpatient therapy, but these patients account for more than 90% of the costs related to the disease treatment.⁶ As a result, various guidelines have been developed to assist clinicians in the assessment of severity of illness at presentation. One such system, termed the *Pneumonia Severity Index (PSI)*, was validated with data from approximately 2300 patients in the Pneumonia Patient Outcomes Research Team (PORT) cohort study.²⁷ Based on clinical parameters obtained at initial presentation, a risk score or class is determined (Fig. 12-4). Patients with a risk class of I, II, or III had a low mortality rate (<1%) and were considered to be at low risk, thus amenable to outpatient management. Patients with a risk class of IV or V were associated with higher mortality rates (9.3 and 27.0, respectively) and were considered to be appropriate candidates for hospitalization. The value of the PSI has since been confirmed in multiple studies,²⁸⁻³³ and the PSI is endorsed within the guidelines set forth by the American Thoracic Society and Infectious Diseases Society of America.³ These guidelines emphasize a multistep process in determining the initial site of treatment, based on (1) assessment of factors that compromise the safety of home care, (2) the PSI score, and (3) clinical judgment. The PSI has been criticized, however, because of the relative complexity of the assessment required.

In contrast, the British Thoracic Society has adopted an alternative prediction rule for risk stratification in the setting of CAP, termed *CURB-65*.³⁴ The CURB-65 uses five prognostic variables: the presence of confusion, a blood urea nitrogen concentration (BUN > 20 mg/dL), respiratory rate (>30 breaths/min), low blood pressure (systolic, <90 mm Hg; diastolic, <60 mm Hg), and age (>65 years). Patients with scores of 0 or 1 were considered to be appropriate for outpatient care; those with scores of 2 or 3 should be considered for admission, perhaps to the ICU; and scores of 4 or 5 should receive mandated ICU care. A simplified version of CURB-65, termed *CRB-65*, drops the use of the BUN measurement and thus is applicable to the outpatient office setting.³⁵

The PSI and the CURB-65 have been compared in a variety of studies,^{28,36,37} with strengths and weaknesses described for both systems. The PSI is particularly good at identifying patients with a low risk of mortality, but it tends to underestimate severity of illness in some patient populations. Alternatively, the CURB-65 more accurately identifies those patients with severe CAP and at high risk of death. It has been proposed that the two assessment tools may be thought of as complementary rather than competitive tests.³⁸

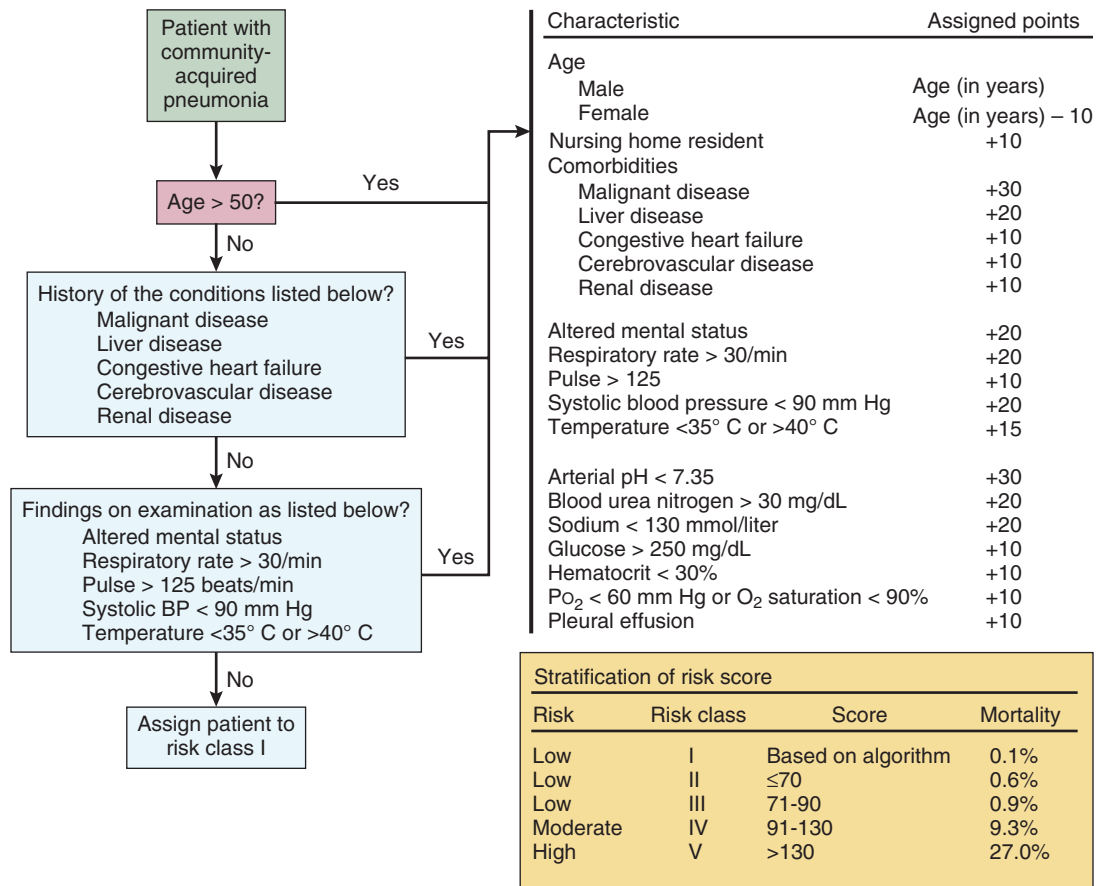


FIGURE 12-4 ■ The Pneumonia Severity Index. BP, Blood pressure; O₂, oxygen; PO₂, partial pressure of oxygen.

Treatment of Community-Acquired Pneumonia

The treatment for CAP at initial presentation is outlined in Figure 12-5, as described by the American Thoracic Society and Infectious Diseases Society of America, stratified by the presence or absence of modifying factors, comorbidities, and site of initial treatment.³ Data from published reports support the use of the published guidelines, leading to better outcomes.^{11,39-46} It should be reinforced that the timing of therapy is important, with the first dose of antibiotic given 4 to 8 hours after initial presentation. Prompt administration of therapy has been associated with improved survival.⁴⁶ The use of the published guidelines facilitates prompt delivery of appropriate therapy. Furthermore, although it is desirable to narrow the spectrum of administered antibiotic agents, this is not possible in up to 50% of cases because the causative organism has not been identified. In addition, a significant proportion of cases represent mixed polymicrobial infections. The use of these guidelines using broad-spectrum therapy allows for appropriate treatment in these patients.

Clinical decisions regarding duration of therapy are poorly supported in the literature. In general, most treatment regimens last 7 to 14 days; the severity of the presenting illness, the response to therapy, and the underlying comorbidities should all be considered when addressing

duration of treatment. Most bacterial infections, including those caused by *S. pneumoniae*, are treated for 7 to 10 days provided a good clinical response is seen. *Mycoplasma*, *Chlamydia*, and *Legionella* infections should be treated for 10 to 14 days, and perhaps longer if significant comorbidity exists.

Successful response to therapy in a patient with CAP usually follows a predictable course. Stabilization of clinical parameters often occurs by 72 hours, with gradual improvement noted thereafter. The severity of the presenting illness and underlying patient disease understandably play a role in the response to therapy. The febrile response and leukocytosis typically resolve by day 4 or 5, with the radiologic findings lagging behind. In fact, the initial radiographic abnormalities may worsen before improvement is documented. Only 15% of chest films are clear at discharge, and many cases take 2 to 3 months to return to normal. With a successful response to treatment, consideration should be given to conversion to oral therapy. The American Thoracic Society describes four criteria that should be met prior to switching to oral therapy: improvement in cough and dyspnea; afebrile (<100° F) at two consecutive assessments 8 hours apart; resolving leukocytosis; and a functioning gastrointestinal tract with oral intake.⁵ Obviously, some leeway may be allowed in these criteria given the clinical situation. Compliance can be an issue with oral therapy, and consideration of drug dosing schedules and side effects

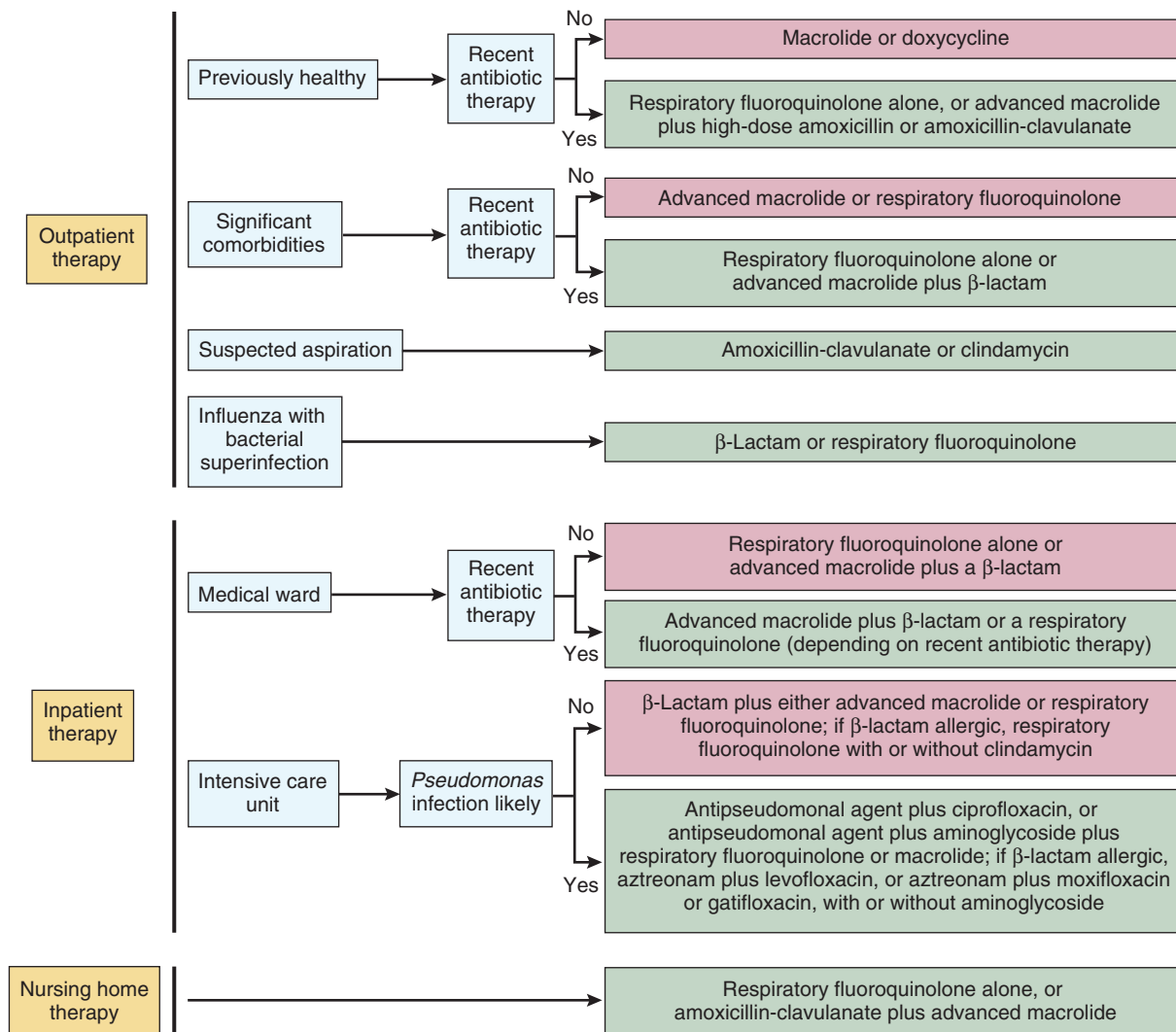


FIGURE 12-5 ■ Empiric therapy for community-acquired pneumonia.

should be taken into account when selecting an oral regimen.⁴²

Two adjunctive therapies have been studied for their effects on outcome in patients with severe CAP. In a retrospective analysis, the administration of activated protein C to a subset of patients in the PROWESS study with CAP was associated with a drop in mortality rates.⁴⁵ Further studies, including prospective randomized trials, remain pending. In at least one randomized study, the use of a continuous infusion of corticosteroids in patients with CAP was associated with lower mortality rates, shorter length of ICU stay, and shorter duration of mechanical ventilation.⁴⁷ No increase in complications was associated with the use of steroids in this patient population.

Two serum markers, C-reactive protein (CRP) and procalcitonin (PCT), have been studied to assess response to CAP therapy, determine outcome, and guide duration of therapy. Of the two, PCT seems the most promising. PCT is the precursor to calcitonin and has no hormonal effects. Serum levels of PCT rise in the setting of acute bacterial infections, stimulated by

cytokines, microbial toxins, and the cell-mediated immune response. One study determined that higher serum levels of PCT, drawn within 24 hours of admission to hospital, were associated with higher PSI levels and a greater risk of mortality.⁴⁸ Other investigators have found PCT levels useful in predicting outcome and guiding duration of therapy.⁴⁹⁻⁵¹

Clinicians should resist the urge to switch antibiotic therapy within the first 72 hours, unless marked clinical deterioration occurs. Failure to respond to initial therapy occurs in up to 10% of patients because of a variety of factors. The presence of a drug-resistant or unusual pathogen may be the cause, which may be remedied by further diagnostic tests for the causative agent, broadening the antibiotic therapy, or both. A complication of the initial pneumonia may be present, at either a local (e.g., lung abscess, empyema) or a distant (e.g., meningitis, endocarditis, septic arthritis) site. Selected imaging, such as computed tomography and echocardiography, as well as sampling of fluid collections based on these studies and physical exam, can often reveal the source of the persistent infection. Finally, several noninfectious illnesses can

mimic pneumonia and should be ruled out. This group of disease states is extensive and includes bronchogenic cancer, lymphoma, and a variety of inflammatory and interstitial lung diseases.

Hospital-Acquired (Nosocomial) Pneumonia

Hospital-acquired pneumonia (HAP) refers to pulmonary infection that occurs after at least 48 to 72 hours of admission to an acute care facility or in intubated patients. The latter situation is termed *ventilator-associated pneumonia*. HAP is the second most common nosocomial infection and has the highest mortality⁵²⁻⁵⁴, with crude mortality rates of 30% previously reported.⁵⁵ Risk factors for nosocomial pneumonia have been described and include the extremes of age, chronic lung disease, previous abdominal or thoracic surgery, endotracheal intubation, and duration of mechanical ventilation.⁵⁶

Two factors predispose patients to nosocomial pneumonia: the aerodigestive tract is colonized with bacteria, and the contaminated secretions are aspirated into the lower respiratory system.⁵⁷ Several of the preventive strategies described later are aimed at interrupting these two processes.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is a nosocomial pulmonary infection that develops in patients receiving mechanical ventilation. VAP that occurs early, within 48 to 72 hours after intubation, is typically caused by bacteria responsive to antibiotic therapy (e.g., pansensitive *S. aureus*, *H. influenzae*, and *S. pneumoniae*) and frequently results from aspiration complicating the intubation process. In contrast, late-onset VAP is often caused by antibiotic-resistant organisms (e.g., methicillin-resistant *S. aureus* [MRSA], *Pseudomonas aeruginosa*, *Acinetobacter* and *Enterobacter* species).⁵⁸ Risk factors for VAP include the duration of mechanical ventilation, age older than 70 years, H₂ or antacid therapy, chronic lung disease, depressed consciousness, need for reintubation, and gastric aspiration.^{52,58-61} The incidence of VAP is significantly higher in surgical ICUs as opposed to medical ICUs, according to the Centers for Disease Control and Prevention.⁶²

There is some controversy in the literature regarding optimal diagnosis of VAP.⁶³ To date, there seems to be little evidence supporting the use of invasive (bronchoscopic) techniques for diagnosis compared with quantitative tracheobronchial aspirates, with no difference in subsequent mortality, length of hospital stay, or duration of mechanical ventilation.⁶⁴⁻⁶⁸ Bronchoscopy may be of use in patients who fail to respond to initial therapy.⁶⁹ The treatment of VAP consists of general supportive care and the administration of empiric broad-spectrum antibiotics, guided by the severity of the illness.^{52,70} The adequacy of initial antibiotic therapy appears to be the most important determinant of outcome.^{71,72} Numerous studies have examined preventive measures to limit the development of VAP. The use of semi-recumbent positioning, sucralfate instead of H₂ antagonists for stress

ulcer prophylaxis, and selective digestive tract decontamination has the strongest support in the literature.⁷³

Health Care–Associated Pneumonia

Health care–associated pneumonia (HCAP) refers to pneumonia that occurs in a nonhospitalized patient with extensive health care contacts. Examples of such contacts include outpatient intravenous therapy, hospitalization, or treatment at a hospital or dialysis unit within the past 30 days; or residence in a nursing home or other long-term care facility. In general, the recommendations for treatment mirror those suggested for HAP.⁵²

Aspiration Pneumonia

Aspiration refers to the inhalation of oropharyngeal or gastric contents into the tracheobronchial tree. This usually results in either a *pneumonitis* caused by a chemical injury from contact with sterile, acidic gastric contents or a *pneumonia* caused by inhalation of infected material. In rare cases, aspiration can lead to airway obstruction, lung abscess, and other findings. Aspiration pneumonia is a common problem, accounting for 5% to 15% of CAP, and is frequently seen in nursing home residents, in patients with swallowing disorders, and in patients with altered mental states. It is also a recognized complication of general anesthesia, occurring in approximately 1 in 3000 operations and accounting for 10% to 30% of deaths related to anesthesia.⁷⁴

The acute lung injury or pneumonitis from gastric aspiration, termed *Mendelson syndrome*,⁷⁵ appears directly related to the acidity and volume of aspirated material. In general, a pH less than 2.5 and a volume in excess of 0.3 mL/kg (approximately 21 mL in a 70-kg adult) are required to initiate lung injury. The injury follows a biphasic pattern, with the initial insult caused by direct damage of the acid on the delicate capillary and alveolar cells, followed several hours later by the rapid accumulation of inflammatory cells and mediators resulting in a local and systemic inflammatory response. Progression to acute respiratory distress syndrome and multiorgan system failure may ensue. Because the gastric contents are sterile because of the acidity, infection is usually not an initial feature in these cases but can become prominent later in the course of the illness with secondary infection of the damaged lung parenchyma. Efforts to modify the gastric pH may lead to gastric colonization with gram-negative bacteria as well as other organisms, leading to infection early following the aspiration episode. Treatment is largely supportive in nature. Particularly if the aspiration is witnessed, bronchoscopy is indicated to remove any residual fluid or debris from the airway. The use of corticosteroids in the treatment of aspiration pneumonitis has not been shown to be of benefit. Although it is common practice to initiate antibiotic therapy in these patients, this often overtreats simple pneumonitis that may resolve with supportive measures alone. Furthermore, the use of antibiotics early may encourage the development of resistant organisms. Antibiotic therapy should be considered early in patients thought to have gastric colonization and in those patients who do not

improve within 48 hours of the inciting event and who show evidence of ongoing lung injury, infection, or infiltrate.⁷⁶ Empiric coverage with broad-spectrum agents is recommended.

Aspiration pneumonia commonly arises from inhalation of colonized oropharyngeal bacteria, causing the signs, symptoms, and radiographic changes representative of pneumonia. Approximately half of normal adults aspirate while asleep,⁷⁷ and for infection to occur, the normal protective mechanisms must either fail or be overwhelmed by the volume or bacterial burden of the aspirate. In supine patients, the dependent lung segments (posterior aspects of upper lobes, superior segments of lower lobes) are affected most frequently. In upright individuals, the basilar segments, particularly on the right side, are at greatest risk of infection. The aspiration episode in patients developing pneumonia is frequently not observed, and the diagnosis is derived from the clinical picture and the characteristic radiographic changes in individuals known to be at risk. Treatment with antimicrobial therapy is appropriate. Use of antibiotics with anaerobic coverage is probably overdone but is appropriate in select cases where severe periodontal disease, alcoholism, and other disorders predominate. In hospitalized patients, coverage of gram-negative bacteria is essential.

BRONCHIECTASIS

Bronchiectasis was first described in 1819 by Laennec. It is defined by the permanent dilation of the bronchi,⁷⁸ caused by a recurrent process of transmural infection and inflammation. The disease process is characterized by the pathologic or radiographic appearance of the airways. Cylindrical or tubular bronchiectasis results in dilated, slightly tapered airways; varicose bronchiectasis resembles the chronic venous state of the same name, with areas of dilation and constriction; and in saccular or cystic bronchiectasis, progressive dilation of the airway can end in saclike, cystic structures resembling a cluster of grapes. The cylindrical changes are frequently seen with tuberculosis infections, whereas the saccular or cystic type is more common after obstruction or bacterial infection. Thick, mucoid secretions are often noted pooled in the dilated airways, causing a chronic inflammatory state involving the airway walls. The lung parenchyma distal to the dilated, ectatic airways are often damaged as well, with fibrosis and emphysematous changes present. The accompanying bronchial arteries and lymph nodes are engorged and hypertrophied as well. The left lower lobe is the area most frequently involved, followed by the lingula and right middle lobe.

The causes and disease states associated with bronchiectasis are listed in Box 12-1. The common pathway for all these disorders is recurrent, transmural infection of the bronchial wall. Bacterial infections, particularly those involving potentially necrotizing agents such as *S. aureus*, *P. aeruginosa*, *S. pneumoniae*, and various anaerobes, remain important causes of bronchiectasis, particularly when there is a delay in treatment or there are factors present to prevent eradication of the infection. Bronchiectasis in patients with allergic bronchopulmonary

BOX 12-1 Conditions Causing or Associated with Bronchiectasis

- Infection
 - Bacterial
 - Mycobacterial
 - Aspergillus*
 - Viral (including HIV)
- Congenital conditions
 - Primary ciliary dyskinesia
 - α_1 -Antitrypsin deficiency
 - Cystic fibrosis
 - Tracheobronchomegaly (Mounier-Kuhn syndrome)
 - Cartilage deficiency (Williams-Campbell syndrome)
 - Pulmonary sequestration
 - Marfan syndrome
- Immunodeficiency
 - Hypogammaglobulinemia
 - Secondary to disease states or therapy
- Sequelae of toxic inhalation or aspiration
 - Chlorine
 - Foreign body
- Rheumatic conditions
 - Rheumatoid arthritis
 - Systemic lupus erythematosus
 - Sjögren syndrome
 - Relapsing polychondritis
- Inflammatory bowel disease

Adapted from Barker AF: Bronchiectasis. *N Engl J Med* 346(18):1383–1393, 2002.

aspergillosis is the result of an immune reaction to the fungal organism, with production of inflammatory mediators and subsequent direct airway invasion by the fungus. Viral infections can lead to bronchiectatic airways both through direct infection and through a reduction in host defenses. This latter theme is common when considering the pathophysiology of bronchiectasis. Primary ciliary dyskinesia and various immune deficiencies such as hypogammaglobulinemia are examples of congenital disorders in which there is impairment in host defense mechanisms. Cystic fibrosis is another important cause of bronchiectasis, with predilection for the upper lobes. Occasionally the appearance of bronchiectasis in middle age will be the presenting symptom in patients with milder forms of cystic fibrosis. Several autoimmune disorders, such as rheumatoid arthritis and inflammatory bowel disease, have been linked to the presence of recurrent pulmonary infections and the development of bronchiectasis.

Both focal and diffuse forms of bronchiectasis are seen. The focal variety is often associated with an isolated abnormality causing relative or complete bronchial obstruction. An aspirated foreign body, a slow-growing tumor, and a broncholith are examples. In rare cases, bronchial compression (as seen with middle lobe syndrome) or angulation of the bronchus (following surgical lobectomy) produce obstruction leading to recurrent infection and the development of localized disease. Bronchiectasis of postinfectious causes is more likely to be localized, whereas disease caused by congenital deficiencies is more likely to be diffuse. A recent study of stable

patients with bronchiectasis revealed a 64% incidence of colonization with what were termed *potential pathogenic microorganisms* (PPMs). The most frequently isolated PPMs were *H. influenzae*, *Pseudomonas* spp., and *S. pneumoniae*. Risk factors for PPM colonization include diagnosis of bronchiectasis before 14 years of age, an FEV₁ that is 80% predicted, and the presence of varicose or saccular bronchiectasis.⁷⁹

Patients with bronchiectasis experience recurrent pulmonary infections characterized by dyspnea and an unremitting chronic cough productive of thick, tenacious purulent sputum. Hemoptysis is common and at times can be massive because of erosion into the enlarged bronchial vessels. Occasionally patients with bronchiectasis will describe a nonproductive cough, indicative of upper lobe involvement. Auscultation reveals crackles, wheeze, or rhonchi in most patients.

The radiographic findings in bronchiectasis are understandably important in establishing the diagnosis. Standard radiographs are abnormal in most cases, demonstrating focal areas of consolidation, atelectasis, evidence of thickened bronchi (best noted as ring shadows when seen on end), and, in advanced cases, delineation of the dilated, cystic changes in the airway (Fig. 12-6). Computed tomography, particularly high-resolution imaging, is more sensitive and specific for the diagnosis of bronchiectasis. Evidence of airway dilation, changes consistent with saccules or varicosities of the airway, and lack of airway tapering toward the periphery are all consistent with bronchiectasis.⁸⁰ Upper lobe involvement suggests the diagnosis of cystic fibrosis or allergic bronchopulmonary aspergillosis, middle lobe and lingular disease is more typical of environmental mycobacterial infection such as *Mycobacterium avium* complex, and lower lobe predominance suggests bacterial involvement.

Therapy for bronchiectasis involves treatment of the underlying disorder if possible; suppression of the bacterial load through appropriate use of antibiotics; encouragement of proper pulmonary hygiene, including the routine use of bronchodilators, mucolytic agents, and postural drainage; and surgery in select cases. The role of surgery is threefold. First, patients with focal areas of

disease causing unremitting symptoms and associated with localized lung parenchymal destruction or antibiotic resistance or intolerance are candidates for resection therapy, usually via a segmentectomy or lobectomy. Most of these resections are amenable to minimally invasive techniques.⁸¹ Second, the rare patient who presents with massive hemoptysis should be considered for surgical therapy if less invasive maneuvers such as bronchial artery embolization are unsuccessful. Finally, some patients with end-stage bronchiectasis may be candidates for lung transplantation.⁸²⁻⁸⁴ As with other patients with end-stage suppurative lung disease, sequential double-lung transplantation is indicated to avoid contamination of the new transplanted lungs.

LUNG ABSCESS

A lung abscess is a circumscribed cavity within the lung parenchyma filled with purulent material and air. The cavity may form as a result of a necrotizing infection or may become secondarily infected. The abscess formation may be singular in nature or multifocal, depending on the causes. The abscess is arbitrarily termed acute if present for 6 weeks or less and chronic if it has been present for longer than 6 weeks. Further classification comes from the underlying cause, as noted earlier: a primary lung abscess arises from a necrotizing infection, whereas a secondary lung abscess forms as a result of another pathologic entity.

Box 12-2 lists the causes of lung abscess. The most common cause is inadvertent aspiration of infected oropharyngeal secretions, which can occur in the setting of impaired consciousness, in the presence of poor dental hygiene, or in association with gastroesophageal reflux

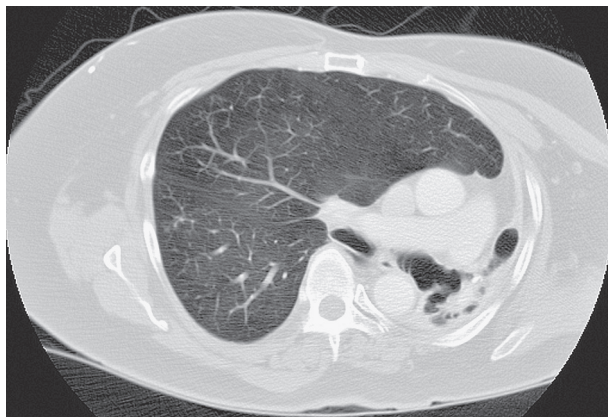


FIGURE 12-6 ■ Computed tomography scan demonstrating end-stage bronchiectasis involving the left lung, with complete parenchymal destruction.

BOX 12-2 Causes of Lung Abscess

PRIMARY

- Aspiration
 - Impaired consciousness
 - Severe periodontal disease
 - Dysphagia syndromes, esophageal reflux
- Necrotizing pneumonia
- Immunocompromised patient

SECONDARY

- Bronchial obstruction
 - Neoplasm
 - Foreign body
 - Lymphadenopathy
- Cavitating lesions
 - Neoplasm
 - Pulmonary infarct
 - Emphysema, bullous disease
- Direct extension
 - Amebiasis (liver)
 - Subphrenic abscess
- Hematogenous dissemination

Adapted from Hodder RV, Cameron R, Todd TRJ: Bacterial infections. In Pearson FG, Deslauriers J, Ginsberg RJ, et al, editors: Thoracic surgery, New York, 1995, Churchill Livingstone, pp 433-469.

disease or various dysphagia syndromes (strictures, Zenker and other diverticula, dysmotility disorders, achalasia, and others). A lung abscess can occur as a sequela of necrotizing lung infections, particularly in the setting of an immunocompromised host. Bronchial obstruction, caused by tumor, foreign body, or external compression of the bronchus, can predispose to distal lung infection and subsequent abscess formation. A preexisting cavity within the lung parenchyma, as a result of a cavitating neoplasm, a resolving infarct, or even structural lung disease, can lead to secondary infection and abscess. Direct extension of an adjacent abscess can occur. Finally, hematogenous seeding from another source can produce abscesses within the lung, often multifocal. Recognition of the secondary nature of the abscess can have direct therapeutic implications—for example, an abscess resulting from a foreign body aspiration will likely respond poorly to treatment if the offending item is not removed.

The location of lung abscesses is determined by the segmental anatomy of the tracheobronchial tree and the underlying cause. Because aspiration is a major cause, the dependent segments—the posterior segment of the right upper lobe and the superior segments of both lower lobes—tend to be involved frequently. The distribution roughly falls into right upper lobe, 25%; right middle lobe, 10%; right lower lobe, 33%; left upper lobe, 12%; and left lower lobe, 20%.⁸⁵

The bacteriology of lung abscesses frequently falls in line with the underlying cause. Many ambulatory patients with lung abscess have gram-positive bacteria (e.g., alpha- and beta-hemolytic streptococcus, *S. aureus*, *S. pneumoniae*, *Streptococcus viridans*) as the source, whereas gram-negative organisms (e.g., *Proteus* spp., *Escherichia coli*, *P. aeruginosa*, *Enterobacter* spp., and *Eikenella* spp.) predominate in nosocomial infections. In lung abscess caused by aspiration, mixed flora are often present and anaerobes play an important part.⁸⁶ Aerobic gram-positive cocci and facultative gram-negative bacilli are commonly found, including *S. aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, and *P. aeruginosa*.

Clinically, patients complain of cough, fever, malaise, weight loss, dyspnea, and occasionally pleuritic chest pain. The symptoms are reminiscent of pneumonia and may be insidious in onset. Hemoptysis may be a complicating factor in rare cases and can vary from blood streaks in the sputum to life-threatening hemorrhage. With cavitation and drainage into the tracheobronchial tree, patients will likely describe production of large volumes of foul-smelling sputum. The uninvolved lung can become soiled through a spillover effect and produce respiratory failure. If large enough, the abscess can exert a mass effect on adjacent structures. Rupture into the pleural space is uncommon but can lead to empyema and fulminant sepsis.

A chest radiograph is likely to show a cavitary space within the lung, accompanied by an air-fluid level (Fig. 12-7). In contrast with a hydropneumothorax, the abscesses are more likely to have equal air-fluid levels on both posteroanterior and lateral films.⁸⁷ Features of a lung abscess may be difficult to appreciate on plain film exam and can be mistaken for alternative diagnoses. Computed tomography is helpful in these cases,

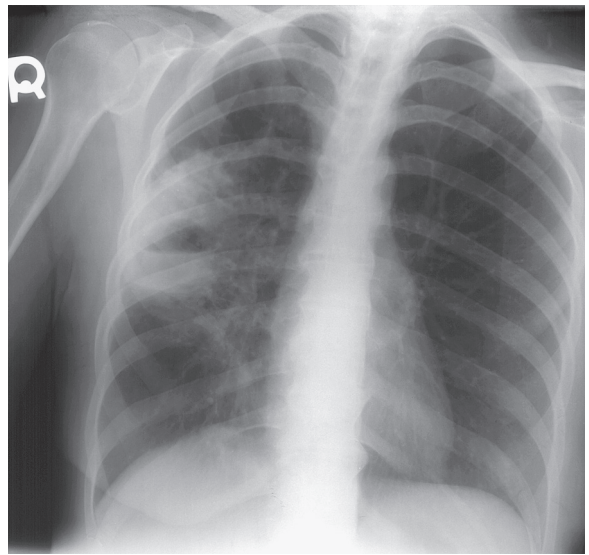


FIGURE 12-7 ■ Posteroanterior chest radiograph demonstrating a lung abscess with air-fluid level.

delineating the exact anatomic features and location of the abscess and its relation to adjacent structures. For example, a cavitary neoplasm may be confused with an abscess. Compared with the thin, smooth walls of the abscess, cavitation secondary to tumor is usually associated with thick, irregular walls, features that do not respond to antibiotic therapy. An interlobar fluid collection or empyema may also be mistaken for a lung abscess. A lenticular shape, obtuse angle with the chest wall, compression of neighboring bronchovascular structures, and a “split pleura” sign signify the presence of pleural fluid in these cases.⁸⁸ In addition to standard laboratory investigation, bronchoscopy should be used to assess for bronchial obstruction caused by tumor or a foreign body and possibly to obtain cultures. Accurate culture data may be best obtained through percutaneous fine-needle aspiration. In a series reported by Yang and colleagues,⁸⁹ fine-needle aspiration yielded a 94% success rate in culturing pathogens, compared with 11% from sputum culture and only 3% from lavage. Attempted drainage via bronchoscopic means should be discouraged in most cases because of the risk of flooding the airways with purulent material.

The successful treatment of lung abscess involves prolonged antimicrobial therapy targeted at the causative organism combined with establishment of adequate drainage. In most cases, the drainage can be accomplished internally, aided by postural techniques and chest physiotherapy. If internal drainage is inadequate, percutaneous drainage may be done, usually with an excellent response (Fig. 12-8). The complications of percutaneous drainage (empyema, pneumothorax, hemothorax) occur in less than 10% of cases, even less so if pleural symphysis is present. The course of antibiotic therapy typically lasts 6 to 8 weeks, with radiographic resolution occurring by 4 to 5 months. Medical therapy for lung abscess is generally successful in 85% to 90% of cases.⁹⁰ Indications for surgical intervention would include empyema, development of a bronchopleural fistula, significant

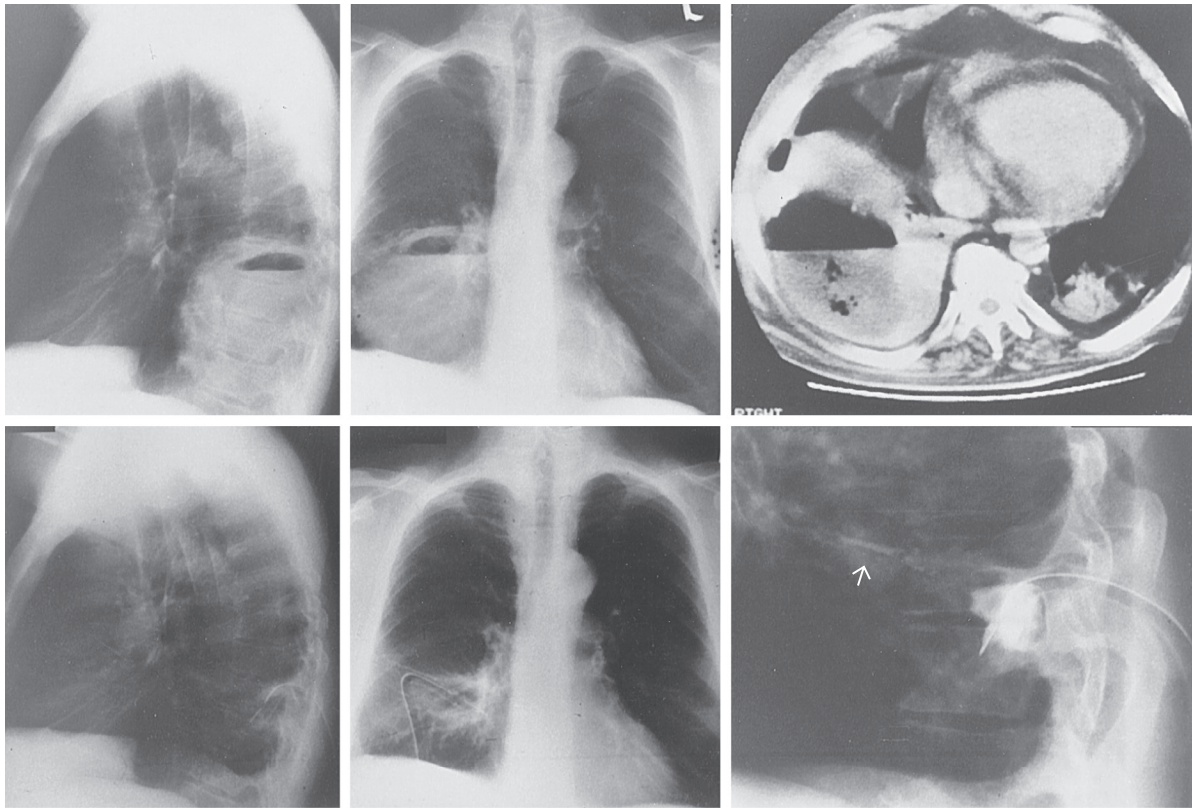


FIGURE 12-8 ■ Computed tomography scan and chest radiographs demonstrating a large lung abscess (*upper panels*) with resolution after appropriate percutaneous drainage (*lower panels*). The arrow depicts the collapsed, contracted abscess cavity.

hemoptysis, persistence of the abscess despite adequate therapy, and suspicion of underlying malignancy. During surgical procedures for lung abscess, special attention should be paid to protecting the contralateral lung from spillage, usually through the use of a double-lumen tube. Resection of the involved segment of lung is usually performed, although in cases of rupture into the pleural space, simple unroofing of the cavity, decortication, and wide drainage will usually suffice. Some success with endoscopic drainage of lung abscesses has been reported.⁹¹

PULMONARY MYCOBACTERIAL DISEASE

Mycobacterial pulmonary diseases include infections with *Mycobacterium tuberculosis* and its more virulent forms, multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).⁹² Other mycobacterial infections caused by organisms have gone through a series of name changes, including atypical mycobacteria, mycobacterium other than tuberculosis, environmental mycobacterial infections, and the most commonly used term, nontuberculous mycobacteria (NTM).⁹³ Whereas good epidemiology studies can be found for tuberculosis infections as well as MDR-TB/XDR-TB, there are poor epidemiology data for NTM infections. This is probably because NTM infections are not transferable from person to person and thus are not reportable to local or national health authorities.

In 2013, there were 9 million patients worldwide who developed tuberculosis, and 1.5 million patients died of the disease.⁹⁴ Unfortunately, most of these cases are in countries where health care systems are in dire need of help. In India, approximately 500,000 people die from tuberculosis yearly. Fortunately, only 10% to 15% of those exposed to the tuberculosis organism acquire the clinical disease; however, this leaves a large number of individuals who make up a latent source for later activation with tuberculosis if their resistance breaks down as a result of disease or aging.

The early treatment of tuberculosis gave rise to the sanatoria system. It was believed that rest and fresh air were beneficial in the treatment of tuberculosis. However, it has never been well documented that this form of therapy produced any long-term benefit.

Surgery for tuberculosis began with collapse therapy. The tuberculosis organism is an obligate aerobe, and it was reasoned that preventing oxygen from entering the cavities would be beneficial in the treatment of patients with cavitary pulmonary tuberculosis. Various forms of collapse therapy have been used, including thoracoplasty, wax or Lucite ball plombage, phrenic nerve crush or interruption, pneumoperitoneum, and induced pneumothorax. Collapse therapy continued to be the treatment of choice for tuberculosis infections until chemotherapy with streptomycin and para-aminosalicylic acid (PAS) was introduced in 1945. It was not until the introduction of isoniazid in 1952 that prolonged cures could be obtained with antibiotic therapy.

Resectional surgery gradually replaced collapse therapy as the primary surgical approach to patients with tuberculosis infections having residual destroyed lung or cavitory disease. With the introduction of rifampin in 1966, the need for surgery was markedly reduced and the sanatoria system gradually became extinct. Drug-sensitive tuberculosis in almost all cases can be cured with antibiotic therapy alone. It is hoped that recent advances in diagnostic testing, including point-of-care recognition using Xpert MTB/RIF (a real-time PCR assay), will aid in identification of infected individuals and initiation of therapy.⁹⁵⁻⁹⁷ The standard treatment of drug-sensitive tuberculosis is 6 to 9 months of isoniazid and rifampin, adding pyrazinamide and ethambutol during the initial 2 months.^{98,99} Patients with drug-sensitive tuberculosis who are treated appropriately are only operated on for complications such as bronchostenosis, massive hemoptysis (>600 mL in 24 hours), bronchopleural fistula, to rule out the presence of cancer, and occasionally decortication of a trapped lung, which occurs when polymicrobial contamination occurs within the pleural cavity in tuberculosis patients who have had a pleural effusion.

Patients with tuberculosis whose organism is resistant to both isoniazid and rifampin are classified as having MDR-TB. XDR-TB strains are resistant not only to isoniazid and rifampin but also to fluoroquinolones and either aminoglycosides (amikacin, kanamycin) or capreomycin or both.^{100,101} These patients with MDR-TB/XDR-TB present a much greater challenge to clinicians, who must use four to five drugs to optimize treatment success.¹⁰¹⁻¹⁰³ Recent approval of new drugs, such as bedaquiline and delamanid, provide new hope in the medical treatment of drug-resistant tuberculosis.^{104,105}

Surgery plays a greater role in the management of drug-resistant tuberculosis. In addition to the previously listed indications for surgery, patients are also operated on for persistent cavitory disease, destroyed lobe, or destroyed lung with or without a positive sputum. In the United States, patients with MDR-TB make up the largest group of patients operated on for pulmonary infections with tuberculosis.¹⁰⁶ The addition of surgery to the treatment regimen has been shown to be beneficial.^{107,108}

Patients with nontuberculous mycobacterial infections (NTMs) present a different challenge. The most common NTM infection is that of the *Mycobacterium avium* complex. This includes both *Mycobacterium avium* and

Mycobacterium intracellulare, which are almost indistinguishable from each other on culture. Infections with the so-called rapid growers, such as *Mycobacterium chelonae*, *Mycobacterium abscessus*, and *Mycobacterium fortuitum*, seem to be increasing in the United States although accurate epidemiology is not available. These infections are more difficult to treat because good antibiotic coverage is not available.¹⁰⁹ Some of these rapid grower infections are extremely virulent and can destroy an entire lung (Figs. 12-9 and 12-10), and surgery, along with continued use of any antibiotics available, offers the only hope to control the process. Specific types of NTM infection include infection of the middle lobe and lingula of women (Fig. 12-11).¹¹⁰ This usually occurs in slender women with little or no body fat and is associated frequently with skeletal abnormalities such as scoliosis or pectus excavatum.¹¹¹ This syndrome has not been found in men, in our experience; however, if it does occur, it is extremely rare.

Preparation for surgery is an important part of the therapeutic approach for patients with mycobacterial infections. The most important aspect of preparation is nutrition. Patients with an albumin concentration below 3.0 g/dL are not operated on. Nutritional supplementation is accomplished either orally or by gastrostomy or jejunostomy feeding tubes to improve the patient's anabolic state prior to surgery. The best available antibiotic

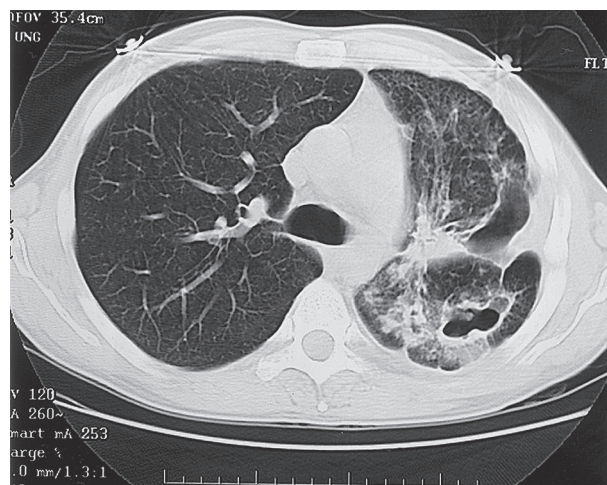


FIGURE 12-9 ■ Computed tomography scan showing severe cavitory disease in a patient with *Mycobacterium chelonae* infection.

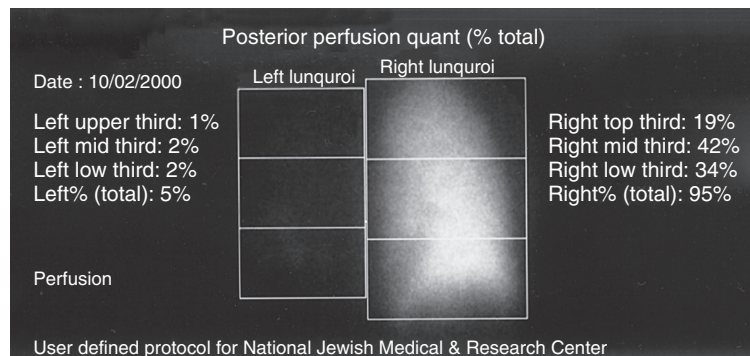


FIGURE 12-10 ■ Perfusion scan of the patient depicted in Figure 12-9, demonstrating absence of perfusion to the left lung.

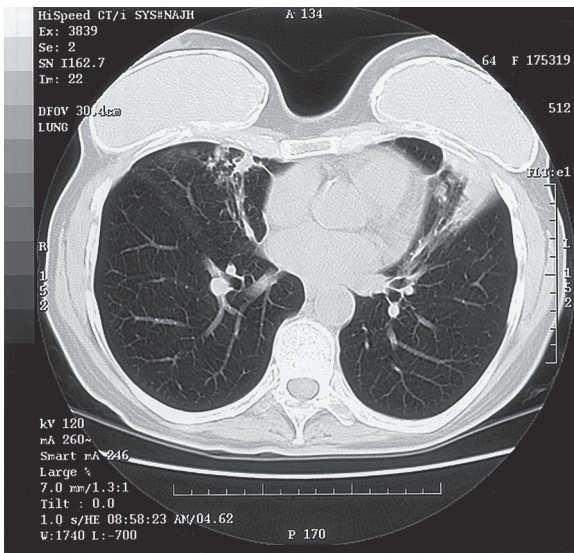


FIGURE 12-11 ■ Computed tomography scan of a woman with *Mycobacterium avium* complex infection of the right middle lobe and lingula.

therapy is given for approximately 3 months prior to surgery. This can be prolonged if bacterial counts are decreasing and can be shortened if the sputum becomes negative for acid-fast bacilli. Approximately 50% of patients with MDR-TB have negative sputum prior to surgery. Routine evaluation, as with other pulmonary surgery, includes pulmonary function tests, ventilation perfusion scans, and computed tomography.

Surgical principles include leaving enough viable lung tissue to have a functional postoperative patient. Double-lumen tubes or bronchial blockers are used in all operations. All grossly involved lung, which includes cavitory disease and destroyed lung should be removed, whereas nodular disease remaining in other parts of the lung can be left behind. The use of muscle flaps is controversial. However, it is our opinion that using muscle flaps to fill space following lobectomies is often helpful. With muscle flaps, we think that the incidence of bronchopleural fistula has been decreased. Muscle flaps are used after pneumonectomy if there is a polymicrobial contamination, significant drug resistance, or positive sputum at the time of surgery. If there is massive contamination, the chest is left open and an omental flap is used. Omental flaps are also used to cover the bronchus in the absence of any muscle as a result of previous surgery or extreme cachexia. If the chest is left open (Eloesser procedure), it is packed with quarter-strength Dakin solution using Kerlix gauze and changed on a daily basis for 5 to 6 weeks. When the opening is closed, assuming the intrathoracic chest wall is clean, Clagett solution is left in the pleural cavity. Pleural tents have been suggested to help eliminate space and seal air leaks. This is not practical in mycobacterial surgery because most of the dissections over the upper lobe are done in the extrapleural plane. The latissimus dorsi muscle is used whenever significant space problems are expected after lobectomy, and it is also used to cover the bronchus and hilum. If only bronchial support is needed following a pneumonectomy, intercostal muscle can be used. Appropriate antibiotic

therapy is continued for at least 12 months following culture conversion.

Whereas tuberculosis infections can infect normal lung tissue, NTM infections most frequently affect previously diseased lungs and have a much more indolent course than does tuberculosis or MDR-TB. Lung damage can result from previous infections such as tuberculosis, bronchiectasis, or chest wall irradiation. NTM patients often are found to have genetic abnormalities such as heterozygous cystic fibrosis, α_1 -antitrypsin deficiency, or cilia dysfunction. It is also of note that over 50% of the patients with NTM infections have esophageal dysfunction. These patients often reflux at night, causing contamination and damage to the lungs and making them more susceptible to pulmonary disease.

In the United States, there is an abnormally high number of patients with NTM disease that are Caucasian. In addition, the overwhelming majority of NTM patients are women (relative to men). The reasons for these two findings are still not clear.

Operative mortality in experienced hands should be less than 3%. The largest study to date involving anatomic lung resection for NTM disease reported a mortality rate of 2.6% in 236 consecutive patients, with no deaths in the second half of the series.¹¹² Complications following mycobacterial surgery are high—in the 25% to 30% range—but with experience, this can be brought down to less than 15%. Specific complications include a high rate of bronchopleural fistula, most often occurring after right pneumonectomy for NTM infections. Wound infection after *M. chelonae* and *M. abscessus* is common, and careful attention to wound closure is necessary. Other complications, such as air leaks, bleeding, and postpneumonectomy pulmonary edema, are similar to those of other thoracic procedures for nonmycobacterial disease.

Results of surgery for tuberculosis or MDR-TB are gratifying, whereas surgery for NTM infections is less successful because of the long duration of indolent disease prior to surgical intervention. Earlier surgery in these patients should improve the results. Persistence in aggressively treating surgical complications is often necessary to obtain good results and requires dedicated thoracic surgeons experienced in these difficult cases.

With 33% to 40% of the world infected with tuberculosis and with the presence of poverty, this disease will not go away. With the increasing number of NTM infections, at least in the United States, surgery will continue to play a role in the therapy of these patients.

MAJOR PULMONARY MYCOTIC INFECTIONS

Of more than 100,000 species of fungi, only 300 or so are associated with pulmonary disease. Fungal infection of the lung results from inhalation of the infectious agent. Colonization or asymptomatic fungal infection is common in the United States: an estimated 30 million are infected with *Histoplasma capsulatum* and another 10 million with *Coccidioides immitis*. Serious infection is rare but is seen with increasing frequency in immunocompromised populations. The increasingly advanced use of chemotherapy

for neoplasms, antibiotics for infections, immunosuppressive therapies for organ transplantation, and corticosteroids for various conditions has increased opportunistic infections by usually harmless saprophytes such as *Aspergillus*, *Candida*, and *Mucor*. Under these conditions, the formerly clear differentiation between so-called pathogenic and nonpathogenic fungi has become blurred.

In addition to detailing the medical conditions that predispose to infection, other areas of the patient history can yield important clues to the causative agent. The three major fungal infections seen in healthy populations—histoplasmosis, coccidioidomycosis, and blastomycosis—are recognized as endemic organisms in specific geographic areas of the United States. These organisms are dimorphic; they exist in nature as a mycelium (mold) that bears infectious spores, which later enter the host and develop into a yeast-like phase that is the tissue pathogen. These morphologic differences occur in response to changes in temperature. The spores invade the host through an aerosolized form via the respiratory tract, resulting in a mild or asymptomatic infection. Chronic pulmonary or disseminated infection is uncommon, with the presence of an intact cell-mediated immune response critical to preventing serious illness. The more common opportunistic fungi—*Aspergillus*, *Cryptococcus*, *Mucor*—are ubiquitous and are located in the soil. Proximity to building or construction sites where aerosolization of these organisms can occur has been linked to an increased incidence of *Aspergillus*, *Histoplasmosis*, *Coccidioidomycosis*, and other infections.^{113,114}

Fungal infection of the lung is best established by recovery of the infecting organism by culture, but recognition in smears or tissue sections may be enough for diagnosis. The best two stains for demonstration of fungi in tissue are periodic acid–Schiff and methenamine silver, but no one stain demonstrates all organisms. Specific immunologic changes in the host response may provide a strong indication of the diagnosis and may often lead to therapy before actual isolation of the organism can be achieved.¹¹⁵ All too often, however, it is not possible to find pathognomonic organisms in the stained specimens and only a presumptive diagnosis can be made. Cultures of fungi can be made from tissues, sputum, pleural fluid, and other clinical specimens. Induced sputum samples, obtained in the morning and at least six in number, are recommended.¹¹⁵ Sabouraud's dextrose agar is an excellent general-purpose culture medium. Prompt delivery of the specimens to the laboratory is essential. Because respiratory tract cultures may simply be the result of fungal colonization, the culture isolates from these sites, which are not sterile, may not correspond to infection. However, risk stratification of the host may aid in this matter. One study demonstrated a positive culture for *Aspergillus* in immunocompromised patients such as bone marrow transplant recipients was associated with invasive infection 50% to 70% of the time, whereas a positive culture in cystic fibrosis patients was rarely combined with invasive aspergillosis.¹¹⁶ Serologic tests for circulating fungal antigens (such as galactomannan in aspergillosis) and circulating antibodies to fungal antigen (histoplasmosis and coccidioidomycosis) can aid in diagnosis. Molecular diagnostic techniques using PCR

technology are being developed for *Aspergillus*, *Candida*, and *Cryptococcus*.^{117,118}

Histoplasmosis

Histoplasmosis is a fungal infection caused by the dimorphic fungus *Histoplasma capsulatum*, which exists in mycelial form in the soil (its natural habitat) and in yeast form at body temperature. It is endemic in the Mississippi and Ohio river valleys, where the incidence of positive skin reactions to the fungus exceeds 80%.¹¹⁹ Furthermore, the incidence of skin test reactivity probably underestimates the true incidence, because the skin test may revert to negative over a period of time.

The yeast phase of the organism is not contagious, and there is no danger of transmission through direct human contact. The microspores from the mycelial phase act as the transmitted agent, inhaled into the distal air spaces in the lung. The critical inoculum is unknown. Within days, the microspores germinate into yeast spores, attracting neutrophils and macrophages to the site of infection. Neutrophils are largely ineffective against the yeast spores, which are ingested by the macrophages. Infected macrophages transport the spores to other areas in the reticuloendothelial system, producing a subclinical disseminated infection. This process is poorly controlled in those with impaired T cell immunity. The outcome of infection is determined by the development of a specific cell-mediated immune reaction within approximately 2 weeks. Granulomas form within the lungs and mediastinal lymph nodes to wall off residual organisms. As the epithelial cell granulomas age, caseating necrosis develops in the central areas and may calcify as the peripheral portions become fibrotic. Within these lesions, *H. capsulatum* organisms are usually found only in the caseous material, seen well with methenamine silver stain. The yeast are often found intracellularly in macrophages.

Approximately half of the cases of acute pulmonary histoplasmosis are asymptomatic. The remaining patients have a flu-like illness with chills, myalgias, headache, nonproductive cough, dyspnea, and pleuritic chest pain. The disease is self-limited, usually lasting a week or two, but frequently with fatigue lasting for several weeks. Occasionally patients will be troubled by pericarditis or persistent symptoms or arthralgia and erythema nodosum.¹²⁰ These symptoms respond well to nonsteroidal anti-inflammatory agents.

Progressive disseminated histoplasmosis develops rarely, usually seen in those with impaired cell-mediated immunity. The liver, spleen, lymphatic system, bone marrow, and adrenal glands are most frequently involved. Diffuse pulmonary infiltrates may appear and progress rapidly, at times accompanied by shock and disseminated intravascular coagulation.

Chronic cavitary pulmonary histoplasmosis occurs in approximately 10% of patients with symptomatic histoplasmosis. Most have chronic obstructive pulmonary disease (COPD) and other structural defects in the lungs, which predispose them to the illness. Clinically, the disease is similar to cavitary tuberculosis, except that the illness is less severe. The radiographic picture mimics that seen in tuberculosis, with fibronodular changes,

often involving both pulmonary apices, cavities, and adjacent pulmonary pleural thickening.

Fibrosing mediastinitis represents excessive scarring from prior histoplasmosis infection. The symptoms are produced by gradual, relentless compression of mediastinal structures, including the superior vena cava, pulmonary vessels, esophagus, and tracheobronchial tree. The calcified nodes may actually erode into the latter two structures, presenting as a broncholith with airway obstruction and hemoptysis or with a localized esophageal leak and dysphagia (Fig. 12-12). The progression is fatal in 10% to 20% of cases, and attempts to surgically bypass or remove the obstructing lesions are difficult and often unrewarding. Antifungal and steroid therapies are of limited use in fibrosing mediastinitis and do not slow the progression of the disease.¹²¹

Histoplasmoses are the residua of healed primary histoplasmosis and are usually seen as asymptomatic coin lesions on routine chest films. Their significance lies in the fact that the lesions, if uncalcified, may be impossible to differentiate from neoplasm, and surgical excision may be indicated. Computed tomography may reveal central calcification or peripheral calcification with a “target” appearance indicating a benign diagnosis.

Definitive diagnosis of active histoplasmosis relies on isolation of the fungus in culture. Serologic immunodiffusion tests detect antibodies to *H. capsulatum* in 24 to 48 hours but may also be positive in those with a remote history of the disease. Furthermore, the test is negative in up to 10% of patients with culture-proven histoplasmosis, usually in immunocompromised patients.

Amphotericin B is the mainstay of significant histoplasmosis infections.¹²² The primary, self-limiting

infection does not require therapy unless progression to severe illness is documented. Treatment is always indicated in the disseminated form of the disease and in immunocompromised populations. Chronic pulmonary histoplasmosis may alternatively be treated with ketoconazole or itraconazole. Surgical intervention in the chronic form of the disease is indicated only if the thick-walled cavities fail to respond to an adequate course of antimicrobial therapy and if pulmonary function permits.

Coccidioidomycosis

Coccidioidomycosis is the illness caused by the pathogenic fungus *Coccidioides immitis*. This dimorphic fungus is found in the soil as a mold and in tissues as an endospore. Relatively hardy, it can withstand periods of high salinity and drought but is intolerant of freezing temperatures. It is endemic in the desert southwest United States, and protection from infection in the endemic area is almost impossible. The infecting structures are termed *arthroconidia*, which are separated from the mold stalk by wind or other disturbances. The arthroconidia are transported through the air, resulting in inhalation into the distal air sacs of the lung and transformation into spherules. The spherules enlarge in the lung and become packed with endospores, which ultimately rupture, liberating the tiny endospores and perpetuating the invasive process. The severity of the clinical course after inhalation of the endospores is determined mainly by the host's ability to develop cell-mediated immunity against *C. immitis* to control infection. Children exposed are more likely to develop a mild or asymptomatic infection, whereas adults are more likely to have a severe

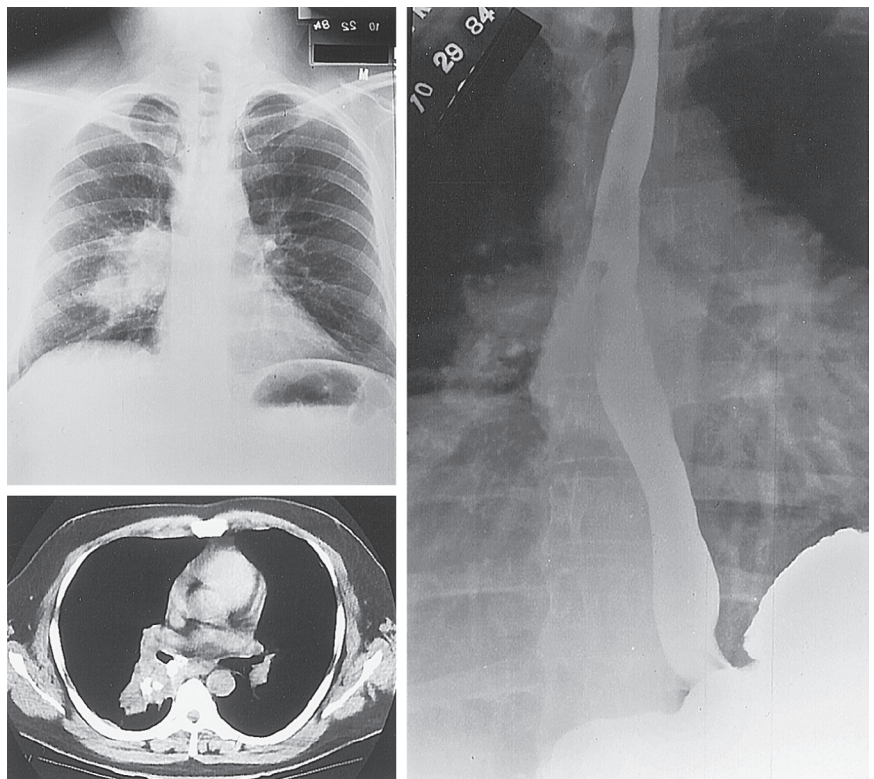


FIGURE 12-12 ■ Computed tomography, contrast esophagography, and chest radiography demonstrating calcified mediastinal granulomatous disease secondary to histoplasmosis, with erosion into the adjacent esophagus.

primary infection with dissemination. African Americans are 12 times more likely to develop disseminated disease than Caucasians, with American Indian, Hispanic, and Filipino ethnic groups also at increased risk.¹²³ Men are at higher risk than women.

The most common clinical manifestations of primary pulmonary coccidioidomycosis, commonly referred to as *desert fever* or *valley fever*, are cough, fever, fatigue, dyspnea, chest pain, and headache. The symptoms develop 1 to 4 weeks after exposure. Approximately 20% of patients will have erythema nodosum or erythema multiforme, indicating an excellent cell-mediated immune response and prognosis. In most cases, the disease is self-limiting and remits in a few days. More severe primary infections can be accompanied by high fever, cough, weight loss, and development of pulmonary infiltrates and may take weeks to resolve. If the symptoms persist for more than 6 weeks with concomitant radiologic findings, treatment is usually started.

Patchy infiltrates are the most common radiographic finding in primary coccidioidomycosis, which range in size from subsegmental to lobar. Infiltrates may be single or multiple. Adenopathy can be present and be so dramatic as to resemble lymphoma. Subsequent necrosis of the infiltrate commonly occurs, resulting in cavitation or coalescence into a granulomatous nodule (Fig. 12-13). The cavities are usually peripheral in location and may rupture into the pleural space, causing a pleural effusion, pneumothorax, bronchopleural fistula, and empyema. Secondary infection of the cavity and hemoptysis may also occur. The nodules that form within the lung parenchyma mimic bronchogenic carcinoma and often require resection to settle the issue.

Disseminated coccidioidomycosis may occur, typically as the result of hematogenous spread. The symptoms are insidious in onset several weeks after the primary infection. Skin and soft tissue lesions, bone and joint lesions, involvement of the genitourinary system, and meningitis can result.

The diagnosis of coccidioidomycosis depends on the identification of *C. immitis* within the body tissues or

fluids. Detection by culture may take several weeks. Serum or cerebrospinal fluid can be tested to detect antibodies to *C. immitis*, through an immunodiffusion method. This test usually becomes positive within 4 weeks after an initial infection and remains positive throughout the clinically active illness. Some individuals continue to produce detectable antibodies for up to 1 year after recovery. Negative serology does not exclude a diagnosis of coccidioidomycosis. A skin test is available that shows a reaction to coccidioidin, prepared from the mycelial phase of the organism. A positive test is highly correlated with protection and a favorable prognosis. Patients with disseminated disease often lose this measure of cell-mediated immunity, and a persistently negative skin test at the end of therapy suggests the possibility of relapse.

Most patients with coccidioidomycosis require no therapy. All patients with disseminated disease and those with extensive pulmonary disease should be treated. Amphotericin B is the treatment of choice in severe disease, with lesser forms treated with fluconazole or itraconazole.¹²² Meningeal involvement is treated with intrathecal therapy. Surgical intervention is indicated for resection of old granulomas suggestive of carcinoma and for complications arising from cavitary disease.

Blastomycosis

Blastomycosis is a systemic mycotic infection caused by the dimorphic fungus *Blastomyces dermatitidis*. The fungus is a soil-dwelling organism endemic to the southeastern and central United States, although interestingly it has been cultured from soil only infrequently.¹²⁴ This fact, as well as the lack of a suitable skin test, has made precise definition of the endemic region problematic. The infecting microconidia are inhaled to the level of the alveolus, where the organism converts to its parasitic yeast-like form. The yeast multiplies rapidly, attracting neutrophils and macrophages and, later, a T cell-mediated immune reaction. An area of pneumonitis forms, with involvement of the regional lymph nodes. As granuloma formation finally occurs, with the organisms walled off, healing begins with "rounding off" of the infiltrate and fibrosis. These produce the late coin lesions suggestive of carcinoma. Late calcification of these lesions is less common than with histoplasmosis or coccidioidomycosis. If delayed hypersensitivity does not develop, the fungus may disseminate throughout the body and involve the skin, bones, meninges, and prostate or adrenal glands, producing disseminated disease. In patients with cell-mediated immune deficiencies, blastomycosis can present as a rapidly progressive infection.¹²⁵

The primary infection site is the lung, although the incidence of asymptomatic infection is difficult to determine. In symptomatic cases, the disease may present acutely with fever, chills, myalgias, arthralgias, and a dry, hacking cough that becomes productive. Hemoptysis and pleuritic pain can occur. Most symptomatic patients recover within 2 to 3 weeks. Occasionally the symptoms will persist, resulting in chronic suppuration and cavitation. Patients who seem to have recovered may develop recurrent infection in areas remote from the primary site.

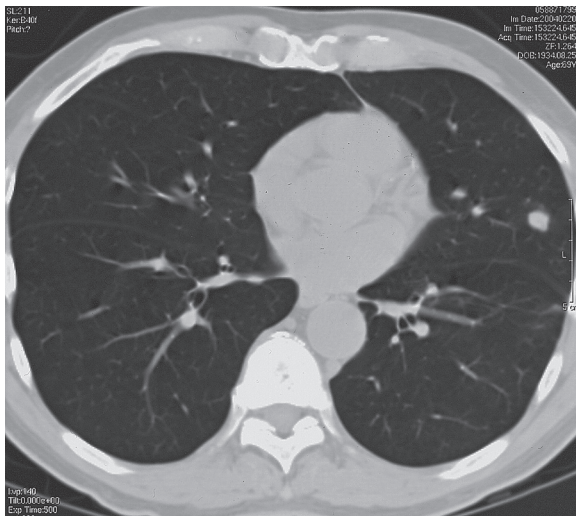


FIGURE 12-13 ■ Computed tomography scan demonstrating a granuloma in the lingula caused by coccidioidomycosis.

Radiologic findings are variable. Single or multiple sites of infiltrate or nodularity can occur, often with a lower lobe predilection. Pleural involvement may be seen, including thick, irregular pleural-based lesions.

B. dermatitidis is readily isolated from infected fluid or tissue if proper care is given in the specimen processing. This round, thick-walled, single budding yeast measuring 8 to 15 μm in diameter may be seen reasonably well with routine hematoxylin and eosin stains, although periodic acid–Schiff and methenamine silver stains usually have many more organisms. Sputum or other fluids should be prepared with a 10% potassium hydroxide solution and examined under a microscope with reduced illumination. A definitive diagnosis may be obtained within an hour. Identification by culture, in contrast, can take weeks. Serodiagnosis of blastomycosis has not been successful to date.

For subclinical disease, treatment may be deferred. In more severe but not life-threatening forms of the illness, itraconazole is used preferentially.¹²² Itraconazole may also be used as an adjunct following therapy with amphotericin B in disseminated cases, those with immune compromise, and in those with mild extrapulmonary disease. For life-threatening and diffuse disease, amphotericin B is the drug of choice.¹²² Meningeal involvement also mandates amphotericin B therapy. The role of surgery in blastomycosis is to help with diagnosis and rule out malignancy.

Aspergillosis

Aspergillus is a ubiquitous soil-dwelling organism that releases small conidiophores that are easily inhaled (Fig. 12-14). It is inevitable that exposure occurs, and thus the development of active infection depends on other influences. Although more than 200 species of *Aspergillus* are known, only a few are thought to be pathogenic for humans. *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus niger* are the most common, with *A. fumigatus* dominating in human disease. In patients with normal immune function, no chronic or structural lung disease, and no hypersensitivity or allergic concerns, an infection is usually averted. In others, three main types of *Aspergillus* infection may occur, with considerable overlap. Patients may develop a noninvasive aspergilloma, invasive aspergillosis, or a hypersensitivity reaction to *Aspergillus*, causing illness. The spectrum of *Aspergillus* infection is detailed in Figure 12-15.

Aspergilloma

Individuals with cavitary lung disease may develop an aspergilloma, a noninvasive infection characterized by a mass of fungal mycelia, inflammatory cells, mucus, and tissue debris, all within a preformed lung cavity (Fig. 12-16). The cavity classically has been attributed to a prior tubercular infection, although this is obviously not always the case. Other types of fungus may produce a fungal ball, yet *Aspergillus* is by far the most common.¹²⁶ The true incidence of aspergilloma is unknown. In a study of 544 patients with a preexisting lung cavity caused by tuberculosis, 11% had radiographic evidence

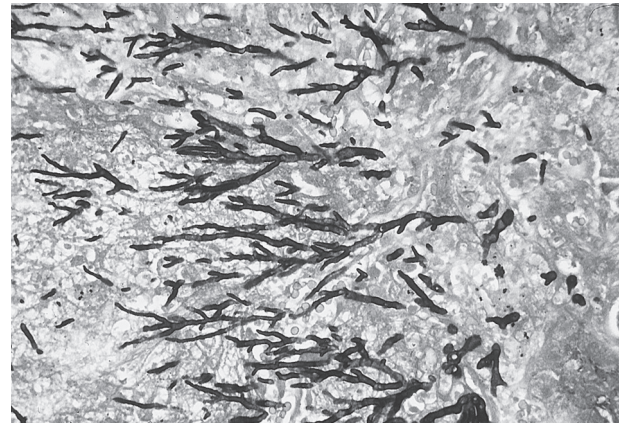


FIGURE 12-14 ■ *Aspergillus fumigatus* infection, demonstrating the branching, septate hyphae of the organism.

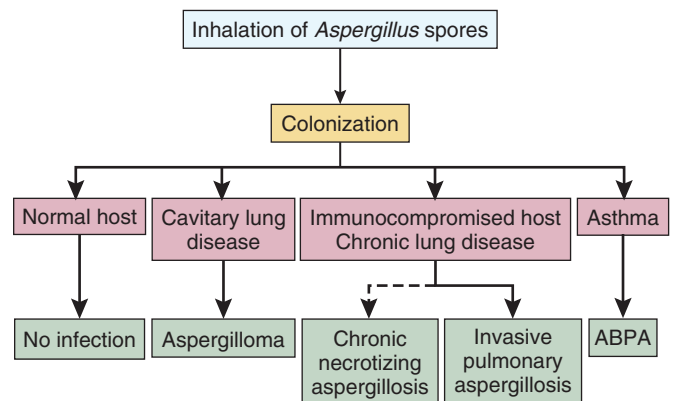


FIGURE 12-15 ■ The spectrum of *Aspergillus* infection. ABPA, Allergic bronchopulmonary aspergillosis.

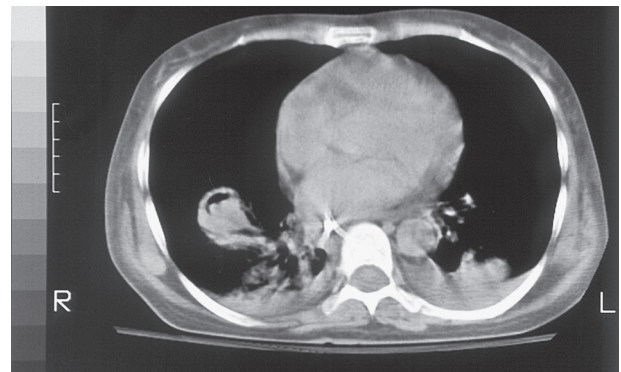


FIGURE 12-16 ■ Computed tomography scan demonstrating an aspergilloma involving the right lower lobe.

of aspergilloma.¹²⁷ Most aspergillomas remain asymptomatic, yet some may increase in size or cause hemoptysis, requiring intervention. On the other hand, some tend to resolve spontaneously. Invasion and dissemination from an aspergilloma rarely occur. In addition to hemoptysis, which is the most common presenting symptom, chronic cough and weight loss can occur. Rupture of the cavity into the pleural space with subsequent empyema and fistula has been reported.

Radiographic imaging reveals a thick-walled cavity, typically in the upper lobe, with a mass or fungal ball within the cavity. Movement of the mass inside the cavity with position change is variable and not a reliable diagnostic test but remains an additional interesting finding (Fig. 12-17). Differential diagnoses include cavitating hematoma, neoplasm, abscess, Wegner granulomatosis, and hydatid cyst; it is important to note that aspergilloma may coexist with any of these diagnoses. Culture of the sputum may yield *Aspergillus* but is frequently negative. Serologic testing will be helpful in the setting of a suggestive radiologic finding.

Systemic antimicrobial agents, including amphotericin B, have limited use in treating aspergilloma because of poor penetration into the cavity.¹²² Asymptomatic mycetomas should be left alone. Surgical resection is indicated

if hemoptysis or other symptoms attributable to the lesion occurs and adequate pulmonary reserve is present.

Invasive Aspergillosis

Acute invasive *Aspergillus* infection is a rare but dramatic occurrence in immunosuppressed and myelosuppressed patients. Myelosuppression appears to be the greatest risk factor for invasive pulmonary aspergillosis: patients with leukemia have an incidence 20 times higher than patients with lymphoma or patients with solid organ transplants.¹²⁸ Risk factors for invasive aspergillosis include prolonged neutropenia, corticosteroid therapy, transplantation (highest risk with lung and bone marrow), hematologic malignancy, cytotoxic therapy, and acquired immune deficiency syndrome (AIDS).¹²⁹

The lower respiratory tract is the focus of the invasive infection. As a result, respiratory symptoms predominate, including fever, cough, sputum production, and dyspnea. The presence of pleuritic chest pain (caused by pulmonary infarction following vascular invasion) and hemoptysis, in the appropriate clinical setting, should alert clinicians to the possibility of the diagnosis.¹³⁰ With vascular invasion, the organism can spread to other organs, particularly the brain but also the heart and intra-abdominal organs.

Radiologic findings can be nonspecific. Rounded densities and peripheral, pleural-based infiltrates are suggestive of infarction. Typical computed tomography findings include multiple nodules, a halo sign (hemorrhage surrounding a nodule), and the air crescent sign (lucency in the region of the original nodule secondary to necrosis). The presence of *Aspergillus* spp. in sputum samples could be the result of colonization, although studies have shown that positive cultures in patients with leukemia and in those who have undergone bone marrow transplant have a positive predictive value of 80% to 90%.¹³¹ Bronchoalveolar lavage (BAL) is helpful in the diagnosis of invasive aspergillosis, particularly in patients with diffuse lung involvement. Transbronchial biopsies add little to the BAL testing except increased risk. Serologic studies are not helpful in this setting. The use of lung biopsy remains the gold standard for diagnosis but should be reserved for equivocal cases.

The mortality for invasive aspergillosis remains high,¹³² and empiric therapy should be initiated as early as possible. The treatment of choice remains amphotericin B or intravenous voriconazole, followed by oral voriconazole or itraconazole.¹²²

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to *Aspergillus* antigens, particularly *A. fumigatus*. It is typically seen in patients with long-standing asthma or cystic fibrosis. It is believed that IgE- and IgG-mediated reactions play a central role in ABPA. The diagnosis is usually made on clinical grounds buttressed by radiologic and serologic testing. Patients present with wheezing, fever, and mucus plugging; radiologic studies show pulmonary infiltrates that tend to be in the upper lobe and central in location. Volume loss

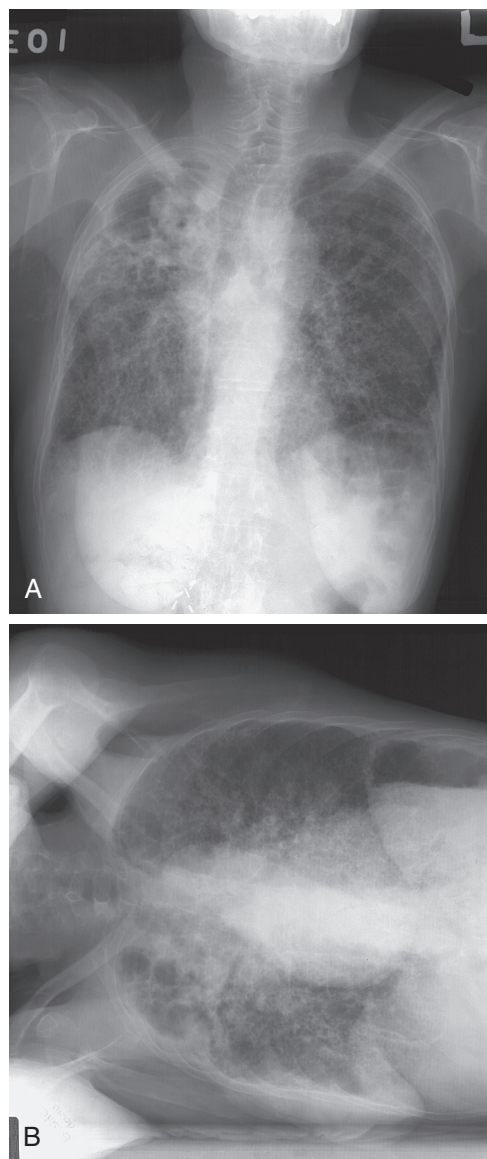


FIGURE 12-17 ■ Posteroanterior (A) and decubitus (B) chest radiographs demonstrating an aspergilloma within a right upper lobe cavity. The fungus ball “moves” with change in patient position.

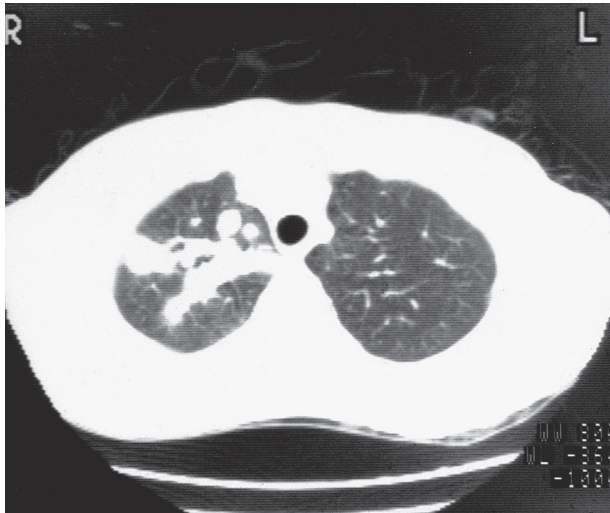


FIGURE 12-18 ■ Computed tomography demonstrating allergic bronchopulmonary aspergillosis involving the right upper lobe.

secondary to mucus impaction may be seen, appearing as bandlike opacities emanating from the hilum with rounded distal margins (Fig. 12-18). Treatment consists of oral corticosteroids to suppress the immunologic response to the *Aspergillus* antigens and the secondary inflammatory reaction. Concurrent itraconazole may be added to the regimen.

Cryptococcosis

Cryptococcus neoformans is an encapsulated yeast that is found worldwide as a soil organism. It is associated with bird (pigeon) droppings, although the birds do not serve as a vector or carrier for the microbe. The portal of entry in humans is the respiratory tract. As a result, pulmonary infection may be the first manifestation of disease but is usually variable and nonspecific. Spontaneous remission usually occurs in most patients. In those with suppressed or impaired immune systems, disseminated disease can result. *C. neoformans* has a special predilection for the meninges, and lethal meningitis can occur.

Treatment of cryptococcosis involves amphotericin B and flucytosine.¹²² Cryptococcal infections usually come to the attention of thoracic surgeons following resection of a pulmonary mass that is found to be a chronic granulomatous reaction to a prior *C. neoformans* infection. Central necrosis and cavitation are not commonly seen, as in other major pulmonary mycotic infections. These lesions often involve the lower lobe and are solid. Up to 10% of patients with a resected pulmonary lesion develop cryptococcal meningitis after resection.¹³³ If incidental resection occurs, sampling of the spinal fluid should be performed. Evidence of extrapulmonary disease or residual pulmonary disease should prompt initiation of therapy.

Mucormycosis

Mucormycosis is a rare fungal infection, commonly fatal, caused by fungi of the subclass Zygomycetes. *Mucor* species are ubiquitous and are found in soil and decaying organic debris. Infection occurs by inhalation of spores

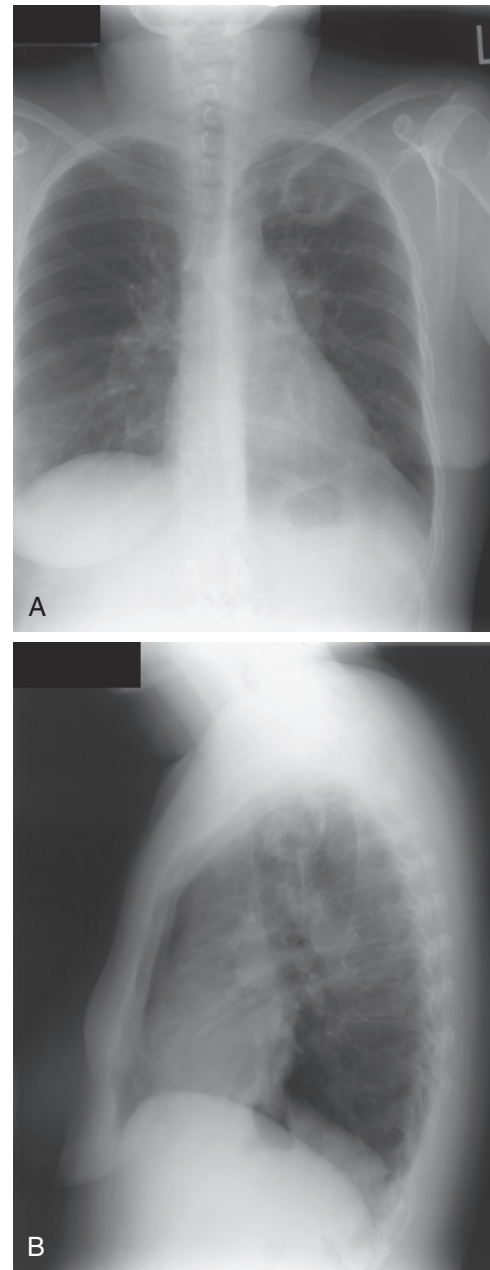


FIGURE 12-19 ■ Posteroanterior (A) and lateral (B) chest radiographs demonstrating mucormycosis involving the left upper lobe.

and is commonly found in immunocompromised hosts. Risk factors for *Mucor* infection include neutropenia, acidosis, hyperglycemia, corticosteroid therapy, and deferrioxamine therapy. This fungus grows best in acidic, hyperglycemic environments, thus accounting for the susceptibility of patients with diabetic ketoacidosis.

Mucor infections may involve several areas of the body, including rhinocerebral, pulmonary, cutaneous, and gastrointestinal areas and the central nervous system. The rhinocerebral involvement is commonly seen in poorly controlled diabetics, and these patients may also have a pulmonary component. The pulmonary aspect typically presents with bronchopneumonia (Fig. 12-19), and progresses to invade pulmonary vessels, causing infarction.

The infection can directly invade the extrapulmonary tissues, including the chest wall and mediastinal structures.

The radiologic findings are variable and contribute little to refining the diagnosis. Culture results are usually negative; positive results strongly suggest invasive disease. Direct pathologic examination of infected tissue should reveal broad, usually nonseptate hyphae invading the tissue. The side branches are short and at a 90-degree angle.

The overall mortality rate for pulmonary mucormycosis exceeds 50%. Therapy consists of three components: correction of underlying abnormalities, such as the hyperglycemic acidotic state seen with diabetic ketoacidosis, and reversal of immunosuppression if possible; early institution of high-dose amphotericin B therapy; and aggressive surgical resection of involved lung and soft tissue, when possible.

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SURGERY FOR EMPHYSEMA

Pamela P. Samson • Bryan Fitch Meyers

CHAPTER OUTLINE

PATHOPHYSIOLOGY

SELECTION OF PATIENTS FOR SURGICAL TREATMENT OF EMPHYSEMA

BULLECTOMY

LUNG TRANSPLANTATION

Techniques

VOLUME REDUCTION

Techniques

COMBINATIONS OF LUNG TRANSPLANTATION AND LUNG VOLUME REDUCTION

BRONCHOSCOPIC TREATMENT OF EMPHYSEMA

Endoscopic Placement of One-Way Valves

Airway Bypass

Nitinol Airway Coils

SUMMARY

The prospect of improving the debilitating symptoms of advanced pulmonary emphysema has long attracted the interest of thoracic surgeons. Previous surgical approaches such as costochondrectomy, phrenic crush, pneumoperitoneum, pleural abrasion, lung denervation, and thoracoplasty have largely fallen out of favor.¹ Today, only three surgical procedures are offered for patients with severe emphysema refractory to intensive medical management: bullectomy, lung transplantation, and lung volume reduction surgery (LVRS). Bullectomy has roots dating to the early 1900s, when external drainage of the giant bulla was attempted to eliminate the space-occupying lesion by collapse rather than by resection. The general approach has evolved to include resection of the bulla with sparing of functional lung tissue. Lung transplantation was first successfully performed in 1963 by Hardy and colleagues,² and after a long period of incremental progress, the operation became clinically feasible in the early 1980s, first as heart-lung transplantation³ and then as isolated lung transplantation.⁴ Today, emphysema is one of the most common diagnoses leading to lung transplantation. LVRS was first proposed by Brantigan and colleagues⁵ in conjunction with lung denervation, but it was discarded after the initial experience because of a 16% mortality rate. Observations about the physiologic behavior of emphysema patients during and after lung transplantation led to the reconsideration and modification of volume reduction by Cooper and associates.⁶

PATHOPHYSIOLOGY

The destruction of pulmonary parenchyma decreases the amount of functioning lung tissue where gas exchange can take place. As lung tissue is destroyed, the organ loses

elastic recoil and expands in volume. This leads to the typical hyperexpanded chest seen in advanced emphysema patients with flattened diaphragms, widened intercostal spaces, and horizontal ribs. These anatomic changes result in the loss of normal biomechanics and bring about increased work of breathing and dyspnea.⁷ When destruction and expansion occur in a nonuniform manner, the most affected lung tissue can expand to crowd the relatively spared lung tissue to impair ventilation of the functioning lung. Obstruction in the small airways is caused by a combination of reversible bronchospasm and irreversible loss of elastic recoil by adjacent lung parenchyma. The suitability of a patient for any surgical treatment of emphysema depends in part on the relative contributions of lung destruction, lung compression, and small airways obstruction to the overall physiologic impairment.

SELECTION OF PATIENTS FOR SURGICAL TREATMENT OF EMPHYSEMA

Bullectomy, lung transplantation, and LVRS may be offered to patients who remain symptomatic despite optimal medical therapy. Initial medical treatment will include bronchodilators to treat any reversible component of airway obstruction and supplemental oxygen therapy. Smoking cessation is an absolute necessity and should be in effect for at least 6 months before surgical therapy is considered. Participation in pulmonary rehabilitation has been shown to relieve subjective dyspnea, to increase functional capabilities, and to improve subjective quality of life.^{8,9} All patients considered by the authors

for surgical treatment of emphysema are enrolled in a supervised pulmonary rehabilitation program, and their subsequent consideration for surgery is based, in part, on their compliance and progress with rehabilitation.

BULLECTOMY

Traditionally, giant bullous emphysema is characterized by a bulla or bullae that occupy approximately one third or more of the hemithorax. Most patients considered for surgery are symptomatic with dyspnea or spontaneous pneumothorax. Other rare symptoms include bleeding or infection within the confines of the bulla. Bullae treated expectantly with observation will typically demonstrate enlargement causing worsening dyspnea, although the rate of expansion is not well described. Factors making surgery less appealing include multiple smaller bullae, advanced emphysema in the nonbullous adjacent lung, and significant comorbidities. Bullectomy is performed relatively infrequently, as demonstrated by a systematic review several years ago that cited 22 individual publications on bullectomy during a 39-year period with a combined total of 476 patients.¹⁰

The operative technique depends on the anatomic details of the bulla as well as the preferred approach of the surgeon. A well-demarcated bulla with a clear pedicle can be excised with a stapler by a muscle-sparing thoracotomy or a video-assisted thoracoscopic approach. Numerous bullae or bullae that merge indistinctly with the comparatively normal adjacent lung will require a large, stapled wedge resection placed to maximize resection of destroyed lung while minimizing resection of spared parenchyma. It is unusual for a formal lobectomy to be necessary, but when a lobe is almost completely destroyed and the fissures are complete, a lobectomy is an attractive option that might reduce the risk of a postoperative air leak and prolonged chest tube drainage. Many surgeons will combine a localized pleurectomy or a pleural tent with the bullectomy to help manage the pleural space and prevent a prolonged chest tube air leak.

The safety of bullectomy in well-selected patients is demonstrated by the 2.3% mortality reported by FitzGerald and colleagues¹¹ more than 30 years ago. Our more recent results are similar, with a single death in 43 operations (2.3%).¹² Properly selected patients will experience a perioperative increase in the first second forced expiratory volume (FEV₁), and subsequently there is a very low rate of respiratory failure or need for tracheostomy. Parenchymal air leaks are the most frequent single postoperative complication. Prolonged chest tube air leaks (more than 7 days) have been reported from 53% to 75% after bullectomy.^{12,13} Air leaks may be minimized intraoperatively with the surgeon's choice of buttressed stapled lines, pleural tent, pleurectomy, biological glues, or postoperatively with ambulatory Heimlich valves.

In a prospective study with 41 patients undergoing elective surgery for bullae, the 1-year mortality rate was 7.3%, and the overall 5-year mortality rate was 12.2%.¹⁴ When a subgroup analysis was performed, it was seen that all mortality cases were from patients whose bullae were surrounded by diffuse, generalized emphysema

(rather than normal lung parenchyma).¹⁴ A small retrospective series in Iceland demonstrated no 30-day mortality, a 5-year survival rate of 100%, and an overall survival rate of 60% at 10 years.¹³ Our clinical series demonstrated a 5-year survival rate of 91%, with two late deaths attributed to pneumonia and one to pulmonary fibrosis.¹²

In general, the freedom from long-term return of dyspnea is proportional to the quality of the remaining lung after bullectomy. Our experience demonstrated an improvement in the FEV₁ from 1.2 ± 0.6 liters preoperatively to 1.9 ± 0.9 liters at 6 months and 1 year postoperatively.¹² The persistence of a measurable airflow obstruction after bullectomy underscores the presence of residual emphysema in the remaining lung, regardless of its seemingly normal appearance compared with the destroyed bullous regions. However, in a prospective series by Palla and colleagues, patients with and without underlying diffuse emphysema experienced a persistent FEV₁ benefit over 5 years of follow-up, with both groups reaching their maximum increase in FEV₁ 2 years after surgery, followed by a gradual decline through postoperative year 5.¹⁴ For all patients in this series, a significant reduction (improvement) in the dyspnea score was seen immediately after surgery and only began to increase 5 years postoperatively. Despite the late progression in dyspnea, the improvement observed in dyspnea at 5 years remained clinically significant compared with preoperative values seen at presentation.¹⁴

LUNG TRANSPLANTATION

After the initial success with single-lung transplantation for emphysema was reported,¹⁵ and the development of techniques to allow safe, bilateral lung transplantation continued to progress,^{16,17} the application of lung transplantation for severe emphysema became increasingly common. From 1995 to 2012, chronic obstructive pulmonary disease (COPD) and emphysema were the most common indications for lung transplantation and comprised 33.5% of all lung transplants.¹⁸ During this period, three single-site studies found significantly higher 5-year survival rates for patients receiving bilateral as compared with single-lung transplantation, with no difference in 30-day mortality.^{19–21} A review of the International Society for Heart and Lung Transplantation (ISHLT) database's single and bilateral lung transplants (9883 cases) from 1987 to 2006 also confirmed a significant long-term survival advantage for patients receiving a bilateral lung transplant (6.41 years vs. 4.59 years; $P < 0.0001$), and a hazard ratio of 0.89 (0.80–0.97) after propensity-based matching to control for potential confounders between these patient groups.²² A retrospective analysis of 1656 lung transplant recipients who were 60 years or older showed no difference among 30-day, 1-year, or 5-year survival rates between those who received single versus bilateral lung transplantation.²³ As an overall result of these findings, there has been an important shift in lung transplantation practice from a 27.5% bilateral rate in 1997 to 72.8% in 2011.¹⁸ Our previously published report included 306 patients, 86 of whom received a single-lung

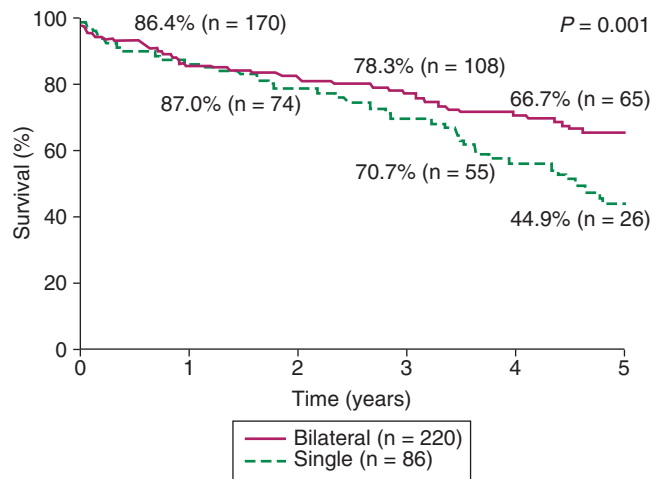


FIGURE 13-1 ■ Survival curves for bilateral and single-lung transplant recipients at Washington University from 1988 to 2002.

transplant and 220 of whom received a bilateral transplant.¹⁹ In contrast to earlier reports from our institution, the morbidity and mortality were comparable for the two groups, with an overall hospital mortality rate of 6.2%. There were no differences in hospital stay, intensive care unit stay, or duration of mechanical ventilation. There was, however, a difference in long-term survival; the 5-year survival rate (Fig. 13-1) of the bilateral transplant recipients was 66.7%, whereas the survival rate of the single-lung recipients was 44.9%. The ISHLT database also demonstrates a significant long-term survival advantage for patients with α_1 -antitrypsin deficiency undergoing bilateral lung transplantation when compared with single-lung transplantation.¹⁸ Of note, among those patients undergoing single-lung transplantation, no difference in 30-day, 1-year, 3-year, or 5-year survival is observed based on right- or left-sided transplantation, and when such transplantations are carried out, they should be based on patient factors such as pretransplant perfusion scans.²⁴

The selection criteria for lung transplantation are chosen to identify patients with sufficient risk of death from lung disease to make the risks of the transplant operation worth bearing. In our experience, the mean supplemental oxygen requirement is slightly in excess of 4 liter/min. The typical profile of a COPD patient listed for lung transplant shows a post-bronchodilator FEV₁ of up to 20% (and frequently as low as 10% of predicted), resting PO₂ less than 55 mm Hg, significant pulmonary hypertension, hypercarbia (>55 mm Hg), life-threatening exacerbations, and severe functional limitations. Progressive elevation in PCO₂ is frequently observed in patients, with several patients undergoing transplantation with the PCO₂ in excess of 100 mm Hg. Although survival of emphysema patients has been notably difficult to predict, these patients typically exhibit an excellent survival rate on the waiting list compared with patients who have other lung diseases. In 2004, the BODE index (an acronym of the four factors that comprise the model: *b*ody mass index, *a*irflow *o*bstruction, *d*yspnea, and *e*xercise capacity) was developed and found to be a better

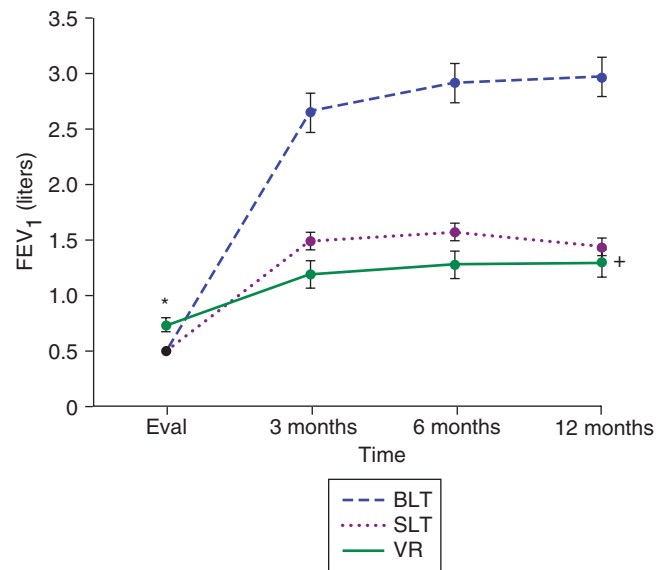


FIGURE 13-2 ■ Changes observed in first second expired volumes in patients after bilateral lung transplantation (BLT), single-lung transplantation (SLT), and lung volume reduction surgery (VR). FEV₁, First second forced expiratory volume.

predictor of both all-cause mortality and respiratory-related mortality than FEV₁.²⁵ For example, the highest index quartile (BODE index 7 to 10) was associated with a mortality rate of 80% at 52 months and an overall median survival of approximately 3 years.²⁵ As a result of studies using the BODE index to stratify mortality risk among patients with emphysema, the ISHLT implemented a BODE index exceeding 5 as indication for referral to a lung transplantation center and an index of 7 to 10 as an independent guideline for lung transplantation listing.²⁶

The implementation of the lung allocation score (LAS) in 2005 by the Organ Procurement and Transplantation Network altered the proportion of patients with emphysema undergoing lung transplantation after listing. Matches for donor lungs are now made on the basis of estimated mortality risk on the waiting list and estimated post-transplant survival probability. In a multicenter retrospective cohort study examining transplant characteristics before and after implementation of the LAS, a significant decrease in rates of lung transplantation for patients with emphysema was seen (from 45.9% of all transplant cases to 33.9%), with an increase in transplantation rates for patients with idiopathic pulmonary fibrosis (from 14.7% of cases to 24.6%).²⁷ No differences in hospital mortality or 1-year survival rates were detected.²⁷ Another analysis, of approximately 8000 patients listed for lung transplantation between 2002 to 2008, demonstrated that COPD patients had the lowest 6- and 12-month mortality rates on the waiting list pre-LAS and had a further significant decline in mortality rates after LAS implementation.²⁸

Initial and long-term function of patients with single or bilateral lung transplantation to treat emphysema shows a dramatic improvement in pulmonary function and exercise tolerance with elimination of the need for supplementary oxygen. Figure 13-2 demonstrates the

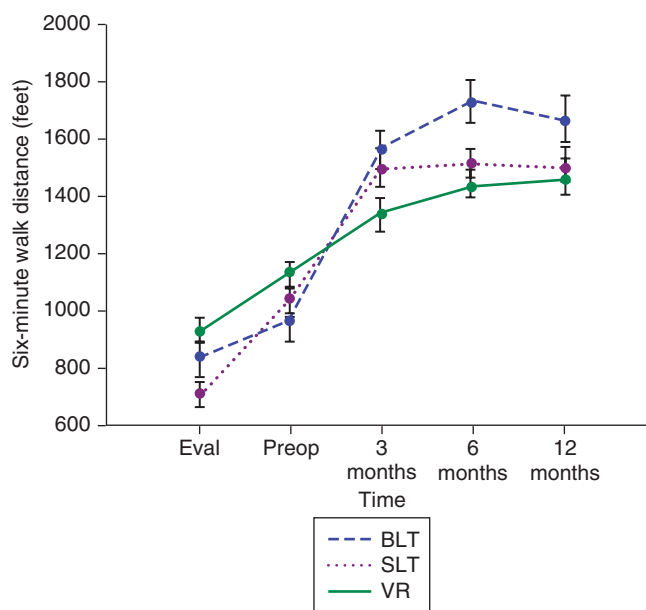


FIGURE 13-3 ■ Changes observed in 6-minute walk test results after single-lung transplantation (SLT), bilateral lung transplantation (BLT), and lung volume reduction surgery (VR).

magnitude of change in the FEV₁ as a result of single-lung transplantation, bilateral lung transplantation, and LVRS as reported by Gaissert and colleagues.²⁹ Figure 13-3 shows a similar stratified analysis for exercise tolerance as measured by 6-minute walking distances. Although the improvement in both outcome measures is greatest for patients who underwent bilateral lung transplantation and least for those who underwent LVRS, the absolute differences in exercise tolerance are much less than those seen in pulmonary function. Improvements in quality-of-life measures have also been documented among lung transplant patients with a BODE index greater than 5 (with mean time of assessment 4 months after lung transplantation).³⁰

The disadvantages of lung transplantation are well known. First, the lack of available donor lungs can lead to wait times in excess of a year. Once lungs become available, the initial morbidity and mortality rates of lung transplantation are higher than those reported for lung volume reduction, with 30-day mortality variously described as 5% to 15% but typically closer to the lower end of that range. The presence of allograft lungs necessitates lifelong immunosuppression, incurring higher medical costs to the individual and society. It also predisposes the patient to increased risk of neoplasm (as well as increased growth rate of occult cancers with poor comparative survival versus non-immunosuppressed patients for any given stage) and infection compared with non-immunosuppressed patients. Finally, the risk for development of chronic lung allograft dysfunction (CLAD) increases as a function of time following transplantation, reaching 50% to 60% by 5 years. A retrospective study of 425 bilateral lung transplants from the ISHLT/United Network for Organ Sharing (UNOS) registry identified a survival difference when analyzed by age, with 30-day, 1-year, and 5-year survival rates for patients younger than

50 years old equal to 94.9%, 84.7%, and 68.2%, respectively, and patients 50 to 60 years old with rates of 93.0, 79.7, and 60.5%.³¹

A controversial aspect of lung transplantation had been the question of whether it conveys a survival benefit to the patient with emphysema, with literature from the past decade divided.²⁴⁻²⁹ Of note, when patients transplanted for emphysema are stratified either by FEV₁ or BODE index, survival benefit with lung transplantation is seen for the most severe categories of each measurement. For example, in a numerical simulation based on a UNOS database of 8182 COPD patients on the waiting list for lung transplantation since 2004, it was calculated that 79% of patients with an FEV₁ less than 16% of the predicted value would gain an average of an additional year of life expectancy (in comparison to only 44.6% of listed patients gaining an additional year when not stratified by FEV₁).³² A survival benefit was also seen in a single-center retrospective analysis when COPD patients receiving lung transplantation were stratified by BODE index of 7 or higher.³³ It is likely that the Lung Allocation System will optimize the life extension caused by lung transplantation by balancing the goals of transplanting the candidates with the lowest life expectancy on the wait list while selecting those most likely to survive and thrive postoperatively (Fig. 13-4).

Techniques

Our current approach to a bilateral sequential transplantation involves bilateral anterior thoracotomies in the fourth (or fifth) interspace. The internal mammary artery is ligated and divided bilaterally. The fourth rib is shingled anteriorly by resecting 1 cm of the costal cartilage at the sternal border. More mobility is obtained by dividing the intercostal muscle from within the pleural space back as far as the posterior axillary line. Should additional access to the thorax become necessary during the operation, the sternum can be divided transversely at the fourth interspace, and the entire chest is clamshelled open. The least functional lung, as determined by preoperative quantitative ventilation and perfusion scans, is resected and replaced first. Preliminary dissection of both lungs shortens the time that the first implanted lung is exposed to the entire cardiac output and thus lessens the likelihood of reperfusion edema.

The pulmonary arteries and veins are dissected beyond their primary bifurcations to preserve the length of the main trunks. The right pulmonary artery is usually transected by a vascular stapling device 1 cm beyond the ligated first branch to the right upper lobe. The left pulmonary artery is kept longer and transected between staple lines beyond the second branch to the left upper lobe. The vein branches are usually not stapled; rather, they are double ligated and divided at their secondary branch points to save length for the future recipient atrial cuff. The arterial and venous dissection and division are accomplished before the bronchial division to avoid prolonged contamination of the operative field by the open distal airway. The bronchus is transected between cartilaginous rings, and the posterior bundle of lymphatics and bronchial arteries is exposed to facilitate ligation and

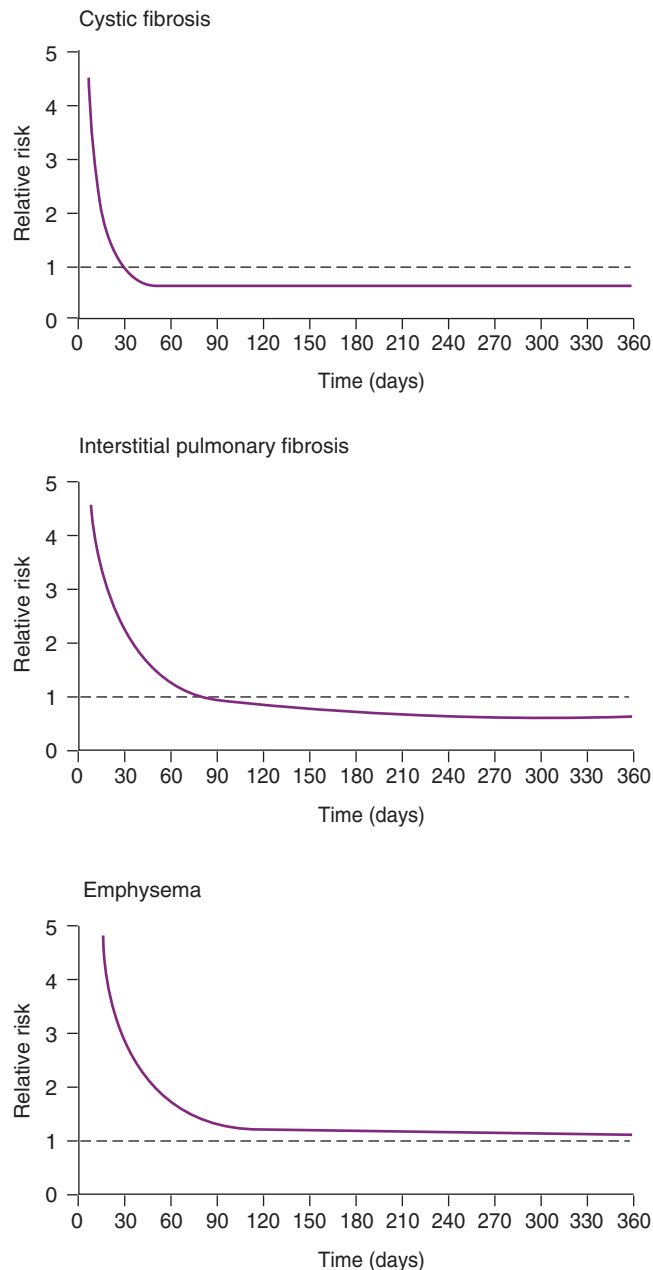


FIGURE 13-4 ■ Relative risk of death after lung transplantation compared with risk faced by remaining on the waiting list, stratified by underlying diagnosis leading to transplantation.

subsequent division. The pulmonary artery stump is mobilized centrally, then grasped with a clamp and retracted anteriorly to afford better access to the posterior bronchus. The pulmonary vein stumps are then grasped and retracted anteriorly and laterally to permit circumferential opening of the pericardium. With the pericardium freed, the vein stumps are then retracted and temporarily fixed anteriorly. This provides an excellent view of the bronchus, which is then mobilized well into the mediastinum and divided. Meticulous hemostasis in the mediastinum is achieved at this point, with the knowledge that reaching this portion of the operative field after implantation of the graft lung will be extremely difficult.

Meanwhile, the donor lung is prepared on the back table. The donor bronchus is divided immediately proximal to the upper lobe orifice. Care is taken to minimize dissection of the donor bronchus to preserve collateral flow through the peribronchial nodal tissue. The pulmonary artery and left atrial cuffs are freed from any pericardial attachments that may cause kinking after the anastomosis is completed.

Once the native lung is removed, the donor lung is placed into the chest and kept cold with iced saline and slush. We conduct the anastomoses from posterior to anterior in the following sequence: bronchus, artery, and atrium. The first stitches are 4-0 polydioxanone (PDS) sutures placed at the two corners of the bronchial anastomosis at the medial and lateral junction of the membranous and cartilaginous airways. These sutures are tied, and one end is used to join the donor and recipient membranous airways in a continuous suture. The cartilaginous rings of the donor and recipient are joined with interrupted figure-of-eight 4-0 PDS sutures.

The second anastomosis is the pulmonary artery. The pulmonary artery (which has already been extensively and circumferentially dissected into the mediastinum) is clamped centrally, with care taken to avoid including the Swan-Ganz catheter in the jaws of the Satinsky clamp. The vascular staple line is resected at a location that matches the size of the donor and recipient artery. A larger recipient artery can be divided beyond the first ligated branch to match a smaller donor artery; a smaller recipient artery is usually divided proximal to the first branch, or through it, to maximize circumference. The donor pulmonary artery is trimmed to an appropriate length, and the anastomosis is created with running 5-0 Prolene suture. This anastomosis must be made with precise, small suture bites to avoid any anastomotic stricture.

The atrial anastomosis is performed last. A Satinsky clamp is placed centrally on the atrium. Placement of this clamp too centrally can reduce venous drainage from the contralateral lung and decrease cardiac output, whereas placement of the clamp too peripherally will compromise the recipient atrial cuff. The ties are then cut off the recipient vein stumps, and the bridge of atrium between vein stumps is divided to create the atrial cuff. The anastomosis is performed with 4-0 Prolene suture, and the last few sutures are left intentionally loose to allow flushing and de-airing of the graft and the recipient atrium. For this maneuver, the lung is partially inflated, and the pulmonary artery clamp is loosened momentarily. The lung is flushed to force out the residual pulmonary perfusate solution. The pulmonary artery clamp is then reapplied, and the atrial clamp is opened momentarily to completely de-air the atrium. The atrial sutures are then secured and the clamps removed. All suture lines are then checked for hemostasis as ventilation and perfusion are restored.

VOLUME REDUCTION

The concept of LVRS is an extension of the bullectomy operation, in which destroyed tissue is resected to facilitate better function of the remaining lung that is

relatively spared from major emphysematous changes. The advantages of lung volume reduction for carefully selected candidates include relief of dyspnea and improvement of functional capabilities without the cost and adverse side effects of organ transplantation. There is no built-in waiting time as with transplantation; as soon as candidates can reach the pulmonary rehabilitation exercise goals, they are ready for the procedure (Box 13-1).

Many groups in previous decades have reported independent results for LVRS, and these results have consistently shown benefit to the recipient with acceptable mortality and varying morbidity.³⁴⁻³⁸ Successful lung volume reduction programs report meticulous selection of patients (Table 13-1), methodical preparation of patients with reduction of risk factors, and attentive post-operative care. In contrast to patients considered for lung transplantation for severe emphysema, patients being considered for LVRS may be slightly older (up to 75 years of age), may have a slightly higher preoperative post-bronchodilator FEV₁ (<40% predicted), and must demonstrate heterogenous emphysematous changes on

high-resolution computed tomography (HRCT). Significant hypercarbia (PCO₂ > 55 mm Hg) or pulmonary hypertension (PA systolic > 45 mm Hg) are contraindications to LVRS. Gains of 20% to 35% in FEV₁ have been reported for unilateral operations, and improvements of 40% to 80% are seen with bilateral operations. Most authors also reported substantial gains in exercise tolerance, freedom from oxygen use, freedom from steroid use, and subjective quality of life.

Ciccone and associates³⁹ reported long-term results in 250 bilateral LVRS recipients. After a median follow-up of 4.4 years, the 5-year survival was estimated to be 68%. Of these 250 patients, 18 had gone on to lung transplantation after a median interval of 4.3 years. Five years after surgery, the mean change in FEV₁ had declined to a 7% increase, yet 53% of the patients demonstrated persistence in benefit over preoperative FEV₁ values. This finding takes on greater importance when considering the relentless deterioration in FEV₁ seen despite maximal medical management.

To date, the National Emphysema Treatment Trial (NETT) has been the largest and most comprehensive

BOX 13-1 Indications and Contraindications for Lung Volume Reduction Surgery and Lung Transplantation

INDICATIONS COMMON TO BOTH PROCEDURES

Emphysema with destruction and hyperinflation
Marked impairment (FEV₁ < 35% predicted)
Marked restriction in activities of daily living
Failure of maximal medical treatment to correct symptoms

CONTRAINDICATIONS TO BOTH PROCEDURES

Abnormal body weight (<70% or >130% of ideal)
Coexisting major medical problems increasing surgical risk
Inability or unwillingness to participate in pulmonary rehabilitation
Unwillingness to accept the risk of morbidity and mortality of surgery
Tobacco use within the past 6 months
Recent or current diagnosis of malignant disease
Increasing age (>65 years for transplantation, >70 years for volume reduction)
Psychological instability, such as depression or anxiety disorder

DISCRIMINATING CONDITIONS FAVORING LUNG VOLUME REDUCTION SURGERY

Marked thoracic distention
Heterogeneous disease with obvious apical target areas
FEV₁ > 20% predicted
Age between 60 and 70 years

DISCRIMINATING CONDITIONS FAVORING LUNG TRANSPLANTATION

Diffuse disease without target areas
FEV₁ < 20% predicted
Hypercapnia with PaCO₂ > 55 mm Hg
Pulmonary hypertension
Age younger than 60 years
α₁-Antitrypsin deficiency

TABLE 13-1 Selection Criteria for Lung Volume Reduction Surgery

Inclusion Criteria	Exclusion Criteria
General	
Disability despite maximal rehabilitation	Inability to participate in rehabilitation
Cessation of tobacco use > 6 months	Continued use of tobacco
Patient's expectation of goals reasonable	Significant comorbidity
	Previous pleurodesis or thoracotomy
	Underweight, overweight
Anatomic-Radiographic Evaluation	
Marked emphysema	Bronchiectasis
	Minimal radiographic emphysema
Heterogeneously distributed emphysema	Homogeneously distributed emphysema
Target zones of poorly perfused lung	No target zones
Areas with better preserved lung	No preserved lung tissue
Marked thoracic hyperinflation	Chest wall or thoracic cage abnormalities
Physiologic Evaluation	
Marked airflow obstruction	Minimal to moderate airflow obstruction
Marked hyperinflation	Minimal to moderate thoracic hyperinflation
Alveolar gas exchange	Markedly disordered alveolar gas exchange
DL _{CO} < 50% (steady state)	DL _{CO} < 10%
	PaCO ₂ > 60 mm Hg
Cardiovascular function	Cardiovascular function
Essentially normal ejection fraction	Mean pulmonary artery pressure > 35 mm Hg
	Left ventricular ejection fraction < 40%
	Significant coronary artery disease

randomized control trial to evaluate the role of LVRS in severe emphysema. After completing a pulmonary rehabilitation program, 1218 patients were randomized to either bilateral LVR surgery or continued best medical therapy between January 1998 and July 2002.⁴⁰ This multicenter trial reported a 90-day surgical mortality of 7.9%, which did not differ according to surgical approach (sternotomy vs. video-assisted thoracoscopic surgery) or by center. Although there was a significant difference between the 90-day surgical mortality and the 90-day mortality of those participants that remained in the medical arm (7.9% vs. 1.3%, respectively; $P < 0.001$), at the 2-year follow-up there was no difference in total mortality.⁴⁰ When high-risk patients were excluded (defined as participants with an FEV₁ of up to 20% predicted and either diffusing capacity for carbon monoxide [DL_{CO}] up to 20% or homogenous emphysema), the 90-day surgical mortality decreased to 5.2%.⁴⁰ Cooper and colleagues refrained from offering LVRS to patients with homogeneous emphysema from the outset of our experience, but the results obtained in this high-risk group were different from those reported by the NETT. Meyers and colleagues reported that patients with both FEV₁ and DL_{CO} of less than 20% predicted values experienced a perioperative mortality of 5% and durability of benefit that was no different from that experienced by the rest of the LVRS cohort.⁴¹ The survival curves from that study are shown in Figure 13-5.

Improvements in exercise capacity, 6-minute walk distance, percent predicted FEV₁, quality-of-life measures, and dyspnea scores were significantly higher in the NETT surgery group at all time points (6, 12, and 24 months).⁴⁰ However, when patients were divided into four subgroups based on location of disease (upper lobe vs. other) and exercise capacity (high vs. low), important outcome differences were detected (Fig. 13-6). For patients with upper lobe disease, those with low exercise capacity had significantly improved survival (risk ratio [RR] for death = 0.47; $P = 0.005$), workload capacity, and quality-of-life measures, whereas those with high exercise capacity preop showed benefits in workload

capacity and quality-of-life measures only.⁴⁰ For patients with non-upper lobe disease, those with low exercise capacity showed significant improvements in quality-of-life measures only, whereas those with high exercise capacity had no improvements in any category and in fact were at increased risk of death (RR = 2.06; $P = 0.02$).⁴⁰ These results still inform surgeons and payers regarding suitable candidate selection for LVRS.

Subgroup analysis of patients with α_1 -antitrypsin deficiency enrolled in NETT demonstrated higher 2-year mortality with surgery compared with medical management (20% vs. 0%) and decreased duration of benefits in FEV₁.⁴² Previous single-center studies had also demonstrated that improvement in dyspnea scores and lung function testing in α_1 -antitrypsin-deficient patients is of lower magnitude and shorter duration when compared with those who had more typical emphysema.^{43,44}

At 5 years of follow-up in NETT, the total mortality rate for all participants in the surgical group was

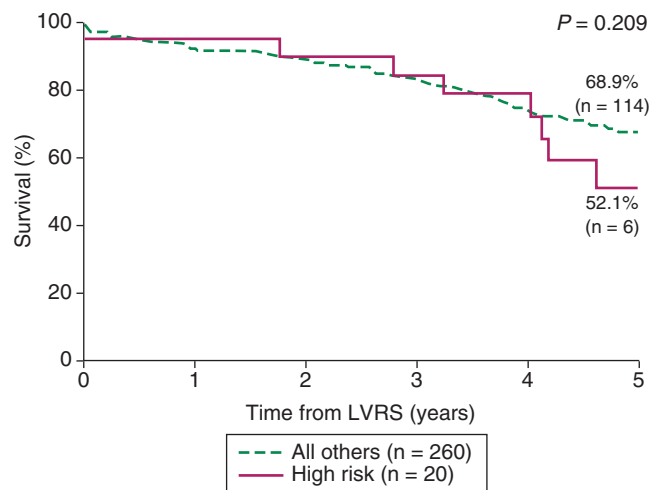


FIGURE 13-5 ■ Kaplan-Meier survival graph after bilateral lung volume reduction surgery (LVRS).

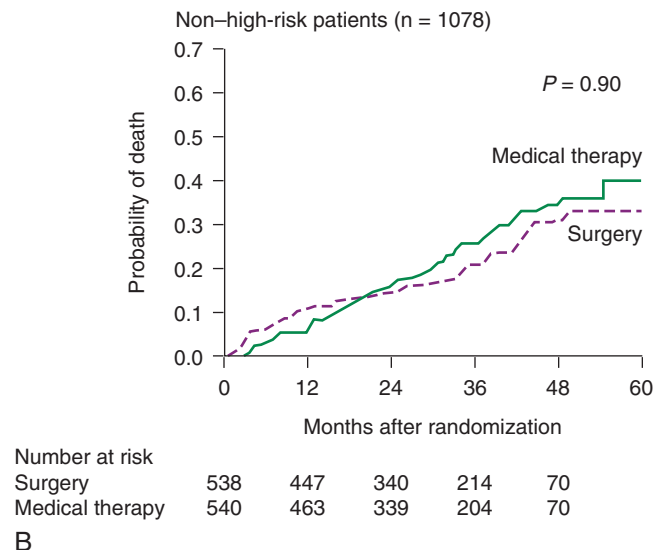
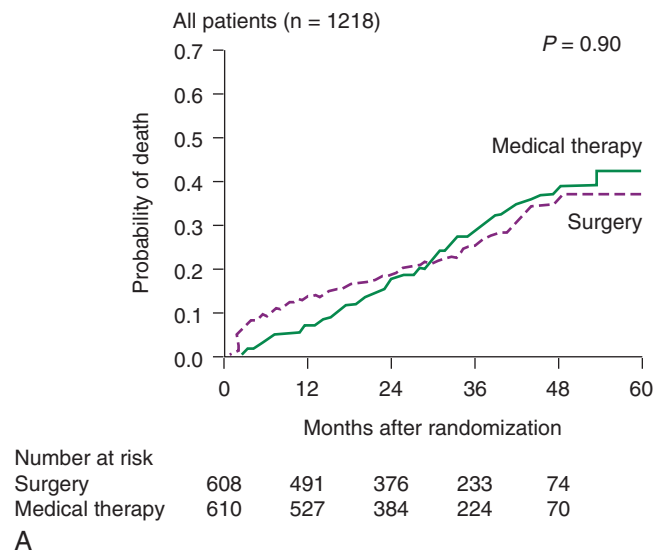


FIGURE 13-6 ■ National Emphysema Treatment Trial survival curves.

significantly lower than that in the “best medical care” cohort (overall RR = 0.85; $P = 0.02$). Quality-of-life measures were persistently higher, and exercise capacity remained significantly improved in the surgical patients for 3 years.⁴⁵ Subgroup analysis at 5 years demonstrated a continued survival advantage for the upper lobe, low exercise capacity participants only (RR = 0.57; $P = 0.01$). For the non-upper lobe disease group with low exercise capacity, the benefit in quality-of-life measures only persisted for 2 years, less than in both of the upper lobe disease groups.⁴⁵ A later exploratory analysis retrospectively analyzed survival data based on perfusion scintigraphy and found that the survival advantage for the upper lobe–predominant disease and low exercise capacity group was only significant when low upper zone perfusion was also documented (defined as less than 20% of total lung perfusion to the upper third of both lungs).⁴⁶ In this analysis, a significant survival advantage was also detected among the upper lobe disease patients with high exercise tolerance and low upper zone perfusion (RR 0.70; $P = 0.02$).⁴⁶ Figure 13-7 shows a perfusion scintigram that demonstrates the absence of apical perfusion—a pattern often seen in ideal candidates for LVRS.

The typical postoperative hospitalization after LVRS is described as 8 to 10 days, with variation in length of stay often attributed to persistent air leaks and atrial fibrillation. In the NETT trial, 90% of patients were

reported as having a postoperative air leak after LVRS, with a median duration of leak of 7 days.⁴⁷ Significant increases in risk for incidence and duration of air leak were found among patients with upper lobe disease, significant pleural adhesions, patients using inhaled steroids, and those with lower predicted FEV₁.⁴⁷ No association was found between rate or duration of air leak and surgical approach, buttressing of staple line, stapler brand, or intraoperative adjunctive procedures (pleural tenting, fibrin glue, or chemical pleurodesis).⁴⁷ Of note, 96.4% of patients in the NETT trial received buttressed staple lines, so the power to detect a difference is small. Other studies have detected a significant reduction in air leak duration and length of stay with buttressing.^{48,49} For patients experiencing air leak in NETT, postoperative stay was significantly longer (11.8 vs. 7.6 days; $P = 0.0005$).⁴⁷ Long-term complications past 30 days are rare, but there have been case reports describing expectoration of staples and bovine pericardial strips ranging from 6 to 20 months after surgery.^{50,51} The most serious sequelae of this have been identification of an associated pneumonitis or pneumonia and treatment with antibiotics.^{50,51} No cases demonstrated a subsequent bronchopleural fistula, likely because of the length of time since the original surgery.

Reoperation for further resection after initial LVRS is extremely rare. One group reported a series of 17 patients that demonstrated recurrent evidence of regional lung hyperinflation and loss of clinical benefit after initial LVRS.⁵² The various methods used for repeat intervention included completion lobectomy in approximately 40%, nonanatomic resection in 30%, and awake lung plication under epidural anesthesia in the remaining 30%.⁵² Although this led to improvements in FEV₁, forced vital capacity (FVC), residual volume (RV), 6-minute walk test, and dyspnea scores at 1-year follow-up, the perioperative mortality rate was 11.7%, higher than typically seen for initial LVRS.⁵²

Techniques

We currently favor a video-assisted thoracoscopic surgery (VATS) approach for bilateral lung volume reduction procedures because of the exposure and flexibility that it provides with a minimum of morbidity. In the NETT experience, there was no difference in mortality between median sternotomy and VATS. However, the cost of operation, median hospital length of stay, and percentage of patients experiencing independent living at 1 month postoperatively showed significant benefits for VATS in comparison with median sternotomy.⁵³

Many patients with severe emphysema have a significant element of chronic bronchitis with increased sputum production. After induction of anesthesia, a single-lumen endotracheal tube is placed and flexible bronchoscopy is performed to suction secretions and to obtain a specimen for Gram stain and culture. If thick, tenacious secretions are encountered, a mini-tracheostomy may be inserted at the end of the operative procedure to facilitate postoperative pulmonary toilet. After bronchoscopy, the single-lumen endotracheal tube is replaced with a left-sided double-lumen tube.

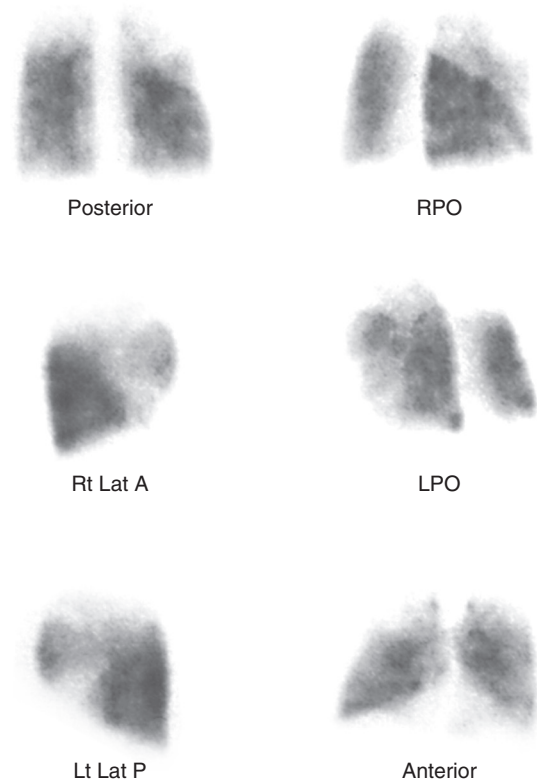


FIGURE 13-7 ■ Pulmonary perfusion scintigraphy demonstrating typical upper lobe–predominant emphysema that is viewed as the most suitable morphology for lung volume reduction surgery. *LPO*, Left posterior oblique; *Lt Lat P*, left lateral posterior; *RPO*, right posterior oblique; *Rt Lat A*, right lateral anterior.

Ventilation to the right lung is then suspended while ventilation to the left lung is continued. Care is taken by the anesthesiologist to avoid overinflation of the left lung, and airway pressures are generally restricted to the range of 15 to 20 cm H₂O pressure. Hypercapnia may well occur, but this is usually well tolerated. The patient may be placed in the supine position or in the respective lateral decubitus position depending on surgeon preference. The first trocar is placed in the seventh intercostal space and will serve as the thoracoscopic port. The working ports can be placed at the fourth or fifth intercostal space lateral to the midclavicular line. Several minutes after ventilation is suspended to the right lung, the right middle and lower lobes are usually well deflated and become progressively atelectatic, while continued inflation from upper lobe disease may still be visualized. Compression with a sponge on a ring clamp through the working port will help gradually deflate the upper lobe. The pulmonary ligament is rarely divided. Dense adhesions may be present if there have been prior episodes of pneumonia.

For upper lobe disease, 70% to 80% of the right upper lobe is excised with multiple applications of a linear stapler buttressed with strips of bovine pericardium or other similar material. Recall that the NETT trial showed no benefit for buttressing, but most cases involved the use of such material. A long curved clamp can be placed through the instrument port and applied to the lung to create a linear “crush” mark before application of the stapler. The staple line (with buttressing strips) is started at the anterior segment of the right upper lobe next to the mediastinum and is continued posteriorly. Of note, adjustments to this staple line trajectory may be made depending on lung perfusion studies. Care should be taken to avoid crossing the fissure because this can damage the superior segment of the lower lobe or tether the apex of the superior segment to the remaining upper lobe and prevent the superior segment from filling the apex of the chest.

We prefer to use a single line of excision to remove most of the right upper lobe rather than using multiple excisions, remembering that the goal is to reduce volume adequately, not to remove all of the severely diseased lung tissue. Occasionally, the apex of the upper lobe will be densely adherent to the apex of the chest and to the superior mediastinum. In such cases, it may be easier first to transect the upper portion of the lobe before attempting to dissect the apical and mediastinal adhesions. Once the transection has been accomplished, the specimen can be more easily detached from the chest wall and mediastinum by blunt dissection, cautery, or even a linear stapler, leaving a small remnant of the lung attached to the mediastinum, if necessary, to avoid injury to the phrenic nerve.

After upper lobe resection, the chest is filled with warm saline and the lung is gently inflated. Ordinarily, there are no air leaks at this time. It is not uncommon to find that the reexpanded, remaining lung does not completely fill the apex of the chest. We have considered the use of a pleural tent in this situation but now reserve it for rare cases, in particular when the remaining lung is tethered in the chest by virtue of adhesions to the chest wall or diaphragm. It has not been our practice to do

pleurodesis either by abrasion or by talc, even if the patient is not a potential candidate for subsequent lung transplantation. One chest tube is placed in the pleural space and brought out through the camera port.

Ventilation is shifted from the left lung to the right lung. With upper lobe–predominant disease, the goal is to excise the superior subdivision of the left upper lobe, leaving the lingula intact, because this is usually much less diseased. Unlike the right side, the superior segment of the left lower lobe usually reaches easily to the apex of the chest after the apical resection.

The upper one half to two thirds of the left upper lobe is excised with multiple applications of the stapler. The line of excision is usually parallel to the oblique fissure separating the upper and lower lobes. As on the right side, care is taken to avoid stapling across the fissure into the superior segment of the left lower lobe. After left upper lobe excision, the lung is reinflated and inspected for air leaks. One chest tube is placed as on the right.

After completion of the operation, the double-lumen tube is removed in the operating room. If a mini-tracheostomy is thought to be necessary on the basis of the initial bronchoscopy, this is placed immediately after removal of the double-lumen tube, generally with a 4-mm-diameter mini-tracheostomy.

COMBINATIONS OF LUNG TRANSPLANTATION AND LUNG VOLUME REDUCTION

Combinations of LVRS and lung transplantation have been reported in anecdotal clusters of patients. The combined approaches include volume reduction as a bridge to transplantation, simultaneous single-lung transplantation and unilateral volume reduction to prevent native lung hyperexpansion, early post-transplantation unilateral volume reduction to treat acute native lung hyperexpansion, and late unilateral volume reduction to treat chronic native lung hyperexpansion.

When single-lung transplantations are performed in patients with emphysema, dynamic hyperinflation is a phenomenon that can arise during ventilation through a standard single-lumen endotracheal tube. Although the transplanted lung may display a restrictive physiology with low compliance (especially in the setting of reperfusion injury) and require significant positive pressure ventilation, this will cause the native high compliance lung to undergo significant inflation, possibly resulting in hemodynamic compromise. This can be minimized by placing a double-lumen endotracheal tube and providing independent ventilation, or expediting extubation as soon as appropriate. However, this phenomenon may also be seen months after transplantation and extubation with more mild to moderate symptoms. Todd and colleagues⁵⁴ reported the Toronto experience with simultaneous unilateral volume reduction after single-lung transplantation to prospectively improve overall lung function. They experienced no additional postoperative complications, and the pulmonary function at 3 months was better than expected compared with historic controls receiving a

single-lung transplant alone. Yonan and colleagues⁵⁵ retrospectively analyzed 12 patients who experienced native lung hyperexpansion after single-lung transplantation. In their analysis of risk factors, lower pretransplantation FEV₁, higher RV, and pulmonary hypertension were all associated with a higher risk for native lung hyperexpansion. They did not perform nor did they advocate volume reduction surgery simultaneously with single-lung transplantation for emphysema.

The concept of a combined procedure was introduced to the medical literature by Zenati and colleagues⁵⁶ in 1995. Meyers and colleagues described 99 of 200 patients who underwent bilateral LVRS and who were thought to have been eligible for transplantation.⁵⁷ With a median follow-up of 5.1 years, 32 of the 99 had been listed for transplantation and 15 had actually undergone transplantation.⁵⁷ The Kaplan-Meier curve depicting freedom from listing and freedom from transplantation is shown in Figure 13-8. The only preoperative or operative factor that was predictive for the subsequent need for transplantation was a lower lobe rather than an upper lobe LVRS procedure.

One potential benefit for the patient successfully completing volume reduction surgery is the possibility that transplantation might be avoided altogether by an excellent response to volume reduction. A second possibility is that transplantation is delayed by several years and the patient is transplanted with a later cohort with the possibility of improved techniques, better immunosuppression, and overall better survival. Finally, because the hazard rate of death after lung transplantation is higher than the hazard rate of death after LVRS, anything that can safely delay entry onto the steeper survival curve may be advantageous.

However, the potential benefit of LVRS as a bridge to transplantation has limitations for many patients with severe emphysema. The anatomic and physiologic criteria that are now known to allow for significant improvement with LVRS are much more restrictive than the

criteria for transplantation, so it is unlikely that a large fraction of emphysema candidates for transplantation could be safely and successfully treated with volume reduction. Also, the challenge of how to treat a patient near the upper age limit eligible for transplantation remains a dilemma. Finally, for many patients with LVRS prior to bilateral lung transplantation, this occurred not as a bridging plan but as a pragmatic response to increasing symptoms after observing loss of the initial respiratory benefit from the LVRS procedure.

The technical logistics of performing bilateral lung transplantation after LVRS can be challenging. Although previous studies reported no differences in the need for reoperation, hospital length of stay, longitudinal lung function testing, or survival in patients receiving LVRS prior to transplantation, it is important to note that most patients received unilateral lung transplantation only.^{58,59} A recent series found that when compared with other bilateral lung transplant patients, patients with a prior history of LVRS had significantly longer operating room times, more frequent use of cardiopulmonary bypass (45% vs. 16%; $P < 0.05$), longer time on cardiopulmonary bypass, higher transfusion rates, and more adhesions to the chest and hilum.⁶⁰ In terms of perioperative outcomes, patients with LVRS prior to bilateral lung transplantation were also found to have significantly more reexplorations because of bleeding, more frequent need for phrenic nerve surgery, a higher rate of renal insufficiency requiring dialysis, longer intensive care unit stay (14.4 vs. 3.2 days; $P < 0.05$), lower FEV₁ (56.7 ± 29.1 vs. 78.8 ± 23.5 ; $P < 0.05$), and shorter distances on 6-minute walk tests.⁶⁰ Of note, longer ischemic time, chylothorax, primary graft disease requiring extracorporeal membrane oxygenation (ECMO), and in-hospital death numbers approached statistical significance.⁶⁰ The realities of the higher risks incurred when performing bilateral lung transplantation after LVRS should certainly influence both the patient consent process and operating room preparation.

The use of LVRS for late or chronic native lung hyperexpansion after single-lung transplantation is increasingly rare and anecdotal as the proportion of single-lung transplants continue to decrease. Kroshus and colleagues⁶¹ described three patients who were treated with unilateral LVRS for native lung hyperinflation and post-transplantation dyspnea that was not attributable to infection or rejection. LVRS was performed 12, 17, and 42 months after the initial lung transplantation, and all patients experienced a substantial relief in dyspnea with an improvement in exercise tolerance and an improvement in the appearance of the chest radiograph. A similar report by Le Pimpec-Barthes and associates⁶² described successful treatment of symptomatic native lung hyperexpansion by volume reduction of the native side in the form of a right upper lobectomy.

BRONCHOSCOPIC TREATMENT OF EMPHYSEMA

On the basis of improvements seen with LVRS, two main endoscopic approaches to reduce hyperinflation in

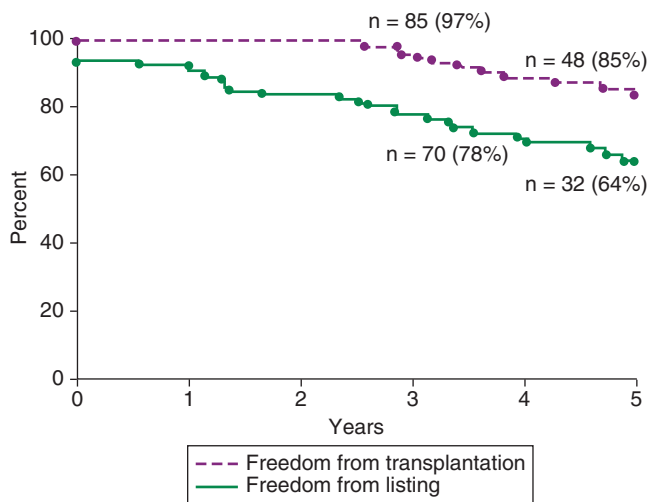


FIGURE 13-8 ■ Freedom from listing and freedom from transplantation in 99 patients thought to be eligible for either lung volume reduction surgery (LVRS) or transplantation at the time of bilateral LVRS operation.

patients with severe emphysema have been developed and investigated.

Endoscopic Placement of One-Way Valves

One approach involves placement of one-way valves with bronchoscopy in the segmental bronchi of markedly destroyed and hyperinflated portions of the lung. It was anticipated that such valves would allow deflation and secretion drainage from these segments while limiting distal airflow in. Over time, it was postulated that this would facilitate atelectasis and volume reduction in those segments. In a single-center nonrandomized trial of patients with heterogeneous emphysema, unilateral one-way intrabronchial valves were placed at target areas defined by HRCT and lung perfusion scans.⁶³ An average of 3.6 valves were placed for each patient, and all lobes were amenable to valve placement. Of note, when performing valve placement in a right middle lobe target area, the right middle lobe was always treated together with the right upper lobe.⁶³ Significant improvements were detected post procedure in supplemental oxygen use, FEV₁, FVC, RV, 6-minute walk test, and dyspnea scores.⁶³ The 6-minute walk test and dyspnea score improvements were the only outcomes that remained significant at the 5-year follow-up.⁶³ When participants' HRCT scans were evaluated for complete versus incomplete fissure demarcation, patients with complete fissures continued to have improvement in supplemental oxygen use and RV at 5 years. Furthermore, this group had a significantly improved survival advantage (83.3% vs. 24% at 100 months; $P = 0.003$).⁶³ An additional technique that has been developed to document the presence of collateral ventilation to a potential target area involves occluding the airway of interest with a catheter balloon and subsequently measuring collateral ventilation through airflow and pressure measurements of the isolated segment through a console system (Chartis).⁶⁴

In a multicenter trial with intrabronchial valve placement in patients with heterogeneous upper lobe-predominant emphysema, significant improvements were detected in the Saint George Respiratory Questionnaire at 1-, 3-, and 6-month follow-ups.⁶⁵ Patients that showed similar criteria to the high-risk category in NETT were excluded. No significant changes in pulmonary function or 6-minute walk test were detected.⁶⁵ Of note, approximately 25% of patients had valves removed at various time points for LVRS (with reasons including pneumonia in the area of the valves, nonresponders requesting removal, and in one episode, acute removal for a patient with wheezing and chest pain).⁶⁵ No episodes of valve erosion, migration, or hemoptysis were reported.⁶⁵ In the Endobronchial Valve for Emphysema Palliation (VENT) trial, another multicenter randomized trial, a small significant difference in the FEV₁ and 6-minute walk test between the endobronchial valve group and the standard medical care group was detected at 6 months, although much of this significance was attributed to continued loss of FEV₁ in the standard care group.⁶⁶ Patients receiving endobronchial valves were noted to have increased rates

of COPD exacerbation requiring hospitalization and pneumonia in the target lobe.⁶⁶

Airway Bypass

Many patients with crippling, end-stage emphysema are not suitable candidates for LVRS because of a homogeneous pattern of destruction. In these patients, there are no "target areas" that could be excised for LVRS or placement sites for endobronchial valves. Nonetheless, these patients are subject to the same crippling effects of hyperinflation as are other end-stage emphysema patients. With the goal of reducing hyperinflation in these patients, airway bypass can be performed to provide direct communication between segmental bronchi and adjacent lung parenchyma. Stents are placed through the bronchial wall, with one end of the stent in the airway and the other in the lung parenchyma. Because of the extensive collateral ventilation that may be present in such patients, several airway bypass stents may be needed. The Exhale Airway Stents for Emphysema (EASE) trial was a randomized, double-blinded international trial that examined the use of airway bypass versus sham control (bronchoscopy only) in patients with homogeneous emphysema and severe hyperinflation.⁶⁷ Patients in the airway bypass arm could receive up to six stents, with a maximum of two stents per lobe (excluding the right middle lobe).⁶⁷ Although postprocedure lung function testing showed significant improvement (increased FEV₁, decreased RV, and increased FVC), these benefits did not persist at 1 month or beyond.⁶⁷ In terms of symptomatic improvement, there was a significant benefit in the St. George's respiratory questionnaire (SGRQ) at 1 month, but that outcome also did not persist in later follow-up (from 3 months to 1 year) when compared with the control group.⁶⁷ On 6-month follow-up imaging, only 25% of patients had all stents present (most presumably lost as a result of expectoration), and of those with remaining stents, only 21% had retained patency.⁶⁷ Based on this trial, it is not likely that airway bypass results in any durable benefits for either treatment or palliation of severe hyperinflation.

Nitinol Airway Coils

At the time of this chapter writing, there is enthusiasm in some centers for another novel approach to improve symptoms of advanced emphysema. Initial pilot studies are under way of the use of nitinol stents to shrink emphysematous upper lobes and enhance ventilation and perfusion of the other, spared, areas of the lung. The procedure has been dubbed LVRC (lung volume reduction endobronchial coils) and the generic procedure to address symptoms endobronchially has been named BLVR (bronchoscopic lung volume reduction). Preliminary small trials have shown encouraging findings with improved pulmonary function, better exercise tolerance, and improved subjective symptom controls. Currently, these devices are for investigational use only and the reader will have to check recent reports for updates on the fate of LVRC and any additional entries to the category of BLVR interventions. A large, multicenter trial

with a planned enrollment of 315 patients (the RENEW trial) will help decide the fate of this latest entry into the arena of nonsurgical LVRS analogues.

SUMMARY

Although bullectomy, LVRS, and lung transplantation are similar in that each represents a surgical procedure aimed at improving the physiology and symptoms of severe pulmonary emphysema, they are unique in their ideal selection criteria and expected outcomes. We favor a meticulous selection process in which all options are considered and ultimately tailored to the patient's anatomic and physiologic features. Patients referred with a functionless, space-occupying bulla that compresses relatively normal adjacent lung will be offered thorascopic or open bullectomy. Patients with ideal circumstances for LVRS—that is, hyperinflation, heterogeneous distribution of disease, FEV₁ greater than 20%, and normal PCO₂—may be offered LVRS. Finally, patients with diffuse disease, lower FEV₁, hypercapnia, and associated pulmonary hypertension are directed toward transplantation. LVRS has not been a satisfactory option for patients with α_1 -antitrypsin deficiency, and we prefer transplantation in these cases. With strict adherence to these criteria, we find that very few emphysema patients are serious candidates for any surgical procedures. Combinations of lung volume reduction and lung transplantation, either simultaneously or sequentially, are possible but rarely necessary. Because many of the intrabronchial valve trials excluded patients that were considered high risk in the NETT trial, the main population for which we have data regarding endobronchial valve palliation are patients that either decline LVRS or have hindering medical comorbidities. Airway bypass at this time remains a procedure with only a short-term benefit, with no evidence of long-term palliation. Novel strategies will need to pass through rigorous challenges that have led to the dismissal of many such interventions in the past.

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LUNG TRANSPLANTATION

Lisa M. Brown • Varun Puri • G. A. Patterson

CHAPTER OUTLINE

HISTORICAL ASPECTS

SELECTION

Recipients
Disease-Specific Guidelines
Donors

DONOR OPERATION

Procurement
Brain-Dead Donor
Non-Heart-Beating Donor
Atrial Cuff and Pulmonary Vein Injuries
Pulmonary Arteries
Congenital Bronchial Anomalies

RECIPIENT OPERATION

Anesthesia and Intraoperative Conduct
Implantation
Incisions
Pneumonectomy
Lung Implantation
Cardiopulmonary Bypass

POSTOPERATIVE MANAGEMENT

Ventilation
Fluid Management
General Care

IMMUNOSUPPRESSION

INFECTION PROPHYLAXIS

COMPLICATIONS

Technical Problems
Primary Graft Dysfunction
Infectious Complications
Bacterial
Viral
Fungal
Acute Rejection
Airway Complications
Failure of Normal Bronchial Healing
Anastomotic Stenosis
Chronic Rejection: Bronchiolitis Obliterans Syndrome
Posttransplant Lymphoproliferative Disorder
Gastrointestinal Complications

RESULTS

PEDIATRIC LUNG TRANSPLANTATION

SUMMARY

The first successful human lung transplant was done in 1983 by the Toronto Lung Transplant Group.¹ Thirty years have passed since this landmark operation and more than 15,000 lung transplants have been done. Lung transplantation is now the preferred treatment option for a variety of end-stage pulmonary diseases. Remarkable progress has been made through refinements in technique and a better understanding of transplant immunology and microbiology. Despite these improvements, a shortage of donors and chronic graft dysfunction continue to prevent lung transplantation from reaching its full potential. Attempts made to address the donor shortage include using marginal donors, living-lobar donors, non-heart-beating donors, and split-lung donor techniques. Chronic graft dysfunction is the major factor that limits long-term survival. Extensive research efforts are underway to find methods to overcome this and prolong survival in patients undergoing lung transplantation.

HISTORICAL ASPECTS

In 1947, Vladimir Demikhov performed the first lung transplant in a dog.^{2,3} The dog survived 7 days, subsequently dying from complications of bronchial dehiscence. Dr. James D. Hardy and colleagues performed the first human lung transplant in 1963.⁴ Although their patient died after 18 days, their brief success demonstrated the technical feasibility of the operation and stimulated worldwide interest in lung transplantation. Over the next 20 years, approximately 40 lung transplants were attempted, but none achieved long-term success.⁵ The only recipient discharged from the hospital was a 23-year-old patient of Derom and colleagues,⁶ who left the hospital 8 months after transplantation and died a short time later as a result of chronic rejection, sepsis, and bronchial stenosis. Most patients in this era died within 2 weeks of lung transplantation as a result of primary graft failure, sepsis, or rejection. The most frequent cause of death

beyond the second week was bronchial anastomotic disruption.

The Toronto Lung Transplant Group's first attempt at lung transplantation, in 1978, ended with the patient dying after a bronchial dehiscence.⁷ Through experimental studies, this group discovered that high-dose perioperative steroids hindered bronchial anastomotic healing,⁸ and that wrapping an omental pedicle around the bronchus restored the blood supply to the ischemic donor bronchus and protected against anastomotic dehiscence.⁹ Recipient selection was also addressed, because most of the early attempts had been in acutely ill, often ventilator-dependent patients. The Toronto group reasoned that patients with end-stage respiratory failure from pulmonary fibrosis would provide the ideal physiologic conditions for single-lung transplantation. The increased resistance to both perfusion and ventilation of the native lung would preferentially direct perfusion and ventilation to the transplanted lung. On November 7, 1983, the first successful isolated lung transplant was performed in a 58-year-old man with pulmonary fibrosis.¹ Use of the omental flap and the withholding of steroids perioperatively are now mainly of historical interest. In the final analysis, it appears to be the attention to detail that this group practiced that led to the transplant's long-term success.

Patterson and colleagues used the en bloc double-lung transplant technique to extend the use of lung transplantation to patients with septic lung diseases and emphysema.¹⁰ The en bloc double-lung transplant, however, had several drawbacks: it was technically difficult, it required cardiopulmonary bypass (CPB), tracheal anastomotic ischemic complications were frequent, cardiac denervation occurred, and bleeding into the posterior mediastinum was troublesome because of poor operative exposure. To circumvent these problems, Pasque and colleagues¹¹ devised the technique of bilateral sequential lung transplantation. A transverse thoracosternotomy provided excellent exposure of the mediastinum and both pleural spaces. Recently, this incision was modified to avoid sternal division, when possible, to eliminate sternal wound complications.

Patients with emphysema were initially felt to be poor candidates for single-lung transplantation, because the overly compliant native lung would be prone to hyperinflation, resulting in mediastinal shift and compression of the transplanted lung. Despite this concern, successful single-lung transplantation for emphysema was reported in 1989 by Mal and colleagues.¹² Pasque and colleagues¹³ reported success with single-lung transplantation for patients with pulmonary hypertension.

The first applications of living related lobar transplants were reported by Starnes and colleagues.¹⁴ Split-lung techniques have been developed to allow a large left donor lung to be bipartitioned and the individual lobes transplanted bilaterally.¹⁵ In addition, the use of lungs from non-heart-beating donors has moved from the research realm to clinical reality.¹⁶ Most recently, the use of extended normothermic ex vivo lung perfusion has led to an increase in the percentage of donor lungs used for transplant by allowing for an objective assessment and subsequent repair (or rejection) of high-risk donor

lungs.¹⁷ Furthermore, when these lungs are transplanted, early outcomes are similar to those with conventionally selected and transplanted lungs.¹⁸

SELECTION

Recipients

General selection criteria for lung transplantation are listed in [Box 14-1](#) and disease-specific guidelines are listed in [Box 14-2](#), adapted from the most recent international guidelines for the selection of lung transplant candidates.¹⁹

Advanced recipient age is associated with decreased survival after lung transplantation.²⁰ Despite this, there has been an increase in lung transplants in patients over the age of 65. From 2006 through mid-2012, 10% of lung transplant recipients were older than 65 years and 3% were older than 70 years, an increase from 3% and 0.3%, respectively, from 2000 to 2005.²⁰ One study of 225 lung transplant recipients 70 years or older demonstrated similar survival to recipients aged 60 to 69 years.²¹

Absolute contraindications to lung transplantation are listed in [Box 14-3](#).¹⁹ A history of malignant disease within the prior 5 years generally prohibits lung transplantation. A potential exception is a patient with lung adenocarcinoma in situ or minimally invasive adenocarcinoma (formerly known as *bronchoalveolar carcinoma*). A recent study of 29 patients with bronchoalveolar carcinoma undergoing lung transplantation demonstrated that these patients have similar 30-day mortality and 5-year survival rates as patients undergoing lung transplantation for noncancer diagnoses.²² Interestingly, the presence of invasive tumor or lymph node metastases did not rule out the possibility of long-term survival.²² The patient with a recent extrathoracic malignancy deemed to be cured might be considered for transplant.

Previous thoracic surgery is not an absolute contraindication to lung transplantation, although it may complicate a transplant operation. Patients receiving high-dose corticosteroid therapy (≥ 20 mg prednisone) are not eligible for lung transplantation, because a well-documented negative influence on bronchial healing and susceptibility to postoperative infection has been demonstrated. However, low- or moderate-dose steroid therapy does not result in an increased incidence of bronchial anastomotic complications. Ventilator dependency is not an

BOX 14-1 Recipient Selection Criteria

- Clinically and physiologically severe disease
- Medical therapy ineffective or unavailable
- Substantial limitations in activities of daily living
- Limited life expectancy
- Adequate cardiac function without significant coronary disease
- Ambulatory, with rehabilitation potential
- Acceptable nutritional status
- Satisfactory psychosocial profile and emotional support system

BOX 14-2 Guidelines for Transplantation by Pulmonary Disease**CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

- Patients with a BODE index* of 7 to 10 or at least one of the following:
 - History of hospitalization for exacerbation associated with acute hypercapnia ($\text{PCO}_2 > 50$ mm Hg)
 - Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy
 - $\text{FEV}_1 < 20\%$ predicted and either $\text{DLCO} < 20\%$ predicted or homogeneous distribution of emphysema

CYSTIC FIBROSIS AND OTHER CAUSES OF BRONCHIECTASIS

- Oxygen-dependent respiratory failure
- Hypercapnia
- Pulmonary hypertension

IDIOPATHIC PULMONARY FIBROSIS AND NSIP

- Histologic or radiographic evidence of usual interstitial pneumonia and any of the following:
 - $\text{DLCO} < 39\%$ predicted
 - 10% or greater decrement in FVC during 6 months of follow-up
 - A decrease in pulse oximetry below 88% during a 6-MWT
 - Honeycombing on high-resolution computed tomography (fibrosis score > 2)
- Histologic evidence of NSIP and any of the following:
 - $\text{DLCO} < 35\%$ predicted
 - 10% or greater decrement in FVC or 15% decrease in DLCO during 6 months of follow-up

PULMONARY ARTERIAL HYPERTENSION

- Persistent New York Heart Association class III or IV on maximal medical therapy
- Low (< 350 m) or declining 6-MWT
- Failing therapy with intravenous epoprostenol or equivalent
- Cardiac index < 2 L/min/m²
- Right atrial pressure > 15 mm Hg

*BODE index includes body mass index, degree of airflow obstruction (assessed by percent predicted FEV_1), degree of dyspnea (assessed by the modified Medical Research Council [MMRC] dyspnea scale), and exercise capacity (assessed by the 6-minute walk distance). The index increases as body mass index, FEV_1 , and distance walked decrease and as the MMRC scale increases.
 6-MWT, 6-minute walk test; DLCO , diffusing capacity of the lungs for carbon monoxide; FVC , forced vital capacity; *NSIP*, nonspecific interstitial pneumonia.

absolute contraindication to transplantation, but it has been identified as a risk factor for increased mortality. This is likely because of the debility associated with long-term ventilation.²⁰

All patients, except those with primary pulmonary hypertension (PPH) or Eisenmenger syndrome, participate in a monitored exercise rehabilitation program while awaiting transplantation. Virtually all patients experience an improvement in strength and exercise tolerance without any measurable change in pulmonary function. This improved endurance enables recipients to better

BOX 14-3 Absolute Contraindications to Lung Transplantation

- Malignancy within the last 2 years, with the exception of cutaneous squamous and basal cell carcinomas; the role of lung transplantation in patients with focal pulmonary adenocarcinoma in situ (formerly known as *bronchoalveolar carcinoma*)
- Untreatable advanced dysfunction of another organ system (heart, liver, kidney); coronary artery disease not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function, is an absolute contraindication to lung transplantation, but heart-lung transplantation could be considered in some cases
- Noncurable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C, and human immunodeficiency virus
- Significant chest wall or spinal deformity
- Nonadherence or inability to follow through with medical therapy or office follow-up
- Untreatable psychiatric or psychological condition associated with the inability to cooperate or comply with medical therapy
- Absence of a consistent or reliable social support system
- Substance addiction (alcohol, tobacco, or narcotics) that is either active or has been within the last 6 months

withstand the rigors of a transplant operation and subsequent recovery.

Lung allocation in the United States was previously based on time on the waitlist, regardless of medical urgency or deterioration in medical condition. This system was flawed because it favored recipients well enough to survive on the transplant list, whereas those who may have benefitted most risked death while waiting. An ideal system of organ allocation balances clinical necessity with the ability to recover from a transplant operation. The United Network for Organ Sharing (UNOS) Thoracic Organ Committee revised the listing algorithm by assigning each patient a lung allocation score (LAS) based on the immediate need for transplant and the probability of post-transplant survival. This led the UNOS, in 2005, to rearrange its waitlist for adult lung transplantation to one based on the LAS score. Details of the allocation system are found on the official Organ Procurement and Transplantation Network website.²³

The LAS score is calculated by estimating waitlist urgency, defined as the expected number of days that could be lived without a transplant (Box 14-4), and post-transplantation survival, defined as the expected number of days lived during the first year after transplantation (Box 14-5). The transplant benefit measure is then derived by subtracting the waitlist urgency from the post-transplantation survival to obtain the raw allocation score (calculated in days). This score is normalized to the LAS on a scale of 1 to 100. The highest scores are listed first for transplantation. Factors used to predict risk of death and posttransplantation survival are regularly reviewed by the Thoracic Organ Transplantation Committee and updated as needed.

BOX 14-4 Factors That Predict Risk of Death for Patients on the Transplant Waiting List

- Forced vital capacity
- Pulmonary artery systolic pressure
- Oxygen required at rest
- Age
- Body mass index
- Diabetes
- Functional status
- Six-minute walk distance
- Continuous mechanical ventilation
- Diagnosis

BOX 14-5 Factors That Predict Survival after Lung Transplantation

- Forced vital capacity
- Pulmonary capillary wedge pressure ≥ 20 mm Hg
- Continuous mechanical ventilation
- Age
- Serum creatinine level
- Functional status
- Diagnosis

Disease-Specific Guidelines

Obstructive lung disease, with and without α_1 -antitrypsin deficiency, is currently the most common indication for lung transplantation, accounting for 39% of the adult lung transplantations reported in the 2013 Registry of the International Society for Heart and Lung Transplantation (ISHLT).²⁰ The second most common indication for lung transplantation was interstitial lung disease, accounting for 24% of lung transplants.²⁰

Before being considered for lung transplantation, patients with obstructive lung disease should have maximization of medical therapy including bronchodilators and oxygen. Consideration should be given to lung volume reduction surgery (LVRS) in ideal patients (with hyperinflation, heterogeneous distribution of disease, forced expiratory volume in 1 second [FEV₁] of more than 20%, and normal PCO₂).²⁴ We have not found LVRS to be an ideal option in patients with α_1 -antitrypsin deficiency, because these patients typically have diffuse disease.²⁴ Preliminary LVRS does not jeopardize subsequent successful lung transplantation²⁵ and may provide benefit while delaying time to lung transplantation.²⁶ We favor a meticulous selection process in which both transplantation and volume reduction are considered, and the best option is selected for each patient. In general, in patients with obstructive lung disease, the FEV₁ should be less than 25% of predicted value, and not reversible, although most patients usually have an FEV₁ of less than 15% of predicted at the time of transplantation. Progressive deterioration as indicated by hypercarbia (PaCO₂ ≥ 55 mm Hg), increasing oxygen requirement (resting PaO₂ < 55 mm Hg), the development of secondary pulmonary hypertension, rapid decline of FEV₁, or frequent

life-threatening infections indicate decreased survival, suggesting the need for transplantation.¹⁹

Septic lung disease is another common indication for lung transplantation. Cystic fibrosis (CF) is a common inherited disorder resulting in diffuse bronchiectatic destruction of both lungs. Without transplantation, the overwhelming majority of patients die as a result of progressive respiratory failure in the second or third decade of life. As reported in the 2013 ISHLT Registry, CF is the second most common indication for bilateral-lung transplantation and the third most common indication for lung transplantation in general.²⁰ The most reliable predictors of mortality in CF patients include an FEV₁ of less than 30% predicted, elevated PaCO₂, requirement for supplemental oxygen, frequent admissions to the hospital for control of acute pulmonary infection, and failure to maintain weight.²⁷ At this stage of disease, patients with CF usually have a rapidly progressive downhill course. To offset this high waitlist mortality, some of these factors have been incorporated into the LAS.

Patients with septic lung disease or those with significant sputum production are evaluated with frequent sputum cultures to determine bacterial sensitivities. Inhaled high-dose aminoglycosides or colistin are frequently used in this population. Patients with multidrug-resistant organisms, especially pan-resistant *Burkholderia cepacia*, are considered high risk, and many centers consider this a contraindication to transplantation. Some studies have shown that early mortality after lung transplantation in patients with CF who have *B. cepacia* infection is significantly increased.^{28,29} However, a recent review found several studies that were clearly in favor of *B. cepacia*-infected or colonized CF patients being listed for lung transplantation, because there was no difference in survival nor mortality risk compared with noninfected patients.³⁰ Successful transplantation in these patients often requires the use of multiple combinations of intravenous antibiotics after in vitro synergy testing to guide antibiotic selection. If no susceptible antibiotic regimen is found on synergy testing, we do not proceed with transplantation.

The diagnoses of pulmonary fibrosis and restrictive lung disease include idiopathic pulmonary fibrosis (IPF), pulmonary fibrosis of other etiologies, sarcoidosis with elevated pulmonary artery pressures, and obliterative bronchiolitis (not re-transplant cases). The 2013 ISHLT Registry report indicated that IPF was the second most common indication for single-lung transplantation and the third most common for bilateral-lung transplantation.²⁰ In our experience, candidates for transplantation had classic restrictive findings on spirometry, with a mean forced vital capacity (FVC) of 1.35 L and an FEV₁ of 1.14 L.³¹ All used supplemental oxygen and demonstrated marked impairments in exercise tolerance. Moderate pulmonary hypertension is common in these patients. Patients with pulmonary fibrosis who require a transplant have been observed to have a rapid downhill course. The lung allocation score has been devised to recognize the medical urgency of these patients.

Before the 1990s, the outlook for patients with pulmonary arterial hypertension (PAH) was poor given a lack of medical therapeutic options; heart lung transplantation

was the only option for long-term survival.³² The introduction of intravenous epoprostenol in the early 1990s and a better understanding of the pathogenesis of PAH led to earlier diagnosis and implementation of effective medical therapy.³³ Over the past three decades, improved medical management of PAH has led to an improvement in pulmonary artery pressures and relief of symptoms in the majority of patients, as well as a decrease in the number of patients needing transplantation.³²⁻³⁴ Transplantation may be delayed as long as these patients remain clinically stable on vasodilator therapy. The current indication for transplantation is progressive deterioration despite optimal medical therapy. This is defined as New York Heart Association (NYHA) class III or IV, low (<350 m) or declining 6-minute walk test, failing therapy with intravenous epoprostenol or equivalent, right atrial pressure (RAP) greater than 15 mm Hg, and cardiac index <2 L/min/m².¹⁹ Since the implementation of the lung allocation score, the probability of transplantation for PAH is low, with an increased mortality on the waiting list compared with other indications for lung transplantation.³² Data from the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) indicate that using a modified LAS score including a mean RAP of ≥14 mm Hg or a 6-minute walk distance ≤300 m would improve predictions of waitlist urgency for patients with PAH.³² Double-lung transplantation has become the operation of choice for PAH in most centers; heart-lung transplantation is rarely necessary for PAH because the right ventricle typically recovers rapidly after lung transplantation. In most centers, heart-lung transplantation is reserved for patients with PAH associated with congenital heart disease. However, patients with Eisenmenger syndrome with associated atrial or ventricular septal defect should be considered for double-lung transplantation and repair of the cardiac defect.

Donors

Rapid progress in the field of transplantation has resulted in a shortage of suitable allografts for all organs. This problem is particularly significant for lung transplantation, because only 15% of otherwise suitable organ donors have lungs satisfactory for transplantation, according to the criteria listed in [Box 14-6](#). Many conditions

resulting in brain death (e.g., trauma, spontaneous intracerebral hemorrhage) also lead to significant pulmonary parenchymal pathologic change because of lung contusion, infection, aspiration, or neurogenic pulmonary edema.

Satisfactory gas exchange is essential for donor lungs. This is confirmed by measuring a PaO₂ of greater than 300 mm Hg with an inspired oxygen fraction (FiO₂) of 100% and peak end-expiratory pressure (PEEP) of 5 cm H₂O. A PaO₂-to-FiO₂ ratio of 300 or greater indicates adequate gas exchange. A donor chest radiograph taken shortly before procurement must reveal clear lung fields. Bronchoscopic assessment at the donor institution often reveals mucopurulent secretions. This is common and is not a specific contraindication to lung transplantation if the donor is otherwise suitable. Bronchoscopic evidence of aspiration or frank pus in the airway, however, is a definite contraindication to transplantation of that lung.

The donor's medical history is obtained, with particular emphasis on and attention paid to the donor's age, cause of death, timing of death, smoking history, and prior thoracic procedures. Older donor age is associated with decreased survival after lung transplantation, and, in general, donors younger than 55 are preferred.²⁰ Despite this, according to the 2013 Registry of ISHLT, although young adults (18-29 years old) comprised 30% of lung donors, the use of lungs from donors older than 50 years old has increased over the past two decades.²⁰ Although a significant smoking history (≥30 pack-years) in the donor is a concern, it is not an absolute contraindication to the use of otherwise suitable donor lungs. In fact, a study from the UK demonstrated that although lungs from donors with a significant smoking history are associated with worse outcomes, the individual probability of survival is greater if those lungs are accepted than if they are declined and the patient waits for a potential transplant from a donor without a smoking history.³⁵ ABO blood type incompatibility between donor and recipient, human immunodeficiency virus positivity, active malignancy (outside the central nervous system), and active hepatitis infection remain absolute contraindications to donor lung procurement. Histocompatibility matching for human leukocyte antigens (HLAs) is not usually performed between donor and recipient before transplantation unless the patient has an elevated panel-reactive antibody or known HLA antibodies from prior sensitization.

Size matching between donor and recipient is an important consideration. An acceptable size match depends on the nature of the recipient's lung disease and the type of transplant anticipated. The most reliable method of size matching predicts donor and recipient lung volumes using standard nomograms based on age, sex, and height, and is used by all pulmonary function laboratories to predict lung volumes. In patients undergoing single-lung transplantation for obstructive lung disease, we try to place allografts with 15% to 20% greater volume than the recipient predicted lung volume. Implantation of a large allograft is easily achieved in a patient with obstructive lung disease because of the enormous size of the recipient pleural space. In patients with pulmonary fibrosis or pulmonary vascular disease,

BOX 14-6 Ideal Lung Donor Selection Criteria

- Age < 55 years
- No history of pulmonary disease
- Normal serial chest radiograph
- Adequate gas exchange: PaO₂ > 300 mm Hg, FiO₂ = 1.0, positive end-expiratory pressure = 5 cm H₂O
- Normal bronchoscopic examination
- Negative serologic screening for hepatitis B and human immunodeficiency virus
- Recipient matching for ABO blood group
- Size matching

however, the pleural spaces are reduced or normal in size, respectively. It is therefore inadvisable to use excessively oversized lungs in these patients. In patients undergoing bilateral-lung transplant, we prefer to match the donor lung volume to the lung volume or anticipated lung dimensions that the recipient would possess in the absence of lung disease. Oversizing a bilateral recipient may cause hemodynamic instability upon chest closure. Donor lungs that are substantially larger than the recipient's chest cavity but are otherwise usable should not preclude transplantation. We prefer to downsize the lungs by doing a lobectomy on the back table. If the size mismatch is noted after implantation, bilateral wedge resection, targeting the lingula and the right middle lobe, is carried out using stapling devices.

Certain circumstances allow for relaxation of the typically strict donor selection criteria. A minor degree of pulmonary infiltrate may be accepted in donor lungs being used for a bilateral transplantation. We analyzed 133 consecutive donor lungs and identified 37 with marginal quality, as judged by arterial blood gas analysis and radiographic assessment. The marginal donors provided postoperative function equivalent to those judged to be excellent.³⁶ Several recent studies have demonstrated no difference in post-lung transplant survival when using lungs from extended-criteria donors.^{37,38}

Novel techniques to optimize use of donor lungs have been introduced. Using the split-lung technique, the left lung of a large cadaveric donor is bipartitioned and the two lobes are used to perform a bilateral-lobar transplant in the smaller recipient. It requires significant expertise in lung transplantation, but it has been done successfully with good outcomes at certain institutions.^{15,39} Living lobar donors are also used to overcome the cadaveric lung donor shortage. Two healthy donors each donate one lobe. Donor right lower lobe and left lower lobe are implanted in the recipient on the respective sides.⁴⁰ Although we have acquired significant experience with this approach, we have not used this option in any patient since adoption of the lung allocation score system in 2005.

Another technique that is regaining popularity is the use of non-heart-beating donors.¹⁶ The lung is unique because it can tolerate warm ischemia for up to 1 hour. This is possible because the lung has a low metabolic requirement and is normally filled with well-saturated blood, and its alveoli are filled with oxygen.⁴¹ This ability of pulmonary parenchymal cells to continue aerobic cellular metabolism by relying on the oxygen in the alveoli make the lung potentially the ideal organ for transplantation after cessation of circulation, so-called "donation after cardiac death" (DCD). There are four types of DCD donors: Categories I (dead on arrival) and II (unsuccessful resuscitation) comprise the uncontrolled donors, and Categories III (awaiting cardiac arrest) and IV (cardiac arrest in brain-dead donors) consist of the controlled donors. Controlled DCD donors are the most common type. The largest series of DCD donors included 70 bilateral and 2 single-lung transplantation recipients.⁴² One- and 5-year survival in this study was 97% and 90%, respectively, and the incidence of grade 3 primary graft dysfunction was only 8.5% at 24 hours. Several other recent series have demonstrated comparable outcomes

between lung transplant recipients of DCD donors and brain dead donors.⁴³⁻⁴⁷ Despite this, DCD is only practiced by a few transplant centers.

The most recent development in the field of lung transplantation is ex vivo lung perfusion (EVLP). Steen and colleagues developed the first ex vivo perfusion system with the goal of using it to assess donor lung function in non-heart-beating donors; they described the first case report of successful transplantation of an unacceptable lung after ex vivo reconditioning.⁴⁸ Keshavjee and colleagues developed a strategy for successful long-term (12 hour) EVLP that would enable careful evaluation and potential repair of the donor lungs.⁴⁹ This strategy was made possible by adhering to several important concepts.⁵⁰ First, an acellular perfusate is used to avoid the problem of limited red blood cell life span; the lungs are oxygenated via the ventilator rather than the vasculature. Second, only 40% of the maximal cardiac output is used to perfuse the lungs thereby decreasing hydrostatic pressure and pulmonary edema without compromising perfusion. Finally, this group discovered that a left atrial pressure of 3-5 mm Hg is an important parameter to maintain. In a landmark study, the Toronto Lung Transplant Program group identified high-risk donor lungs and subjected these lungs to EVLP for 4 hours.¹⁸ The main outcome was primary graft dysfunction (PGD) at 72 hours. The incidence of PGD was 15% in the EVLP group (20 lungs) and 30% in the control group (116 lungs) and there was no difference in the secondary end points: 30-day mortality, bronchial complications, duration of mechanical ventilation, and hospital and intensive care unit (ICU) lengths of stay. Ultimately, it may be possible to treat donor lungs with medications to reduce pulmonary edema and inflammation or gene and cell therapy to prepare the lungs to deal with reperfusion and immunologic insults.⁵⁰

To ensure the most efficient transfer of data, the transplant network for the United States requires a complex computer system. UNet is a secure Internet-based transplant information database created by UNOS for the nation's organ transplant centers and organ procurement organizations to register patients for transplants, match donated organs to transplant candidates, and manage the critical data of all patients. In 2006, DonorNetSM was launched to increase the efficiency and accuracy of the organ placement process. It is a central electronic environment in which organ procurement coordinators send out offers of newly donated organs to transplant centers with compatible candidates. Organ offers can now be made to multiple transplant centers simultaneously, ensuring that organs can be matched and placed efficiently.

DONOR OPERATION

Procurement

Brain-Dead Donor

Once a candidate is determined to be a suitable donor for lung transplantation on the basis of history, chest radiograph, and arterial blood gas analysis, a flexible

bronchoscopy is done to ensure that there are no copious purulent secretions or signs of aspiration and to thoroughly suction the tracheobronchial tree.⁵¹ A small amount of purulent secretions that clears away with the initial suction is not a contraindication to procurement. Anatomic variations that may complicate implantation are noted. Clear and effective communication between the heart and lung procurement teams should be established. The sites of left and right heart venting, division of the left atrial cuff, and cannulation and division of the main pulmonary artery (PA) should be discussed and agreed upon.

Using a standard median sternotomy approach, the pericardium and both pleural spaces are widely opened. Recruitment of all atelectatic lung segments is done in situ using a sustained inflation pressure of 30 cm H₂O pressure. A compliance check is performed on the lungs by disconnecting the ventilator at end inspiration; this should result in a prompt deflation of the lungs. The lungs are manually palpated to rule out any unsuspected pathology. The pericardium is retracted with heavy silk sutures that are not tied, to allow access to both pleural spaces. At this point, we communicate with the implantation team about the quality of lungs and any concerns before proceeding.

The thoracic organ dissection begins by dissecting the aortopulmonary window in preparation for the aortic cross clamp. The main and right pulmonary arteries are separated from the ascending aorta. The superior vena cava (SVC) is dissected circumferentially to free it from all its mediastinal attachments. A heavy silk tie is passed around the SVC cephalad to the azygos vein and a Rommel tourniquet is loosely applied. A 2-0 silk tie is passed around the azygos vein and tied off about one-half centimeter away from its take off of the SVC. The SVC and the aorta are gently retracted, and the posterior pericardium is incised above the right PA, allowing access to the trachea. The plane around the trachea is developed using finger dissection. The Waterson interatrial groove is then carefully sharply dissected. This maneuver allows access to the left atrium for left ventricular venting and easier differentiation of cardiac and pulmonary left atrial cuffs when excising the heart and lungs.

After completion of the thoracic dissection and ensuring that abdominal organ procurement teams are ready, the donor is systemically heparinized (250 to 300 U/kg). The ascending aorta is cannulated with a routine cardioplegia cannula for cardiac preservation. A prolene U-stitch is placed near the pulmonary valve and a Sarns (Ann Arbor, MI) 6.5-mm curved metal cannula is placed into the main PA, with the tip pointing toward the PA bifurcation if the lungs only and not the heart are being procured. If both heart and lungs are being procured, the PA is cannulated at a minimum of 1.5 cm from the pulmonary valve, with the cannula tip pointing toward the pulmonary valve.

Using a fine needle, a 500- μ g bolus dose of prostaglandin-E₁ is injected directly into the PA; this may cause hypotension. Next, three maneuvers are done to decompress the heart before cross-clamping the aorta. First, the SVC silk tie is cinched down using the Rommel tourniquet. Second, a small incision is made in the left

atrium via the Waterson groove dissection, and a Yankauer suction is advanced across the mitral valve into the left ventricle. This incision will later be extended during the division of the left atrium into cardiac and pulmonary cuffs. Finally, the inferior vena cava (IVC) is transected with scissors. The aorta is then cross-clamped and cardioplegia initiated. The pulmonary preservation solution, 50 to 75 mL/kg of cold (4°C) Perfadex (Addmedica, Paris, France), is administered via gravity into the PA cannula. Ice slush is generously used to topically cool the heart and both pleural spaces. Gentle ventilation is continued to prevent atelectasis and homogeneously distribute the perfusate. Both lungs should blanch equally with the pulmoplegia infusion.

After completion of the cardioplegia and the ante-grade pulmonary flush, the cannulae are removed. The IVC is now freed posteriorly and dissected up to the level of the right atrium, ensuring that the right inferior pulmonary vein is not injured during this maneuver. Division of the left atrium ensues with the cooperation of the heart and lung teams. The left atrial incision begins halfway between the left inferior pulmonary vein and the atrioventricular (AV) groove (coronary sinus). This incision is extended in a plane parallel to the AV groove toward the base of the left atrial appendage on the left and toward the inferior edge of the IVC on the right. The left atrial incision is completed from inside the left atrium; all four pulmonary vein orifices can be visualized with preservation of optimal atrial cuff lengths on both the heart and lung blocks. An optimal residual atrial cuff should have a rim of left atrial muscle around each of the pulmonary vein orifices (Fig. 14-1). The SVC and azygos vein are transected. This is followed by division of the aortic arch vessels and the main PA at the site of cannulation. The heart is then passed off the field. Next, a Foley

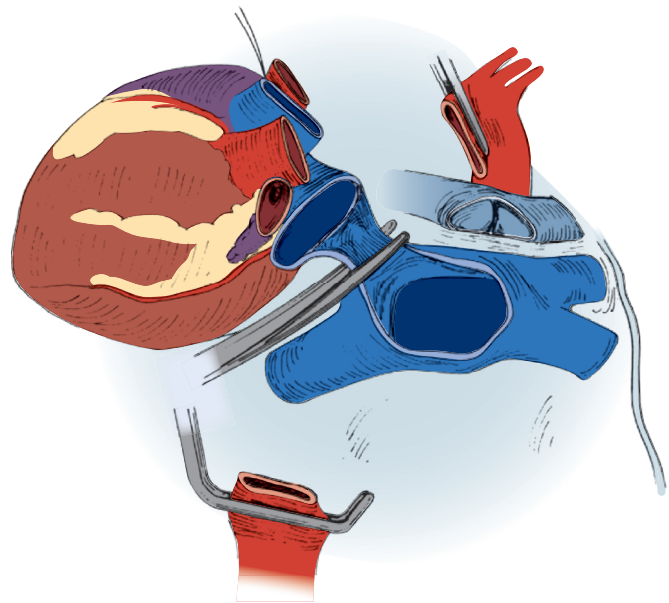


FIGURE 14-1 ■ The heart is being explanted, leaving a rim of atrium around each pulmonary vein orifice. (From Sundaresan S, Trachiotis GD, Aoe M, et al: Donor lung procurement: assessment and operative technique. *Ann Thorac Surg* 56:1409-1413, 1993.)

catheter is used to deliver 250 mL of retrograde pulmonary flush via each of the pulmonary vein orifices, which often delivers residual blood and small clots out of the open PA bifurcation. Retrograde pulmonary perfusion results in improved oxygenation, higher compliance, and a lower extravascular lung water index in transplanted lungs in the experimental setting.⁵²

We then proceed with en bloc removal of the mediastinal contents. This technique avoids injury to the membranous trachea, pulmonary arteries, and pulmonary veins, and it preserves maximal soft tissue for collateral flow to the airway. At the level of the aortic arch vessels, the mediastinal tissues are divided down to the level of the trachea. The donor is then extubated and the trachea is divided sharply between two TA-30 staple lines (Fig. 14-2). We do not inflate the lungs before this maneuver. The proximal esophagus is divided using an Endo GIA linear stapler (Covidien, Boulder, Colo.). The remaining mediastinal tissue is divided straight back to the thoracic spine, and this organ bloc is gently lifted and dissected off of the spine to the level of the midthorax. Attention is then turned to the lower thorax. The pericardium is divided near its attachments to the diaphragm, taking care not to injure the lung parenchyma. The inferior pulmonary ligaments are mobilized and divided while protecting the lung by gently retracting each lower lobe cephalad. The distal esophagus is divided using an Endo GIA linear stapler. The remaining mediastinal tissue is again divided straight back toward the spine and then cephalad along the spine until the previous dissection is met, allowing removal of the mediastinal/lung bloc from the thoracic cavity.

If the lungs are to be used at separate institutions, they are separated on the back table. Otherwise, they are placed in three layers of plastic bags, with cold preservation solution, and transported on ice. Upon arrival in the recipient operating room, separation of the two lungs is

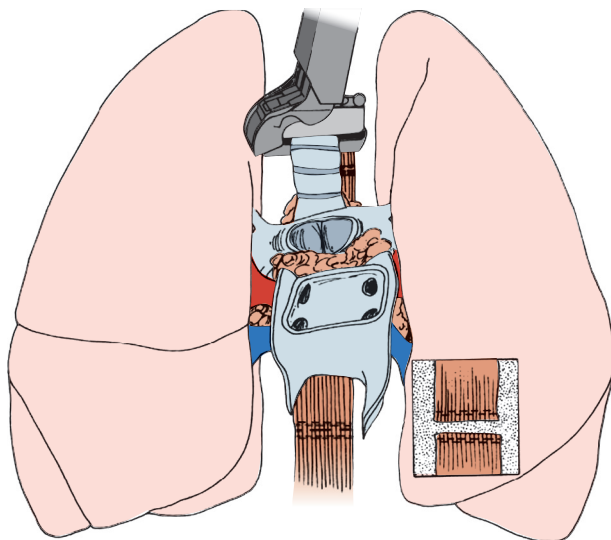


FIGURE 14-2 ■ Division of the trachea and esophagus before double-lung en bloc extraction and after removal of the heart. *Inset*, Division of the distal donor esophagus. (From Sundaresan S, Trachiotis GD, Aoe M, et al: Donor lung procurement: assessment and operative technique. *Ann Thorac Surg* 56:1409-1413, 1993.)

done in an ice slush bath. The donor esophagus and aorta are removed. The lungs are separated by division of the posterior pericardium, of the left atrium between the pulmonary veins, of the main PA at the bifurcation, and of the left bronchus close to the carina—in this order. A 15-blade is used to sharply cut across the left mainstem bronchus where it takes off of the carina; the carina is initially left with the right side. The donor bronchi are divided one ring proximal to the upper lobe orifice while minimizing proximal peribronchial dissection to preserve collateral flow. The right and left pulmonary arteries are dissected back to their first branches.

Non-Heart-Beating Donor

Our approach to non-heart-beating donors is similar to the heart-beating approach, with the exception that there is a significant time constraint. Gomez-de-Antonio and colleagues have described an alternative approach involving venoarterial extracorporeal membrane oxygenation and bilateral chest tube placement for topical cooling.⁵³

Atrial Cuff and Pulmonary Vein Injuries

Injuries most frequently involve the right inferior pulmonary vein and occur during the division of the left atrial cuff or division of the IVC. Pulmonary venous injuries can also occur as a result of excessive dissection of the inferior pulmonary ligament or unnecessary dissection of the atrial cuff within the pericardium. Unidentified, these injuries can lead to troublesome bleeding at reperfusion.

If the donor left atrial cuff is inadequate, or the superior and inferior veins are completely separated, a reconstructive salvage technique using donor pericardium has been described⁵⁴ (Fig. 14-3). It is estimated that as much as 2.7% of patients may need atrial cuff reconstruction, and Oto and colleagues have elegantly illustrated their techniques (Fig. 14-4).⁵⁵

Pulmonary Arteries

The right PA is more commonly injured because it courses behind the aorta and SVC. Because the right PA is substantially longer than the left, injury to this vessel under the aorta often does not require repair, and the artery is simply trimmed distal to the laceration. If necessary, repair is accomplished by simple suture or reconstruction using available donor pulmonary artery, azygos vein, or pericardium.

Congenital Bronchial Anomalies

A tracheal upper lobe bronchus, the most common anomaly, may be a segmental or a lobar bronchus. If the bronchus is a segmental bronchus, it may be either oversewn or reimplanted. If the entire right upper lobe bronchus arises as an abnormal tracheal bronchus, the options are donor right upper lobectomy, left single-lung transplantation, or incorporation of the bronchus intermedium and the aberrant right upper lobe bronchus into a modified anastomosis with the recipient bronchus.⁵⁶

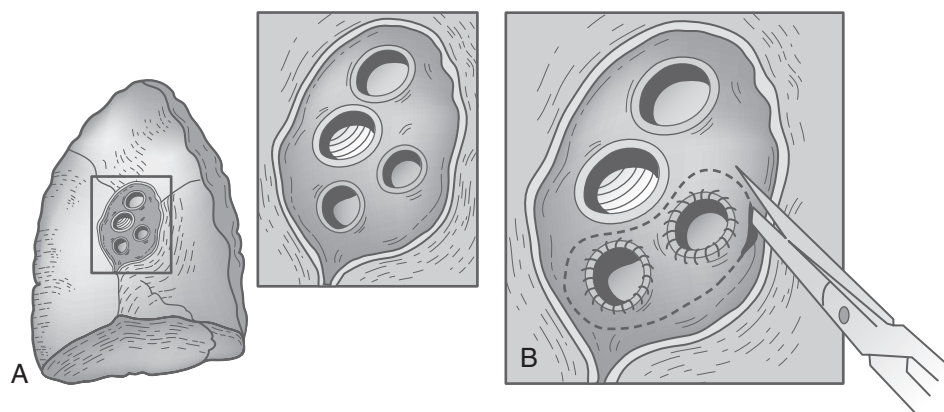


FIGURE 14-3 ■ Creation of a new atrial cuff after suboptimal harvest. **A**, There is complete separation of the superior and inferior pulmonary veins. **B**, Attaching the intima of each vein to the pericardium and then incising pericardium to reconstruct an atrial cuff. (From Casula RP, Stoica SC, Wallwork J, et al: Pulmonary vein augmentation for single lung transplantation. *Ann Thorac Surg* 71:1373–1374, 2001. Copyright The Society of Thoracic Surgeons.)

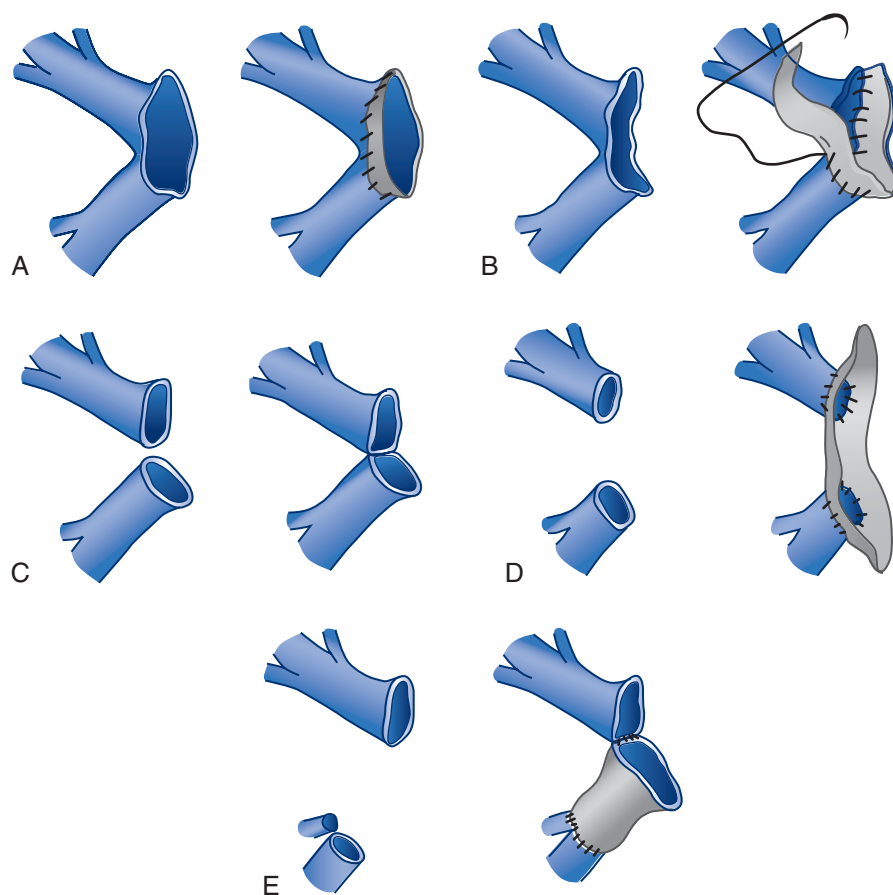


FIGURE 14-4 ■ Reconstruction for an inadequate left atrial cuff. **A**, Anterior pericardial patch augmentation. **B**, Anterior and posterior pericardial patch augmentation. **C**, Separated but close venous orifices united by suture repair to create oval cross-sectional cuff. **D**, Widely separated veins, cuff reconstruction using pericardium. **E**, Donor pulmonary artery used to reconstruct the inferior vein in lung transplantation. (From Oto T, Rabinov M, Negri J, et al: Techniques of reconstruction for inadequate donor left atrial cuff in lung transplantation. *Ann Thorac Surg* 81:1199–1204, 2006.)

RECIPIENT OPERATION

Anesthesia and Intraoperative Conduct

An experienced anesthesiologist who is adept in double-lumen tube management, bronchoscopy, and the use of

transesophageal echocardiography (TEE) is an invaluable part of the transplant team. Our patients undergo placement of an epidural catheter unless systemic heparinization for cardiopulmonary bypass is anticipated. If the indication for transplantation is septic lung disease, patients undergo therapeutic bronchoscopy and

suctioning via a large single-lumen endotracheal tube. Radial and femoral arterial lines, a PA catheter, a TEE probe, and heating blankets on both the operating table and lower body are routine. The patient is positioned supine with both arms tucked. Minimizing intravenous fluids without compromising end-organ perfusion may avoid or reduce postoperative respiratory insufficiency. We use vasopressors as indicated and avoid excessive volume resuscitation.

TEE is useful at various junctures in the operation.⁵⁷ Specifically, TEE monitoring is used to identify any intracardiac shunts, evaluate the right ventricle during PA clamping, determine the need for CPB based on classic signs of impending right ventricular decompensation, assess the arterial and venous anastomoses, and check for air in the left atrium. We use epoprostenol or nitric oxide (or both) for acute refractory pulmonary hypertension in the perioperative period. Inhaled nitric oxide is also indicated for poor oxygenation.

Implantation

Incisions

Bilateral anterolateral thoracotomy without sternal division is our preferred incision for bilateral sequential lung transplant.⁵⁸ The skin incision follows the inframammary crease at the level of the fourth intercostal space and extends from the lateral sternal edge to the anterior axillary line. The breast tissue is elevated and the pectoralis major muscle is divided. The chest cavity is entered in the fourth interspace. Bilateral internal mammary arteries are ligated and divided. Alternatively, the internal mammary arteries can be preserved if a 1-cm segment of costal cartilage of the fourth rib is resected at the sternal border, allowing upward mobility of the fourth rib when retracted. Further mobility for retraction is obtained by dividing the intercostal muscles from within the pleural space laterally to the paraspinal muscles. We place two chest wall retractors at 90-degree angles to one another (Fig. 14-5).

The *clamshell incision* (sternothoracotomy) involves connecting the bilateral anterolateral thoracotomy incisions across the midline by dividing the sternum (Fig. 14-6). This incision provides excellent exposure and requires the division of both mammary arteries. It is used to provide additional exposure when CPB is needed or when cardiomegaly and/or a relatively small thoracic cavity makes hilar exposure difficult. The sternum is reapproximated using two figure-of-eight #5 sternal wires.

A *median sternotomy* is used if the recipient is undergoing concomitant cardiac surgery. This approach may also be useful for women with large breasts that compromise the exposure obtained by anterolateral thoracotomy.

Posterolateral thoracotomy and anterolateral thoracotomy are used when the patient has significant cardiomegaly, which can make exposing the left hilum through an anterolateral thoracotomy difficult. This difficulty can be circumvented by transplanting the left lung via a left posterolateral thoracotomy incision and then repositioning the patient for a right anterolateral thoracotomy to transplant the right lung.

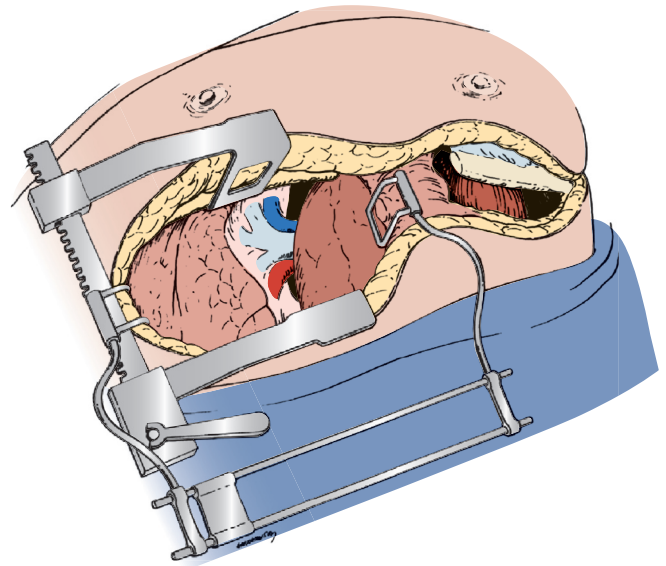


FIGURE 14-5 ■ Bilateral anterolateral thoracotomy. Two retractors are placed at right angles. (From Meyers BF, Patterson GA: Technical aspects of adult lung transplantation. *Semin Thorac Cardiovasc Surg* 10:213–220, 1998.)

The anterior axillary muscle-sparing thoracotomy incision, which may lead to improved chest wall and shoulder girdle mechanics, was initially described for single-lung transplant in recipients with chronic obstructive pulmonary disease.⁵⁹ The small anterior axillary thoracotomy is comparable with the more conventional posterolateral or clamshell incision in terms of operating times and ability to cannulate for central CPB.^{60,61}

Pneumonectomy

Before excision of the recipient lungs, the donor lungs should be separated and ready for implantation, and bilateral hilar dissection and adhesiolysis completed. This allows expeditious removal of the second lung, minimizing the amount of time that the newly implanted contralateral lung is exposed to the entire cardiac output. The lung with the poorer function, based on a preoperative ventilation perfusion scan, is transplanted first, because the other lung will more likely support single-lung ventilation.

During pneumonectomy, meticulous hemostasis is of prime importance in taking down pleural adhesions, particularly in patients with septic lung disease and prior thoracic procedures. The phrenic, vagus, and recurrent laryngeal nerves must be protected. During hilar dissection, the pulmonary arteries and veins are dissected beyond their first bifurcations to preserve the length of the main trunks. The right PA is transected approximately 1 cm beyond the truncus anterior branch and the left PA beyond the second branch to the left upper lobe. Vascular staplers are used on the central side of division, and ties are used peripherally. This maneuver downsizes the recipient PA, which may provide a better donor-recipient size match, and the ligated first branch of the recipient PA provides an anatomic landmark for orientation during the anastomosis. Next, the pulmonary veins

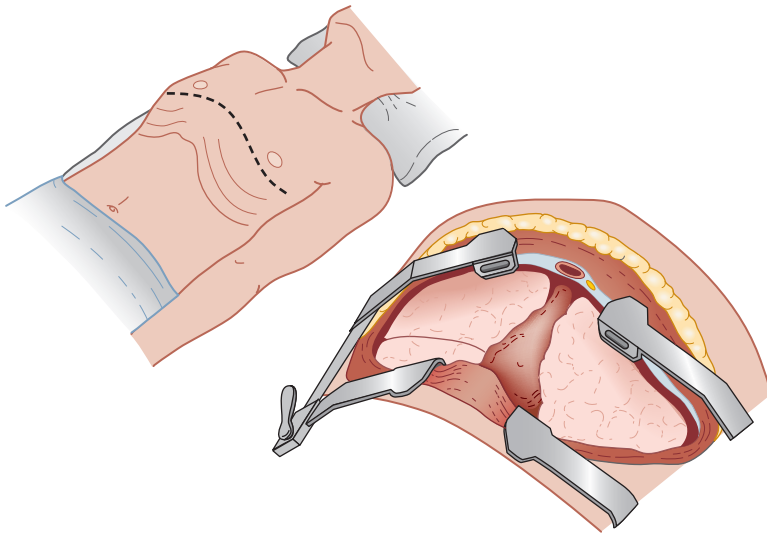


FIGURE 14-6 ■ The sternum has been divided for a clamshell incision that provides excellent exposure to the thorax. (From Lau CL, Patterson GA: Technical considerations in lung transplantation. *Chest Surg Clin North Am* 13:463–483, 2003.)

are divided at secondary branch points. The peribronchial tissue is divided, and bronchial artery bleeding is controlled with cautery or ligatures; bronchial arteries are often significantly enlarged in patients with septic lung disease. The bronchus is divided sharply just proximal to the upper lobe origin, and the lung is removed. All posterior mediastinal and posterior chest wall bleeding is controlled, because this is the only opportunity to access this area safely. Next, we prepare for implantation by exposing the hilum. The pulmonary artery is gently grasped in a clamp, freed centrally, and retracted anteromedially. The superior and inferior pulmonary veins are similarly grasped in clamps, the pericardium around them is widely opened, and the veins are retracted anteriorly. We are now ready for lung implantation.

Lung Implantation

The donor lung is covered with a cold lap pad and placed in a bed of ice slush into the thoracic cavity. We start with the bronchial anastomosis. Our preference is an end-to-end anastomosis using two 4-0 polydioxanone (PDS) sutures in a running fashion. A retraction suture (0 silk) is placed into the anterior aspect of the recipient bronchus to aid exposure. The anastomosis is started on the membranous portion of the airway in running fashion and carried around over the anterior cartilaginous portion with the second suture (Fig. 14-7). In case of significant size mismatch between the bronchi, the membranous portion is completed using a running 4-0 PDS suture, and the cartilaginous part is approximated with simple interrupted 3-0 VICRYL sutures (Ethicon Endo-Surgery, Cincinnati, Ohio; Fig. 14-8). The peribronchial tissue on the donor and recipient sides is used to cover the anterior aspect of the anastomosis to offer some protection to the overlying vascular anastomoses in case of bronchial anastomotic breakdown. End-to-end airway anastomosis is superior to the telescoped anastomosis technique.⁶²

Next, a vascular clamp is placed as proximal as possible on the recipient PA and the staple line resected. The donor and recipient PAs are trimmed to prevent excessive length and possible kinking, and an end-to-end

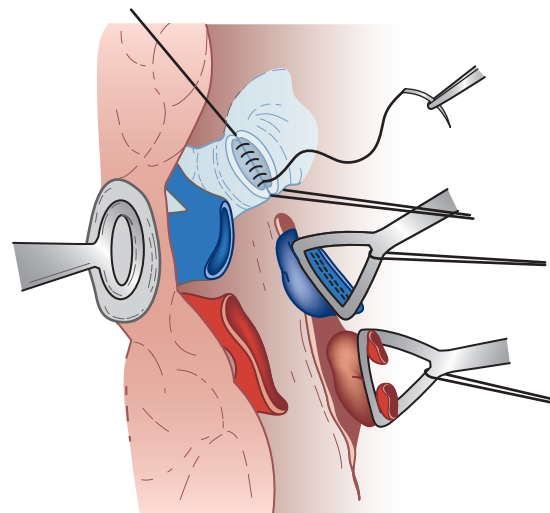


FIGURE 14-7 ■ Retraction on the pulmonary artery and pulmonary vein stumps provides exposure for the airway anastomosis. The bronchial anastomosis is being performed with 4-0 polydioxanone (PDS) suture. (From Meyers BF, Patterson GA: Technical aspects of adult lung transplantation. *Semin Thorac Cardiovasc Surg* 10:213–220, 1998.)

anastomosis is fashioned using a continuous 5-0 polypropylene stitch, using precise small bites to prevent anastomotic stricture (Fig. 14-9).

The pericardium is then opened circumferentially around the pulmonary vein stumps. The vein stumps are then retracted laterally and a Satinsky-type clamp is placed centrally on the recipient's left atrium. The recipient pulmonary venous stumps are amputated, and the two openings connected to create the atrial cuff. The anastomosis is fashioned with continuous 4-0 polypropylene suture. Stitches are placed via a mattress technique, which achieves intima-to-intima apposition and excludes potentially thrombogenic atrial muscle (Fig. 14-10).

The last few sutures of the venous anastomosis are left loose, the lung is partially inflated, and the PA clamp is released momentarily. This maneuver flushes air and perfusate out of the lung. The left atrial clamp is then opened

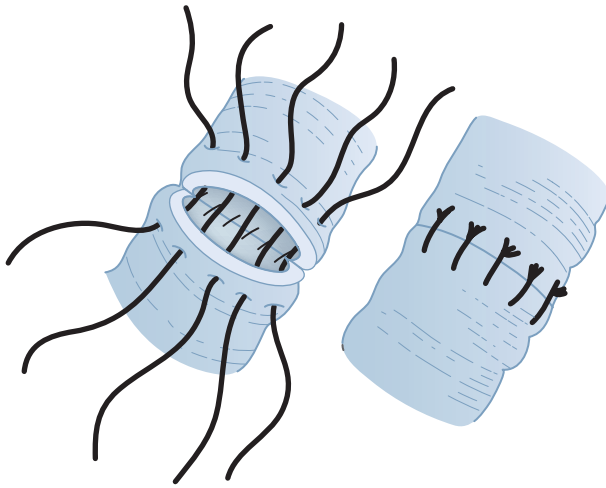


FIGURE 14-8 ■ The anterior wall of the bronchial anastomosis is performed with interrupted 3-0 Vicryl suture when a significant size mismatch is present. (From Meyers BF, Patterson GA: Technical aspects of adult lung transplantation. *Semin Thorac Cardiovasc Surg* 10:213–220, 1998.)

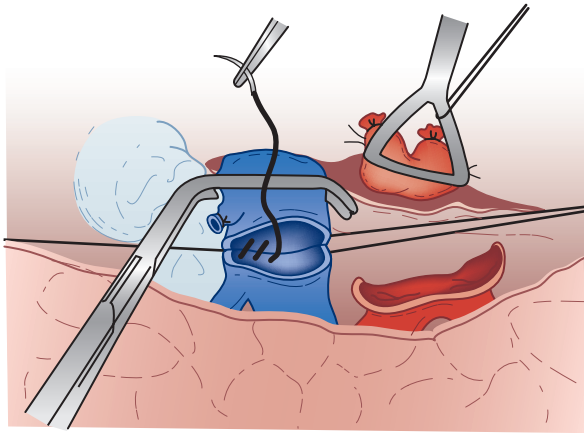


FIGURE 14-9 ■ The pulmonary artery anastomosis is fashioned using a running 5-0 polypropylene suture. (From Meyers BF, Patterson GA: Technical aspects of adult lung transplantation. *Semin Thorac Cardiovasc Surg* 10:213–220, 1998)

to completely de-air the atrium. The atrial suture line is pulled up tight and tied down. All clamps are removed.

If the operation is being done without CPB, it is important to stabilize the patient after the first lung is implanted. Pulmonary hypertension may result from hypercarbia that is corrected with a period of dual-lung ventilation. Using this maneuver, CPB for implantation of the second lung can often be avoided.

The pleural spaces are drained with two 24-Fr Blake drains (Ethicon, Somerville, N.J.) in each pleural space, one placed apically and one along the diaphragm. If significant postoperative bleeding is expected, two 28-Fr conventional chest tubes are preferred over Blake drains. The sternum is reapproximated with two figure-of-eight #5 sternal wires. The ribs are reapproximated with heavy interrupted figure-of-eight monofilament nonabsorbable suture. The chest wall is closed in layers.

A flexible bronchoscopy is done after exchanging the double-lumen tube for a single-lumen tube to evaluate

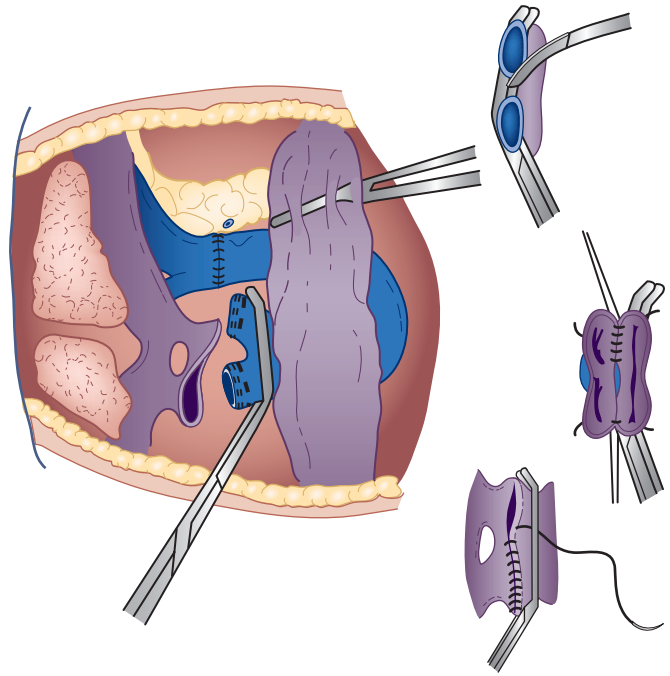


FIGURE 14-10 ■ A large Satinsky clamp is placed centrally across the left atrium. Both vein stumps are amputated, and the bridge between is connected to create a left atriotomy suitable for anastomosis. (From Patterson GA: Bilateral lung transplant: indications and technique. *Semin Thorac Cardiovasc Surg* 4:95–100, 1992.)

the airway anastomoses and remove blood and secretions. The patient is now transported, intubated, to the ICU.

Cardiopulmonary Bypass

We use CPB selectively in our patients. It is, however, indicated for children, small-statured patients when a double-lumen tube cannot be placed, lobar transplants, concomitant intracardiac procedures, and most patients with pulmonary hypertension. CPB is also indicated if at any point during the operation the patient develops refractory hypoxemia, hypercarbia, pulmonary hypertension, or hemodynamic instability. Difficult exposure is another indication for CPB. This is typically seen in patients with idiopathic pulmonary fibrosis who have a small pleural space with the heart shifted to the left, making exposure of the left hilum difficult (Fig. 14-11). A traction suture in the fibrous portion of the diaphragm, brought extracorporeally through a planned chest tube site, can improve exposure. Inadequate exposure of the left hilum is sometimes the only indication for CPB. We have also used the Urchin heart-positioning device (Medtronic, Minneapolis, MN) to improve exposure in these situations (Fig. 14-12).⁶³

When CPB is used electively, we do most of the dissection before systemic heparinization. Standard aortic cannulation is carried out, and a two-stage venous cannula is introduced via the right atrial appendage. We avoid the use of pump suckers. After implantation of the first lung, the left atrium is de-aired and the venous clamp removed. This also allows the placement of an atrial clamp for venous anastomosis on the contralateral side.

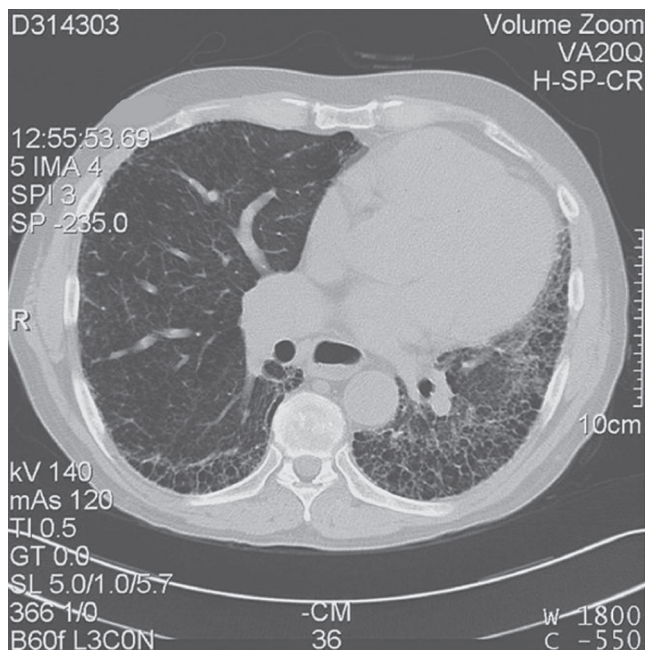


FIGURE 14-11 ■ Axial computed tomographic image from a patient with idiopathic pulmonary fibrosis shows a markedly diminished left pleural space with the mediastinum shifted to the left. This finding mandates the use of cardiopulmonary bypass for adequate exposure.

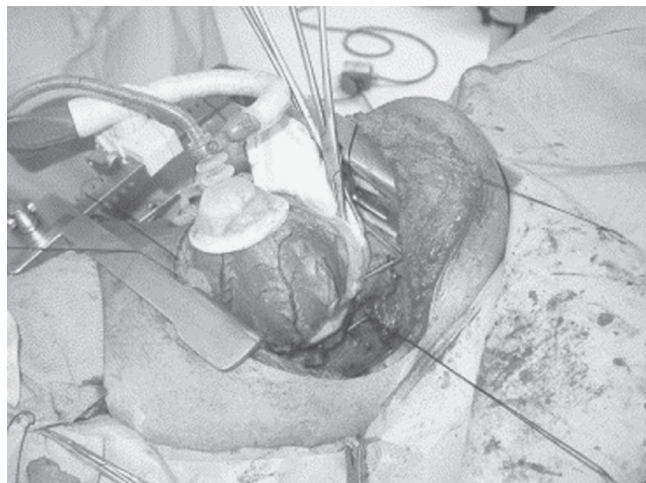


FIGURE 14-12 ■ An apical suction device is in place, lifting the apex of the heart and improving exposure to the left hilum. (From Lau CL, Hoganson DM, Meyers BF, et al: Use of an apical heart suction device for exposure in lung transplantation. *Ann Thorac Surg* 81:1524–1525, 2006)

POSTOPERATIVE MANAGEMENT

Ventilation

Patients are transported to the ICU and are ventilated using standard techniques. Tidal volumes of 7 to 10 mL/kg are usually sufficient. The FiO_2 is adjusted to keep the PaO_2 greater than 70 mm Hg, and PEEP of 5 to 7.5 cm H_2O is used in most patients. Frequent arterial blood gas analyses are performed. After an initial period of

evaluation, if the patients are hemodynamically normal and have no significant bleeding, and gas exchange is adequate, ventilator weaning is started. Patients are extubated according to standard criteria for gas exchange and respiratory mechanics. Most patients are extubated within 24 to 48 hours of transplantation after standard intermittent mandatory ventilation or pressure-support weaning. Before extubation, patients undergo bronchoscopy to ensure adequate clearance of secretions. This standard management is applied in all bilateral-lung transplant recipients and single-lung recipients undergoing transplantation for pulmonary fibrosis.

After single-lung transplantation for emphysema or pulmonary vascular disease, patients are managed using a different approach.⁶⁴ Preventing hyperinflation of the native lung and compression of the newly implanted lung are the main goals in patients with emphysema. This is accomplished by avoiding the use of PEEP and using lower tidal volumes. If air trapping occurs in the native lung, it leads to high airway pressures, inadequate removal of carbon dioxide, and hypotension from decreased venous return to the heart. This sometimes requires volume reduction of the native lung by lobectomy or even pneumonectomy.^{65,66}

In single-lung recipients with pulmonary vascular disease, we use a prolonged period (48–72 hours) of elective ventilation. The patient is positioned to keep the native lung dependent to maintain inflation and appropriate drainage of the transplanted lung. Tidal volumes are standard, but a higher PEEP of 7.5 to 10 cm H_2O is applied. If early graft dysfunction, rejection, or infection occurs, leading to a prolonged period of mechanical ventilation, tracheostomy should be done early in the postoperative course.

Fluid Management

In the early postoperative period, the Swan-Ganz catheter and daily weight measurement provide objective assessment of fluid status. The patients often return from the operating room with a significant positive fluid balance. Diuretics are used aggressively during the early postoperative period. Sometimes, patients undergoing single-lung transplantation for PPH develop hemodynamic instability if the filling pressures on the right side of the heart are excessively reduced, and these patients may require somewhat higher filling pressures.

General Care

Postoperatively, a quantitative lung perfusion scan to assess graft flow is done only if there are any major concerns. If a lobar or greater perfusion defect is appreciated, further interrogation for the cause should be undertaken either by catheterization or operative exploration. Aggressive clearance of airway secretions and inhalation of bronchodilators are required postoperatively. Early and constant involvement of the physical therapy team ensures that transplant recipients are out of bed to chair, walking with assistance, and using the treadmill or exercise bike as soon as possible.

IMMUNOSUPPRESSION

Immunosuppression after solid organ transplantation was revolutionized by the introduction of cyclosporine in the 1980s. Immunosuppression for lung transplantation is used for induction, maintenance, and treatment for rejection.

Induction therapy is controversial. High-dose methylprednisolone is routinely administered intraoperatively before reperfusion. However, there is no consensus on the routine use of induction immunosuppression.⁶⁷ Potential benefits include lower rates of acute rejection, protection from nephrotoxicity as a result of delayed introduction of a calcineurin inhibitor, and a decrease in bronchiolitis obliterans syndrome (BOS). Disadvantages are the higher risk of infectious complications and posttransplantation malignancies. Practice patterns vary significantly, and approximately 50% of patients undergoing lung transplantation receive induction immunosuppression.

Two types of induction immunosuppression agents are available: antithymocyte globulin and interleukin-2 receptor (IL-2R) antagonists.⁶⁷ Antithymocyte globulin is a formulation of polyclonal antibodies directed against T- and B-lymphocyte cell-surface antigens. In the United States, two types are available, Thymoglobulin (Genzyme, Cambridge, Mass.), derived from rabbits, and Atgam (Pfizer, New York, N.Y.), derived from horses. The animals are injected with human thymic cells or lymphocytes, leading to the formation of anti-human antibodies that are then isolated, purified, and used for induction therapy. IL-2R antagonists are humanized monoclonal antibodies directed against the IL-2 receptor on activated T cells, thereby interfering with T cell proliferation. Basiliximab (Simulect; Novartis Pharma, East Hanover, N.J.) is currently the only IL-2R antagonist used for induction therapy. This agent is generally well tolerated and is not associated with an increased incidence of post-transplant infections.⁶⁸

For maintenance therapy, the majority of lung transplant patients are placed on a three-drug regimen, consisting of a calcineurin inhibitor, an antimetabolite, and a low-dose corticosteroid. On a case-by-case basis, a mammalian target of rapamycin (mTOR) inhibitor may be used instead of either the calcineurin inhibitor or the antimetabolite. Tacrolimus (Prograf; Astellas Pharma, Northbrook, Ill.) is a calcineurin inhibitor that suppresses the transcription of IL-2, inhibiting the proliferation of T cells; it is 10 to 100 more times more effective at inhibiting T cell activation than cyclosporine. Mycophenolate fofetil (MMF) (Cellcept; Genentech, South San Francisco, Calif.) is an antimetabolite that noncompetitively blocks an enzyme in the purine synthesis pathway. Sirolimus (Rapamune; Pfizer, New York, N.Y.) is an mTOR inhibitor similar in structure to tacrolimus and binds the same cytosolic immunophilin, but this complex binds mTOR downstream from IL-2 in the T cell activation cascade. mTOR inhibitors should not be used until wounds and anastomoses are completely healed because of several reports of airway dehiscence in the early postoperative period.^{69,70} Everolimus (Zortess; Novartis) is a newer mTOR inhibitor with improved bioavailability and a similar side-effect profile. Most programs give

moderate-dose corticosteroid therapy (methylprednisolone, 0.5-1 mg/kg per day intravenously) for several days before starting an oral dose of prednisone 0.5 mg/kg per day. At both 1 and 5 years after transplantation, tacrolimus is the most common calcineurin inhibitor used and MMF the most common antimetabolite.⁷¹

INFECTION PROPHYLAXIS

We routinely administer broad-spectrum antibiotics (usually cefepime and vancomycin) for several days after transplantation. Results from donor and recipient airway cultures are used to adjust this empiric regimen. In patients with CF, aerosolized colistin or tobramycin is added, and special emphasis is placed on coverage for *Pseudomonas*.

Cytomegalovirus (CMV) reactivation in lung transplant recipients has been associated with CMV pneumonitis and gastrointestinal disease, as well as increased risk for development of BOS. The risk of development of CMV-related complications after lung transplantation is highly dependent on the CMV status of both the donor and the recipient, with donor-positive/recipient-negative at highest risk.⁷² A recent randomized controlled trial demonstrated that extending prophylaxis with valgancyclovir from the standard 3 months to 12 months after transplantation decreased the incidence of CMV disease from 32% to 4%.⁷³ During a mean follow-up of almost 4 years, extended-course CMV prophylaxis provided a sustained protective benefit over short-course prophylaxis with a lifetime CMV incidence of 12% versus 55%, respectively.⁷⁴ For mismatched recipients, we administer prophylactic therapy for 3 to 6 months. Otherwise, we use a preemptive treatment approach, where recipients are screened weekly by polymerase chain reaction (PCR) for CMV in the blood, and treatment is initiated if the PCR test becomes positive. For the first year after transplantation, we also routinely prescribe acyclovir (unless the patient is on ganciclovir or valganciclovir) for herpes simplex prophylaxis.

Aspergillus is the most common cause of invasive fungal infection in lung transplant recipients. Therefore, many transplant centers use routine antifungal prophylaxis. A recent meta-analysis evaluated the available literature to compare the development of invasive aspergillosis (IA) and colonization with and without fungal prophylaxis.⁷⁵ The results were that 19 of 235 (8.1%) and 28 of 196 (14.3%) developed IA in the prophylaxis and no-prophylaxis groups, respectively (relative risk 0.36, 95% confidence interval 0.05-2.62). There was no significant reduction in either IA or *Aspergillus* colonization with prophylaxis.

Lifelong *Pneumocystis jiroveci* pneumonia prophylaxis is started 3 weeks after transplantation. Our current strategy includes Bactrim DS (Roche Laboratories/Genentech, South San Francisco, Calif.) three times per week. One study of *Pneumocystis jiroveci* pneumonia in solid organ transplant recipients demonstrated that the highest incidence of *Pneumocystis* pneumonia occurred among lung transplant recipients and that there was no decrease in the incidence beyond 1 year as was seen with other types

of solid organ transplantation.⁷⁶ Therefore, lifelong prophylaxis is recommended. Alternative agents, such as monthly application of inhaled pentamidine, are administered when there is an allergy to sulfa medications.

As part of the frequent bronchoscopies performed in these patients, we routinely obtain samples from the bronchoalveolar lavage (BAL) for cytology, Gram stain, KOH test (potassium hydroxide), acid-fast bacilli stain, and immunostains for respiratory viruses, herpes simplex virus, and CMV. In addition, bacterial, mycobacterial, fungal, and viral cultures are obtained.

It is difficult to distinguish infectious pulmonary problems from rejection in the early posttransplantation lung recipient using radiographic, clinical, and physiologic criteria. This has led to the frequent use of fiberoptic bronchoscopy in these patients. BAL and transbronchial biopsies are done to examine for opportunistic infection and evidence of rejection, respectively. These studies are routinely performed at 2 to 3 weeks; at 2, 3, 6, and 12 months; and annually thereafter.

COMPLICATIONS

Technical Problems

With increasing experience, the technical aspects of lung transplantation have become more sophisticated and reproducible. However, as with any major operation, technical complications may occur perioperatively. Perioperative hemorrhage may be related to a large raw surface that is created after explantation from a patient with septic lung disease or one who has undergone previous pleurodesis. CPB usually exacerbates this problem. In addition to meticulous attention to stopping all surgically correctable bleeding, we aggressively correct any coagulopathy with blood products and use recombinant factor VII as needed. In this situation, we delay final chest closure and proceed to the ICU after approximating the skin and applying a transparent sterile dressing. Final chest closure is usually possible within the next 24 to 48 hours. This strategy does not increase the incidence of wound complications.⁷⁷

A technically unsatisfactory bronchial anastomosis is easily identified in the operating room during postimplantation bronchoscopy. Inadequate anastomotic caliber mandates immediate surgical revision. Pulmonary arterial anastomotic compromise manifests as persistent pulmonary hypertension and unexplained hypoxemia. Intraoperative TEE can be used to assess flow through the anastomoses intraoperatively. A nuclear perfusion scan performed immediately postoperatively will demonstrate less-than-anticipated flow to the affected side. The gold standard for studying the PA anastomosis is contrast angiography, which can additionally look for a gradient across the anastomosis. A gradient of 15 to 20 mm Hg may be found, especially in single-lung recipients, in whom most cardiac output is directed to the transplanted lung, or in bilateral recipients with a high cardiac output. The need for anastomotic revision is dictated by the clinical situation. Significant reduction in flow in the appropriate clinical setting indicates surgical correction,

because the donor bronchus depends entirely on pulmonary arterial collateral flow. Pulmonary venous anastomotic compromise can be technical or may be caused by a clot causing compression in the setting of hemorrhage. Similarly, TEE and contrast angiography, with close attention to the venous phase, will identify the problem. Sometimes, surgical exploration is necessary to confirm the diagnosis and repair the problem.

Primary Graft Dysfunction

Primary graft dysfunction develops in as much as 25% of lung transplant recipients.^{78,79} Mortality from PGD is as high as 30% and is the main cause of mortality in the perioperative period. The major diagnostic criteria for PGD are a decreased PaO₂-to-FiO₂ ratio in the first 48 hours after transplantation, and the presence of pan-lobar alveolar infiltrates on postoperative chest radiographs (Fig. 14-13). The ISHLT devised a grading system for primary graft dysfunction based on these criteria (Table 14-1).⁸⁰

Ischemia-reperfusion injury accounts for most cases of primary graft dysfunction (see Fig. 14-13). Other suspected causes include donor lung pathologic conditions

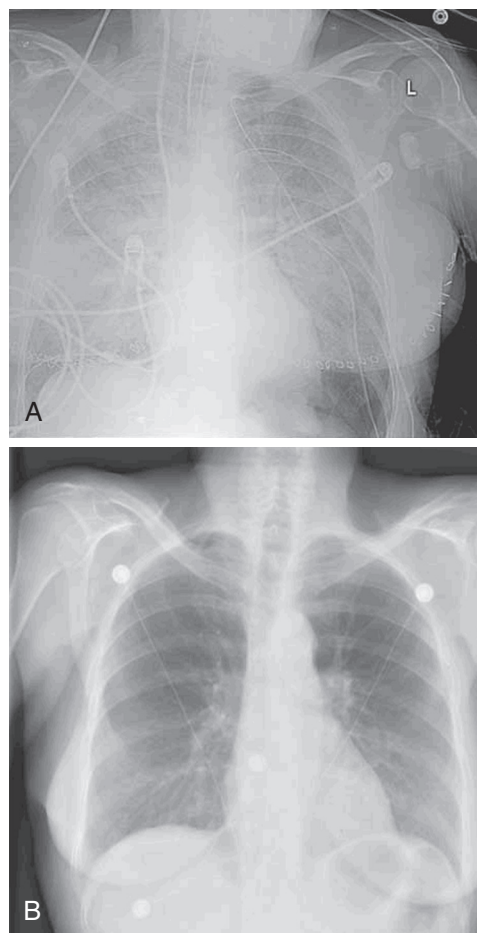


FIGURE 14-13 ■ **A**, Chest radiograph showing diffuse consolidation typical of ischemic reperfusion injury. The right lung was implanted first, which explains the increased injury appreciated on this side. **B**, Radiograph of the same patient after complete recovery.

TABLE 14-1 Grading System for Primary Graft Dysfunction

Grade	PaO ₂ /Fio ₂	Radiographic Infiltrates
0	>300	Absent
1	>300	Present
2	200-300	Present
3	<200	Present

From Christie JD, Carby M, Bag R, et al: Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 24:1454-1459, 2005.

such as aspiration, infection, or contusion. The pathogenesis of PGD begins with the pathophysiologic changes that occur in the donor after brain death; it continues during the cold ischemia time period and then during reperfusion.⁸¹ The ischemia-reperfusion injury generates reactive oxygen species that go on to injure the pulmonary endothelium and epithelium. This injury leads to capillary leak, pulmonary edema, and decreased lung compliance that manifests as hypoxia and bilateral infiltrates on chest radiograph. In addition, macrophages in the donor lungs initiate an inflammatory cascade that leads to the release of mediators that then recruit and activate recipient leukocytes. Elevated recipient pulmonary artery pressure and prolonged ischemic time have been consistently identified as strong risk factors for the development of PGD.

Primary graft dysfunction is managed with aggressive cardiopulmonary support in the ICU. Lung protective ventilation strategies, diuresis, inhaled nitric oxide,⁸² and aerosolized prostacyclin⁸³ are used. In most patients, PGD resolves over several days of intensive care support, and they obtain satisfactory long-term allograft function.⁷⁹ ECMO support is used if conservative management is unsuccessful. In a review of our experience with 983 lung transplant recipients, 47 required ECMO for PGD during the immediate postoperative phase. ECMO was used in 9.7% of pediatric and 2.8% of adult lung transplant recipients.⁷⁹ Only 38% of patients who needed ECMO survived to discharge from the hospital. Eleven patients underwent retransplantation for PGD. There is a direct relationship between the severity of PGD and the development of BOS.⁸⁴

Infectious Complications

Infectious complications are a major cause of posttransplant morbidity and mortality. PGD and non-CMV infection are the major causes of death within the first year after transplant.⁸⁵ After the first year, the most common causes of death are BOS and non-CMV infection.

Bacterial

Gram-negative organisms are the most common cause of bacterial pneumonia, with *Pseudomonas aeruginosa* being the most frequent, followed closely by *Staphylococcus*

aureus.⁸⁶ Patients infected with *Burkholderia cenocepacia* have a sixfold higher risk of death at 1 year compared with patients infected with *Burkholderia cepacia complex*, and they have an eightfold higher risk than patients without *Burkholderia* infection.⁸⁵ Patients with CF need to be carefully evaluated before lung transplantation to determine whether *Burkholderia* spp. are present. Typical symptoms of pneumonia such as fever and cough are commonly masked by immunosuppressive therapy. Therefore, a thorough work-up in all lung transplant recipients with deteriorating lung function regardless of symptoms is mandatory. This includes a chest radiograph, complete blood cell count, bronchoscopy with BAL, and, possibly, transbronchial biopsies. Empiric antibiotic treatments for pneumonia should cover for methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and atypical bacterial infections.

Lung abscess is sometimes encountered in lung transplantation recipients, and patients with CF are susceptible to having multifocal lung abscesses resulting from inhalation of organisms colonized from an upper airway or sinus infection. The care of these patients is the same as it is for any other patient with lung abscess. Broad-spectrum antibiotic therapy is initiated, and bronchoscopy is done to ensure that there is no airway obstruction.

Viral

Cytomegalovirus disease is the most common postoperative infectious complication in lung transplant recipients (Fig. 14-14).^{85,86} It occurs in as much as one-third of transplant patients in the first year.⁸⁶ Because the lung can harbor high latent CMV loads, the incidence of CMV infection is higher after lung transplantation than after transplantation of other solid organs. The greatest risk of CMV infection occurs when a CMV⁺ recipient is transplanted with lungs from a CMV-positive donor. Therefore, most programs match seronegative donors with seronegative recipients. In addition, CMV may predispose a patient to the development of chronic allograft rejection. CMV also leads to further immunosuppression, such that patients are at an increased risk for other opportunistic infections and posttransplant lymphoproliferative disease.⁸⁷ The diagnosis of CMV infection (viral replication) at our institution is based on a positive PCR test on a blood sample, whereas the presence of cytomegalic cells (CMV inclusion bodies or positive immunoperoxidase stain) in tissue biopsies is considered indicative of CMV disease (CMV infection with symptoms) (see Fig. 14-14). If symptoms are present, patients are treated with intravenous ganciclovir or oral valganciclovir for at least 1 week after viral replication is no longer detectable.⁸⁵ CMV immunoglobulin can be given to patients who do not respond to standard antiviral treatment.

Although less common, non-CMV viral respiratory tract infections have been reported.^{88,89} These include herpesvirus, respiratory syncytial virus, parainfluenza virus, influenza virus, and adenovirus. These infections have also been linked to later development of chronic allograft rejection.^{90,91} Treatment includes supportive care and antiviral therapy.

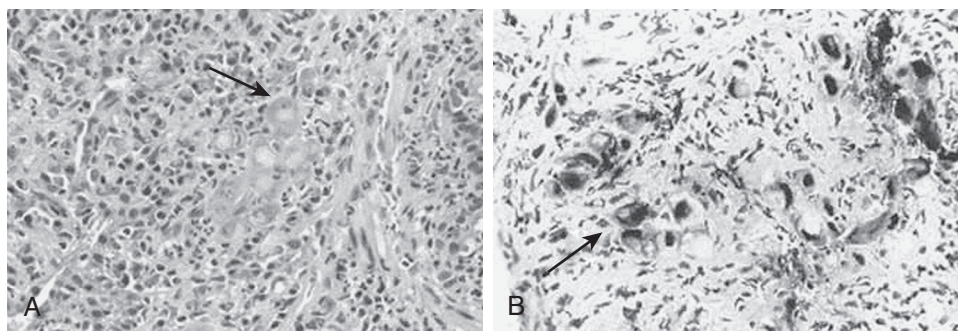


FIGURE 14-14 ■ **A**, Transbronchial lung biopsy showing cytomegalovirus (CMV) pneumonitis with CMV inclusion bodies (*arrow*), using hematoxylin and eosin stain. **B**, Demonstration of CMV inclusion bodies by immunoperoxidase staining (*arrow*).

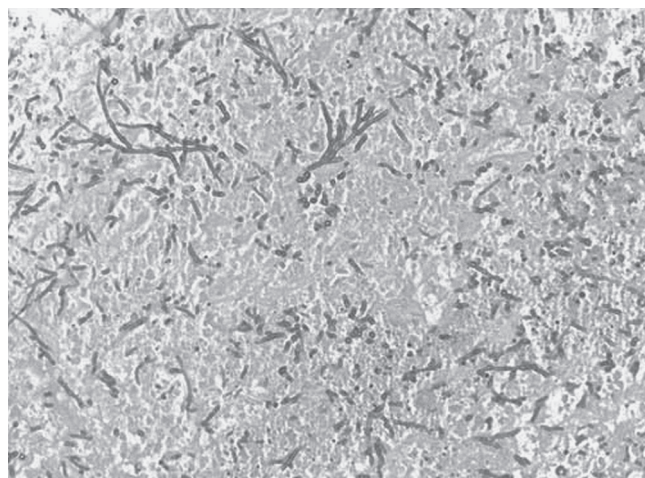


FIGURE 14-15 ■ Histopathologic examination of a patient with *Aspergillus* spp., infection (hematoxylin and eosin stain, original magnification $\times 20$).

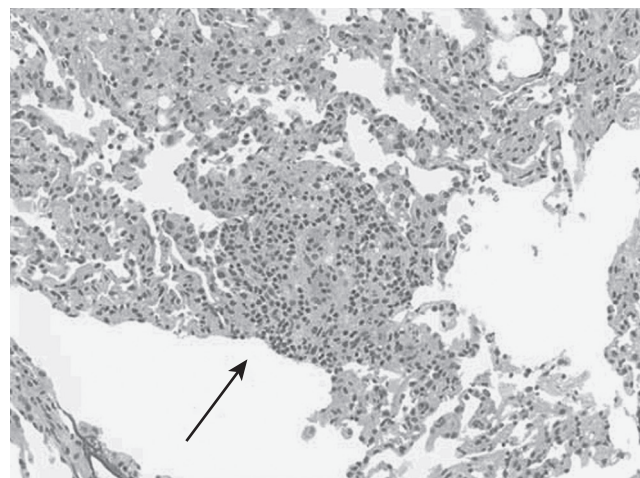


FIGURE 14-16 ■ Histopathologic examination of acute rejection (*arrow*; hematoxylin and eosin stain, original magnification $\times 20$).

Fungal

Candida albicans is commonly isolated after transplantation; it usually represents colonization, but it may also be invasive.⁸⁶ These infections may be symptomatic or may be discovered on surveillance bronchoscopy. Candidal infections are most commonly associated with airway anastomotic complications.^{92,93} They can be treated with a combination of systemic and inhaled amphotericin B and fluconazole (some species are resistant).

The most frequent cause of significant fungal infection after transplantation is *Aspergillus* (Fig. 14-15). More commonly, however, *Aspergillus* spp. growing in sputum or BAL cultures represents colonization (see Fig. 14-15). Colonization is a risk factor for invasive disease, but only a fraction of colonized patients develop more serious infections.⁹⁴ *Aspergillus* infections are classified as either localized airway infection or invasive disease. Invasive disease is further subclassified as tracheobronchitis, invasive pulmonary aspergillosis, and disseminated aspergillosis. Aspergillosis tracheobronchitis tends to localize to the bronchial anastomoses. This can result in erosion involving the adjacent pulmonary artery, causing massive hemoptysis and death. Overall mortality for patients with invasive pulmonary aspergillosis or disseminated disease approaches 60%.⁹⁵ In less severe cases, it increases the

risk of airway complications including stenosis and bronchomalacia.⁹⁶ Voriconazole is the mainstay treatment for invasive aspergillosis; parenteral lipid formulations of amphotericin B is the second-line therapy. Prevention of aspergillosis involves infection-control measures such as wearing masks while near areas of hospital construction, as well as avoiding gardening, compost, and other outdoor exposures. Once *Aspergillus* sp. has colonized the airways, it is difficult to clear.

Acute Rejection

Acute rejection is seen more commonly after lung transplantation than after any other solid organ transplant (Fig. 14-16).⁹⁷ Although it is an uncommon cause of mortality, it is associated with the development of chronic rejection. The majority of episodes of acute rejection occur early in the postoperative period, and the incidence steadily declines after the first 3 months.⁹⁸⁻¹⁰⁰ Between July 2004 and June 2012, one-third of adult lung recipients experienced at least one episode of acute rejection between discharge and 1-year follow-up.²⁰

Patients with symptomatic episodes of acute rejection present with dyspnea, hypoxemia, low-grade fever, and moderate leukocytosis, which can be difficult to differentiate from infection. The chest radiograph often shows

TABLE 14-2 Revised Working Formulation for Classification and Grading of Pulmonary Allograft Rejection

A: Acute Rejection	
Grade 0	None
Grade 1	Minimal
Grade 2	Mild
Grade 3	Moderate
Grade 4	Severe
B: Airway Inflammation	
Grade 0	None
Grade 1R	Low grade
Grade 2R	High grade
Grade X	Ungradeable
C: Chronic Airway Rejection-Obliterative Bronchiolitis	
	0-Absent
	1-Present
D: Chronic Vascular Rejection	
	Accelerated graft vascular sclerosis

From Stewart S, Fishbein MC, Snell GI, et al: Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant* 26:1229–1242, 2007.

diffuse, perihilar interstitial infiltrates; however, episodes occurring after the first month may appear as a normal chest radiograph. Episodes of acute rejection may also present with a decrease in lung function: 10% or greater decline in baseline FEV₁ or FVC. Bronchoscopy with transbronchial biopsy is used to confirm the diagnosis and rule out infection. Acute rejection is present if there is perivascular or peribronchial mononuclear inflammation. A grading system based on histologic criteria for classification of pulmonary transplant rejection was revised by the ISHLT in 2007 (Table 14-2).¹⁰¹

Acute rejection is usually treated with intravenous methylprednisolone, 10 to 15 mg/kg per day for 3 to 5 days. Most commonly, there is dramatic improvement in symptoms and radiographic findings within 8 to 12 hours; this is followed with a tapered steroid dose over 2 to 3 weeks. Baseline immunosuppression is reevaluated with recurrent acute rejection. We repeat bronchoscopy in 3 to 6 weeks to confirm an appropriate response to therapy. In approximately one-third of cases, persistent acute rejection is detected at follow-up.¹⁰² For refractory acute rejection, a trial of cytolytic therapy is often initiated.¹⁰³ Other therapies have included aerosolized cyclosporine,¹⁰⁴ alemtuzumab,¹⁰⁵ methotrexate,¹⁰⁶ extracorporeal photopheresis,^{107,108} and total lymphoid irradiation.¹⁰⁹ Despite the introduction of new immunosuppressant agents in the maintenance regimens of lung transplant recipients, none has been associated with a clear reduction in acute rejection.^{110,111}

Airway Complications

With standard methods of implantation, the donor bronchus is rendered ischemic as the systemic bronchial circulation is interrupted. The donor bronchus relies on collateral pulmonary arterial flow during the first few days after transplantation. Anastomotic complications

resulting from airway ischemia include infection, dehiscence, stenosis, and malacia. The reported incidence of these complications is 7% to 14%, although improvements in anastomotic techniques, pulmonary preservation, and care in preserving collateral circulation during the donor operation have decreased the incidence.¹¹²⁻¹¹⁴

In a review of our experience at Washington University in St. Louis, Missouri, the incidence of airway complications was associated with the time period during which the transplantation was performed. The incidence of airway complications during the initial period, from 1988 through 1993, was almost 16%; this decreased to less than 10% during later time periods. Importantly, airway complications did not seem to have an adverse impact on overall survival.⁷⁹

From a technical standpoint, a shortened donor bronchial length (one ring proximal to the upper lobe takeoff) reduces the length of the donor bronchus that is dependent on collateral flow. Peribronchial tissue on the donor bronchus is preserved during preparation of the lung. Telescoping the bronchial anastomosis has not been shown to reduce the rate of airway complications, and we do not use the telescoping technique unless we encounter a significant size mismatch between donor and recipient. Improved preservation techniques have also resulted in increased bronchial viability after transplantation. Post-transplantation pulmonary parenchymal pathology also compromises collateral flow, rendering the ischemic donor bronchus at increased risk for necrosis and dehiscence. Therefore, pulmonary allograft preservation and adequate postoperative pulmonary blood flow are important. Surprisingly, laboratory evidence points to the beneficial role of steroids in bronchial revascularization and epithelial regeneration.^{115,116}

Postoperative surveillance bronchoscopy leads to early identification of anastomotic complications. Computed tomography (CT) is a useful diagnostic tool for the evaluation of documented or suspected donor airway complications. Patients with late airway stenoses have symptoms of dyspnea, wheeze, or decreased FEV₁. Bronchoscopic assessment confirms the diagnosis.

Failure of Normal Bronchial Healing

Sometimes patchy areas of superficial necrosis of donor bronchial epithelium are seen. These areas are of no concern and ultimately heal. Minor degrees of bronchial dehiscence are also of little long-term consequence. Membranous wall defects typically heal without airway compromise, whereas cartilaginous defects usually result in some degree of late stricture. Significant dehiscence (>50% of the bronchial circumference) may result in compromise of the airway. This problem should be managed expectantly using laser or mechanical débridement of the area to maintain a patent airway. A stent can be placed only if the distal main airway remains intact. A significant dehiscence sometimes results in direct communication with the pleural space, resulting in pneumothorax and a significant air leak. If the lung remains completely expanded and the pleural space is evacuated, however, the leak will ultimately seal, and the airway may heal without significant stenosis.¹¹⁷

Similarly, a dehiscence may communicate directly with the mediastinum, resulting in mediastinal emphysema. If the lung remains completely expanded and the pleural space is filled, adequate drainage of the mediastinum can be achieved by placing a drain in close proximity to the anastomotic line by mediastinoscopy. This step will also lead to healing of the anastomosis, often without stricture.

Surgical revision of the anastomosis is possible only if an adequate length of donor airway is available for resuturing. This procedure is rarely possible, however, if the donor bronchus was cut to an appropriately short length at the time of the initial procedure. Massive dehiscence of the airway with uncontrolled leak or mediastinal contamination has been treated by retransplantation.

Necrotic tissue at the bronchial anastomosis is an ideal medium for the growth of saprophytic fungi. These infections can be a significant source of morbidity. In one study, saprophytic fungal infections involving the bronchial anastomosis occurred in 25% of recipients surviving a minimum of 75 days after transplantation. In 47% of those patients with fungal involvement of the anastomosis, airway complications occurred.⁹⁶

Anastomotic Stenosis

Chronic airway stenoses result from surgical stenosis, granulation tissue, infection, or bronchomalacia, with ischemia as the universal common denominator. Bronchoscopic balloon dilation may be attempted, and this may avoid the need for stent placement.¹¹⁸ We have used Silastic endobronchial stents to treat this problem.¹¹⁹ Daily inhalation of *N*-acetylcysteine is required to keep the stents patent. Most of these stents are only needed temporarily, because after several months, most patients are able to maintain satisfactory airway patency without a stent. When airways distal to an anastomotic stricture are too small to accept a Silastic stent, or when a Silastic stent will obstruct one bronchus while stenting another, a self-expanding metal stent may be used. However, granulation tissue rapidly overgrows a bare metal mesh stent, sometimes making it impossible to remove. Self-expandable silicone stents have also been used. Treatment of the granulation tissue consists of a combination of laser or forceps débridement, dilation, and stenting.¹¹² Recurrent airway stenoses have been managed with topical application of mitomycin C¹²⁰ and with high-dose brachytherapy.¹²¹ Finally, if bronchial strictures prove unmanageable by dilation or stent insertion, sleeve resection¹²² and retransplantation are available options.¹²³

Chronic Rejection: Bronchiolitis Obliterans Syndrome

Chronic rejection of the lung allograft is the major limitation to long-term recipient survival (Fig. 14-17). Within 5 years of transplantation, BOS develops in 49% of recipients, and in 76% of recipients by 10 years post-transplant.²⁰ In addition, 5 years after transplantation, BOS accounts for 20% of deaths.²⁰ The hallmark clinical feature of BOS is the development of airway obstruction with a reduction of FEV₁ that does not respond to

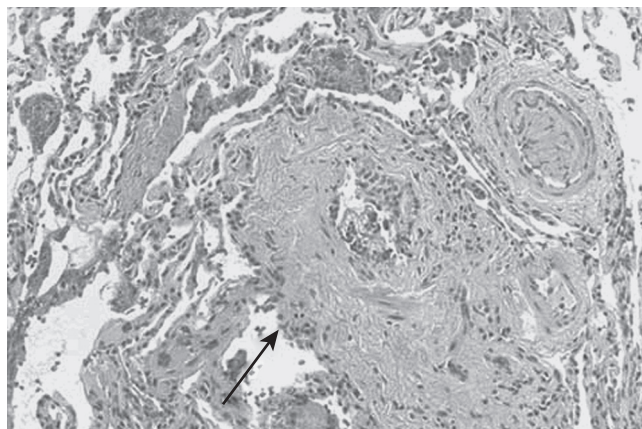


FIGURE 14-17 ■ Transbronchial lung biopsy showing bronchiolitis obliterans with scarring and fibrosis of the small airways (arrow; hematoxylin and eosin stain).

bronchodilators. The key histologic finding of chronic rejection is obliterative bronchiolitis, an inflammatory process that affects small noncartilagenous airways (see Fig. 14-17).¹²⁴ Bronchiolitis obliterans is a patchy heterogeneous process, thus transbronchial biopsy has a sensitivity of only 22% to 73% in the diagnosis of chronic rejection.¹²⁵ The clinical diagnosis of BOS requires a sustained decline in FEV₁ for more than 3 weeks and other causes of a decrease in lung function need to be excluded: acute rejection, anastomotic complications, and infection.¹²⁴ The diagnosis of BOS does not require the presence of histologically documented bronchiolitis obliterans.

The best posttransplant FEV₁ is determined and used as the baseline against which future measurements are compared. A decline from this baseline determines the stage of BOS. Patients cannot receive a diagnosis of BOS until at least 3 months after transplantation. The absence or presence of bronchiolitis obliterans is noted by subcategories “a” and “b,” respectively. Table 14-3 shows the current classification system.¹²⁶ The forced expiratory flow 25% to 75% (FEF₂₅₋₇₅) is part of the classification and has been shown to be more sensitive than FEV₁ for the detection of early airflow obstruction in bilateral-lung transplant recipients,¹²⁷ but it has wide variability with single-lung transplants. Airway neutrophilia detected on BAL,¹²⁷ elevated exhaled nitric oxide fraction,¹²⁸ and air trapping on an expiratory CT scan¹²⁹ are additional diagnostic tests that indicate BOS. A recent review reported the risk factors for development of BOS (Box 14-7).¹²⁴ Interestingly, gastroesophageal reflux disease is a potential risk factor for BOS. In lung transplant patients who undergo early fundoplication, both freedom from BOS and survival were improved when compared with patients with reflux and no fundoplication.¹³⁰

Therapeutic options for bronchiolitis obliterans are limited, and once present, it is generally irreversible. Standard treatment protocols consist of augmenting immunosuppression in an attempt to stabilize the disease process. Regimens such as high-dose corticosteroids,

TABLE 14-3 Criteria for Bronchiolitis Obliterans Syndrome*

BOS Score	Degree	Baseline FEV ₁ (%)
0	None	>90, and FEF ₂₅₋₇₅ >75%
0-p	Potential	81-90 and/or FEF ₂₅₋₇₅ ≤75%
1	Mild	66-80
2	Moderate	51-65
3	Severe	≤50

*Each bronchiolitis obliterans syndrome (BOS) score has a subcategory noting the histologically documented absence or presence of bronchiolitis obliterans: *a* indicates "without pathologic evidence of bronchiolitis obliterans," and *b* indicates "with pathologic evidence of bronchiolitis obliterans."

FEV₁, Forced expiratory volume in 1 second; FEF, forced expiratory flow.

Adapted from Cooper JD, Billingham M, Egan T, et al: A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. *International Society for Heart and Lung Transplantation. J Heart Lung Transplant* 12:713-716, 1993; and Estenne M, Maurer JR, Boehler A, et al: Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 21:297-310, 2002.

BOX 14-7 Risk Factors for Bronchiolitis Obliterans Syndrome after Lung Transplantation

PROBABLE ROLE

- Acute rejection
- Cytomegalovirus (CMV) pneumonitis
- HLA mismatching
- Lymphocytic bronchitis/bronchiolitis
- Noncompliance with medications
- Primary graft dysfunction

POTENTIAL ROLE

- *Aspergillus* spp. colonization of lower airways
- Aspiration
- CMV infection (without pneumonitis)
- Donor antigen-specific activity
- Epstein-Barr virus reactivation
- Etiology of native lung disease
- Gastroesophageal reflux
- Older donor age
- Pneumonia (gram-negatives, gram-positives, fungi)
- Prolonged allograft ischemia
- Recurrent infection other than CMV

From Hayes D, Jr: A review of bronchiolitis obliterans syndrome and therapeutic strategies. *J Cardiothorac Surg* 6:92, 2011.

cytolytic therapy, substitution of MMF for azathioprine, and conversion of cyclosporine to tacrolimus have sometimes been successful at preserving pulmonary function.^{131,132} A single-center, randomized controlled trial of aerosolized cyclosporine given within 6 weeks of lung transplant along with routine systemic immunosuppression showed that, although the rate of acute rejection was unaffected, the patients receiving inhaled cyclosporine had improved survival and longer periods of chronic

rejection-free survival.¹³³ Several studies have demonstrated an improvement in FEV₁ with azithromycin therapy for 3 to 6 months.^{134,135} Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have immunomodulatory effects, and one report showed that acute rejection in lung transplant patients was less common in those taking statins.¹³⁶ In addition, none of the lung transplant patients taking statins developed BOS, but 37% of those not taking them did develop it, and the 6-year survival rate of patients taking statins was greater than those not (91% versus 54%, respectively).¹³⁶ Extracorporeal photopheresis therapy has also been shown to reduce the rate of decline in lung function, and 25% of patients in one study had an improvement in FEV₁.¹³⁷

Unfortunately, most patients either acquire progressive bronchiolitis obliterans or a lethal opportunistic infection as a result of the augmented immunosuppression. Retransplantation may be an option in carefully selected patients with BOS. BOS does not appear to occur in an accelerated manner after retransplantation. In the pulmonary retransplant registry, 81% and 56% were free of BOS at 1 and 4 years after retransplantation, respectively.¹³⁸ More recent studies indicate that the 1- and 5-year survival rates after retransplantation for BOS are similar to those for primary lung transplantation.¹³³

Posttransplant Lymphoproliferative Disorder

Posttransplant lymphoproliferative disorder (PTLD) is a well-recognized complication after solid-organ and bone marrow transplantation, with an incidence between 2% and 6% after lung transplantation (Fig. 14-18).^{139,140} It encompasses a spectrum of disease entities ranging from atypical lymphoid proliferation to malignant non-Hodgkin lymphoma.¹⁴¹ Most commonly, the cells are of B cell origin. There is an association between PTLD and Epstein-Barr virus (EBV).¹⁴² In lung transplant recipients, a strong correlation between negative EBV serology before transplantation and the development of PTLD has been reported. Studies have reported a 6.8- to 20-fold increased risk of development of PTLD in recipients who were EBV-negative before transplantation.¹⁴³

When it occurs in the first year after transplantation, PTLD shows a predilection for the thorax and commonly arises in the lung allograft.¹⁴⁰ In contrast, when patients present with PTLD after the first year, it is usually extrathoracic, commonly arising in the abdomen and pelvis (Fig. 14-19).¹⁴⁴ In our series, late-occurring abdominal and pelvic PTLD cases were most commonly malignant non-Hodgkin lymphomas, and, despite aggressive therapy, the prognosis was poor. In contrast, patients who had early-stage PTLD, unless disseminated disease was present at diagnosis, had a favorable prognosis and often responded to decreased immunosuppression.¹⁴⁴

The choice of treatment for PTLD is based on the stage and progression of disease. First, a trial of reduced immunosuppression is attempted, particularly with disease limited to the allograft. Others also have recommended the simultaneous use of antiviral therapy.¹⁴⁵ Although chemotherapy (cyclophosphamide, adriamycin,

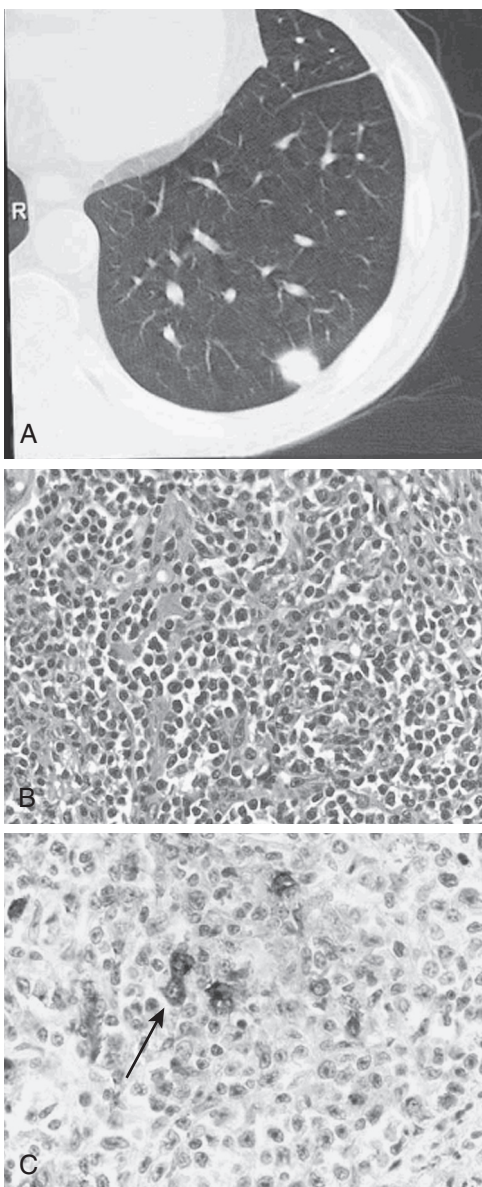


FIGURE 14-18 ■ **A**, Computed tomographic scan of a patient with multiple pulmonary nodules that developed several months after bilateral lung transplantation. The patient was found to have posttransplantation lymphoproliferative disease (PTLD). **B**, Histopathologic examination of a posttransplantation lymphoproliferative nodule (hematoxylin and eosin stain). **C**, Immunostaining of a PTLN nodule found to be positive for Epstein-Barr virus (arrow).

vincristine, and prednisone [CHOP]) has been used in patients with widespread disease or with progression of disease, treatment-related mortality is considerable. Rituximab has been shown to be effective against CD20-positive B cell tumor cells and has been proposed as a first-line agent against PTLN. Several studies cite a response rate of approximately 66%.^{146,147} Preventive strategies for children may include matching recipient and donor EBV status, but this is not effective in adults because greater than 90% of the population are EBV-positive by the time they are 35 years old. One group reported that prophylactic use of antiviral therapy may reduce the incidence of PTLN.¹⁴⁸

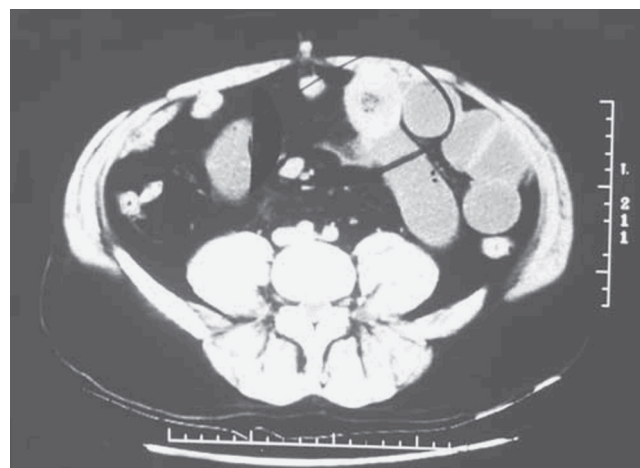


FIGURE 14-19 ■ Computed tomographic scan from a patient with small bowel intussusception secondary to posttransplantation lymphoproliferative disease.

Gastrointestinal Complications

Gastrointestinal (GI) complications are common in lung transplant recipients, occurring in as many as 50% of patients in some series.¹⁴⁹ Nonsurgical GI complications, including esophagitis, gastroesophageal reflux, gastritis, gastric atony, peptic ulcer disease, pancreatitis, cholecystitis, CMV hepatitis, CMV colitis, GI bleeding, adynamic colonic ileus, diverticulitis, and *Clostridium difficile* colitis, or diarrhea, commonly occur in the first month postoperatively, and most patients respond to conservative therapy. Acute abdominal processes requiring an operation can occur at any point after transplantation and have an incidence of 4% to 17%. They include, in decreasing frequency, bowel perforation, appendicitis, cholecystitis, colitis, and pneumatosis intestinalis.¹⁵⁰ PTLN may appear as an acute abdominal process, secondary to intussusception (see Fig. 14-19) or bowel perforation. A high index of suspicion is needed to diagnose these GI complications, because immunosuppression can mask clinical signs and symptoms. Emergent operative exploration is associated with significant morbidity and mortality. Elective procedures, however, can be performed safely in this population with acceptable morbidity rates.¹⁵¹

RESULTS

Among survivors, functional results are excellent (Fig. 14-20). Patients usually return to normal levels of exercise tolerance without oxygen supplementation within 6 to 8 weeks after transplantation. Long-term results of more than 300 patients with emphysema who received transplants at Washington University from 1988 to 2000 have been reported,¹⁵² and updated data are available through 2012. The overall hospital mortality rate during the 13-year period (1988 to 2000) was 6.2%, but from 1995 to 2000, it was only 3.9%. All patients showed a significant improvement in posttransplantation functional outcomes measured by parameters such as FVC, FEV₁, and a 6-minute walk test. Since the

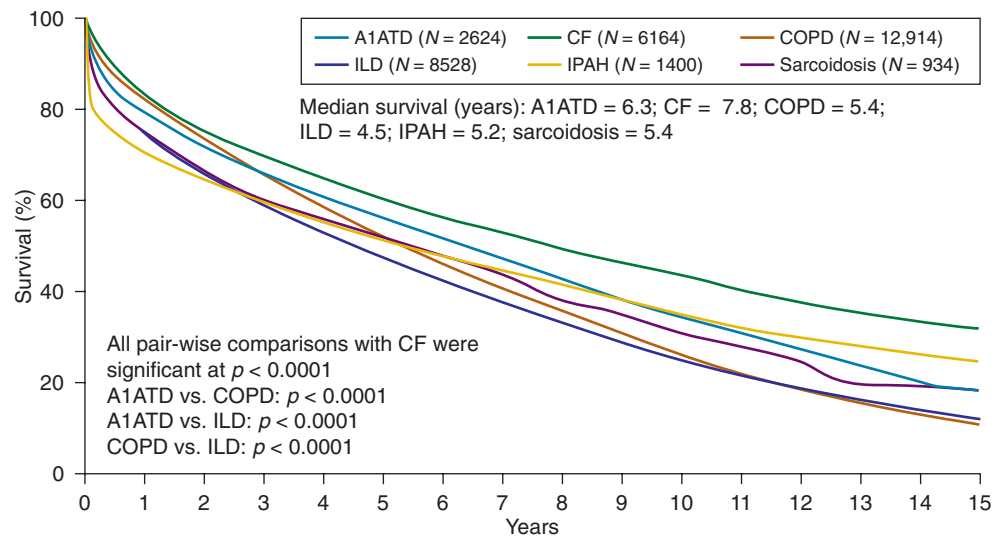


FIGURE 14-20 ■ Adult lung transplant recipient Kaplan-Meier survival by diagnosis, conditional on survival to 1 year (transplants: January 1990 to June 2011). A1ATD, α_1 -Antitrypsin deficiency–associated chronic obstructive pulmonary disease; CF, bronchiectasia associated with cystic fibrosis; COPD, non-A1ATD–associated COPD; ILD, interstitial lung disease, which includes idiopathic pulmonary fibrosis; IPAH, idiopathic pulmonary arterial hypertension. (From Yusef RD, Christie JD, Edwards LB, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report—2013; focus theme: age. *J Heart Lung Transplant* 32:965–978, 2013.)

implementation of the lung allocation score, IPF (29%) has become the most common indication for lung transplantation at our center, followed by chronic obstructive pulmonary disease (COPD) (25%) and cystic fibrosis (17%). From 1988 through 2012, 1216 primary transplants and 35 retransplants were done for a total of 1251 transplants; 1038 of these were bilateral-lung transplants and 194 were single-lung transplants. During this same time frame, 10-year survival rates were similar for all indications for lung transplantation, ranging from 31% to 43%. However, 15-year survival was highest for CF patients (32%), followed by IPF patients (25%), PPH/idiopathic pulmonary arterial hypertension (20%), α_1 -antitrypsin deficiency (17%), and COPD (16%).

Several centers have reported satisfactory results for patients with septic lung disease undergoing lung transplantation. The Toronto Lung Transplant Group reported excellent gas exchange, pulmonary function, and exercise ability among operative survivors.¹⁵³ The Washington University experience was similar, with overall survival comparable with that of patients with other indications for lung transplantation.

Fibrotic lung diseases such as IPF have been the indication for lung transplantation in more than one-third of all patients transplanted at our center since revision of the allocation system. The long-term survival is lower than that of patients with other diagnoses at early and later time points (see Fig. 14-20). Early mortality is probably affected by the complexity of transplants in fibrotic patients, whereas the late mortality may be affected by the older age of recipients relative to those transplanted for CF, PPH, or α_1 -antitrypsin deficiency.²⁰

From 1989 to 2001, our program performed 100 transplants for either PPH or secondary pulmonary hypertension, with 55 adult and 45 pediatric recipients of 51 bilateral-lung, 39 single-lung, and 10 combined heart-lung transplantations.¹⁵⁴ The overall hospital mortality

rate in this complicated group of patients was 17%, with a mortality rate of 10.4% among those transplanted for PPH and 23.1% among those transplanted for secondary pulmonary hypertension. The morbidity rate was also significantly higher compared with patients transplanted for emphysema: almost 25% of patients were taken back to the operating room for bleeding, 24% were reintubated, 17% needed a tracheostomy for prolonged ventilator support, and 16% required ECMO support. Among the surviving patients, there was a significant and sustained improvement in right ventricular function as well as pulmonary artery pressure and resistance.

PEDIATRIC LUNG TRANSPLANTATION

Lung transplantation was expanded to the pediatric population in a judicious manner in the late 1980s. The number of lung transplantations for recipients younger than 18 years of age was 107 for the year 2011, as reported by the ISHLT.¹⁵⁵ This number has remained stable over the past decade and represents a small proportion of the total lung transplantation procedures performed. The most common indications for lung transplantation in infants (<1 year) are congenital heart disease and surfactant protein B deficiency, each representing 16.7% of the transplants done in this age group between 1990 and 2012.¹⁵⁵ Of children between 1 and 5 years of age, 22.4% of lung transplantations were done for PPH and 16.8% for IPF. CF is the predominant indication for lung transplantation in children between 6 and 10 years of age (53%) and teenagers between 11 and 17 years of age (70.6%). With the revision of the lung allocation system, lungs are allocated to potential recipients younger than 12 years of age on the basis of wait time on the transplant list. Potential recipients aged 12 to 17 years are prioritized based on their lung allocation score.¹⁵⁶

Survival after pediatric lung transplantation is comparable with that reported in adults with a median survival of 4.9 years versus 5.4 years, respectively.¹⁵⁵ Bilateral-lung transplant recipients show an improved survival compared with single-lung transplant recipients, but this may be an effect of underlying disease and other recipient factors. The vast majority of pediatric lung transplants are bilateral. As in adults, early mortality after pediatric lung transplantation is secondary to infections and graft failure, and late mortality is attributed mostly to bronchiolitis obliterans, with greater than 50% developing bronchiolitis obliterans by 5 years.¹⁵⁵

Only 20 to 30 centers are currently performing pediatric lung transplants. Our center began its pediatric lung transplant program in July 1990. Since its inception, 410 lung transplants have been done. Almost half of the lung transplants were done in patients with CF (47%). The second and third most common indications for lung transplant were pulmonary hypertension (12%) and bronchiolitis obliterans (7%). The age of recipients ranges from less than 1 month to 25 years. From 1998 through 2002, actuarial survival at our center was 77% at 1 year, 62% at 3 years, and 55% at 5 years. The most common cause of early mortality was graft failure. Late mortality was most commonly secondary to bronchiolitis obliterans (57%), infection (21%), and posttransplant malignancies (18%).¹⁵⁷

SUMMARY

Lung transplantation is an effective therapeutic option for selected patients with end-stage pulmonary disease. The use of marginal donors, non-beating-heart donors, and ex vivo lung perfusion has been implemented in an attempt to increase the donor pool. Lung preservation and immunosuppression strategies continue to evolve. Extensive research efforts are underway to find methods to overcome chronic rejection and prolong survival in patients undergoing lung transplantation.

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PART F

LUNG CANCER

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SCREENING FOR LUNG CANCER: CHALLENGES FOR THE THORACIC SURGEON

Brendon M. Stiles • Bradley Pua • Nasser K. Altorki

CHAPTER OUTLINE

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SUMMARY

Lung cancer is a global health burden and is among the most common and deadliest of all malignancies worldwide. In the United States, lung cancer accounts for more than 25% of all cancer deaths, exceeding deaths from breast, colon, and prostate cancers combined.¹ More than 80% of individuals with lung cancer die of the disease, primarily because a large proportion of patients with lung cancer present with locally advanced or metastatic disease. Intuitively, early detection of resectable and potentially curable disease could reduce the overall death rate from lung cancer. Historically, screening for lung cancer was not recommended by the majority of clinical societies and health care agencies in the United States. However, following the mortality benefit identified in the National Lung Screening Trial (NLST) in 2011,² most U.S. guidelines now recommend screening with low-dose computed tomography (LDCT) in at-risk populations.³⁻⁶ This shift in policy can be expected to increase significantly the number of patients found to have lung cancer, but also those found to have benign lung nodules. Much of the current debate has turned toward identifying the most appropriate “at-risk” populations for screening, ensuring appropriate management of screen detected nodules, and defining the optimum duration of CT screening. This chapter briefly discusses the history of and rationale for lung cancer screening and addresses optimization of screening protocols.

HISTORY OF LUNG CANCER SCREENING

Chest Radiograph Screening

Interest in screening high-risk patients for lung cancer was sparked when the association between cigarette smoking and lung cancer was first appreciated by Doll and Hill in the 1950s.⁷ The first mass screening project was conducted by Brett in London from 1960 to 1964.⁸ Although not a randomized trial, 55,034 men were assigned to undergo either chest radiography (CXR) every 6 months for three years (the screened group) or a single CXR at the beginning of the study, followed by a repeat CXR at the end of the 3-year period (the “unscreened” group). At the end of the 3-year period, more lung cancers were detected in the screened group compared to the unscreened group (132 vs. 96 cases). In addition, resectability was enhanced in the screened group. Despite these findings, lung cancer–specific mortality was not different between the two groups.

In the 1970s, the National Cancer Institute funded three randomized trials for lung cancer screening using both CXR and sputum cytology at Johns Hopkins, Memorial Sloan-Kettering Cancer Center, and the Mayo Clinic.⁹⁻¹¹ Again, more cancers were found in the

screened groups of patients, and resectability rates were significantly higher in the screened group. Nonetheless, again there was no statistically significant difference in the lung cancer–specific mortality between the screened and unscreened populations in any of the trials.

Early Computed Tomography Screening Studies

In the 1990s, increased resolution and data-acquisition speeds of modern computed tomographic (CT) scanners rekindled interest in screening for lung cancer. Initial findings from Henschke and colleagues of the Early Lung Cancer Action Project (ELCAP) showed that in a high-risk population, LDCT was superior to CXR in detection of lung nodules.¹² Notably, 2.7% of those enrolled in the CT screening program had lung cancer, the great majority of which were stage I.^{13,14} A subsequent report by the I-ELCAP group addressed overall curability estimated through 10-year survival rates of patients found to have stage I lung cancer by CT screening.¹⁵ The authors reported an estimated 88% 10-year survival rate, markedly higher than survival rates predicted by the current staging system or among those presenting as a result of symptoms. They inferred that because CT screening leads to early detection of lung cancer and because those lung cancers found as a result of CT screening are curable, that CT screening leads to a reduction in lung cancer mortality. Several other groups subsequently evaluated CT screening for lung cancer. A review by Black and colleagues¹⁶ published in 2007 identified 12 studies, including two randomized and 10 single-arm observational studies. Significant variability existed in the study populations and in the definition of a positive finding in each. The percentage of positive screenings ranged from 5.1% to 51%. From baseline screenings, 1.8% to 18% of positive findings led to a diagnosis of cancer. The majority of the tumors were stage I (53% to 100%), with a high resectability rate (>78%). Only one of the studies reported 5-year survival: 76% for patients with cancer detected at baseline screening and 65% for patients with cancer detected at annual repeat scanning.¹⁷

Screening for lung cancer with LDCT was not universally embraced, however. Bach and colleagues¹⁸ reported the findings from CT screening of 3246 high-risk patients from multiple institutions. The authors reported a threefold increase in individuals diagnosed with lung cancer and a tenfold increase in patients undergoing lung resection (compared to expected cases). They also found no evidence of a decline in the number of patients with advanced stages of disease or of deaths from lung cancer in the screened groups. The authors concluded that CT screening might not meaningfully reduce the risk of dying from lung cancer and suggested that CT screening is inherently prone to overdiagnosis, thus exposing patients to unnecessary surgery. The study generated controversy given that the follow-up was relatively short (3.9 years) and that at least one of the three studies did not require the exclusion of symptomatic individuals, possibly undermining the core concept of screening.

MODELING APPROACHES TO ESTIMATE MORTALITY BENEFIT

Given the inability of early randomized trials and prospective studies to prove a mortality benefit to screening, others have attempted to address the magnitude of lung cancer mortality reduction using modeling approaches. McMahon and colleagues from the Mayo Clinic used 1520 current or former smokers undergoing CT screening to model predicted cases of lung cancer and deaths, which were compared to a simulated unscreened control arm.¹⁹ The model ultimately simulated 500,000 cases per study arm based on five annual screening examinations, to generate precise estimates of mortality. At 6 years of follow-up, the screening arm had an estimated 37% relative increase in lung cancer detection compared with the simulated control arm and a 28% relative reduction in cumulative lung cancer–specific mortality. The model included many assumptions such as lung cancer incidence rates, adherence to the screening protocol, and treatment by established guidelines, yet the study made a compelling argument for a mortality benefit from CT screening.

Similarly, Foy and colleagues used a lung cancer mortality model developed within the Cancer Intervention and Surveillance Modeling Network (CISNET) to address the potential for mortality reduction by CT screening for lung cancer.²⁰ The comparison matched members of a CT screening trial (NY-ELCAP) with age, sex, and tobacco exposure-matched control patients from the Beta-Carotene and Retinol Efficacy Trial, with well-established lung cancer incidence rates. The simulation was repeated 5000 times to compare expected lung cancer mortality between the two groups. Although again subject to inherent assumptions made for the purposes of modeling, the study suggested a 45.6% relative reduction in lung cancer mortality in the group of patients screened with CT.

More recently, a modeling study was performed by the CISNET on behalf of the USPTF. Models were created using de-identified data from the NLST and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial.²¹ The authors judged a strategy of screening patients aged 55–80, with at least 30 pack-years, and no more than 15 years since quitting as the optimal scenario balancing benefits and harms. In this scenario, the estimated reduction in lung cancer mortality is between 8.6% and 23.5%. All these studies, albeit models, suggested that LDCT screening protocols, logically followed by earlier treatment of lung cancer, do likely provide a mortality benefit.

The Gold Standard: The National Lung Screening Trial

Between 2002 and 2009, the NLST enrolled 53,456 patients between the ages of 55 and 74 years.² Patients had a history of smoking at least 30 pack-years and were either current smokers or former smokers who had quit within the past 15 years. The majority of patients were male (59%) and younger than 65 years (73%). The group compared low-dose CT screening (26,723) with CXR screening (27,733) using three annual screening rounds with 8

TABLE 15-1 Results of the National Lung Screening Trial (2011)

Study Characteristics	CT-Screened Arm	CXR-Screened Arm
Total no. of patients	26,722	26,732
Screening interval and follow-up	Three annual screens with eight years of follow-up	Three annual screens with eight years of follow-up
Rate of positive screening over 3 rounds	24.2%	6.9%
False positive rate	96.4%	94.5%
Lung cancers confirmed after positive test	649 (2.4%)	279 (1.0%)
Surgical procedures following positive screening test	713	239
Total lung cancers in group	1060	941
Total lung cancer deaths	354	442
Relative decreases in lung cancer mortality in CT screened group	20.3%	
Relative decrease in overall mortality in CT screened group	7%	

CT, Computed tomography; CXR, chest radiography.

years of follow-up (Table 15-1). In the CT screening arm, there were 354 deaths from lung cancer, compared with 442 in the CXR group, translating into a 20.3% reduction in lung cancer–related mortality. Additionally, there was a 7% reduction in overall mortality in the CT arm of the trial. This absolute mortality reduction was unprecedented in the history of lung cancer screening and was greeted with much enthusiasm by advocates of CT screening. The NLST secondary analyses will continue to provide data over the coming years. In addition, several European randomized trials (MILD, DANTE, ITALUNG, NELSON, DLCST, LUSI, and UKLS)^{22–28} have or are comparing lung cancer CT screening with no screening. It is expected that pooling the results of these trials and the NLST will further clarify the role for CT screening and better define screening protocols. It should be noted that both the DANTE²³ and DLCST²⁶ trials failed to show a decrease in lung cancer mortality in the CT-screened patients; however, they were likely underpowered. The largest trial among these, the NELSON²⁵ study, has not yet reported end results.

Important Statistical Concepts

The efficacy of screening in reducing cancer-specific mortality may be confounded by lead time, length, and overdiagnosis biases. Although the statistical arguments may be examined from many different vantage points and are sometimes difficult to interpret, they have been well described previously by Strauss.²⁹ We will highlight some of those important concepts here.

In all screening trials, one must distinguish lead time from lead time bias. The success of any screening program

depends on a lead time in diagnosis and treatment, which itself does not present a problem. Bias can arise when short-term survival rates are used to assess the value of screening in populations with and without lead time. Lead time bias should not affect resectability or more importantly, curability. In the subpopulations of patients with lung cancer in the older screening trials, there were an increased proportion of 5-year survivors in the screen-detected cases compared with those in the control arms in both the Mayo and Czech studies.^{9,30} The survival curves never converged, suggesting that screening increased the cure rate of patients with cancer. These mature data imply that lead time bias does not explain differences in survival between those groups. The I-ELCAP investigators' effort to estimate 10-year survival rates, rather than shorter-term rates, was also an attempt to avoid any possible lead time bias.¹⁵ The estimated cure rate occurs at the plateau phase of the survival curve, its asymptote, at which point the additional deaths that occur are from competing causes. Ongoing analysis of mature NLST data as well as data from other randomized trials will help further to clarify any potential effect of lead time bias.

Length-bias essentially refers to the tendency of screening to lead to the diagnosis of slower growing cancers more frequently in the baseline round, as these tumors potentially may have been present for a considerable amount of time prior to the screening study. For tumors detected only on repeat rounds of screening, this is far less of a concern. A review of the Mayo data, however, demonstrates that survival rates were only slightly better in the prevalence cases when compared to incidence cases (40% vs. 33%), those diagnosed at repeat screening.²⁹ In the I-ELCAP, no distinction was made in survival rates between the prevalence and incidence groups. In the CT screening arm of the NLST trial, 270 (48%) cancers were diagnosed on the incident CT, compared with 379 (62%) following repeat screening.² Survival differences between the two groups were not reported, but they will be important to evaluate in future reports.

Similar to the length bias argument, the overdiagnosis hypothesis is based on the idea that screen-detected cancers may be indolent and perhaps even clinically insignificant. The lung cancer detection rates were higher in the screened groups in both the Mayo and Czech studies. Despite this, mortality for the entire screened cohort in both studies was actually slightly higher. Similarly, in the CT-based study by Bach and colleagues,¹⁸ there was an increased rate of lung cancer detection, 144 cases versus 45 expected cases. Despite this increase in detection, there was no decrease in the expected lung cancer mortality rate. The possibility of overdiagnosis has been used to explain these findings, as well as the excellent projected 10-year survival in the I-ELCAP study. Several authorities suggest that many lung cancers detected by screening would not progress rapidly to the point of clinical detection and would therefore be unlikely to account for a meaningful share of deaths among screened individuals.

Perhaps the most challenging aspect of understanding the issue of “overdiagnosis” is defining the term itself. The phrase is often used synonymously with “pseudo-disease,” which implies that the disease would progress slowly and would not lead to death before that

caused from a competing illness. This definition allows for patients with lung cancer who die of competing (or accidental) causes to be considered as examples of overdiagnosis regardless of tumor stage. The concept of overdiagnosis was first proposed based on data from the Mayo Lung Project. In that study, there was an excess of early-stage lung cancers in the screened group, yet no difference in mortality. Therefore, it was concluded that those excess predominantly early stage cancers were overdiagnosed. However, when examined critically, they did not fit the profile of indolent cancers. They were on average 2 cm in diameter, not present on the baseline round, had a median growth rate of 101 days, and were nearly all invasive pathologically.⁹ Thus, in the screened arm, lung cancers were far more likely to be identified and they cannot be thought of as indolent. The similar disease-specific survival rate between the groups could be explained by the high rate of competing causes of death in the screened group, in which the number of cardiovascular deaths was nearly four times the rate of lung cancer deaths.

There are several other arguments against overdiagnosis. For example, studies reported by Sobue and colleagues³¹ and by Flehinger and colleagues³² have documented mortality rates in excess of 80% for untreated screen-detected lung cancers. The high mortality of screen-detected small tumors argues against their presumed indolent or nonfatal nature. In fact, it seems that even the smallest lung cancers are almost always deadly. An analysis by Henschke and colleagues of the Surveillance, Epidemiology and End Results (SEER) database revealed an 87% 8-year fatality rate for untreated 6-15-mm primary non-small cell lung cancer (NSCLC).³³ A more recent review of the California Cancer Center registry by Raz and colleagues³⁴ examined long-term survival in untreated stage I NSCLC. Five-year overall survival was only 6%, with a median survival of 9 months.

More evidence against overdiagnosis can be found from autopsy studies. McFarlane and colleagues³⁵ reported that the rate of "surprise" lung cancer at autopsy was less than 1% and that many of these patients had in fact died from those cancers. Another study found a slightly higher (3.3%) rate of lung cancer at autopsy, but deemed none of the cancers to have been clinically insignificant, as lung cancer was thought to be the direct cause of death in over half of the cases.³⁶ Further evidence against overdiagnosis can also be found in the I-ELCAP data. Henschke and colleagues reported that for the I-ELCAP screening trial, an expert panel of pulmonary pathologists confirmed that 95% of the patients with stage I cancer had invasive tumors that were morphologically indistinguishable from "garden variety" lung cancers.¹⁵ In addition, a subgroup of the I-ELCAP screen-detected cancers was analyzed for biomarkers using immunohistochemistry and fluorescence in situ hybridization.³⁷ The molecular alterations were found to be similar to those found in conventionally diagnosed cancers. Of note, all eight I-ELCAP patients with untreated stage I cancer died within 5 years of screening.

Recently, Patz and colleagues³⁸ cited overdiagnosis as a potential reason for the mortality benefit in the NLST study. They used modeling estimates to determine that the probability is 18.5% (95% confidence interval [CI],

5.4% to 30.6%) that any lung cancer detected by screening with LDCT was an overdiagnosis, in particular that when a bronchioloalveolar (*noninvasive* in new terminology) lung cancer was detected with LDCT there was a 78.9% (95% CI, 62.2% to 93.5%) chance of overdiagnosis. In the NLST, there were 110 bronchioloalveolar cell carcinomas in the CT-screened arm, 95 of which were screen detected. In the CXR arm, there were only 35 bronchioloalveolar cell carcinomas, of which 13 were screen detected.² Given the lack of longitudinal studies to date, it is impossible to determine whether these were overdiagnosed indolent cancers or whether they would have progressed. The authors concede that as their model was based on only three annual screens and an average of 7 years of follow-up, any estimate of overdiagnosis based on lifetime follow-up scenarios must be treated cautiously. Although the natural history of noninvasive lung carcinomas is not well understood, in general, the balance of both epidemiologic and pathologic evidence does not appear to make lung cancer a good candidate for high rates of overdiagnosis by screening.

OTHER APPROACHES TO SCREENING

As reviewed by Brower³⁹ and by Hensing and Salgia,⁴⁰ a number of molecular alterations have been identified in premalignant bronchial lesions and in early lung cancer. These molecular abnormalities may be potentially identified in the sputum or blood of high risk patients. Common approaches to molecular biomarkers include novel high-throughput technologies for analysis of DNA, RNA, protein, and autoantibody expression in biological samples. Whereas all of these blood- or sputum-based tests offer promise for lung cancer detection, none have been extensively evaluated or applied to large screening populations. Several obstacles exist to developing a sensitive and specific test for early lung cancer, most importantly the heterogeneity of the disease. As such, it remains to be seen whether these techniques will play a role in screening for lung cancer. Currently there are no adequate standards to evaluate samples, with resulting large disparities among quantitative and qualitative reports. The hope, however, is that one day it will be possible to develop accurate blood and sputum tests to facilitate the diagnosis of lung cancer. Such tests will likely be combined with CT screening protocols, either using the biomarker to select patients for screening or to further risk stratify patients found to have nodules on CT screening.

CURRENT RECOMMENDATIONS

The American Association for Thoracic Surgery (AATS) created an interdisciplinary task force to structure recommendations for lung cancer screening to extend the findings of the NLST to long-term clinical practice and to address issues related to screening.⁴ Six unanimous recommendations were presented and accepted at the AATS 2012 annual meeting (Box 15-1). The group recommends screening smokers and former smokers with at least a 30 pack-year history from the ages of 55 to 79 years. In

BOX 15-1 American Association for Thoracic Surgery Guidelines Task Force Recommendations Regarding Low-Dose Computed Tomography Screening for Lung Cancer

1. Annual lung cancer screening with LDCT for smokers and former smokers between 55 and 79 years old with 30 pack-year history of smoking
2. Annual LDCT until the age of 79 in long-term lung cancer survivors to detect second primary lung cancers
3. Annual lung cancer screening with LDCT for smokers and former smokers between 55 and 79 years old with 20 pack-year history of smoking and additional comorbidities that infer increased risk of lung cancer greater than 5% over the following 5 years
4. Multidisciplinary approach to lung cancer screening, evaluation, and treatment
5. Development of a web-based application for patient self-risk assessment
6. Continue AATS engagement with other specialties to develop and refine further guidelines

AATS, American Association for Thoracic Surgery; LDCT, low-dose computed tomography.

Modified from Jaklitsch MT, Jacobson FL, Austin JH, et al: *The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups*. *J Thorac Cardiovasc Surg* 144:33–38, 2012.

addition, the AATS recommended screening patients aged 50 to 54 years with a 20-pack history if additional risk factors are present. Recommendations also addressed the need for surveillance with annual LDCT in lung cancer survivors, the need for patient self-risk assessment, and the need for multidisciplinary evaluation. Importantly, the AATS made no recommendation to stop screening after the 3-year time point used in the NLST, citing lack of scientific evidence for cessation of screening. The AATS also proposed that long-term cancer survivors should have an annual LDCT until the age of 79 years to screen for second primary lung cancers.

The U.S. Preventive Services Task Force³ recommendations are similar to those of the AATS. They recommend annual screening for patients aged 55 to 80 years with a 30 pack-year smoking history, but suggest discontinuing screening when patients have not smoked for 15 years. The USPSTF also addressed implementation of screening programs, smoking cessation counseling, shared decision making, and standardization of follow-up of abnormal findings. The National Comprehensive Cancer Network (NCCN) has also recommended LDCT screening in selected patients at risk for lung cancer.⁴¹ *High risk* is defined as patients aged 55 to 74 years with at least a 30 pack-year smoking history without cessation greater than 15 years prior. They also recommended that patients aged 50 years or older undergo screening when they have at least a 20 pack-year smoking history and one additional risk factor. In addition to the AATS, USPSTF, and NCCN, several other groups, including the American College of Chest Physicians, the American Society of Clinical Oncology, the American Cancer Society, and the American Thoracic Society, have all recommended screening for lung cancer with LDCT scan based on the

results of the NLST. Regardless of the method used to screen patients for lung cancer, controversy over the value and best paradigm of screening will likely continue to exist, much as it does for other cancers, including breast and prostate cancer. In 2009, the United States Preventive Services Task Force (USPSTF) released new recommendations for breast cancer screening, which were quite different from their 2002 recommendations.⁴² The Task Force raised the recommended age to begin screening from 40 to 50 years and recommended stopping screening at age 74. These recommendations generated significant national controversy. The USPSTF's interpretation of the screening data was subsequently refuted by some investigators who continued to claim a benefit for screening in the 40- to 84-year age range.⁴³ Similarly, the value of screening for prostate cancer has also been called into question by the results of two disparate landmark studies.⁴⁴ The European Randomized Study of Screening for Prostate Cancer reported a statistically significant cancer-specific mortality reduction of 20% favoring prostate-specific antigen-based screening.⁴⁵ In contrast, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial showed no mortality reduction.⁴⁶ Undoubtedly, different structures of competing clinical trials, heterogeneous unscreened populations, and evolving technological advances will also continue to make an absolute application of the data for lung cancer screening to clinical practice difficult.

Screening Regimen

Screening regimens currently vary by institution. There are two major published guidelines from the NCCN and from the I-ELCAP group suggesting algorithms for lung screening, but no consensus currently exists. The American College of Radiology (ACR) is expected to present a structured assessment, management, and categorization algorithm for LDCT screened detected nodules in late 2014 termed Lung-RADS (Table 15-2). This is comparable to the BI-RADS and LI-RADS lexicons used for screening mammography as well as CT and MR imaging for hepatocellular carcinoma, respectively. Widespread adoption is anticipated, allowing for uniformity among screening centers and the ability to compare results with the ACR National Data Registry (NRDR: <http://www.acr.org/Quality-Safety/eNews/Issue-05-March-2014/CT-Lung-Screening>).

Our current local screening regimen begins with a definition of what constitutes a positive or negative screening result. A nodule must first, before entering into a management algorithm, be assessed for signs of benignity which would exclude it from further assessment. A nodule containing calcification, unless eccentric, is most likely benign.⁴⁷ Therefore, if it is the only finding, it is considered a negative result. Noncalcified nodules or nodules containing eccentric calcifications are subsequently evaluated by size criteria. Another sign of benignity is a nodule which contains fatty attenuation. These nodules are likely to represent hamartomas. In addition, there is mounting evidence that perifissural nodules—solid nodules attached to a fissural surface which are lentiform or triangular in shape—are most

TABLE 15-2 Lung-RADS Version 1.0 Category Descriptors and Management Recommendations

Category	Descriptor	Management	Probability of Malignancy	Estimated Population Prevalence
1. Negative	No nodules/definitely benign nodules	Continue annual screening with LDCT in 12 months	<1%	90%
2. Benign appearance or behavior	Low likelihood of cancer due to size or lack of growth			
3. Probably benign	Low likelihood of becoming clinically active cancer	6-month LDCT	1-2%	5%
4A/4B. Suspicious	Additional diagnostic testing and/or tissue sampling recommended	4A. 3-month LDCT or PET/CT	5-15%	2%
		4B. PET/CT or tissue sampling	>15%	2%

CT, Computed tomography; LDCT, low-dose computed tomography; PET, positron emission tomography.

Modified from Lung-RADS Version 1.0 Assessment Categories release date: April 28, 2014. Available at <http://www.acr.org/~media/ACR/Documents/PDF/QualitySafety/Resources/LungRADS/AssessmentCategories>.

likely benign.⁴⁸ This group evaluated participants of the NELSON trial and classified nodules on the baseline examination into those that fit the periferous nodule criteria. None of these nodules turned out to be malignant after 5.5 years of follow-up. Once a nodule is identified that does not meet the benign criteria, its density is evaluated and separated into those that are purely subsolid (ground glass attenuation) or contain any solid component. If the initial test result is positive, as defined by a diagnostic algorithm (Fig. 15-1), then this algorithm is followed until cancer is confirmed or the suspicion level is lowered to allow the patient to return to annual screening. If the initial test is negative, the patient is referred to the next screening round (annual).

Current helical CT scanning allows for images of less than 1 mm in slice thickness to be obtained in a single breath hold. As most lung screening centers obtain and interpret images using these thinner slices, it has resulted in detection of smaller nodules. NLST used a 4-mm cutoff in their diagnostic algorithm to consider a baseline scan as positive. Concerns with a relatively high false-positive rate in that trial have led some investigators to suggest using a larger size cutoff for considering a nodule to warrant closer follow-up than the recommended annual screening. Henschke and colleagues⁴⁹ retrospectively analyzed their screening cohort of 21,136 participants in I-ELCAP and applied more restrictive thresholds for identifying a nodule as positive. They found that using alternative threshold values of 6, 7, 8, and 9 mm resulted in a positive study frequency of 10.2% (95% CI, 9.8% to 10.6%), 7.1% (CI, 6.7% to 7.4%), 5.1% (CI, 4.8% to 5.4%), and 4.0% (CI, 3.7% to 4.2%), respectively. Use of these alternative definitions would have reduced the workup by 36%, 56%, 68%, and 75%, respectively, thus leading investigators to suggest further study using these higher threshold values. We currently use a cutoff of 6 mm for solid and subsolid nodules.

MANAGEMENT OF THE SCREEN-DETECTED NODULE

No matter how the current debate on screening unfolds or how the technology evolves, thoracic surgeons will

continue to be asked to evaluate individuals with either screen-detected or incidentally discovered small pulmonary nodules. The management of these patients presents several challenges. It is important to understand the likelihood of malignancy in relationship to nodule size. The overwhelming majority of nodules found by screening or on incidental studies are not cancer. A large proportion of these nodules are less than 6 mm on the baseline round of screening and therefore do not actually constitute a positive result. Even for larger nodules, it is important to reassure patients that a positive CT scan does not mean that they have cancer.

Several factors can influence the probability of cancer in a pulmonary nodule. Of these factors, nodule size is the most critical. Early studies suggested that the rate of malignant disease was 1% in nodules less than or equal to 5 mm, 24% in those 6 to 10 mm, 33% in those 11 to 20 mm, and 80% for those greater than 20 mm.¹² In addition, change in size is also one of the most important factors to consider, as nodules that demonstrate growth are considered to be active. Time to follow-up CT scanning is in part dependent on the initial size of the nodule (as measurement of the growth in small nodules is more challenging) and on whether the nodules were initially detected on the baseline or repeat round. The time to follow-up is typically shorter on the repeat round, as cancers found on repeat screening are typically faster growing.

Several factors other than size play a role in the probability of malignancy. Patients with numerous small nodules (>6) are generally thought to be at low risk for malignancy and more likely to have inflammatory lung disease. The consistency of the nodule also affects the probability of cancer, with some investigators suggesting that part-solid nodules have a higher rate of malignancy (63%) than nonsolid nodules do (18%), whereas solid nodules have the lowest malignancy rate (7%).⁵⁰ Other factors to consider are patient age, smoking history, occupational history, personal and family history of cancers, and endemic rates of granulomatous disease.

Our general algorithm for radiographic follow-up is presented in Figure 15-1. For nodules less than 6 mm in diameter or for nonsolid nodules less than 10 mm found on baseline CT, we recommend a repeat CT scan in 1 year. For solid or part-solid nodules measuring 6 to

10 mm in diameter, we obtain a repeat CT scan in 3 months to assess for growth or resolution. For nodules found on annual repeat screening, those less than 3 mm in diameter should return to annual screening, while those larger than 3 mm and smaller than 6 mm should have CT follow-up within 6 months. For those larger than 6 mm, a course of antibiotics and repeat in 1 month is an additional option. Libby and colleagues¹⁵ suggested that an initial 7- to 10-day course of antibiotics resulted in partial or complete resolution of 29% of nodules on baseline screening and 74% of nodules on repeat screening. In all instances, nodule growth should prompt careful consideration of a biopsy or closer follow-up. Positron emission tomography (PET) scans may be an additional diagnostic option for screen detected nodules, particularly for patients with nodules larger than 1 cm in diameter. Veronesi and colleagues⁵¹ reported the sensitivity and specificity of PET for screen detected lung nodules to be 89% and 93%, respectively. Median nodule size was 14 mm for their cohort of patients. Even for nodules less than 10 mm, sensitivity and specificity were 83% and 100%.

Once the possibility of cancer exists, it is imperative to establish an accurate tissue diagnosis. When a nodule is deemed to be suspicious for malignancy—based on baseline characteristics, positive PET scan findings, or the demonstration of growth—we typically proceed to percutaneous transthoracic needle biopsy, typically by fine-needle aspiration (FNA), even for nodules smaller than 10 mm. FNA performed at high-volume centers can be extremely accurate, with a sensitivity of 82% to 99% and a diagnostic accuracy of up to 97%.⁵² FNA can result in four possible outcomes: malignant, specific benign, nonspecific benign, and nondiagnostic. For malignant and specific benign nodules, the treatment course is clear. Patients with nonspecific benign and nondiagnostic results require further workup. A review by Savage and colleagues⁵³ of 74 cases of FNA with either nonspecific benign or nondiagnostic findings demonstrated an eventual malignancy rate of almost 18%. Such nonspecific diagnoses can include atypical cells or inflammation. Furthermore, as described by Travis and colleagues,⁵⁴ the histologic heterogeneity of lung adenocarcinoma continues to be defined, leading to the recent refinement of the algorithm for adenocarcinoma diagnosis in small biopsies.

We will typically repeat CT scans at short intervals (within 3 months), with or without a course of antibiotics, and gradually increase the interval to the subsequent scan so that nodule stability can be ascertained. Volumetric analysis with serial CT scans can also be performed to assess nodule growth over time and to infer malignancy. Unfortunately, such techniques are not universally available and are costly, and their feasibility of use is still questioned with part-solid nodules and nodules adjacent to vessels. Further growth necessitates repeat FNA or

surgical biopsy, depending on clinical suspicion and surgical risk.

In institutions in which CT-guided FNA is not routinely performed, there should be a higher reliance on more invasive diagnostic techniques for suspicious nodules, such as bronchoscopic biopsy or surgical biopsy, either by open thoracotomy or video-assisted thoracoscopic surgery (VATS). Bronchoscopic biopsy is an option for establishing tissue diagnosis, although the yield for flexible bronchoscopy has historically been low, especially in small peripheral nodules. Newer techniques, including endobronchial ultrasound and electromagnetic navigational bronchoscopy, have been reported to increase the diagnostic yield of transbronchial biopsy to upwards of 60%, even for small, peripheral lesions.^{55,56}

When surgical biopsy is necessary, VATS is thought to decrease postoperative morbidity when compared with open thoracotomy, but comes with the occasional difficulty of palpating and visualizing small lesions that are often found on screening studies. Several techniques are available to localize and excise small pulmonary nodules using a minimally invasive approach.⁵⁷⁻⁶² Preoperative marking with methylene blue, wire hooks, and metallic coils has been described. Reported complications are rare, but include marker dislodgement, pneumothorax, intrapulmonary hemorrhage, and air embolism. Sortini and colleagues⁶³ and other investigators have also reported good results with ultrasound localization, although this method is strongly operator dependent. Other groups have described a VATS radiotracer localization technique, with a success rate of 92% for nodules with a median size of 8 mm.⁶⁴ The technique can be applied to all pleural surfaces including interlobar regions with complete fissures and enables rapid and predictable intraoperative localization. The procedure uses readily available technical components with minimal additional cost. Regardless of the method used to localize small nodules, VATS resection typically can be performed with low morbidity, short hospital stays, and excellent diagnostic accuracy.

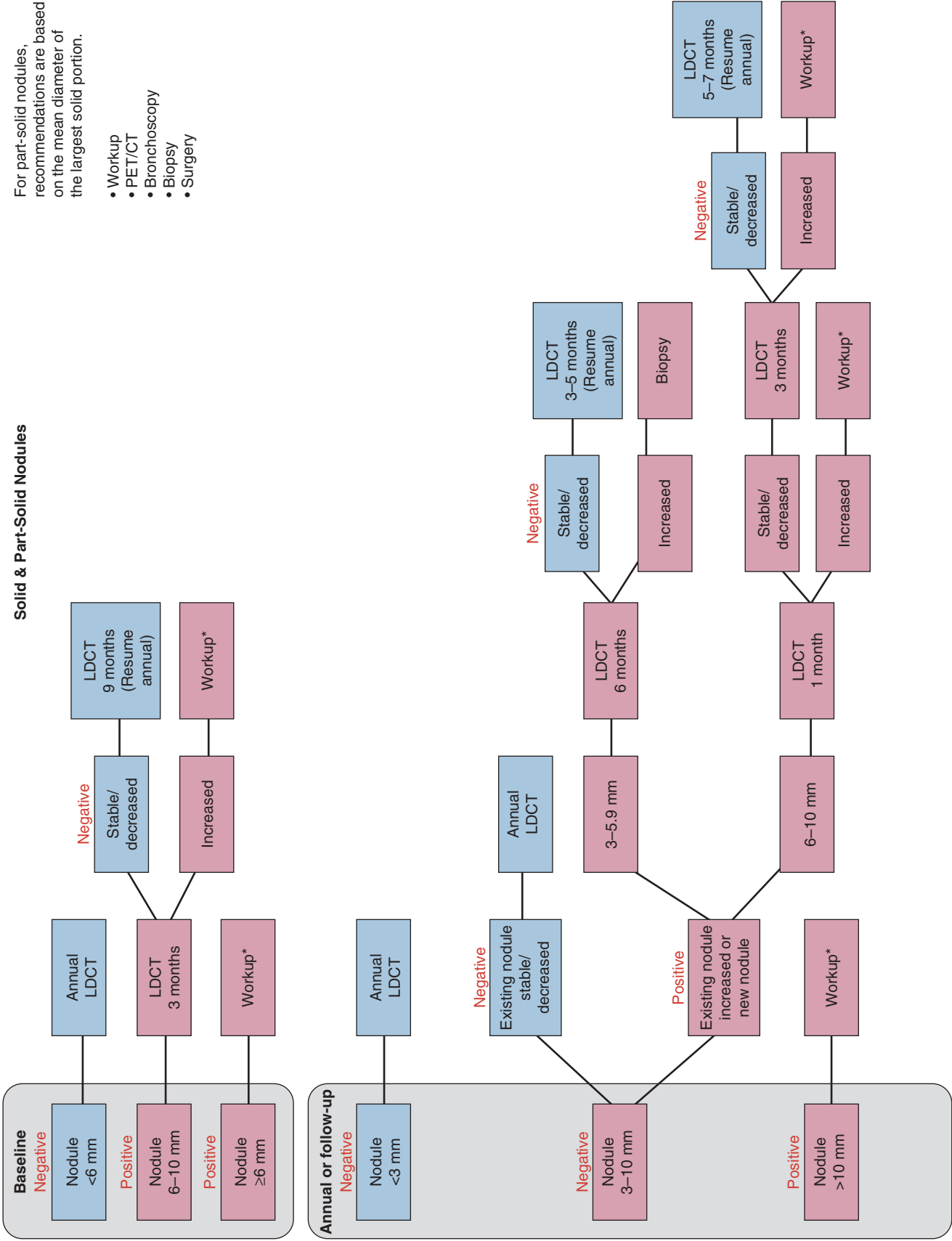
SUMMARY

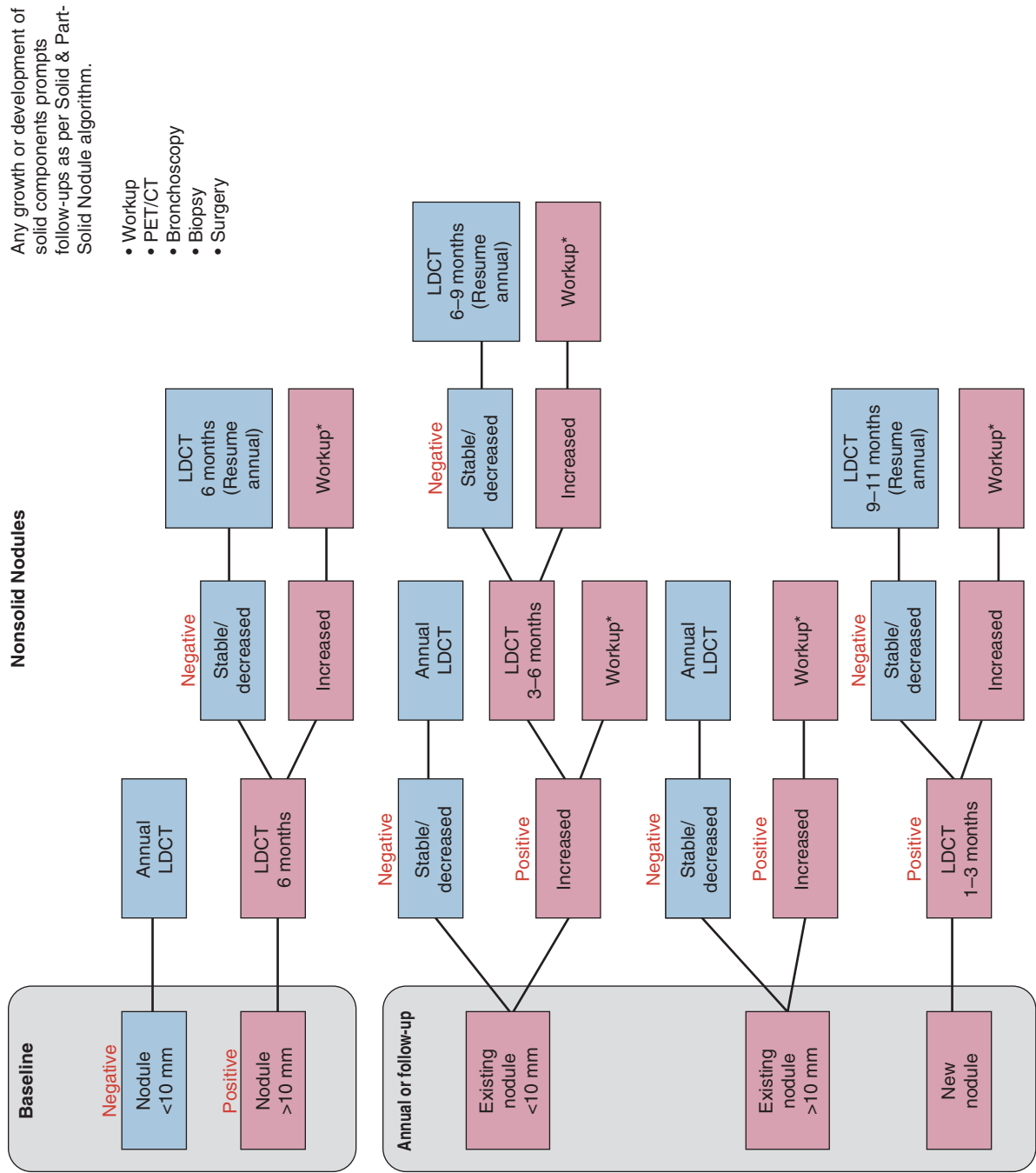
Lung cancer continues to be a deadly disease. The goal of screening programs is to detect tumors in earlier, curable stages, consequently reducing disease-specific mortality. The issue of screening has great relevance to thoracic surgeons, who should play a leading role in the debate over screening and its consequences. This is especially important as screening protocols may generate a tenfold increase in the number of patients presenting for surgical resection.¹⁸ The burden is on thoracic surgeons to work in a multidisciplinary setting to guide and treat these patients safely and responsibly, with low morbidity and mortality rates of potential diagnostic or therapeutic interventions.

For part-solid nodules, recommendations are based on the mean diameter of the largest solid portion.

- Workup
- PET/CT
- Bronchoscopy
- Biopsy
- Surgery

Solid & Part-Solid Nodules





B

FIGURE 15-1 ■ The diagnostic algorithm for (A) solid or part-solid nodules and (B) nonsolid nodules. This algorithm was created through discussion by a multidisciplinary group composed of thoracic surgeons, radiologists, pulmonologists, oncologists, and pathologists. *Workup is at the discretion of the treating physicians but typically consists of a PET/CT and tissue diagnosis, either by bronchoscopy, CT-guided biopsy, or for highly suspicious nodules, minimally invasive surgery. CT, Computed tomography; LDCT, low-dose computed tomography; PET, positron emission tomography.

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LUNG CANCER WORKUP AND STAGING

Valerie W. Rusch

CHAPTER OUTLINE

THE STAGING SYSTEM

DIAGNOSIS AND STAGING

History and Physical Examination

NONINVASIVE MODALITIES

Chest Radiography

Sputum Cytology

Low-Dose Computed Tomography

High-Resolution Computed Tomography

Positron Emission Tomography

Bone Scan

Magnetic Resonance Imaging

INVASIVE MODALITIES

Bronchoscopy

Endobronchial Ultrasound

Autofluorescence Bronchoscopy

Percutaneous Transthoracic Needle Biopsy

Cervical Mediastinoscopy

Left Anterior Mediastinotomy and Extended
Cervical Mediastinoscopy

Scalene Node Biopsy

Video-Assisted Thoracic Surgery

Thoracotomy

METASTATIC WORKUP

SUMMARY

In 2010, the most recent year for which numbers are available, there were 201,144 new cases of lung cancer (107,164 men and 93,984 women) in the United States.¹ With 158,248 deaths, lung cancer remains the leading cause of cancer-related deaths in both men and women. Of newly diagnosed cases, approximately 80% will be non-small cell lung cancer (NSCLC), and of these, 80% will involve metastatic or locally advanced disease. Only 20% will be in potentially surgically curable patients with early-stage disease, where complete resection yields 5-year survivals of 40% to 75%.²

Careful staging of newly diagnosed lung cancer is critical for several reasons. First, determining the patient's clinical TNM (tumor, nodes, metastasis) stage allows appropriate therapeutic decisions to be made on the basis of the specific stage of disease. This is particularly important for locally advanced disease in which multimodality therapy (induction or adjuvant) is standard care, as well as for metastatic disease when surgery should be avoided. Second, accurate staging allows the clinician to give the patient valuable prognostic information. Third, staging allows evaluation of new therapeutic interventions, and comparison of results of treatments between studies and institutions.

There are controversies about the extent of workup, and the methods used for staging have evolved during the past decade.

THE STAGING SYSTEM

Staging is a process through which the extent of lung cancer in a patient is determined by a combination of techniques including history, physical examination, imaging studies, and invasive procedures where appropriate. Before initiation of treatment, a clinical stage (cTNM) is generated. If surgical resection occurs, the operative findings and pathologic features determine the final pathologic stage (pTNM).

In 1974, the American Joint Committee for Cancer (AJCC) Staging developed a lung cancer staging system based on TNM descriptors.³ Naruke and coauthors⁴ devised the original lymph node map that placed nodes into stations on the basis of defined anatomic boundaries. This was subsequently modified for North America by the American Thoracic Society⁵ and by Mountain and Dresler.⁶ In 1986, the AJCC, International Union Against Cancer (UICC), and representatives from Japan proposed an International Staging System (ISS) for lung cancer that grouped patients with similar survival outcomes using anatomic criteria.⁷ This system was derived from analyses of a 3000-patient database at the M. D. Anderson Cancer Center (MDACC). The accuracy of the ISS was further confirmed by studies from Naruke⁸ and Watanabe.⁹ In 1997, analyses of the updated MDACC database of 5319 patients¹⁰ led to revision of the ISS,

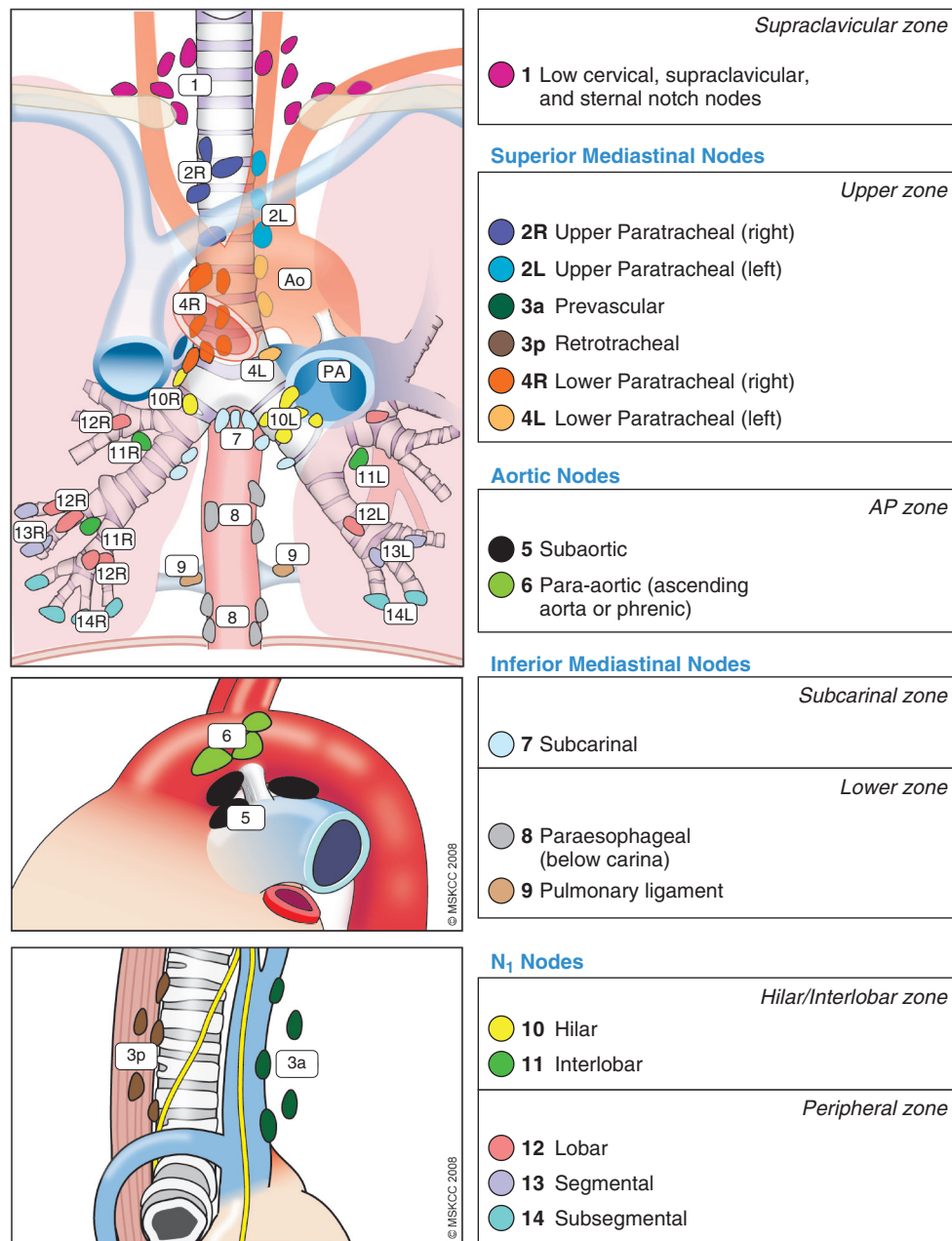


FIGURE 16-1 ■ Regional lymph node stations for the staging of non-small cell lung cancer. Ao, Aorta; PA, pulmonary artery. (From Rusch VW, Asamura H, Watanabe H, et al: The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 4:568–577, 2009.)

incorporated into the sixth edition of the AJCC and UICC staging manuals.

In 1996, the International Association for the Study of Lung Cancer (IASLC) initiated an international staging project to form the basis of the seventh edition of the TNM staging system.¹¹ The goals of the project were to validate the individual T, N, and M descriptors using a larger database made up of medical and surgical patients from a wide geographic distribution.¹² Data on 100,869 patients, including 67,725 cases of NSCLC, were submitted to the database, and several changes were proposed.¹³ The existing N descriptors were validated and

not changed (Fig. 16-1).¹⁴ For the T descriptors, size cutoffs were added to the T1 and T2 tumors, and tumors greater than 7 cm in greatest dimension were designated as T3, in light of the prognostic significance of increasing size of the primary tumor (Table 16-1).¹⁵ Additional tumor nodules in the same lobe as the primary, previously known as “satellite nodules,” were reclassified from T4 to T3, and additional nodules in the ipsilateral lung became T4. The M descriptor was divided into M1a (for pleural metastases, malignant effusion, or contralateral pulmonary disease) and M1b (for extrathoracic metastases).¹⁶ After incorporating the suggested changes into

TABLE 16-1 Definitions for T, N, and M Descriptors in the Seventh Edition of the AJCC and UICC Staging Manuals**T (Primary Tumor)**

TX	Primary tumor cannot be assessed, or tumor is proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm) Involves main bronchus, ≤ 2 cm distal to the carina Invades visceral pleura (PL1 or PL2) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (<2 cm distal to the carina*) but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

N (Regional Lymph Nodes)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M (Distant Metastasis)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion†
M1b	Distant metastasis

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

†Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

AJCC, American Joint Committee for Cancer; UICC, International Union Against Cancer.

From Goldstraw P, Crowley J, Chansky K, et al: *The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours*. *J Thorac Oncol* 2(8):709, 2007.

TNM subsets, new stage groupings were identified that yield even distributions of overall survival among stages, particularly between stages IIA and IIB (Table 16-2).^{17,18}

DIAGNOSIS AND STAGING

Diagnosis and clinical staging begin with the initial history and physical examination. A single study may serve the dual purpose of securing a diagnosis and staging the patient. If a patient's treatment is nonsurgical or involves multimodality therapy, obtaining a tissue diagnosis prior to treatment is mandatory. If it appears that the patient's clinical stage will be most appropriately managed by surgical resection alone, tissue confirmation of malignancy can be secured either preoperatively or at

the time of exploration, depending on the preference of the operating surgeon.

History and Physical Examination

Patients often come to the surgeon for evaluation with some studies already performed. However, the history and physical examination remain important in the initial evaluation. A detailed history focusing on risk factors—such as duration of cigarette smoking, exposure to asbestos and other industrial hazards, a prior history of lung cancer, and the presence of symptoms—allows the clinician to assess the likelihood of a diagnosis of lung cancer. Bach and associates showed that the duration of tobacco smoking, more so than the amount of daily usage, increases an individual's risk of developing lung cancer.¹⁹

TABLE 16-2 Descriptors, Proposed T and M Categories, and Proposed Stage Groupings*

Sixth Edition T/M Descriptor	Seventh Edition T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (>5-7 cm)	T2b	IIA	IIIB	IIIA	IIIB
T2 (>7 cm)	T3	IIIB	IIIA	IIIA	IIIB
T3 invasion		IIIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		IIIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)		IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

*These revisions were incorporated into the seventh edition of the AJCC and UICC staging manuals.

From Goldstraw P, Crowley J, Chansky K, et al: The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol* 2(8):709, 2007.

The lung cancer risk associated with asbestos exposure also increases with the intensity and length of exposure, and together, tobacco use and asbestos exposure have a multiplicative effect. Symptoms, such as bone pain, hoarseness, weight loss, and neurologic changes, can indicate the presence of metastatic disease and direct further investigation.

A physical examination is also important. It provides an estimate of a patient's overall health status, which influences treatment selection. Physical findings, such as Horner syndrome, or the presence of clubbing, may support the suspicion of lung cancer. Physical examination may also demonstrate advanced disease. For example, palpation of the supraclavicular fossae can reveal lymph node metastases, and auscultation of the lung fields can identify the presence of a malignant pleural effusion.

NONINVASIVE MODALITIES

Chest Radiography

Posteroanterior and lateral chest radiographs, often done for unrelated reasons, are a common initial study in which a suspected lung cancer is identified. However, most lesions are not visible until they are at least 7 to 10 mm in diameter.²⁰ A chest radiograph can localize the site of suspect lesions (central or peripheral) and the associated effects of disease, such as atelectasis, consolidation, or proximity to the pleural surface. The presence of a pleural effusion of chest wall invasion or of phrenic nerve involvement causing elevation of the hemidiaphragm may also be seen. Advanced disease may be identified in the case of rib destruction from bone metastases or synchronous lesions in the pulmonary parenchyma. Hilar and mediastinal lymph node metastasis is more

difficult to identify, unless there is substantial enlargement.

Sputum Cytology

Cytologic analysis of sputum for malignant cells is a simple diagnostic technique but is rarely used in North America because of the epidemiologic shift from centrally located squamous cell to more peripherally located adenocarcinomas. However, sputum cytology is still a potentially relevant test in other parts of the world where squamous cell cancers are more common. Samples may be induced by saline nebulization or collected as a 3-day pool of sputum produced from spontaneous coughing in the morning. Based on 16 published studies of at least 50 patients each, the overall sensitivity is 66% (range, 42% to 97%) and the overall specificity is 99% (range, 68% to 100%). When sputum cytology is used for patients suspected of having lung cancer on clinical grounds, the diagnostic yield is higher, with a sensitivity of 87% and a specificity of 90%.²¹

Low-Dose Computed Tomography

An increasing number of patients, particularly in developed countries, now have lung cancers identified by low-dose computed tomography (CT) because of the results of a large prospective U.S. randomized clinical trial. The National Lung Screening Trial (NLST) enrolled 53,454 persons at high risk (participants between ages 55 and 74 years with at least 30 pack years of smoking) for lung cancer at 33 medical centers and randomized them to undergo three annual screenings with either low-dose CT or posteroanterior chest radiography. Patients in the low-dose CT group had a significantly lower risk of death from lung cancer (20% relative risk reduction) and from any cause. The majority (63%) of lung cancers detected by low-dose CT were stage I tumors.^{22,23} The use of low-dose CT will likely increase in the future, largely supplanting chest radiography.

High-Resolution Computed Tomography

Once a suspect lesion has been detected on a chest radiograph or a low-dose CT, the next step is a high-resolution CT of the chest and upper abdomen, preferably performed with intravenous contrast. This yields information about the size, characteristics (e.g., spiculation, ground-glass opacification, lack of calcification), and local extent of a potential lung cancer. Potential invasion of contiguous chest wall or mediastinal structures can be assessed.

CT also provides details about the remaining lung parenchyma and pleural spaces. "Satellite" or additional nodules, bullous or emphysematous changes, pleural thickening, masses, or effusion may be identified. The chest CT for a suspected lung cancer should include the upper abdomen, through the liver and adrenal glands. Although most asymptomatic incidental lesions in the upper abdomen are benign (adrenal adenoma, hepatic cysts), unsuspected metastases are identified in a small percentage of patients.

Chest CT also allows assessment of mediastinal lymph nodes. The use of intravenous contrast is important in distinguishing nodes from vascular structures. The most widely used criterion to define abnormal lymph nodes is a short-axis diameter of 1 cm or greater. Although CT is the most accurate radiographic method of measuring lymph node enlargement, it does not reliably predict metastatic disease. Toloza and colleagues²⁴ reported results of a meta-analysis of 20 studies with 3438 evaluable patients that showed an overall sensitivity of 57% and specificity of 82%. Therefore, staging of the mediastinum and subsequent therapeutic decisions should not be based solely on the results of the CT.

Positron Emission Tomography

Whole-body positron emission tomography (PET) is a physiologic imaging technique based on the detection of positrons emitted by low-atomic-weight isotopes (carbon, fluorine, oxygen, nitrogen). Fluorodeoxyglucose (FDG) labeled with radioactive fluoride (¹⁸F) is a D-glucose analog that is phosphorylated after cellular uptake and accumulates intracellularly, rather than being metabolized. Because lung cancer cells have an increased rate of glycolysis and overexpress the glucose transporter, there is preferential accumulation and visualization of FDG in the primary tumor and in potentially metastatic sites (Fig. 16-2).²⁵ The criterion for an abnormal PET scan is either a standardized uptake value (SUV) of greater than 2.5 or uptake in the lesion that is greater than the background activity of the mediastinum. The lower limit of resolution of PET is approximately 1.0 to 1.2 cm and thus PET may not detect very small malignant lesions. Benign inflammatory or infectious conditions (e.g., granulomas, sarcoidosis) can also produce false-positive PET findings.

Despite these limitations, PET has become an invaluable tool in lung cancer staging.

Several studies have shown that PET is superior to CT in staging the mediastinum in lung cancer patients. Pieterman and colleagues²⁶ prospectively compared standard staging approaches to PET for detection of mediastinal lymph node and distant metastases in 102 patients with resectable NSCLC who underwent histologic staging of the mediastinum. The sensitivity and specificity of PET for detection of mediastinal nodal metastases were 91% and 86%, respectively, compared with a sensitivity of 75% and a specificity of 66% for CT. A meta-analysis of 18 studies demonstrated an overall sensitivity of 84% and specificity of 89%.^{24,26} Toloza and associates²⁴ also showed that combining CT and PET resulted in the highest diagnostic accuracy, with a sensitivity of 94% and a specificity of 86%, supporting the use of both modalities for staging of the mediastinum. PET also resulted in a stage different from the one arrived at by the standard methods in 62 of 102 patients, correctly indicating a lower stage in 20 patients and a higher stage of disease in 42 patients. PET was effective in identifying occult metastatic disease. In 11 patients (11%), PET demonstrated distant metastatic disease in bone, liver, and adrenal glands not detected by CT.

During the past decade, integrated PET-CT scanners have replaced PET alone, leading to improved diagnostic accuracy and anatomic localization of disease.²⁷ Cerfolio and coauthors compared PET with and without integrated CT in 129 patients with biopsy-proved or suspected NSCLC who subsequently underwent surgical staging.²⁸ PET-CT was a significantly better predictor of stages I and II disease and demonstrated superior accuracy for both T status (70% versus 47%, $P = 0.001$) and N status (78% versus 56%, $P = 0.008$) compared with



FIGURE 16-2 ■ Positron emission tomography–computed tomography (PET-CT) showing a right superior sulcus tumor (A) and the presence of an asymptomatic retroperitoneal metastasis (B).

PET alone. Moreover, PET-CT was more sensitive and more specific and had a higher positive predictive value for the status of N1 and N2 disease ($P < 0.05$). As in prior studies, PET-CT identified 19 (14.7%) patients with M1 disease.

PET-CT has proved to be more accurate than a bone scan, with a similar sensitivity and a higher specificity.²⁹⁻³² In the largest study comparing PET with bone scan, Song and colleagues retrospectively analyzed 1000 newly diagnosed patients, 105 of whom were eventually diagnosed with bone metastases and underwent PET-CT and bone scan.³¹ PET-CT was more accurate (98.3% versus 95.1%, $P < 0.001$), sensitive (94.3% versus 78.1%, $P = 0.001$), and specific (98.8% versus 97.4%, $P = 0.006$) than bone scan. PET-CT also showed a lower incidence of false positives (1.2% versus 2.9%) and false-negative results (5.7% versus 21.9%) compared with a bone scan. Agreement between PET-CT and bone scan findings was good, with a calculated $\kappa = 0.732$. Based on its clear advantages in both intra- and extrathoracic staging, PET-CT is now a routine part of pretreatment staging.

Bone Scan

Although PET-CT has essentially replaced bone scans for evaluation of potential skeletal metastases, when used in the setting of a positive clinical assessment (e.g., bone pain or tenderness), a technetium-99m methylene diphosphate (99mTc MDP) whole-body bone scan is relatively sensitive but not specific. In their meta-analysis of seven studies and 633 patients, Toloza and colleagues²⁴ showed that bone scans have an overall sensitivity of 87% and specificity of 67%. False-positive abnormalities are more common when scans are done in asymptomatic patients and can be the result of degenerative or traumatic skeletal injury. Follow-up with magnetic resonance imaging may or may not aid in establishing a definitive diagnosis. False-negative results, although uncommon, do occur, and in one series 6% of patients with an initially negative bone scan developed confirmed skeletal metastases within 1 year.³³

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the chest offers few advantages over CT in the diagnosis or staging of lung cancer. Heelan and coworkers³⁴ evaluated both CT and MRI in otherwise operable patients with NSCLC and found that MRI was no more accurate than CT in identifying hilar or mediastinal lymph node metastases and actually had a higher false-positive rate. In a recent study, whole-body MRI with diffusion-weighted imaging was compared with FDG-PET-CT in 33 patients before surgery for lung cancer. Whole-body MRI had comparable sensitivity, specificity, and accuracy for tumor detection and staging but showed no superiority to PET-CT.³⁵ However, MRI can be useful in some situations. When tumors are adjacent to the spine, MRI provides superior visualization of the spinal canal and can more accurately detect subtle changes in the marrow suggestive of invasion. It also delineates the relationship of a superior

sulcus carcinoma (Pancoast tumor) to the subclavian vessels and brachial plexus more accurately than CT.

INVASIVE MODALITIES

Bronchoscopy

Rigid or flexible bronchoscopy with conventional white light allows visualization of the tracheobronchial tree and is a standard part of evaluating patients with known or suspected lung cancer. It serves several critical purposes: diagnosis, staging, assessment of resectability, and visualization of the remaining bronchial tree. Flexible video-assisted bronchoscopy has replaced rigid bronchoscopy for all but a few special circumstances. It is generally performed as an outpatient procedure on a spontaneously breathing patient through the nasal or oral route, following topical anesthesia and sedation. The tracheobronchial tree up to the second or third subsegmental bronchi is easily visualized. The options available to secure a diagnosis include direct biopsy, brushing, saline lavage for cytology, and transbronchial needle aspiration (TBNA) with or without fluoroscopic guidance. Using more than one technique (e.g., biopsy, brushing, and cytologic lavage) generally improves the diagnostic yield.

When bronchoscopy reveals an endobronchial tumor, biopsy is best accomplished with either a forceps or brush biopsy, with sensitivities in the range of 80% to 100%.^{36,37} Positive endobronchial findings are common in cases of squamous and small cell cancers because of their central location. In contrast, a bronchoscopic examination is likely to yield normal findings when there are peripheral lesions, and the diagnostic sensitivity of bronchoscopy varies widely from 37% to 98%, depending on the size and location of the target lesion. Increasing size and presence of a bronchus sign (a bronchus leading to or contained in a lesion on CT) portend a higher diagnostic yield.³⁷ The use of fluoroscopy to guide a transbronchial biopsy or TBNA and lavage can improve diagnostic accuracy up to 80%.³⁸ Electromagnetic navigation bronchoscopy (ENB) is a new technology that uses high-resolution CT to guide transbronchial biopsy in real time during bronchoscopy. The CT-based "navigation" of the bronchoscope allows accurate biopsy of small peripheral lung lesions, especially when coupled with rapid on-site cytologic evaluation.³⁹

TBNA can also be used when there is bronchial distortion (thickening or blunting of the carina, extrinsic compression) secondary to the lesion or metastatic lymph nodes. Popularized by Wang and Terry, TBNA is performed with a 20- to 22-gauge, rigid needle through the channel of the fiberoptic bronchoscope to puncture the airway in the area of interest.⁴⁰ It is a safe and inexpensive procedure with an overall sensitivity of 50% and a specificity of 96%.^{36,37} As previously mentioned, diagnostic yield is enhanced by the use of fluoroscopy, as well as the use of rapid, on-site cytopathology. A positive result, especially from a mediastinal lymph node station, can obviate further surgical staging, although a negative result should still be confirmed surgically. Limitations include a sensitivity of only 30% for small (<2 cm),

peripheral lesions and inaccessibility of certain lymph node stations, including anterior, aortopulmonary, paraesophageal, and pulmonary ligament nodes. This technique has now been largely supplanted by the more recent development of endobronchial ultrasound.

Endobronchial Ultrasound

In an effort to improve on the diagnostic accuracy of TBNA, endobronchial ultrasound (EBUS) was developed and commercially introduced in the early 1990s.⁴¹ The original probe was radial, and radial EBUS guidance was shown to improve the yield of TBNA in the lymph node staging of lung cancer.^{42,43} Subsequently, an ultrasonic endoscope with a built-in linear-array, convex probe at the tip was developed by the Olympus Corporation (Tokyo) to enable real-time EBUS-guided TBNA. This EBUS is integrated with a convex transducer at 7.5 MHz at the tip of a flexible bronchoscope (XBF-UC260F-OL8, Olympus), whose angle of view is 90 degrees and direction of view is 30 degrees forward oblique. The ultrasound scans parallel to the insertion direction of the scope, and images are obtained by directly contacting the probe, with or without a saline-filled balloon at the tip. The ultrasound image is processed by a dedicated scanner (EU-C2000) that allows for image freezing, size measurement, and Doppler mode. A special 22-gauge needle is passed under direct visualization through the instrument channel to biopsy the target lesion through the bronchial wall (Fig. 16-3). The procedure can be done under monitored anesthesia care or general anesthesia. Indications for EBUS-TBNA include diagnosis of lung and mediastinal tumors and assessment of mediastinal and hilar lymph nodes. Accessible nodal stations include levels 2, 3, 4, 7, 10, and 11. Subaortic, paraesophageal, peribronchial, segmental, and subsegmental nodes are generally not approachable.

Several studies have shown the accuracy of EBUS-TBNA for mediastinal and hilar nodal staging in NSCLC.⁴⁴⁻⁴⁶ In one of the earliest series, Yasufuku and colleagues⁴⁵ successfully performed EBUS-TBNA in 105 patients with proved or suspected lung cancer and adenopathy by CT criteria alone. They sampled 163 lymph

nodes and reported an overall diagnostic accuracy rate of 96.3%, with a sensitivity of 94.6% and a specificity of 100%. Of note, patients who proved to have benign disease were excluded from analysis, and not all patients had confirmatory surgical biopsy of the nodal stations biopsied by EBUS. In a subsequent prospective controlled trial, Yasufuku and colleagues performed EBUS-TBNA followed immediately by cervical mediastinoscopy, in 153 patients with known or suspected lung cancer. No significant differences were found between EBUS-TBNA and mediastinoscopy with respect to sensitivity, negative predictive value, diagnostic accuracy, and determination of true pathologic N stage.⁴⁷ The same group of investigators has also reported that EBUS-TBNA can accurately access hilar and interlobar lymph nodes.⁴⁸ The accuracy of EBUS-TBNA is enhanced by rapid on-site evaluation (ROSE) of cytology specimens during the procedure, which also optimizes specimen submission for tumor molecular profiling.⁴⁹ A recent meta-analysis of 1066 patients from nine studies confirms the excellent accuracy of EBUS-TBNA.⁵⁰ In many centers, EBUS-TBNA has largely replaced mediastinoscopy in the staging of resectable NSCLC.

Autofluorescence Bronchoscopy

Detection and treatment of dysplastic or early invasive centrally located neoplastic lesions whose presence is suggested by positive sputum cytology remain a challenge. Approximately one third of patients with positive sputum cytology, but radiographically occult lung cancers, require more than one bronchoscopy for localization.⁵¹ In an effort to improve identification of superficial bronchial mucosal malignancy, Hung and associates⁵² were able to demonstrate that normal and malignant bronchial mucosa have different autofluorescence intensities under blue light (wavelength, 442 nm). This led to the development of the LIFE (light imaging fluorescence endoscope) Lung system (Xillix Technologies, Richmond, BC, Canada). Whereas normal bronchial mucosa appears green, premalignant and malignant tissue appears brown-red.⁵³ Subsequent prospective trials comparing white-light bronchoscopy alone with white-light bronchoscopy

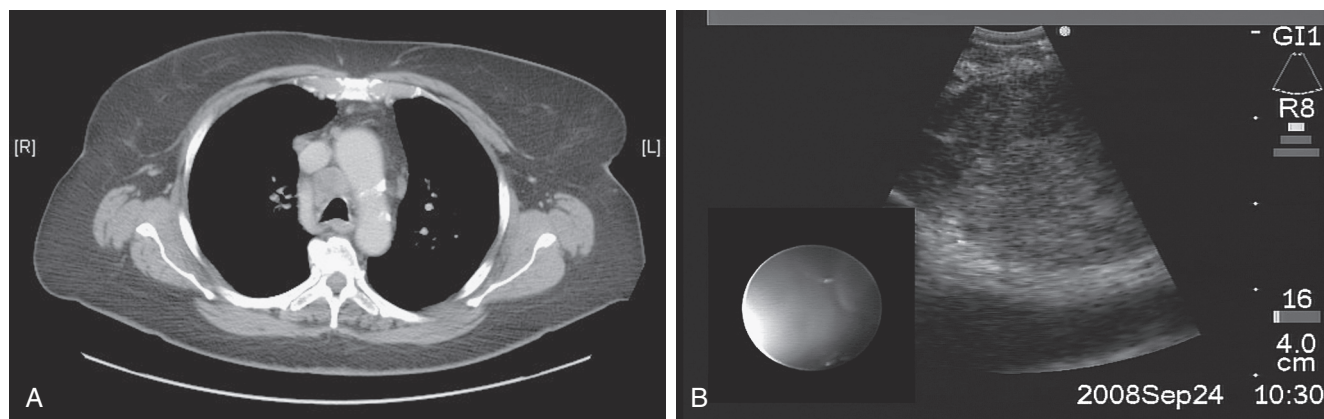


FIGURE 16-3 ■ **A**, CT scan of the chest revealing enlarged right paratracheal lymph node. **B**, Endobronchial ultrasound (EBUS)-guided transbronchial needle aspirate of an enlarged right paratracheal lymph node.

plus LIFE have shown enhanced sensitivity in detection of intraepithelial neoplasms and invasive carcinoma.⁵³⁻⁵⁶ Lam and coauthors⁵⁶ reported the results of a multicenter North American trial of 173 patients that showed the relative sensitivity of white-light bronchoscopy plus LIFE versus white-light bronchoscopy alone to be 6.3 for intraepithelial lesions and 2.71 if invasive cancers were included. The role of LIFE was in preoperative screening for synchronous squamous carcinomas but in follow-up for recurrence or second primary tumors, and for monitoring intraepithelial dysplasia in some chemoprevention trials, it is not currently in widespread use. This relates in part to the epidemiologic shift away from centrally located squamous cancers and in part to the lack of development of more advanced autofluorescence technology than can be used outside of the research setting.

Percutaneous Transthoracic Needle Biopsy

Percutaneous transthoracic needle biopsy is a well-established procedure used to obtain a tissue diagnosis of lung cancer in patients who are not surgical candidates because of advanced disease or medical contraindications. However, with the identification of increasing numbers of noncalcified peripherally located pulmonary nodules by low-dose CT, transthoracic needle biopsy has become a critical tool in the detection of early-stage lung cancer. The accuracy of percutaneous needle biopsies has been enhanced by the development of fluoroscopy CT, which allows precise targeting of very small peripheral nodules for biopsy.^{57,58} The most common complications of the procedure are pneumothorax and mild hemoptysis. Although the reported incidence of pneumothorax varies greatly, the rate of postprocedure pneumothoraces requiring intervention ranges from 1.6% to 17%.^{59,60} The most important risk factor is underlying chronic obstructive pulmonary disease (COPD).⁶¹ Hemoptysis occurs in 5% to 10% of cases and is usually self-limited. Massive hemoptysis is rare with the use of 20-gauge or smaller needles.^{62,63} Relative contraindications to transthoracic biopsy, therefore, are the presence of severe COPD, a bleeding disorder, contralateral pneumonectomy, and severe pulmonary hypertension. When successful, the results of percutaneous transthoracic biopsy are positive in patients with lung cancer in roughly 90% of cases, with a low false-positive rate of less than 2%.⁶⁴ However, false-negative results can be frequent, so all results should be considered indeterminate unless a specific benign diagnosis is made.

Cervical Mediastinoscopy

Accurate assessment of the mediastinum is paramount as mediastinal lymph node involvement by metastatic carcinoma strongly influences treatment decisions. Until the development of EBUS, cervical mediastinoscopy was the most accurate pre-resection method of staging the mediastinum in lung cancer. Described by Carlens in 1959, mediastinoscopy is performed with a rigid, lighted scope placed in the avascular, pretracheal space to access the superior mediastinum.⁶⁵ Its efficacy is well established, with a pooled procedural sensitivity of 81% and a specificity of 100% in a recent meta-analysis of 5687 patients.^{65a} A negative mediastinoscopy also predicts a high rate of complete resection at thoracotomy. Luke and colleagues⁶⁶ demonstrated that of 590 patients with a negative mediastinoscopy, 93% had complete tumor resection. Cervical mediastinoscopy is an outpatient procedure that is extremely safe. In a review of 2137 patients, Hammoud and coworkers⁶⁷ reported overall morbidity and mortality rates of 0.6% and 0.05%, respectively.

In the pre-EBUS era, the indications for mediastinoscopy were often debated and routine mediastinoscopy was controversial. Most thoracic surgeons agreed that mediastinoscopy should be performed for the following: (1) lymph node enlargement greater than 1 cm in the short axis on CT, (2) hypermetabolic uptake on PET, and (3) possible enrollment into induction therapy protocols. Relative indications included the presence of T2 or T3 tumor or poor prognostic tumor histologies such as large cell carcinoma.⁶⁸ Those who supported the practice of routine mediastinoscopy emphasized its low complication rate and high level of accuracy, the high rate of complete resection after a negative mediastinoscopy, the relatively low sensitivity of CT, the prevalence of nodal disease even in T1 tumors (Table 16-3), and the ability to select patients who might benefit from induction therapy. During the past decade, the combination of PET-CT and EBUS-TBNA has gradually replaced mediastinoscopy in the staging of NSCLC. However, mediastinoscopy remains appropriate in situations where EBUS-TBNA samples are inadequate for diagnosis or for tumor molecular profiling.

Left Anterior Mediastinotomy and Extended Cervical Mediastinoscopy

One limitation of mediastinoscopy can be in the setting of a left upper lobe cancer, in which aortopulmonary window and para-aortic lymph nodes (levels 5 and 6) may

TABLE 16-3 Prevalence of Nodal Metastases in Clinical T1 Non-Small Cell Lung Cancer

Author (ref)	Patients (N)	Node+ (%)	N1 (%)	N2 (%)	Skip N (%)
Ishida et al ⁸⁷	221	28	9	19	28
Naruke ⁸⁸	714	33	18	15	30
Asamura et al ⁸⁹	337	26	10	16	25
Oda et al ⁹⁰	524	22	8	14	51
Graham et al ⁹¹	86	29	19	10	34

need to be sampled. In this situation, there are two options for surgical staging. Levels 5 and 6 mediastinal lymph nodes can be accessed from a left anterior or parasternal approach, as described by McNeill and Chamberlain.⁶⁹ A transverse incision is placed over the second rib, and the costal cartilage is removed. The retrosternal extrapleural space is entered by blunt dissection, and the para-aortic space is explored. Modifications of the procedure include preservation of the internal mammary vessels, use of the mediastinoscope for better visualization, and preservation of the cartilaginous rib. In three reported series totaling 194 patients with left upper lobe cancers who underwent a Chamberlain procedure, 38% (73 of 194) had positive biopsy results, and resectability in those patients with a negative anterior mediastinotomy was 95%.⁷⁰ As with cervical mediastinoscopy, morbidity and mortality rates in previously reported series are low—8% and 0%, respectively.

Another surgical approach to the anterior mediastinum in left upper lobe cancers is extended mediastinoscopy, described by Ginsberg and associates.⁷¹ After a pathologically negative standard cervical mediastinoscopy, the mediastinoscope is withdrawn, and blunt digital dissection is used to create a window between the innominate and left carotid arteries posterior to the innominate vein. The mediastinoscope is reinserted and advanced along the anterolateral surface of the aortic arch into the node-containing fat pad. Extended mediastinoscopy should be avoided in patients with a dilated or calcified aortic arch or previous sternotomy. Because of the challenging nature of the dissection required for extended mediastinoscopy and the development of other minimally invasive alternatives to accessing the aortopulmonary window, such as EUS and video-assisted thoracic surgery, extended mediastinoscopy is no longer widely performed.

Scalene Node Biopsy

Scalene node biopsy is used to assess suspect nodes in the supraclavicular fossa, identified by either palpation or imaging (specifically, PET-CT). If there are palpable nodes in the supraclavicular fossa, a fine-needle aspiration (FNA) in the office is often sufficient. If an FNA is nondiagnostic, or metastatic disease is suspected on imaging, formal excision of the fat pad may be performed. A 3- to 4-cm incision is placed over the insertion of the sternocleidomastoid muscle parallel to the clavicle. Dissection is performed between the clavicular and sternal heads, exposing the scalene fat pad on top of the scalenus anterior muscle. Care must be taken to preserve the phrenic nerve lying posterior on the scalenus anterior muscle. Scalene node biopsy can also be done during a mediastinoscopy using a single incision. Lee and Ginsberg reported that 15.4% of patients (6 of 39) with positive N2 disease had positive scalene nodes as well, indicating N3 disease.⁷²

Video-Assisted Thoracic Surgery

Video-assisted thoracic surgery (VATS), now performed with a videothoracoscope, is a valuable tool for the

diagnosis and staging of NSCLC. It requires general anesthesia and a patient who can tolerate single-lung ventilation. With the patient in a standard lateral decubitus position, the thoracoscope and endoscopic instruments are inserted through one or more operating ports placed via small intercostal incisions. The entire hemithorax can be explored, including the hilum, mediastinum, visceral and parietal pleural surfaces, and chest wall. The principal use of VATS has been to perform the excisional biopsy of peripheral lung nodules for the diagnosis of primary lung cancer or to rule out synchronous or metastatic disease.⁷³ It can be used to evaluate mediastinal lymph nodes—in particular, those inaccessible by cervical mediastinoscopy (anterior, aortopulmonary, para-aortic) or anterior mediastinotomy (hilar, inferior pulmonary ligament).^{74,75} Several studies have shown that the sensitivity and accuracy of VATS are almost 100% for diagnosis and staging of lung cancer, with minimal morbidity and mortality.

Thoracotomy

With the myriad of accurate, less invasive diagnostic methods available, more than 95% of tumors can be characterized without thoracotomy. Exploratory thoracotomy, however, still allows the most thorough assessment of the primary lesion, the pleural space, and the ipsilateral mediastinal lymph nodes. The tumor is typically biopsied with a Tru-Cut needle, and the local extent and status of the mediastinal lymph nodes are assessed while the pathologists analyze the specimen by frozen section.

METASTATIC WORKUP

Approximately 40% of patients with newly diagnosed lung cancer are found to have extrathoracic metastases. Identifying these patients is critical to avoid unnecessary thoracotomy and a delay in appropriate systemic therapy. Currently, the standard multiorgan imaging techniques used to rule out the most common metastases in patients with NSCLC (adrenal, liver, brain, bone) are CT of the chest and upper abdomen, CT or MRI of the brain with contrast, and whole-body PET-CT.

Who should undergo evaluation for distant metastatic disease? There are few prospective randomized trials of extrathoracic imaging for NSCLC. It is well accepted that patients who have certain symptoms, abnormal physical findings, or laboratory abnormalities are at increased risk of having metastatic disease. Silvestri and coauthors showed in a large meta-analysis that a positive clinical evaluation was associated with a roughly 50% rate of abnormal scans.⁷⁶ These results underscore how critical the findings of the initial history, physical examination, and laboratory tests are in guiding subsequent workup. Patients with a positive clinical evaluation (Table 16-4) should undergo multiorgan scanning.

What about asymptomatic patients? Routine multiorgan imaging in patients without symptoms or signs is controversial. Several studies have shown that routine preoperative scanning in asymptomatic patients is

TABLE 16-4 Clinical Evaluation for Metastatic Disease

Clinical Evaluation	Finding
Symptoms	Constitutional: weight loss > 5% of body weight, malaise Musculoskeletal: focal skeletal pain Neurologic: headache, seizure, mental status or personality changes
Physical signs	Focal neurologic deficit Supraclavicular lymphadenopathy Hoarseness Superior vena cava syndrome Bony tenderness Skin or soft tissue mass Hepatomegaly
Laboratory tests	Anemia Elevated liver function tests Hypercalcemia

associated with a low percentage (3% to 10%) of positive results, with silent metastases found in 2.7% to 15%.⁷⁷ In their meta-analysis, Silvestri and colleagues⁷⁶ calculated the probability that a scan will be negative if the clinical evaluation is negative (i.e., the negative predictive value of the clinical evaluation). For CT of the abdomen or brain, and for bone scan, the negative predictive values were 94%, 95%, and 89%, respectively. The only prospective, randomized trial that compared routine multi-organ scanning with chest CT and mediastinoscopy in asymptomatic patients with clinically operable lung cancer showed no statistically significant difference in the rate of unnecessary thoracotomy, postoperative recurrence, or overall survival.⁷⁸ Despite this, more recent data have shown whole-body PET and PET-CT to be invaluable in disclosing non-central nervous system metastatic disease in up to 10% to 20% of cases missed by standard methods.^{26,79,80} On this basis, PET-CT should be considered a standard staging modality in all cases of biopsy-proved or suspected lung cancer, and it obviates the need for bone scan as well.

In addition, some authors have reported that more locally advanced lesions (T3 or N2) have a higher rate of asymptomatic distant metastases.^{81,82} Others have shown that adenocarcinomas have a higher rate of asymptomatic cerebral metastases than squamous carcinomas.^{77,83} However, the evidence to support routine brain imaging in the evaluation of potentially resectable NSCLC is scant and is based primarily on retrospective series. MRI with or without intravenous gadolinium is considered the optimal imaging study. A generally accepted approach is to add brain MRI to CT and PET-CT for evaluation of clinically higher stage tumors (stages II and III) but not for stage I tumors where the frequency of asymptomatic brain metastases is only about 5%.⁸⁴⁻⁸⁶

Based on available information, it is appropriate for all patients with established or suspected lung cancer to undergo high-resolution, contrast CT of the chest and whole-body PET-CT. Selected patients should undergo brain MRI. Multiorgan scanning should be considered for (1) any patient with a positive clinical evaluation

(symptoms, signs, blood work), (2) patients with locally advanced disease (stage IIIA) being considered for multimodality therapy, and (3) patients with earlier stage disease (stages I, II) who are marginal operative candidates.

SUMMARY

Lung cancer remains a challenging and deadly disease. Proper diagnosis and staging are critical for determining the best treatment strategy for each patient. The most important components of the workup are the initial history and the physical examination. Numerous noninvasive and invasive techniques can be used to establish an accurate and valid clinical estimate of tumor stage.

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LUNG CANCER: SURGICAL TREATMENT

Masaki Anraku • Shaf Keshavjee

CHAPTER OUTLINE

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SPECIAL CONSIDERATIONS

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SURGICAL TREATMENT OF SMALL CELL LUNG CANCER

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- Improved Local Control
- Mixed-Histology Tumors
- Surgery as a Salvage Treatment
- TNM Staging (Seventh Edition) and Surgical
Outcome

SUMMARY

This chapter provides an overview of the surgical treatment for lung cancer. The indications for surgery, types and extent of lung resection, and mediastinal lymphadenectomy are reviewed, with an emphasis on recent published evidence and the new international tumor-node-metastasis (TNM) staging system (seventh edition, 2009). Minimally invasive lung resection (see [Chapter 18](#)), tracheal lesions (see [Chapter 8](#)), tumor invading the chest wall (see [Chapter 20](#)), and multimodality approaches (see [Chapter 19](#)) are specifically covered separately.

Lung cancer remains the leading cause of cancer death worldwide, with an estimated 159,480 deaths and 228,190 new cases in the United States in 2013.¹ Complete surgical resection is the treatment of choice for patients with early-stage (stages I and II) and selected locally advanced (stage III) non-small cell lung cancer (NSCLC). Surgery may have a role to play in the following cases as well: NSCLC with isolated adrenal metastasis, isolated brain metastasis, or highly selected small cell lung cancer. Adjuvant chemotherapy has been established as a modality to improve survival in selected resectable NSCLC on the basis of published clinical studies including phase III randomized trials.²⁻⁶ Neoadjuvant therapy (induction chemotherapy or chemoradiotherapy) improves outcome in patients with N2 disease or resectable, locally advanced NSCLC.⁷

HISTORICAL NOTE

The first lobectomy for lung cancer was described by Davies⁸ in 1913-1914; the patient died 8 days after resection, with empyema. As water-sealed drainage system and anesthetic techniques advanced, surgical resection for lung cancer became prevalent. In 1933, Graham and Singer⁹ reported the first successful one-stage pneumonectomy. Since then, the standard operation for lung cancer became pneumonectomy with the technique of individual hilar ligation of the pulmonary vessels and suturing of the bronchus. Around the same time, Churchill and coworkers¹⁰ described their experience of lobectomies with hilar dissections. The technique of segmentectomy for lung cancer was described by Overholt and Langer.¹¹ As refinements progressed, more advanced techniques were developed, including sleeve resection by Price-Thomas¹² in 1956, carinal resection by Mathey and colleagues¹³ and Thompson,¹⁴ and Pancoast tumor resection by Chardak and MacCallum.¹⁵ Grillo and colleagues¹⁶ reported on carinal resection with airway reconstruction in 1963. In 1973, Jensik and colleagues¹⁷ reported a large series of segmental resections as intentional curative procedures for the treatment of bronchogenic carcinoma. Since the early 1990s, as the system of video endoscopy and endoscopic instruments have evolved, video-assisted thoracoscopic surgery (VATS) for major pulmonary resection has continued to develop worldwide.¹⁸ More recently, studies have demonstrated that robot-assisted surgery is a safe and feasible operation for pulmonary resection.^{19,20}

PULMONARY SURGICAL OPERATIONS: INDICATIONS AND TECHNIQUES

Lobectomy

Lobectomy with complete en bloc tumor removal remains the standard surgical procedure in patients with resectable NSCLC. Resections less extensive than lobectomy (i.e., segmentectomy and wedge resection) are chosen in patients with limited pulmonary reserve or, recently, in those with small peripheral tumors without nodal disease for curative intent. The indications for curative-intent sublobar resection are discussed later. On occasion, sleeve lobectomy is required when the tumor protrudes into the mainstem bronchus. A concern with sleeve lobectomy is that it might be an inferior oncologic resection compared with pneumonectomy; however, sleeve lobectomy, compared with pneumonectomy, has demonstrated better long-term outcome, that is, lower morbidity and mortality rates.^{21,22}

Positioning and Incisions

The patient is placed into the lateral decubitus position. Entry into the pleural space via a posterolateral incision is the standard that provides an excellent exposure to the hilum of the lung. The anterior serratus muscle can be mobilized and spared whenever possible. The intercostal muscle, in most cases the fifth intercostal, is cut along the rib both anteriorly and posteriorly to obtain wider rib spreading. Anterior, lateral, or axillary thoracotomies are other alternatives. Occasionally, a hemi-clamshell incision or median sternotomy is selected for extended resection of apical tumors because either provides excellent exposure of the thoracic inlet, superior pulmonary veins, and main pulmonary arteries.

Mobilization and Hilar Dissection

After the pleural cavity is entered, careful inspection of the pleural space is performed. Any pleural fluid is sampled for cytology and culture. All lobes of the lung are then palpated to assess the extent of the disease, to identify unexpected pleural or parenchymal lesions, and to confirm resectability. The inferior pulmonary ligament is incised up to the inferior pulmonary vein, and the mediastinal pleura of the hilum is incised circumferentially to totally mobilize the lung. Care must be taken to prevent injury to the phrenic nerve by electrocautery when the anterior hilum is opened. The posterior views of right and left pulmonary hila are shown in [Figure 17-1](#).

The hilar vascular structures (the main pulmonary artery and the superior and inferior pulmonary veins) are identified and dissected. The fissures between the lobes are often not completely open, so dissection is required to reach the interlobar structures. The incomplete fissures usually necessitate a combination of sharp and blunt dissection. Care must be taken to avoid violation of the tumor if an extension of the tumor from one lobe to another is seen. The interlobar views of right and left lungs are shown in [Figure 17-2](#).

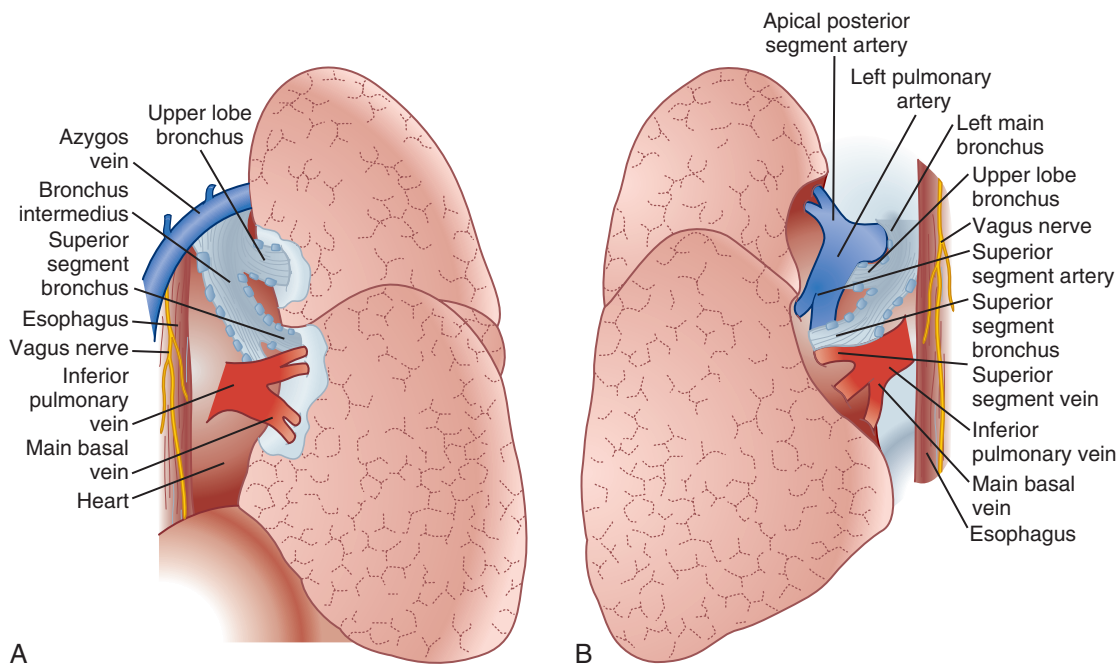


FIGURE 17-1 ■ Posterior views of the right (A) and left (B) pulmonary hila. The mediastinal pleura is opened and the lung retracted anteriorly. (Illustrations by Dennis Wei.)

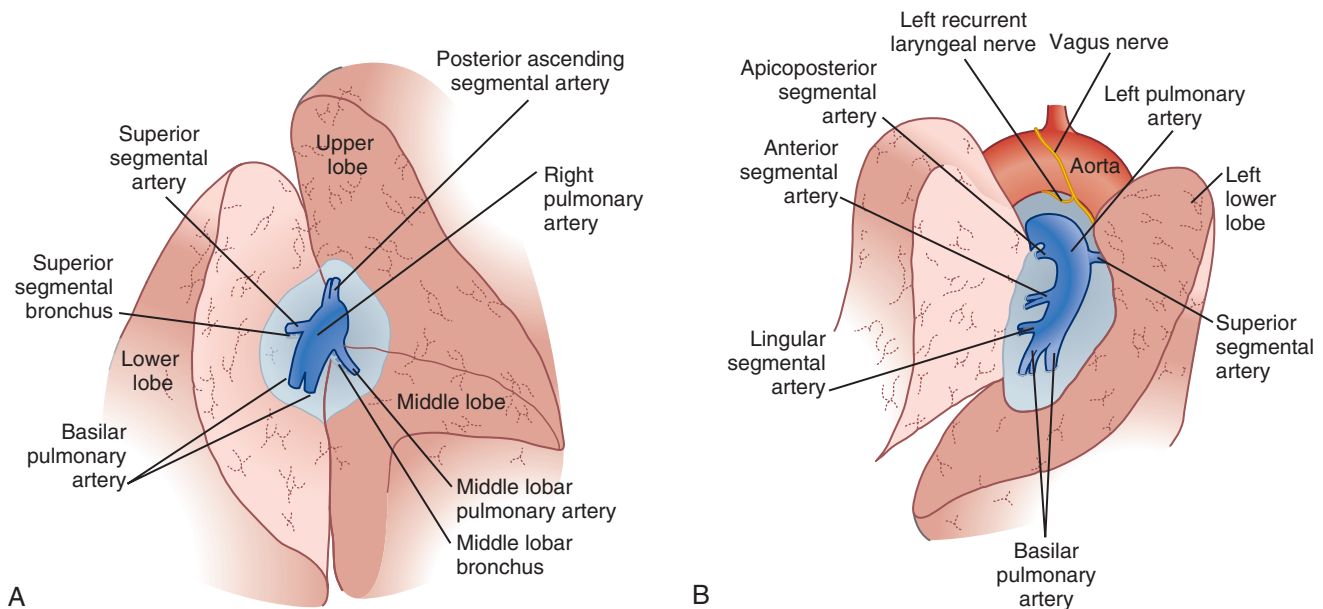


FIGURE 17-2 ■ The interlobar views of the right (A) and left (B) lungs. The fissures are incised and pulmonary artery branches are exposed. (Illustrations by Dennis Wei.)

Management of Vessels

Once the interlobar pulmonary artery is identified, the segmental arteries are exposed to the appropriate plane by dissecting down onto the pulmonary arterial vascular plane. The fissures can be divided with electrocautery or with a mechanical stapler, depending on the amount of parenchymal tissue to be transected. For division of pulmonary arteries, some surgeons prefer transfixing ligatures (especially for larger vessels), and others apply simple nonabsorbable ligatures. The

mechanical stapler can be also used to divide large vessels. It is preferable to isolate and tape the main pulmonary artery and pulmonary veins for control before starting vessel dissections in the following cases: (1) tumor invasion to the main trunk of the pulmonary artery, (2) tumor involving the roots of segmental arterial branches, or (3) significant inflammatory scarring or adhesions encountered around the pulmonary arteries. Using this technique, the main pulmonary artery and veins can be easily clamped for control if an arterial injury occurs.

The order of division of the vasculature is flexible; however, it is safe to divide pulmonary artery branches, then veins, followed by the bronchus, in most cases. Some prefer to divide veins first to avoid possible tumor cell dissemination into the blood circulation during the manipulation of the lung, but it has not been proven that this maneuver affects long-term outcome. The disadvantage of dividing the pulmonary veins before the artery branches is that the diseased lobe may become congested with retained blood, making the surgery difficult. It is often advantageous to first divide the structure whose absence allows better exposure of the remaining structures. For example, the bronchus can be divided first to obtain better exposure and dissection of the pulmonary artery branches if needed.

Management of Bronchus

After obtaining the proposed bronchial margin by clearing peribronchial lymph nodes of the diseased lobe, bronchial closure is performed with a bronchial stapler. Excessive devascularization of the bronchial stump should be avoided to prevent bronchopleural fistula (BPF). Although closure can be performed by hand-suturing techniques, the stapling technique is faster and equally safe. Before firing the bronchial stapler, the anesthesiologist is asked to inflate the operative lung to confirm no impingement of the main bronchus or other remaining bronchi. Frozen-section pathologic examination of the bronchial margins should be obtained if there is any concern of tumor invasion. For poor-risk patients or those who received induction chemoradiotherapy, the bronchial stump should be covered with pericardial fat pad, pericardium, pleura, or intercostal muscle to minimize the chances of a postoperative BPF. In cases of sleeve lobectomy, cancer-free margins on both proximal and distal bronchial ends should be confirmed by frozen section. For the bronchial anastomosis, two traction stitches are placed on both bronchial ends. Interrupted 4-0 monofilament absorbable sutures are placed on the cartilaginous portion and a running monofilament absorbable suture on the membranous portion without any tension on the bronchial anastomosis.

Placement of Chest Tubes

Chest tubes are placed for evacuation of residual fluid and air to reexpand the residual lung. Another purpose of tube placement is for monitoring of postoperative bleeding. Although there are no standardized rules in terms of the tube size and number, we usually place an apical chest tube and an angled basilar chest tube above the diaphragm (28 Fr).

Pneumonectomy

As anatomic lobectomy has become the standard form of curative resection for bronchogenic carcinoma, pneumonectomy has become less prevalent. Pneumonectomy is reserved for central lesions, traditionally, but even in patients with tumor invasion of the mainstem bronchus or bronchus intermedius, sleeve lobectomy is the

procedure of choice, with acceptable morbidity, mortality, and long-term survival.²³ After careful assessment and patient selection, pneumonectomy is used for patients with centrally located NSCLC that cannot be completely resected using bronchoplastic procedures.

Incision

Posterolateral thoracotomy via the fifth intercostal space is the standard approach because it provides excellent access to both the anterior and the posterior hila. Anterior thoracotomy or muscle-sparing (e.g., anterior serratus muscle or latissimus dorsi muscle) thoracotomy is another option of choice. On entering the pleural cavity, a careful assessment is performed to identify the extent of tumor. This includes bronchoscopic assessment at the time of surgery. The decision to perform pneumonectomy is usually made preoperatively on the basis of the tumor location and the cardiopulmonary reserve; however, occasionally, it is not possible to make a decision before the intraoperative assessment. A lesser resection such as sleeve lobectomy with or without pulmonary arterioplasty should always be considered as long as a complete en bloc tumor resection can be achieved.

Hilar Dissection

Once the need for pneumonectomy is confirmed, the hilum is dissected to identify the main pulmonary artery and the superior and inferior pulmonary veins. After retracting the lung anterosuperiorly, the inferior pulmonary ligament is divided up to the level of the inferior pulmonary vein. The inferior pulmonary vein is exposed and isolated by dissecting surrounding connective tissues. On the right side, a plane between the main pulmonary artery and the superior pulmonary vein should be developed for dissection. On the left side, the superior pulmonary vein resides anterior to the left main bronchus, so a plane for dissection should be found between these structures. The division of the superior and inferior pulmonary veins can be performed by double ligation or stapling. When the tumor involves the pericardial reflection, the pericardium is opened for more proximal vessel isolation, and a vascular clamp is applied across the atrium for division of the pulmonary vein. After division of the vein, the stump is closed with a double-layer nonabsorbable suture.

When the tumor is in close proximity to the proximal pulmonary artery, and thus it is not possible to obtain a sufficient margin to apply a stapler, the pericardium should be opened to obtain additional length for division (Fig. 17-3). On the right side, mobilization of the superior vena cava is often required to encircle the proximal right main pulmonary artery. On the left side, division of the ligamentum arteriosum produces additional length for division of the left main pulmonary artery proximally. During this maneuver, special attention should be paid to avoiding injury to the left recurrent laryngeal nerve, if the nerve is not involved by the tumor. Dissecting proximally after opening the pericardium at its reflection, one can divide the left pulmonary artery at its origin. It is important not to impinge on the right pulmonary artery

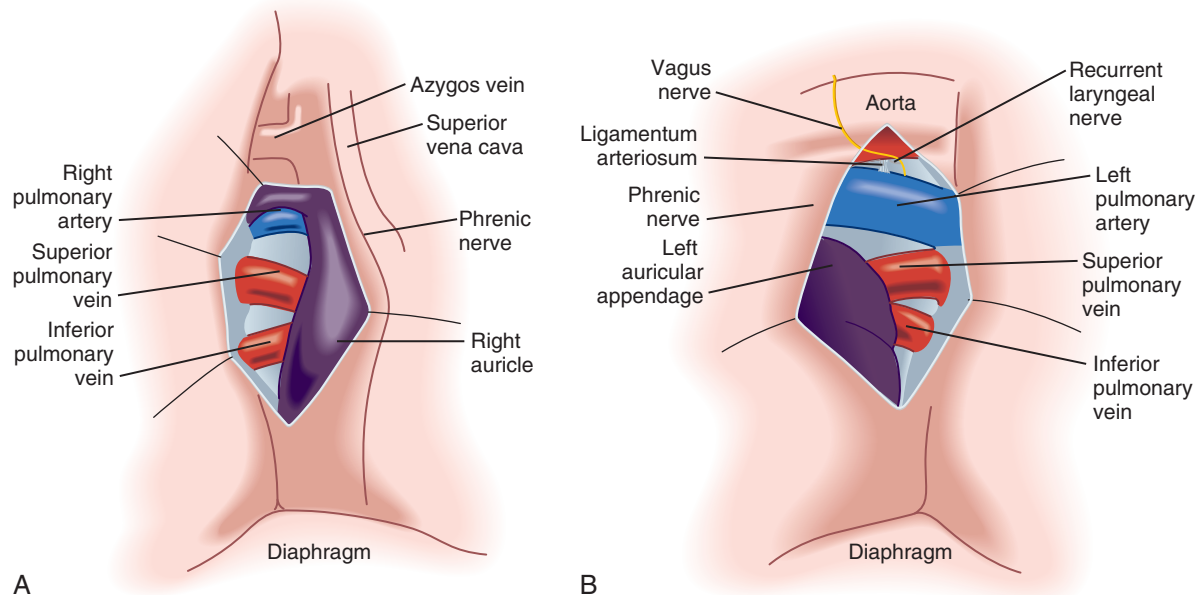


FIGURE 17-3 ■ The anterior intrapericardial views of the right (A) and left (B) hila. (Illustrations by Dennis Wei.)

when applying traction to staple the left main pulmonary artery.

Management of Bronchus

The division of the mainstem bronchus should be performed as proximally as possible (3 to 5 mm from the carina) to avoid creating an unnecessarily long bronchial stump. On the right side, the carina and the anticipated point of bronchial division is often visualized easily. The division of the left mainstem bronchus requires some traction on the bronchus, because the carina is poorly visualized from the left side. Peribronchial tissues and lymph nodes around the bronchus are cleared to better expose the bronchus, but an excessive devascularization should be avoided to preclude poor healing that could lead to postoperative BPF. In patients who received induction radiotherapy, the stump of the right main bronchus should be covered by a pericardial fat pad, mediastinal pleura, pericardium, intercostal muscle flap, or even omentum. Although it is generally desirable to protect the right main bronchial stump, it is not always necessary on the left side because the left main stump retracts into mediastinal tissues after division. Darling and colleagues²⁴ reported the rates of BPF were approximately 13% on the right side and 5% on the left side, with 8% overall.

Management of the Postpneumonectomy Space

The goal of management of the postpneumonectomy space is to normalize (i.e., reposition) mediastinum to the midline. To accomplish this, some leave a small chest tube to evacuate a measured quantity of air immediately after surgery in the operating room, and then remove the tube, whereas others leave a chest tube with balanced

pneumonectomy drainage systems (e.g., Pleur-evac [Teleflex Medical, Research Triangle Park, NC] balanced pneumonectomy drainage system) to avoid mediastinal shift while maintaining normal pressures. Alternatively, a chest tube can be left clamped and intermittently unclamped briefly to reposition the mediastinum. In any case, negative pressure to the chest tube must not be applied because it may cause a significant mediastinal shift to the operative side.

Sublobar Resection (Segmentectomy and Wedge Resection)

Sublobar resection was originally developed for the surgical management of infectious lung diseases such as tuberculosis and bronchiectasis, in which bilateral or multisegmental disease is frequently seen. For the treatment of NSCLC, this has generally been the option for patients with poor pulmonary function who may not tolerate anatomic lobectomy, because limited resections have demonstrated a higher local recurrence rate and worse long-term outcome than anatomic lobectomy.²⁵ However, recent evidence suggests that sublobar resection, especially anatomic segmentectomy, may in fact be the surgical procedure of choice, not only for patients with poor cardiopulmonary reserve but also for those with early stage NSCLC at low risk.²⁶ In general, anatomic segmentectomy is preferred over simple wedge resection to clear the lymphatics draining the tumor bed. Generous wedge resection with cancer-free margins may be acceptable for small, peripheral, “nonsolid” bronchioalveolar carcinoma.²⁷ Sampling or formal dissection of hilar and mediastinal lymph nodes with intraoperative frozen-section pathology should be performed to confirm any nodal disease. If proven positive for nodal disease intraoperatively, the surgical resection should be converted to anatomic lobectomy whenever possible.

Surgical Principles

Because the landmark of a diseased segment used to guide resection is its bronchus, identification of the bronchus of the diseased segment is a key step. The division of segmental structures tends to begin with the segmental arterial branch, because this often allows good exposure of the segmental bronchus, which runs along with the segmental artery. The segmental vein is best divided last, after identification of the intersegmental plane. Intersegmental veins, the venous drainage of adjacent segments, are usually preserved. The separation at the intersegmental lung parenchymal plane is performed with differential lung deflation and inflation. First, the segmental bronchus of the diseased segment is clamped in a deflated state. Then the lung is inflated, and the demarcation line can be identified because the diseased segment remains airless while other parts of the lung are expanded. Alternatively, the lung is expanded first, followed by clamping the bronchus of the diseased segment; then the lung is deflated to demarcate the diseased segment that remains expanded. Manual monofilament absorbable interrupted suturing (4-0 polydioxanone [PDS] or Maxon) is usually used for the bronchial closure. Stapling may be performed if sufficient length of the diseased segmental bronchus is available. In this case, care must be taken to

avoid compromising adjacent segmental bronchi. Blunt or sharp dissection of the intersegmental plane is traditionally performed by scissors, a sponge on a stick, or the surgeon's fingers. Small bridging veins or bronchi are individually clipped or ligated for division. Stapling the intersegmental plane is also applicable and desirable, and this is achievable if the resection is extended into an adjacent segment to achieve an adequate margin from the tumor. Any air leaks from the dissecting plane are controlled by nonabsorbable suturing. Various types of segmentectomy are shown in Figure 17-4.

The use of wedge resection as a surgical procedure for primary lung cancer should be strictly limited to small, peripheral, early-stage NSCLC. Although wedge resection is often accomplished by VATS, it is often difficult to assess the interlobar lymph nodes. Whenever there is any doubt about the resection margins, the procedure should be converted to anatomic segmentectomy.

Mediastinal Lymph Node Dissection

Rationale

Recent advances in mediastinal staging with computed tomography (CT), positron emission tomography (PET), and endobronchial ultrasound-guided fine-needle

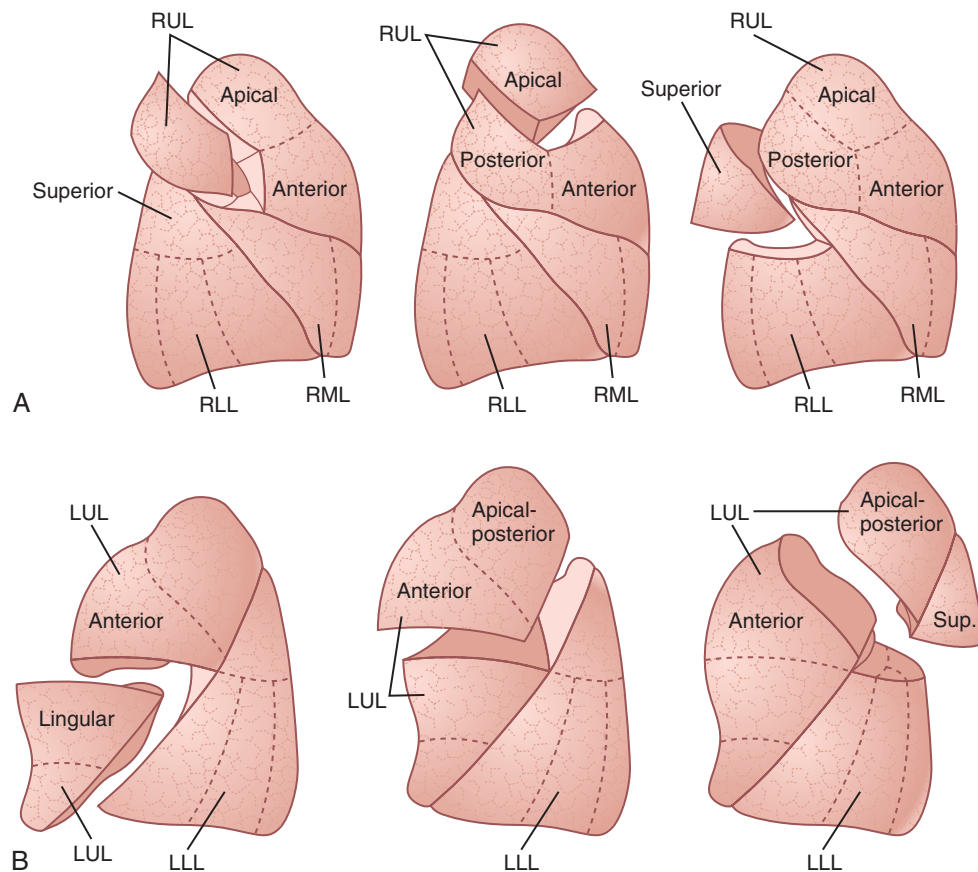


FIGURE 17-4 ■ Segmental resections of the lung. **A**, Right lung. Upper lobe: posterior and apical segmentectomies. Lower lobe: superior segmentectomy. **B**, Left lung. Upper lobe: lingular and superior division segmentectomies. Combined segmentectomies of apical-posterior (upper lobe) and superior (Sup.) segments (lower lobe). LLL, Left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe. (From Jensik RJ, Faber LP, Milloy FJ, et al: Segmental resection for lung cancer. A fifteen-year experience. *J Thorac Cardiovasc Surg* 66:563–572, 1973.)

aspiration (EBUS-FNA) have improved diagnostic accuracy.^{28,29} However, there is no doubt that intraoperative mediastinal lymph node staging remains the gold standard, and it is an integral part of the surgical treatment of lung cancer to determine accurate nodal (N) status, which is a significant outcome predictor.³⁰ Generally, *lymph node sampling* indicates the removal of macroscopically abnormal lymph nodes. When biopsies are performed from all lymph node stations, it is said to be *systematic sampling*. If systematic removal of all the mediastinal tissue containing lymph nodes within anatomic landmarks is performed, it is referred to as *complete lymph node dissection*. Bilateral mediastinal and cervical lymph node clearance is referred to as *extended lymph node dissection*.³¹ It has been a subject of controversy as to whether complete lymph node dissection is superior to systematic sampling in diagnostic accuracy and long-term survival. These issues are discussed later. The classification and graphic representation of lymph node levels for lung cancer staging by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC)³² are shown in Figure 17-5.

Techniques

Mediastinal lymph node dissection (MLND) is almost always accompanied by lung resection for lung cancer, so the procedure is most frequently performed via a posterolateral thoracotomy. It can also be achieved via median sternotomy, anterior thoracotomy, or, more recently, VATS incisions. Although the surgical procedure and extent of MLND may vary from surgeon to surgeon, dissection of stations 2R, 4R, 7, 8, 9, and 10R for the right side and stations 5, 6, 7, 8, 9, and 10L on the left side is generally accepted. On the right side, the superior mediastinum bordered by the superior vena cava anteriorly, the trachea posteriorly, the innominate artery superiorly, and the azygos vein inferiorly, is dissected for lymphadenectomy. After incision of the mediastinal pleura, the mediastinal fat pad is dissected from the posterior aspect of the superior vena cava and the anterolateral surface of the trachea. One or two small draining veins are frequently seen from the mediastinal fat pad into the superior vena cava, and they are ligated or simply clipped. Right station 2 (2R) nodes are located between the cephalic border of the aortic arch and the cephalic border of the right innominate artery. Right station 4 (4R) nodes are found between the cephalic border of the aortic arch and the origin of the right upper lobe bronchus. Lymph nodes at station 3 posterior (3p) are dissected between the esophagus and the membranous portion of the trachea, and at station 3 anterior (3a) are taken anterior to the superior vena cava (anterior to the right phrenic nerve) where necessary. Right station 10 (10R) nodes are dissected along the anterior border of the right bronchus distal to the pleural reflection.

To expose the subcarinal lymph nodes (7), the lung is retracted anteriorly. After incision of the mediastinal pleura along with the anterior border of the esophagus, the subcarinal fat pad is dissected from the medial border of the right main bronchus laterally, the anterior aspect

of the esophagus posteriorly, and the pericardium anteriorly. The attachments between the main bronchus and the fatty tissues containing subcarinal nodes are freed. The bronchial arterial branches running into the fat tissues are clipped before division to avoid unnecessary bleeding. The inferior pulmonary ligament nodes (9) are easy to dissect, and the paraesophageal nodes (8) are taken if they are present. On the left side, aortopulmonary (5 and 6) and subcarinal (7) nodes are dissected. For the upper mediastinal node dissection, the mediastinal pleura is incised just above the left main pulmonary artery, all the way up to the cephalic border of the aortic arch, midway between the phrenic nerve and the vagus nerve. Para-aortic (6) nodes are dissected from the phrenic nerve posteriorly and the ligamentum arteriosum anteriorly, and subaortic (5) nodes are removed posterior to the ligamentum arteriosum. During dissection, small arteries or veins should be controlled by ligation or clipping to avoid any thermal injury of the phrenic, vagus, and recurrent laryngeal nerves by electrocautery. Subcarinal (7) nodes can be removed in the same way as on the right side.

SURGICAL TREATMENT OF NON-SMALL CELL LUNG CANCER

Surgical resection is generally considered in patients with stage I or II NSCLC. Those with locally advanced stage IIIA or IIIB NSCLC are usually treated with chemotherapy and radiotherapy. However, stages IIIA and IIIB represent heterogeneous groups of patients, and select patients will benefit from surgical resection.

The decision regarding surgical intervention is based on several variables, including the extent of disease (both T and N factors), age, cardiopulmonary reserve, performance status, and comorbid risk factors. Induction or adjuvant (postsurgical) chemotherapy with or without radiotherapy is offered to surgical candidates with locally advanced NSCLC. Recently, adjuvant or neoadjuvant chemotherapy has been also offered to patients with early-stage resectable NSCLC in clinical trial settings, and the combined approach appears to prolong survival.

The UICC and the AJCC published the seventh edition of the TNM classification for lung cancer in 2009.³³

The recently revised TNM descriptors are shown in Table 17-1. Specific surgical issues related to each stage (T, N, and M) are discussed here.

T Category: T1 and T2

T1 and T2 tumors are subcategorized in the seventh edition of the TNM staging according to the proposals by the IASLC Lung Cancer Staging Project.³⁴ The changes in the T classification in the T1 and T2 categories are as follows: (1) T1 is subcategorized into T1a, if the tumor is 2 cm or less, and T1b, if the tumor is greater than 2 cm but not greater than 3 cm; (2) T2 tumors are greater than 3 cm, and they are T2a if equal to or less than 5 cm, and T2b if greater than 5 cm and equal to or

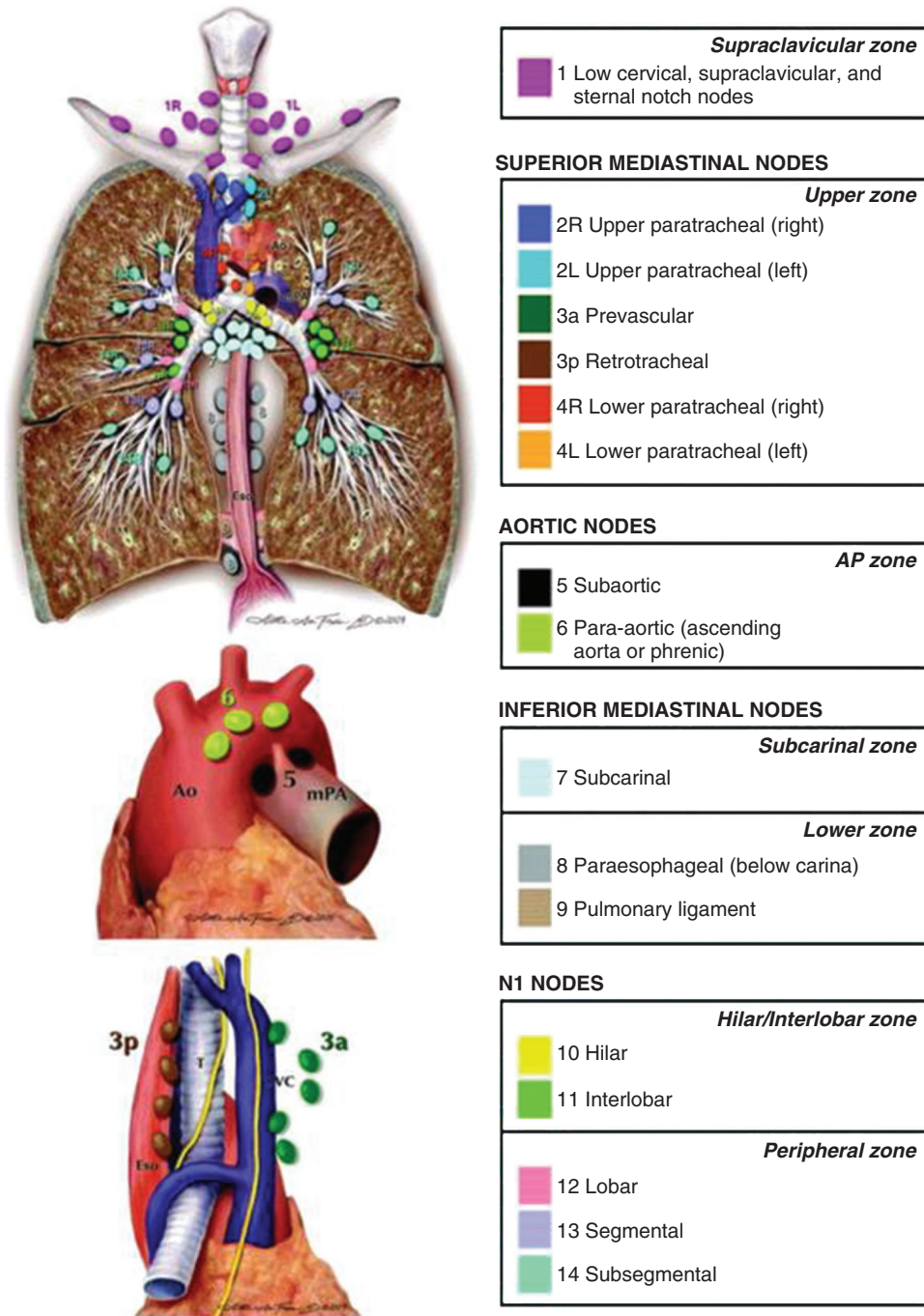


FIGURE 17-5 ■ The International Association for the Study of Lung Cancer (IASLC) lymph node map. (From Rusch VW, Asamura H, Watanabe H, et al: The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 4:568–577, 2009.)

less than 7 cm. Tumors greater than 7 cm are in the T3 category (see Table 17-1).

For the T1 and T2 categories, the surgical procedure of choice is essentially the same if patients are medically fit and have good cardiopulmonary reserve; anatomic lobectomy is the preferred mode of resection.³⁵ However, recent refinements of prognostication suggest that sublobar resection (segmentectomy or wide wedge resection)

may be performed on patients with small, peripheral, early-stage NSCLC, or those older than 71 years without jeopardizing the clinical outcome.³⁶ Additional multicenter trials comparing lobectomy with lesser resections are under way.^{37,38} On another front, a growing body of evidence suggests that surgical resection alone is not adequate for the treatment of large-sized NSCLC without any nodal disease.²

TABLE 17-1 Definitions for T, N, and M Descriptors by the International Association for the Study of Lung Cancer (IASLC)**T (Primary Tumor)**

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor $\leq$ 3 cm in greatest dimension, surrounded by lung or pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a	Tumor $\leq$ 2 cm in greatest dimension
T1b	Tumor $>$ 2 cm but $\leq$ 3 cm in greatest dimension
T2	Tumor $>$ 3 cm but $\leq$ 7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if $\leq$ 5 cm) Involves main bronchus, $\geq$ 2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor $>$ 3 cm but $\leq$ 5 cm in greatest dimension
T2b	Tumor $>$ 5 cm but $\leq$ 7 cm in greatest dimension
T3	Tumor $>$ 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus $<$ 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe

N (Regional Lymph Nodes)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M (Distant Metastasis)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion [†]
M1b	Distant metastasis

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1.

[†]Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

Adapted from Goldstraw P, Crowley J, Chansky K, et al: *The IASLC lung cancer staging project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours*. *J Thorac Oncol* 2:706–714, 2007.

Sublobar Resection versus Lobectomy for Node-Negative, Small-Size Non-Small Cell Lung Cancer

Jensik and coworkers¹⁷ reported their 15-year experience of segmental resections of peripheral lung cancer as a curative-intent procedure in 1973. The 5-year survival rate of 69 patients who underwent curative resections by segmentectomy was 56%. Of these, six (9%) developed local recurrence in the primary lobe. The authors concluded that segmentectomy can be a valid procedure for selected, peripherally located lung cancer. In the early 1980s, the Lung Cancer Study Group (LCSG) performed a multicenter randomized clinical trial of lobectomy versus a lesser resection by wedge or segmentectomy in T1N0 NSCLC in patients with small peripheral tumors, and the report suggested a threefold increase

in the incidence of local recurrence in patients treated by resections smaller than lobectomy.²⁵ Therefore, the authors recommended that the use of sublobar resection should be limited to poor-risk patients with compromised pulmonary function.

However, more recent evidence suggests that radical, curative-intent sublobar resection can be offered for clinical T1N0 NSCLC even in good-risk patients. The survival outcome and locoregional recurrence rates of anatomic segmentectomy in comparison with lobectomy are summarized in Table 17-2.^{25,39-42} Although most of the evidence is from retrospective studies comparing the outcome of segmentectomy with that of lobectomy, several key factors have been identified to obtain optimal results by anatomic segmentectomy. The factors include (1) surgical margins, (2) tumor size, and (3) lymph node assessment.

TABLE 17-2 Long-Term Outcome and Local Recurrence Rate of Sublobar Resection in Comparison to Lobectomy in Patients with Early-Stage Non–Small Cell Lung Cancer

Author (Year)	N (Sublobar/ Lobectomy)	Stage	<i>Sublobar Resection versus Lobectomy</i>	
			Local Recurrence (%)	5-Year Survival (%)
Ginsberg, Rubenstein ²⁵ (1995)	125/122	cT1N0	6.3 vs. 2.1*	83 vs. 89
Koike et al ³⁹ (2003)	74/159	cT1N0	2.7 vs. 1.3	89 vs. 90
Fernando et al ⁴⁰ (2005)	124/167	pT1N0	17.5 vs. 10.0 (tumor size < 2 cm)	56 vs. 85 months (MS)
			4.4 vs. 3.5 (tumor size, 2–3 cm)	45 vs. 70 months* (MS)
Okada et al ⁴¹ (2006)	305/262	cT1N0	4.9 vs. 6.9	90 vs. 90
Okumura et al ⁴² (2007)	55/187	pT1N0†	NS	83 vs. 81

*Statistically significant.

†Large cell carcinoma excluded.

c, Clinical; NS, not stated; MS, median survival; p, pathologic.

It is clear that positive surgical margins must be avoided to achieve complete resection; however, it remains unresolved as to what is the optimal adequate surgical margin (i.e., the distance from the tumor to the cut margin) for localized tumors in the setting of segmentectomy. Sawabata and colleagues⁴³ conducted a prospective study to define optimal surgical margins in excision of NSCLC. In the study, the surgical margins were microscopically 100% negative for malignancy when the margin distance was greater than 20 mm or when the resected tumors had a margin distance greater than the maximum tumor diameter (a margin-to-tumor size ratio > 1). Schuchert and coworkers⁴⁴ reported that the local recurrence rate was significantly higher in patients with a margin-to-tumor ratio less than 1 than in those with the ratio greater than 1 (25% versus 6.2%). In the study, the mean surgical margin in patients with local recurrence was 12.8 mm and the margin in those without local recurrence was 18.6 mm. Therefore, lobectomy or extended segmentectomy should be performed when an adequate surgical margin (preferably 2 cm) cannot be obtained, especially if tumors are located centrally. Intraoperative pathologic assessment of surgical margins should generally be performed to confirm the margins.

Tumor size is also an important factor when segmental resection is considered. A large tumor size is associated with increased risk of local recurrence and distant metastasis. Fernando and colleagues reported that there was no difference in survival between sublobar resection and lobar resection groups when the tumor size was smaller than 2 cm in pathologic T1N0 NSCLC, whereas the median survival was significantly better in the lobar resection group when tumor size was greater than 2 cm (68.7 versus 50.6 months).⁴⁰ Okada and colleagues⁴⁵ reported the 5-year cancer-specific survivals of patients with pathologic stage I disease with tumors of 2 cm or less and 2.1 to 3 cm in diameter were similar: 92.4% and 87.4% after lobectomy, and 96.7% and 84.6% after segmentectomy, respectively. On the other hand, in patients with a tumor greater than 3 cm in diameter, survivals were significantly worse in the segmentectomy group than in the lobectomy group (62.9% versus 81.3%). Bando and colleagues⁴⁶ reported a higher locoregional recurrence rate of segmentectomy in patients with tumors 2.1 to 3 cm than in those with tumors 2 cm or smaller. In the report by Schuchert and associates,⁴⁴ recurrence was observed more frequently

in stage IB patients than in stage IA patients. Jones and coworkers⁴⁷ reported no locoregional recurrence in 43 patients with pathologic T1N0 NSCLC who underwent segmentectomy. El-Sherif and colleagues⁴⁸ recently reviewed their experience of sublobar resection versus lobectomy and demonstrated that the disease-free survival rate of sublobar resection was equivalent to that of lobectomy in patients with stage IA NSCLC, but in those with stage IB NSCLC, survival was worse in the sublobar resection group. Several recent series have also reported comparable long-term outcomes of segmentectomy and lobectomy in small (tumor size, <2 cm) T1N0 NSCLC.^{39,41,49} Based on the current evidence, patients with early-stage small NSCLC (tumor size, preferably ≤2 cm) may undergo anatomic segmentectomy if negative nodal disease is confirmed.

Intraoperative lymph node assessment is an integral part of sublobar resection. Miller and colleagues⁵⁰ evaluated the frequency of lymph node metastasis in patients who underwent resection of NSCLC 1 cm or less. The tumors were located in the periphery in 89 patients, centrally in 3, and endobronchially in 8. Of these, seven (7%) had lymph node metastasis (N1 = 5 and N2 = 2). In the prospective nonrandomized trial of sublobar resection reported by Okada and colleagues,⁴¹ of 305 patients with clinical T1 (tumor size, <2 cm) N0 NSCLC who were assigned to undergo sublobar resection, 20 (7%) were found to have lymph node metastasis (N1 = 11 and N2 = 9) intraoperatively, so the procedure was converted to lobectomy. Therefore, even for tumors smaller than 1 cm, intraoperative hilar and mediastinal lymph node sampling or dissection is recommended whenever sublobar resection is performed.

Wedge resection has appeared to be suboptimal for the surgical treatment of lung cancer except for localized, small-size pure bronchioloalveolar carcinoma because of a higher local recurrence rate. Landreneau and associates⁵¹ documented high local recurrence rates in patients with T1N0 NSCLC who underwent wedge resection (wedge versus lobectomy: 24% versus 9%). Sienel and coworkers⁵² analyzed local recurrence rates in patients with pathologic T1N0 NSCLC who underwent either segmentectomy or wedge resection. Segmentectomies were followed by systematic lymph node dissection, and wedge resections by lymph node sampling. The local recurrence rate was significantly higher in the wedge

resection group than in the segmentectomy group (55% versus 16%), and the difference of recurrence rates was significant even in patients with tumors 2 cm or less (40% versus 11%). The observed higher locoregional recurrence rates may be partly explained by an inadequate lymph node assessment, because sampling of interlobar lymph nodes or segmental hilar nodes is often impractical or impossible, resulting in the missing of positive nodes and false downstaging. Wedge resection may also leave draining lymphatic vessels containing cancer cells behind in the residual diseased segment, thus increasing the risk of local recurrence. Therefore, anatomic segmentectomy, but not wedge resection, is recommended for patients with early-stage small NSCLC when sublobar resection is considered. If anatomic segmentectomy might not be tolerated because of poor cardiopulmonary reserve, wedge resection combined with radiotherapy or brachytherapy could be an alternative approach to reduce the risk of local recurrence.^{40,53}

Although much of the evidence for sublobar resection is from retrospective studies, two large-scale prospective randomized trials are currently under way to obtain solid evidence of sublobar resection for stage IA, peripheral NSCLC. Both the Cancer and Lymphoma Group B trial (CALBG 140503)³⁷ and the Japan Clinical Oncology Group and the West Japan Oncology Group trial (JCOG0802/WJOG4607L)³⁸ aimed to recruit more than 1000 cases. The difference between the studies is that the former study allows both segmentectomy and wedge resection for the experimental arm, but the latter Japanese study specifies only segmentectomy for the sublobar resection arm.

T Category: T3

The T3 category includes (1) tumors greater than 7 cm; (2) additional nodules in the primary lobe; (3) tumors of any size invading the chest wall, diaphragm, mediastinal pleura, or parietal pericardium; (4) tumors in the main-stem bronchus less than 2 cm from the carina without invading the carina; and (5) tumor-associated atelectasis or obstructive pneumonitis of the entire lung (see [Table 17-1](#)). Some of these subsets are discussed with respect to their specific surgical considerations later.

Tumors Invading the Chest Wall

Technical details and the outcome of this subset are reviewed in [Chapter 20](#). NSCLC invading the chest wall is usually peripheral in location, so mediastinal lymph nodes are less likely to be involved. The degree of chest wall involvement with tumor varies from the parietal pleura to the muscles and ribs of the chest wall. Those with NSCLC involving the chest wall, but without mediastinal node disease, are good candidates for surgical treatment whenever medically fit. Postoperative mortality has continued to be reduced, in recent reports ranging from 0% to 6.3%.⁵⁴⁻⁶⁰ In general, factors affecting long-term survival include (1) completeness of resection,^{54,56,60} (2) extent of invasion of the chest wall,^{55,56,60} and (3) nodal status.^{54,56,57,59,60} In patients with incomplete resection (macroscopic or microscopic disease) or unresectable

tumors, the 5-year survival was essentially zero.^{54,60} It is a matter of controversy as to whether en bloc (full-thickness chest wall) resection is necessary for all depths of tumors invading the chest wall, but some authors advocate a full-thickness resection to achieve complete tumor clearance.^{56,57,59} A large study of surgically resected T3 NSCLC was recently published by Kawaguchi and coworkers from Japan.⁶¹ In the study, 407 patients having chest wall invasion had 5-year survival of 43.2%. The roles of chemotherapy and radiotherapy for this group of patients are still uncertain and clearly require further investigation.⁵⁹

Superior Sulcus Tumors

Superior sulcus tumors (Pancoast tumors) are a unique subset of carcinomas of the lung, invading the thoracic inlet. Because of the close proximity to thoracic inlet structures, the tumors often invade adjacent tissues early, with symptomatic consequences. In case of tumor invasion to the posterior compartment of the thoracic inlet, involvement of the lower brachial plexus, particularly the T1 nerve root, is common. Shoulder and arm pain radiating to the inner aspect of the upper arm (T1) or the ulnar distribution in the fourth and fifth fingers of the hand (C8), or both, are commonly seen in these cases. Extension to the stellate ganglion with consequent Horner syndrome, or extension to the ribs or vertebrae, is also observed. Tumors invading the anterior compartment of the thoracic inlet may involve the subclavian vessels.

Advances in surgical techniques and combined-modality approaches recently led to the conduct of two prospective multicenter phase II clinical trials, where induction chemoradiotherapy was performed followed by surgical resection in patients with superior sulcus NSCLC.^{62,63} The North American Intergroup trial (Southwest Oncology Group 9416, INT 0160) report by Rusch and colleagues⁶² suggested that both T3N0-1 and T4N0-1 tumors benefit from preoperative chemoradiation with high response rates by pathologic examination (61% with complete pathologic response or minimal microscopic tumor) and high complete resection rates (76% overall, and 94% of patients who underwent thoracotomy). The median survival was 33 months for all patients, and 94 months for the patients who achieved an R0 resection. Kunitoh and coworkers⁶³ reported mature results of induction chemoradiotherapy followed by surgical resection in patients with T3 ($n = 56$) or T4 ($n = 20$) NSCLC (Japan Clinical Oncology Group Trial, JCOG 9806). Of these, 57 patients (76%) underwent surgical resection and, again, a high R0 resection rate (68% overall, and 90% of patients who received surgical resection) was achieved. The overall 5-year survival rate was 56%. In both studies, the pattern of cancer recurrence was predominantly distant, and the brain is the leading organ of relapse. In the INT 0160 trial, 19 of 57 patients (41%) who developed recurrence had brain metastasis only, and 5 of 39 patients (13%) did so in the JCOG 9806 trial. On the other hand, the MD Anderson Cancer Center reported a prospective phase II study of upfront surgery followed by chemotherapy (cisplatin and etoposide) and radiotherapy (50-60 Gy) for superior

sulcus tumors.⁶⁴ The study demonstrated overall survival rates of 50% at 5 years and 45% at 10 years after the treatment. Interestingly, as a part of the study protocol, 11 of 32 underwent prophylactic cranial irradiation (PCI, 25 Gy in 2.5-Gy fractions). Although the PCI regimen was terminated during the study period because of the lack of definitive evidence of its efficacy, those who underwent PCI did not develop brain metastasis. Given that the main pattern of recurrence is distant, especially in the brain, further refinement of the multimodal treatment regimen is required to obtain better outcome.

Tumors in Proximity to the Carina

A tumor extending to within 2 cm of the carina is said to be a T3 tumor, and patients with this subset of tumors benefit from surgical resection in published series. Since the introduction of lung-sparing techniques by Price-Thomas¹² in 1947, sleeve lobectomy has been adopted by many thoracic surgeons,⁶⁵ and it is now the standard of procedure for NSCLC extending into the large airway whenever appropriate. The techniques can be applied to not only tumors in proximity to the carina but also those located at the origin of a lobar bronchus, those with positive margin after standard lobectomy, and those that are N1 disease and can be completely resected. Pneumonectomy or sleeve pneumonectomy should be strictly considered for lesions that cannot be completely removed by a lung-sparing procedure because of the higher postoperative morbidity and mortality. Deslauriers and colleagues²² reported a lower operative mortality in the sleeve lobectomy group compared with the pneumonectomy group (1.6% versus 5.3%). The authors reported the 5-year survival rates of 52% in the sleeve lobectomy group and 31% in the pneumonectomy group. The 5-year survival rates in the sleeve lobectomy group by nodal involvement were 63% in N0, 48% in N1, and 8% in N2. Although no series specifically reported on results of surgical resection of T3 tumors defined by proximity to the carina, negative mediastinal node disease and complete resection are keys for improved survival.^{22,66}

When a tumor involves not only the mainstem bronchus but also the proximal pulmonary artery, vascular sleeve resection is combined for complete resection. In the report by Yildizeli and coworkers⁶⁶ of 218 patients with sleeve lobectomy, 28 patients (13%) underwent vascular sleeve resection and most of them (20/28) were associated with left upper lobectomy. A meta-analysis reported by Ma and associates²³ suggested that sleeve lobectomy with or without vascular reconstruction can be performed without increasing mortality or morbidity compared with pneumonectomy, and it offers better survival than pneumonectomy.

Tumors Invading the Mediastinum or Diaphragm

The outcome in patients with mediastinal pleural involvement is generally poor because of frequent mediastinal node involvement. Riquet and colleagues⁶⁷ documented that 25 out of 68 patients (36%) with mediastinal pleural invasion who underwent surgical resection had N2

disease. The 5-year survival rate was reported as 31% in the study. Pitz and associates⁶⁸ documented a 5-year survival rate of 25% in patients with complete resection.

NSCLC invading the diaphragm is a rare condition and infrequently diagnosed preoperatively. Yokoi and coworkers⁶⁹ noted only one third of these patients (17 of 63 patients) had a diagnosis of diaphragmatic invasion before surgery, and Riquet and colleagues⁷⁰ reported only 3 out of 68 patients (4%) had the diagnosis preoperatively. Prognostic factors reported in this subset were nodal disease, completeness of resection, and the depth of diaphragmatic invasion. In the series of Yokoi and coworkers, 5-year survival rates by nodal disease were 28% (N0) versus 18% (N1/2), and those by the depth of diaphragmatic invasion were 33% (parietal pleura) versus 14% (diaphragmatic muscle or deeper). Rocco and colleagues⁷¹ reported the 5-year survival rate of 27% in patients with N0 disease and diaphragmatic invasion. The relatively poor prognosis of mediastinal or diaphragmatic involvement even in patients with N0 disease after complete resection can be explained by the extensive lymphatic and venous drainage,^{67,70} so adjuvant or neoadjuvant therapy should probably be offered for these subsets of patients.

Additional Nodules in the Primary Lobe

It is recognized that patients with pulmonary metastasis in a primary lobe have better survival than those with contralateral pulmonary metastasis or with other metastatic disease. In addition, it is often not possible to determine preoperatively whether a satellite nodule seen on a CT scan is a metastatic lesion or an inflammatory lesion, so satellite lesions in a primary lobe still warrant surgical resection. In recent surgical series, the 5-year survival rates in patients with pathologically proven pulmonary metastasis in a primary lobe have been reported to be from 45% to 57%.⁷²⁻⁷⁵ The node status is a significant prognostic factor in this subset of patients who underwent complete surgical resection, but whether the number of satellite lesions is a prognostic factor has yet to be clarified.

T Category: T4

The T4 category includes tumors directly invading important mediastinal structures such as the heart, esophagus, great vessels, trachea, vertebral body, or carina (see Table 17-1). Tumors with a malignant pleural effusion are reclassified into the M1 category, because the prognosis of this subset of patients is comparable with that of those with metastatic disease. The median survival of patients with malignant pleural dissemination is only 8 months, and the 5-year survival rate is 2%.³⁴ On the other hand, M1 based on additional nodules in the ipsilateral lung (different lobe) is reclassified as T4.

Generally, T4 tumors are deemed unresectable; however, curative surgical resection can be performed in highly selected patients with surgery alone or with a combined multimodality approach including chemotherapy, radiotherapy, or both. Patients with T4 tumors with mediastinal node disease (N2) are generally excluded

from being surgical candidates, because their prognosis is in general not improved. Therefore, every effort should be made to exclude N2 disease if surgical resection is considered. Furthermore, it is recommended by the American College of Chest Physicians' practice guideline that resection be undertaken only at an experienced, highly specialized center.⁷⁶

Heart and Great Vessels

Patients with T4 tumors by virtue of invasion to the heart are rarely candidates for surgical treatment. On occasion, central tumors extending around the inferior pulmonary vein and the left atrium may be amenable to complete surgical resection.⁷⁷ The tumor resection can be achieved by clamping the left atrium and then suturing the defect, or by removing tumors with the patient on cardiopulmonary bypass, if indicated (e.g., for cardiac chamber invasion with main pulmonary artery involvement).^{77,78} Tsuchiya and coworkers⁷⁹ reported a 5-year survival after left atrium resection of 22% in 44 patients with NSCLC. Riquet et al reported a surgical series of lung cancers invading to pericardium alone ($n = 32$), pericardium and pulmonary vein ($n = 34$), and pericardium and atrium ($n = 34$).⁸⁰ The mode of lung resection was predominantly pneumonectomy (>90%) in all three subsets. In the group with pericardium invasion, R0 resection was achieved in 81.3% of cases, but only 52.9% of cases in the group with pericardium and pulmonary vein invasion and 40% in the group with pericardium and atrium invasion. In the three subsets, the 5-year survival rates were 15.2%, 19.1%, and 7.2%, respectively.

Surgical resection of NSCLC involving great vessels, including the aorta, the main pulmonary artery, and the superior vena cava, can be performed either primarily or as a part of multimodality treatment. In patients with tumors invading the thoracic aorta or the subclavian artery, the surgical procedure varies from intra-adventitial dissection or direct lateral clamping and suturing with or without a patch, to replacement of a portion of artery with a prosthetic graft.^{81,82} These aggressive surgical resections are further justified when tumors extend into the arterial wall, because they carry a risk of sudden rupture or embolism. Several reports of superior vena cava resections for NSCLC have depicted survival rates according to the degree of primary tumor or nodal involvement. In general, a poor prognosis is seen in patients with mediastinal node disease (5-year survival, 52% in N0-1 versus 21% in N2),⁸³ those with superior vena cava invasion by metastatic lymph nodes (5-year survival, 36% in superior vena cava tumor invasion versus 6.6% in superior vena cava lymph nodal invasion),⁸⁴ or those with pneumonectomy (hazard ratio = 2.9 compared with lobectomy).⁸⁵ Induction treatment should be considered, because it may allow less pulmonary resection (i.e., lobectomy or sleeve lobectomy) by reducing tumor burden, and it may also decrease the distant failure rate.^{85,86}

Carina and Trachea

Carinal resection has been performed for patients with NSCLC invading the carina or extending to the lower

part of the trachea since the 1950s as a potentially curative treatment.⁸⁷ As a result of improvements in surgical techniques, perioperative management, and patient selection, the surgery-related hospital mortality continues to decrease. In the past decade, acceptable mortality rates in patients who underwent carinal pneumonectomy have been reported from several experienced institutions, ranging from 4% to 15%.⁸⁸⁻⁹³

As a part of mediastinal staging, some prefer to perform mediastinoscopy at the time of planned thoracotomy to avoid the development of scar tissue along the trachea, to help in reducing anastomotic tension by allowing good tracheal mobilization.^{88,90} Others perform mediastinoscopy preoperatively for possible induction chemoradiotherapy if pathologic N2 disease is confirmed.^{89,91} Recent advancement of EBUS-FNA may take the role of mediastinoscopy in the setting.⁹² A rigid bronchoscopy can be used to better assess the involved tracheobronchial tree, to determine resectability, and to plan airway reconstruction.

Various tracheobronchial anastomoses after carinal resection have been described by Mitchell and associates,⁹⁴ who reviewed the surgical experience at Massachusetts General Hospital. The techniques are described in [Chapter 8](#). A right carinal pneumonectomy is generally performed via right posterolateral thoracotomy, or occasionally bilateral thoracotomy, or sometimes median sternotomy is performed for bilateral reconstruction of the tracheobronchial tree. The approach for a left carinal pneumonectomy varies: median sternotomy, clamshell incision, left thoracotomy, or bilateral thoracotomy is used.

Mediastinal lymph node involvement is a strong prognostic factor.^{88-93,95} Whether adjuvant or neoadjuvant, or chemotherapy or chemoradiotherapy, should be used for those with N2 disease in this subset is still under debate. Recent series of carinal resection are summarized in [Table 17-3](#).

Ipsilateral Pulmonary Metastasis in Nonprimary Lobes

A recent report of a surgical series by Nagai and colleagues⁹⁶ demonstrated 5-year survival rates of patients with nonprimary lobe lung metastases of 42.1% (p-N0, $n = 38$), 7.9% (p-N1, $n = 19$), and 10.0% (p-N2, $n = 52$). In the study, approximately 60% of these patients received R0 (complete) resection, and 11% of cases received pneumonectomy. Significant survival differences were detected between node-negative (N0) and node-positive (N1 or N2) groups. Because the stage of the mediastinal node disease is a key prognostic factor, careful preoperative mediastinal investigation is necessary if surgical resection is to be considered in this subset of patients.

Vertebral Body

Patients with vertebral body involvement historically have been deemed unresectable; however, advances in surgical techniques, postoperative care, and induction chemoradiotherapy allow aggressive complete resection with an acceptable mortality for patients with vertebral

TABLE 17-3 Recent Series of Carinal Resection in Non–Small Cell Lung Cancer

Author (Year)	N (Number of N2/3)	Mortality (%)	Overall	5-Year Survival (%)	
				N0/1	N2/3
Mitchell et al ⁸⁸ (2001)	60 (11)	15	42	51 (N0), 32 (N1)	12
Regnard et al ⁸⁹ (2005)	65 (23)	7.7	26.5	38	5.3
de Perrot et al ⁹⁰ (2006)	100 (27)	7.6	44	53	15
Macchiarini et al ⁹¹ (2006)	50 (18)	4	51	NS*	NS
Roviaro et al ⁹³ (2006)	53 (NS)	7.5	33	NS	NS
Jiang et al ⁹⁵ (2009)	41 (14)	2.4	26.8	37.0	7.1

*Nodal status was a significant prognostic factor in multivariate analysis.

body invasion.^{97,98} Several groups have reported outcomes of vertebral body resection (either total or hemi) in patients with NSCLC invading the spine. Grunenwald and associates⁹⁷ reported a 53% 2-year survival rate in 19 patients treated with vertebral body resection. Gandhi and coworkers⁹⁹ primarily performed surgery followed by radiotherapy in this subset and achieved a 2-year survival rate of 54%. Fadel and colleagues¹⁰⁰ documented a 3-year survival rate of 39%. Anraku and colleagues¹⁰¹ reported a 3-year survival rate of 58% in patients ($n = 23$) with T4 (vertebral body) N0 disease who underwent surgery including multiple total vertebrectomy (Fig. 17-6A). In the study, all patients received preoperative chemotherapy or chemoradiotherapy, and 45% of them achieved complete response to the neoadjuvant therapy by pathologic examination. R0 resection rate was high: 19 out of 23 patients (83%) achieved complete resection. The outcome in patients who demonstrated pathologic complete response or near-complete response (viable cells <1% in the resected specimen) was excellent, whereas the outcome in those who did not was poor (3-year survival, 93% versus 20%; see Fig. 17-6B). Because the high rates of both R0 resection and pathologic complete response were associated with better survival, a multimodality treatment approach with induction chemoradiotherapy should be strongly considered in carefully selected patients. Recent series of vertebral body resection are summarized in Table 17-4.

Esophagus

NSCLC invading the esophagus is rarely amenable to complete resection and the outcomes have been disappointing, so the presence of frank invasion to the esophagus is considered unresectable. Pitz and associates¹⁰² reported that only 3 out of 12 patients (25%) achieved complete resection in this subset of patients. The 5-year survival rate of resected NSCLC invading to the esophagus reported by Bernard et al was only 12%.¹⁰³

N Category: N0 and N1

Decision making in the treatment of patients with stage I/II (N0 or N1) NSCLC is relatively straightforward. Surgical resection (in most cases, lobectomy) is the mainstay of therapy if patients have good cardiopulmonary reserve. However, there is a growing body of evidence on types of surgical resection and combined neoadjuvant and

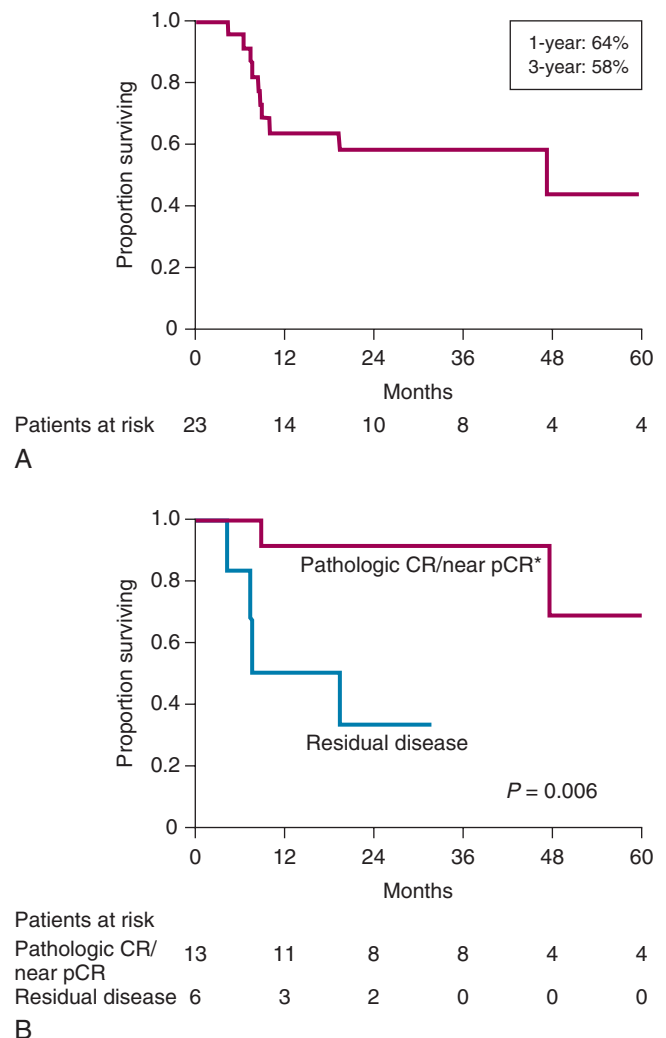


FIGURE 17-6 ■ Survival after induction chemoradiotherapy followed by radical vertebrectomy for patients with non-small cell lung cancer invading the spine. **A**, Overall survival ($n = 23$). **B**, Survival according to the pathologic complete response (pCR) in the resected specimen in patients with R0 resection (pCR, $n = 10$; near pCR*, $n = 3$; pathologic residual disease, $n = 6$). *Viable tumor cells less than 1% in a resected tumor. (From Anraku M, Waddell TK, de Perrot M, et al: Induction chemoradiotherapy facilitates radical resection of T4 non-small cell lung cancer invading the spine. *J Thorac Cardiovasc Surg* 137:441–447, 2009.)

TABLE 17-4 Recent Surgical Series of Vertebrectomy in Non–Small Cell Lung Cancer

Author (Year)	All Patients (N)	Vertebrectomy (n of Patients)			Treatment Protocol (n)	R0 Resection (%)	Survival (%)
		Total	Hemi*	Multilevel† (%)			
Gandhi et al ⁹⁹ (1999)	17	7	10	3 (18)	S alone (1), R → S (1) S → R (6), C+R → S (3) S → C+R (6)	65	54 (2-year)
Grunenwald et al ⁹⁷ (2002)	19	4	15	3 (16)	S(8), R → S (2) C → S (5), C+R → S (4)	79	53 (2-year)
Fadel et al ¹⁰⁰ (2002)	17 [‡]	1	16	1 (6)	S → R (9), C → S → R (7) C+R → S → R (1)	77	39 (3-year)
Anraku et al ¹⁰¹ (2009)	23	6	17	4 (17)	C+R → S (22), C → S (1)	83	58 (3-year)

*Partial vertebrectomy and transverse process resection included.

†Number of cases with two or more total vertebrectomies.

‡All had direct tumor spread into the intervertebral foramina without spinal canal or vertebral body invasion.

C, Chemotherapy; NS, not stated; R, radiotherapy; S, surgery.

From Anraku M, Waddell TK, de Perrot M, et al: Induction chemoradiotherapy facilitates radical resection of T4 non-small cell lung cancer invading the spine. *J Thorac Cardiovasc Surg* 137:441–447, 2009.

adjuvant therapy in the management of stage I/II disease. Therefore, accurate hilar/interlobar nodal staging is required. Preoperative EBUS-guided aspiration cytology of the N1 nodes (hilar and interlobar) may be useful in differentiating N0 and N1 disease to consider induction treatment before surgical resection as described by Yasufuku et al.¹⁰⁴ In clinical (CT- and PET-based noninvasive staging) N0 patients, the authors were able to confirm N0 disease in 87 (53.4%), upstaged 1 (0.6%) to N1 disease, and 6 (3.7%) to N2 disease.

In patients with clinical N0-1 disease, the type of pulmonary resection is dependent on T category and intraoperative assessment of nodal disease. As described (see “Sublobar Resection versus Lobectomy,” earlier), lesser resection such as segmentectomy would be an option for small-size peripheral NSCLC (T1 disease) if no nodal disease is confirmed intraoperatively. Therefore, intraoperative interlobar or hilar nodal assessment (or both) is critical in decision making for sublobar resection. VATS has been widely accepted for resection in this category. On the other hand, for patients with N0 NSCLC with local tumor invasion (T3 disease), an extended en bloc resection such as pneumonectomy, sleeve resection, chest wall resection, or other procedures can be performed to obtain cancer-free margins. Mediastinal lymph node sampling is essential for accurate cancer staging. The controversy as to whether complete MLND is included is discussed later in this chapter.

Cisplatin-based adjuvant chemotherapy has been shown to improve survival in patients with N1 and even in pathologic N0 disease, with completely resected, T1b or higher NSCLC based on phase III randomized clinical trials.^{105–107} Various combinations of chemotherapeutic agents; new nonplatinum agents, including molecular targeted drugs; and techniques of tumor molecular profiling are under investigation in efforts to further improve outcomes in patients with NSCLC.

N Category: N2

The option of offering surgery to patients with N2 disease (ipsilateral mediastinal or subcarinal node involvement) has been long debated. N2 disease comprises heterogeneous groups of patients, from those with micrometastatic mediastinal node involvement found intraoperatively (on frozen section) or postoperatively (on final pathologic examination) to those with bulky mediastinal node involvement recognized by the pre-treatment staging workup. In a study by Andre and coworkers,¹⁰⁸ patients with N2 disease proven before surgery (either by CT or mediastinoscopy) had significantly worse survival than those who did not have a diagnosis of N2 disease before surgery (Fig. 17-7). Patients with N2 disease are subjected to a combined treatment strategy including chemotherapy, radiotherapy, and surgery, but it remains controversial as to which of these treatment modalities should be included or in what sequence (i.e., before or after surgery). Albain et al conducted a randomized phase III study of 396 patients with stage IIIa NSCLC.⁷ In the study, patients with no progression after chemoradiotherapy were randomly assigned to either surgery or definitive radiotherapy. There was no significant difference in overall 5-year survival following surgery versus definitive radiotherapy (27% versus 20%; $P = 0.24$). However, improved progression-free and overall 5-year survivals of patients with lobectomy in the surgery arm were observed when compared to those of the radiotherapy arm (22 and 36% versus 11% and 18%; Fig. 17-8).

In the context of decision making in the treatment of N2 disease, there are two distinct scenarios according to when the nodal disease is definitely confirmed: (1) N2 disease confirmed by the pretreatment staging workup, and (2) N2 disease found at thoracotomy or at postsurgical pathologic examination (unexpected N2 disease).

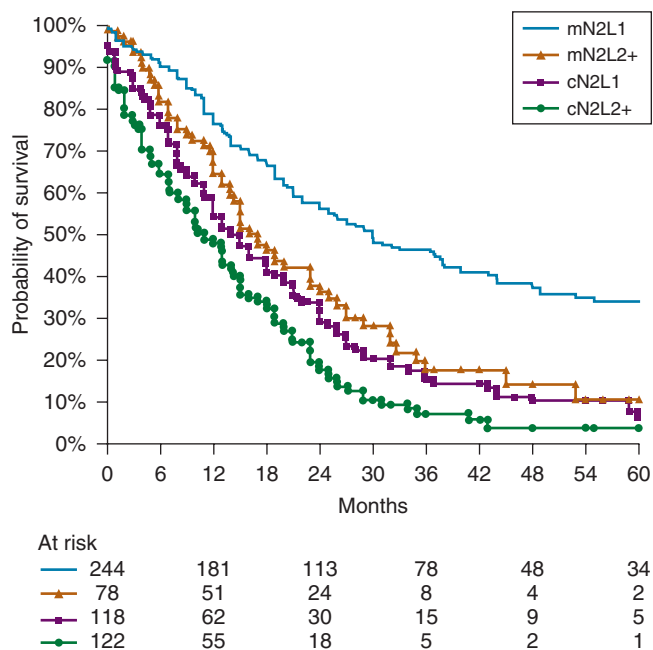


FIGURE 17-7 ■ Survival of patients with N2 disease treated with primary surgery according to N2 status and number of levels involved. *cN2*, N2 disease proven by CT (lymph node > 1 cm in short-axis diameter) or mediastinoscopy before surgical resection; *mN2*, N2 disease not proven before surgery (all lymph nodes < 1 cm in short-axis diameter by CT or negative mediastinoscopy); *L1*, a single lymph node level involved; *L2+*, multiple lymph node levels involved. (From Andre F, Grunewald D, Pignon JP, et al: Survival of patients with resected N2 non-small cell lung cancer. *J Clin Oncol* 18:2981–2989, 2000.)

N2 Found on Pretreatment Staging

Patients with multistation, bulky (involved lymph nodes > 2 cm in short-axis diameter measured by CT scan), histologically or cytologically proven N2 disease are generally treated with nonsurgical modalities (i.e., chemotherapy or chemoradiotherapy), because complete resection would not be expected. On the other hand, those with nonbulky, multistation or single-station N2 disease found at staging, but without any sign of distant metastasis, are still potential candidates for curative surgical resection.^{7,109} Theoretical advantages of neoadjuvant treatment include (1) downsizing of the primary and nodal disease that may facilitate complete clearance of the nodal disease, (2) decreased chance of surgical seeding of tumor cells, (3) in vivo chemosensitivity or radiosensitivity checking of the tumor, and (4) better patient compliance with the treatment.¹¹⁰ Uy and colleagues¹¹¹ reported an improved overall median survival of 40 months in patients with biopsy-proven N2 NSCLC treated with induction chemoradiation followed by surgery, and in this patient population, pathologic response to induction treatment was also prognostic. However, the decision to proceed with surgical resection requires careful assessment after induction treatment including restaging, performance status, and pulmonary function tests. Especially for poor-risk patients who respond to induction chemotherapy, definitive radiotherapy is an option for treatment, as a recent randomized clinical trial conducted by the

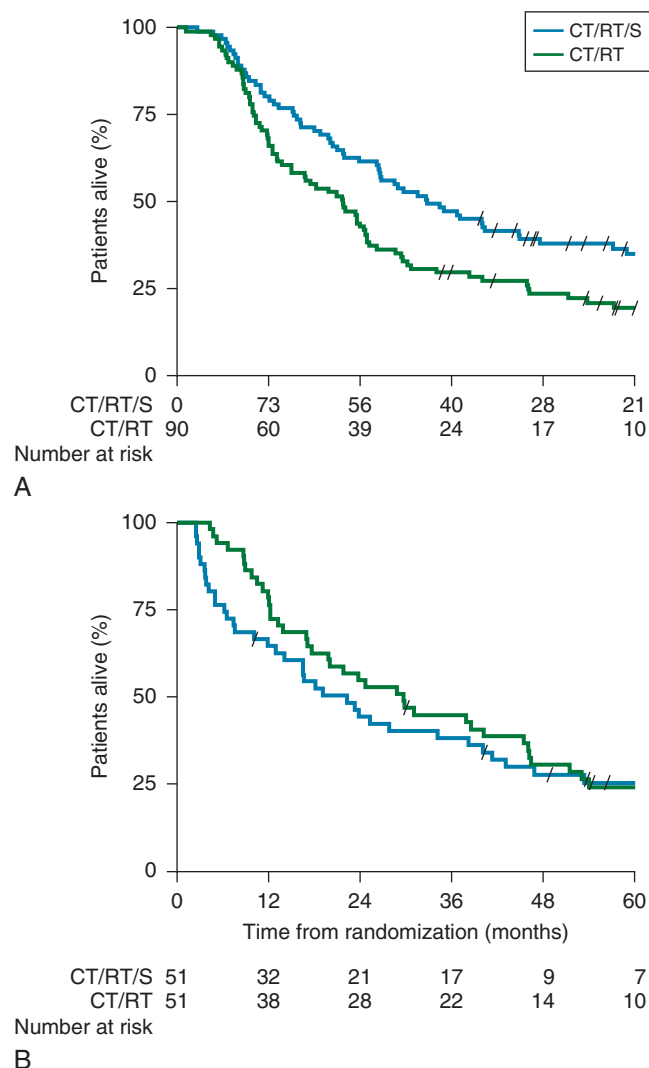


FIGURE 17-8 ■ Survival after induction chemoradiotherapy followed by surgical resection (lobectomy or pneumonectomy) versus chemotherapy plus definitive radiotherapy in patients with stage IIIA (T1-3 pN2) non-small cell lung cancer. **A**, Lobectomy versus a matched cohort of chemoradiotherapy. **B**, Pneumonectomy versus chemoradiotherapy. *CT/RT*, Chemotherapy plus radiotherapy; *CT/RT/S*, chemotherapy plus radiotherapy followed by surgery. (From Albain KS, Swann RS, Rusch VW, et al: Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 374:379–386, 2009.)

European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group demonstrated comparable outcomes in the radiotherapy arm and the surgery arm.¹¹²

Mediastinal restaging and assessment after neoadjuvant treatment is of great importance, because residual N2 disease after chemotherapy appears to be an unfavorable prognostic factor, and surgical resection for these patients remains controversial. Although clinical restaging with chest CT is suboptimal for predicting pathologic response of metastatic lymph nodes to induction chemotherapy, integrated PET and CT^{113,114} and endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA)^{92,104} have been used and may be promising in this

context. In a prospective study by Cerfolio and colleagues¹¹⁴ in patients with biopsy-proven N2 disease treated with induction chemoradiotherapy, PET plus CT was more accurate than CT alone for restaging. In their study, a greater than 50% decrease in the maximum standardized uptake value (SUV_{max}) in the metastatic lymph nodes was highly suggestive of pathologic clearance of cancer. Repeat mediastinoscopy after induction chemotherapy has been reported as useful with high sensitivity by Marra and colleagues.¹¹⁵ However, because it is an invasive procedure and known to be technically demanding, it is not regularly performed in clinical practice.

In a phase II study of induction chemotherapy followed by surgery in patients with mediastinoscopy-proven N2 disease, reported by Garrido and coworkers,¹⁰⁹ the 5-year survival was 17.6% in patients with residual pN1-3 disease (Fig. 17-9). In their study, patients downstaged to pN0 had significantly better survival (5-year survival, 51.6%) than those with pN1-3 disease. However, persistent minor mediastinal disease after induction chemotherapy may not always exclude surgical resection; in other words, some of those may be cured by surgical clearance of residual mediastinal disease. Doms and colleagues¹¹⁶ tried to select this subset of patients by means of serial ¹⁸F-fluoro-2-deoxyglucose (FDG)-PET scans taken before and after induction therapy. The authors demonstrated significantly better survival in patients with persistent minor mediastinal disease and a more than 60% decrease in the SUV_{max} than in patients with persistent minor disease but with a less than 60% decrease in SUV_{max} .

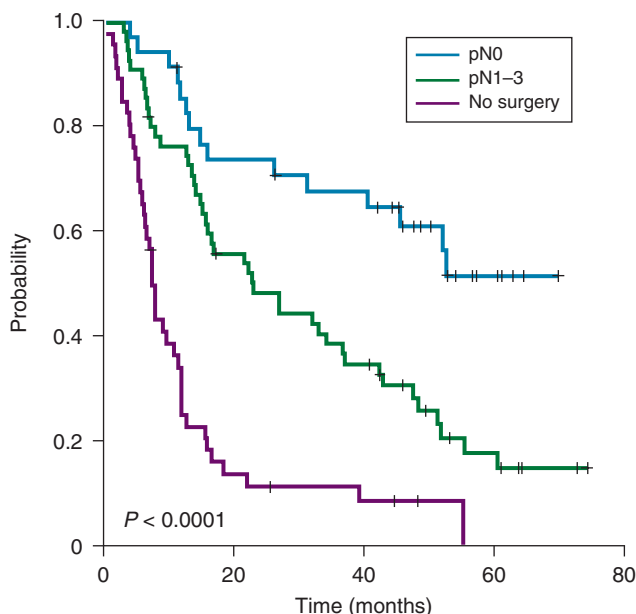


FIGURE 17-9 ■ Median survival according to pathologic downstaging in patients with mediastinoscopy-proof N2 with induction chemotherapy followed by surgery. (From Garrido P, González-Larriba JL, Insa A, et al: Long-term survival associated with complete resection after induction chemotherapy in stage IIIA [N2] and IIIB [T4N0-1] non small-cell lung cancer patients: the Spanish Lung Cancer Group Trial 9901. *J Clin Oncol* 25:4736-4742, 2007.)

N2 Found at Thoracotomy

The optimal management in patients with N2 disease found at thoracotomy (unsuspected N2 disease) is controversial. Treatment options include aborting lung resection followed by induction therapy and possibly followed by surgical resection, or proceeding with lung resection followed by adjuvant therapy. The rationale for the former decision is based on the favorable outcome of induction therapy followed by surgery obtained from published evidence including randomized clinical trials.¹¹⁷ In this era of VATS lung resection, however, it is reasonable to stop lung resection for induction therapy if N2 disease is discovered at the time of a VATS lobectomy, in which case the morbidity of the incision is small. On the other hand, with open thoracotomy, one may favor the latter option because the patient has already been exposed to the risks of general anesthetic and thoracotomy. In addition, patients who underwent thoracotomy (even without lung resection) may not be as compliant as those who undergo induction therapy before surgery. Cerfolio and colleagues¹¹⁸ reported a 5-year survival of 35% in patients who have completely resected unsuspected N2 disease after PET plus CT and thin-slice CT assessments (most likely reflecting minimal disease N2 status).

Controlling distant relapse is critical in patients with resected N2 NSCLC, because presence of N2 disease is known to be an indicator for high risk of metastatic relapse. Pisters and Le Chevalier¹¹⁹ summarized similar relapse rates in operable stage IIIA (N2) NSCLC (Table 17-5).

On this background, the use of adjuvant chemotherapy or radiotherapy has been extensively studied in resected N2 NSCLC, and adjuvant cisplatin-based chemotherapy appears to be beneficial, as proven by two recent randomized clinical trials. The Adjuvant Navelbine International Trialist Association (ANITA) trial demonstrated a reduced risk for death (hazard ratio, 0.69), with prolonged survival in patients who received adjuvant chemotherapy with or without radiotherapy compared with those without adjuvant therapy after complete surgical resection (Table 17-6).¹⁰⁶ A hazard ratio of 0.79 was reported in the International Adjuvant Lung

TABLE 17-5 Expected Outcome after Surgical Resection in Operable Non-Small Cell Lung Cancer

Surgical Stage			Relapse (%)	
			Local	Distant
IA	T1N0	67	10	15
IB	T2N0	57	10	30
IIA	T1N1	55	—	—
IIB	T2N1	39	12	40
	T3N0	38		
IIIA	T3N1	25	15	60
	T1-3N2	23		

Adapted from Pisters KM, Le Chevalier T: Adjuvant chemotherapy in completely resected non-small-cell lung cancer. *J Clin Oncol* 23:3270-3278, 2005.

TABLE 17-6 Overall Survival Estimates for Resected Patients* with N2 Non–Small Cell Lung Cancer with or without Cisplatin-Based Adjuvant Chemotherapy

Survival Interval	Survival (%)			
	Chemotherapy		Control	
	Radiotherapy	No Radiotherapy	Radiotherapy	No Radiotherapy
1-year	98	71	74	57
2-year	77	49	48	35
5-year	47	34	21	17

*N = 224.

Adapted from Douillard JY, Rosell R, De Lena M, et al: Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 7:719–727, 2006.

Cancer Trial (IALT), in favor of adjuvant chemotherapy compared with observation alone.¹⁰⁷

A past meta-analysis showed that postoperative mediastinal radiotherapy for patients with resected NSCLC has not been proven to be effective.¹²⁰ However, a more recent meta-analysis using the Surveillance, Epidemiology, and End Results (SEER) database of postoperative radiotherapy demonstrated prolonged survival in patients with stage IIIA (N2) disease.¹²¹ Results from the ANITA trial (nonrandomized subanalysis) also showed a benefit with postoperative radiation (see Table 17-6).

N Category: N3

Contralateral mediastinal lymph node metastases are considered a contraindication for surgery because long-term outcome with surgery has been dismal. The Southwest Oncology Group¹²² reported a 0% 3-year survival rate of patients with N3 NSCLC who underwent induction chemotherapy and radiotherapy followed by surgery. Because N3 lymph nodes are outside the surgical field and considered to be extensive lymphatic spread of cancer, complete surgical resection cannot be achieved. Therefore, we believe that patients with N3 disease should be treated nonsurgically.

M Category: M1a

M1a includes separate tumor nodules in a contralateral lobe, tumor with pleural nodules, and tumor with malignant pleural effusion.

Additional Nodules in the Contralateral Lung

Additional nodules in the *contralateral lung* are designated as M1a (previously M1), whereas those in the *primary lobe* are designated as T3, and those in the *ipsilateral lung (different lobe)* as T4, according to the seventh edition of the *TNM Classification for Lung Cancer*.³³ Based on the IASLC data, the median survival of patients with M1a disease was 10 months, with a 5-year survival rate of 3%,¹²³ which was significantly worse than that of same-lobe nodules or ipsilateral lung nodules (5-year survival, 28% and 21%, respectively). The median survivals of this subset of patients in the IASLC database and the SEER database

were 6 and 7 months, respectively. Therefore, additional nodules in the contralateral lung generally preclude surgery, although surgery may be offered for the primary NSCLC if the contralateral pulmonary lesions are questionable and mediastinal staging is negative. FDG-PET has appeared to be sensitive for detecting malignant metastatic disease,¹²⁴ but pathologic confirmation should be made by a percutaneous transthoracic needle biopsy or an excisional biopsy of those identified by PET, especially in the case of a solitary lesion.¹²⁵

When tumors represent double primaries (synchronous primaries) without mediastinal disease, the optimal treatment is two-staged lobectomy for contralateral tumors if the patient's lung function permits. When the cardiopulmonary reserve is limited, a lobectomy could be performed for the more advanced tumor and a limited resection (segmentectomy or wedge resection) for the contralateral tumor. Limited resection is in general reserved for smaller tumors or squamous carcinomas, because they are less likely to spread via the local lymphatic system, although this concept needs further study. Alternatively, bilateral segmentectomies can be considered for patients with very limited pulmonary function. A recent pooled analysis (N = 467) of completely resected synchronous NSCLC in multiple lobes revealed that advanced age, male gender, nodal involvement, and unilateral tumor location are poor prognostic factors.^{125a} In those who completed all their resections within a 6-month period (N = 412), median survival was 50.7 months.

A subtype of adenocarcinoma of the lung, adenocarcinoma in situ (AIS), is characterized as being multicentric and is frequently identified in its early stage with the advent of high-resolution CT. AIS can also exist with other types of NSCLC. The management of multifocal AIS or AIS with other non-small cell types is discussed later (see "Multifocal Adenocarcinoma In Situ").

Malignant Pleural Effusion

A histologically documented malignant pleural effusion is a contraindication for surgery because it is not amenable to complete resection. However, Ichinose and coworkers¹²⁶ reported a 5-year survival rate of 23% in surgical patients with a minimal amount of malignant pleural effusions (average, 37 mL) found at thoracotomy.

Long-term survivals (>5 years) have also been reported by Yokoi and colleagues¹²⁷ in highly selected patients with carcinomatous pleuritis without N2 disease who underwent extrapleural pneumonectomy.

M Category: M1b

Category M1b includes all distant metastasis outside the lung. The vast majority of lung cancer patients with distant metastasis are not curable by surgical treatment, and surgery is therefore precluded. However, there is some evidence for a potential role for surgical resection in patients with NSCLC who have an isolated distant metastasis in the adrenal gland or brain.

Adrenal Gland

A solitary adrenal metastasis in patients with otherwise operable NSCLC is a rare condition (incidence, 1.6%), because adrenal metastases are usually accompanied by other metastatic disease.¹²⁸ Based on reported series of adrenalectomy for isolated adrenal metastases in NSCLC, complete surgical resection of both the primary tumor and adrenal metastasis may improve survival in selected cases. Mercier and associates¹²⁹ reported a 5-year survival rate of 23% in 23 patients with NSCLC who underwent complete resection of an adrenal metastasis after surgical treatment of lung cancer. In the study, 6 patients presented with an adrenal metastasis found on the preoperative workup, and the remaining 17 patients were found to have an isolated adrenal metastasis during follow-up after lung resection. The complete adrenalectomy necessitated combined kidney ($n = 2$), inferior vena cava ($n = 1$), or liver ($n = 1$) resection. In the case series by Pfannschmidt and coworkers,¹³⁰ the median survival after adrenalectomy was 12.6 months ($n = 11$). Tanvetyanon and colleagues¹³¹ analyzed the pooled data from 114 cases in 10 publications describing outcomes of adrenalectomy in NSCLC. The authors concluded that the time between diagnosis of primary lung cancer and the discovery of adrenal metastasis (disease-free interval [DFI]) was prognostic. Patients with a DFI of 6 months or less demonstrated significantly shorter median survival than those with a DFI greater than 6 months (12 versus 31 months). An evidence-based clinical practice guideline published by the American College of Chest Physicians (ACCP) recommends curative resection of the primary N0-1 lung tumor and the isolated adrenal metastasis for those who are medically fit.¹³² The impact of adjuvant chemotherapy or radiation to the adrenal bed on long-term outcome remains undefined because of the scarcity of this population subset; however, the treatment strategy should be refined further because this subset may be detected more frequently as a result of improvements in diagnostics, including CT, magnetic resonance imaging, and PET.¹³³

Brain

NSCLC is known for its propensity to metastasize to the brain, and the form of dissemination is often multiple. It has been reported that 30% to 50% of patients with NSCLC are found to develop brain metastasis during the

course of their disease.¹³⁴ A solitary brain metastasis from lung cancer can be categorized into three subsets: (1) a synchronous primary lung cancer with a single brain metastasis, (2) a solitary brain metastasis found after successful treatment of the primary tumors, and (3) a single brain metastasis from an uncontrolled primary lung cancer. Here we will discuss only the first presentation of the brain metastases, because thoracic surgical oncologists may encounter such cases and be involved in the decision-making process. Thoracic surgeons should be aware, when they advise new surgical colleagues, that resection of a solitary brain metastasis in a patient with completely resected NSCLC carries a potential cure rate.

In a retrospective report from the Mayo Clinic by Billing and coworkers,¹³⁵ 28 out of 220 patients underwent surgical treatment of brain metastases from NSCLC. These patients were treated with surgical resection of synchronous brain metastases and the primary lung cancer. In this series, all craniotomies were performed before the primary lung cancer resections, with a median time between craniotomy and thoracotomy of 14 days. The most responsible factor influencing survival after surgery was the presence of thoracic lymph node metastases. The overall 5-year survival rate was 21.4%, but no patient with lymph node metastases (N1 and N2) survived longer than 3 years.

The advent of stereotactic radiosurgery (SRS) has offered another treatment option for patients with a solitary brain metastasis. Hu and coworkers¹³⁴ reported on outcomes of NSCLC patients with a solitary brain metastasis treated with either SRS or neurosurgery, in conjunction with chemotherapy, radiotherapy, or both, for the lung primary site. The median survivals for patients who had received treatment for their primary cancers and those who had not were 15.5 and 5.9 months, respectively. In addition, the survival times were thoracic stage dependent: median survivals by thoracic stage (I, II, and III) were 25.6, 9.5, and 9.9 months, respectively. The ACCP guideline summarized that the favorable prognostic factors in patients with isolated brain metastasis were young female gender, metachronous presentation, good performance status, or lower T stage.¹³² In the guideline, one can consider curative surgical approach for both the brain metastasis and the primary tumor if complete resection is likely to be achieved. Surgical resection or SRS, with or without whole brain radiation therapy to a solitary brain lesion, is the treatment of choice. Based on the reported series and the aforementioned guideline, patients with thoracic stage I NSCLC with a solitary brain metastasis appear to benefit from aggressive treatment including surgical resection of the primary site. Those with N2 disease should be excluded because the cancer involvement of mediastinal nodes portends a worse prognosis.

SPECIAL CONSIDERATIONS

Mediastinal Lymph Node Dissection versus Systematic Sampling

Tumor staging is critical for predicting prognosis, for comparing clinical studies, and, most importantly, for

planning therapy in lung cancer. To obtain more accurate mediastinal lymph node staging, intraoperative lymph node examination is necessary in early-stage (I and II) or selected stage III resectable disease. However, current practice varies from simple visual inspection of the mediastinum to radical MLND without having solid consensus among thoracic surgeons. In fact, it was reported that nodes were sampled at any mediastinal level during surgery in only 42% of patients with lung cancer in the United States.¹³⁶ The points of current debate with regard to surgical mediastinal staging, in particular, in comparing MLND with systematic sampling (SS) include safety, staging accuracy, and local control and long-term survival.

Operative Morbidity

The argument against MLND is that it might be associated with higher morbidity compared with SS. It can be assumed that chylothorax, phrenic or recurrent laryngeal nerve injury, increased lymphatic drainage/bleeding, or decreased host defense may occur because of resection of whole lymphatic drainage pathways and lymphatic tissues along with the local blood supply. However, recent reports, including a randomized clinical trial, demonstrated that MLND does not increase operative morbidity.¹³⁷⁻¹³⁹ Allen and colleagues¹³⁹ reported a large multi-institutional randomized trial (the American College of Surgeons Oncology Group trial, ACOSOG Z0030), in which patients with lung cancer were randomized to either lymph node sampling ($n = 498$) or lymph node dissection ($n = 525$). Operative mortality was 2.0% for the sampling group and 0.76% for the dissection group. Morbidity including minor complications was 38% in each group. Specifically, there were no statistical differences in the rates of chylothoraces, postoperative hemorrhage, recurrent nerve injuries, or BPFs. No statistical difference was observed in the duration of chest tube drainage (sampling versus dissection, 4 versus 5 days), median total chest tube drainage (1.34 versus 1.46 L), or the length of hospitalization (6 days in both groups).

Staging Accuracy

One of the critical questions is whether SS is as accurate as MLND in surgical mediastinal staging. If mediastinal lymph node assessment is not adequately performed, the true N stage remains unrecognized, which may result in false downstaging. In the ACOSOG Z0030 trial, all patients first received lymph node sampling with frozen section examination. When all required lymph nodes biopsied were negative for malignancy on frozen section, then those patients were randomized to either sampling only, with no further dissection, or to complete MLND. Positive mediastinal nodes were found in 20 patients (3.8%) who had negative sampling and were randomized to MLND. Therefore, these patients would have unrecognized N2 disease without the dissection.

In the nonrandomized trial reported by Keller and colleagues,¹³⁷ SS was as efficacious as MLND in accurate nodal staging, with rates of detected N2 disease of 60%

in the SS group ($n = 112/187$) and 59% in the MLND group ($n = 110/186$). However, MLND detected significantly more levels of N2 disease (multiple N2 levels: 30% in MLND versus 12% in SS) in the study. The result is comparable to prospective randomized trials reported by Izbicki and associates (17.4% in SS versus 57.2% in MLND)¹⁴⁰ and by Wu and colleagues (28% in SS versus 48% in MLND).¹⁴¹

One might ask whether complete MLND is always necessary for patients with early-stage, small-size NSCLC, as such cases are frequently and increasingly identified today. In a prospective randomized trial for patients with clinical T1N0 NSCLC less than 2 cm in diameter ($n = 115$), Sugi and coworkers¹⁴² found no statistical differences in N2 detection rates (13% in both groups) or in survival rates between the groups and thus concluded that SS is adequate.

A unique multicenter cross-sectional study was performed by Massard and associates¹⁴³ to answer the question of whether MLND elevates diagnostic accuracy. The authors performed lymph node sampling first, followed by complete MLND in each patient enrolled in the study ($N = 208$). The sampled nodes and the nodes from MLND were examined separately, so each case served as its own control. Of 60 patients with pathologic N2 disease, lymph node sampling identified only 31 patients (52%) as having N2 disease. Furthermore, multilevel N2 disease was detected by sampling in 10 out of 25 patients (40%). The authors concluded that lymph node sampling is inadequate in determining accurate N stage.

Local Control and Long-Term Survival

A postulated argument is that MLND contributes not only to improved staging but also to tumor control and long-term prognosis; however, the therapeutic efficacy of MLND remains under debate. If SS fails to identify positive mediastinal nodes, it may result in an increased risk of local recurrence in comparison with MLND. On the other hand, it might be hypothesized that MLND may help in clearing occult micrometastatic cells in the mediastinal lymph nodes that are not identified by conventional histopathologic methods¹⁴⁴ and thus may increase the rate of complete resection. The latter hypothesis is supported by the fact that local tumor recurrence is significantly higher in patients with pathologic stage I or pathologic N0-1 disease who underwent SS than in those who underwent MLND (45% versus 13%, and 46% versus 13%, respectively).¹³⁸

A few prospective randomized studies have examined these issues. A study by Izbicki and colleagues¹⁴⁵ demonstrated that MLND appeared to prolong the relapse-free interval compared with SS in patients with pathologic N1-2 disease; however, there was no significant difference in survival. Sugi and associates¹⁴² conducted a prospective randomized study of SS and MLND in patients with clinically diagnosed peripheral NSCLC less than 2 cm in diameter. The patients were assigned to a lobectomy with SS ($n = 56$) or a lobectomy with MLND ($n = 59$). In the study, no significant differences were found in recurrence rate or survival between the groups. On the other hand, a more recent prospective randomized trial

conducted by Wu and coworkers¹⁴¹ demonstrated a survival benefit of MLND over SS (median survival, 59 versus 34 months) with a reduced local recurrence rate (2.9% versus 4.8%). The difference in survival was prominent in stage I (5-year survival, 82.2% versus 57.5%) and stage IIIA (27.0% versus 6.2%). Recent evidence from the literature relating to the potential benefit of MLND on both local control and long-term outcome are summarized in Table 17-7.

The large, prospective, randomized multicenter trial of MLND ($N = 525$) versus SS ($N = 498$) during pulmonary resection in patients with early-stage NSCLC (N0 or nonhilar N1, T1, or T2) (ACOSOG Z0030) demonstrated no significant difference in local, regional, or distant recurrence between the two groups.¹⁴⁶ Furthermore, MLND did not improve survival if thorough pre-resection sampling of the mediastinal and hilar lymph node was negative for cancer metastasis. The median survival rates were 8.1 years for SS and 8.5 years for MLND, and the 5-year survival rates were 69% and 68%, respectively.

Multifocal Adenocarcinomas In Situ or Minimally Invasive Adenocarcinomas

The terms *bronchioloalveolar carcinoma* and *mixed subtype adenocarcinoma* (WHO 1999 and 2004 definitions) have been discontinued in the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) lung adenocarcinoma classification.^{146a} New classifications have been introduced, such as *adenocarcinoma in situ* (AIS) and *minimally invasive adenocarcinoma* (MIA) for small solitary adenocarcinomas with pure lepidic growth and predominant lepidic growth with 5 mm or greater invasion, respectively.

AIS and MIA are known for their multifocal nature, including bilateral lung involvement, although the cause

of the multifocality is under debate.¹⁴⁷ One radiographic appearance of AIS, known as ground-glass nodule (GGN), is characterized as a localized, mild-to-moderate increase in density on a CT scan without obscuring preexisting bronchovascular structures. A focal GGN can contain solid parts in the lesion that often represent invasive components. High-resolution CT is useful for correlating the radiographic appearance of GGN with pathologic features, including mediastinal node involvement.^{148,149}

Treatment Strategy and Outcome

A single lesion of AIS or MIA can be cured surgically by standard lobectomy with lymph node dissection. Asamura et al reported excellent surgical results of clinical stage IA patients with radiographically determined noninvasive lung adenocarcinoma who underwent lobectomy with MLND.¹⁵⁰ Specifically, if the ratio of maximum diameter of consolidation (C) divided by the maximum tumor diameter (T) (the C/T ratio) on high-resolution CT images was less than 0.5, the 5-year survival was 96.7%.

Given its multifocal process and better outcome compared with other non-small cell types, attempts have been made with complete surgical resection for multifocal AIS and/or MIA, or for those with other non-small cell types. Clinically, invasive lung adenocarcinomas can present with synchronous, multifocal, AIS or MIA lesions that appear as pure or near-pure GGNs. The optimal approach in this circumstance remains unclear. Gu et al took a strategy of anatomic pulmonary resection of a dominant, invasive lesion and wedge resection of accessible ipsilateral GGNs.¹⁵¹ On the other hand, Kim et al reported the long-term outcome of multifocal pure GGNs found in patients who had surgical resection for bronchioloalveolar carcinoma (BAC).¹⁵² In the latter study, 18 patients had some of the ground-glass lesions resected and the remaining lesions followed by serial CT scans with a median follow-up of 40.3 months. The

TABLE 17-7 Impact of Mediastinal Lymph Node Dissection (MLND) or Systematic Sampling (SS) on Local Recurrence and Long-Term Outcome in Patients with Resectable Non-Small Cell Lung Cancer

Author (Year)	Study Design (N of Patients)	Clinical Stage	MLND vs. SS	
			Local Recurrence (%)	Disease-Free Median Survival (mo, but % when 5-yr)
Izbicki et al ¹⁴⁵ (1998)	Randomized (169)	I-III	28.9 vs. 34.4 (NS)	48 vs. 24 (NS)
Sugi et al ¹⁴² (1998)	Randomized (115)	I	10 vs. 13 (NS)*	81.4% vs. 83.9% (overall 5-yr, NS)
Keller et al ¹³⁷ (2000)	Nonrandomized (373)	II, IIIA	52 vs. 58 (NS)*	57.5% vs. 29.2 [†]
Wu et al ¹⁴¹ (2002)	Randomized (471)	I-IIIA	2.9 vs. 4.8	59 vs. 34 [†] p-St. I, 82.2% vs. 57.5% [†] (5-yr) p-St. II, 50.4% vs. 34.1% (5-yr, NS) p-St. IIIA, 27.0% vs. 6.2% [†] (5-yr)
Lardinois et al ¹³⁸ (2005)	Nonrandomized (100)	I, II	p-St. I, 13 vs. 45 [†] p-St. II, 17 vs. 55 (NS) p-St. IIIA, 23 vs. 10 (NS)	p-St. I, 60.2 vs. 44.8 [†] p-N0, 52.8 vs. 44.8 [†] All, 46.2 vs. 41.1 (NS)

*Statistically significant.

[†]Distant recurrence included.

NS, Not significant; p-St., pathologic stage.

ground-glass lesions either did not change in size ($n = 15$) or they disappeared ($n = 3$). The authors concluded that a close follow-up with CT scan can be an alternative if resection(s) of pure GGNs is not feasible. Mun and colleagues¹⁵³ reported clinicopathologic results of thorascopic resections for patients with small, peripheral, multifocal BAC (105 BAC lesions in 27 patients). In the study, the surgeons performed lobectomies or lesser resections (segmentectomy or wedge resection) with or without lymph node dissection. All lesions demonstrated GGN with no solid components (pure GGN) on the preoperative high-resolution CT scan. There was no local recurrence observed; however, interestingly, de novo BAC lesions developed in 26% of the patients after the surgical treatment.

In summary, sublobar resection may be offered for solitary, small, peripheral ground-glass lesions with no radiographic sign of invasive growth, whereas standard lobectomy should be performed for those with invasive growth features radiographically. Complete surgical resection appears to be a preferable option for multifocal GGNs if mediastinal nodes are not involved, because these cases should not be considered as T4 or M1a disease.

SURGICAL TREATMENT OF SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) represents 15% of all lung cancer in North America¹⁵⁴ and is characterized by rapid growth and early dissemination. Only approximately 30% of the patients with SCLC have limited disease (LD). LD-SCLC is treated with curative intent with chemoradiotherapy with median survival of 23 months and a 5-year survival rate of 12% to 17%, whereas extensive-disease SCLC is treated primarily with chemotherapy with a median survival of approximately 7 to 12 months, and the proportion surviving 5 years is only 2%.¹⁵⁴

The treatment for patients with lung cancer including SCLC was primarily surgery before 1970, but surgery was largely discouraged after a report from the Medical Research Council in the United Kingdom.¹⁵⁵ This trial showed a small but significant difference in the survival rate—a 4-year survival of 3% in the surgery arm versus 7% in the radiotherapy arm. Because all patients who survived 5 years were treated in the radiotherapy arm, this became the standard form of treatment for LD-SCLC. The role of surgery as initial treatment was reevaluated after introduction of the TNM staging system. Shields and colleagues¹⁵⁶ reported the experience of the Veterans Administration Surgical Oncology Group (VASOG) and concluded that surgical resection is indicated in patients with T1N0 SCLC. At approximately the same time, the reduction of local recurrence of LD-SCLC by surgical resection was emphasized by the Toronto group.¹⁵⁷ These findings revived interest in the role of surgery in the treatment of early-stage SCLC. Furthermore, the role of adjuvant chemotherapy after surgical resection was investigated by several groups,¹⁵⁸⁻¹⁶⁰ which enhanced the benefit on improved survival. In 1983, the Lung Cancer

Study Group initiated a prospective randomized trial in which patients treated with induction chemotherapy were randomized to undergo surgical resection or to receive radiotherapy.¹⁶¹ Although several criticisms can be made, this is the only prospective randomized trial for LD-SCLC comparing surgery with radiotherapy to date. Median survival was 15.4 months in the surgery arm ($n = 70$) and 18.6 months in the radiation arm ($n = 76$). The authors concluded that surgical resection did not contribute to either prolonged survival or local control. Conclusions are limited by the fact that in the surgical arm, only 77% ($n = 54$) of patients underwent complete resection. Also, neither platinum-based chemotherapy nor concurrent chemoradiotherapy was used, and the modern preoperative neoadjuvant therapy might be more potent. Finally, patients with peripheral nodules, assumed to be T1N0, who might be the best candidates for surgery, were specifically excluded from this study.

Rationale for Surgery

Evolving from a number of case-series reports and prospective phase II trials, the role of surgery in LD-SCLC has been shaped by several rationales: (1) Small peripheral lesions without any nodal involvement can occasionally be misdiagnosed as SCLC when they are in fact typical or atypical carcinoid tumors. (2) Surgical resection for LD-SCLC (T1N0, T2N0) may improve local control compared with chemoradiotherapy. (3) Mixed-histology tumors (a SCLC tumor with an NSCLC component) may not be completely eradicated by chemoradiotherapy because the NSCLC component is less sensitive to chemotherapy. (4) Salvage surgery for chemoresistant localized SCLC or local relapse after an initial response to chemotherapy or chemoradiotherapy may be more effective than current second-line chemotherapy. A final indication for surgery is a second primary tumor with NSCLC histology after cure of initial SCLC. Although only a small percentage of patients with SCLC survive longer than 2 years, the occurrence of a second primary NSCLC is becoming more common with current advances in the treatment of SCLC. It is worth noting that any new tumor arising more than 2 years after initial treatment for SCLC is in fact more likely to be of non-small cell histology. Patients without mediastinal node metastases can be treated with surgery. However, survival is reduced in patients with a stage I second NSCLC who underwent wedge resection compared with patients with primary stage I NSCLC receiving wedge resection (median survival, 24.5 versus 58.4 months).¹⁶²

Improved Local Control

Although the mainstay of the current treatment for LD-SCLC is chemotherapy with or without radiotherapy, even the current active chemoradiotherapy protocols have demonstrated local failure rates of 36% and 52%.¹⁶³ The first site of recurrence in patients with LD-SCLC who achieve complete remission is the primary tumor site, followed by hilar or mediastinal lymph nodes.¹⁶⁴ In an autopsy series, only 31% of patients who underwent surgery had residual primary tumor, whereas 92% of

patients with LD-SCLC who had negative mediastinoscopy but were treated without surgery had residual disease at the primary site. Shepherd and colleagues¹⁵⁷ reported on the Toronto experience, with a combined treatment program including surgical resection, and demonstrated local relapse in only 2 of 35 patients. A recent report from a German group has demonstrated 100% local or locoregional control after complete surgical resection following induction chemoradiotherapy for LD-SCLC, with a 5-year survival rate of 63%.¹⁶⁵ There are no available data from randomized control trials comparing modern chemoradiotherapy protocols with chemoradiotherapy with surgery; however, the impact of surgical resection on local control seems to be evident. In this context, surgical treatment for SCLC appearing as a solitary pulmonary nodule without nodal involvement would be a justifiable strategy. Particularly if the diagnosis is uncertain or in question, surgery can be an initial step in the management of T1-2 N0 SCLC. In a recent Japanese trial, the 5-year survival rates in patients with clinical stage IA (T1N0) and IB (T2N0) postoperatively proven SCLC who underwent complete resection followed by chemotherapy were an encouraging 73% and 67%, respectively.¹⁶⁶

Mixed-Histology Tumors

According to the World Health Organization classification of lung carcinoma (1999), the variants of SCLC admixed with various other histologic types are defined as combined small cell carcinoma. Recent surgical series of neuroendocrine lung tumors revealed that 26.6% of resected SCLC fell into this category.¹⁶⁷ In studies of induction chemotherapy followed by adjuvant surgery for pathologically confirmed SCLC, an NSCLC component was found in the resected specimen in 11% to 15% of cases.^{161,168} The high percentage of combined SCLC in surgical reports is partially because combined SCLC tends to be in the periphery rather than in the hilum and thus surgical resection may be more feasible. In addition, because of the large amount of tissue available in surgical cases (i.e., the entire tumor), the chance of finding other components may increase. Another possible reason is that, because the NSCLC component is less sensitive to chemotherapy than the SCLC component, residual tumors, which are more likely to be surgically treated, may be more likely to contain an NSCLC component. Therefore, it is reasonable to offer surgical resection to improve local control if a histologic diagnosis of mixed SCLC without nodal involvement is obtained. It must be part of a combined modality approach, because surgery alone is not adequate for the SCLC component. An NSCLC component may be responsible for local relapse or the poor response to chemoradiotherapy, so surgery may be offered as salvage treatment.

Surgery as a Salvage Treatment

Because the treatment of relapsed or unresponsive LD-SCLC with second-line chemotherapy is generally unsatisfactory, salvage surgery for these cases offers another treatment option. The Toronto group has

identified a small but curable subset of patients who benefit from salvage surgery.¹⁶⁹ In this prospective study, the authors offered surgery for patients with residual disease after chemotherapy, radiotherapy, or both, or with local failure after the initial response to chemotherapy. After resection, 10 of 28 patients were found to have a mixed histology or pure-NSCLC tumor, although 25 of 28 patients were thought to have a pure-SCLC tumor preoperatively. The 10 patients with mixed histology or pure-NSCLC tumor achieved a median survival of more than 2 years. In contrast, patients with pure-SCLC tumors rarely survived more than 2 years. Therefore, patients with mixed histology in their residual or nonresponsive tumor without nodal disease may be good candidates for salvage surgery. In this view, it is worth considering a second biopsy to reevaluate the cell type.

TNM Staging (Seventh Edition) and Surgical Outcome

The revised TNM staging is now applied not only to NSCLC but to SCLC based on the recent analysis of the SCLC cases in the IASLC database.¹⁷⁰ Applying pathologic TNM staging to the data of 349 cases of resected SCLC clearly separated patient subgroups with different prognoses (Fig. 17-10). Overall 5-year survival rates of resected stages IA and IB were 56% and 57%, respectively. Even in the groups of stages IIA and IIB, 38% and 40% 5-year survival rates were obtained. The results support the use of surgical resection as a part of the multimodal treatment for SCLC. Subsequent analysis of the SEER database, the 5-year survival rate of patients with stage I SCLC who underwent lobectomy without radiotherapy was 50.3%.¹⁷¹ Another recent analysis of the English National Cancer Repository (NCDR) showed that the 5-year survival rate of SCLC undergoing surgical resection was 31% despite its inherent poor prognosis.¹⁷² In summary, surgery is indeed a viable option for the treatment of LD-SCLC. How best to integrate it into multimodal treatment programs and how to improve patient selection for surgery are key considerations for further refinement of the treatment strategy in these patients.

SUMMARY

Surgical resection in patients with NSCLC continues to be the mainstay of curative treatment, and the techniques continue to evolve. VATS and, more recently, robot-assisted surgery allow thoracic surgeons to perform minimally invasive surgery on early-stage tumors without violating key oncologic principles. On the other hand, improvements in surgical techniques, intraoperative management, and postoperative care allow more radical resections of tumors invading other organs. Neoadjuvant, adjuvant, or both therapies should be considered in the treatment for most patients with resectable NSCLC (excluding stage IA) if medically fit. Accurate tumor staging continues to be the key to determining optimal treatment strategy.

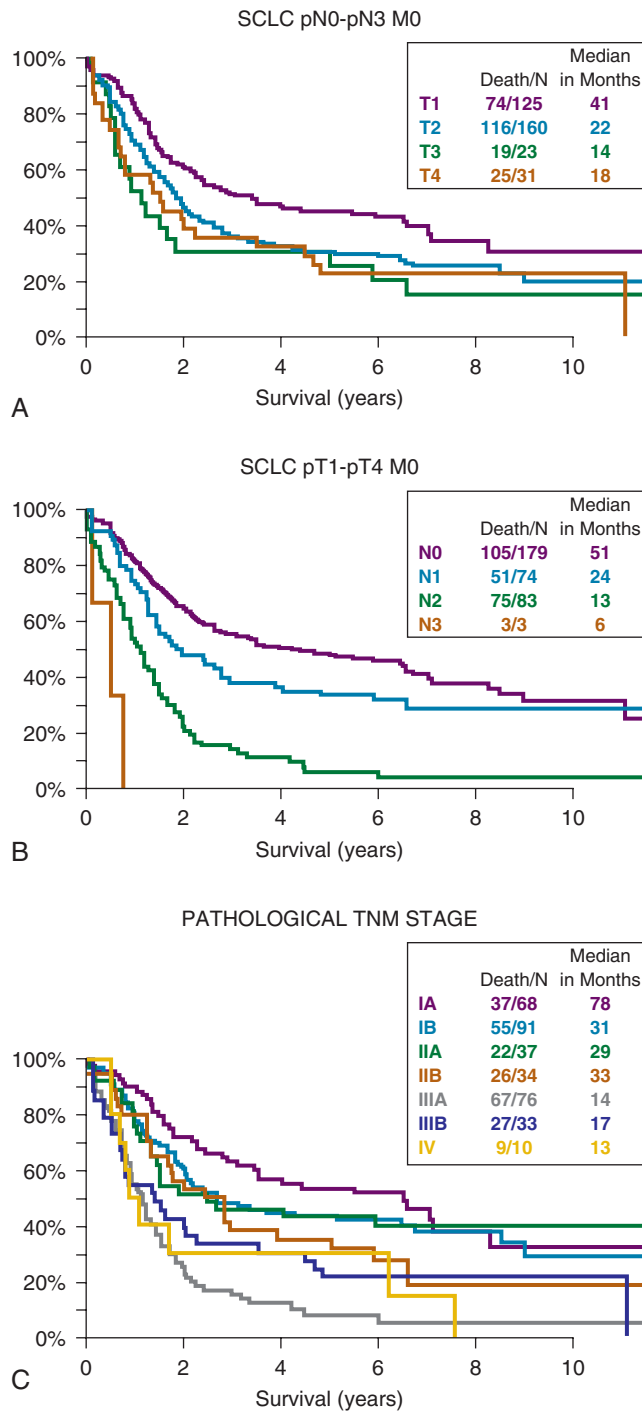


FIGURE 17-10 ■ Survival of resected small cell lung cancer (SCLC) by pathologic T category (A), pathologic N category (B), and pathologic tumor, node, metastasis (TNM) stages (C) (Union for International Cancer Control [UICC], 6th edition). (From Vallières E, Shepherd, Crowley J, et al: The IASLC lung cancer staging project: proposals regarding the relevance of TNM in the pathological staging of small-cell lung cancer in the forthcoming [seventh] edition of the TNM classification for lung cancer. *J Thorac Oncol* 4:1049–1059, 2009.)

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LUNG CANCER: MINIMALLY INVASIVE APPROACHES

Jennifer M. Hanna • Mark W. Onaitis • Thomas A. D'Amico

CHAPTER OUTLINE

DEFINITION

BRIEF HISTORY

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SUMMARY

The surgical approach in the management of patients with lung cancer continues to evolve and improve. Conventional surgical approaches (including standard posterolateral thoracotomy, muscle-sparing thoracotomy, trans-sternal thoracotomy, and median sternotomy) remain viable options for some patients with resectable lung cancer. However, minimally invasive procedures have increasingly gained acceptance as a standard surgical modality for early-stage lung cancer, with increasing application to more advanced disease, as a means of minimizing operative morbidity without sacrificing oncologic efficacy.

DEFINITION

Minimally invasive procedures, using operative telescopes and video technology, are referred to synonymously as thoracoscopic procedures or video-assisted thoracic surgery (VATS). For clarity, the terms *VATS* and *thoracoscopic* refer to totally thoracoscopic approaches, where rib spreading is avoided and visualization depends on video monitors.¹ A hybrid procedure, which employs rib spreading and direct visualization in addition to thoracoscopy, may be referred to as *video-assisted thoracotomy*. Thoracoscopy has been widely used diagnostically in the management of patients with lung cancer; thoracoscopic

wedge resection to confirm malignancy prior to thoracotomy for anatomic resection is commonly performed. In addition, thoracoscopic therapeutic procedures, including pleurodesis for malignant pleural effusion and pericardial window for pericardial effusions, are also frequently performed. The application of thoracoscopic anatomic resections is no longer new and is increasingly used internationally. In the most recent analysis of the Society of Thoracic Surgeons (STS) General Thoracic Surgery Database, thoracoscopic lobectomy constituted 45% of all lobectomies performed.²

Thoracoscopic lobectomy is defined as the anatomic resection of an entire lobe of the lung, using a videoscope and an access incision (<8 cm), without the use of a mechanical retractor and without rib spreading.¹ The anatomic resection includes individual dissection and stapling of the involved pulmonary vein, pulmonary artery, and bronchus and appropriate management of the mediastinal lymph nodes, as would be performed with thoracotomy. In selected patients, thoracoscopic anatomic segmentectomy may be performed, adhering to the same oncologic principles that guide resection at thoracotomy.³ Theoretical advantages to minimally invasive resection include reduced surgical trauma and inflammation, decreased postoperative pain, shorter chest tube duration, shorter length of stay, preserved pulmonary function, and numerous short-term and long-term outcomes.⁴⁻⁹

BRIEF HISTORY

The history of minimally invasive thoracic surgery began in 1910 when Jacobaeus used a cystoscope to lyse adhesions to collapse the lung to treat tuberculosis.¹⁰ This technique was widely applied in the early part of the century but was largely abandoned after streptomycin was introduced in 1945. However, with the emergence of laparoscopic cholecystectomy, minimally invasive approaches were applied more widely. The first descriptions of the use of VATS for anatomic lobectomy were published in 1993 by Walker and colleagues.¹¹ The first large single institution series, published in 2006,^{12,13} supported the safety and feasibility demonstrated in the Cancer and Leukemia Group B multi-institutional, prospective study.¹

INDICATIONS

In general, the indications for thoracoscopic lobectomy are similar to those for lobectomy using the open approach.^{1,12-15} Thus, the procedure is applied to patients with known or suspected lung cancer (clinical stage I-II) if the disease appears amenable to complete resection by lobectomy. Preoperative staging and patient selection for thoracoscopic lobectomy should be conducted as for conventional thoracotomy.¹⁶ With increasing focus on operative planning and experience with the VATS techniques, the indications for thoracoscopic lobectomy are evolving. Whereas initially a history of prior surgery, the presence of an endobronchial lesion, or even the administration of induction chemotherapy were once regarded as contraindications, the experience that has since been gained, together with improvements in instrumentation and thoracoscopic imaging, have now changed this situation in most hospitals with experience in VATS. As such, recent studies have shown that lobectomy by VATS in cases of lung cancer with prior chemotherapy can be carried out safely and effectively, without an increase in the rate of complications.¹⁷ And although endobronchial lesions were previously considered a contraindication to VATS resections, bronchoplastic procedures and pneumonectomy are now commonly performed minimally invasively.^{15,18}

Tumor size may preclude the option of thoracoscopic lobectomy in some patients, as some large specimens (tumors greater than 6 to 8 cm in diameter) may not be amenable to removal without rib spreading, possibly negating the benefit of minimal access surgery. However, no absolute size criteria have been applied. Although it is controversial, some have argued that the thoracoscopic approach may allow recruitment and resection of some patients considered medically inoperable, who could not undergo conventional thoracotomy.^{1,14,19,20} A study by Cattaneo and colleagues²¹ demonstrated improved tolerance of thoracoscopic lobectomy as compared with thoracotomy lobectomy in patients older than 70 years of age. Several studies have further demonstrated that VATS lobectomy is beneficial in reducing pulmonary complications in patients with poor preoperative pulmonary function.^{2,22} The minimal physiologic requirements for

resection have not been agreed on; however, the selection of patients for thoracoscopic lobectomy must take into account that conversion to thoracotomy may be necessary.

CONTRAINDICATIONS

Absolute contraindications to thoracoscopic lobectomy include the inability to achieve complete resection with lobectomy, T3 (chest wall) or T4 (local invasion) tumors, active N2 or N3 disease, and inability to achieve single-lung ventilation.^{14,15} Relative contraindications include tumors visualized in the lobar orifice at bronchoscopy (although successful thoracoscopic sleeve resection has been reported),¹⁸ the presence of complex, calcified benign hilar lymphadenopathy that would complicate vascular dissection, and prior thoracic irradiation. Prior thoracic surgery; T3 tumors that involve the pericardium, mediastinal pleura, or diaphragm; incomplete or absent fissures; and benign noncalcified mediastinal adenopathy should not be considered contraindications.^{15,23} Increasing experience has allowed successful thoracoscopic lobectomy after induction therapy, including for patients with stage IIIA (N2) disease.¹⁷ Finally, chest wall involvement would obviate thoracoscopic resection for most patients, but successful hybrid thoracoscopic lobectomy with en bloc chest wall resection has been demonstrated to be safe and feasible.²⁴

The efficacy of mediastinal lymph node dissection (MLND) has been questioned.²⁵ Several studies have examined the extent of MLND by VATS versus open lobectomy. In one study by Kondo and coworkers,²⁶ thoracotomy was performed for reassessment of lymph nodes following MLND using VATS and yielded few additional lymph nodes (mean = 1.3 lymph nodes, median 0 lymph nodes). Similarly, Sugi et al²⁷ found no difference between the number of lymph nodes dissected among patients who underwent VATS (mean = 8.4 ± 1.0) versus patients who had open lobectomy (mean = 8.2 ± 1.5). More recently, a retrospective review by Watanabe and colleagues²⁸ of 770 patients with cN0-pN2 non-small cell lung cancer who underwent VATS ($n = 450$) or open lobectomy ($n = 320$) examined the total number of lymph nodes, number of lymph node stations, and number of mediastinal nodes and mediastinal stations by VATS versus open lobectomy, and found no difference in any of these categories. Data from the recent American College of Surgeons Oncology Group Z0030 trial ($N = 752$, VATS = 66, open = 686) has also confirmed the efficacy of MLND during VATS procedures by demonstrating a similar number of lymph nodes removed and lymph node stations assessed as compared with thoracotomy.²⁹

Other studies comparing the efficacy of a lymph node dissection of a VATS lobectomy with standard thoracotomy have demonstrated similar results.^{30,31} Nevertheless, it remains that some surgeons doubt the efficacy of VATS MLND. To date, few studies have disputed the efficacy of MLND by VATS, with one study by Denlinger and colleagues³² ($n = 79$ VATS, $n = 464$ open) showing fewer lymph nodes sampled by VATS compared

with thoracotomy (7.4 ± 0.6 versus 8.9 ± 0.2 , $P = 0.03$) and fewer N2 nodes (2.5 ± 3.0 versus 3.7 ± 3.0 , $P = 0.004$). In a recent study by D'Amico et al³³ analyzing data from the National Comprehensive Cancer Network database with a more balanced number of VATS versus open procedures ($N = 388$, $n = 199$ VATS, $n = 189$ open), VATS and thoracotomy were found to result in a similar number of mediastinal lymph nodes resected (median = 4 for both groups) and N2 nodes resected (median = 3 for both groups). The percentage of patients with at least three mediastinal lymph node stations assessed, as recommended by the current guidelines, was also similar in the VATS and open group (66% VATS versus 58% open, $P = 0.12$).

STRATEGY FOR THORACOSCOPIC LOBECTOMY

After bronchoscopy and mediastinoscopy (when indicated), single-lung anesthesia is established using a dual-lumen endotracheal tube or bronchial blocker. The patient is positioned in a full lateral decubitus position with slight flexion of the table at the level of the hip, which provides splaying of the ribs to improve thoracoscopic access and exposure. Care must be taken to secure and pad the patient so that the risk of neurologic injury is minimized. Once the patient is positioned, the anesthesiologist should reconfirm the desired position of the endotracheal tube. Before sterile preparation and draping, the chest is marked for the placement of thoracoscopic incisions.

Port placement is a matter of surgeon preference. Most surgeons use three or four incisions, although lobectomy can usually be accomplished using only two incisions.¹⁵ Using this strategy, the first incision, either a 5-mm or 10-mm port access used predominantly for the thoracoscope, is placed in the seventh or eighth intercostal space in the mid-axillary line. The location of this incision is chosen so that it does not compete with the anterior incision, yet it still provides anterior and superior visualization of the hilum. A port is used for placement of the thoracoscope, but ports are not used for the other incisions. Before making the second incision, evidence that the patient is unresectable, such as parietal pleural involvement, should be sought.

The second incision, an anterior access incision (usually 4.5, but up to 6.0 cm) for dissection and specimen retrieval, is placed in the fifth or sixth intercostal space, just inferior to the breast. The location of this incision, where the intercostal spaces are the widest, is chosen to provide access for hilar dissection and is usually not dependent on whether the planned procedure is an upper or lower lobectomy. A wound protector may be used in the access incision to improve soft tissue retraction, to facilitate suctioning, and to protect the incision during specimen removal. Additional incisions may be used, either in the axilla or posteriorly, to improve visualization or to provide retraction.

Instrumentation for thoracoscopic lobectomy is critical to successful completion of the procedure. The thoracoscope should be a 30-degree angled scope to optimize

the ability to achieve panoramic visualization during dissection and to minimize competition with the operative instruments. Alternatively, a 45-degree angled scope or a flexible scope may be used, although this may be more difficult for an assistant to navigate. A spectrum of surgical instruments may be used for dissection, including conventional instruments and dedicated thoracoscopic or laparoscopic instruments. It is especially beneficial to use curved instruments for retraction during dissection, as they minimize the tendency for instruments to compete or collide with each other. Thoracoscopic (linear) mechanical staplers, such as the Endo GIA (Covidien, Norwalk, CT), are employed for control of the vessels (2.0- or 2.5-mm staples), bronchus (3.5- or 4.8-mm staples), and fissure.

After placing the access incision, the surgeon performs thoracoscopic exploration, which includes confirming the location of the tumor, excluding the presence of pleural metastases, and dividing the pulmonary ligament for lower lobectomy. If a malignant diagnosis has not been achieved preoperatively, thoracoscopic wedge resection is performed using an automatic stapling device, and the specimen is removed, either in a protective bag or with a wound protector. After frozen section confirms a malignant diagnosis, thoracoscopic lobectomy may be completed. MLND may be performed at this point or may be deferred until the lobectomy is completed.²⁵

The approach to the staging of mediastinal lymph nodes is controversial. Many advocate systematic sampling of mediastinal lymph nodes because of concerns about the adequacy and safety of formal dissection.^{25,34} Others accomplish MLND by complete resection of the mediastinal nodes thoracoscopically, including levels 2, 4, 7, 8, and 9 on the right and levels 5, 6, 7, 8, and 9 on the left.²⁵ A minimum of three mediastinal stations should be assessed.^{16,33}

Hilar dissection is carried out through the access incision, to achieve visualization and mobilization of the hilar structures. When upper lobectomy is being performed, division of the posterior pleural reflection permits elongation of the hilum and facilitates further resection. For any anatomic thoracoscopic lobectomy, hilar dissection is begun with mobilization of the pulmonary vein, although alternative strategies may be employed depending on the size and location of the tumor. For upper lobectomy, the lung is reflected posteriorly and inferiorly to facilitate dissection. For lower lobectomy, the lung is retracted superiorly. Moving the thoracoscope to the anterior incision may improve visualization of the superior hilum and may facilitate placement of the linear stapler for upper lobectomy if it is introduced through the mid-axillary (camera) port.

The risk of intraoperative hemorrhage is minimized with careful hilar dissection, which is facilitated with the visual clarity and magnification available with the video thoracoscope. Unexpected bleeding from a major branch of the pulmonary artery or pulmonary vein may occur, however. In most cases, the source of the bleeding is easily identifiable and tamponade is possible, allowing conversion to thoracotomy. To minimize the risk of vascular injury, surgeons have employed various techniques to isolate the pulmonary arterial and venous branches,

including ligatures to retract the vessels, and catheters to guide the stapling devices. These techniques may be helpful in difficult cases but are not required for most patients.

All lobectomy specimens are removed using a protective specimen bag to prevent implantation of tumor cells in the incision. The lobectomy specimen and hilum are inspected to ascertain that anatomic lobectomy has been performed. After retrieval, the hemithorax is irrigated with warm saline and the bronchial stump is inspected. If an air leak is encountered, repeat stapling or endoscopic suturing may be performed.

SPECIFIC TECHNICAL CONSIDERATIONS

Left Upper Lobectomy

With the thoracoscope in the mid-axillary incision, the horizontal and oblique fissures are inspected and the presence of the tumor in the left upper lobe is confirmed. The lung is retracted posteriorly, and the superior pulmonary vein is identified and mobilized. The left superior pulmonary vein is then encircled using a curved clamp; dissection behind the superior pulmonary vein allows identification of the pulmonary artery (Fig. 18-1). The stapling device is then applied (Fig. 18-2), and the superior pulmonary vein is divided, exposing the pulmonary artery. The pulmonary artery is mobilized, focusing on the apical and anterior branches (Fig. 18-3), which may then be stapled and divided. The left upper lobe bronchus is now visualized and may be stapled and divided (Fig. 18-4). Subsequently, the branches of the posterior and lingular arteries are stapled (Fig. 18-5). Finally, the fissures are completed and the specimen is retrieved.

Right Upper Lobectomy

Right upper lobectomy is slightly more difficult than left upper lobectomy because both horizontal and oblique fissures must be managed. With the thoracoscope in the

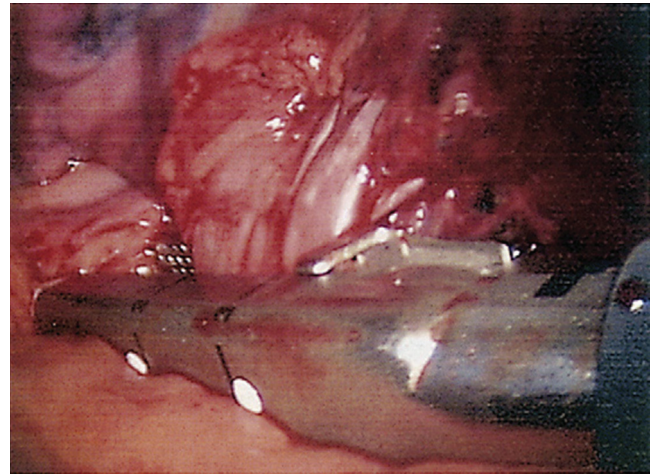


FIGURE 18-2 ■ Left superior pulmonary vein, just prior to division with stapler.

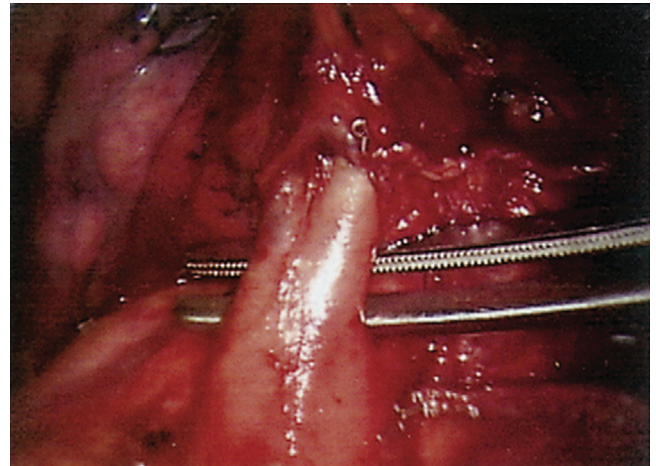


FIGURE 18-3 ■ Apical anterior branches of the left pulmonary artery.

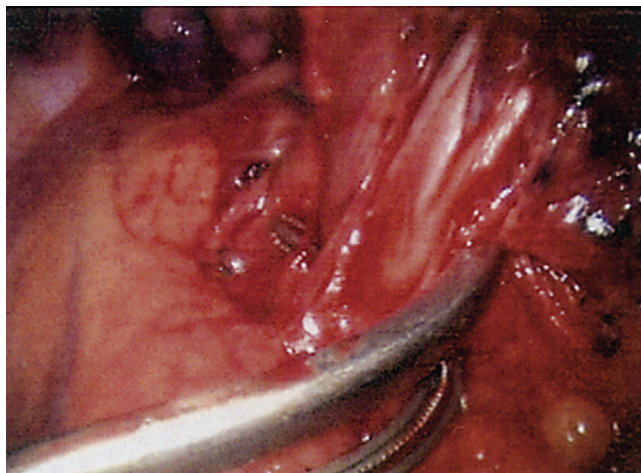


FIGURE 18-1 ■ Left superior pulmonary vein, encircled with a curved clamp.

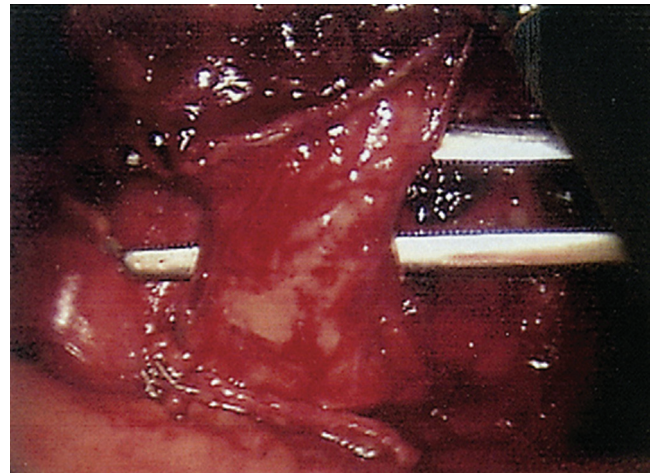


FIGURE 18-4 ■ Left upper lobe bronchus, encircled with a curved clamp.

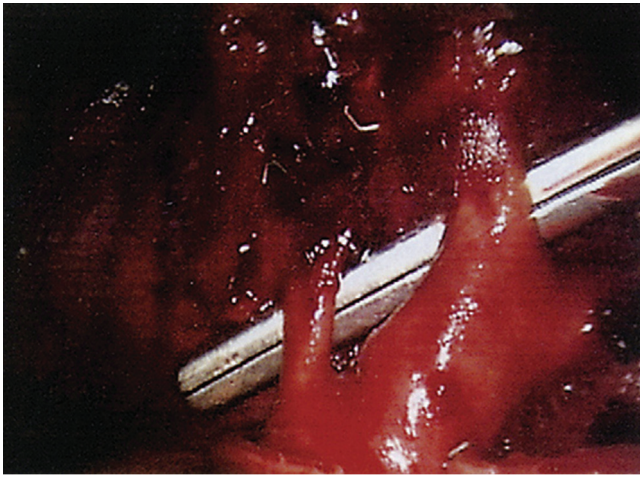


FIGURE 18-5 ■ Posterior and lingular branches of the left pulmonary artery.

mid-axillary incision, the horizontal and oblique fissures are inspected and the presence of the tumor in the right upper lobe is confirmed. After the completion of the division of the posterior pleural reflection, dissection of the bronchus and removal of the level 11 lymph nodes may be undertaken. At this point, stapling and division of the right upper lobe bronchus is often feasible, facilitating future arterial dissection.

The right lung is then retracted posteriorly, and the superior pulmonary vein is identified and mobilized to identify the division between the middle lobe and upper lobe venous branches. The upper lobe branches are encircled using a curved clamp; dissection behind the superior pulmonary vein allows identification of the pulmonary artery. The stapling device is then applied and the vein is divided, exposing the pulmonary artery. The pulmonary artery is mobilized, and the apical anterior trunk (truncus anterior) may then be stapled and divided. Subsequently, the posterior ascending arterial branch is stapled. The right bronchus is now exposed, and if not already managed, the upper lobe bronchus may be stapled and divided. Finally, the horizontal fissure (anteriorly) and the oblique fissure (posteriorly) are completed and the specimen is retrieved.

Right Middle Lobectomy

With the thoracoscope in the mid-axillary incision, the horizontal and oblique fissures are inspected and the presence of the tumor in the middle lobe is confirmed. The lung is retracted posteriorly, and the superior pulmonary vein is identified and mobilized to identify the division between the middle lobe and upper lobe venous branches. The middle lobe vein is encircled and stapled, exposing the middle lobe bronchus and artery. Retraction of the middle lobe laterally and posteriorly optimizes exposure of the bronchus. At this point, the bronchus is encircled and stapled, further exposing the middle lobe artery. The middle lobe artery is then stapled and divided as well, allowing completion of the fissures.

Lower Lobectomy (Right or Left)

The strategy for lower lobectomy is similar on the right and left sides. With the thoracoscope in the mid-axillary incision, the presence of the tumor in the lower lobe is confirmed. The lung is retracted anteriorly, and the pleura is incised between the lung and the esophagus. The lung is then retracted laterally and superiorly to incise the pleura overlying the inferior pulmonary vein, which can then be encircled and stapled after ascertaining that the superior segment branch is included in the dissection. Further superior retraction of the lower lobe improves exposure of the bronchus at the bifurcation of the lower lobe bronchus and the middle lobe bronchus (right lung) or lingular bronchus (left lung). The lower lobe bronchus is then encircled and stapled, exposing the lower lobe arterial trunk, which is then stapled and divided. Finally, the fissure is completed and the specimen retrieved.

Segmentectomy

Thoracoscopic segmentectomy is an option for anatomic resection in patients with poor lung function (forced expiratory volume in 1 second [FEV₁] or diffusion capacity less than 50% of predicted) or synchronous primary tumors. In addition, small (≤ 2 cm), peripheral primary tumors (particularly with minimally invasive histology), well-centered in the segment of interest, may be candidates.^{3,35-39} These resections may be successfully completed thoracoscopically.⁴⁰

The segments that are technically easiest to resect are the superior segments of the lower lobes, the lingular segment of the left upper lobe, the composite basilar segments of the lower lobes (sparing the superior segment), the upper division of the left upper lobe (sparing the lingua), and the posterior segment of the right upper lobe. A segmentectomy should not be performed when the tumor is immediately encroaching on the intersegmental fissure. The closest segmental margin should exceed 2.0 cm or the diameter of the tumor. The surgeon should always resect all intersegmental lymph nodes in addition to the hilar and mediastinal nodes that are routinely taken at the time of lobectomy.⁴⁰

Wedge Resection

Lobectomy is considered the procedure of choice in most patients with early-stage lung cancer, as it is associated with a lower rate of local recurrence and higher overall survival compared with sublobar resections.¹⁶ When sublobar resections are an option, anatomic segmentectomy is preferred. However, in patients with small peripheral tumors who will not tolerate anatomic resection or in whom anatomic resection would be extraordinarily difficult, wedge resection (sometimes followed by radiotherapy) may be the best surgical option.¹⁶ VATS wedge resections of small (<3 cm) peripheral nodules are usually carried out using endoscopic stapling devices to transect lung parenchyma. Larger and more centrally located nodules are more challenging.

RESULTS

The safety and efficacy of thoracoscopic lobectomy for patients with early-stage lung cancer have been established. Although there are no prospective, randomized series that compare thoracoscopic lobectomy with conventional approaches, a sufficient number of series have been published, including single-institution and multi-institution experiences, as well as meta-analyses, to conclude that thoracoscopic lobectomy is a reasonable strategy for patients with clinical stage I lung cancer.

The Cancer and Leukemia Group B (CALGB) reported on the results of a prospective, multi-institutional registry series of 127 patients who underwent thoracoscopic lobectomy.¹ In this series, the mortality was 2.7%, the operative time was 130 minutes, and the median length of stay was 3 days. Since that first multi-institutional study demonstrated the safety and feasibility of minimally invasive lobectomy, numerous subsequent studies have analyzed the potential advantages of this approach.

Postoperative Pain

One of the best studied advantages of thoracoscopic lobectomy is a reduction in postoperative pain.^{19,40,41,42} Nomori and colleagues⁴¹ compared a group of age- and sex-matched patients who underwent thoracoscopic lobectomy ($n = 33$) or limited anterior thoracotomy ($n = 33$). The patients who underwent thoracoscopic lobectomy experienced less pain between postoperative day (POD) 1 and POD 7 ($P < 0.05$ - 0.001) and had lower analgesic requirements up to POD 7 ($P < 0.001$). Demmy and Curtis¹⁹ reported on their results in a series of patients who underwent either thoracoscopic lobectomy or conventional thoracotomy. In this series, the percentage of patients reporting severe pain was 6% after thoracoscopic lobectomy and 65% after thoracotomy. Moreover, the percentage of patients reporting minimal or no pain was 63% after thoracoscopic lobectomy and 6% after thoracotomy.

Chronic discomfort is also an important issue in postoperative recovery. Although more difficult to measure than acute pain, chronic pain and shoulder dysfunction have been studied. Stammberger and colleagues,⁴³ in addressing long-term quality of life following VATS, reported that 53% of 173 patients undergoing VATS had insignificant pain 2 weeks after the operation. At 6 months, 75% had no complaints, and only 4% had mild or moderate discomfort at 2 years.

Postoperative Pulmonary Function

Many have theorized that smaller incisions and absence of rib spreading may improve lung function in the postoperative period, and several studies have reported pulmonary function test (PFT) data after thoracoscopic resection. Two studies examined postoperative arterial oxygen tension (PaO_2) after both VATS and muscle-sparing thoracotomy and found that VATS patients had better oxygenation during the first postoperative

week.^{44,45} Others have demonstrated improvements in early postoperative FEV_1 and forced vital capacity in the first weeks and months after VATS.^{8,19}

Systemic Inflammatory Effects

Minimally invasive procedures appear to produce less of a systemic insult than more conventional, invasive procedures.^{7,8,46-50} Many groups have studied inflammatory mediators after VATS and open resection and have found lower levels of C-reactive protein and interleukins (ILs) in those having undergone VATS.^{7,8,46} Yim and colleagues⁷ analyzed the cytokine responses in a series of 36 matched patients who underwent thoracoscopic lobectomy or conventional thoracotomy and lobectomy. Analgesic requirements were significantly lower in the patients who underwent VATS lobectomy. In addition, the levels of IL-6 and IL-8 were lower in the VATS group than in the group that underwent thoracotomy. Leaver and coworkers⁴⁶ examined immunosuppression due to systemic effects of surgery and found higher numbers of CD4 lymphocytes and natural killer cells and less suppression of lymphocyte oxidation in the VATS group. These studies have shown that VATS lobectomy leads to a reduced inflammatory response, less postoperative reduction in immunosuppression, and less impairment of cellular cytotoxicity than does open lobectomy. These findings could partially explain why perioperative outcomes of VATS lobectomy are superior to the perioperative outcomes of open lobectomy. Whether these trends toward more effective immune function after VATS resection lead to faster recovery or better long-term oncologic outcomes will be important endpoints of future studies.

Oncologic Effectiveness

The ultimate acceptance of thoracoscopic lobectomy will be dependent on its oncologic effectiveness as compared with conventional lobectomy. To date, only one small prospective, randomized trial has compared oncologic results of VATS with open lobectomy. In this study, published in 2000, Sugi and colleagues²⁷ reported that for 100 patients with stage IA non-small cell lung cancer undergoing either open ($n = 52$) or VATS ($n = 48$) lobectomy, there was no difference in 3- and 5-year survival rates. Although this trial is without sufficient power to assess differences between the operations, several additional retrospective studies performed are sufficient for limited analysis. First, most studies demonstrate no differences in number of lymph nodes obtained either by dissection or sampling between conventional and VATS lobectomy.^{25-31,33} Second, data from existing series reveal survival rates for patients with stage I disease that were at least as good as those published in the literature for conventional thoracotomy.³⁴ Some analyses have further documented improved survival when VATS was used.^{4,5} Reasons for the possible differences are unclear, but it has been postulated that preservation of immune function and less systemic release of inflammatory cytokines may be contributing factors.³⁴ In addition, the benefit of adjuvant treatment for resected stage II lung cancer necessitates attempts to maximize planned chemotherapy doses

postoperatively. Thoracoscopic lobectomy, with its lower morbidity rates, allows a high proportion of patients to receive all intended doses.^{51,52}

Cost-Effectiveness

The assessment of cost-effectiveness is controversial because of the difficulty in identifying and including all costs. It is clear that VATS can be associated with high costs of consumables and with longer operative times in inexperienced hands. However, numerous disposable instruments essential to performing thoracoscopic lobectomies, such as linear endoscopic staplers, are also used by many in performing either conventional or limited thoracotomies. Nakajima and colleagues⁵³ published a study from Japan demonstrating that hospital charges were actually lower for the VATS approach. One important variable in the assessment of cost-effectiveness is length of hospital stay. In most series of thoracoscopic lobectomy, the median length of stay was only 3 days.^{1-3,6,13,14} As surgeon experience increases with thoracoscopic lobectomy, the operative times will become comparable to those of conventional approaches. In fact, the mean operative time in the CALGB multi-institutional study was only 130 minutes.¹

A recent study by Swanson et al⁵⁴ used the Premier Perspective Database to compare hospital costs for VATS and open lobectomy procedures in the United States. A total of 3,961 patients underwent either open lobectomy ($n = 2907$) or VATS lobectomy ($n = 1054$). Hospital costs took into account costs associated with the operation, length of stay, and adverse events. Hospital costs were found to be significantly higher for open versus VATS lobectomy, though costs associated with VATS lobectomy were influenced by surgeon experience, whereas this was not the case with open lobectomy.

Overall Complications

The observation that thoracoscopic lobectomy may have a lower complication profile has been supported in multiple studies analyzing outcomes of series including patients undergoing thoracoscopic lobectomy and patients undergoing open lobectomy. In one study, 122 patients undergoing thoracoscopic lobectomy and 122 patients undergoing thoracotomy were compared.⁵⁵ Overall, the incidence of postoperative complications was lower in the thoracoscopic group (17.2% versus 27.9%, $P = 0.046$); however, these patients were matched for age and sex only, and there was no significant difference in the incidence of any of the specific complications reported. Whitson and colleagues⁵⁶ analyzed the outcomes of 147 (unmatched) patients who underwent lobectomy, including 88 by thoracotomy and 59 by thoracoscopy. Thoracoscopic lobectomy was associated with a lower incidence of pneumonia but with no difference in other complications, including blood loss, atrial fibrillation, or number of ventilator days.

Using a prospective database, the outcomes of patients who underwent lobectomy at Duke from 1999 to 2009 were analyzed with respect to postoperative complications.⁵⁷ Propensity-matched groups were analyzed, based on preoperative variables and stage. Of the 1079 patients

in the study, 697 underwent thoracoscopic lobectomy and 382 underwent lobectomy by thoracotomy. In the overall analysis, thoracoscopic lobectomy was associated with a lower incidence of prolonged air leak ($P = 0.0004$), atrial fibrillation ($P = 0.01$), atelectasis ($P = 0.0001$), transfusion ($P = 0.0001$), pneumonia ($P = 0.001$), sepsis ($P = 0.008$), renal failure ($P = 0.003$), and death ($P = 0.003$). In the propensity-matched analysis based on preoperative variables comparing 284 patients in each group, 196 patients (69%) who underwent thoracoscopic lobectomy had no complications versus 144 patients (51%) who underwent thoracotomy ($P = 0.0001$). In addition, thoracoscopic lobectomy was associated with fewer prolonged air leaks (13% versus 19%; $P = 0.05$), a lower incidence of atrial fibrillation (13% versus 21%; $P = 0.01$), less atelectasis (5% versus 12%; $P = 0.006$), fewer transfusions (4% versus 13%; $P = 0.002$), less pneumonia (5% versus 10%; $P = 0.05$), less renal failure (1.4% versus 5%; $P = 0.02$), shorter chest tube duration (median 3 versus 4 days; $P < 0.0001$) and shorter length of hospital stay (median 4 versus 5 days; $P < 0.0001$).³

Similar results were obtained when the STS database was analyzed by Paul and colleagues.⁶ All patients undergoing lobectomy as the primary procedure via thoracoscopy or thoracotomy were identified in the STS database from 2002 to 2007. After exclusions, 6323 patients were identified: 5042 underwent thoracotomy, 1281 underwent VATS. A propensity analysis was performed, incorporating preoperative variables, and the incidence of postoperative complications was compared. Matching based on propensity scores produced 1281 patients in each group for analysis of postoperative outcomes. After VATS lobectomy, 945 patients (73.8%) had no complications, compared with 847 patients (65.3%) who had lobectomy via thoracotomy ($P < 0.0001$). Compared to open lobectomy, VATS lobectomy was associated with a lower incidence of arrhythmias ($n = 93$ [7.3%] versus $n = 147$ [11.5%]; $P = 0.0004$), reintubation ($n = 18$ [1.4%] versus $n = 40$ [3.1%]; $P = 0.0046$), and blood transfusion ($n = 31$ [2.4%] versus $n = 60$ [4.7%]; $P = 0.0028$), as well as a shorter length of stay (4.0 versus 6.0 days; $P < 0.0001$) and shorter chest tube duration (3.0 versus 4.0 days; $P < 0.0001$). No difference was found in operative mortality between the two groups.⁴

Finally, two important meta-analyses assessed the advantages of the thoracoscopic approach. In the first, analyzing the outcomes of 21 studies comparing VATS and open approaches, Yan and colleagues⁴ demonstrated that there were no significant differences in locoregional recurrence but that VATS lobectomy was associated with a reduced systemic recurrence rate ($P = 0.03$) and improved 5-year mortality rate ($P = 0.04$). Cao and colleagues⁵ performed a similar analysis, focusing on studies that included propensity matching. In this meta-analysis, VATS was associated with a lower risk of perioperative morbidity ($P = 0.0004$), confirming the single and multiple institution series in the literature.^{6,58}

LOCALLY ADVANCED DISEASE

The results of patients who underwent lobectomy with chest wall resection were recently reviewed. Of 78

patients who underwent lobectomy and chest wall resection, 68 patients had resection via thoracotomy and 10 patients had a hybrid thoroscopic approach.²⁴ Preoperative, perioperative, and outcome variables were assessed using standard descriptive statistics. All patients underwent complete resection with negative margins. Patients who underwent the hybrid thoroscopic approach had shorter lengths of stay and fewer complications. Advantages of this approach include smaller incision size overall, precision of dissection, and avoidance of rib spreading and scapular retraction/rotation.

Nwogu and colleagues⁵⁹ studied the feasibility of VATS pneumonectomy. In their review of 70 patients who underwent pneumonectomy for malignancy from 2002 to 2008, 24 were done via a VATS approach and 35 via an open approach with 8 conversions to open procedures. In this series, 34% of patients had induction therapy, and these patients were proportionally distributed between the groups. Patients who underwent VATS had shorter lengths of stay and less blood loss. Patients who required conversion had significantly more operative blood loss. Complication rates were similar among all three groups.

Finally, it has been demonstrated that neither T status (>3 cm), nor N status ($>N0$), nor central location is a contraindication to thoroscopic lobectomy.⁵⁸ In a study of 1195 patients who underwent thoroscopic lobectomy, the results of patients with small, peripheral, and clinically node-negative tumors were compared with results of patients who had tumors larger than 3 cm, central tumors, or node-positive tumors. In this study, larger and more central tumors did not increase the complication rates or the conversion rates. While the conversion rate was higher in patients with N1 disease, the complication rate was similar in this subgroup as well.

SUMMARY

Minimally invasive approaches to lung cancer treatment have been demonstrated to be safe and effective for patients with early-stage lung cancer. Thoroscopic lobectomy is designed to achieve the same oncologic result as conventional lobectomy: complete hilar dissection and individual vessel control. The recognized advantages of thoroscopic anatomic resection include less short-term postoperative pain, shorter hospital stay, preserved pulmonary function, better compliance with adjuvant chemotherapy, and fewer complications. As techniques evolve, thoroscopic strategies are increasingly applied to locally advanced lung cancer as well. Although there are no sufficiently powered prospective randomized studies comparing the thoroscopic approach with conventional thoracotomy, there are no data from published series to suggest any difference in oncologic efficacy.

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LUNG CANCER: MULTIMODAL THERAPY

Stefan S. Kachala • David P. Mason • Sudish C. Murthy

CHAPTER OUTLINE

ADJUVANT THERAPY

Adjuvant Chemotherapy

Adjuvant Radiotherapy

INDUCTION THERAPY

Induction Chemotherapy for Early-Stage
Non-Small Cell Lung Cancer

Induction Therapy for Stage IIIA/B Non-
Small Cell Lung Cancer

Induction Chemoradiotherapy

Special Circumstance: Superior Sulcus
Tumors

RECOMMENDATIONS

Although long regarded as the best chance for cure, surgery alone has significant shortcomings in the management of non-small cell lung cancer (NSCLC). Even in the most favorable of circumstances (stage I), failure of therapy is anticipated in 20% to 40% of patients.¹⁻³ Moreover, because most patients do not have localized disease at time of initial diagnosis, surgical resection is offered to only a minority of all patients with NSCLC.

Considerable effort has been directed toward developing preoperative (induction or neoadjuvant) and postoperative (adjuvant) strategies to improve long-term outcome after surgery and to increase the total number of resectable patients. These strategies use chemotherapy and radiation singly, sequentially, or concurrently.

Predicting which patients will not be cured by resection alone would clearly permit identification of appropriate candidates for multimodality treatment. To this end, locoregional lymph node involvement is a powerful predictor of cancer recurrence and should be thoroughly investigated during treatment planning.^{4,5} Tumor histology and size also affect cancer-related and overall survival of resected patients.⁶⁻⁸ Numerous genetic markers are being discovered that may further refine outcome prediction when combined with current imaging modalities (e.g., positron emission tomography).⁹⁻¹¹ Recent reports have proposed systems using histologic and molecular criteria to stratify predicted survival of resected patients.¹²⁻¹⁴

In developing strategies for combined therapies, patterns of failure must be considered. Locoregional recurrence after resection of stage I cancers is rare, but it is fairly common when regional lymph nodes are involved. The impact of improving local control with adjuvant radiotherapy may not translate to a survival advantage because patients seldom die from local recurrence. Even

in the presence of local lymph node involvement, completely resected patients with stage II cancers are still twice as likely to fail systemically as locally.¹⁵ Moreover, patients (stage IB-IIIa) who recur after resection with curative intent show distant sites of disease in up to 75% of cases.¹⁶ Consequently, effective adjuvant systemic therapy (chemotherapy) would be favored to adjuvant local therapy (radiotherapy) for resected cancers at high risk for recurrence.

ADJUVANT THERAPY

Despite enthusiasm for 35 years of promising clinical trials of multimodality treatment of NSCLC, it has only recently become apparent that there is a clear and consistent benefit of adjuvant therapy for resected lung cancer. This ambiguity may have been partly because chemotherapy and radiation protocols are changed frequently, resulting in large numbers of studies that cannot be compared. Also, few studies have been designed to critically examine treatment effects on specific NSCLC stages, as most studies tend to group stages I through III in their treatment arms. This shortcoming has been compounded by lack of accurate, sophisticated staging in most trials.

Unfortunately the promising results generated at high-volume academic centers do not, for a number of reasons, easily translate to less specialized, smaller institutions.^{17,18} Regardless, all patients with the diagnosis of NSCLC should be evaluated by a multidisciplinary team or physician adept in the care of patients with lung cancer in order to recommend and coordinate the optimal therapeutic approach.^{19,20} It is also essential that treated patients are carefully followed.

Adjuvant Chemotherapy

Early randomized trials of adjuvant chemotherapy focused on the use of nitrogen mustard,²¹ cyclophosphamide,²² and a combination of lomustine and hydroxyurea.²³ Cumulatively, these trials demonstrated that treated patients had more postoperative complications without survival benefit. In fact, patients treated with adjuvant cyclophosphamide experienced a worse long-term survival rate than untreated patients.²² This was independently confirmed by meta-analysis.²³ Findings from these early studies have since been discounted because histologic type and pathologic stage were not considered during trial design and chemotherapeutic agents used in these trials have since been demonstrated to be ineffective, if not detrimental, for patients with NSCLC.

As several studies began documenting the efficacy of platinum-based agents for advanced (stage IV) NSCLC, platinum-based adjuvant regimens were trialed with resected patients. Initial enthusiasm was generated when the Lung Cancer Study Group trial²⁴ suggested a disease-free and overall survival benefit in the adjuvant treatment arm. Although the survival advantage was not considered statistically significant, sufficient optimism was generated to continue investigations of platinum-based chemotherapeutic protocols. However, several subsequent trials continued to demonstrate minimal efficacy, even though continued trial design flaws were identified.

A randomized study of cyclophosphamide, doxorubicin, and cisplatin adjuvant therapy for resected stage I to II NSCLC²⁵ did not demonstrate treatment efficacy. This trial suffered from inability to deliver the prescribed chemotherapeutic regimen over the prescribed time and also the toxicity and limited usefulness of doxorubicin in the treatment of NSCLC. Less than 30% of patients in the treatment arm actually received chemotherapy as intended. Other randomized studies have been similarly plagued by incomplete delivery of prescribed postoperative therapies,^{26,27} which in part contributes to the negative findings. Additionally, the dose of cisplatin (40 to 60 mg/m²/cycle) used in most previous trials is substantially lower than currently recommended (80 to 120 mg/m²/cycle).²⁸

Although all of these early platinum trials were considered statistically negative, subtle survival differences were noted between control and treated patients in essentially every study. Not surprisingly, a 1995 meta-analysis of several randomized adjuvant platinum-based trials demonstrated a 13% reduction in the risk of death ($P = 0.08$) for treated patients.²⁹ This finding fueled continued interest in this platinum-based adjuvant treatment and spawned several modern trials. Platinum dosage was adjusted so that patients were scheduled to receive 300 to 400 mg/m² (total dose). Adjuvant radiation therapy was often left to the discretion of participating centers. Two such studies demonstrated trends favoring a survival benefit in treated patients, but neither was considered to be a positive trial.^{30,31} However, the International Adjuvant Lung Cancer Trial^{32,33} demonstrated a clear survival benefit of adjuvant platinum-based chemotherapy. This study included resected stage I to III patients and found a survival advantage, 5% benefit after 5 years ($P = 0.003$),

favoring the adjuvant chemotherapy arm versus surgery alone. This survival advantage is similar in magnitude to that achieved by adjuvant chemotherapy for resected breast and colon cancers.^{34,35}

The Lung Adjuvant Cisplatin Evaluation (LACE) pooled data from the five largest randomized trials at the time and reanalyzed this collective.³⁶ This study amassed information from more than 4500 patients and concluded that postoperative cisplatin-based chemotherapy significantly improves survival in patients with NSCLC. Trials contributing to LACE were heterogeneous with regard to stage (I to III), and subsequent subgroup analysis of pooled data provided insight into the differential effect of adjuvant therapy on specific stages of resected cancer. Based on results from LACE, there is little doubt that resected stage II and III patients experience a meaningful survival advantage from adjuvant chemotherapy—at least 5% for overall survival and 6% for disease-free survival.³⁶ Patients with resected stage IB disease, however, have much less benefit, although there is a trend toward some advantage in much the same way as in Cancer and Leukemia Group B (CALGB) 9633, a trial of adjuvant carboplatin and paclitaxel for resected stage IB patients only.³⁷ An important finding of CALGB 9633 was that patients with resected tumors larger than 4 cm do, indeed, benefit from adjuvant chemotherapy.³⁷ Current guidelines recommend that patients with stage IIA-B and IIIA (with occult N2 disease) receive a platinum-based postoperative chemotherapy regimen.^{19,20} Stage IA-B NSCLC patients who have been completely resected (R0) are advised not to receive postoperative chemotherapy at this time.¹⁹

The application of molecular inhibitors as adjuvant therapy in lung cancer is an area of intense current interest. However, a recent phase III adjuvant clinical trial of gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), versus placebo in resected NSCLC was closed early as interim analyses demonstrated either no benefit or potential detrimental impact.³⁸

Adjuvant Radiotherapy

Studies of the efficacy of adjuvant radiotherapy are confounded by many of the same factors that have plagued, and continue to plague, chemotherapy trials. Many randomized adjuvant radiotherapy trials are composed of patients from all stages of resected NSCLC. Consequently, the expected negligible (or deleterious) effects on patients with early-stage cancer may obscure small beneficial effects for patients with more advanced disease. Also, because the field of radiation oncology has evolved so quickly, many early randomized studies became obsolete before their data had matured. Moreover, most early randomized trials were underpowered. Consequently, it is not surprising that, although feasibility and retrospective studies often yield promising results, no randomized data exist to suggest a survival benefit of postoperative radiotherapy (PORT).

At this time, there is no justification to include adjuvant radiotherapy for resected stages I and II NSCLC. Three randomized trials,³⁹⁻⁴¹ as well as meta-analyses of trials (PORT studies),^{42,43} document a deleterious effect on survival of adjuvant radiotherapy for early-stage

NSCLC. Postulated reasons for this include poor radiotherapy planning,⁴¹ larger fraction sizes,³⁹ greater total radiation dosage,³⁹⁻⁴¹ outdated equipment, and poor quality control.⁴⁴

Although there was some optimism that hilar lymph node (N1)-positive patients (stage II) would provide a good substrate for adjuvant radiotherapy, this does not appear to be the case. Based on subgroup analysis of several randomized trials,^{42,43,45,46} radiotherapy has no significant effect on either local control or overall survival for these patients.

Finally, there are insufficient data to defend use of adjuvant radiotherapy for resected stage III (N2/N3) disease, as well. Even though improved local control has been reported,^{45,46} this has not translated into a meaningful survival benefit. The strongest argument to support adjuvant radiotherapy for resected stage III NSCLC comes from a nonrandomized, single-institution, retrospective study.⁴⁷ Investigators in this study found that PORT was the strongest independent predictor of survival for resected N2-positive disease. This study, however, has been widely criticized,⁴⁴ and PORT meta-analyses consistently fail to demonstrate efficacy for adjuvant radiotherapy for stage III disease.^{42,43} Yet, controversy remains over radiotherapy used in this setting, as one recent trial of adjuvant chemotherapy demonstrated improved 5-year overall survival when patients received thoracic radiation (after their chemotherapy) for resected stage III disease.⁴⁸

INDUCTION THERAPY

Induction or neoadjuvant therapy is any systemic or regional cytoreductive treatment (e.g., chemotherapy, radiotherapy, chemoradiotherapy) administered before definitive locoregional therapy (e.g., surgery). Aggressive surgical (mediastinoscopy or video-assisted thoracoscopic surgery [VATS]) or interventional (transbronchial needle aspiration or endoscopic ultrasound-guided fine-needle aspiration) staging is imperative to ensure that induction therapy protocols are applied to homogeneous patient populations. Some patients may be rendered inoperable because of grade 3 or 4 induction therapy toxicities, and this must be considered and discussed with patients during treatment planning.

Use of chemotherapy in the induction setting has several potential advantages. First, there is earlier initiation of treatment for possible micrometastatic (systemic) disease. Because distant recurrence is the most common mode of failure,¹⁶ early eradication of systemic disease might translate into a survival advantage, and chemotherapy is most effective when the tumor burden is small.⁴⁹ Also, drug delivery and cytotoxic effects may be enhanced as a result of preservation of mediastinal (and possibly tumor) blood supply. Perhaps most important, however, is that a higher percentage of patients will receive their intended dose of chemotherapy when drugs are delivered preoperatively.^{50,51} Neoadjuvant therapy also allows for a period of smoking cessation before resection, a critical element in improving NSCLC patient outcomes.^{52,53}

Induction radiotherapy in combination with chemotherapy has and continues to be investigated vigorously. Two large phase III trials comparing only induction radiotherapy (40 to 50 Gy) were reported several decades ago.^{54,55} Both demonstrated inferior survival rates for irradiated patients. Since then, limited data have emerged to suggest a role for radiotherapy alone as an induction modality. Consequently, induction radiotherapy is discussed primarily in the context of chemoradiotherapy protocols.

Wide adoption of induction therapy is not without concern. Subsequent resections are generally more technically challenging and may result in lung-sparing operations becoming less feasible. Morbidity and mortality rates for surgery after induction therapy may be greater,^{30,56} and for an early-stage cancer, given the expected relatively good survival, the risks may well exceed any tangible benefit. Despite these concerns, several groups are pursuing rigorous induction strategies and demonstrating excellent safety profiles.^{57,58}

Induction Chemotherapy for Early-Stage Non-Small Cell Lung Cancer

Observations from other solid tumor treatment trials suggest that chemotherapy response rates improve as similar drug regimens are applied to earlier stages of disease.⁵⁹ The feasibility of induction chemotherapy for early-stage lung cancer was demonstrated in 2000 by the Bimodality Lung Oncology Team study.⁵⁰ This phase II trial examined the response, toxicity, resectability rate, surgical morbidity, and intermediate survival for patients treated preoperatively with carboplatin and paclitaxel. Two preoperative cycles were administered and three postoperative cycles planned for patients undergoing complete resections. After induction therapy, 56% of patients had a major objective response; 86% of patients underwent complete resection. An impressive percentage, 96%, of patients received the intended preoperative chemotherapy, and 46% received the planned postoperative courses. Treated patients appeared to have normal postoperative recoveries.

The results of a more recent randomized trial suggest a benefit of induction chemotherapy for stages I and II NSCLC.³⁰ The induction regimen consisted of two cycles of mitomycin, ifosfamide, and cisplatin. Two additional cycles were given postoperatively for responding patients. The patient population was heterogeneous, with some stage IIIA patients included in the study. Nonetheless, despite a slightly higher mortality rate for chemotherapy-treated patients, disease-free survival was longer than for untreated patients with stage I or II cancers. However, postoperative platinum-based chemotherapy in stage II and no adjuvant therapy for stage I remains the preferred approach.¹⁹

Induction Therapy for Stage IIIA/B Non-Small Cell Lung Cancer

In 1982, Pearson and colleagues reported on the dismal outcome of surgery alone for stage IIIA (N2 lymph node-positive) patients.⁶⁰ They noted a 9% 5-year survival rate

for gross mediastinal lymph node involvement and a 24% survival rate for patients with microscopically positive nodes. Even for occult, single-station N2 disease, the best reported survival rate is less than 30% after 5 years.⁶¹ Local recurrence seldom contributes to mortality, because most of these patients die of metastatic disease. Consequently, induction chemotherapy as the systemic component of multimodality treatment for patients with locally advanced NSCLC has been investigated.

By the mid-1990s, the recognized standard of care for resectable stage IIIA (N2-positive) NSCLC was changed by the near-simultaneous publication of two small randomized trials designed to study the efficacy of induction chemotherapy followed by resection. Until this time, most had considered combined definitive chemoradiotherapy as the standard of care. Collectively, these two reports represented data acquired from only 120 patients. Rosell and associates⁶² compared surgery alone with three cycles of induction chemotherapy (platinum based) followed by surgery. All patients in the study were scheduled to receive postoperative thoracic irradiation. A second, more chemotherapy-intensive trial consisted of three cycles of a cisplatin regimen given as induction with three additional cycles planned postoperatively for responding patients.⁶³ In this trial, radiotherapy was reserved for unresectable or incompletely resected patients. Entry into either trial required pathologic confirmation of mediastinal lymph node involvement (N2 disease) by mediastinoscopy, or T3 disease. Although neither study was without shortcomings, both trials were stopped early because interim analyses demonstrated a significant advantage favoring patients given induction chemotherapy. Mature, actual (not actuarial) survival updates have been published, with an average of 7 years of follow-up and these results appear to hold up.^{64,65}

In 2012, the results from the Chemotherapy for Early Stages Trial (CHEST) were reported.⁶⁶ This study sought to capitalize on the results from EORTC 08955 in which gemcitabine and cisplatin induction therapy had produced response rates of 70% and almost 19-month median survival.⁶⁷ CHEST was terminated early because of enrollment, but even with this limitation demonstrated an absolute difference at 3 years of 5.1% progression free survival and 7.8% overall survival benefits.⁶⁶ Taken together, these reports document a durable and statistically significant survival benefit of induction chemotherapy with surgery versus surgery alone, and they translate into a 20% better 5-year survival rate.

Induction Chemoradiotherapy

Radiotherapy in sequence after chemotherapy (with or without surgery) has long been used to consolidate the local component of therapy for stage III NSCLC.⁶⁸⁻⁷⁰ Concurrent chemoradiotherapy has several theoretical advantages over the sequential strategy. Contemporary drugs active in NSCLC (e.g., cisplatin, paclitaxel) are radiation sensitizers and allow a synergistic tumoricidal effect when given concurrently with ionizing radiation. Although combined therapy is clearly more toxic,⁷¹ several investigators have found the subsequent operative mortality and morbidity rates to be similar to those of

induction chemotherapy alone if appropriate perioperative safeguards and patient selection are optimized.^{56,72} A hypothetical advantage of concurrent chemoradiation induction therapy is reduction in tumor bulk, permitting unresectable lesions to be removed with negative margins, or the potential for lesser resections to be performed (lobectomy as opposed to pneumonectomy). Finally, delivery of ionizing radiation when tumor vascularity has not yet been disrupted by surgical dissection may enhance response.

Since 1990, the standard of care for patients with unresectable stage IIIA disease (bulky N2 involvement), and for most patients with stage IIIB NSCLC, has been concurrent chemoradiotherapy.⁷³ Based on encouraging observations with regard to clinical response rates but a disappointing rate of local failure, trials were devised to examine the addition of surgery to provide “more definitive” local control.⁷⁴ The Southwest Oncology Group (SWOG) organized the most widely reported, multi-institutional feasibility trial of this strategy, SWOG 8805. The treatment protocol consisted of two cycles of induction chemotherapy (cisplatin and etoposide) and 45 Gy of concurrent radiotherapy for patients with stage IIIA or IIIB NSCLC.⁷⁵ Of the 126 patients enrolled, 60% had stage IIIA and 40% had stage IIIB disease. Fifty-three percent of the stage IIIB patients had N3 lymph node involvement. A 6% operative mortality rate resulted, even though almost one third of the operations required pneumonectomy.⁷⁶ This compared favorably with contemporary surgical series without induction therapies,^{77,78} and it underscored the possibility of safely performing resection after combined neoadjuvant therapy.⁷⁵ This notion has since been reaffirmed by more recent studies.^{57,58}

Stage IIIB disease with N3 lymph node involvement is generally considered inoperable because of an inability to obtain a complete resection and a near-universal pattern of systemic failure after aggressive local therapy. Growing experience with surgery after induction chemoradiation has allowed certain centers to offer resection to selected stage IIIB patients. In SWOG 8805, patients with stage IIIA and IIIB disease had equivalent clinical and pathologic responses and similar survival rates.⁷⁵ These investigators and others⁷⁹⁻⁸² noted that only patients who had sterilization of their mediastinal disease after induction treatment benefited from treatment. For patients experiencing complete pathologic responses (i.e., no viable tumor found in the resected specimen), a 40% to 55% 5-year survival rate is expected.^{72,82} Because of this, more recent therapeutic regimens have attempted to improve the preoperative sterilization rate by increasing the dosage of radiation in the induction chemoradiation treatment to greater than 5900 cGy.^{57,58}

A single-institution experience using hyperfractionated radiotherapy with concurrent induction chemotherapy (cisplatin and paclitaxel) has identified an intermediate prognostic group.^{83,84} Patients with stage IIIA/B disease who were treated with this regimen were equally likely to benefit whether they had N2 or N3 disease before treatment (Figure 19-1). Patients downstaged from N3 to N2, or those IIIA patients with residual N2 disease at surgery, still had a median survival rate of 27 months and a 31% 5-year survival rate.⁷²

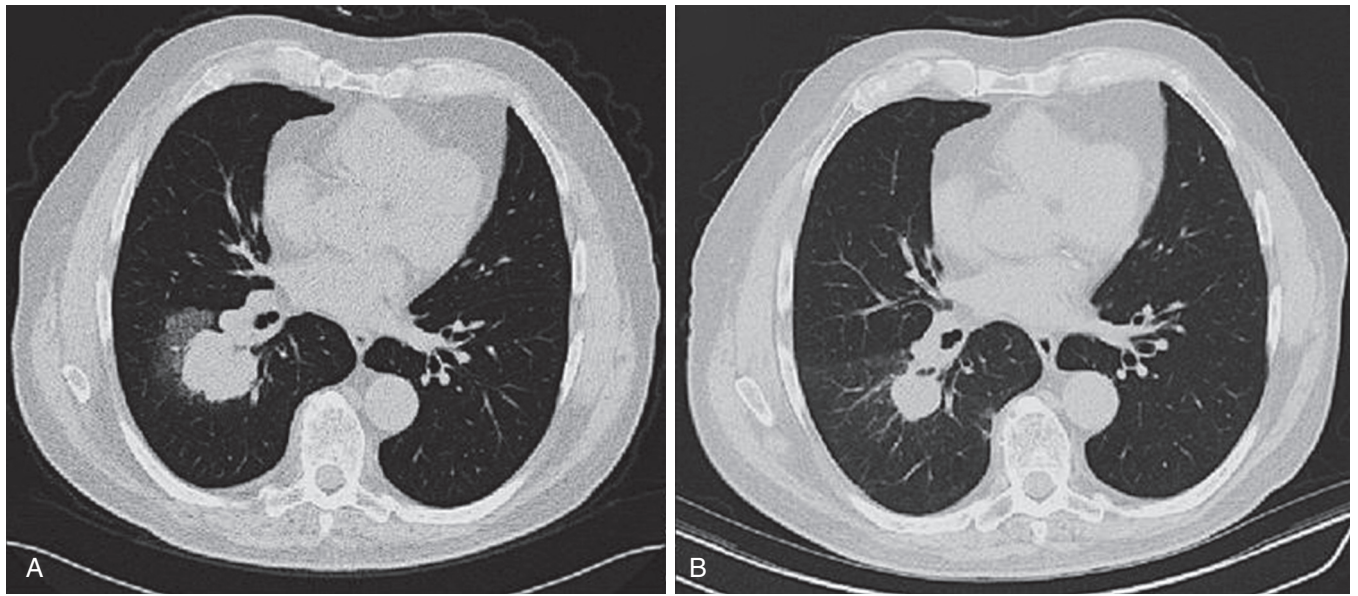


FIGURE 19-1 ■ Pre- (A) and post-induction (B) chemoradiotherapy chest computed tomographic images in a patient with stage IIIA non-small cell lung cancer (NSCLC). Note the reduction in size of the primary lesion and peritumoral ground-glass opacity after therapy.

A few recent randomized studies of induction chemotherapy and chemoradiotherapy for stage IIIA NSCLC question the usefulness of surgery as part of any treatment algorithm. In SWOG 8805, 21% of resected patients had a complete pathologic response with sterilization of primary lesion and regional lymph nodes (i.e., primary T0N0). An additional 37% of patients had only microscopic residual cancer.⁷⁵ Such observations led some investigators to speculate whether resection actually contributed to survival at all or merely provided prognostic information of response to therapy.

To address whether surgery benefits patients with stage III NSCLC, the National Cancer Institute sponsored a multi-institutional phase III trial (INT 0139), in which 429 patients received two cycles of cisplatin and etoposide with concurrent thoracic radiotherapy (45 Gy), followed by either resection or additional chemoradiation therapy. Resected patients were scheduled for two postoperative cycles of chemotherapy, whereas patients randomized to the no-surgery arm were to receive uninterrupted radiation up to 61 Gy with two additional cycles of chemotherapy. Although there were more early deaths in the surgical arm (14 versus 3), disease-free survival rates were superior when resection was a component of treatment (log-rank, $P = 0.02$). The 3-year survival rate in the operated group was 29% compared with only 19% in the chemoradiation-alone cohort.⁸⁵ The outcomes update, however, did not demonstrate a clear survival advantage for the whole group, although subgroup analysis showed a benefit favoring addition of surgery when the resection was lobectomy and not pneumonectomy.⁸⁵

Another randomized trial of induction chemotherapy followed by either resection or definitive radiotherapy demonstrated equivalence of the two treatment arms.⁸⁶ The 5-year overall survival rates were 15.7% and 14% for surgery and radiotherapy, respectively. The authors were left to conclude that, because of the lower

side-effect profile and lower treatment-related mortality, radiotherapy, and not surgical resection, should be considered the preferred locoregional treatment for these patients.

Current investigative efforts to enhance survival in patients with stage III disease are focused on novel induction chemotherapy drug combinations, different dosage schedules and intensities, altered radiation fractionation schemes, and the use of biological response modifiers targeting inflammation, angiogenesis, tissue invasion, cellular proliferation, apoptosis, and metastasis.⁸⁷⁻⁸⁹

Surgery remains central in the accurate staging of these patients and enhances survival for some patients with stage IIIA or IIIB NSCLC. Unfortunately, no patient or tumor characteristics can predict response to induction therapy. Moreover, clinical, noninvasive, and radiographic assessments of response have been disappointing.⁷⁰ Semiquantitative positron emission tomography (PET)^{90,91} and some minimally invasive techniques (e.g., endoscopic ultrasound-guided fine-needle aspiration,⁹² VATS,⁹³ repeat mediastinoscopy^{94,95}) may permit identification of patients most likely to benefit from resection after induction therapies. Nonresponders might be best served by alternative or experimental therapies.

For these reasons, the optimal treatment of patients with stage III NSCLC remains undefined. Although the role of surgery is unclear and the impact of improved post-induction staging unknown, it is clear that complete resection can provide improved long-term outcomes in appropriately selected patients.^{96,97}

Special Circumstance: Superior Sulcus Tumors

Patients with superior sulcus (Pancoast) tumors represent a unique group who serve as attractive candidates for induction protocols. The biological behavior of some of

these tumors seems to differ from that of other NSCLC in that extensive local disease can occur without the obligate systemic disease that accompanies other T3 tumors.⁹⁸ Nonetheless, presence of regional lymph node involvement remains a powerful negative predictor of survival after Pancoast tumor resection. In approximately one third of Pancoast tumor resections, complete resection is not obtained.⁹⁹ This is significant because an incomplete resection does not benefit the patient.⁹⁹⁻¹⁰²

Long-term survival after resection of a superior sulcus tumor was first observed only after the addition of adjuvant radiation therapy.¹⁰³ Subsequently, an induction radiation therapy strategy was developed that dramatically improved survival compared with historical controls.¹⁰⁴ Despite these advances, complete resection for node-negative T3 tumors was possible in less than two thirds of patients. Unlike standard stage II/III disease, locoregional disease was the most common form of recurrence.¹⁰⁵

The feasibility of induction chemoradiation therapy for patients with superior sulcus tumors was evaluated in a 2001 multi-institutional trial.¹⁰⁶ The study population included patients who had N2/N3 node-negative disease with T3 or T4 tumors and adequate cardiopulmonary fitness to tolerate resection. Patients were given two cycles of cisplatin and etoposide with concurrent radiation (45 Gy). The radiation field included the primary tumor and ipsilateral supraclavicular fossa, but it excluded the hilum or mediastinum. Surgery was performed 3 to 5 weeks after the end of the induction therapy. Two cycles of “boost” (adjuvant) chemotherapy were scheduled after recovery from surgery.

The induction therapy was completed as planned in 92% of patients. The related mortality rate was 3%. Of the enrolled patients, 75% underwent surgery. Of these, 92% underwent complete resection. The 2-year survival for completely resected patients was a surprising 70%. Updated mature results of this phase II trial demonstrated a 44% 5-year survival for the entire cohort

and a 12% local relapse rate versus 40% for historical controls.^{106,107}

RECOMMENDATIONS

The extent of NSCLC at initial diagnosis, as defined by American Joint Committee on Cancer staging,¹ is currently the only reliable predictor of survival. It is therefore essential to exhaust all reasonable efforts to obtain accurate staging information before consideration of adjuvant or induction therapies. Multimodality therapy should be used in a stage-dependent manner, guided and coordinated by a multidisciplinary team. This is summarized in Table 19-1.^{19,20}

Staging protocols must include a thorough search for distant metastatic disease and provide accurate information regarding locoregional lymph node involvement. We currently favor using PET as part of the metastatic survey and prefer mediastinoscopy for evaluation of mediastinal lymph nodes, although we recognize that endoscopic and endobronchial staging modalities are rapidly becoming an equivalent standard of care. Our institutional experience with PET to stage the mediastinum has not measured up to that reported elsewhere^{108,109} and has not replaced invasive mediastinal staging for this purpose in our practice.

There is little doubt that adjuvant chemotherapy has a role in the management of resected stage II/III NSCLC and is the standard of care at this time.^{19,20} Chemotherapy should revolve around a platinum-based regimen, and it is becoming increasingly apparent that patients benefit most when the intended dose of chemotherapy is delivered.

There is still active debate regarding the use of adjuvant chemotherapy for stage IB disease. Ongoing trials should help clarify this issue, although on the basis of current data, adjuvant chemotherapy for patients with stage I tumors should not be used.¹⁹

TABLE 19-1 Summary of Multimodality Guidelines

Stage	Surgery	Adjuvant Therapy	Radiation	Chemotherapy	Level of Evidence
I	Yes	No	No	No	1B—Surgical resection 1B—Against postoperative chemotherapy 1A—Against postoperative radiation therapy
II	Yes	Yes	No	Yes	1B—Surgical resection 1A—Postoperative chemotherapy 2A—Against postoperative radiation therapy
IIIA (N2-occult)	Yes	Yes	May be considered	Yes	1A—Adjuvant chemo 2C—Adjuvant radiation
(N2-discrete)	Yes	No	Yes (Definitive or induction recommended)	Yes	1A—Definite or induction followed by surgery 1C—Against primary resection followed by adjuvant therapy
IIIB (N2, N3)	No	No	Yes (Definitive concurrent)	Yes	1A—Definitive concurrent 1A—Against induction followed by surgery

Patients with stage IIIA/B NSCLC do poorly with surgery alone. After numerous studies and much debate, the optimal use of induction chemoradiation therapy remains largely unresolved. Although recent randomized trials do not favor the inclusion of surgery, complete resection can provide improved long-term outcomes in appropriately selected patients.^{96,97}

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LUNG CANCER: SURGICAL STRATEGIES FOR TUMORS INVADING THE CHEST WALL

Rajeev Dhupar • Michaela Straznicka • Garrett L. Walsh

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INTRODUCTION AND HISTORY

Lung cancer continues to be the leading cause of cancer-related deaths in both men and women. Over 75% of non-small cell lung cancer (NSCLC) is advanced in stage at presentation, with extensive locoregional disease or distant metastasis. Most resectable lung cancers are confined to the pulmonary parenchyma, but 5% to 8% extend beyond the lungs and invade the pleura, soft tissues, or osseous structures of the chest wall.^{1,2} Chest wall invasion for surgical staging (T3) is defined as any tumor involvement into or beyond the parietal pleura. Pathologists can further describe these tumors by their depth of chest wall invasion, but this is infrequently reported in this subset of T3 patients.

Historically, chest wall invasion by a tumor of any histology was considered unresectable. Early surgical experience demonstrated that the surgical violation of the parietal pleura resulted in a sucking chest wound with immediate pulmonary collapse, often leading to the rapid demise of the patient. Dr. M. Michellau presented to the Institute of France in Paris in March of 1818 with a fungating mass protruding from his left chest wall. Dr. Richerand proposed a resection of the involved rib and pleura, an unprecedented operation at that time. On March 31, 1818, Dr. Richerand resected the left sixth and seventh ribs of Dr. Michellau with an unexpected occurrence of acute respiratory distress on entrance into the chest cavity. The patient was saved by covering the aperture with a linen cloth plastered with cerate. Despite a

rocky postoperative course, Dr. Michellau survived and returned home 27 days postoperatively. The pathology of the lesion is not known, but a primary rib malignancy is suspected.³

In the summer of 1883, a brilliant young surgeon, H. M. Block, in what was then called Danzig, East Prussia (now Gdansk, Poland), carried out the first planned pulmonary resection. Dr. Block had performed successful open chest surgery on experimental animals and was eager to apply his experience to humans.⁴ He chose a young female relative with a diagnosis of bilateral pulmonary tuberculosis and performed a thoracotomy to resect her diseased lung. Although the details of the operation are not known, we do know that the operation had a tragic end. A few days later, the short, brilliant career of Dr. Block ended with a self-inflicted gunshot wound to the head.⁵

Murphy⁶ described his experiments and clinical experiences with open pneumothorax during his address to the American Medical Association in 1898. Parham,⁷ in 1898, was the first in the United States to report resection of a bony chest wall tumor involving three ribs. A controlled pneumothorax with soft tissue coverage was created. This patient survived, although many others who followed did not.

The difficulties of operating with an opened pleural space in a spontaneously breathing patient were all too apparent to the surgeons of those times. Working without adequate control of the airway and ventilator support was difficult, and the patient quickly deteriorated once the

chest was open. Many ideas were investigated to overcome these deficiencies of the anesthetic techniques.

Major surgical and anesthesia advances were introduced in 1904 at the German Surgical Congress in Berlin. Two techniques, designed to surmount the open chest problem, were proposed. Ferdinand Sauerbruch,⁸ from the surgical clinic of von Mickylykz at the University of Breslau, introduced his method of *unterdruck* (low-pressure) ventilation. Lung expansion was maintained after thoracotomy by keeping an experimental animal's entire body inside a negative-pressure chamber (at -15 cm H_2O) while the head remained outside the chamber with the anesthesiologist. Brauer⁹ described the benefits of *uberdruck* (high-pressure) anesthesia, in which the lung was kept expanded by placing the patient's head in a glass positive-pressure chamber.

Surprisingly, the *unterdruck* method initially was the preferred technique. Sauerbruch and von Mickylykz built a negative-pressure operating room large enough to accommodate an entire surgical team, in which successful thoracic operations were carried out. These rooms continued to be built as late as 1918 in Munich by Sauerbruch, making this approach the favored method in Germany throughout the 1930s. Sauerbruch's ideas and methods so dominated his associates and contemporaries that little progress in other anesthetic techniques issued from Germany during this era.

Major progress, however, had already begun and would continue in France, England, and the United States during roughly the same period. The use of positive-pressure ventilation of the lungs was slowly being developed. Reliable delivery of positive pressure to the lungs was possible only by direct intubation of the trachea, and at that time, a tracheotomy was the only technique for tracheal intubation. Most surgeons were unwilling to perform a tracheotomy simply to deliver an anesthetic under positive pressure. The first systematic use of intubation through the mouth using bellows to inflate the lung was by the Frenchman DePaul, who intubated and resuscitated neonates in the mid-1800s. Other French surgeons, Tuffier, Quenu, and Doyen, and Milton in Egypt, also used positive pressure during thoracotomies in the last few years of the 19th century.

In the late 1800s, two physicians from New York, Joseph O'Dwyer and George Fell, described intubation techniques and positive-pressure ventilation. Dr. O'Dwyer developed a practical method of endotracheal intubation for the treatment of diphtheria, which was applied in thousands of cases and resulted in a gratifying decrease in the mortality rate of that dreaded disease.^{10,11} Dr. Fell also used a crude device to maintain ventilation in patients suffering from drug overdoses.¹² In New Orleans, Parham and Matas used the combined Fell-O'Dwyer apparatus in 1886 to administer positive-pressure surgical anesthesia.¹³

The use of positive-pressure ventilation identified the need for cuffed endotracheal tubes for the reliable delivery of anesthesia to the lungs. Eisenmenger first described a cuffed endotracheal tube in 1893. Placement of such tubes was facilitated by Kirstein,¹⁴ who introduced direct laryngoscopy in 1895 for safe, reliable placement of endotracheal tubes in the trachea. In 1907, Chevalier

Jackson improved the laryngoscope and produced the instrument that is still in use today and bears his name.¹⁵ A practical endotracheal tube design for general use was introduced by Guedel in 1928,¹⁶ and its use became widespread starting in the 1930s. In 1938, the first operative use of ventilators was made with the Freckner Spiropul-sator, developed in Sweden. In 1942, Griffith and Johnson, in Montreal, Canada, introduced curare to facilitate intraoperative controlled ventilation.¹⁷

With these international advances in intubation techniques and airway management, positive-pressure anesthesia slowly became a clinical reality during the last few years of the 19th century and the first few decades of the 20th century. As a direct result, surgeons were now willing to transgress the parietal pleura to address the complex pathologies of the thoracic cavity with increasing frequency. From 1904 to 1929, surgeons began to specialize and perform a series of pulmonary resections, and by 1929, thoracic surgery had become an established specialty. Most early lung resections and thoracoplasties were performed because of infections. Surgical morbidity and mortality rates were horrifying at first, and only the bravest patients and the most resilient surgeons chose to continue to work in the field. Sepsis was the predominant cause of death and was correlated mainly with an open pleural cavity.

In 1947, Coleman¹⁸ reported long-term survival after en bloc excision of the chest wall with pulmonary resection. Concurrently, significant strides in chest wall reconstructive techniques were occurring through the use of fascia lata grafts, autogenous rib grafts, large cutaneous flaps, and latissimus dorsi muscle flaps, as described by Campbell in 1950¹⁹ and Grillo et al in 1966.²⁰ Over the past 40 years, we have witnessed further refinements in surgical procedures, the use of prophylactic antibiotics, improved anesthesia delivery and monitoring, and the implementation and use of critical care units for postoperative ventilation. Today these advances permit the safe and effective resection of locally advanced lung cancer with extensive chest wall involvement on a routine basis.

Pancoast tumors comprise a distinct surgical entity and are discussed separately.

DEMOGRAPHICS AND SYMPTOMS

Patients with lung cancer are usually 50 to 70 years old; lung cancer is rarely seen in patients younger than 30 years, although with the ongoing epidemic of children and young teenage smokers, advanced lung cancer can be seen even in these younger age groups (Fig. 20-1). Lung cancer with chest wall invasion most typically presents in patients in their seventh decade, with a median age of 64 to 66 years (range, 38-93 years).²¹⁻²³ Overall, lung cancer incidence and mortality continue to be disproportionately higher in men than in women, although the gap is narrowing. Lung cancer with chest wall invasion has an overwhelming predominance in men; women represent only 10% to 30% of patients in several recent studies.^{2,21-23} Current or previous smoking history is elicited in approximately two thirds of patients, with an average 50-pack-year history per patient.^{2,21}

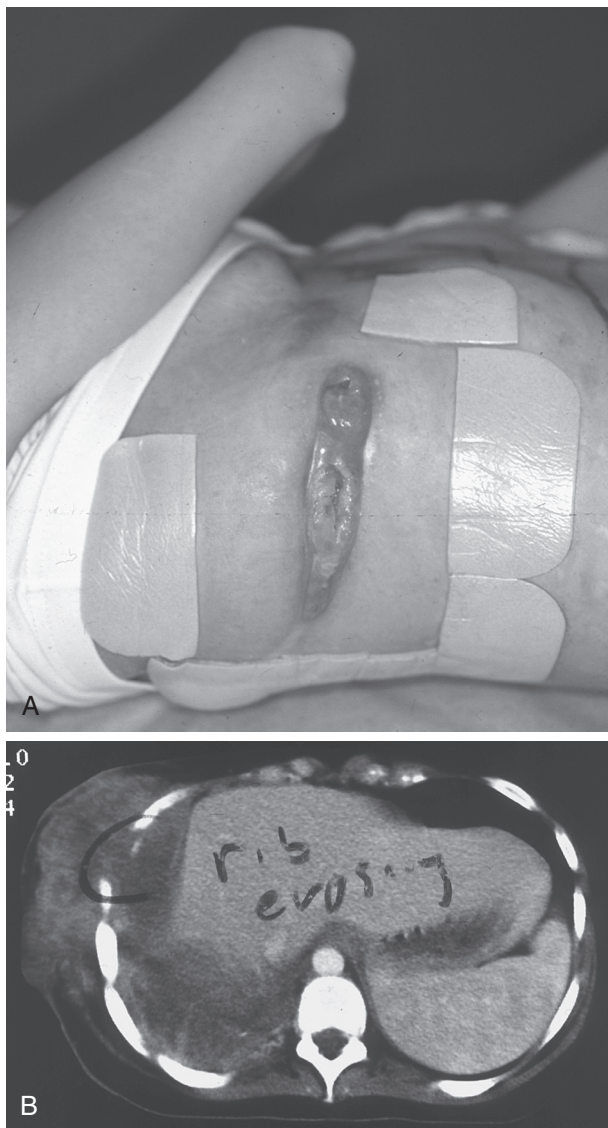


FIGURE 20-1 ■ **A**, A 25-year-old woman presents to our institution with a nonhealing thoracotomy incision with a draining wound after an attempted decortication for what was initially felt to be a postpneumonic empyema. **B**, A CT scan demonstrates a large right lower lobe adenocarcinoma of the lung with direct invasion of the chest wall as the cause of the nonhealing wound.

The lung parenchyma has no sensory nerve fibers, which accounts for the often late clinical presentation of most bronchogenic tumors. Most patients have presenting symptoms related to compression, invasion, or obstruction of the lung parenchyma or airways, or invasion of the chest wall or mediastinal structures. Metastasis to distant organs, including neurologic symptoms and bone pain, unfortunately are common.

Patients whose lung cancer has invaded the chest wall have similar presenting symptoms, including chest pain (40%-60%), cough (14%), recurrent lower respiratory tract infection (10%-25%), weight loss (10%-18%), hemoptysis (12%), and dyspnea (11%). As many as 25% of patients can be asymptomatic (Table 20-1).^{2,21,22}

TABLE 20-1 Presenting Symptoms in Lung Cancers with Chest Wall Invasion

Presenting Symptom	Percentage
Chest wall pain	40%-60%
Recurrent lower respiratory tract infection	10%-25%
Weight loss	10%-18%
Hemoptysis	12%
Dyspnea	11%
Cough	11%
Asymptomatic	25%

The right lung has a slight predominance in location of lung cancers, both in general and for those with chest wall invasion.² Okada and colleagues described a marked predilection for the upper lobes in his series of lung cancers that invade the chest wall, although not all series confirm this finding.²³ Lung cancers in general have a slight predilection for upper lobes rather than lower lobes, which theoretically may be related to the relative increase in ventilation (and associated carcinogens) to the upper portions of the lungs.

Squamous cell carcinoma is the classic smoking-related tumor, and for many years it was the most common histology. In recent years, however, adenocarcinoma has overtaken squamous cell carcinoma as the most common lung cancer worldwide. Several series of patients with lung cancer that invades the chest wall have demonstrated that the histologic diagnosis of squamous cell carcinoma remains the most common, followed closely by adenocarcinoma; large cell carcinoma and adenosquamous carcinoma comprise fewer of these tumors.^{2,22-24} Average tumor diameter in these patients, by computed tomography (CT) measurements, was 6.5 cm; tumors ranged from 2 to 18 cm in maximum diameter.²

DIAGNOSIS

Chest roentgenography is useful for the identification of parenchymal lesions, although it has poor specificity and sensitivity for detecting chest wall involvement. Rib destruction is a reliable indicator of chest wall invasion, although it is identified on routine chest x-rays in only a fraction of cases. Tissue diagnosis of malignancy in these T3 lesions usually is obtained by transthoracic needle aspiration by our interventional radiologists.

Peripheral lung lesions with the suggestion of chest wall involvement may require additional radiographic testing to confirm invasion. These radiographic techniques include CT scans, nuclear medicine (scintigraphic) bone scans, magnetic resonance imaging (MRI), and positron emission tomography (PET) scans. Although gross tumor involvement of the chest wall is easily diagnosed with these radiographic modalities, confirmation of isolated parietal or mediastinal pleural invasion is more difficult and often unreliable.²⁵⁻²⁸

The use of CT scans has greatly increased the precision of tumor localization, allowed accurate evaluation of contiguous organ involvement, improved assessment of lymph nodes, and improved the identification

of pulmonary metastasis. A CT scan is excellent for assessing rib destruction and intercostal muscle tumor extension but is relatively inaccurate for invasion limited to the parietal or mediastinal pleura.^{25,26,28} Shirakawa and associates²⁹ identified patients who had parietal pleural invasion by using inspiratory/expiratory CT scans. They demonstrated that a respiratory phase shift of greater than half of a vertebral body height in middle and lower lobe tumors reliably predicted the absence of parietal pleural invasion. The accuracy and negative predictive value were 90% and 86%, respectively, in tumors located in the lower and middle lobes. For upper lobe tumors, however, the respiratory phase shift did not correlate with operative findings regardless of whether invasion was present. This discrepancy is a result of the minimal normal respiratory phase shift of these lung fields when the patients were studied in the supine position.

MRI has the advantages of multiplanar imaging and high differential signal intensity, which are invaluable for determining vascular invasion and spinal involvement. Conventional MRI, unfortunately, is just as limited as CT scans for evaluation of parietal and mediastinal pleural invasion. Kodalli and associates²⁷ used breath-hold inspiration and expiration MRI to assess parietal pleural invasion. Pleural invasion was excluded when tumor displacement exceeded 5 mm in reference to chest wall structures or relevant mediastinal structures (e.g., the aortic arch).

This study identified 100% sensitivity and specificity for pleural invasion for tumors located in the middle lobe and basilar segments of the lower lobes. Studies of upper lobe tumors and those located in the apical segments of the lower lobes demonstrated a positive predictive value of only 40% but a negative predictive value of 100%. The superiority of MRI to CT scans lies in its ability to assess lung and diaphragm movement in a coronal plane. Insufficient respiratory motion is evident by less than 1-cm movement of the diaphragm on coronal images, and necessary scans could be repeated by asking the patient to take a deeper breath. Although more recent reports have also commented on high sensitivity, specificity, and accuracy of respiratory dynamic cine MRI in evaluating lesions that do not have clearly demonstrated invasion on standard CT or MRI, this modality is not widely available outside of specialized centers.³⁰

Ultrasonography (US) has been compared with CT for detection of chest wall involvement. In a series from 2008, 90 patients with suspicion for chest wall involvement were evaluated preoperatively with CT and US. Their ultrasound criteria for determining chest wall invasion were any two of the following: (1) tumor ingrowth seen into the chest wall, (2) interruption of the pleural reflection, (3) invasion of the ribs, (4) impairment of movement with respiration. Based on these criteria, US was deemed more sensitive than CT (89% vs. 42%) with similar specificity (95% vs. 100%).³¹ Perhaps the real-time imaging of ultrasound during respiration leads to more accurate imaging data.

More invasive methods have been used for detection of parietal pleural invasion, including use of expiratory dynamic CT scans after the introduction of a diagnostic pneumothorax.^{32,33} Lack of invasion was diagnosed on the

basis of appearance of an air space between the mass and adjacent structures. Sensitivity was 100% in both studies for chest wall invasion, although sensitivity dropped to 76% in cases of mediastinal invasion.

Specificity for tumor involvement was 80% in a study by Watanabe and coworkers.³² Benign pleural adhesions caused false-positive results. Complications were reported as mild and included chest pain, shortness of breath, and subcutaneous emphysema. Despite these results from a variety of imaging techniques, we do not feel that these tests are warranted because they potentially subject high-risk patients to a pneumothorax and ultimately are unlikely to alter the planned operative procedure. In some cases, review of the CT images obtained during transthoracic needle biopsy can reveal minimal pneumothoraces incidentally obtained as a result of biopsy. Often, these images will show clear separation from the chest wall (Fig. 20-2).

For most patients, preoperative assessment of chest wall involvement is not critical, because it does not often alter resectability or treatment strategy. However, for the marginal patient, who may be borderline for toleration of lung resection, identifying chest wall invasion, and thus the necessity for combined pulmonary and chest wall resection, may lead the clinician to pursue definitive non-operative treatment with chemoradiotherapy.

STAGING

Accurate staging of NSCLC is critical for effective clinical management. Standard staging includes a complete history and physical examination, laboratory tests (including calcium, alkaline phosphatase, and liver function tests), chest x-ray, CT scan of the chest and upper abdomen to include the adrenal glands, and full body PET scan. In addition, brain MRI is obtained when a patient has neurologic symptoms or when the lesion is locally advanced or nodal disease is suspected.

Surgical-pathologic staging is performed according to the International Staging System for Lung Cancer, using information about the primary tumor (T), nodal status (N), and distant metastasis (M) (Table 20-2).³⁴ “T” status denotes characteristics of the primary tumor, including size and local aggressiveness. Chest wall invasion denotes at least T3 status (for a full description of TNM staging, refer to the most current AJCC Lung Cancer Staging guidelines). “Chest wall involvement,” however, includes a wide pathologic spectrum, from invasion of the parietal pleura only to full-thickness chest wall replacement by tumor.

Nodal status (N) comprises the second feature of the staging system. Clinical evidence of ipsilateral hilar node involvement is classified as N1, which is not considered a contraindication for surgical resection. Ipsilateral adenopathy of the mediastinum increases the nodal status to N2. The most effective treatment modality for these patients is controversial and is discussed later. Spread of tumor to the contralateral mediastinal, contralateral hilar, or any scalene or supraclavicular nodal basins denotes an N3 status; patients with N3 disease generally are not considered surgical candidates.

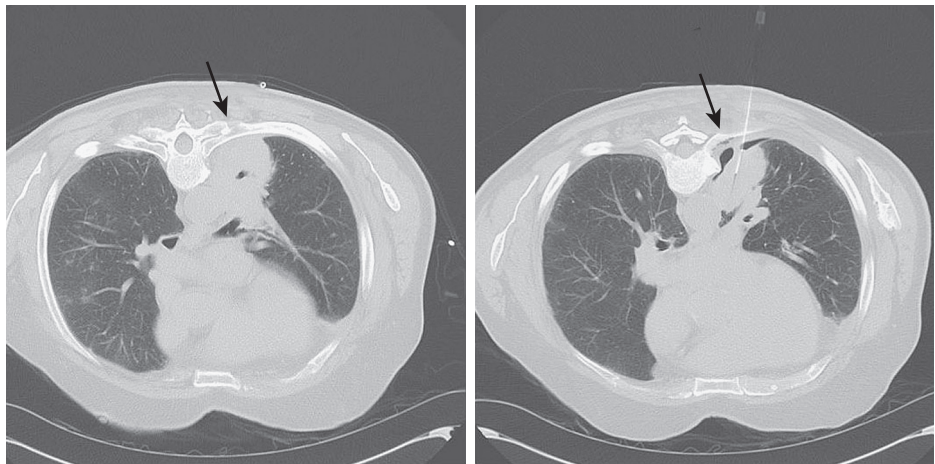


FIGURE 20-2 ■ A CT of the chest reveals a lung mass abutting the posterior rib (arrow in left image). A review of the images obtained during transthoracic needle biopsy showed the mass moving away from the chest wall with a minimal focal area of pneumothorax (arrow in right image). Other images revealed complete separation from the chest wall. Note: The patient is prone in these scans for obtaining the biopsy.

TABLE 20-2 Brief Description of the TNM Stage Groups for Lung Cancer						
Stage 0	Carcinoma in situ					
Stage IA	T1a,b	N0	M0			
Stage IB	T2a	N0	M0			
Stage IIA	T1a,b, T2a	N1	M0	T2b N0 M0		
Stage IIB	T2b	N1	M0	T3	N0 M0	
Stage IIIA	T3	N1	M0	T1-3	N2 M0	T4 N0-1 M0
Stage IIIB	T4	N2	M0	Any T N3 M0		
Stage IV	Any T	Any N	M1a,b			

Patients without evidence of distant metastatic disease are considered to have M0 disease, and they may be candidates for surgical resection. However, in patients with distant metastatic disease (M1), systemic treatment in the form of chemotherapy is currently the treatment of choice, often in combination with radiation therapy for local control.

In 1997 an important change was made to the TNM staging system regarding tumors with chest wall involvement. Before 1997 a NSCLC that was defined as T3 N0 M0 was classified as stage IIIA. Survival data of patients with these tumors revealed that their clinical course with surgery alone was more favorable than the clinical course of other patients with stage IIIA disease (i.e., those with hilar or mediastinal lymph node involvement; T3N1, T3N2, T1N2, or T2N2). Subsequently, T3 N0 M0 tumors had been downstaged to stage IIB with this revision.

Because the survival rate of lung cancer patients with chest wall involvement and nodal disease is significantly worse than that of patients with chest involvement alone, the clinical challenge for surgeons is to identify nodal involvement by noninvasive imaging or minimally invasive biopsy techniques before subjecting patients to extensive chest wall resections.

The importance of correct pretreatment staging cannot be overemphasized. Hilar and mediastinal lymph nodes can be assessed before surgery by using CT scans, MRI, and PET scans. Integrated CT-PET scans measure metabolic activity of tissues and can detect disease in

otherwise normal size-appearing nodal tissue; however, the accuracy for subcentimeter nodules is reduced.

Despite advances in nuclear imaging techniques, mediastinoscopy remains the most sensitive and specific test for evaluating the mediastinal nodes and should be considered before undertaking any major chest wall resection. Another option available for staging the mediastinum is endobronchial ultrasound (EBUS)-guided fine-needle aspiration. EBUS involves the use of a specially designed bronchoscope with an ultrasound transducer at the tip that allows real-time image guided biopsy of nodes adjacent to the airway and can access some nodes at levels 10, 11, and 12.^{35,36} Sensitivity and specificity of EBUS have been reported to be higher than those of CT or PET and comparable to those of mediastinoscopy; in addition, it is less invasive.³⁷ Because of the anatomic location, the preoperative assessment of N1 disease is more problematic via mediastinoscopy. Patients with T3N1 disease still should be considered for en bloc resections, and these patients have a better survival rate than those with N2 disease.

Flexible bronchoscopy is performed for transbronchial biopsies, brushings, and washings. Although it is unlikely that peripheral lung tumors involving the chest wall extend into the airway, it is the authors' practice to perform bronchoscopy immediately before resection to identify any unsuspected endobronchial disease and to assess the airway anatomy.

Bone scintigraphy scans can be used to detect occult bony metastases and confirm bony lesions in symptomatic

patients. The vertebral column is the most commonly affected region for bone metastases. MRI is accepted as the most accurate imaging modality in detecting bone metastases within the vertebral column, and focal imaging can be guided by bone scan abnormalities or symptoms.³⁸⁻⁴⁰ Suspicious uptake in bones other than the vertebral column also requires further investigation, although MRI scans become less useful. False positives are seen in the bony thorax when a history of rib fractures or trauma is noted. False negatives can be appreciated when bone scans are correlated with PET scans. Positive lesions on PET scans, which are not seen on bone scans, may represent soft tissue metastasis.⁴¹ Durski and associates⁴¹ recommend that all patients be staged with a PET scan, and bone scans should be performed only if symptomatically indicated when PET scans are negative. In their series, the use of bone scans in addition to PET scans did not change the clinical stage of any of their patients, although it allowed more precise localization of skeletal abnormalities.

PET scans using ¹⁸F-fluorodeoxyglucose (FDG) are routinely used in addition to CT scans for both initial diagnosis and staging of NSCLC. One study suggests that obtaining both a PET and a CT scan is more cost-effective than performing a CT scan alone for staging.⁴² The reported sensitivity and specificity of PET for thoracic lymph node involvement are 70% to 100% and 81% to 100%, respectively. CT has sensitivity and specificity of 25% to 81% and 56% to 94%, respectively.⁴³⁻⁴⁷ The ACOSOG trial Z0050 evaluated the usefulness of PET for staging NSCLC. Their results support staging NSCLC patients with PET to reduce the rate of non-therapeutic thoracotomy but recommend confirming PET-positive mediastinal nodes with mediastinoscopy. In addition, their recommendations include using PET to guide tissue biopsy in the cases of suspected single-site distant metastases.⁴⁸ Integrated PET-CT was compared with PET alone in a prospective blinded trial in which the same radiologist read an integrated scan and, at a later date, was asked to read the PET images only. Integrated PET-CT was shown to be more accurate at predicting T and N status of patients and was better at determining stage I and stage II disease.⁴⁹ Integrated scans have become standard for preoperative evaluation of all our NSCLC patients.

TREATMENT

Patients with confirmed N2 disease who are devoid of distant metastatic disease are offered treatment on protocol with neoadjuvant chemotherapy. Surgery is offered to those patients whose tumors show an objective response to chemotherapy and whose disease can be completely resected.²² Progression of disease while on chemotherapy is generally regarded as a contraindication to surgery, as is evidence of N3 disease. Preoperative radiation therapy has not been shown to increase survival in several studies but has demonstrated an increased operative mortality.^{1,22,50} Preoperative radiation therapy therefore is not widely used and is not recommended at our institution.

Patients with evidence of metastatic spread should not be considered surgical candidates except in extraordinary circumstances. These circumstances may include isolated brain metastases that can be resected before lung resection.

PREOPERATIVE ASSESSMENT

The most important risk factors for perioperative complications for patients who are undergoing resection of lung tumors are cardiovascular and pulmonary disease, metabolic disorders (e.g., diabetes), and malnutrition. A complete preoperative assessment therefore includes physiologic testing for cardiac and pulmonary reserve, optimal management of diabetes, and nutritional support when needed. Spirometry, arterial blood gases, alveolo-capillary diffusion (D_{LCO}), and xenon ventilation scans determine pulmonary reserve and predict postoperative function. Cardiac evaluation—including electrocardiography (ECG), echocardiography, stress testing, and even cardiac catheterization—may be required to identify correctable disease in high-risk patients. Nutritional assessment includes aggressive diabetic control, optimization of protein stores, and possible enteral or parenteral feeds for severely malnourished patients. Serial measurements of prealbumin levels may be used as a guide to nutritional improvement.

The overall effect on chest wall mechanics and respiratory physiology must be taken into account when evaluating the medical condition of the patient and the extent of pulmonary resection. Most surgeons try to leave a patient with at least 33% of predicted forced expiratory volume in one second (FEV_1) postoperatively. Spirometry, xenon scanning, and exercise oxygen testing are helpful in identifying patients who are truly medically inoperable based on these pulmonary function criteria. No tests, however, can accurately predict the postoperative pulmonary compromise of patients who require chest wall resections. It is often difficult to predict the extent of required rib resections and the requirement for chest wall stabilization and reconstruction. Phrenic nerve or diaphragmatic involvement may lead to further impaired respiratory physiology. Occasionally, in patients with marginal lung function, a nonanatomic or subsegmental resection of the lung may be required if the chest wall component of the operation is extensive.

OPERATIVE TECHNIQUES

Good communication and cooperation with our anesthesia and pain management colleagues is crucial to the success of these operations. Several pain management and anesthetic techniques have dramatically improved the intraoperative and postoperative course for our patients. A plan for adequate pain control, either with epidural catheters or long-acting local anesthetics with non-narcotic and narcotic analgesics, is of vital importance to prevent postoperative morbidity. In addition, a double-lumen endotracheal tube is useful for these cases and greatly facilitates visualization during the surgery.

In most patients, the tumor can be approached via a posterolateral thoracotomy. In tumors that involve the chest wall and the apex of the chest (either superior sulcus tumors proper or large upper lobe tumors with chest wall and neck extensions), an initial anterior neck approach to dissect the subclavian vessels and the brachial plexus may be beneficial before addressing the posterior chest wall component (Fig. 20-3). Depending on the tumor location, the incision may be tailored more posteriorly and extended superiorly between the scapula and spinous processes. Review of the radiographic studies and palpation of the interspaces should identify an intercostal space

at least one rib space below the inferior margin of the tumor for entry into the chest cavity. On entry into the hemithorax, digital examination of the lung and chest wall is performed to determine tumor attachment and assess chest wall fixation. The chest cavity is examined for pleural dissemination or metastatic deposits at other sites. Great care should be taken to prevent disruption of thin adhesions of the tumor to the parietal pleura that may be involved with tumor.

When tumor invasion into the chest wall is radiographically evident before surgery, an en bloc chest wall resection should be carried out with at least one

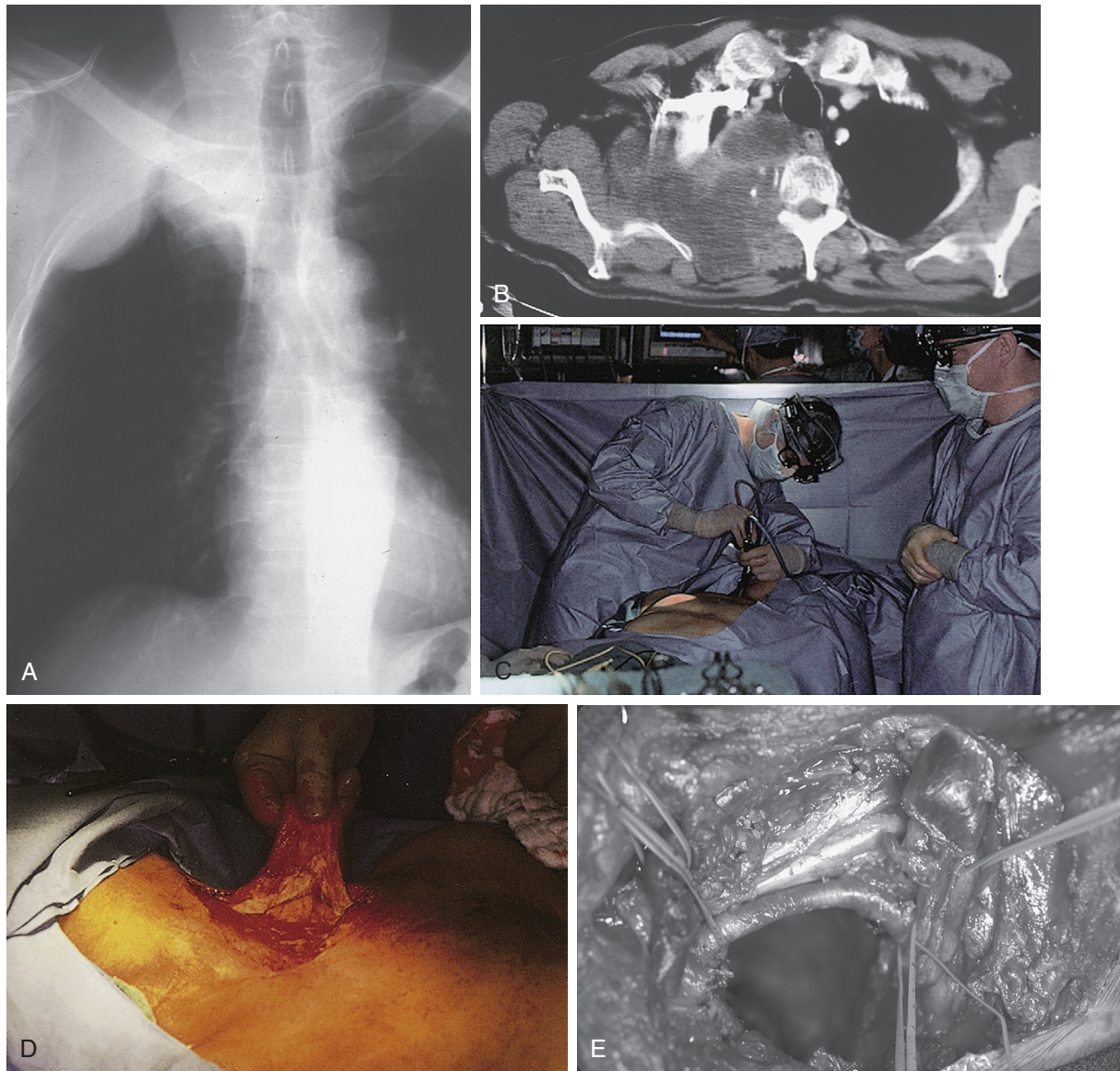


FIGURE 20-3 ■ **A**, Chest radiograph demonstrating a large right upper lobe apical tumor, which was diagnosed a sarcomatoid carcinoma based on transthoracic needle biopsy. **B**, A CT scan demonstrates the full-thickness chest wall involvement with tumor extension into the posterior chest wall musculature. **C**, A mediastinoscopy is performed routinely to rule out N2 or N3 nodal involvement before proceeding with the extensive lung and chest wall resection. **D**, An initial supraclavicular neck dissection is performed to dissect the subclavian vessels and brachial plexus. This is the initial hockey-stick skin incision along the anterior border of the sternocleidomastoid muscle and along the clavicle. **E**, A close-up of the resection of the first and second ribs from the anterior approach with resection of the subclavian vein and preservation of the subclavian artery and brachial plexus as shown.

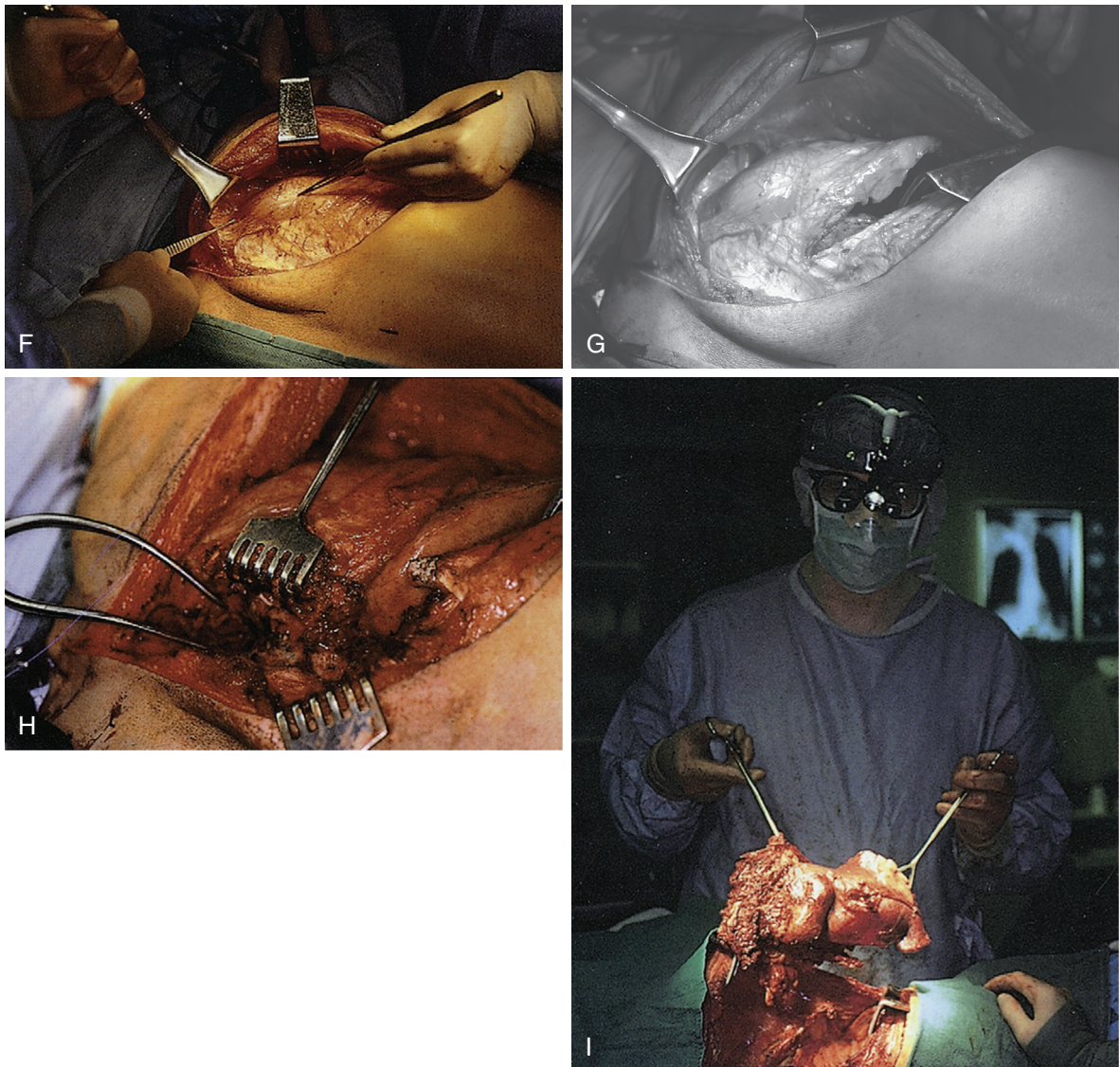


FIGURE 20-3, cont'd ■ **F**, The patient is repositioned. The initial dissection is through a posterolateral thoracotomy with elevation of the scapula after division of the latissimus dorsi muscle and reflection of the serratus anterior muscle. The tumor bulge into the interspaces of the chest wall can be appreciated. There is no gross tumor involvement of the external surface of the chest wall, however. **G**, An interspace is entered caudal to the inferior extent of the tumor involvement. **H**, The posterior elevation of the paraspinous muscles and disarticulation of the posterior ribs from the transverse processes and vertebral bodies. **I**, Complete en bloc removal of the chest wall (ribs one to five) and the right upper lobe.

uninvolved rib and intercostal muscle above and below the mass.⁵¹ An en bloc resection is defined as removal of lung parenchyma in continuity with a portion of the adjacent parietal pleura and chest wall soft tissues. The overlying integument generally is left intact, although complete extension of tumors through the skin can be seen (Fig. 20-4).

On rare occasions when the tumor is large, its bulk can impede the exposure of the hilar structures. In this situation, several firings of a stapler through normal, uninvolved pulmonary parenchyma can permit the initial removal of the tumor and chest wall, with safer dissection of the delicate hilar vessels without the risk of torsion and traction created by the weight of the tumor and attached chest wall. An en bloc resection is preferred whenever it is feasible.

It is more difficult to determine the extent of malignant pleural involvement when the adhesions are thin and filmy between the tumor and the chest wall. The tumor may be somewhat mobile on palpation. A surgeon must resist the temptation to simply lyse these adhesions. An extrapleural dissection must be initiated away from the site of attachment. If the plane is not easily identified at any time during the extrapleural dissection, then the extrapleural dissection must be immediately halted and a full-thickness chest wall resection performed. If the extrapleural dissection appears to proceed easily, frozen section analysis of the parietal pleura is recommended.² If the tumor transgresses the parietal pleura on frozen section, then an additional resection of the chest wall is required. When performing an extrapleural dissection, marking the extent of the extrapleural dissection with

metal clips on the chest wall leaves a permanent radiographic landmark to guide adjuvant radiotherapy if required.

Circumferential margins of 2 cm generally are regarded as adequate, although some surgeons advocate



FIGURE 20-4 ■ A 75-year-old man with a fungating tumor in the left anterior chest wall originating from a bronchogenic carcinoma of the lingula with transmural invasion of the chest wall and skin.

a larger margin of 4 cm on the rib resection.^{21,52} In these studies the mean number of ribs resected was three, with a range of one to five.^{2,21} The oncologic resection should never be compromised by less than a complete resection.

Several circumstances deserve additional mention. Special attention needs to be paid to tumors extending into the intervertebral foramen without intraspinal extension. Disarticulation of the ribs is performed through the costotransverse joints with ligation of the nerve roots as they exit the spinal column.⁵³ Tumors that extend into the vertebral column may require a laminectomy to expose the epidural tumor and involved nerve root. The tumor is dissected free from the dura, and the nerve roots are identified and transected. In cases where the tumor invades the vertebral bodies themselves, a partial resection of the vertebral body may be performed without the need for instrumentation. Resection should be carried out to grossly uninvolved bone and can include complete vertebrectomy with spinal reconstruction (Fig. 20-5). Further discussion regarding vertebral resection and reconstruction is beyond the scope of this chapter.

Anterior tumors that invade into the sternum are resected en bloc with the involved portion of the sternum and attached ribs. A complete resection is mandatory and

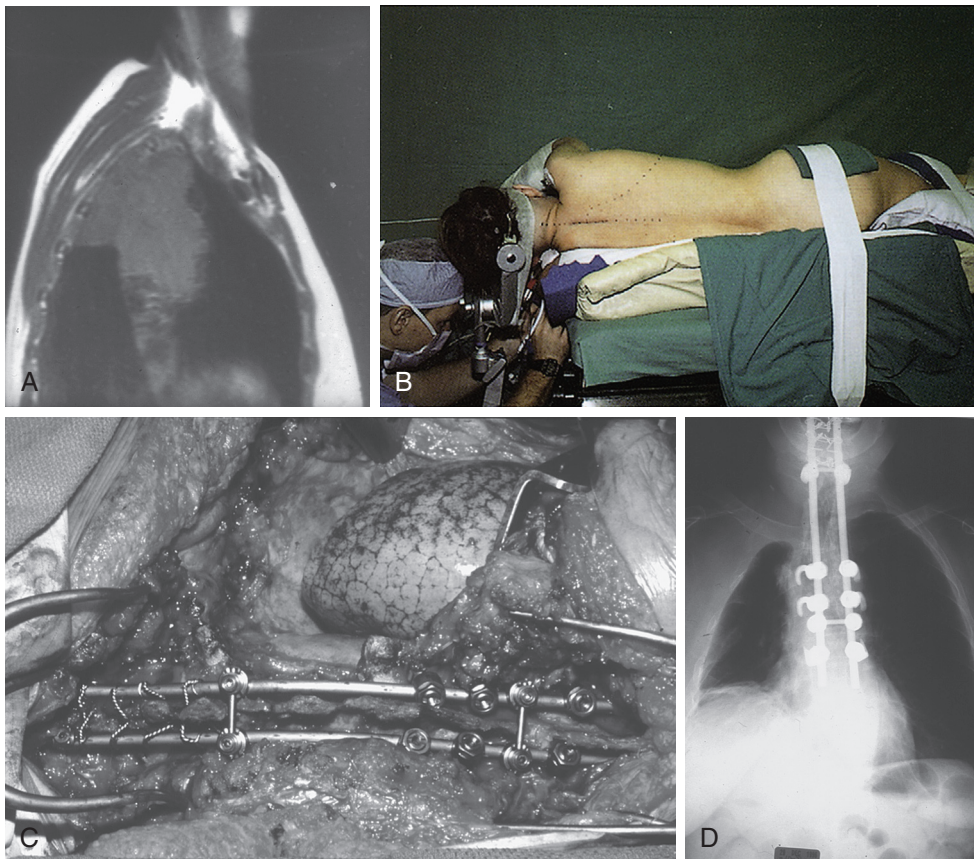


FIGURE 20-5 ■ **A**, A lateral chest radiograph demonstrating a large right upper lobe lung cancer with involvement of the chest wall and T1 through T3 vertebral bodies. **B**, Operative positioning of the patient with the head in cervical tongs to immobilize it and to maintain the alignment of the cervical and thoracic spines. The patient is additionally secured on a beanbag and taped with the appropriate padding of the anterior superior iliac spine. **C**, Intraoperative photograph showing the resected chest wall, right upper lobe, and multilevel vertebral body resection with reconstruction with posterior rods and anterior stabilization. **D**, Chest radiograph posteroanterior demonstrating postoperative instrumentation.

may necessitate a complete sternectomy. Reconstruction with a rigid prosthesis to prevent flail usually is required after a complete sternectomy. If the resection is limited to either the manubrium or less than one third of the sternum, reconstruction is often unnecessary.⁵⁴

The resected portion of the chest wall remains attached to the lung and is allowed to drop into the hemithorax, where pulmonary resection is then carried out in the usual manner. The extent of pulmonary resection is determined by the amount of parenchymal involvement, as well as the pulmonary reserve of the patient. A crucial determinant for long-term survival is the ability to achieve a complete (R0) resection.¹ The survival rate of patients who undergo incomplete resection (R1) is comparable to that of patients who have not had a resection at all.¹ Most frequently, lobectomy is sufficient to achieve an R0 resection.

Burkhardt and associates,²¹ in 95 operations for bronchogenic carcinoma with chest wall involvement, performed a lobectomy in 80% of patients in their series, pneumonectomy in 13%, bilobectomy in 4%, and sublobar resection in 3%. Okada,²³ in his series of 132 patients, favored a more lung-preserving approach, with 49% undergoing lobectomy, 15% segmentectomy, 13% sleeve lobectomy, 10% pneumonectomy, 8% lobectomy with partial resection, and 5% sleeve bilobectomy or sleeve pneumonectomy. In both series a complete mediastinal and hilar lymph node dissection was performed in each patient. In all cases the operating surgeon confirmed the clinical impression of an R0 resection. In our practice we would agree with the general recommendation to perform a complete mediastinal and hilar nodal dissection in these patients.

Recent reports have described en bloc chest wall resections and anatomic pulmonary resections using completely minimally invasive thoracoscopic techniques, or thoroscopes as an adjunct to assist in the resection.⁵⁵⁻⁵⁷ The basic principles of oncologic resection should remain the same as with more traditional techniques.

RECONSTRUCTION

Reconstruction of the chest wall defect is controversial. Some surgeons do not routinely reconstruct chest wall defects in any patients, and they report minimal morbidity. Facciolo and associates² performed 104 thoracotomies with full-thickness chest wall resection without prosthetic reconstruction of the costal elements in any patient. Chest wall defects were closed with scapula repositioning or chest wall muscle transfers. Exact details regarding location and complexity of the defects were not described, although the results were excellent.

In general, all full-thickness skeletal defects that have the potential for paradox should be considered for reconstruction. Both the size and location of the chest wall resection should guide the decision for reconstruction. When the defect is small, approximately 5 cm or less, the skeletal component can be ignored and the defect closed with overlying soft tissues only. Posterior defects up to 10 cm in diameter may not require reconstruction because the overlying scapula provides support.

Exceptions include midthoracic posterior defects that allow the scapular tip to become entrapped in the bony thorax during full range of motion of the ipsilateral arm. In these cases either the chest wall can be reconstructed or the scapular tip can be amputated.

Many complex chest wall defects require not only skeletal stabilization but also skin and soft tissue coverage to protect the reconstruction. Indications for reconstruction include the need for structural stability, cosmesis for anterior and lateral chest wall defects, obliteration of dead space, and recruitment of healthy soft tissue from nonanatomic areas to restore the chest wall integrity.

Reconstruction can be performed using autogenous tissues, such as fascia lata grafts or muscle transpositions, or various prosthetic materials, including mesh, metals, or soft tissue patches. The use of autogenous tissue is favored when the wound to be closed is contaminated. Grossly contaminated wounds may need to remain open for a period of time for aggressive local wound care before attempted closure, sometimes at the expense of prolonged mechanical ventilation.

The most commonly used autogenous grafts are locally advanced muscle flaps. Although transposition of the latissimus dorsi muscle for chest wall coverage was described in 1896 by Tansini, it was Brown and associates who reintroduced the musculocutaneous concept in 1977 and created a surge of interest in muscle and musculocutaneous flap reconstruction of the thoracic cavity.⁵⁸ The use of muscle flaps should be anticipated before surgery, and the operation should be conducted to protect the muscle of choice and its vascular pedicle at all times (Fig. 20-6).

The most widely used local muscle flaps are the latissimus dorsi, pectoralis major, rectus abdominis, serratus anterior, trapezius, and deltoid muscles. The latissimus dorsi muscle has excellent versatility because of its large size and wide arc of motion, allowing it to reach both the anterior and posterior thorax. The pectoralis major muscle also displays great versatility, with significant limitations seen only when posterior thoracic coverage is needed. In those cases it can be used as a free flap. Less frequently, the transverse rectus abdominis musculocutaneous (TRAM) flap is used. It is used almost exclusively for anterior defects and is rotated about its vascular pedicle.

When muscle flaps are not available or cannot be used, prosthetic materials are used. Because of the availability and easy handling of synthetic materials, many surgeons prefer to use synthetic grafts for reconstruction even if muscle flaps are available. The choice of prosthetic material can vary, but the type of material used often depends on the surgeon's preference. LeRoux and Shama have set forth the ideal characteristics of a prosthetic material: rigidity to abolish paradoxical chest motion, inertness to permit ingrowth of fibrous tissues and decrease the likelihood of infection, malleability so that it can be fashioned to the appropriate shape at the time of the operation, and radiolucency to allow for follow-up of the underlying problem.⁵⁹

Additional desirable features include hypoallergenicity, lack of proven carcinogenicity, the ability to withstand sterilization, the ability to not be modified by bodily

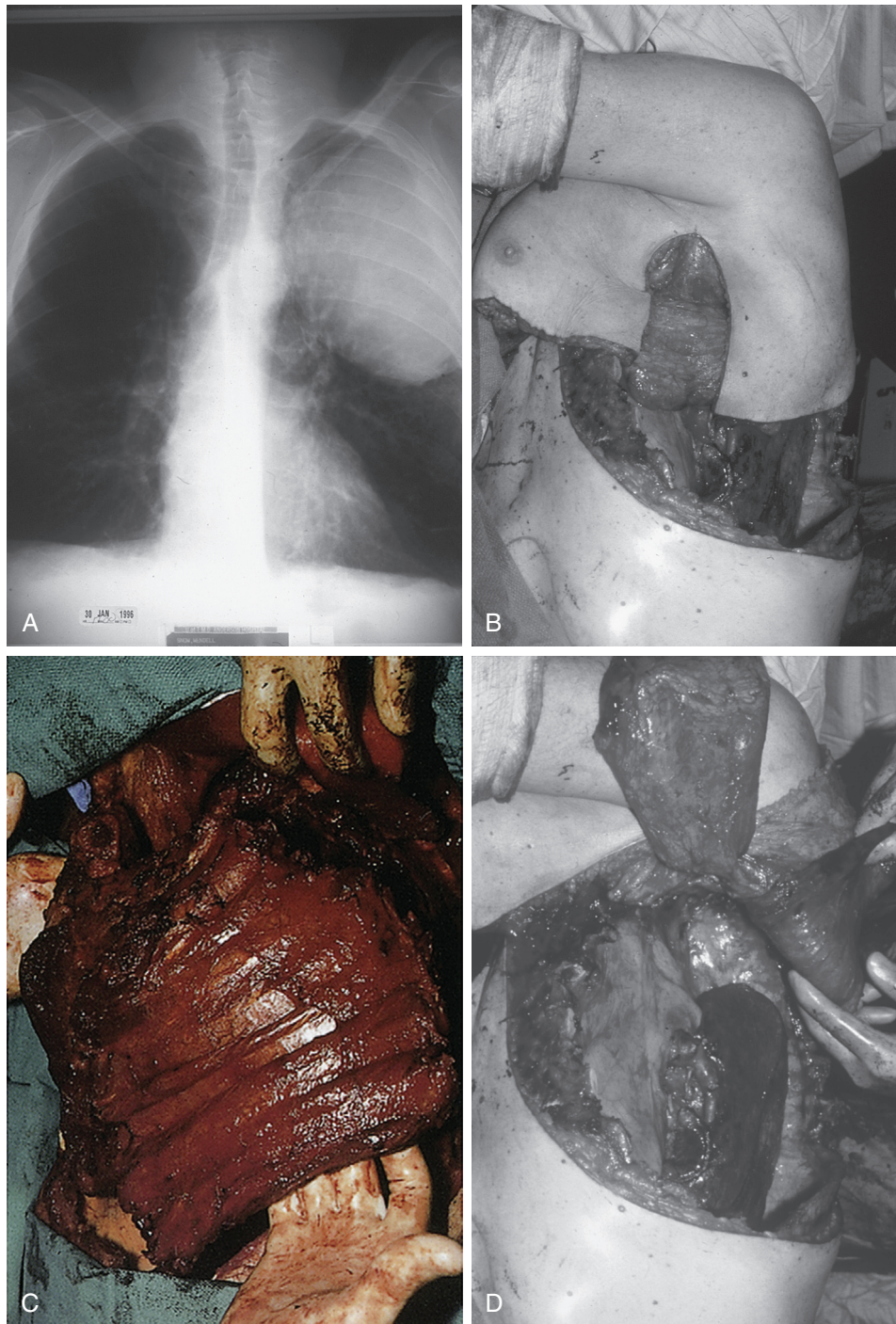


FIGURE 20-6 ■ **A**, Chest radiograph posteroanterior demonstrating a large squamous cell carcinoma of the left upper lobe involving ribs one through seven. Mediastinoscopy was negative. **B**, Lateral operative positioning with the entail skin incision raised for muscle flaps. **C**, Operative photo demonstrating extensive chest wall resection of seven ribs with en bloc left upper lobe attached. **D**, Resulting surgical chest wall defect with previously mobilized muscle flaps (latissimus, serratus, and pectoralis) that are used to cover the prosthetic chest wall reconstruction.

fluids, and adequate strength. Although no substance to date perfectly fulfills all of these criteria, various synthetic and alloplastic materials can be used with satisfactory results.

Polypropylene mesh (PM) (Marlex, Cranston, RI) with or without methylmethacrylate sandwich, polytetrafluoroethylene (PTFE) mesh, and Vicryl mesh are

examples of materials that have been used in different situations. PTFE is made in a variety of thickness sizes; 2-mm thickness is required for chest wall reconstruction to tolerate the tension generated during closure. Some surgeons consider PTFE to be easier to handle than PM because it lends itself to a slight stretch, can be sutured with fewer wrinkles and surface irregularities, and may

create a watertight seal of the pleural space.⁵⁴ However, Deschamps and associates⁶⁰ compared PM to PTFE and observed no significant differences in outcomes or complications.

Polypropylene mesh with methylmethacrylate (PPMM) sandwich provides the most rigidity and perhaps the best cosmetic result, at the price of greater difficulty of implantation. In cases where the chest wall resection is extensive and the possibility of paradoxical movement of the reconstruction is suspected, this level of rigidity is desired. A few key points need to be kept in mind when working with this unyielding material. After the specimen is removed, the patient is returned to a neutral position by unflexing the operating table if initially flexed on positioning. An imprint of the defect is made to determine the size of the reconstruction, and the mesh is tailored to leave approximately 2 to 3 cm of extra material circumferentially with which to secure the patch to the remaining chest wall. A thin layer of methylmethacrylate is applied directly to the mesh, leaving 2 to 3 cm of mesh circumferentially overlapping the chest wall and free of cement. The layer of cement should not extend completely to the edges of the ribs, but leave at least one centimeter gap. If the cement is allowed to extend to the rib edges, respiratory motion and movement of the torso can lead to undesirable and often painful "clicking" of the movement of the unyielding solid prosthesis against bony elements of the chest wall. A second layer of mesh, of identical size, is quickly applied to the cement, thereby creating the "sandwich." The cement generates a significant amount of heat as it hardens, so care must be taken to avoid contact with unprotected tissue. When the reconstruction is of the lateral chest wall, it is important to re-create the curvature of the thorax. This may be accomplished by allowing the sandwich to harden on a malleable retractor that has been shaped appropriately or by allowing the sandwich to harden on the patient's (protected) iliac crest.

Regardless of the material used, the patch is secured taut with heavy interrupted nonabsorbable sutures either through or around the remaining ribs. If the spine constitutes the posterior border of the defect, the sutures may be placed through drill holes in the transverse processes. The patch is then covered with adequate healthy soft tissue. Intrathoracic chest tubes are tunneled a distance from the reconstruction and positioned to avoid direct contact with the synthetic material. Subcutaneous closed suction drains should be used when extensive flaps have been raised and a large potential dead space has been created.

The simplest and most practical method of coverage is local tissue advancement. This is particularly important in patients who have received high doses of radiation; the local tissues may have impaired healing potential, and in many cases rotation of a pedicled muscle flap from a nonradiated area may be advantageous. There are occasional cases in which the local muscle flaps may be unavailable because the muscles have been extirpated or the vascular pedicle has been destroyed by surgical ablation or irradiation. In those cases free tissue transfer of flaps using microvascular reconstruction can be used with excellent results.⁶¹ Often these complex cases require the

close interaction of the thoracic surgical team with our plastic surgeon colleagues. Available grafts can include contralateral latissimus dorsi and serratus anterior muscles, as well as both ipsilateral and contralateral TRAM flaps.⁶¹ The omentum is an excellent salvage flap that can be used in cases where the pedicled muscle flap fails. Suction drains frequently are used to eliminate dead space or are used in cases of large raw surfaces over the prosthetic reconstruction. Drains usually are removed when the daily output is less than 25 mL/day from each drain.

Titanium plating systems are also available for reconstructing chest wall defects, either alone or in conjunction with soft tissue or synthetic materials. The multiple titanium plates can be used to span a defect to provide skeletal stability and prevent paradoxical chest wall movement. These are secured to healthy bone with drill and screw systems, prior to coverage with soft tissue. The same precautions against infection must be used as with implantation of any synthetic material, but results from initial reports for reconstruction of sternal and chest wall resections appear to be satisfactory in short follow-up.^{62,63}

Lung tumors that involve the chest wall are exceedingly rare in children, but children present a unique challenge to the thoracic surgeon when reconstruction is necessary. Depending on the age of the child, growth of the chest wall continues, thereby limiting the ability to use prosthetic materials for reconstruction. As the child outgrows the reconstruction, the mesh may cut through its anchors and re-create the defect. If a more solid reconstruction is used, permanent mesh can act as a tether, eventually leading to contracture and deformity. Tuggle and colleagues have reported successful chest wall reconstruction using bioabsorbable copolymer plates in four children. This material has been used for cranial and facial reconstruction in the pediatric population. They cite benefits that include excellent tensile strength, moldability, and resorbability, which would leave residual firm fibrous tissue but theoretically not limit growth. Their report in this limited series indicates follow-up to only 2 years without instability or growth limitation at that point.⁶⁴ Ideally reconstruction should be performed with rotational muscle flaps whose nerve supplies are carefully preserved, to allow for growth and a dynamic contribution to chest wall development.⁶⁵

POSTOPERATIVE CARE

Postoperative care should be tailored to each individual patient. A patient with good preoperative pulmonary function who had a limited resection and reconstruction should be extubated in the operating room at the conclusion of the case and convalesced on a telemetry ward. A frailer patient with an extensive resection and reconstruction may require intubation for 24 to 48 hours in the intensive care unit, with meticulous respiratory hygiene. For all patients the authors prefer to continue epidural analgesia either until the chest tubes are removed or up to 7 days after surgery, whichever comes first. Aggressive pulmonary hygiene, including early ambulation, incentive spirometry, and bronchodilators, is essential and is

attended by a full-time respiratory therapy staff on the wards. All patients remain on telemetry monitors throughout their hospital stay. The use of antibiotics postoperatively usually is limited to 24 hours of a broad-spectrum cephalosporin. Chest tubes are removed when air leaks have been sealed and when drainage is less than 100 mL per 8-hour shift. Additional postoperative care is similar to that of other thoracotomy patients.

COMPLICATIONS

Complications specific to chest wall resection and reconstruction include wound seroma formation, wound infection involving the prosthesis, and respiratory mechanical changes subsequent to prosthetic placement.^{60,66} Small seromas are best managed with observation because most resolve with time. Large or symptomatic seromas can be repeatedly aspirated under strict sterile conditions with little risk of contamination. Surgical obliteration is infrequently necessary and is reserved for recalcitrant seromas.⁶⁰

Wound infections that occur with synthetic grafts usually require removal of the prosthesis and replacement with either autogenous reconstruction or open wound care with delayed closure. Prolonged air leaks from violated visceral pleural surfaces or fissures can allow respiratory bacteria to infect the overlying prosthesis. Every attempt must be made to seal or oversee any raw lung surfaces and decrease the remaining free space within the hemithorax before placement of the prosthetic material. In all pulmonary resections, including the upper lobes, the inferior pulmonary ligament should be divided to permit sufficient mobility of the remaining lung in the hemithorax. Chest tubes should be placed in the hemithorax, minimizing their direct contact with the mesh. PM is preferable to PTFE when significant air leaks are present. The smooth surface of PTFE often makes it more difficult for a lung prosthesis apposition to occur and can result in a localized bronchopleural fistula that declares itself months later. PM permits more vigorous adhesions, leading to rapid ingrowth of the lung, and is better suited for a “contaminated” environment of an air leak.

The development of a bronchopleural fistula after pneumonectomy is an extremely morbid complication to treat, and in cases with chest wall resection and synthetic reconstruction, the treatment options are limited and complex. Most cases require removal of the prosthesis and prolonged open wound care. Patients who survive the initial sepsis and demonstrate signs of wound healing may be considered for complex reconstructions, which may include muscle flaps, omental flaps, and even thoracoplasty. Frequently these complicated cases are best handled using a multispecialty approach, with the aid of talented plastic surgeons familiar in reconstructive techniques.

Delayed wound infections can occur as a result of seroma aspiration or hematogenous seeding from distant infection. In these cases careful inspection of the prosthesis in the operating room is required. Most early prosthesis infections require removal of the prosthesis,

followed by local wound care. In infections that present months after the primary surgery, removal of the prosthesis without replacement is often well tolerated without pulmonary compromise. After several months, sufficient fibrous tissue has developed to support the chest wall mechanics. Delayed wound infections may have had adequate time for incorporation of the prosthesis by granulation tissue, especially polypropylene, making prosthesis removal difficult and even unnecessary. Deschamps and associates⁶⁰ allowed those prostheses that were well incorporated by granulation tissue to remain in situ, using aggressive wound débridement and frequent dressing changes. They were able to salvage approximately one half of these infected reconstructions without removal of their prosthesis and without development of delayed wound infections or draining sinus tracts.

In rare cases, complications may occur related to mechanical failure of the prosthesis, with patch dehiscence resulting in lung herniation, or flail physiology. We had encountered one case in which a particularly active young patient fell and fractured his PPMM prosthesis, resulting in uncomfortable clicking and instability. This necessitated replacement (Fig. 20-7).

Postoperative respiratory mechanical changes often are difficult to measure, and they vary based on the type of prosthesis used. The loss of viscoelasticity and inhomogeneity is a result of the replacement of a dynamic chest wall with a rigid structure that prevents chest wall mobility. Animal studies suggest that PTFE is favorable to PPMM because it allows the chest wall to remain dynamic during the respiratory cycle.⁶⁶ Human studies are limited but demonstrate good pulmonary function 6 months postoperatively. Lardinois and associates⁶⁷ studied patients preoperatively and 6 months postoperatively and found no significant deterioration of FEV₁, and they noted concordant chest wall to prosthesis movements in most patients.

Cerebrospinal fluid (CSF) leaks can occur when the dura is violated during dissection within the intervertebral foramina or during partial or complete



FIGURE 20-7 ■ An active young patient cracked his polypropylene-methylmethacrylate chest prosthesis. The instability and the uncomfortable clicking necessitated replacement.

vertebrectomies. The nerve roots should be ligated distal to the emergence of the external sheath covering the cord. Potential spinal fluid leaks should be carefully evaluated during the initial operation. If a small dural tear has occurred during the resection, it needs to be repaired with fine monofilament sutures and covered with an autogenous tissue transfer using intercostal muscle, diaphragm, or pleura. Negative intrathoracic pressure coupled with positive pressure created in the CSF can lead to a chronic CSF leak. Initial treatment includes a lumbar drain and patient immobility in a supine position to minimize the CSF pressure. Supine bed rest of a post-thoracotomy patient can be associated with significant pulmonary complications.

Caution with hemostasis around the vertebral foramina is of paramount importance. Excessive use of monopolar electrocautery in this region could lead to transmitted cautery current with nerve or even spinal injury; judicious use of bipolar cautery is warranted. Aggressive packing of oxycellulose to control hemorrhage at an intervertebral foramen has led to a report of paraplegia caused by swelling of the oxycellulose. Fortunately this was reversible with immediate reoperation, removal of the oxycellulose and coverage with fibrin glue, and a pericardial fat pad.⁶⁸

Patients who have required extensive combined lung and chest wall resections that extend to the vertebral bodies and dural sac can have fascinating delayed complications. For example, a patient in whom a small dural rent was identified and repaired during the resection of a tumor involving the vertebrae required a chest tube for 10 days for a prolonged air leak that occurred during the dissection of the interlobar fissure. The patient had no problems after the removal of the chest tubes and discharge from the hospital. Several months later, he had mental status changes and a seizure that was believed, on clinical grounds, to likely represent metastatic disease to the brain. A CT scan was done and demonstrated a significant amount of air within the brain (Fig. 20-8), which originated from a small bronchopleural subarachnoid fistula. This required an additional thoracotomy with interposition of a pedicled omental flap between the lung and the dural sac to close the small communication. Within 48 hours, the patient's neurologic status normalized.

PATHOLOGY

A complete resection (R0) is defined as pathologic evidence of disease-free (negative) tissue margins on final pathology and an assessment by the surgeon that all grossly detectable disease, including nodal disease, has been removed. Patients who had complete gross resection at thoracotomy but were found to have positive margins on final microscopic pathologic review are classified as having undergone an incomplete (R1) resection. Gross residual disease after an attempted resection is classified as an R2 resection, including residual nodal disease that could not be removed.

Depth of chest wall invasion can be grouped into three levels on the basis of the final pathologic examination:

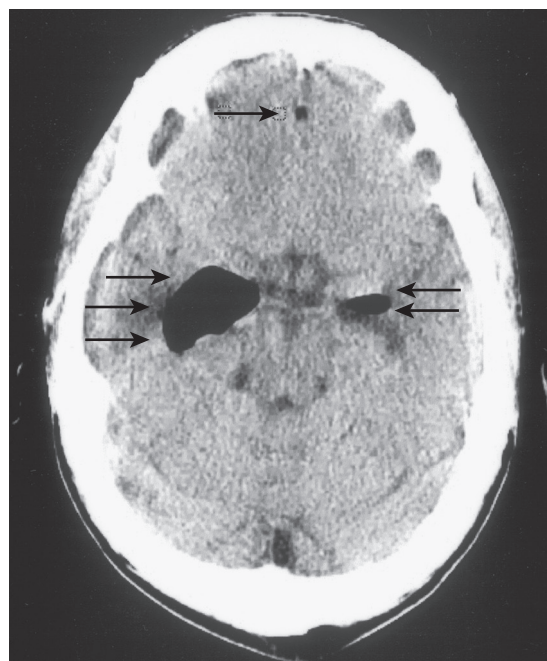


FIGURE 20-8 ■ A CT scan of the brain demonstrating the pathognomonic finding of air within the ventricular system of the brain (arrows) secondary to a bronchopleural-subarachnoid fistula from a combined chest wall, lung, and vertebral body resection.

parietal pleura only; parietal pleura and soft tissues; and parietal pleura, soft tissues, and bone. Complete pathologic stage (TNM) is based on microscopic examination of the primary mass, all surrounding margins, and nodes.

The evaluation of the world literature pertaining to chest wall resections in patients with lung cancer often is complicated, based on varied surgical practices. Some surgeons proceed directly to en bloc full-thickness chest wall resections rather than attempting to strip the parietal pleura by extrapleural maneuvers. In Facciolo and associates' series of 104 patients who underwent full-thickness, en bloc resections of lung with attached chest wall, the pathologic depth of invasion was limited to parietal pleura only (in 27% of patients), parietal pleura and soft tissues (35%), and parietal pleura, soft tissue, and bone (38%).² All margins were microscopically negative on final pathologic review. All lymph nodes were negative in 80% (N0), 5% had positive hilar or lobar nodes (N1), and 15% had positive mediastinal (N2) nodes.

Chapelier and associates⁶⁹ also exclusively performed full-thickness resection of any tumors found by the naked eye to be invading at least the parietal pleura. A total of 100 patients were treated by this method. Pathologic evaluation revealed parietal pleural invasion in 29% of cases, parietal pleura and intercostal muscle invasion in 47% of cases, and osseous invasion in 24% of cases. Microscopically negative margins were attained in all but one patient. Nodal status was 65% N0, 28% N1, and 7% N2.

Burkhart and associates²¹ reviewed their experience with 95 resections with bronchogenic carcinoma with invasion of the chest wall, all treated with full-thickness chest wall resection. Depth of invasion extended into the

parietal pleura only in 31% of patients, into the parietal pleura and soft tissues in 45% of patients, and into the osseous structures in 24% of patients. Seventeen percent of patients had pathologically involved N1 nodes, and 15% had pathologically involved N2 nodes. A presumed R0 resection was obtained in all cases.

Downey and associates¹ reported on 334 patients who underwent thoracic exploration for T3 tumors involving the chest wall at Memorial Sloan Kettering Hospital. Intraoperative results included 175 patients who achieved an R0 resection, 94 who achieved an R1 or R2 resection, and 65 who underwent exploration only. Of the 175 patients who attained an R0 resection, 80 (46%) underwent an extrapleural resection based on intraoperative surgeon judgment of the level of invasion. All 80 had evidence of parietal invasion only. The remaining 95 patients underwent full-thickness chest wall resection, of which 19% had parietal pleural invasion, 25% had parietal pleural and soft tissue invasion, and 56% had invasion involving the osseous structures.

Magdeleinat and associates²² attempted an extrapleural resection in all patients whose parietal pleura could be easily removed. Intraoperative frozen sections were obtained when any doubt existed about negative margins. Tumors fixed to the deeper structures were removed with the associated full-thickness chest wall. A total of 201 patients were studied, of which 89 (44%) had tumor invasion limited to the parietal pleura. Ten of these patients underwent a full-thickness chest wall resection because the surgeon suspected deeper invasion intraoperatively. Only one patient who underwent an extrapleural resection had an underestimation of invasion, with microscopic residual identified at final pathology. Thirty-four patients (17%) did not achieve an R0 resection, most often because of residual tumor at the lateral edges of the resection. Nodal disease was absent in 58% (N0), lobar or hilar nodal disease was seen in 26% (N1), and mediastinal nodal disease was seen in 13% (N2). Three percent of patients had T4 disease.

Pathologic staging with standard histopathologic evaluation has been augmented with the use of immunohistochemical (IHC) stains to detect micrometastatic disease in lymph nodes and at resection margins. Mineo and colleagues analyzed nodes and margins of their en bloc lung and chest wall resections ($N = 47$) with IHC stains and found over 10% of patients had only margins positive on IHC, which strongly correlated with local failure, and 12% had only nodal micrometastases seen on IHC staining, which correlated with distant relapse.⁷⁰ None of their patients who were IHC positive in the lymph nodes or margins lived to the 4-year follow-up, whereas those who were node negative and margin negative by IHC had a 73% 5-year survival. This appears to be a strong prognostic factor, but whether IHC detection of disease can lead to improved delivery of adjuvant therapy and subsequent survival advantage remains to be seen.

RESULTS

Operative mortality is defined as mortality within 30 days of surgery or within the same hospitalization. Improve-

ments in preoperative screening, anesthetic techniques, and postoperative care have decreased the incidence of postoperative mortality in many studies. Long-term results are affected most importantly by complete resection to microscopically negative margins and by absence of N2 nodal involvement.⁷¹ The extent (number of ribs) of chest wall resection is not a determinant for 5-year survival as long as an R0 resection is accomplished. These results are validated by several studies.

Overall complications and mortality in patients with combined pulmonary and chest wall resections are greater than of pulmonary resection alone. This is not only because of the added potential complications unique to chest wall resection but also because of the increased surgical insult and physiologic impairment from chest wall resection. A review by Martin-Ucar and colleagues from Leicester of their experience with lung and chest wall resection in 41 patients indicated increased 60-day mortality in those with any of the following: significant weight loss ($BMI < 18.5$), advanced age (>75 years old) and decreased preoperative FEV_1 ($<70\%$ predicted) with a 47% 60-day mortality for patients with one or more of the aforementioned risks, and 0% mortality for patients who did not have any of the three factors.⁷²

Weyant and colleagues reported on 262 chest wall reconstructions (141 were pulmonary resections with chest wall resection). In their series the greatest predictor of postoperative respiratory complications was the size of the chest wall resection, and they advocated rigid repair with PPM sandwich for physiologic stability of the chest wall. Although some groups have reported reasonable outcomes for patients undergoing pneumonectomy with chest wall resection,⁷³ they caution against it; in a series, four of nine patients who underwent pneumonectomy with chest wall resection died postoperatively.⁷⁴

Facciolo and associates² reported no operative mortality and a major complication rate of 20%, which included atrial fibrillation, bleeding, prolonged air leak, and empyema. Forty percent of patients received postoperative radiation therapy, and all patients with N2 disease received postoperative chemotherapy. The overall 5-year survival rate was 61%, with a median survival period of 74 months. Statistically worse 5-year survival rates were noted in patients with N2 disease when compared with patients with N0 disease (18% vs. 67%). Depth of invasion also affected survival rates, with a 79% survival rate at 5 years for pleural involvement only compared with a 56% survival rate for pleural, soft tissue, and bone involvement. An impressive 90% 5-year survival rate was noted in the subset of patients with N0 disease whose tumors were limited to the parietal pleural invasion only. The addition of postoperative radiation therapy dramatically increased 5-year estimated survival rates from 47% to 74%, although the criteria for administering postoperative radiation are not clearly defined.

Chapelier and associates⁶⁹ had different results. The operative mortality rate was 4%, and postoperative complications were noted in 16% of patients. The median survival period was 18 months, the 2-year survival rate was 41%, and the 5-year survival rate was 18%. Significantly worse 5-year survival rates were noted with N2

disease when compared with N0 or N1 disease (0% vs. 22% vs. 9%, respectively). Patients with more than two ribs resected had better survival rates when compared with patients with fewer than two ribs resected ($P=0.03$). Invasion limited to the pleura only was an independent factor favoring long-term survival when compared with deeper invasion ($P=0.02$). The long-term survival rate for patients with well-differentiated tumors was significantly better than that for patients with poorly differentiated or undifferentiated tumors ($P=0.005$). Postoperative radiation therapy or adjuvant chemotherapy did not improve survival in this study.

Burkhardt and associates²¹ summarized the Mayo Clinic experience, with somewhat higher mortality and morbidity rates. The operative mortality rate was 6.3%, and the complication rate was 45%. The overall 5-year actuarial survival rate was 39%, with best survival rates noted in stage IIB (T3 N0 M0) patients (44%), and worse rates for stage IIIA patients (26%). Interestingly, women in their study had a significantly improved 5-year survival rate compared with men (53% vs. 39%, respectively), and women without evidence of nodal disease had the best survival rate (61% 5-year survival). Survival rates in all groups were affected by depth of invasion; tumors that invaded the parietal pleura only resulted in a 5-year survival rate of 50%, compared with 35% in patients with tumor invasion into the soft tissues and 31% in patients with osseous involvement. Although these results did not reach statistical significance, the trend is suggestive of results seen at other institutions. Of their patients, 10% received neoadjuvant chemotherapy and/or radiation therapy, with a disappointing increase in operative mortality rates noted in those patients who had received radiation. No improvement in survival rates was seen in pretreated patients.

Voltolini and colleagues⁷⁵ retrospectively analyzed outcomes of their lung resections with chest wall involvement in 68 patients. A multivariate analysis revealed that survival was impacted by nodal status, complete resection, and depth of chest wall invasion. Their node-negative patients had a 42% 5-year survival, but those who were node positive (N1 or N2) had 17% survival at 5 years. Those with tumors involving the parietal pleura had significantly better 5-year survival than those with deeper invasion (43% vs. 9%). They had three patients with positive margins; none lived to the 1-year follow-up.

Matsuoka and colleagues⁷⁶ reported similar conclusions with their experience of lung resections involving the chest wall. They also found poorer 5-year survival for N2-positive patients compared with node-negative patients (6.2% vs. 44%) and poorer survival for those with incomplete resections (14% compared to 34% for complete resections). They did not, however, find depth of chest wall invasion to correlate with outcome.

Doddoli and colleagues⁷⁷ in France reported their series of 309 patients from three institutions. In their experience lung resections involving the chest wall were associated with an 8% operative mortality rate and a 33% complication rate. They reported a 5-year survival rate for stage IIB (T3N0) patients of 40% but only 12% for stage IIIA (T3N1 or T3N2). In their population of stage IIB (T3N0) patients, en bloc resection afforded a better

5-year survival (60%) rate than did extrapleural resection (39%). The impact of R1 or R2 resection could not be determined because their series included only those with R0 resection. The Memorial Sloan Kettering Hospital experience, as summarized by Downey and associates,¹ is comparable with other reports. The operative mortality rate, including all patients who underwent surgery, was 3%. Patients who left the operating room with either R1 or R2 disease had a dismal 5-year survival rate of 4%, which was comparable to the survival rate of those patients who underwent exploration without resection (0%). Patients who received R0 resection had a 6% postoperative mortality rate and an overall 5-year survival rate of 32%. Further analysis in the R0 group demonstrated survival advantage in node-free patients; 5-year survival rate in T3 N0 M0 = 49%, T3 N1 M0 = 27%, and T3 N2 M0 = 15% ($P<0.0003$). After either complete extrapleural or en bloc resection, there was no significant difference in survival rates between histologic groups, nor was there any difference in survival rates by univariate analysis of pathologic demonstration of depth of tumor invasion in the chest wall. Overall there was no observed significant difference in survival rates after a complete extrapleural resection compared with after a complete en bloc resection. However, further subgroup analysis demonstrated that patients with N0 disease had a prolonged survival period when receiving an extrapleural resection versus an en bloc resection (65 months vs. 21 months, respectively, $P<0.01$). This conflicts with the aforementioned series by Doddoli where stage IIB patients had better survival with en bloc resection.⁷⁷ They also noted no survival advantage to radiation therapy given preoperatively, intraoperatively, or postoperatively.

Magdeleinat and associates²² documented a 7% operative mortality rate and a 36% complication rate. Predictably, perioperative complications were more frequent in older patients and in patients with limited pulmonary reserve. Actuarial 5-year and 10-year survival rates for the entire population were 21% and 13%, respectively. After complete and incomplete resection, 5-year survival rates were 24% and 13%, respectively. The highest survival rate was noted again in the subgroup of patients without nodal involvement. The authors noted an increased 5-year survival rate in patients whose tumor did not extend beyond the parietal pleura (37%) as compared with those whose tumor extended past the parietal pleura into the chest wall proper (15%). Of note, in patients with disease limited to the pleura, the type of resection (extrapleural or chest wall) did not affect survival rates (37% and 31%, respectively).

Elia and colleagues⁷⁸ from Italy reported similar outcomes in their 110 patients. They reported a 0% mortality rate and 28% complication rate. Again, nodal status was strongly correlated with 5-year survival (47% for N0 vs. 0% for N1 or N2) (Table 20-3). They also analyzed survival of their N0 patients by type of resection and found no difference in survival rate for extrapleural versus en bloc resection. The survival rate of patients who had R1 resections was not reported, and breakdown of survival by depth of chest wall involvement was not analyzed.

TABLE 20-3 Results of Surgical Resection of Lung Cancer with Chest Wall Invasion

Lead Author Date	Mortality (%)	Major Morbidity (%)	5-year Survival Overall (%)	5-year Survival with N0 (%)	5-year Survival with N2 (%)	5-year Survival: Pleural Invasion Only (%)	5-year Survival: Invasion beyond Pleura (%)	5-year Survival: R1 or R2 Resection (%)
Burkhardt et al (2002) ²¹	6	45	39	44	26	30	31	N/A
Chapelier et al (2000) ⁶⁹	4	16	18	22	0	N/A	N/A	N/A
Doddoli et al (2005) ⁷⁷	8	33	31	40	8	45	N/A	N/A
Downey et al (1999) ¹	6	N/A	32	49	15	33	34	4
Elia et al (2001) ⁷⁸	0	28	35	47	0	N/A	N/A	N/A
Facciolo et al (2001) ²	0	19	61	67	18	79	54	N/A
Magdeleinat et al (2001) ²²	7	36	24	25	21	37	15	13
Matsuoka et al (2004) ⁷⁶	N/A	N/A	30	44	6	33	36	14
Voltolini et al (2006) ⁷⁵	4	N/A	32	42	17 (N1 or N2)	43	9	0
Lee et al (2012) ²⁴	5	21	26	37	5	N/A	N/A	8

Lee and colleagues²⁴ recently reported the outcomes of 107 patients undergoing chest wall resection for NSCLC. Pneumonectomy was performed in 42% of these patients with a 5% operative mortality rate and a 21% complication rate. The 1-year mortality rate for survivors was 59%. Multivariate analysis found five main factors that were prognostic for survival: depth of invasion, tumor size, node status (N0 and N1 vs. N2), complete resection, and completion of adjuvant therapy. Comparison of outcomes between the various studies can be seen in Table 20-3.

SUMMARY

In summary, bronchogenic lung cancer with invasion into the chest wall is seen in less than 10% of patients with resectable disease. Extensive preoperative staging is required because metastatic disease is a contraindication for surgical treatment. Patients with N2 disease should not be considered candidates for primary surgical treatment. These patients should be considered for protocol treatments, when available, that may include neoadjuvant chemotherapy and/or radiation therapy followed by surgery if an appropriate response is seen.

The operative approach may include an extrapleural resection only when tumor invasion is limited to the parietal pleura, or it may include a more extensive en bloc resection when deeper soft tissue and bony chest wall invasion is demonstrated. The most important predictors of long-term patient survival are (1) the achievement of an R0 resection and (2) nodal status. Reconstruction generally is required for anterior and lateral defects when a flail segment is created and for large posterior defects that may cause a trapped scapula. Reconstruction options are numerous, including autogenous tissue flaps, rotational muscle flaps, and a variety of prosthetic materials. The choice of reconstruction is based on each patient and his or her clinical situation, surgeon preference, and the availability of specialized plastic surgical assistance.

Long-term results are encouraging in those patients who, after final pathologic review, are found to have N0 disease (stage IIB). The role of postoperative adjuvant

treatment in patients with incidental N1 or N2 (IIIA) disease is not defined.

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ANTERIOR APPROACH TO SUPERIOR SULCUS LESIONS

Philippe G. Darteville • Sacha Mussot

CHAPTER OUTLINE

HISTORICAL NOTE

PRESENTATION

PREOPERATIVE STUDIES

TREATMENT

ANTERIOR TRANSCERVICAL TECHNIQUE

SURGICAL MORBIDITY AND MORTALITY

RESULTS AND PROGNOSIS

HISTORICAL NOTE

Henry K. Pancoast, a radiologist at the University of Pennsylvania, described a patient afflicted with a carcinoma of uncertain histologic origin occupying the extreme apex of the chest, associated with shoulder and arm pain, atrophy of the hand muscles, and Horner syndrome.¹ This clinical entity has become known as Pancoast syndrome. Unknown to Pancoast, Tobias had already characterized the anatomic and clinical aspects of this lesion, correctly recognizing that the tumor was a peripheral lung cancer. Anatomically, the pulmonary sulcus refers to the costovertebral gutter extending from the first rib to the diaphragm. The superior pulmonary sulcus lies at the uppermost extent of this recess, as reviewed by Teixeira.² Generally, it is understood that non-small cell lung carcinomas of this region are termed Pancoast tumors, and we refer to this association throughout the chapter. However, the term *superior sulcus lesion* encompasses other, more diverse causes, both benign and malignant. Furthermore, this definition has been expanded to include patients who do not have evidence of brachial plexus or stellate ganglion involvement. Chest wall involvement in this region might be restricted to involvement of the parietal pleura or could extend deeper to the upper ribs, vertebral bodies, or subclavian vessels, according to Detterbeck.³ Invasion of the chest wall at or lower than the level of the second rib, or of the visceral pleura only, does not meet the criteria for a superior sulcus lesion. Additionally, Macchiarini and colleagues⁴ reported that a wide variety of superior sulcus lesions can result in Pancoast syndrome (Box 21-1); thus, a histologic diagnosis is mandatory when the syndrome is encountered.

PRESENTATION

Superior sulcus lesions of non-small cell histology account for less than 5% of all bronchial carcinomas, as reported by Ginsberg and associates.⁵ These tumors may arise from either upper lobe and tend to invade parietal pleura, endothoracic fascia, subclavian vessels, brachial plexus, vertebral bodies, or the first rib. However, their clinical features are influenced by their location.

Tumors located anterior to the anterior scalene muscle may invade the platysma and sternocleidomastoid muscles; the external and anterior jugular veins; the inferior belly of the omohyoid muscle; the subclavian and internal jugular veins, including major branches; and the scalene fat pad (Fig. 21-1). They invade the first intercostal nerve and the first rib more frequently than the phrenic nerve or superior vena cava. Patients usually complain of pain distributed to the upper anterior chest wall.

Tumors located between the anterior and middle scalene muscles may invade the anterior scalene muscle (phrenic nerve lying on its anterior aspect); the subclavian artery, including primary branches, except the posterior scapular artery; and the trunks of the brachial plexus and middle scalene muscle (Fig. 21-2). These tumors manifest with signs and symptoms related to the compression or infiltration of the middle and lower trunks of the brachial plexus (e.g., pain and paresthesia radiating to the shoulder and upper limb).

Tumors lying posterior to the middle scalene muscles are usually located in the costovertebral groove and invade the nerve roots of T1, the posterior aspect of the subclavian and vertebral arteries, the paravertebral sympathetic chain, the inferior cervical (stellate) ganglion,

BOX 21-1 Causes of Pancoast Syndrome**NEOPLASMS**

- Primary bronchogenic carcinomas
- Other primary thoracic neoplasms: adenoid cystic carcinomas
- Hemangiopericytoma
- Mesothelioma
- Metastatic neoplasms: carcinoma of the larynx, cervix, urinary bladder, and thyroid gland
- Hematologic neoplasms: plasmacytoma, lymphoid granulomatosis, lymphoma

INFECTIOUS PROCESSES

- Bacterial: staphylococcal and pseudomonal pneumonia, thoracic actinomycosis
- Fungal: aspergillosis,allescheriasis, cryptococcosis
- Tuberculosis
- Parasitic: echinococcosis (hydatid cyst)

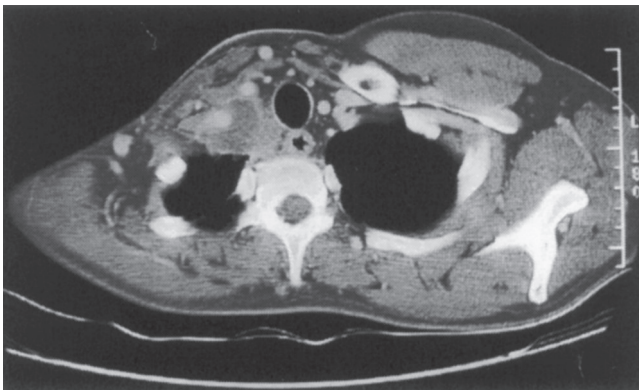


FIGURE 21-1 ■ Computed tomographic scan showing a right superior sulcus bronchial carcinoma invading the anterior thoracic inlet, including the subclavian vein.

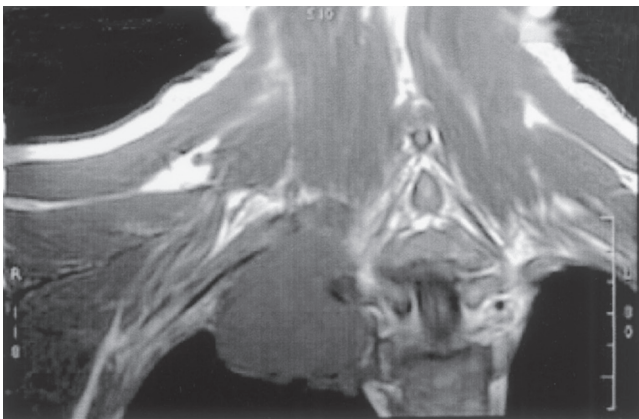


FIGURE 21-2 ■ Magnetic resonance image showing a left superior sulcus bronchial carcinoma invading the middle thoracic inlet, including the subclavian artery.

and the prevertebral muscles. Some of these posterior tumors can invade transverse processes (Fig. 21-3) or extend to the vertebral bodies (only those without intraspinal extension may be resected).

Because of the peripheral location of these lesions, pulmonary symptoms, such as cough, hemoptysis, and

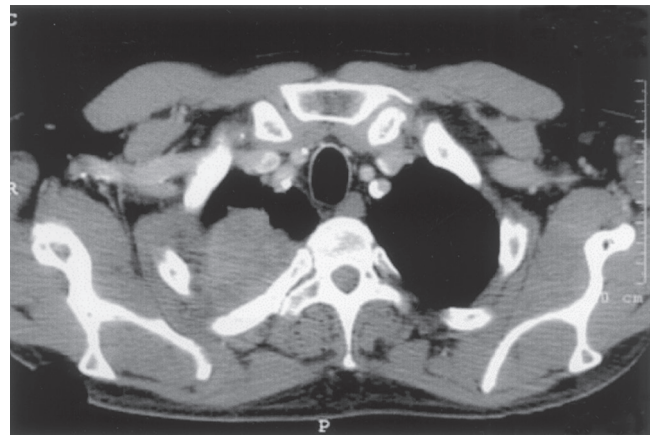


FIGURE 21-3 ■ Computed tomographic scan showing a right superior sulcus bronchial carcinoma invading the posterior arch and the transverse process of the first rib and abutting the costovertebral angle.

dyspnea, are uncommon in the initial stages of the disease. Abnormal sensation and pain in the axilla and medial aspect of the upper arm in the distribution of the intercostobrachial (T2) nerve are more frequently observed in the early stage of the disease process. With further tumor growth, patients can develop overt Pancoast syndrome.

PREOPERATIVE STUDIES

Any patient with signs and symptoms that suggest the involvement of the thoracic inlet should undergo a detailed preoperative evaluation to establish the diagnosis of bronchial carcinoma and to assess for operability. These patients usually have small apical tumors that are hidden behind the clavicle and the first rib on routine chest radiographs. The diagnosis is established by history and physical examination, biochemical profile, chest radiographs, bronchoscopy with sputum cytology, fine-needle transthoracic or transcutaneous biopsy, and computed tomography of the chest. A tissue diagnosis via video-assisted thoracoscopy is rarely indicated when other investigations are negative; thus it eliminates the possibility of pleural metastatic disease. If there is evidence of mediastinal adenopathy on computed tomographic scanning and/or on positron emission tomography, mediastinoscopy is mandatory because patients with histologically proven N2 disease are not operative candidates most of the time.

Neurologic examination, magnetic resonance imaging (MRI), or electromyography may delineate the tumor's extension to the brachial plexus, phrenic nerve, or epidural space. Vascular invasion is evaluated by venous angiography, subclavian arteriography, Doppler ultrasonography (cerebrovascular disorders may contraindicate resection of the vertebral artery), or MRI (Fig. 21-4). If the workup suggests tumor encroachment into the intervertebral foramina, additional MRI is mandatory to rule out invasion of the extradural space (Fig. 21-5).

The initial evaluation also includes routine cardiopulmonary function tests and investigative procedures; positron emission tomography has become mandatory to

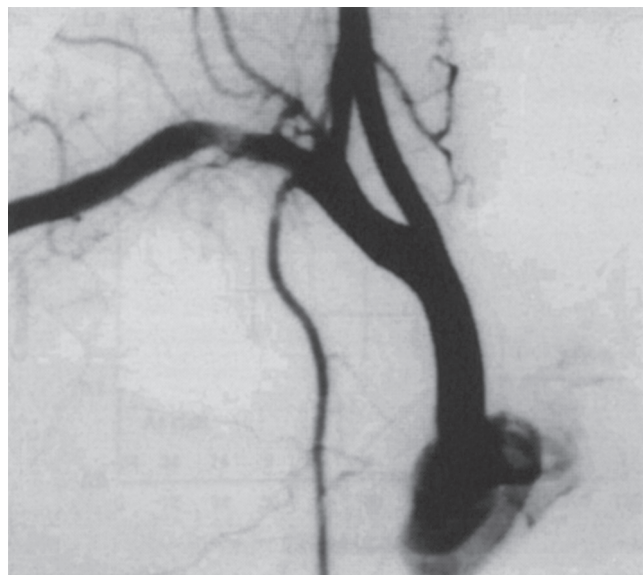


FIGURE 21-4 ■ Angiogram illustrating a massive tumoral invasion of the intrascapular left subclavian artery.

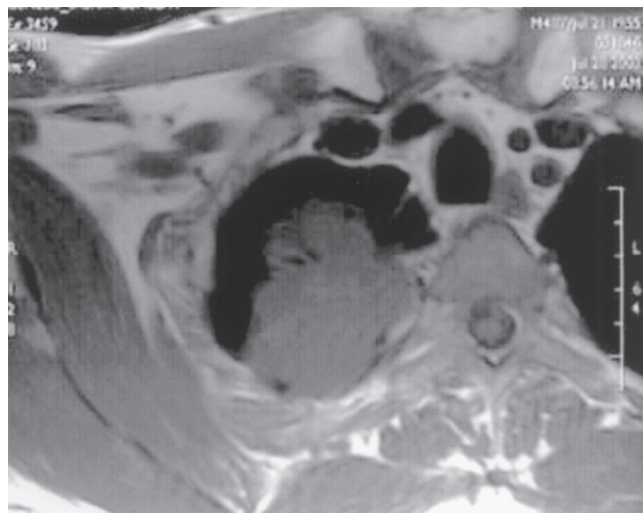


FIGURE 21-5 ■ Magnetic resonance image that rules out invasion of the intervertebral foramina by the tumor.

identify the presence of any metastatic disease that precludes surgical treatment.

TREATMENT

Tumors of the superior sulcus are deemed universally and rapidly fatal lesions. For many years, it was believed that these tumors were not amenable to surgery, until Chardack and MacCallum⁶ successfully performed a lobectomy and chest wall excision followed by radiation therapy. Eight years later, Shaw and colleagues⁷ approached superior sulcus tumors with preoperative radiation therapy (30 to 45 Gy in 4 weeks, including the primary tumor, mediastinum, and supraclavicular region) followed by surgical resection. This radiosurgical approach shortly became the standard treatment, yielding

better disease control and survival compared with other treatments. More recently, Ginsberg and colleagues⁵ provided evidence that en bloc resection of the tumor combined with external radiation (preoperative, postoperative, or both) must be considered the standard therapeutic approach for superior sulcus tumors. The goal of resection is the complete removal of the upper lobe in continuity with the invaded ribs, transverse processes, subclavian vessels, T1 nerve root, upper dorsal sympathetic chain, and prevertebral muscles.

In 1999, we reviewed various surgical approaches for treating superior sulcus lesions.⁸ In general, superior sulcus lesions not invading the thoracic inlet are completely resectable through the classic posterior approach of Shaw and colleagues.⁷ However, the posterior approach does not allow direct, safe visualization, manipulation, or complete oncologic clearance of all anatomic structures of the thoracic inlet. Superior sulcus lesions extending to the thoracic inlet should be resected by an anterior transcervical approach according to our previous description.⁹

This operation has been increasingly accepted as a standard approach for all benign and malignant lesions of the thoracic inlet. Additionally, this approach facilitates exposure of the anterolateral aspects of the upper thoracic vertebrae. Contraindications to this approach include extrathoracic metastasis, invasion of the brachial plexus above the T1 nerve root, invasion of the vertebral canal or sheath of the medulla, massive invasion of the scalene muscles or extrathoracic muscles, mediastinal lymph node involvement (multiple N2 disease), and advanced cardiopulmonary disease.

ANTERIOR TRANSCERVICAL TECHNIQUE

One-lung anesthesia with measurements of urine output and body temperature is necessary. An arterial line opposite to the primary lesion and at least two venous lines for volume expansion should be used. The patient is supine with the neck hyperextended and the head turned away from the involved side. A bolster behind the shoulder elevates the operative field. The skin preparation extends from the mastoid downward to the xiphoid process and from the midaxillary line laterally to the contralateral midclavicular line medially. An L-shaped cervicotomy incision is made, including a vertical pre-sternocleidomastoid incision carried horizontally below the clavicle up to the deltopectoral groove (Fig. 21-6). To increase the exposure, the interception between the vertical and horizontal branches of the L-shaped incision is lowered to the level of the second or third intercostal space, depending on tumor extent. The incision is then deepened with cautery. The sternal attachment of the sternocleidomastoid muscle is divided. The cleidomastoid muscle, along with the upper digitations of the ipsilateral pectoralis major muscle, is scraped from the clavicle. A myocutaneous flap is then folded back, providing full exposure of the neck and cervicothoracic junction.

Once the inferior belly of the omohyoid muscle is divided, the scalene fat pad is dissected and sent for

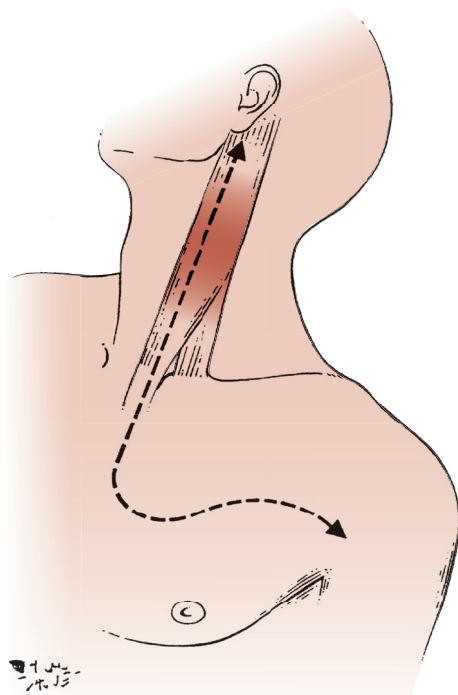


FIGURE 21-6 ■ Anterior transcervical approach. (As described in Darteville PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

pathologic examination to exclude scalene lymph node metastasis. Inspection of the ipsilateral superior mediastinum after division of the sternothyroid and sternohyoid muscles is made by the surgeon's finger along the tracheoesophageal groove. Next, tumor extension to the thoracic inlet is carefully assessed. We recommend resection of the medial half of the clavicle only if the tumor is deemed resectable. The jugular veins are dissected first, so that branches to the subclavian vein can eventually be divided. On the left side, ligation of the thoracic duct is usually required. Division of the distal part of the external and anterior jugular veins facilitates visualization of the venous confluence at the origin of the innominate vein. The internal jugular vein may be ligated to increase exposure of the subclavian vein (Fig. 21-7) but can be conserved most of the time. If the subclavian vein is involved, it can be easily resected after proximal and distal control has been achieved. Direct extension of the tumor to the innominate vein does not preclude resection. Next, the anterior scalene muscle is divided with cautery either at its insertion on the scalene tubercle of the first rib or in a tumor-free margin (Fig. 21-8). If the tumor has invaded the upper part of this muscle, it needs to be divided at its insertions on the anterior tubercles of the transverse processes of C3 to C6. Before dealing with the anterior scalene muscle, the status of the phrenic nerve is carefully assessed because its unnecessary division has a deleterious influence on postoperative respiratory function. It should be preserved whenever possible.

The subclavian artery is dissected (Fig. 21-9). To improve mobilization, branches are divided. The verte-

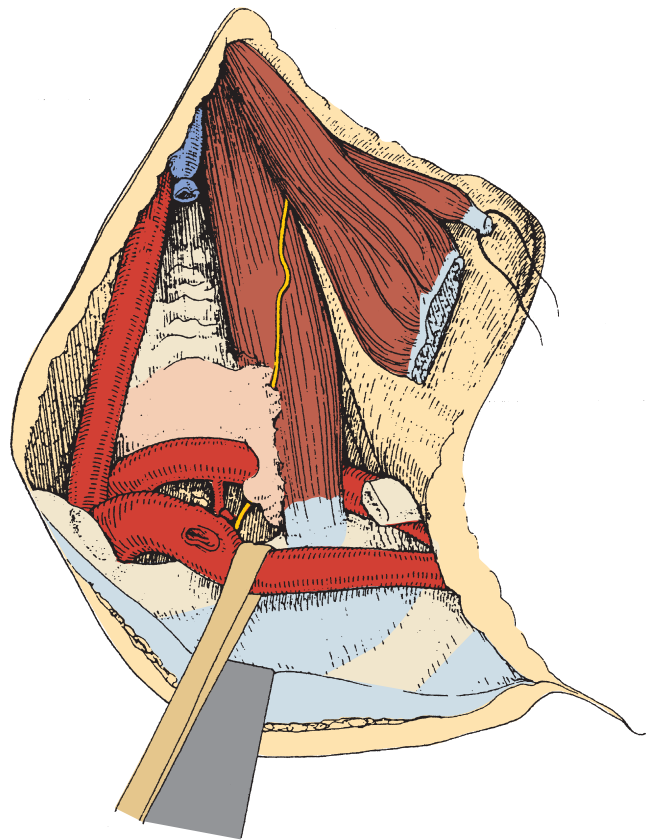


FIGURE 21-7 ■ Illustration of the resected scalene fat pad and the internal half of the clavicle after division of the sternal head of the sternocleidomastoid and the inferior belly of the omohyoid muscles. The exposure, dissection, and division of the external and internal jugular vein greatly facilitates the exposure of the subclavian vein and permits assessment of tumor resectability. (Adapted from Darteville PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

bral artery is resected only if invaded and if no significant extracranial occlusive disease was detected on preoperative Doppler ultrasound. If the tumor rests against the subclavian artery wall, the artery can be freed following a subadventitial plane. If there is invasion of the arterial wall, resection is necessary to obtain tumor-free margins. After proximal and distal control is obtained, the artery is divided on either side of the tumor (Fig. 21-10). Revascularization is performed using either polytetrafluoroethylene graft (6 or 8 mm) or, more often, an end-to-end primary anastomosis after freeing the carotid and subclavian arteries. During these maneuvers, the pleural space is usually opened by dividing Sibson fascia.

The middle scalene muscle is divided above its insertion on the first rib or higher, as dictated by tumor extent. This may require division of its insertions on the posterior tubercles of the transverse processes of vertebrae C2 to C7, especially for apical tumors invading the middle compartment of the thoracic inlet. The nerve roots of C8 and T1 are easily identified and dissected free from outside to inside, up to where they join to form the lower trunk of the brachial plexus. Thereafter, the ipsilateral prevertebral muscles are resected, along with the

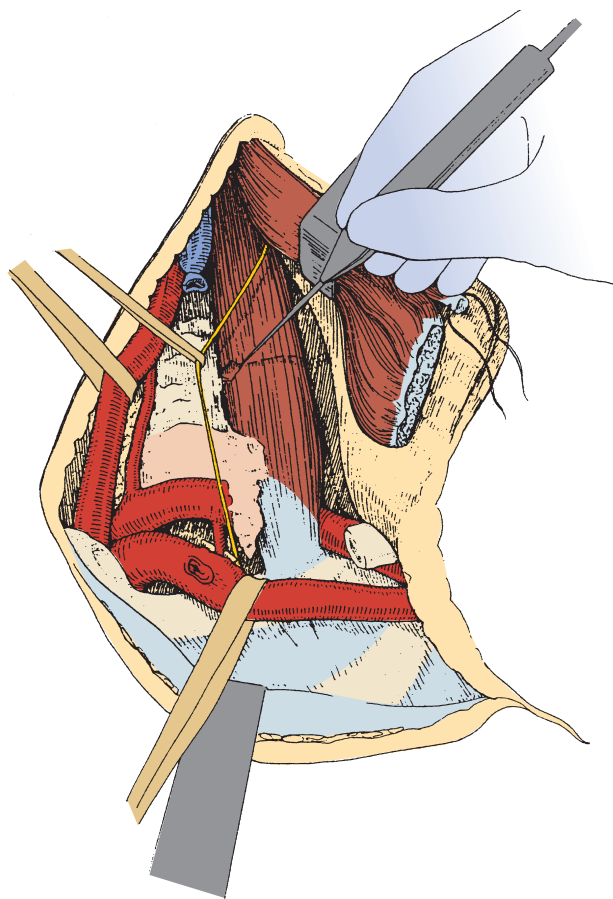


FIGURE 21-8 ■ The subclavian artery is exposed after division of the insertion of the anterior scalenus muscle on the first rib. The phrenic nerve is protected and preserved. (Adapted from Dartevelle PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

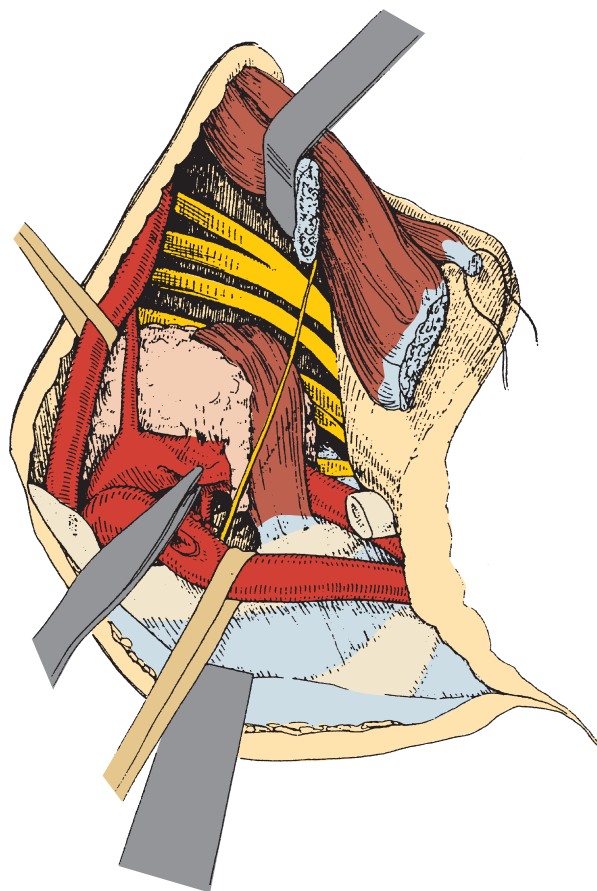


FIGURE 21-9 ■ Retraction of the anterior scalenus muscles allows identification of the interscalenic trunks of the brachial plexus. The subclavian artery can be gently freed from the tumor by dividing all collateral branches (the vertebral artery is generally preserved if not invaded). (Adapted from Dartevelle PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

paravertebral sympathetic chain and stellate ganglion, from the anterior surface of the vertebral bodies of C7 and T1 (Fig. 21-11). This permits oncologic clearance of the major lymphatic vessel draining the thoracic inlet and the visualization of the intervertebral foramina. The T1 nerve root is usually divided proximally beyond visible tumor, just lateral to the T1 intervertebral foramen. Although tumor involvement of the brachial plexus may be high, neurolysis is usually achieved without division of the nerve roots above T1 (Fig. 21-12). Lateral and long thoracic nerves should be preserved to avoid winged scapula.

The chest wall resection is completed before the upper lobectomy (Fig. 21-13). The anterolateral arch of the first rib is divided at the costochondral junction. The second rib is divided at the middle arch. The third rib is scraped on the superior border toward the costovertebral angle. The specimen is progressively freed. The divided ribs are disarticulated from the transverse processes of the first two or three thoracic vertebrae. An upper lobectomy can be accomplished through this cavity, although it is technically more demanding. The additional posterior thoracotomy, as in our original description,⁶ is usually not

required. The cervical incision is closed in two layers after the sternal insertion of the sternocleidomastoid muscle is sutured. Conventional tube drainage of the ipsilateral chest cavity is carried out.

There is increasing concern about the functional and aesthetic benefit of preserving the clavicle. We believe that the indications for preserving and reconstructing the clavicle are limited to the combined resection of the serratus anterior muscle and the long thoracic nerve, because this causes the scapula to rotate and draw forward. This entity (scapula alata), combined with the resection of the internal half of the clavicle, pushes the shoulder anteriorly and medially, leading to severe cosmetic, functional discomfort. If this circumstance is anticipated, we recommend an oblique section of the manubrium that fully preserves the sternoclavicular articulation, its intra-articular disc, and the costoclavicular ligaments, rather than the simple sternoclavicular disarticulation. Clavicular osteosynthesis can be accomplished by placing metallic wires across the lateral clavicular edges and across the divided manubrium.

We developed a technique for resecting superior sulcus tumors extending into the intervertebral foramen

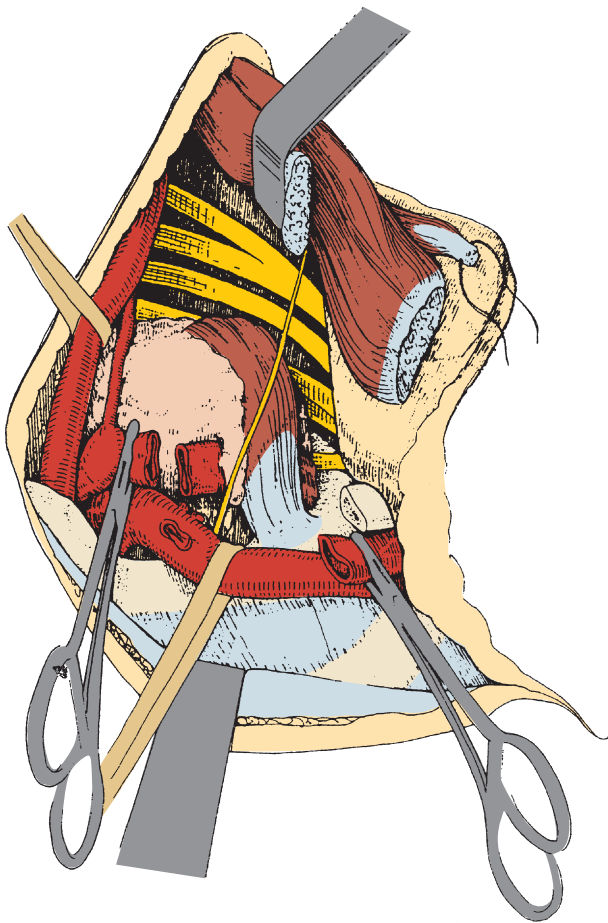


FIGURE 21-10 ■ If involved by the tumor, the subclavian artery can be divided after its proximal and distal control has been obtained. (Adapted from Darteville PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

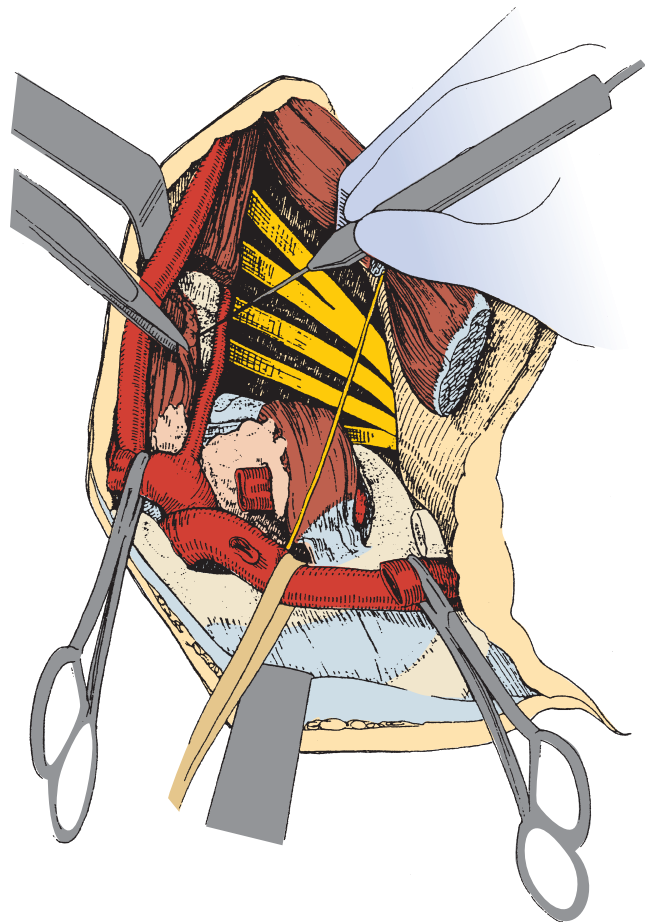


FIGURE 21-11 ■ The prevertebral muscles are extensively detached from the vertebral bodies, and both the stellate ganglion and the dorsal sympathetic chain are isolated and finally released, using raspatories, from all surrounding attachments. (Adapted from Darteville PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

without intraspinal extension¹⁰ (Fig. 21-14). The underlying principle is the use of a combined anterior transcervical and posterior midline approach, allowing resection of the intervertebral foramen and division of the nerve roots inside the spinal canal. The procedure starts with a transcervical approach; resectability is assessed. All tumor-involved areas are resected with tumor-free margins, as described. Next, the patient is placed in a ventral position, and a median vertical incision is extended from spinal processes C7 to T4.

After a unilateral laminectomy on three levels, the nerve roots are divided inside the spinal canal at their emergence from the external sheath covering the spinal cord. The specimen is resected en bloc, with the lung, ribs, and vessels through the posterior incision (Fig. 21-15) after division of the ipsilateral hemivertebral bodies. On the side of the tumor, spinal fixation is performed from the pedicle above to the pedicle below the resected hemivertebrae. On the contralateral side, a screw is placed in each pedicle (Fig. 21-16). However, if an anterior spinal artery is discovered to be penetrating the spinal canal through an invaded intervertebral foramen, surgery is contraindicated. Tumors involving

transverse processes should be resected with the anterior approach. The maneuver is similar to that used with the posterior approach but from the front to the back, with a finger placed behind the transverse process of T1 and T2 to direct the chisel correctly (Fig. 21-17).

SURGICAL MORBIDITY AND MORTALITY

Surgical complications are numerous and vary in severity. Horner syndrome occurs after injury to the stellate ganglion. The clinical consequences are usually well tolerated. Various nerve deficits can occur as well. Although division of the T1 nerve root does not induce significant muscular palsy in the nerve distribution, resection of the lower trunk of the brachial plexus can result in atrophic paralysis of the forearm and small muscles of the hand, with paralysis of the cervical sympathetic system (Dejerine-Klumpke syndrome). This scenario should be discussed with the patient before surgery. Relief of the preoperative pain and potential cancer cure are worth

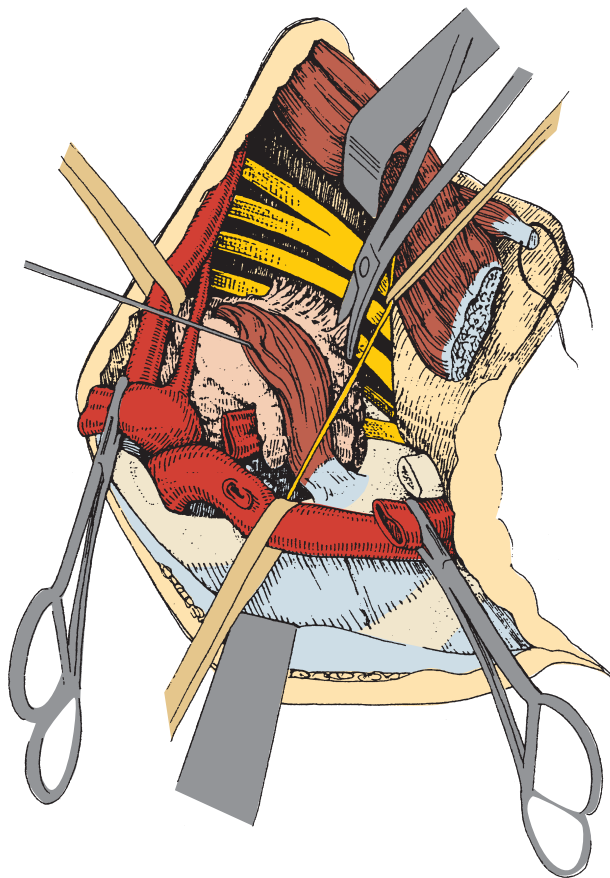


FIGURE 21-12 ■ Tumoral involvement of the brachial plexus requires an inside-out neurolysis if the upper trunks are involved, or a resection of T1 if the lower trunk or nerve roots are involved. (Adapted from Dartevielle PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

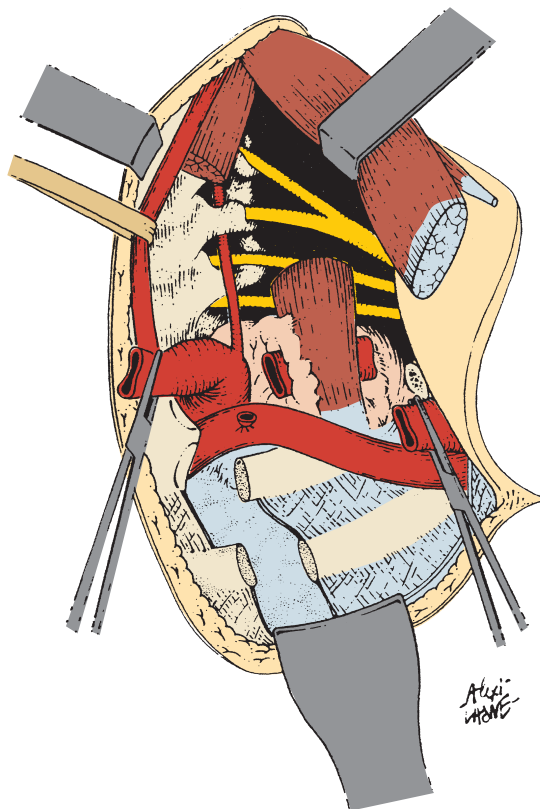


FIGURE 21-13 ■ Once structures above the thoracic inlet are freed from the tumor, the first two ribs might be separated anteriorly at its chondrocostal junction and resected posteriorly in tumor-free margins. The third rib is scribed on its superior border toward the costovertebral angle and retracted inferiorly. (Adapted from Dartevielle PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

the nerve sacrifice, however, and adaptation is usually reasonable.

Hemothorax can result from the extensive pleural adhesions encountered during resection, the chest wall resection, or the blood spillage from veins around the intervertebral foramina. Chylothorax should be prevented intraoperatively by extensive ligation of the cervical and intrathoracic lymphatic vessels after meticulous dissection. Whenever this occurs, continued chest tube drainage, lung expansion, or reoperation may be necessary.

Patients having a combined transcervical and midline approach are more likely than others to develop postoperative atelectasis and perfusion-ventilation mismatch. This is a result of chest wall dyskinesia and phrenic nerve resection or even temporary paresis from the dissection. Thus, these patients are unable to breathe spontaneously in the early postoperative course.

The postoperative course is characterized by atelectasis because of the extended chest wall resection, with or without phrenic nerve sacrifice. Treatment involves measures to achieve complete lung expansion by ensuring the following: ventilation (mechanical support as necessary); chest tube function; prevention of retained secretions by

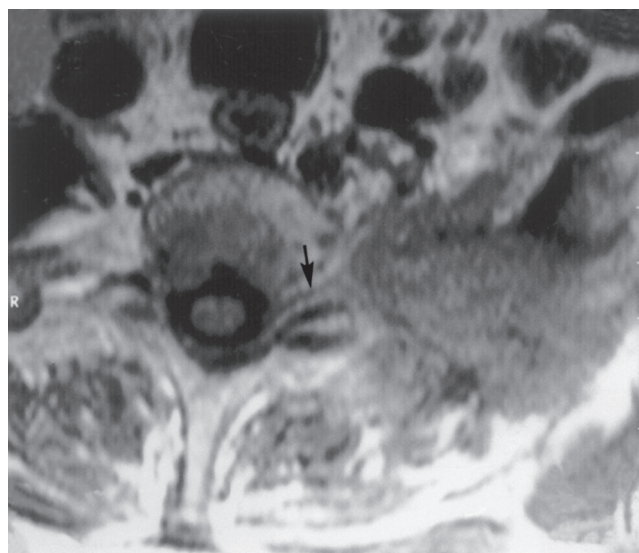


FIGURE 21-14 ■ Magnetic resonance image of a right superior sulcus bronchial carcinoma extending into the intervertebral foramen (arrow) without intraspinal extension.

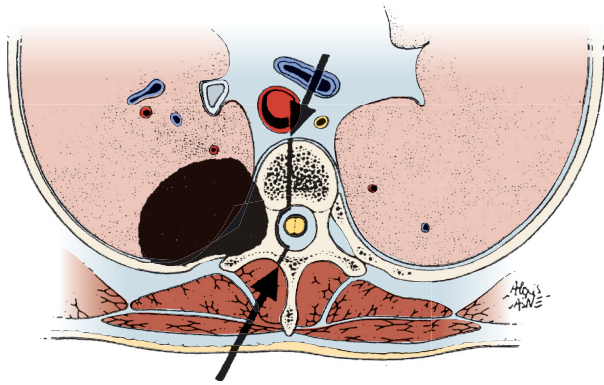


FIGURE 21-15 ■ Right-sided apical tumor involving the costovertebral space, intervertebral foramen, and part of the ipsilateral vertebral body. This tumor is first approached anteriorly as described in the text, and then the operation is completed through a hemivertebrectomy performed via the posterior midline approach. Arrows show the line of vertebral resection. (Adapted from Darteville PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

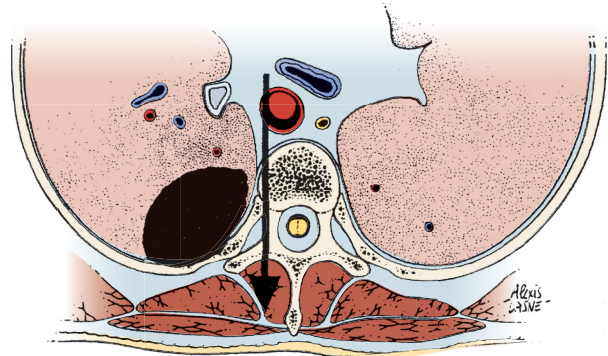


FIGURE 21-17 ■ Right-sided apical tumor involving the posterior arch of the rib only and resected from the anterior cervical approach by a vertical en bloc resection of part of the lateral vertebral body, the costovertebral space, and transverse process. Arrow shows the line of vertebral resection. (Adapted from Darteville PG, Chapelier AR, Macchiarini P, et al: Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. *J Thorac Cardiovasc Surg* 105:1025, 1993.)

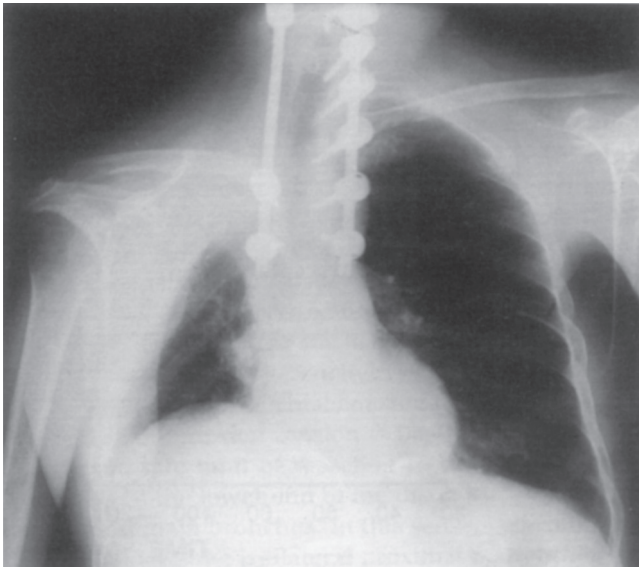


FIGURE 21-16 ■ Chest radiograph showing bilateral spinal fixation with metal rods interposed. (From Darteville PG: Extended operations for lung cancer. *Ann Thorac Surg* 63:12, 1997, with permission.)

mobilization, coughing, chest physiotherapy, and airway suctioning (even a temporary tracheostomy); optimal analgesia; and incentive spirometry.

Fluid overload should be avoided and diuretics used judiciously to avoid adult respiratory distress syndrome. Chest tubes remain in place until all air leaks have stopped and there is complete lung expansion. Fluid drainage should be minimal. Incomplete lung expansion with persistent intrapleural air space should be ignored because the space will ultimately be filled with serous fluid.

Resection of the subclavian vein should be accompanied by elevation of the ipsilateral forearm to facilitate venous drainage and generation of a collateral venous pathway (within 1 to 2 months). The radial pulse should

be followed closely to control the patency of the revascularized subclavian artery; after a preoperative loading dose of intravenous heparin, anticoagulant treatment should be switched to oral doses for a 6-month postoperative period only.

Neurologic complications are infrequent: spinal fluid leakage occurs secondary to injury to the spinal cord sheath. The risks of air embolism into the subarachnoid space, ventricles, central canal of the brain, and spinal cord space justify reoperation, during which a cerebral ventricular-venous shunt may be required.

RESULTS AND PROGNOSIS

The overall 5-year survival rates after combined radio-surgical (posterior approach) treatment of superior sulcus tumors caused by bronchial carcinoma range from 10% to 56% (Table 21-1). The best prognosis is found in patients without nodal involvement who have had a complete resection, as noted by Arcasoy and Jett¹¹ and Ginsberg and colleagues.⁵ We reported a complete resection rate of 100% with no postoperative mortality or major complications.¹² The 5-year and median survival rates were approximately 35% and 18 months, respectively. The local recurrence rate was less than 1.8% using our approach. Fadel and coworkers reported 17 en bloc resections of non-small cell lung cancers invading the thoracic inlet and intervertebral foramina, with 5-year and median survival rates of 20% and 27 months, respectively.¹³ Among the adverse prognostic factors, the nodal status is the only predictor of disease-free survival (Box 21-2). A review of our experience with superior sulcus tumors in 126 patients revealed that complete resection was achieved in 90% of cases, resulting in a median survival time of 28 months and a 5-year survival of 39.3%.¹⁴ There was one death during the study period. By multivariate analysis, incomplete resection and subclavian artery involvement adversely affected survival ($P = 0.01$,

TABLE 21-1 Results of Surgical Treatment for Superior Sulcus Tumors

Author (year)	Cases (N)	5-Year Survival (%)	Mortality (%)
Paulson (1985) ¹⁵	79	35	3
Anderson et al (1986) ¹⁶	28	34	7
Devine et al (1986) ¹⁷	40	10	8
Miller et al (1987) ¹⁸	36	31	NS
Wright et al (1987) ¹⁹	21	27	—
Shahian et al (1987) ²⁰	18	56	—
McKneally et al (1987) ²¹	25	51	NS
Komaki et al (1990) ²²	25	40	NS
Sartori et al (1992) ²³	42	25	2.3
Maggi et al (1994) ²⁴	60	17.4	5
Ginsberg et al (1994) ⁵	100	26	4
Okubo et al (1995) ²⁵	18	38.5	5.6
Dartevelle, Macchiarini (1998) ²⁶	70	34	—
Totals	562	33 ± 12*	3.5 ± 3*

*Values are percent ± standard deviation.

Adapted from Dartevelle P, Macchiarini P: Optimal management of tumors in the superior sulcus. In Franco KL, Putman J Jr, editors: *Advanced therapy in thoracic surgery*. Hamilton, Ontario, 1998, BC Decker, with permission.

BOX 21-2 Factors Influencing Survival and Disease-Free Survival* of Patients with Superior Sulcus Tumor†

ADVERSE PROGNOSTIC FACTORS

- Female sex
- Positive bronchoscopy
- Abnormal serum carcinoembryonic antigen (CEA)
- Full-blown Pancoast-Tobias syndrome
- Positive lymph nodes (N1-N3)

FACTORS WITHOUT PROGNOSTIC INFLUENCE

- Side and site of the tumor
- Invasion of the intervertebral foramen

*By multivariate analysis, only the nodal status adversely affected disease-free survival.

†The superior sulcus tumors had invaded the thoracic inlet, and they were completely resected through the anterior approach.

each). More recently we reviewed 54 en bloc resections of non-small cell lung cancer invading the thoracic inlet and spine.²⁷ Complete resection was achieved in 91% of cases and the 1-, 5-, and 10-year survival rates were 82%, 31%, and 31%, respectively. These results have been emphasized by an even more recent review and pooled data analysis.²⁸ Overall, these results suggest that radical surgery for superior sulcus tumors may be performed in experienced centers with low mortality and favorable survival rates.

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OTHER LUNG MALIGNANCY

PART OUTLINE

22 OTHER PRIMARY TUMORS OF THE LUNG

23 SECONDARY LUNG TUMORS

OTHER PRIMARY TUMORS OF THE LUNG

Dustin M. Walters • David R. Jones

CHAPTER OUTLINE

BRONCHOPULMONARY CARCINOIDS

Epidemiology
Pathology
Genetics and Biochemistry
Clinical Presentation
Diagnosis
Imaging
Bronchoscopy
Tumor Markers
Staging
Management and Treatment
Surgery
Endobronchial Management
Adjuvant Therapies: Radiation,
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PRIMARY PULMONARY CARCINOSARCOMA

Epidemiology and Pathology
Diagnosis
Treatment and Prognosis

Most primary lung cancers comprise the histologic variants described in other chapters of this text. On occasion, however, the thoracic surgeon must diagnose and treat an unusual primary lung cancer. These tumors frequently have a similar clinical presentation to more common tumors, but there are often subtle differences in treatment. Hence, knowledge of these tumors, their characteristics, and the ensuing diagnostic and treatment paradigms are important for the practicing thoracic surgeon.

BRONCHOPULMONARY CARCINOIDS

Epidemiology

Bronchopulmonary carcinoid tumors account for one quarter of all carcinoid tumors, represent 1.2% of all primary lung tumors in adults,^{1,2} and are the most common primary lung tumor in children.³ Overall, when all carcinoids are accounted for, they are distributed almost equally between males and females; however, in

the bronchopulmonary subset, they are found predominantly in females.^{4,5} The incidence is significantly higher in white patients than in black, Asian, and Hispanic patients.¹ Compared with bronchogenic carcinomas, carcinoid tumors occur more frequently in younger patients and are less likely to be associated with a significant smoking history.⁵

Bronchopulmonary carcinoid tumors arise from neuroendocrine cells and are thus positioned on the neuroendocrine tumor spectrum, which includes the more aggressive large-cell neuroendocrine carcinomas and small-cell lung carcinomas. Bronchopulmonary carcinoid tumors are classified as either typical or atypical on the basis of histologic features. Typical carcinoid tumors account for three quarters of bronchopulmonary carcinoids, are often centrally located, and rarely metastasize.⁵ In contrast, atypical carcinoid tumors are located more frequently in the lung periphery and metastasize in more than 40% of cases. Atypical carcinoid tumors occur more often with increasing age and are rarely seen in patients younger than 30 years.⁶ Unlike high-grade bronchopulmonary neuroendocrine tumors (large-cell and small-cell variants), typical and atypical bronchopulmonary carcinoids rarely occur in combination with other adenocarcinomas; however, the risk of synchronous breast and prostate cancer is slightly elevated.⁷

Pathology

Most bronchopulmonary carcinoid tumors, particularly typical carcinoids, are centrally located.⁸ Fink et al reported that 68% of bronchopulmonary carcinoid tumors were located in the major bronchi (13% in the mainstem bronchi and 55% in lobar bronchi), with the remaining 32% in peripheral locations.⁸ Because of the predominance of central location, these tumors can often be visualized bronchoscopically, demonstrating a sessile, red-brown to bluish-tan endobronchial mass with variable vascularity and a smooth surface. On gross pathologic examination, typical carcinoids appear as a white or gray cut surface without evidence of hemorrhage

or necrosis.⁹ In contrast, atypical carcinoids tend to be located peripherally in the lungs.¹⁰ On gross pathologic examination, atypical carcinoids appear white-gray on section but can exhibit a color of tan, pink to yellow-brown, and red.¹¹

The World Health Organization (WHO) classification of pulmonary neuroendocrine tumors is based on morphologic and histologic features, which clearly influence tumor behavior and prognosis.¹² The spectrum of neuroendocrine tumors includes low-grade typical carcinoids, intermediate-grade atypical carcinoids, and high-grade large- and small-cell variants. Typical carcinoid tumors have fewer than 2 mitoses per 10 high power fields (HPF), have no evidence of necrosis, and are larger than 0.5 cm. Tumors smaller than 0.5 cm are classified as carcinoid tumorlets and are addressed later in this chapter. Atypical carcinoid tumors have 2 to 10 mitoses per 10 HPF or necrosis. [Figure 22-1](#) demonstrates the histologic appearance of a typical and an atypical carcinoid tumor. In comparison, large- and small-cell carcinomas contain greater than 10 mitoses per 10 HPF and are further distinguished on the basis of other morphologic characteristics. Although the WHO classification places these four subtypes under the general heading of bronchopulmonary neuroendocrine tumors, the results of histopathologic and immunochemical studies support the idea that bronchopulmonary carcinoids are distinct from the more malignant and high-grade neuroendocrine tumors.¹³

Gustafsson and colleagues¹³ discussed a separate entity termed *diffuse idiopathic pulmonary neuroendocrine cell hyperplasia* (DIPNECH). This rare preneoplastic condition features proliferation of pulmonary neuroendocrine cells and neuroepithelial bodies. When this proliferation extends beyond the basement membrane, the group of cells is identified as a carcinoid tumorlet. These tumorlets are nodular, carcinoid-like proliferations of neuroendocrine cells less than 5 mm in size; those that proliferate to greater than 5 mm are classified as carcinoid tumors. DIPNECH can be both an adaptive response, as seen in persons living at high altitudes, and a reactive response

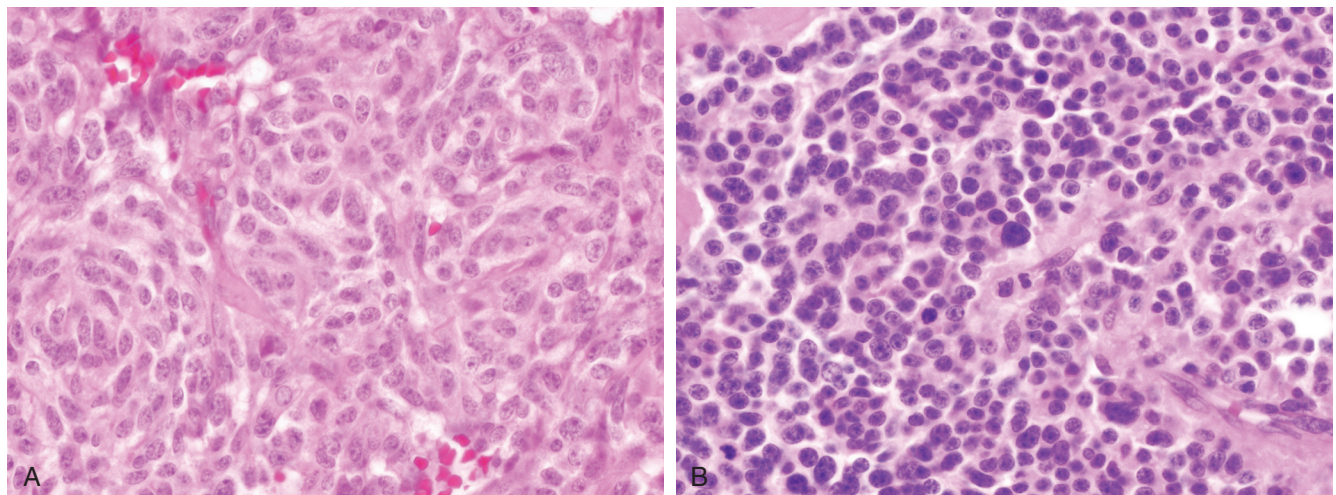


FIGURE 22-1 ■ **A**, H&E stain of a typical carcinoid. **B**, H&E stain of an atypical carcinoid.

TABLE 22-1 Pathologic Criteria for Carcinoid and Associated Tumors

Type of Tumor	Location	Nodal Metastases	Gross Pathologic Examination	Histologic/WHO Criteria
DIPNECH	Variable	None	Nodular bronchial wall thickening	No extension beyond basement membrane
Carcinoid tumorlet	Variable	None	Small, similar appearance to carcinoid tumors	Carcinoid-like, but <0.5 cm in size, mitoses very uncommon
Typical carcinoid	Central	Rare	White or gray with minimal evidence of necrosis or hemorrhage	<2 mitoses/2 mm ² >0.5 cm in size Lack of necrosis
Atypical carcinoid	Peripheral	Frequent	White-gray that on section appears tan, pink, red, or yellow-brown	2-10 mitoses/2 mm ² >0.5 cm in size Necrosis

DIPNECH, Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; WHO, World Health Organization.

to lung injury, as seen in patients with obliterative bronchiolitis,¹⁴ chronic cough,¹⁵ and interstitial lung disease.¹⁶ Table 22-1 describes the major distinctions among DIPNECHs, tumorlets, and carcinoids.

Genetics and Biochemistry

Molecular genetic analysis has demonstrated that multiple genes are involved in the development and progression of carcinoid tumors. One important genetic mechanism is loss of heterozygosity (LOH), which can occur in multiple chromosomes, including but not limited to 3p, 5q21 (MCC/APC), 9p21 (*p16* gene), 11q13 (*MEN1* gene), 13q14 (retinoblastoma [*RB*] gene), and 17p13 (*p53* gene).^{17,18} LOH at chromosome 3p is the most frequent change in bronchopulmonary neuroendocrine tumors and has been observed in 40% of typical carcinoids and 73% of atypical carcinoids.¹⁸ *p53* mutations and loss of 5q21 occur in higher-grade tumors and are associated with worse survival.^{17,18}

Bronchopulmonary carcinoids are known to occur as components of familial endocrine cancer syndromes, namely multiple endocrine neoplasia 1 (MEN1), although this rarely occurs. The *MEN1* gene is inactivated by mutation in approximately 47% of typical carcinoids and 70% of atypical carcinoids.¹⁹⁻²¹ More recently, a study evaluated 129 patients with MEN1 and found that 6 of these (5%) had been diagnosed with bronchopulmonary carcinoids on initial diagnosis.²² An additional 32 patients had chest computed tomography (CT) scans for review, and 12 of these (38%) had pulmonary nodules suspicious for bronchopulmonary carcinoid, 4 of which were histologically confirmed to be a carcinoid. This study demonstrated that the incidence of bronchopulmonary carcinoid in MEN1 is much higher than previously believed; therefore, it is recommended that patients with MEN1 be screened for bronchopulmonary carcinoids with chest CT imaging every 3 years, with onset at 20 years of age.^{22,23}

The *p53* gene (chromosome 17p13) is important for maintaining genomic stability, in addition to numerous other functions. LOH or abnormal expression at the *p53* locus has been detected in 4% of typical carcinoids and 29% of atypical carcinoids.^{24,25} Kobayashi et al²⁶

BOX 22-1 Endocrinopathies Seen in Bronchopulmonary Carcinoids

Carcinoid syndrome
Cushing syndrome
Acromegaly
Hypercalcemia
Hypoglycemia

evaluated the frequency of *p53* protein expression in several bronchopulmonary carcinoid tumors and found that the sampled typical carcinoids did not demonstrate any expression; in contrast, 20% of the sampled atypical carcinoids had expression.

Clinical Presentation

The presentation of bronchopulmonary carcinoid tumors is dependent on both the size and the location of the tumor; given the high proportion of centrally located carcinoid tumors, most patients are symptomatic at presentation. The most common symptoms are cough, hemoptysis, dyspnea, wheezing, and recurrent upper respiratory infections or pneumonia, caused by endoluminal obstruction by the tumor. Symptoms may be present for many years before diagnosis is made and almost entirely reflect the anatomic location of the lesion, as opposed to the secreted bioactive products.²⁷ Although some patients with bronchopulmonary carcinoid tumors may initially have carcinoid syndrome²⁸ (diarrhea, flushing, bronchoconstriction, and heart failure), in general this is exceedingly rare.⁸ Infrequently, bronchopulmonary carcinoids may secrete adrenocorticotrophic hormone (ACTH) (Cushing syndrome),²⁹ growth hormone,³⁰ or other bioactive substances. Carcinoid tumors are one of the most frequent causes of ectopic secretion of ACTH.³¹ Box 22-1 depicts common endocrinopathies associated with carcinoid tumors. A quarter of patients are asymptomatic,³² and thus many of these tumors are found incidentally or are never discovered. A population-based study in Denmark showed that 24% of typical carcinoids and 7% of atypical carcinoids were discovered on autopsy.²⁷

Diagnosis

Imaging

Chest radiographs (CXR) are nonspecific for bronchopulmonary carcinoids but may demonstrate an isolated, well-defined hilar or perihilar mass, occasionally with associated atelectasis or postobstructive pneumonia. Suspicious lesions should be examined further with chest CT, which is the preferred diagnostic imaging study and which allows for determination of tumor size, location, and potential lymph node involvement. On CT, carcinoids appear as well-defined, homogeneous, spherical/ovoid, endobronchial masses (Fig. 22-2) that exert mass effect or cause distal airway obstruction.³³ Spiculation is absent. Typical carcinoids are often vascular and more commonly centrally located. In contrast, atypical carcinoids are usually located peripherally, and 30% have calcifications.¹⁰

Most bronchopulmonary neuroendocrine tumors (80%) express somatostatin receptors, predominantly SST₂ receptors.³⁴ Somatostatin receptor scintigraphy (SRS) with radiolabeled somatostatin analogs (¹¹¹In-octreotide and ¹¹¹In-lanreotide) can be used to locate bronchopulmonary carcinoid tumors or metastatic lesions. However, only two thirds of these carcinoids will have positive findings on SRS, and CT is generally superior for visualizing both primary and metastatic lesions.³⁵ Furthermore, benign pathologic results can produce false-positive findings on SRS. Given these limitations and the superiority of CT scans, SRS should rarely be used in the diagnosis or workup of bronchopulmonary carcinoids.

The role of positron emission tomography (PET) in diagnosing bronchopulmonary carcinoids is not as well defined as that of either CT or SRS but has been investigated in several small, single-institution series and may benefit select patients. PET functions by detecting the accumulation of radiolabeled biological molecules (most commonly ¹⁸F-fluorodeoxyglucose [FDG]) within

neoplastic cells. Historically, the use of FDG-PET has been fraught with false-negative results in patients with solitary bronchopulmonary carcinoids, because they are often hypometabolic on FDG-PET.³⁶ More recently, however, FDG-PET, particularly when combined with CT, has shown improvement in the staging of select patients, particularly those with atypical carcinoid tumors.³⁷ Typical carcinoids generally demonstrate significantly lower average standardized uptake values (SUVs), compared with atypical carcinoids. Chong et al³⁸ reviewed FDG-PET scans of typical carcinoids ($n = 2$) and atypical carcinoids ($n = 5$) for maximum SUV. The typical carcinoids had an SUV range of 3.2 to 3.4, with both specimens exhibiting less than mediastinal uptake. Three of the five atypical carcinoids had a higher SUV (4.0 to 7.1) than the mediastinum. One of the five atypical carcinoids had a maximum SUV of 1.7, with an ipsilateral hilar lymph node measuring an SUV of 11.2.³⁸ A further potential benefit of FDG-PET is its ability to identify lymph node and distant metastases in some cases, although it does not identify these metastases in all cases.^{37,39} In summary, the role of FDG-PET is evolving, and in the future it will likely play a role in the workup of select patients, particularly those with suspected atypical carcinoid tumors. Given the possibility for false-negative results in FDG-PET scans, a lesion that is suspicious for carcinoid on CT should be treated as such.

Bronchoscopy

After the identification of an endobronchial or centrally located tumor, the next step in the diagnostic workup should be bronchoscopic evaluation. Rivera et al⁴⁰ reviewed almost 3800 patients with central, endobronchial lesions and found that the overall sensitivity of flexible fiberoptic bronchoscopy for detecting lesions was 88%. As mentioned previously, most bronchopulmonary carcinoids (75%) are centrally located and are thus amenable to bronchoscopic evaluation. Recently, electromagnetic navigational bronchoscopy (ENB) has proven to be an effective means of obtaining tissue in peripheral lesions not amenable to biopsy by standard bronchoscopic techniques. In a recent study, ENB was able to establish a diagnosis in 37 of 48 patients (77%) with such lesions who were at high risk for requiring more invasive procedures.⁴¹ On bronchoscopic evaluation, carcinoid tumors are often smooth with a distinct reddish-brown appearance. Biopsy should be performed in an effort to establish a diagnosis, although distinguishing typical from atypical carcinoids can sometimes be challenging because of the small tissue sample typically obtained with flexible bronchoscopy.⁴² Given this difficulty and the fact that 5% to 20% of typical carcinoids and 30% to 70% of atypical carcinoids metastasize to regional lymph nodes, lymphadenectomy at the time of surgery should be strongly considered for accurate staging.¹¹ Additionally, there are several cases in the literature of carcinoid tumors overdiagnosed as small-cell carcinomas on the basis of bronchoscopic biopsies.⁴³ An accurate diagnosis is best achieved by careful evaluation of hematoxylin and eosin sections and mitotic index, as treatments differ radically among these separate entities.

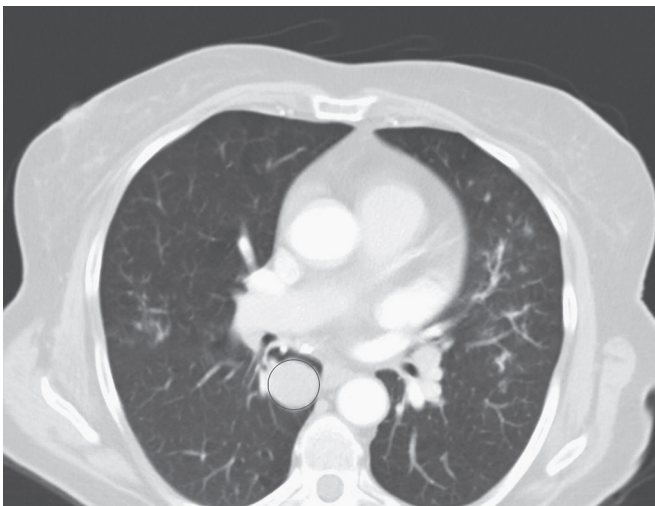


FIGURE 22-2 ■ Chest CT scan of a typical carcinoid.

In the past, a feared complication of bronchoscopic biopsy of carcinoid tumors was major hemorrhage; however, several more recent studies have shown this to be a rare occurrence, and biopsy is considered a safe venture. In a review of 587 biopsies by flexible and rigid bronchoscopy, there was significant hemorrhage in 15 patients (2.6%), with only 4 (0.7%) requiring emergency intervention secondary to massive uncontrollable hemorrhage.⁴⁴ Mucosal injection of an epinephrine solution before biopsy can mitigate some of the risk of hemorrhage. In the event of significant bleeding that is difficult to control, a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser is helpful.^{45,46} If standard bronchoscopic and ENB biopsy techniques are unable to successfully biopsy peripheral tumors, CT-guided percutaneous transthoracic needle biopsy, video-assisted thoracic surgery, and thoracotomy are other options.

Tumor Markers

Serotonin and urinary 5-HIAA are well-known markers of hormonally active carcinoid tumors; however, they are not specific for bronchopulmonary carcinoids. Chromogranin A (CgA) elevation in plasma is a relatively sensitive (75%) marker of bronchopulmonary carcinoids.⁴⁷ Care must be taken in patients with renal impairment and atrophic gastritis and during proton pump inhibitor therapy, because these conditions cause elevations in CgA and thus false-positive results. In clinical practice, there is no evidence that measurement of tumor marker levels adds value or alters patient management; therefore, it is not routinely performed.

Staging

The TNM (tumor, nodes, metastasis) classification for lung cancer remains the most widely used staging classification for bronchopulmonary carcinoid tumors.⁴⁸ Fink et al analyzed 142 bronchopulmonary carcinoids, of which 128 were typical and 14 were atypical. Lymph node metastases were less common in the subset of typical carcinoids (N0 = 87%, N1 = 10%, N2 = 3%), compared with atypical carcinoids (N0 = 43% N1 = 29%, N2 = 14%, N3 = 14%). As for other histologic variants of lung cancer, for bronchopulmonary carcinoids, N1 disease is defined as ipsilateral hilar lymph node involvement, N2 disease is defined as ipsilateral mediastinal lymph node involvement, and N3 disease is defined as contralateral or distant nodal involvement. None of the patients with typical carcinoid was found to exhibit N3 disease. Distant metastatic disease (M1) was found in 2% of typical and 21% of atypical carcinoid tumors.⁸

A larger, more recent Italian study⁴⁹ retrospectively analyzed 252 patients, 174 with typical and 78 with atypical carcinoid tumors, during a 38-year period and found that 96% of patients with typical carcinoids presented without nodal metastases, 3.4% presented with N1 disease, and 0.6% presented with N2 disease. In contrast, only 72% of patients with atypical carcinoids presented without nodal metastases, 17% presented with N1 disease, and 11% presented with N2 disease. Thus, typical carcinoids rarely have nodal disease, whereas

atypical carcinoids commonly have either N1 or N2 disease—again highlighting the different tumor biology between these two tumors. The two previously mentioned studies and others are summarized in Table 22-2.

Management and Treatment

Surgery

Complete surgical resection with preservation of normal lung tissue remains the only curative treatment of bronchopulmonary carcinoids.¹³ When considering bronchopulmonary carcinoid tumors, there should be three surgical goals: (1) complete resection of the tumor (R0 resection), (2) sparing of the parenchyma whenever possible, and (3) lymph node staging by either ipsilateral lymph node sampling or mediastinal lymph node dissection.

Centrally located typical carcinoids should be resected using lung parenchyma-sparing resections, such as sleeve resection, or anatomic segmentectomy.⁵⁰⁻⁵¹ Because local recurrence is rare, surgical treatment of typical carcinoids does not require a wide margin of resection.⁴⁹ Ferguson and coworkers, in a multicenter retrospective study, found that wide nonanatomic wedge resection or segmentectomy was justified in the case of peripheral typical carcinoid tumors because of the low likelihood of local recurrence.⁵² Additionally, sleeve bronchial resections without parenchymal resection have been described for select patients with typical carcinoid tumors who have no evidence of nodal metastasis.⁵³

Although most agree that nonanatomic resection, when possible, is acceptable for the management of typical carcinoids, the surgical approach for atypical carcinoids is typically lobectomy or, rarely, pneumonectomy. When sleeve lobectomy is a reasonable alternative to pneumonectomy, this approach is preferred.⁵⁴ Given the greater propensity of atypical carcinoids to metastasize to lymph nodes, a more extensive and aggressive resection (lobectomy, bilobectomy, and pneumonectomy) and nodal dissection are recommended.⁵⁵⁻⁵⁷

Surgical resection of bronchopulmonary carcinoids should be combined with ipsilateral mediastinal lymph node dissection or sampling.⁴⁹ The necessity of lymph node dissection is justified by the possibility of lymph node metastasis, which has an incidence of 4% to 13% in typical carcinoids and 28% to 67% in atypical carcinoids.^{8,49,50,58}

Endobronchial Management

Endobronchial intervention using Nd:YAG laser removal or mechanical tumor removal has been described in highly selected patients with intraluminal typical carcinoid tumors, with excellent local control and low rates of recurrence.⁵⁹ Bertoletti and colleagues⁶⁰ conducted a study of 18 patients (all with typical carcinoid, strict endoluminal disease, and no evidence of lymph node invasion) treated with flexible bronchoscopy and cryotherapy. Patients were monitored for 55 months; there was one recurrence in 7 years, with no long-term complications. Finally, in a recent retrospective review, 25

TABLE 22-2 Summary of Studies Comparing Typical and Atypical Carcinoid Tumors

Author	Year	BP Carcinoid	Patients	N0	N1	N2	5-year Survival (Histology)	10-year Survival (Histology)	5-year Survival (Node Negative)	10-year Survival (Node Negative)	5-year Survival (Node Positive)	10-year Survival (Node Positive)
Fink et al ⁸	2001	Typical	128	111	13	4	89%	82%	n/a	n/a	n/a	n/a
		Atypical	14	6	4	2	75%	56%				
Filosso et al ⁵⁰	2002	Typical	75	69	2	4	97%	93%	92%	87%	85%	52%
		Atypical	38	24	7	7	77%	52%				
Cardillo et al ⁵⁸	2004	Typical	121	107	14	0	99%	n/a	100%	n/a	90%	n/a
		Atypical	42	15	18	9	70%	n/a	100%	n/a	59%	n/a
Garcia-Yuste et al ⁶⁸	2007	Typical	569	517	32	20	97%	92%	97%	92%	100%	66%
		Atypical	92	59	14	19	78%	67%	83%	70%	60%	60%
Rea et al ⁴⁹	2007	Typical	174	167	6	1	n/a	93%	n/a	87%	n/a	50%
		Atypical	78	56	13	9	n/a	64%				
Total		Typical	1067	971	67	29	89-99%	82-93%				
		Atypical	262	160	56	46	70-77%	52-67%				

BP, Bronchopulmonary.

endoscopically treated patients were compared with 48 patients who underwent surgical resection, and there was no difference in mortality.⁶¹ No recurrences were noted in either group. Although these results are encouraging, the current standard of care is surgical resection, and endobronchial resection should be reserved for patients who are not candidates for surgical intervention because of medical risk factors.

Adjuvant Therapies: Radiation, Chemotherapy, and Targeted Therapy

Bronchopulmonary carcinoids respond poorly to radiotherapy, and this treatment modality is generally reserved for use when surgical resection is impractical or as an adjunct when resection is incomplete.^{13,62}

There is no role for adjuvant chemotherapy following resection of a typical carcinoid tumor, regardless of lymph node status. In patients with atypical carcinoids, chemotherapy can be used as an adjunct, but response rates are typically low.⁶³ The recommendations for adjuvant doublet, platinum-based chemotherapy are largely based on similar indications for other non-small cell lung cancer (NSCLC) histologic profiles and the presence of N1 or N2 disease. No clinical trials to date have specifically addressed the role, agent, or dosing regimen for atypical carcinoids.

Whereas cytotoxic chemotherapy regimens have had limited success, more recent evidence suggests that targeted therapies against mammalian target of rapamycin,^{64,65} vascular endothelial growth factor,⁶⁶ and platelet-derived growth factor⁶⁷ may be efficacious, although more clinical data are needed.

Prognosis

With an increase in the number of chest imaging studies performed, as well as the enhanced quality of the imaging techniques, there has been an increase in the incidence of bronchopulmonary carcinoids. Despite what could be perceived as earlier detection of all carcinoid tumors, a review of the SEER database demonstrated a decrease in the 5-year survival of patients with all carcinoids (including atypical ones) during the past 30 years.² Reasons for this decrease in survival are unclear but may be related to an increase in the incidence of the atypical carcinoid histologic profile.

It is well known that typical carcinoids have a superior prognosis, compared with atypical carcinoids. This difference is primarily attributable to the differences in tumor biology between the two histologic profiles. Recent studies have shown the 5-year and 10-year survival rates for patients with typical carcinoids to be 89% to 99% and 82% to 93%, respectively. In contrast, the 5-year and 10-year survival rates for patients with atypical carcinoids are 70% to 77% and 52% to 67%, respectively.^{8,49,50,58}

The prognostic significance of lymph node involvement in atypical carcinoid tumors cannot be overstated and has been addressed by multiple studies (see [Table 22-2](#)). The 5-year survival for atypical carcinoids with node-positive disease is 59% to 60%, compared with 83% to 100% for node-negative disease. For typical

carcinoids, however, the presence or absence of nodal disease does not correlate with survival.^{58,68}

CARCINOID TUMORLETS

Epidemiology

A carcinoid tumorlet is a nodular proliferation of pulmonary neuroendocrine cells that extends beyond the basement membrane but is less than 5 mm in size; those that proliferate to greater than 5 mm are classified as carcinoid tumors.¹³ Carcinoid tumorlets and carcinoid tumors have long been associated in the literature, but a definitive relationship has not been firmly established. Studies have demonstrated the presence of tumorlets in normal lungs or in association with carcinoid tumors.^{69,70} There have also been case reports of isolated peribronchial⁷¹ and hilar⁷² lymph node metastases, which point to the possible neoplastic potential of carcinoid tumorlets. In each of these circumstances, the lymph nodes appeared normal on gross examination; however, on pathologic examination, microscopic metastases were found.

Pathology

Carcinoid tumorlets develop from Kulchitsky cells, which are hyperplastic neuroendocrine cells in the bronchial and bronchiolar mucosa. Tumorlets can be single or multiple, are less than 5 mm in size, and have a carcinoid-like appearance. It has been suggested that these cells secrete neuropeptides that can elicit peribronchiolar reaction, leading to fibrotic lung disease.^{14,73,74}

Clinical Presentation and Diagnosis

Most pulmonary carcinoid tumorlets are asymptomatic and thus are discovered incidentally, even if multiple tumorlets are present. Pulmonary symptoms, dysfunction, and radiologic abnormalities have occasionally been attributed to multiple tumorlets.⁷⁵ In a retrospective review of 28 patients, those with multiple nodules were most likely to present with cough (59%) and dyspnea (47%); however, 41% of patients had no symptoms at presentation. Almost half of the patients (47%) with multiple nodules were nonsmokers, but 59% demonstrated obstructive patterns on pulmonary function testing.⁷⁵

Management and Treatment

There is no consensus on the management of carcinoid tumorlets. If, on pathologic examination, a carcinoid tumorlet is discovered at the resection margin, further surgical resection is not advocated. In cases where carcinoid tumorlets are associated with bronchopulmonary carcinoids, the appropriate management and treatment are dictated by the histologic profile and stage of the carcinoid tumor. Clinical surveillance may be indicated for patients with carcinoid tumorlets, because they are believed by some to progress, in rare cases, to a true carcinoid tumor; the evidence for this, however, is conflicting.⁷⁶⁻⁷⁸

Prognosis

The risk of progression to carcinoid tumor, although unproven, is at least uncommon, and although there are reports in the literature of metastatic progression,^{71,72} this is an exceedingly rare event. There is a small risk of fibrotic lung disease secondary to carcinoid tumorlets. One study demonstrated that, when tumorlets occur in conjunction with true carcinoid tumors, the multicentricity may confer a poorer prognosis.⁷⁹ Most patients with tumorlets will have persistent and stable disease without the need for additional therapy.

PRIMARY PULMONARY SALIVARY GLAND-TYPE NEOPLASMS

Epidemiology

Primary salivary gland-type lung tumors are rare, low-grade, intrathoracic malignancies, and they account for 0.2% of all lung tumors.⁸⁰ These tumors include adenoid cystic carcinomas (ACCs), mucoepidermoid carcinomas (MECs), and mixed tumors (ACC and MEC)⁸¹ (Table 22-3). It has been postulated that these tumors arise from the submucosal glands of the tracheobronchial tree and are probably related to structural homology between exocrine glands.^{81,82}

Molina et al performed a retrospective review of 62 patients with primary salivary gland-type lung cancer and found that ACC was the most frequent histologic profile (64.5% of patients), followed by MEC (32.3%) and mixed tumor (3.2%).⁸³ These results are largely consistent with those of previous series, although in some series MEC is reported to be the most frequent histologic form. Patients diagnosed with ACC generally have more advanced age than those with MEC (54 vs. 40 years; $P = 0.02$) and are more likely to have a history of smoking or to currently smoke.⁸³

Pathology

On bronchoscopic or gross evaluation, MECs will often have a smooth appearance and are typically pink, gray, or tan in color. In contrast, ACCs are typically exophytic, have less defined borders, and may ulcerate or infiltrate surrounding tissue. On histologic examination, MECs demonstrate mucous cells in conjunction with varied proportions of epidermoid, clear, and "intermediate" cells.⁸³

Several staging systems have been described for MECs, with the Brandwein⁸⁴ and the Armed Forces Institute of Pathology (AFIP)⁸⁵ systems being two of the more commonly used options. The Brandwein system is a three-stage grading system (low, intermediate, and high) that assigns points for different histologic features. Two points are assigned for an intracystic component (<25%), invasion in small nests or islands, or nuclear atypia. Three points are assigned if there is lymphatic/vascular invasion, bony invasion, greater than 4 mitoses per 10 HPF, perineural spread, or necrosis. Summation of these points grades the MEC as low (0 points), intermediate (2-3 points), or high grade (4-21 points).⁸⁴ Similarly, the AFIP system is a points-based system: 2 points are given for intracystic components or neural invasion, 3 points are given for necrosis or greater than 4 mitoses per 10 HPF, and 4 points are given for anaplasia. Once again, the points are summed, and tumors are categorized as low (0-4 points), intermediate (5-6 points), or high grade (7-14 points).⁸⁵ Table 22-4 summarizes these grading systems.

ACC tumors exhibit myoepithelial cells with various degrees of ductal type cells and are graded on the basis of their predominant architectural pattern. According to the Perzin⁸⁶ and Szanto⁸⁷ grading systems, grade 1 tumors are predominantly tubular without a solid component, grade 2 tumors are predominantly cribriform with less than 30% solid component, and grade 3 tumors have greater than 30% solid component. The other commonly used staging system, discussed by Spiro et al,⁸⁸ describes grade 1 tumors as mostly tubular or cribriform with only minor solid components, grade 2 tumors as having 50% solid component, and grade 3 tumors as mostly solid. Table 22-5 summarizes the grading systems for ACCs.

Clinical Presentation

Most salivary gland tumors are endobronchial lesions that arise centrally within large airways, although primary peripheral ACC of the lung has rarely been reported.^{81,89} Symptoms are typically related to the sequelae of either endoluminal obstruction or extraluminal compression secondary to the central tumor location.

Molina et al retrospectively reviewed 49 patients with MEC and 115 patients with ACC and found the most common symptoms to be cough, dyspnea, hemoptysis, wheezing, and fever. Dyspnea (60% vs. 35%) and wheezing (42.5% vs. 30%) were more common in ACC patients than MEC patients.⁸³

TABLE 22-3 Primary Pulmonary Salivary Gland-Type Tumors

Tumor Type	Location	Pathologic Profile	Sputum Cytologic Result	Treatment
ACC	Trachea, bronchi, lung	Myoepithelial cells, ductal type cells	Negative	Surgery, radiation therapy
MEC	Bronchi	Mucus cells, epidermoid cells, clear-type cells, "intermediate" cells	Negative	Surgery
Mixed tumor	Trachea, bronchi	Mix of ACC and MEC	Negative	Surgery

ACC, Adenoid cystic carcinoma; MEC, mucoepidermoid carcinoma.

TABLE 22-4 Grading Systems for Pulmonary Mucoepidermoid Carcinomas

	Brandwein et al ⁸⁴	AFIP ⁸⁵
Variables	Intracystic component <25% (2 points) Invasion in small nests/islands (2 points) Nuclear atypia (2 points) Lymphatic/vascular invasion (3 points) Bony invasion (3 points) >4 mitoses/10 HPF (3 points) Perineural spread (3 points) Necrosis (3 points)	Intracystic component (2 points) Neural invasion (2 points) Necrosis (3 points) >4 mitoses/10 HPF (3 points) Anaplasia (4 points)
Grading	Low grade: 0 points Intermediate grade: 2-3 points High grade: 4 or more points	Low grade: 0-4 points Intermediate grade: 5-6 points High grade: 7-14 points

AFIP, Armed Forces Institute of Pathology; HPF, high power field.

TABLE 22-5 Grading Systems for Adenoid Cystic Carcinomas

Grade Number	Perzin et al ⁸⁶ and Szanto et al ⁸⁷	Spiro, Huvos ⁸⁸
Grade 1 (Low)	Predominantly tubular, no solid component	Mostly tubular or cribriform, minor solid components
Grade 2 (Intermediate)	Predominantly cribriform, <30% solid component	50% solid component
Grade 3 (High)	Solid component >30%	Mostly solid

Diagnosis

CXRs will most likely appear normal, unless the tumor obstructs the airway. The imaging study of choice is chest CT, which is recommended to obtain more detail about both the intraluminal and the extraluminal extent of ACCs and MECs.⁹⁰ Given the predominance of centrally located primary salivary gland-type lung tumors, flexible bronchoscopy is the primary diagnostic modality because it offers opportunities for direct visualization and tissue diagnosis.

Management and Treatment

Surgery

Complete surgical resection remains the only curative treatment of ACCs and MECs and should be performed with parenchyma-sparing techniques when possible. Given the propensity for ACCs to spread submucosally and perineurally, intraoperative frozen sections should be

used to confirm negative margins.⁹¹ It should be noted, however, that ACCs have a propensity to extend longitudinally in a perineural manner, and in some cases a microscopically negative surgical margin may not be obtainable. In these cases, the surgeon should resist the temptation to resect further, if additional resection would jeopardize a successful tracheobronchial anastomosis.⁹² A recent review of patients with primary salivary gland-type lung tumors revealed the most commonly performed resections were lobectomy (44%), tracheal resection (26%), and pneumonectomy (19%).⁸³ To spare lung parenchyma, sleeve resection should be considered when feasible.⁹³ Because of the high recurrence rate (23-27%) of these tumors,^{93,94} an R0 resection, when possible, should be the goal. For patients who experience recurrence, repeat resection results in good outcomes and excellent long-term survival.⁹³

Endobronchial Treatment Strategies

Brutinel et al compiled a 2-year experience with endobronchial Nd:YAG laser therapy to relieve endobronchial obstruction. Of the 116 patients in the study, 8 had ACC. When these patients were treated with laser therapy for palliation, they remained asymptomatic for longer periods, compared with those with more common forms of lung cancer.⁹⁵ Endobronchial laser therapy should precede radiation therapy if possible, because edema from radiation therapy may temporarily exacerbate the airway obstruction.^{96,97} Endobronchial brachytherapy can be used for recurrent ACC, with good palliative results.⁹⁸

Adjuvant Treatment

ACCs are relatively radiosensitive; the role of radiation therapy for MEC is more controversial. The likelihood of achieving a complete response for ACC correlates significantly with a dose of ≥ 60 Gy.⁹⁹ The role of radiation therapy for patients with ACC is most often in the adjuvant setting, particularly for those with positive resection margins at the time of surgery or for palliation.⁸³ However, there have been reports of using radiation as the primary treatment for ACC, with complete clinical response and long-term disease-free survival.^{100,101} It is generally recommended to use adjuvant radiation for centrally located ACC lesions, regardless of whether the resection is R₀, R₁, or R₂.¹⁰²

The role of chemotherapy is not well defined for ACC or MEC, but chemotherapy may be considered in cases of metastatic ACC. Hotte et al conducted a phase II consortium study to assess the antitumor activity of imatinib (Gleevec) in ACCs, which are known to express a high level of *c-kit*. Of the 16 patients enrolled in the study, 15 had an assessable response. After two cycles, 9 patients had stable disease, and 6 had progressive disease. Therefore, there is no role for routine administration of imatinib in the treatment of patients with ACC.¹⁰³

Prognosis

Patients with primary salivary gland-type lung tumors have significantly better outcomes than those with

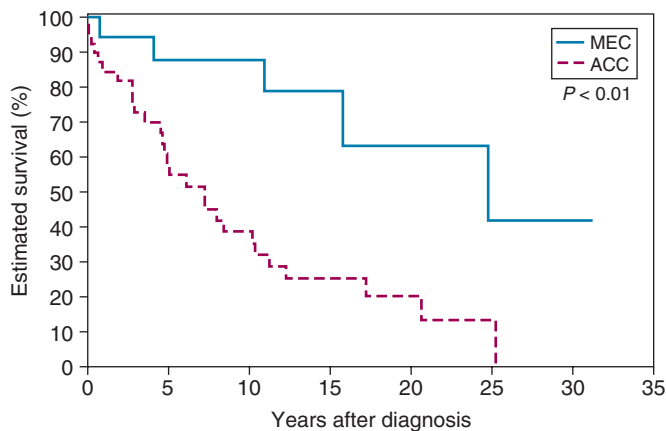


FIGURE 22-3 ■ Kaplan-Meier survival curve for MEC versus ACC. (From Molina JR, Aubry MC, Lewis JE, et al: Primary salivary gland-type lung cancer: spectrum of clinical presentation, histopathologic and prognostic factors. *Cancer* 110:2253–2259, 2007.)

NSCLCs, because these lung tumors are considered low-grade malignancies. Five- and 10-year survival rates for ACC have been reported to be 55% to 79% and 39% to 57%, respectively,^{83,94} compared with 88% and 88% for MEC.^{83,94} Figure 22-3 shows the survival curves for patients with MEC and ACC.

Tumor grade is both a prognostic marker and a factor in determining adjuvant therapy for MEC.¹⁰⁴ Yousem and Hochholzer reported a 95% survival rate for patients with low-grade MEC tumors and found that almost 25% of patients with high-grade MEC tumors experienced recurrences.¹⁰⁴ The rate of nodal metastases is related to tumor grade, with 2% of low-grade and 15% of high-grade MEC tumors presenting with regional lymph node metastases.⁸²

PRIMARY PULMONARY SARCOMAS

Primary pulmonary sarcomas are rare neoplasms accounting for only 1% of lung cancers. They must be distinguished from the more common sarcomas metastatic to the lung, primary pulmonary sarcomatoid carcinomas, and diffuse malignant mesotheliomas involving the lung.^{105,106} An accurate history of the patient is important, particularly confirming the absence of a personal history of cancer. The history and physical examination should also focus on a search for occult neoplasm. Ultimately, however, a tissue biopsy is paramount to making an accurate diagnosis.

Historically, the distinction in the literature between true sarcomas and carcinomas with sarcomatous components has been somewhat cloudy, which makes the older literature challenging to interpret. In 2004, the WHO, in an effort to better define these distinctions, updated the classifications of primary pulmonary sarcomas and similar lesions. The WHO identified a distinct group of poorly differentiated non-small cell carcinomas that contain sarcoma or sarcoma-like components and labeled these “sarcomatoid carcinomas.” There are five distinct subgroups in the 2004 WHO classification of sarcomatoid carcinomas: pleomorphic carcinoma, spindle cell

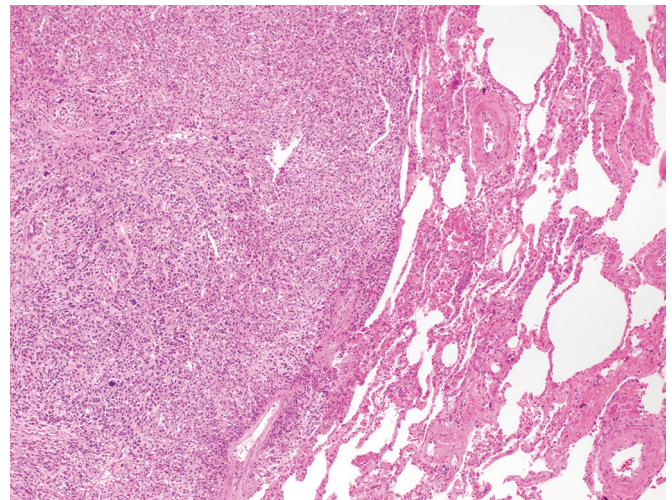


FIGURE 22-4 ■ Histologic slide of a leiomyosarcoma.

carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma.¹⁰⁵ The primary pulmonary sarcomas described in the subsequent subsections have maintained their own classification and presence in the current literature.

Primary Pulmonary Leiomyosarcoma

Primary pulmonary leiomyosarcomas can arise in several areas of the lung, including the pulmonary artery (10%), the bronchus (20%), and the pulmonary parenchyma (70%).¹⁰⁷ A review of 18 patients with primary leiomyosarcomas of the lung showed a mean age of 50 years (range, 5 to 76 years).¹⁰⁸ Most of the patients were asymptomatic on presentation, with the neoplasms discovered incidentally. On gross pathologic examination, these lesions are well circumscribed, grayish-white, firm, and rubbery.¹⁰⁸ A typical histologic appearance is shown in Figure 22-4. Moran et al classified these lesions as low, intermediate, or high grade based on cytologic findings. Low-grade tumors showed an orderly proliferation of spindle cells, minimal pleomorphism, and few mitoses without hemorrhage or necrosis. Intermediate-grade lesions maintained the orderly proliferative pattern but had increased cellular atypia, occasional pleomorphism, and a higher mitotic index. High-grade lesions were highly cellular with marked pleomorphism and atypia, high mitotic index, and areas of hemorrhage and necrosis.¹⁰⁸ Radiographically, pulmonary leiomyosarcomas are usually well-demarcated, smooth, or lobular masses that may exhibit intratumoral hemorrhage or necrosis^{109,110} (Fig. 22-5).

Given the rarity of primary pulmonary leiomyosarcomas, there is little consensus on treatment. The most commonly accepted therapy is radical surgical excision, as is the case for other pulmonary sarcomas.¹¹¹ There is a lack of evidence for the effectiveness of radiation and chemotherapy in the treatment of primary pulmonary leiomyosarcomas; however, doxorubicin and ifosfamide are considered the most effective agents for soft-tissue sarcomas.¹¹² Grade is one of the most important prognostic indicators. In one study, high-grade lesions had



FIGURE 22-5 ■ Chest CT scan of a large primary pulmonary leiomyosarcoma. (From Gladish GW, Sabloff BM, Munden RF, et al: Primary thoracic sarcomas. *Radiographics* 22:621–637, 2002.)

significantly poorer prognosis (8 of 9 patients [89%] died within 2 years of diagnosis), compared with low- or intermediate-grade lesions (all 6 patients were alive at the end of the study period; mean follow-up, 6 years).¹⁰⁸

Primary Pulmonary Synovial Sarcoma

Primary pulmonary synovial sarcoma is a mesenchymal spindle cell tumor that accounts for 0.5% of all lung malignancies. Tumors may arise from the lung parenchyma, the bronchial tree, or the pulmonary arteries.¹¹³ Most pulmonary tumors are peripheral, with occasional endobronchial lesions.^{114,115} The median age of patients at diagnosis is 40 years, and there is no significant difference between men and women.^{116,117} On gross pathologic examination, the tumors are soft, tan masses often with foci of necrosis, hemorrhage, and cystic changes, and they are histologically indistinguishable from other soft-tissue synovial sarcomas.¹⁰⁸ Molecular testing for a characteristic t(X;18) chromosomal translocation, present in 90% of these tumors, confirms the diagnosis.¹¹⁵ Additionally, the presence of two embryonic tumor markers, epithelial membrane antigen and vimentin, may help differentiate primary pulmonary synovial sarcomas from other lesions.¹¹³

Similar to patients with other pulmonary sarcomas, most patients with pulmonary synovial sarcoma are asymptomatic at presentation. When symptoms are present, cough (21%), chest pain (20%), and hemoptysis (20%) are the most common.¹¹³ Metastatic synovial sarcoma to the lungs is more common than its primary counterpart; therefore, metastatic disease must be ruled out before therapy. The standardized therapy for patients with primary pulmonary synovial sarcoma is surgical resection and adjuvant radiation or chemotherapy, depending on the findings at the time of surgery. Synovial sarcoma is chemosensitive to doxorubicin and ifosfamide,

with an overall response rate of 24%.¹¹⁸ Tumors tend to recur locally, with extension into the chest wall, pericardium, paraspinal soft tissue, diaphragm, and abdomen.¹⁰⁵ The overall prognosis for patients with primary pulmonary synovial sarcoma is poor, with an overall 5-year survival rate of 50%.¹¹⁹ Risk factors that predict a poorer prognosis for patients with primary pulmonary synovial sarcoma are age 20 years and older, tumor size greater than 5 cm, incomplete resection, and large number of mitotic figures.¹¹³

Primary Pulmonary Epithelioid Hemangioendothelioma

Pulmonary epithelioid hemangioendothelioma, previously referred to as intravascular bronchioloalveolar tumor, is a primary pulmonary sarcoma that is considered a low- to intermediate-grade vascular tumor. Pulmonary epithelioid hemangioendothelioma affects young patients and is more common in women than in men.¹²⁰ On gross pathologic examination, the tumor is gray-white or gray-tan in appearance. The cut surface is of cartilaginous consistency with occasional calcification. Histologically, the tumor has a distinctive appearance, with short cords and nests of epithelioid cells associated with a myxohyaline matrix.¹⁰⁵

Preoperative diagnosis remains difficult, and most diagnoses are made from pathologic evaluation of surgical biopsy specimens. Immunohistochemical analysis shows diffuse cytoplasmic staining of the malignant cells with factor VIII-related antigen, confirming the lineage of tumor cells.¹²⁰ Half of patients present with nonspecific respiratory symptoms similar to those of other lung neoplasms (cough, dyspnea, or chest pain). Imaging often demonstrates the presence of multiple bilateral nodules with occasional calcification.^{121–124}

Because primary pulmonary epithelioid hemangioendothelioma is rare, few data exist regarding a standard treatment strategy. In patients with a unilateral nodule, wedge resection seems to offer similar survival benefits to anatomic resection.¹²⁰ The prognostic value of lymph node sampling is unknown because of the small number of patients who demonstrate lymph node metastases.¹²⁵ Patients with bilateral nodules have undergone a variety of treatments, ranging from interferon alfa-2a¹²⁶ to azathioprine¹²⁷ to multiple wedge resections¹²⁸ to no treatment. Bagan and colleagues endorse the consideration of lung transplantation for patients with vascular aggressiveness and pleural hemorrhagic effusion because these patients have a life expectancy of less than 1 year.¹²⁰

Prognosis is, in part, dependent on sites of metastases; however, unlike for other lung cancers, for pulmonary epithelioid hemangioendothelioma, simultaneous lesions in the lung and the liver do not necessarily mean metastases. Epithelioid hemangioendothelioma may also be found as a second concurrent primary in the liver. This is important in the transplant community because surgeons who manage transplantation for hepatic hemangioendothelioma do not consider a focal lesion in the lung to be a metastasis.¹²⁹ Bagan et al indicate that the current staging system for lung cancer does not predict outcomes for primary pulmonary epithelioid

hemangioendothelioma, and they advocate the use of clinical and radiologic disease to guide prognosis.¹²⁰ Prognosis in patients with primary pulmonary epithelioid hemangioendothelioma can be sorted into two groups: (1) asymptomatic patients with nodules, who have a median survival of 180 months, and (2) patients with symptoms of vascular endothelial cell proliferation (alveolar hemorrhage, hemoptysis, hemorrhagic pleural effusion), who have a significantly worse survival of generally less than 1 year.¹²⁰

Primary Pulmonary Angiosarcoma

Malignant vascular tumors are highly uncommon, with angiosarcomas constituting less than 1% of all sarcomas.¹³⁰ Pulmonary angiosarcomas are usually the consequence of metastasis from the skin or subcutaneous tissue, breast, liver, or heart. Primary pulmonary angiosarcoma is characterized by an insidious growth pattern, with the tumor showing extensive local invasion and hematogenous metastases at the time of presentation.¹³¹ Demographically, angiosarcomas typically arise in middle-aged adults. These tumors have been tied to radiation therapy and to exposure to vinyl chloride and arsenic.¹³²

Histologically, these lesions can mimic carcinomas and exhibit cytokeratin positivity.¹³³ Some patients may have bilateral infiltrates that mask pulmonary hemorrhage. The most common clinical characteristic at presentation is hemoptysis.¹³³ Radiographically, these lesions usually present as multiple bilateral nodules.¹³⁴

Surgery remains the mainstay treatment for primary pulmonary angiosarcomas, with radical resection the preferred choice. Angiosarcomas are radiosensitive. Paclitaxel, which exerts antiangiogenic and apoptotic effects, has been shown to be effective against angiosarcoma.¹³⁵ The prognosis of patients with angiosarcomas is quite poor, with most patients dying within months of initial presentation.¹³⁰

PRIMARY SOLITARY PULMONARY PLASMACYTOMA

Epidemiology and Pathology

Extramedullary plasmacytomas are uncommon neoplasms of plasma cell origin. Most of these tumors arise in the head and neck region; in rare occurrences they may arise in the lung as a solitary nodule or less commonly as a lobar consolidation or as diffuse pulmonary infiltrates.¹³⁶ Joseph and colleagues evaluated 19 cases of primary pulmonary plasmacytoma and found that males and females were affected equally and that the median age at diagnosis was 42 years.¹³⁷

Clinical Presentation and Diagnosis

Patients are either asymptomatic on presentation or have nonspecific pulmonary symptoms of cough, wheeze, or shortness of breath.¹³⁶ Diagnosis of primary pulmonary plasmacytoma is difficult. The clinician should undertake the workup of a lung nodule or mass, including CT scan.

Most commonly, the diagnosis is made after excision of the tumor and proper histopathologic examination.

Treatment and Prognosis

Treatment for primary pulmonary plasmacytomas is usually resection alone or a combination of surgery and chemotherapy or radiotherapy. A review of 19 patients with primary pulmonary plasmacytomas found that a variety of treatment modalities had been used: surgery alone ($n = 11$), radiation therapy ($n = 3$), surgery with radiation ($n = 3$), and surgery with chemotherapy ($n = 2$). The authors concluded that surgery and radiotherapy are both effective treatments with low rates of local recurrence.¹³⁷ Solitary pulmonary plasmacytoma has been shown to occasionally progress to multiple myeloma over time.^{138,139} Thus, once the diagnosis is made, it is essential that a complete evaluation be performed, to exclude systemic disease. After resection, patients should be monitored closely by use of serum and urine electrophoresis, skeletal bone survey, and bone marrow examination.¹³⁶

PRIMARY PULMONARY LYMPHOMA

Epidemiology

Primary pulmonary lymphomas are uncommon, representing less than 1% of lung cancers¹⁴⁰ and less than 1% of malignant lymphomas¹⁴¹ and accounting for only 3.6% of extranodal lymphomas.¹⁴² The peak incidence of primary pulmonary lymphomas is in the sixth and seventh decades of life, with an equal distribution between men and women.¹⁴³ It has been well documented that immunosuppression is a risk factor for the development of lymphoma.¹⁴⁴

Pathology

The vast majority of primary pulmonary lymphomas are of B cell origin. One study of 62 cases of primary pulmonary lymphoma demonstrated 58 B cell cases, 2 T cell cases, and 2 indeterminate cases.¹⁴³ B cell mucosal-associated lymphoid tissue (MALT) lymphomas are the predominant tumor type. Most MALT lymphomas are low grade, but transition to higher grade can occur in a minority of cases.¹⁴⁵

Clinical Presentation and Diagnosis

Graham and coworkers¹⁴⁵ reported a series of 18 patients with primary pulmonary lymphoma. The most common pulmonary symptoms at presentation were cough (50%), dyspnea (39%), and chest pain (17%). Additionally, some patients suffered from systemic symptoms of fatigue (11%) and weight loss (6%). Twenty-two percent of patients were asymptomatic at presentation.

Management and Treatment

Once diagnosed, the primary pulmonary lymphoma must be appropriately staged to rule out extrathoracic

disease. This includes additional imaging, possible bone marrow biopsy, and laboratory tests (lactate dehydrogenase and β_2 -microglobulin).^{146,147} In the case of an isolated primary pulmonary MALT lymphoma diagnosed by CT-guided biopsy, management is observation only, reserving treatment for possible future progression of disease on the basis of symptoms and radiographic progression. In cases where the diagnosis was established after wedge resection or lobectomy with negative margins and no evidence of high-grade transformation or disease elsewhere, a complete resection is considered definitive, and no further therapy is required. If there is residual disease, disease in the contralateral chest, high-grade lymphoma, or extrathoracic disease, then chemotherapy and, rarely, radiation should be considered.¹⁴⁵

Prognosis

Cordier et al¹⁴⁸ reported a 5-year survival of 94% for low-grade primary pulmonary lymphoma and a median survival of 3 years for high-grade disease. Ferraro et al¹⁴⁹ reported a 5-year survival of 68% for primary pulmonary MALT lymphoma.

PRIMARY PULMONARY MELANOMA

Epidemiology

Primary pulmonary melanomas are among the rarest of primary lung tumors: only a few dozen cases have been reported in the English-language literature.^{150,151} Because of the scarcity of these tumors, their clinical presentation, natural history, treatment, and prognosis are not well defined.

Pathology

Making a diagnosis of primary pulmonary melanoma and distinguishing it from the much more common metastatic melanoma is not an easy task. Authors have suggested that several criteria should be required for a diagnosis of a primary pulmonary tumor.¹⁵²⁻¹⁵⁴ These include (1) "nesting" of melanoma cells beneath the bronchial epithelium; (2) invasion of melanoma cells into the bronchial epithelium; (3) solitary lung tumor; (4) lack of a personal history of cutaneous, mucosal, or ocular melanoma; and (5) negative findings from a thorough search for occult melanoma. Even so, there is still some controversy about whether this lesion is a primary pulmonary lesion. At the heart of the controversy is the belief that, to have a primary pulmonary melanoma there must be a melanin-containing precursor cell. However, melanin-containing cells have not been demonstrated in the normal tracheobronchial tree.¹⁵⁰ Despite this, it has been postulated that, because the trachea shares an embryologic origin with the pharynx and esophagus, both of which are known to give rise to primary melanomas, the primary pulmonary melanoma is a consequence of residual melanoblasts.

Clinical Presentation and Diagnosis

In a review of 20 cases, Ost and colleagues found the common presenting symptoms of primary pulmonary melanoma to be cough (50%), hemoptysis (40%), and postobstructive pneumonia (25%). Of note, 30% of patients were asymptomatic (the lesion was found incidentally). Constitutional symptoms of weight loss, night sweats, or fever were present in 25% of patients.¹⁵⁰ In addition to the pathologic criteria for the identification of primary pulmonary melanomas, a complete evaluation of the patient must be conducted to rule out any other primary source.

Treatment

If a pulmonary melanoma is encountered and, after a thorough examination, is determined to be a primary lesion, the appropriate treatment is anatomic resection (usually lobectomy) with lymph node dissection.¹⁵⁰

PRIMARY PULMONARY CARCINOSARCOMA

Epidemiology and Pathology

Primary pulmonary carcinosarcomas were once considered to be primary pulmonary sarcomas, but given their varied histologic makeup, these neoplasms now occupy a designation of their own. Carcinosarcomas contain a mixture of carcinomatous and sarcomatous components¹⁵⁵ and generally arise in middle-aged to older adult populations.¹⁵⁵⁻¹⁵⁷

Diagnosis

The presence of cytokeratin and vimentin antibodies can be used to readily distinguish carcinomatous and sarcomatous tumor formation from each other, with the difference in reaction to the tumor markers used to make the diagnosis of a carcinosarcoma.¹⁵⁵ Carcinosarcomas are rarely diagnosed preoperatively. On occasion, diagnosis can be made by cytologic analysis of sputum¹⁵⁸ and, when a nodule is present, by transthoracic needle biopsy.¹⁵⁹

Treatment and Prognosis

Complete surgical resection with clear margins is the most commonly accepted treatment for primary pulmonary carcinosarcomas. Huwer and colleagues¹⁵⁵ have advocated that chemotherapy and radiation (the standard modalities for treatment of soft-tissue sarcoma) should be administered to those with primary pulmonary carcinosarcoma, arguing that the prognosis is largely dependent on the sarcoma component of the tumor.

Given its propensity to metastasize to distant sites and its high rate of local recurrence, primary pulmonary carcinosarcoma has a poor prognosis.^{160,161} Petrov et al¹⁶² reported a 5-year survival of 49%, with a mean survival of 37 months.

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SECONDARY LUNG TUMORS

Michael Friscia • Melissa Culligan • Joseph Friedberg

CHAPTER OUTLINE

HISTORY OF METASTASECTOMY

PATHOPHYSIOLOGY OF PULMONARY METASTASES

Do Metastases Metastasize?

Does Lung Cancer Metastasize to Lung?

EVALUATION OF THE PATIENT WITH SECONDARY PULMONARY TUMORS

Symptoms and Presentation

Radiographic Evaluation

Tissue Diagnosis

INDICATIONS FOR SURGERY

SURGICAL APPROACH

LYMPH NODE DISSECTION

RESULTS OF PULMONARY METASTASECTOMY

SPECIFIC SECONDARY LUNG TUMORS

Soft Tissue Sarcoma

Osteosarcoma (Osteogenic Sarcoma)

Colorectal Cancer

Breast Carcinoma

Head and Neck Carcinoma

Renal Cell Carcinoma

Germ Cell Tumors

Gynecologic Tumors

Melanoma

Endocrine Tumors

Other Tumors

ALTERNATIVE TREATMENT OPTIONS

PALLIATIVE THERAPY

CONCLUSIONS

After the liver, the lung is the second most common site for metastatic involvement in neoplastic disease when all tissues and organs are considered, and 20% to 54% of patients with cancer will have pulmonary metastases at some point in the natural history of their disease (Boxes 23-1 and 23-2). In the absence of extrathoracic metastases (i.e., in approximately 25% of patients with disseminated disease), retrospective data have shown that complete resection can be associated with increased survival, regardless of histology, in appropriately selected patients. Cures have been reported with either resection alone or in combination with chemotherapy.^{1,2} Surgical forms of palliation can improve quality of life. For some patients, surgery may have a complementary role, such as defining residual disease that is potentially amenable to salvage forms of therapy or obtaining adequate tissue for molecular testing for targeted therapies.

HISTORY OF METASTASECTOMY

During the 19th century, in the European literature there were sporadic reports of lung resections for metastatic tumors. The first of these reports was in 1855, by the French surgeon Sédillot, who removed a chest wall tumor and excised disease extending into the lung.³ The first case of a true pulmonary metastasectomy was described by Weinlechner in 1882 in a patient with a rib sarcoma,

who was found to have two incidental pulmonary metastases at the time of the sarcoma resection.⁴ Kronlein reported the first long-term survivor after pulmonary metastasectomy in a patient with recurrent chest wall sarcoma and a metastatic lung nodule. The patient went on to survive 7 years, eventually succumbing to recurrent pulmonary disease.⁵⁻⁷

The first, and perhaps most famous, report of a planned pulmonary metastasectomy in the United States was performed in 1933 by Barney and Churchill.¹ Soon after resection of a renal cell carcinoma, they noted that the patient's pulmonary nodule, seen on a chest radiograph preoperatively and presumed to be tuberculosis, had doubled in size. The lesion, now thought to represent metastatic disease, was treated with radiation therapy. They noted a poor response and elected to resect the nodule. The patient went on to live 23 years, eventually dying of coronary artery disease with no evidence of tumor recurrence at autopsy. Despite the early discovery (in the late 1800s) that survival could be improved by resection of metastatic disease, it was not for another 40 years that metastasectomy was performed as a separate procedure by Divis in Europe.⁸ This was followed soon after by similar reports in the American literature by Torek and Tudor Edwards in the early 20th century.^{9,10}

These early reports, and others like them, paved the way toward general acceptance of pulmonary metastasectomy. Although initial indication for surgery was reserved

BOX 23-1 Primaries Most Commonly Metastatic to the Lung*

- Breast
- Colon
- Kidney
- Uterus
- Prostate
- Oropharyngeal carcinoma

*Most common because of greater prevalence.

BOX 23-2 Tumors with the Highest Predisposition for Pulmonary Metastasis

- Choriocarcinoma
- Osteosarcoma
- Testicular tumors
- Melanoma
- Ewing sarcoma
- Kaposi sarcoma

for those with a solitary metastasis, with time and experience, surgeons began to perform more aggressive metastasectomies. In 1947, Alexander and Haight described the first case series of 24 patients who underwent pulmonary metastasectomy.¹¹ In this series, they described a young woman with a spindle cell neurogenic sarcoma. She initially underwent a right lower lobectomy for metastatic disease in 1939. She had a recurrence in 1940 for which she underwent a left upper lobectomy. This article was the first to define criteria for resection of pulmonary metastases, including control of the primary tumor, absence of extrathoracic disease, and sufficient pulmonary reserve.

The largest effort aimed at evaluating patients undergoing pulmonary metastasectomy was undertaken by the International Registry of Lung Metastases (IRLM). Established in 1991, the IRLM accrued 5206 patients in North America and Europe. This landmark report demonstrated that complete resection, long disease-free interval, and single lesions were associated with better long-term survival. This and other studies have helped to develop current criteria for performing pulmonary metastasectomies and to define anticipated survival after resection.¹²⁻¹⁴

PATHOPHYSIOLOGY OF PULMONARY METASTASES

In 1889, British surgeon Stephen Paget observed that metastatic disease followed a nonrandom pattern. Using autopsy records of patients with a variety of primary tumors, he hypothesized that factors in certain tumors have an affinity for certain factors in target organs. Theories have subsequently evolved that attempt to explain the propensity for metastases to spread to specific organs. The “cascade spread” theory hypothesizes that a single organ represents the first site of spread, followed by systemic dissemination.¹⁵ This metastatic cascade is considered to be a complex series of events culminating in the

generation of metastases. The initial phase of the cascade involves tumor growth via neovascularization, which is stimulated by growth factors secreted by the tumor cells and local host cells. The invasive phase of tumor growth involves the local production and activation of proteolytic enzymes (matrix metalloproteinases, collagenases, serine proteinases, cysteine proteinases) derived from both the host and tumor tissue. These enzymes decrease cell adhesiveness, stimulate cell migration, and enhance chemotaxis and subsequent tumor cell detachment.

Metastasis is most likely initiated after cell detachment from the primary tumor mass. Typically, epithelial cells undergo anoikis (apoptosis) because of the loss of cell-cell interactions once they are separated from parent tissue. Metastatic cells are thought to resist anoikis by forming cell-cell attachments with other tumor cells or host cells and through the overexpression of proteins that inhibit anoikis.

Movement from the extracellular space into a vascular compartment is termed *intravasation*. Cancer cells have been shown to degrade basement membranes via local release of extracellular matrix-degrading proteins (matrix metalloproteinases), facilitating migration into the lymphatic and circulatory system. Once in the circulatory system, tumor cells must avoid recognition and destruction by the host immune system. Only 0.1% of tumors cells in circulation go on to generate metastases.¹⁶ Mechanisms that cancer cells use to survive include human leukocyte antigen (HLA) class I downregulation (mediator of immune cell recognition) and loss of immunogenic antigens. Cancer cells also downregulate the immune system via the production of immunosuppressive cytokines. Some evidence suggests that clots form around tumor cells that protect these cells from immunologic and physiologic stresses in the bloodstream.¹⁷

Tumor cells bind to pulmonary vasculature, which, via a platelet-induced reaction, stimulates endothelial cell retraction.¹⁸ The lung is thought to play a role as the primary capillary filter for drainage of most organs, and its rich capillary network provides an ideal environment for deposition. Movement of tumor cells from the circulatory system into the interstitium is called *extravasation*. Basement membrane disruption is thought to occur in a manner similar to intravasation.

Once extravasated, tumor cells may remain quiescent or they may proliferate. Proliferation and local invasion require neovascularization, which is induced via a shift toward the intracellular and extracellular production of pro-angiogenic factors. Epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and transforming growth factor- α (TGF- α) foster tumor cell proliferation in the new environment. On the other hand, the host organ produces inhibitors, such as TGF- β , mammastatin, and amphiregulin, to prevent metastatic implantations.¹⁹ These compounds are under investigation to assess their ability to control metastatic disease.

Do Metastases Metastasize?

It is thought that metastases need to follow the same steps as the primary tumor to metastasize: angiogenesis, intravasation, arrest, and extravasation. In 1975, Hoover and

Ketcham demonstrated, experimentally, that metastases do have the ability to metastasize.²⁰ In this experiment, the primary tumor in mice was amputated after pulmonary metastasis developed. These mice were then placed into parabiosis with normal syngeneic partners. Metastases were demonstrated in the non-tumor-bearing partners, supporting the theory that metastases can re-metastasize. In addition, both autopsy and experimental data have defined the concept of metastases from metastatic disease.²¹ Further support of this concept is provided by the presence of intrathoracic lymph node metastases among patients who undergo anatomic resection and lymph node dissection for metastatic lung disease, especially for renal cell carcinoma (46.6%)²² and colon cancer (9.8%).²³ On the other hand, Sugarbaker and colleagues took pieces of healthy lungs and transplanted them into mice that had established pulmonary metastases. Their results demonstrated no evidence of secondary tumor development, thus leading to the conclusion that metastases do not metastasize.²⁴

Whether metastases metastasize is still poorly understood and remains a challenge for medical oncologists and surgeons as they struggle to determine the best treatment and the proper timing of that treatment for patients with pulmonary metastases.²⁵

Does Lung Cancer Metastasize to Lung?

Lung cancer can metastasize via lymphatic channels to the ipsilateral lung and, as suggested by some autopsy series, less commonly to the contralateral lung. These are patients with one primary lung cancer and intrapulmonary metastases. According to the seventh revision of the lung cancer staging system of the International Association for the Study of Lung Cancer (IASLC), ipsilateral nodules in the same lobe as the primary tumor will be considered T3 and nodules in a different ipsilateral lobe from the primary tumor will be considered T4.²⁶ It is difficult, however, to determine if these patients have synchronous lesions or a primary lung cancer with intrapulmonary metastases. Ichinose and coworkers have used DNA flow cytometry to evaluate these lesions.^{27,28} Using this technique, lesions are determined to be synchronous if they demonstrate completely different DNA ploidy. If both tumors show diploidy, or when at least one DNA index of abnormal clones between two aneuploidy tumors is the same or almost identical, they are considered metastatic. In addition, loss of heterozygosity and p53 mutational status have been used to distinguish multicentric lung cancers from intrapulmonary metastases.^{29,30} Using these criteria, it appears that lung cancer can metastasize to lung, albeit less commonly than synchronous tumors.

EVALUATION OF THE PATIENT WITH SECONDARY PULMONARY TUMORS

Symptoms and Presentation

Because approximately 75% to 90% of patients with secondary pulmonary malignancies are asymptomatic, their disease is most commonly discovered incidentally on

routine or follow-up radiologic examinations.^{31,32} Absence of symptoms is predominantly due to the usual peripheral location of pulmonary metastases. The asymptomatic nature of pulmonary metastases makes necessary the practice of obtaining lung-imaging studies in the follow-up of most cancer patients.

Symptoms, when they do occur, typically occur with endobronchial or pleural involvement, large bulky disease, or central venous obstruction. Patients may have symptoms of cough and hemoptysis suggesting an endobronchial lesion and thus warrant bronchoscopic examination. Endobronchial metastatic lesions are extremely rare in patients who die of solid tumors, with breast, kidney, pancreas, colon, and melanoma as the most common sources.³³ Dyspnea may occur, which is usually secondary to airway obstruction, a pleural effusion, extensive parenchymal replacement by multiple metastatic lesions, or lymphatic spread. Finally, chest pain, wheezing, or pneumothorax may occur, but these are unusual presenting symptoms.

During physical examination, wheezing may be heard, which is a sign of airway obstruction. Occasionally, a pericardial rub is heard, representing pericardial involvement. Pleural or pericardial involvement is usually the result of ovarian, breast, or lung adenocarcinomas. Thymic malignancies are notorious for pleural involvement when they metastasize.³⁴ In addition, decreased breath sounds and egophony may be appreciated when an obstructing lesion is present with associated lobar or segmental atelectasis, which could be seen on a chest radiograph as postobstructive pneumonia.

Radiographic Evaluation

Most pulmonary metastases are detected by chest radiography (Fig. 23-1) or computed tomography (CT) (Fig. 23-2) during routine follow-up for the primary cancer. Radiologic testing is used to define the extent of the disease and to determine whether an individual is a candidate for pulmonary metastasectomy. A search for extrathoracic disease may involve imaging the original primary disease site as well as looking for distant disease. A new pulmonary nodule in a patient with a prior malignancy should be considered cancer until proven otherwise.

Because of its higher resolution, helical CT is the gold standard imaging modality for evaluation of the lungs and characterization of metastatic lesions. Lung metastases can be small (usually less than 1 cm), and they appear as multiple lesions in 75% of cases. Most metastatic lesions to the lung are found on the lung periphery, and they have a predilection for the basilar lung fields, probably because of increased blood flow to this region when the patient is in an upright position.^{35,36} Distinguishing between a metastatic lesion and other malignant or benign lung lesions can be difficult. CT characteristics of metastatic lesions include spherical shape with well-circumscribed, smooth borders. Lesions with irregular or spiculated borders with associated linear densities are more commonly associated with primary lung cancers, although this is not a universal finding.³⁵ Calcifications in lung nodules are rarely seen in metastatic pulmonary disease. Metastases that may have associated calcifications

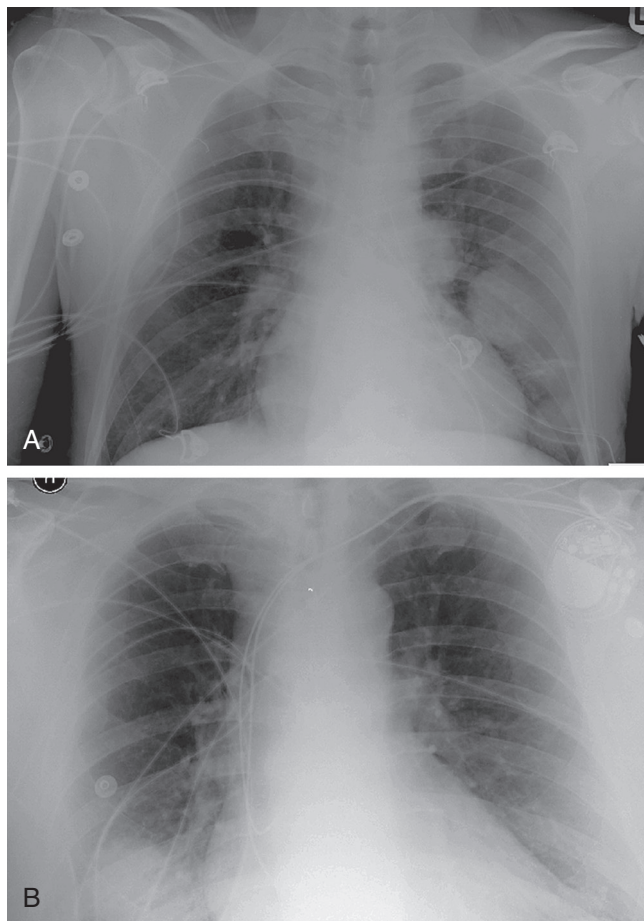


FIGURE 23-1 ■ Pulmonary metastases as detected by chest radiography. **A**, Left lower lobe metastasis. **B**, Left upper lobe metastasis.

include osteosarcomas, chondrosarcomas, and breast and ovarian cancer. Cavitation can occur in benign lesions such as those caused by lung abscess, aspergillosis, or tuberculosis. Malignant nodules that can cavitate include squamous cell carcinoma (primary lung or metastatic carcinomas), sarcoma, and testicular tumors.

Positron emission tomography (PET) is imperative when considering patients for metastasectomy. In a series of patients with melanoma, ^{18}F -fluorodeoxyglucose (FDG)-PET had a sensitivity of 92%, a specificity of 88%, and accuracy of 91%.³⁷ PET is helpful in assessing extent of disease, including the primary disease site as well as thoracic and extrathoracic potential sites of metastases. However, PET positive findings should be interpreted with caution because of the low specificity of positive results. When considering surgical management of metastatic lung disease, all potential sites of metastatic disease identified on CT and PET should be thoroughly evaluated, particularly in the mediastinum, because tissue confirmation of multiple organ involvement will likely change management. Although CT is useful for identifying and characterizing pulmonary metastases, caution must be exercised because intraoperative pulmonary palpation may identify smaller parenchymal lesions not detected with imaging.

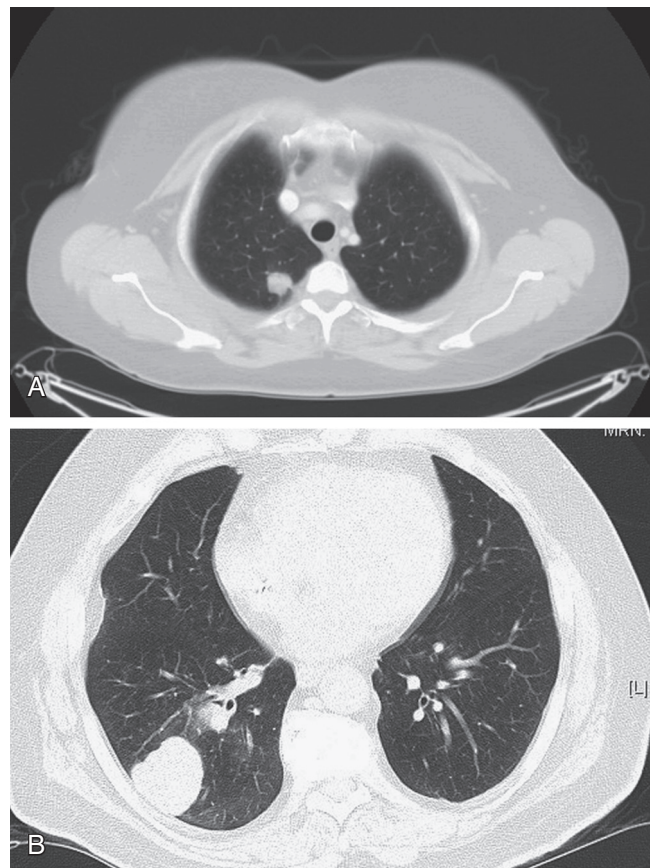


FIGURE 23-2 ■ Pulmonary metastases as detected by chest CT. **A**, Metastatic lesion in the right upper lobe. **B**, Metastatic lesion in the superior segment of the right lower lobe.

Tissue Diagnosis

Multiple nonsurgical options are available for confirmation of a histologic diagnosis. These options, including endoscopic procedures and percutaneous needle aspiration, should be used when management will change based on the results. This is particularly true for patients that are borderline surgical candidates or who refuse surgery but desire alternative treatment.

Sputum cytology is of historical interest and has been replaced by bronchoscopy, as it is often nondiagnostic because of the peripheral location of most pulmonary metastases.³⁸ Bronchoscopic examination and diagnosis of pulmonary metastases is useful in the case of endobronchial or centrally located lesions. Peripheral radial ultrasound probes or electromagnetic guidance systems may increase the yield of endobronchial sampling. Percutaneous fine-needle aspiration (FNA) is another option for obtaining a tissue diagnosis. It is associated with a risk of pneumothorax, in some series as high as 27%.³⁹ Unfortunately these procedures are plagued by low sensitivity, such that equivocal or “negative” results do not establish a diagnosis of benign disease. In addition, in the current era of molecular and genomic testing, obtaining ample tissue for processing with these less invasive techniques can be difficult and could require multiple procedures. If tissue diagnosis is desired but less invasive means have failed to obtain adequate tissue, video-assisted thoracic

surgery (VATS) with excisional biopsy is recommended. VATS has a sensitivity and specificity approaching 100%.⁴⁰⁻⁴² It is a more invasive procedure than FNA and requires general anesthesia with selective lung ventilation. Also, when extent of metastatic disease is limited, it may be therapeutic as well as diagnostic, as the nodules can be completely excised. Occasionally, there is a role for thoroscopic core needle biopsy, such as in cases of multiple lesions not amenable to complete surgical resection when treatment hinges on a tissue diagnosis and all less-invasive diagnostic modalities have proved fruitless or are deemed less safe than a VATS approach.⁴³

Because the pretest probability of malignancy is high in a patient with a lung nodule and history of malignancy, the negative predictive value is low if cancer is not identified on a specimen obtained percutaneously or with bronchoscopy.⁴⁴ For this reason, nonsurgical procedures aimed at obtaining a histologic diagnosis should be used selectively, and multidisciplinary evaluation with a surgeon and oncologist is of the utmost importance. In this setting, diagnostic procedures can be selected based on risk profile, local expertise, and anatomic location of the lesion with the aim of proceeding to an appropriate therapy.

INDICATIONS FOR SURGERY

Reasons to perform surgery for secondary pulmonary malignancy include curative resection, tissue diagnosis, or evaluation of residual disease. Before proceeding with resection, a number of questions should be considered in the preoperative assessment of the patient.

Does the pulmonary nodule represent one site of multiorgan spread, thereby contraindicating resection? Pulmonary metastases are common in the advanced stages of cancer, with as many as one third of patients presenting with secondary nodules. Of these patients, however, most pulmonary nodules (75% to 85%) are a manifestation of widespread disease. Consequently, only 15% to 25% of patients have lesions confined to the lung and are appropriate candidates for curative resection (Table 23-1). Preoperative evaluation, therefore, should exclude extrathoracic disease.

When pleural or pericardial effusion is present, thoracentesis or pericardiocentesis should be performed to

evaluate for malignancy. Positive cytology contraindicates resection. Cytology may be falsely negative, however, in up to 40% to 60% of cases.^{45,46} Consequently, a negative cytology returned in the context of a high index of suspicion for malignant effusion warrants pericardial or pleural biopsy, or both. A VATS approach can be used to access the pleural space, and it offers a minimally invasive transthoracic approach to the pericardium. It also affords the option of visualizing and palpating the lung as well as sampling the mediastinal lymph nodes. Bronchoscopy should always be performed before thoracoscopy or thoracotomy, to evaluate for endobronchial lesions.

Is a nonsurgical therapeutic option available? Although surgical resection of secondary pulmonary malignancies may give patients a significant survival advantage, nonsurgical management may be more appropriate for certain cancers. For example, in the context of nonseminomatous germ cell tumors, great success has been obtained with chemotherapy, with cure rates approaching 90% (see “[Germ Cell Tumors](#),” later). In addition, alternative therapies such as radiofrequency ablation or stereotactic body radiation may be appropriate in selected cases (see “[Alternative Treatment Options](#),” later).

Will the patient tolerate the procedure? Risk factors associated with metastatic disease (e.g., smoking and advanced age) require that patients being considered for surgical resection receive a thorough medical assessment with particular attention to their pulmonary and cardiac status. Stress testing, echocardiograms, arterial blood gases, pulmonary function testing, and ventilation-perfusion scans may be necessary to assess patients’ tolerance for a proposed resection or their ability to undergo single-lung ventilation. Also, previously administered chemotherapeutic agents such as bleomycin or mitomycin may result in additional compromise of pulmonary function, and doxorubicin may be associated with cardiac impairment. In addition, the thoracic surgeon expecting to perform a metastasectomy must always be prepared to perform a formal lobectomy should the pathology reveal a primary lung cancer or should wedge resection result in incomplete resection. Thus, performing the preoperative assessment with consideration for anatomic resection and its attendant risk is prudent.

Are the lesions resectable? *Unresectability* is defined as noncontiguous involvement beyond the visceral pleural

TABLE 23-1 Most Common Site of Metastasis and Percentage with Isolated Disease

Histology	Most Common Site of Metastasis (%)	Second Most Common Site of Metastasis	Those with Isolated Pulmonary Metastases (% of All Patients)
Breast carcinoma	Lung ¹⁴¹ (59-65)		22 ¹⁰³
Colorectal	Liver ¹⁴²	Lung ¹⁴²	2-4 ²
Germ cell tumors	Lung ¹⁴³		
Head and neck squamous cell carcinoma	Lung ¹⁴⁴ (75)		
Melanoma	Lung ^{128*} † (18-36)		5 ¹²⁸
Osteosarcoma	Lung ⁸³ (85)		
Renal cell carcinoma	Lung ¹⁰⁴		4 ¹⁰⁴
Soft tissue sarcoma	Lung ¹⁴⁵ (80-90)		20 ⁷⁶
All histologies	Liver	Lung ¹⁴⁶	15-20 ^{147,148}

*Secondary to skin, subcutaneous, lymph nodes.

†In clinical series; however, 70% to 87% in autopsy series.

BOX 23-3 Selection Criteria* for Metastasectomy

- Local control of the primary tumor or ability to completely resect the primary with synchronous presentations²⁰
- Radiologic findings consistent with metastatic disease
- Absence of extrathoracic metastases (i.e., metastasis is confined to the lung)
- Ability to perform a complete resection of the metastases
- No significant comorbidity that would preclude surgery
- No alternative therapy that is superior to surgery

*Approximately one third of patients with metastatic disease meet these criteria.

envelope.³¹ This is best determined at operation. Preoperatively, imaging modalities can only provide an estimate of resectability. In addition, thoracoscopy can sometimes be useful to assess for disseminated disease or bulky tumors that involve major structures and preclude complete resection. If the pericardium or pleura is involved with neoplastic disease from direct extension of an underlying parenchymal lesion, but there is no associated effusion, they should be resected en bloc with the specimen. Direct metastases to the pleura or pericardium in a discontinuous manner (i.e., disseminated spread) and malignant pleural or pericardial effusions are generally contraindications for resection.

Is the primary tumor controlled? Efficacy of pulmonary metastasectomy depends on, among other factors, the ability to control the primary site of disease. The primary neoplasm should generally be addressed before resection of the pulmonary metastases. Therefore, thorough preoperative testing should be performed to rule out other possible metastatic sites or local recurrence of the primary tumor prior to pulmonary metastasectomy (Box 23-3).

Alexander and Haight, in the 1940s, were the first to describe specific selection criteria for consideration of pulmonary metastasectomy. They realized that the benefits of surgical resection depended on primary tumor control, absence of extrathoracic spread, and adequate patient selection. Approximately one third of patients meet these selection criteria and can appropriately undergo metastatic resection.

SURGICAL APPROACH

Surgery for pulmonary metastases is based on the principle of performing a complete resection while preserving as much lung tissue as possible.⁴⁷ The specific location of the tumor in the lung plays a role in determining the resection volume necessary to remove all disease. Wedge resection of the lung to include a negative resection margin is the standard therapy. Deeply located lesions or central lesions may require an anatomic resection—segmentectomy, lobectomy, or, in rare cases, pneumonectomy.

Bronchoscopy is performed routinely at the time of resection to exclude endobronchial involvement, which

may alter surgical approach or preclude resection with curative intent. Epidural analgesia has become the gold standard in thoracic surgery for managing postoperative pain and facilitating postoperative secretion clearance, particularly when thoracotomy is required. Single-lung ventilation using a double-lumen endotracheal tube or a bronchial blocker allows the surgeon to perform a thorough manual inspection of the superficial and deep parenchyma of the deflated lung. An articulating stapler that cuts and staples simultaneously is useful for removing palpable nodules while sparing lung tissue. A 1-cm margin is considered adequate when excising metastases to the lung, but this has not been systematically evaluated.

The choice of incision should reflect the extent of disease, the goal of complete resection, and the patient's ability to undergo the procedure. The surgical options for metastasectomy include VATS, thoracotomy, and midline approaches (which allow simultaneous access to both thoracic cavities). VATS procedures typically involve two- or three-port access to the pleural space, ipsilateral lung collapse via a double-lumen tube with digital palpation of the lung, and nodule localization through the nearest trocar site. Central lesions may be difficult to palpate through the smaller incisions, which may justify an open procedure for their removal. In addition, direct bimanual palpation, which is difficult with VATS, may aid in identification of additional lesions not seen on imaging. In 1996, McCormack and colleagues prospectively performed VATS resections based on CT findings, followed by thoracotomies with lung palpation, and found additional lesions in 14 of 18 patients.⁴⁸ Cerfolio and coworkers confirmed that 64-slice helical CT scan missed pathologically proven metastases in 18% of cases when thoracotomy with bimanual palpation was performed.⁴⁹ Other studies have shown that, at least for patients who underwent metastasectomy for colorectal cancer, there is no statistically significant difference in survival between the open and the thoracoscopic approaches.⁵⁰ Lin and colleagues reported on 99 potentially curative resections of metastases using a VATS approach and demonstrated long-term survival comparable to historic results with an open approach.⁵¹ Landreneau and coworkers observed less pain and a shorter hospital stay after VATS resection of colorectal metastases to the lungs.⁵² Furthermore, as CT scanning technology evolves, the detection of nodules as small as 1 mm may be achieved, further narrowing the disparity between CT scanning and manual palpation.⁵³ At this point, the data support thoracotomy and manual palpation as being the more sensitive method for detecting nodules. However, the choice between thoracotomy and VATS involves many factors and should be individualized for every patient.

Open approaches include standard thoracotomy, bilateral simultaneous or staged thoracotomy, a clamshell and hemi-clamshell incision, and median sternotomy. Standard thoracotomy can be performed as the definitive procedure in patients with unilateral disease or as a staged procedure, with a contralateral thoracotomy performed approximately 6 weeks later in patients with bilateral disease. Bilateral submammary incisions including a transverse sternotomy (a clamshell incision) are useful for

accessing both thoracic cavities for metastasectomy. A hemi-clamshell incision, consisting of a unilateral anterior thoracotomy with a partial or complete sternotomy, has been described. Each of these incisions may at times be the correct approach, but, generally, each of them tends to be more morbid and painful than VATS or a median sternotomy. Morbidity and mortality rates for lung metastasectomy by conventional means range between 0% and 31.6% and between 0% and 7.6%, respectively.⁵⁴

Median sternotomy, preferred by some surgeons, provides access to both thoracic cavities, but it provides limited exposure to lesions in the left lower lobe and large posterior central lesions. Patients with a history of radiation therapy, obesity, chronic obstructive pulmonary disease, diabetes, and steroid use may be at higher risk for wound complications after median sternotomy.

The metastasectomy itself usually consists of a wedge resection. This is facilitated by the tendency of metastatic disease to be found at the periphery of the lung, and it is easily performed with lung clamps and a pulmonary stapling device. Excision with electrocautery or laser may also be performed under select circumstances.⁵⁵⁻⁵⁸ Posterior areas of the lung may be better assessed by filling the hemithorax with saline to float the lung anteriorly. Resection with a 1- to 2-cm margin of uninvolved tissue is adequate in this setting. Lobectomy is indicated if a lesser procedure would result in an incomplete resection or is not technically possible. This is most commonly the case with large, centrally located lesions or lesions in such close proximity to bronchovascular structures that an anatomic resection is required to avoid leaving fatally compromised lung tissue behind. Chest wall resection of contiguous lesions not associated with other disease, or even pneumonectomy, has been shown to improve survival when used in the appropriate setting.^{3,59,60}

When considering surgery for the treatment of presumed (based on preoperative imaging) unilateral pulmonary metastases, one must consider whether this approach will miss undiagnosed contralateral disease and whether this would be detrimental to the patient. One study tried to answer this question by comparing sternotomy to unilateral thoracotomy in patients with metastases that appeared unilateral in preoperative imaging studies.⁶¹ Unilateral thoracotomy was used, and the contralateral lung was not assessed. One might expect residual disease in the unevaluated thorax, resulting in a worse prognosis for this group. In fact, no difference in long-term survival was found. Furthermore, repeat resection of recurrences have been shown to improve survival, thus making the argument that any missed subclinical disease could be resected subsequently.^{61,62} These results have been corroborated by Younes and colleagues.⁶³ In this study, patients undergoing unilateral thoracotomy for unilateral disease ($n = 179$) and patients undergoing bilateral thoracotomies for bilateral disease ($n = 88$) were investigated. The two groups of patients with confirmed bilateral metastases (synchronous or metachronous) were compared. Patients who experienced recurrence in the contralateral lung within 3, 6, or 12 months had overall 5-year survival rates of 24%, 30%, and 37%, respectively. When patients with recurrence in the contralateral lung

were compared with patients with bilateral metastases on admission, there was no significant difference in overall survival. The only two predictors of contralateral recurrence were histology and the number of pathologically proven metastases. Younes and colleagues concluded that bilateral exploration of unilateral lung metastases is not warranted in all cases.

LYMPH NODE DISSECTION

The role of systematic lymph node dissection performed during pulmonary resection for metastases is not well defined. Many studies do not include nodal data because traditionally a lymph node dissection was not routinely performed as part of the operation. The reported incidence of mediastinal nodal metastases varies according to histology.^{14,64} In patients undergoing metastasectomy for renal cell carcinoma, intrathoracic lymph node involvement can be as high as 46.6%.²² Alternatively, Putnam and coworkers demonstrated a very low incidence of lymph node metastases in patients with sarcomatous pulmonary metastases.⁶⁵

There is evidence that the presence of nonsarcomatous lymph node metastases at the time of metastasectomy has an adverse effect on survival, which suggests preoperative identification of mediastinal nodal metastasis may lead one away from a surgical approach.⁶⁴ In addition, the omission of lymphadenectomy from the surgical resection of metastases may incorrectly classify patients as being free of disease. Furthermore, lymph node involvement may influence the ensuing postoperative treatment plan

RESULTS OF PULMONARY METASTASECTOMY

Pulmonary metastasectomy in appropriately selected patients has been shown in retrospective studies to improve survival. When all histologies are considered, the 5-year survival rate for patients undergoing resection of secondary pulmonary malignancy is 25% to 40% (Table 23-2). Many series have evaluated potential prognostic indicators to more clearly define the patients who are most likely to benefit from metastasectomy. For example, short tumor doubling time is frequently a sign of an aggressive lesion, and it has been proposed that patients with these tumors, therefore, might not derive a survival benefit from resection. The results seen in these studies, however, have not been conclusive.⁶⁶⁻⁶⁹ Moreover, the practical application of such a measurement is difficult. Disease-free interval has also been studied in an attempt to predict outcomes. Longer disease-free interval, however, has not been consistently associated with a better prognosis.^{65,69-71} It is not clear whether there is a number of nodules above which resection is unwarranted. As many as 20 to 30 metastasectomies have been performed at one operation with good results.⁷² Thus, multiplicity may be more appropriately used to assist in the assessment of tumor resectability. None of these criteria for predicting positive outcome from metastasectomy has

TABLE 23-2 Five-Year Survival Rates of Various Histologic Metastatic Resections

Histology	5-Yr Survival Rate without Metastasectomy (%)	5-Yr Survival Rate with Metastasectomy (%)
All histologies	—	25-40 ^{65,149}
Breast cancer	11 ¹⁰³	35-50 ^{105,150,151}
Colorectal cancer	<5 ⁵⁴	40-45 ^{25,152}
Germ cell tumors	—	68 ⁶⁵
Head and neck squamous cell carcinoma	—	29-60 ⁶⁵
Melanoma	3-4 ^{128,129}	21-36 ^{77,128,129}
Osteosarcoma	0-17 ^{83,153}	20-40 ^{65,154,155}
Renal cell carcinoma	—	13-54 ^{22,156}
Soft tissue sarcoma	—	20-40 ^{65,79}
Urinary tract cancer	—	25-43 ¹⁵⁶

TABLE 23-3 Prognostic Factors in Metastasectomy

Absolute	Equivocal
Complete resectability	Tumor doubling time Disease-free survival Number of nodules Histology Nodal status

been universally established. Most studies have proposed that complete resectability is the only universal determinant of prognosis across histologies (Table 23-3).

Many of the aforementioned studies attempting to evaluate prognostic determinants in pulmonary metastasectomy have been faulted because they lack sufficient statistical power to demonstrate clinical significance. One group, however, reported 5206 cases of pulmonary metastases from various sites from the 18 medical centers of the International Registry of Lung Metastases. In this retrospective review, three indicators were shown to have prognostic significance regardless of primary histology: resectability, a disease-free interval of greater than 36 months, and solitary versus multiple lesions. As a result, the authors proposed a four-group staging system based on the number of prognostic indicators present in a given patient (Table 23-4). Although staging systems such as this may better define the patients most likely to benefit from metastasectomy, survival rates after surgery, even with poor prognostic indicators, may be better than after any other treatment. Consequently, some surgeons believe that metastasectomy should be offered to appropriate patients regardless of these factors, with the possible exception of inability to perform complete resection.¹⁴

In addition to the aforementioned factors equivocally associated with prognosis, other factors have been shown to clearly not affect outcome. These factors include unilateral (as opposed to bilateral) disease, age, sex, and wedge resection versus formal lobectomy (Box 23-4).

After complete pulmonary resection of metastatic disease, recurrence is the most common cause of death. Despite this, repeat resections have contributed to prolonged survival for a number of histologies.^{62,65,73,74} The most studied histology is soft tissue sarcoma. For example,

TABLE 23-4 Prognostic Staging System

Prognostic Stage	Number of Prognostic Indicators*	5-Yr Survival Rate (%)
Stage I	None	61
Stage II	Two	34
Stage III	Three	24
Stage IV	Unresectable	14

*The three possible indicators are resectability, disease-free interval greater than 36 months, and solitary (as opposed to multiple) metastases.
From Pastorino U, McCormack PM, Ginsberg RJ: A new staging proposal for pulmonary metastases. The results of analysis of 5206 cases of resected pulmonary metastases. Chest Surg Clin N Am 8:197-202, 1998.

BOX 23-4 Factors Not Affecting Prognosis in Patients with Metastasectomy

- Age
- Sex
- Unilateral versus bilateral disease
- Wedge resection versus formal lobectomy

in a study by the National Cancer Institute in which patients underwent re-resection for soft tissue sarcomas, no difference in the actuarial 5-year survival was found in those undergoing one, two, and even three resections for recurrence.⁷³ To appropriately choose patients for repeat resection, it is important to use preoperative selection criteria that are similar to those used for the initial resection. This ensures the absence of disseminated disease and the ability of a given patient to tolerate the proposed procedure.

SPECIFIC SECONDARY LUNG TUMORS

Soft Tissue Sarcoma

Soft tissue sarcomas consist of a heterogeneous group of nonossifying malignant neoplasms derived from mesenchymal connective tissue. In a 1997 report from the International Pulmonary Metastases Registry, soft tissue sarcomas were the most common type of pulmonary metastases resected, and they accounted for 42% of all

patients undergoing metastasectomy.⁷⁵ Unfortunately, only 50% of patients with lung metastases from sarcoma are operative candidates, and of those, 80% undergo complete resection. It is from that 80% that the 5-year survival rates of 20% to 40% are obtained.⁷⁶ Soft tissue sarcomas typically respond poorly to systemic chemotherapy, making surgery the only potentially curative treatment option. However, in the absence of a randomized trial, it is impossible to know whether these results reflect careful patient selection and favorable biology rather than a specific benefit of surgery.

Patients with extremity soft tissue sarcomas tend to develop pulmonary metastases more frequently than those with sarcomas at other sites.⁷⁷ Gadd and coworkers analyzed histopathologic findings of soft tissue extremity sarcomas and their relationship to pulmonary metastases.⁷⁶ The probability of pulmonary metastases developing from a soft tissue sarcoma is influenced by histopathologic factors such as grade, size, and location of the primary tumor. Patients with spindle cell sarcoma had the highest incidence of pulmonary metastases, whereas those with liposarcomas had the lowest incidence.

Regardless of histology, primary and repeat metastasectomy has been associated with improved long-term survival. A study from Memorial Sloan-Kettering focusing on 719 patients with sarcoma who had pulmonary metastases showed a 3-year survival rate of 46% for patients undergoing resection, compared with 17% for those treated nonsurgically.⁷⁸ Favorable prognostic indicators include completeness of resection, disease-free interval, tumor doubling time greater than 40 days, number of nodules (four or fewer), grade, tumor histology, radicality of resection, and age.^{66,78-80}

Pulmonary re-recurrence after complete resection of metastatic soft tissue sarcomas has been reported to occur in 45% to 83% of patients, and the lungs represent the main reason for ultimate treatment failure in up to 80% of patients.⁸¹ Five-year survival rate of 36% after re-resection of soft tissue sarcomas has been reported.⁸² Patients whose metastases cannot be completely resected, those with large metastases (>2 cm), and those with high-grade primary tumor pathology tend to have worse outcomes.⁸³

Osteosarcoma (Osteogenic Sarcoma)

Like soft tissue sarcomas, osteosarcoma has a strong predilection for metastasis to the lung. In addition, the lesions themselves are frequently multiple and often recur despite resection. Consequently, pulmonary involvement is responsible for most deaths in patients with this disease. Approximately 10% to 20% of patients have distant metastases on initial evaluation and, as with other histologies, CT of the chest is the imaging modality of choice for detection.

Before the introduction of chemotherapy, the overall survival from osteogenic sarcoma was only 10% to 20%.^{70,83} In the early 1970s, however, the use of chemotherapy, especially high-dose methotrexate, substantially improved outcomes.⁸⁴ Later, with the introduction of multimodality therapy, chemotherapy (doxorubicin, high-dose cyclophosphamide, and cisplatin) combined

with resection improved 5-year survival rates to 32% to 40%.^{14,85} In some cases, treatment resulted in cure. As a consequence of these improved results early in the history of metastasectomy, a more aggressive approach toward resection of pulmonary metastases developed. These favorable outcomes in selected patients treated aggressively with multimodality therapy, including pulmonary metastasectomy, have been duplicated by others in recent years.^{86,87} Despite the survival advantage imparted by surgical resection in osteogenic carcinoma, tumor recurs in 50% of patients within 1 year. Eventually, 85% of these patients relapse with recurrent pulmonary disease, despite adequate removal of the primary tumor and no earlier evidence of gross secondary disease. Resection of these recurrences is indicated if feasible, as numerous studies have demonstrated improved survival.^{29,88} If the patient is not a surgical candidate, radiotherapy or radiofrequency ablation may be an option.

No prognostic factors, except complete resection, have consistently been associated with improved survival after metastasectomy. A number of studies have looked at the aforementioned characteristics (age, sex, location, doubling time, disease-free survival, number of nodules, resectability) but found that few consistent conclusions could be drawn. In most studies, a worse outcome correlated with an increased number of nodules.^{14,89} All studies conclude that complete surgical resection is indicated, and when resectability was studied, incomplete resection was always associated with a worse outcome.^{14,90,91} In addition, the location of the primary lesion has been associated with worse prognosis in the case of pelvic and vertebral tumors.⁹²

Colorectal Cancer

The lung and liver are the most common sites of metastatic disease in colorectal cancer. Marked improvements in the survival of patients with metastatic colorectal cancer have been seen in the past decade, which is attributed mostly to several new drugs. Despite this, surgical resection is widely accepted as having a prominent role in the treatment of patients with synchronous or metachronous metastatic disease in the lungs. Because of the increasing number of active agents at the oncologist's disposal, surgical resection and its timing need to be planned carefully in a multidisciplinary fashion.

The evidence of survival benefit continues to be limited due to a lack of prospective data. However, multiple studies of pulmonary resection of metastatic colorectal carcinoma have demonstrated that the survival in selected patients at 5 years ranges from 27% to 61%. Prognostic factors associated with improved prognosis in patients with pulmonary metastases from colorectal cancer include primary tumor stage and completeness of the resection. Other prognostic factors may include number of pulmonary metastases, pre-thoracotomy carcinoembryonic antigen (CEA) serum level, and presence of lymph node metastases.⁹³⁻⁹⁹ Even in the presence of synchronous and metachronous colorectal metastases to the lung and liver, surgical management of both can result in long-term survival, albeit less favorable than those with more limited metastatic disease. Barlow and colleagues observed a

median survival of 44 months after combined liver and lung resection.¹⁰⁰ Gonzalez and colleagues observed a median disease-free survival of 13 months after pulmonary metastasectomy in patients who had previously undergone liver resection for liver metastasis.¹⁰¹

These retrospective studies have formed the rationale for the recommendation of surgical resection in patients with colorectal cancer metastases to the lung, but the perception of selection bias continues to bring into question whether this practice is truly improving survival. A prospective randomized trial (PulMiCC) is currently under way in the United Kingdom to attempt to answer this question.¹⁰²

Breast Carcinoma

Pulmonary involvement in breast cancer is most commonly associated with widespread disease, such that a thorough search for extrathoracic disease is warranted before considering metastasectomy. In a series of 5143 patients with breast cancer, Staren and coworkers reported lung metastases in 284 patients, and only 1% of these had metastatic disease confined to the lung.¹⁰³ They observed a significant 5-year survival advantage for patients who underwent metastasectomy (36% versus 11%). Factors conferring a more favorable prognosis include estrogen and progesterone receptor (ER/PR) status and a complete resection.^{104,105} Meimarakis et al recently published their favorable results of lung metastasectomy in breast cancer, including statistically significant overall survival in surgical patients in a matched pair analysis when matched for age and tumor-nodes-metastasis (TNM) status of original tumor.¹⁰⁶

In addition to a possible therapeutic benefit, resection of a breast cancer metastasis offers reassessment of molecular markers (ER, PR, and HER2) because of the 5% to 30% discordance rate between receptor status of primary lesions when compared with subsequent metastasis. These changes can dramatically affect the type of adjuvant therapy offered.¹⁰⁷

Head and Neck Carcinoma

Head and neck carcinomas most commonly spread through local lymphatics. The lung is among the more common sites of distant spread, followed by bone and liver. Patients with head and neck cancer and a history of frequent tobacco use are at risk for other foregut malignancies. A solitary nodule in a patient with a history of head and neck cancer has a greater chance of being a lung primary tumor and should be treated as such. Five-year survival rates after metastasectomy for head and neck cancers range from 29% to 59%.¹⁰⁸ Shiono et al recently reported overall 5-year survival following pulmonary metastasectomy of 26.5%, with male gender and oral cavity primary tumor associated with very poor outcomes.¹⁰⁹

Renal Cell Carcinoma

The lung is a frequent site of renal cell metastases, with prevalence rates as high as 72% to 76% in autopsy

studies.^{110,111} Over the past decade, tyrosine kinase inhibitors such as sorafenib and sunitinib have been shown to delay disease progression in patients with metastatic renal cell carcinoma, but surgical resection in selected patients continues to demonstrate a survival benefit in retrospective series and even cure, as first reported by Barney and Churchill in 1939.¹¹² Several retrospective studies have been published demonstrating the beneficial effect of resecting renal cell cancer metastases to the lung, with reported 5-year survival rates ranging from 20% to 50%. Han and colleagues reported that patients with evidence of disease in multiple organs fare significantly worse than those with metastatic disease limited to the lungs.¹¹³ Patients with a solitary renal metastasis fare best, with a 5-year survival of up to 54%.¹¹⁴ Assouad and colleagues observed that 5-year survival was significantly affected by the size of the largest metastasis and by mediastinal lymph node involvement.¹¹⁵ Synchronous metastases, greater than six metastases, absence of regional and mediastinal nodes, and resectability have been identified as being important prognostic factors.^{104,116} Results of long-term follow-up studies support an aggressive surgical approach in patients with renal carcinoma metastases to the lungs.^{22,117}

Germ Cell Tumors

Germ cell tumors account for only 1% of all cancers, but they are the most common malignancy in male patients between the ages of 15 and 35 years. Most germ cell tumors are highly responsive to chemotherapy and even patients with metastatic disease have an excellent prognosis. Most patients with metastatic testicular tumors demonstrate a complete clinical remission after treatment with chemotherapy. Surgical intervention for pulmonary metastases from germ cell tumors is primarily reserved for evaluation of a residual mass after chemotherapy, particularly in nonseminomatous types. In these cases, resection of the metastatic sites of residual disease results in removal of chemotherapy-resistant elements as well as identification of residual viable cancer that may require additional chemotherapy.

In the 25% to 30% of patients with a residual mass after chemotherapy for nonseminomatous germ cell tumors, it is difficult to differentiate necrosis from a mature teratoma or persistent tumor. Cagini and coworkers reported on a series of 144 patients who underwent resection of a residual mass after chemotherapy for metastatic germ cell tumors.¹¹⁸ Viable malignant elements were found in 44 patients, and 63 patients were found to have a differentiated teratoma. An overall 5-year survival rate of 77% was observed, with a worse rate (51%) in patients with malignant teratomatous elements. Special considerations in this group include prior exposure to bleomycin, which results in increased risk of pulmonary complications following surgery.¹¹⁹

Gynecologic Tumors

The lung represents the most common organ involved in uterine cancer spread, with isolated pulmonary metastases observed in approximately 6% of patients.¹²⁰

Pulmonary metastasectomy for uterine cancer is associated with a 5-year survival rate of approximately 50% in well-selected patients.¹²¹ Anderson and colleagues observed improved median survival in patients undergoing pulmonary metastasectomy for adenocarcinomas (46 months) compared with leiomyosarcomas (25 months), although median survival reported by Clavero and colleagues was similar.^{120,122} Completeness of resection, longer disease-free interval, and three or fewer metastases have been associated with an improved survival rate in this patient population.¹²³ Additionally, ER/PR status of pulmonary metastases is significant with cancers of uterine origin, as patients with positive ER/PR receptors have an 80% response rate and average survival rates of up to 33 months.¹²⁴

Most patients with ovarian cancer metastatic to the lung have malignant effusions.¹²⁵ Disease confined to the lung amenable to metastasectomy is exceedingly rare.

Melanoma

Patients with metastatic melanoma often present with widely disseminated disease, and isolated pulmonary metastases are rare. The lungs are the second most common site of metastases in patients with melanoma, with a prevalence of between 12% and 36%.^{126,127} The annual probability of developing pulmonary metastases increases progressively from 10% at 5 years to 17% at 15 years.

An aggressive surgical approach to pulmonary metastatic disease from melanoma is warranted as long as a complete metastasectomy can be performed. Evidence for this is based in part on studies from Harpole and colleagues and Taft and coworkers, who reported 5-year survival rates of 20% and 27%, respectively, in patients undergoing pulmonary metastasectomy, versus 4% and 3%, respectively, in patients treated medically.^{128,129}

If a complete resection cannot be performed, little or no benefit is provided in terms of prolonging patient survival. Additional factors influencing survival include disease-free interval less than 5 years, prior chemotherapy, nodular histology, the presence of more than two pulmonary nodules, and positive lymph nodes.^{128,130}

Endocrine Tumors

The lungs represent an uncommon site of metastases for malignant endocrine tumors. A select group of patients with slow-growing endocrine tumors, including carcinoids, well-differentiated thyroid cancers, and parathyroid cancers, may benefit from resection of their metastases. In a retrospective review, Khan and coworkers reported shorter survival in patients with positive mediastinal lymph nodes at the time of resection and a shorter disease-free interval.¹³¹ Occasionally, metastases may be resected to alleviate symptoms of hormone production.^{132,133}

Other Tumors

Small retrospective series have demonstrated encouraging survival rates when compared with historical data when

lung metastases have been identified for other histologies. These included hepatocellular carcinoma,¹³⁴ gastric cancer,¹³⁵ and pancreatic adenocarcinoma.^{136,137} In fact, in addition to considering disease-free interval, limited sites of disease, complete resectability, and low anticipated morbidity, surgeons should also consider resection of suspected lung metastasis for patients with cancer.

ALTERNATIVE TREATMENT OPTIONS

In patients with lung metastases deemed appropriate for locoregional therapy, several options are available to patients who are medically inoperable or who decline surgery. The data for these therapies are substantially limited compared with the data for surgery, and no randomized data exist. Options include stereotactic body radiation therapy, radiofrequency ablation, and cryoablation.

Stereotactic body radiation therapy (SBRT) is a technique that uses localized radiation treatments delivered in a limited number of fractions. The end result in the lung is high-dose radiation to a small area of lung tissue, minimizing damage to adjacent lung and mediastinal structures. Successful use of SBRT to treat intracranial and skull base tumors led to applications in other regions, including the lung. Side effects include chest wall pain and rib fractures when treating lesions abutting the pleura and lung toxicity, because of airway necrosis, when treating central lesions. Local control rates (defined as stabilization or decrease in size of the treated lesion) in oligometastatic disease have been reported in the 87% to 100% range.¹³⁸

Radiofrequency ablation (RFA) is a thermal energy delivery system that applies an alternating current through a needle electrode into a tissue. The result of energy delivery is coagulative necrosis and tissue destruction in the vicinity of the probe. Lung parenchyma is thought to be a good place to use RFA because pulmonary tissue surrounding solid tumors acts as a thermal insulator, allowing energy to focus on the area of the solid tumor.¹³⁹ Lesions can be approached percutaneously with CT guidance or through an incision in the operating suite.

Inclusion criteria for RFA are lesions no larger than 5 cm in diameter, inoperable non-small cell lung cancer, and no more than four secondary lesions in both lungs. The feasibility of RFA depends on factors such as the presence of an "access window" and proximity to hilar structures. Complications of RFA include pneumothorax requiring intervention (30%), pleural effusion, hyperpyrexia, infection, and hemorrhage. Chua and colleagues reported their experience using RFA for lung tumors (73% were colorectal cancer metastases) in 148 patients who were not candidates for surgical resection. They found 46% had a complete response, 39% had stable disease, 16% had progressive disease, and median progression-free survival was 11 months.¹⁴⁰

PALLIATIVE THERAPY

Palliative therapies include laser ablation of airway lesions, tracheobronchial photodynamic therapy (PDT),

radiation modalities, and airway stenting. Hemoptysis resulting from pulmonary metastases is usually controlled with external beam radiation, laser ablation, or PDT. The neodymium:yttrium-aluminum garnet laser provides effective coagulation and tumor necrosis, and it is helpful in the removal of endobronchial tumors causing obstruction. It can be used effectively via a flexible or rigid endoscope. PDT has been shown to prolong airway patency and can be used as the primary treatment modality or in conjunction with the laser. Finally, airway stenting is frequently used either alone or in conjunction with other palliative therapies to improve patient quality of life.

CONCLUSIONS

Currently, metastasectomy is the treatment of choice in appropriately selected patients with metastatic disease to the lungs for most neoplastic histologies. Selection guidelines now available are useful in determining which patients benefit from metastasectomy. The role of pulmonary metastasectomy is changing as more effective systemic chemotherapy treatment regimens become available, and more experience is obtained with less invasive techniques. Controlled clinical trials will be needed to aid the clinician in selecting the most appropriate treatment for each individual patient.

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PART H

CHEST WALL

PART OUTLINE

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SYMPATHECTOMY

CONGENITAL CHEST WALL DEFORMITIES

Konstantinos Papadakis • Robert C. Shamberger

CHAPTER OUTLINE

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A great variety of congenital abnormalities of the chest wall occur. Their physiologic implications are also quite varied and span the spectrum from the rare entities of ectopia cordis and asphyxiating thoracic dystrophy, which are often lethal, to the much more common pectus excavatum and pectus carinatum with their limited physiologic impact. In this chapter anterior thoracic deformities will be considered in five categories: pectus excavatum, pectus carinatum, Poland syndrome, sternal defects (including ectopia cordis), and miscellaneous conditions (including asphyxiating thoracic dystrophy [Jeune syndrome]).

PECTUS EXCAVATUM

Pectus excavatum is the most frequent anterior chest wall deformity. The central depression of the chest is produced by posterior angulation of the sternum and the costal cartilages. The first and second costal cartilages and the manubrium are usually in a normal position (Fig. 24-1), but the lower costal cartilages, which insert into the sternum and the body of the sternum, are depressed.

The most anterior segment of the ossified portion of the ribs may also be curved posteriorly in older adolescents and adults. The extent of sternal and cartilaginous deformity is variable. Numerous methods of grading these deformities have been proposed by Hümmer and Willital,¹ Oelsnitz,² Welch,³ Haller and associates,⁴ and others, but none has been universally accepted. Asymmetry of the depression is often present. The right side is frequently more depressed than the left, and the sternum may be rotated as well. A system to quantify the asymmetry based on computed tomography (CT) scan of the chest has been reported.⁵ Many children with pectus excavatum have a characteristic physique with a broad thin chest, dorsal lordosis, “hook shoulder” deformity, costal flaring, and poor posture.

Pectus excavatum is present at birth or within the first year of life in most affected children (86%), as shown in Figure 24-2. The deformity rarely resolves with increasing age, and it may worsen during the period of rapid growth in adolescence. Waters and associates identified scoliosis in 26% of 508 patients with pectus excavatum. Hence, it is important that all patients with pectus deformities are evaluated clinically for scoliosis. Asymmetrical

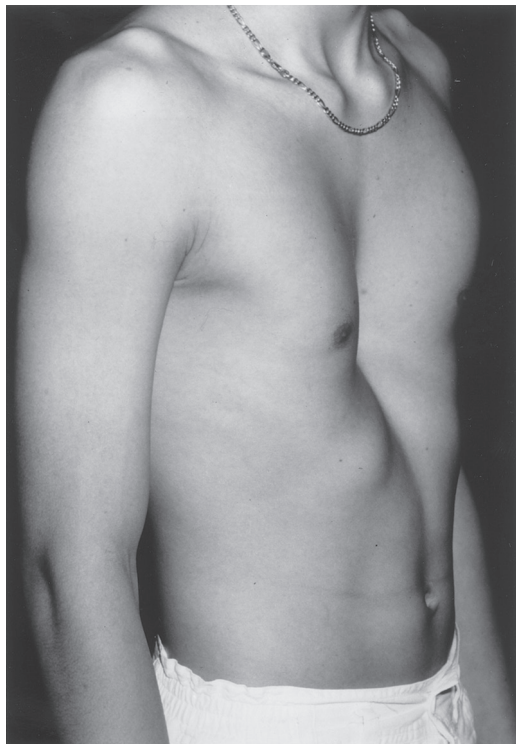


FIGURE 24-1 ■ A 16½-year-old boy with a symmetrical pectus excavatum deformity. Note that the depression extends to the sternal notch.

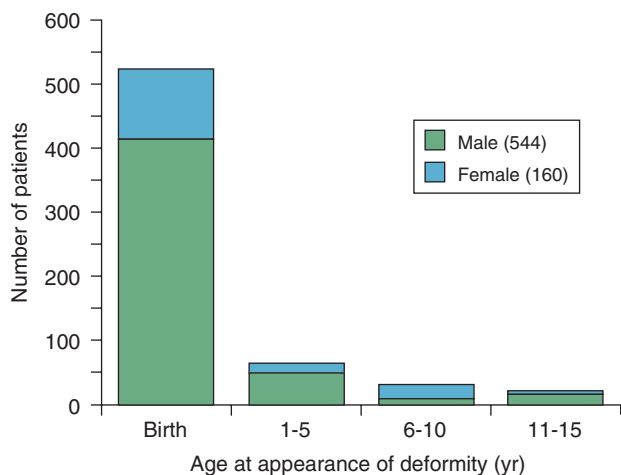


FIGURE 24-2 ■ Age at appearance of pectus excavatum deformity in 704 infants and children. Note the large proportion identified at birth or within the first year of life and the predominance of males with this deformity. (From Shamberger RC, Welch, KJ: Surgical repair of pectus excavatum. *J Pediatr Surg* 23:615, 1988. With permission.)

pectus excavatum with a deep right gutter and sternal rotation often is accompanied by scoliosis.⁶ Congenital heart disease was identified in 1.5% of infants and children undergoing chest wall correction at Boston Children's Hospital (Table 24-1).⁷ The frequency of chest wall deformities among all patients with congenital heart disease evaluated at this institution was only 0.17%.

Asthma may be identified in association with pectus excavatum and carinatum. In a review of 694 consecutive

TABLE 24-1 Congenital Heart Disease Associated with Pectus Excavatum and Carinatum

	Number of Cases
Aortic ring	1
Aortic regurgitation	1
Atrial septal defect primum	2
Atrial septal defect secundum	3
Complete atrioventricular canal	3
Dextrocardia	3
Ebstein malformation	1
Idiopathic hypertrophic subaortic stenosis	2
Patent ductus arteriosus	1
Pulmonic stenosis	1
Tetralogy of Fallot	3
Total anomalous pulmonary venous return	1
Transposition of great arteries	6
Tricuspid atresia	1
Truncus arteriosus	1
Ventricular septal defect	6

From Shamberger RC, et al: Anterior chest wall deformities and congenital heart disease. *J Thorac Cardiovasc Surg* 96:427-432, 1988. With permission.

cases, 35 patients with asthma were identified (5.2%), a frequency comparable to that of asthma in the general pediatric population.⁸

Cause and Incidence

Ravitch reported that pectus excavatum may occur as frequently as 1 in 300 to 400 live births and that it is rare in blacks. It occurs more frequently in boys than girls, by an almost 4:1 ratio.⁹ Although the sternal depression appears to be caused by overgrowth of costal cartilages, the cause of pectus deformities is unknown. Lester attributed its development to an abnormality of the diaphragm, which tethered the sternum posteriorly.¹⁰ This theory was supported by the occurrence of pectus excavatum in children after repair of agenesis of the diaphragm and the frequent association of pectus excavatum and congenital diaphragmatic hernia.^{11,12} Histopathologic changes in the costal cartilages similar to those seen in scoliosis, aseptic osteonecrosis, and inflammatory processes are reported, but the cause of these changes and their significance are unknown.¹³

A family history of chest wall deformity in 37% of 704 patients suggests a genetic predisposition to pectus excavatum.¹⁴ Three of four siblings were affected in one family. Analysis of 34 families with more than one family member with pectus excavatum has shown a variable pattern of inheritance that appears to be multifactorial.¹⁵

A high incidence of chest wall deformities occurs in children with Marfan syndrome, and these deformities are often severe and usually accompanied by scoliosis.¹⁶ Pectus excavatum is also commonly seen in individuals with the abdominal musculature deficiency syndrome (prune-belly syndrome).¹⁷ Pectus excavatum also occurs in association with other myopathies and chromosomal

TABLE 24-2 Musculoskeletal Abnormalities Identified in 130 of 704 Cases of Pectus Excavatum

	Number of Cases
Scoliosis	107
Kyphosis	4
Myopathy	3
Marfan syndrome	2
Pierre Robin syndrome	2
Prune-belly syndrome	2
Neurofibromatosis	3
Cerebral palsy	4
Tuberous sclerosis	1
Congenital diaphragmatic hernia	2

From Shamberger RC, Welch KJ: Surgical repair of pectus excavatum. *J Pediatr Surg* 23:615–622, 1988. With permission.

defects such as Turner syndrome. A summary of the associated musculoskeletal abnormalities is shown in Table 24-2.

Symptoms

Pectus excavatum is well tolerated in infancy and childhood. The anterior depression in an infant with a flexible chest may be accentuated by upper airway obstruction as from tonsillar and adenoidal hypertrophy, but this obstruction does not produce the pectus deformity. Older children may complain of pain in the area of the deformed cartilages or of precordial pain after sustained exercise. Symptomatic limitations to sustained exercise may also appear in these children and teenagers and limit their participation in athletic activities. Palpitations, presumably caused by transient atrial arrhythmias, are occasionally reported. These patients may have mitral valve prolapse.

Pathophysiology

The cardiopulmonary implications of the pectus excavatum deformity have been debated for many decades. Although some authors believe this deformity has a limited physiologic effect, many patients report increased stamina after surgical repair. These findings date back to the first surgical repair performed by Sauerbruch in 1913.¹⁸ The patient was an 18-year-old boy who developed dyspnea and palpitations with very limited exercise. Three years after his operation, he could work 12 to 14 hours a day without tiring and without palpitations. Anecdotal reports during the next 3 decades repeated this observation. Investigators have sought to identify the physiologic abnormality or combination of abnormalities that could explain this symptomatic improvement after surgery. Early physiologic measurements of cardiac and pulmonary function were crude and did not yield convincing evidence of a cardiopulmonary deficit. In many early studies the results fell within the broad range of normal values, if often at the lower limit.⁷ A recent analysis of a large multi-institutional cohort of 408 patients with pectus excavatum found that the median values for forced vital capacity (FVC) and forced expiratory volume

in 1 second (FEV₁) were 13% below predicted values and forced expiratory flow (FEF_{2.5%-75%}) median was 20% below the predicted value.¹⁹

A systolic ejection murmur is frequently present in individuals with pectus excavatum and it is magnified by a short interval of exercise. This murmur is attributed to the close proximity between the sternum and the pulmonary artery, which results in transmission of a flow murmur.

Electrocardiographic abnormalities are common and result from the abnormal configuration of the chest wall producing displacement of the heart into the left thoracic cavity.²⁰ Patients with a history of palpitations should have a 24-hour electrocardiogram to document the presence or absence of arrhythmias as well as an echocardiogram to evaluate for mitral valve prolapse. Resolution of these supraventricular arrhythmias has been anecdotally reported after correction of a pectus excavatum deformity.

Many authors attribute the symptomatic improvement in exercise tolerance after surgery to improvement in pulmonary function. This has been difficult to prove, however, with the wide range of pulmonary function that exists from individual to individual and its dependence on physical training and body habitus. Several of the key studies will be reviewed.

Pulmonary Function Studies

As early as 1951, Brown and Cook performed pulmonary evaluations on patients before and after surgical repair.²¹ They demonstrated that although vital capacity (VC) was normal, the maximum breathing capacity was diminished (50% or more) in 9 of 11 cases and increased an average of 31% after surgical repair. Weg and associates in 1967 evaluated 25 Air Force recruits with pectus excavatum and compared them with 50 unselected basic trainees.²² Although the lung compartments of both groups were equal, as were the VCs, the maximum voluntary ventilation was significantly lower in those with pectus excavatum than in the control population. Castile and coworkers in 1982 evaluated seven patients with pectus excavatum, five of whom were symptomatic with exercise.²³ The mean total lung capacity of the group was 79% of predicted. Flow volume configurations were normal, excluding airway obstruction as a cause of the symptoms. Workload tests demonstrated normal response to exercise in the dead space to tidal volume ratio and alveolar-arterial oxygen difference. The measured oxygen uptake, however, increasingly exceeded predicted values as workload approached maximum in the four “symptomatic” subjects with pectus excavatum. This pattern of oxygen consumption was different from that in normal subjects and in the three asymptomatic subjects with pectus excavatum in whom a linear response was seen. The mean oxygen uptake in the symptomatic subjects at maximal effort exceeded the predicted values by 25.4%. The three asymptomatic subjects, on the other hand, demonstrated normal linear oxygen uptake during exercise. Increased oxygen uptake suggests increased work of breathing in these symptomatic individuals despite the normal or mildly reduced VCs. Increases in tidal volume with

exercise were uniformly depressed in those with pectus excavatum.

Cahill and coworkers in 1984 performed pre- and postoperative studies in 5 children and adolescents with pectus carinatum and in 14 with pectus excavatum.²⁴ No abnormalities were demonstrated in the pectus carinatum group. The low normal VCs in excavatum patients were unchanged by operation, but a small improvement in the total lung capacity and a significant improvement in the maximal voluntary ventilation were seen. Exercise tolerance improved in those with pectus excavatum after operation, as determined by both total exercise time and maximal oxygen consumption. In addition, at any given workload, those with pectus excavatum demonstrated a lower heart rate, stable oxygen consumption, and higher minute ventilation after repair. Mead and associates in 1985 studied rib cage mobility by assessing intra-abdominal pressure.²⁵ Normal abdominal pressure tracings in pectus excavatum suggested normal rib cage mobility.

Blickman and colleagues in 1985 assessed pulmonary function in 17 children with pectus excavatum by xenon perfusion and ventilation scintigraphy before and after surgery.²⁶ Ventilation studies were abnormal in 12 children before surgery and improved in 7 after repair. Perfusion scans were abnormal in 10 children before surgery and improved after operation in 6 children. The ventilation-perfusion ratios were abnormal in 10 of the 17 children preoperatively and normalized after repair in 6 children.

Derveaux and associates in 1989 evaluated 88 patients with pectus excavatum and carinatum by pulmonary function tests before and 1 to 20 years after repair (mean was 8 years).²⁷ The surgical technique used a fairly extensive chest wall dissection. Preoperative studies were within the normal range (>80% of predicted) except in subjects who had both scoliosis and pectus excavatum. The postoperative values for FEV₁ and VC expressed as percentage of expected were decreased in all groups, although the absolute values at follow-up may have been greater than at preoperative evaluation. Improved chest wall configuration was confirmed by radiologic evaluation, so the relative deterioration in pulmonary function was not the result of recurrence of the pectus deformity. An inverse relationship was found between preoperative and postoperative function. Those with less than 75% of predicted function had improved function after surgery, but function was worse after repair if the preoperative values were greater than 75% of predicted. Almost identical results were found in a study by Morshuis and coworkers in 1994.²⁸ They evaluated 152 subjects before and a mean of eight years after surgery for pectus excavatum. These results of pulmonary evaluation were in contrast to the subjective symptomatic improvement reported by the patients and their improved chest wall configuration. The decline in pulmonary function in the postoperative studies was attributed to the operation because the preoperative pulmonary defect appeared to be stable regardless of the age at initial repair. Both studies were marred by the obvious lack of an age- and severity-matched control group without surgery.

Derveaux and colleagues in 1988 evaluated transpulmonary and transdiaphragmatic pressures at total lung capacity in 17 individuals with pectus excavatum.²⁹ Preoperative and long-term follow-up evaluations were performed a mean of 12 years apart. Reduced transpulmonary and transdiaphragmatic pressures demonstrated that the increased restrictive defect was produced by extrapulmonary rather than pulmonary factors, suggesting that surgery produced increased rigidity of the chest wall.

Wynn and others in 1990 assessed 12 children with pectus excavatum by pulmonary function tests and exercise testing.³⁰ Eight children had repair and were evaluated pre- and postoperatively. Four children had two sets of evaluations but no operation. A decline in total lung capacity was identified in the repaired children compared with stable values in the control group. Cardiac output and stroke volume increased appropriately with exercise before and after operation in both groups, and the operation was believed to have produced no physiologically significant effect on the response to exercise.

Kaguraoka and associates in 1992 evaluated pulmonary function in 138 individuals before and after repair of pectus excavatum.³¹ A decrease in VC occurred during the first 2 months after surgery, with recovery to preoperative levels by 1 year after operation. At 42 months, the values were maintained at baseline, despite a significant improvement in the chest wall configuration. Tanaka and coworkers in 1993 found similar results in individuals who had the more extensive sternal turnover technique; in fact, they demonstrated a more significant and long-term decrease in VC.³² Morshuis and coworkers in 1994 evaluated 35 subjects who had had pectus excavatum repaired as teenagers or young adults; their ages were 17.9 ± 5.6 years.³³ Preoperative evaluations were performed and repeated 1 year after surgery. Preoperative total lung capacity ($86.0 \pm 14.4\%$ of predicted) and VC ($79.7 \pm 16.2\%$) were significantly decreased from predicted values and decreased further after surgery ($-9.2 \pm 9.2\%$ and $-6.6 \pm 10.7\%$, respectively). The efficiency of breathing at maximal exercise improved significantly after operation. Exercise was limited by ventilation in 43% of the subjects before repair. A tendency toward improvement occurred after operation. However, the group with no ventilatory limitation initially demonstrated one after operation with a significant increase in oxygen consumption.

Quigley and colleagues in 1996 evaluated 36 adolescents with pectus excavatum and 10 age-matched healthy controls at baseline and then an average of 8 months after surgery in 15 subjects and 9 months in controls.³⁴ Adolescents with pectus excavatum had a decrease in VC compared with controls, although the mean values remained in the normal range. The mean total lung capacity was also normal. There was no difference in workload performance between subjects with pectus excavatum and the controls, with both groups achieving a similar duration and level of exercise. No significant change in pulmonary function tests was seen in follow-up in either group. The duration of exercise as well as the level of work increased significantly in those who had surgery but not in the controls. The absence of adverse effects on pulmonary function after surgery was

attributed to a less extensive surgical procedure than was used in the studies reported by Derveaux²⁹ and Morshuis^{28,33} and their colleagues. Several series report the effects on pulmonary function of the new minimally invasive repair of pectus excavatum (MIRPE) described by Nuss.^{35,36} In these series there were limited or no preoperative abnormalities and mild or no significant change after repair. Similar results were reported in a prospective study of 145 patients having MIRPE.³⁷ There was no improvement in static values 6 months after removal of the struts. The most recent study evaluated 77 patients who had pre- and postoperative testing.³⁸ This study demonstrated statistically significant improvements in the FEV₁, the FVC, and the oxygen pulse.

In a recent, multicenter study of patients with pectus excavatum, patients demonstrated a relatively small decrease in lung function preoperatively with improvement postsurgical correction of approximately 6% to 10%.³⁹ The improvement in lung function was slightly greater in those with the most severe degrees of depression of the sternum (CT index > 3.2). When pre- and postoperative exercise pulmonary function tests were compared, the exercise studies in postsurgical patients revealed a 10.2% increase in maximum oxygen uptake and a 19% increase in oxygen pulse. It is postulated that the latter is probably attributable to an increase in stroke volume. As in previous studies, although the mean decrease in pulmonary function preoperatively and the mean improvement postoperatively were statistically significant, the changes were only modest in magnitude after repair.

In composite, these studies of pulmonary function over the past 4 decades have failed to document consistent improvement in pulmonary function resulting from surgical repair. In fact, some studies have demonstrated deterioration in pulmonary function at long-term evaluation that was attributed to increased chest wall rigidity after repair. A meta-analysis of 12 of these studies revealed no statistically significant change in pulmonary function.⁴⁰ Despite this finding, workload studies have shown improvement in exercise tolerance after repair, suggesting there is a cardiac basis for this enhanced performance.^{24,41}

Cardiovascular Studies

Posterior displacement of the sternum can produce a deformity of the heart, particularly indentation of the right ventricle. Displacement of the heart to the left, often with a sternal "imprint" on the anterior wall of the right ventricle was demonstrated angiographically by Garusi and D'Ettorre in 1964,⁴² and Howard⁴³ demonstrated its resolution after surgical repair. Elevated right heart pressures have been reported by some authors, as have pressure curves similar to those seen in constrictive pericarditis. In 1962, Bevegård studied 16 individuals with pectus excavatum by right heart catheterization and exercise testing.⁴⁴ The physical work capacity in pectus excavatum at a given heart rate was significantly lower in the sitting than the supine position. Those with 20% or greater decline in physical work capacity from the supine to the sitting position had shorter

sternovertebral distances than did those with less decrease in their physical work capacity. The measured stroke volume at rest decreased from supine to sitting positions a mean of 40.3%, similar to normal subjects. In the supine position, stroke volume increased with exercise 13.2%. In the sitting position, the increase in stroke volume from rest to exercise was 18.5% for the pectus excavatum group, significantly lower ($P < 0.001$) than the 51% increase seen in normal subjects. Thus, in the pectus excavatum group, an increased cardiac output could be achieved primarily by increased heart rate because only limited enhancement of the stroke volume could occur. Intracardiac pressures measured at rest and with exercise were normal in all subjects despite this apparent limitation of ventricular volume.

Gattiker and Bühlmann in 1967 confirmed this limitation of the stroke volume in a study of 19 subjects.⁴⁵ In the upright position at a heart rate of 170 beats per minute, the physical work capacity was lower than in the supine position (mean 18% decrease) because of the decrease in stroke volume. Beiser and associates in 1972 performed cardiac catheterization in six adolescents and young adults with moderate degrees of pectus excavatum.⁴⁶ Normal pressure and cardiac index were obtained at rest in the supine position. The cardiac index during moderate exercise was normal, but the response to upright exercise was below that predicted in two patients and at the lower limit of normal in three patients. The cardiac index was 6.8 ± 0.8 L/min/m² compared with 8.9 ± 0.3 liter/min/m² in a group of 16 normal controls ($P < 0.01$). The difference in cardiac performance again appeared to be produced primarily by a smaller stroke volume in the group with pectus excavatum in an upright position. Stroke volume was 31% lower and cardiac output 28% lower during upright as compared with supine exercise. Postoperative studies were performed in three individuals, two of whom achieved a higher level of exercise tolerance after surgery. The cardiac index increased an average of 38%. Because heart rate at maximal exercise was not higher after repair, an enhanced stroke-volume response was responsible for this increase.

Peterson and associates in 1985 performed radionuclide angiography and exercise studies in 13 children with pectus excavatum.⁴⁷ Ten of 13 were able to reach the target heart rate before surgical repair, 4 without symptoms. After operation, all but 1 child reached the target heart rate during the exercise protocol, and 9 of 13 reached the target without becoming symptomatic. The left and right ventricular end-diastolic volumes were consistently increased after repair at rest, and the mean stroke volume was increased 19% after repair. These findings substantiated the ventricular volume changes previously demonstrated by cardiac catheterization, although an increase in the cardiac index was not demonstrated. Recent echocardiographic studies by Kowalewski and associates of 42 patients before and 6 months after surgery revealed statistically significant changes in the right ventricular volume indices after surgery.⁴⁸ There was no correlation seen, however, between the pectus index and the changes in the right ventricular volume indices.

Malek and coauthors (2003) performed maximal exercise testing and pulmonary function tests on 21 individuals with pectus excavatum, 18 of whom routinely did aerobic exercise.⁴¹ Their maximum oxygen uptake and oxygen pulse were significantly lower than expected. These limitations were attributed to cardiovascular and not ventilatory factors and resulted in an abnormally low threshold for lactate accumulation. Of note, subjects with a Haller index greater than 4.0 were eight times more likely to have reduced aerobic capacity than those with a lower severity index.

Results of cardiac function have more recently been assessed in patients having the MIRPE procedure.³⁶ In 11 patients, an increase was demonstrated in the stroke volume measured echocardiographically 3 months after repair to which subjective improvement in exercise tolerance was attributed.

A meta-analysis was performed of eight studies (representing 169 patients), which reported quantitative data on the cardiovascular function of patients before and following repair.⁴⁹ The analysis suggested that surgical repair did not significantly improve cardiovascular function.

A recent study of 75 teenagers (49 with pectus excavatum and 26 controls) demonstrated a lower cardiac index in those with pectus excavatum during submaximal exercise, whereas there was no difference in heart rate or increase in heart rate between the two groups.⁵⁰ A follow-up study a year following surgery with a modified Nuss procedure demonstrated a significant increase in the patients following surgery, although the cardiac index was still significantly lower compared with the controls. Repeat studies 3 years after surgery and following strut removal revealed no difference in cardiac index or FEV₁ between the patients and controls.⁵¹ Additional studies are needed to further define the relationship between pectus excavatum and cardiopulmonary function. Recent dynamic or exercise studies have been most promising in this area. Methods to more effectively evaluate preoperative cardiopulmonary function are needed to identify which children may achieve symptomatic and physiologic improvement from surgical repair.

Echocardiographic Studies of Mitral Valve Prolapse

Bon Tempo, Salomon, and Schutte and their associates reported mitral valve prolapse in patients with narrow anterior-posterior chest diameters, anterior chest wall deformities, and scoliosis.⁵²⁻⁵⁴ Prospective echocardiographic studies of adults with pectus excavatum demonstrated mitral valve prolapse in six of 33 (18%) subjects studied by Udoshi and associates and in 11 of 17 subjects (65%) of Saint-Mezard and colleagues.^{55,56} Anterior compression of the heart by the depressed sternum may deform the mitral annulus or the ventricular chamber and produce mitral valve prolapse in these patients. Preoperative evaluation by echocardiogram of children and adolescents with pectus excavatum by Shamberger and associates identified 23 with mitral valve prolapse.⁵⁷ Postoperative studies did not demonstrate mitral valve prolapse in 10 (43%) of these children, suggesting its resolution after correction of the chest wall deformity.

Coln and coauthors performed echocardiography on subjects during exercise (123 preoperative and 107 postoperative).⁵⁸ They demonstrated chamber compression in 117 (95%) before surgery and in none of the patients after repair. They also found in subjects with chamber compression resolution of mitral valve prolapse (16 of 23) and mitral valve regurgitation (28 of 29) following repair as had been previously demonstrated by the author. Symptoms related to exertion reported in 106 (86%) of the subjects resolved remarkably in all, which was attributed to the cardiac effects of repair.

Surgical Repair

The first surgical corrections of pectus excavatum were reported by Meyer in 1911 and Sauerbruch in 1920, and Ochsner and DeBakey summarized the early experience with various techniques.^{18,59,60} In 1949, Ravitch reported a technique that included excision of all deformed costal cartilages with the perichondrium, division of the xiphoid from the sternum, division of the intercostal bundles from the sternum, and a transverse sternal osteotomy securing the sternum anteriorly in an overcorrected position.⁶¹ Kirschner wire fixation was used in the first two patients and silk suture fixation in later patients.

Baronofsky (1957) and Welch (1958) subsequently reported a technique for the correction of pectus excavatum that emphasized total preservation of the perichondrial sheaths as well as the attachment of the upper sheaths and intercostal bundles to the sternum.^{62,63} Anterior fixation of the sternum was achieved with silk sutures. Haller and associates later developed a technique which they labeled as *tripod fixation*.⁶⁴ Subperichondrial resection of the abnormal cartilages is performed followed by a posterior sternal osteotomy. The most cephalad normal cartilages are then divided obliquely in a posterolateral direction. When the sternum is elevated, the sternal ends of the cartilage rest on the costal ends, providing further anterior support of the sternum. Support of the sternum by metallic struts after mobilization of the costal cartilages has been promoted by several authors. Rehbein and Wernicke developed struts that could be placed into the marrow cavity of the ribs at the costochondral junction.⁶⁵ An arch was then formed by the struts anterior to the sternum, and the sternum was secured to this arch. Paltia and associates placed a transverse strut through the caudal end of the sternum, firmly fixing its location.⁶⁶ The two ends of the strut are supported by the ribs laterally. Adkins and Blades, and Jensen and associates, used retrosternal elevation by a metallic strut.^{67,67a} Willital used a similar retrosternal strut after creating multiple chondrotomies in the costal cartilages to provide flexibility.⁶⁸ Recent innovations in these methods include bioabsorbable struts, or use of Marlex mesh or a Dacron vascular graft as a strut, but there is no evidence these methods are preferable to traditional methods with metallic struts.⁶⁹ Robicsek and Fokin described a large series of chest wall deformities.⁷⁰ For those patients with pectus excavatum, the sternum is mobilized more extensively with this technique than in others, except for the sternal turnover. The sternum is divided from the intercostal muscles and perichondrial sheaths from its tip to

the upper extent of the deformity. It is then supported in an anterior position by a “hammock” of Marlex mesh, which is sewn to the ends of the ribs to each side. The advantages of this extensive mobilization and permanent implantation of the mesh are not clear. No randomized studies have compared the recurrence or complication rates between suture or strut fixation techniques. Oelsnitz and Hecker and coworkers, using suture fixation, reported satisfactory repairs in their large series in 90% to 95%.^{2,13}

The *sternal turnover* was first proposed by Judet and Judet in 1954 and Jung in 1956 in the French literature.^{71,72} The sternum is mobilized and the costal cartilages are divided, allowing the sternum to be rotated 180 degrees. Wada and colleagues in 1970⁷³ reported a very large series from Japan using this technique, which is essentially a free graft of sternum. It is a radical approach and has been associated with major complications if infection occurs. Modifications of this technique by Taguchi and associates in 1975 have involved either preservation of the internal mammary vessels by wide dissection or reimplantation of the internal mammary artery.⁷⁴ These modifications were developed because of the reported incidence of osteonecrosis and fistula formation, which occurred in up to 46% of patients older than 15 years.

Allen and Douglas implanted Silastic molds into the subcutaneous space to fill the depression in pectus excavatum.⁷⁵ Although this approach may improve the external contour of the chest, extrusion of the molds has occurred, and this method does nothing to increase the volume of the thoracic cavity or relieve compression on the heart. Other authors have reported favorable cosmetic results in adults with no pulmonary restrictions but with a significant frequency of seroma and hematoma formation.^{76,77} Schier and colleagues described use of a suction device placed over the chest in children and adults with pectus excavatum and early results were encouraging, although the durability of the correction was not established.⁷⁷ Haecker and Mayr⁷⁸ described a similar device. Although improvement was seen, only 14.7% of the patients had the sternum lifted to a “normal” position after 12 months of therapy.

A randomized postoperative study comparing the use of an epidural catheter versus patient-controlled analgesia for pain control demonstrated that pain scores favored the epidural approach early in the postoperative period and patient-controlled analgesia in the later period.⁷⁹ The epidural analgesia technique required longer time in the operating room, an increased number of calls to the pain service, and greater hospital charges.

Minimally Invasive Repair of Pectus Excavatum

A method of elevation of the sternum with a retrosternal bar without resection or division of the costal cartilages was first reported by Nuss in 1998.⁸⁰ He repaired 42 patients under 15 years of age (median age 5 years) by placing a convex steel bar under the sternum and anterior to the heart through small bilateral thoracic incisions. A long clamp was passed blindly behind the sternum and

out an opening in the contralateral chest (Fig. 24-3). A tape was then drawn across the chest in the clamp and used to pull the bar through the pleural cavity and anterior to the pericardium. The bar was initially placed with the concave side anteriorly and then it was rotated once it was in position (see Fig. 24-3). The bar was left in position for 2 years before removal when presumed permanent remodeling of the cartilages had occurred. Although Nuss in his initial report warned that the “upper limits of age for this procedure require further evaluation,” the technique has been widely used in older patients and Hebra and colleagues have reported the use of this technique in adults.⁸¹ In 2002 the results by Nuss and his associates using this technique in 303 patients were reported by Croitoru.⁸² This included an older group of children than in the initial report (range 21 months to 29 years; median age 12.4 years). Two bars were required in 12.5% of the patients. Routine use of thoracoscopy to avoid cardiac injury was instituted in 1998. Lateral stabilizers were placed in 69.4% of the cases and were routinely used after 1998 and were wired to the bar in 65.4% of cases. Recommended duration for leaving the bars in the chest is now 3 years. Epidural analgesic was used for 2 to 4 days and the median length of stay was 5 days with a range of 3 to 10 days. The frequency of early complications was low. They included pneumothorax requiring aspiration 1.0%, pericarditis 2.3%, with only 0.3% requiring drainage, pneumonia 0.7%, hemothorax 0.3%, transient extremity paralysis 0.3%, superficial wound infection 2.3%, and bar infection requiring eventual removal of the bar 0.7%.

Late complications in this series included bar displacement requiring repositioning in 8.6% of cases, which included a high proportion (over 50%) of patients in whom a stabilizer was not used or in patients where the stabilizer was not wired to the bar. When both modifications were used, displacement occurred in only 5% of the patients. An unexpected occurrence of allergies to the metal bar was encountered in 1% of the patients who presented with rashes in the area of the bars. This required conversion to bars composed of other alloys. Late hemothorax occurred in two patients, one secondary to undefined trauma. The occurrence of a mild overcorrection in the deformity was seen in 3.6% and a pectus carinatum deformity developed in 1.3%, all of whom had either Marfan syndrome or Ehlers-Danlos syndrome. The reported outcome of children in this large series was excellent appearance in 84.5%, good in 14.8%, and failed in only 1 patient; however, the bars had been removed at the time of the report in only 23.4% of the patients.

A more recent summary by Shin and associates of the infectious complications in a consecutive series of 863 patients showed a 1.5% incidence.⁸³ This included six bar infections, four cases of cellulitis, and three stitch abscesses. Antibiotics and surgical drainage resolved the infection in three of the bar infections, and removal of the bar was required in three patients (in one patient 3 months after surgery and in the other two patients 18 months after surgery). Organisms involved were predominantly *Staphylococcus aureus* in 83% of the cases. This success of preserving the struts despite infectious

complications was mirrored by the experience in two subsequent reports.^{84,85}

Allergy to the retrosternal bars was also identified in 2.2% of the patients having MIRPE by Nuss and his group.⁸⁶ Most patients (63%) presented with rash and erythema, 32% had pleural effusions, and 15% were diagnosed on preoperative screening. It is obviously critical to distinguish between allergic and infectious complications. The importance of placing the bars and stabilizers in a subcutaneous and not a submuscular position to

avoid extra osseous bone formation around the strut and increased blood loss at the time of removal has been demonstrated.⁸⁷

Hebra and associates reported the results of a survey of members of the American Pediatric Surgery Association who had used the minimally invasive (Nuss) technique.⁸⁸ Thirty institutions contributed 251 cases, although it should be noted that 42% were performed by one surgeon. The complications reported were similar to those of Nuss and his associates, but the frequency was

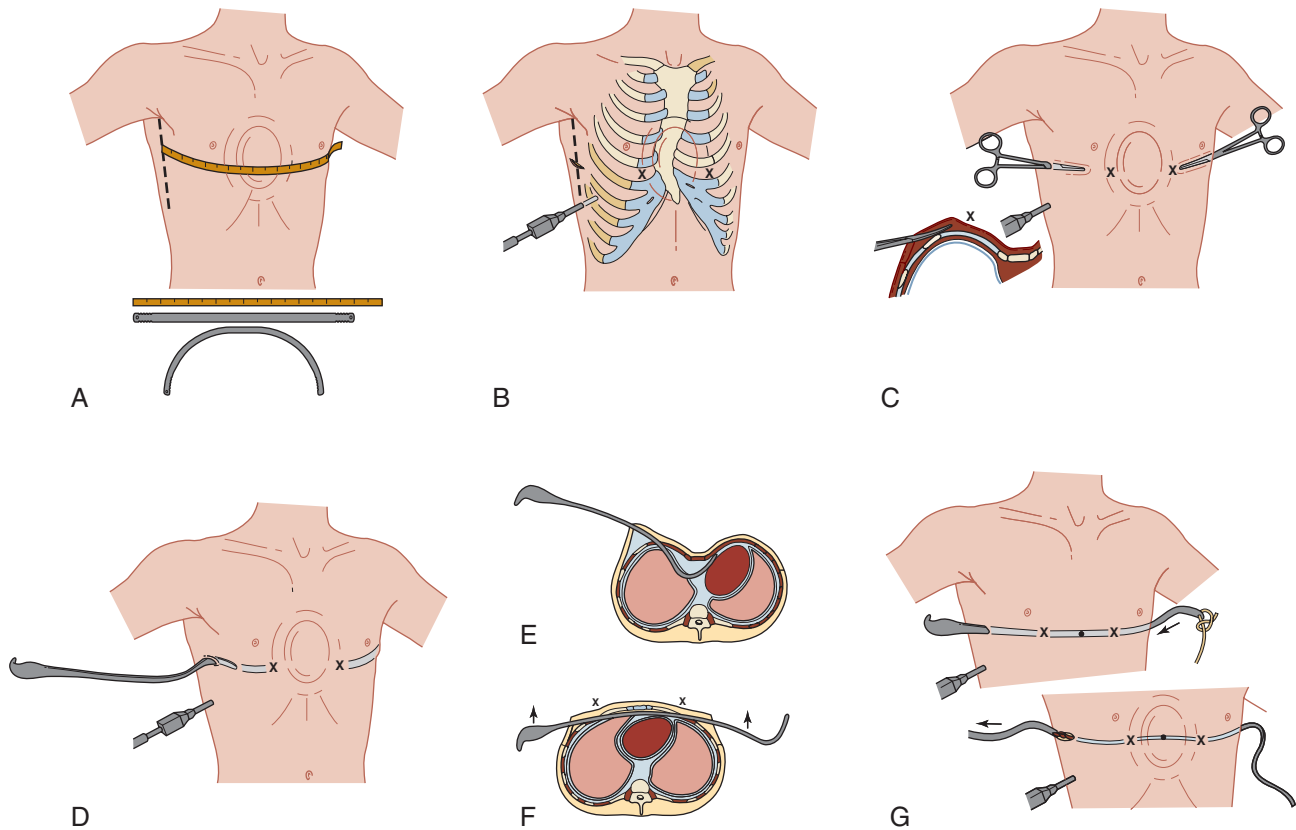


FIGURE 24-3 ■ **A**, The length of the pectus bar is determined by measuring the distance from the right midaxillary line to the left midaxillary line and subtracting 2 cm or 1 inch, because the bar takes a shorter course than the tape measure. The measurement is done over the area of the deepest depression that is still part of the sternum. The bar is bent to the desired convex configuration, making note that the center of the bar should be flat for 2 to 4 cm to allow greater stability. **B**, A thoracoscope is inserted into the right chest two intercostal spaces below the planned bar placement to check that the internal anatomy corresponds with the external markings and to look for unexpected pathology. If all is well, then the lateral thoracic incisions are made in the region of the midaxillary line and subcutaneous tunnels are created to the greatest apex of the pectus deformity (X). The X's represent the entrance and exit sites of the bar from inside the chest. They are in the intercostal space that is in the same horizontal place as the deepest depression, and care should be taken that they are placed medial to the greatest apex of the chest. **C**, Skin tunnels are created above the muscle starting from each of the lateral thoracic incisions to the top of the pectus ridge on each side. The tunnels should be created so that the entry and exit sites of the bar from inside the chest are medial to the top of the pectus ridge on each side. With the thoracoscope in place, a tonsil clamp is inserted into the subcutaneous tunnel on the right and a blunt thoracostomy is created at the site marked X, taking care not to injure the intercostal vessels, lung, or pericardium. **D**, Under continued thoracoscopic visualization, a pectus introducer (Biomet Microfixation, Jacksonville, FL) is inserted into the chest through the right tunnel and thoracostomy site at the top of the pectus ridge. With great care and thoracoscopic guidance, the pleura and pericardium are dissected off the undersurface of the sternum, creating a substernal tunnel. The introducer is slowly advanced across the mediastinum and brought out through the corresponding intercostal space on the left and advanced out of the incision on the contralateral side. Again, this exit site is medial to the top of the pectus ridge. **E**, A 30-degree thoracoscope facilitates visualization during the substernal dissection, and care is taken to keep the point of the dissector underneath the sternum at all times to push the heart out of the way of the dissection plane. During the dissection the ECG monitor should be turned to maximum volume to listen for any ectopy or arrhythmias. **F**, The introducer is pushed out of the thorax through the previously marked intercostal space (x) on the left and advanced out through the corresponding tunnel and incision. When the introducer is fully in place, the sternum is elevated by lifting the introducer on each side, thus correcting the pectus excavatum. The sternum is lifted out of its depressed position with the introducer numerous times. This is facilitated by pressing down on the lower chest wall while lifting the introducer. **G**, Once the sternal depression has been corrected, umbilical tape is attached to the introducer and the introducer is slowly withdrawn from the chest cavity with the umbilical tape attached.

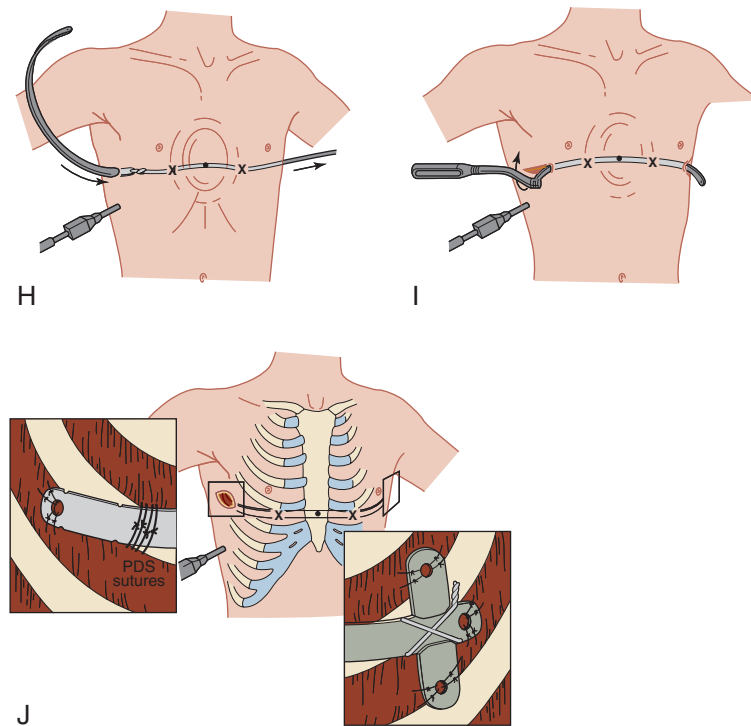


FIGURE 24-3, cont'd ■ H, The pectus bar that was previously bent into a convex shape is then attached to the umbilical tape and slowly guided through the right subcutaneous tunnel under thoracoscopic visualization and guided through the substernal tunnel with its convexity facing posteriorly until it emerges on the contralateral side. **I,** The pectus bar is positioned inside the chest with its convexity facing posteriorly and an equal amount of bar protruding on each side. Using the specially designed bar flippers (Biomet Microfixation, Jacksonville, FL), the bar is rotated 180 degrees giving instant correction to the pectus deformity. The sides of the bar should be resting comfortably against the musculature and should not be too tight or too loose. If the bar does not fit snugly on each side because of pressure on the middle, the bar can be reflipped and molded as necessary while still in place in the chest. **J,** The bar is stabilized by attaching a stabilizer to the left end of the bar and wiring the bar and stabilizer together with No. 3 surgical steel wire. The stabilizer and bar are also secured by placing numerous interrupted absorbable sutures through the holes in the bar and adjacent fascia. An additional stabilizing technique uses a laparoscopic "auto-suture" needle to place multiple 0 PDS or Vicryl sutures around the bar and underlying ribs with thoracoscopic guidance. (From Shamberger RC, Nuss D, Goretsky MJ: Surgical treatment of chest wall deformities. In Spitz L, Coran AG, editors: *Operative pediatric surgery*, ed 6, London, 2006, Hodder Arnold. With permission.)

higher, presumably because the procedures were performed by more individuals less familiar with the operation. Displacement of the bar occurred in 9.2% of cases and pneumothorax requiring tube thoracostomy in 4.8%. Less frequently encountered complications included thoracic outlet syndrome, pericarditis, blood loss requiring a transfusion, cardiac injury, persistent cardiac arrhythmias, and erosion of the sternum by the bar. Many of the surgeons had adopted the use of thoracoscopy to improve the safety of passing the clamp anterior to the heart. Other surgeons elevate the sternum with a bone hook during passage of the clamp to open the retrosternal space anterior to the heart.

Engum and coauthors reported their series of 21 patients with a mean age of 8.2 years.⁸⁹ Their patients had an average hospital stay of 4.9 days, which was comparable with that of the open repair. Complications encountered in their series were similar to the experience of others and included rotation of the bar, production of a marked pectus carinatum deformity, progressive chest wall asymmetry, and chronic persistent pain requiring removal of the bar in one case.

Molik and colleagues later enlarged this single institution review and in a retrospective analysis compared 68

patients with standard surgical repair with 35 patients with a Nuss repair.⁹⁰ The Nuss procedure required less time (3.3 hours) compared with the open technique (4.7 hours), but had a higher complication rate (43%) than the open method (20%). Four patients with the standard operation (6%) and eight with the Nuss technique (29%) required reoperation. Length of stay was comparable between the open (4.8 days) and Nuss (4.0 days) techniques. The Nuss patients had a higher frequency of epidural analgesics postoperatively and an increased duration of patient-controlled analgesia after surgery.

Fonkalsrud and associates reported a similar retrospective comparison of the two techniques, each used at one institution.⁹¹ During a 5-year interval, 68 patients had the minimally invasive procedure and 139 had the open technique. There was a higher incidence of reoperations and hospitalizations in the Nuss group, but it was noted that 90% of the complications of this method occurred in the first 25 cases, again clearly demonstrating the role of experience in determining the frequency of surgical complications. It was difficult to determine in this study whether the differences noted in the use of epidural catheters and intravenous narcotics was attributable to truly different patient requirements or was a

manifestation of institutional bias for analgesic techniques. There was a shorter mean hospitalization noted for the open procedure (2.9 days) compared with the minimal access procedure (6.5 days), and a similar difference between mean time before return to work or school (12 vs. 18 days). These authors concluded that “long-term follow-up also will be required to assure both health professionals and the public that this is the procedure of choice for patients with pectus excavatum.”

The occurrence of “overcorrection” of the deformity or production of a true carinate deformity was first reported by Croitoru and associates and was associated with underlying connective tissue disorders (Marfan syndrome and Ehlers-Danlos syndromes).⁸² It was reported, however, by Hebra to have occurred in an otherwise healthy 13-year-old boy 1 year after Nuss repair and by others following both MIRPE and open repair.^{92,93} What factors predispose some patients to this complication is not understood.

Other rare complications for the MIRPE include those of exsanguinating hemorrhage during removal of the strut resulting from laceration of a pulmonary vessel and bilateral sternoclavicular dislocation; cardiac tamponade and shock produced by erosion of the aorta by a strut that had rotated 90 degrees; and a near-fatal hemorrhage from erosion of the internal mammary vessel by a bar that had rotated 45 degrees.⁹⁴⁻⁹⁶ Thoracic outlet syndrome presenting with brachial plexus compression has also been reported following repair of a severe asymmetrical depression,⁹⁷ as has mechanical occlusion of the inferior vena cava at the level of the diaphragm, both of which were relieved by removal of the strut.⁹⁸

Kelly and colleagues have recently summarized their large experience with 1,215 patients with the MIRPE and reviewed the changes they have made to the procedure.⁹⁹ One bar was placed in 69% and two bars were required in 30% of their patients; 95.8% of the patients had a good or excellent surgical outcome at the time of bar removal. Complications with bar displacement decreased from 12% in the first decade to 1% in the second. Allergy to nickel was identified in 2.8% of patients, the vast majority prior to surgery. Wound infection occurred in 1.4% (17 patients) of whom 4 required surgical drainage. During the interval of this study, the median age at surgery has gone from 6 years to 14 years. Modifications of the technique that occurred during the duration of the study include routine use of unilateral or bilateral thoracoscopy; techniques to minimize risk of dissection between the sternum and heart in patients with severe depressions, including elevation of the sternum manually through an infraxiphoid incision or first placing a more superior transmediastinal tunnel and leaving the introducer in place, elevating the sternum while dissecting the lower tunnel; use of titanium bars when a metal allergy is identified; using a bar length that is 1 inch shorter than the measurement from right to left midaxillary line; more frequent use of two bars in patients with severe depressions or older patients; and use of a metal stabilizer to decrease the risk of rotation of the bar.

The MIRPE has also been used for patients with recurrent pectus depressions. A report of 100 patients demonstrated that this approach was generally safe and

effective but that patients with a prior MIRPE may have extensive pleural adhesions requiring decortication and patients with a prior open procedure may have acquired thoracic dystrophy and require multiple bars and are at a greater risk of complications.¹⁰⁰

A prospective multi-institutional study of patients undergoing repair of pectus excavatum has been completed. Early reports from this study suggest that the pain and complications from the MIRPE and open procedures are similar and that repair can be accomplished with limited risks to the patients.¹⁰¹ A subsequent report from this study demonstrated by use of a validated survey tool that preoperative psychosocial functioning was unrelated to the objective severity of the pectus depression by CT index.¹⁰² Both patients and their parents reported significant positive postoperative changes in both physical and psychosocial functioning, including less social self-consciousness and a more favorable body image.

Children should be followed long-term after repair by any technique until they reach full stature. Only by so doing can each surgeon assess the ultimate results of his or her surgical technique. Regrettably, recurrence can occur until full stature is achieved.

Open Surgical Repair of Pectus Excavatum

The open surgical technique for correction of pectus excavatum is depicted in [Figure 24-4](#). In girls, particular attention is taken to place the incision within the projected inframammary crease, thus avoiding the complications of breast deformity and development described by Hougaard and Arendrup.¹⁰³ Skin flaps are mobilized by electrocautery to the angle of Louis superiorly and a shorter distance to the xiphoid inferiorly. Pectoral muscle flaps are elevated off the sternum and costal cartilages, preserving the entire pectoralis major and portions of the pectoralis minor and serratus anterior muscles in the flap (see [Fig. 24-4A](#)). Ellis and associates have described elevating the skin and muscle together in a single flap, which is a reasonable but not widely adopted alternative method.¹⁰⁴

Perioperative antibiotics are used, giving one dose of cefazolin immediately before operation and three postoperative doses. The Hemovac drain (Snyder Laboratories, New Philadelphia, OH) is removed when the drainage is less than 15 mL for an 8-hour period. All patients are warned to avoid aspirin and nonsteroidal anti-inflammatory agent-containing compounds for 2 weeks before surgery.

The authors currently use the retrosternal bar (Baxter Healthcare, Deerfield, IL) for internal fixation to secure the sternum firmly in an anterior position and to avoid the need to skeletonize the sternum to achieve adequate mobility for suture fixation. Although correction of pectus excavatum is technically most easily performed in a young child, there is increasing concern about long-term recurrence in these children as well as impairment in the growth of the chest wall. Current practice is to delay surgery until the children are well into their pubertal growth. At this age, the chest has less remaining growth and opportunity for recurrence of the pectus

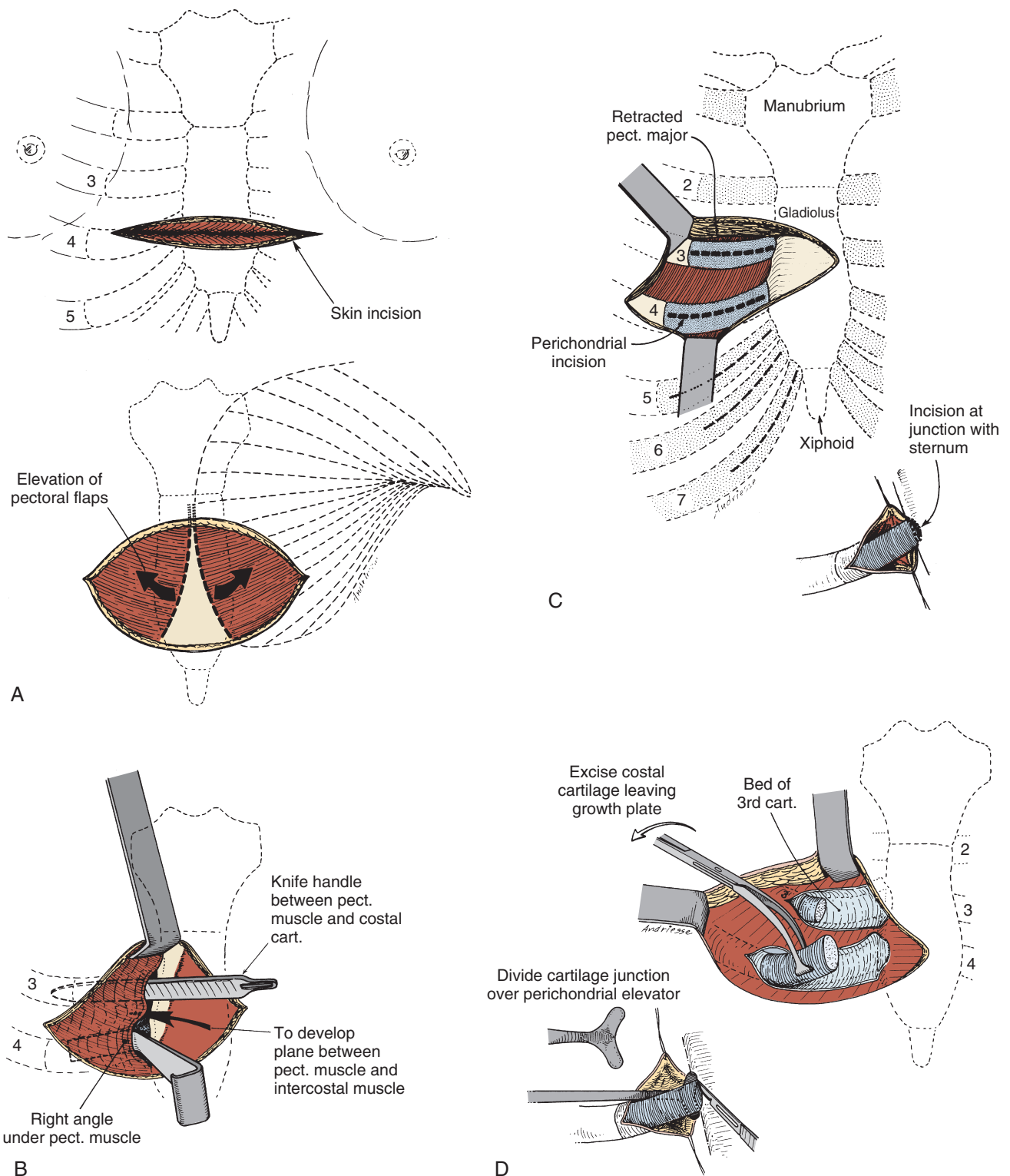


FIGURE 24-4 ■ Open surgical technique for repair of pectus excavatum. **A**, A transverse incision is placed below and well within the nipple lines and, in females, at the site of the future inframammary crease. The pectoralis major muscle is elevated from the sternum along with portions of the pectoralis minor and serratus anterior bundles. **B**, The correct plane of dissection of the pectoral muscle flap is defined by passing an empty knife handle directly anterior to a costal cartilage after the medial aspect of the muscle is elevated with electrocautery. The knife handle is then replaced with a right-angle retractor, which is pulled anteriorly. The process is then repeated anterior to an adjoining costal cartilage. Anterior distraction of the muscles during the dissection facilitates identification of the avascular areolar plane and avoids entry into the intercostal muscle bundles. Muscle elevation is extended bilaterally to the costochondral junctions of the third to fifth ribs and a comparable distance for ribs 6 and 7. **C**, Subperichondrial resection of the costal cartilages is achieved by incising the perichondrium anteriorly. It is then dissected away from the costal cartilages in the bloodless plane between perichondrium and costal cartilage. Cutting back the perichondrium 90 degrees in each direction at its junction with the sternum (*inset*) facilitates visualization of the back wall of the costal cartilage. **D**, The cartilages are divided at their junction with the sternum with a knife having a Welch perichondrial elevator held posteriorly to elevate the cartilage and protect the mediastinum (*inset*). The divided cartilage can then be held with an Allis clamp and elevated. The costochondral junction is preserved with a segment of costal cartilage on the osseous ribs by incising the cartilage with a scalpel. Costal cartilages three through seven are generally resected, but occasionally the second costal cartilages must be removed if posterior displacement or funneling of the sternum extends to this level, as may be seen in older patients (see Fig. 24-1). Segments of the sixth and seventh costal cartilages are resected to the point where they flatten to join the costal arch. Familiarity with the cross-sectional shape of the medial ends of the costal cartilages facilitates their dissection. The second and third cartilages are broad and flat, the fourth and fifth are circular, and the sixth and seventh are narrow and deep.

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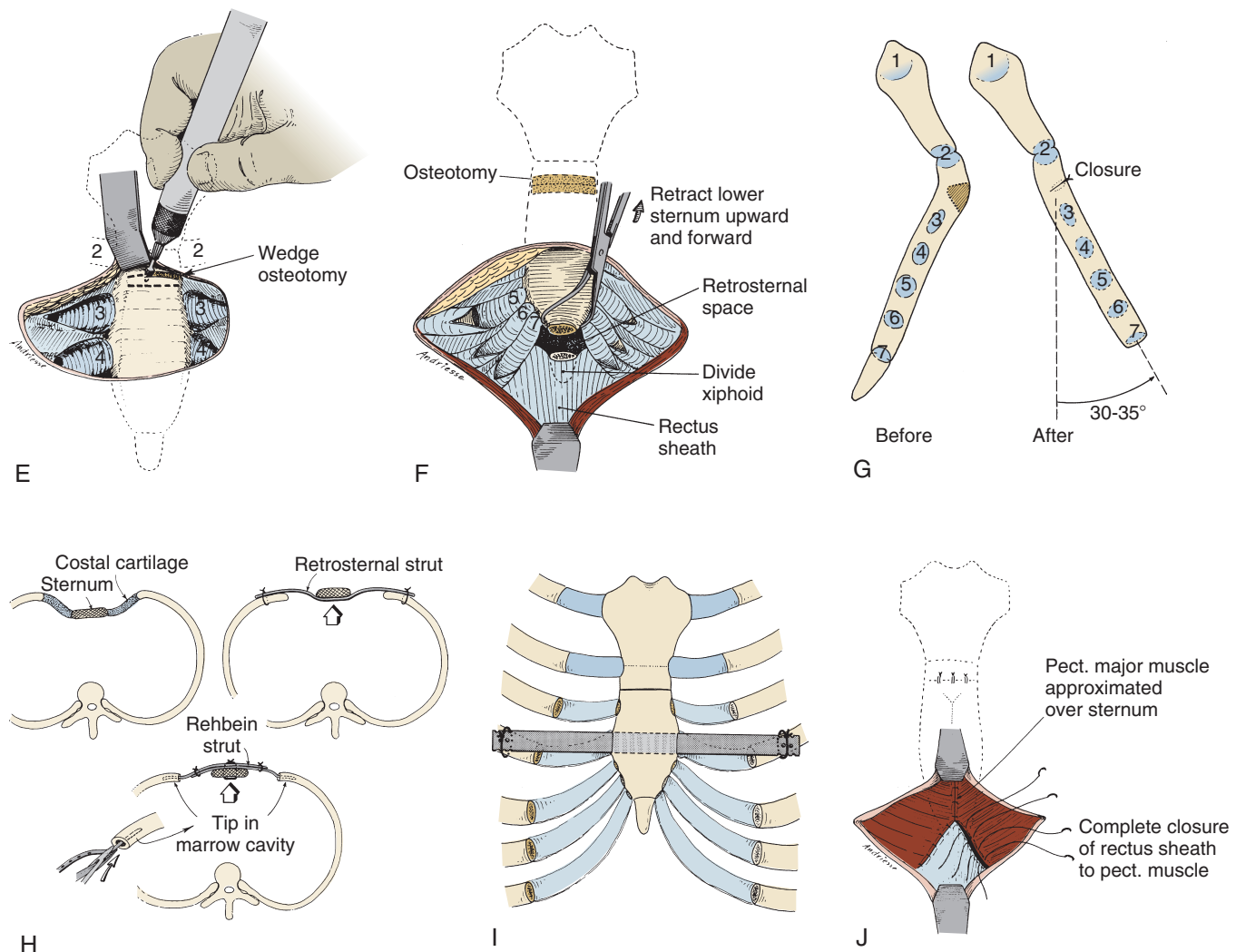


FIGURE 24-4, cont'd ■ **E**, The sternal osteotomy is created above the level of the last deformed cartilage and the posterior angulation of the sternum, generally the third cartilage but occasionally the second. Two transverse sternal osteotomies are created through the anterior cortex with a Hall air drill (Zimmer USA, Warsaw, IN) 3 to 5 mm apart. **F**, The base of the sternum and the rectus muscle flap are elevated with two towel clips, and the posterior plate of the sternum is fractured. The xiphoid can be divided from the sternum with electrocautery, allowing entry into the retrosternal space. This step is not necessary with the use of a retrosternal strut unless the xiphoid is protruding anteriorly when the sternum is in its corrected position. Preservation of the attachment of the perichondrial sheaths and xiphoid avoids an unsightly depression that can occur below the sternum. **G**, Correction of the abnormal position of the sternum is achieved by creation of a wedge-shaped osteotomy, which is then closed with elevation by the strut, bringing the sternum anteriorly into a slightly overcorrected position. **H**, This figure demonstrates the use of both retrosternal struts and Rehbein struts. Rehbein struts are inserted into the marrow cavity (*inset*) of the third or fourth rib, and the struts are then joined medially to create an arch anterior to the sternum. The sternum is sewn to the arch to secure it in its new anterior position. The retrosternal strut is placed behind the sternum and is secured to the rib ends laterally to prevent migration. **I**, Anterior depiction of the retrosternal strut. The perichondrial sheath to either the third or the fourth rib is divided from its junction with the sternum, and the retrosternal space is bluntly dissected to allow passage of the strut behind the sternum. It is secured with two pericostal sutures laterally to prevent migration. The wound is then flooded with warm saline and cefazolin solution to remove clots and inspect for a pleural entry. A single-limb medial Hemovac drain (Snyder Laboratories, New Philadelphia, OH) is brought through the inferior skin flap to the left of the sternum and placed in a parasternal position to the level of the highest resected costal cartilage. **J**, The pectoral muscle flaps are secured to the midline of the sternum, advancing the flaps inferiorly to obtain coverage of the entire sternum. The rectus muscle is then joined to the pectoral muscle flaps, closing the mediastinum. (**A-G** and **J**, From Shamberger RC, Welch KJ: Surgical repair of pectus excavatum. *J Pediatr Surg* 23:615–622, 1988. With permission; **D** and **F**, Adapted from original figures; **H** and **I**, From Shamberger RC: Chest wall deformities. In Shields TW, et al, editors: *General thoracic surgery*, ed 5, Philadelphia, 2000, Lippincott Williams & Wilkins.)

excavatum (Fig. 24-5). Fonkalsrud also recommends delay until at least 10 years of age because of recurrence most frequently occurring during pubertal growth.⁹¹ In contrast, Humphreys and Jaretzki and Backer and associates have found no correlation between the age at repair and frequency of recurrence.^{105,106}

Complications are few and relatively unimportant, except for major recurrence, which occurred in 17 of 704 patients in one series (Table 24-3).¹⁴ Pneumothorax occurred in 2% of the patients and required only observation or aspiration. Tube thoracostomy was required in only four patients in the entire series and in no patients

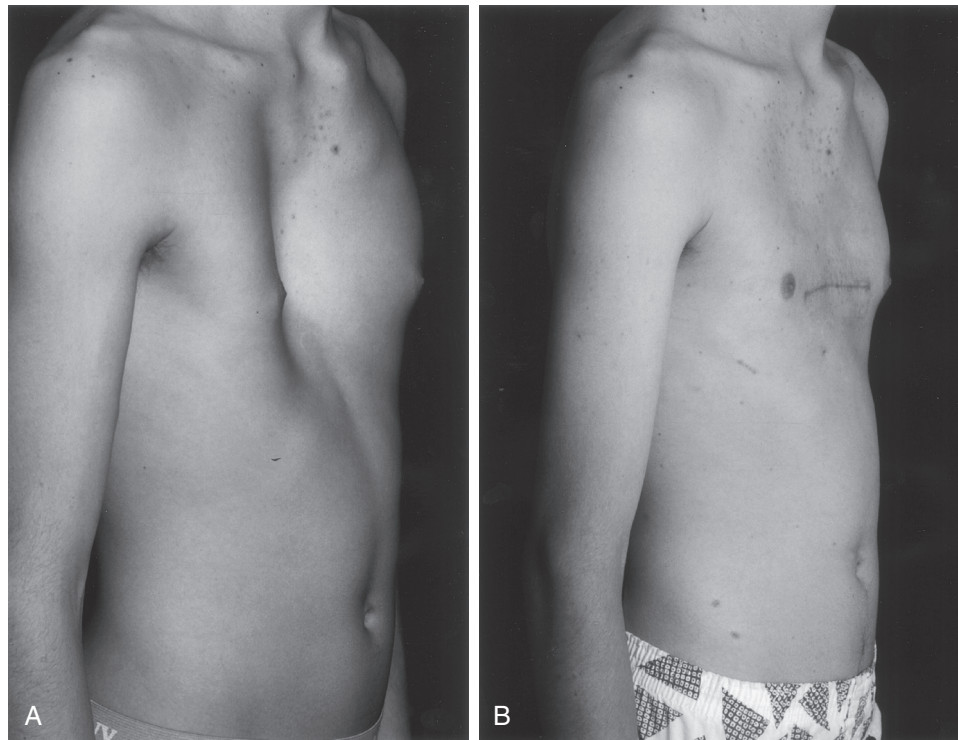


FIGURE 24-5 ■ **A**, Preoperative photograph of a 14-year-old boy with pectus excavatum. **B**, Postoperative photograph 7 months after repair using a retrosternal strut.

TABLE 24-3 Complications of Pectus Excavatum Repair: 70 Cases in 704 Patients

	Number of Cases
Pneumothorax*	11
Wound infection	5
Wound hematoma	3
Wound dehiscence	5
Pneumonia	3
Seroma	1
Hemoptysis	1
Hemopericardium	1
Major recurrence	17
Mild recurrence	23

*Four patients required chest tube placement.

From Shamberger RC, Welch KJ: *Surgical repair of pectus excavatum*. *J Pediatr Surg* 23:615–622, 1988. With permission.

during the last 2 decades of the report. Wound infection is rare with use of perioperative antibiotic coverage.

The most distressing complication after surgical correction of pectus excavatum is major recurrence of the deformity. It is difficult to predict which patients will have a major recurrence, but it appears to occur with increased frequency in children with poor muscular development and an asthenic or “marfanoid” habitus. All children with Marfan syndrome should be repaired with strut fixation because of the high risk of recurrence reported without strut fixation. Scherer and associates reported a low recurrence rate (1 of 8 cases) using a retrosternal strut.¹⁶ Redlinger and colleagues reported their results with the MIRPE procedure in patients with

Marfan syndrome (33 patients) and marfanoid features (212 patients).¹⁰⁷ The patients with Marfan syndrome had more severe deformities and required multiple bars for correction. The recurrence rate of these two groups was not significantly different from patients without Marfan syndrome or marfanoid features, and clinical results were similar between all groups.

Although recurrences appear symmetrical, many are in fact right sided, with a deep right parasternal gutter and sternal obliquity. The third, fourth, and fifth rib ends migrate medially, with apparent “foreshortening” of the costal cartilages. Correction of recurrent pectus excavatum is generally a formidable task. Sanger and associates reported their experience in secondary correction.¹⁰⁸ They resected the regenerated fibrocartilage plate, repeated the sternal osteotomy, and closed the pectoral muscles behind the sternum. Ten patients had an early good result. In the Boston Children’s Hospital experience, 12 children and adolescents underwent secondary repair. Resection of the segments of the third to fifth costal cartilages was necessary to correct the deformity. After clearing the tip of the sternum, resection of the left fibrocartilage plate to the level of the third or second perichondrial sheath allowed the sternum to be brought forward and rotated into an acceptable position. Ten of 12 repeat operations were accomplished without pleural entry. Follow-up of patients with secondary correction ranged from 10 to 17 years. Eight had acceptable thoracic contour, two had a broad shallow depression, and two had frank recurrence. I recommend use of strut fixation on all patients with secondary repair because cartilage regeneration will be slower and less adequate than that after primary operation. Successful repair of recurrent pectus

excavatum has also been reported using the MIRPE technique.^{109,110}

In 1990, Martinez and associates first described a deficiency in thoracic growth in children after repair of pectus excavatum during the preschool years.¹¹¹ Subsequently in 1996, Haller reported three boys who presented in their teens with apparent limited growth of the ribs after resection of the costal cartilages at an early age.¹¹² This produced a bandlike narrowing of the mid chest, which was labeled acquired Jeune disease by the authors (Fig. 24-6). In some cases, the first and second ribs in which the costal cartilages had not been resected had relative overgrowth, producing anterior protrusion of the upper sternum (see Fig. 24-6C). Haller attributed this to injury of the costochondral junctions during surgical repair.¹¹² As these junctions are the longitudinal growth centers for the ribs, early operation resulted in decreased growth of the ribs and of the sternum resulting from injury to its growth centers or vascular supply. Martinez and associates demonstrated experimentally in 6-week-old rabbits that resection of the costal cartilages produced a marked impairment in chest growth, particularly the anterior-posterior diameter, during a 5.5-month period of observation.¹¹¹ Less severe impairment occurred if only the medial three fourths of the costal cartilage was resected, preserving the growth centers at the costochondral junction. This impairment was attributed to fibrosis and scarring within the perichondrial sheaths. Perichondrial sheaths, bone, or other prosthetic tissues that cannot grow also should not be joined posterior to the sternum because they will form a bandlike stricture across the chest. This complication of delayed thoracic growth was described primarily in children repaired in early childhood and can be avoided by delaying surgery until the children are older. Preservation of the costochondral junction by leaving a segment of the cartilage on the osseous portion of the rib may partially minimize growth impairment. Weber and Kurkchubasche described a method of improving the severe pulmonary impairment

encountered in one patient with the “acquired Jeune syndrome.”¹¹³ A sternotomy was performed and wedged open permanently with rib struts. The pleura was opened bilaterally along with subperichondrial resection of six ribs. Pulmonary function was improved after the procedure in this patient. A subsequent report involving 10 patients further substantiates the efficacy of this technique to improve pulmonary function in 8 of the 10 cases.¹¹⁴ Patients are followed after surgery to full growth: age 16 for girls and age 19 for boys. Use of clinical and Moiré photography for initial evaluation and follow-up studies leads to improved clinical assessment of results and obviates the need for multiple radiographic examinations.¹¹⁵

PECTUS CARINATUM

Pectus carinatum, an anterior protrusion of the sternum or chest wall, is much less frequent than pectus excavatum: 16.7% of all chest wall deformities in the Boston Children’s Hospital experience. The anterior protrusion occurs in a spectrum of configurations often divided into four categories (Table 24-4).¹¹⁶ The most frequent form, termed *chondrogladiolar* by Brodtkin, consists of anterior protrusion of the body of the sternum with protrusion of the lower costal cartilages.¹¹⁷ It is described as appearing as if a giant hand had pinched the chest from the front, forcing the sternum and medial portion of the costal cartilages forward and the lateral costal cartilages and ribs inward (Fig. 24-7).¹¹⁸ Asymmetrical deformities with anterior displacement of the costal cartilages on one side and normal cartilages on the contralateral side are less common (Fig. 24-8). Mixed lesions have a carinate deformity on one side and a depression or excavatum deformity on the contralateral side, often with sternal rotation. Some authors classify these as a variant of the excavatum deformities. The least frequent deformity is the *chondromanubrial* or “pouter pigeon” deformity with protrusion

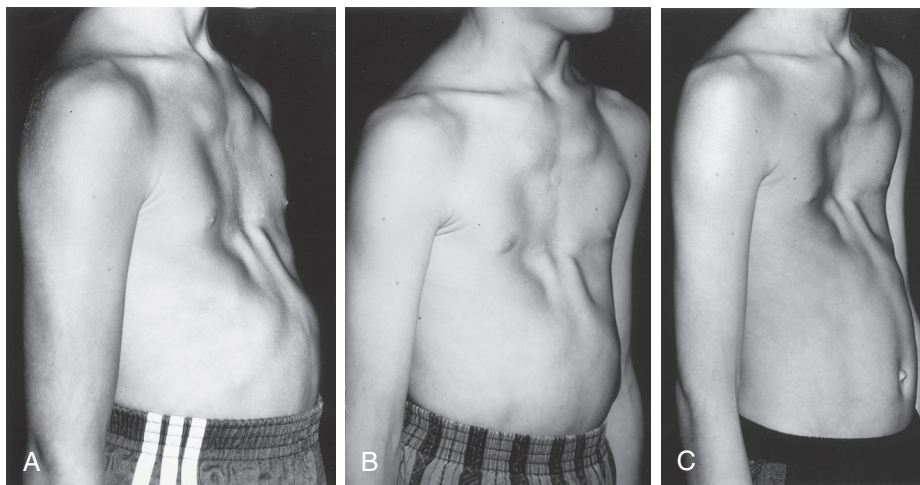


FIGURE 24-6 ■ Sequence of photographs demonstrating deterioration in the quality of a repair that can occur with time. This boy had an initial excellent result from a Welch repair with suture fixation of the sternum at age 4 years 3 months. The follow-up photographs at 7 years 6 months (A), 9 years 3 months (B), and 12 years 9 months (C) demonstrate progressive depression of the sternum and costal cartilages and relative “overgrowth” of the upper chest.

TABLE 24-4 Frequency of Pectus Carinatum Deformities

	Number of Cases
Chondrogladiolar	
Symmetrical	89
Asymmetrical	49
Mixed carinatum and excavatum	14
Chondromanubrial	3
Total number of cases	155

From Shamberger RC, Welch KJ: *Surgical correction of pectus carinatum*. *J Pediatr Surg* 22:48–53, 1987.

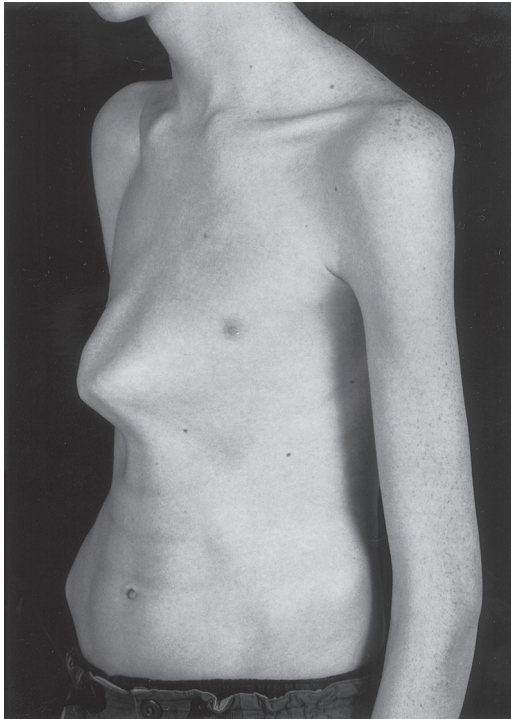


FIGURE 24-7 ■ Symmetrical chondrogladiolar pectus carinatum in a 11½-year-old boy.

of the upper chest involving the manubrium and second and third costal cartilages with relative depression of the body of the sternum (Fig. 24-9).

Cause

The cause of pectus carinatum is no better understood than that of pectus excavatum. It appears as an overgrowth of the costal cartilages with forward buckling of the cartilages and anterior displacement of the sternum. Again, there is a clear-cut increased family incidence, which suggests a genetic basis. In a review by the author and colleagues of 152 patients, 26% had a family history of chest wall deformity and 12% of scoliosis.¹¹⁶ It is much more frequent in boys than in girls by a 3 : 1 ratio. Scoliosis and other deformities of the spine are the most common associated musculoskeletal anomalies (Table 24-5).¹¹⁶

Pectus carinatum is rarely present at birth, and in almost one half of the patients, the deformity was not

TABLE 24-5 Musculoskeletal Abnormalities Identified in 30 of 152 Cases of Pectus Carinatum

	Number of Cases
Scoliosis	23
Neurofibromatosis	2
Morquio disease	2
Vertebral anomalies	1
Hyperlordosis	1
Kyphosis	1

From Shamberger RC, Welch KJ: *Surgical correction of pectus carinatum*. *J Pediatr Surg* 22:48–53, 1987. With permission.

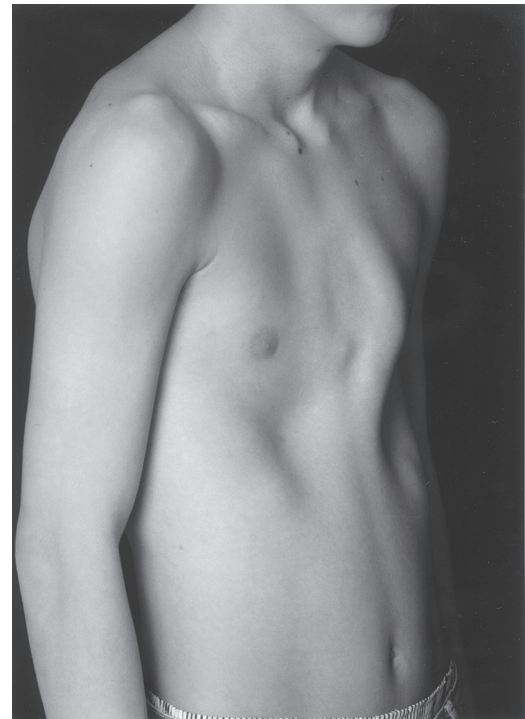


FIGURE 24-8 ■ A 15-year-old boy with marked asymmetrical pectus carinatum demonstrates protrusion of the costal cartilages limited to the left side of his chest.

identified until after the 11th birthday (Fig. 24-10). The deformity often progresses during early childhood, particularly in the period of rapid growth at puberty. The chondromanubrial deformity, in contrast with the chondrogladiolar form, is often noted at birth and is associated with a truncated, comma-shaped sternum with absent sternal segmentation or premature obliteration of the sternal sutures (Fig. 24-11). Currarino and Silverman described its association with an increased risk of congenital heart disease.¹¹⁹ Lees and Caldicott reviewed 1915 thoracic radiographs and identified 135 children with sternal fusion anomalies.¹²⁰ Eighteen percent of these children had documented congenital heart disease.

Surgical Repair

Correction of carinate deformities has had a colorful history, beginning with the first repair by Ravitch in 1952

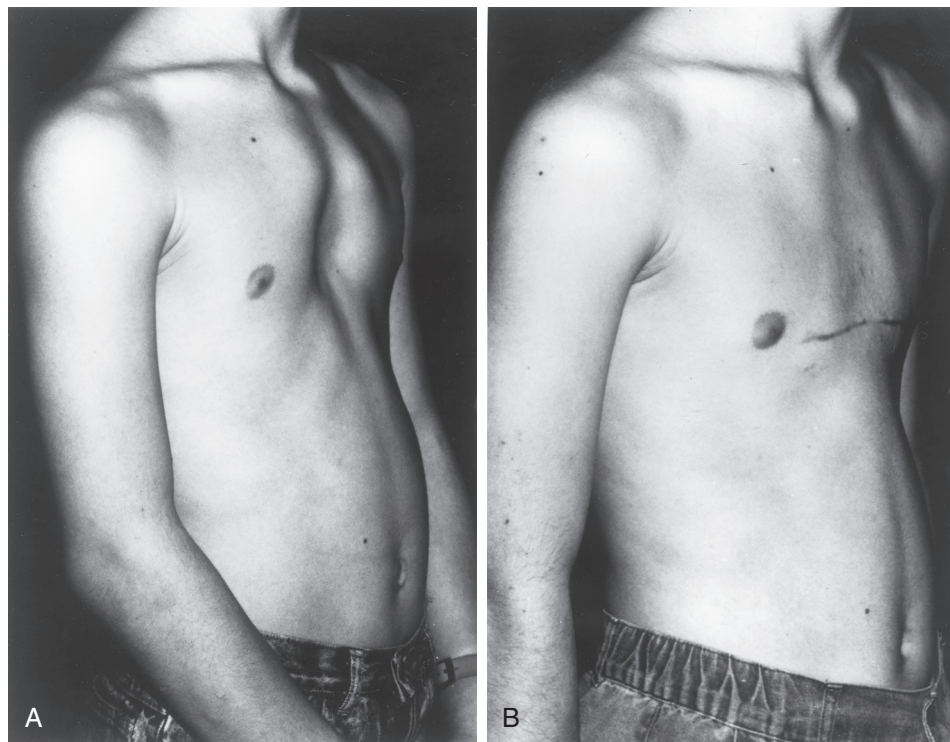


FIGURE 24-9 ■ **A**, A 15-year-old boy with the chondromanubrial deformity. Note the posterior depression of the lower sternum, accentuated by the anterior bowing of the second and third costal cartilages. **B**, After repair, the sternal contour is improved and costal cartilages are reformed in a more appropriate fashion.

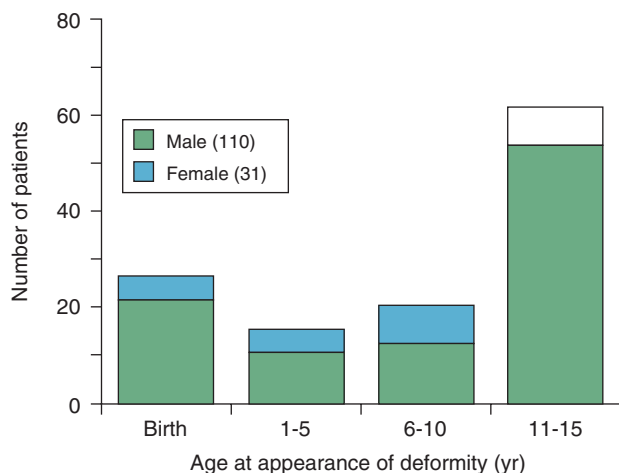


FIGURE 24-10 ■ Age at appearance of pectus carinatum deformity in 141 infants and children. Note the appearance of protrusion in almost one-half of the children at puberty. (From Shamberger RC, Welch KJ: Surgical correction of pectus carinatum. *J Pediatr Surg* 22:48–53, 1987. With permission.)

of an upper chondromanubrial deformity.¹²¹ He resected multiple costal cartilages and performed a double sternal osteotomy. In 1953, Lester reported two methods of repair for a lower chondrogladiolar deformity.¹²² The first approach, resection of the anterior portion of the sternum, was abandoned because of excessive blood loss and unsatisfactory results. The second method, subperiosteal resection of the entire sternum, was a no less radical technique. Chin (1957) and later Brodtkin (1958),

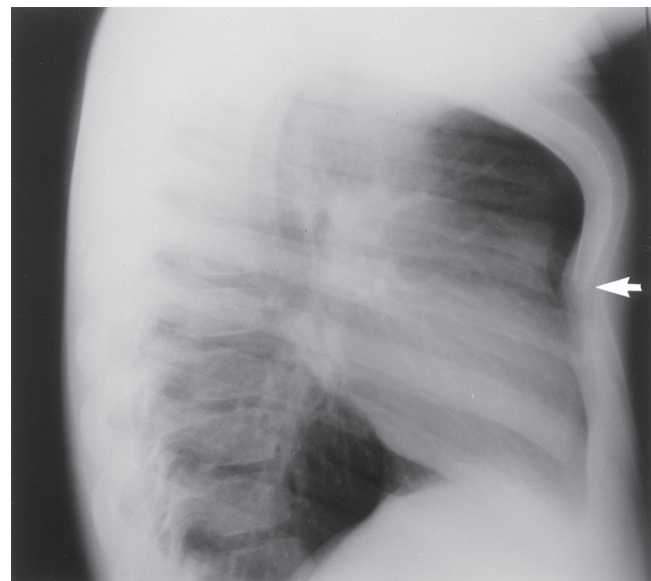


FIGURE 24-11 ■ Lateral chest radiograph of a boy with chondromanubrial pectus carinatum. The short, comma-shaped sternum lacking segmentation is apparent. Arrow is at the tip of the truncated sternum. (From Shamberger RC, Welch KJ: Surgical correction of chondromanubrial deformity [Currarino Silverman syndrome]. *J Pediatr Surg* 23:319–322, 1988. With permission.)

in a technique called the xiphosternopexy, advanced the transected xiphoid and the attached rectus muscles to a higher site on the sternum.^{123,124} This produced posterior displacement of the sternum in younger patients with a flexible chest wall. Howard combined this method with

subperichondrial resection of the costal cartilages and a sternal osteotomy.¹¹⁸ Ravitch reported repair of the chondrogladiolar deformity by resection of costal cartilage in a one- or two-stage procedure, with placement of “reefing” sutures to shorten and posteriorly displace the perichondrium.¹²⁵ A sternal osteotomy was used in one of three cases. Robicsek and associates described repair by subperichondrial resection of costal cartilages, transverse sternal osteotomy, and resection of the protruding lower portion of the sternum.¹²⁶ The xiphoid and rectus muscles were reattached to the new lower margin of the sternum, pulling it posteriorly. In 1973, Welch and Vos reported an approach to these deformities that I continue to use today.¹²⁷

Surgical Technique

The placement of the skin incision, mobilization of the pectoral muscle flaps, and subperichondrial resection of the involved costal cartilage are identical to the method described for pectus excavatum. Management of the sternum is shown in Figure 24-12 for the various deformities. In the chondromanubrial deformity, the costal cartilages must be resected from the second cartilage inferiorly.¹²⁸ A single-limb medium Hemovac drain (Snyder Laboratories, New Philadelphia, OH) is brought through the inferior skin flap, as for excavatum patients, with the suction ports in a parasternal position to the level of the highest resected costal cartilage. The pectoralis muscle flaps and skin flaps are closed. Perioperative antibiotics are used as in pectus excavatum.

Abramson and colleagues have reported a minimally invasive operation for pectus carinatum.¹²⁹ The technique involves placement of a subcutaneous curved steel bar via lateral thoracic incisions. Subperiosteal wires attach small

fixation plates to the ribs laterally, and the convex bar is secured to the small fixation plates with screws. Satisfactory results have been reported. Best results are seen in younger patients with a flexible chest wall, submuscular insertion of the bar, and use of stronger pericostal wire.

Operative Results

Results are overwhelmingly¹³⁰ successful in these patients. In a review of 152 cases, postoperative recovery was generally uneventful.¹¹⁶ Blood transfusions are rarely required, and none has been given in the last 10 years of the report. There is a 3.9% complication rate (Table 24-6). Only three patients have required revision, each having additional lower costal cartilages resected for persistent unilateral malformation of the costal arch.

Nonoperative Correction

Attempts to treat pectus carinatum by orthotic bracing have been reported, beginning in 1992 in Brazil. Evolution of bracing devices has led to an increased success rate, and presently several reports suggest that 65% to

TABLE 24-6 Complications of Pectus Carinatum Repair: 7 Cases in 152 Patients

	Number of Cases
Pneumothorax*	4
Atelectasis	1
Wound infection	1
Local tissue necrosis	1

*Two patients required chest tube placement.

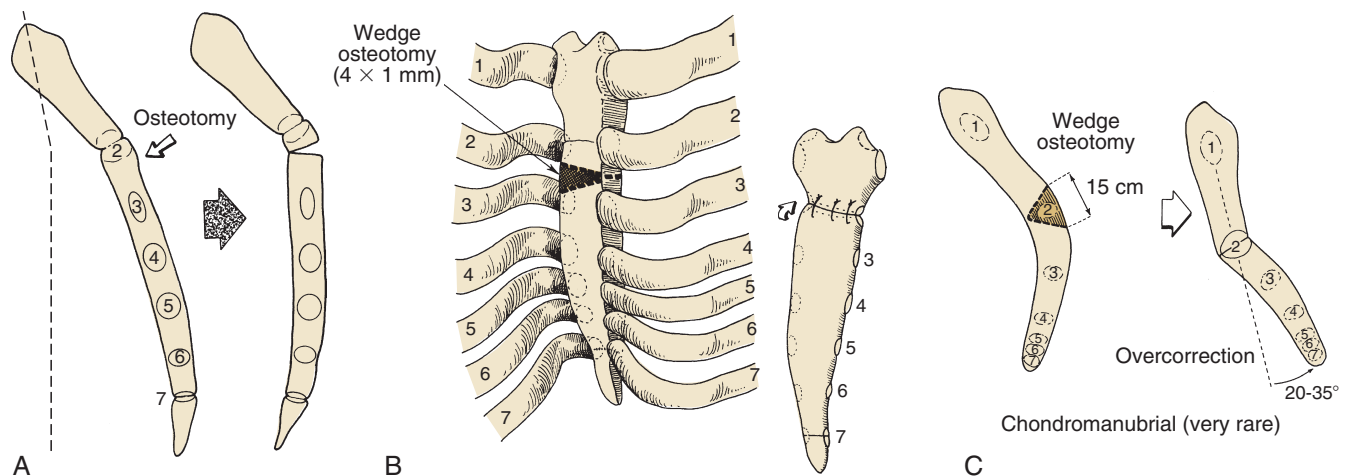


FIGURE 24-12 ■ **A**, A single or double osteotomy after resection of the costal cartilages allows posterior displacement of the sternum to an orthotopic position. **B**, The mixed pectus deformity is corrected by full and symmetrical resection of the third to seventh costal cartilages, followed by transverse offset (0- to 10-degree wedge-shaped sternal osteotomy). Closure of this defect achieves both anterior displacement and rotation of the sternum. **C**, The chondromanubrial type of deformity is depicted with a broad, wedge-shaped sternal osteotomy placed through the anterior cortex of the obliterated sternomanubrial junction. Closure of the osteotomy after fracture of the posterior cortex achieves a posterior displacement of the superior portion of the sternum, which is secured only by its attachment to the first rib. The lower portion of the sternum is overcorrected 20 to 35 degrees and is secured in position by strut or suture fixation. (**A** and **B**, From Shamberger RC, Welch KJ: Surgical correction of pectus carinatum. *J Pediatr Surg* 22:48-53, 1987. With permission; **C**, From Shamberger RC, Welch KJ: Surgical correction of chondromanubrial deformity. *J Pediatr Surg* 23:319-322, 1988. With permission.)

80% of children will have resolution with brace treatment alone.^{131-133,134,135} Compliance in using the brace is clearly the rate-limiting factor for success in older patients. Recently efforts have focused on making the brace easy to conceal and comfortable to wear. Bracing strategies that work toward incremental correction over several months have met with better success than previous efforts.^{132,136,137} In teenagers, poor compliance with bracing programs can be addressed by peer pressure at a bracing clinic along the lines of a spina bifida clinic.

This approach works optimally in patients with a symmetrical deformity and has been shown to result in acceptable results even in those with an asymmetrical configuration. The brace varies between institutions, but the primary factor in success of the brace is the patient's compliance with its use.^{138,139,140} Colozza recently reported on a quality-of-life questionnaire survey on patients who had treatment by bracing.^{140a} It revealed that most of the patients were satisfied with their appearance after treatment, experienced minimal pain from the bracing, and would use the brace again. Their self-esteem increased significantly after bracing.

POLAND SYNDROME

In 1841, Poland, while he was a medical student, described congenital absence of the pectoralis major and minor muscles associated with syndactyly.¹⁴¹ Despite a prior report of this entity by Froriep in 1839, the eponym Poland syndrome has been used since 1962, when Clarkson first applied it to a group of similar patients.^{142,143} Subsequent reports have described other components of the syndrome, including absence of ribs, chest wall depression, and abnormalities of the breasts. Each component of the syndrome occurs with variable severity. The extent of thoracic involvement may range from hypoplasia of the sternal head of the pectoralis major and minor muscles with normal underlying ribs to complete absence of the anterior portions of the second to fifth ribs and costal cartilages (Figs. 24-13 and 24-14). Breast involvement is frequent, ranging from mild hypoplasia to complete absence of the breast (amastia) and nipple (athelia) (see Fig. 24-13C).¹⁴⁴ Minimal subcutaneous fat and an absence of axillary hair are additional components of the syndrome. Hand deformities may include hypoplasia of the fingers (brachydactyly) and fused fingers (syndactyly), primarily involving the central three digits. The most severe expression of the anomaly, mitten or claw deformity (ectromelia), is rare.^{143,145} Extensive classification systems of the associated hand anomalies has been developed.¹⁴⁶ Poland syndrome may also occur in combination with Sprengel deformity, in which there is decreased size, elevation, and winging of the scapula.

Poland syndrome is present at birth and has an estimated incidence of 1 in 30,000 to 1 in 32,000.^{147,148} Abnormalities of the breast can be defined at birth by absence of the underlying breast bud and the hypoplastic nipple, which is often superiorly displaced. The cause of Poland syndrome is unknown. Bouvet and associates proposed hypoplasia of the ipsilateral subclavian artery as the origin of this malformation, but, as noted by David,

decreased blood flow to the extremity may be the result of decreased muscle mass of the hypoplastic limb rather than its cause.^{149,150} Although some forms of syndactyly are autosomal dominant traits, a similar pattern has not been demonstrated in patients with Poland syndrome, which is generally sporadic. Multiple cases within a family are rare although its appearance in one of two identical twins was described.¹⁵¹⁻¹⁵⁴ Poland syndrome is associated with a second rare syndrome, the Möbius syndrome: bilateral or unilateral facial palsy and abducens oculi palsy. Nineteen such cases have been identified, but a unifying cause is lacking. Familial occurrence of these two syndromes was reported.^{155,156} An unusual association between Poland syndrome and childhood leukemia has also been reported.^{157,158}

The Boston Children's Hospital experience with Poland syndrome (1970 to 1987) included 41 children and adolescents, of whom 21 were males.¹⁵⁹ The lesion was right sided in 23 patients, left sided in 17 patients, and bilateral in 1 patient. Hand anomalies were noted in 23 (56%) and breast anomalies in 25 (61%). In 10 children, the underlying thoracic abnormality required reconstruction, and in 3 children, rib or cartilage grafts were needed for complete repair.

Surgical Repair

Assessment of the extent of involvement of the various musculoskeletal components is critical for optimal thoracic reconstruction. If the deformity is limited to the sternal component of the pectoralis major and minor muscles without underlying chest wall deformity, there is little functional deficit and repair is unnecessary, except to facilitate breast augmentation in females (see Fig. 24-14). If the underlying costal cartilages are depressed or absent, repair must be considered to minimize the concavity, to eliminate the paradoxical motion of the chest wall if ribs are absent, and in girls to provide an optimal base for breast reconstruction. Ravitch reported correction of posteriorly displaced costal cartilages by unilateral resection of the cartilages; a wedge osteotomy of the sternum allowing rotation of the sternum; and fixation with Rehbein struts and Steinmann pins.¹⁰⁰ I have achieved suitable repair in most cases with bilateral costal cartilage resection and an oblique osteotomy, which corrects both sternal rotation and posterior displacement, as in the patients with mixed pectus carinatum and excavatum deformity (Fig. 24-15). The sternum is then displaced anteriorly and is supported with a retrosternal strut, which allows correction of the posteriorly displaced costal cartilages. An unappreciated carinate deformity is often present on the contralateral side, which accentuates the ipsilateral concavity (see Fig. 24-14B).

Absence of the medial portion of the ribs can be managed with split rib grafts taken from the contralateral side. These must be secured to the sternum medially and to the "dagger point" ends of the hypoplastic ribs laterally. The grafts can be covered with a prosthetic mesh if needed for further support. In these cases, it must be remembered that there is little tissue present between the endothoracic fascia and the fascial remnants of the pectoral muscles. Soft tissue coverage of the area can be

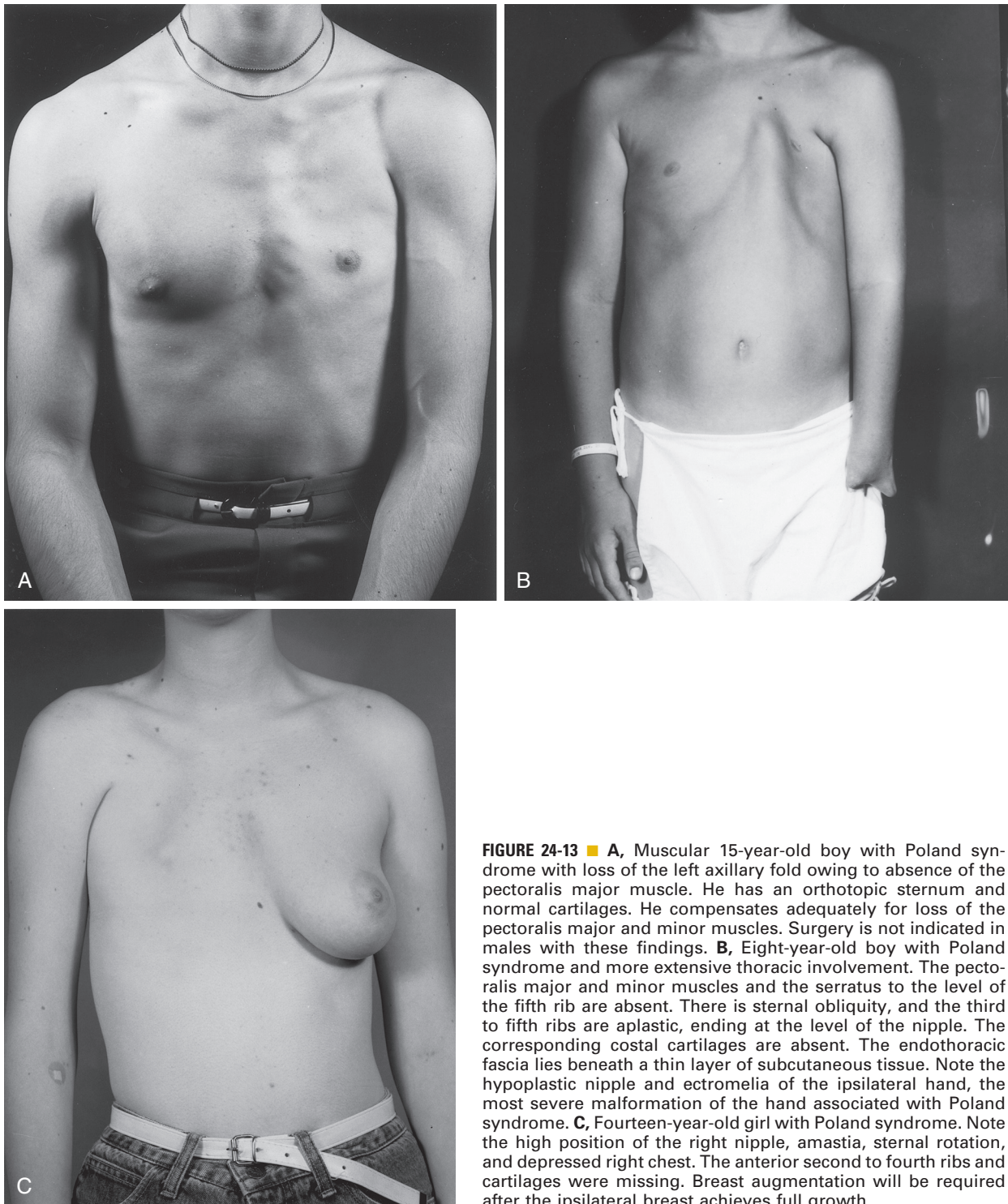


FIGURE 24-13 ■ **A**, Muscular 15-year-old boy with Poland syndrome with loss of the left axillary fold owing to absence of the pectoralis major muscle. He has an orthotopic sternum and normal cartilages. He compensates adequately for loss of the pectoralis major and minor muscles. Surgery is not indicated in males with these findings. **B**, Eight-year-old boy with Poland syndrome and more extensive thoracic involvement. The pectoralis major and minor muscles and the serratus to the level of the fifth rib are absent. There is sternal obliquity, and the third to fifth ribs are aplastic, ending at the level of the nipple. The corresponding costal cartilages are absent. The endothoracic fascia lies beneath a thin layer of subcutaneous tissue. Note the hypoplastic nipple and ectromelia of the ipsilateral hand, the most severe malformation of the hand associated with Poland syndrome. **C**, Fourteen-year-old girl with Poland syndrome. Note the high position of the right nipple, amastia, sternal rotation, and depressed right chest. The anterior second to fourth ribs and cartilages were missing. Breast augmentation will be required after the ipsilateral breast achieves full growth.

augmented with transfer of a latissimus dorsi muscle flap. This is particularly helpful in girls who will require breast augmentation.¹⁶⁰⁻¹⁶² Flap rotation is seldom, if ever, required in boys and has the disadvantage of adding a second posterior thoracic scar and decreasing the strength of the latissimus dorsi muscle.

Customized silicone prostheses can be used to correct both the chest wall depression and the absence of the breast.¹⁶³ Other recent innovations in repair include use

of Surgisis and a “swinging rib” or of a vertical expandable prosthetic rib system.¹⁶⁴

STERNAL DEFECTS

Sternal defects are rare compared with pectus excavatum and pectus carinatum, yet they have received a great deal of attention in the medical literature because of their

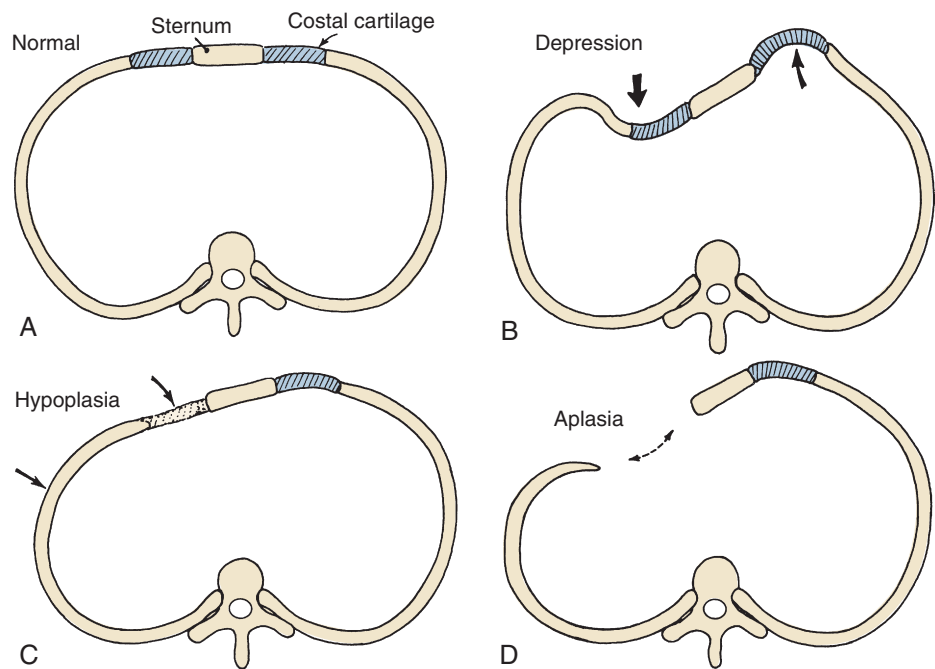


FIGURE 24-14 ■ The spectrum of thoracic abnormality seen in Poland syndrome. **A**, Most frequently, an entirely normal thorax is present, and only pectoral muscles are absent. **B**, Depression of the involved side of the chest wall, with rotation and often depression of the sternum. A carinate protrusion of the contralateral side is frequently present. **C**, Hypoplasia of ribs on the involved side but without significant depression may be seen. It usually does not require surgical correction. **D**, Aplasia of one or more ribs is usually associated with depression of adjacent ribs on the involved side and rotation of the sternum. (From Shamberger RC, Welch KJ, Upton J, III: Surgical treatment of thoracic deformity in Poland syndrome. *J Pediatr Surg* 24:760–765, 1989. With permission).

dramatic presentation and often fatal outcome. Deformities resulting from failure of ventral fusion of the sternum can be divided into four groups: (1) cleft sternum, (2) thoracic ectopia cordis, (3) thoracoabdominal ectopia cordis, and (4) cervical ectopia cordis. The heart is in a normal position in cleft sternum but is displaced in the other three entities. In thoracic ectopia cordis, the heart protrudes anteriorly and there are no tissues covering the heart. In cervical ectopia cordis, the protrusion is even more pronounced, and the heart is often fused with the head. In thoracoabdominal ectopia cordis, the heart is covered but often displaced into the abdomen through a defect in the diaphragm.

Cleft Sternum

An infant with cleft sternum has a complete or partial separation of the sternum but a normally positioned intrathoracic heart. This deformity results from failure of fusion of the sternal bars, which should occur approximately the eighth week of gestation. In all such cases, despite the sternal separation, normal skin coverage is present, with an intact pericardium and a normal diaphragm. Abdominal wall defects such as omphalocele do not occur in these children. The condition causes few functional problems. A dramatic increase in the protrusion of the deformity occurs with crying or Valsalva maneuver. The sternal defects described in 109 cases are summarized in Table 24-7.¹⁶⁵ The cleft involves primarily the upper sternum, whereas patients with thoracic or thoracoabdominal ectopia cordis have clefts primarily of the lower sternum.

TABLE 24-7 Sternal Defects Reported in 109 Cases of Cleft Sternum

	Number of Cases
Upper cleft	46
Upper cleft to xiphoid	33
Complete cleft	23
Lower defect with manubrium or midsegment intact	5
Central (skin ulceration noted in only three cases) defect with manubrium and xiphoid intact	2

From Shamberger RC, Welch KJ: Sternal defects. *Pediatr Surg Int* 5:156–164, 1990. With permission.

The second distinction between cleft sternum and the other sternal defects is that children with cleft sternum rarely have intrinsic congenital heart disease. An unexplained association does exist, however, between cleft sternum and cervicofacial hemangiomas, which were reported in 14 cases since the first description of this association by Fischer in 1879.¹⁶⁶

Surgical Repair

Maier and Bortone accomplished the first primary repair of cleft sternum in 1949 in a 6-week-old infant.¹⁶⁷ The flexibility of the newborn chest allows approximation of the sternal bars without producing cardiac compression (Fig. 24-16). A summary of the reported repairs for cleft sternum in 69 cases is shown in Table 24-8.

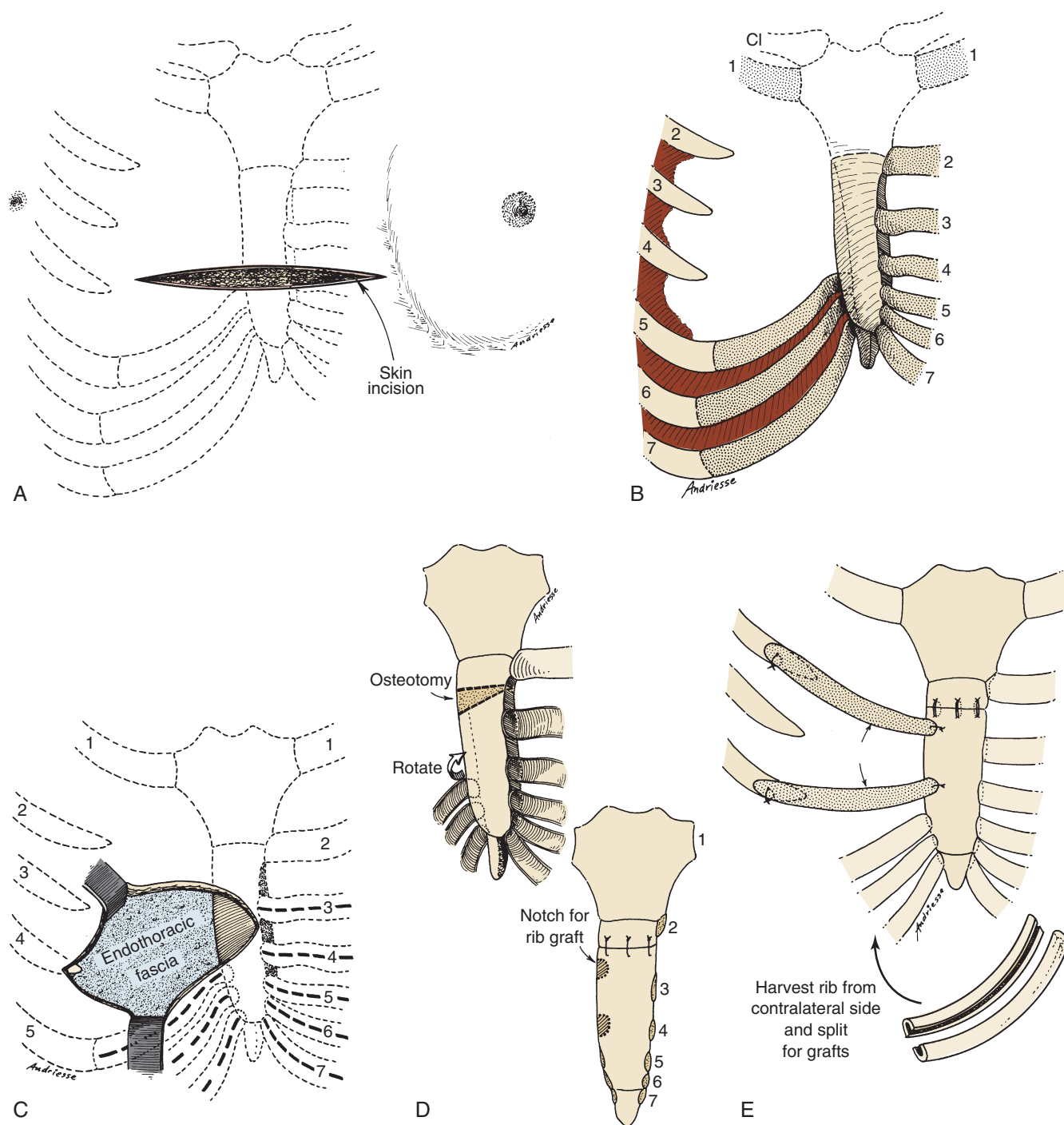


FIGURE 24-15 ■ **A**, A transverse incision is placed below the nipple lines and, in females, in the inframammary crease. **B**, Schematic depiction of the deformity, with rotation of the sternum, depression of the cartilages of the involved side, and carinate protrusion of the contralateral side. **C**, In patients with aplasia of the ribs, the endo-thoracic fascia is encountered directly below the attenuated subcutaneous tissue and pectoral fascia. The pectoral muscle flap is elevated on the contralateral side and the pectoral fascia, if present, on the involved side. Subperichondrial resection of the costal cartilages is then carried out, as shown by the **bold dashed lines**. Rarely, this must be carried to the level of the second costal cartilages. **D**, A transverse, offset, wedge-shaped sternal osteotomy is created below the second costal cartilage. Elevation of the sternum with a retrosternal strut corrects both the posterior displacement and the rotation of the sternum. **E**, In patients with rib aplasia, split rib grafts are harvested from the contralateral fifth or sixth rib and then secured medially with wire sutures into previously created sternal notches and with wire to the native ribs laterally. Ribs are split, as shown, along their short axis to maintain maximum mechanical strength. (From Shamberger RC, Welch KJ, Upton J, III: Surgical treatment of thoracic deformity in Poland's syndrome. *J Pediatr Surg* 24:760-765, 1989. With permission.)

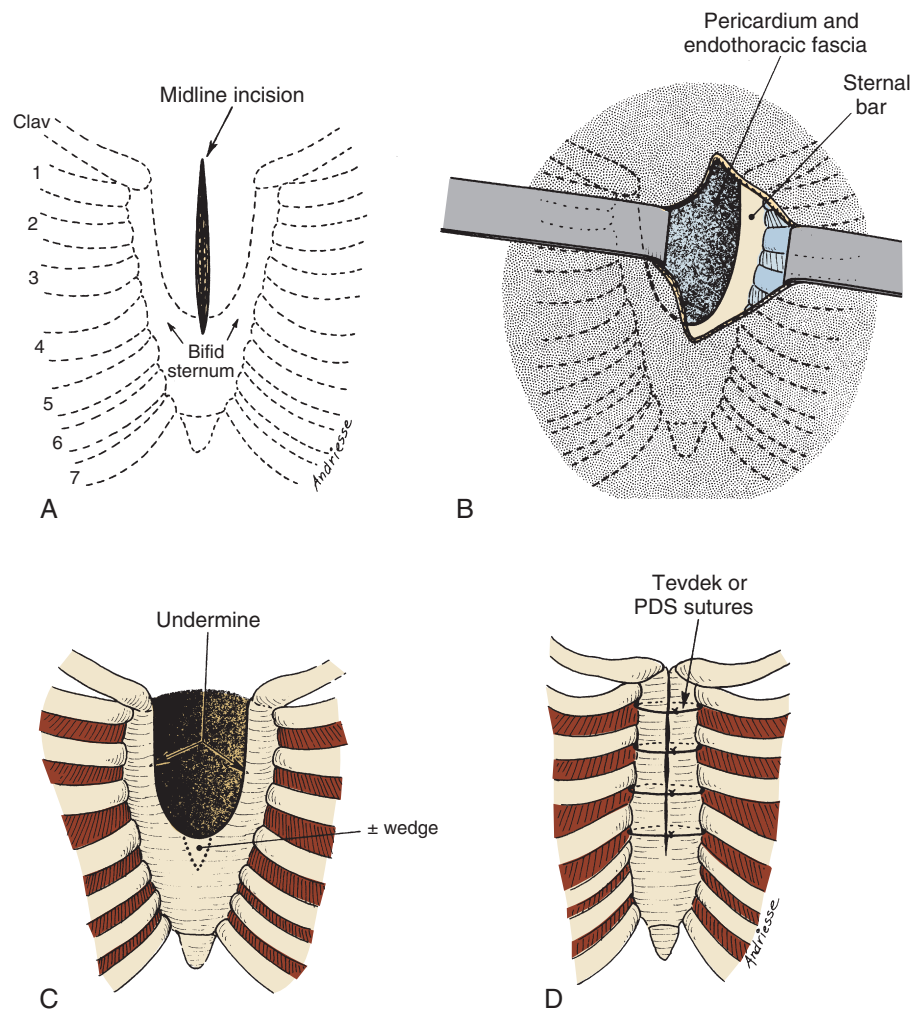


FIGURE 24-16 ■ **A**, Repair of bifid sternum is best performed through a longitudinal incision extending the length of the defect. **B**, Directly beneath the subcutaneous tissues the sternal bars are encountered, with pectoral muscles present lateral to the bars. **C**, The endothoracic fascia is mobilized off the sternal bars posteriorly with blunt dissection to allow safe placement of the sutures. Approximation of the sternal bars may be facilitated by excising a wedge of cartilage inferiorly. **D**, Closure of the defect is achieved with 2-0 Tevdek or PDS (Ethicon, Sommerville, NJ) sutures. (From Shamberger RC, Welch KJ: Sternal defects. *Pediatr Surg Int* 5:156–164, 1990. With permission.)

TABLE 24-8 Methods of Repair of Cleft Sternum in 69 Cases	
	Number of Cases
Primary approximation and repair	25
Primary repair with sliding chondrotomies (Sabiston)	19
Primary repair with rotating chondrotomies (Meissner)	3
Primary repair with other chondrotomy	4
Bone or cartilage graft	8
Prosthetic mesh graft	4
Sternocleidomastoid muscle transposition	3
Transposition of local soft tissues	2
Skin closure with excision of ulcer	1

From Shamberger RC, Welch KJ: Sternal defects. *Pediatr Surg Int* 5:156–164, 1990. With permission.

Sabiston reported reconstruction of cleft sternum using multiple oblique chondrotomies.¹⁶⁸ The chondrotomies increase the chest wall dimensions and flexibility. The technique is useful in older infants and children with a less flexible chest and a wide defect. Meissner described a variation of repair in which the cartilages are divided laterally and swung medially to cover the defect.¹⁶⁹ Autologous grafts of costal cartilage, split ribs, and segments of the costal arch have been used since Burton first repaired this defect with a portion of the costal arch.¹⁷⁰ Repairs with prosthetic material are far less satisfactory because of the risks of infection and the inability of these tissues to grow with the child. Most authors now recommend treatment of cleft sternum in the newborn period, when simple direct closure is possible without the use of prosthetic materials or grafts.

Ectopia Cordis

Although treatment of isolated cleft sternum is routinely successful, surgical repair of ectopia cordis, particularly

thoracic ectopia cordis, has a high mortality rate. The lethal factor in thoracic ectopia cordis and cervical ectopia cordis is the extrathoracic location of the heart, which makes tissue coverage difficult. In thoracoabdominal ectopia cordis (the Cantrell pentalogy), the major impediment to survival is the high incidence of intrinsic congenital heart disease.¹⁷¹

Cause

The cause of thoracic ectopia cordis and thoracoabdominal ectopia cordis is much debated. Some consider these anomalies to be the result of disruption of the amnion and possibly disruption of the chorionic layer or yolk sac as well.¹⁷²⁻¹⁷⁵ This disruption occurs during the third or fourth week of gestation at a time when cardiac chamber formation is occurring rapidly. This timing may account for the high incidence of abnormal cardiac development. Von Praagh (personal communication, 1987) has the intriguing notion, based on embryology studies by Patten and Bremer, that acute hyperflexion of the craniocervical segment of the embryo pins the heart down in the extrathoracic position with the submental cardiac apex.^{176,177} The abnormal fetal configuration produced by oligohydramnios may persist to delivery and oppose traction by the gubernaculum cordis, which normally pulls the cardiac apex into caudal alignment. Chromosome abnormalities have been reported.¹⁷⁸⁻¹⁸⁰

Thoracic Ectopia Cordis

Thoracic ectopia cordis is one of the most dramatic occurrences in the delivery room (Fig. 24-17). The naked beating heart is external to the thorax. Clearly visible are the atrial appendages, coronary vasculature, and cephalic orientation of the cardiac apex. The gubernaculum cordis initially extends to the supraumbilical raphe. Thoracic ectopia cordis was first reported by Stensen in 1671.¹⁸¹ Stensen's report was later translated by Willis.¹⁸² Stensen identified the four components of the tetralogy of Fallot in this patient with thoracic ectopia cordis. Cardiac anomalies are unusually frequent in thoracic ectopia



FIGURE 24-17 ■ An infant with thoracic ectopia cordis with no abdominal wall defect. The cardiac apex is cephalad. Any movement of the heart resulted in bradycardia and arrest. The patient had complex tetralogy of Fallot.

cordis. Table 24-9 lists the associated cardiac anomalies reported up to 1990. Only 4 of 75 cases had no intrinsic cardiac anomalies.

Infants with thoracic ectopia cordis are severely deficient in the midline somatic tissues that normally cover the heart. Many attempts at primary closure fail because of the inability to mobilize adequate tissues for coverage. An abdominal defect is often present as well. Recent computed tomogram evaluation by Haynor and associates also shows reduced intrathoracic volume in these infants.¹⁸³ Most allegedly successful repairs have been not of true thoracic ectopia cordis but, rather, of thoracoabdominal ectopia cordis. Cutler and Wilens first attempted repair in 1925 by skin flap coverage but failed because of cessation of cardiac function, presumably from compression of the heart.¹⁸⁴ Only 3 survivors of more than 29 attempts have been recorded (Table 24-10).

The first successful repair of ectopia cordis was achieved by Koop in 1975 and was reported by Saxena.¹⁸⁵ An infant with a normal heart had skin flap coverage at 5 hours of age, with inferior mobilization of the anterior attachments of the diaphragm. The sternal bars were 2 inches apart and could not be approximated primarily without cardiac compression and compromise. When the infant was 7 months old, an acrylic resin of Dacron and Marlex mesh was inserted to close the sternal cleft, followed by primary skin closure. Necrosis of the skin flaps complicated the postoperative course with infection of the prosthetic material, which was later removed. This child was well at 20-year follow-up.

Successful closure in two other infants is reported. Dobell and associates also achieved closure in two

TABLE 24-9 Intrinsic Cardiac Lesions Reported: 75 Cases of Thoracic Ectopia Cordis

	Number of Cases
Tetralogy of Fallot	16
Pulmonary artery stenosis	6
Transposition of great arteries and pulmonary artery stenosis or atresia	8
Patent ductus arteriosus (PDA)	2
Tricuspid and pulmonary atresia	3
Ventricular septal defect (VSD) and atrial septal defect (ASD)	6
VSD	5
ASD and PDA	4
ASD	1
Truncus arteriosus	3
Coarctation, ASD, and PDA	1
Coarctation	1
Aortic hypoplasia	1
Double-outlet left ventricle	2
Double-outlet right ventricle	2
Aortic stenosis, ASD, and PDA	1
Single atrium, single ventricle	3
Double atrium, single ventricle	3
Cor triatriatum	1
Aberrant right subclavian artery	1
Bilateral superior vena cava*	1
Normal	4

*Also present in association with many of the listed anomalies.
From Shamberger RC, Welch KJ: Sternal defects. *Pediatr Surg Int* 5:156-164, 1990. With permission.

TABLE 24-10 Reported Survivors of Thoracic Ectopia Cordis and Their Repair

Author	Year	Cardiac Lesion	Method of Sternal Closure
Koop and Saxena	1975	None	Skin flap closure at 5 hr. Acrylic resin applied to sternal cleft at 7 months.
Dobell	1982	None	Perinatal skin closure in one stage. Second-stage repair with skin grafts.
Amato, Cotroneo, & Gladieri	1988	None	Skin flaps mobilized, diaphragm moved inferiorly, Gore-Tex* membrane used to close defect with skin flaps over it. Child survived but died of aspiration at 11 months of age.

*Gore-Tex: W. L. Gore & Associates, Flagstaff, AZ.
From Shamberger RC, Welch KJ: Sternal defects. *Pediatr Surg Int* 5:156–164, 1990. With permission.

stages.¹⁸⁶ Skin flap coverage was provided for the newborn. Rib strut grafts were placed over the sternal defect at 19 months of age and covered with pectoral muscle flaps. The pericardium was divided from its anterior attachments to the chest wall, allowing the heart to fall back partially into the thoracic cavity. Only Amato and colleagues achieved complete coverage of the heart in one stage.¹⁸⁷ The unifying theme of successfully managed cases is mobilization of adequate soft tissue to cover the heart in its extrathoracic location and avoiding attempts to return the heart to an orthotopic location. Of note, in the successful cases, intrinsic cardiac lesions and associated abdominal defects were absent. These are the characteristics that most distinguish the successes from the failures, rather than any differences in surgical techniques. Coverage of the heart with autologous tissues, whether by flap rotation or bipedicle flaps, generally produces excessive compression on the heart, which limits cardiac output either by kinking outflow vessels or by impeding cardiac filling. In most cases, attempts are abandoned in the operating room because of severe impairment of cardiac function. In patients who are repaired with autologous tissue grafts (bone or cartilage) or synthetic materials, infection and extrusion of the graft invariably occur. Ultimate success with this lesion will be achieved only by accomplishing tissue coverage of the heart that avoids posterior displacement into an already limited thoracic space. This will require use of tissues from sites distant from the chest wall or engineered tissue materials. Severe intracardiac defects associated with thoracic ectopia cordis in most cases also limit survival. The only recent advancement in management of this lesion has been early ultrasonographic diagnosis, including definition of the intracardiac lesion and termination of the pregnancy, if acceptable to the parents.^{188,189}

Abdominal wall defects are also frequent in these patients, including an upper abdominal omphalocele or diastasis recti and, rarely, eventration of the abdominal viscera (Fig. 24-18). Associated abdominal wall defects are summarized in Table 24-11. The presence of abdominal defects should not, however, lead to classification of these lesions as thoracoabdominal ectopia cordis. This term should be reserved for those infants in whom the heart is covered at birth.

Thoracoabdominal Ectopia Cordis (Cantrell Pentalogy)

In thoracoabdominal ectopia cordis, the heart is covered by an omphalocele-like membrane or thin skin, which is



FIGURE 24-18 ■ Infant with thoracic ectopia cordis (arrow) and eventration of the abdominal viscera. (From Shamberger RC, Welch KJ: Sternal defects. *Pediatr Surg Int* 5:156–164, 1990. With permission.)

TABLE 24-11 Abdominal Wall Defects Reported in 75 Cases of Thoracic Ectopia Cordis

	Number of Cases
Omphalocele	36
Diastasis recti (or ventral hernia)*	6
Eventration	4

*Often covered by thin, pigmented dermis.
From Shamberger RC, Welch KJ: Sternal defects. *Pediatr Surg Int* 5:156–164, 1990. With permission.

often pigmented. The sternum is generally cleft inferiorly, and the heart lacks the severe anterior rotation present in thoracic ectopia cordis. An early report of this lesion by Wilson in 1798 clearly defined the associated somatic defects of the abdominal wall, diaphragm, and pericardium (Fig. 24-19), as well as the intrinsic cardiac anomalies. This entity was subsequently reviewed by Major in 1953 and Cantrell and associates in 1958.^{171,190} It is now frequently called Cantrell pentalogy, although it was described long before Cantrell's relatively recent review. The five essential features of thoracoabdominal ectopia cordis are a cleft lower sternum, a half moon-shaped anterior diaphragmatic defect resulting from lack of development of the septum transversum, absence of the parietal pericardium at the diaphragmatic defect,



FIGURE 24-19 ■ Newborn male with thoracoabdominal ectopia cordis. The head is to the left. Note the epigastric omphalocele extending superior to the umbilicus. The cardiac apex was visible below the costal arch just at the superior aspect of the omphalocele.

TABLE 24-12 Abdominal Wall Defects Reported in Patients with Thoracoabdominal Ectopia Cordis

	Number of Cases
Omphalocele	64
Diastasis recti (or ventral hernia)	40
Diaphragmatic defect	71
Pericardial defect	46

From Shamberger RC, Welch KJ: *Sternal defects. Pediatr Surg Int* 5:156–164, 1990. With permission.

omphalocele (Table 24-12), and, in most patients, an intrinsic cardiac anomaly (Table 24-13; see Fig. 24-19). A left ventricular diverticulum occurs with surprising frequency in patients with this anomaly. In many cases, the diverticulum protrudes through the diaphragmatic and pericardial defects into the abdominal cavity.

Successful repair and long-term survival are more frequent in thoracoabdominal ectopia cordis than in thoracic ectopia cordis. Arndt attempted the first repair in 1896, but return of the heart to the thoracic cavity resulted in death.¹⁹¹ Wieting performed the first successful surgical repair in 1912.¹⁹² He achieved primary closure of the diaphragm and abdominal wall fascia but ignored the ventricular diverticulum. Initial surgical intervention must address the skin defects overlying the heart and abdominal cavity. Primary excision of the omphalocele with skin closure avoids infection and mediastinitis, although several cases have been successfully managed by local application of topical astringents, thus allowing secondary epithelialization to occur. Several early cases, as in that of Cullerier in 1806, document the long-term viability of individuals with thoracoabdominal ectopia cordis with intact skin coverage despite the abnormal location and coverage of the heart.¹⁹³

Advances in cardiac surgery now allow correction of the intrinsic cardiac lesions, which were previously fatal.

TABLE 24-13 Intrinsic Cardiac Lesions Reported in Patients with Thoracoabdominal Ectopia Cordis

	Number of Cases
Tetralogy of Fallot	13
Tetralogy of Fallot and diverticulum of left ventricle	1
Diverticulum of left ventricle	16
Diverticulum of left ventricle and VSD	9
Diverticulum of left ventricle, pulmonary stenosis, and VSD	1
Diverticulum of left ventricle and ASD	1
Diverticulum of left ventricle, ASD, and VSD	1
Diverticulum of left ventricle, VSD, and mitral stenosis	1
Diverticulum left ventricle, hypoplastic left ventricle, and VSD	1
VSD	8
VSD and ASD	2
VSD and single atrium	1
ASD	3
ASD, VSD, and total anomalous pulmonary venous connection	1
Truncus arteriosus	5
Single atrium and single ventricle	5
Pulmonary atresia and single ventricle	2
Pulmonary atresia, VSD, and PDA	1
Pulmonary stenosis and VSD	3
Tricuspid atresia	4
Double-outlet left ventricle	2
Double-outlet right ventricle	2
Transposition of the great arteries, mitral atresia, and pulmonary artery hypoplasia	1
Transposition of the great arteries and pulmonary artery stenosis	2
Transposition great arteries and VSD	1
Aortic stenosis, ASD, and VSD	1
Bilateral superior vena cava	1
Normal	5

ASD, Atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

From Shamberger RC, Welch KJ: *Sternal defects. Pediatr Surg Int* 5:156–164, 1990. With permission.

An aggressive approach to repair in infants with thoracoabdominal ectopia cordis is appropriate. Repair of the abdominal wall defect or diastasis has been achieved by primary closure or prosthetic mesh (Table 24-14). Primary closure of the thoracoabdominal defect may be difficult to achieve because of the wide separation of the rectus muscles and their superior attachment to the costal arches. A resorbable poly-L-lactic polyglycolic acid plate and other prosthetic materials have been used for this repair.¹⁹⁴ Complete repair of the intracardiac defect is best performed before placement of prosthetic mesh overlying the heart. Repair of the abdomen and chest wall is important primarily for mechanical protection of the heart and abdominal viscera. Early diagnosis by prenatal ultrasound has not altered the surgical approach or overall mortality of this lesion. Three cases in the Boston Children's Hospital series had severe pulmonary hypoplasia, which was lethal in two, a previously unreported association.¹⁶⁵

TABLE 24-14 Reported Methods of Repair of Thoracoabdominal Ectopia Cordis

	Number of Cases
Primary closure of diaphragm and abdominal wall defect	8
Primary closure of skin only and excision of omphalocele	7
Primary closure of diaphragm	4
Primary closure of abdominal wall defect	2
Coverage of abdominal defect with Silastic pouch and secondary epithelialization	3
Resection of lower ribs and sternum to increase room in chest with inferior attachment of diaphragm and primary skin coverage	1
Staged repair with initial skin closure with secondary prosthetic mesh closure of the abdominal and thoracic defect	1
Staged repair with initial skin closure with secondary closure of abdominal wall and diaphragm	1

From Shamberger RC, Welch KJ: Sternal defects. *Pediatr Surg Int* 5:156–164, 1990. With permission.

THORACIC DEFORMITIES IN DIFFUSE SKELETAL DISORDERS

Asphyxiating Thoracic Dystrophy (Jeune Disease)

In 1954, Jeune and colleagues described a newborn with a narrow rigid chest and multiple cartilage anomalies.¹⁹⁵ The patient died of respiratory insufficiency early in the perinatal period. Subsequent authors have further characterized this form of osteochondrodystrophy, which has variable degrees of skeletal involvement. It is inherited in an autosomal recessive pattern and is not associated with chromosomal abnormalities. Its most prominent feature is a narrow, bell-shaped thorax and protuberant abdomen. The thorax is narrow in both transverse and sagittal axes and has little respiratory motion because of the horizontal direction of the ribs (Fig. 24-20). The ribs are short and wide, and the splayed costochondral junctions barely reach the anterior axillary line. The costal cartilage is abundant and irregular, like a rachitic rosary. Microscopic examination of the costochondral junction demonstrates disordered and poorly progressing endochondral ossification, resulting in decreased rib length.

Skeletal abnormalities associated with this syndrome include short stubby extremities with relatively short and wide bones. The clavicles are in a fixed and elevated position, and the pelvis is small and hypoplastic, with square iliac bones.

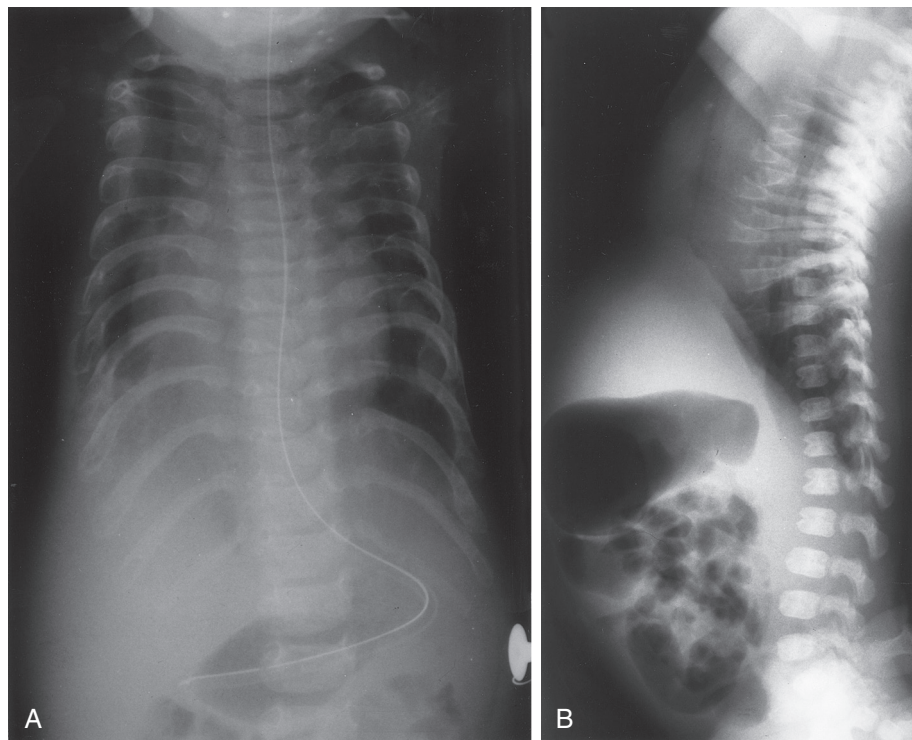


FIGURE 24-20 ■ Jeune disease (asphyxiating thoracic dystrophy). **A**, Anteroposterior radiograph shows short horizontal ribs and narrow chest. **B**, Lateral radiograph demonstrates that the short ribs end at the midaxillary line. Abnormal flaring at the costochondral junctions is also present. The patient died of progressive respiratory insufficiency at 1 month of age. There was no surgical intervention. Postmortem examination revealed alveolar hypoplasia.

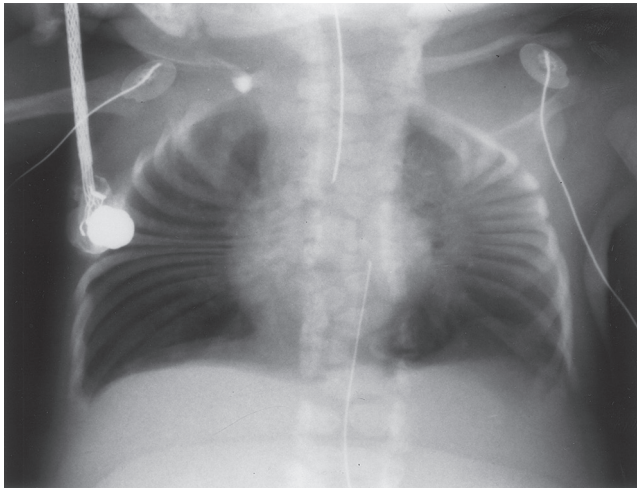


FIGURE 24-21 ■ Chest radiograph of an infant with spondylothoracic dysplasia. Severe abnormality of the spine is apparent, with multiple alternating hemivertebrae producing a crablike configuration to the ribs.

The syndrome has a variable extent of pulmonary impairment. Although the initial cases reported resulted in neonatal deaths, subsequent reports by Kozlowski and Masel and others have documented that infants can survive for longer intervals of time with this syndrome.¹⁹⁶ The pathologic findings in autopsy cases reveal a range of abnormal pulmonary development. In most cases, the bronchial development is normal and there are fewer alveolar divisions, as described by Williams and associates.¹⁹⁷

Spondylothoracic Dysplasia (Jarcho-Levin Syndrome)

Spondylothoracic dysplasia is an autosomal recessive deformity with multiple vertebral and rib malformations, described by Jarcho and Levin in 1938.¹⁹⁸ Infants and children with this syndrome have multiple alternating hemivertebrae in most, if not all, of the thoracic and lumbar spine. The vertebral ossification centers rarely cross the midline, although bone formation is normal. Multiple posterior fusions of the ribs and remarkable shortening of the thoracic spine result in a crablike appearance of the ribs on the chest radiograph (Fig. 24-21).

The thoracic deformity is secondary to the spine anomaly, which results in close posterior approximation of the origin of the ribs. Although most infants with the entity succumb before 15 months of age, as reviewed by Roberts and colleagues, no surgical efforts have been proposed or attempted.¹⁰³ One third of patients with this syndrome have associated malformations, including congenital heart disease and renal anomalies. Heilbronner and Renshaw have reported its occurrence primarily in Puerto Rican families (15 of 18 cases).¹⁹⁹

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CHEST WALL TUMORS

Mark S. Allen

CHAPTER OUTLINE

PRESENTATION AND EVALUATION

History
Physical Examination
Imaging
Chest Radiographs
Preoperative Evaluation

SURGICAL MANAGEMENT

Preoperative Biopsy
Anesthetic Considerations
Intraoperative Considerations
Reconstruction
Postoperative Care
Follow-up

SPECIFIC LESIONS

Benign
Osteochondroma

Chondroma
Fibrous Dysplasia
Eosinophilic Granuloma
Hemangioma
Neurofibroma/Neurolemmoma
Desmoid Tumors

Malignant Lesions

Chondrosarcoma
Osteosarcoma
Ewing Sarcoma (Small Round Cell)
Plasmacytoma
Other Sarcomas

SUMMARY

Chest wall tumors are relatively rare tumors that include a variety of soft tissue and bone tumors. Although rarely seen by physicians practicing in a nonspecialized practice, patients who have these tumors need careful consideration because the evaluation and management are varied and full of pitfalls. Some of the tumors need no therapy, others need radical surgical resection, some need preoperative chemotherapy or radiation therapy, and reconstruction is always an important issue in the planning of resection. Even a simple biopsy of a chest wall tumor is important, because improperly performed biopsy can make future treatment more difficult. In general, the management of chest wall tumors should be referred to a specialized center for optimal outcome.

Ostias Aimaz is credited with the first chest wall resection in 1778.¹ As surgical and anesthetic techniques evolved, therapy for chest wall tumors evolved. O. T. Clagett, at the Mayo Clinic in Rochester did much of the initial pioneering work and published his findings in 1957.² Drs. Pairolero and Arnold subsequently built on this foundation and advanced the surgical resection and reconstruction of chest wall tumors.³⁻⁶

Because the lesions are rare, most (if not all) of the data on management of these patients are based on retrospective series. There are no randomized trials; thus much of what we know is not evidence based but rather based on trial and error. Most of the larger series are from specialized cancer centers such as the MD Anderson

Cancer Center, Memorial Sloan Kettering Hospital, and the Mayo Clinic, but in recent years there has been an effort to pool information from many institutions to improve knowledge.^{5,7-10}

Metastatic lesions are the most common chest wall tumor, and their management depends on the status of the primary disease.¹¹ Occasionally, metastatic disease should be resected or radiated for symptom control or cure. Infections of the chest wall could also be considered “tumors.” This chapter, however, will deal with primary chest wall tumors.

PRESENTATION AND EVALUATION

History

As with most problems in medicine, a careful history and physical examination can help establish a diagnosis and prevent errors. Although approximately 20% of patients with primary chest wall tumors have their tumors discovered as incidental findings, most present with a mass or pain. Patients should be questioned about when the pain started, where it is located, what the intensity of the pain is, and what makes it better or worse. Pain usually, but not always, implies a malignant lesion. Severe pain that requires narcotics for relief should alert the clinician that the tumor might infiltrate nerves. When a mass is present,

the patient should be questioned about when it was first discovered and questions asked to determine its growth rate. A history of fever, weight loss, and malaise should be sought, which could help narrow the diagnostic possibilities.

A history of trauma to the area should be elicited, because there seems to be a correlation between trauma to an area and the development of a sarcoma. The history should include data about prior cancers, radiation therapy, operations, infections, travel, and hereditary disease (e.g. Gardner or von Recklinghausen disease).

Physical Examination

After the history, a physical examination should be completed with emphasis on the lesion in question. If a mass is present, it should be palpated to see if it hard or soft, mobile or fixed, and tender or not tender. Its location should be carefully documented. It is often helpful to palpate the lesion with the patient in the same position he or she will be in for surgery, which may prevent any intraoperative surprises. The extremities should be moved to see if the mass moves with any arm movements. Lymphadenopathy, if present, should be palpated and other lumps, scars, or tender spots examined.

Imaging

Chest Radiographs

Although not very sensitive, a plain chest radiograph (CXR) may be the initial radiograph that discovers the chest wall lesion. Old CXRs should be obtained and examined in an attempt to establish a growth rate of the lesion. Rib films can be used to help determine bony erosion or lytic lesions, but computed tomography (CT) is much more sensitive. The CT gives information about the location of the lesion and its relationship to the rib, soft tissue, pleura, and any vascular structures or nerves in the local area (Fig. 25-1). It is very helpful for surgical planning as well.¹² Careful viewing of the CT will usually narrow the diagnostic possibilities and in some patients is diagnostic.¹³ Examples include fibrous dysplasia, which has a characteristic lytic appearance with an intact cortex; Ewing sarcoma, which elevates the periosteum (Fig. 25-2) and leads to a radiographic sign known as Codman triangle (this is a pseudotriangle because it is only two sided: the original bone and the elevated cortex); and the characteristic stippled or ring-and-arc calcification seen in a chondrosarcoma.¹⁴ Magnetic resonance imaging (MRI) is useful as well because it can delineate between soft tissue, bone, nerve, or vascular structures in a multiplanar fashion (Fig. 25-3).¹⁵ Occasionally MRI can lead to a specific diagnosis such as in the case of myxoid chondrosarcoma where the lesion will have markedly high signal intensity on T2-weighted images secondary to the myxoid component.¹²

Proton emission tomography (PET) and bone scanning can be used to search for metastatic disease. The standard uptake value (SUV) obtained in PET may help with prognosis, but there is not enough data to support this supposition. It is also not known whether obtaining



FIGURE 25-1 ■ CT scan of a right anterior chest wall mass.

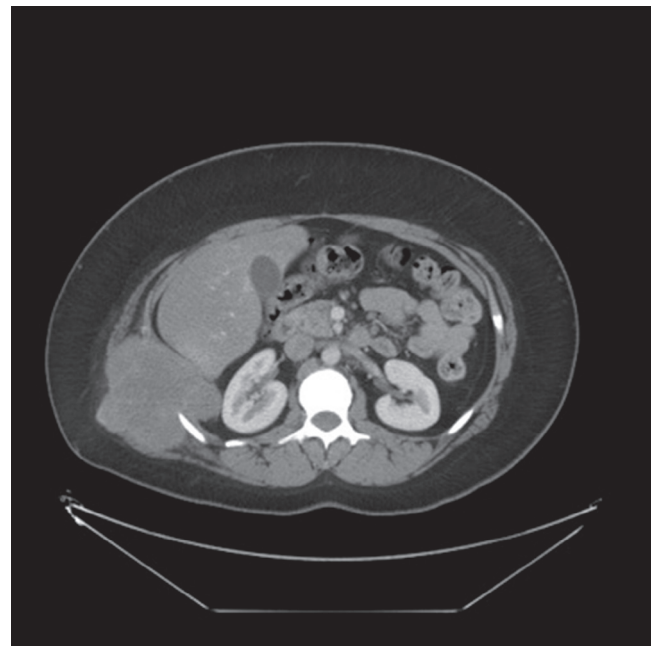


FIGURE 25-2 ■ CT scan of a right posterior Ewing tumor.

a PET on all patients with a malignant primary chest wall is cost effective. At present, if there is suspicion of a metastatic deposit, obtaining a PET seems like a reasonable option. PET is not a method to definitively determine if a mass is malignant or benign.

Preoperative Evaluation

Because primary chest wall tumors are usually treated with surgery, preoperative evaluation of other medical issues is warranted. The cardiovascular system should be investigated with regard to possible ischemic heart disease

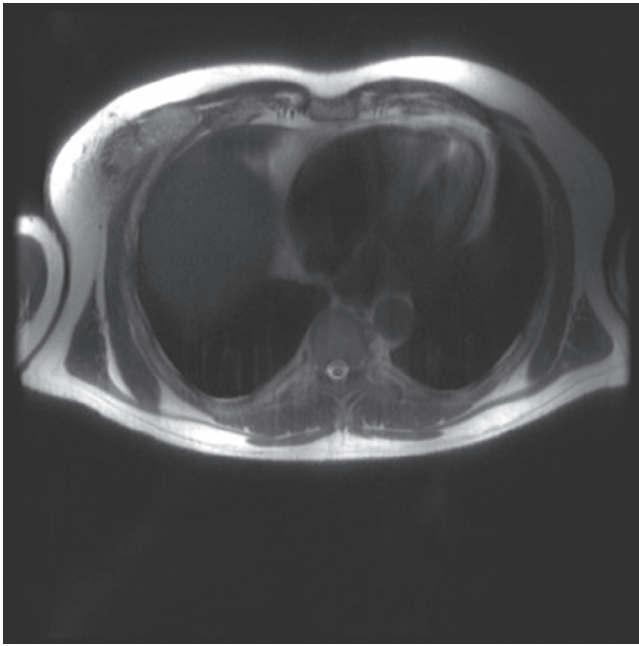


FIGURE 25-3 ■ MRI of the right anterior chest wall mass seen in Figure 25-1. The MRI is often a better way to delineate the tumor from surrounding tissue.

and pulmonary dysfunction. Pulmonary function testing should be done to determine the risks of removing a portion of the chest wall and its deleterious effects on pulmonary mechanics. If patients are smoking, they should stop. This will reduce the risk of pulmonary infections and improve the blood flow to any tissue flaps that are necessary to cover the resection. As in all surgery, diabetes should be under control. Patients should also be counseled on postoperative physical therapy that may be necessary.

SURGICAL MANAGEMENT

Preoperative Biopsy

One of the major problems with primary chest wall lesions is how to obtain a tissue diagnosis.¹⁶ If biopsy is not performed correctly, future therapy and even survival can be jeopardized. If the lesion is small (i.e., <3 cm) and in a favorable location (lateral chest wall away from vital structures), an excisional biopsy can be undertaken.¹⁷ Because pathologic examination often requires overnight decalcification, frozen section may not be available. If the pathology cannot be determined based on excisional biopsy, the incision should be closed with careful attention to prevention of a postoperative hematoma, which could spread potentially malignant cells into the surrounding area. The incision for the biopsy should also be placed with consideration for further resection, because if the pathology returns malignant, the biopsy site should be excised. Extensive flaps or dissection should be avoided in the initial biopsy, because cure rate is related to margins of resection.

For large tumors (i.e., ≥ 3 cm) or tumors located in a critical area (near great vessels), a core needle biopsy can be done. Fine-needle aspiration (FNA) is not useful except when a metastatic lesion is suspected because FNA limits the amount of histologic tissue and tissue architecture.¹⁷ A core needle biopsy is approximately 95% accurate.¹⁸ Even though pathology is not 100% accurate, between a good history, physical examination, and radiographic imaging, the diagnosis should be highly reliable.

Anesthetic Considerations

Chest wall resections are usually done under general endotracheal anesthesia. If lung resection is anticipated or special exposure is required, a double-lumen tube can be used, but usually single-lumen anesthesia will suffice. Pain control postoperatively is accomplished with epidural analgesia and supplemented with parenteral narcotics and nonsteroidal anti-inflammatory medications. The routine use of standard perioperative antibiotics (one dose of a cephalosporin just prior to the incision and one dose postoperatively) has been clearly established and should be used. Control of glucose in all patients, but especially in diabetics, has been shown to lower postoperative complication rates.¹⁹

Intraoperative Considerations

Resection of the mass should be complete, the margin of resection depending on the histologic type of the tumor and its location on the chest wall. The initial resection is the best, and perhaps only, chance for a curative operation as reoperations for recurrent tumors are unlikely to be curative. The resection should be en bloc, including overlying skin, soft tissue, and muscle and with an adequate margin. No randomized trials are available to help determine the optimal margin; only retrospective series are available to determine the extent of resection. In 1986, King and colleagues, from the Mayo clinic, published their series of 90 patients who underwent chest wall resection for primary chest wall tumors.⁵ Approximately 80% of the patients had a malignant lesion; one quarter of these classified as a malignant fibrous histiocytoma (now called pleomorphic sarcoma), one quarter chondrosarcoma, and one half a mixture of other lesions. The researchers found that patients that had a margin of at least 4 cm had a lower recurrence rate than those with a lesser margin. They also recommended resecting the adjacent marrow cavity (rib or sternum) if the tumor could invade into the marrow. In a separate study from the same institution that just included 96 patients with primary chest wall chondrosarcoma, McAfee and coworkers reported a statistically significant survival advantage for resections with at least a 4-cm margin.²⁰ For tumors that are too close to vital structures for the recommended margin, a compromise must be made. However, fear of reconstruction should not limit the extent of resection. With modern reconstructive techniques, many options are available and cure should not be compromised. Thoracoscopic techniques have been used to resect these types of lesions, but the data on long-term outcome are limited.²¹

Reconstruction

After wide excision, the goals of reconstruction are to replace the rigid chest wall to provide protection to the underlying viscera and restore the mechanics of respiration.²² In the noninfected patient, the rigid chest wall can be reconstructed with a variety of material. Sheets of 2-mm-thick polytetrafluoroethylene (Gore-Tex, W. L. Gore and Associates) are the easiest to use for chest wall reconstruction. The sheets are sewn into the chest wall with nonabsorbable sutures and then covered with soft tissue. Other options include a methylmethacrylate Marlex mesh sandwich, which allows placing curved shapes into the chest wall, which can be useful for larger defects.²³ Polypropylene (Prolene, Ethicon, Inc.) or polyglactin (Vicryl, Ethicon, Inc.) mesh can also be used for bony chest wall reconstruction.²⁴

Soft tissue reconstruction is required to cover the defect. If the defect is small, local tissue can be elevated and primarily closed over the defect. For larger defects, muscle or musculocutaneous flaps are used to cover the defect. These include latissimus dorsi, pectoralis major, rectus abdominis, serratus anterior, and external oblique flaps. In rare circumstances, a free flap is required to cover the defect if no local rotational flaps are available. Omentum can also be brought into the area, if necessary, to provide a vascular bed for tissue ingrowth. Series by Arnold and Pairolero are excellent resources for details about chest wall reconstruction after resection.^{3,4,25-27}

Postoperative Care

Postoperative care should be routine in most chest wall resections unless the amount of chest wall removed was so large that it severely compromises pulmonary mechanics. If ventilation mechanics are difficult postoperatively, mechanical ventilation may be necessary, but this is quite unusual. Even complete sternal resections for tumors do not commonly require prolonged ventilator support. Aggressive chest physiotherapy and early ambulation are important aspects of care, although randomized trials proving their efficacy are limited. Appropriate analgesia is important for early ambulation and deep breathing and coughing. If the pleural space was entered during the resection, chest tubes can be removed when the drainage is below 300 mL in a 24-hour period and no air leak is present.

If infection occurs and foreign material was used for reconstruction, the foreign material will need to be removed. A thick fibrous layer forms under the material within the first several weeks, so removal will not result in an open pneumothorax. The foreign material can be removed, the soft tissue replaced, and the patient treated with appropriate antibiotic. If the long-term cosmetic result is unsatisfactory, a subsequent reconstruction can be undertaken later, after the infection has fully resolved.

Follow-up

Patients should return for follow-up several weeks after discharge from the hospital to be sure they are healing

properly, their pain is under control, and any questions they have are answered. Additional therapy, such as radiation or chemotherapy, depends on the margins of resection and the histology of the tumor. Patients should be followed long term to look for signs of recurrence. Periodic MRIs or CTs are useful to image the resected area after surgery. A yearly interval seems reasonable, but no standard currently exists.

SPECIFIC LESIONS

Benign

Osteochondroma

The most common benign chest wall tumor is an osteochondroma. This type of chest wall tumor occurs three times more frequently in males than females. Osteochondromas are cartilage-capped bony projections arising on the external surface of bone that contains a marrow cavity that is continuous with that of the underlying bone.²⁸ Approximately 85% of these tumors arise as a solitary event with no hereditary link. Hereditary multiple osteochondromas (HMOs) is a disorder caused by mutation in the exostosis (multiple)-1 (EXT1) or exostosis (multiple)-2 (EXT2) gene and is inherited in an autosomal dominant fashion.²⁹ Patients with HMOs may have multiple lesions.

These lesions can present as a painless mass or a pathologic fracture, or they may be found incidentally on a chest roentgenogram. They have a characteristic radiographic appearance, "a sessile or stalked exostosis whose pedicle merges with the adjacent cortex, a peripheral rim of calcification and stippled calcification within the tumor mass."³⁰

The lesions can be safely observed with serial imaging. Indications for resection include enlargement, concern about the accuracy of the diagnosis, and development of pain. Occasionally the lesions can impinge on the spine or vascular system and require resection for relief. Resection requires only a negative margin.

Chondroma

Chondroma is a benign cartilaginous tumor that typically occurs at the costocartilage junction on the chest wall. It is most commonly seen in 20- to 30-year-olds and makes up approximately 20% to 30% of the benign chest wall tumors. The history of the lesion is usually a slowly enlarging nonpainful mass that the patient has noticed recently. On palpation it is fixed to the bony chest wall and nontender. Radiographically it appears as a soft tissue periosteal mass with a thin cortex but sclerotic. Calcification is often present and can be in a diffuse or stippled pattern. Histologic analysis shows mature hyaline cartilage cells with foci of myxoid degeneration and calcium.

Chondroma is difficult to differentiate from its malignant counterpart, chondrosarcoma, so tumors of this type should be resected to establish a diagnosis. Resection is usually straightforward with a 2-cm margin sufficing. Recurrence, if benign, is uncommon.

Fibrous Dysplasia

Fibrous dysplasia is thought to be a developmental disorder in which normal bone is replaced by fibrous stroma and immature bone. It occurs most commonly in 20- to 30-year-olds and is equally distributed between men and women. The lesion presents as a painless mass and in over 80% of the patients is a solitary lesion. Multiple lesions can occur as part of the McCune-Albright syndrome, which includes café au lait spots, endocrine disorders, short stature, and precocious puberty.³¹ The radiographic appearance shows a central fibrous area in the rib with a thinned cortex and a lytic component. The lesion can have the appearance of “soap bubbles” or ground glass. Histologic analysis reveals irregular shaped speckles of bone cells that often have bizarre shapes. They have been described as “Chinese characters” by some to signify the odd appearance.³¹ Treatment is observation, unless the lesion becomes painful or enlarges. Resection with negative margins is curative.

Eosinophilic Granuloma

These tumors are a disorder of the lymphoreticular system and not really a true bone tumor. They involve proliferation of histiocytes, Langerhans cells, giant cells, and eosinophils. They can affect the rib or the sternum with a peak incidence in 5- to 15-year-old patients. They present with pain, fevers, and an isolated tender mass in the chest wall. CT scan shows the lesion destroys the cortex, makes new subperiosteal bone, and can mimic osteomyelitis or malignancy. Core biopsy shows Birbeck granules on electron microscopy.³² Treatment is local excision for diagnosis or relief of symptoms. Alternatively, if the diagnosis is known, intralesional or systemic corticosteroid or low-dose radiation can be used.³³

Hemangioma

Hemangiomas are thought to be congenital vascular malformations that occur in the rib or intercostal space. They may be related to trauma, hormonal imbalance, or liver disease, but most are thought to be congenital. They appear, similar to other benign chest wall tumors, as a painless mass, usually in children. The radiographic appearance on CXR shows the shadow of a soft tissue tumor (Fig. 25-4). CT scan shows characteristic fatty tumor with an occasional phlebolith. They are said to have a “honeycomb” appearance. On MRI the fat portion will have high signal intensity on T1-weighted images, and the vascular portion will be high intensity on T2-weighted images (Fig. 25-5).

Resection is necessary for enlargement, pain, or if the diagnosis is in doubt. Occasionally the mass will be large enough to cause congestive heart failure, but this is extremely rare. Extension of the mass into the spinal canal should be checked, for this will greatly complicate the resection. Preoperative embolization has been used for large tumors to decrease intraoperative blood loss but is not necessary for smaller lesions and is not curative alone. Resection with negative margins is curative.

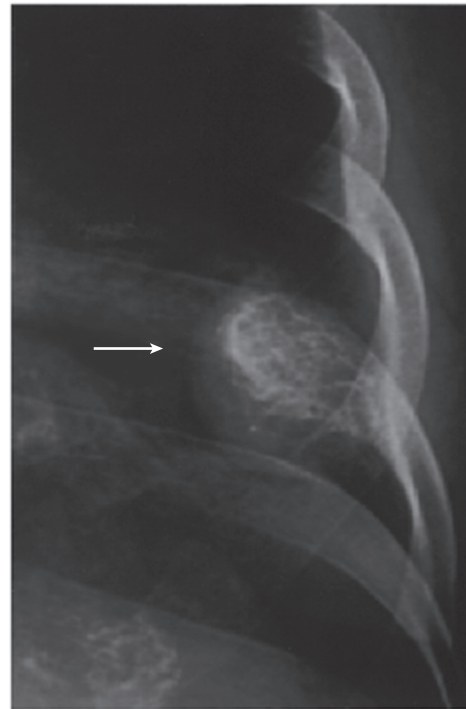


FIGURE 25-4 ■ Rib radiograph showing a mass (arrow) that is located on the seventh rib and expands beyond the irregular cortex. Calcification inside the mass presents a so-called honeycomb appearance. (Reprinted with permission from Okumura T, et al: Hemangioma of the rib: a case report. *Jpn J Clin Oncol* 30:354–357, 2000.)

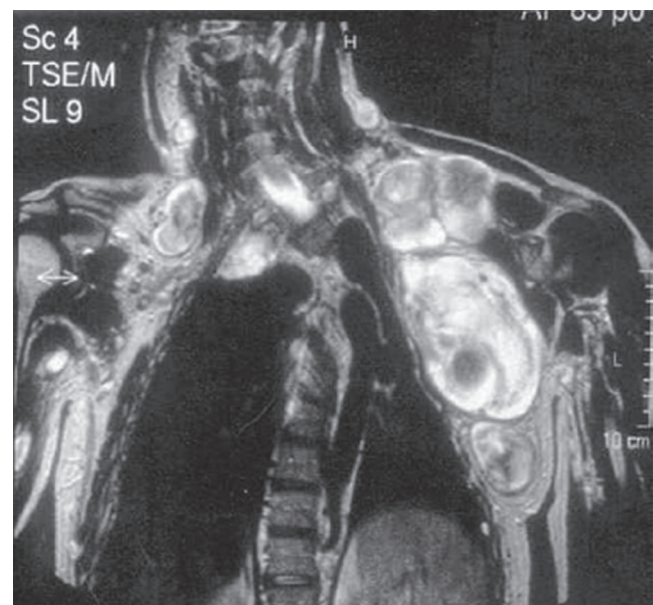


FIGURE 25-5 ■ MRI showing the coronal plan of T1 image demonstrating lobulated masses in the chest wall. The involvement of the supra- and subclavicular region, severe deformity of the chest, and thoracic scoliosis are clearly evident. (Reprinted with permission from Margaritora S, et al: Giant neurofibroma of the chest wall. *Eur J Cardiothorac Surg* 21:339, 2002.)

Neurofibroma/Neurolemmoma

These are tumors that arise from nerve cells (neurofibroma) or nerve sheath cells (neurolemmoma or schwannoma) that are in the chest wall. Neurofibromas can be associated with neurofibromatosis type I, a disorder caused by the mutation of a gene on chromosome 17 that codes for neurofibromin, a negative regulator of the Ras oncogene signal transduction pathway.³⁴ These tumors present either as singular painless enlargements in the isolated form or numerous tumors on the chest wall and in other areas. They can cause electric shock-like symptoms. Radiographically they are smooth bordered masses that enhance with gadolinium with MRI.³⁵ The neurofibromas can enlarge markedly, indicating they have undergone malignant transformation. The tumors should be removed for symptom control and if malignant transformation is suspected.

Desmoid Tumors

These tumors, although classified as benign because they do not metastasize, are locally aggressive low-grade sarcomas that arise from fascia and connective tissue. Approximately 20% develop in the chest wall. The cause is unknown, but they are associated with trauma, familial adenomatous polyposis, and Gardner syndrome. Some of the tumors are positive for estrogen and/or progesterone receptors, implying that hormonal therapy with agents like tamoxifen may be helpful. Radiographically they tend to be homogenous masses with indistinct borders. Surgical resection with wide margins is the treatment of choice. This may be difficult with tumors that involve the axilla, clavicular area, or the brachial plexus.

Abbas's series from the Mayo Clinic studied 53 patients (24 men and 29 women) whose median age was 39 years old.³⁶ A palpable mass was present in 66%, pain was present in 42%, and no signs or symptoms were present in 10% of the patients. All the patients had wide radical excision attempted, and it was completed in 44. Seven had microscopic margins and two (R1 resection) had grossly positive margins (R2 resection). Follow-up was complete in 51 patients for a median of 53 months. The 5-year survival was 93%; however, 30% had a local recurrence. Radiation therapy was used in some of the recurrent tumors, but whether or not it was useful to prevent further recurrence is unknown. These patients should be followed for life because some of the recurrences occurred long after the initial resection.³⁷

Malignant Lesions

Chondrosarcoma

Chondrosarcomas are the most common malignant primary chest wall tumor in adults. They arise de novo or from degeneration of a chondroma, exostosis, or osteochondroma. They may have a relationship to remote trauma. In large series, approximately 80% occur in the ribs and 20% occur in the sternum.^{20,38} Presentation is typically a hard, slowly enlarging painful mass. On radiographic imaging it is a poorly defined lobulated mass,

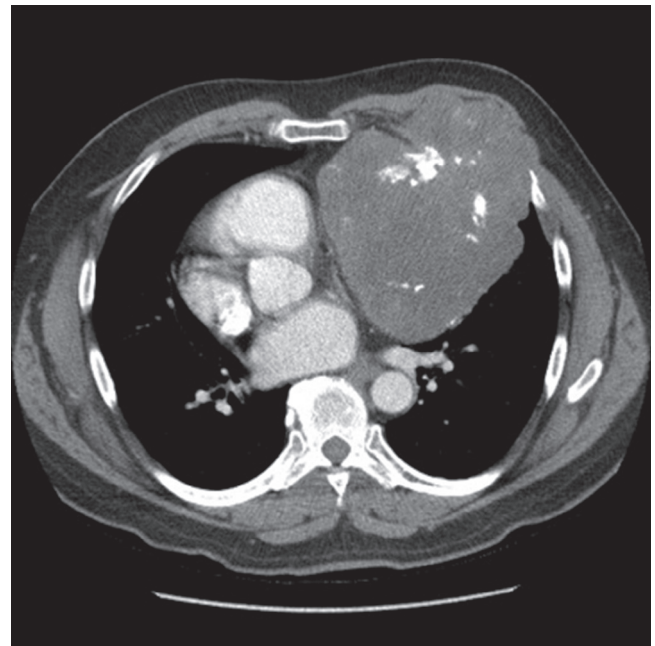


FIGURE 25-6 ■ Large left anterior chest wall chondrosarcoma.

often with cortical destruction and varying amounts of calcification (Fig. 25-6). Metastatic lesions are seen in roughly 10% of patients, with higher-grade tumors more often presenting with metastases.

Definitive diagnosis is made by pathologic examination, which shows chondroid matrix with increased cellularity, binucleate cells, and increased mitotic activity.³¹ Therapy is wide surgical excision when possible; radiation and chemotherapy have little to offer these patients.

In a large series from Scandinavia, 106 patients treated over a 22-year (1980-2002) period were analyzed.³⁸ The average age was 59 years old and there were 59 men and 47 women. All patients were treated with surgical excision, except for 9 who were deemed too ill to undergo resection. The overall 10-year survival was 64% and was improved for those that could undergo wide excision.

In another series from the Mayo clinic that examined 96 patients with chondrosarcoma of the chest wall, researchers found a similar age at presentation (median age 53.5) and a similar distribution of gender (55 men, 41 women).²⁰ Seventy-two of the patients had their initial resection at Mayo clinic, 28 underwent wide excision (2 to 4 cm margin), 25 had local excision (<2-cm margin), and 19 underwent palliative resection. The long-term survival was dependent on the extent of resection; those that had wide excision had a 96.4% 10-year survival, those with a local resection had a 65.4% 10-year survival, and those with a palliative resection only had a 14% 10-year survival (Fig. 25-7).

Patients that present with a chondrosarcoma should undergo wide excision (at least 4-cm margins) if possible. Radiation therapy is usually given to patients who cannot undergo a wide excision because the tumor is too close to vital structures. Follow-up should last for the rest of the patients' lives, because these tumors have been known to recur late after surgical resection.

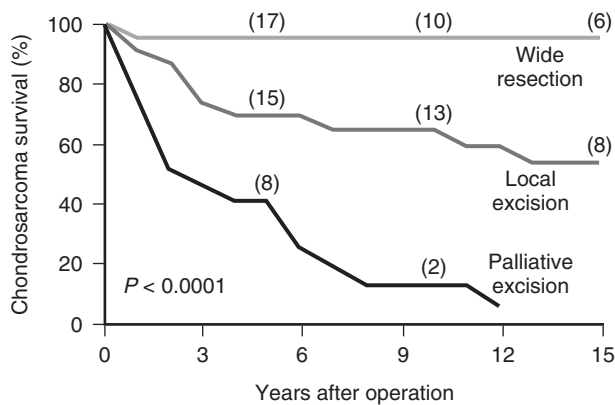


FIGURE 25-7 ■ Survival rate of resected chondrosarcoma according to margin of resection. (From McAfee MK, et al: Chondrosarcoma of the chest wall: factors affecting survival. *Ann Thorac Surg* 40:535–541, 1985.)

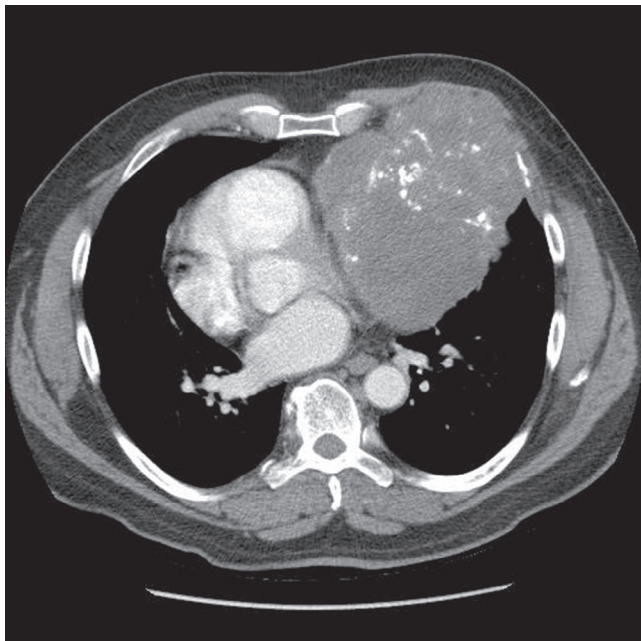


FIGURE 25-8 ■ Computed tomography scan of an osteosarcoma of the left chest wall.

Osteosarcoma

Osteosarcoma are the most common bone tumor overall, but less common than chondrosarcoma in the chest wall. They occur in younger patients (10 to 25 years old) and can occur later in life in association with Paget disease, prior radiation therapy (with at least a 10-year latency period), or in old bone infarcts.³⁹ There is a higher risk in patients with retinoblastoma (*RB1* mutation on chromosome 13q14) and in Li-Fraumeni syndrome (*p53* mutation). The tumor presents as a rapidly expanding painful mass. Elevations in alkaline phosphatase can be seen, but this is a nonspecific finding. On radiograph a classic sunburst pattern is sometimes seen. Osteosarcomas are typically more calcified than chondrosarcomas (Fig. 25-8). Codman triangle refers to the shape formed by the elevated periosteum and the cortex seen in some tumors. A CT of the chest is an important study, because

at least 20% of patients will present with pulmonary metastases.

Treatment is neoadjuvant chemotherapy (doxorubicin, methotrexate, and cisplatin and wide local excision.⁴⁰ Radiation therapy is ineffective. The 5-year survival ranges from 14% to 50% and is related to response rate to chemotherapy and the ability to undergo wide excision. Pulmonary metastasectomy can prolong life, so patients should be followed carefully.

Ewing Sarcoma (Small Round Cell)

Ewing sarcoma, along with Askin tumors and primitive neuroectodermal tumors (PNETs), make up a group of small round cell tumors that have a neural origin.⁴¹ Most of these tumors have a translocation mutation between the long arms of chromosomes 11 and 22 [t(11:22)(q24;q12)].⁴² This is the most common tumor in pediatric and young adult patients, and approximately 6% occur in the rib. Only 15% of Ewing sarcomas occur on the chest wall, whereas 50% of PNETs are found here.

Ewing sarcomas present as a painful mass, often accompanied by fever, malaise, and weight loss. The erythrocyte sedimentation rate (ESR) may be elevated. Radiologically they are large uncalcified tumors with soft tissue and bone destruction. An onion peel or sunburst pattern can be seen on CT. Pathology shows small round blue cells with scant clear cytoplasm, which stain positive with periodic acid–Schiff because of the presence of glycogen.³¹ PNETs have rosettes, dark oval nuclei with neurofibrillary cores that allow them to be differentiated from Ewing tumors.

Treatment of Ewing tumor is with neoadjuvant chemotherapy followed by wide resection if possible. Because this tumor may spread within the marrow of the rib, consideration should be given to removal of the entire rib during the resection. Survival rates depend on the response to chemotherapy and the ability to perform a wide complete resection.

Plasmacytoma

Plasmacytoma of the chest wall is a growth of monoclonal plasma cells in the rib that, unlike multiple myeloma, is a solitary lesion. It usually appears in elderly men as a pain in the rib without a palpable mass. Radiographically it appears as an osteolytic process with paracostal opacities frequently present. A core biopsy is performed to make the diagnosis, and then the lesion is treated with radiation therapy. A dose of 5000 to 6000 cGy is recommended.¹⁶ If disseminated multiple myeloma does not develop, the cure rate is quite good. Unfortunately approximately two thirds of patients progress to systemic disease within 3 years.³¹

Other Sarcomas

Almost any other type of sarcoma can occur primarily in the chest wall, although they are quite rare. More frequent types include undifferentiated pleomorphic sarcoma (formerly known as malignant fibrous histiocytoma [MFH]), liposarcoma, neurofibrosarcoma,

rhabdomyosarcoma, and radiation-induced sarcomas. All have a common presentation as a painful mass that is enlarging. The treatment, in general, is wide excision with or without additional radiation and/or chemotherapy.⁴³ Long-term survival depends on grade of tumor and the ability to perform wide excision.

SUMMARY

Primary chest wall tumors comprise a wide variety of cell types with often confusing presentations. Establishment of an accurate pathologic diagnosis without interfering with subsequent treatment options is an important principle. For most tumors, wide excision is the key to therapy and should be performed at a center where physicians have experience treating these unusual lesions.

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THORACIC OUTLET SYNDROME AND DORSAL SYMPATHECTOMY

Harmik J. Soukiasian • Harold C. Urschel, Jr.[†] • Robert J. McKenna, Jr.

CHAPTER OUTLINE

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REOPERATION FOR RECURRENT THORACIC OUTLET SYNDROME

OPERATIVE TECHNIQUE FOR REDO THORACIC OUTLET SYNDROME SURGERY

SUMMARY

Thoracic outlet syndrome, a term coined by Rob and Standover,¹ refers to compression of the subclavian vessels and brachial plexus at the superior aperture of the chest. It was previously designated, according to presumed etiologies, as *scalenus anticus*, *costoclavicular*, *hyperabduction*, *cervical rib*, and *first thoracic rib syndromes*. The various syndromes are similar, and the compression mechanism is often difficult to identify. Most compressive factors operate against the first rib (Fig. 26-1).^{2,3}

The various symptoms and presentations of thoracic outlet syndrome (TOS) are related to which structure or

structures are affected, the subclavian vein, subclavian artery or brachial plexus.⁴⁻⁶

Neurovascular compression can occur between the anterior and middle scalene muscles while passing over the first rib, in the space between the clavicle and first rib, or in the subcoracoid tunnel at the insertion of the pectoralis minor muscle.⁷⁻¹¹

HISTORICAL ASPECTS

Until 1927, the cervical rib was commonly thought to be the cause of symptoms of this syndrome. Galen and Vesalius first described the presence of a cervical rib.¹² Hunauld, who published an article in 1742, is credited by

[†]Deceased.

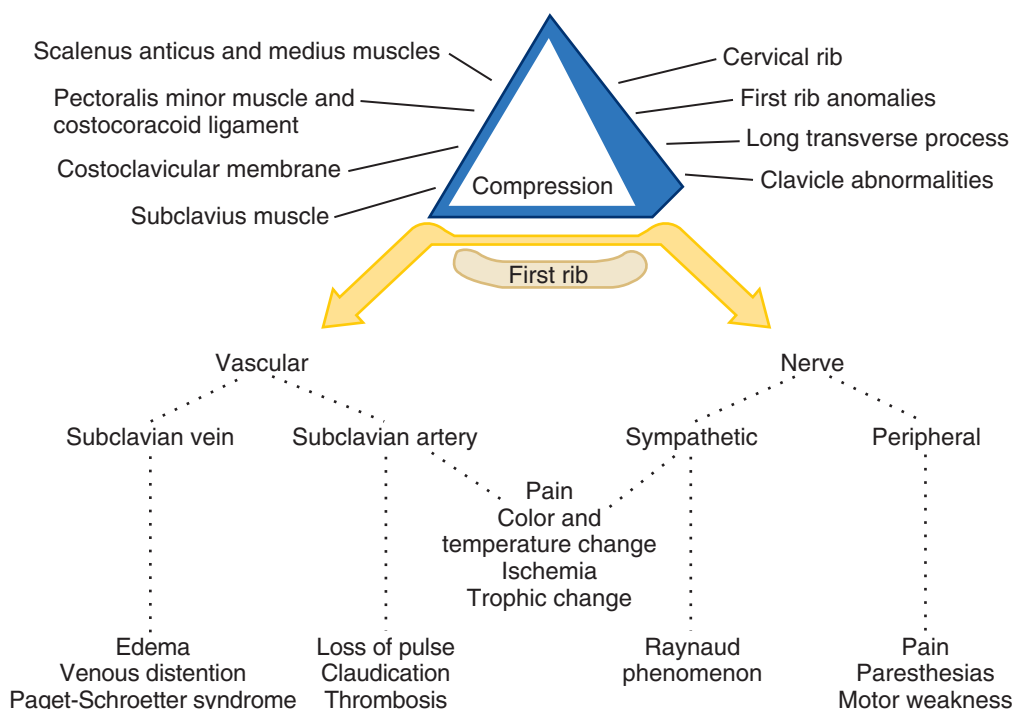


FIGURE 26-1 ■ Diagram of the relationships of muscle, ligament, and bone abnormalities in the thoracic outlet that can compress neurovascular structures against the first rib.

Keen¹³ as being the first to describe the importance of the cervical rib in causing symptoms. In 1818, Cooper treated symptoms of cervical rib with some success,¹⁴ and in 1861, Coote¹⁵ performed the first cervical rib removal. Halsted¹⁶ stimulated interest in dilation of the subclavian artery distal to cervical ribs, and Law¹⁷ reported the role of adventitious ligaments in the cervical rib syndrome. In 1927, Adson and Coffey¹⁴ suggested the role of the scalenus anticus muscle in cervical rib syndrome. Naffziger and Grant¹⁸ and Ochsner and associates¹⁹ popularized sectioning of the scalenus anticus muscle. Falconer and Weddell²⁰ and Brintnall and colleagues²¹ incriminated the costoclavicular membrane in the production of neurovascular compression. In 1945, Wright²² described the hyperabduction syndrome with compression in the costoclavicular area by the tendon of the pectoralis minor. Rosati and Lord²³ added claviclectomy to anterior exploration, scalenotomy, cervical rib resection (when one was present), and sectioning of the pectoralis minor and subclavian muscles and of the costoclavicular membrane. The role of the first rib in causing symptoms of neurovascular compression was recognized by Bramwell²⁴ in 1903. Murphy²⁵ is credited with the initial resection of the first rib in 1910. He used a supraclavicular approach to the resection, whereas the primary surgical approach for decades had been a supraclavicular scalenotomy, without rib resection.²⁶

Brickner,²⁷ Brickner and Milch,²⁸ and Telford and coworkers^{29,30} suggested that the first rib was the culprit. Clagett² emphasized the first rib and its resection through the posterior thoracoplasty approach to relieve neurovascular compression. In 1962, Falconer and Li³¹ reported the anterior approach for first rib resection, whereas

Roos³² in 1966 introduced the transaxillary route for first rib resection and extirpation. Caldwell and colleagues³³ introduced the method of measuring motor conduction velocities across the thoracic outlet in diagnosing TOS. Urschel and Razzuk³⁴ popularized reoperation for recurrent TOS.

Regardless of the mode of presentation, the optimal diagnosis and treatment of TOS remains elusive, and treatments have therefore varied.^{35,36,37}

SURGICAL ANATOMY

At the superior aperture of the thorax, the subclavian vessels and the brachial plexus traverse the cervicoaxillary canal to reach the upper extremity. The cervicoaxillary canal is divided by the first rib into two sections: the proximal one, composed of the scalene triangle and the costoclavicular space, and the distal one, composed of the axilla. The proximal division is the more critical for neurovascular compression. It is bounded superiorly by the clavicle, inferiorly by the first rib, anteromedially by the costoclavicular ligament, and posterolaterally by the scalenus medius muscle and the long thoracic nerve. The scalenus anticus muscle, which inserts on the scalene tubercle of the first rib, divides the costoclavicular space into two compartments: the anteromedial one containing the subclavian vein and the posterolateral one containing the subclavian artery and the brachial plexus (Fig. 26-2). The latter compartment, which is bounded by the scalenus anticus anteriorly, the scalenus medius posteriorly, and the first rib inferiorly, is called the *scalene triangle*.

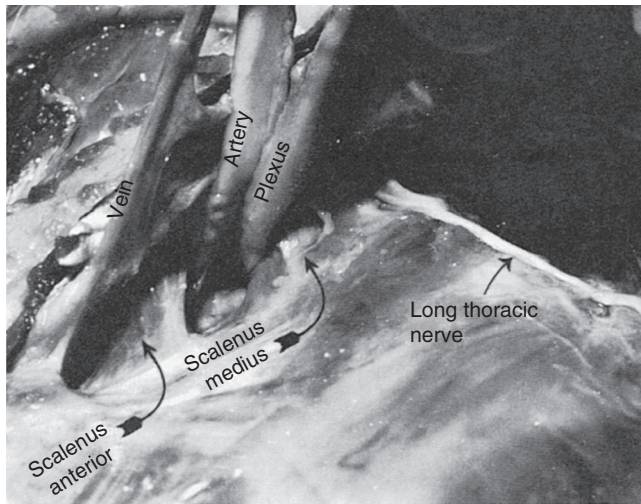


FIGURE 26-2 ■ Anatomic dissection from the transaxillary approach, showing the relationship of the neurovascular bundle, the scalenus anterior muscle, and the long thoracic nerve along the posterior border of the scalenus medius muscle.

FUNCTIONAL ANATOMY

The cervicoaxillary canal, particularly its proximal segment (the costoclavicular area), normally has ample space for passage of the neurovascular bundle without compression. Narrowing of this space occurs during functional maneuvers. It narrows during abduction of the arm because the clavicle rotates backward toward the first rib and the insertion of the scalenus anticus muscle. In hyperabduction, the neurovascular bundle is pulled around the pectoralis minor tendon, the coracoid process, and the head of the humerus. During this maneuver, the coracoid process tilts downward and thus exaggerates the tension on the bundle. The sternoclavicular joint, which ordinarily forms an angle of 15 to 20 degrees, forms a smaller angle when the outer end of the clavicle descends (as in drooping of the shoulders in poor posture), and narrowing of the costoclavicular space may occur.¹⁵ Normally during inspiration, the scalenus anticus muscle raises the first rib and thus narrows the costoclavicular space. This muscle can cause an abnormal lift of the first rib, as in cases of severe emphysema or excessive muscular development, which is seen in young adults.

The scalene triangle, which normally occurs between the scalenus anticus anteriorly, the scalenus medius posteriorly, and the first rib inferiorly, permits the passage of the subclavian artery and the brachial plexus, which are in direct contact with the first rib. The space of the triangle is 1.2 cm at its base and approximately 6.7 cm in height (Fig. 26-3). There is a close-fitting relationship between the neurovascular bundle and this triangular space. Anatomic variations can narrow the superior angle of the triangle, cause impingement on the upper components of the brachial plexus, and produce the upper type of scalenus anticus syndrome that involves the trunk containing elements of C5 and C6. If the base of the triangle is raised, compression of the subclavian artery and the trunk containing components of C7, C8, and T1 results in the lower type of scalenus anticus syndrome. Both types have been described by Swank and Simeone.³⁸

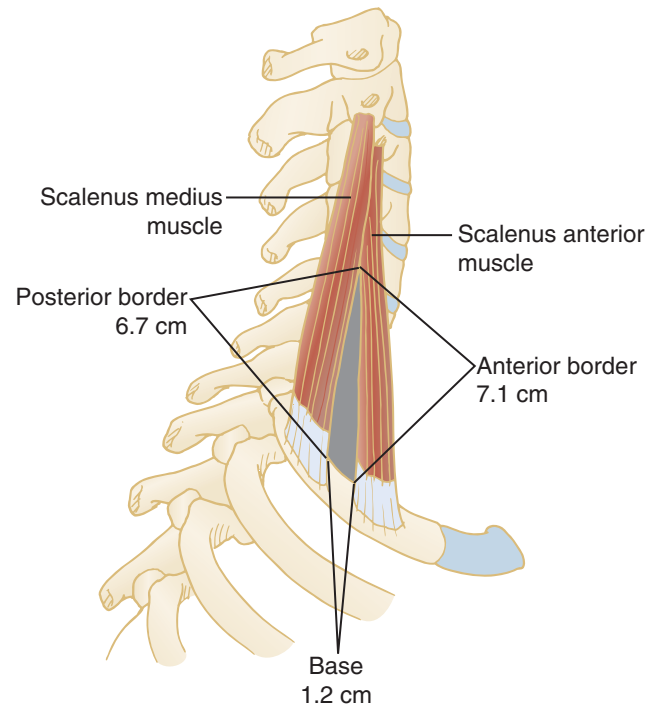


FIGURE 26-3 ■ The scalene (anterior) triangle, with its measurements and the narrow interval through which the neurovascular bundle passes. (From Rosati LM, Lord JV: *Neurovascular compression syndromes of the shoulder girdle*, New York, 1961, Grune & Stratton.)

COMPRESSION FACTORS

Many factors may cause compression of the neurovascular bundle at the thoracic outlet, but the basic factor is deranged anatomy, to which congenital, traumatic, and, occasionally, atherosclerotic factors may contribute (Box 26-1).²³ Bony abnormalities are present in approximately 30% of patients as cervical rib, bifid first rib, and fusion of first and second ribs; clavicular deformities; or previous thoracoplasties.³ These abnormalities can be visualized on the plain posteroanterior chest film, but special radiographic views of the lower cervical spine may be required in some cases of cervical ribs.

SYMPTOMS AND SIGNS

The symptoms of TOS depend on whether the nerves or blood vessels, or both, are compressed in the cervicoaxillary canal. Neurogenic manifestations are observed more frequently than vascular ones. Symptoms consist of pain and paresthesias, which are present in approximately 95% of cases, and motor weakness and occasionally atrophy of hypothenar and interosseous muscles, which is the ulnar type of atrophy, in approximately 10%. The symptoms occur most commonly in areas supplied by the ulnar nerve, which include the medial aspects of the arm and hand, the fifth finger, and the lateral aspects of the fourth finger. The onset of pain is usually insidious and commonly involves the neck, shoulder, arm, and hand. The pain and paresthesias may be precipitated by

BOX 26-1 Causes of Neurovascular Compression Syndromes

ANATOMIC

- Potential sites of neurovascular compression
 - Interscalene triangle
 - Costoclavicular space
 - Subcoracoid area

CONGENITAL

- Cervical rib and its fascial remnants
- Rudimentary first thoracic rib
- Scalene muscles
 - Anterior
 - Middle
 - Minimus
- Adventitious fibrous bands
- Bifid clavicle or first rib
- Exostosis of first thoracic rib
- Enlarged transverse process of C7
- Omohyoid muscle
- Anomalous course of transverse cervical artery
- Abnormal lateral insertion of costoclavicular ligament
- Flat clavicle

TRAUMATIC

- Fracture of clavicle
- Dislocation of head of humerus
- Crushing injury to upper thorax
- Sudden, unaccustomed muscular efforts involving shoulder girdle muscles
- Cervical spondylosis and injuries to cervical spine

ATHEROSCLEROSIS

strenuous physical exercise or sustained physical effort with the arm in abduction and the neck in hyperextension. Symptoms may be initiated by sleeping with the arms abducted and the hands clasped behind the neck. In other cases, trauma to the upper extremities or the cervical spine is a precipitating factor. Physical examination may be noncontributory. When present, objective physical findings usually consist of hypesthesia along the medial aspects of the forearm and hand. Atrophy, when evident, is usually described in the hypothenar and interosseous muscles with clawing of the fourth and fifth fingers. In the upper type of TOS, in which components of C5 and C6 are involved in compression, pain is usually in the deltoid area and the lateral aspects of the arm. The presence of this pain should induce action to exclude a herniated cervical disc.²³ Entrapment of C7 and C8 components that contribute to the median nerve produces symptoms in the index finger and sometimes the middle finger. Components of C5, C6, C7, C8, and T1 can occur at the thoracic outlet by a cervical rib and produce symptoms of various degrees in the distribution of these nerves (Fig. 26-4).

In some patients, the pain is atypical, involving the anterior chest wall or parascapular area, and is termed *pseudoangina* because it simulates angina pectoris. These patients may have normal coronary arteriograms and ulnar nerve conduction velocities decreased to values of

48 m/sec and less, which strongly suggests the diagnosis of TOS. The shoulder, arm, and hand symptoms that usually provide the clue for the diagnosis of TOS may initially be absent or minimal compared with the severity of the chest pain. The diagnosis of TOS is frequently overlooked; many of these patients are committed to becoming “cardiac cripples” without an appropriate diagnosis, or they develop severe psychological depression when told that their coronary arteries are normal and that they have no significant cause for their pain.³⁹

Symptoms of arterial compression include coldness, weakness, easy fatigability of the arm and hand, and pain that is usually diffuse.^{40,41} Raynaud phenomenon is noted in approximately 7.5% of patients with TOS.⁴⁰ Unlike Raynaud disease, which is usually bilateral and symmetrical and elicited by cold or emotion, Raynaud phenomenon in neurovascular compression is usually unilateral and is more likely to be precipitated by hyperabduction of the involved arm, turning of the head, or carrying of heavy objects. Sensitivity to cold may also be present. Symptoms include sudden onset of cold and blanching of one or more fingers, followed slowly by cyanosis and persistent rubor. Vascular symptoms in neurovascular compression may be precursors of permanent arterial thrombosis.²³ Arterial occlusion, usually of the subclavian artery, when present, is manifested by persistent coldness, cyanosis or pallor of the fingers, and in some instances, ulceration or gangrene. Palpation in the parascapular area may reveal prominent pulsation, which indicates poststenotic dilation or aneurysm of the subclavian artery (Fig. 26-5).⁴²

Less frequently, the symptoms are those of venous obstruction or occlusion, commonly recognized as effort thrombosis, or Paget-Schroetter syndrome. The condition characteristically results in edema, discoloration of the arm, distention of the superficial veins of the limb and shoulder, and some degree of aches and pains. In some patients, the condition is observed on waking; in others, it follows sustained efforts with the arm in abduction. Sudden backward and downward bracing of the shoulders or heavy lifting or strenuous physical activity involving the arm may constrict the vein and initiate venospasm, with or without subsequent thrombosis. On examination, in cases of definite venous thrombosis, there is usually moderate tenderness over the axillary vein, and a cordlike structure may be felt that corresponds to the course of the vein. The acute symptoms may subside in a few weeks or days as the collateral circulation develops. Recurrence follows with inadequacy of the collateral circulation.⁴³

Objective physical findings are more common in patients with primarily vascular rather than neural compression. Loss or diminution of radial pulse and reproduction of symptoms can be elicited by the three classic clinical maneuvers: the Adson or scalene test,⁴⁴ the costoclavicular test, and the hyperabduction test.⁴⁵

DIAGNOSIS

The diagnosis of TOS includes history, physical and neurologic examinations, radiography of the chest and cervical spine, electromyography, and ulnar nerve conduction

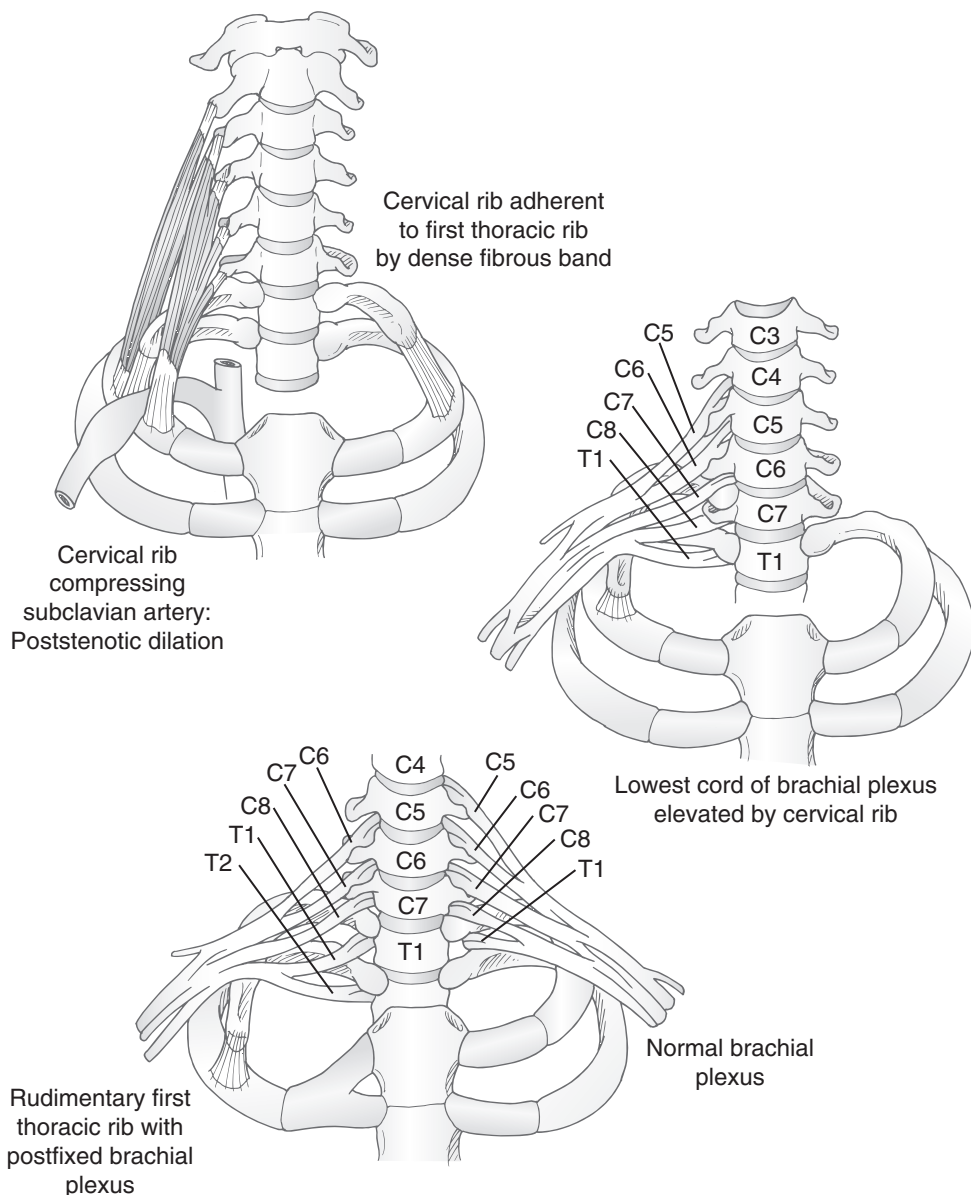


FIGURE 26-4 ■ Compression caused by congenital rib abnormalities. (Reprinted from www.netterimages.com. © Elsevier, Inc. All rights reserved.)

velocity (UNCV). In some cases with atypical manifestations, other diagnostic procedures such as cervical myelography, periphery⁴² or coronary arteriography, or phlebography⁴⁶ should be considered. A detailed history and physical and neurologic examinations can often result in a tentative diagnosis of neurovascular compression. This diagnosis is strengthened when one or more of the classic clinical maneuvers is positive and is confirmed by the finding of decreased UNCV.⁴⁷

Clinical Maneuvers

The clinical evaluation is best based on the physical findings of loss or decrease of radial pulses and reproduction of symptoms that can be elicited by the following three classic maneuvers.^{23,45}

The Adson or scalene test (Fig. 26-6)⁴⁴ tightens the anterior and middle scalene muscles and thus decreases

the interspace and magnifies any preexisting compression of the subclavian artery and brachial plexus. The patient is instructed to take and hold a deep breath, extend the neck fully, and turn the head toward the side. Obliteration or decrease of the radial pulse suggests compression.

For the costoclavicular test (military position; Fig. 26-7), the shoulders are drawn downward and backward. This maneuver narrows the costoclavicular space by approximating the clavicle to the first rib and thus tends to compress the neurovascular bundle. Changes in the radial pulse with production of symptoms indicate compression.

For the hyperabduction test (Fig. 26-8), the arm is hyperabducted to 180 degrees, resulting in the components of the neurovascular bundle being pulled around the pectoralis minor tendon, the coracoid process, and the head of the humerus. A decrease in the radial pulse suggests compression.

Radiographic Findings

Films of the chest and cervical spine are helpful in revealing bony abnormalities, particularly cervical ribs (Fig. 26-9) and bony degenerative changes. If osteophytic changes and intervertebral space narrowing are present on plain cervical films, a cervical computed tomographic scan should be obtained to rule out bony encroachment and narrowing of the spinal canal and the intervertebral foramina.

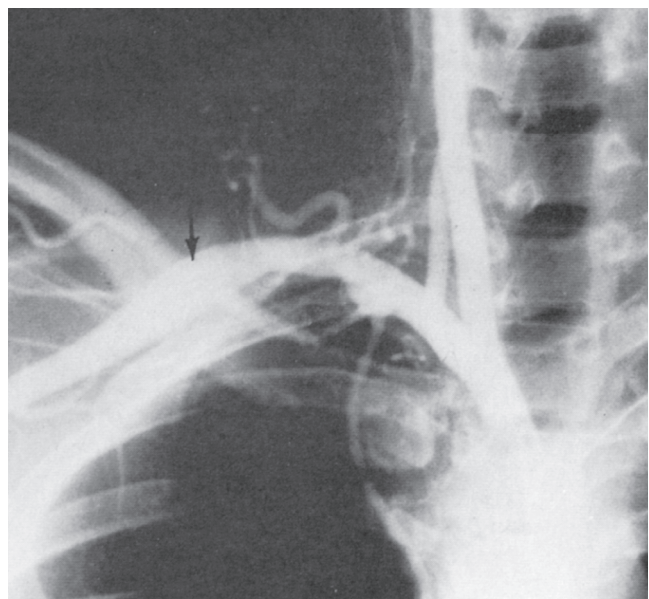


FIGURE 26-5 ■ Arteriogram showing poststenotic dilation (arrow) of the right subclavian artery secondary to thoracic outlet compression.

Nerve Conduction Velocity and Electromyography

This test is widely used in differential diagnosis of the causes of arm pain, tingling, and numbness with or without motor weakness of the hand. Such symptoms can result from compression at various sites: in the spine; at the thoracic outlet; around the elbow, where it causes tardy ulnar nerve palsy; or on the flexor aspects of the wrist, where it produces carpal tunnel syndrome. For diagnosis and localization of the site of compression, cathodal stimulation is applied at various points along the course of the nerve. Motor conduction velocities of the ulnar, median, radial, and musculocutaneous nerves can be measured reliably.⁴⁸ Caldwell and colleagues³³ have improved the technique of measuring UNCV for evaluation of patients with thoracic outlet compression. Conduction velocities over proximal and distal segments of the ulnar nerve are determined by recording the action potentials generated in the hypothenar or first dorsal interosseous muscles. The points of stimulation are the supraclavicular fossa, middle upper arm, below the elbow, and at the wrist (Fig. 26-10).⁴¹

Method of Measuring Conduction Velocities

Equipment

Electromyographic examination of each upper extremity and determination of the conduction velocities are done with the Meditron 201 AD or 312 or the TECA-3 electromyograph. Coaxial cable with three needles or surface electrodes is used to record muscle potentials, which appear on the fluorescent screen (Fig. 26-11).

Adson maneuver
for diagnosis of
scalenus anticus syndrome

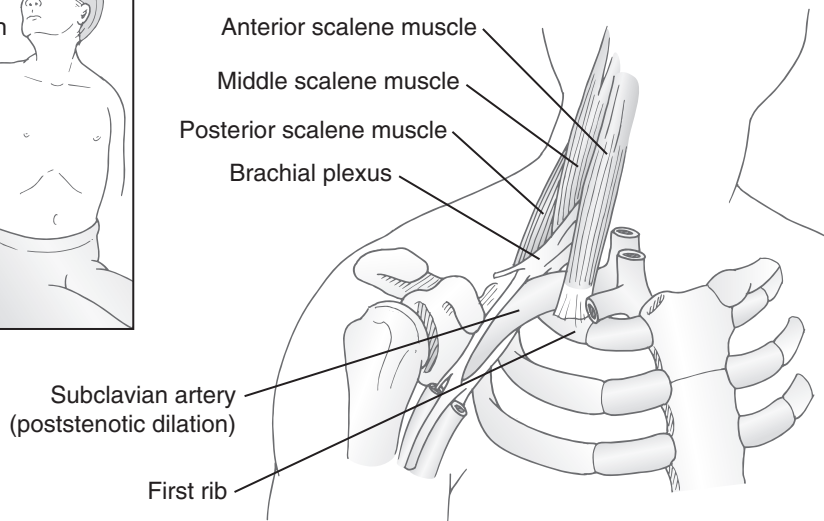
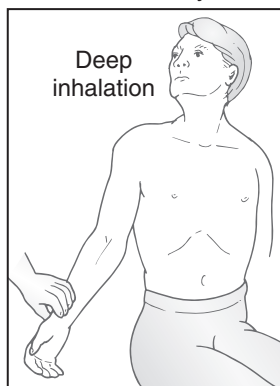


FIGURE 26-6 ■ Adson maneuver. Relationship of the scalene triangle to the neurovascular bundle. (Reprinted from www.netterimages.com. © Elsevier, Inc. All rights reserved.)

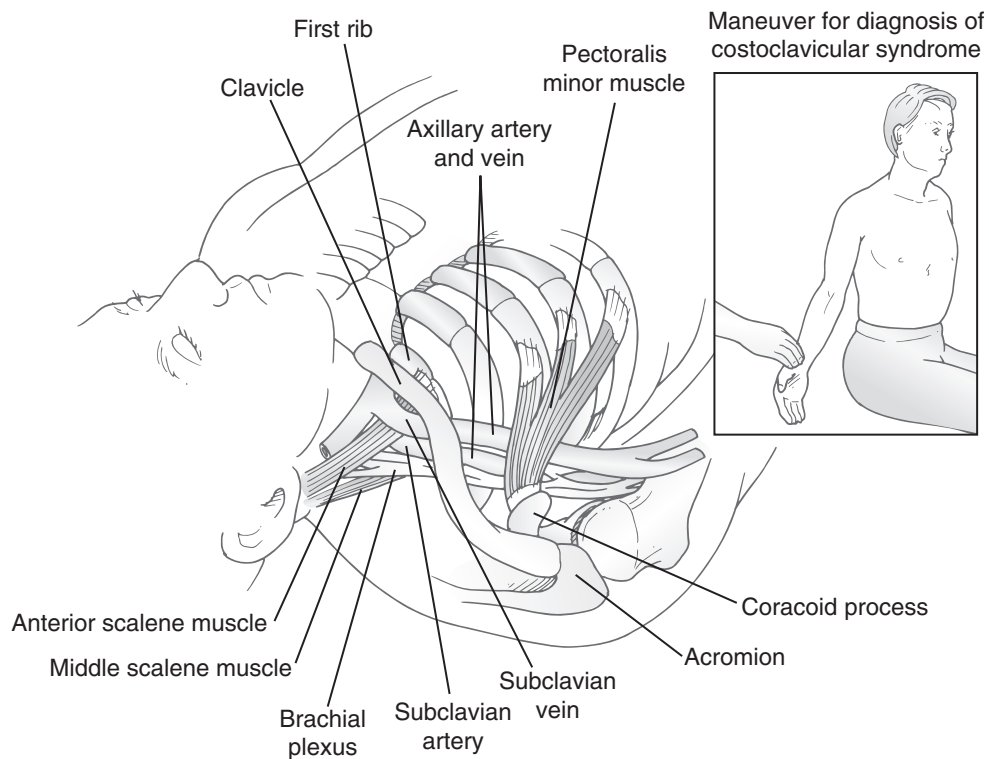


FIGURE 26-7 ■ Costoclavicular maneuver (military position). Relationship of the costoclavicular space to the neurovascular bundle. (Reprinted from www.netterimages.com. © Elsevier, Inc. All rights reserved.)

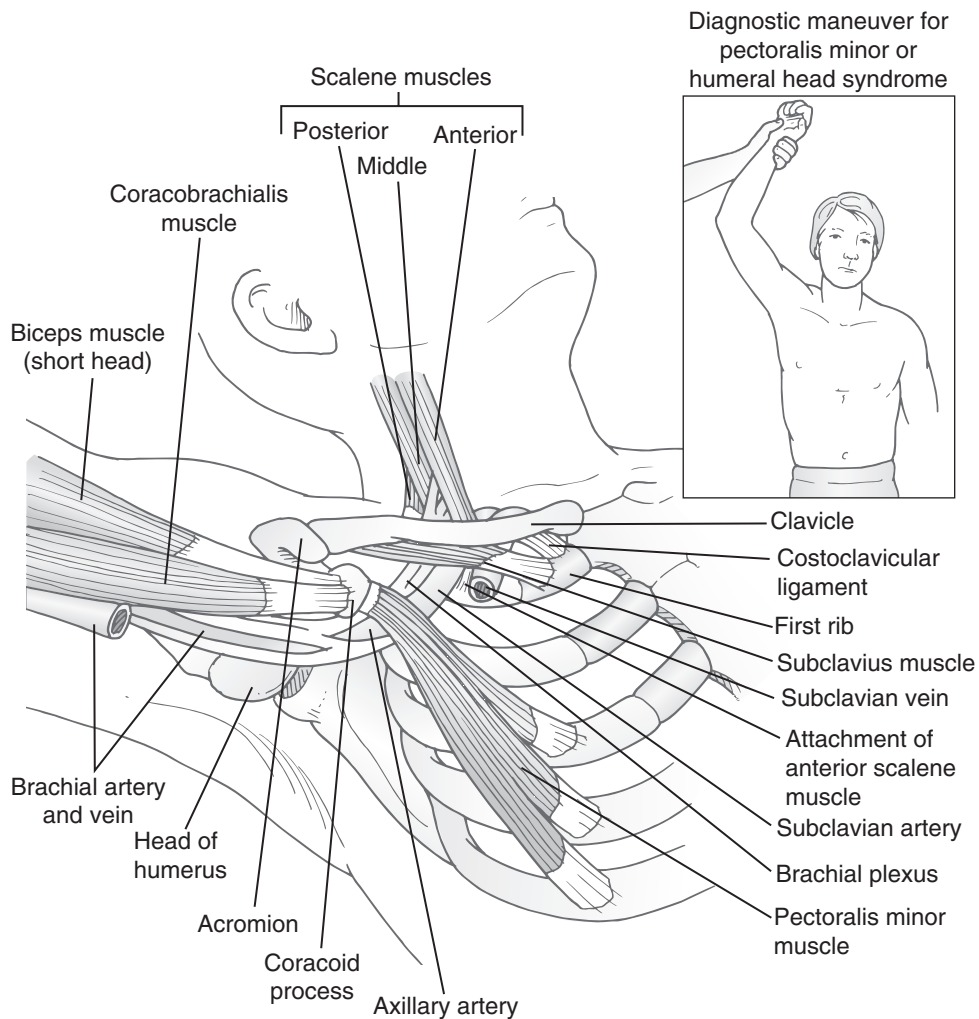


FIGURE 26-8 ■ Hyperabduction maneuver. Relationship of the neurovascular bundle to the pectoralis minor tendon, the coracoid process, and the humeral head (pulley effect). (Reprinted from www.netterimages.com. © Elsevier, Inc. All rights reserved.)

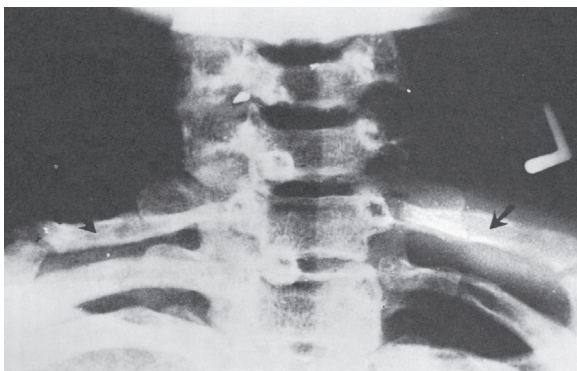


FIGURE 26-9 ■ Radiographic film showing bilateral cervical ribs (arrows).



FIGURE 26-11 ■ TECA-3 electromyograph using a coaxial cable and three needles to record generated action potentials.

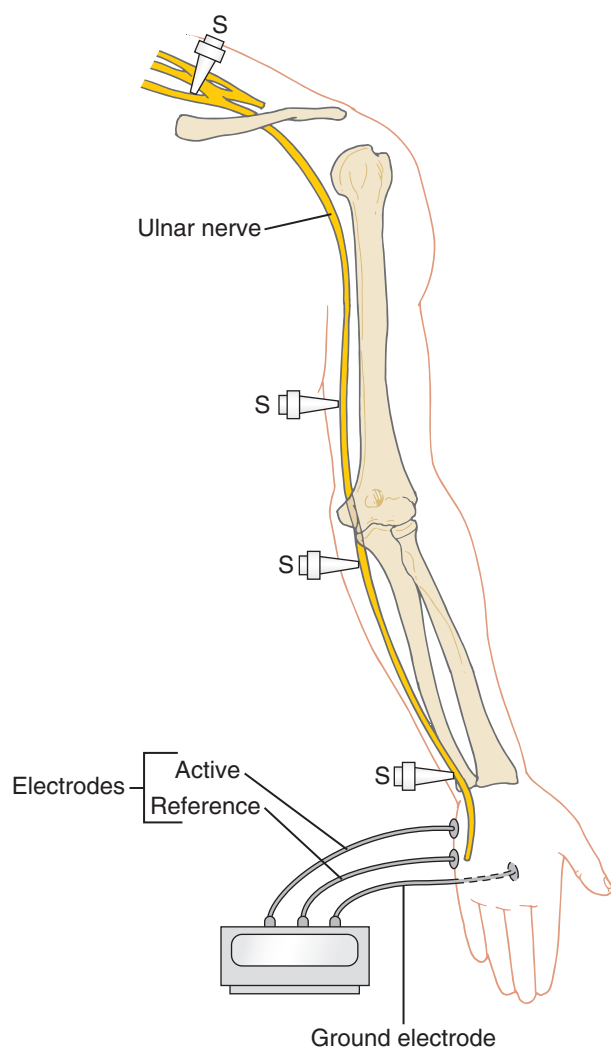


FIGURE 26-10 ■ The four ulnar nerve stimulation points: in the supraclavicular fossa (Erb point over the trunks of the plexus), above the elbow, below the elbow, and at the wrist.

Technique

The conduction velocity is determined with the Krusen-Caldwell technique.³³ The patient is placed on the examination table with the arm fully extended at the elbow and in approximately 20 degrees of abduction at the shoulder



FIGURE 26-12 ■ A stimulating electrode positioned over the cords of the brachial plexus at Erb point in the supraclavicular fossa posterior to the sternocleidomastoid muscle, which is the stimulation site of the brachial plexus across the outlet.

to facilitate stimulation over the course of the ulnar nerve. The ulnar nerve is stimulated at the four points by a special stimulation unit (Fig. 26-12) that imparts an electrical stimulus with strength of 350 V with the patient's load, which is approximately equal to 300 V with the patient's load with a skin resistance of 5000 Ω . Supramaximal stimulation is used at all points to obtain maximal response. The duration of the stimulation is 0.2 msec, except for muscular individuals, for whom it is 0.5 msec. Time of stimulation, conduction delay, and muscle response appear on the TECA screen; time markers occur each millisecond on the sweep.

The latency period to stimulation from the four points of stimulation to the recording electrode is obtained from the TECA digital recorder or calculated from the tracing on the screen.

Calculation of Velocities

After the latencies, which are expressed in milliseconds, are obtained, the distance in millimeters between two

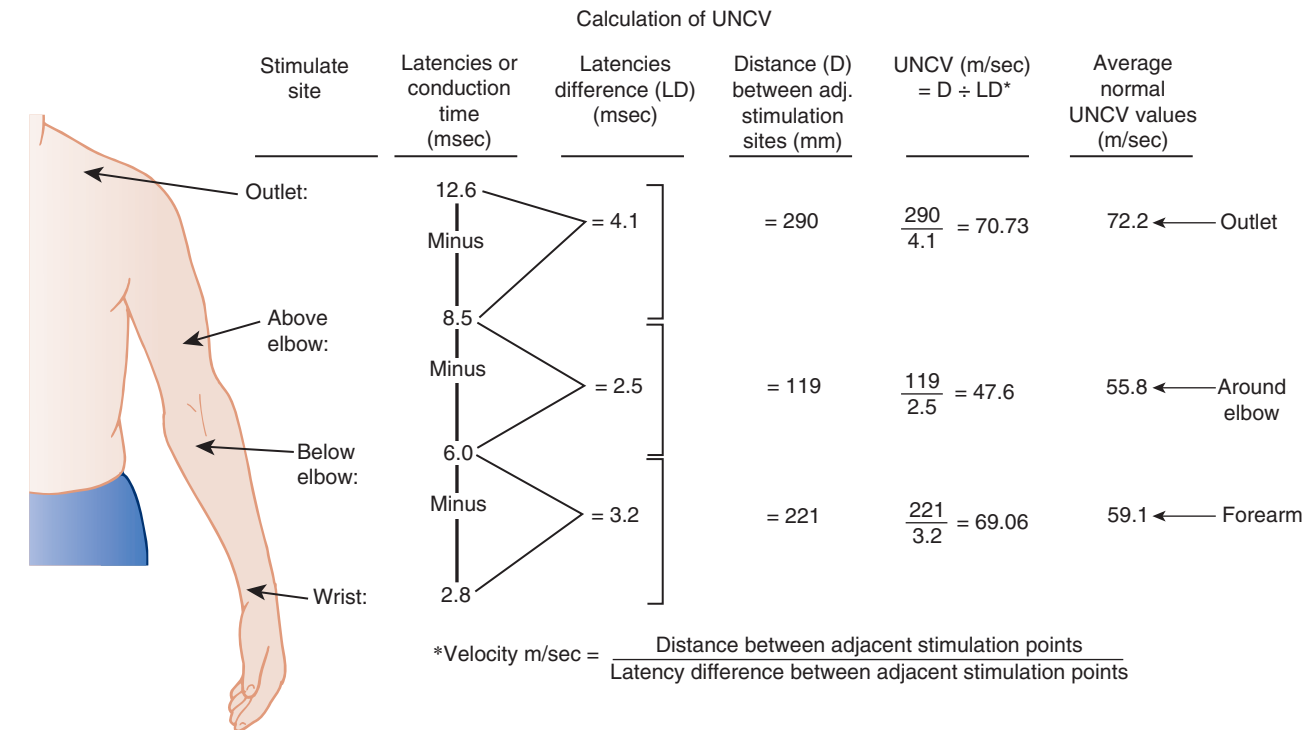


FIGURE 26-13 ■ The sites of stimulation and the formula for calculating ulnar nerve conduction velocity (UNCV).

adjacent sites of stimulation is measured with steel tape. The velocities, which are expressed in meters per second, are calculated by subtracting the distal latency from the proximal latency and dividing the distance between two points of stimulation by the latency difference (Fig. 26-13) according to the following formula:

velocity (m/sec) = distance between adjacent stimulation points (mm) ÷ difference in latency between adjacent stimulation points (msec)

Normal Ulnar Nerve Conduction Velocities

The normal values of the UNCVs according to the Krusen-Caldwell technique³³ are 72 m/sec or greater across the outlet, 55 m/sec or greater around the elbow, and 59 m/sec or greater in the forearm. Wrist delay is 2.5 to 3.5 msec. Decreased velocity in a segment or increased delay at the wrist indicates compression, injury, neuropathy, or neurologic disorders. Decreased velocity across the outlet is consistent with TOS. Decreased velocity around the elbow signifies ulnar nerve entrapment or neuropathy. Increased delay at the wrist is encountered in carpal tunnel syndrome.

Grading of Compression

The clinical picture of TOS correlates fairly well with the conduction velocity across the outlet. Any value less than 70 m/sec indicates neurovascular compression. The severity is graded according to decrease of velocity across the thoracic outlet: compression is called *slight* when the velocity is 66 to 69 m/sec, *mild* when the velocity is 60 to 65 m/sec, *moderate* when the velocity is 55 to 59 m/sec, and *severe* when the velocity is 54 m/sec or less.

Angiography

Simple clinical observations usually suffice to determine the degree of vascular impairment in the upper extremity. Peripheral angiography^{42,49} is indicated in some cases, as in the presence of a paraclavicular pulsating mass, the absence of radial pulse, or the presence of supraclavicular or infraclavicular bruits. Retrograde or antegrade arteriograms of the subclavian and brachial arteries should be obtained to demonstrate or localize the pathology. In cases of venous stenosis or obstruction, as in Paget-Schroetter syndrome, phlebography is used to determine the extent of thrombosis and the status of the collateral circulation (Fig. 26-14).

Magnetic resonance imaging in association with postural maneuvers is gaining popularity in the workup and diagnosis of TOS. Magnetic resonance imaging allows for better visualization and identification of the different compartments of the cervicothoracic-brachial junction as well as demonstration of any compression of the neural or vascular structures involved.⁵⁰⁻⁵²

The study involves imaging of the involved shoulder with the patient's affected arm at the side and over the head to determine the impact of the first rib on the vessels and nerves.

DIFFERENTIAL DIAGNOSIS

TOS should be differentiated from various neurologic, vascular, cardiac, pulmonary, and esophageal conditions (Box 26-2).^{3,23,47,53}

Neurologic causes of pain in the shoulder and arm are more difficult to recognize and may arise from involvement of the nervous system in the spine, the brachial plexus, or the peripheral nerves. A common neurologic

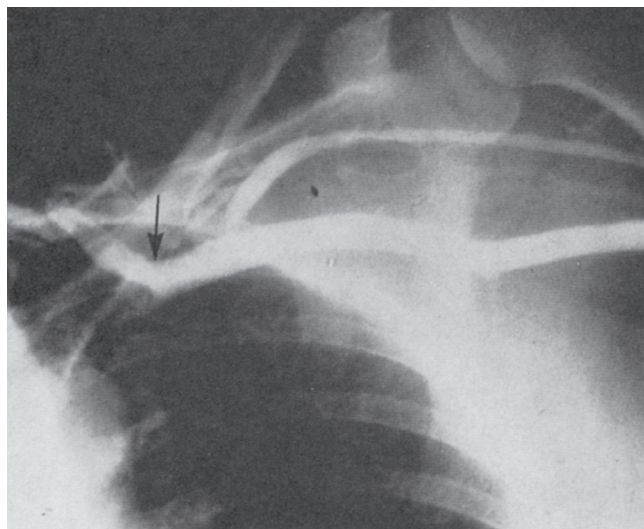


FIGURE 26-14 ■ Phlebogram showing total occlusion (arrow) with minimal collateral circulation of the left subclavian vein resulting from thoracic outlet compression. At operation, no thrombus was present in the vein, and obstruction was relieved by removing the first rib.

BOX 26-2 Differential Diagnoses of Thoracic Outlet Syndrome Nerve Compression

CERVICAL SPINE

- Ruptured intervertebral disc
- Degenerative disease
- Osteoarthritis

TUMORS

- Spinal cord tumors
- Brachial plexus superior pulmonary sulcus tumors

PERIPHERAL NERVE

- Postural palsy
- Peripheral nerves entrapment neuropathy
- Carpal tunnel—median nerve
- Ulnar nerve—elbow
- Radial nerve
- Suprascapular nerve
- Medical neuropathies

VASCULAR PHENOMENA

- Arterial arteriosclerosis-aneurysm occlusive
- Thromboangiitis obliterans
- Embolism
- Vasculitis, collagen disease, panniculitis
- Venous thrombophlebitis
- Mediastinal venous obstruction
- Raynaud disease
- Reflex vasomotor dystrophy
- Causalgia

OTHER DISEASES

- Angina pectoris
- Esophageal spasm

cause of pain in the upper extremities is a herniated cervical intervertebral disc. The herniation almost invariably occurs at the interspace between the fifth and the sixth or the sixth and the seventh cervical vertebrae and produces characteristic symptoms. Onset of pain and stiffness of the neck is manifested with varying frequency. The pain radiates along the medial border of the scapula into the shoulder, occasionally into the anterior chest wall, and down the lateral aspect of the arm, at times into the fingers. Numbness and paresthesias in the fingers may be present. The segmental distribution of pain is a prominent feature. A herniated disc between the C5 and the C6 vertebrae, which compresses the C6 nerve root, causes pain or numbness primarily in the thumb and to a lesser extent in the index finger. The biceps muscle and the radial wrist extensor are weak, and the reflex of the biceps muscle is reduced or abolished. A herniated disc between the C6 and the C7 vertebrae, which compresses the C7 nerve root, produces pain or numbness in the index finger and weakness of index finger flexion and ulnar wrist extension; the triceps muscle is weak and its reflex is reduced or abolished. Any of these herniated discs can cause numbness along the ulnar border of the arm and hand because of spasm of the scalenus anticus muscle. Rarely, pain and paresthesias in the ulnar distribution may be related to herniation between the C7 and the T1 vertebrae, which causes compression of the C8 nerve root. Compression of the latter nerve root produces weakness of intrinsic hand muscles.^{23,54} Although rupture of the fifth and sixth discs produces hypesthesia in this area, only rupture of the seventh disc produces pain down the medial aspect of the arm.²³

The diagnosis of a ruptured cervical disc is based primarily on the history and physical findings; lateral radiography of the cervical spine reveals a loss or reversal of cervical curvature, with the apex of the reversal of curvature at the level of the disc being involved. Electromyography can localize the site and extent of the nerve root irritation. When a herniated disc is suggested, cervical myelography should be used to confirm the diagnosis.^{23,54}

Another condition that causes upper extremity pain is cervical spondylosis, a degenerative disease of the intervertebral disc and the adjacent vertebral margin that causes spur formation and the production of ridges into the spinal canal or intervertebral foramina. Radiographic films and a computed tomographic scan of the cervical spine and electromyography help in making the diagnosis of this condition (Fig. 26-15).

Several arterial and venous conditions can be confused with TOS (see Box 26-2). The differentiation can often be made clinically.²³

In atypical patients with chest pain alone, it is important to consider TOS in addition to angina pectoris. Exercise stress testing and coronary angiography may exclude coronary artery disease when there is a high index of suspicion of angina pectoris.^{39,45}

THERAPY

Patients with neurogenic TOS should be given physiotherapy when the diagnosis is made. Proper physiotherapy

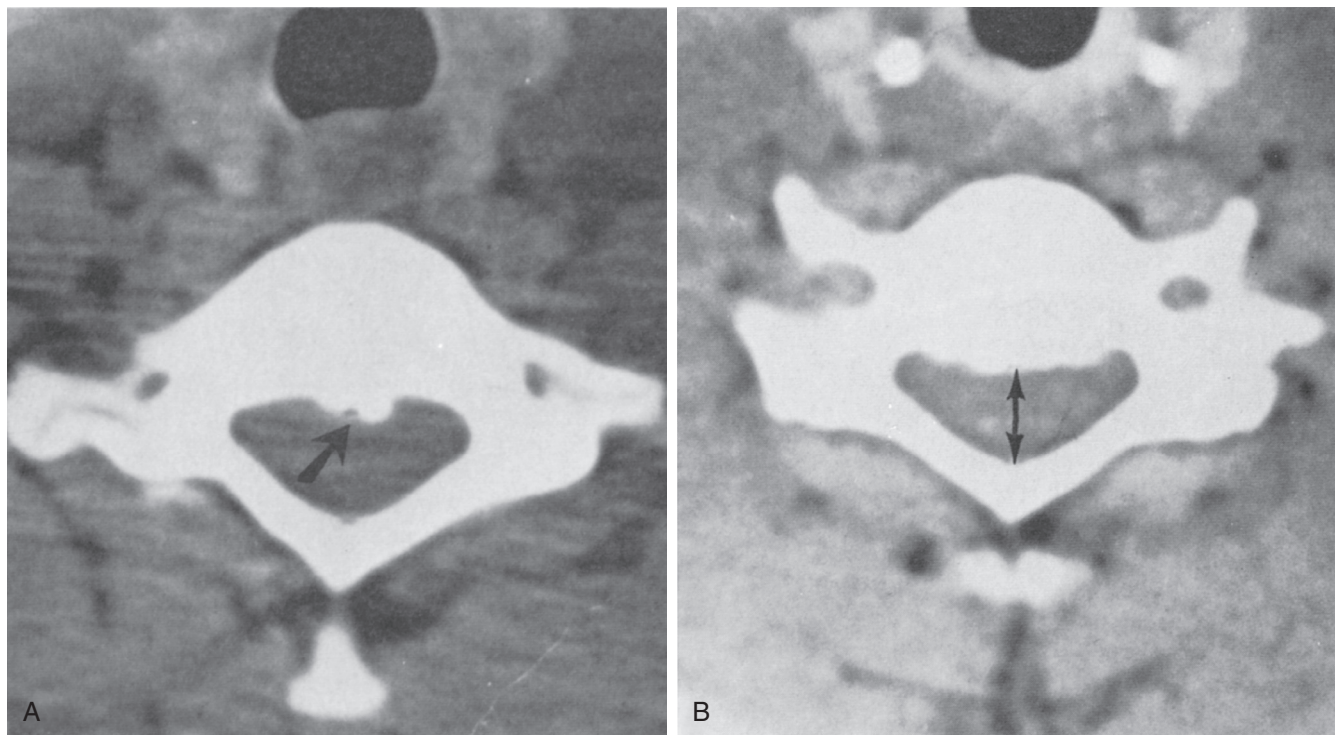


FIGURE 26-15 ■ Computed tomographic scan showing osteophytic ingrowth (arrow) in the spinal canal (A) and narrowing of the anteroposterior diameter of the spinal canal (B; double-headed arrow) in a patient with the typical clinical picture of thoracic outlet syndrome.

includes heat massages, active neck exercises, stretching of the scalenus muscles, strengthening of the upper trapezius muscle, and posture instruction. Because sagging of the shoulder girdle, which is common among middle-aged people, is a major cause in this syndrome, many patients with less severe cases are improved by strengthening the shoulder girdle and by improving posture.⁵⁴

Most patients with TOS who have UNCVs of more than 60 m/sec improve with conservative management. If the conduction velocity is below that level, most patients, despite physiotherapy, may remain symptomatic, and surgical resection of the first rib and correction of other bony abnormalities may be needed to provide relief of symptoms.^{40,41,55}

If symptoms of neurovascular compression continue after physiotherapy, and the conduction velocity shows slight or no improvement or regression, surgical resection of the first rib and cervical rib, when present, should be considered.^{40,41,55} Clagett² popularized the high posterior thoracoplasty approach for first rib resection, Falconer and Li³¹ emphasized the anterior approach, and Roos³² introduced the transaxillary route in 1966.

The transaxillary route is an expedient approach for complete removal of the first rib with decompression of the seventh and eighth cervical and first thoracic nerve roots and the lower trunks of the brachial plexus. First rib resection can be performed without the need for major muscle division, as in the posterior approach²; the need for retraction of the brachial plexus, as in the anterior supraclavicular approach³¹; and the difficulty of removing the posterior segment of the rib, as in the infraclavicular approach. In addition, first rib resection shortens the postoperative disability and provides better

cosmetic results than the anterior and posterior approaches do, particularly because 80% of patients are female.^{40,41,47,56}

Technique of Transaxillary Resection of the First Rib

The patient is placed in the lateral position with the involved extremity abducted to 90 degrees by traction straps wrapped around the forearm and attached to an overhead pulley. An appropriate weight, usually 2 lb (907 g), is used to maintain this position without undue traction (Fig. 26-16).^{3,45} Two arm holders are used to hold the arm at 90 degrees from the body and to prevent further hyperabduction.

A 3- to 4-inch transverse incision is made in the axilla below the hairline between the pectoralis major and the latissimus dorsi muscles and is then deepened to the external thoracic fascia (Fig. 26-17). Care should be taken to prevent injury to the intercostobrachial cutaneous nerve, which passes from the chest wall to the subcutaneous tissue in the center of the operative field. The use of electrocautery in that area should be minimized.

The dissection is extended cephalad along the external thoracic fascia up to the first rib. With gentle dissection, the neurovascular bundle and its relationship to the first rib and both scalenus muscles are clearly outlined, which helps to avoid injury to its components (Fig. 26-18). The insertion of the scalenus anticus muscle is identified, skeletonized, and divided (Fig. 26-19). The first rib is dissected subperiosteally with a periosteal elevator and is separated carefully from the underlying pleura to avoid pneumothorax. A segment of the middle portion of the rib is

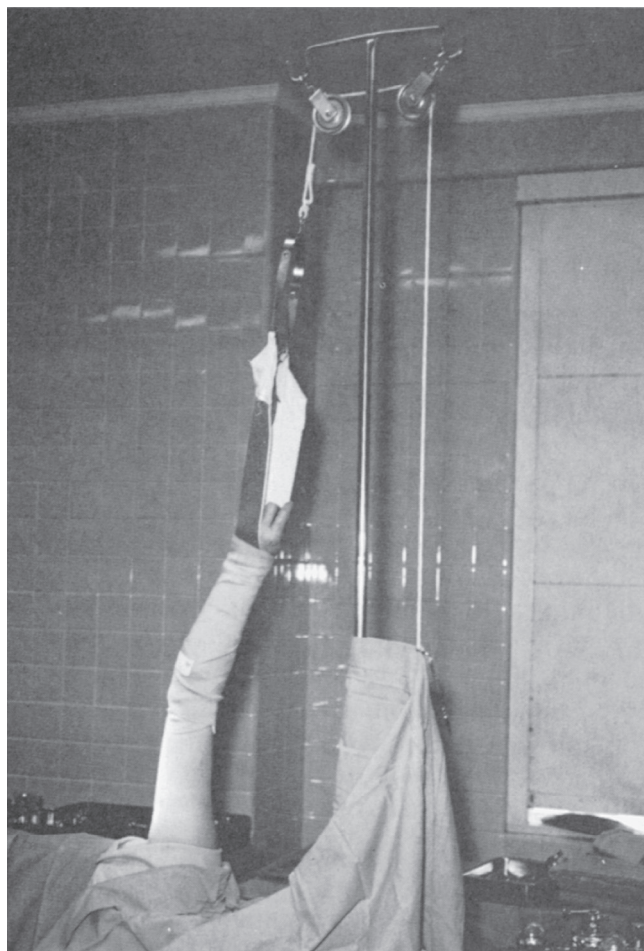


FIGURE 26-16 ■ The arm is abducted to 90 degrees by traction straps on the forearm and is attached to an overhead pulley.

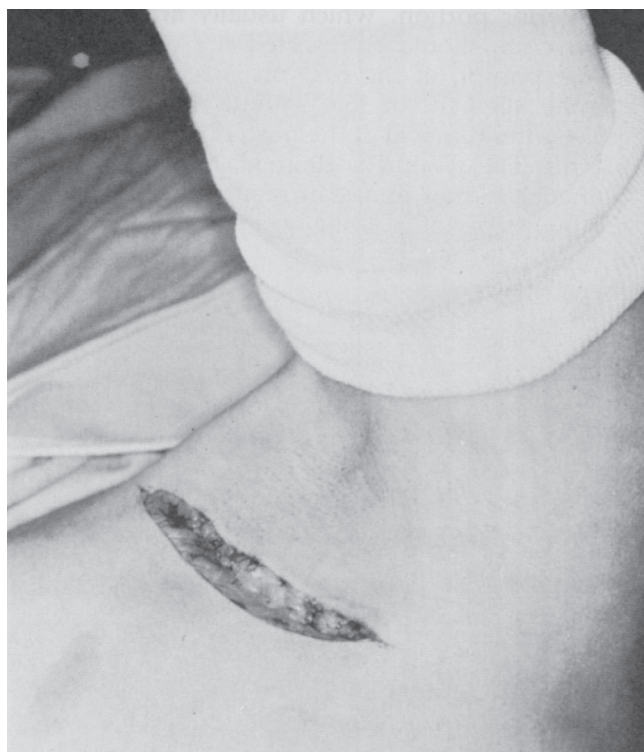


FIGURE 26-17 ■ A transverse incision is made in the axilla below the hairline between the pectoralis major and the latissimus dorsi muscles and is extended to the chest wall.

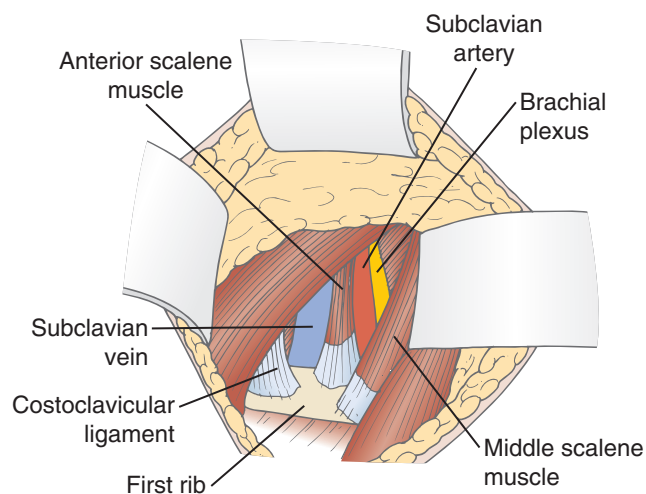


FIGURE 26-18 ■ Schematic drawing showing the relationship of the neurovascular bundle to the scalene muscles, first rib, costoclavicular ligament, and subclavius muscle.

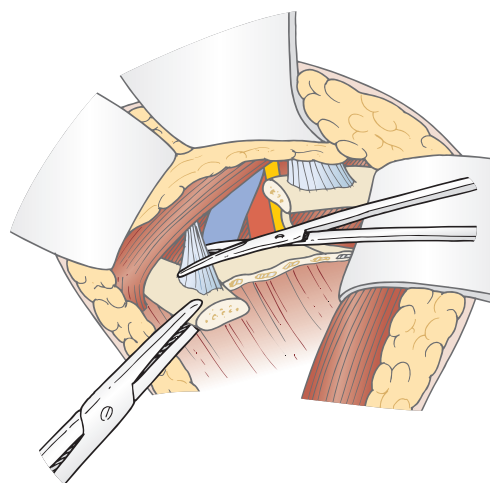


FIGURE 26-19 ■ Schematic drawing showing division of the insertion of the scalenus anterior muscle on the first rib and removal of a segment of the midportion of the first rib.

resected, followed by subperiosteal dissection and resection of the anterior portion of the rib at the costochondral junction. After the costoclavicular ligament is cut, the posterior segment of the rib is similarly dissected subperiosteally and resected in fragments, including the articulation with the transverse process, the neck, and the head. The scalenus medius muscle should not be cut from its insertion on the second rib, but rather stripped with a periosteal elevator to avoid injury to the long thoracic nerve that lies on its posterior margin. The neck and head of the first rib are removed completely with a long, special Urschel double-action pituitary and Urschel Lexel rongeurs. The eighth cervical and first thoracic nerve roots can be visualized at this point. If a cervical rib is present, its anterior portion, which usually articulates with the first rib, should be resected when the middle portion of the first rib is removed. The remaining segment of the cervical rib should be removed after removal of the posterior segments of the first rib. The wound is drained,

and only the subcutaneous tissues and skin require closure, because no large muscles have been divided. The patient is encouraged to use the arm for self-care, but to avoid heavy lifting until at least 3 months after operation. Cervical muscle stretching should be started at the end of the first week, and gentle exercising of the arm can be started at the end of the third week after operation.

It is preferable to remove the first rib entirely, including the head and neck, to avoid future irritation of the plexus, because a residual portion, particularly if long, will cause recurrence of symptoms.

Technique of Using Video-Assisted Thoracic Surgery for Transaxillary Resection of the First Rib

A more recent option for the transaxillary resection of the first rib is a video-assisted thoracic surgery (VATS) approach for TOS.

After the administration of single-lung, general anesthesia with a double lumen endotracheal tube, the patient is placed in the lateral decubitus position with the arm resting on pillows for support or on an airplane arm support. VATS is performed with a 5-mm, 30-degree thoracoscope introduced through the fifth intercostal space at the midaxillary line. Optimal exposure for the first rib is achieved with reverse Trendelenburg and CO₂ insufflation to an intrathoracic pressure of 6 to 10 mm Hg. A 3-cm incision is made at the bottom of the hair line in the midaxillary line between the pectoralis and latissimus dorsi muscles (Fig. 26-20). Care is taken to minimize the use of electrocautery near the intercostobrachial cutaneous nerve.

Through the axillary incision, blunt dissection is performed on the surface of the chest wall superiorly to the first rib. The first rib is identified by its characteristic flat, broad surface, which is different from the other ribs and

visualization of the subclavian artery in the cupola. A periosteal elevator is then used to dissect the lateral surface of the rib. To protect the neurovascular bundle, the surgeon's index finger is kept between the brachial plexus and the area of the rib being dissected. The dissection is sequentially carried out on the lateral, inferior, and the pleural surfaces of the rib. At that point, the pleura near the second rib is opened to see the surface of the dissected rib. By opening the pleura near the second rib, the intercostal muscle that hangs in to the pleural space obstructs the view of the first rib less than if the pleura is entered near the first rib (Figs. 26-21 and 26-22).

The first rib can now be seen easily. An index finger is placed between the superior aspect of the first rib and the brachial plexus to protect the nerves, as a right angle clamp is passed over the superior aspect of the first rib to ensure that complete circumferential dissection has been achieved. The right angle clamp is spread widely, resecting a 1-cm portion of the first rib in the midaxillary line (Figs. 26-23 and 26-24) so that the surgeon can push the

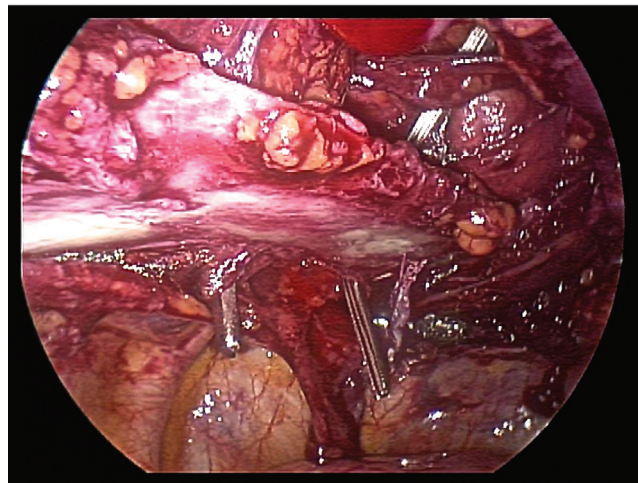


FIGURE 26-21 ■ Dissection and mobilization of the first rib.



FIGURE 26-20 ■ The incisions for a video-assisted thoracic surgery (VATS) first rib resection are shown (arrows). A 2-cm incision is made over the third intercostal space at the bottom of the hair line in the midaxillary line between the pectoralis and latissimus dorsi muscles. VATS is performed with a 5-mm, 30-degree thoracoscope introduced into the fifth intercostal space at the midaxillary line, where a chest tube is eventually introduced.

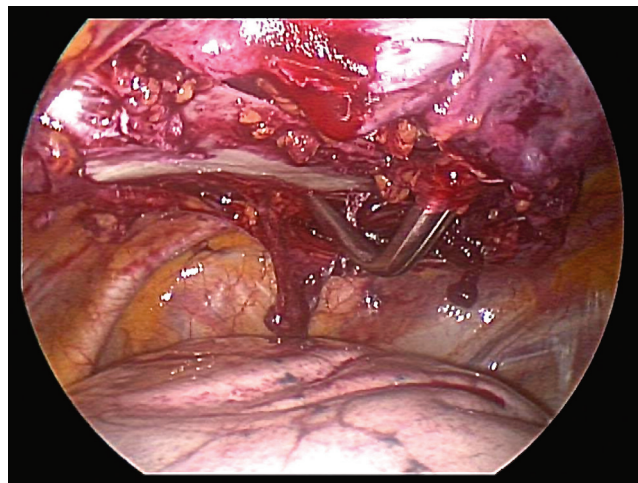


FIGURE 26-22 ■ The first rib is mobilized, and a right angle is shown dissecting along the superior and inferior aspect of the rib.

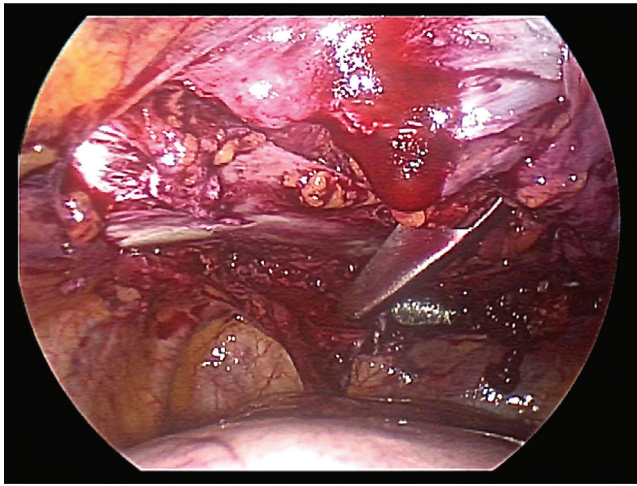


FIGURE 26-23 ■ A rongeur is used to resect a 1-cm portion of the first rib in the midaxillary line. This transection allows the rib to become destabilized to facilitate disarticulation.

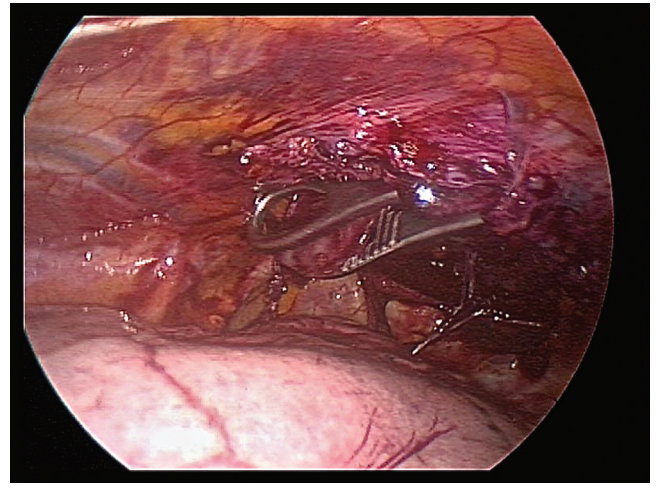


FIGURE 26-25 ■ Disarticulation and removal of the first rib anteriorly from its sternal attachment.

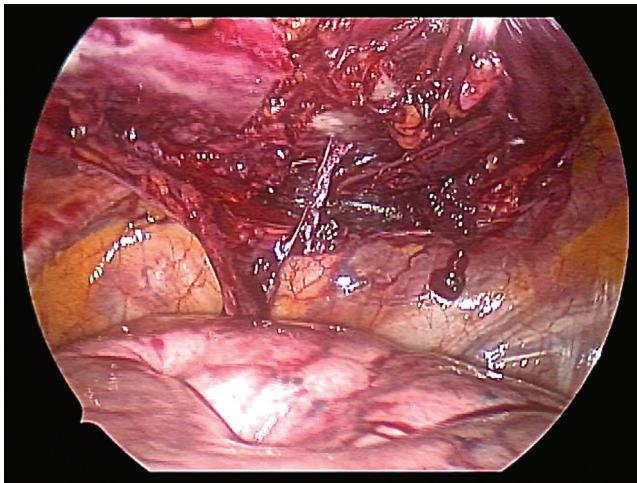


FIGURE 26-24 ■ A 1-cm portion of the rib has been removed by the rongeur. The rib is now destabilized, allowing for easier disarticulation.

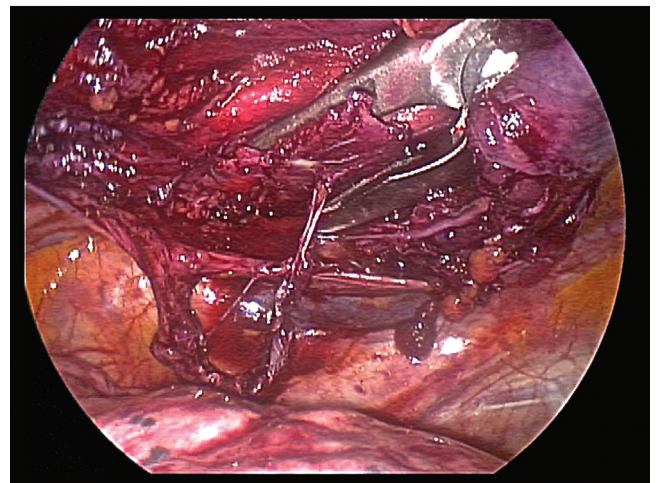


FIGURE 26-26 ■ Disarticulation and removal of the first rib posteriorly from its vertebral attachment.

rib caudally. This greatly facilitates complete mobilization of the rib to the sternum (anteriorly) and the vertebral bodies (posteriorly). Once the rib is completely mobilized, it is cut adjacent to the sternum anteriorly and disarticulated from the vertebral body posteriorly (Figs. 26-25 and 26-26). If there is difficulty with disarticulation, the rib is cut flush with the vertebral bodies posteriorly. Once the rib is completely removed, the axillary structures are easily visualized in their decompressed state (Fig. 26-27).

EFFORT THROMBOSIS: PAGET-SCHROETTER SYNDROME

Effort thrombosis of the axillary-subclavian vein (Paget-Schroetter syndrome) is generally secondary to unusual or excessive use of the arm in addition to the presence of one or more compressive elements in the thoracic outlet.^{46,57}

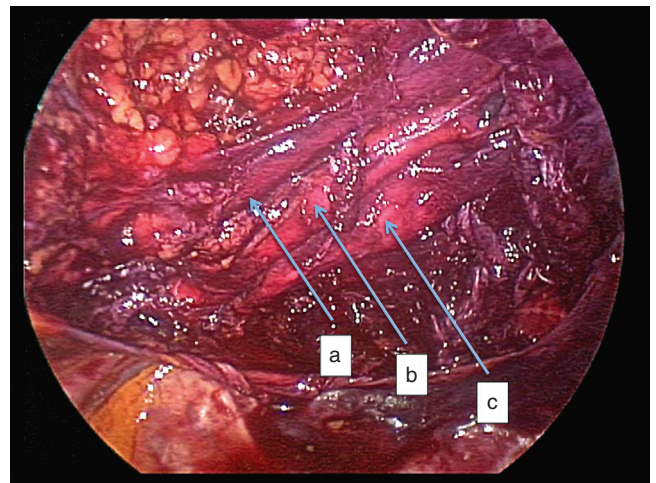


FIGURE 26-27 ■ Once the rib is completely removed, the axillary structures can be visualized in their decompressed state: (a) subclavian vein, (b) subclavian artery, (c) brachial plexus.

Historically, Paget⁵⁸ in 1875 in London and Von Schroetter⁵⁹ in 1884 in Vienna described this syndrome of thrombosis of the axillary-subclavian vein, which bears their names. The word *effort* was added to thrombosis because of the frequent association with exertion producing either direct or indirect compression of the vein.⁶⁰ The thrombosis is caused by trauma⁶¹ or is associated with unusual occupations requiring repetitive muscular activity, as has been observed in professional athletes, linotype operators, painters, and beauticians. The combination of cold temperature and traumatic factors, such as carrying skis over the shoulder, tends to increase the proclivity for thrombosis.⁶² Elements of increased thrombogenicity also increase the incidence of the problem and exacerbate its symptoms on a long-term basis.

In Paget-Schroetter syndrome, which is always secondary to TOS, the costoclavicular ligament congenitally inserts into the first rib much farther laterally than normal in all cases we have seen (Fig. 26-28 is normal; Fig. 26-29 is abnormal). Subsequent hypertrophy of the scalenus anticus muscle (e.g., in weightlifters), which is lateral to the axillary-subclavian vein, produces severe external compression of the vein. This establishes the abnormal anatomic structure that can produce vein occlusion—the Paget-Schroetter syndrome.⁶³

Adams and colleagues^{46,64} reported long-term results in patients treated conservatively with elevation of the

arm and warfarin sodium (Coumadin). There was a 12% incidence of pulmonary embolism. Development of venous distention occurred in 18% of patients, and late residual arm symptoms of swelling, pain, and superficial thrombophlebitis were noted in 68% of patients (deep venous thrombosis with postphlebotic syndrome). Phlegmasia cerulea dolens was present in one patient.

For many years, therapy included elevation of the arm and use of anticoagulants, with subsequent return to work. If symptoms recurred, the patient was considered for a first rib resection, with or without thrombectomy,⁶⁴ as well as resection of the scalenus anterior muscle and removal of any other compressive element in the thoracic outlet, such as the cervical rib or abnormal bands.⁶⁵⁻⁶⁷

Increased use of local thrombolytic agents,⁶⁸⁻⁷⁰ combined with prompt surgical decompression of the neurovascular compressive elements in the thoracic outlet,⁷¹ has reduced morbidity of Paget-Schroetter syndrome and the necessity for thrombectomy, and it has substantially improved clinical results, including the ability to return to work.⁵³

One advantage of urokinase over streptokinase is the direct action of urokinase on the thrombosis distal to the catheter to produce a local thrombolytic effect.⁷²⁻⁷⁴ Streptokinase produces a systemic effect that can potentially cause complications. Heparin is given postoperatively until the catheter is removed. Another advantage is that

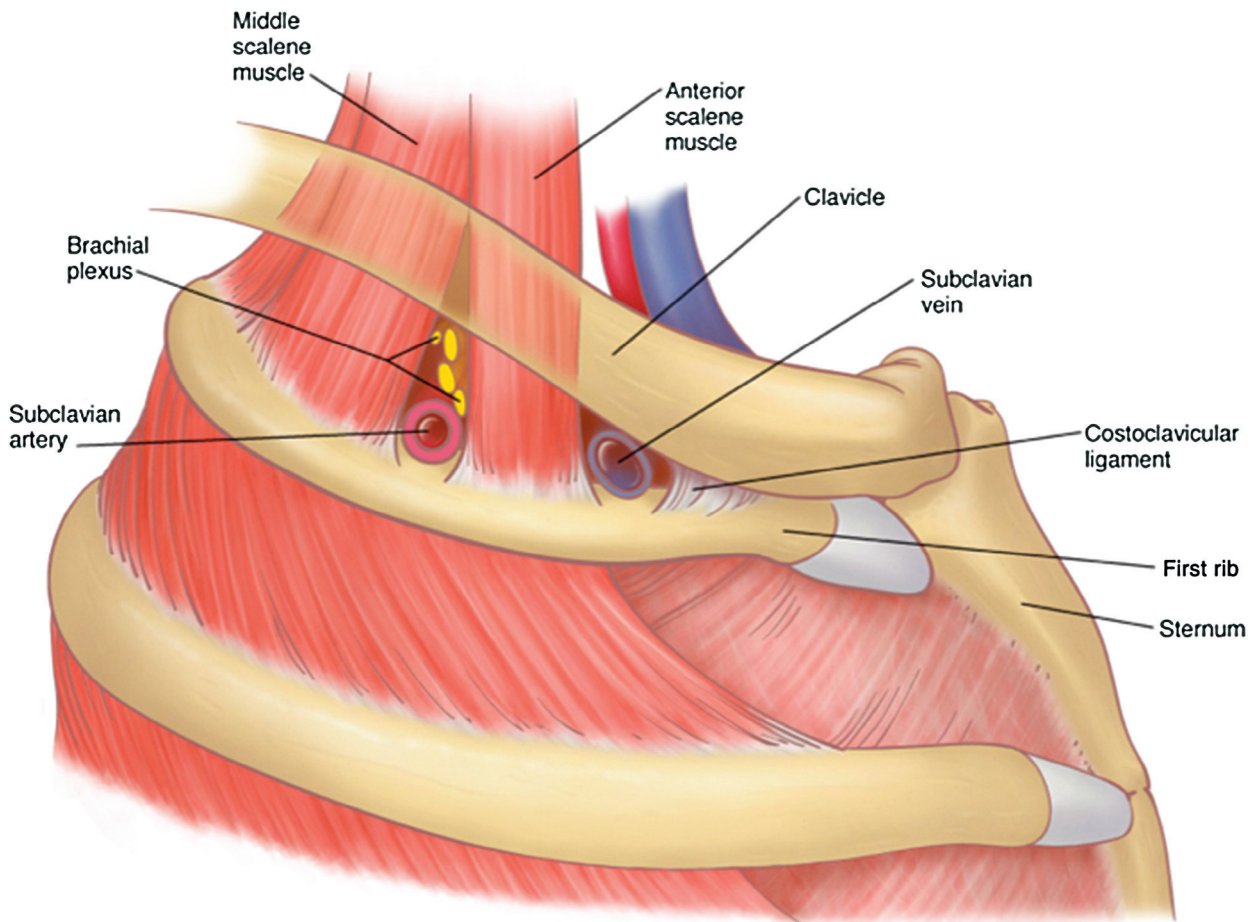


FIGURE 26-28 ■ The cross-sectional view of the neurovascular structures traversing the thoracic outlet, with the clavicle above and the first rib below.

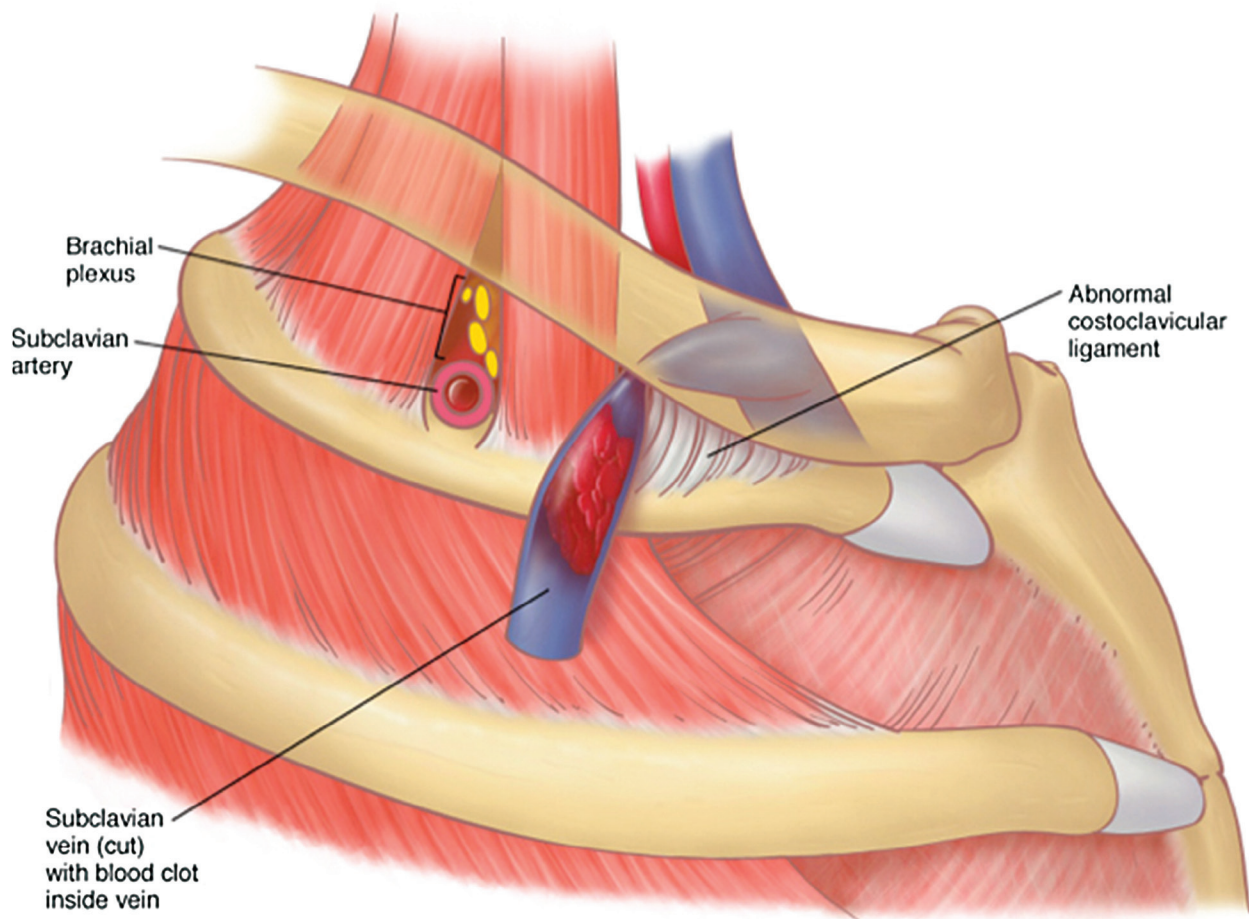


FIGURE 26-29 ■ The costoclavicular ligament inserts much farther laterally on the first rib, causing vein occlusion.

the need for thrombectomy is reduced by the use of a thrombolytic agent followed by aggressive surgical intervention because some of the long-term disability is due to the morbidity of a thrombectomy as well as recurrent thrombosis.⁷⁵⁻⁷⁷

The natural history of Paget-Schroetter syndrome suggests moderate morbidity⁷⁸⁻⁸⁰ with conservative treatment alone. Bypass with vein or other conduits⁸¹⁻⁸³ has a limited application in this low-pressure system. Causes other than TOS must be treated individually^{84,85} using the basic principles mentioned. Intermittent obstruction of the subclavian vein⁸⁶ can lead to thrombosis, and decompression should be used prophylactically.^{82,83} More than 600 patients with Paget-Schroetter syndrome underwent operations by Urshel. By far the best results were seen when the clots were lysed less than 6 weeks after the axillary-subclavian vein was occluded, and then the first rib was promptly removed and neurovascular decompression was provided. This technique uniformly gave good results. If the time of treatment is greater than 6 weeks from the time of the initial thrombosis, the results are less good, but the same procedure should be performed to obtain optimal results.^{47,87,88}

After successful thrombolysis, there often appears to be a stenosis in the vein on venography. Therefore, interventional radiologists or cardiologists sometimes dilate this vein, suspecting an “internal” problem rather than

seeing it as the result of external compression. Because the stenosis immediately closes down after balloon dilation, they may insert intravascular stents. These techniques have all failed in our experience⁸⁷⁻⁸⁹ and in the experiences of others.⁹⁰ In general, if the vein is not patent, then rib resection is not indicated.

DORSAL SYMPATHECTOMY FOR THORACIC OUTLET SYNDROME MANAGEMENT WITH VIDEO-ASSISTED THORACIC SURGERY

Dorsal sympathectomy and the management of TOS are significantly improved with video assistance through magnification and improved video systems. An open transaxillary approach for TOS can be slow, exposure can be challenging, and can require someone to lift the arm up for a protracted time. Video-assisted thoracic surgery addresses these issues. A VATS view from inside the pleura offers excellent visualization of anatomic structures, does not require anyone to lift the arm, and comes with an additional bonus of excellent visualization for other members of the team, which is particularly helpful for surgical residents. In addition, for sympathectomy

alone, VATS offers less pain to the patient and a shorter hospitalization.

Video assistance is used in two techniques. One technique involves the sympathectomy through two ports, with the standard VATS. The second technique involves a transaxillary incision with removal of the first rib using video-assistance magnification and light; the surgeon operates either directly or secondarily while visualizing the image on the television screen. This last technique was popularized by Martinez.⁹¹

The primary indications for dorsal sympathectomy include hyperhidrosis, Raynaud phenomenon and Raynaud disease, causalgia, reflex sympathetic dystrophy (RSD), and vascular insufficiency of the upper extremity. Except for hyperhidrosis, all these indications require the usual diagnostic techniques, including cervical sympathetic block to assess whether the symptoms are relieved by temporary blockade of the sympathetic ganglia. When Raynaud phenomenon of a minor to moderate degree is associated with TOS, the simple removal of the first rib with any cervical rib, in addition to stripping the axillary-subclavian artery (neurectomy), will relieve most symptoms after the initial operation.⁴⁰

It is rarely necessary to perform a sympathectomy unless Raynaud disease is a very severe type, in which case a dorsal sympathectomy is performed with first rib resection. In contrast, for patients with recurrent TOS and causalgia, dorsal sympathectomy should be performed with the initial reoperation procedure.^{37,39}

Pathophysiology

The principal physiologic effect expected of sympathectomy is the release of vasomotor control and hyperactive tone of the arterioles and smaller arteries that have a muscular element in the vessel wall. Circulation to the skin, peripheral extremity, and bone receives major improvement, but the effect on skeletal muscle of the arm is minimal. The other known function is the reduction of cutaneous sweating, when it is profuse and undesirable. Sympathectomy is often associated with compensatory sweating. RSD is associated with pain, neurasthenia, and cutaneous atrophy (Sudeck-Leriche) and posttraumatic limb. These patients also benefit from a sympathectomy if a diagnostic block is effective. Sympathectomy is not recommended for patients with diabetic neuropathy. Nor should it be performed in any of the vascular vasospastic syndromes until after conservative management, including cessation of tobacco products and institution of β -blockers, peripheral vasodilators, and calcium channel blockers, has failed.⁹²

Preganglionic sympathetic nerves derived from the spinal cord do not follow a corresponding relationship to the accompanying somatic nerves. The cervical ganglia of C1 to C4 are fused into a superior cervical ganglion, C5 and C6 into the middle cervical ganglion, and C7 and C8 into the inferior ganglion, which combines with the ganglion from T1 to the larger stellate ganglion. Cervical ganglionectomy is not used for denervation of the upper extremity, because the preganglionic sympathetic outflow from the spinal cord to the arm is usually from T2

through T9, mostly from T2 through T4. In approximately 10% of cases, T1 preganglionic fibers also supply the upper extremity. For removal of preganglionic fibers to the upper extremity in most patients, removal of paravertebral ganglia T2 and T3 with the interconnecting chain is sufficient. Postganglionic fibers from these two segments often join and branches then follow the nerves of the brachial plexus. The joined T2 and T3 fibers that bypass the stellate ganglion are known as the nerve of Kuntz.⁹³ For the remaining patients who have a T1 connection through the stellate ganglion to obtain adequate sympathetic denervation, the lower third of the stellate ganglion should also be removed, as recommended by Palumbo.^{94,95}

Patients with RSD or sympathetic maintained pain syndrome (SMPS) must complain of pain outside a peripheral nerve distribution.⁹⁶ Although the injury itself may have been minor, the pain appears out of proportion to the injury. We have seen two types of RSD or SMPS. One type involves the hand or even a greater majority of the upper extremity, and a second is localized to one or more digits. In no instance can the patient's pain be completely accounted for by an injury to a specific nerve, although injury to a specific nerve may cause the more diffuse symptoms. The patient also demonstrates diminished hand function. Several patients have been referred with a diagnosis of SMPS, and, on examination, it is apparent that although they may complain of diffuse pain, the hand functions normally with a full range of movement, and motor power is demonstrated. These patients, of course, do not have SMPS. The patient must also demonstrate some joint stiffness. The skin and soft tissue trophic changes demonstrate varying amounts of vasomotor instability, depending on the stage of SMPS.

According to Mackinnon and Dellon,⁹⁶ there are early, intermediate, and late stages of SMPS. In the early stages, vasomotor instability is noted with dramatic sympathetic overactivity apparent in the hand or digit involved. Instability, with symptoms varying between redness and warmth and cyanosis and sweating, is noted in this early stage. Edema is also a classic finding in the early stage. In the intermediate stage of SMPS, pain is a less dramatic component and is usually elicited by attempts to move the joints. At rest, the patient may be comfortable. The edema and vasomotor changes have settled by this time, and the hand has the appearance of a "burned out" dystrophic hand, with marked stiffness and atrophy of the soft tissue noted. The normal wrinkles on the dorsum of the hand are no longer apparent. The fingertips may have a tapered appearance. The nail growth is usually more exaggerated than in the normal hand, and the hand is often cool and pale. The intermediate stage extends over a number of months. During the late stage, all the superimposed problems of disuse atrophy may take effect. During this stage, problems with the elbow and shoulder are common, although the initial SMPS involved only the hand or one or more digits. The degree of pain experienced during the late phase is variable and is often the result of disuse and stiffness. SMPS can affect other areas of the body and has been observed in the foot, face, and penis.

Complications

Horner Syndrome

If the fibers of C7 and C8 (the upper part of the stellate ganglion) are removed, Horner syndrome results. This syndrome involves miosis, enophthalmos, drooping of the eyelid (ptosis), and flushing of that side of the face, with loss of sweating in that area.⁹⁷ Currently, sympathectomy procedures are usually not performed at the level of the second rib or higher so that the risk of Horner syndrome is low.

Postsympathectomy Neuralgia

The complication of postsympathectomy neuralgia is less common in the upper extremities than in the lower extremities. The pain usually occurs in the shoulder and upper arm on the lateral aspect. Clinical history usually substantiates this diagnosis if the symptoms occur within the first 3 months. The confirmation can be obtained with a test involving skin resistance and sudomotor activity detection. Test results reveal increased sympathetic activity and suggest a rebound phenomenon from the nonsympathectomized adjacent dermatomes. Rebound may be a regeneration of nerve fibers or an increased response of peripheral nerves to catecholamines. Symptoms usually resolve in 3 to 6 weeks with conservative management. Phenytoin sodium (Dilantin), carbamazepine (Tegretol), and calcium-channel blockers are all used in the medical management of these symptoms.⁹⁸

Recurrent Symptoms

Occasionally, after an excellent sympathectomy, with a warm hand and good circulation, recurrent symptoms occur as early as 3 months. These symptoms may be secondary to the regeneration or sprouting and rehooking of nerves, or to failure to strip the sympathetic nerves from the artery and the transfer of sympathetic tone through these nerves. Therefore, stripping of the axillary-subclavian artery of its local sympathetic nerves is performed in each case at the initial operation.⁹⁹ In addition, during the initial procedure, cauterization of the bed of the sympathectomy area produces sympathetic effects that usually last at least 3 years. We have also had good success with redo sympathectomy if symptoms recur after the initial procedure.

Surgical Approaches for Dorsal Sympathectomy

Historically, the anterior cervical approach has been used, with the division of the scalenus-anticus muscle as the approach to the cervical sympathetic chain.⁵⁹ The stellate ganglion lies on the transverse process of C6, and this approach is used primarily by neurosurgeons and vascular surgeons. For hypertension, Smithwick¹⁰⁰ and Urschel and Razzuk¹⁰¹ popularized the posterior approach using a longitudinal parasternal incision with the patient in the prone position. A small piece of both the first and the

second rib is removed and the sympathetic chain is identified in the usual position. This approach has the advantage of allowing bilateral procedures at the same time without changing the patient's surgical position, but with the advent of VATS, this approach is only of historic interest.

Another approach is the transaxillary transthoracic approach, which is performed through the second or third interspace with the transverse subhairline incision.^{94,95,102,103} This approach is more painful for the patient than others, but with VATS, it can be performed with minimal discomfort. The approach used most frequently when the patient also has TOS is the transaxillary approach, with resection of the first rib, retraction of the pleura caudad, and a dorsal sympathectomy.^{40,55} This combined procedure causes minimal pain and low morbidity. Video assistance is used frequently for this approach as well.

Variations of Dorsal Sympathectomy

Standard sympathectomy involves removal of the sympathetic chain with thoracic ganglia 1, 2, and 3. This approach involves removing the lower third of the stellate ganglion⁴⁰ with the second and third ganglia and the interconnecting sympathetic chain. This is the standard approach for Raynaud phenomenon, causalgia, and RSD. The standard VATS approach for hyperhidrosis involves either a 1-cm incision in the axilla or two 3-mm trocars for insufflation and transection of the nerve. The Society of Thoracic Surgeons workforce on sympathectomy recommends transecting the sympathetic chain at the third rib.¹⁰⁴ Horner syndrome occurs after removal of C8 or the upper two thirds of the stellate ganglia. Complete dorsal sympathectomy includes the removal of the lower third of the stellate ganglion and the sympathetic chain at the second and third ribs. This procedure is primarily for patients with ulceration of the fingers associated with Raynaud disease. Previous evidence suggests that removal of only the T2 and T3 ganglia, avoiding the stellate ganglia altogether, offers adequate sympathectomy for the standard indications of hyperhidrosis, Raynaud phenomenon, causalgia, and RSD. That was not Urshel's experience, because careful attention to anatomy virtually eliminates the possibility of Horner syndrome; thus, he believed that there is no advantage in leaving T1 for the treatment of ulcerations associated with Raynaud disease. Currently, the operation is performed at the third rib, plus the fourth rib if there is significant axillary or plantar sweating.¹⁰⁴

Technique

Two approaches are used for sympathectomy to treat TOS. The first is the transaxillary approach with a transthoracic sympathectomy.¹⁰⁵ This involves leaving the first rib, collapsing the lung, and performing the sympathectomy with video-assisted technique.¹⁰⁶ The second is a transaxillary removal of the first rib and the retraction of the pleura with a dorsal sympathectomy, which was used in most patients.

Urshel Transaxillary Approach with a Transthoracic Sympathectomy

The patient is placed in the lateral thoracotomy position with an axillary roll under the downside arm. The upper arm is suspended at 90 degrees from the chest wall over a pulley system with a 1-lb (453-g) weight.¹⁰³ An arm holder is used to ensure that no hyperabduction or hyperextension of the shoulder occurs and that relaxation occurs every 3 minutes. Three ports are used between the second and the fourth interspaces. The camera should be placed either anteriorly or in the midaxillary port. A double-lumen endobrachial tube is used, and the upside lung is collapsed, ventilating only the downside lung.¹⁰⁷ This selectively shunts blood through the downside lung, and excellent oxygenation usually results.

The lung is retracted and the sympathectomy is performed. The mediastinal pleurae are cut open and the sympathetic chain is identified on the vertebral body near the neck of the ribs. Nerve hooks are used to elevate the dorsal sympathetic chain; the nerve connections, including the gray and white rami, are clipped before transection or cauterization. The stellate ganglion is divided at the junction of the lower third and upper third, where it looks like a cat's claw. The stellate ganglion is cut, but it is not photoablated or cauterized, because Horner syndrome can result from either heat or light injury to the adjacent C8 ganglion. The lower ganglia can be cauterized, photoablated with the laser, or cut. Hemostasis can be achieved with the cautery, but its use is usually minimal to reduce the chances of Horner syndrome. The pleurae are left open and a chest tube is placed through one of the ports for drainage. There is a curvature of the sympathetic chain, so in many cases the stellate ganglion lies transversely, rather than vertically, on the transverse process of the vertebral body. Special knowledge of the anatomy is important, especially the location of the thoracic duct, which can simulate the sympathetic chain and be injured if not appropriately identified.

Urshel Transaxillary First Rib Resection for Thoracic Outlet Syndrome with Retraction of the Pleura and Sympathectomy

This technique differs slightly from other VATS procedures in that an actual incision is made transversely below the axillary hairline and the technique for rib resection is carried out. A right-angle breast retractor with a light is used, and a Dever retractor is placed on the other side of the incision. The video camera is a standard thoracoscope, a Wolf scope, or an Olympus flexible operating esophagogastroscope.

The pleurae are retracted inferiorly using a sponge stick, and the sympathetic chain is identified on the transverse process of the vertebral bodies. It is vertical between the T2 and T3 ganglia. However, T1, the lower part of the stellate ganglion, angles anteriorly and lies in almost a transverse position. Clips are placed on all the communicating rami of the sympathetic chain. T2 and T3 ganglia are resected. The stellate ganglion is divided at the junction of its lower third, and T1 is removed. This division is made with a sharp knife. Cauterization or laser

photoablation is not used in the stellate ganglion. Cautery is used after the removal of the sympathetic chain to prevent sprouting. Hemostasis is secured. A large, round Jackson-Pratt drain is placed, and methylprednisolone acetate (Depo-Medrol) is injected over the nerve roots and plexus that have undergone neurolysis. The camera is removed and the wound is closed in the usual manner.

Results

In 926 patients, sympathectomy alone or in conjunction with first rib removal for TOS has been successful.¹⁰⁸ In only six patients has sympathetic activity recurred in less than 6 months. All these patients were initially treated conservatively. Three of the six patients required repeated sympathectomy. Postsympathectomy neuralgia occurred in only 2 of 926 patients. Both patients were managed successfully in a conservative manner. Among the patients in whom Horner syndrome was not created deliberately, four patients developed the syndrome. All resolved spontaneously in several months. Forty-two cases of Raynaud phenomenon were treated successfully with first rib resection alone or with periarterial neurectomy without initial sympathectomy.^{47,89}

REOPERATION FOR RECURRENT THORACIC OUTLET SYNDROME

Extirpation of the first rib relieves symptoms in patients with TOS not relieved by physiotherapy. Of the surgically treated patients, 10% develop various degrees of shoulder, arm, and hand pain and paresthesias that are usually mild and short-lasting and that respond well to a brief course of physiotherapy and muscle relaxants. In a few patients (1.6%), symptoms persist, become progressively more severe, and often involve a wider area of distribution because of entrapment of the immediate trunk in addition to the lower trunk and C8 and T1 nerve roots. Symptoms can recur 1 month to 7 years after rib resection; in most patients, they recur within the first 3 months. Symptoms consist of an aching or burning type of pain, often associated with paresthesias, involving the neck, shoulder, parascapular area, anterior chest wall, arm, and hand. Vascular lesions are uncommon and consist of causalgia minor and an occasional injury of the subclavian artery with subsequent false aneurysm formation caused by the sharp edge of a remaining posterior stump of an incompletely resected first rib (Fig. 26-30). Recurrence is diagnosed on the basis of history, physical examination, and decreased nerve conduction velocity across the outlet. Diagnostic evaluation should also include thorough neurologic evaluation, chest and cervical spine radiography (Fig. 26-31), cervical myelography, subclavian artery angiography, and magnetic resonance imaging of cervical spine and brachial plexus,¹⁰⁹ when indicated.

Two groups of patients who require reoperation can be identified. Pseudorecurrence occurred in patients who did not have relief of symptoms after the initial operation. These patients can be separated etiologically as those in whom the second rib was mistakenly resected instead of

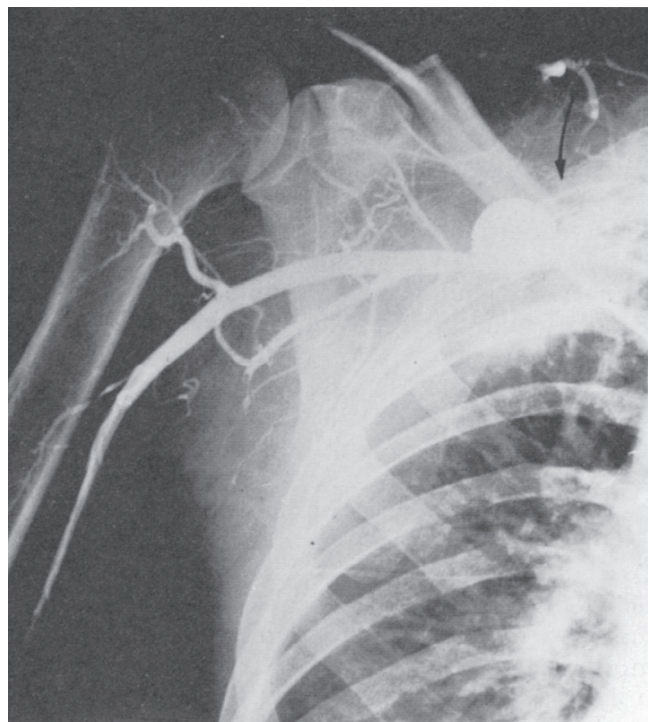


FIGURE 26-30 ■ Arteriogram showing a false aneurysm of the right subclavian artery caused by the pointed end of a posterior stump (arrow) of an incompletely resected first rib.

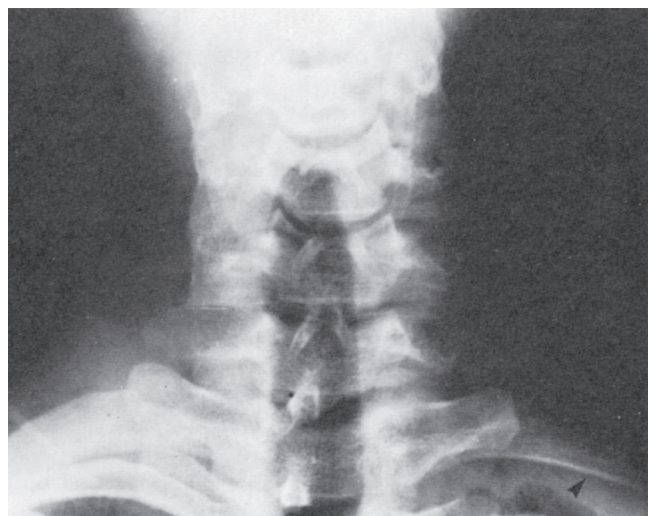


FIGURE 26-31 ■ Cervical film showing a posterior remnant (arrowhead at lower right) of an incompletely resected first rib in a patient who developed recurrent thoracic outlet syndrome.

the first; the first rib was resected, leaving a cervical rib; a cervical rib was resected, leaving an abnormal first rib; or a second rib was resected, leaving a rudimentary first rib. True recurrence occurred in patients whose symptoms were relieved after the first operation but who retained a significant segment of the first rib or who had complete resection of the first rib but showed excessive scar formation around the brachial plexus.

Physiotherapy should be given to all patients with symptoms of neurovascular compression after first rib

resection. If the symptoms persist and the conduction velocity remains below normal, reoperation is indicated.

Reoperation for TOS is performed with the posterior thoracoplasty approach to provide better exposure of the nerve roots and brachial plexus, to thus reduce the danger of injury to these structures and to provide adequate exposure of the subclavian artery and vein. This incision also provides a wider field for resection of any bony abnormalities or fibrous bands and allows extensive neurolysis of the nerve roots and brachial plexus, which is not always possible with the limited exposure of the transaxillary approach. The anterior or supraclavicular approach is inadequate for reoperation.

The basic elements of reoperation include resection of persistent or recurrent bony remnants of a cervical first rib, neurolysis of the brachial plexus and nerve roots, and dorsal sympathectomy. Sympathectomy removes T1, T2, and T3 thoracic ganglia. Care is taken to avoid damage to the C8 ganglion (upper aspect of the stellate ganglion), which produces Horner syndrome. The reoperation provides relief of major and minor causalgia and alleviates the paresthesias in the supraclavicular and infraclavicular areas. The incidence of "postsympathetic" syndrome has been negligible in this group of patients. A nerve stimulator is used to differentiate scar from nerve root to avoid damage with reoperations in these patients.

OPERATIVE TECHNIQUE FOR REDO THORACIC OUTLET SYNDROME SURGERY

The technique of the operation includes a high thoracoplasty incision that extends from 3 cm above the angle of the scapula, halfway between the angle of the scapula and the spinous processes, and caudad 5 cm from the angle of the scapula. The trapezius and rhomboid muscles are split the length of the incision. The scapula is retracted from the chest wall by making a subperiosteal incision over the fourth rib. The posterior superior serratus muscle is divided, and the sacrospinalis muscle is retracted medially. The first rib remnant and cervical rib remnant, if present, are located and removed subperiosteally. After the rib remnants (Fig. 26-32) have been resected, the regenerated periosteum is removed (Fig. 26-33). In our experience, most regenerated ribs occur from the end of an unresected rib segment rather than from periosteum, although the latter is possible. For a reduction in the incidence of bony regeneration, it is important in the initial operation to remove the first rib totally in all patients with primarily nerve compression and pain.

If there is excessive scar after removal of a bony rib remnant, it may be prudent to do the sympathectomy initially. A 1-inch segment of the second rib is resected posteriorly to locate the sympathetic ganglion. In that way, the first thoracic nerve may be easier to locate below rather than through the scar.

Neurolysis of the nerve root and brachial plexus is done with a nerve stimulator and is carried down to, but not into, the nerve sheath. Neurolysis is extended peripherally over the brachial plexus as far as any scarring persists. Excessive neurolysis is not indicated, and opening of the

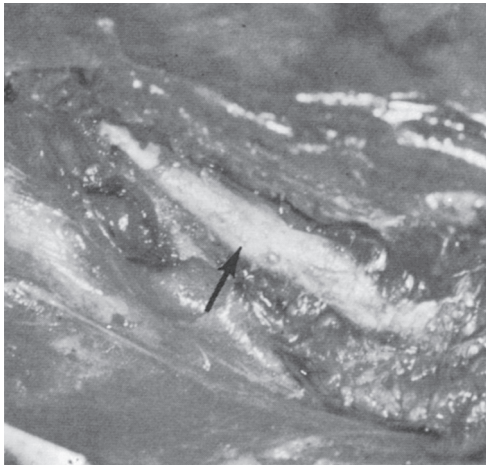


FIGURE 26-32 ■ A long posterior remnant (arrow) of an incompletely resected first rib in a patient with recurrent thoracic outlet syndrome.

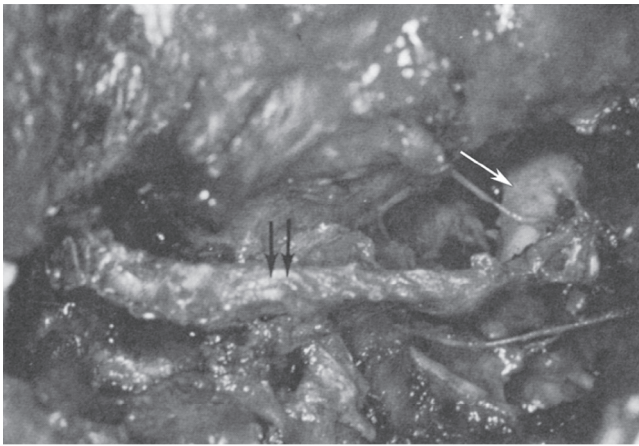


FIGURE 26-33 ■ Fibrocalcific band (two black arrows) of regenerated periosteum in continuity with a posterior remnant (white arrow) of the first rib in a patient with recurrent thoracic outlet syndrome.

nerve sheath produces more scarring than it relieves. For scarring to be minimized, the initial operation for TOS should include complete extirpation of the first rib, avoidance of hematomas with adequate drainage either by catheter or by opening the pleura, and avoidance of infection.

The subclavian artery and vein are released if symptoms indicate. The scalenus medius muscle is débrided. The dorsal sympathectomy is completed by extrapleural dissection. Meticulous hemostasis is achieved, and a large, round Jackson-Pratt catheter drain placed in the area of, but not touching, the brachial plexus is brought out through the subscapular space via a stab wound into the axilla. SeptraSeal (hyaluronidase) and methylprednisolone acetate (Depo-Medrol; 80 mg) are left in the area of the brachial plexus, but the patient is not given systemic steroids unless keloid formation has occurred. The wound is closed in layers with running Vicryl. Range-of-motion exercises are performed to prevent shoulder limitation, but overactivity is avoided to minimize excessive scar formation.

When the problem is vascular and involves false or mycotic aneurysms, special techniques are used for reoperation. A bypass graft is interposed from the innominate

or carotid artery proximally, through a separate tunnel distally, to the brachial artery. The graft is usually performed with the saphenous vein, although other conduits may be used. The arteries supplying and leaving the infected aneurysm are ligated. Subsequently, the aneurysm is resected by a transaxillary approach with no fear of bleeding or ischemia of the arm.

Special instruments have been devised to provide adequate resection through the transaxillary or posterior route. These instruments include a modified strengthened pituitary rongeur and a modified Leksell double-action rongeur for removal of the first rib without danger to the nerve root.

The sympathectomy relieves chest wall pain that resembles angina pectoris, esophageal disease, or even a tumor in the lung by denervating the deep fibers that accompany the arteries and bone.

The results of reoperation are good if an accurate diagnosis is made and the proper procedure is used.⁴⁰ More than 1200 patients have been followed for 6 months to 15 years. All patients improved initially after reoperation, and in 79%, the improvement was maintained for more than 5 years. In 14% of the patients, symptoms were managed with physiotherapy; 7% required a second reoperation, in every case because of rescarring. There were no deaths, and only two patients had infections that required drainage.¹⁰⁷

SUMMARY

Thoracic outlet syndrome is recognized in approximately 8% of the population. Its manifestations may be neurologic, vascular, or both, depending on the component of the neurovascular bundle predominantly compressed. The diagnosis is suspected from the clinical picture and is usually substantiated by determination of the UNCV. Treatment is initially conservative, but persistence of significant symptoms, which occurs in approximately 5% of patients with diagnosed TOS, is an indication for first rib resection. Primary resection is performed preferably through the transaxillary approach; however, VATS, supraclavicular, and posterior approaches are all reasonable.

It can be argued that overall there is no significant difference in outcomes and complications between the most widely accepted approaches and that neither is clearly superior to the other.¹¹⁰⁻¹¹³

As such, surgeon preference, comfort, and mastery of the technique are integral to optimizing outcomes with the chosen approach. Symptoms of various degrees recur after first rib resection in approximately 10% of patients. Most patients improve with physiotherapy, and only 1.6% require reoperation. Reoperation for recurrent symptoms is performed through a high posterior thoracoplasty incision.^{37,107}

Acknowledgments

Dr. Urschel was a leader in the treatment of TOS, and his contributions to the topic will aid in the education of many current and future surgeons. The crux of his input

into this chapter has been preserved with updates added, where appropriate. He will be missed. In addition, we are grateful to Rachel Montano and Brenda Knee for their assistance in organizing, preparing, and transcribing the original chapter.

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PART I

PLEURA

PART OUTLINE

- | | | | |
|----|--------------------------|----|---|
| 27 | SPONTANEOUS PNEUMOTHORAX | 30 | MALIGNANT PLEURAL AND PERICARDIAL EFFUSIONS |
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SPONTANEOUS PNEUMOTHORAX

Neal G. Moores • Karl G. Reyes • Siva Raja • David P. Mason

CHAPTER OUTLINE

EPIDEMIOLOGY

CAUSES

CLINICAL PRESENTATION

IMAGING

MANAGEMENT

Observation

Aspiration

Tube Thoracostomy

Pleurodesis

Surgery

SPECIAL CONSIDERATIONS

Secondary Spontaneous Pneumothorax

Catamenial Pneumothorax

The term *pneumothorax* was first coined by Jean Marc Gaspard Itard¹ in 1803, when he called attention to five cases in which free air was found in the thorax after trauma. Derived from the Greek words *pneuma* (air) and *thorakos* (breastplate or chest), it is an apt description for the accumulation of air in the pleural space that leads to partial or total collapse of the affected lung. The clinical features of pneumothorax were first described in 1819 by René Laennec,² who postulated the relationship to pre-existing blebs and unprovoked rupture and, hence, the term *spontaneous pneumothorax*. This pathophysiologic mechanism was confirmed by Kjærgaard³ in later decades. Today, the classification of pneumothoraces is based on clinical presentation and underlying lung disease. Multiple management strategies range from simple evacuation of air from the pleural space to potential prevention of future pneumothoraces.

EPIDEMIOLOGY

Spontaneous pneumothorax (SP) may be termed either a primary or secondary event, dependent on underlying lung disease. Primary spontaneous pneumothorax (PSP) typically occurs in young patients with localized blebs but otherwise normal lungs. Secondary spontaneous pneumothorax (SSP) occurs in patients with marked structural lung disease and directly contributes to SP. Approximately 20,000 new cases of PSP are diagnosed annually in the United States,⁴ with an estimated economic impact of \$130 million per year in lost wages. The annual estimated incidence of PSP is between 7.4 and 18 cases per 100,000 population among men and between 1.2 and 6 cases per 100,000 population among women.⁴ Patients prone to PSP are usually tall and thin and between 10 and 30 years of age.⁵ A significant factor is cigarette smoking, which can increase the risk of PSP by a factor as high as 20.⁶

SSP develops as a complication of underlying lung disease, most commonly chronic obstructive pulmonary disease (COPD).⁷ The annual incidence of SSP is approximately 6.3 cases per 100,000 population among men and 2 cases per 100,000 population among women.⁴ The peak incidence occurs between the ages of 60 and 65 years.⁵

CAUSES

PSP manifests without forewarning signs or symptoms and is most likely caused by rupture of a subpleural bleb. This premise is based on cumulative results of patients undergoing computed tomography (CT), which demonstrated subpleural blebs in as many as 80%.^{8,9} Surgical experience confirmed the presence of bullae in more than 75% of patients who underwent video-assisted thoracoscopic surgery (VATS) and thoracotomy.¹⁰⁻¹² Recent research may indicate a more diffuse pathologic etiology than simple bleb rupture. Fluorescein-enhanced pathologic assay of resected lung tissue in PSP patients reveals significant inflammatory changes and potential air-leak sites remote from blebs and other visible abnormalities.¹³

After the first episode of PSP, recurrence varies, ranging from 16% to 54%. Most studies indicate an average of 30%.^{14,15} Recent research indicates that the presence of subpleural blebs on high-resolution CT confers a recurrence risk of up to 68.1%, whereas the absence of blebs carries a recurrence risk of only 6.1%.¹⁶ Most recurrences develop between 6 months and 2 years after the initial episode.¹⁵ Men who are tall and have a history of smoking are at the greatest risk of recurrence. Counseling for smoking cessation should be strongly encouraged.¹⁵ After the second episode of PSP, the likelihood of recurrence increases markedly and can reach as high as 83%.^{7,14}

CLINICAL PRESENTATION

PSP typically manifests with sudden pleuritic chest pain and dyspnea.^{6,17} Classic findings on physical examination include diminished breath sounds, hyperresonance, and fremitus; however, patients with small pneumothoraces may have normal findings on physical examination. Most patients with PSP are stable, primarily because of their young age and otherwise normal lung function. Patients with SSP are more likely to present with respiratory distress, a result of respiratory compromise caused by SP superimposed on preexisting lung disease.¹² Whereas tension SP is unusual, indicators include tachycardia, cyanosis, and hypotension.

IMAGING

Chest radiography is the most common diagnostic tool for SP. A thin pleural line can be identified that has been displaced from the chest wall. A small SP may be difficult to identify on plain radiography; an expiratory view may prove more beneficial in determining the presence of SP. Frequently, attempts are made to measure the size of the SP as a percentage of the hemithorax it occupies, although this method is typically inaccurate.^{18,19} On occasion, a giant bulla can mimic a pneumothorax. Subtle lines demarcate a bulla, which tends to be surrounded by thickened visceral pleura. In addition, a pleural line can frequently be seen with lung markings visible beyond the suspected bulla (double wall sign).^{20,21}

Controversy exists about the significance of routine chest CT to evaluate for subpleural blebs. Proponents contend that identification of large or multiple subpleural blebs on CT is an indication for early surgical intervention to prevent recurrence.^{11,22,23} Opponents of this principle argue that management should not be influenced by these findings alone.^{24,25} Although CT is seldom required for routine diagnosis of SP, when subpleural blebs are diagnosed on CT, recurrence rates are high and some will elect early intervention such as bleb resection.¹⁶

MANAGEMENT

Algorithms for the management of SP range from established management protocols (American College of Chest Physicians [ACCP] Consensus Statement) to operative intervention (Table 27-1). Selected therapies depend on a number of variables: SP size, stability of the patient, symptom complex, initial SP onset or recurrent episode, and presence or absence of structural lung disease.^{19,26} The principal procedure is evacuation of air from the pleural space (spontaneous resolution versus instrumentation). Additional procedures targeted to prevent future SP episodes may also be considered in cases of SP recurrence.

Observation

Small pneumothoraces are those that are less than 3 cm in distance between the apical parietal pleura and the

TABLE 27-1 American College of Chest Physicians Delphi Consensus Statement on Spontaneous Pneumothoraces

Clinically stable with small pneumothorax	• Observation 3-6 hr • Follow-up CXR excludes progression: discharge and 1-2 day follow-up • Unreliable or impractical follow-up: observation 24 hr
Clinically stable with large pneumothorax	• Admission • Aspiration (or) tube thoracostomy • Heimlich valve (or) water seal • Highly reliable patients • May discharge to home with Heimlich valve with < 48 hr follow-up
Clinically unstable with large pneumothorax	• Admission • Tube thoracostomy (24-28 Fr) • Pneumothorax catheter and Heimlich valve • Acceptable in small subset of patients • If initial placement does not resolve instability: rapid conversion to suction/water seal device and standard chest tube
Management of persistent air leak	• >4 days • Consider VATS and pleurodesis • Recommends against sclerosing agents through chest tubes • Surgical risk prohibitive, or patient refuses surgery • Pleurodesis via chest tube • Talc slurry • Doxycycline
Recurrence prevention	• Treatment reserved for second spontaneous pneumothorax • Operative intervention • Apical bullae resected, if present • Abrasive pleurodesis • Talc slurry: acceptable (alternative sclerosants rarely acceptable in this setting) • Parietal pleurectomy: acceptable (weak consensus) • Chemical pleurodesis an acceptable alternative • Talc slurry • Doxycycline

CXR, Chest x-ray; VATS, video-assisted thoracic surgery.

From Baumann MH, Strange C, Heffner JE, et al: *Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement*. *Chest* 119:590-602, 2001.

thoracic cupula, with no lateral component. Asymptomatic patients should be managed expectantly²⁶⁻²⁸ by close monitoring, physical examination, continuous pulse oximetry, and repeated chest radiography within 3 to 6 hours. The ACCP recommends against the placement of chest tubes, or aspiration of small pneumothoraces. Our practice is to monitor patients in the hospital for a minimum of 24 hours. Even though some patients with stable radiographic features may be discharged from the hospital with follow-up within 12 to 24 hours,^{16,26} the potential for catastrophic consequences from a missed tension pneumothorax is a great risk.²⁹ Small pneumothoraces usually resolve without intervention, but

recurrence is possible. If chest radiography reveals that the SP is enlarging, immediate intervention is crucial.

Aspiration

Aspiration allows evacuation of pleural air and complete reexpansion of the lung. This technique can be applied even for larger pneumothoraces if the patient is stable. We prefer the Seldinger technique,^{30,31} which uses a small, single-lumen central line placed over the superior rib edge in the second interspace in the midclavicular line. A three-way stopcock and large syringe are used to aspirate until resistance is felt, usually signifying full lung expansion. Chest radiography is then performed to confirm the findings, and the catheter is removed.^{27,28,32-36} Commercially prepared kits with one-way valves (Heimlich valve)⁷ allow air to exit but prevent air entry. These valves can be left in place until full lung expansion is achieved. For more rapid resolution, however, it is our preference to perform tube thoracostomy with a small chest tube. Complications of aspiration, although rare, may include bleeding and possible lung injury. Reported success is higher in resolving PSP (66% to 83%) than for SSP (37%).^{27,35} SP that does not respond successfully to aspiration requires tube thoracostomy.

Tube Thoracostomy

Tube thoracostomy is recommended for patients with large or symptomatic SP and for most patients with SSPs. Patients with signs of a tension pneumothorax should be treated without hesitation, even before chest radiography is performed. Tube placement is through the fifth intercostal space in the midaxillary line. In our experience, as with chest tubes placed through port sites following VATS, there is no need to tunnel chest tubes placed at bedside.

A small chest tube can be difficult to direct to the apex of the chest, so a 28 Fr is preferable. The chest tube is left in place for 24 to 48 hours. Our practice is to place the chest tube on water seal once lung expansion has been confirmed. If an air leak persists and nonoperative management is preferred, a Heimlich valve can be placed. The patient can then be discharged for outpatient management. The efficacy of suction is debated, but there is no evidence that it speeds the resolution of SP. If it is used, it should be used judiciously.³⁷ Tube thoracostomy successfully resolves PSP in approximately 90% of patients for the first occurrence, 50% for the first recurrence, and 15% after a second recurrence.³⁸ For this reason, definitive management of SP recurrences will require either surgical intervention or chemical pleurodesis.

Pleurodesis

After tube thoracostomy, chemical pleurodesis may help prevent SP recurrence. Sclerosing agents are instilled to create pleural symphysis. The most commonly used agents are sterile talc slurry and doxycycline solution. Because adult respiratory distress syndrome may be triggered by high doses of talc, use should be limited to

5 g.^{39,40} In theory, talc has the potential to induce malignant transformation after decades of use, but thus far, this has not been demonstrated in humans.⁴¹ Nonetheless, our agent of preference is doxycycline to sclerose benign pleural processes. A total of 500 mg of doxycycline combined with lidocaine is infused through the chest tube, and the patient's position is shifted from side to side to distribute the sclerosant. Suction is then placed for 48 hours. Recurrence of SP in patients treated with bedside pleurodesis is high, ranging from 8% to 40%.^{40,42,43} In our institution, this treatment is reserved for patients who are not considered good operative candidates, most commonly patients with SSP.

Surgery

Surgical indications for PSP are recurrence, large or persistent air leaks, and incomplete lung expansion after tube thoracostomy. Other surgical indications include patients with a history of bilateral SP and patients in occupations that would place them at high risk if a pneumothorax recurred, such as commercial pilots and professional scuba divers.^{19,26,37,38} Although some thoracic surgeons recommend surgery in patients with a first-time PSP if bullae are detected on CT scan,²² we think that this strategy is highly aggressive, unnecessary, and unproven; thus we do not incorporate this practice into our treatment strategies.

VATS is the surgical procedure of choice for SP, replacing the previous procedure, axillary thoracotomy.^{44,45} The goals of surgery are resection of the offending bulla, complete lung expansion, and pleurodesis to prevent recurrence. A standard three-port VATS technique is used with lung isolation through a double-lumen endotracheal tube. The entire lung is carefully inspected, with particular attention to the apex and superior segments, because these are typical bullae locations. Saline flooding of the hemithorax during gentle lung inflation can help locate a ruptured bleb. Some surgeons resect the apex of the lung even if no bleb is located, although our practice is to perform lung resection only when a bleb is identified (Fig. 27-1). Buttressed staple lines are not necessary with otherwise normal lung parenchyma.

Intraoperative pleurodesis should be performed in addition to blebectomy. Mechanical pleurodesis is our most common method and is performed with use of a Bovie scratch pad with aggressive abrasion of the parietal pleura (Fig. 27-2). It is our practice to infuse doxycycline as an additional chemical sclerosant, although some surgeons choose to infuse talc at the time of surgery with good results and minimal impairment of pulmonary function over time.^{46,47} This is in spite of a recent study out of Korea suggesting that there is no difference in recurrence with mechanical pleurodesis following bleb resection.⁴⁸

Another effective method of obtaining pleural symphysis is parietal pleurectomy, by either VATS or open techniques. Results are similar to those of mechanical abrasion.^{49,50} Surgeons should make every effort to control air leak before leaving the operating room. Apical chest tube placement is crucial to full lung expansion. Postoperatively, chest tubes are placed to water seal as soon as

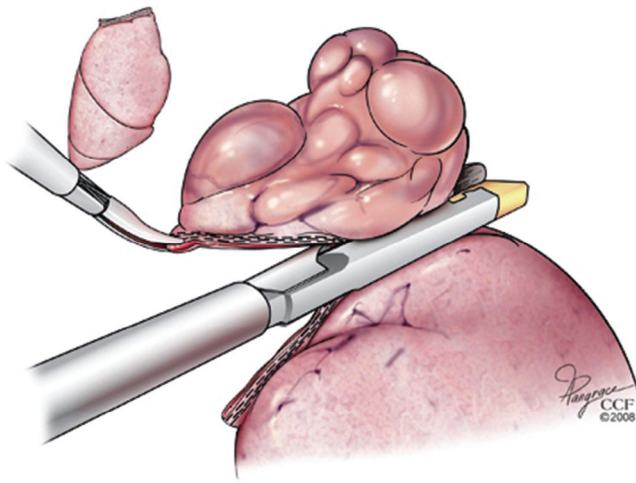


FIGURE 27-1 ■ Video-assisted technique of apical bleb resection. (Reprinted with permission of the Cleveland Clinic Center for Medical Art Photography. © 2008.)

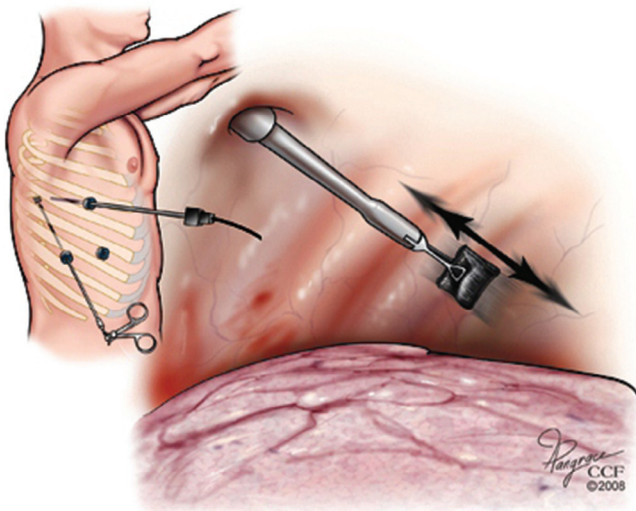


FIGURE 27-2 ■ Video-assisted mechanical pleurodesis with use of an electrocautery scratch pad. (Reprinted with permission of the Cleveland Clinic Center for Medical Art Photography. © 2008.)

a chest x-ray demonstrates full expansion, and no air leak is present. VATS successfully resolves SP and prevents recurrence in more than 90% of patients.⁵¹ Whereas some studies show that recurrence of SP is slightly higher with VATS compared with thoracotomy, this small increment does not justify the discomfort and lost work days in this generally young population.⁵² Thoracotomy is reserved for VATS failures and complex giant bleb resections not amenable to VATS.

SPECIAL CONSIDERATIONS

Secondary Spontaneous Pneumothorax

Clinical presentation of SSP is similar to that of PSP; however, dyspnea and respiratory compromise are often more profound, given the presence of underlying lung

disease, even with small pneumothoraces. In this setting, intervention should be performed quickly with tube thoracostomy. Major causes of SSP are COPD with bleb rupture followed by *Pneumocystis* infection in patients with HIV infection, asthma, cystic fibrosis, necrotizing pneumonia, or tuberculosis. Less common causes are idiopathic pulmonary fibrosis, Langerhans cell histiocytosis, lung cancer, lymphangioleiomyomatosis, sarcoidosis, and catamenial pneumothorax.¹² SP in patients with COPD portends poor long-term prognosis.⁵³ Management strategies must be tailored to the individual patient. Operative risk in a markedly compromised patient must be weighed against the potential morbidity and prolonged hospital course that can accompany nonoperative intervention. We have found Heimlich valves particularly valuable in managing patients with prolonged air leak because they allow easy ambulation and outpatient management.

Catamenial Pneumothorax

Catamenial pneumothorax is a rare form of SP usually occurring within 72 hours of menstruation. The typical patient is between 30 and 40 years of age, although age may range substantially. Theories are unproven but suggest that catamenial pneumothorax is caused by congenital diaphragmatic fenestrations that allow passage of air through the peritoneum to the pleura or pathologic intrathoracic endometrial implants that cause perforation of the visceral pleura.^{54,55} Right-sided catamenial pneumothorax is more common, but the reasons for this are unclear. When catamenial pneumothorax recurs despite intervention, treatment can be challenging. Hormonal manipulation with gonadotropin-releasing hormone agonists has been recommended; however, side effects can be unpleasant, and it should be combined with surgery for optimal results.⁵⁵ Our approach is to inspect the diaphragm for fenestrations thoracoscopically. If they are identified, fenestrations should be closed. This should be combined with mechanical pleurodesis or pleurectomy. Hormonal manipulation for one or two menstrual cycles can be considered while awaiting complete pleural symphysis.⁵⁵

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EMPHYEMA

Yaron Perry • Philip A. Linden

CHAPTER OUTLINE

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EPIDEMIOLOGY

In the United States, empyema is seen in approximately 60,000 patients annually, with a mortality rate of 15%.¹ Approximately 50% of empyemas in the United States today result from pneumonia. Pleural infection may also result from lung surgery, trauma, esophageal perforation, or transdiaphragmatic spread of an intra-abdominal infection. At least 40% of all patients hospitalized with pneumonia have an ipsilateral pleural effusion.¹ The average length of stay for patients with parapneumonic empyema in the United States was approximately 15 days and is shorter for children than adults. The in-hospital fatality rate was 7.2% in the NIS database and was lower for children (0.4%) than for adults older than 65 years (16.1%).²

HISTORICAL REVIEW

Empyema is most often used to refer to collections of pus in the space around the lungs (pleural cavity). The word is derived from the Greek word *empyein*, meaning “pus-producing.” Hippocrates first described the serious nature of thoracic empyema more than 2400 years ago.³ Even then, the need for surgical intervention was recognized, and open drainage was essentially the only treatment available until the late 19th century. Gotthard Bülow was among the first to use a closed method of drainage of infected pleural fluid, which he reported in 1891.⁴ It was not, however, a widely recognized treatment

option until the findings of the U.S. Army Empyema Commission led by Graham and Bell in 1918.⁵ The influenza epidemic of 1917-1919 resulted in a dramatic rise in the incidence of streptococcal empyema. During the early period of the epidemic, open thoracic drainage was commonly used in military hospitals to treat parapneumonic fluid. Often this was done early in the acute empyema phase, prior to the development of adhesions, and resulted in lung collapse and respiratory compromise. The early mortality rate from such a condition was 30.2% in this group of otherwise healthy, young men. A much better understanding of the pathology and evolution of empyema was obtained as a result of the Empyema Commission. As a result, with the use of closed drainage, the mortality rate for empyema dropped to 4.3%. The principles outlined by Graham, consisting of avoidance of open drainage during the acute phase and sterilization and obliteration of the infected space, constitute the fundamentals of modern therapy.⁶ With the discovery of effective antibiotics in the mid-20th century, the incidence of empyema was significantly reduced. The introduction of antibiotics, however, led to the emergence of resistant infections, polymicrobial infection, and partially treated empyemas. The incidence of streptococcal empyema decreased markedly with the introduction of antibiotics, and *Staphylococcus aureus* emerged as the predominant pathogen. More recently, gram-negative and anaerobic bacteria have become important pathogens. In spite of current medical advances, thoracic empyema continues to be a challenging problem, associated with significant morbidity and mortality.^{7,8}

BACTERIOLOGY

The bacteria traditionally associated with parapneumonic empyema are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and, more recently, *Streptococcus anginosus* (formerly *Streptococcus milleri*). Anaerobes have been identified as sole or coexisting pathogens in 25% to 76% of cases. A recent review of the NIS database between 1996 and 2008 characterized the changing epidemiology of parapneumonic empyema in community hospitals across the United States. The largest increase in relative incidence of empyema occurred in young adults. The most serious cases of empyema were associated with staphylococcal infections. For patients older than 40 years, staphylococcal empyema had a significantly higher in-hospital mortality rate than those associated with other pathogens. The mortality rate was 8.9 for patients aged 40 to 64 with staphylococcal empyema compared to 4.4% to 6.1% for other pathogens. For individuals older than 65 years, the mortality rate for staphylococcal empyema was 21.8% versus 12% to 16% for other pathogens.²

Most empyemas were categorized as having unknown pathogens. Among the pathogen specified cases, staphylococcal empyema accounted for most of the increased incidence of empyema, and these patients had the longest lengths of stay and highest mortality rate. This increase in staphylococcal empyema has also been noted in previous studies involving tertiary care facilities.^{9,10}

The incidence of pneumococcal empyema has remained relatively stable in both children and adults. Infant vaccination with a seven-valent pneumococcal conjugate vaccine (PCV7) started in 2000.¹¹⁻¹⁴ Studies documented significant reductions in the incidence of pneumonia hospitalizations after the introduction of this vaccine.^{15,16} Overall, national rates of childhood pneumococcal empyema remained relatively stable during the study period. The introduction of a 13-valent pneumococcal conjugate vaccine in 2010 in the United States may provide protection against several pneumococcal serotypes commonly associated with empyema.^{17,18}

The number of parapneumonic empyemas classified as being caused by unknown pathogens has increased significantly. Defining the etiology of empyema is difficult, and it is unclear whether this increase is related to truly unknown organisms, to imperfect laboratory testing, or to the increased use of antibiotics prior to hospitalization. Some studies using molecular techniques have suggested that a significant percentage of culture-negative empyema may be caused by pneumococci, mainly serotype 1.¹⁹⁻²³ Although recent studies suggest *Streptococcus anginosus* may be a leading cause of empyema,²⁴⁻²⁶ it can be difficult to distinguish between streptococcal species. Mixed bacterial infections are found in some parapneumonic empyemas.²⁶

The cause of the observed increase in the incidence of empyema is not clear. Part of the increase may be related to the increased incidence of antibiotic-resistant pathogens. The increase in cases of staphylococcal empyema seems to correlate with the increase in methicillin-resistant organisms.^{27,28} *Streptococcus pneumoniae* is an

exception—the incidence of resistant pneumococcal disease decreased markedly following the introduction of PCV7.²⁹

PATHOGENESIS

Classically, the development of empyema occurs in three clinical stages: the exudative stage, the fibrinopurulent stage, and the organizing stage. When initially presented with an infectious organism, the pleura responds with edema formation, and exudation of proteins and neutrophils into the pleural space. Inflammatory cytokines result in increased pleural mesothelial and capillary cells permeability, resulting in an effusion. Activated by bacteria, mesothelial cells act as phagocytes and trigger an inflammatory cascade with the release of chemokines, cytokines, oxidants, and proteases. Polymorphonuclear cells are recruited.¹

Early in the exudative stage, bacterial growth may be minimal, and the exudate may be sterile. The rapidity of progression depends on the type and virulence of the organism, host defenses, and initiation of antibiotic treatment. Staphylococcal pneumonias are almost always associated with pleural effusions. With uncomplicated parapneumonic effusions, the pleural fluid has a pH greater than 7.20, relatively normal glucose levels, and lactate dehydrogenase (LDH) levels that, although elevated, are typically less than 3 times the upper limit of normal. Most patients with uncomplicated parapneumonic effusions respond to antibiotics alone.

Untreated exudative effusions may develop into fibrinopurulent effusions or complex parapneumonic effusions. The fibrinopurulent stage represents the deposition of fibrin on visceral and parietal pleural membranes and the formation of loculations. Ongoing phagocytosis and cell lysis result in pleural fluid with a pH less than 7.20, LDH levels more than 3 times normal, and low glucose. A complex parapneumonic effusion develops into a pleural empyema when the concentration of leukocytes becomes sufficient to form frank pus. Empyema fluid consists of fibrin, cellular debris, and viable or dead bacteria. As fibrin is deposited into the pleural space, lymphatic channels may become occluded, further increasing the amount of pleural fluid. The fibrin strands result in loculations of the pleural space, which prevent drainage of the pleural fluid using a single needle or tube.³⁰ This stage is more likely to result in a positive Gram stain and/or positive bacterial cultures. This stage of pleural effusion requires catheter drainage and often surgical drainage.

The third and final phase is the organizing phase. This stage is characterized by the influx of fibroblasts and the formation of a thick, fibrous pleural peel along with continued maturation of dense septations. Both the visceral and the parietal pleura may become severely thickened with significant fluid remaining in the pleural space. During this stage of disease, simple drainage of the fluid may be possible, but the thick peel prevents reexpansion of the underlying lung. Failure of the “trapped” lung to reexpand will not allow for improved aeration of the lung or any improvement in breathing. The residual space quickly refills with infected fluid.

DIAGNOSIS: CLINICAL SIGNS AND SYMPTOMS, FLUID ANALYSIS, AND RADIOLOGIC APPEARANCE

The clinical presentation may vary depending on the underlying bacterial cause. Patients with aerobic infections tend to be more acutely ill with an initial presentation similar to that of pneumonia. This can be followed by a nonresolving picture with pleuritic chest pain, fever spikes, and failure to improve after receiving appropriate antibiotic therapy. Immunocompromised patients, older adults, and those with anaerobic infections may have a more indolent course and may experience weight loss, cough, fever, and anemia.²⁵ The pleural effusions are generally evident on upright chest radiographs. Lateral decubitus films are useful in determining whether the fluid is free flowing and amenable to complete percutaneous drainage.

The presence of leukocytosis, radiographic evidence of a pleural effusion, and the presence of purulent fluid on thoracentesis are classic findings of empyema. Signs or symptoms of infection, history of malignancy, or associated medical diseases such as cardiac failure or kidney or liver disease can be helpful in determining the cause of an effusion.

Ultrasound can detect loculations and can determine an appropriate site for thoracentesis. A computed axial tomographic (CAT) scan can determine the size and the location of the effusion and provides information regarding associated underlying parenchymal and pleural abnormalities. A CAT scan with intravenous contrast can further characterize the empyema, suggesting loculations or a thickened pleura or rind. Inspection of the lung-fluid interface may suggest entrapped lung and may reveal an underlying parenchymal process such as an abscess or tumor. The appearance of the effusion and fluid-lung interface can give indications as to the need for operative intervention (Figs. 28-1 to 28-4).

Thoracentesis is useful in determining the cause of an effusion. Pleural fluid evaluation should include a cytologic evaluation, pH level, gram stain and culture, cell

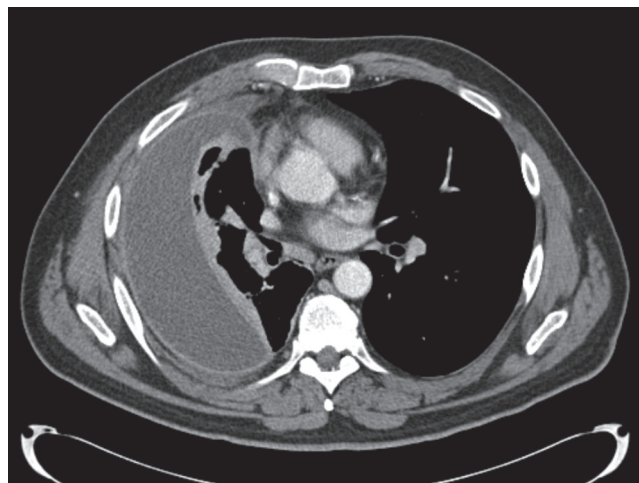


FIGURE 28-2 ■ CT scan of patient who required open decortication. The nonlayering of the effusion and the thickened visceral pleura peel suggest that extensive decortication may be required.

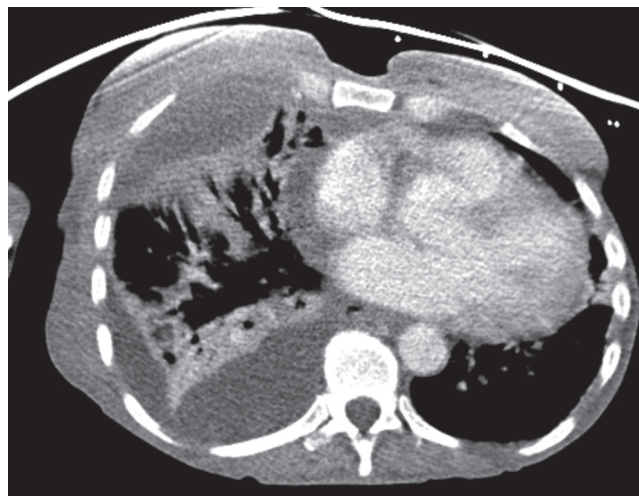


FIGURE 28-3 ■ CT scan showing separate basilar loculations of fluid, suggesting the need for intraoperative drainage.

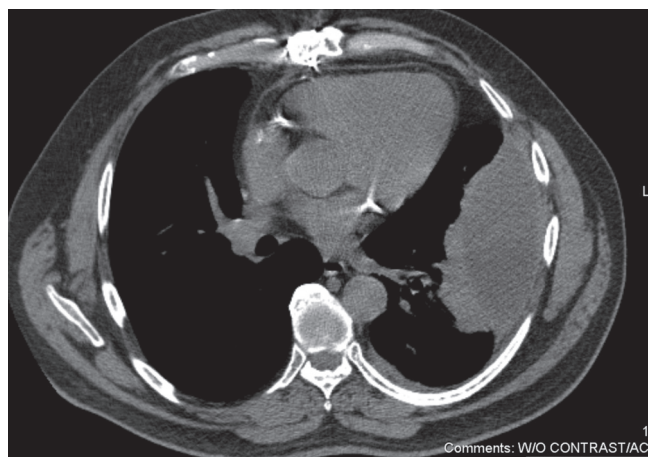


FIGURE 28-1 ■ CT scan of a patient who required VATS decortication. The lenticular, loculated appearance suggests intraoperative drainage is required.

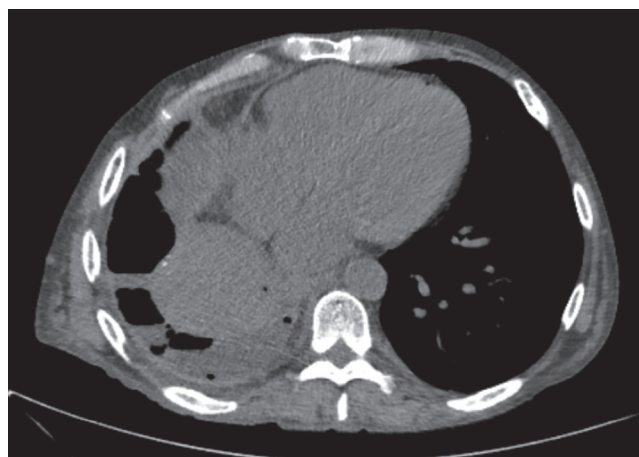


FIGURE 28-4 ■ CT scan showing an uneven, lobulated, circumferential effusion suggesting the presence of a thickened visceral peel that requires operative drainage and decortication.

count, and total protein, glucose, and LDH levels. Effusions are classified as exudative or transudative based on protein and LDH levels. Exudate effusions will have a pleural fluid protein/serum protein level higher than 0.5 and a pleural fluid LDH/serum LDH level higher than 0.6. The presence of an increased white blood cell count in the pleural fluid, particularly with a preponderance of neutrophils, may indicate pleural infection. Low pleural fluid glucose and a pH less than 7.20 are indicators of active pleural infection and the need for pleural drainage.

TREATMENT

Initial antibiotic coverage of patients with parapneumonic effusions is generally dictated by treatment guidelines for pneumonia and may be modified according to blood and pleural fluid microbial cultures and sensitivities. Empiric anaerobic antibiotic coverage may be initiated although anaerobes are much less likely to be cultured. Patients with nosocomial empyema need adequate gram-negative coverage. Vancomycin may be added for suspected methicillin-resistant infection. Reported bacteriology of pleural sepsis varies significantly between community acquired and nosocomial infections.³⁰ Early appropriate antibiotic therapy represents the cornerstone of therapy for pneumonia and parapneumonic effusion. Minimal size free-flowing effusions may be observed without a diagnostic aspiration because the risk of a complicated course is remote. All other free-flowing effusions should be aspirated for diagnostic purposes.

Uncomplicated parapneumonic, exudative effusions that are of small volume, free flowing without loculations, with a negative Gram stain, pH greater than 7.20, and negative cultures are usually inflammatory in nature. Most of these resolve with antibiotic treatment of the underlying pneumonia and can be observed without formal drainage.¹ Early drainage of pleural fluid becomes necessary when a parapneumonic effusion advances beyond the exudative stage to the fibrinopurulent stage and becomes a complicated parapneumonic effusion. Indications for immediate drainage are large effusions (larger than half the hemithorax), effusions with loculations, pH less than 7.20, positive Gram stain or culture, and low glucose levels. The presence of frank pus on aspiration is also an indication for immediate and complete drainage.¹

Options for drainage include serial thoracenteses, tube thoracostomy (with or without intrapleural fibrinolytics), thorascopic drainage, thoracotomy and drainage (decortication), and chronic open drainage. Choice of drainage is dependent on the viscosity of the pleural fluid; location, volume, and extent of loculations; and the general condition of the patient.

In theory, in the absence of loculations, either thoracentesis or tube thoracostomy should adequately drain any fluid. With significant ongoing infection and inflammation, however, continued production of fluid will occur, requiring repeat thoracentesis. Serial

thoracenteses are generally not recommended. Using such strategy, one study showed that the average patient required 7.7 aspirates with an average hospital stay of 31 days.³¹ Tube thoracostomy is generally performed with a size 24 to 32 Fr chest tube placed in a dependent area (usually the posterior costophrenic recess). If pleural infection is confirmed and all fluid is drained, then the tube is generally left in place until drainage is very low, typically less than 30 to 40 mL/day.

Complicated parapneumonic effusions and empyema are characterized by a procoagulant state within the pleural space, which results in the progressive development of dense layers of fibrin and loculations, as discussed earlier. These complex loculated effusions are unlikely to be adequately drained with simple tube thoracostomy. In an attempt to aid drainage of loculated areas of empyema, instillation of fibrinolytic agents via the chest tube has been proposed as a means of avoiding operation.

Intrapleural instillation of fibrinolytic agents can theoretically dissolve fibrinous clots and adhesions and prevent pleural loculations. The use of fibrinolytic agents is appealing because the most common reason for failure of pleural drainage among patients with an appropriately positioned catheter is occlusion of the catheter by viscous fibrin-rich fluid and/or debris, or partitioning of the pleural space with fibrin bands that loculate pleural fluid and prevent it from reaching the chest tube. Side effects with fibrinolytics are minimal with rare reports of fever and bleeding.³²

Streptokinase, urokinase, and tissue plasminogen activator have all been instilled via chest tube. Streptokinase is usually administered as 250,000 IU in 100 to 200 mL saline daily for up to 7 days. Urokinase is usually administered as 100,000 to 200,000 IU in 100 mL saline daily up to 3 days. Tissue plasminogen activator is administered as 10 to 25 mg twice daily up to 3 days. Drains are typically clamped for several hours following the administration of the fibrinolytic. Tissue plasminogen activator, a recombinant agent, provides fibrinolytic activity without the risk of antigenic-based reactions that can be seen with repeated administration of streptokinase.³³

Tuncozgur and colleagues³⁴ looked at fibrinolytic versus saline instillation via chest tube in 49 patients. They found a significantly lower decortication rate (60% vs. 29%) and shorter duration of hospitalization (14 vs. 21 days) with the addition of intrapleural fibrinolysis as well as a greater volume of chest tube drainage (1.8 liters vs. 0.8 liters). It should be noted, however, that even a 14-day hospital stay is considerably longer than what is expected following an expeditious video-assisted thoracic surgery (VATS) decortication. A single-center randomized placebo-controlled study by Diacon and colleagues³² reported that intrapleural streptokinase resulted in faster resolution of infection, reduced need for surgery (13.6% vs. 45.5%), and improved outcomes in patients with complex parapneumonic effusions and empyema.

Another prospective study by Mithos and colleagues³³ investigated tube thoracostomy versus tube thoracostomy and streptokinase. Tube thoracostomy alone

was successful in 67% of cases. Instillation of streptokinase led to a favorable outcome in 87% and significantly shortened hospital stay, reduced the mortality rate, and reduced the rate of surgical intervention. Davies and colleagues³⁵ compared fibrinolysis versus saline control in the second to fifth hospital day in 24 patients with tube thoracostomy for empyema. These investigators looked at volume of drainage and improvement in chest radiographs. Fibrinolytics caused an increased rate of fluid drainage and greater improvement on chest radiograph. No bleeding complications were seen. Three patients in the control group and none in the fibrinolytic group required surgical drainage.

Bouros and colleagues³¹ compared fibrinolytics with saline control in 31 patients. Fibrinolytic patients had a larger volume of drainage and higher rates of successful chest tube drainage (87% vs. 25%) compared with saline control patients. Two patients treated with fibrinolytic therapy required surgical drainage and 12 patients with saline crossed over to fibrinolytic therapy, with 6 of 12 ultimately requiring surgical drainage.

Tokuda and coworkers³⁶ performed a meta-analysis of all the major placebo controlled studies involving intrapleural fibrinolysis. The meta-analysis showed a trend toward improved survival and a decreased need for surgical interventions. The differences, however, failed to be statistically significant.

In the largest prospective, multicenter, double-blind controlled trial to date, the Multicenter Intrapleural Sepsis Trial (MIST) studied the use of intrapleural streptokinase for the treatment of empyema.³⁷ A total of 454 patients with pleural pus, pH less than 7.20, or positive bacterial culture from the pleural space were randomized to chest tube drainage with streptokinase (250,000 IU twice daily for 3 days) versus chest tube drainage with saline placebo. Primary endpoints of the study were death and need for surgical drainage. The proportion of patients who died or needed surgery at 3 months (primary endpoints) was similar between streptokinase and control (31% vs. 27%). No differences in mortality, rate of surgery, radiographic outcomes, or length of hospital stay were shown. This large study showed that intrapleural streptokinase offered no additional benefit in the treatment of empyema over chest tube drainage alone.

For free-flowing uncomplicated parapneumonic effusions or empyema, tube thoracostomy or percutaneous catheter drainage remains the standard of care. No high-grade evidence from a large-scale randomized controlled study exists to support the administration of fibrinolytic therapy.

Fibrinolytic therapy may be considered in poor surgical candidates who fail chest tube drainage, in patients who require a period of medical stabilization before surgery is performed, and in centers where surgical facilities are limited. Patient factors, local expertise, and surgical availability to a certain extent dictate the initial choice between tube thoracostomy and fibrinolytics or thoracoscopy.

Surgical drainage via thoracoscopy is indicated in patients who fail chest tube drainage, in patients whose lung does not reexpand following either thoracentesis or

tube thoracostomy, or as the initial treatment in patients who, based on chest computed tomography (CT) appearance, are unlikely to be effectively treated with a chest tube. These include patients with very loculated effusions, patients with thick pus, or with a thick pleural rind on CT scan. Loculations can be broken down, thick pleural fluid and debris completely evacuated, the pleural space can be extensively lavaged, and chest tubes can be carefully placed. Several small retrospective and non-blinded prospective studies suggest that thoracoscopy is superior to tube thoracostomy with fibrinolytics, with the need for thoracotomy halved.³⁸⁻⁴⁰

In the only prospective randomized controlled trial of fibrinolytic therapy versus thoracoscopy for empyema, Wait and coworkers⁴¹ randomly assigned 20 patients with complicated multiloculated parapneumonic empyema to streptokinase (250,000 IU daily for 3 days) via tube thoracostomy or immediate thoracoscopic drainage. Thoracoscopy had a higher treatment success rate (91% vs. 44%), lower duration of chest tube drainage (5.8 vs. 9.8 days), and a shorter hospital stay (8.7 vs. 12.8 days). This study supports the preferred approach of primary thoracoscopic drainage in patients presenting with loculated collections, provided that they are suitable candidates for surgical intervention.

Often in the chronic organizing phase of empyema, a thick fibrous peel builds up on the visceral pleura that restricts lung mechanics and prevents lung reexpansion, even after fluid drainage. The procedure allows for excision of all the fibrous tissue from the pleura to permit lung reexpansion.⁴² Decortication relies on lung elasticity to fill the cavity. Failure of reexpansion of the lung in the acute phase may result when there is densely consolidated lung that does not fully reexpand after drainage of fluid, even with decortication. Lung constriction after empyema can reduce lung perfusion by 20% to 25% on the involved side. The pulmonary function of patients who undergo decortication can increase significantly. Decortication can improve lung perfusion and improve vital capacity from 62% up to 80% and the forced expiratory volume after 1 second (FEV₁) from 50% to 69%. Nonetheless, decortication remains a procedure with significant morbidity and a reported mortality rate of up to 10%.⁴² Some investigators have suggested that pleural thickening may resolve over time and recommend deferring decortication for up to 6 months, but this opinion is in the minority.⁴³ In patients suffering from overwhelming sepsis, pleural drainage by tube thoracostomy or expeditious VATS is the immediate goal. Decortication may then be performed at a later date when the patient is stable. Delayed decortication is advised if there remains significant restriction of the affected lung and if the patient is a good operative risk.

For patients in whom sepsis cannot be controlled acutely with thoracoscopic drainage and in whom decortication is not appropriate, window thoracostomy may be performed. Open thoracostomy may be the procedure of choice if there is a permanent supply of causative organisms as a result of a bronchopleural fistula or if there is a space issue such as in a postpneumectomy empyema (Figs. 28-5 to 28-8).

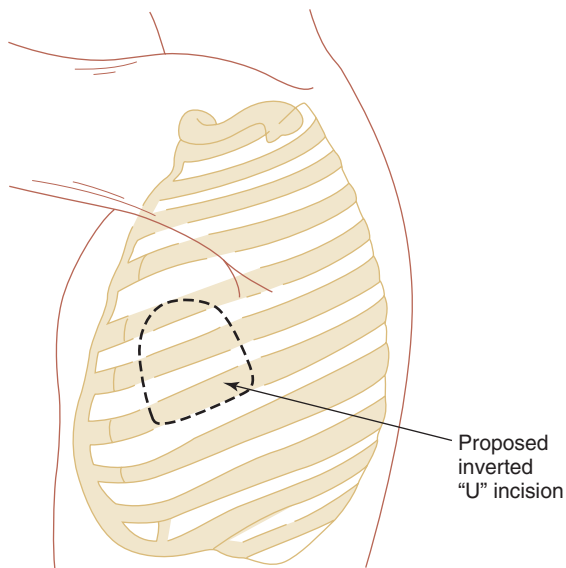


FIGURE 28-5 ■ Proposed incision for modified Eloesser flap. The proposed inverted U incision is in the left side of the chest.

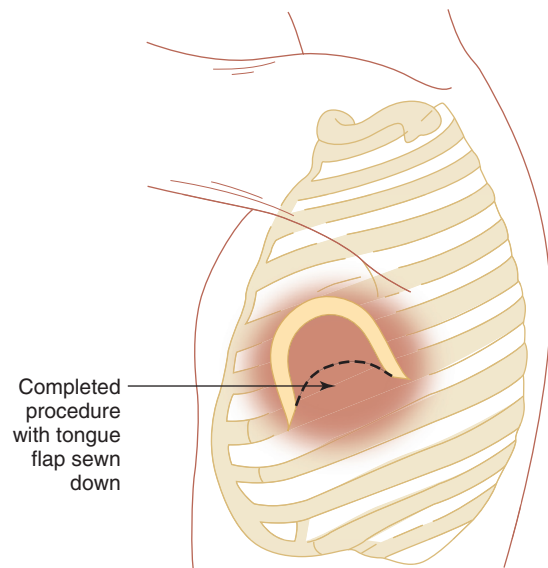


FIGURE 28-7 ■ Completed modified Eloesser flap with tongue flap sewn to the base of the empyema cavity.

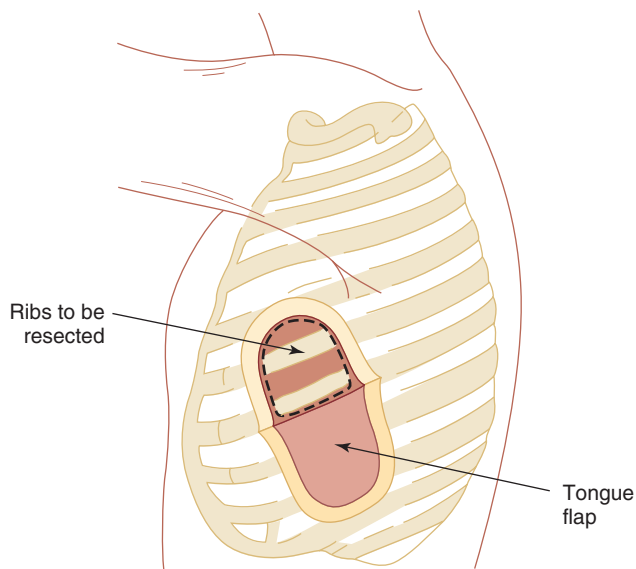


FIGURE 28-6 ■ Incision, with tongue flap reflected. The ribs to be resected are identified.

SPECIAL CONSIDERATIONS: POSTPNEUMONECTOMY EMPYEMA AND BRONCHOPLEURAL FISTULA

Incidence

Empyema is uncommon following pulmonary resection, occurring in only 2% to 16% of patients.⁴⁴⁻⁴⁶ Most (80% to 90%) postpneumonectomy empyemas are the result of a bronchopleural fistula (BPF) and carry a mortality rate of 5% to 35%.^{47,48} BPFs have been noted to occur in 2% to 10% of pneumonectomies.⁴⁴ Deschamps et al⁴⁹ reviewed 713 patients who underwent pneumonectomy at the Mayo Clinic between 1985 and 1998. Ten percent of the pneumonectomies were performed for benign

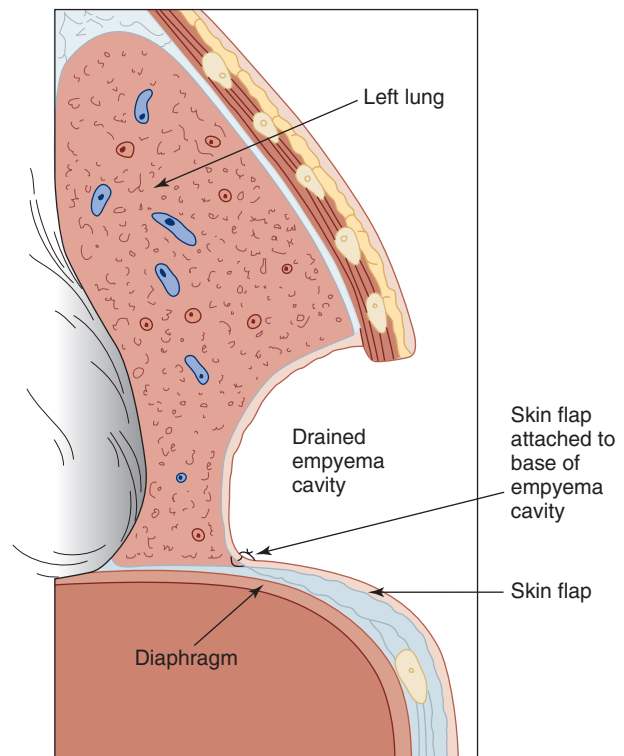


FIGURE 28-8 ■ Cross-sectional view of the drained empyema cavity and the completed modified Eloesser flap, with tongue flap sewn to the base of the empyema cavity.

disease. The incidence of postpneumonectomy empyema was 7.5% and the incidence of postpneumonectomy BPF was 4.5%. Variables associated with an increased incidence of postpneumonectomy empyema were benign disease, lower preoperative FEV₁, lower preoperative diffusion of carbon dioxide in the lung (DLCO), lower preoperative serum hemoglobin, right pneumonectomy, stump reinforcement, completion pneumonectomy,

timing of chest tube removal, and blood transfusion. Variables associated with the occurrence of BPF were benign disease, lower preoperative FEV₁ and DLCO, right pneumonectomy, bronchial stump reinforcement, timing of chest tube removal, increased intravenous fluid in the first 12 hours, and overall amount of blood transfused.

It is generally accepted that bronchial stump reinforcement is protective against BPF. The unexpected findings in this study may be related to the surgeon's choice to use bronchial stump reinforcement for those patients believed to be at highest risk for stump breakdown. Bronchial stump closure with staples had a protective effect against BPF compared with suture closure. Factors not affecting the incidence of PPE or BPF were gender, age, smoking history, associated cardiovascular disease, corticosteroid use, chronic renal failure, diabetes mellitus, hematologic disease, cirrhosis, nonpulmonary malignancy, body mass index, weight loss, stage, preoperative chemotherapy or radiation therapy, preoperative percentage of predicted total lung capacity and residual volume, PaO₂, and PaCO₂, extended resection, and duration of postoperative mechanical ventilation.

The signs and symptoms of postpneumonectomy empyema initially consist of low-grade fever, malaise, and leukocytosis. The appearance of air in the pleural fluid after pneumonectomy is nondiagnostic; however, a drop in the air-fluid level is strongly suggestive of a BPF even in the absence of other symptoms. Computed tomography can be helpful in demonstrating the size and location of loculated air-fluid pockets. It may also show reversal of the normal concavity of the mediastinal margin with increased thickening of the residual parietal pleura.^{50,51} Air in continuity with the bronchial stump may raise suspicion of a BPF but is not diagnostic. Bronchoscopy should be performed if the diagnosis of empyema is suspected after pulmonary resection. The bronchial stump should be thoroughly inspected for a small BPF. Similarly, the contralateral airway should be inspected and sputum collected for cultures. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the organisms most frequently involved.⁴⁹ In patients with suspected early empyema who have no evidence of a fistula, systemic antibiotics and observation may be the most appropriate management option. In cases of confirmed postpneumonectomy empyema, however, treatment follows the well-established rules of managing any abscess.⁴⁹ These management rules include adequate pleural drainage, appropriate parenteral antibiotics, removal of necrotic tissue, and obliteration of residual space. Obliteration of the empyema space can be accomplished by transposition of viable tissue such as omentum or skeletal muscle; this can be performed as a primary procedure to manage an empyema space or as a staged procedure some months after an open thoracostomy.

Treatment

When the patient presents acutely with clinical features of a BPF, contralateral pneumonitis, and respiratory distress, initial management begins with emergency chest tube drainage of the cavity to control infection and stop

contralateral spillage. The patient should be positioned in the lateral decubitus position with the pneumonectomy side down until adequate drainage of the pleural space is achieved. Simultaneously, respiratory support is provided as clinically needed. When a large BPF is present and mechanical ventilation is required, a double-lumen endotracheal tube or a straight, long single-lumen tube is used to ventilate the remaining lung and bypass the fistula. The ventilation of these patients can be extremely challenging. If the fistula occurs in the perioperative period (i.e., within the first month or so), repeat thoracotomy and attempted closure of the stump with muscle flap reinforcement and drainage of the pleural space are recommended. After this time, scarring and granulation tissue prevent the precise placement of bronchial stump sutures. Other treatment options include thoracoplasty,⁵²⁻⁵⁴ open pleural drainage,⁵⁵⁻⁵⁷ and transsternal, transpericardial closure of the fistula.⁵⁸⁻⁶⁰ If bronchoscopy reveals a long main bronchus stump (i.e., >1 cm), then transsternal, transpericardial closure with a thoracoabdominal (TA) stapler may be a good option.

Rarely, carinal resections have been used for treatment of a pneumonectomy stump BPF.⁶¹ Clagett and Geraci in 1963⁶² showed that post-pneumonectomy empyema could be successfully treated by open pleural drainage, frequent wet-to-dry dressing changes, and, when the thorax was clean, secondary chest wall closure with obliteration of the pleural cavity with an antibiotic solution. Failure was most often due to a persistent or recurrent fistula.⁶⁰ Because of this, the original Clagett technique is modified when a BPF is present to include transposition of a well-vascularized muscle to cover the stump at the time of open drainage to prevent further ischemia and necrosis.⁶³ Our preference is intrathoracic transposition of extrathoracic skeletal muscle.⁶³⁻⁶⁷ Usually, the serratus anterior muscle is intact despite a previous thoracotomy. Other available muscles include the pectoralis major, the cephalic portion of the previously transected latissimus dorsi, and the rectus abdominis. The advantages of using these muscles include adequate bulk, an axial blood supply, and the muscle's availability in the same visceral cavity. Transposition of the latissimus dorsi and pectoralis major muscles results in minimal cosmetic or functional abnormality; transposition of the serratus anterior muscle, however, may result in scapular winging.

CONCLUSIONS

Patients with pneumonia and associated pleural effusion should initially be evaluated with thoracentesis. Presence of loculations or pleural fluid analysis showing bacteria on Gram stain or culture, low glucose or low pH, and frank pus are all indications for immediate drainage. Nonloculated parapneumonic effusion and empyema may be adequately treated with tube thoracoscopy, but loculated effusions, or those inadequately drained with a chest tube, are best treated with thoracoscopic drainage. The fundamental principles of therapy are to remove infection and allow for lung reexpansion to obliterate dead space. If visceral scarring results in lung entrapment, then decortication is required. With recent advances in

VATS technology and skills, most decortications can be performed using minimally invasive techniques. Open decortication is usually reserved for patients with severe scarring after remote pleural empyema. If a significant pleural space exists and decortication is not possible, then the options are thoracoplasty, muscle flap transposition, or open window drainage.

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CHYLOTHORAX

Gaetano Rocco

CHAPTER OUTLINE

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DEFINITION

Chylothorax is the collection of an excessive amount of chyle in the pleural space. The continued loss of chyle, which can add up to 2 to 3 liters a day after a thoracic duct injury,¹ leads to significant depletion of fats (up to 70% of dietary intake), proteins, and T lymphocytes.² As a consequence, marked disturbances in the immunologic and nutritional profile are the rule in these patients along with a mass effect created by dislocation of intrathoracic structures by the enlarging fluid collection. Indeed, the flow rate of chyle within the thoracic duct can be as high as 110 mL/hr.¹ If left untreated, chylothorax may yield an overall 50% mortality rate.³

CLASSIFICATION AND CAUSE

The term *traumatic* is often used to include both iatrogenic and postinjury chylothoraces,² which usually represent the most common causes of significant chyle accumulation in the chest. Neoplastic causes can account to up to 20% of chylothoraces.² In a recent report from the Mayo Clinic, the cause was surgery or trauma in 50% of the patients, medical conditions in 44%, and unknown in 6%.⁴ This unusual distribution, compared to the commonly reported series,⁵ was explained by the high volume of surgical cases being performed each year at that institution.

In the pediatric group, congenital chylothorax manifests itself early after birth possibly as a result of a combination of thoracic duct malformation and sudden elevation of venous pressure.⁶ Neonatal chylothorax has been reported in conjunction with several syndromes, such as Noonan and Down.^{2,6} In addition, the incidence of chylothorax after cardiothoracic procedures in children is reported to be as high as 3.8%.⁷ The detection of a pleural effusion in this age group should immediately

raise the suspicion of chylothorax.⁶ Tuberculosis with significant mediastinal adenopathy may still be responsible for “spontaneous” bilateral chylothoraces in children because of the obstruction to centripetal flow.⁸

Excessive chyle collection in the pleural space may occur in association with benign and malignant tumors. Reportedly, almost 50% of the patients with chylothorax have cancer. Of these, 70% have lymphoma.⁵ Conversely, chylothorax was reported in 10% of the patients with lymphangioliomyomatosis (LAM) treated at the Mayo Clinic over a 24-year period.⁹

Intraoperative injuries may ensue from surgical procedures conducted in the proximity of the thoracic duct anatomic course.^{2,10,11} Even minor maneuvers such as raising a pleural flap over the thoracic aorta or dividing the inferior pulmonary ligament can cause this complication.¹² In 1999, the Mayo Clinic reported that out of 11,315 general thoracic surgical procedures, 47 patients (0.42%) had postoperative chylothorax.¹

Chylothorax can complicate the postoperative course of 1% of esophagectomy patients,¹³ requiring surgical reexploration in almost 90% of the cases.³ Conversely, despite chylothorax occurring in less than 1% of the patients subjected to pulmonary resection, only 38% undergo reoperation for final treatment.¹ A detailed list of possible causes of chylothorax was reported by De Meester¹⁴ in a previous edition of this textbook and later modified by Nair.²

ANATOMIC CONSIDERATIONS

A certain variability in the distribution of the thoracic duct and its tributaries represents the rule rather than an exception. At some point in the embryogenesis, the thoracic duct itself is a bilateral structure¹⁵ and can triplicate in up to 40% of the population.¹⁵ The single thoracic duct anatomy is found in approximately 65% of the individuals. Chylothorax can result from leak of lymph from

major collectors—the most sizeable being the thoracic duct—or from multiple lymphatic channels, which define a network of tributaries consistently demonstrated by several anatomic studies.¹¹

The centripetal flow toward the left subclavian vein is regulated by three factors¹⁷: (1) the vis a tergo created by the continuous enteral absorption of chyle constituents, which pushes the chyle from the cisterna chyli to the left subclavian vein; (2) the aspiration effect given by the negative effect of the intrathoracic pressure facilitating the cephalad flow; and (3) lymphatic vessel contractions, generated by smooth musculature, aiming at emptying the duct into the subclavian vein.

PATHOPHYSIOLOGY

A chylothorax can result from a chyle leak (direct injury or obstruction of the major lymphatic vessel), generalized oozing, or transdiaphragmatic flow from chylous ascites.⁹ The distinction between idiopathic (sometimes called spontaneous) and secondary causes of chylothorax depend on the presence of an identified etiology. Secondary causes include neoplastic and inflammatory conditions because chylothorax may ensue from the obstruction to centripetal flow or increased flow rate with extreme dilation of lymphatic vessels leading to extravasation of lymph in a space that changes from virtual to actual despite the presence of an expanded lung. As a consequence, lymphatic vessels are thought to preserve, at the beginning, their structural integrity at the expense of an increased permeability into the pleural space.^{2,9} Constrictive pericarditis, superior vena cava obstruction, and mediastinal fibrosis resulting from cancer treatment can generate chylothorax according to this pathophysiologic model.⁵ In this setting, patients with liver cirrhosis can develop spontaneous chylothorax as a result of a twofold or threefold increase in diameter of the thoracic duct from an unusual backflow and pressure in the thoracic duct.¹⁶ Another factor implied in the onset of chylothorax is valve competency in the lymphatic vessels as demonstrated by the rarity of such complication following pulmonary resection and extensive mediastinal nodal dissection. Valve insufficiency–induced backflow from the thoracic duct into the areas of nodal dissection and injury of the lymphatic network may explain the chylous effusion¹¹ after pulmonary resections with concurrent nodal dissection.

From a clinical standpoint, chylothorax resulting from pleural carcinomatosis or from tubercular involvement may denote a gradual onset and development. This observation can be also explained by progressive lung trapping caused by the visceral pleura thickened by the persistent chemical irritation by chyle components.¹² In time, fibrotic visceral pleura may impose a restrictive physiology on the affected lung by significantly reducing its compliance. This scenario is more often the case with the so-called pseudochylothorax (see later).

Induced or secondary causes of chylothorax include traumatic and iatrogenic causes, which have in common the interruption of the vessel caused by direct injury, inadvertent division, or blunt trauma to the thoracic duct

or its tributaries. Rupture of the thoracic duct may also occur following sudden hyperextension of the spine (seat belt injury),¹⁸ vertebral fractures or dislocation, or after protracted and vigorous vomiting or coughing.⁶

SYMPTOMS AND DIAGNOSIS

Biochemically, chyle is usually characterized by a content of triglycerides in the pleural fluid greater than the one detected in the plasma (>110 mg/dL¹), a cholesterol/triglycerides ratio less than 1, and, the presence of chylomicrons.^{2,6,19–21} A detailed description of the chemical components of chyle is already available in the surgical literature.^{1,6} A differential diagnosis with pseudochylothorax sometimes has to be made.² Pseudochylothorax refers to those chronic effusions that may resemble chylothorax but do not have its biochemical composition.² The pleural effusions in patients with tuberculosis or rheumatoid arthritis may have these features (i.e., yellowish or milky color, sterile, high cholesterol levels).

One interesting observation is that chyle does not contain fibrinogen, which could seal a small leak.³ Chyle is bacteriostatic and can be a chemical irritant for the pleural surfaces,¹² even though this finding is disputed.^{2,17} In addition, chylothorax can affect the bioavailability of drugs like amiodarone, digoxin, and, cyclosporine.²

The acute onset of a significant chyle leak may be characterized by dyspnea and cough associated with a sense of pressure in the chest.² Hemodynamic disturbance is also common with high-flow chylous fistulas.² Conversely, severe malnourishment and cachexia may ensue as a result of persistent chylothorax.² Symptoms related to chyle accumulation were described in a report by the Mayo Clinic.⁴ Over a 21-year observation period, 203 patients developed chylothorax (male-female ratio, 1.21; median age, 54 years). Of these patients, 57% presented with dyspnea, whereas 37% were asymptomatic. More than 7 weeks elapsed from symptom development to diagnosis.⁴

A milky pleural effusion accumulating at a rate of more than 400 to 700 mL per day is suggestive of chylothorax.¹² An empty pleural space after pneumonectomy may accommodate a greater chyle flow.¹² The administration of a high-fat meal 3 hours before surgery, with or without dye, or the subcutaneous injection of dye 1 hour before surgical exploration can facilitate the identification of the site of leakage when the decision for surgery to ligate the duct is made.¹²

Some authors rely on the findings of pedal lymphography to define further management.^{16,22} Indeed, the discontinuation of chyle leak after lymphography represents a distinct therapeutic possibility¹⁶ because of the sclerosing effect of the iodine contrast medium. Controversies exist whether to proceed to lymphography only in candidates for surgical reexploration or to routinely proceed in all patients developing chylothorax after pulmonary resection.²³ However, the reported success rate in minimizing the need for reoperation through the adoption of a rigorous management protocol, including lymphography, seems to support the latter option.²²

Nevertheless, the lymphographic finding of a leak from small tributaries may predict the success of conservative management.¹⁶

PRINCIPLES OF MANAGEMENT
(Table 29-1)

Three approaches to managing chylothorax are:

- 1. Conservative (nonsurgical)
- 2. Surgical, aimed at identifying and isolating the lymphatic duct causing the leak so that it can be closed
- 3. Surgical, aimed at obliterating the space otherwise to be filled by chyle

Conservative management represents a mainstay of treatment of postoperative chylothorax developing in children following cardiothoracic interventions.⁷ The principles of conservative treatment include (1) nothing by mouth (NPO), (2) medium-chain triglyceride diet, or (3) parenteral nutrition.¹²

In adults, it has been suggested that the detection of recurrent chylothorax greater than 1 liter/day after 1 week or between 0.1 and 1 liter chyle loss during the first two weeks¹⁶ is evidence of failure of conservative management. Others¹² suggest opting for a surgical intervention if the leak is greater than 1 liter/day for 5 days, if the chylothorax does not subside after 2 weeks, or if there is severe nutritional or metabolic imbalance. Advocates of early surgical intervention following esophagectomy support the idea of reintervention if the leak is consistently greater than 2 liters during 2 consecutive days.³ An interesting perspective for chylothorax treatment has been outlined by Cope, who suggested percutaneously injecting a sclerosing agent into the cisterna chyli.²⁴

Surgical intervention or reintervention can be performed via an open or a video-assisted thoracic surgery

(VATS)/robotic approach.²⁵ The increasingly frequent resort to safe minimally invasive techniques to achieve control of the thoracic duct may change the balance between conservative and operative approaches. Indeed, the therapeutic possibilities revolve around the identification of the leak, closure of the fistula, and obliteration of the pleural space, especially if the chylothorax complicates an esophagectomy (see Table 29-1). On principle, the side of the identified leak should be preferentially approached and surgically treated.³ In the event of a bilateral chylothorax, the right side should be preferentially entered to ligate the supradiaphragmatic thoracic duct. If the duct cannot be isolated, mass ligation of the fibrotic area around the duct should be performed.¹² The treatment options suggested in the literature are listed in Table 29-1.

Chylothorax after Pulmonary Resection

Despite the fact that a well-expanded residual lung after lobectomy and postpneumonectomy chylothorax have similar etiologies and pathophysiologies, the former usually responds better to a conservative approach.²¹ In the latter, sudden accumulation of chyle in the empty hemithorax can cause a contralateral shift of the mediastinum with the attendant cardiorespiratory functional impairment. This rare clinical scenario, reported in almost half of the pneumonectomy patients who develop chylothorax,²⁶ mandates a more aggressive protocol to ensure early ligation of the thoracic duct—within 3 to 5 days of onset if the chyle loss is greater than 400 mL after an observation period lasting two consecutive 8-hour shifts.²¹

Reportedly, chylothorax occurs more frequently on the right side, possibly because of a more radical mediastinal nodal dissection following resection for bronchial carcinoma.¹⁶

Chylothorax after Esophagectomy

Patients undergoing esophagectomy are often older adults with significant cardiorespiratory comorbidities and malnourishment.¹³ In addition, multiple operative fields are necessary to complete the esophageal resection and restore the gastrointestinal continuity. The resort to VATS has reduced the impact of this operation on patients' overall condition. In a series of 1787 patients operated on during an 18-year period, 26% underwent a transhiatal esophagectomy as a result of their substantial cardiorespiratory comorbidities.¹³ However, no significant difference in the prevalence of chylothorax was noted between trans-thoracic and transhiatal approaches.¹³ In a Mayo Clinic series, the incidence of this complication following esophagectomy was reported to be 2.9%.¹ Investigators renowned for their long-standing experience with transhiatal esophagectomy (reaching almost 2000 patients subjected to this procedure) have reported an incidence of chylothorax of 1.5%, favorably comparing with the 2% to 4% range reported in the literature.²¹

Early reoperation with mass ligation of the thoracic duct is advocated to limit the immunologic and nutritional imbalances that can heavily affect the postoperative course of these patients.¹³ The mortality rates for

TABLE 29-1 Therapeutic Modalities in the Management of Chylothorax

Nonsurgical	Operative: Open or VATS/Robotic
Chest drain only ⁵	Fibrin glue plugging ^{3,12}
Medium-chain triglyceride diet/Total parenteral nutrition ¹²	Mass ligation ^{1,12}
Somatostatin ¹²	Thoracoscopic clipping ^{3,12}
Octreotide ¹²	Ultrasonic coagulation ³
Etilefrine ¹²	Pledget suturing ³
Up to 20 Gy postoperative radiation ^{2,12}	Pleurovenous or peritoneal shunting ^{12,20,28}
Nitric oxide ¹²	Decortication/pleurectomy ³
Tetracycline/doxycycline pleurodesis ^{12,20}	VATS talc pleurodesis ¹²
Povidone pleurodesis ²⁹	
OK-432 interferon/interleukins ²⁰	
Bleomycin ²⁰	
Embolization during lymphangiography ²⁷	
Positive pressure ventilation ²⁰	

VATS, Video-assisted thoracoscopic surgery.

TABLE 29-2 Outcomes after Treatment of Postoperative Chylothorax

Type of Operation	Source (Year)	% Total	No. of Patients	First-Line Treatment	Success
Lobectomy or greater	Takuwa et al ³⁰ (2013)	2.3	37/1580	LFD OK432	84%
Iatrogenic injury	Itkin et al ³¹ (2010)	NR	109	Catheter embolization	67%
Esophagectomy	Shah et al ³² (2012)	3.8	34/892	Conservative (38%) + surgical ligation (62%)	100%
Pediatric cardiothoracic surgery	Yeh et al ³³ (2013)	—	163	NPO/TPN/octreotide vs. MCT/LFD + surgical ligation	100%
Esophagectomy after neoadjuvant therapy	Merritt et al ³⁴ (2011)	7.4	4/54	—	—
Esophagectomy after neoadjuvant therapy	Kranzfelder et al ³⁵ (2013)	2%	39/1856	Surgical ligation in 69%	—
Lung cancer resections	Kozower et al ³⁶ (2010)	0.24	46/18,800	—	—
STS database					

LFD, Low-fat diet; MCT, medium-chain triglyceride [diet]; NPO, nothing by mouth; NR, not reported; STS, Society of Thoracic Surgeons; TPN, total parenteral nutrition.

reoperation reach 16% compared with more than 80% after conservative treatment,³ making an early surgery option to control chylothorax a preferable option. However, the prophylactic ligation of the immediately supradiaphragmatic azygos vein along with the thoracic duct during esophagectomy has been recommended to drastically reduce the incidence of chylothorax.^{2,13}

CONCLUSION

Among different types of chylothoraces, postoperative chylothorax represents a serious challenge, especially when esophagectomy is performed after induction therapy (Table 29-2). Current conservative treatment, in addition to time-honored strategies, tends to include diagnostic lymphangiography³⁷ and midodrine, an α -adrenergic drug available for oral administration.³⁸ Conservative treatment, combined with surgical treatment when necessary, leads to resolution in most patients.

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MALIGNANT PLEURAL AND PERICARDIAL EFFUSIONS

Sai Yendamuri • Chukwumere Nwogu • Todd L. Demmy

CHAPTER OUTLINE

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MALIGNANT PLEURAL EFFUSIONS

Pleural effusions are common clinical problems occurring in more than 1 million patients each year.¹ In some settings, up to 22% of these effusions are caused by malignant disease and more than 100,000 malignant effusions require treatment annually.² Affected patients with advanced neoplastic diseases experience considerable morbidity as a result of these pleural fluid collections.

Physiology

Pleural effusion results from a derangement in the normal physiology such that there is increased production of pleural fluid or a change of its composition with or without a reduction in the absorption of the fluid. This may be to the result of primary or secondary tumors of the pleura with seeding of the intrapleural space and lymphatic obstruction. Free-floating tumor cells block absorption of fluid and produce vasoactive substances that in turn increase the production and block the absorption of intrapleural protein and fluid.^{3,4}

Demographics

In adults, 95% of neoplastic pleural effusions arise from a metastatic source, with lung and breast carcinoma accounting for 75% of all cases.⁵ Other common

causes are lymphoma, gastric cancer, and ovarian cancer. Approximately half of patients with breast cancer develop a pleural effusion within their lifetime, as compared with one fourth of patients with lung cancer and one third of patients with lymphoma.

Most pediatric effusions, on the other hand, are benign. If malignant, lymphomas or leukemias account for half with the remainder a mix of tumors such as neuroblastoma, Wilms tumor, and germ cell neoplasms.⁶

Adenocarcinomas whose primary is unknown constitute a distinct entity in patients in whom the source of the pleural malignancy is never found. They are associated with exposure to environmental tobacco smoke.⁷

Evaluation

Historical and Physical Findings

Patients with malignant pleural effusions are typically symptomatic and complain of dyspnea, cough, or chest pain. The discomfort often is independent of respiration but is aggravated by activity. With invasive pleural metastases, the affected nerve roots may radiate pain. Like pericardial effusions, rapid fluid accumulation amplifies the symptoms. For at least 10% of patients, the dyspnea is multifactorial and does not improve after drainage. Physical findings indicating pleural effusion are decreased tactile fremitus and dullness to percussion

on examination of the posterior chest, accompanied by decreased breath sounds. As the effusion increases in size, there may be hyperresonance on percussion immediately above the fluid level because of compression and overdistention of the lung. Bronchial breath sounds may be prominent. As effusions become massive, tracheal deviations from mediastinal shifts are detectable. Malignant pleural effusions rarely cause hemodynamic compromise from tension hydrothorax.

Imaging

Early evidence of pleural effusion by chest radiograph is costodiaphragmatic sulcus blunting caused by as little as 125 to 250 mL of fluid, depending on the quality of the film (Fig. 30-1). Occasionally, a spurlike shadow projects into the fissure. Massive effusions are uncommon; however, when they occur, they are more likely malignant. In patients in whom the finding is uncertain, a decubitus film might show shifting of the fluid. Effusions wider than 10 mm by decubitus film often are tapped successfully.⁸

There are specific computed tomography (CT) criteria for pleural effusions. In general, loculation, pleural thickening, pleural nodules, and extrapleural fat of increased density are present only in exudative effusions. Multiple pleural nodules and nodular pleural thickening are generally limited to effusions of malignant origin (Fig. 30-2). Pleural thickening greater than 1 cm also is a reliable criterion.⁹ Magnetic resonance imaging (MRI) has limited use, but it may be slightly more useful for certain pleural tumors such as lipoma; it also can be helpful in determining the extent of invasion for mesothelioma.¹⁰ Thoracic ultrasound shows the optimal site for diagnostic thoracentesis of a small pleural effusion. It also helps in the selection of ideal entry points for thoroscopes or pleural biopsy instruments by avoiding adhesions.¹¹ In addition, ultrasound has moderate accuracy in predicting the malignant nature of the effusion.¹²

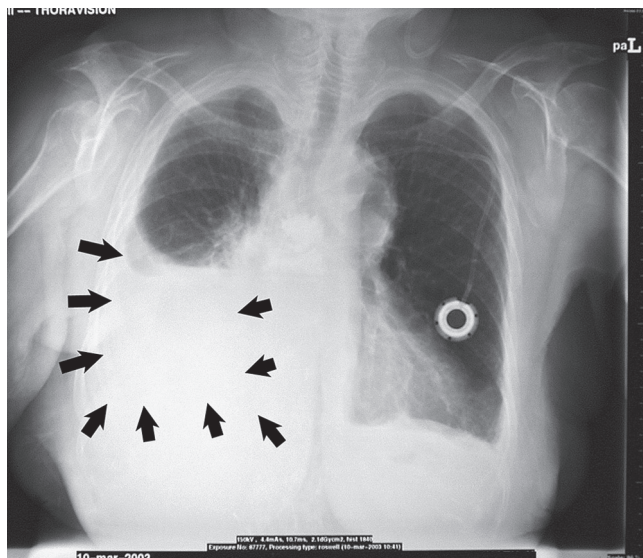


FIGURE 30-1 ■ Chest roentgenogram showing large right pleural effusion (outlined by arrows).

Positron emission tomography (PET)–CT scans may detect early pleural metastases before other imaging tests. If nuclear imaging reveals pleural activity and pleural fluid is scant, diagnostic thoracoscopy is necessary to exclude pleural disease provided this staging is relevant. Limited data suggest a high degree of diagnostic accuracy in differentiating benign from malignant pleural effusions.¹³ Figure 30-3 shows an image of a PET scan demonstrating a malignant pleural effusion.

Diagnostic Procedures

The diagnosis of pleural effusion is confirmed by thoracentesis. Withdrawing only a small portion of pleural fluid is indicated occasionally when full lung reexpansion is unlikely or as a prelude to a definitive drainage procedure. It is usually preferable to attempt drainage of as much pleural fluid as possible (Fig. 30-4).

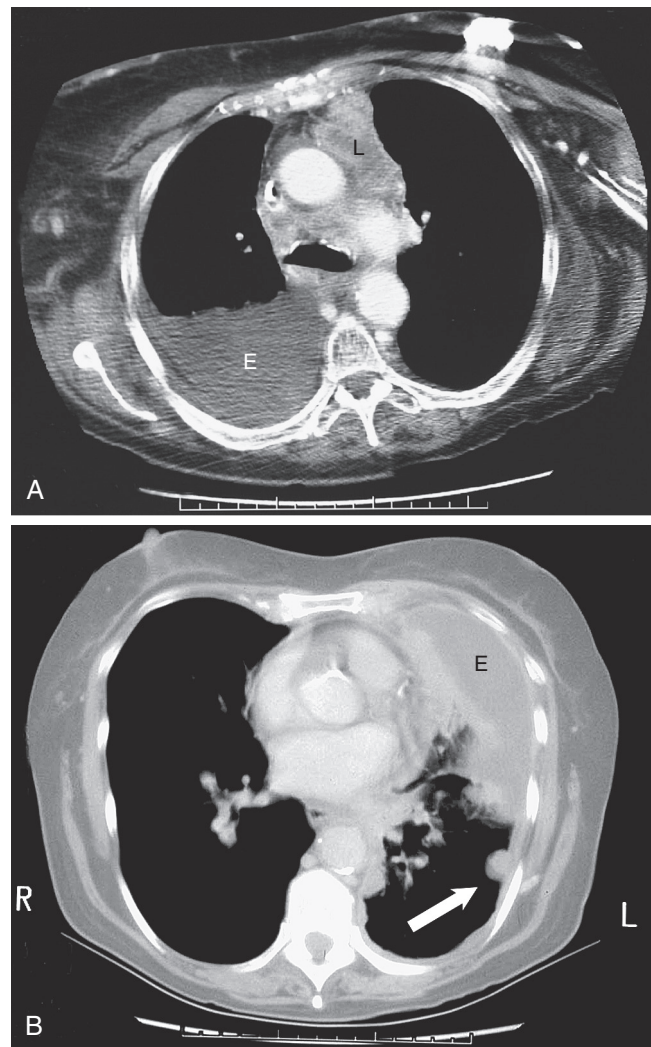


FIGURE 30-2 ■ **A**, CT images of a malignant pleural effusion. **B**, Chest CT from a patient with breast carcinoma, with recurrent basilar left pleural effusion after partially successful chemical sclerosis. The image shows partial pleurodesis, pleural thickening, and a pleural nodule (arrow) at the level of the mid thorax. E, Effusion; L, prevascular lymphadenopathy.

Several commercial kits facilitate drainage by allowing insertion of soft catheters with side holes to completely evacuate the fluid. The catheters can be readjusted during drainage in case the lung temporarily occludes the holes. Needles with retractable blunt obturators (e.g., Turkel needle) also prevent lung injury during pleural entry. Physical examination can guide a pleural tap. On the other hand, ultrasound or other imaging can optimize needle or chest tube placement for effusion drainage in more complex situations (Fig. 30-5). This is particularly useful for a small effusion or pleural disease of long

duration complicated by lung consolidation or pleural loculation. Although marking of the area of “deepest” fluid is useful, it is important to perform the thoracentesis with the patient in the same position as during the imaging. Attempts to completely aspirate chronic effusions should be undertaken carefully. High vacuum applied to the pleural space, by either syringe aspiration or vacuum bottle, is sufficient to rupture alveoli and cause a complicated hydropneumothorax.

Standard Chemistry and Cell Counts

Practically all malignant pleural effusions are exudates. Laboratory criteria to establish exudative effusions are based on absolute values or ratios to systemic parameters. One of the most useful sets of criteria used to classify effusions as exudative was described by Light: pleural fluid/serum total protein ratio greater than 0.5, pleural fluid/serum lactate dehydrogenase (LDH) ratio greater than 0.6, and pleural fluid LDH greater than 200 U/liter (greater than two thirds of the laboratories' upper limit of normal for serum).^{1,14}

Low glucose (<60 mg/dL) and low pH (<7.20) levels are common in malignant pleural effusions.¹⁵ This is attributed to glucose usage and acid production by the malignant cells, leukocytes within the pleural fluid, and also increased pleural membrane metabolism. Investigators have alternatively implicated abnormal pleural membrane transport of glucose, carbon dioxide, and hydrogen ion.¹⁶ Pleural fluid amylase is elevated in approximately 10% patients with malignant pleural effusions, even without pancreas gland disease.¹⁷ In fact, the most common cause of an amylase-rich pleural effusion is neoplasm.¹⁸ The cell count can also indicate malignancy. For some investigators, bloody fluid is the strongest positive predictor of malignant effusion. Fluid viscosity has also been studied as a diagnostic test.¹⁹

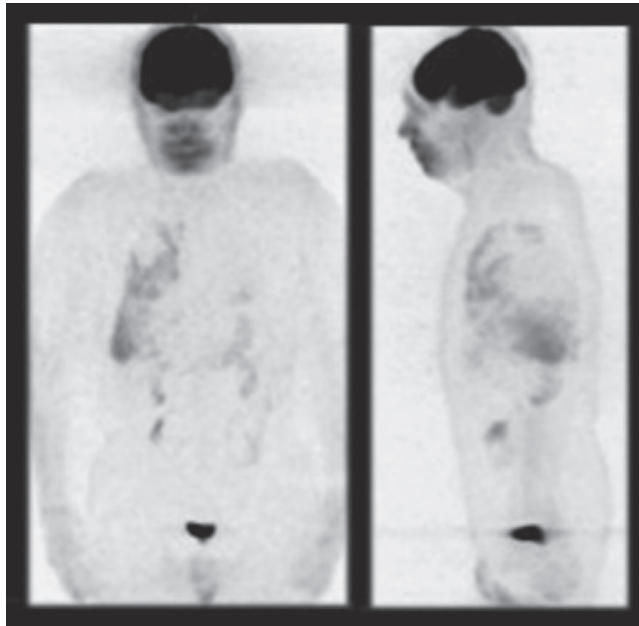


FIGURE 30-3 ■ PET scan demonstrating uptake on the side of the chest with the malignant pleural effusion.

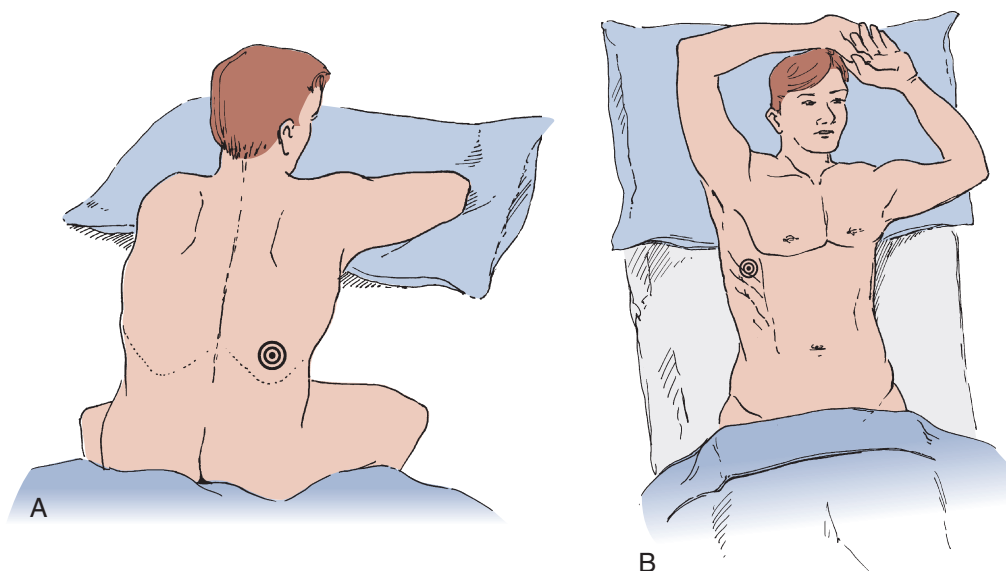


FIGURE 30-4 ■ **A**, Common patient position for insertion of a thoracentesis needle or catheter. Posterior approach allows access to the most dependent (posterior pleural) sulcus to allow maximal drainage of nonloculated fluid. **B**, Lateral patient positioning for thoracentesis or chest tube placement is also useful for effusions with large lateral collections of fluid. The patient's arm is abducted and flexed over his head to facilitate access to the lateral chest.

Immunocytochemistry and Special Chemistry

Many investigators focused their explorations on staining patterns of cells obtained from pleural fluid to confirm

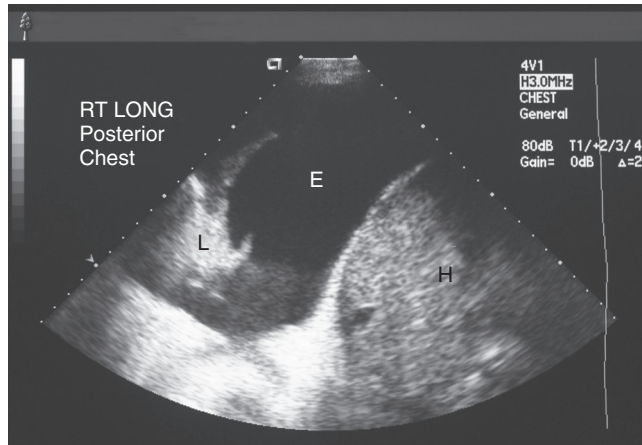


FIGURE 30-5 ■ Ultrasound of right lateral chest to facilitate safe pleural access. E, Effusion; H, hepatic lobe; L, lung.

malignancy, and, if present, correctly classify its origin. Unfortunately, markers are not yet sufficiently sensitive and specific, but they generally show twice the positivity of cytology alone (80% versus 40%).²⁰ These tests usually are used after standard cytologic screening and in combination with cytogenetic and other miscellaneous tests to establish a diagnosis. A more complete list is displayed in [Table 30-1](#).

Some of these markers, such as p53, predict a worse prognosis for malignant effusions that are p53-negative.²¹ Another marker, Ki-67, is associated with a worse prognosis when its labeling index is low.²²

Vascular endothelial growth factor (VEGF) has been found to be a useful discriminator for malignant effusions.²³ Other special chemistry values, displayed in [Table 30-2](#), are occasionally useful to categorize malignancy. The sensitivities and specificities vary by specific cell types.

In the past few years, epigenetic biomarkers for cancer have been studied. These include markers to differentiate benign from malignant pleural effusions.^{24,25} These markers often have the advantage of easier sample processing and, if validated, may impact the field significantly.

TABLE 30-1 Immunocytochemistry Markers

Ref	Test	Benign Mesothelial	MM	General CA*	Adeno CA [†]	Other CA [‡]	Other Type
20	AFP					++	Hepatocellular
88	Alcian Blue	0		+			
89	B 72.3		0	++	+++		
20	B-19					++	Prostate
90	BCA-225	0		++			
91	BER-EP4	0	0	++ / +++	+++		
20	CA 15.3					+++	Breast
20	CA 19.9					+++	Gastric
92	Calretinin	+++	+++	0	0		
93	CD44 s	+++		-			
93	CD44 v 3-10	0		+			
92, 94	CEA	0		+++	++	+++	Colorectal
95	Desmin	++/+++	0	0			
96	E-cadherin	0	+++	++			
91	EMA	-	+++	+++			
97	GATA	0				+++	Breast
98	GLUT1	-		+++			
88	Keratin	0	+++	+	+++		
99	Ki67	0		++			
100	Leu M1				++		
20	MCA					++	Breast
91	MCA-b-12	-		+++			
101	MOC31	0			+++		
92	Mucicarmine				+		
102	Mucin	0			+		
95	N-cadherin	++	+++	+			
103	p53	-/0		+			
104	UEA	0		+			
105	TIMP-2				++		
106	Vimentin			+			
106	CKMNF 116			+			

*Nonspecific diagnosis of cancer.

[†]Specific diagnosis of adenocarcinoma.

[‡]Specific diagnosis of certain histologic type.

Scale: +++, >90%; ++, 60%-90%; +, 30%-59%; -, 10%-29%; 0, <10%.

AFP, α -Fetoprotein; CA, carcinoma; CKMNF, cytokeratin; EMA, epithelial membrane antigen; GLUT1, glucose transport protein; MCA, mucin-like carcinoma-associated antigen; MM, malignant mesothelioma; TIMP, tissue inhibitor of metalloproteinase; UEA, *Ulex europaeus* agglutinin.

TABLE 30-2 Sensitivity and Specificity of Various Pleural Fluid Assays in the Detection of Malignancy

Ref	Assay	Sensitivity (%)	Specificity (%)
107	Ca 19-9	36	83
107	Ca15.3	80-95	93
108	Calprotectin	100	83.15
107	CEA	52	77
107	CYFRA 21-1	91	90
109	MUC-1 > 0.126	64	95.7
109	MUC-5AC > 0.028	72	98
110	Sialic acid > 0.075	68	77
111	Sialyl EA	64	95
112	TNF ratio	84	90
107	TSA	80	67
113	CYFRA 21-1	47	92
114	MN/CA9	89	91
115	Mammaglobin by RT-PCR	82	75

CEA, Carcinoembryonic antigen; CYFRA, cytokeratin fragment; EA, embryonic antigen; RT-PCR, reverse transcriptase-polymerase chain reaction; TNF, tumor necrosis factor; TSA, total sialic acid.

Cytogenetics

DNA testing by flow cytometry or chromosome analysis predicts the likelihood of malignancy. The evidence of a marker chromosome, aneuploidy, or a hyperdiploid state suggests malignancy. Aneuploid samples (by flow cytometry) yield predictive values as high as 96%.²⁶ No aneuploidy was found in benign reactive effusions in one series.²⁷ Telomerase activity occurs in 92% of malignant effusions and in only 6% of benign effusions (with a specificity of 94.2%).²⁸

Pleural Cytology and Biopsy

Cytologic evaluations with standard staining (Papanicolaou smears) can sometimes confirm malignant pleural effusions. In very unusual cases (0.5%), the results are falsely positive.²⁹ In cytologic specimen reviews, lung adenocarcinoma is the most frequent diagnosis. Breast cancer effusion specimens have a higher cytology diagnostic yield (approximately 78%) than lung or other tissue primaries.³⁰ The sensitivity of pleural fluid cytology frequently is greater than undirected pleural biopsy.

When standard pleural effusion cytology is nondiagnostic, pleural needle biopsy occasionally provides some additional useful diagnostic information (48% in one series).³¹ However, whether pleural biopsy adds much over fluid cytologic evaluation in cases of suspected malignancy is controversial. In another series, only 7% of the cases had a diagnosis made by use of pleural biopsy when the cytology result was negative.³² This can be enhanced by the use of ultrasound to perform a directed biopsy.³³ For difficult cases, cytology combined with needle biopsy results are inferior to those obtained by video-assisted thoracic surgery (VATS) (41% versus 97%).³⁴ In several series, a typical yield of undirected pleural needle biopsy of 50% to 60% was far inferior to biopsies obtained by VATS. Use of a directed VATS

approach in these cases achieves greater than 90% success.³⁵ With idiopathic effusions (20% in some series), uncertainty is reduced to 4% using thoracoscopy. The complication rate from thoracoscopic biopsy is low, with mortality rates less than 1% and complication rates less than 10%.³⁶ Figure 30-6 shows thoracoscopy images that confirmed pleural malignancy.

A technique variation that might shift results of “blind” biopsy toward those by directed means is the use of a pleural brush to increase the cytologic yield. In one series, this technique was positive in 90% of the cases, as opposed to 67% with the routine cytologic aspirate and 58% with biopsy.³⁷ Thoracotomy to perform pleural biopsy is unusual given successful directed methods such as VATS.

When patients remain without a definitive diagnosis following VATS or thoracotomy, approximately one third will demonstrate a cause (typically lymphoma or mesothelioma) months to years later.³⁸ For patients with massive malignant effusions for which the cause is unknown, fiberoptic bronchoscopy may establish lung cancer. When effusions are mild to moderate and without associated symptoms, the chance of finding a neoplasm is not great enough to warrant bronchoscopy.

In summary, clinical information, conventional cytology results, immunocytochemistry, flow cytometry, and special chemistry test results must be integrated to yield the most accurate diagnosis.

Treatment

The optimal treatment for malignant pleural effusion is controversial. Multiple technologies exist that control malignant pleural effusions successfully. The best selection for a patient is guided by factors such as the individual's frailty and the prognosis of the primary malignancy. The need for additional pleural tissue or directed biopsy, as well as concomitant diagnostic or therapeutic procedures requiring general anesthesia, also guides the choice and timing of pleural interventions.

The anatomic state of the affected thorax is important. For example, a pleural effusion of relatively rapid onset typically yields full expansion of the lung and pleural coaptation after the effusion is evacuated. On the other hand, malignant disease of long duration can prevent full lung expansion because of visceral pleural restriction, endobronchial obstruction, parenchymal fibrosis, or replacement by tumor. To help with planning, good diagnostic imaging is important.

Treatment options can be classified into those that rely on drainage alone or those that also obliterate the pleural space. Because an inflammatory response is associated with most pleural effusions, persistent and complete pleural drainage may also achieve pleural fusion. Recent evidence shows cytokine activation from repetitive pleural draining that supports this view.³⁹ Although pleural malignancy traditionally means surgical incurability, some investigational multidisciplinary methods include operations for selected cases designed to improve the chance for cure.⁴⁰

A chest radiograph after pleurodesis commonly shows multiloculated fluid collections suggestive of empyema. This finding probably represents regions of rapid pleural

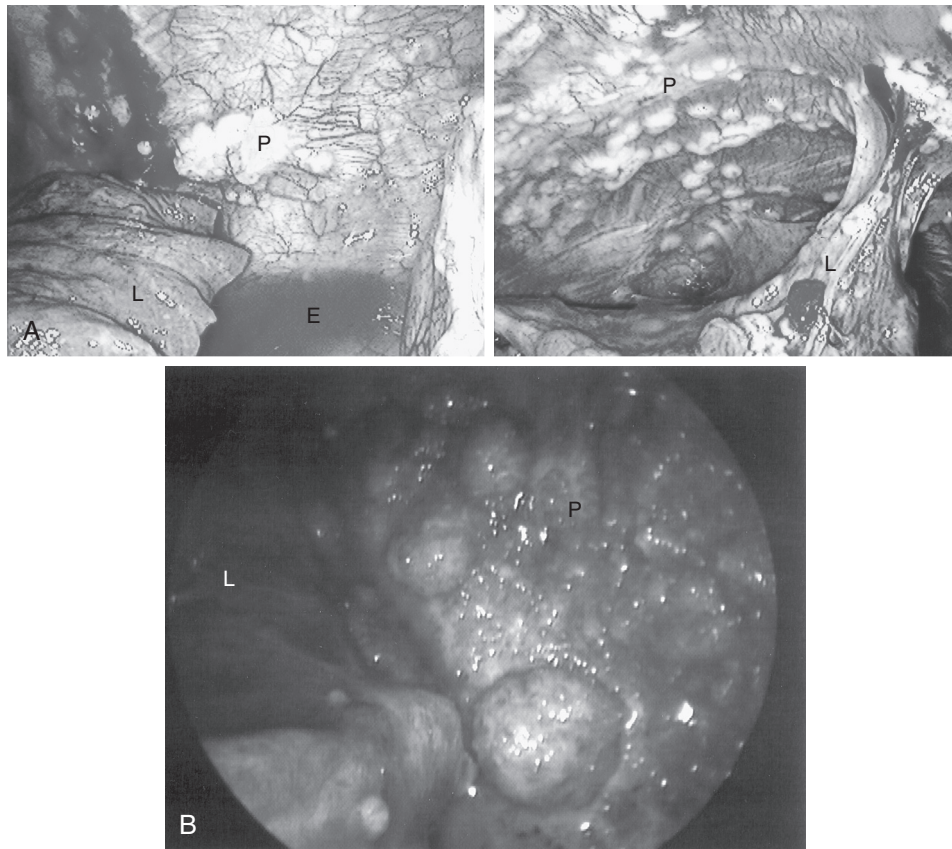


FIGURE 30-6 ■ **A**, Lung carcinoma. Parietal and visceral pleural implants with residual effusion are displayed. **B**, Malignant mesothelioma with the “grape cluster” pattern characteristic of pleural tumors. *E*, Effusion (residual); *L*, lung; *P*, parietal pleura.

adhesion formation with intervening accumulations of inflammatory fluid. This is probably an acceptable variation of treatment effect rather than a nonuniform distribution of sclerosing agent.

This imaging appearance generally resolves by 1 to 3 weeks; however, to avoid this phenomenon, some physicians wait for effusion drainage rates to decrease before instilling pleurodesis agents. It is not clear whether this practice is necessary. Long delays before pleurodesis may simply reduce the thoracic cavity area to which the instilled agent is exposed when significant pleural adhesions have already occurred in regions remote to the drainage catheter. Occasionally, significant pleural thickening or even fibrothoraxes occur as long-term sequelae of pleurodesis. The use of thoracic ultrasound (see Fig. 30-5) can guide the optimal drainage site for small pleural effusions or the optimal point of entry of a thoracoscope to avoid adhesions.

Drainage-Based Methods of Malignant Effusion Control

Serial thoracenteses appropriately control malignant pleural effusions for some patients. This option is not effective for durable effusion control but provides temporary symptomatic relief in cases with extremely poor prognoses. Thoracentesis is also ideal when alternate therapy should cause a major reduction in the patient's

effusion. For example, a lymphoma-related effusion may resolve with chemotherapy.

Occasionally, thoracentesis creates a hydropneumothorax because of poor compliance or entrapment of the ipsilateral lung. If the pneumothorax and dyspnea symptoms remain stable and noncompelling, tube thoracostomy should be avoided, because pleural coaptation and effective ventilation from that lung are unlikely. Fluid will replace the air space over time. Lung entrapment can probably be predicted by measurement of pleural pressure swings.⁴¹

Small Catheter Drainage. Implantation of a long-term pleural catheter or placement of a percutaneous medium-durability pleural catheter for continuous or intermittent drainage is better than serial percutaneous aspirations.⁴² The pleural catheters have the advantage of obtaining near complete removal of the pleural fluid in the same way that a tube thoracostomy evacuates the pleural space. Needle aspiration rarely evacuates the fluid completely and rarely maintains the lung expansion long enough for a spontaneous pleurodesis to occur. Even without introduction of any pleural sclerosing agents, pleurodesis occurs simply by maintaining pleural apposition in a select group of patients probably from the underlying inflammation and invasive effects of the neoplasms.⁴³

Using a small silicone catheter (Fig. 30-7) with a valve that allows drainage only when connected to a closed

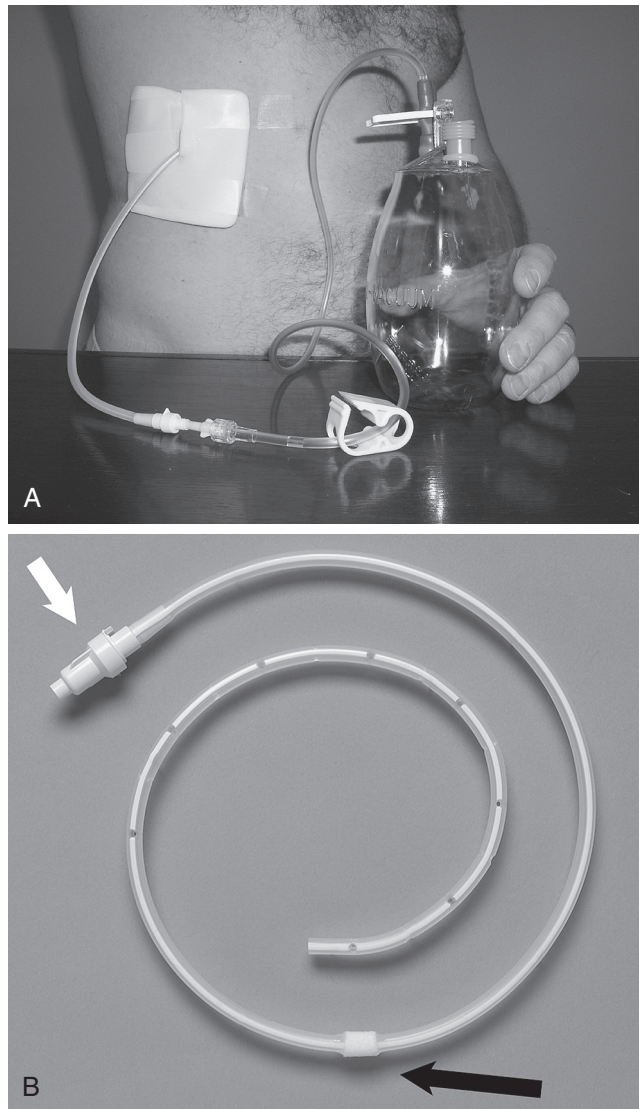


FIGURE 30-7 ■ PleurX catheter. **A**, Patient connects the PleurX catheter to a bottle for self-drainage. **B**, Close-up of the catheter. Note the one-way valve mechanism (white arrow) and Velcro cuff to provide tissue ingrowth (black arrow).

system, approximately 50% success at 30 days has been achieved in prospective randomized clinical trials compared with traditional pleurodesis methods.

This research was replicated with the Tenckhoff catheter, the pigtail catheter, and the Pleuracan device.⁴⁴⁻⁴⁶ Each of these devices controlled dyspnea in greater than 90% of the cases. Intermittent pleural drainage is an attractive option for patients in whom pleurodesis is less likely to occur because of the inability of the visceral pleura to touch the parietal pleura. As a consequence, this method is often used to complement sclerosis options at various centers.

Pleuroperitoneal Shunting. Another way to drain pleural fluid is to pump it into the peritoneal cavity using a device similar to that crafted to drain ascites into the venous system. This generally requires the patient to pump the shunt chamber (Fig. 30-8) at least 20 times four

times a day and perhaps more because of the need to overcome the negative intrapleural pressure.⁴⁷

More than 80% of patients reported excellent results with this method, and it obviated the need for an appliance to traverse the skin. Unfortunately, with this technology, at least 10% to 20% of the patients will occlude their shunt, possibly requiring revision; furthermore, determination of shunt obstruction may be difficult.⁴⁸ Otherwise, this shunt appears to have survival rates similar to those of talc pleurodesis. Also, there is generally no evidence of peritoneal deposits resulting from this pleuroperitoneal shunting technology. The decision to use the shunt can be made during thoracoscopy when pleural coaptation seems unlikely and placement of the shunt is relatively easy because the patient is under general anesthesia.

Sclerosis-Based Pleural Effusion Management

Generally, accelerating the process of pleurodesis (which might not occur by prolonged drainage alone) is done by accessing the pleural space, draining most of the fluid, and then inserting a substance that increases the inflammatory response and thus causes intense adhesions within the pleural envelope. There is controversy regarding how pleural fluid characteristics affect the success of pleurodesis or the prognosis of the patient. For instance, investigators have shown that a low pleural fluid glucose (<60 mg), low pH (<7.2), low performance status (Karnofsky score < 70), massive effusion, and high pleural LDH levels (>600 U/liter) are associated with a higher rate of failure with pleurodesis efforts. These values also predict positive pleural fluid cytology and a poor overall prognosis.⁴⁹ However, other investigators have contradicted this finding particularly with respect to pleural effusion pH.⁵⁰ Experimental evidence supports the concept that the inflammatory effect needed by some sclerosant agents is inhibited by steroid use, thereby decreasing the effectiveness of the pleurodesis.⁵¹

Rolling the patient into different positions after instilling the desired sclerosant is another common practice. This is unnecessary in patients with normal pleural spaces in whom aqueous sclerosing agents were used. Rapid intrapleural dispersion occurs in just one position as demonstrated by radiopharmaceutical labeling and nuclear medicine imaging.⁵² However, when the pleural space is loculated or there is lack of full lung expansion, rolling may be useful. Sclerosing agents that are particulate, like talc slurry, might have more uniform distribution by rolling, but this has been disproved in one small prospective trial.⁵³ There also appears to be variations in the practice of pleurodesis with surgeons more likely to use an agent such as talc and other physicians using bleomycin or cycline-based drugs.

Another practice that is controversial is the need for the pleural effusion drainage rate to taper off before instilling a sclerosing agent. This may be unnecessary. Investigators have shown that the daily amount of pleural fluid drainage is much less useful than having full pleural fluid evacuation and lung reexpansion on chest roentgenogram.⁵⁴ Pleurodesis appears to have only a minor

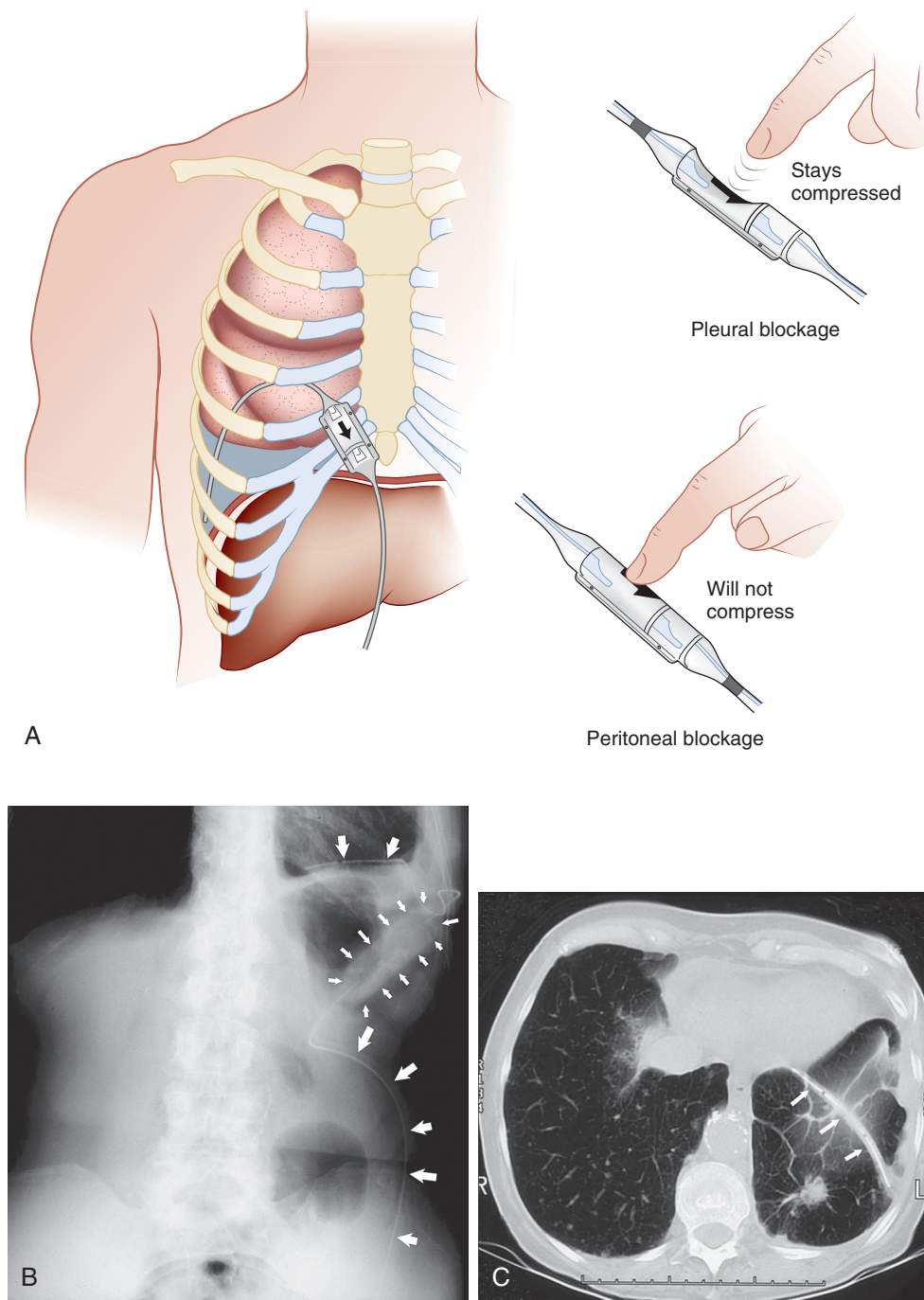


FIGURE 30-8 ■ Pleuroperitoneal shunt. **A**, Diagram of shunt position and demonstration of proximal and distal obstruction. **B**, Roentgenogram of lower chest and upper abdomen, showing left pleuroperitoneal shunt (*arrows*) with chamber placed at costal margin for patient self-pumping. **C**, CT image showing the catheter (*arrows*) in the left lower pleural space. This image was obtained 3 months after shunt placement in the patient whose left lower lung loculated pleural breast carcinoma effusion as depicted in [Figure 30-2B](#). (**A**, Reprinted with permission from Ponn RB, Blancaflor J, D'Agostino RS, et al: Pleuroperitoneal shunting for intractable pleural effusions. *Ann Thorac Surg* 51:605–609, 1991.)

adverse effect on respiratory function, although the studies on this are limited.⁵⁵ Finally, whereas sclerosis of the pleural cavity is generally practiced on inpatients, there have been successful outpatient pleurodesis programs.

When pleurodesis is performed as an inpatient procedure, a chest tube is generally inserted. Chest tube size can vary significantly, ranging from 20 to 36 Fr

depending on local institution or operator preference. Also, there appears to be considerable variation in sedation practices with occasional episodes of high discomfort and anxiety during the insertion of chest tubes. Generally, patients with dyspnea from malignant effusions are not decompensated enough to require emergent placement without analgesic preparation. It is appropriate to establish a protocol to standardize intravenous sedative

and analgesic use to supplement the generous use of local anesthetics during placement of a chest catheter.

The trend has been toward the use of smaller catheters, both for drainage and for the pleurodesis of malignant pleural effusions. In a prospective randomized study, a 12-Fr catheter was comparable to a standard large-bore tube.⁵⁶ This result has been reproduced in other studies using both inpatient and outpatient pleurodeses with the pigtail, Cystofix, Elecath, and PleurX catheters and talc, doxycycline, or similar traditional sclerosing agents.

Chemical Sclerosis—Talc. Talc was first used to create pleural adhesions in 1935 for tuberculosis management, and approximately 25 years later, it started to become popular for controlling malignant effusions. Generally, there are two ways to administer talc into the pleural space. One is in an insufflated powder (talc poudrage) and the other is instillation of particulate slurry with talc in a liquid vehicle. The dose of talc needed depends somewhat on the route of delivery and its preparation method. A fine powder from an aerosol gives a broader distribution with less mass (Fig. 30-9). Nevertheless, reported successful talc pleurodeses generally used between 2 and 8 g with a dose of 5 g being the most common used in multicenter trials.

Talc is often prepared preferentially in the hospital pharmacy rather than purchased from expensive vendors.

In fact, the cost compares favorably with that of most other agents. The use of purified but not sterilized talc may be acceptable because a tremendous inflammatory response kills contaminating bacteria. Nevertheless, the standard, preferred practice is to use talc sterilized by prolonged baking at 132° C, ethylene oxide sterilization (talc in cellophane pouches), or gamma radiation.

Although the use of talc for malignant pleural effusions has become widespread and is considered a safe clinical practice, some patients sustain an inflammatory response severe enough to cause respiratory insufficiency. Such responses have prompted experts to question its use. Clinical outcomes and laboratory testing show that talc administered intrapleurally is distributed systemically. The extent to which this might adversely affect somewhat frail patients who receive it is unclear. Some investigators have suggested that the patient should be observed as an inpatient for up to 72 hours after its use. Talc causes mesothelial denuding and an exudative neutrophilic pleural effusion similar to what occurs with the tetracycline class of sclerosis agents. For some tumors, such as mesothelioma, talc may also induce apoptosis. On the other hand, if there is evidence of increased fibrinolytic activity, then talc sclerosis may be less effective.

Table 30-3 lists good to excellent results of talc and other sclerosant agents in noncomparative studies. Hospital stays ranged from 3.3 to 4.4 days.^{57,58} Associated

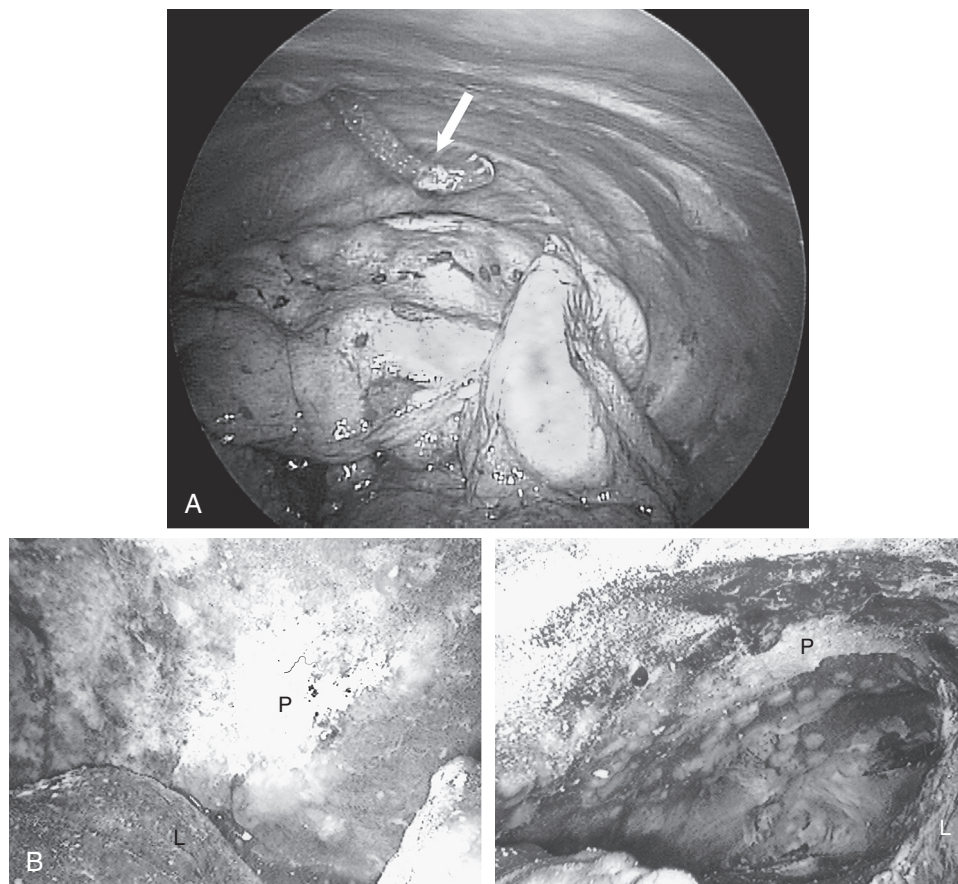


FIGURE 30-9 ■ **A**, Thoracoscopic image of left chest before insufflation of talc. Angled tip on insufflation catheter (arrow) facilitates directing talc to desired areas. **B**, Thoracoscopic image of left chest after insufflation of talc (see same patient, Fig. 30-6A). *L*, Lung; *P*, parietal pleura.

mortality ranges from 0% to 16% and morbidity ranges between 4% and 14% with respiratory complications being most frequent.

When talc is tested in comparison trials (Table 30-4), the results are not as favorable but still are equal or

superior to other common pleurodesis methods. Most of these investigations had good risk profiles with complication rates less than 20% and mortality attributed to the talc less than 5%. Are the differences in results dependent on the patient population or, perhaps, the method or composition of the talcum powder used? Particle size might affect dissemination. At least 20% of the patients who receive talc pleurodesis will have a transient interstitial haziness occur on the chest roentgenogram, possibly from endothelial damage and capillary leak syndrome. Talc slurry was thought to be a riskier delivery route because there seemed to be more anecdotal reports of respiratory distress associated with this method. Some investigators believe that intraoperative talc leads to shorter hospital stays. Another development is the use of awake anesthesia with a thoracic epidural, purported to decrease hospital length of stay and hasten recovery.⁵⁹ A prospective study has not shown a significant difference between talc poudrage administered in the operating room compared with bedside talc slurry based on 30-day prevention of an effusion.⁶⁰

Chemical Sclerosis—Cycline Drugs and Bleomycin. Multiple doses of chemical sclerosants have been studied, but a single dose is probably sufficient. A dose of tetracycline at 20 mg/kg was found to be effective as a single-dose regimen.⁶¹ Now doxycycline is available for clinical use instead of tetracycline. A dose of doxycycline is typically 500 mg in 100 to 200 mL of 0.9% saline. Although there has been interest in using cycline-based drugs intraoperatively, there is no advantage to this over bedside use. Results of noncomparison studies with tetracycline and bleomycin are presented in Table 30-3.

Bleomycin, in general, shows success rates that are equivalent or just less than those of talc pleurodesis. Pleural effusions from breast tumors may respond better than those of other tumors to this drug. Many times these drugs may work better in the pleural cavity than in other spaces such as the peritoneal cavity.

TABLE 30-3 Nonrandomized Trials of Common Sclerosant Agents

Agent (Ref)	Patients (N)	Success (%)*
Talc Poudrage		
116	40	90%
117	42	82%
118	44	96%
58	24	88%
119	125	87%
Talc Slurry		
120	58	81%
121	34	100%
Bleomycin		
122	38	63%
123	20	85%
124	19	79%
Cyclines		
125	25	59%
126	21	88%
127	31	100%
Others		
Iodopovidone		
128	52	96%
Vincristine		
129	15	80%

*Most investigators defined 100% success as complete or near complete control of pleural effusion at 30 days after pleurodesis based on both symptom control and repeat chest imaging. Although 1 month was a uniform interval for assessing this endpoint, some investigators used longer follow-up. Studies also differed on whether early deaths were considered failures.

TABLE 30-4 Randomized Trials of Common Sclerosant Agents and Percent Success*

Reference	Patients (N)	Talc Slurry	Talc Poudrage	Bleomycin	Tetracycline	Other	Other Compound Name
60	469 [†]	70%	79%				
130	26	79%		75%			
131	33	92%			48%		
132	134		97%	64%	33%		
133	36		87%	59%			
134	62			64%	52%		
135	115 [†]			64%	33%		
63	60			25%	35%	70%	Bleomycin & tetracycline
136	106			72%		79%	Doxycycline
137	38			74%		43%	Corynebacterium parvum
138	32			13%		65%	Corynebacterium parvum
139	40			50%		80%	Mepacrine
140	40				80%	60%	Methenamine
141	102			69%		76%; 71%	OK-432; cisplatin + etoposide
142	160			85		62	Interferon alfa-2b
143	49	84%				96%	Silver nitrate
144	18				83%	90%	Quinacrine

*Most investigators defined 100% success as complete or near complete control of pleural effusion at 30 days after pleurodesis based on symptom control and repeat chest imaging.

[†]Multicenter trial.

Pain and transient fever occurred in 5% of patients after intrapleural instillation in one multicenter trial.⁶² In other studies, the fever occurred in as high as 60% of patients. It is unclear why there is so much variation in the reporting of these side effects.

Reports of pleural sclerosis need to be compared based on how long the treatment effects are followed. One investigation found 70% long-term success with combined bleomycin and tetracycline. Although a favorable early result was found with either agent, after 4 months the single-sclerosant success rate fell to 25% to 35%.⁶³

Other Sclerosing Compounds. Other compounds have been used, including three doses of *Corynebacterium parvum* (7 mg in 20 mL saline). Good results (76% to 100% success) were obtained, but this drug is no longer available. Intrapleural interferon- β (5 to 20 million units, maximum of three administrations) can be used alone, but there is only a 30% remission rate. Yet, when interferon- β is cycled with immunotherapy such as interleukin-2 and interferon- α , a 56% to 70% response rate occurs.⁶⁴ Tumor necrosis factor therapy yielded an 87% recurrence-free rate at 4 weeks with a dose of 0.15 to 1.01 mg/patient. These patients have flu-like symptoms, including fevers, chills, and fatigue.⁶⁵

Radiopharmaceutical Interventions

Radioactive compounds were used in the 1960s to control malignant pleural effusions, and they have gained renewed interest. The most commonly used is an intracavitary colloidal suspension of chromic phosphate (^{32}P) because of its safer emission and faster decay compared with elements such as gold. Results of these therapies in uncontrolled trials have 75% success rates.⁶⁶ Generally, a dose of 6 to 12 mCi of ^{32}P is used, which has a half-life of 14 days. A therapeutic thoracentesis (maximal drainage) is performed with a temporary thoracentesis catheter. The catheter remains in place until the ^{32}P is instilled. It is then flushed and withdrawn. The patient may then be discharged if there are no complications.

Mechanical Abrasion or Laser

Limited data exist regarding the use of mechanical pleural abrasion that is effective for other types of pleural disease such as pneumothorax. Experimental data suggest that the mechanical abrasions are no better than the addition of sclerosing agents such as talc. Similarly, laser treatments that cause superficial pleural destruction are probably not as effective in controlling effusions. Both are inhibited by their erratic effects in poorly healing neoplastic tissue.

Pleurectomy

The poor prognoses of patients with malignant pleural effusions limit enthusiasm for aggressive surgical options given the anticipated recovery times for such operations. However, the less invasive therapies noted earlier are used when thoracoscopy is needed to achieve a directed diagnosis of the pleural pathology. The use of

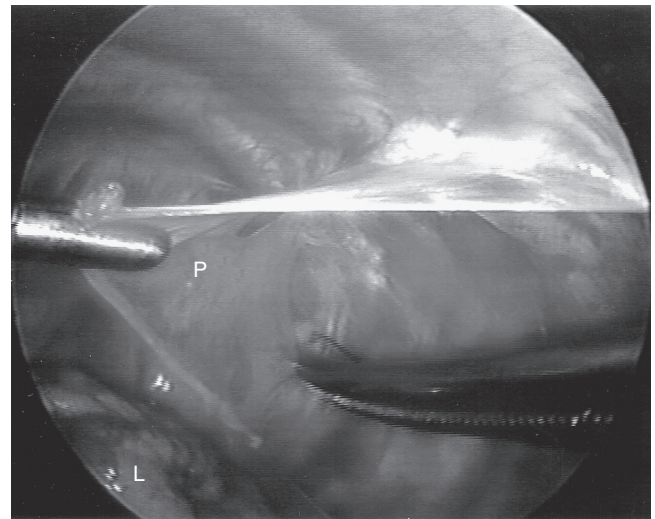


FIGURE 30-10 ■ Video-assisted thoracic surgery (VATS) image of parietal pleurectomy. L, Lung; P, parietal pleural peel.

thoracotomy and pleurectomy is accepted more for patients with malignant mesothelioma in whom early mortality from distant metastases is less certain. The mortality rate for pleurectomy of malignant effusions is at least 12%. Patients were considered for pleurectomy if they failed traditional drainage and sclerosing agents, had trapped lung, or were diagnosed as having malignant pleural effusion or pleural carcinomatosis at the time of thoracotomy. Nevertheless, these indications are now unusual outside a clinical trial. To reduce the concern regarding thoracotomy morbidity, there is interest in VATS pleurectomy (Fig. 30-10), which results in a shorter hospital stay and good effusion control. In a series of patients who underwent VATS pleurectomy,⁶⁷ there was 0% mortality with a mean hospital stay of 5 days. Six of 19 patients died within 12 months, and of the remaining 13 patients, 2 developed recurrent effusions.

Prognosis and Future Trends

The prognoses of patients with malignant effusions vary among clinical settings because of population variations in primary cell types and regional preferences in therapies used to control effusions. A survival rate of less than 50% at 6 months and 6% at 2 years after malignant pleural effusion diagnosis is typical. Also in these series, patients treated only by serial thoracenteses rather than more aggressive therapies had a particularly short survival (13.9 weeks). Alternatively, a longer interval between the initial diagnosis of cancer and the malignant effusion favors survival.

Breast cancer effusions are associated with a more favorable survival rate, particularly when they are estrogen receptor positive and the cells show a morula clustering pattern on cytology. The presence of large clusters of malignant cells on smears also has a favorable prognosis in other cancers. Unfavorable tumor surface receptors adversely affect prognosis (see “[Immunocytochemistry and Special Chemistry](#)”).

As with other treatment modalities, patient performance status is an important factor in determining optimal therapy. A Karnovsky score of 70 or higher is preferred before more aggressive surgical approaches (e.g., thoracoscopy) that require general anesthesia are taken. This yields a survival rate that makes the morbidity risk tenable.

Occasionally, trivial malignant effusions are discovered with minimal nearby carcinomatous pleuritis at the time of thoracotomy. If there is only a small primary tumor with little other regional disease, it may be reasonable to perform a formal resection if the patient has good pulmonary function. Although this approach is controversial, the logic for taking this approach follows from the finding that patients who have occult pleural metastases treated by pleural washings may have prolonged survival times or even cure. Accordingly, for patients with minimal pleural carcinomatosis and N0 tumors, there is interest in performing ablative therapy of the pleura to improve cancer control and possibly effect a cure. One of these treatments has been pleurectomy and intracavitary photodynamic therapy, which has been used to treat mesothelioma and may also be useful for treating primary lung cancer. A phase II trial on carefully selected patients demonstrated a 6-month local control rate of 73% and a median survival of 21.7 months.⁶⁸

Hyperthermic chemotherapy and hypotonic chemotherapy are other investigational methods of effusion control. Experience in mesothelioma work has led to use of hyperthermic pleural chemoperfusion in isolated metastatic pleural disease with favorable results in small series.⁶⁹ Thrombolytic agents may disrupt loculations for more effective pleurodesis or pleural ablation therapy. Transfer of lymphokine-activated killer cells improved tumor lysis in the pleural space, and intrapleural interleukin-2 induced a 37% complete response in a multi-institutional study, possibly by restoring the immunocompetence of effusion-associated lymphocytes.⁷⁰ Cytokine therapy, particularly the use of VEGF receptor blocker, can control some pleural effusions. In related research, indomethacin was shown to block prostanoïd-related endothelial cell permeability associated with adenocarcinomas. Intrapleural steroids, however, do not slow effusion reaccumulation. Gene therapy approaches, such as suicide gene therapy, continue to show steady progress but should still be considered investigational.⁷¹

Finally, intrapleural chemotherapy can control effusions without pleurodesis, per se. Mixed results have occurred with agents such as cisplatin and cytarabine, and doxorubicin. One of the trials by the Lung Cancer Study Group showed a combined complete and partial response at 3 weeks of 49%.⁷² More commonly, systemic chemotherapy is administered; recent drugs used for this include gemcitabine and vinorelbine or combinations with cisplatin, ifosfamide, and irinotecan. Zoledronic acid and hypotonic cisplatin therapy have also been proposed.^{73,74} Gene therapy is yet another strategy being explored.⁷⁵

Fusing of a sclerosing agent with a chemotherapy agent is another novel approach. A bioadhesion compound linked to Adriamycin achieved a 100% response rate in 14 patients in a preliminary report.⁷⁶ Similarly, microspheres can deliver chemotherapy intrapleurally at high local concentrations with low systemic exposures.

Diverse managements are offered for patients with malignant pleural effusions. Optimally, the treatment conforms to the patient's anticipated survival based on histologic diagnosis, molecular markers, extent of metastatic disease, and other comorbidities. Despite some promising research, the overall prognoses of these patients are limited and therapy should focus on improving quality of life. Accordingly, less invasive outpatient small catheter-based methods are replacing inpatient therapies such as the traditional chest tube with talc slurry. A randomized controlled trial (CALGB 30102) was designed to compare chest tube talc slurry (inpatient) with intermittent small catheter drainage (outpatient). However, this study closed early because of poor accrual; nevertheless, data analysis demonstrated better palliation by catheter-based drainage.⁷⁷ A cost-effectiveness analysis performed by Puri and colleagues suggests that tunneled catheters are the most cost effective in patients with limited prognosis and bedside pleurodesis is most cost effective in patients with better prognosis.⁷⁸

MALIGNANT PERICARDIAL EFFUSIONS

Pericardial effusion is the most common cardiac problem in patients with malignant disease and is reported in 1.5% to 21% of patients with cancer.⁷⁹ Nonmalignant conditions also cause pericardial effusions in patients with cancer. Examples of these conditions are infection, uremia, congestive heart failure, hypothyroidism, and autoimmune disorders. Radiation, drug-induced pericarditis, and idiopathic pericarditis are also known causes of pericardial effusions.

The most common malignancies to involve the pericardium are metastatic lung cancer, breast cancer, leukemia, lymphoma, and melanoma. Less commonly, secondary involvement by esophageal, gastric, colonic, oral, nasopharyngeal, prostate, and ovarian carcinoma may be seen. Primary tumors of the pericardium are rare and include mesothelioma, fibrosarcoma, angiosarcoma, and malignant teratoma.

Mechanism

Tumors spread to the pericardium by direct extension or by hematogenous or lymphatic spread. Mediastinal lymph node metastases subsequently spread to the pericardium by retrograde movement through lymphatic vessels draining that space. Increased visceral pericardial fluid production may result from direct involvement of the serosal surface by tumor. Flow obstruction by tumor increases lymphatic and venous hydrostatic pressure, which also drives pericardial fluid accumulation. The hemodynamic consequences of a pericardial effusion depend on its rate of accumulation and the pericardial compliance. Thus, large effusions may cause no symptoms if they accumulate slowly within compliant pericardia.

Evaluation

Frequent pericardial effusion symptoms are dyspnea, cough, and chest pain. Physical examination findings are

tachycardia, pulsus paradoxus, diminished heart sounds, elevated jugular venous pressure, hypotension, and pulsus alternans. Pericardial tamponade is more likely after rapid accumulations of fluid and may be the initial clinical presentation of malignant pericardial disease.

The chest radiograph often shows an enlarged cardiac silhouette, mediastinal widening, or hilar densities. Alternatively, a normal plain radiograph does not exclude pericardial effusion. Electrocardiographic effusion criteria are sinus tachycardia, nonspecific ST segment or T wave changes, low-voltage tracings, and electrical alternans.

Echocardiography is very sensitive in detecting the presence of fluid and has become the most useful tool for diagnosing pericardial effusions (Fig. 30-11). Right atrial or right ventricular compression with decreased left ventricular dimension and failure of the inferior vena cava to collapse on deep inspiration suggests hemodynamic compromise. The echocardiogram also guides pericardiocentesis, drainage catheter placement, or both, safely. Cytologic examination of the pericardial fluid may then be performed. The rate of positive cytologic results reported in published series ranges from 57% to 100% among patients with malignancy.⁸⁰ Both CT and MRI provide excellent anatomic detail of the pericardial space but do not yield physiologic or functional information (Fig. 30-12).

Treatment

Various therapeutic interventions are used alone or in combination to treat patients with malignant pericardial effusions. One of the main objectives is obliteration of any potential pericardial space by fusion of the epicardium and pericardium. Patient performance status, medical comorbidities, malignant disease stage, prognosis, and response to other cancer treatments influence selections of these options.

Pericardiocentesis provides immediate decompression of the pericardial space and is usually performed with echocardiographic guidance. Hemodynamic impairment is thereby relieved but can recur quickly. Recurrence

rates as high as 25% have been reported.⁸¹ Thus, this procedure is seldom durable enough except for terminal patients with brief anticipated survival.

A pericardial catheter left in place at the time of pericardiocentesis allows drainage of additional fluid with or without administration of a sclerosing agent. Numerous investigators have induced pericardial sclerosis to prevent pericardial effusion recurrences. Some of the agents administered were thiopeta, tetracyclines, OK-432 (an immunomodulator), bleomycin, aclarubicin, mitomycin C, 5-fluorouracil, and radiocolloids such as ³²P and ¹⁵⁴Au. Doxycycline may produce intense pain and, as with bleomycin, may produce a febrile response in a significant number of patients. Thiopeta does not cause pain and rarely evokes a fever. It is inexpensive and is the sclerosant of choice at some centers because of these advantages. Intrapericardial sclerosis has an overall success rate over 80%.⁸¹ A few centers have used intrapericardial radiocolloids, but their popularity is limited in part because of logistic problems related to their administration. Intrapericardial interferon has also been used.⁸² It reportedly enhances cell-mediated cytotoxicity and has an antiproliferative effect. Colchicine has also been described to have an inhibitory effect on leukocyte chemotaxis and decreases the production of interleukin-1 by monocytes.⁸³ These effects have been exploited in the use of colchicine in the treatment of refractory malignant pericardial effusion. The minimally invasive nature of these catheter-based interventions is attractive and reduces the recurrence rate after simple pericardiocentesis to an acceptable level. When less invasive options fail, surgical treatment can be offered to appropriate candidates.

Of the surgical options, subxiphoid pericardial “window” creation has been used most extensively (Fig. 30-13). It can be performed using local or general anesthesia, it has low complication rates, and it does not require single-lung ventilation like some thoracoscopic methods.

Success rates over 90% have been reported.⁸¹ Much of the pericardial fluid drainage occurs in the space posterior to the ascending aorta through abundant

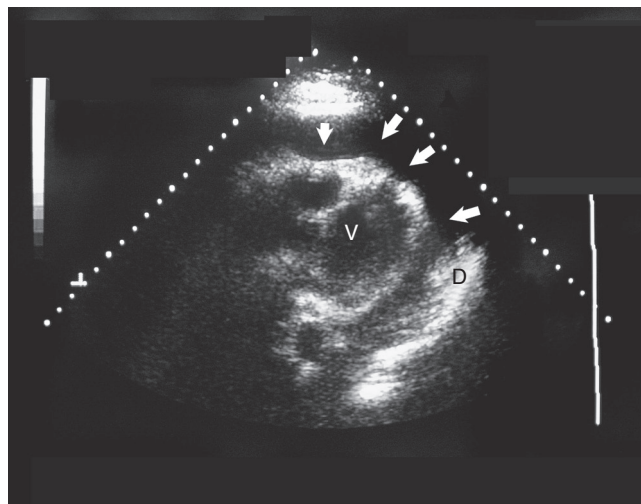


FIGURE 30-11 ■ Echocardiogram shows a large pericardial effusion (arrows). D, Diaphragmatic pericardium; V, ventricle.

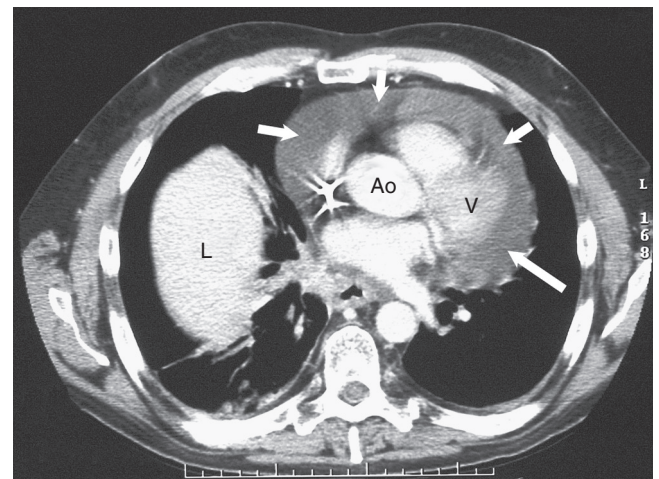


FIGURE 30-12 ■ CT scan shows moderately large pericardial effusion (arrows). Ao, Aortic root; L, liver dome; V, atrioventricular junction with adjacent pulmonary outflow tract.

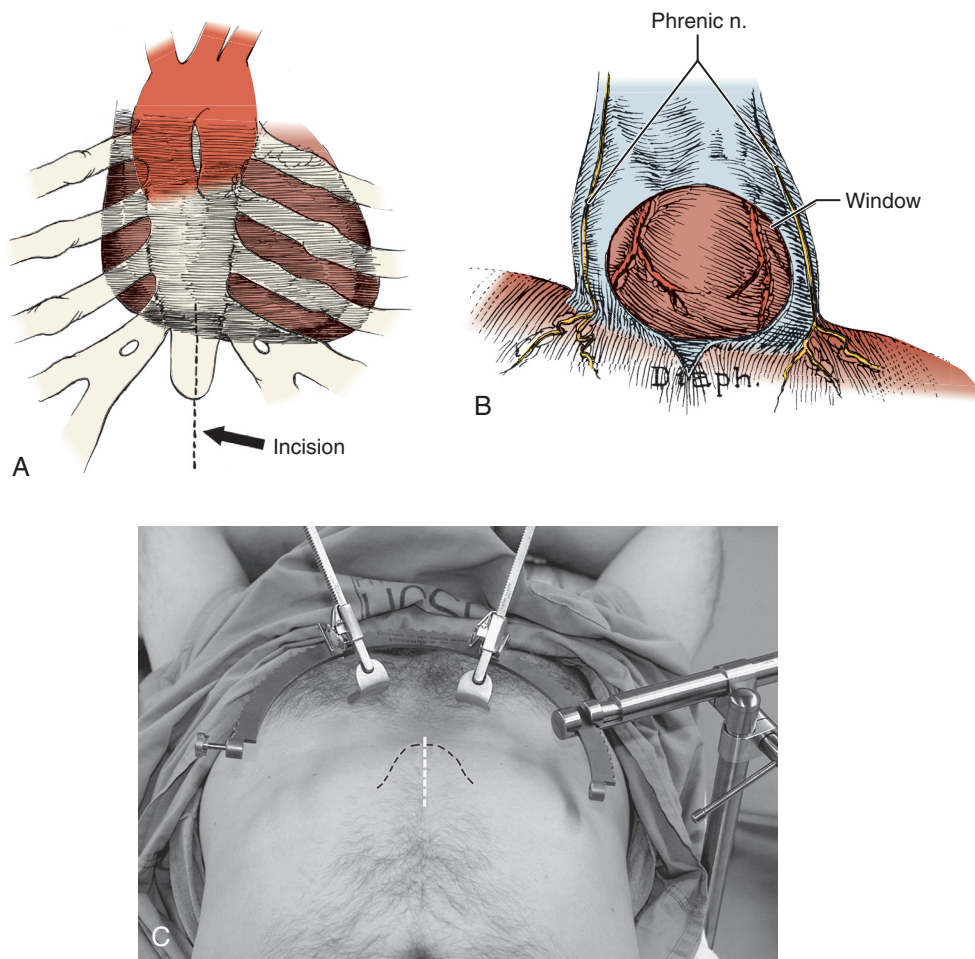


FIGURE 30-13 ■ **A**, Relation of pericardial effusion to planned subxiphoid incision (arrow). **B**, Large pericardial window has been resected. Exposure can be facilitated by partial excision of the subxiphoid cartilage. Drainage may be facilitated by placement of a drainage tube, opening of the pleural spaces, or a preperitoneal space, depending on the surgeon's preference. **C**, Exposure can also be facilitated by a self-retaining retractor system that lifts the costal margin and sternum anteriorly to expose the superior pericardium. The model is positioned under partial ring of the Bookwalter retractor system with small blades that provide this traction. Black dashed line shows the costal margin and the white dashed line overlies the xiphoid process, denoting the planned incision. (**A** and **B**, Reprinted with permission from Ravitch M, Steichen F: *Atlas of general thoracic surgery*, Philadelphia, 1988, WB Saunders, p 175.)

carinal lymphatic systems. A relatively small tumor burden in that space (which is not visible to surgeons performing subxiphoid pericardial windows) may create an effusion. This accounts for some pericardial window specimens that do not show malignancy by pathologic review.

Thoracotomy may be used to either create a pleuro-pericardial window or perform pericardiectomy. The latter has been claimed to have the greatest durability of all the surgical procedures. However, it requires general anesthesia and optimal single-lung ventilation, and it has relatively high morbidity and mortality rates.

Thoracoscopic approaches aim to provide the same quality of pericardial drainage without the morbidity of a thoracotomy.⁸⁴ Thoracoscopic approaches have been well tolerated in very ill patients but still require single-lung ventilation and general anesthesia. When both pleural and pericardial effusions are present, a thoracoscopic approach should be favored (Fig. 30-14). This permits treatment of both spaces. Also, excellent

visualization of the thoracic cavity permits directed biopsies in undiagnosed cases.

Percutaneous balloon pericardial window creation has been reported.⁸⁵ Complications included pleural effusions requiring drainage, transient fever, and small pneumothoraces. This was performed with patients under local anesthesia and usually permitted prompt hospital discharge.

The Denver pleuroperitoneal shunt has also been used to drain pericardial effusions into the peritoneal space.⁸⁶ This requires only local anesthesia and a short hospital stay. The patients need to compress the pumping chamber of the device several times daily. Possible shortcomings of this drainage method include lack of patient cooperation and shunt thrombosis.

Passive pericardioperitoneal shunting can be accomplished using a video-assisted technique.⁸⁷ This technique essentially involves a laparoscopic approach to creating a generous transdiaphragmatic pericardial window without an external drain.

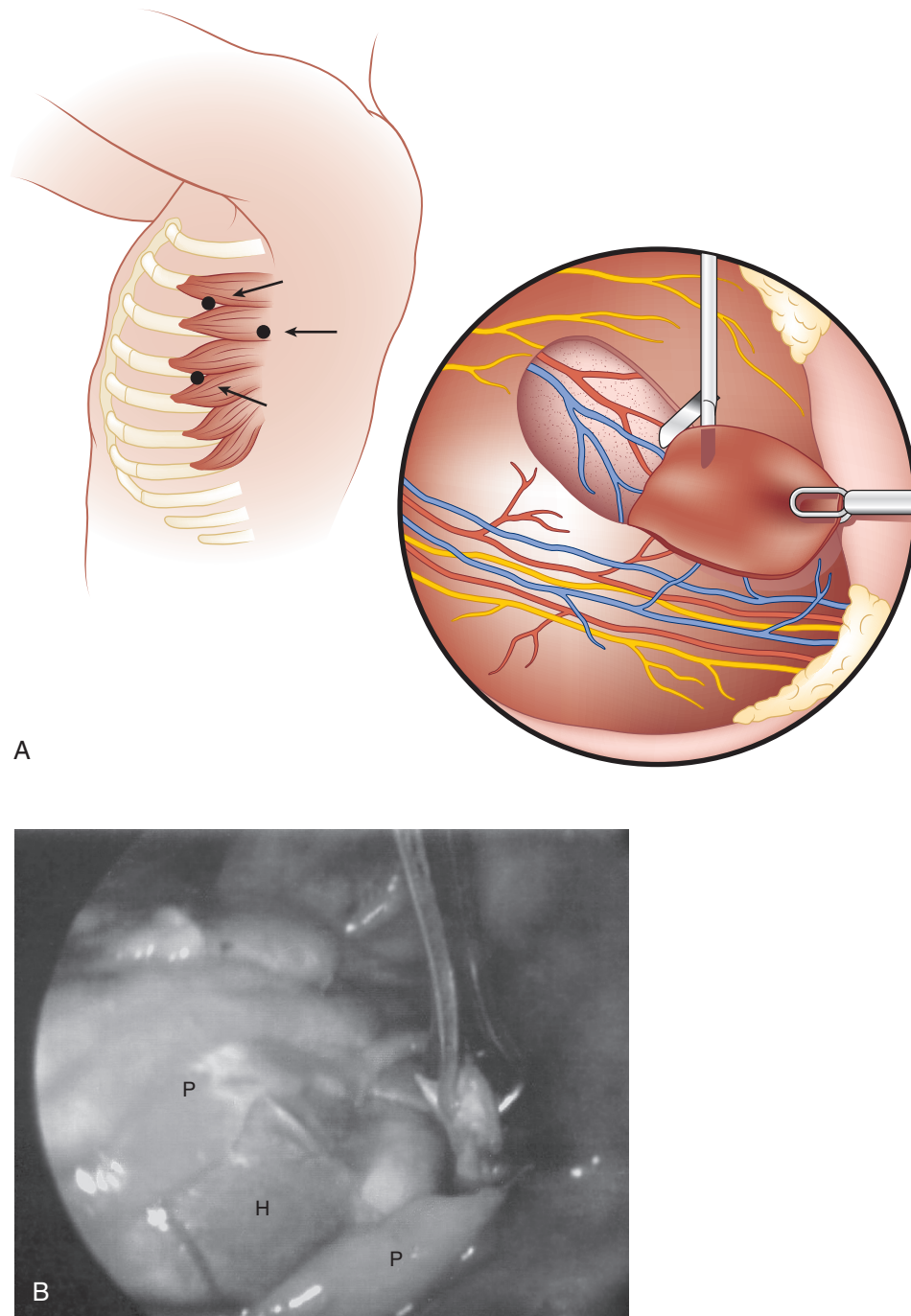


FIGURE 30-14 ■ **A**, Trocar positions in preparation for creation of a thoracoscopic pericardial window. The patient is in the decubitus position. The camera trocar site lies most posteriorly, and the remaining two sites are used for manipulating instruments. **B**, Thoracoscopic image of left thoracoscopic pericardial window (left chest). *H*, Heart; *P*, pericardium. (**A**, From Inderbitzi R, Furrer M, Leupi F: Pericardial biopsy and fenestration. *Eur Heart J* 14:135–137, 1993.)

Chemotherapy and radiation therapy can be quite effective in patients with neoplasms that are sensitive to these modalities. These therapies can be used in conjunction with direct pericardial interventions.

The choice of procedure is patient dependent and must be individualized. No modality is clearly superior to others, but the degree of invasiveness, morbidity, and cost vary widely. The clinical focus should be placed on providing rapid and durable relief from the effusion with the least possible morbidity.

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PLEURAL TUMORS

Ciaran McNamee • Jeffrey B. Velotta • David J. Sugarbaker

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Desmoplastic Small Round Cell Tumor

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PLEURAL EMBRYOLOGY AND ANATOMY

The pleura is a thin continuous membrane that separates during embryologic development into two layers as the developing lung buds encroach on the pleural cavity. The component of the pleural membrane that envelopes the lung is called the visceral pleura, which then continues as a contiguous serosal layer, called the parietal pleura, to cover the chest wall, the mediastinum, and the diaphragm. These layers fuse at the hilum, creating the pleural space. The pleural space contains a small quantity of glycoprotein-rich fluid that allows the opposing pleural surfaces to glide over each other during respiration. These pleural membranes are derived from the mesoderm during embryogenesis; the separation by the ingrowth of the lung bud permits the parietal pleura to fuse with the ectoderm to form the somatopleure and the visceral pleura to fuse with the endoderm to form the splanchnopleure. Thus, all three germ layers are represented in the histogenesis of the pleurae, which explains

the later de-differentiation of pleural tumors into both epithelial and mesenchymal elements.

The blood supply of the parietal pleura emanates from systemic sources: intercostal arteries, subclavian artery, internal thoracic artery, and phrenic arteries. The visceral pleura derives its arterial blood supply from the bronchial arterial circulation and from the lung parenchyma. The lymphatic drainage for the parietal pleura follows the arterial blood supply and drains to systemic sources. The visceral pleura drains into the pulmonary parenchyma. Naturally occurring pores or stomata in the caudal aspect of the parietal and mediastinal pleurae transfer particulate matter into lymphatic channels for drainage. Most of the fluid that accumulates in the pleural space is derived from the lung and is absorbed by the parietal pleura. The visceral pleura is devoid of somatic innervation, whereas the parietal pleura has a rich network of somatic, sympathetic, and parasympathetic neural innervation.

The pleural membrane is thin and translucent. It is composed of five separate layers: (1) the mesothelial layer (flattened mesothelial cells joined by tight junctions),

(2) a thin submesothelial connective tissue layer, (3) a superficial elastic tissue layer, (4) a loose subpleural connective tissue layer in which run lymphatics, nerves, arteries, and veins, and (5) a fibroelastic layer that is adherent to the underlying structures (lung, mediastinum, diaphragm, and chest wall). The mesothelial cell features long slender microvilli that extend into the pleural space and are believed to release hyaluronic acid into the pleural fluid.¹

The pleural response to injury is characterized by edema and exudation of protein and neutrophils. This response is known as an exudative pleural reaction. It is orchestrated by the release of inflammatory mediators (cytokines, chemokines, oxidants, and proteases) from mesothelial cells, which also have phagocytic capabilities. Lesser inflammatory conditions can be resolved by the absorption of inflammatory products by mesothelial cells aided by the lymphatic evacuation of fluid and particles. Severe or persistent damage encourages a submesothelial fibroblastic response and the formation of dense adhesions.

The pleural reaction can occur in response to an infectious or a noninfectious injury, usually acquired through the respiratory system. Infectious organisms are associated with empyema. However, the visceral pleura responds to autoimmune diseases, drug reactions, radiation, or pneumoconiosis by creating cytokines (transforming growth factor- β [TGF- β] and tumor necrosis factor- α [TNF- α]), which in turn lead to the formation of a fibrin matrix. Asbestos, silica, and coal dust are associated with the development of circumferential plaques of dense hyaline fibrosis on the parietal pleural surface that typically involve the diaphragm and chest wall.

ASBESTOS-ASSOCIATED PLEURAL PATHOLOGY

Biologic Capabilities of Asbestos Fibers

Asbestos is divided into two main types based on fiber length and other physical properties that may account for its biopersistence in humans. The fibers of the first type are short and serpentine. Chrysotile (or white asbestos) is the predominant member. The second type, known as amphibole asbestos, has long, thin, straight fibers. It has several subtypes, including crocidolite, actinolite, tremolite, anthophyllite, and amosite.² Approximately 95% of the asbestos currently used worldwide is chrysotile. The remaining 5% is amosite and crocidolite, although these groups of fibers are commonly mixed together.³

Two conflicting theories have been advanced to explain the oncogenic potential of asbestos fibers based on their physical properties of dimension, shape, and length. The amphibole hypothesis proposes that amphibole fibers owe their durability and their biopersistence in the lung to their long length. Proponents of this hypothesis believe that the short serpentine chrysotile fibers are broken down and cleared too quickly to provoke cancer.⁴ The Stanton theory postulates that amphibole asbestos is carcinogenic because the long fibers are able to penetrate deeper into the pleura, where they come in contact with

and incite mesothelial cell proliferation.⁵ Whatever the cause, it appears that chrysotile fibers are cleared from the body by macrophages much more quickly than are amphibole fibers, which can remain in the lung for many years after exposure, accounting for their high degree of biopersistence.

There is evidence that the biopersistence of asbestos fibers is associated with malignancy in animals^{6,7} and in humans.⁸ Although consensus has not been reached on the precise carcinogenic potential of the different fiber types, or the level or length of exposure needed for the malignant transformation to mesothelioma, an expert panel (level 4 evidence) published an opinion on this matter in 2003. The consensus decision of this panel suggests that the longer, biopersistent fibers associated with amphibole asbestos (particularly, crocidolite) have greater carcinogenic potential than the short fibers of the serpentine asbestos.⁹

Epidemiology of Mesothelioma

The causal association between asbestos exposure and the later development of pleural tumors is strong. However, the lack of a clinically recognizable, premalignant, non-invasive form of malignant mesothelioma, coupled with the difficulty of obtaining invasive biopsy material, has hampered the identification of the agent or agents responsible for initiating or promoting the development of pleural tumors *in vivo*. Thus, much of the current knowledge is empirically derived from three sources: epidemiologic data, *in vitro* investigation of asbestos and mesothelial cell lines, and retrograde assumptions made from mesothelioma chromosome studies.

Malignant mesothelioma was first identified as a discrete diagnosis in 1870.¹⁰ The name was coined in the 1930s.¹¹ Suspicion of an association between asbestos exposure and mesothelioma development was initially documented in the medical literature between 1920 and 1950.¹²⁻¹⁴ Despite the numerous case reports, it was not until 1960 that Wagner and colleagues reported a series of cases that demonstrated a strong association between mesothelioma and occupational exposure to asbestos in asbestos miners in South Africa.¹⁰ A clear link between asbestos exposure and pleural tumor development was documented in the United States by Selikoff and colleagues in the 1960s and 1970s.^{15,16} Further evidence of this association followed, with multiple case-control series from 1965 to 1975. These reports were summarized in an epidemiologic review of mesothelioma by Britton.¹⁷ In this review, the most notable risk of mesothelioma was associated with occupational exposure to asbestos, primarily in shipyards where crocidolite asbestos was used in naval insulation materials. Other defined exposure groups with varied relative risks of mesothelioma development included workers who installed insulation and workers in the asbestos product manufacturing industry or in heating and construction industries.¹⁷ After Wagner's publication, further worldwide case series comparing amphibole and chrysotile fiber exposures from 1980 to 1999 confirmed the association of asbestos exposure (particularly amphibole fibers) and mesothelioma. Even chrysotile miners were identified to be at high risk

for mesothelioma, although contamination of the chrysotile asbestos by amphibole fibers (particularly tremolite) as the true cause of disease in these miners has been questioned.^{17,18}

Based on the suspicion of an association between asbestos and cancer development, industrial regulations emerged. As early as 1932, the United Kingdom issued the first anti-asbestos regulation, titled "Asbestos Industry Regulation 1931." Crocidolite asbestos was not banned in the United Kingdom, however, until 1970. By 1980, most western European countries had followed suit. The U.S. Environmental Protection Agency listed asbestos as a hazardous air pollutant in 1971. By 1972, exposure limits for asbestos had been published, and by 1979 asbestos use was curtailed. Asbestos control or regulation in many other world regions has yet to be achieved.

The latency period (20 to 50 years) between exposure to asbestos and mesothelioma development is substantial.¹⁹ Although the epidemiologic data linking asbestos exposure to mesothelioma are clear, the lifetime risk of mesothelioma development in workers exposed to asbestos ranges from 4.5% to 10.0%.²⁰⁻²³ Thus, the lack of a strong, direct, quantifiable association between asbestos exposure and pleural tumor development impedes the prediction of individual disease development, and future predictions are relevant only in broad demographic terms.

Western populations were exposed to asbestos as an environmental hazard when it was used in an uncontrolled fashion in the shipbuilding and construction industries between 1940 and 1970. Despite worldwide attention by environmental regulatory bodies, the latency of the disease suggests that the peak incidence of the disease in Europe, North America, and Australia may be in the next 10 to 15 years.^{24,25} Prediction risks for mesothelioma development suggest that the disease will continue to increase in Europe, to peak in 2020, and thereafter to rapidly decline, because the workforce exposure should affect only the population born before 1950 (assuming the commencement of work at age 20, when asbestos regulations were initiated).^{17,24} The prediction for a mesothelioma peak in the United States is 2004; Australia, 2015; and Japan, 2025. However, these assumptions do not include many unanticipated factors such as the attack on the World Trade Center in 2001, where an estimated 10 million New Yorkers were exposed to asbestos dust.^{26,27}

Population Exposure

Individuals with asbestos disease can be divided into four groups based on the degree of exposure to asbestos: direct occupational exposure, secondary occupational exposure, passive occupational exposure, and nonoccupational exposure.

The first group comprises individuals with direct exposure either through work or by direct inadvertent exposure to asbestos fibers. An example of this exposure group is the miners of asbestos in Wittenoom, Australia. These miners were exposed at work, but because asbestos was used in lieu of grass to cover the schoolyards and playgrounds, their children also received direct exposure.²⁵

The secondary exposure group represents persons whose exposure could be termed as *occasional*, such as plumbers, carpenters, navy personnel, and installers of asbestos as insulation.

The third group represents those who are passively exposed through other family members who work directly with asbestos and carry the fibers home on their clothing. This group includes persons in close contact with the first two groups (e.g., wives of asbestos workers).²⁸

A small number of individuals have mesothelioma but no history of occupational exposure to asbestos. Some may have contacted asbestos fibers in their natural habitat,²⁹ or they may have a genetic predisposition.^{30,31} It has been postulated that simian virus 40 (SV40) plays a synergistic role with asbestos in the development of mesothelioma, either as a clastogenic transformer (an inducer of chromosomal damage) or as a cytologic protector, which permits chromosomally damaged cells to survive and propagate rather than die (apoptosis).^{32,33} SV40 was identified as a contaminant in polio vaccines from 1950 to 1963, and the extent of its role in mesothelioma development is still controversial and undetermined.

Finally, 2% to 5% of mesothelioma cases arise in a pediatric population, which suggests a genetic rather than an environmental cause of mesothelioma in these individuals.³⁴

Pathogenesis of Asbestos Fibers

Benign asbestos-related pleural disease is thought to manifest as either discrete parietal pleural plaques or diffuse disease involving visceral pleural hyperplasia and fibrosis.³⁵ The mechanism whereby asbestos fibers reach the parietal pleura to evoke pleural plaque formation is unknown. However, as described earlier, it is suspected that the inability of pulmonary macrophages to phagocytose these particles is a result of their length and that the fibers burrow through the lung and eventually come into contact with the mesothelial cells in the pleural membranes. Several theories have been proposed to explain how the fibers pass from the visceral to the parietal mesothelial cells. There are several putative causes. The fibers may protrude through the visceral pleura, abrading and irritating the parietal pleural surface. The fibers may migrate across the pleura from the visceral to the parietal surface, or they may disseminate via lymphatic drainage to the parietal mesothelial cells.^{27,35}

The effect of asbestos on mesothelial cells is complex, multifactorial, and difficult to explain. It has been shown, for example, that human mesothelial cells often die in vitro after contact with, or phagocytosis of, asbestos fibers.^{36,37} A possible explanation is that asbestos fibers may induce the proliferation of cellular cytokines that have cytoprotective effects and that allow asbestos-transformed mesothelial cells to survive and proliferate. TNF- α expression has been shown to increase after mesothelial cells and macrophages are exposed to asbestos, and this factor may enable the asbestos-damaged cells to survive.³⁸ Fiber persistence may lead to chronic inflammation with increased cycles of cell growth that might induce cellular mitotic changes. These changes may

gradually cause the mesothelial cells to acquire genetic and epigenetic changes that lead to neoplasia. Even without directly interfering with the DNA machinery of the cell, these fibers may secondarily select for cells with oncologic potential.

In addition to inducing cellular proliferation, asbestos fibers have other cytologic and clastogenic properties that could lead to neoplasia. Incorporation of asbestos fibers into the mesothelial cell, for example, produces oxygen free radicals,^{39,40} cytokines, chemokines, and growth factors such as epidermal growth factor (EGF) and TGF- α .⁴¹⁻⁴³ These elements can promote the proliferation of mesothelial cells, rendering them more susceptible to DNA and genetic damage.⁴⁴ Asbestos induces phosphorylation of mitogen-activated protein (MAP) kinases and of the extracellular signal-regulated kinases (ERKs) 1 and 2 with increased downstream expression of tumor proto-oncogenes.⁴³

Asbestos fibers also have clastogenic properties—that is, they may act directly on the chromosomes.⁴⁵ They may sever or disrupt the mitotic spindle of cells, causing chromosomal abnormalities such as aneuploidy to occur.⁴⁶ Finally, they may induce epigenetic tumor suppressor silencing via promoter DNA CpG methylation, which permits tumorigenic cells to enter the cell cycle instead of halting them at the G₁/S interphase of mitosis.⁴⁷

Mesothelial Cell Neoplastic Changes Attributed to Asbestos Exposure

Retrograde analysis of molecular biologic changes in the malignant mesothelial cell has revealed several different areas of molecular variance from normal mesothelial cellular mechanics. These variations are thought to lead to neoplasia.

Chromosomal Abnormalities in Mesothelioma. Karyotypic alterations result from somatic mutations; however, gene deletions, gene silencing, and RNA editing are also common chromosomal aberrations in malignant mesothelioma. DNA sequencing techniques and comparative genomic hybridization permit discrimination between clonal proliferations of tumor cells.^{48,49} These techniques may also help in the histologic identification and sorting of mesothelioma subtypes. They may aid by distinguishing mesothelioma from similar-appearing tumors such as adenocarcinoma.⁵⁰ Whole-transcriptome, deep sequencing of single mesothelioma tumors has revealed unique individual tumor profiles of chromosomal and mRNA expression.⁵¹

These chromosomal changes in malignant mesothelioma often are multiple, leading to clonal proliferations that show individual variation (losses are more common than gains).⁵⁰ In mesothelioma, a common deletion occurs at the 9p21 locus. This occurs at a frequency of 70% in mesothelioma cell lines and in up to 22% of primary tumor specimens.^{52,53} This locus encodes two inhibitors of the cyclin-dependent kinases (CDKs)—namely, p16^{INK4a} (CDKN2A) and p15^{INK4b} (CDKN2B), which prevent the phosphorylation of retinoblastoma (Rb) protein. The Rb protein modulates cell entrance into the S phase from G₁ of the cell cycle.

Phosphorylation of this protein, which is prevented by CDK inhibitors, allows uncontrolled cellular entry into S phase. The 9p21 gene also codes for p14^{ARF}, which acts as a regulator for an important tumor suppressor oncogene, p53. This gene encodes tumor protein p53, which responds to diverse cellular stresses such as hypoxia, DNA damage, and oncogene activation, to regulate target genes that induce cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. P53 protein is expressed at a low level in normal cells and at a high level in various transformed cell lines, where it is believed to contribute to transformation and malignancy. P53 is a DNA-binding protein containing transcription activation, DNA-binding, and oligomerization domains. It is postulated to bind to a p53-binding site and activate expression of downstream genes that inhibit growth and invasion and thus function as a tumor suppressor by initiating the transcription of genes leading to downstream effects on cell cycle arrest in G₀ and apoptosis. A downstream target of p53 is p21, a multifunctional CDK inhibitor. Loss of p21 expression is associated with decreased patient survival.⁵⁴ Also, there is a frequent loss of chromosome 22 in malignant mesothelioma.⁵⁵ The tumor suppressor gene *NF2* is located on this chromosome.

Tumor Suppressor Genes in Mesothelioma

Tumor Suppressor Genes and CDK Inhibitor Loss. Ironically, malignant mesothelial cells lack mutation of the two most common genetic mutations found in most cancers—namely, tumor suppressor genes *p53* and *pRb*.⁵⁶ The tumor suppressor gene *p53* is important for cell cycle arrest because it prevents propagation of DNA-damaged cells or genetically unstable cells. It acts by stimulating the expression of p21, which, in turn, acts as a CDK inhibitor. In an equivalent manner, the retinoblastoma gene (*Rb*), as noted earlier, also halts chromosomal synthesis and therefore tumor proliferation.

However, the chromosomal aberrations of malignant mesothelioma cells ultimately adversely affect these two tumor suppressor genes by upstream regulation of their gene products. Mutational deletion of the 9p21 locus in mesothelioma cells affects p14^{ARF}, an upstream regulator of p53. Deletional interruptions of this gene inactivate TP53-MDM2, which is extremely important for intrinsic cellular control of chromosomally damaged cells. Inactivation of this pathway by decreasing p21 gene products allows CDK to phosphorylate Rb protein, which then allows damaged cells to enter the S phase of the cell cycle.⁵⁷ Viral transduction of p14^{ARF} into mesothelioma cells in culture leads to increased production of p53 and p21, resulting in an increase in dephosphorylated Rb and G₁ arrest and an inhibition of mesothelioma cell growth.⁵⁸

In an equivalent manner, the loss of p16^{INK4a} leads to loss of CDK 4 and 6, leading to phosphorylation of *Rb* gene by the lack of CDK inhibition.⁵⁷ Deletion of p16/CDKN2A has been reported in greater than 70% of mesothelioma cells.^{50,59} As seen with p53, mesothelioma cells transfected with adenovirus expressing p16^{INK4a} demonstrate decreased phosphorylation of Rb,⁶⁰ leading to cell cycle arrest, cell death, and tumor regression.

Merlin and RAS-ERK Pathway. Changes in chromosome 22 may lead to altered expression of *NF2*, or somatic mutational changes may lead to *NF2* alterations, which occur in approximately 50% of patients with mesothelioma.⁶¹ *NF2* encodes for a protein named merlin (alternatively called schwannomin). This protein is important in the connection between the plasma membrane and the cytoskeleton of the cell and may act as a tumor suppressor gene by inhibiting the RAS-ERK pathway and inducing cyclin D1 expression. Inhibition or abrogation of *NF2* function and its downstream product merlin may lead to a lack of contact-dependent growth arrest,⁶²⁻⁶⁴ leading to tumor proliferation at the expense of neighboring normal cells.

Oncogene Activation in Mesothelioma. The transcription factors AP-1 and β -catenin are often upregulated in malignant mesothelioma; AP-1 is upregulated by Fra-1 which is a member of the Fos family of transcription factors. Fra-1 expression is increased in malignant mesothelioma cells, in response to asbestos or EGF, and reduced with inhibitors of ERK. Mesothelioma cells transfected with either an ERK inhibitor or a dominant negative Fra-1 reverse their transformed phenotype.⁶⁵

The transcription factor β -catenin is controlled by Wnt signaling, so that the presence of Wnt inhibits phosphorylation of adenomatous polyposis coli (APC) and axin, allowing persistence of β -catenin. Increased presence of β -catenin leads to nuclear binding of T cell factor/lymphoid-enhancer factor (Tcf/Lef) proteins with downstream activation of transcription factors. Mesothelioma cells have been shown to have altered APC expression,⁶⁶ and they may express upstream negative inhibitors of the Wnt pathway (Wnt inhibitory factor [WIF-1] and secreted frizzled-related protein [sFRP]).^{67,68} Extracellular signaling, through the overexpression of membrane disheveled proteins with downstream activation of β -catenin, may play an important role in malignant mesothelioma.⁵⁷

Epigenetic Maneuvers. Promoter methylation has been shown to be effective in inactivating WIF-1 and sFRP.^{69,70} Hypermethylation of DNA is a common epigenetic method of inhibition of tumor suppressor gene function.^{71,72} In the context of asbestos exposure, however, there may be a dose-dependent increased induction of methylation as a result of asbestos fibers.⁴⁷ The precise mechanism for hypermethylation of this phenotypically important pathway is still not established. It may also be directly attributable to the clastogenic properties of asbestos fibers, or alternatively to repeated inflammatory insults of asbestos-generating reactive oxygen species, which may lead to increased mitotic stimulation and promoter methylation. Acquired generations of accrued genetic and epigenetic chromosomal changes leading to malignancy may thus be induced.⁴⁷

Growth Factors in Mesothelioma. Platelet-derived growth factor (PDGF) chains A and B increase in response to asbestos exposure; they have been implicated in the development and progression of malignant mesothelioma.^{50,73} Asbestos also induces autophosphorylation of EGF receptor (EGFR). This may result in the activation

of the MAP kinase cascade and ERK1 and ERK2 kinases, leading to expression of proto-oncogenes that encode members of the fos-jun and activator protein 1 families.⁴³ Hepatocyte growth factor (HGF) can promote cell growth and migration mediated via downstream AKT and ERK pathways by binding to its receptor c-Met. Circulating levels of this growth factor are elevated in patients with mesothelioma, so inhibition of HGF receptor c-Met may be a therapeutic option.⁷⁴ EGFR (member of the ErbB family of tyrosine kinase receptors) is overexpressed in malignant mesothelioma in association with angiogenesis and proliferation.⁷⁵ Multiple ligands can bind to and activate this receptor, leading to intracellular tyrosine kinase autophosphorylation and signaling pathways of cell proliferation, differentiation, and immortality. The two most important ligands are EGFR and TGF α , both of which are increased by mesothelial asbestos exposure. Inhibition of EGFR and vascular endothelial growth factor (VEGF) pathways by tyrosine kinase inhibitors⁷⁶ and inhibitors to VEGF production or VEGF receptors⁷⁷ will decrease or inhibit mesothelioma cell growth. VEGF production is increased by SV40 infection of mesothelioma cells.⁷⁸ Inhibitors of VEGF^{79,80} and EGFR pathways⁷⁶ in patients with mesothelioma are currently used in clinical studies.

Viral Activation of Mesothelioma Cells

SV40 is a double-stranded circular polyomavirus that contaminated polio vaccines in the United States, Canada, Europe, Asia, and Africa between 1955 and 1963. This virus has the potential, based on molecular, pathologic, and clinical evidence, to cause cancer.⁸¹ It has two major chromosomal regions, one of which harbors latent oncogenic potential. The early region encodes for SV40Tag (large tumor antigen), SV40tag (small tumor antigen), and 17 KT; the late region encodes for structural proteins of the virus.

It has been postulated that SV40 infection may increase the cellular production of growth factors, such as VEGF⁸² and HGF, through autocrine and paracrine mechanisms.⁷⁸ It may also protect cells from apoptosis by the ectopic production of telomerase, which prevents chromosomal shortening with successive cell division.⁸³

SV40Tag can bind to and inactivate the tumor suppressor genes *p53* and *Rb*, unleashing uncontrolled tumor growth. Small tumor antigen (SV40tag) may inhibit PP2A, leading to dephosphorylation of members of the MAPK family and deactivation of Wnt and ERK, which may lead to increased cellular transcription.⁸⁴

Despite the powerful putative oncologic attributes of SV40 virus, however, there is much debate in the literature as to the role of SV40 in cellular transformation; the oncologic potential of SV40 is very controversial and current opinion discounts its oncologic potential.^{85,86} The counterargument to the role of SV40 in inducing neoplasia in mesothelial cells is supported by the lack of viral particles identified within mesothelioma cells.⁸⁷ Further support for this counterargument is empirically derived from the knowledge that p14^{ARF} and p16^{INK4a} cause mesothelioma mutational changes, with upstream deactivation of *p53* and *Rb*, thus rendering SV40

inactivation of these tumor suppressor genes redundant and therefore obsolete.

Apoptotic Processes

Extracellular ligands of the caspase pathway, such as TNF, TNF-related apoptosis-inducing ligand (TRAIL), and Fas ligand, induce programmed cell death in normal cells. Intracellular mediators of apoptosis, including telomerase (see “[Viral Activation of Mesothelioma Cells](#)”) and proteins from the *bcl-2* family, which may have proapoptotic and antiapoptotic properties, are increased in mesothelioma patients. Protein expression from this family may have a diagnostic and prognostic role in clinical medicine.^{75,88} Proapoptotic Bcl-2 proteins induce apoptosis by increasing mitochondrial membrane permeability, in turn leading to caspase pathway activation. Antiapoptotic Bcl-xl expression is increased in mesothelioma. This can also be targeted by inhibitors of antisense oligonucleotides⁸⁹ or viral vector transfection of mesothelioma cells.⁹⁰

CLINICAL ASPECTS OF PLEURAL TUMORS

Pleural tumors are recognized by the characteristic radiographic appearance of a thickened pleural layer that contains fluid, solid tumor, or a combination of both. Patients may or may not have symptoms of chest pain or dyspnea consequent to lung restriction or compression. In rare cases, pleural tumors are associated with other symptoms, such as hypoglycemia or hypertrophic pulmonary osteoarthropathy. Radiographic evidence of pleural thickening in either symptomatic or asymptomatic patients is often the stimulus to initiate clinical studies to confirm the benign or malignant nature of the pathology or to redress, if possible, the underlying lung compression.

It is often difficult to distinguish benign from malignant pleural reactions ([Box 31-1](#)). As with other benign pleural conditions, the mesothelial cell also may release mediators such as cytokines, chemokines, oxidants, and proteases. These mediators may induce an exudative pleural reaction that gives rise to a proliferative hyperplasia of the mesothelial and submesothelial layers.^{1,35} This reaction can resemble a malignant process. Thus, pleural thickening can be attributable to multiple causes, ranging from benign inflammation to malignancy, as summarized in [Box 31-2](#).

Inflammatory Pleural Reactions

The pleura reacts to pleural injury either by development of a reactive mesothelial hyperplasia or organizing pleuritis (as opposed to atypical mesothelial hyperplasia, described later) or by the formation of nodular pleural plaques. Plaques are acellular deposits on the parietal pleura that often calcify. They are usually associated with asbestos exposure.^{91,92} These benign lesions are often multiple and occur bilaterally. Their presence raises the possibility of mesothelioma or lung cancer, either on presentation or in the future.

BOX 31-1 Benign Causes of Pleural Hyperplasia

- Pleural infections
- Radiation
- Surgery
- Trauma
- Intracavitary treatments (chemotherapy or sclerosing agents)
- Collagen vascular diseases
- Systemic immune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, Wegener granulomatosis)
- Subpleural pulmonary abnormalities (infarction, infection, neoplasia)
- Pneumothorax
- Drug reactions (nitrofurantoin, bromocriptine, methysergide, procabazine)
- Pancreatitis, uremia
- Pneumoconiosis (asbestosis)

BOX 31-2 Causes of Pleural Masses

- Inflammatory pleural reactions
 - Reactive mesothelial hyperplasia or organizing pleuritis versus atypical mesothelial hyperplasia
 - Nodular pleural plaques
- Pulmonary tumors that may resemble pleural tumors
 - Inflammatory pseudotumor of the lung
- Benign pleural tumors
 - Solitary fibrous tumor
 - Lipomas and lipoblastomas
 - Adenomatous tumors
 - Calcifying fibrous tumors
 - Mesothelial cysts
 - Multicystic mesothelioma
 - Schwannoma
- Pleural tumors with low malignant potential
 - Desmoid tumors
 - Well-differentiated papillary mesothelioma
 - Pleural thymoma
- Primary malignant pleural tumors that may look like benign tumors
 - Malignant solitary fibrous tumor
 - Pleuropulmonary blastoma
 - Localized malignant mesothelioma
 - Vascular sarcoma
 - Liposarcoma
 - Pleuropulmonary synovial sarcoma
 - Askin tumor or primitive neuroectodermal tumor (PNET)
 - Desmoplastic small round cell tumor
- Malignant pleural tumors
 - Metastatic malignancies to the pleura
 - Malignant mesothelioma

Pulmonary Tumors That May Resemble Pleural Tumors

Inflammatory pseudotumor of the lung is a rare pulmonary tumor in adults, but it is the most common primary pulmonary tumor in children.⁹³ These tumors may be associated with a pleural thickening that responds to steroid therapy.⁹⁴

The specific histologic features of a *benign reactive mesothelial hyperplasia* that mimics malignancy include high cellularity, cytologic mitoses, necrosis, papillary excrescences, and entrapment of mesothelial cells in organizing pleuritis. Immunohistochemistry may be of limited help in differentiating benign from malignant pleural pathology. Its primary value may be in the demonstration of invasion by immunostaining of invasive cells. Invasion is a key marker for malignancy and must be differentiated pathologically from entrapment, pseudo-invasion, or sequestration.^{95,96}

Indeterminate lesions may appear on pleural biopsy as a proliferation of atypical mesothelial cells, either in a monolayer or piled up with cellular accumulations. These lesions may demonstrate increased cytologic atypia without evidence of true invasion; they may remain benign or degenerate into malignancy.^{95,97}

Benign Pleural Tumors

Benign pleural tumors comprise less than 5% of all pleural tumors. Far more commonly, they represent either metastatic cancer or a diffuse malignant pleural mesothelioma. These malignant tumors share common properties with benign pleural tumors, which can make it difficult to establish the diagnosis, particularly with small biopsies of minimal amounts of tissue. The common properties of benign and malignant pleural tumors are that both originate from, or metastasize to, mesothelial or submesothelial surfaces; both may recur after surgical removal; and both are difficult to identify with limited tissue biopsy material because of patterns of heterogeneous cellularity.⁹⁸

However, it is important to be able to distinguish a benign from a malignant pleural tumor, because the benign form confers excellent survival potential. Some benign tumors may recur after complete resection, and they may still be treated surgically with curative intent.

A radiograph of a patient with benign tumors of the pleura reveals a thickened parietal layer with underlying lung compression. Occasionally, these tumors have the appearance of lung invasion (particularly if they are visceral pleura based), as in the inverted fibroma form of solitary fibrous tumors. These pleural abnormalities are identified by a variable thickening of either the visceral or parietal pleura. This imposes a diagnostic dilemma because of the many possible causes of pleural masses in the differential diagnosis. Furthermore, fine-needle aspirates of these abnormalities are often unreliable for confirming a diagnosis as a benign pleural tumor.^{96,99-101}

From a clinical perspective, primary pleural tumors span a pathologic spectrum ranging from benign tumors, to benign tumors with some malignant features, to frankly malignant tumors. The most common pleural tumor (solitary fibrous tumor of the pleura) can occur in either a benign or a malignant form; they may also recur in either a benign or a malignant form.^{98,102}

Benign Pleural Tumors That May Remain Benign

Solitary Fibrous Tumors. The solitary fibrous tumor is the most common benign pleural tumor, and it is rare (by

2002, only 800 cases had been reported).⁹⁸ (In contrast, 3000 new cases of diffuse mesothelioma are diagnosed yearly in the United States.¹⁰³) This tumor arises from the submesothelial layer of the mesothelioma and it is usually solitary, although it may occur in multiple sites.^{104,105} It is associated with hypertrophic pulmonary osteoarthropathy in up to 22% of cases, and with severe hypoglycemia in 3% to 4% of cases.¹⁰⁶ The latter syndrome (Doege-Potter syndrome) is attributable to tumor-derived growth factor (insulin-like growth factor II).¹⁰⁷

These tumors are often (>80%) attached to the visceral pleura, and they are often pedunculated (80%). In the remaining 20% of cases, they originate from the parietal pleura on the diaphragmatic or mediastinal surface, and parietal-based tumors are more likely to be sessile than pedunculated.¹⁰⁵ Pedunculated tumors have a 2% recurrence rate, whereas sessile tumors have an 8% recurrence rate.⁹⁸

Because the solitary fibrous tumor is often pedunculated, it is amenable to resection by video-assisted thoracic surgery (VATS). However, resection should be complete and without tumor disruption to prevent tumor recurrence from either incomplete resection or microscopic seeding of the resected bed. It is important to remove not only the tumor but also the stalk with a 1-cm base of underlying lung. If the tumor is too large for VATS surgery, a thoracotomy may be required.^{98,100} Tumors originating from the parietal pleura require at least a partial pleurectomy with the tumor resection. Occasionally, chest wall resection along with tumor removal is required if there is concern about recurrence or invasion from possible malignant transformation.

Sessile lesions larger than 5 cm should probably be removed by thoracotomy to prevent recurrences.¹⁰⁰ These tumors may appear to invade the lung if visceral growth (inverted fibroma) is seen, so lung resection may be required. Peritumoral adhesions, in which microscopic tumor deposits may hide, are common (60%), so a wide resection is needed. This can include lung, diaphragm, chest wall, and pericardium with frozen section determination that all margins are free of tumor at resection.¹⁰⁰ Recurrent tumors may be multifocal and may undergo malignant transformation.¹⁰² Because histologic characteristics do not always predict the potential for recurrence, long-term follow-up is necessary.

Lipomas and Lipoblastomas. Chest wall lipoma is a common incidental finding, occurring in 0.1% of all computed tomography (CT) scans of the chest.¹⁰⁸ Lipoblastoma is a tumor of embryonic white fat that typically occurs in infancy or early childhood.¹⁰⁹ Both lipomas and lipoblastomas are benign and are best treated by surgical excision of the involved area.

Adenomatoid Tumors. Adenomatoid tumors are very rare incidental findings appearing as solitary circumscribed lesions on either the parietal or visceral pleura. They are usually identified at the time of pulmonary resection for unrelated pathology. They occur more commonly in other sites (most commonly the genital tract), and resection is performed to exclude other malignant pleural tumors.¹¹⁰

Calcifying Fibrous Tumors. Calcifying fibrous tumors are rare and are characterized by dense collagenous tissue with psammoma bodies containing dystrophic calcifications. They commonly occur in subcutaneous tissue or in deep soft tissue, but rarely in the pleura (there have been nine reports of this tumor since the initial report in 1996). They can occur as solitary tumors or in multiple sites; calcifications are typically not seen on plain chest films but are seen on a CT scan.¹¹¹⁻¹¹⁸

Simple Mesothelial Cysts. The pleura is an uncommon site for the development of a mesothelial cyst, which is thought to arise from persistence of the ventral pericardial recess after embryonic development. These lesions often occur in the anterior right cardiophrenic angle. The cysts that retain a connection to the pericardium are called pleuropericardial cysts, and if the neck to the pericardium is pinched off, they are classified as mesothelial cysts. They can be treated with surveillance unless symptoms develop, and then they can be treated by either aspiration or excision by VATS.^{119,120}

Multicystic Mesothelial Cysts. Multicystic inclusion cysts (multicystic mesothelioma or multilocular inclusion cysts) appear as multilocular fluid-filled cysts spread along the serosal surface of the pleura. These are extremely rare abnormalities occurring in asymptomatic individuals, and their removal to exclude other pathologies can be accomplished by VATS surgery.¹²¹

Schwannoma. Schwannomas are peripheral nerve sheath tumors that may occur spontaneously or after radiotherapy.¹²² They may arise in paraspinal intrathoracic locations and may mimic loculated fibrous deposits or localized pleural tumors. The key to the removal of this tumor is to exclude the possibility of spinal extension to prevent paraplegia from compressive spinal cord hematoma formation caused by bleeding into the peritumoral area.

Pleural Tumors with Low Malignant Potential

Well-Differentiated Papillary Mesothelioma

Well-differentiated papillary mesothelioma typically occurs with a diffuse nodular growth over the mesothelial surface, although there is only superficial invasion without deep invasion except in recurrent or long-standing lesions. Diagnosing this lesion is difficult because it looks similar to invasive mesothelioma (diffuse malignant mesothelioma) on small biopsy specimens. These lesions have an indolent course in the absence of invasive features, and in most cases they do not shorten life expectancy.¹²³

Desmoid Tumors

Desmoid tumors, which usually arise from facial or musculoaponeurotic structures, commonly arise from the chest wall with visceral invasion, although pleural desmoid tumors have been documented.^{124,125} They may be

associated with aggressive fibromatosis via the APC tumor suppressor gene or the β -catenin oncogene acting through the main intracellular effector pathway of the Wntless/Wnt signaling pathway.^{126,127}

The treatment of these tumors requires complete resection with negative margins,^{124,125,128} although recurrence may occur even with negative margins.¹²⁵ However, surgical resection of recurrences has excellent potential for long-term cure.¹²⁸

Pleural Thymoma

Pleural thymomas may arise from the pleura and can appear in either a localized or diffuse form. They probably arise from ectopic thymic tissue in the pleura, although this occurrence is rare (only 15 cases reported by 2002).¹²⁹ The localized form can be surgically removed for cure; the diffuse form may require radiotherapy.^{123,130}

Primary Malignant Pleural Tumors That May Look Like Benign Tumors

Malignant Solitary Fibrous Tumor

Patients with this tumor, which arises from mesenchymal cells in the submesothelial layer with malignant degeneration, are more likely to have larger, symptomatic, sessile tumors than their benign pedunculated counterparts.^{98,99,131} Visceral-based tumors are less likely to be malignant,¹³² and they are more often pedunculated than the parietal-based tumors.^{98,100} Malignancy is also more often associated with CT heterogeneity of these tumors, pleural effusions, chest wall invasion, and positivity with positron emission tomography (PET).^{99,100} CT-guided aspiration to determine malignancy is notoriously inaccurate,^{99,100} possibly because the tumor heterogeneity results in sampling error.

After tumor removal, malignancy is determined on the basis of cellularity and high mitotic counts, nuclear pleomorphism, presence of areas of tumor necrosis, and stromal or vascular invasion. Malignancy occurs in approximately 37% of case series of solitary fibrous tumors (range, 7% to 60%).¹⁰⁰ Recurrence is usually local and strongly associated with malignancy. It occurs with the following frequencies: benign pedunculated, 2%; benign sessile, 8%; malignant pedunculated, 14%; malignant sessile, 63%.⁹⁸

Benign tumors may also recur as malignant tumors,^{102,133} indicating the need for long-term follow-up. All tumors and recurrences are best treated with aggressive surgical resection or extended resection if necessary.^{98,100} The value of adjuvant therapy for malignant tumors is debated.^{98,100,131}

Pleuropulmonary Blastoma

Pleuropulmonary blastoma (PPB) arises from either the lung or the visceral pleural lining and affects children younger than 6 years. This tumor is unique in its progression from a cystic stage (type I, multilocular cystic tumors), to a more aggressive stage (type II, mixed cystic

and solid tumors), and finally to the most aggressive stage (type III, solid tumor). Age correlates with the type of PPB: younger patients (median age, 9 months) tend to have type I, whereas older patients (median age, 42 months) tend to have type III.¹³⁴ There is strong evidence for sequential progression of tumor from type I to type II to type III, and recurrences after surgical removal of type I tumors always arise as type II or III tumors, with a low salvage rate.¹³⁵ The survival rate after successful resection of type I tumors is 85% to 90%, but it drops to 60% for type II and 45% for type III tumors.^{134,136} Important treatment points concerning this tumor are a thorough histologic review of any multiloculated pediatric lung cyst, continued CT surveillance of these patients, and consideration of adjuvant chemotherapy for resected type I tumors.¹³⁶

Localized Malignant Mesothelioma

Localized malignant mesothelioma is a rare tumor: by 2007, only 46 cases had been reported in the English literature.¹³⁷ By all histologic, immunohistochemical, and ultrastructural criteria, these tumors are similar to diffuse malignant mesothelioma.¹³⁸ Their diagnosis depends on the following factors: (1) radiologic, surgical, or pathologic evidence of a localized serosal or subserosal tumor mass without evidence of diffuse serosal spread, and (2) a microscopic pattern identical to that of diffuse malignant mesothelioma.¹³⁹ The small number of case series in the literature do not show it to have a strong association with asbestos exposure.¹³⁷ Recurrence after surgical resection may occur either locally or with distant metastases, although only rarely does diffuse pleural spread occur with recurrence, and, in contradistinction to diffuse malignant mesothelioma, many cases are cured by surgical excision.^{137,138}

Vascular Sarcoma

The two types of pleural vascular sarcomas are epithelioid hemangioendothelioma and angiosarcoma, and the former has a lesser histologic grade. Both may demonstrate smooth to nodular pleural thickening resembling diffuse malignant mesothelioma. Differentiating these vascular sarcomas from mesothelioma can be done by immunostaining for vascular markers (CD34, CD31, factor VIII).^{123,138} Both types are very aggressive, and the outcome is often poor despite aggressive treatment.¹⁴⁰

Liposarcoma

Liposarcomas are rare (15 cases in the English literature to 2007). They are thought to be derived from residual nests of primitive mesenchymal cells in the pleural cavity. Surgical resection with consideration of postoperative chemotherapy is the recommended treatment for patients with these tumors.^{123,141}

Pleuropulmonary Synovial Sarcoma

Pleuropulmonary synovial sarcoma is a distinct histologic subtype of sarcoma that is identified as a mesenchymal

spindle cell tumor with a specific chromosomal translocation of t(X;18)(p11.2;q11.2). The name is a misnomer—these tumors have no relationship to synovial tissue. They are thought to derive from totipotent mesenchymal cells with epithelial differentiation. Most of these tumors are large and pleural based with heterogeneous areas of necrosis or hemorrhage; it is important to differentiate these rare primary pleural tumors from the more frequently seen metastatic synovial sarcoma to the lungs.¹⁴² Only a few anecdotal reports about treatment of this tumor appear in the literature. Treatment includes surgical resection and adjuvant therapy. Chemotherapy or radiotherapy may be added to the treatment regimen, based on soft tissue synovial sarcoma experiences and anecdotes of poor results with this tumor in thoracic locations.^{142,143}

Askin Tumor or Primitive Neuroectodermal Tumor (PNET)

The Askin tumor, or primitive neuroectodermal tumor (PNET), is a soft tissue tumor that appears either as a single lesion or as multiple pleural nodules in children and young adults. It is classified as a member of the Ewing sarcoma family because the chromosomal aberration t(11;22)(q24;q12) is peculiar to both tumors. However, PNET originates from soft tissue, whereas Ewing sarcoma is a tumor of bone. Extrapolated data from a single-center report of treatment of PNET¹⁴⁴ or the combined results of both tumors¹⁴⁵ suggest consideration of neoadjuvant chemotherapy, surgical resection, and adjuvant chemoradiotherapy.

Desmoplastic Small Round Cell Tumor

The desmoplastic small round cell tumor is a rare aggressive malignancy that affects adolescents and young men; fewer than 10 thoracic cases have been described.^{95,146,147} These tumors may remain localized, but more commonly they involve the pleura diffusely. They have a unique expression of epithelial, muscle, and neural markers, with a characteristic fusion protein as a result of gene fusion transcript between the Ewing sarcoma gene on chromosome 22 and the Wilms tumor gene on chromosome 11, t(11;22)(p13;q22).^{123,138} The prognosis is poor, as it is in patients with abdominal presentations of this tumor.

Malignant Pleural Tumors

Metastatic Malignant Tumors

Metastatic tumors to the pleura are common (>150,000 new cases each year in the United States); the tumor of origin in 75% of cases is lung, breast, or lymphoma, with minor contributions from ovary and stomach. In 5% to 10% of cases, the primary site is unknown.^{148,149} Patients with metastatic pleural tumors often present with symptoms from a pleural effusion because of lymphatic obstruction of pleural fluid or because of increased capillary permeability in response to tumor invasion, either by direct local tumor extension or by tumors (ovary, breast) with a predilection for serosal invasion by

a hematogenous route.¹⁵⁰ Examples of secondary pleural effusions (paramalignant effusions) caused by tumor-associated effusions without direct neoplastic involvement of serosal surfaces are chylothoraces, proximal bronchus obstruction with postobstructive atelectasis, and effusions resulting from cancer cachexia.¹⁴⁹ Metastatic tumors to serosal surfaces resulting in effusions develop site-based cellular differences between effusion tumor cells and cells from the primary or other metastatic sites. Such differences include upregulation of matrix metalloprotein (MMP)-2, and other adhesion molecules (cadherins, integrins), reduced reliance on ERK-driven pathways or chemokines for proliferation, and apoptosis resistance despite increased death receptor expression and in accordance with increased inhibitors of apoptosis proteins.¹⁵⁰

Determination of malignancy by cytologic examination of pleural effusions ranges from 62% to 90% of patients with malignant pleural effusions; increased test sensitivity can be achieved by repeated thoracenteses, electro-chemiluminescence immunoassay, genetic analysis by microsatellite analysis, DNA methylation, determination of aneuploidy, and immunocytochemistry by a variety of techniques.¹⁵¹ Gene expression tests such as EGFR mutation and receptor analysis can be useful both for tumor differentiation and for response to treatment.¹⁵² Malignant pleural effusions can be managed by a variety of techniques with a goal of creating a pleural symphysis. Such techniques range from a variety of catheter drainage procedures with the option of several different sclerosing agents, to pleuroperitoneal shunting or a surgical pleurectomy and decortication.^{148,149,151,153,154}

Restraint with respect to aggressive surgical strategies is appropriate, because, apart from breast cancer, the median survival from malignant pleural effusions is less than 6 months.¹⁵⁵ Massive effusions fare worse than lesser effusions.¹⁵⁶

Diffuse Malignant Pleural Mesothelioma

Diffuse malignant pleural mesothelioma (MPM) is the most common primary pleural tumor, but it occurs less commonly than distant malignancy with metastatic involvement of the pleural surfaces.^{151,154} An aggressive tumor, MPM arises from the mesothelial cells of the pleura. Although it can spread systemically, it grows preferentially over serosal surfaces, penetrating the interlobar fissure and eventually encasing the lung. The disease can occur at any site where mesothelial cells de-differentiate from mesenchymal cells, including the peritoneum, pericardium, tunica vaginalis of the testes, and ovary. The pleura, however, is the most common site of involvement of MPM. In the United States, there are approximately 2000 to 3000 new cases each year. Annual mortality rates in Britain and the rest of the world are projected to continue to rise, peaking in 2020.^{24,157}

Mesothelioma has several histologic subtypes (Fig. 31-1). Epithelial mesothelioma is the most prevalent type, followed by mixed/biphasic, sarcomatous, and, rarely, desmoplastic types.¹⁵⁸ In a study of 1517 cases, the epithelial cell type was found in 61.5% of the specimens,

followed by the biphasic type in 22%, and the sarcomatous type in 16.4%.¹⁵⁹ Unusual histologic subtypes of mesothelioma include tubular, capillary, solid, large or giant cell, small cell, clear cell, signet cell, glandular, microcystic, myxoid, and adenoid cystic.¹⁶⁰

Clinical Presentation. In early-stage disease, the symptoms are often subtle and the disease may be identified only because of a serendipitous finding on a chest radiograph performed for other complaints. The most common presenting symptom associated with mesothelioma is dyspnea (80%) caused by restrictive compression of the affected lung. Cough (69%) and weight loss (40%) may also occur; fatigue and weakness are generally later symptoms.¹⁶¹ Mesothelioma is usually not associated with pleuritic chest pain,¹⁶² which may suggest chest wall invasion. If invasion is confined to a localized area of the chest wall, this may still permit surgical resection. If diffuse, it may indicate nonresectable disease.

Physical examination may reveal a spectrum of signs from minimal disease to an absence of breath sounds suggestive of a unilateral pleural reaction in the involved hemithorax.

The chest radiographs typically reveal a large pleural opacity; this may also be associated with evidence of pleural-based masses (identified as nodular or irregular pleural thickening).¹⁶³ In advanced cases, mediastinal compression or intercostal narrowing can be seen on the chest radiograph; rib erosion or periosteal reaction is indicative of chest wall invasion. The chest CT scan is more accurate than plain films for identifying the extent of disease, the potential for lung compression or invasion of local structures, and metastatic spread to the mediastinal nodes. Magnetic resonance imaging (MRI) is generally superior to CT for evaluating diaphragmatic or mediastinal invasion. However, neither mode is 100% accurate, and operative exploration may be required to determine resectability.

Recently, PET-CT imaging has been shown to increase the accuracy of MPM staging¹⁶⁴ and to indicate extrathoracic occult disease. PET-CT scans are 91% sensitive and 100% specific in differentiating benign from malignant pleural disease.¹⁶⁵

Histologic identification of the pleural abnormality is required to determine the malignant nature of the pleural mass, as well as to identify the tumor type and subtype. Often, thoracentesis is the initial step for symptomatic relief of a pleural effusion and for diagnosis. However, the cytologic yield from this type of sample is relatively poor, only 62%.¹⁶⁶ The yield from pleural needle biopsy is somewhat better, at 86%.¹⁶⁷ VATS has been shown to be an effective method of enhancing the diagnosis of MPM, and it provides specimens from selected biopsy areas of parietal, visceral, and diaphragmatic pleura.¹⁶⁸ Extensive sampling is often still needed, but collection in this fashion is diagnostic in 98% of patients.

The visual manifestations of mesothelioma as seen either at open thoracotomy or by VATS can be described as localized mass lesions (rarest form), pleural studding and small plaques (discontinuous), pleural masses with variable confluence, and lung encasement with tumor invasion of chest wall and lung.^{139,169}

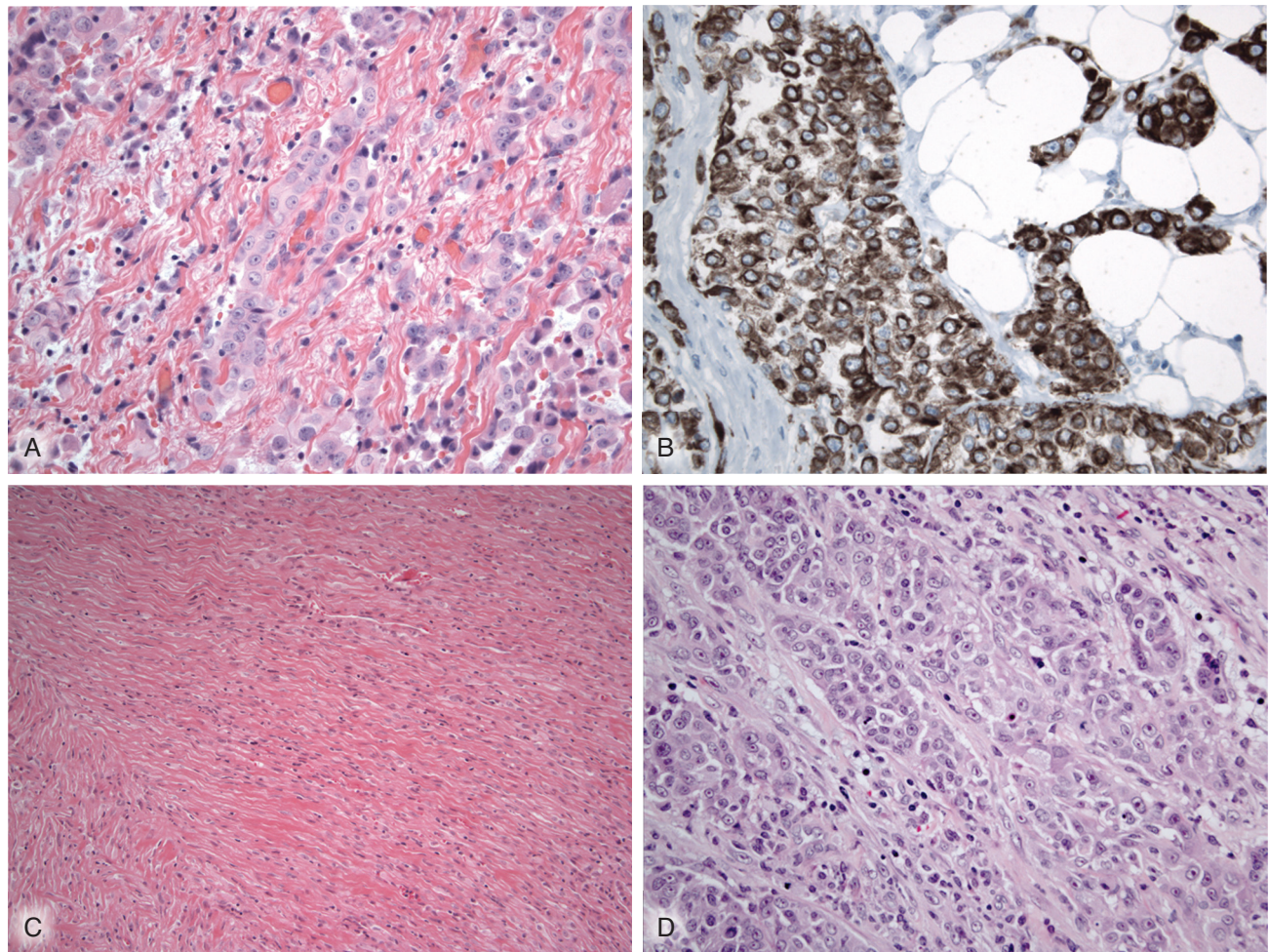


FIGURE 31-1 ■ The pathologic classification of mesothelioma reveals three histologic patterns. Diffuse malignant mesothelioma is categorized as epithelioid, sarcomatoid, or biphasic (mixed) epithelioid mesothelioma. **A**, Epithelioid subtype (hematoxylin & eosin [H&E], ×400). In this typical photomicrograph of epithelioid mesothelioma, the cells are arranged in a tubular pattern. **B**, Immunostaining pattern of malignant mesothelioma, epithelioid subtype. Note the more solid pattern of cells highlighted with cytokeratin immunostaining (AE1/AE3, ×400). The photomicrograph also demonstrates invasion of tumor cells into the chest wall adipose tissue. **C**, Sarcomatoid subtype (H&E, ×400). Spindle-shaped cells are arranged in sheets or fascicles that form nonspecific architectural patterns resembling those seen in the various sarcomas. **D**, The biphasic or mixed subtype is characterized by the presence of both epithelioid and sarcomatoid components (H&E, ×400). (Courtesy Lucian Chirieac, MD, Brigham and Women's Hospital, Boston.)

Tissue samples that are removed for histologic evaluation must be carefully evaluated to differentiate between benign proliferative mesothelial processes and malignant mesothelioma. It is also difficult to determine differences between epithelial mesothelioma, sarcomatoid mesothelioma, and sarcoma. Definite stromal invasion is the most reliable indicator of malignancy in both epithelial and spindle cell neoplasms.¹⁷⁰ Densely packed mesothelial cells in the pleural space are consistent with a benign disease process, but if they are found in the stroma, it is more suggestive of malignant mesothelioma. The three histologic subtypes of malignant mesothelioma are classified according to the relative proportions of epithelial and spindle cells. These include epithelial, sarcomatoid (spindle), and mixed (see Fig. 30-1). The epithelial subtype accounts for more than 50% of tumors and needs to be carefully differentiated from adenocarcinoma.^{171,172} Electron microscopy may aid in this differentiation. The basement membrane underlying adenocarcinoma cells

has a more complete structure than that which underlies mesothelioma cells.¹⁷³ Mucopolysaccharide stains (i.e., periodic acid–Schiff, Mayer mucicarmine) are strongly positive in adenocarcinomas and usually absent in mesotheliomas. The presence of hyaluronic acid strongly supports the diagnosis of mesothelioma. Epithelial mesotheliomas are further characterized not only by their architectural pattern, including tubular, tubulopapillary, papillary, solid, or microcystic types, but also on the basis of their cytologic features, including small cell, large cell, deciduoid, or clear cell types.¹⁷⁴ The sarcomatoid subtype accounts for 15% to 20% of tumors and must be distinguished from sarcomas.^{175,176}

Although no single immunohistochemical marker is sufficiently sensitive and specific to differentiate mesothelioma from adenocarcinoma, sarcoma, or reactive mesothelial hyperplasia, a panel of markers is currently used to aid in this distinction.¹⁷⁷ The antibody calretinin demonstrates good specificity for mesothelial cells,

whereas carcinoembryonic antigen (CEA) is highly specific for adenocarcinoma.¹⁷⁸ Low-molecular-weight cytokeratin is a general marker of mesothelioma, whereas the high-molecular-weight cytokeratins favor epithelial mesothelioma in particular.¹⁷⁹ Thyroid transcription factor-1 (TTF-1) and E-cadherin stains also help differentiate mesothelioma from adenocarcinoma: mesothelioma specimens are negative for TTF-1 and adenocarcinomas are positive for E-cadherin.¹⁸⁰ These two markers serve as the frontline immunohistochemical staining for mesothelioma, which can be followed by a secondary panel of antibodies including BerEP4, Leu M1, calretinin, cytokeratin 5/6, and N-cadherin, if necessary. Gene expression techniques involving microarray RNA profiling may be helpful to distinguish between mesothelioma and adenocarcinoma.¹⁸¹ This work uses gene product ratios and is a novel approach to diagnosing MPM, with an accuracy of between 95% and 99%.

After histologic confirmation of mesothelioma, the staging of this disease becomes central to determining the best therapy for a particular patient. Staging is equally important in assessing the effectiveness of a new therapy, and it helps to ensure that proper comparisons are made between treatment groups. When study results are reported or compared, it is important to distinguish between clinical and pathologic staging. Unfortunately, there is lack of consensus for a single mesothelioma staging system, and several staging systems are in use today. These include the Butchart staging system,¹⁸² the tumor-nodes-metastasis (TNM) staging system set forth by the Union for International Cancer Control (UICC),¹⁸³ the International Mesothelioma Interest Group (IMIG) staging system based on TNM status,¹⁸⁴ and the Brigham and Women's Hospital/Dana-Farber Cancer Institute staging system.¹⁸⁵

The Butchart classification system for MPM, described in 1976, was the first to be introduced and is quite simple, but it fails to provide any prognostic information because anything beyond stage I is considered unresectable.¹⁸²

The UICC staging system, described in 1990, was based on the TNM cancer staging system used for non-small cell lung cancer (NSCLC).¹⁸³ Because of the nature of mesothelioma tumor growth in the pleural space, the T variable as it is described in terms of NSCLC is not always applicable in patients with mesothelioma. Furthermore, although the N nodal description is the same as for NSCLC, in mesothelioma it is often difficult to evaluate nodal stations when the pleural space is completely filled with tumor or effusion. Because of the short overall survival in mesothelioma, patients often do not live long enough for metastatic disease (M) to be found. Once again, this staging system falls short clinically because it fails to correlate with patient survival and prognosis.

In 1994, another staging system was proposed by the IMIG (Box 31-3). This classification system attempts to account for the unique features of mesothelioma while using the accepted T and N status indicators. In this system, T1a tumors involve the ipsilateral parietal pleura with or without diaphragmatic involvement, and T1b tumors involve the visceral pleura. T2 disease invades the

lung parenchyma, so that lung resection would be necessary for complete removal of tumor. These tumors are associated with a pleural effusion. T3 tumors are locally advanced but are still amenable to resection in that there is involvement of endothoracic fascia, mediastinal fat, localized chest wall, or pericardium. T4 disease is technically unresectable and involves invasion of tumor into the chest wall, through the diaphragm into the peritoneum, or into the contralateral pleura, mediastinal organs, spine, internal pericardial surface, or myocardium. Staging of nodal involvement in the IMIG system is similar to NSCLC staging. Stages Ia and Ib correlate with T1aN0 and T1bN0, respectively. Stage II includes T2N0 tumors. Stage III is any T3 or any N1 or N2, and stage IV involves any T4, N3, or M1 disease.

The Brigham and Women's Hospital/Dana-Farber Cancer Institute staging system is simpler than a TNM-based system (Table 31-1) and offers better prognostic value for patients treated with different modalities. Stage I disease is resectable without lymph node involvement. Stage II tumors are also confined to the pleural envelope, but they include positive lymph node (N0 or N1) involvement. Stage III disease is unresectable, with locally aggressive tumors invading the mediastinum, diaphragm, or chest wall with or without extrathoracic or contralateral (N2 or N3) lymph node involvement. Stage IV tumors are associated with extrathoracic metastases. This system stratifies patients according to survival and accounts for resectability, tumor histology, and nodal status. The validity of this staging system has been confirmed in an analysis of a series of 120 patients.¹⁸⁶

Prognosis. MPM is a rare but highly aggressive tumor of the pleura that has defied a standard approach to treatment. Without treatment, the median survival ranges from 4 to 12 months.¹⁸⁷⁻¹⁸⁹ Recommended treatment strategies are based on the same principles applied to other solid tumors and include chemotherapy, radiation, surgery, and combinations thereof. Assessment of response to treatment can be measured according to certain criteria.¹⁹⁰ However, mesothelioma tumors have a unique growth pattern with a preference for serosal spreading, which makes the application of conventional response criteria sometimes difficult.¹⁹¹ A modification of these criteria for tumor response correlates with survival and lung function and can be used to measure outcome

TABLE 31-1 Brigham Women's Hospital Revised Staging System

I	Disease confined to the capsule of the parietal pleura: ipsilateral pleura, lung, pericardium, diaphragm, or chest wall disease limited to previous biopsy sites
II	All stage I with positive intrathoracic (N0, N1) lymph nodes
III	Local extension of disease into chest wall, mediastinum, or heart, or through diaphragm or peritoneum, with or without extrathoracic or contralateral (N2, N3) lymph node involvement
IV	Distant metastatic disease

BOX 31-3 International Mesothelioma Interest Group (IMIG) Staging System**T PRIMARY TUMOR AND EXTENT**

- T1**
- Tumor limited to ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; no involvement of the visceral pleura
 - Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; scattered foci or tumor also involving the visceral pleura
- T2** Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic pleura); scattered foci or tumor also involving the visceral pleura
Involvement of diaphragmatic muscle
Confluent visceral pleura (including the fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma
- T3** Locally advanced but potentially resectable tumor; tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
Involvement of the endothoracic fascia
Extension into mediastinal fat
Solitary, complete resectable focus or tumor extending into the soft tissues of the chest wall
Nontransmural involvement of the pericardium
- T4** Locally advanced, technically nonresectable tumor; tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
Diffuse extension or multifocal mass of tumor in the chest wall, with or without associated rib destruction
Direct transdiaphragmatic extension of the tumor to the peritoneum

Direct extension of tumor to the contralateral pleura
Direct extension of tumor to one or more mediastinal organs
Direct extension of tumor into the spine
Tumor extending through the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium

N LYMPH NODES

- Nx** Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases in ipsilateral bronchopulmonary or hilar lymph nodes
N2 Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3 Metastases in contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular scalene lymph nodes

M METASTASES

- Mx** Presence of distant metastases cannot be assessed
M0 No (known) metastasis
M1 Distant metastasis present

STAGE GROUPING

- I**
- T1aN0M0
 - T1bN0M0
- II** T2N0M0
III Any T3M0, any N1M0, any N2M0
IV Any T4, any N3, any M1

in mesothelioma treatments.¹⁹² In addition to tumor stage, several independent prognostic variables are important and have been defined in two scoring systems.^{193,194} These include age, performance status, and histologic subtype. Less important variables include chest pain, dyspnea, presence of pleural effusion, asbestos exposure, weight loss, anemia, leukocytosis, thrombocytosis (platelet count > 400,000/ μ L), and elevated lactate dehydrogenase (>500 IU/liter). The prognostic value of these scoring systems was confirmed in a retrospective review of an independent cohort of patients.¹⁹⁵ Tumors with epithelial histology carry a better prognosis.¹⁹⁶

Treatment. To date, there are no evidence-based consensus guidelines on the management of MPM. Because of its rare incidence, there are no randomized controlled trials that compare different surgical approaches with one another or that compare surgery to alternative treatments. The cumulative evidence in the literature lies in retrospective case series reports and prospective non-controlled studies. These data are further confounded by the changing classification and staging systems for mesothelioma.

Radiation Therapy. Mesothelioma cells have a modest sensitivity to radiation, less sensitive than small cell lung cancer but more sensitive than NSCLC.¹⁹⁷ Effective

treatment with an intact lung is largely limited by the collateral damage associated with the vital organs in the necessary radiation field.¹⁹⁸ It is difficult to assess the value of radiation therapy because no large study has compared radiation therapy to no treatment at all. In a small series of 23 patients reported by Ball and Cruickshank, those patients who received less than 40 Gy did not have effective palliation, whereas those receiving higher dosages were better palliated.¹⁹⁹

Radiation therapy has been shown to be effective in the prevention of local recurrence after thoracentesis or thoracoscopic biopsy.²⁰⁰ However, radiation is usually ineffective in controlling disease after partial surgical resections. Dosages must be limited to 20 Gy because of toxicity to the remaining lung. When a patient can undergo extrapleural pneumonectomy (EPP), adjuvant radiation can help reduce local recurrence, which arises in the ipsilateral hemithorax in more than 60% of cases. In one nonrandomized study, which did not reach statistical significance, 31% of patients treated with radiation after EPP had local recurrence, as opposed to 45% of patients not treated with adjuvant radiation.²⁰⁰ Those patients with negative margins did not show any decrease in local recurrence after postoperative radiation, whereas postoperative radiation was found to possibly benefit those with positive resection margins. External beam

radiation therapy, previously based on chest radiographs, has evolved to include intensity-modulated regimens based on three-dimensional field planning.²⁰¹ With careful intraoperative marking by the surgeon and postoperative planning by the radiation oncologist, intensity-modulated radiation beams maximize targeting of the tumor bed and avoid toxicity to surrounding vital structures.²⁰²

Chemotherapy. Mesothelioma is relatively chemoresistant, with response rates to single agents less than 20% and no effect on overall survival. The antimetabolites, anthracyclines, and platinum compounds seem to be the most active in mesothelioma. Methotrexate showed a 37% response rate in a phase II trial of 63 patients.²⁰³ However, toxicity was seen in 58% of patients. Detorubicin showed a greater response than doxorubicin in 35 patients, where a response rate of 26% was found.²⁰⁴ Cisplatin was demonstrated to have a 14% response rate in a Southwest Oncology Group study.²⁰⁵ At a higher dosing schedule, a 36% response rate was seen.²⁰⁶ However, there were significant side effects, and these prompted discontinuation in 34% of patients because of toxicity. Carboplatin showed a similar response rate of 11% and is somewhat better tolerated than cisplatin.²⁰⁴ Vinorelbine also has single-agent activity against mesothelioma, with a low incidence of serious side effects.²⁰⁷ Partial response with 50% reduction in tumor thickness was seen in 24% of patients, whereas 55% had stable disease (neither 25% increase nor 50% decrease in tumor thickness). Gemcitabine has limited activity when used alone.²⁰⁸ Pemetrexed has shown some encouraging results in single-agent therapy in 64 patients, where 14% experienced a partial response.²⁰⁹

Response rates are increased for combination therapies compared with single-agent treatments.²¹⁰ Therefore, single-agent treatment has given way to combination regimens. The results reported by Vogelzang and colleagues showed superior survival time, time to progression, and response rates for patients treated with pemetrexed plus cisplatin versus cisplatin alone.²¹¹ This was a randomized, multicenter, phase III trial in 456 patients. Epithelial histology dominated in more than two thirds of the patients, and stage III or IV disease was seen in 78% of cases. Median survival time was 12.1 months in the combined group versus 9.3 months for cisplatin alone, with response rates of 41.3% versus 16.7%, respectively. This combination is now generally accepted as the standard treatment for patients with mesothelioma,²¹² and further investigations into second-line chemotherapy regimens have begun.²¹³

Surgery. Patients must be suitable surgical candidates for thoracotomy before being considered for pleurectomy/decortication (P/D) or EPP. Age and functional status are the first markers to assess. There is no upper age limit; however, caution is required for patients older than 70 years or with a Karnofsky performance status of less than 70. Cardiopulmonary function is closely studied: a preoperative forced expiratory volume in 1 second (FEV₁) of less than 2 liters, or a predicted postoperative FEV₁ of less than 0.8 liters requires more intensive pulmonary investigation. A marginal preoperative FEV₁ warrants a quantitative radionuclide perfusion scan to predict the

postoperative pulmonary capacity.²¹⁴ Echocardiography provides valuable information, with its ability to assess cardiac function, wall motion abnormalities, valvular disease, and particularly pulmonary artery pressure. If required for further assessment, right heart catheterization may be performed. Left and right ventricular function must be preserved (>45%). Pulmonary hypertension (>45 mm Hg) is a contraindication to EPP.

CT and MRI are used to define the anatomic extent of the tumor and mediastinal or chest wall invasion, and to rule out abdominal extension of disease. CT-PET scanning and cervical mediastinoscopy provide additional staging for extrathoracic disease and lymph node involvement. Metastatic mediastinal node disease confirmed at mediastinoscopy is treated with neoadjuvant chemotherapy in an attempt to downstage the tumor, followed by restaging. The primary goal of surgery is to remove all gross visible tumor (macroscopic complete resection). The eligibility criteria for EPP are listed in [Box 31-4](#).^{17,32,82,182,215-219} Patients who do not meet these criteria may still be candidates for pleurectomy.

Extrapleural pneumonectomy: With routine hemodynamic monitoring, an epidural and a double-lumen endotracheal tube in position, a posterolateral thoracotomy is made. The incision begins midway between the posterior scapula and the spine and extends under the scapular tip along the course of the sixth rib to the costochondral junction.²²⁰ The latissimus and serratus muscles are divided. In general, any prior thoracoscopy port sites or incisions are excised and incorporated into the thoracotomy incision when feasible. The sixth rib is carefully identified and removed from just anterior to the paraspinous ligament posteriorly to the costochondral junction anteriorly. This sets up the start of the extrapleural dissection plane, which is established next. The fused pleura is dissected away from the chest wall until there is room to insert a retractor. Then, the dissection proceeds in an organized manner, packing off any dissected planes to tamponade bleeding during mobilization elsewhere. Blunt dissection using a sponge stick or a finger complements sharp dissection with scissors. Careful attention is given to the subclavian vessels superiorly; the contralateral pleural space and internal thoracic vessels medially;

BOX 31-4 Eligibility Criteria for Extrapleural Pneumonectomy

- Karnofsky performance > 70
- Renal function: creatinine < 2
- Liver function: AST < 80 IU/L; total bilirubin < 1.9 mg/dL; PT < 15 sec
- Pulmonary function: postoperative FEV₁ > 0.8 L, as calculated from PFTs and quantitative $\dot{V}/\dot{Q}$ scans
- Cardiac function: normal electrocardiogram and echocardiogram (EF > 45%)
- Extent of disease: limited to ipsilateral hemithorax, with no transdiaphragmatic, transpericardial, or extensive chest wall involvement

AST, Aspartate aminotransferase; EF, ejection fraction; FEV₁, forced expiratory volume in 1 sec; PFTs, pulmonary function tests; PT, prothrombin time; $\dot{V}/\dot{Q}$, lung ventilation/perfusion quotient.

and the azygos vein, superior vena cava, and esophagus (right side) and aorta, intercostal arteries, and esophagus (left side) posteriorly. Continuous reorientation helps avoid inadvertent injury, as does palpation of a properly positioned nasogastric tube.

At this point, a determination is made as to the resectability of the tumor. Once this has been confirmed, the diaphragm is dissected at the anterior border with the chest wall and pericardium. The diaphragm is avulsed from the chest wall by careful manual traction, as opposed to sharp dissection, which can actually lead to more bleeding. Care must be taken to ensure removal of all gross tumor, but it is necessary to leave a rim of the diaphragmatic crus intact for later patch reconstruction. The peritoneum is left intact if at all possible. Next, the pericardium is opened caudally. It is incised anteromedially toward the phrenic nerve and the hilar vessels. The pulmonary veins are divided intrapericardially. The pulmonary artery is taken in similar fashion on the right, but extrapericardially on the left. Each vascular division is done using the endoleader technique and the endoscopic stapling device. Posteriorly, the pericardium is opened at the level of the esophagus on the right and the aorta on the left. The subcarinal lymph nodes are then removed, and the bronchus is divided last using a heavy-wire stapler. The ability to visualize this bronchoscopically during the dissection aids in achieving the proper bronchus length. A short, almost flush bronchial stump reduces the possibility of stump syndrome from airway secretions and helps minimize stump breakdown.

Once the specimen has been removed, additional lymph node stations are sampled and the bronchial stump is leak tested. At this point, a chemical wash is performed, followed by intracavitary heated chemotherapy consisting of cisplatin and gemcitabine for 1 hour. If the patient has a creatinine clearance of less than 60 mL/min or crowded optic disc on preoperative assessment, the length of intracavitary chemotherapy should be reduced by half. Next, the omentum is mobilized for use as a bronchial stump buttress. Alternatively, this can be covered with a pericardial fat pad buttress. Next, the diaphragm and pericardium are reconstructed using 2- and 1-mm expanded polytetrafluoroethylene (e-PTFE) patches, respectively (Gore-Tex Dual Mesh; WL Gore, Flagstaff, AZ) (Fig. 31-2). A series of nine stitches is used to secure the patch circumferentially from the posterior paraspinous ligament around to the sixth costal cartilage anteriorly. Gore-Tex buttons or bumpers are used to keep the sutures from pulling through the chest wall (Fig. 31-3). The dynamic two-piece diaphragm patch is then sewn to the base of the pericardium from the anterior costophrenic angle posteriorly toward the esophagus and inferior vena cava (right) or aorta and crus (left) (Fig. 31-4). The impermeable nature of the patch prevents peritoneal fluid from freely crossing into the pleural space postoperatively.

The pericardial patch is fenestrated and sewn in place posteriorly first. It is then secured to the diaphragmatic patch inferiorly and the residual pericardium anteriorly and superiorly (Fig. 31-5). It should not be made too tight because this may constrict filling of the heart, causing a tamponade effect. This is more important on

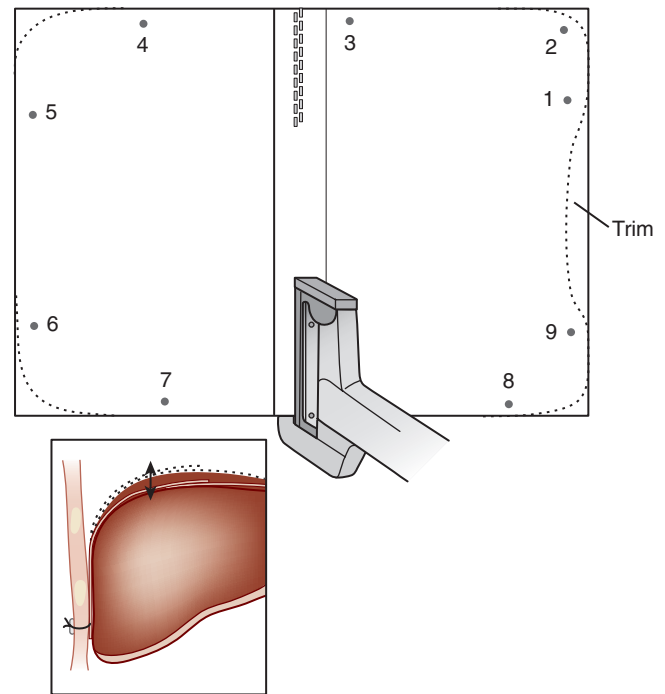


FIGURE 31-2 ■ Creation of the diaphragmatic patch. Two 2-mm impermeable Gore-Tex patches (Gore-Tex Dual Mesh; WL Gore, Flagstaff, AZ) are overlapped, stapled together, and trimmed to create a dynamic patch with reduced tension along its edges. Nine holes are made along the periphery of the patch to receive interrupted 0 Gore-Tex sutures.

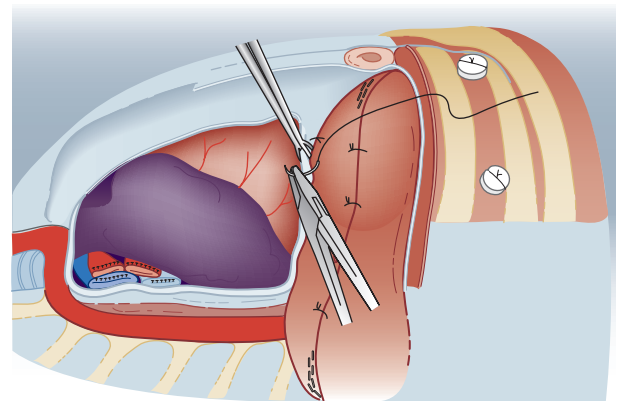


FIGURE 31-3 ■ Diaphragmatic reconstruction. The sutures on the patch are pulled through the chest wall with an awl and securely tied, from the paraspinous ligament posteriorly to the sixth rib anteriorly. Polytetrafluoroethylene (PTFE) buttons or bumpers are placed to prevent the sutures from pulling through the chest wall.

the right side, given the potential for the heart to turn about the axis of the cavae and herniate. In fact, the left-sided pericardium does not always have to be patched. Once the patches have been placed, an elliptical opening is made in the diaphragmatic patch, and the omentum is pulled through this aperture (Fig. 31-6). It is secured to the bronchus, primarily, with additional bites taken along the surrounding tissues to minimize direct tension. The diaphragmatic patch can be reefed up between the two pieces that make up the dynamic patch, with care not to

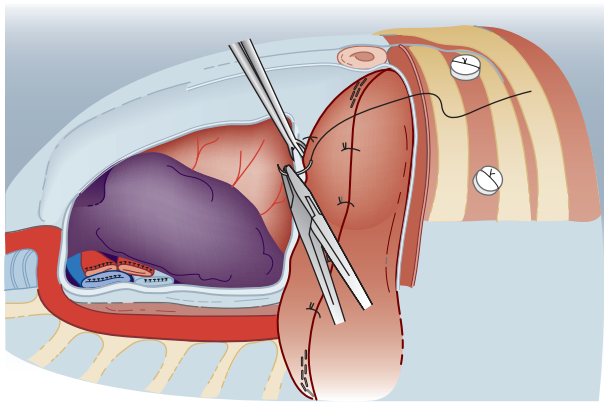


FIGURE 31-4 ■ Completion of patch reconstruction. The posterior or mediastinal edge of the diaphragmatic patch is sutured to the inferior cut edge of the pericardium. Care is taken to avoid constriction of the inferior vena cava (right side), slitting the patch if necessary, and to avoid intra-abdominal herniation (left side) with healthy bites along the crus and posterior chest wall.

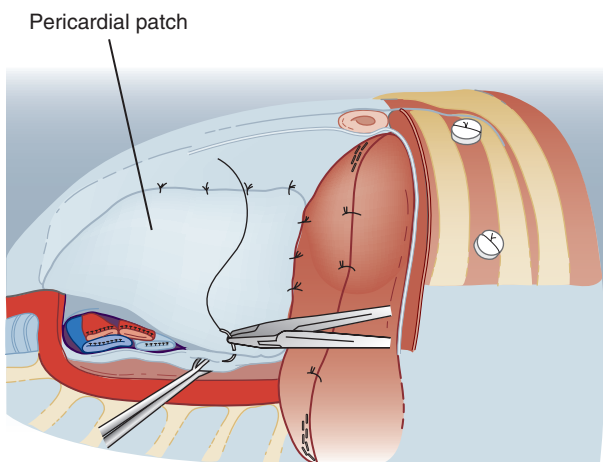


FIGURE 31-5 ■ The pericardial patch is secured to the posterior, anterior, and superior cut edges of the pericardium. Inferiorly, it is sutured to the diaphragmatic patch itself. Depending on patient size, it may be necessary to splice in an additional patch to avoid cardiac or caval constriction. Displacement of the heart into the pneumonectomy space after closure needs to be taken into account when sizing the pericardial patch during implantation. The pericardial patch should be fenestrated before reconstruction to reduce the chance of pericardial tamponade from fluid accumulation behind the patch.

make the neodiaphragm too tight. Additional bites are taken to secure this patch with the chest wall and diaphragmatic crura posterolaterally. Thorough hemostasis is achieved with an argon beam coagulator. The thoracotomy is closed in standard fashion with care to make it watertight. A 12-Fr red rubber catheter is left in place for use in balancing the mediastinum intraoperatively. In men, 1000 mL is removed initially after a right EPP (750 mL from the left), whereas in women, 750 mL is taken from the right chest (500 mL from the left side). Additional air is removed in the postoperative setting as needed based on the chest radiograph, with the intention of removing the catheter altogether by the third day to reduce infection.

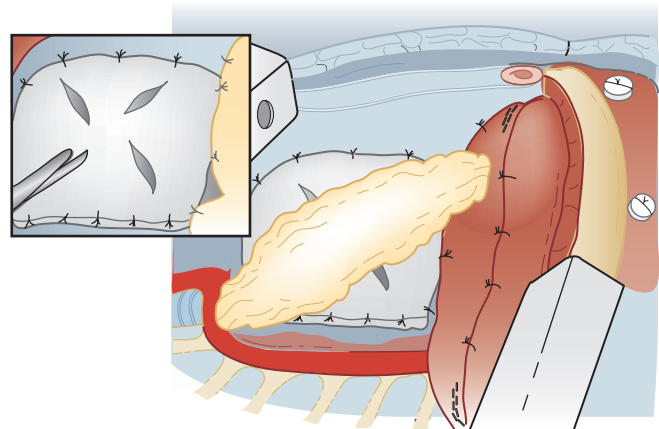


FIGURE 31-6 ■ A portion of omentum can be mobilized and carefully pulled through the patch to serve as a buttress on the bronchial stump to help prevent bronchopleural fistula.

Pleurectomy is a palliative debulking procedure that is combined with decortication for patients with mesothelioma whose pulmonary function or physiologic status contraindicates pneumonectomy. The incision and initial dissection are identical to that described for an EPP. Once the parietal pleura has been dissected free, the tumor itself is incised down to the visceral pleura for an internal pleurectomy. Bleeding can be controlled with an argon beam coagulator or hilar clamping, if needed. It is important to remove as much tumor tissue as possible, especially that extending into the fissures, for a macroscopic complete resection.²²¹ On the right side, reconstruction of the diaphragm is not always needed, because the liver is there and the lung is left in place.

Postoperative Management. Key points in successful recovery of patients in the postoperative setting include pain management, careful fluid balance, and early vigilance for, and diagnosis of, common postoperative complications, which include deep venous thrombosis, pulmonary embolism, vocal cord paralysis, chylothorax, empyema, bronchopleural fistula, and mediastinal shift.²²² Pain is controlled with a thoracic epidural and a patient-controlled analgesia (PCA) pump when needed. Proper pain control and vigorous ambulation (after an initial 48-hour period of mediastinal equilibration for pneumonectomy patients) are critical to preventing contralateral lung atelectasis. The Swan-Ganz catheter is left in place and removed on postoperative day 2 with the expectation that there will be massive fluid shifts. Patients are often vasoplegic as a result of the systemic inflammatory response of the intracavitary chemotherapy and dissection of the sympathetic trunk. Aggressive ambulation begins after the pulmonary artery catheter is removed and will progress over the ensuing days. Patients are given a nasogastric tube and nothing by mouth for the first 48 hours. Diet is then advanced as tolerated. Because aspiration can have devastating consequences in any patient with a voice change or signs of aspiration, there is a low threshold for evaluating the vocal cords in this patient population. Fluid restriction and liberal use of diuretics help achieve proper fluid balance: pulmonary

edema is a dreaded complication of pneumonectomy. Perioperative beta blockade is administered for prophylaxis of atrial fibrillation. Aggressive screening and prophylaxis for deep venous thrombosis is carried out in every patient with venous duplex Doppler exams on a weekly basis for the first several weeks after surgery.

Operative Results. Several large studies of pleurectomy for mesothelioma have been reported. A series from Memorial Sloan Kettering Cancer Center listed a mortality rate of 1.8%, complication rate of 25%, and 1-year survival of 49% in 64 patients.²²³ In Germany, Achatz and colleagues reviewed 245 partial and complete pleurectomy cases and showed a 30-day mortality of 8.5% with a median survival of 9.2 months.²²⁴ In 1991, Brancatisano and associates described a series of 45 pleurectomy patients with a mortality rate of 2.2%, morbidity rate of 16%, and median survival of 16 months.²²⁵ Allen and coworkers reported a series of 56 patients with a perioperative mortality of 5.4%, morbidity of 26.8%, and 1-year survival of 30%.²²⁶ More recently, Richards and colleagues reported a retrospective analysis of patients under a protocol for a combined regimen of cytoreduction surgery (pleurectomy or EPP) plus intraoperative intracavitary chemotherapeutic lavage with hyperthermic cisplatin.²²¹ In a subgroup of patients undergoing pleurectomy at two different dosages of hyperthermic drug delivery—low dosage (50 to 150 mg/m²) versus high dosage (175 to 250 mg/m²)—the study found that the subset of patients receiving high-dose chemotherapy demonstrated an apparent survival benefit warranting further investigation. The EPP arm of this phase I study, published in 2009, reported overall median survival of 17 months (resected 20 months; unresected 10 months). Median survivals for patients receiving the higher cisplatin dose was 26 months, and for patients receiving the lower dose, median survival was 16 months ($P = 0.35$).²⁷⁴

Extrapleural pneumonectomy carries a higher mortality rate compared with that of pleurectomy in most series. The perioperative mortality in Butchart's original series was 30%, which was comparable to that of contemporary studies in the 1970s.¹⁸² Since then, experience from high-volume centers has shown a significant reduction in mortality from EPP to rates of less than 10%. DaValle and colleagues²²⁷ published a mortality rate of 9%, and Rusch and coworkers²²⁸ reported a rate of 6%. Recently, Sugarbaker's group reported a perioperative mortality of 4% and morbidity of 66% for this procedure.^{229a}

In addition to the surgical approach, lymph node involvement has also been an important factor in overall survival after EPP or P/D. Hysi et al conducted a multicenter retrospective study in France and concluded that lymph node involvement and metastatic lymph node ratio influence survival.²²⁹ They found that node-positive resection specimens significantly reduced median survival (22.4 months for N0 versus 12.7 months for N+ patients, $P = 0.002$). The lymph node ratio was also important in that a lower metastatic lymph node ratio (<13%) was associated with a significantly improved median survival (19.9 months versus 11.7 months, $P = 0.01$). Interestingly the number of lymph nodes removed or involved was not related to survival; only the lymph node ratio was related

to survival, therefore promoting lymph node ratio as a more reliable prognostic factor.

Multimodality Therapy

Early efforts to treat MPM with single therapies failed to have a significant impact on patient survival (Box 31-5). As a result of these failures, a multimodality strategy evolved. The multidisciplinary approach for surgical candidates includes P/D or EPP, external beam radiation to the hemithorax, and systemic combined chemotherapy. Treatment plans involving two modalities, such as chemotherapy and surgery, radiation and surgery, or chemotherapy and radiation, have shown some improvement over single-modality treatment in nonrandomized studies. Chemotherapy or radiation without surgery has had very limited success.²³⁰ Surgery, either as P/D or EPP, combined with chemotherapy or radiation has been found to show some improvement in survival when compared with historical controls. Rusch and colleagues from Memorial Sloan Kettering Cancer Center reported a series of 105 patients with MPM who underwent P/D combined with intraoperative brachytherapy plus adjuvant external beam radiation.¹⁸³ Median survival was 12.5 months, with local relapse the most common treatment failure. In another study from the same institution, 28 patients with mesothelioma underwent P/D, this time in conjunction with intrapleural and adjuvant systemic chemotherapy.²³¹ Overall survival was 68% at 1 year and 40% at 2 years, with locoregional disease the most common relapse.

A seminal article in 1980 by Antman and associates advocated a multimodality approach to malignant mesothelioma after a retrospective review suggested an advantage to aggressive intervention.²³² Antman initiated a prospective multimodality protocol that included EPP followed by adjuvant chemoradiation. In 1991, Sugarbaker reported his first case series of 31 patients who

BOX 31-5 Therapeutic Options for Malignant Pleural Mesothelioma

SINGLE-MODALITY THERAPY

- Debulking surgery (pleurectomy/decortication or extrapleural pneumonectomy)
- Radiation (external beam, brachytherapy)
- Chemotherapy (single- or double-agent approach: doxorubicin, cyclophosphamide, cisplatin; gemcitabine, pemetrexed [see reference 267], and cisplatin)

MULTIMODALITY THERAPY

- Surgery and adjuvant radiation
- Surgery and adjuvant chemotherapy
- Surgery and adjuvant chemoradiotherapy

INNOVATIVE THERAPIES UNDER INVESTIGATION

- Intracavitary lavage with hyperthermic chemotherapy
- Photodynamic therapy
- Gene therapy
- Angiogenesis
- Immunogenic therapy

underwent EPP in a trimodality setting. The mortality rate was low (6%), and this study identified trends toward improved survival in the subset of patients with negative histologic margins.²³³ During this period, other centers produced case series with improved mortality rates after EPP.^{189,227}

A prospective trial by Rusch and coworkers noted a longer progression-free survival with EPP but showed no difference in survival when compared with patients who underwent less radical procedures or nonsurgical treatment.²²⁸ Allen and colleagues published a retrospective case series of patients who underwent either pleurectomy or EPP with adjuvant chemotherapy or radiation therapy.²²⁶ There was a trend toward higher median survival in those who underwent EPP, but it was not statistically significant. Sugarbaker's group described a substantial reduction in operative mortality (4.6%), and in 1993, the Brigham and Women's Hospital/Dana-Farber Cancer Institute combined cancer treatment program identified a subset of patients with epithelial histology and node-negative status that exhibited improved survival.^{234,235} The next update in the Brigham series reported a median survival of 21 months in 120 patients.¹⁸⁶ Based on the Brigham staging system, median survival was 22 months for stage I, 17 months for stage II, and 11 months for stage III disease. These data were subsequently updated in 183 patients using the revised Brigham staging system, where N2 disease was reclassified as stage III (instead of stage II) disease, beyond the pleural envelope.¹⁸⁵ This reclassification was in response to a multivariate analysis that showed that the most important predictor of poor outcome after EPP in a trimodal setting was histologic subtype (nonepithelial), positive N2 nodal disease, and positive resection margins.

During this time, the IMIG consortium led by Rusch developed another staging system (see [Box 31-3](#)).¹⁸⁴ TNM staging designates most patients as stage III, which has the effect of coalescing patients with different tumor characteristics and obscuring survival benefits associated with such prognostic markers. Nonetheless, the TNM staging system continues to be more widely used. Rusch published a prospective noncontrolled study of a cohort of mesothelioma patients treated with either EPP or pleurectomy followed by adjuvant treatment. Tumor stage had a significant impact on overall survival when considered across all stage groups: stage I had a median survival of 30 months, stage II 19 months, stage III 10 months, and stage IV 8 months. Although there was no significant difference in survival based on type of surgical resection, it should be noted that pleurectomy was performed in patients with minimal visceral pleural tumor, whereas those with more locally advanced tumors underwent EPP.¹⁸⁴ It is important to recognize such a selection bias in operative planning when interpreting results.

As there is much controversy as to the importance of type of surgical resection (P/D versus EPP), the issue is likely to remain unresolved in the absence of randomized controlled trials comparing the two approaches. A recent case series by Stewart and colleagues supports the benefit of EPP over P/D by demonstrating a longer progression-free survival and longer time to local disease progression with EPP.²³⁶ Studies of patterns of failure

after multimodality therapy have implicated locoregional recurrence as the most common site of treatment failure. Baldini and colleagues revealed that 25 of 46 patients (54%) developed documented recurrences, with a median time to recurrence of 19 months. The ipsilateral hemithorax was the most common site of recurrence (35%), followed by the abdomen (26%), contralateral hemithorax (17%), and distant disease (8%).²³⁷ This study clearly indicates the locally aggressive nature of malignant mesothelioma and suggests that more effective methods to prevent locoregional recurrence are needed after macroscopic complete resection of this tumor.

Local Recurrence. The ipsilateral hemithorax is the most common site of recurrence after malignant mesothelioma. Burt and colleagues recently illustrated the beneficial effects of local chest wall resection for recurrent mesothelioma.²³⁸ They found that, out of 1142 patients from 1988 to 2011 who underwent EPP or radical pleurectomy for mesothelioma, 47 (4.1%) had chest wall recurrence amenable to resection. The predominant area of recurrence was peri-incisional (49% of cases), followed by the costophrenic angle (38%). There was no 30-day mortality following chest wall resection, and median length of stay in the hospital was 3 days. Overall median survival duration after resection for recurrence was associated positively with time to recurrence. Patients with epithelial pathology had median survival of 8.9, 17.2, and 35.8 months with a time to recurrence of less than 12 months, 12 to 24 months, and more than 24 months, respectively. The authors concluded that chest wall resection is a safe and effective method of managing local recurrence and that time to recurrence appears to predict survival, with decreased time to recurrence being associated with worsening overall survival.

Innovative Adjunctive Therapies

Intraoperative Heated Chemotherapy. Intracavitary chemotherapy has been studied in patients with abdominal malignancies as a means of improving locoregional control.^{239,240} With intracavitary administration, the chemotherapy agent enters the tumor cells directly by diffusion, thereby minimizing the toxicity associated with systemic delivery. The depth of penetration for chemotherapy agents is only several centimeters deep from surface application²⁴¹; however, this may be sufficient for locoregional control if microscopic control is needed after gross tumor removal. It is important to achieve a macroscopic complete resection before the administration of intracavitary chemotherapy to ensure complete exposure of the chemotherapeutic agent to all surfaces that may harbor cancer cells.²²¹ The optimal timing for chemotherapy lavage is in the operating room immediately after tumor resection and before the development of adhesions. This allows maximal drug exposure to occur before tumor cells become entrapped in fibrinous exudates and loculated adhesion pockets. In addition, the best time for drug delivery is immediately after resection, when the volume of residual tumor cells is small enough to be penetrated by the chemotherapy drug.

Systemic absorption of intrapleural chemotherapy will occur, with peak plasma levels occurring within 1 hour of intrapleural administration of cisplatin; however, there is a local advantage with respect to pleural in comparison to plasma levels using this drug delivery system.²⁴² Intraoperative caution is needed with respect to crystalloid infusion to prevent postpneumectomy pulmonary edema, and there is also significant concern about renal toxicity because of potential systemic absorption of

cisplatin. Adjunctive methods to mitigate the potential for renal toxicity include the intraoperative administration of thiosulfate and amifostine as cytoprotective agents in combination with intravenous hydration postoperatively.

Hyperthermia has been shown to increase cell permeability, alter cellular metabolism, and improve membrane transport of drugs.²⁴³ A synergistic effect of hyperthermia and cisplatin has been demonstrated (Table 31-2).^{244,245} Initial studies with this approach after EPP suggested

TABLE 31-2 Hyperthermic Intracavitary Chemotherapy Studies

Study	Patients (N)	Surgery (Number of Patients)	Intracavitary Chemotherapy	Overall Median Survival (mo)	Cytoprotection	Renal Toxicity (Number of Patients)
Rusch et al, 1994 ²⁶⁸	27	P/D	Cisplatin (100-75 mg/m ²) Mitomycin C (8 mg/m ²)	18.3	IV hydration	(2)
Rice et al, 1994 ²⁶⁹	19	P/D (9) EPP (10)	Cisplatin (100 mg/m ²) Mitomycin C (8 mg/m ²)	13	IV hydration	None
Lee et al, 1995 ²⁷⁰	15	P/D	Cisplatin (100 mg/m ²) Cytosine arabinoside (1200 mg)	11.5	IV hydration	(1) Grade III
Sauter et al, 1995 ²⁷¹	13	P/D	Cisplatin (100 mg/m ²) Cytosine arabinoside (1200 mg)	9	IV hydration	(1) Grade IV
Colleoni et al, 1996 ²⁷²	20	P/D	Cisplatin (100 mg/m ²) Cytarabine (1000 mg/m ²)	11.5	IV hydration	(2) Grade III/IV
Yellin et al, 2001 ²⁴⁷	7	EPP (4) P/D (1) Thor (2)	Cisplatin (150 mg or 200 mg)	NR	IV hydration	None
Monneuse et al, 2003 ²⁴⁶	16	P/D	Mitomycin C (max, 60 mg), +/- cisplatin (max, 80 mg)	18	IV hydration	None
van Ruth et al, 2003 ²⁷³	20	P/D (12) EPP (8)	Cisplatin (80 mg/m ²) Doxorubicin (20-35 mg/m ²)	11	IV hydration	None
Chang and Sugarbaker, 2004 ²⁷⁴	50	EPP	Dosage-escalation study. Cisplatin (MTD 250 mg/m ²)	NR	IV sodium thiosulfate concomitant with lavage	NR
Richards et al, 2006 ²²¹	44	P/D	Cisplatin (MTD 225 mg/m ²)	Survival benefit for high dosage range (18 mo versus 6 mo)	IV sodium thiosulfate after lavage (16 g/m ² for 6 hr)	(1) Grade IV, (2) grade III, (4) grade II
Zellos et al, 2009 ²⁷⁵	29	EPP	Cisplatin (225 mg/m ²)*	20	IV amifostine (910 mg/m ²) after EPP/before lavage	(8) Grade III/IV (reversible in all but 1)
Tilleman et al, 2009 ²⁷⁶	92	EPP	Cisplatin (225 mg/m ²)	13.1	IV sodium thiosulfate after lavage with and without amifostine (910 mg/m ²) before lavage	(9) Grade III/IV (1 not attributable to cisplatin)

*Renal toxicity not related to cisplatin dose; MTD could not be established.

EPP, Extrapleural pneumonectomy; MTD, maximum tolerated dose; NR, not reported; P/D, pleurectomy/decortication; Thor, thoracotomy. Reproduced with permission from Mujoomdar A, Sugarbaker D: Hyperthermic chemoperfusion for the treatment of malignant pleural mesothelioma. *Semin Thorac Cardiovasc Surg* 20:298-304, 2008.

that median survival could be increased to 18 months²⁴⁶ and, in selected patients, long-term control could be achieved.²⁴⁷ Tilleman and colleagues have recently reported a series of 121 patients treated with heated intraoperative chemotherapy after EPP.²⁷⁶ In this series, in the group of patients who completed the protocol, there was a mortality of 1.1% and a postoperative morbidity of 48.9%, with significant renal toxicity of 9.8%. The overall median survival of the treatment cohort was 13.1 months, with a cancer-specific survival of 16.9 months. However, in patients with epithelial histology and early-stage disease (Brigham and Women's Hospital stage I or II), there was an improved cancer-specific median survival of 21.4 months and 22 months, respectively.²⁴⁸

Because of the potential for local recurrence in the hemithorax and for regional relapse in the abdomen, the practice of bicavitary intraoperative heated chemotherapy is now used in conjunction with EPP or P/D as part of a multimodality treatment approach in patients with mesothelioma.

Antiangiogenic Therapy. Angiogenesis plays a central role in tumor growth and therefore lends itself as a target in the treatment of cancer patients. Three antiangiogenesis inhibitors currently under trial are thalidomide, SU5416, and bevacizumab. Thalidomide is one of the few antiangiogenic agents available for oral administration. It has shown promise in prolonging disease stabilization with a relatively mild toxicity profile.²⁴⁹ Studies involving the other two drugs involve VEGF, and endpoints include time to progression of disease and tumor response rate. SU5416 is an inhibitor of the VEGF-1 receptor Flk-1 and is being studied by the National Cancer Institute, and bevacizumab is a recombinant anti-VEGF monoclonal antibody under investigation at M. D. Anderson Cancer Center, the University of Chicago, and the University of Pennsylvania.²⁵⁰

Photodynamic Therapy. Photodynamic therapy (PDT) is a two-step process that involves first the administration of a photosensitizing agent, such as Photofrin or Foscan. Tumor cells preferentially take up these compounds. The second step involves exposing the affected tumor tissue to light at a certain wavelength. This light catalyzes a cellular reaction in which free radicals are produced and ischemic necrosis occurs. These events lead to damage from direct cytotoxic effects on cellular membranes and from vascular occlusion. Because the depth of tissue penetration of the light is limited, PDT is well suited for use as an intraoperative adjunct after surgical debulking.

Applications of this therapy in mesothelioma patients have been ongoing at a few centers.²⁵¹⁻²⁵⁴ Takita and his group studied Photofrin in 40 patients from 1991 to 1996.²⁵³ Patients underwent pleurectomy or extrapleural pneumonectomy for removal of all gross disease or had their tumors debulked to a depth of less than 0.5 cm; intraoperative PDT followed. Median survival for patients in stages I and II was 36 months and was 10 months for patients in stage III and IV. Because of its better profile in terms of increased oxygen singlet

production and decreased duration of skin photosensitivity, the photosensitizer Foscan was studied in 26 patients undergoing P/D or EPP in a phase I trial from 1997 to 2001.²⁵¹ Median progression-free survival and overall survival were each 12.4 months. These preliminary results will probably lead to a phase II trial.

Immunotherapy. Several studies suggest that mesothelioma cells are susceptible to destruction by immunologic means.²⁵⁵ Boutin described the activity of intrapleural recombinant interferon- γ (IFN- γ) against malignant mesothelioma in 1991.²⁵⁶ His group has also made use of an implantable access system for prolonged administration of the immunotherapy agents directly into the affected hemithorax, reducing the toxicity and allowing treatment on an outpatient basis.²⁵⁷ A prospective multicenter study of 89 patients with early-stage disease showed an overall response rate of 20%, and the treatment was well tolerated.²⁵⁸ The exact mechanism of action is not clear, but it may relate to an IFN- γ -mediated inhibitory effect on interleukin-6 (IL-6) production, which may abrogate the systemic manifestations associated with mesothelioma cells.²⁵⁹

Other work has been done using the cytokine interleukin-2 (IL-2), which is known to stimulate proliferation of T cells, natural killer cells, and lymphokine activated killer cells. Repeated intrapleural instillation of IL-2 was given twice weekly for 4 weeks during a phase II trial in 31 patients, 22 of whom were in stage I.²⁶⁰ Pleural fluid collections were effectively treated in 90% of patients, and median overall survival was 15 months. In another study, treatment with IL-2 yielded an overall response rate of 47% in a phase I trial and 55% in phase II testing.²⁶¹ Monti and coworkers demonstrated the *in situ* activation of CD8⁺ cells and macrophages after the administration of IFN- γ .²⁶² Despite the theoretical considerations, a phase II trial using an infusion of activated macrophages and IFN- γ did not show an improvement in antitumoral activity.²⁶³

Gene Therapy. Gene transfer techniques can be used to alter cells to enhance immunogenicity. This can be done in several ways, including by transfection and expression of genes for various cytokines and costimulatory molecules.²⁶⁴ In a murine model of mesothelioma, flank tumors were treated with adenovirus-encoding interferon- β (IFN- β).²⁶⁵ Tumors treated before debulking increased long-term tumor-free survival and resulted in twofold to sixfold smaller foci of implanted tumor cells at 2 weeks postoperatively. It was postulated that elimination of residual tumor cells occurred because of an amplification of the cytotoxic T-lymphocyte antitumor response mediated by adenovirus-encoding IFN- β .

Recently, a small study of 21 patients with mesothelioma used high-dose therapy with a vector that encoded the herpes simplex virus thymidine kinase.²⁶⁶ A spectrum of clinical responses was observed, including in two patients followed for 6 years after gene transfer therapy. It is thought that in the future, augmenting the immune effects of gene transfers may lead to increased numbers of therapeutic responses.

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DIAPHRAGM

PART OUTLINE

32 SURGERY OF THE DIAPHRAGM:
A DEDUCTIVE APPROACH

33 CONGENITAL DIAPHRAGMATIC HERNIA

SURGERY OF THE DIAPHRAGM: A DEDUCTIVE APPROACH

Carlos E. Bravo Iñiguez • Mauricio Perez Martinez • Daniel C. Wiener • Michael T. Jaklitsch

*And on a day we meet to walk the line
And set the wall between us once again.
We keep the wall between us as we go. ...
He only says, "Good fences make good neighbors."
ROBERT FROST, "MENDING WALL"*

CHAPTER OUTLINE

EMBRYOLOGY

STRUCTURE AND FUNCTION

PLEURAL AND PERITONEAL ATTACHMENTS

ARTERIAL AND VENOUS ANATOMY

LYMPHATICS

DIAPHRAGMATIC INNERVATION

DIAPHRAGMATIC INCISIONS

TRAUMATIC DIAPHRAGMATIC INJURY

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DIAPHRAGMATIC PACING

ONCOLOGY OF THE DIAPHRAGM

DIAPHRAGMATIC RESECTION AND REPAIR WITH PROSTHETIC PATCH

SUMMARY

The muscular diaphragm acts as a boundary between the positive-pressure abdominal cavity and the negative-pressure thoracic cavity. Perhaps because it is a boundary structure, or perhaps because the horizontal diaphragm is poorly visualized on a plain chest radiograph and computed tomography (CT) scan, discussion of the surgical approach to the diaphragm is neglected in many surgical textbooks.

In our opinion, there is some misinformation about the surgical treatment of the diaphragm in the current literature. This misinformation seems to reflect a lack of understanding of the basic anatomy and physiology of the diaphragm. Although diaphragmatic disease is infrequent, exposure to the diaphragm is commonplace because it is visualized during every thoracic surgical procedure and most intra-abdominal operations. Therefore, the basic principles advocated by this chapter can be verified or denied in the operating room.

Two fundamental principles can be applied to all surgical approaches to the diaphragm: (1) the muscles contract in a radial manner like the spokes of a wheel; and (2) the balance of positive pressure pushing up from the abdomen and negative pressure within the thorax created by the elastic recoil of the lung during quiet expiration displaces

the central tendon into the chest, whereas contraction of the diaphragmatic muscle pulls the tendon back toward the costal margin and elevates the lower ribs, enlarging the volume of the thorax. We hope to apply these two fundamental principles in an understanding of the physiology and pathophysiology of the diaphragm. Furthermore, we believe that these two principles will allow physicians to use new technologies and to develop better operations to treat diaphragmatic disease.

EMBRYOLOGY

In utero, the diaphragm forms from the septum transversum and pleuroperitoneal folds.¹ The septum transversum is an unpaired ventral membrane that separates the pericardium from the remainder of the thorax and creates the central trileaflet of the diaphragmatic tendon (Fig. 32-1).² One of the trileaflet tendons lies within the right hemithorax, one within the left hemithorax, and the third beneath the pericardium. The dorsolateral portions of the diaphragm start with the formation of pleuroperitoneal folds. The mesothelium of the pleura binds to the mesothelium of the peritoneum in a membrane only two

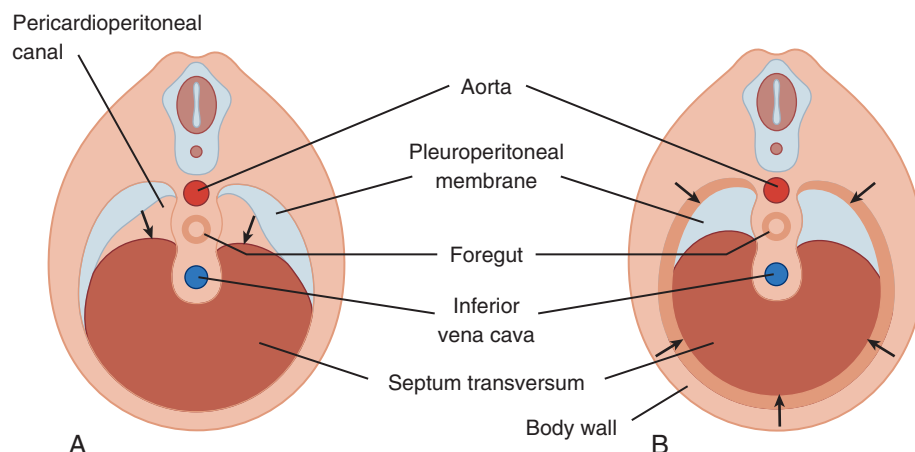


FIGURE 32-1 ■ **A** and **B**, Transverse schematic of developing embryo during weeks 5 to 7. Bilateral pleuroperitoneal folds extend anteriorly to reach the posterior edge of the septum transversum, thus forming the posterior portions of the diaphragm. The septum transversum develops into most of the central tendon. (From Larsen W: *Human embryology*, ed 2, New York, 1997, Churchill Livingstone.)

cell layers deep. Myotomes from C3, C4, and C5 then migrate from the lateral border toward the center of each hemithorax within the interspace between these two mesothelial layers in the seventh week of life. The outer rim of muscle of the diaphragm is from myotomes that carry nerve innervation from T7 through T12.² The intestines return to the abdomen from the yolk sac in the 10th week of life and will be displaced into the chest if the diaphragm has not successfully formed (a congenital diaphragmatic hernia).

STRUCTURE AND FUNCTION

This simplified embryologic description provides several fundamental concepts of diaphragm function and pathology. Muscle contraction is in a radial manner along the lines of migration of the myotomes. Thus, fiber shortening is along the lines of a wheel spoke, between the central tendon and the circumferential rib cage. Furthermore, any congenital loss of muscle or tendon may present as a hernia within the diaphragm.

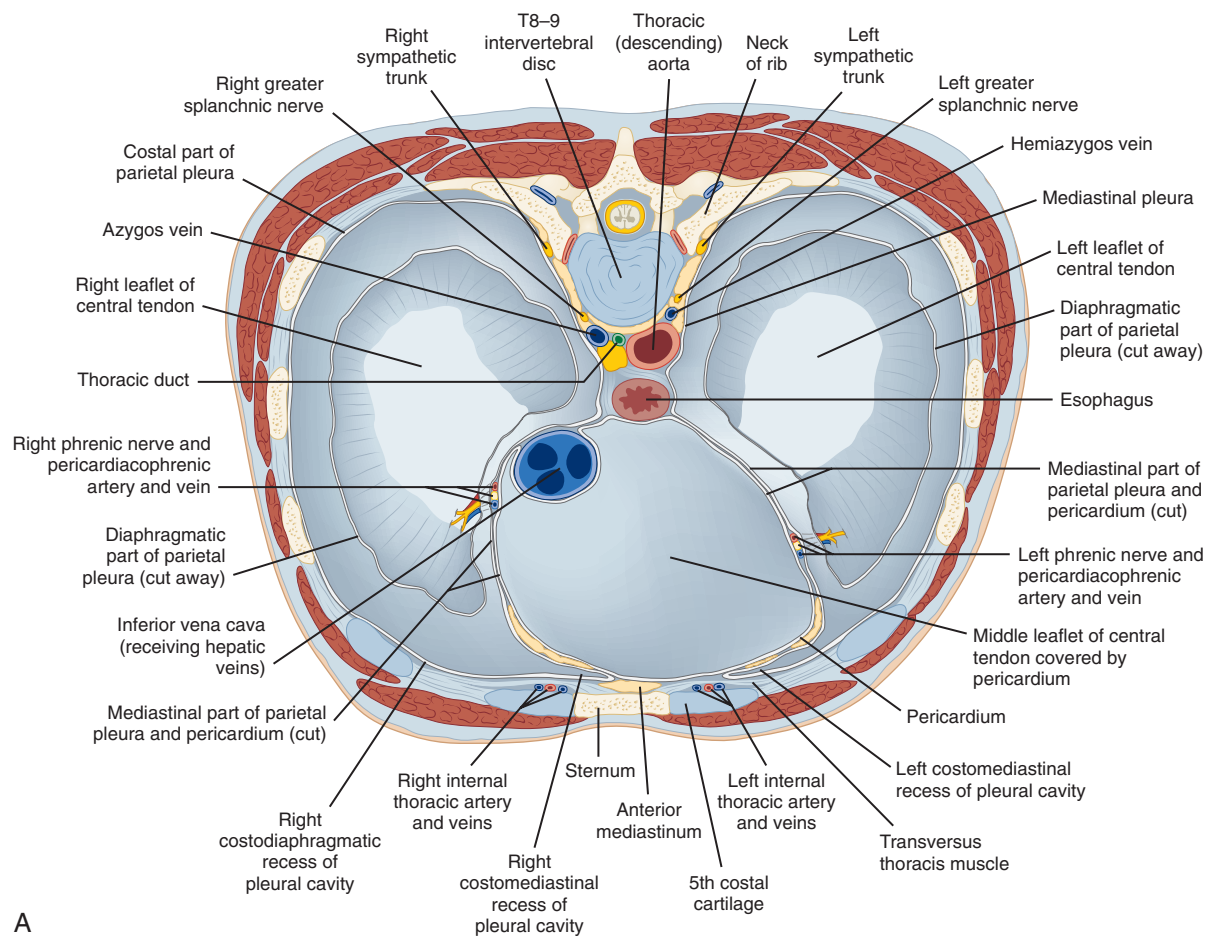
In the adult, each hemidiaphragm resembles the surface of an upside-down fairway wooden golf club. The fan-shaped tendon is like the flat metal sole plate, and the circumferential muscle curves away into the sulcus like the curved wooden club head. The muscle fascicles of the crus coalesce and attach to the lumbar spine, just as the wooden club curves down to attach to the metal shaft.

The diaphragm has three natural openings (Fig. 32-2). The aortic opening is the most posterior of the three and is formed from fibers composing the right and left diaphragmatic crura.³ This tunnel is actually behind the diaphragm, not within it, and contains the aorta, azygos vein, and thoracic duct. The esophageal hiatus is slightly more ventral from the aortic hiatus and consists of fibers passing between the aorta and the esophagus toward the right crus and fibers converging on the pericardial tendon. The opening of the inferior vena cava lies within the confluence of the tendons of the right hemithorax and the tendon beneath the pericardium.

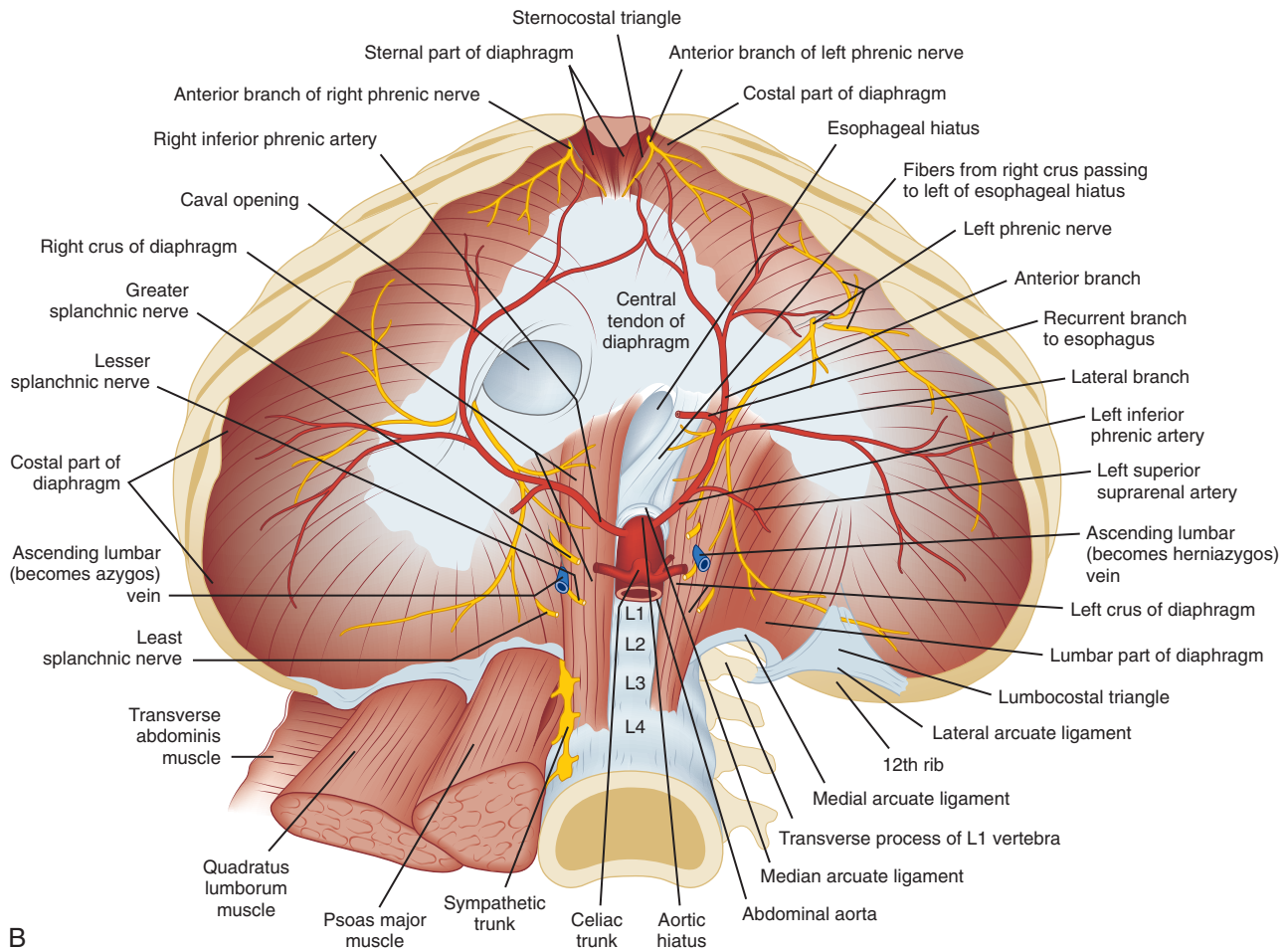
The fan-shaped muscle of the diaphragm arises from the internal circumference of the thorax, with attachments to the sternum, the lower six or seven ribs, and the vertebral bodies of the lumbar vertebrae. Posteriorly, the muscle fibers originate from the aponeurotic arch of the ligamentum arcuatum externum, which overrides the psoas and quadratus lumborum muscle. Laterally, the fibers of the diaphragm interdigitate with slips from the transversalis muscle of the abdomen as they originate from the ribs.³ The right crus is larger and longer than the left and arises from the bodies of the upper three or four lumbar vertebrae. The left crus arises from the upper two lumbar vertebral bodies.

During inspiration, the first rib is elevated and fixed by the scalene muscles of the neck. The external intercostal muscles raise, in turn, each of the lower ribs. Raising these ribs, like a bucket handle that is attached to the sternum and vertebral column, enlarges the thorax and creates the negative pressure that ventilates the lung.³

The diaphragm is the major muscle of inspiration.⁴ In the resting state, the central tendon is displaced cephalad into the thorax by the positive intra-abdominal pressure. During contraction, the radial muscle fibers pull the tendon down toward the abdominal cavity like a drum-head. This further augments the negative intrathoracic pressure and further increases the positive pressure in the abdomen. The diaphragmatic crura contribute to the magnitude of displacement of the central tendon. In fact, if there were only circumferential attachments to the rib cage, the diaphragm would be limited in its ability to displace the lower ribs and to enlarge the thoracic cavity. The thicker fascicles of the crura, which lie at a 45- to 90-degree angle to the plane of the fan, pull on the anchoring lumbar spine like a lever and thus fix the central tendon in place. In descending, the fan of the diaphragm displaces the intra-abdominal viscera, which do not yield completely because they are bolstered by the anterior abdominal wall. The central tendon becomes a fixed point from which the radial muscles of the fan contract and are thus able to elevate the lower ribs. Even though the points of muscle attachment to the



A



B

FIGURE 32-2 ■ Superior (A) and inferior (B) views of the diaphragm, including phrenic nerve anatomy. The intradiaphragmatic course of the phrenic nerves is often difficult to visualize at the time of surgery. Familiarity with the nerve's path as it traverses the muscle is helpful in deciding where to make diaphragmatic incisions.

lumbar spine are more caudal than the attachments to the rib cage, the domed tendon acts as a fulcrum cephalad to the attachments to the rib cage. In fact, contraction of the diaphragm can raise the lower ribs only if the intra-abdominal viscera are in situ and not if the organs have been removed.³ Injuries to the crura have a more disproportionate effect on the respiratory function of the ipsilateral diaphragm than a similar injury to the peripheral muscle.

A forced inspiration descends the central tendon one or two rib interspaces. Under normal respiration, each hemidiaphragm provides between 15% and 25% of respiratory muscle function, with each side of the combined intercostals providing the remaining percentage.^{5,6} Under strained respiration, however, the diaphragm can increase its workload to provide up to 80% of the work of breathing.

PLEURAL AND PERITONEAL ATTACHMENTS

The pleura adheres tightly to the top surface of the diaphragmatic central tendon and most of the musculature. It is impossible to separate the pleura from the central tendon of each hemidiaphragm. As the pleura curves off the chest wall and folds back on itself on the surface of the diaphragm, there is a circumferential diaphragmatic recess of approximately 1 cm that does not contain pleura.⁷ This recess of uncovered diaphragm is used to good advantage during an extrapleural dissection when the surgeon wraps his or her fingers into this recess and pulls downward, thus exposing the diaphragmatic musculature for division (Fig. 32-3).

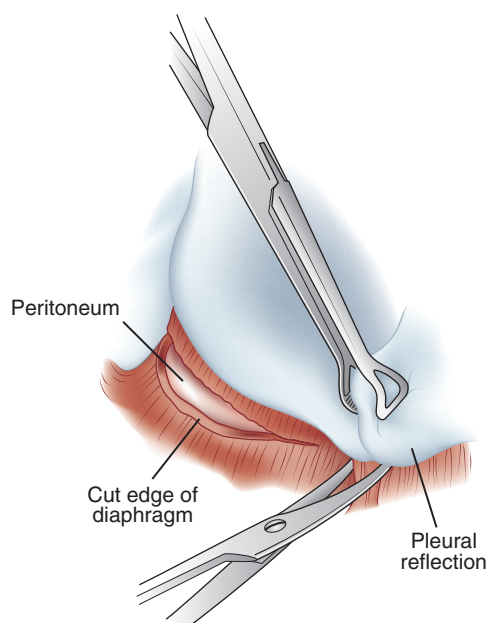


FIGURE 32-3 ■ The parietal pleura folds off the rib cage and onto the diaphragm but does not extend into the deep recess of the diaphragmatic sulcus. A bare area of diaphragmatic muscle can be exposed with traction on the parietal pleura.

The peritoneum is less adherent to the undersurface of the diaphragm and can be bluntly mobilized off the diaphragm during extraperitoneal approaches to the abdominal aorta. The plane of dissection lies between the inferior phrenic artery and vein on the muscle side and the peritoneal membrane. The peritoneum separates from the central tendon of the right diaphragm to form the falciform ligament and produces an area directly under the central tendon that does not have peritoneal covering. This is known as the bare area.

ARTERIAL AND VENOUS ANATOMY

The superior phrenic arteries are located on the thoracic surface of the diaphragm. They are small branches from the lower thoracic aorta and traverse the posterior diaphragm over the top portion of each crus close to the mediastinum.³ They terminate in small anastomoses with the musculophrenic and pericardiophrenic arteries, which are both branches from the internal mammary artery. These two arteries also supply blood to the phrenic nerve and the pericardial fat pad.⁸

The inferior phrenic arteries lie on the undersurface of the crus and the dome of the diaphragm (Fig. 32-4). They are small paired vessels with frequent anatomic variations. They can originate separately or as a common trunk from the aorta above the celiac artery or from the celiac artery itself. Alternatively, a common trunk arising from either the aorta or the celiac artery gives rise to these two arteries. On occasion, one vessel originates from the aorta and the other emerges from one of the renal arteries. Diverging near the crura, the inferior phrenic arteries then course obliquely superior and lateral

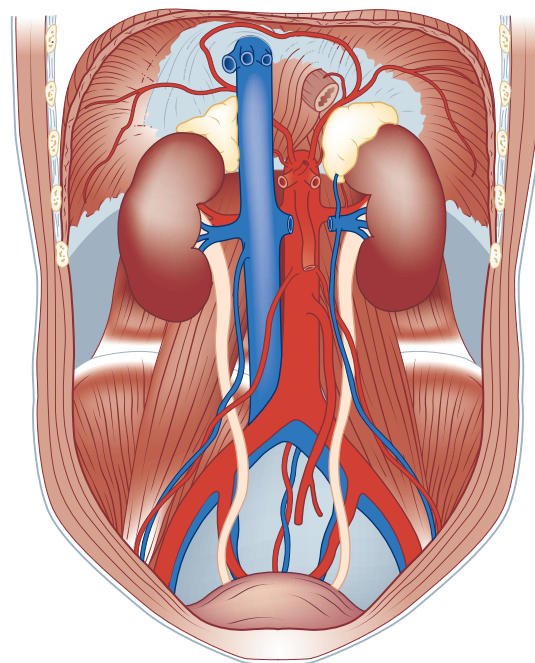


FIGURE 32-4 ■ Arterial anatomy of the inferior diaphragmatic surface.

along the inferior surface of the diaphragm. The left inferior phrenic artery passes posterior to the esophagus and then runs anteriorly along the lateral side of the esophageal hiatus. The right inferior phrenic artery passes behind the inferior vena cava.³

Close to the posterior aspect of the central tendon, both the left and the right inferior phrenic arteries divide into a medial and a lateral branch. The medial branch extends anteriorly, close to the mediastinum. Branches of this vessel traverse the muscular portion of the diaphragm to anastomose with the musculophrenic and pericardiophrenic arteries. The lateral branch of the inferior phrenic artery courses laterally and forms anastomoses with the lower intercostal arteries. The left inferior phrenic artery provides a minor contribution to the blood supply of the lower esophagus. Both right and left inferior phrenic arteries have branches to the ipsilateral suprarenal gland; these branches are called the right and left superior suprarenal arteries.³

In general, the venous anatomy in this region parallels that of the arteries. The superior phrenic veins are small and drain anteriorly to the internal mammary vein. The much larger inferior phrenic veins parallel the course of the inferior phrenic arteries. The right vein empties directly into the inferior vena cava. The left vein usually has two branches, one of which drains into the left renal or suprarenal vein, the other of which passes anterior to the esophageal hiatus and empties into the inferior vena cava.³

LYMPHATICS

The lymphatics of the diaphragm drain toward the internal mammary chain anteriorly and the thoracic duct posteriorly. Smaller lateral lymphatic branches follow the course of the intercostal vessels along the lateral and posterior margins of the chest wall.³ Although these vessels are rarely seen in the nonpathologic state, engorged vessels are frequently seen on both upper and lower surfaces of the diaphragm in patients who have congenital heart disease with elevated central venous pressures and in primary pathologic conditions of the lymphatics, such as cavernous lymphangioma.

DIAPHRAGMATIC INNERVATION

The phrenic nerve originates from the C3, C4, and C5 nerve roots and then enters the chest anterior to the subclavian artery. On the left side, the nerve lies medial to the internal mammary artery 64% of the time; on the right side, it lies medial to the internal mammary artery only 46% of the time.⁹ Thus, the left nerve is more susceptible to injury during mobilization of the left internal mammary artery through a median sternotomy incision.

Most diaphragmatic muscle originates from cervical myotomes innervated by fibers from the spinal nerve roots at cervical levels C3, C4, and C5. These fibers join and form the phrenic nerve, which elongates as the septum transversum migrates caudally. There is, however,

an outer rim of diaphragmatic muscle that originates from migrating mesenchymal cells of the nearby body wall innervated by spinal nerves from thoracic levels T7 to T12. In addition, a contribution from mesenchyme associated with the foregut at levels L1 to L3 coalesces to form the right and left crura.^{2,3}

Despite the contributions from the thoracic and spinal nerve roots, most of the diaphragm is innervated by the phrenic nerve. Although the origin of the phrenic nerve and its proximal course through the mediastinum are well known, the distal extent of the nerve as it branches into the diaphragm proper is not as well described. In 1956, Merendino and colleagues¹⁰ published the most descriptive and often-cited reference regarding this intradiaphragmatic portion of the phrenic nerve. Their anatomic findings and frequently adapted schematized drawings are based on electrical stimulation studies and gross dissection in dogs as well as on intraoperative dissection of approximately 40 human diaphragms.

The phrenic nerve usually divides at the level of the diaphragm or just above it. The right phrenic nerve enters the diaphragm just lateral to the inferior vena cava within the central tendon. The left phrenic nerve enters lateral to the left border of the heart just anterior to the central tendon within the muscle itself. The intradiaphragmatic course of the phrenic nerve can be predicted, even when it is not directly seen, by knowing the distribution of the four main motor divisions. The phrenic nerve first splits into an anterior and a posterior trunk (see Fig. 32-2B). The anterior trunk subsequently divides into a sternal and an anterolateral branch near the anteromedial border of the central tendon. The posterior trunk likewise divides into a crural and a posterolateral branch along the posteromedial border of the central tendon. The sternal and crural branches are short and continue to run in an anteromedial and posteromedial direction, respectively. The anterolateral and posterolateral branches are much longer and run close to the muscular fiber insertions into the central tendon. These two branches innervate most of the diaphragm. Their anatomic relation to one another is often described as a pair of handcuffs or manacles. These branches are often within the muscle layers and are not readily visible.

DIAPHRAGMATIC INCISIONS

Diaphragmatic incisions can be made in various locations. Certain areas of the diaphragm can be incised safely without causing significant damage or loss of function. Other regions are likely to result in bleeding, structural weakness, or diaphragmatic hemiparesis if they are incised or cauterized inappropriately.

Diaphragmatic incisions can be divided into three groups: circumferential, central tendon, and radial. Circumferential incisions in the periphery result in little loss of function. These circumferential incisions, however, must be at least 5 cm lateral to the edge of the central tendon to avoid the posterolateral and anterolateral branches of the phrenic nerve. These incisions can be difficult to realign correctly after a long operation. Placement of surgical clips on each side of the muscular

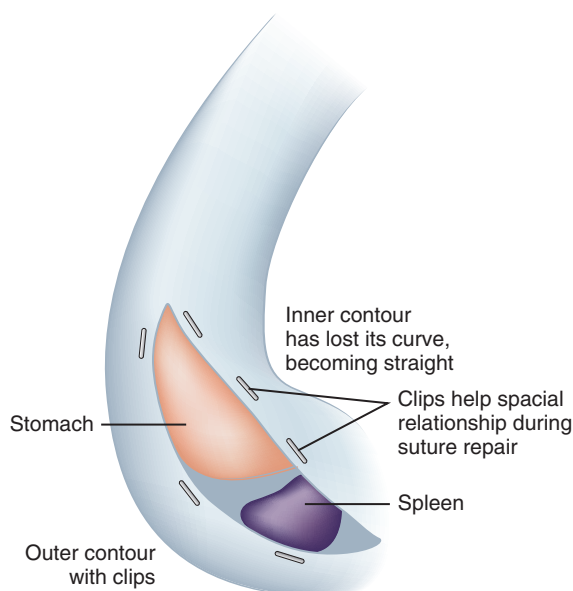


FIGURE 32-5 ■ Curvilinear diaphragmatic incision between strategically placed surgical clips. Diaphragmatic incisions disrupt the radial tension and distort the muscular anatomy. Placement of surgical clips before incision facilitates closure with proper realignment of the diaphragmatic musculature.

incision can greatly facilitate the correct spatial orientation on closing (Fig. 32-5).

Incisions in the central tendon, as far centrally as within 2 cm of the entrance of the phrenic nerve, do not interrupt any major branch of the nerve itself. This type of incision can provide excellent visualization of the abdomen from the thorax, and vice versa. These incisions are easy to open and to close.

A transverse radial incision made from the midaxillary line centrally is relatively safe because it courses between the distal aspects of the anterolateral and posterolateral branches of the phrenic nerve (i.e., through the opening of the handcuffs). Radial incisions from the costal margin extending all the way to the esophageal hiatus, however, may result in segmental diaphragmatic paralysis if the incision transects the crural or posterolateral branches of the phrenic nerve.

TRAUMATIC DIAPHRAGMATIC INJURY

Both blunt and penetrating trauma can injure the diaphragm. Penetrating injuries to the lower thorax and upper abdomen place the diaphragm at risk of injury. The nipples, marking the most cephalad displacement of the central tendon, and the base of the 12th rib, marking the most caudal attachment of the muscle, are important landmarks that help the surgeon identify a potential diaphragmatic injury from penetrating trauma. Any missile traversing this area or knife wound within this zone may create a diaphragmatic laceration.

Blunt trauma that dramatically increases the intra-abdominal pressure may cause a central tendon rupture of the diaphragm. A common mechanism for rupture is seen in patients involved in high-speed motor collisions

who are wearing seat belts. Imminent awareness of an approaching accident can cause inspiration with tensing of abdominal muscles and contraction of the diaphragm. This increases intra-abdominal pressure and, in combination with additional force from the seat belt at impact, can result in rupture of the diaphragm at the dome or central attachments. Diaphragmatic rupture occurs in 0.8% to 1.6% of patients arriving at the emergency department with blunt trauma.¹¹ Because the liver protects the right hemidiaphragm from this mechanism of injury, most diaphragmatic ruptures from blunt trauma are recognized on the left side.

An abnormal diaphragm contour on plain chest radiograph or CT scan after a traumatic injury should raise the possibility of diaphragmatic injury. These findings may be easier to appreciate if a radiopaque nasogastric tube is in place at the time of imaging. Nonetheless, radiographic findings may still be as subtle as blurring of the costophrenic angle. Because of this subtlety, delayed diagnoses are not uncommon. Review of the literature suggests that the diagnosis is missed in as many as 66% in some series.¹² One reason for this may be that traditional CT imaging has yielded poor detection of diaphragmatic injury; however, reports of new helical CT scanners show increasing sensitivity as high as 84%.¹³ If clinical suspicion is high, minimally invasive techniques with laparoscopy or thoracoscopy may be used based on their improved detection of occult diaphragmatic laceration, especially in penetrating left thoracoabdominal injuries.

Diaphragmatic injuries that are diagnosed promptly should be explored from the abdomen with either laparotomy or laparoscopy because of the frequent association of other abdominal organ injury (liver, spleen, stomach, kidney). During insufflation, the surgeon must be prepared to place an emergent chest tube in the event that a tension pneumothorax arises from communication through the diaphragmatic hole. In those cases with a significant delay in diagnosis, injuries generally should be explored from the thorax, with either thoracotomy or thoracoscopy, because the herniated abdominal structure is frequently adherent to the ipsilateral lung.

Diaphragmatic injuries need to be repaired when they are recognized. Repair corrects or prevents complications such as respiratory compromise or herniation of abdominal viscera with the associated risk of incarceration and strangulation. If no other indication for surgical exploration is present and the diagnosis of diaphragmatic rupture remains in question, exploratory thoracoscopy, a simple and effective diagnostic procedure, should be considered. Small tears can be sutured with thoracoscopic techniques after reduction of abdominal contents displaced across the defect. Thoracoscopic exploration and repair require general anesthesia with single-lung ventilation. Timing therefore depends on underlying pulmonary and neurologic function.

Lateral avulsions of the diaphragm may require reattachment to a rib at a higher level. Diaphragmatic lacerations can be closed with nonabsorbable heavy suture, with care taken to prevent injury to the main phrenic nerve branches. If the defect is large and cannot be repaired primarily, a prosthetic mesh is a good option. In

the presence of heavy contamination during damage control surgery, use of an absorbable or biological substitute is preferable to prevent continued retraction of the defect and pleural contamination. At reoperation, if there is no remaining soilage, the mesh can be exchanged for a permanent prosthetic.

DIAPHRAGMATIC ELEVATION

The two most common causes of diaphragmatic elevation are congenital eventration of the diaphragm and phrenic nerve palsy (Fig. 32-6).

Congenital eventration of the diaphragm is a spectrum of disorders that share the underlying cause of impaired fetal myotome migration.¹⁴ Mild cases may lack only the central tendon, whereas severe cases may lack the central tendon as well as the entire muscular diaphragm. The area of congenitally missing muscle tissue is usually closed with a fused single membrane of pleura and peritoneum. This membrane is generally displaced within the ipsilateral hemithorax because of the absence of muscle.

Phrenic nerve paralysis in the child can be caused by a viral palsy, an iatrogenic injury (typically after pediatric thoracic surgery), or a traction injury to the phrenic nerve at the base of the neck after a forceps delivery. In addition, there can be congenital absence of the phrenic nerve.

Diaphragmatic elevation is poorly tolerated in neonates. The flaccid diaphragm compresses the lower lobe of the ipsilateral lung. In addition, if there is a large displacement of abdominal components into the negative-pressure thorax, this bulk mechanically shifts the mediastinum with compression of the contralateral lung. Thus, there is atelectasis of the ipsilateral lower lobe, compression of the left atrium and impediment to pulmonary venous blood flow, and contralateral lung compression with additional atelectasis.¹⁵ The end result may be complete pulmonary failure requiring intubation. Mechanical ventilation reinflates the atelectatic lungs and balances the mobile mediastinum. The ipsilateral diaphragm is shifted into the abdomen.

Surgical intervention is almost mandatory in symptomatic infants with eventration, but in the adult

population, the indications for surgery are less clear. In children, plication is readily successful in achieving weaning from ventilation. In adults, however, this is not the case. In addition, regarding nonventilated patients, the condition is better tolerated in adults, and in general, only patients with progressive symptoms should be offered surgery. Causes of eventration in adults are usually related to phrenic nerve involvement through spinal cord disease, cervical trauma, infiltration of the nerve by tumors or lymph nodes, and iatrogenic injury. In certain conditions, conservative management will eventually lead to recovery of function; however, in the remaining patients, plication remains a low-risk procedure that continues to be underused. A study of patients who underwent unilateral plication by video-assisted thoracoscopic surgery (VATS) documented substantial increases in spirometry readings at 6 months after the procedure.¹⁶ The mechanism for improvement in these patients is because of increased tension of the diaphragmatic barrier between the thorax and abdomen. This allows patients to generate a more negative intrapleural pressure than is possible with a floppy, paralytic diaphragm.

Various techniques have been described in the literature for plication of the diaphragm. Severe forms of congenital eventration of the diaphragm with only a pleuroperitoneal membrane will require patching.¹⁴ A rim of rudimentary diaphragmatic tissue can generally be found around the lateral contour of the chest with enough substance to hold sutures to anchor the patch. Along the medial side, the patch can be stitched to the pericardium and the anterior thoracic spinal ligaments.

The easiest technique of plication is to place imbricating stitches within the central tendon of the diaphragm.^{17,18} If the sutures extend far enough from the edge of the diaphragmatic tendon, they can produce substantial caudal displacement of the tendon toward the abdominal cavity and allow expansion of the ipsilateral lower lobe as well as balancing of the mediastinum (Fig. 32-7).¹⁹ The central tendon can be repaired with thoracoscopic, laparoscopic, or hybrid techniques. With improved video-scopic equipment and experience, the trend toward less invasive procedures will continue and may encourage more physicians to refer their patients for surgery. Mouroux and colleagues²⁰ described a series of 12 patients

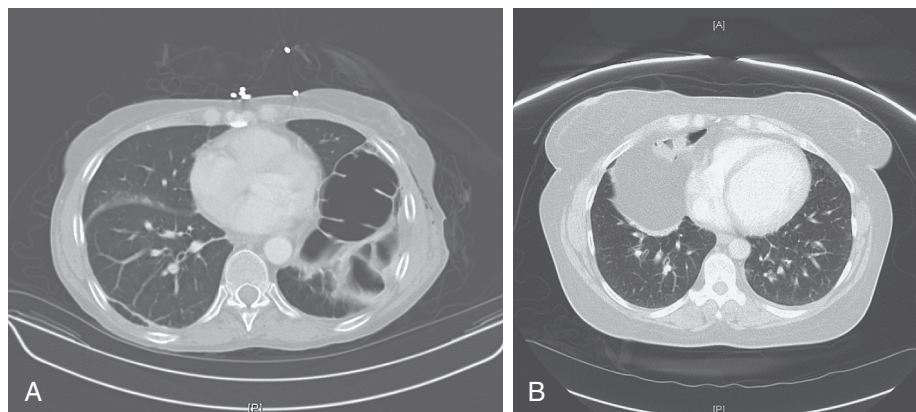


FIGURE 32-6 ■ **A**, CT scan of left diaphragmatic elevation. Note the lung tissue at the anterior and posterior thorax. **B**, CT scan of Morgagni hernia. Note the lack of lung tissue at the extreme hemithorax.

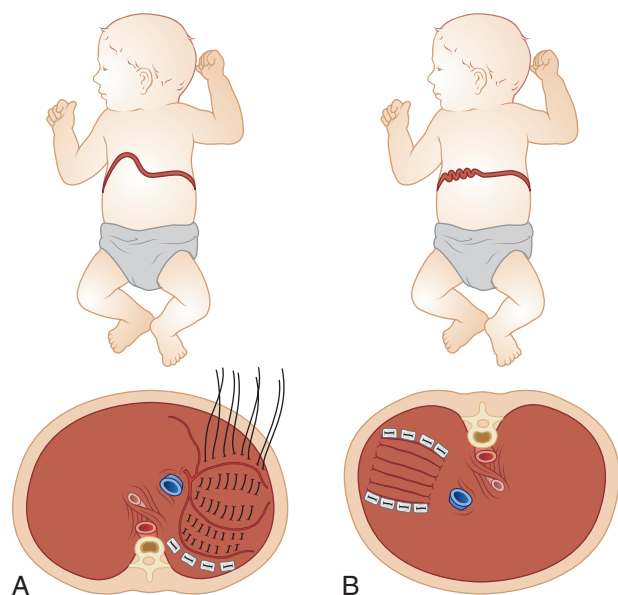


FIGURE 32-7 ■ **A** and **B**, Diaphragmatic plication by pleating of the central tendon. Sutures extend beyond the junction of the central tendon with the muscle and should not directly strike the branches of the phrenic nerve. Unfortunately, the phrenic branches lie within the muscle and frequently cannot be visualized.

who underwent thoroscopically assisted plication with a utility 5-cm incision. A Duval grasper is used to invaginate the apex of the eventration caudad, creating a fold that is closed in two layers. A VATS reproduction of the traditional pleating or “accordion” repair was performed by Freeman and colleagues¹⁶ in 22 patients with use of an Endo Stitch device (Ethicon Endo-Surgery, Cincinnati, OH) to create six to eight parallel U stitches for patients with unilateral diaphragm paralysis. Improvement in pulmonary function and quality of life was seen along with a shortened hospital stay compared with patients who underwent thoracotomy. A total thoroscopic technique with three ports has been described by Kim and associates²¹ and uses the additional adjuncts of carbon dioxide insufflation and steep reverse Trendelenburg position to push the diaphragm down and to increase the effective working space. Laparoscopic plication with four working trocars has been performed by Huttel and colleagues.²² Retention sutures are placed on the dome of the diaphragm and then used for traction. This allows creation of an intra-abdominal fold for plication with 12 to 15 U-type sutures. Finally, to counter the difficulty in placing adequate sutures through minimal access techniques, Moon and coworkers²³ reported grasping and rolling of the redundant diaphragm followed by placement of noncutting linear endoscopic staplers underneath for creation of folds that are left in situ.

Because of the rarity of diaphragmatic surgery for eventration and the multitude of presentations, a true randomized study to compare these methods is difficult, and at present, most surgeons will continue to practice the procedure with which they are most familiar. The drawback of the previous techniques, however, is that most of the pleats will fold the noncompliant central

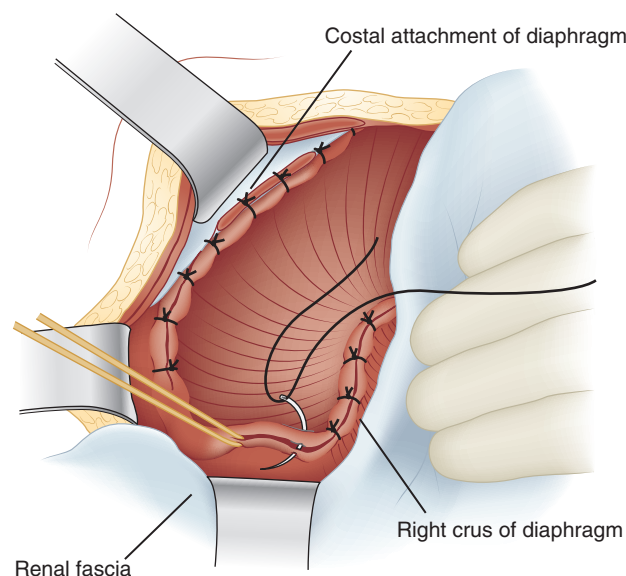


FIGURE 32-8 ■ Original description of a radial plication technique by David State in 1949. A generous subcostal incision was used, and the muscle was sewn circumferentially to the lateral chest wall and crus to make the tendon taut.

tendon. The compliant muscular remnant can be expected to stretch with time. It has been our experience that the central tendon pleating technique is associated with re-elevation of the diaphragm to the level of the hilum within several years. Long-term follow-up of this technique has included reports of recurrent diaphragmatic elevation requiring additional intervention in as many as 19% of treated patients.²⁴ Furthermore, the phrenic vessels and branches of the nerve travel near the insertion of the muscle into the edge of the tendon and cannot be visualized from the thoracic surface of the diaphragm. Yet, to adequately displace the central tendon, these stitches need to extend into the muscle area, and this places the branches of the nerve at risk of injury. For these reasons, our preference is the radial plication method, which we believe more closely approximates the natural physiology of the diaphragm.

David State first described a subcostal radial plication technique for congenital eventration of the diaphragm in 1949.²⁵ The original description of this technique included a generous incision across the right upper quadrant of the abdomen and placement of radial sutures along the muscular portion of the diaphragm, pulling it toward the lateral chest wall (Fig. 32-8). A transthoracic radial plication has also been described.^{19,26}

John Foker at the University of Minnesota has used a transthoracic radial plication technique since 1976 to treat 35 children with elevation of the diaphragm as described by Jaklitsch and colleagues.²⁷ The repairs were performed with interrupted horizontal mattress pledgeted sutures, imbricating the muscular portion of the diaphragm in a radial manner toward the chest wall through a posterolateral thoracotomy (Fig. 32-9). The plication sutures extended in an unbroken band from the xiphoid area to the vertebral body. No sutures were placed along the mediastinal pleura. The goal was to

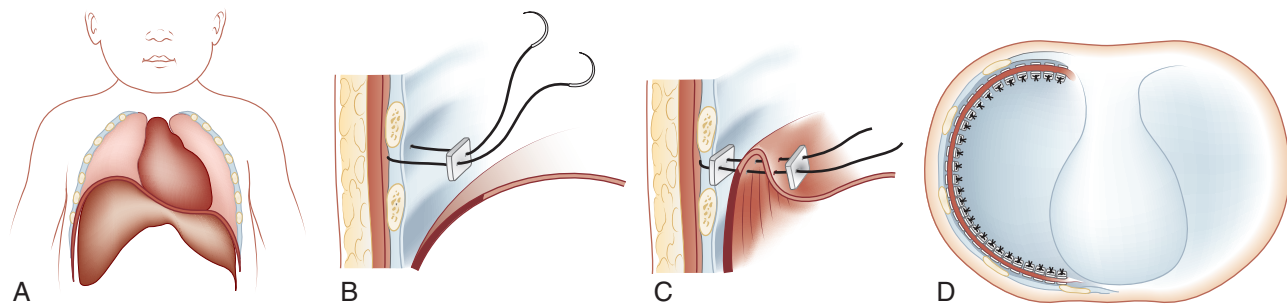


FIGURE 32-9 ■ A-D, Radial plication of the diaphragm with interrupted double-pledgeted sutures extending from the xiphoid to the vertebral spine. Each suture pleats the flaccid muscle to the lateral chest wall.

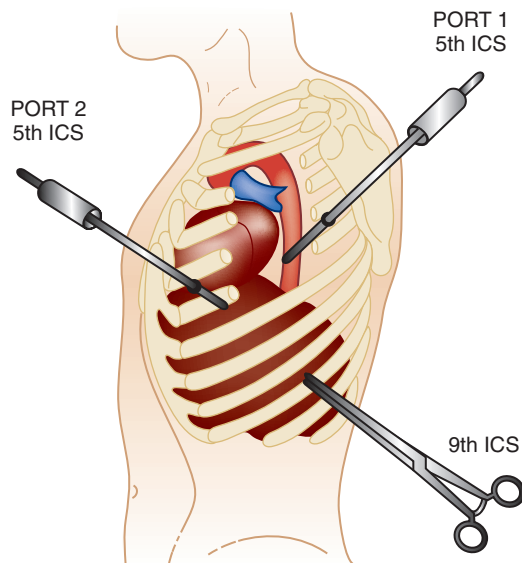


FIGURE 32-10 ■ Thoracoscopic port placement for radial plication in an adult. ICS, Intercostal space. (From Mouroux J, Padovani B, Poirier NC, et al: Technique for the repair of diaphragmatic eventration. *Ann Thorac Surg* 62:905–907, 1996.)

produce a taut diaphragm that appeared as a straight-angled line from mediastinum to chest wall on the anteroposterior view of the chest radiograph. We believe that this produces a plication that mimics the contraction of the fan-shaped muscle while minimizing injury to the branches of the nerve or vessels.

In this series, 31 of the 36 operations (86%) led to extubation within 3 days, even though 15 patients had been ventilator dependent before plication.²⁷ There were no deaths within 30 days, and no morbidity was directly attributed to plication. Only one patient (3%) suffered a recurrence requiring repeated plication. Twenty-six of these patients survived long term (median, 12 years at time of analysis), and 18 of these patients were reevaluated with diaphragmatic ultrasound examination in 1996. Some degree of function had returned to 14 (78%) of the diaphragms.

We have extended this technique, with some success, to a thoracoscopic approach in adults with elevated hemidiaphragms (Fig. 32-10). Currently, we use a three-port technique, with an anterior and posterior port at the sixth and eighth intercostal space, respectively. The third port is subcostal and is used to pass an O-ring clamp through the abdominal cavity to grasp the undersurface of the

central tendon of the diaphragm. This allows the caudal displacement of the muscle to see the muscular imbrications for plication. The posterior thoracic port is then used to plicate the anterior and lateral borders of the muscle; the anterior thoracic port is used to plicate the lateral and posterior borders.

DIAPHRAGMATIC HERNIAS

Several types of hernias involve the diaphragm, including hernias of the foramen of Morgagni, hernias of the foramen of Bochdalek, and central tendon and paraesophageal hernias.

The foramen of Morgagni is a potential space that lies in the parasternal area where the internal mammary vessels pass from the thoracic cavity into the upper abdominal cavity. Slips of diaphragmatic muscle insert medially onto the back of the xiphisternum and laterally to the costal margin (see Fig. 32-2B). This produces a small triangular gap of muscle tissue around the mammary vessels.

In the presence of increased intra-abdominal pressure, omentum, small intestine, or colon can pass through this defect into the anterior mediastinum. Dull pain along the right subcostal area is the most common presenting symptom. Other hernias are found incidentally on radiographic imaging for unrelated reasons. Foramen of Morgagni hernias are more common in women, in obese individuals, and on the right side because the left side is partially occluded by the pericardial sac. These hernias appear as a density in the parasternal area. CT scans of the chest are helpful in distinguishing these hernias from the pericardial fat pad or a pericardial cyst (see Fig. 32-6B).²⁸

Foramen of Morgagni hernias are frequently repaired from an abdominal approach. Both laparoscopic and thoracoscopic repairs have been described.^{29,30} A small rim of the internal transthoracic muscle is frequently found behind the sternum and is sutured to the diaphragm to close the hernia. We perform this closure with interrupted mattress sutures using a heavy nonabsorbable suture. Alternatively, the posterior rectus sheath or a rib can be used to help close the hernia. Rarely, the hernia cannot be closed without tension, and a patch is used.

Foramen of Bochdalek hernias can occur in adults. These are rare disorders that either are found incidentally on radiographs for other reasons or are recognized after

organ incarceration or volvulus.³¹ Most of these hernias are small and are repaired primarily. This can be performed with minimally invasive techniques. Larger defects may require a patch.

Congenital hernias can occur in each of the three central tendons of the trileaflet diaphragm and can be confused radiographically with tumors lying over the dome of the diaphragm. When the hernia occurs in the central trileaflet, it is frequently associated with a congenital absence of the inferior pericardial sac. This can lead to the phenomenon of abdominal contents within the pericardial sac. Repair of these hernias is straightforward because of the laxity of the central tendon. Primary repair is frequently possible. Very large defects may require patching.

The most frequent diaphragmatic hernia is the paraesophageal hernia. The most commonly used descriptive classification system defines four types of hiatal hernias. A sliding or type I hiatal hernia accounts for as many as 95% of paraesophageal hernias and involves the circumferential weakening of the phrenoesophageal ligament with symmetric displacement of the proximal stomach into the thoracic cavity. This is frequently associated with a shortened esophagus. Most type I hernias are asymptomatic and are discovered incidentally on radiographic studies or endoscopy. When symptoms occur, they are related primarily to the associated loss of lower esophageal sphincter tone and gastroesophageal reflux. The likelihood of these symptoms increases in proportion to the size of the hernia.³²

A paraesophageal or type II hiatal hernia involves a focal weakening of the phrenoesophageal ligament. These hernias tend to occur either anterior or lateral to the esophagus. The gastric cardia remains within the abdomen, and the lower esophageal sphincter remains at the level of the diaphragm. A portion of the gastric fundus, however, rolls through the defect into the chest and produces extrinsic compression of the lower esophagus.

A mixed or type III hiatal hernia has both a sliding and a rolling component. The lower esophageal sphincter has been displaced up into the thorax because of a shortened esophagus. A portion of the gastric fundus then rolls through the enlarged hiatal hernia, producing extrinsic compression of the distal esophagus as well. We agree with Pearson and colleagues³³ that a type II hernia with the gastroesophageal junction below the diaphragm is rarely seen, and type I and type III with the gastroesophageal junction displaced into the thorax are far more common.

Type IV hernias are associated with a large enough defect in the phrenoesophageal membrane to allow other organs, such as the colon, spleen, and small intestine, to enter the hernia sac and the chest cavity. Unrepaired type I, II, or III hiatal hernias can progress, resulting in a large defect between the crura of the diaphragm. As the hernia enlarges, the stomach has a tendency to migrate into the thoracic cavity. The positive pressure in the abdomen and the negative thoracic pressure can lead to the herniation of the greater curvature of the stomach into the right side of the chest and twisting of the stomach on itself. This gastric volvulus produces a gastric outlet obstruction. If

air or gastric juices distend the proximal stomach above the gastric outlet, the intraluminal pressure can exceed the perfusion pressure of the organ. This leads to ulceration, bleeding, and the potential for gastric rupture. Recognition of a gastric volvulus or displacement of intra-abdominal organs into the chest is an indication for urgent surgical repair. Because of this potential life-threatening complication, most surgeons recommend repair of these hernias even in the asymptomatic patient.

The initial step in operative repair of a hiatal hernia is to clearly delineate the muscular limits of the hiatal defect. Some experienced surgeons advocate a transthoracic approach for long-standing hernias to facilitate lysis of inflammatory adhesions under direct vision but at the cost of more postoperative pain. More recently, laparoscopic approaches have proved somewhat superior in this goal of identifying the limits of hiatal hernia because of the cephalad displacement of the diaphragmatic muscle during insufflation of carbon dioxide into the abdomen, making the two crura of the diaphragm taut. This tautness and extra space between the stomach and the diaphragmatic muscle greatly facilitate the dissection.

The fat between the proximal stomach and the diaphragmatic muscle needs to be removed. Dividing the muscular fibers of the left diaphragmatic crus in a straight lateral manner can enlarge tight hiatal rings. This will divide neither the branches of the phrenic nerve that lie far anteriorly nor the phrenic vein, which lies medially. The left inferior phrenic artery may be divided without causing ischemia because anastomosing vessels continue to perfuse the area. The enlargement of the tight hiatal ring can greatly facilitate the reduction of a large bulky hernia. Alternatively, a red rubber catheter can be passed across the neck of the hiatal hernia and air insufflated within the sac to facilitate reduction of the hernia contents. This breaks the natural vacuum that occurs in trying to reduce the abdominal contents through the hiatal neck.

The diaphragmatic defect needs to be closed as part of the surgical repair of the hiatal hernia. In fact, it is the pathologic process of the diaphragm that has contributed to the disease of gastroesophageal reflux by disrupting the lower esophageal sphincter. Closure of the dilated esophageal diaphragmatic hiatus is frequently performed by placement of sutures reapproximating the right and left crura of the diaphragm. In large hiatal hernias, this defect can be sizable. If the fibers of the diaphragmatic crura have been thinned, we frequently use pledgeted nonabsorbable sutures to reapproximate the right and left muscle bundles. The tenet of all hernia repairs is to prevent tension at closure, and some defects may require patch or mesh reinforcement. Two randomized studies comparing mesh with primary crural closure are available. Frantzides and colleagues³⁴ randomized 36 patients to closure with or without a polytetrafluoroethylene (PTFE) mesh onlay. At 3-year follow-up, 22% in the primary group had hernia recurrence compared with 0% in the mesh group. Another study with 50 patients used polypropylene rather than PTFE. The simple cruroplasty cohort had a 26% recurrence rate compared with 8% in the mesh group.³⁵

A late complication of the use of prosthetic mesh for this indication has been mesh migration and esophageal or gastric erosion, often ending in sepsis and the need for esophageal exclusion. Biological mesh options now exist that decrease the risk of this complication. The use of porcine small intestine submucosa has been described for closure of large hiatal defects.³⁶ This is now our preferred approach to reinforcement of the crura associated with giant paraesophageal hernias. A radial incision leading to a keyhole slit is made in the mesh to accommodate the esophagus, and the mesh incision is then closed with endoscopic placement of sutures. The material allows a remodeling of the hiatus and is eventually incorporated with the neighboring tissue so that a permanent material is not left in place.

The postoperative complication rate after laparoscopic antireflux surgery is approximately 8%. Between 3% and 6% of all patients undergoing antireflux surgery require reoperation for recurrent, persistent, or new symptoms secondary to complications of the initial repair.³⁷ In one published series of 627 patients, 7% of the entire group had demonstrable anatomic failure, most of which were the result of intrathoracic migration of the wrap with or without disruption of the fundoplication.³⁸ A number of factors have been attributed to this problem, including inadequate closure of the crura, lack of appreciation of a shortened esophagus, and physiologic factors that increase intra-abdominal pressure, such as the Valsalva maneuver, coughing, or retching in the postoperative period.

We believe that one of the most common errors in the surgical repair of hiatal hernias is not recognizing that an esophagus has shortened. If the esophagus is not of adequate length to allow the fundoplication to reside within the abdomen without undue pressure, the fundoplication will likely herniate into the thorax within a few years. We have a low threshold for extending the length of the esophagus with a Collis gastroplasty to ensure that the fundoplication will lie beneath the diaphragmatic hiatus without tension.

A rare but devastating complication of fundoplication herniation into the chest from an unrecognized shortened esophagus is a gastropericardial fistula³⁹ (Fig. 32-11). This rare condition has an associated mortality rate of more than 50% and is seen most often in patients with prior gastroesophageal surgery. It is most likely that these fistulas originate at the site of gastric ulcerations. Approximately 3% to 5% of open Nissen fundoplication procedures are complicated by gastric ulceration. In most cases, the ulcerations occur high on the lesser curvature of the stomach, in proximity to the fundoplication, and are seen most often in patients with recurrent hiatal hernias. Fistulas from the stomach to the aorta, diaphragm, pericardium, right ventricle, and bronchus have been reported as late complications from open Nissen fundoplication.³⁹

Repair of a gastropericardial fistula involves the removal of a circle of pericardium (see Fig. 32-11) and the fistulous entry into the stomach. The muscle of the diaphragm can then be used as a pedicled muscle flap to lie between the exposed heart and the staple line along the lesser curve of the stomach. In our experience, we

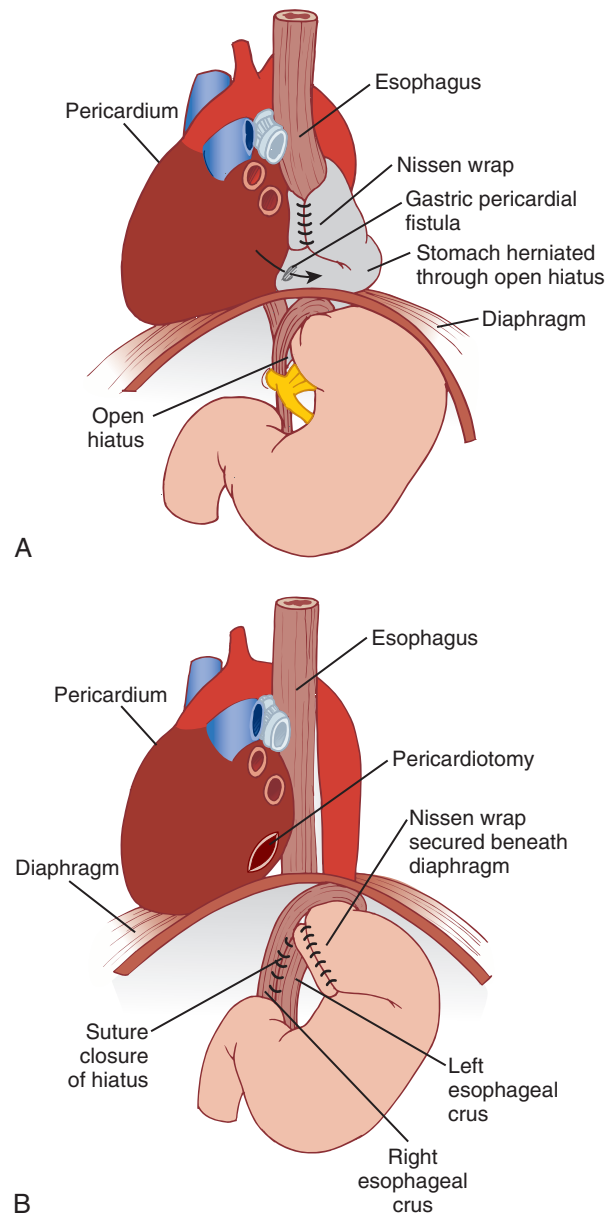


FIGURE 32-11 ■ **A**, Gastropericardial fistula is a devastating complication of a fundoplication herniating into the chest from failure to close the diaphragmatic crura. The fistula is typically along the lesser curve of the stomach distal to the fundoplication. **B**, This fistula was repaired by using the diaphragm as a muscle flap to place between the heart and the stomach. (From Murthy S, Looney J, Jaklitsch MT: Gastropericardial fistula after laparoscopic surgery for reflux disease. *N Engl J Med* 346:328–332, 2002.)

have used pledgeted sutures to close the muscles of the crura and secure the wrap beneath the diaphragm.³⁹

DIAPHRAGMATIC PACING

Diaphragmatic pacing may have a role to play for patients with compromised pulmonary function and diaphragmatic paralysis. The technology was first used clinically in 1967, and more than 700 patients with chronic hypoventilation have been treated in this manner, some

for as long as 18 years.⁴⁰ Expertise in this technique, however, is limited to a few centers. Technical details of long-term continuous pacing were mostly worked out by William Glenn of Yale. He and his colleagues rapidly moved from a successful animal model in 1964⁴¹ to treatment of a patient with central hypoventilation in 1967.⁴² Excellent detailed reviews of this subject have been published by Glenn and Koda⁴⁰ and Elefteriades and Quin,⁴³ also from Yale.

Diaphragmatic pacing has largely been supplanted by noninvasive methods of ventilatory support, including bilevel positive airway pressure and continuous positive airway pressure, particularly in the setting of temporary respiratory compromise or comorbid disease, such as chronic obstructive pulmonary disease. A select subset of patients, however, may be helped by this diaphragmatic pacing. The ideal patient for this technique has central nervous system or upper motor neuron disease and an intact phrenic nerve and diaphragm.^{43,44} The major experience with phrenic nerve pacing has come from quadriplegic patients and central alveolar hypoventilation patients. Patients with spinal cord injury above C3 are especially good candidates because the whole phrenic nerve is denervated from upper motor neurons but intact within the chest. Because pacing will not produce normal excursion of an atrophied diaphragmatic muscle, it is recommended that the pacemaker be placed soon after the neurologic insult.

The major therapeutic objective of diaphragmatic pacing is oxygenation rather than the elimination of carbon dioxide. Expiratory flow must be adequate, thus limiting the use of pacing in patients with severe chronic obstructive pulmonary disease or other conditions that have significantly altered the shape of the chest wall or diaphragm.⁴³ Sufficient diaphragmatic strength, almost normal function of the distal phrenic nerve, and satisfactory excursion of the thoracic skeleton must be demonstrated.

The topic of phrenic nerve pacing is frequently discussed in the setting of phrenic nerve palsy. The inherent lack of electrical conductivity of skeletal muscle, unlike the heart, does not allow uniform contraction of the muscle by multiple surface electrodes. An intact lower motor neuron (i.e., phrenic nerves) is thus required to deliver the electrical impulse by neurotransmitters throughout the muscle for coordinated contraction. Because axonal damage precludes conduction of electrical impulses to the neuromuscular junction, direct phrenic nerve injury is not amenable to pacing. These patients may be better treated with direct intervention (i.e., primary phrenic nerve repair or nerve transplantation with an intercostal or recurrent laryngeal nerve) or supportive measures (i.e., diaphragmatic plication, nocturnal bilevel positive airway pressure, or tracheostomy).⁴³

The best placement of the phrenic nerve pacemaker with current technology is within the upper thorax by an anterolateral thoracotomy through the third intercostal space. This allows placement of the electrode around the main phrenic trunk below the entry of the accessory nerve from the C5 nerve root, which frequently joins the phrenic nerve within the upper thorax.⁴⁵ It is important to avoid handling of the nerve because injury would

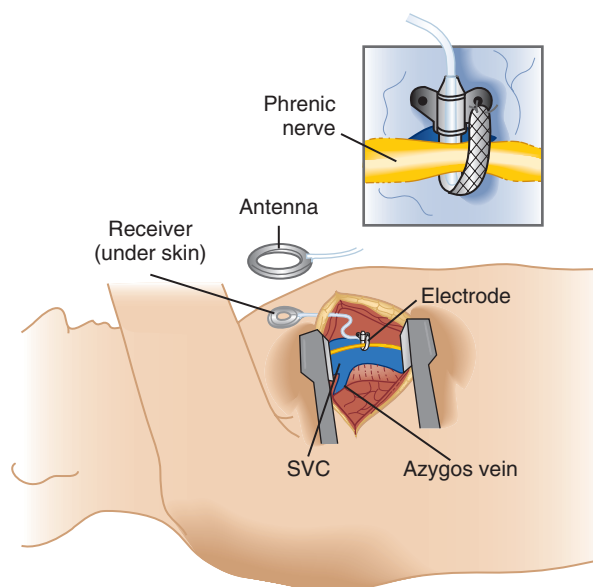


FIGURE 32-12 ■ Placement of phrenic nerve pacing lead to an intralateral thoracotomy. SVC, Superior vena cava. (From Kanaan S, Ducko CT: Disorders of ventilation: diaphragmatic pacing. In Fauci AS, et al, eds: *Harrison's principles of internal medicine*, ed 17, online update, New York, 2008, McGraw-Hill.)

prevent accurate pacing. The site of implantation of the electrode is above the azygos vein and superior vena cava on the right (Fig. 32-12).⁴⁴ In the left side of the chest, the preferred site is between the aortic arch and the pulmonary artery.⁴⁶ The wire attached to the electrode is then tunneled to the receiver in the chest wall. Although the nerve trunk is easily found in the neck, the phrenic nerve is missing the C5 accessory nerve at this level in 76% of patients.⁴⁷ Furthermore, placement of the electrode over the superior vena cava avoids direct conduction of the electrical signal to the atrium, which can occur lower in the thorax. Electrodes can now be placed thoracoscopically.⁴³ Implantation through the cervical approach has largely been abandoned because of its inability to bring the pacing electrode in proximity to the C5 branch of the phrenic nerve.

The phrenic nerve should be tested transcutaneously for patients with a central nervous system cause of hypoventilation to verify intact nerve and muscle function. This test was described by Shaw and colleagues in 1975.⁴⁸ An indifferent electrode is placed on the skin of the neck, and a pacing electrode delivering 5 to 10 mA for 1 msec is placed at the lateral border of the sternocleidomastoid muscle. A forceful contraction of the diaphragm signifies normal or almost normal diaphragmatic function. Forceful diaphragmatic movement can be observed by physical examination. Quantification of diaphragmatic excursion can be made by fluoroscopy or ultrasonography. An excursion of at least 5 cm should be seen for pacing intervention to be considered.^{43,44}

The initial diaphragmatic pacemaker consisted of a monopolar electrode attached to an antenna and a radio-frequency generator. A bipolar electrode would be used if the patient also has a cardiac pacemaker. To overcome the lack of natural electrical conductivity of the skeletal

muscle of the diaphragm, a train of pulse currents with increasing amplitude is delivered by the pacemaker to stimulate all axons within the nerve.⁴³ One consequence of the pulse train to induce uniform muscle contraction is that every fascicle is stimulated to contract. Because 24% of the fascicles are fast-twitch, fatigue-prone type IIB fibers,⁴⁹ full-time pacing can occur only after a period of muscle conditioning. Part-time pacing in quadriplegic patients does not start for 14 days so that pleural effusion can be avoided.⁴³ Pacing starts at 15 minutes per hour and changes every 7 to 14 days. Conditioning thus takes 3 to 6 months. A permanent tracheostomy is recommended for all patients on full-time, continuous phrenic nerve pacing.⁴³

Four pacing systems are available worldwide: the Avery model (Avery Laboratories, Glen Cove, NY), the Atrostim (Atrotech, Tampere, Finland), the Vienna Phrenic Pacemaker (MedImplant Biotechnisches Labor, Vienna, Austria), and the NeuRx Diaphragm Pacing System (DPS; Synapse Biomedical Inc., Oberlin, OH).⁴⁴ The first three models have a two-part system with an extracorporeal radiofrequency generator and implantable receiver-nerve electrode. Further technological improvements may make diaphragmatic pacing a more generalizable technique for patients with long-term but ultimately reversible dysfunction, such as viral palsies and iatrogenic injuries. The largest reported series of diaphragmatic implantation pacers observed 165 patients; 68% were paced for less than 5 years, 20% for 5 to 10 years, and 10% for 10 to 15 years.⁵⁰

Onders and colleagues⁵¹ have developed a separate diaphragm pacing system that can be implanted through a laparoscopic technique. For this form of pacing to be effective, an intact phrenic nerve is still required to recruit muscle contraction by conduction pathways. After laparoscopic ports are placed, the initial step is to map the diaphragm with a specially developed probe to see which point causes the greatest diaphragmatic excursion. Once this point has been identified, electrodes are placed on each side and retested. The lead wires are then tunneled to exit from the chest wall. Limited studies have shown results comparable to those of standard phrenic nerve pacing.⁵² Potential advantages compared with currently available phrenic nerve pacing include less expensive equipment and the ability to implant electrodes in both diaphragms without the need for repositioning or single-lung ventilation that is required during VATS procedures. Current experimentation with natural orifice transluminal endoscopic surgery may further decrease the invasiveness of this procedure and make temporary pacing in the intensive care unit a more realistic possibility.⁵³

At present, improved quality of life for patients is the reason for continued research into the science of diaphragmatic pacing. In addition to the obvious benefit of freedom from mechanical ventilation, pacing can also lead to improved speech patterns, conversion from tracheostomy to stoma devices, and return of olfactory sensation.^{44,46}

In summary, diaphragmatic pacing is useful for carefully selected patients with intact phrenic nerve and diaphragmatic muscle function but impaired upper motor

neurons. Results of unilateral pacing are not beneficial because the phrenic nerve is usually not functional. Patient selection and preoperative evaluation are crucial to successful, long-term diaphragmatic pacing.⁴⁴ The potential exists for a large group of patients with lower motor neuron disease (i.e., temporary or permanent phrenic nerve injury) to benefit once further advances in technology can produce smooth, coordinated muscle contraction of the diaphragm with direct muscle stimulation.

ONCOLOGY OF THE DIAPHRAGM

Primary tumors of the diaphragm are rare, and the literature is notable for scattered case reports only. Benign tumors include variants of fibrous tumors and lipomas, neurogenic tumors, and cysts. These tumors generally present as incidental findings on imaging studies, and most patients are asymptomatic. Surgical resection with primary closure or reconstruction is the standard treatment. Primary malignant tumors may arise from muscles, tendon, or mesothelial elements on either side of the diaphragm. Most of these lesions are sarcomatous in origin and are locally aggressive and best treated with complete diaphragmatic resection. The benefits of chemotherapy are limited. Because recurrence is usually local, various methods of irradiation delivered preoperatively or postoperatively have been used. We have also used intraoperative placement of brachytherapy seeds after resection of primary or secondary tumors of the diaphragm.

Invasion of the diaphragm from tumors on either side of the “fence” can occur. In the abdomen, this is most commonly seen with large retroperitoneal sarcomas, hepatocellular carcinoma, or upper gastrointestinal tumors, including direct extension into the hiatus by gastroesophageal junction adenocarcinomas.

Mesothelioma and chest wall sarcomas are thoracic malignant neoplasms that may involve the diaphragm and are discussed elsewhere in greater detail. Invasion of the diaphragm by primary lower lobe lung adenocarcinomas is considered T3 disease, and patients with T3 disease are often not considered for surgery on the basis of preoperative imaging because a corresponding pleural effusion is present that upstages the disease to T4. Others are given chemotherapy first to determine responders who will most benefit from surgery. Between 0.17% and 0.4% of patients are found to have diaphragm disease at explorative thoracotomy.^{54,55} Because of the rarity of this occurrence, limited data have been published about this topic. Weksler and associates⁵⁶ were the first to address this population of patients, describing eight patients between 1974 and 1995 who underwent exploratory thoracotomy for non-small cell lung cancer. All patients underwent en bloc resection with an overall survival of 52.8 weeks.

To improve on the limited data from the previous series, two multicentric retrospective studies have been done. Riquet and colleagues⁵⁶ reviewed 68 patients from 17 centers who underwent thoracotomy with resection of non-small cell lung cancer invading the diaphragm and found a 67% rate of lymph node involvement. This was

thought to be the result of the extensive lymphatic drainage of the diaphragm. Sixty-three patients in a study from the Lung Cancer Surgical Study Group of Japan were identified from 31 institutions. Complete resection was performed in 55 patients (87.3%), and the 5-year survival in these patients was 22.6%.⁵⁴ The depth of diaphragm involvement was noted to affect prognosis; patients with shallow invasion of the diaphragm had a 33% 5-year survival rate versus 14.3% in those with deep muscular or peritoneal invasion. The overall survival rate of these patients after complete resection compared with T3 lung cancers with chest wall involvement was significantly less.

DIAPHRAGMATIC RESECTION AND REPAIR WITH PROSTHETIC PATCH

Partial diaphragmatic resections are necessary to remove tumors that have invaded a portion of the diaphragm. The redundancy of the muscle frequently allows primary repair for small to modest resections. Larger defects are easily repaired with a mesh or impermeable graft sutured to the remnant of muscle. We use mesh for patients with lung tissue remaining in the ipsilateral hemithorax and impermeable grafts for patients who have had a pneumonectomy to prevent fluid shifts between the thorax and abdomen.

Complete diaphragmatic resection may be required for large tumors invading the diaphragm, such as lung cancer of the lower lobe or sarcomas of the chest. We have gained our extensive experience with complete diaphragmatic resection as part of an extrapleural pneumonectomy for mesothelioma.⁷

An extrapleural pneumonectomy is the complete removal of the pleural envelope and all its contents, including the ipsilateral lung, lateral pericardium, and underlying diaphragm. Because the pleura cannot be separated from the central tendon of the diaphragm, the diaphragm must be resected if the pleural envelope is to be kept intact during removal.

Diaphragmatic resection begins with traction of the pleura away from the chest wall deep into the diaphragmatic sulcus. This exposes the bare area of the lateral diaphragm where the pleura folds off the rib cage and back onto the upper surface of the diaphragm (Fig. 32-13).⁷ The division of these lateral radial bands of the fan-shaped portion of the diaphragm is started at the most anterior portion of the chest close to the pericardium. The fingers of the surgeon bluntly dissect the peritoneum from beneath the muscle, then pull the fibers taut to facilitate visualization to divide the muscle with cautery. It is not unusual for the posterolateral portion of the diaphragm to be beyond the direct vision of the surgeon. Fibers in this area can be bluntly avulsed with minimal risk of bleeding. Once the ligamentum arcuatum externum (external arcuate ligament) is reached in the paravertebral sulcus, the perinephric fat of Gerota fascia not the peritoneum, is directly beneath the fan-shaped muscle. This part of the dissection quickly progresses to the lateral margin of the crus. The diaphragm can then be separated from the peritoneum up toward the lateral

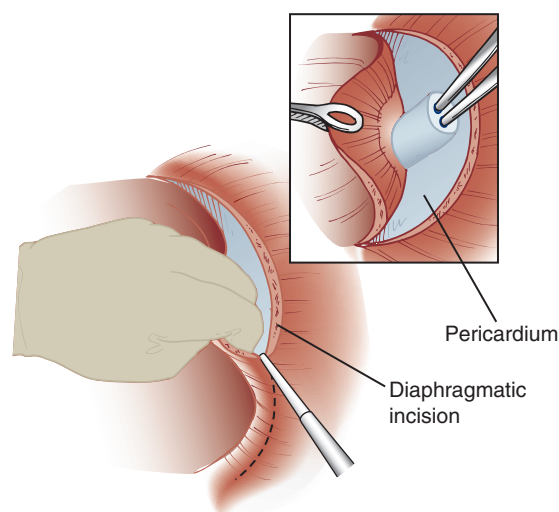


FIGURE 32-13 ■ Circumferential incision of the right hemidiaphragm exposing the underlying peritoneum. Pericardial and crural attachments remain after division of the fan-shaped muscle. (From Kanaan S, Ducko CT: Disorders of ventilation: diaphragmatic pacing. In Fauci AS, et al, eds: *Harrison's principles of internal medicine*, ed 17, online update, New York, 2008, McGraw-Hill.)

border of the pericardium. Defects in the peritoneum are closed as they are recognized.

An extrapleural pneumonectomy requires the removal of the lateral portion of the pericardium because the mediastinal pleura cannot be removed from that structure. The pericardium is opened anteriorly. The phrenic nerve is divided cephalad to the pulmonary artery. The trileaflet of the diaphragmatic tendon is divided along the line demarcating the central tendon of the ipsilateral muscle from the tendon lying beneath the pericardium. This cut is made medial to the insertion of the phrenic nerve into the anterior muscle. This medial cut is extended along the fused portion of diaphragmatic tendon and pericardium to the inferior vena cava on the right or the esophageal hiatus on the left.

At this point, the only attachment of the diaphragm remaining is the crus. Blunt dissection of the pleura of the deep diaphragmatic sulcus needs to be completed before division of the crus to prevent buttonholing of the inferior extent of the posterolateral pleura. The superior phrenic arteries are surgically inconsequential and rarely identified. The inferior phrenic vessels, however, lie on the deep surface of the crus and are easily seen and ligated. These vessels may bifurcate low over the crus, and a second branch may therefore be found after ligation of a branch thought to be the main trunk. The left inferior phrenic vein usually has two branches, one of which drains into the left renal or suprarenal vein and another that passes anterior to the esophageal hiatus and empties into the inferior vena cava. The right inferior phrenic vein empties directly into the inferior vena cava and therefore requires careful dissection and ligation. Vigorous lateral traction can avulse this vessel from the inferior vena cava, close to the insertion of the hepatic veins. Once these vessels have been divided, the crus is easily divided. This completes the diaphragmatic resection.

The postpneumonectomy space fills with fluid. To prevent fluid shifts between the thorax and abdomen, we use a 2-mm impermeable Gore-Tex prosthetic patch to reconstruct the resected diaphragm. This patch prevents herniation of abdominal contents into the chest, holds the abdominal viscera out of the thoracic irradiation field, and bolsters the contralateral diaphragm by fixing the medial edge of the fan into place. This then facilitates the function of the opposite diaphragm by allowing its central tendon to become the anchor point for the lateral fan fascicles. Without patching of the ipsilateral diaphragmatic defect, the contralateral muscle function is compromised.

After the patch has been cut to the shape of the removed diaphragm, the medial edge is sewn to the pericardial tendon with a soft nonabsorbable suture. We prefer 0 Ethibond for this suture. This suture line runs from the free edge of the divided anterior fan muscles, along the pericardial edge, to either the inferior vena cava or esophageal hiatus. A reliable lateral anchorage system has been devised, requiring a sterilized leatherworking awl (Fig. 32-14). Loops of suture material that have been passed through the lateral edge of the patch are then brought through the chest wall with the awl. The sutures are then passed through a small postage stamp-sized patch of the same material as well as a sterile polypropylene button, with the assistance of two angiocatheters. The loop of suture is then tied down to itself onto the button, resulting in excellent lateral displacement of the patch.

The posterior mediastinum between the thoracic spine and the inferior vena cava or esophagus is the area where patch ruptures occur, with abdominal contents herniating into the chest. This is the result of a lack of strong mediastinal tissue available to anchor the patch.

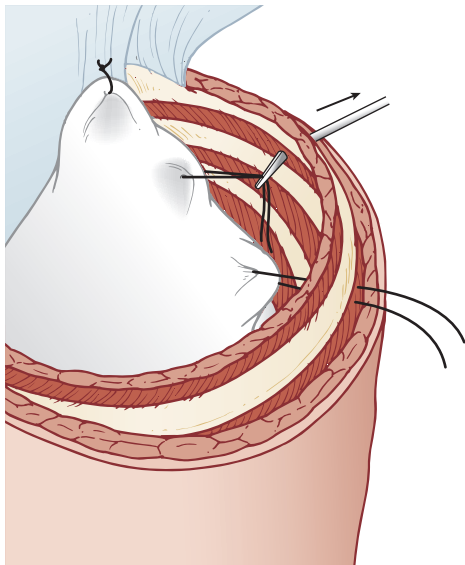


FIGURE 32-14 ■ Diaphragmatic resection for extrapleural pneumonectomy necessitates patch closure. A sterile leatherworking awl is used to pass anchoring sutures through the chest wall to re-create radial lines of tension. These sutures are secured along the outside of the rib cage with use of angiocatheters through the holes of sterile buttons.

Our group of surgeons have developed the following three potential solutions: (1) a suture anchoring the patch to the anterior spinal ligament, (2) a tongue of extra patch material folded inferiorly along the lumbar spine in simulation of the diaphragmatic crus, and (3) a composite of two patches of 2-mm Gore-Tex stapled together in the middle with a thoracoabdominal stapler to create a dynamic patch at the center with less tension at the lateral suture lines. The first technique uses the dense spinous ligament to anchor the posterior mediastinal portion of the patch and decreases the free defect between the anterior suture line at the inferior vena cava and the thoracic spine to a few centimeters. The second technique allows the medial portion of the patch to be partially displaced into the chest but prevents visceral herniation unless the entire tongue becomes displaced into the chest. The last technique allows the prosthetic patch to “give” without rupture if the patient experiences abdominal distention.

SUMMARY

The diaphragm serves several functions as a result of its unique anatomic location. It is the major muscle of respiration, by creating the intrathoracic vacuum and moving the lower ribs. It is a barrier between the positive-pressure abdomen and the negative-pressure thorax. It is important in the function of the lower esophageal sphincter.

Surgical approaches to the diaphragm are easily learned and depend on an understanding of the anatomy and physiology of the muscle, nerve, and blood vessels. Various incisions are possible once the locations of the nerve and vessel branches have been learned. These structures frequently lie within the muscle itself and are not seen on the surface of the structure. Therefore, the concept of a handcuff around the junction of the central tendon to the muscle is helpful.

Diaphragmatic repair and patching are helpful in traumatic injuries, congenital absence of a part of the diaphragm, and diaphragmatic hernias. Diaphragmatic pacing is not useful in phrenic nerve palsies because an intact lower motor neuron is required for the current level of technology to function. Plication of the diaphragm for these cases is useful. We prefer a radial plication technique that mimics the radial contraction of the fan-shaped muscle to that of a central tendon pleat.

Repair of gastroesophageal reflux depends on the construction of a new lower esophageal sphincter. A major contributor of the pathologic process, however, is a diaphragmatic hernia between the crura: a hiatal hernia. Therefore, we believe that tightening of the crus around the repair and lengthening of a shortened esophagus are important steps to keep the repair within the abdomen and to prevent complications such as gastropericardial fistula.

The entire hemidiaphragm can be resected. Small resections can be repaired primarily, but large resections should be patched to assist the function of the contralateral muscle. The choice between permeable and impermeable patches depends on the remaining presence of ipsilateral lung. The principles of the patch repair include

a tight apposition to the medial remnant of the diaphragm and then radial lateral displacement of anchoring sutures.

Although the diaphragm acts as a boundary between the thorax and abdomen, it should not serve as a boundary between the realm of thoracic surgeons and gastrointestinal surgeons. The diaphragm makes a good fence, but neighbors on both sides of that fence should know its anatomy, physiology, and surgical principles of resection and repair.

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CONGENITAL DIAPHRAGMATIC HERNIA

Dario O. Fauza • Jay M. Wilson

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DEFINITION

Different congenital diaphragmatic anomalies include one or more defects that allow for herniation of abdominal contents into the chest. However, the term *congenital diaphragmatic hernia* (CDH), also referred to as *Bochdalek hernia*, refers specifically to congenital defects located on the posterior-lateral aspect of the diaphragm. Despite the name diaphragmatic “hernia,” there is a true hernia sac in only 15% to 20% of cases.

HISTORY

The first known written description of a diaphragmatic herniation was made by Ambroise Paré in 1579.¹ However, the two cases described by Paré were caused by trauma. In his *Sepulchretum* of 1679, Teophile Bonet attributed the first description of a congenital case to Lazare Rivere at the beginning of the seventeenth century,

even if from the necropsy of an adult.² The first report of a CDH in a newborn was made by George Macaulay in 1754, also as a necropsy finding, in an infant who died from respiratory failure a little over 1 hour after birth.³

In 1761, Giambattista Morgagni, then a pupil of Valsalva, wrote a review of diaphragmatic herniations and credited Stehenius with the first observation that CDH was associated with pulmonary hypoplasia.⁴ In the review, Morgagni described the first case of a parasternal hernia in an older man, henceforth termed *Morgagni hernia*. In 1848, Vincent Alexander Bochdalek reported two cases in which he described the location of the diaphragmatic defect as being in the posterior-lateral aspect of the muscle, hence the origins of the terms Bochdalek hernia and Bochdalek foramen.⁵ Although widely used, these terms are actually improper given that the mechanisms and exact location proposed by Bochdalek, namely “rupture of the lumbocostal triangle,” are inaccurate.⁶⁻⁸

The link between CDH and deviations of the embryonic development of the pleuroperitoneal membrane only started to be established from the studies by Broman

in 1902 and 1905.^{9,10} Nevertheless, although this anatomic location for the diaphragmatic defect is universally accepted, it is not yet known where the primary disorder that leads to CDH takes place.

The first successful repair of a CDH was performed by Aue in a 9-year-old boy in 1901, but published only in 1920.¹¹ The first publication of a successful CDH repair was by Hedenhain in 1905; he reports a procedure, also in a 9-year-old boy, occurred in 1902.¹² In 1940, the first survival of a neonate, who underwent CDH repair on the second day of life, was reported by Ladd and Gross.¹³ Gross was also the first to report on a good outcome after repair before the first 24 hours of life, in 1946.¹⁴

In 1977, German and colleagues¹⁵ reported the first child with CDH to survive after being placed on extracorporeal membrane oxygenation (ECMO). Ever since the mid-1980s, it has become clear that ECMO plays a major role in maximizing the survival rates of neonates with CDH.¹⁶⁻¹⁸

In 1989, Harrison presented the first series of CDH treated by open prenatal repair of the diaphragmatic defect in humans, leading to live births but no midterm survival.¹⁹ Survival after this procedure was reported by this same group in 1992, but only in 28.6% of the operated fetuses.²⁰

In the early 1990s, from the work of Wung and coworkers, the concept of avoiding hyperventilation and minimizing barotrauma was introduced.^{21,22} These principles have since led to marked reduction in iatrogenic insult to the lungs, which was common in the old, aggressive ventilation strategies, and consequently significant improvement in survival.^{16,23-25}

The first successful lung transplantation for the treatment of CDH was performed in a newborn in 1992, by the groups of Shochat and Starnes.²⁶ Also in 1992, Wilson first showed, in an ovine model of CDH, that fetal lung growth could be significantly accelerated after occlusion of the fetal trachea, leading to reversal of the pulmonary hypoplasia associated with experimental CDH.²⁸ In 1994, Harrison's group first applied this maneuver successfully in a human fetus with CDH.²⁹ Nonetheless, the results of fetal tracheal occlusion, be it done open or videofetoscopically, remain worse than those of postnatal care, at least at the referral centers in North America.³⁰⁻³² Still, fetal tracheal occlusion continues to be offered systematically at a few European centers and anecdotally elsewhere, though its current indications, if any, remain to be clearly defined.^{33,34} A prospective randomized trial of fetal tracheal occlusion (TOTAL) is currently underway in Europe.

In 1994, the Congenital Diaphragmatic Hernia Registry was created, as a meta-institutional organization dedicated to the exchange and analysis of data related to this disease, as well as to the design and implementation of multicentric prospective trials. This initiative was molded after the pediatric oncology groups first established in the 1980s and, as such, has had a major beneficial impact on CDH survival and management guidelines.³⁵

In 1995, we demonstrated experimentally that lung growth could also be accelerated after birth, through

continuous intrapulmonary distention with a perfluorocarbon.^{36,37} The first series of patients that received this treatment, under ECMO support, was presented in 2000.³⁸ A multicentric prospective trial of this principle has proven difficult to pursue due to regulatory and logistical hurdles, yet it remains an anticipated perspective. Also in 2000, the use of a tissue engineered construct for the repair of the diaphragmatic defect was first proposed in an animal model.³⁹ Further experimental developments have validated engineered diaphragmatic repair and a clinical trial is expected in the not too distant future, pending regulatory clearance.⁴⁰⁻⁴⁴

In general, current development efforts are aimed at further refining pre- and postnatal prognostic markers, defining the patients that would benefit from lung growth acceleration (whether pre- or postnatal), enhancing diaphragmatic repair through tissue engineering, and minimizing morbidity of the increasingly more common long term survivors.

EPIDEMIOLOGY

The prevalence of CDH has been reported as being anywhere between 1:1,200 and 1:12,000 births.⁴⁵⁻⁵⁴ Likely, the main reason for such disparities is the so-called hidden mortality of CDH, which relates to the fact that many babies die before making it to a referral center and thus are not included in the statistics. The better controlled studies show CDH as occurring in 1:2,107 to 1:3,163 births.^{45,47-50,52} One of the largest series ever studied, by Torfs and colleagues,⁵² involving over 718,000 births and stillbirths in part of California, revealed that CDH occurred in 1:3,163 births and in 1:3,340 live births. Among the major congenital anomalies, CDH is one of the most common, accounting for approximately 8% of the cases.⁵⁵

There are no clear racial differences in the prevalence of CDH.^{50,52} The study by Torfs and colleagues⁵² showed a higher prevalence in rural rather than urban areas, but this has not yet been confirmed by other series. The prevalence of prematurity and weight deviations in neonates with CDH is no different from that of the general population.⁵² While isolated CDH is a little more common in boys than in girls (1.5:1), sex distribution is normal in CDH associated with other congenital anomalies and in the whole CDH population.^{52,56}

There is limited controversy as to the risk of CDH recurrence within families. In the vast majority of cases, CDH is sporadic, with no genetic component described to date and with the risk for further offspring being practically equal to that of the general population.^{45,47} At the same time, many families with more than one case of CDH, usually siblings, have been identified.^{48,52,55,57-63} Less frequently, relatives other than siblings can also present with this anomaly.^{58,64,65} The epidemiologic profile of familial cases of CDH differs little from that of the total of cases: it is slightly more common in males (approximately 2:1)^{57,60,64} and there is conflicting data as to the other variables.^{59,65} The occurrence of familial CDH follows a pattern suggestive of multifactorial inheritance as the most likely mode of transmission, with

recurrence estimated between 1.3% and 2%.^{52,55,59,62} The possibility that a genomic imprinting phenomenon takes place has also been proposed.⁶³ A somewhat recent extensive review of a single hospital-based malformation surveillance program (the largest to date of consecutively collected cases of CDH) showed low recurrence among siblings.⁶⁶

EMBRYOLOGY OF THE DIAPHRAGM

The diaphragm comes from the mesoderm. Its development is complex and not yet fully understood. It results from the fusion of four embryonic components: two odd ones, namely the transverse septum and the mediastinum (also known as the dorsal mesentery of the esophagus), and two paired structures, namely both sides of the body wall musculature and both pleuroperitoneal membranes⁹ (Fig. 33-1).

The diaphragm begins to develop during the 3rd and 4th weeks of gestation, with the appearance of the first component of the diaphragm, the transverse septum (see Fig. 33-1). At this point, the transverse septum is an incomplete mesenchymal divider, related cranially to the pericardial cavity and caudally to the midgut. Dorsally, the transverse septum blends with the mediastinum. On each side of the mediastinum there are the pleural canals, which connect the pericardial and peritoneal cavities. The subsequent development of the diaphragm depends on the closure of these dorsal pleural canals, which will give rise to the pleural cavities.

During the 4th week, the pulmonary buds, which are developing inside the mediastinum, begin to protrude into the pleural canals. At this stage, the pleural canals are very small and the pericardial cavity is very large. Crests formed on both extremities of the pleural canals will separate the future pleural cavities from the pericardial cavity, cranially, and from the peritoneal cavity, caudally. The cranial crest will give rise to the pleuropericardial membrane and the caudal crest will form the pleuroperitoneal membrane (see Fig. 33-1).

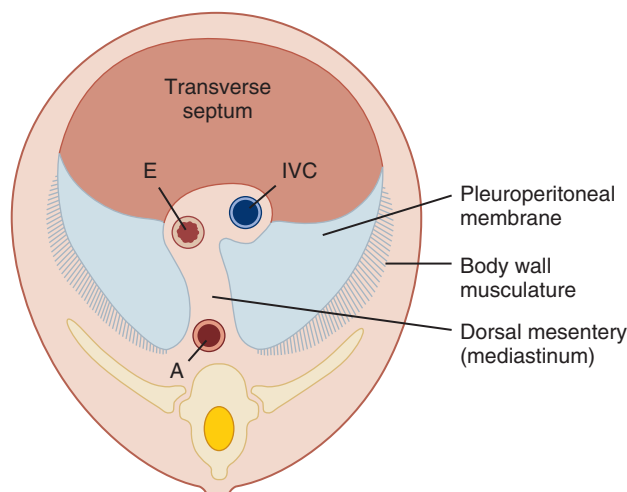


FIGURE 33-1 ■ The four embryonic components of the diaphragm. A, Aorta; E, esophagus; IVC, inferior vena cava.

The enlargement of what are now the pleural cavities leads to a progressive narrowing of the opening between them and the pericardial cavity, as well as to the development of the pleuropericardial membrane. In like manner, there is progressive narrowing of the pleuroperitoneal canals and the development of the pleuroperitoneal membranes.^{6,7} The definitive closure of the pleuroperitoneal canals, now small, will occur during the 8th week of gestation.⁶

After closure of the pleuroperitoneal canals, the pleural cavities continue to expand, in parallel to lung growth. Cranially, they spread out beyond the limits of the pericardial space. Caudally, they extend into the body wall.⁶ During this process, which takes place from the 9th to the 12th week, the mesoderm in the posterior thoracic wall is carved by the caudal borders of the expanding pleural cavities, so that its inner portion will become part of the diaphragm. At the same time, a similar process happens at another, more lateral and anterior portion of both the thoracic and the abdominal walls. As a consequence, part of the diaphragmatic muscle originates from the musculature of the thoracic and the abdominal walls.^{6,67}

Despite the almost universal acceptance of this explanation for the development of the diaphragmatic muscle, there is some controversy related to the role of the phrenic nerve in that process. In accordance with the principle that muscles in general retain their original segmental innervation, certain authors believe that myoblasts derived from the caudal portion of the infra-hyoid mesoderm migrate, together with the phrenic nerve, from the third and fourth cervical somites, towards the diaphragm, so that this would be the origin of the diaphragmatic muscle.^{68,69} However, the phenomenon of myoblast migration together with the phrenic nerve has not yet been proven; it is but a partially accepted theory. The fact that the tendinous center of the diaphragm is a fibrous structure completely devoid of muscle fibers speaks against this theory.⁷ In any event, even if myoblasts from the superior cervical myotomes do follow the phrenic nerve, at least part of the diaphragmatic innervation should be later transferred to muscular portions derived from the thoracic and abdominal walls.

Deviations from the normal development of each one of the various components of the diaphragm bring about different variants of diaphragmatic anomalies. Table 33-1 shows the diverse embryonic origins of the diaphragm and their relation to different diaphragmatic defects.

PATHOLOGY

Etiology

The etiology of CDH is unknown. In a few rare syndromes in which a diaphragmatic defect is present is there a well-defined genetic cause, such as in trisomies of the chromosomes 13 and 18. On the other hand, a single institution review showed that 17% of all cases of CDH (i.e., both isolated and in association with other congenital anomalies) had a recognizable genetic etiology.⁶⁶ In addition, there was no concordance for CDH among five

TABLE 33-1 Embryologic Origins of the Diaphragm and Corresponding Diaphragmatic Defects

Embryonic Structure	Time (wk)	Portion Formed	Diaphragmatic Defect
Transverse septum	3 and 4	Central tendon	Pericardial hernia (ventral defect)
Pleuroperitoneal membranes	7 and 8	Primitive diaphragm	Bochdalek hernia (posterolateral defect)
Mediastinum (dorsal mesentery)	—	Median portion and crura	—
Body wall	9-12	Muscle periphery (ventral-lateral and dorsal)	Morgagni hernia (parasternal defect) and eventration

monozygotic twin pairs. These findings, in conjunction with previous reports of *de novo* dominant mutations in CDH patients, suggest that new mutations may be an important mechanism in the etiology of this disease. At the same time, the discovery of CDH loci using standard methodology has been hindered by the genetic heterogeneity of this disease. Relatively novel techniques such as array comparative genomic hybridization, whole-transcriptome expression profiling, and whole-exome sequencing, among others, are now being pursued and already shedding new light upon the extent and relevance of specific genetic abnormalities associated with CDH.⁷⁰⁻⁷⁵

Even so, the twin data also point to the possibility that epigenetic abnormalities contribute to its development. Indeed, experimental CDH can be produced in diverse animal species through a variety of interventions, other than surgical creation of the defect, including: exposure to diet deficient in either vitamin A,^{76,77} zinc,⁷⁸ or cadmium⁷⁹; administration of either thalidomide,⁸⁰ anti-rat rabbit serum,⁸¹ 2,4-dichlorophenyl-p-nitrofenilic ether (nitrofen, an herbicide),⁸²⁻⁸⁴ or polibromate biphenils^{85,86}; induction of endothelial heparan sulfate deficiency⁸⁷; and genetic manipulations, such as FOG-2, COUP-TFII, GATA-4, SOX7, and Slit3 mutations.⁸⁸⁻⁹² However, to date, there's been no conclusive relationship between these experimental models and clinical/epidemiological data in humans.

Pathogenesis

The pathogenesis of CDH is also unknown. Normally, before the return of the bowel from the umbilical cord to the abdominal cavity, which occurs during the 10th week of gestation, it is necessary for the pleuroperitoneal canal and the lumbocostal triangle to firmly close, which happens between the 8th and 10th weeks. In case such closure does not take place, the bowel will pass through the pleuroperitoneal canal, sometimes also through the lumbocostal triangle, and will invade the chest, resulting in a "herniation" without a hernia sac. In case there is only a membranous closure, the same phenomenon will happen, albeit with a hernia sac that may, or not, rupture sometime later. In any case, although it is well established that the diaphragmatic defect is at the level of the pleuroperitoneal canal,^{6,7,9,10} the sequence of events that culminates in disturbances of its closure remain to be determined.

The prevailing theory as to CDH development has been that the incomplete closure of the pleuroperitoneal canal was a primarily diaphragmatic defect and that the abdominal viscera herniated to the thorax impeded

normal lung development and resulted in the pulmonary hypoplasia and hypertension observed almost universally in association with CDH. This perception was widely confirmed by animal models in which a diaphragmatic defect was surgically produced in fetuses of different species,⁹³⁻⁹⁵ or in which the diaphragmatic herniation was mimicked by an inflatable prosthesis placed in the pleural cavity.⁹⁶ All these models resulted in lung hypoplasia and pulmonary hypertension at birth.

Nonetheless, the foremost notion today is that the primary defect is not in the diaphragm, but in the lung buds, and that the diaphragmatic defect would actually be secondary to a primary pulmonary hypoplasia. Such pulmonary hypoplasia, in turn, could be intensified even more by the presence of abdominal viscera herniated into the chest. Starting at the 4th week of gestation, the growth of the pulmonary buds and of the pleural cavities result in a progressive narrowing of the pleuroperitoneal canals and in the formation of the pleuroperitoneal membranes.^{6,7} The development of the diaphragm, more specifically of the pleuroperitoneal membranes, is intimately related to lung development itself. Researchers that have worked with the experimental model of CDH induced by nitrofen have shown that, in that model, the pulmonary hypoplasia precedes the diaphragmatic defect.^{83,84,97,98} These findings are in accordance with the fact that nitrofen exposure can lead to pulmonary hypoplasia independently of the existence of CDH.⁹⁹⁻¹⁰¹ Iritani⁸³ has concluded that the lung buds, which are primarily hypoplastic because of the exposure to nitrofen, cause hypoplasia of the post-hepatic mesenchymal plate, which in turn develops in intimate association with the lung buds. The hypoplasia of this mesenchymal plate, which is one of the precursor portions of the primitive diaphragm, would then give rise to the diaphragmatic defect and, consequently, the CDH.⁸³ Moreover, it is thought that the morphogenesis and differentiation of the pulmonary respiratory epithelium is intimately dependent on the kind of extra-cellular matrix synthesized by the mesenchyme.^{84,102,103} Kluth and colleagues¹⁰³ have shown that lungs of embryos exposed to nitrofen display an abnormal expression of factors normally found in the extracellular mesenchymal matrix, with a delayed pattern of epithelial differentiation. Iritani speculates further that the fact that CDH is more common on the left in humans is because lung bud development tends to be slower on the left than on the right.^{83,104,105} and, also, the fusion of the pleuroperitoneal membranes happens later on the left side than on the right.⁹³ Independently of the possibility of a primary pulmonary hypoplasia in the nitrofen model, Alles and colleagues¹⁰⁶ have shown that there is also cell death in the mesoderm of some cervical somites which are

precursors of the diaphragm, suggesting a concomitant primary disorder of diaphragmatic development. Consequently, the mechanism behind the emergence of CDH in this model is still to be clarified.¹⁰⁶ Knock-out models, such as FOG-2^{-/-} mice, are also further evidence of a primary pulmonary hypoplasia associated with CDH.⁸⁹

The possibility of a primary endothelial defect in the diaphragm and/or the lungs being a culprit has been suggested more recently, for example from the observation that experimentally induced heparan sulfate deficiency disrupts developmental angiogenesis and leads to CDH, at least in mice.⁸⁷ The identification of parathyroid and thymic anomalies related to embryonic neural crest dysfunction in a rat model, as well as in human infants with CDH, have pointed to a potential involvement of neural crest dysregulation in the pathogenesis of CDH, which however remains to be better recognized.¹⁰⁷ A so-called “smooth muscle hypothesis,” pointing to abnormalities in airway smooth muscle development as central to the pathogenesis of CDH has also been proposed, but not yet fully validated.¹⁰⁸ There are still a number of other, less accepted theories for the pathogenesis of CDH.^{69,109-111} Whichever the location and nature of the primary defect may be, the presence of a diaphragmatic defect *per se* usually leads to herniation of abdominal viscera to the chest, which, in turn, at least contributes to worsening the pulmonary hypoplasia.⁹³⁻⁹⁵ The sooner the herniation occurs in gestation and/or the larger the herniation content, the more intense the pulmonary hypoplasia tends to be.

Pathologic Anatomy

Gross Findings

The diaphragmatic defect, or Bochdalek foramen, is located in the posterior-lateral aspect of the diaphragm, involving at least the area that would have originated from the pleuroperitoneal membrane and, many times, also the area immediately posterior to it, namely the lumbocostal triangle (Fig. 33-2). The size of the defect is highly variable, from less than 1 cm in diameter, to an

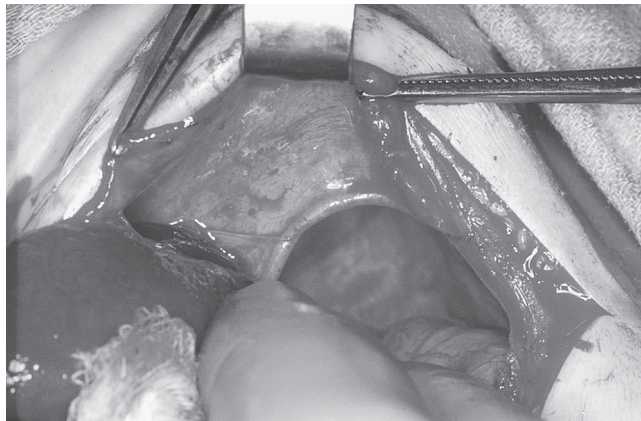


FIGURE 33-2 ■ Typical intraoperative finding, through a left subcostal laparotomy, in a neonate with congenital diaphragmatic hernia. Note the defect on the posterolateral aspect of the left diaphragm.

almost complete absence of the hemi-diaphragm, extending beyond the dome, practically to the midline, preserving merely a small anterior-lateral band of muscle. There is no fibrosis or any evidence of inflammation at the level of the diaphragmatic opening. The left side is affected in approximately 80% to 90% of the cases, the right side in 10% to 20%, and bilateral cases are rare, occurring in approximately 1% of the patients.^{17,112}

In most cases, the pleura and the peritoneum are in continuity over the borders of the diaphragmatic defect, which may render the identification of the residual posterior muscle band difficult. In only approximately 15% of the patients is there a hernia sac. The size of the diaphragmatic opening does not necessarily relate to the volume of the herniation.

Because of the herniation to the chest, the mediastinum is usually deviated to the contralateral side of the hernia (Fig. 33-3). Both lungs, but particularly the one ipsilateral to the defect, are smaller than normal in both volume and weight (Fig. 33-4).¹¹³⁻¹¹⁵ Pulmonary lobulation is ordinarily normal, but may be compromised in a few cases.^{113,116} On the other hand, the shape of the pulmonary lobes is commonly distorted.^{113,116} The pulmonary ligament is almost always absent on the side of the hernia.¹¹³ The number of airway generations and their dimensions are reduced, especially in the ipsilateral side of the defect.^{113,116} The pulmonary arteries, as well as the number and dimensions of their branches, are smaller than normal, in proportion to the reduced size of the lungs, also particularly on the side of the hernia.¹¹³



FIGURE 33-3 ■ Typical gross autopsy finding from a neonate with congenital diaphragmatic hernia. Note the abdominal organs herniated to the left hemithorax through the posterolateral defect on the ipsilateral diaphragm, and the mediastinal deviation to the right. There is no hernia sac.

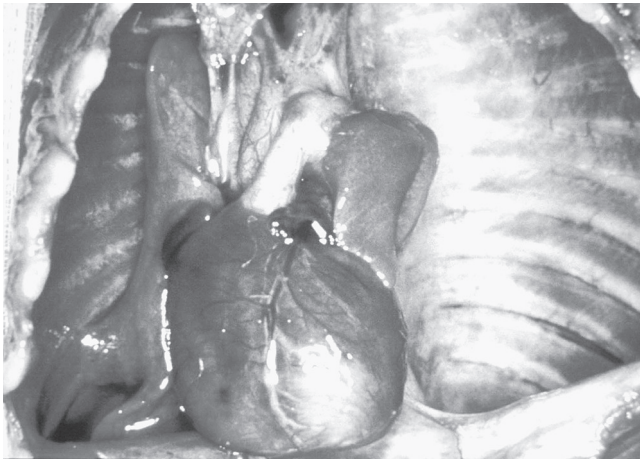


FIGURE 33-4 ■ Thoracic cavity in the neonate shown on Figure 33-3, after removal of the abdominal organs herniated to the left hemithorax. Note the reduced size of the lungs, especially on the left.

The herniation of abdominal contents to the thorax and the pulmonary hypoplasia may both lead to the appearance of many other abnormalities. Because of that, such abnormalities are not exactly considered other anomalies associated with CDH, but actually integral components of the so-called “CDH syndrome.”¹¹⁷ The most frequent of such abnormalities are: persistent *ductus arteriosus*, persistent foramen ovale, and intestinal malrotation.¹¹⁷ Less frequently, the following abnormalities can also be a direct consequence of CDH: gastric volvulus, abnormally sized chest cavity, accessory spleen and/or congenital splenic fibrosis in left CDH, abnormal hepatic lobulation and/or hepatopulmonary fusion in right CDH, and hypoplasia and/or fibrosis of the lobe of the liver ipsilateral to the hernia.¹¹⁷⁻¹¹⁹ Also, expectedly, the volume of the abdominal cavity is frequently reduced.

Microscopy

Except for the defect itself, the diaphragm does not exhibit any other deformity. A local decrease of the density of branches of the phrenic and intercostal nerves has been described by some,⁶⁹ but not yet confirmed by others and is considered of limited value.¹⁰⁶

The impact of CDH on the lungs varies within an ample spectrum. The lung ipsilateral to the hernia is impaired the most, but both lungs are affected. In a given patient, the effects of the hernia are not uniform on the different portions of each lung.

The airway branching order is abnormal, with a reduced number of generations of lower bronchi and bronchioli, often with complete absence of the latter, so that bronchi may end directly in alveoli.^{113,115,116} Given that normal airway branching is complete by 16 weeks of gestation,^{104,120} the reduction in airway generations observed both grossly and microscopically is further evidence of the fact that CDH and/or pulmonary hypoplasia start before this time, more specifically between the 10th and 12th weeks. On the other hand, the development of airway cartilage itself does not seem to be affected, so that

the proportion of cartilage-bearing airways to the total number of airways is normal.^{113,116} Yet, the number of bronchi containing mucous glands is diminished.¹¹⁶

The total alveolar number is reduced, both in absolute terms, as well as in relation to total lung volume.^{113,115,116} However, the number of alveoli per acinus may be either reduced or normal, suggesting that the reduction in total alveolar number is mostly a consequence of the lower number of terminal bronchioli.^{113,115} The alveoli are also smaller than normal.¹¹³ The fate of type II pneumocytes is not yet completely clear. Many studies uncover evidence that the surfactant system is depressed, but it is not absolutely clear whether this has to do with a reduction in the density of type II pneumocytes, or not.¹²¹⁻¹²⁷ Defects in bronchopulmonary innervation have also been identified.¹²⁸

In parallel to the lower number of airway generations, the absolute number of arterial branches is reduced,¹¹³ yet the density of intra-acinar arteries may be normal.¹¹⁵ The arterial diameters are reduced.^{113,115} There is hypertrophy of the arterial muscle layer at all levels, as well as extension of such muscle layers into more distal branches, which normally would not bear any muscle.^{113,115,129,130} There seems to be a direct relationship between pulmonary hypoplasia and arterial muscularization, so that the more hypoplastic the lung, the more intense is the abnormally augmented muscularization.¹²⁹ Abnormal pulmonary lymphatic development has been identified in experimental CDH, but remains to be definitely described in human infants.¹³¹

Pathophysiology

The cardinal aspects of CDH pathophysiology are pulmonary hypertension with persistence of a fetal circulatory pattern, along with a reduction in both pulmonary tidal volume and compliance. The intensity of such manifestations varies a great deal, going from almost nonexistent to incompatible with life, depending mostly on the severity of the anatomical abnormalities of a given patient. According to some, a deficiency of the surfactant system is also part of CDH pathophysiology.¹²¹⁻¹²⁴ However, this notion has been increasingly challenged by more recent data.^{127,132,133}

In children, total peripheral airway cross section area is proportionally larger than in adults, hence the reduction in airway generation present in CDH usually does not lead to significant increases in airway resistance.¹³⁴ The difficulty in ventilating children with CDH stems mostly from the lower pulmonary compliance and lower tidal volumes. The pressure-volume curves of these hypoplastic lungs are abnormal, so that, at a given pressure, lung volume is lower than normal.¹³⁵ Microscopic analyses under insufflation show that, while certain airspaces may open at 15–20 cm H₂O, many are still closed at 30–35 cm H₂O.¹³⁶ Thus, higher inspiratory pressures are transferred only to the alveoli that are open, leading to alveolar rupture and a tendency to develop pneumothorax.¹³⁷ It is not yet clear whether the decreased pulmonary compliance is a result of a quantitative and/or qualitative depression of the surfactant system, or a relative increase in the total amount of collagen in the

lungs.^{121-123,138} The lower tidal volumes are a direct consequence of the reductions in both lung volume and total alveolar number.¹¹³⁻¹¹⁶ All these ventilatory abnormalities are the main reasons for the tendency of infants with CDH to retain CO₂.¹³⁷

Contrary to what happens with the airways, the peripheral vessels (lower arteries, arterioles, and capillaries) account for most of the pulmonary vascular resistance (PVR). Therefore, as a result of the reduction in the total number of arterial branches and their lower than normal diameters, the total arterial cross sectional area is diminished and the PVR is usually significantly increased in CDH.^{139,140} Further contributing factors to the increased PVR are the hypermuscularization of the arteries and amplified arterial reactivity. Because of the latter, certain physiological stimuli such as alveolar hypoxia, hypoxemia, hypercapnia, acidosis, cyanosis, hypothermia, as well as any “disturbances,” such as certain inflammatory mediators and simple manipulations of the patient, may trigger intense pulmonary vasoconstriction and marked increase in PVR.^{141,142} Other than the possibility of a role played by the muscular hypertrophy present in pulmonary arteries and arterioles, the reason why these vessels tend to overreact to stimuli is not yet known. Recent data suggest that the pulmonary vasculature’s ability to synthesize nitric oxide is depressed in CDH and thus may be part of the mechanism.¹⁴³ The possibility of an imbalance involving prostanooids, which are vasoactive agents that include prostaglandins, playing a role has been suggested.^{140,144-146} A potential role for other endogenous vasoactive agents, such as endothelin, in the increase in PVR has proved debatable.^{140,147,148}

This increase in PVR leads to pulmonary hypertension, which is almost universally observed in neonates with CDH.^{136,140,149} Pulmonary hypertension leads to a decrease in total blood flow to the lungs, an increase in end-diastolic pressure in the right ventricle, and a tendency for persistence of a fetal circulatory pattern, with right-to-left shunt through the ductus arteriosus and foramen ovale.^{136,141} The decrease in total pulmonary blood flow and the right-to-left shunt lead to hypoxemia, hypercapnia, and acidosis, which in turn are stimuli to pulmonary vasoconstriction, which worsens the pulmonary hypertension, with consequent intensification of the fetal circulatory pattern and so forth, establishing a vicious circle difficult to break. Not infrequently, patients may be satisfactorily oxygenated and fairly stable, until a random stimulus, or nothing immediately discernible, triggers the vicious circle of fetal circulation. Such a period of temporary stability that precedes the emergence or worsening of pulmonary hypertension has been coined *honeymoon*. It was described for the first time by Collins and colleagues^{140,150} in the mid-1970s and remains a frequent observation in neonates with CDH. The mechanisms responsible for the end of the honeymoon have been elusive until the last few years, when mounting evidence points to it being a cardiac event, more specifically variable degrees of right heart failure.¹⁵¹ Patients who present soon after birth with persistent hypoxemia, without ever going through a honeymoon period, usually have severe pulmonary hypoplasia and serious abnormalities of the pulmonary vasculature.¹³⁰

In the fetus, the oxygenated blood that comes from the placenta returns to the right heart through the umbilical vein and crosses either the foramen ovale or the ductus arteriosus toward the aorta, so that only approximately 7% of the cardiac output goes through the lungs.¹⁵² Therefore, the hemodynamic disturbances associated to pulmonary hypertension almost never manifest in utero. After birth, however, the hemodynamic status tends to deteriorate, often with overload and potential failure of the right heart. Thus, cardiac failure is typically part of the pathophysiology of CDH^{151,153,154} and survival depends, to a great extent, on the ability of the myocardium to withstand the overload imposed by the pulmonary vasculature.^{136,151,153} The deviation of the mediastinum by the herniated content may lead to a decrease in the venous return to the heart, possibly contributing to further worsening of the patient’s hemodynamic status.

It has been suggested that neonates with CDH may have adrenal insufficiency, with an inadequate response to stress.¹⁵⁵ At the same time, there is preliminary experimental evidence pointing to the possibility that lower than normal glucocorticoid levels can contribute to the abnormal lung development and maturation found in CDH.¹⁵⁶ The true meaning of these findings in CDH pathophysiology remains to be better defined. Indeed, at least as far as receptors are concerned, hypoplastic lungs of fetuses and newborns with CDH seem to be as responsive to glucocorticoids, thyroid hormone, and retinoic acid (all relevant to normal pulmonary development) as the lungs of normal children.¹⁵⁷

Among the different aspects of the pathophysiology of CDH, it is the pulmonary hypertension that is most responsible for mortality in the neonatal period. Since otherwise healthy neonates who undergo total pneumonectomy are often able to maintain good oxygenation and ventilation, without clinically relevant pulmonary hypertension, the lack of pulmonary parenchyma alone cannot explain all the manifestations commonly observed in infants with CDH.¹⁵⁸ Rarely in CDH is the bilateral lung impairment intense enough to cause a neonate to have less than half of the normal total alveolar surface area. Consequently, it would appear that, more often than not, the pulmonary vasculature abnormalities are clinically much more relevant than the lack of alveoli (pulmonary hypoplasia).

CLINICAL MANIFESTATIONS

Approximately 90% of the patients with CDH are symptomatic within the first 24 hours of life.¹⁵⁹ Yet, this disease can first manifest at any age and, more rarely, go unnoticed until late in life, or even never be diagnosed.¹⁶⁰⁻¹⁶²

When a child is symptomatic within the first 24 hours of life, the main clinical manifestation is respiratory distress. The earlier the onset of signs and symptoms, the more severe the pulmonary disease. Newborns that are symptomatic in the first 6 hours after birth are considered high risk and account for 88% of the cases.¹⁵⁹ Tachypnea associated with sternal, subcostal, and supraclavicular retraction is common. Cyanosis and pallor are also frequent. Apgar scores tend to be low. If untreated, the

dyspnea tends to worsen over time for three reasons: the progressive distention of the intrathoracic bowel by gas, which is accelerated by aerophagy, common in children in respiratory distress; the gradual increase of the volume herniated to the chest, which is a result of the negative pressure exerted during respiration; and the escalating hypoxemia, hypercapnia, and acidosis because of the vicious circle generated by persistent pulmonary hypertension. The abdomen is often scaphoid because of the migration of abdominal viscera to the chest. However, because of possible bowel distention inside the abdominal cavity, the abdomen can assume a normal appearance over time. The chest may be asymmetrical and larger on the side of the hernia, especially after the bowel fills with gas. The heart sounds are commonly dislocated to the contralateral side of the hernia. Sometimes, the same happens with the trachea. In the ipsilateral hemithorax, the respiratory sounds may be diminished or absent altogether, while bowel sounds may be present. There may be hemodynamic instability, with a tendency to arterial hypotension, because of a decreased venous return to the heart due to the mediastinal deviation and/or because of right heart failure due to pulmonary hypertension. Occasionally, mediastinal deviation can also lead to superior vena cava syndrome.¹⁶³ If it goes untreated, a symptomatic newborn usually dies within a few minutes or hours.

Rarely in the neonatal period, there are manifestations stemming from perforations or strangulation of a hollow viscus, gastric or midgut volvulus, or rupture of a herniated spleen, such as gastrointestinal obstructions, empyema, hemothorax, fever, arterial hypotension, coagulopathy, anemia, or hypovolemic shock. Anecdotal associations between CDH and septicemia with group B streptococcus in premature babies have also been described.¹⁶⁴

When CDH first manifests after the neonatal period, partial or complete gastrointestinal (GI) obstructions are more common than respiratory distress, which, if at all present, tends to be mild. Unlike in the neonates, the spectrum of manifestations of late presentation CDH is broad, including (in addition to GI obstruction and respiratory distress) sudden death, growth retardation, perforations or strangulations of intrathoracic hollow viscus (which can lead to sepsis, empyema, pneumothorax, or hemothorax), rupture of a herniated spleen (with hemothorax, anemia, and possibly hypovolemic shock), airway infections or recurrent pneumonias, urinary tract obstruction owing to herniation of the ureter, chest pain, abdominal pain, vomiting, diarrhea, anorexia, acute abdomen, intrathoracic appendicitis, and other rare presentations.^{160,161}

In bilateral CDH, both sides do not always manifest at the same time. Staggered presentation has been described previously.¹⁶⁵

DIAGNOSIS

The majority of cases are diagnosed before birth, during routine prenatal ultrasound.¹⁶⁶ The relative proportion of cases diagnosed in utero is constantly climbing, because of the increasing application of prenatal ultrasound

screening and improvements in ultrasound technology and resolution. Fetal ultrasonography should always be performed whenever there is polyhydramnios, given that CDH is one of its causes, apparently because of a reduction in the volume of amniotic fluid swallowed by the fetus and probably because of the GI obstruction caused by the hernia. A few authors also recommend careful ultrasonographic examination whenever an amniocentesis shows abnormally low levels of lecithin and sphingomyelin, because of the possibility of an association between CDH and a deficiency in the surfactant system.^{123,124} Such an association, however, has become less accepted.^{126,127,132,133} CDH can be diagnosed with prenatal ultrasound from the eleventh week of gestation until term; previously negative examination results can become positive at any time during pregnancy.^{166,167} False-negative and false-positive examination results can occur; fetal ultrasonography is precise in approximately 90% of cases.^{141,168} Not infrequently, the herniated content identified by prenatal ultrasound can move in and out of the chest, as if the hernia were a dynamic process.¹⁶⁹ A case of CDH diagnosed in the second trimester of pregnancy that seemed to have resolved spontaneously during the third trimester, with delivery of a normal infant, has been reported.¹⁷⁰ There may be inaccuracies as to the side of the hernia, when it is unilateral, and sometimes a bilateral CDH may be diagnosed as unilateral.¹⁶⁹ The differential diagnosis of CDH identified by prenatal ultrasound includes congenital cystic adenomatoid malformation (CCAM) of the lung, diaphragmatic eventration, Morgagni hernia, hiatal hernia, pentalogy of Cantrell, primary diaphragmatic agenesis, pericardial hernia, pulmonary sequestration, lung cysts, diaphragmatic duplication, leiomyosarcoma of the lung, mediastinal teratoma, esophageal atresia with tracheoesophageal fistula, primary pulmonary agenesis, primary pulmonary hypoplasia, and intrathoracic duplications of the GI tract.^{141,171} Color Doppler, three-dimensional ultrasonography, and magnetic resonance imaging (MRI) may all facilitate the prenatal diagnosis of CDH.^{172,173} In the past, in extremely rare, select cases, if in doubt, more invasive exams, such as amniography, computed tomography (CT), or ultrasonography with concomitant intrathoracic or intra-abdominal injection of saline as a "contrast" were considered.^{169,174} But, as fetal MRI has become the new gold standard, these more invasive examinations are of historical interest only. At most referral centers, the prenatal diagnosis of CDH with ultrasound automatically leads to confirmation by fetal MRI, and often an amniocentesis as well, so that the fetal karyotype can be determined. Should certain chromosomal abnormalities be detected, pregnancy termination may be considered.

After birth, a plain chest radiograph is almost always enough to confirm the diagnosis. The typical image is that of bowel loops seen within the lung fields, with deviation of the mediastinum to the contralateral side of the hernia, and decrease or absence of gas in the abdomen (Fig. 33-5). When the radiograph is obtained before the GI tract can be filled with gas, or if the intestines are not herniated (which is more common in right hernias), there may be confusion in the diagnosis. The introduction of a radiopaque gastric tube often helps, in case the stomach

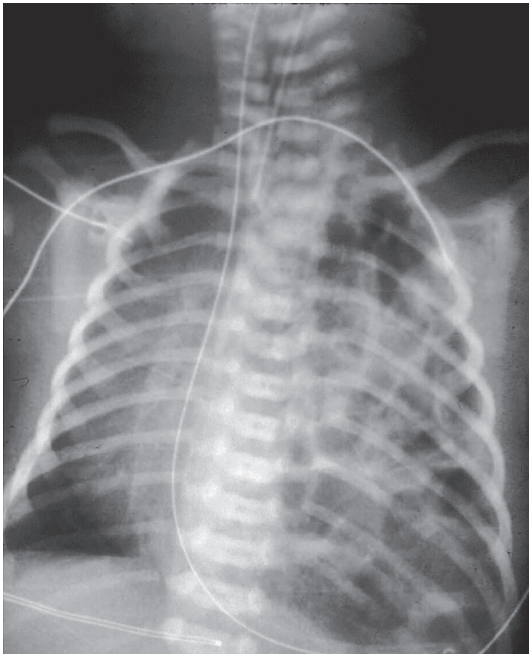


FIGURE 33-5 ■ Typical aspect of plain radiograph from a neonate with a left congenital diaphragmatic hernia. Note the presence of bowel loops in the left hemithorax, the mediastinal deviation to the right, and the gastric tube in the chest.

is herniated (see Fig. 33-5). Should any uncertainty persist, which is uncommon, the diagnosis can be confirmed with a radiograph performed after infusion of contrast through the gastric tube. Even less frequently, an ultrasound may be of help. More rarely, CT, MRI, or a contrast enema can have a role. The differential diagnosis of CDH after birth includes diaphragmatic eventration, pneumonia, CCAM, lung cysts, pneumothorax, pleural collections, Morgagni hernia, hiatal hernia, primary agenesis of the diaphragm, primary pulmonary agenesis, primary pulmonary hypoplasia, pericardial hernia, pulmonary sequestration, cardiac tumors, and duplication of the diaphragm. Despite all these possibilities, the diagnosis of CDH after birth tends to be relatively easy.

On late presentation CDH, the diagnosis is usually made with a simple chest radiograph as well. Also in these cases, a gastric tube may be of help during the interpretation of the radiograph. Sometimes there is previous history of a normal chest radiograph. One must always remember the possibility of late presentation CDH, otherwise the diagnosis will likely be delayed and confused with either pneumonia, pneumatoceles, CCAM, pneumothorax, pleural collections, diaphragmatic eventration, lung cysts, lung nodules, or pulmonary sequestrations. Given that late presentation CDH is relatively rare, the need for other examinations in addition to the chest radiograph is somewhat more common. Such examinations can include an upper GI (often with the patient in Trendelenburg position), ultrasound, CT, MRI, fluoroscopy, and, more rarely, a contrast enema. CDH may be diagnosed as an incidental imaging finding in an asymptomatic patient.

ASSOCIATED ANOMALIES

Children bearing any major congenital anomaly are known to carry a much higher risk of having another anomaly than the general population. Neonates with CDH are no exception to that rule. The incidence of other anomalies associated with CDH in the literature varies from rare to as much as 60%.^{52,54,117,175} There are several different explanations for this disparity: the inclusion, or not, of the other anomalies directly linked to CDH and considered integral components of the so-called CDH syndrome, as described earlier; the inclusion, or not, of stillbirths or patients who die before reaching a referral center; variable diagnostic routines; variable autopsy rates; variable patient populations in terms of the proportion of high risk neonates included in the analysis; and variable regional prevalences of certain congenital anomalies. These studies have identified many different associated anomalies, in all body systems, usually with a predominance of cardiac malformations.

In a detailed review of 166 high-risk neonates (i.e., symptomatic within the first 6 hours of life), we noticed that approximately 40% of the children had one or more congenital anomaly associated with CDH.¹¹⁷ This index was obtained even after exclusion of all the other anomalies that are part of the “CDH syndrome.” Cardiac anomalies were by far the most common, found in 63% of the patients with an associated anomaly, followed by anomalies in the genitourinary tract (23%), GI tract (17%), central nervous system (14%), muscles and skeleton (10%), chromosomes (10%), lungs (5%), and others (5%); in many children there were more than one associated anomaly (Table 33-2).¹¹⁷ Our results were comparable to those from another large series.^{52,175}

The high proportion of cardiac anomalies associated with CDH in many series deserves special attention. In our review, for example, they were more frequent than all other anomalies put together (see Table 33-2).¹¹⁷ Among the cardiac anomalies, heart hypoplasia was the most common.¹¹⁷ This finding is in accordance with many observations pointing to the fact that the cardiac hypoplasia associated with CDH, especially that of the cardiac chambers ipsilateral to the hernia, occurs, like the pulmonary hypoplasia itself, at least in part due to compression of the heart by the herniated content and, perhaps, should also be considered part of the CDH syndrome, as it likely plays a role in the cardiac failure often manifested clinically.^{117,176,177} The presence of an associated cardiac anomaly can lead to significant further reduction of the postductal pO_2 when compared with isolated CDH.¹¹⁷ In fact, in neonates with an excessively low postductal pO_2 , one should be particularly careful in searching for a potential associated cardiac anomaly.

The side of the hernia has been linked to differences in the frequency and pattern of associated malformations.¹⁷⁸ This interesting first observation needs further validation. Patients with late presentation CDH also seem to have a higher prevalence of other anomalies than the general population. However, the related series published thus far are too small for definitive conclusions. For example, in a review of 26 patients spanning 20 years,

TABLE 33-2 Associated Anomalies Identified in 166 High-Risk Patients with Congenital Diaphragmatic Hernia*

Anomaly	Patients (N)	Anomaly	Patients (N)
Cardiac		Absent vermiform appendix	1
Heart hypoplasia	13	Accessory pancreas	1
Atrial septal defect	10	Annular pancreas	1
Ventricular septal defect	9	Duodenal atresia	1
Hypoplasia of aortic isthmus	3	Ectopic liver	1
Aortic coarctation	3	Ectopic pancreas	1
Persistent left superior vena cava	3	Esophageal atresia with transesophageal fistula	1
Ebstein's anomaly	2	Imperforate anus	1
Parachute mitral valve	2	Neuroenteric cyst	1
Abnormal mitral valve	1	Phrygian cap deformity of gallbladder	1
Abnormal tricuspid valve	1	Musculoskeletal	
Absent left pericardium	1	Hemivertebrae	2
Absent right pulmonary artery	1	Absent rib	1
Bicommissural aortic valve	1	Abnormal rib	1
Bifid apex of the heart	1	Accessory rib	1
Common atrioventricular canal	1	Hip dislocation	1
Cor triatriatum	1	Limb dystrophy	1
Double outlet of right ventricle	1	Polydactyly	1
Double coronary ostia	1	Sacral dysgenesis	1
Scimitar syndrome	1	Scoliosis	1
Single coronary artery	1	Chromosomal	
Genitourinary		Trisomy 18	2
Undescended testes	6	Abnormal chromosome 14 centromere	1
Bicornuate uterus	2	Balanced 12/15 translocation	1
Hydronephrosis	2	Chromosome 7Q deletion	1
Horseshoe kidneys	1	Chromosome 12P	1
Hypospadias	1	Mosaic trisomy	1
Renal dysplasia	1	Tetraploidy 21	1
Single kidney	1	Trisomy 13	1
Ureteropelvic junction obstruction	1	Pulmonary	
Vaginal or uterine atresia	1	Pulmonary sequestration	2
Central Nervous System		Pulmonary lymphangiectasia	1
Hydrocephalus	4	Trifurcated trachea	1
Rachischisis	2	Other	
Circle of Willis anomaly	1	Inguinal hernia	2
Microcephaly	1	Omphalocele	2
Myelomeningocele	1	Cleft lip or palate	1
Open spine	1	Conotruncal facies	1
Vascular malformation of cord	1	Torticollis	1
Gastrointestinal			
Meckel diverticulum	6		
Absent gallbladder	1		

*Excluding pulmonary hypoplasia, persistent ductus arteriosus, persistent foramen ovale, intestinal malrotation, gastric volvulus, size abnormalities of the chest wall, accessory spleen or congenital splenic fibrosis in left congenital diaphragmatic hernia (CDH), abnormalities of liver lobulation in right CDH, and hypoplasia or fibrosis of the liver lobe ipsilateral to the hernia.

Reproduced with permission from Fauza DO, Wilson JM: Congenital diaphragmatic hernia and associated anomalies: their incidence, identification, and impact on prognosis. *J Pediatr Surg* 29:1113–1117, 1994.

Berman and colleagues¹⁷⁹ found one or more associated anomalies in 31% of patients.

PROGNOSTIC FACTORS

The search for reliable prognostic markers has been an essential aspect of the study of CDH for decades. Given the broad pathology spectrum related to CDH, such markers are critical for any meaningful comparisons among different therapeutic strategies, and for the identification of cases incompatible with life, in which further efforts would not be justified.

Certain clinical variables are known to be associated with different survival rates. Ever since the study by Young in 1969,¹⁸⁰ there is a well-established reverse relationship between age at the beginning of symptoms and mortality rates.⁵³ Neonates that are symptomatic within the first 6 hours of life are considered high risk, as the lowest survival rates are found in this group of patients.⁵³ There is no difference in mortality between the sexes in isolated CDH; however, higher mortality rates have been reported in females than in males when CDH is associated with other anomalies.⁵² Some studies have shown that the lower the gestational age at birth, or the lower the birth weight, the lower the survival rate.^{53,181} Lower

Apgar scores, particularly in the fifth minute, are also linked to higher mortality.⁵³ Contrary to what a few studies have suggested, the side of the hernia has not had any prognostic effect in the larger series.⁵³ At the same time, the size of the defect is well established as a determining factor not only in survival, but also in the presence of associated anomalies, and in long-term outcome of survivors.^{24,53,182-184} More recently, it has been shown that the presence of a hernia sac also is of prognostic significance, being correlated with better outcomes.¹⁸⁵ The variable with the greatest effect on CDH survival rates is the presence, or not, of other associated congenital anomalies. The prognosis of neonates with associated anomalies, especially cardiac, is overall worse than that of infants with isolated CDH, although it has improved appreciably over time.^{53,117,186,187}

Since the early 1970s, countless studies have tried to correlate mortality to blood gas values or to ventilation parameters, independently, or mutually integrated in often intricate equations. Examples include pH values; best pCO₂ or best pO₂, either postductal or preductal; alveolar-arterial O₂ gradient; mean airway pressure; respiratory rate; pulmonary compliance; dead space; and tidal volume.¹⁸⁸⁻¹⁹³ In the past, perhaps the most popular of these markers was the “best” postductal pO₂ obtained during maximal mechanical ventilation, before either surgically repairing the hernia or placing the patient on ECMO. Children with values greater than 100 mm Hg were labeled *responsive* and had a better prognosis, and vice versa.^{191,192} Other parameters also previously used were the so-called Bohn criteria, which related pCO₂ with the ventilation index (VI = respiratory rate multiplied by mean airway pressure); among the many different combinations, for example, pCO₂ greater than 40 mm Hg with VI ≥ 1000 would suggest high mortality.^{189,191,192} Some authors have proposed that preductal blood gases are more predictive of the degree of pulmonary hypoplasia than postductal blood gases, given that the latter are more influenced by the intensity of pulmonary hypertension and right-to-left shunt; a preductal pO₂ < 100 mm Hg and a preductal pCO₂ > 60 mm Hg would be related to high mortality.^{190,194} As a result of the now universal acceptance of the principle of gentle ventilation, permissive hypercapnia, and minimization of iatrogenic injury related to mechanical ventilation, even preductal blood gases have had increasingly limited prognostic value, at the same time that postductal gases such as best pO₂ during maximal ventilation have been practically abandoned. A recent study from our group has shown that pulmonary support on hospital day 30 is a strong predictor of length of stay, oxygen requirements at discharge, and in-patient mortality, and it can be used as a simple prognostic indicator for family counseling, discharge planning, and a potentially more refined identification of high-risk infants.¹⁹⁵

Imaging criteria as severity predictors have also been extensively studied. One example is the value of prenatal ultrasonography. Until the early 1990s, a positive prenatal ultrasound was considered a marker of bad prognosis, particularly if the hernia was diagnosed before 25 weeks’ gestation.^{196,197} Lately, probably because of the widespread use of fetal ultrasound during routine prenatal

care, the improvements in ultrasound technology, and the novel therapeutic strategies for CDH, it is clear that the prenatal diagnosis of an isolated CDH is, by itself, of no prognostic value, regardless of the gestational age at which it is made.¹⁶⁶ In the event that other associated anomalies, especially cardiac, are diagnosed prenatally in addition to the diaphragmatic hernia, the prognosis is still comparable to that if the diagnosis is made after birth.¹¹⁷ Several specific findings on fetal ultrasound have been proposed as bad prognostic markers, such as polyhydramnios, herniation of the liver and/or the stomach into the chest, “underdevelopment” of the left side of the heart, disproportionate cardiac ventricles, high ratio of the herniated area over the cardiac area, low ratio of the lung area over the total thoracic area, depression or absence of fetal breathing movements, severe mediastinal deviation, reduction of liquid flow through the nose and oropharynx during fetal breathing movements, and disturbances of blood flow modulation through the ductus arteriosus.^{167,196-199} The merit of all these markers, however, is highly controversial and of limited acceptance. The value of liver herniation and the so-called lung-to-head ratio (LHR), which measures the relative proportion between the areas of the lung and the head at predetermined locations, has been emphasized by a few groups.^{200,201} For example, fetuses with liver in the chest and an LHR less than 1 would have a particularly bad prognosis. While there continues to be a debate on the value of the presence, or not, of the liver in the chest, the same cannot be said of the LHR, which at best has been shown to be significantly inconsistent, especially across different institutions.^{159,202,203} Three-dimensional measurements of fetal lung volume with MRI are being increasingly refined and adopted as a seemingly more reliable imaging-based prognostic marker, including at our institution.^{172,204} A so-called CDH congenital composite index, consisting of an amalgam of 10 mainly imaging-based prenatal parameters, has recently been proposed from a single-center study; however, it has yet to be validated by multiple other institutions.²⁰⁵

In like manner, some studies suggest that certain postnatal imaging findings, either independently or in combination, can also be linked to poor outcome. On plain chest radiograph, examples of such findings are the presence of the stomach in the chest, ipsilateral or contralateral pneumothorax, the presence of interstitial emphysema, and a low ratio of aerated ipsilateral lung area over that of the contralateral lung.²⁰⁶⁻²⁰⁸ On an echocardiogram, examples are decreased left ventricular mass, disproportionate dimensions between both pulmonary arteries, and a disproportionately large pulmonary artery trunk in relation to the aorta.^{209,210} Finally, on a pulmonary arteriogram, examples are reduced dimensions of both pulmonary arteries, reduced size of the ipsilateral lung, and severe peripheral compromise.¹⁹¹ Analogous to what happens with prenatal imaging, the predictive value of these proposed postnatal findings is questionable, and few institutions have adopted any of them.

To date, only the following variables have been clearly validated by well-controlled, extensive multicentric data as being of predictive value in CDH: age at the onset of symptoms, birth weight, 5-minute Apgar score, defect

size, and the presence of an associated cardiac anomaly.^{24,53} The meaning of all other suggested prognostic markers is debatable and of limited acceptance. The effect of various prognostic markers seems to differ, depending on the side of the hernia.²¹¹ One of the most common shortcomings of the studies involving prognostic markers is the fact that most of them are reviews from a single institution. Hence, the data are unavoidably linked to the unique patient population and peculiar therapeutic strategies of each service, which are aspects known to still be highly variable from one center to another in CDH. On the other hand, even if well-controlled multicentric trials were conducted, the fact that the treatment of CDH is a constantly evolving moving target could lessen the significance of their results. The introduction of ECMO and of the principle of gentle ventilation are clear examples of the vulnerability of this kind of data, as these therapies rendered the conclusions obtained before their availability nearly useless, even within a given institution. Relatively recently, an empirically weighted mortality prediction score for CDH patients on ECMO has been generated from an extensive retrospective analysis of data from the Extracorporeal Life Support Organization registry, but it has yet to receive widespread acceptance.²¹²

TREATMENT

Except for the rare cases in which there is strangulation of the herniated content, CDH is not a surgical emergency. Rather, CDH is a physiologic emergency. In fact, not infrequently, mechanical aspects of respiration tend to deteriorate after the repair of the hernia.^{213,214} Indeed, emergency surgery is not only unnecessary and often deleterious; a period of preoperative stabilization is known to improve outcome.^{22,215} The child should not go to the operating room while in unstable condition. The time needed for stabilization can vary from less than 12 hours to several days. A few authors even suggest waiting until well beyond stabilization has been reached.²² This recommendation, however, remains somewhat controversial, in that multicentric data have shown good survival even when strict criteria for preoperative stability are not met, suggesting some flexibility in such standards.²¹⁶ At the same time, in certain premature neonates of higher surgical risk, one can wait weeks to a month or longer before proceeding to the repair.¹⁵⁹

The therapeutic strategy in children with CDH and other associated anomalies must be individualized for each patient. The hernia is often repaired before the other anomalies are; however, when CDH is associated with cardiac anomalies, this strategy can lead to unacceptably high mortality.^{117,159} Unless the cardiac defect is mild, the current tendency is to repair the heart before the diaphragm, or, occasionally, both during the same intervention. Yet, the best guidelines for the different scenarios are still being defined.

One of the benefits of the prenatal diagnosis of CDH is the fact that delivery can be planned at a tertiary referral center. The initial results of postnatal resuscitation are known to be maximized when the presence of CDH is detected before birth.¹⁶⁶ At our institution and others,

high-risk outborn infants have a significantly lower survival rate when compared with inborn neonates. Unless there is any obstetrical contraindication, vaginal delivery is preferred over cesarean section.

Preoperative Care

The neonate should be intubated in the delivery room. Ventilation by mask before intubation should be avoided because of the risk for distention of hollow viscera inside the chest. A gastric tube should be introduced and kept under mild continuous suction to minimize such distention and to drain air that might have been swallowed. Central venous access is established, usually through the umbilical vein (occasionally, however, particularly in right-sided CDH, there may be significant distortions of the liver anatomy because of the herniation, which can impede the use of this vein). One of the umbilical arteries is catheterized for blood pressure and postductal blood gas monitoring. Preductal blood gases are obtained through access to the right radial artery, or to one of the superficial temporal arteries. Transcutaneous pulse oximetry monitors and, if available, transcutaneous pO₂ and pCO₂ monitors are placed on preductal and postductal territories. Monitors for body temperature and respiratory rate should also be positioned. At least in the high-risk cases, a Foley catheter is introduced. The volumes of intravenous infusions should be carefully controlled to minimize the chances of a pulmonary edema developing. Prophylactic antibiotics covering both gram-positive and gram-negative bacteria are commonly administered. Whenever possible, inotropic agents should be avoided, given that these drugs usually not only increase cardiac output, but also peripheral vascular resistance, both of which may, together with the ever present pulmonary hypertension, lead to excessive cardiac overload not always tolerated, especially when there is some degree of cardiac hypoplasia.^{117,176} When the use of these drugs is unescapable, many prefer dobutamine, amrinone, or epinephrine to dopamine or norepinephrine, because the former drugs can produce pulmonary vasodilation at low doses.¹⁴¹ One should limit any manipulation or interaction with the infant to a minimum, because of the high volatility of the pulmonary vasculature.

Every neonate with CDH should undergo an echocardiogram with Doppler, given the relatively common occurrence and prognostic effects of both right heart failure and associated cardiac anomalies. Should any functional or structural cardiac disease be identified, its treatment must be carefully coordinated with that of the hernia. A pediatric cardiologist is sometimes a member of the multidisciplinary team caring for these patients. Certain variables, namely prenatal diagnosis before 25 weeks' gestation, low Apgar scores, and "excessive low" postductal pO₂ have shown to be risk factors for the presence of other associated anomalies.¹¹⁷ Should these variables be present, additional examinations such as genitourinary tract and head ultrasounds and a karyotype (if this was not already done during pregnancy) are strongly urged, in addition to the echocardiogram.¹¹⁷

Until the early 1990s, typically neonates were sedated, paralyzed, and hyperventilated, and they received

systemic alkalization with sodium bicarbonate or throtamine to minimize pulmonary hypertension. Ventilation parameters used to be controlled by postductal blood gases. This strategy, which unfortunately is still practiced by many centers today, is clearly associated with unacceptably high risks for iatrogenic lung injury. Pulmonary hypoplasia and, in particular, pulmonary hypertension are both expected to lead to low pO_2 and high pCO_2 , especially in postductal gases. Attempts to normalize postductal blood gas values often lead to marked increases in ventilator parameters, namely respiratory rate (RR), inspired O_2 fraction (FiO_2), peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), and mean airway pressure (MAP), which, in turn, commonly lead to hyperdistention of the lungs and severe barotrauma, not to mention the toxicity of high FiO_2 levels. A survey involving clinical and autopsy data for 68 children with CDH treated in this fashion showed a tremendously high frequency and severity of iatrogenic insult to the pulmonary parenchyma.¹⁷⁷ In that study, 91% of the patients had evidence of diffuse alveolar damage with development of hyaline membrane, more obvious in the ipsilateral lung. Moreover, 65% of the children developed pneumothorax, 51% had pulmonary hemorrhage, and 6% already had variable degrees of interstitial fibrosis.¹⁷⁷ Other studies also showed alveolar ruptures, damage to the alveolar basal membrane, alveolar hemorrhage, and edema, all of which contributed to atelectasis, a decline in lung compliance, and even further deterioration of gas exchange.^{16,127} In addition to barotrauma, to which CDH neonates are particularly vulnerable,¹³⁶ pulmonary hyperdistention leads to even further increase of the already elevated pulmonary vascular resistance, thus worsening the effects associated with pulmonary hypertension.^{217,218} Systemic alkalization with sodium bicarbonate can lead to increases in pCO_2 and to volume and sodium overloads. Throtamine can be useful at times in the short term, but relatively large volumes of this drug are usually necessary, which tends to result in both generalized and pulmonary edema.

It is clear that a completely different strategy, first proposed by Wung and colleagues,^{21,22} should be offered to high-risk neonates with CDH. It is based on the following guidelines: minimal sedation; no muscle paralysis; respiration merely assisted by the mechanical ventilator, if possible through pressure support under flow synchronization, or, if this is not available, then through simple or synchronized intermittent mandatory volume; permissive hypercapnia with no hyperventilation; and no systemic alkalization. Patient monitoring is mostly through preductal gases. Ventilator parameters are left at a minimum necessary to maintain preductal O_2 saturation (SaO_2) greater than or equal to 90%, whichever the postductal values may be, with tolerance to high pCO_2 levels. In general, the ventilator parameters are left at: base RR ≤ 40 breaths per minute, PIP and PEEP no greater than 30 and 5 cm H_2O , respectively, and the FiO_2 should be the lowest possible to prevent severe preductal hypoxemia. That is to say, unless there is metabolic acidosis, suggesting excessively low O_2 delivery, one should tolerate low postductal pO_2 and SaO_2 , as long as there is an adequate amount of oxygen in the preductal blood that is going to the brain

and to the heart. As long as the pH is at "acceptable" levels, one should tolerate hypercapnia. The main goal of this therapeutic strategy is the prevention of barotrauma, probably the most common cause of death whenever the old "conventional" hyperventilation strategy is used.^{16,22,194,219} Despite the known benefits of sedation in CDH, which raises the excitability threshold of the pulmonary vasculature, in this "new" strategy, one must use sedation with great caution, so that the child may be able to effectively activate the mechanical ventilator, preferably in pressure support under flow synchronization. When the child is able to control both the RR and the air flow from the respirator, he or she can contribute more to the minute volume without compromising the functional residual capacity. This therapeutic strategy also avoids the side effects of systemic alkalization.

As discussed, the lungs of newborns with CDH are particularly vulnerable to barotrauma, so the occurrence of pneumothorax is relatively common. Except for rare occasions, one should not drain a pneumothorax ipsilateral to the hernia before surgical repair, given the risk of iatrogenic injury to the herniated content.

Pulmonary Vasodilators

Regardless of the ventilation strategy, many vasodilators administered systemically have been used in an attempt to control the pulmonary hypertension. Examples of these agents are: tolazoline, nitroglycerin, nitroprusside, acetylcholine, prostaglandin E1, prostaglandin D2, prostacyclin, isoprenaline, and nifedipine. Despite the theoretical appeal of these drugs, they are not selective enough to the pulmonary vasculature, and they usually lead to a drop in both total peripheral vascular resistance and systemic arterial pressure. Therefore, their effects on the pressure gradient through the ductus arteriosus is either minimal or inexistent, so that the tendency to right-to-left shunt is unchanged. Furthermore, they can lead to vasodilation of poorly ventilated areas of the lungs, which can worsen the intrapulmonary right-to-left shunt. The drop in systemic arterial pressure, on the other hand, can lead to the administration of volume or inotropic agents, both of which should be avoided. Bos and colleagues²²⁰ reported a reduction of both the alveolar-arterial O_2 gradient and the oxygenation index ($OI = MAP \times FiO_2 / pO_2$) after administration of prostacyclin in high-risk CDH patients, but this had no effect on survival. The use of prostacyclin is also associated with an increase of the bleeding time, which is obviously undesirable in surgical patients.^{220,221} Inhaled prostacyclin has been investigated experimentally, but no clinical applicability has been found.^{222,223} The response to prostaglandin D2 is variable, and systemic hypotension is a common side effect.^{140,220,223} The most popular of these vasodilators was, perhaps, tolazoline, an α -adrenergic receptor blocking agent with a mild inotropic and chronotropic effect on the myocardium. This drug also lowers the levels of thromboxane B2, which is possibly a mediator of pulmonary hypertension in CDH and which also has histamine-like effects.^{141,224} Children who respond to tolazoline usually do so within 4 hours after an initial bolus of 1 to 2 mg/kg, which may be noticed by an increase in the postductal

pO₂. This bolus is commonly followed by a continuous infusion of 1 mg/kg per hour. The infusion of vasodilators directly into the pulmonary artery has been shown not to have any advantage over their systemic or peripheral administration.²²⁵ Tolazoline side effects can be severe and include systemic arterial hypotension, upper GI hemorrhage, thrombocytopenia, hyponatremia, and skin rubor.^{141,224} In case there is upper GI hemorrhage, one should give priority to antacids and gastric lavage, given that tolazoline may inhibit the effects of cimetidine.²²⁶ Tolazoline, as well as these other vasodilators, can occasionally contribute to the stabilization of the patient, sometimes lengthening the honeymoon period. However, this is not often the case and, even when there is some improvement in oxygenation, no beneficial effect on survival has been demonstrated.^{22,215,220} Indeed, most referral centers no longer use systemically administered pulmonary vasodilators.

Sildenafil has been proposed as beneficial in the management of pulmonary hypertension associated with CDH.²²⁷⁻²²⁹ The initial reports were arguably encouraging, but its therapeutic value remains to be defined.

Nitric Oxide

The most potent selective pulmonary vasodilator known is nitric oxide (NO) administered by the endotracheal route. NO is a natural mediator of smooth muscle relaxation in general, but acts only locally because of its extremely short half-life. It is responsible for the biological activity of the so-called endothelial-derived relaxing factor.²³⁰ When given as part of the inspired air, NO crosses the alveolar-capillary membrane by diffusion and stimulates the cyclic guanosine 3',5'-monophosphate (cyclic GMP) in the smooth muscle of the pulmonary arterioles, inducing vasodilation. Its effects are limited to the pulmonary vasculature because it quickly combines with hemoglobin and is deactivated.

At first, there was great enthusiasm in relation to the use of NO for the treatment of CDH; however, clinical experience has been disappointing. Occasionally, NO does help in stabilizing the patient; however, even when there is an initially satisfactory response, there may be tachyphylaxis and, to date, improvements in outcome related to its use remain to be demonstrated.^{159,231,232} In fact, studies involving term neonates with respiratory failure of different causes have shown that inhaled NO improves oxygenation and lowers the need for ECMO in all diagnosis, except in CDH.²³³ The underlying reason why CDH neonates are often unresponsive to NO remains unknown. There has been some evidence that, if combined with the administration of surfactant or with liquid ventilation, NO can improve oxygenation and lower the pulmonary vascular resistance of children with CDH.^{127,234} At most referral centers, the role of NO in CDH remains confined to the management of right cardiac failure, when present.

Surfactant

Given the possibility of a deficiency in the surfactant system in children with CDH, endotracheal instillation

of exogenous surfactant has been studied as a therapeutic adjunct for many years. The results obtained thus far, however, do not justify its widespread application—that is, other than when prematurity itself is the indication for its use.^{132,133}

Prenatal administration of corticosteroids is known to induce, or at least increase, the production of endogenous surfactant.²³⁵ Although the precise mechanisms behind this phenomenon have yet to be elucidated, studies exploring this response in the treatment of CDH have been proposed.²³⁵

Alternative Forms of Mechanical Ventilation

Alternative forms of mechanical ventilation have also been used in CDH. One example is high-frequency oscillatory ventilation (HFOV), which mobilizes volumes smaller than the anatomic dead space, at frequencies of up to 40 Hz. Gas exchange seems to occur not from the delivery of gas under positive pressure, as in conventional mechanical ventilation, but through a diffusion process. Compared with conventional ventilation, it is thought that HFOV minimizes barotrauma and facilitates gas exchange, especially CO₂ elimination, in select circumstances. This form of ventilation, either isolated or combined with NO, has been tested in many institutions for the support of CDH patients, usually with less than satisfactory results.^{159,236} Similar to NO, HFOV seems to be an option only in select cases, yet to be better defined. When analyzed as a whole, the experience with HFOV in CDH has been disappointing.¹²⁷ However, Bohn has proposed that, as long as HFOV is not used for lung recruitment, but with mean airway pressures no higher than 14 to 16 cm H₂O and peak-to-peak airway pressures limited to 35 to 45 cm H₂O, it can lead to improved survival, especially if used early, rather than in a rescue mode.²³⁷ Other authors have also advocated the value of HFOV in CDH, within specific guidelines.¹⁸⁶

Intratracheal pulmonary ventilation, a form of ventilation that promotes active expiration, drastically lowering dead space and thus enhancing CO₂ elimination and minimizing barotrauma, has been used in a handful of CDH cases, with promising preliminary results.²³⁸ Regrettably, broader, definitive studies have been stalled by regulatory constraints and conflicting patent interests.

Liquid ventilation with a perfluorocarbon (PFC) has also been examined for some time. PFCs are bioinert, nonabsorbable by the alveolar-capillary membrane, and may carry large amounts of both O₂ (in particular) and CO₂. Besides, they display low surface tension levels, thus acting as truly artificial surfactants. Hybrid liquid ventilation (i.e., with a PFC and a gas) is known to increase pulmonary compliance and to improve gas exchange, especially oxygenation.²³⁹ The improved oxygenation, in turn, optimizes redistribution of pulmonary blood flow, hence alleviating the pulmonary hypertension.²³⁹ Liquid ventilation, either isolated or in combination with NO, has been applied in a few CDH cases, with encouraging results.^{239,240} However, its effect on outcome and role in the treatment of CDH, if any, is yet to be established.^{127,241}

Extracorporeal Membrane Oxygenation

Since the mid-1980s, extracorporeal life support has left the realm of experimental therapy and has become part of the standard therapeutic options in CDH. Several early studies showed that the introduction of ECMO resulted in a significant increase in survival of these patients.^{16,215,242-244} The significance of these studies, however, was limited by the relatively small number of patients and by the fact that each involved a single institution. A multicentric review by the Congenital Diaphragmatic Hernia Registry, involving 632 patients from 65 centers, showed that ECMO improved survival from 53% to 77% in children with high mortality markers and comparable prognosis.¹²⁷ That same study also showed a direct relationship between the severity of the cases and the beneficial impact of ECMO on outcome.

During extracorporeal support, there is not enough time for the lungs to grow to the point of reversing the pulmonary hypoplasia. However, ECMO acts as a bridge, lessening if not eliminating the component of pulmonary vascular hyperreactivity, allowing for maximum pulmonary remodeling, with an increase in compliance of the pulmonary arteries and arterioles, which normally takes place after birth,^{115,130} as well as reducing barotrauma to a minimum. There is still some debate regarding the best moment to administer ECMO in relation to the time of surgical repair of the hernia.¹⁷ There were no differences in survival when preoperative versus postoperative commencement of ECMO was compared.^{245,246} The current trend at most referral centers, however, is to use ECMO during preoperative stabilization, with repair of the hernia done either after ECMO decannulation, or while still under bypass.^{16,247,248} Despite the need for anticoagulation during ECMO, it has been shown that certain pharmacologic precautions and technical principles allow for safe surgical intervention during bypass, with a minimum risk of hemorrhagic complications.^{16,248-250} Occasionally, a patient may be in stable condition without the need for ECMO in the preoperative period, deteriorating either during or soon after the operation, and needs to then undergo bypass.

A few authors have proposed criteria for the contraindication of both ECMO and surgical repair, which would supposedly be linked to pulmonary disease incompatible with life.^{22,114,190,194,215} Given the many reports by other groups showing survival of patients who had met such criteria,^{16,243,245,251} not to mention the controversies related to the prognostic markers of CDH in general, we offer ECMO and surgery to virtually every patient, unless the presence of other associated anomalies is deemed incompatible with life.

The specific criteria for placing a patient on ECMO are equally debatable. Given the many controversies surrounding prognostic markers in CDH, it is no surprise that the many proposed indications for ECMO in this disease have not been widely accepted. Usually, the indications for ECMO in other diseases do not apply to CDH, mainly because the mechanical ventilation parameters used in other diagnosis before considering ECMO would be unacceptably toxic to the lungs of children with CDH, which are particularly vulnerable to iatrogenic

injury. In most centers, ECMO is considered when the patient with CDH cannot be adequately maintained without the use of toxic ventilator parameters. The definition of such toxic parameters is highly variable from one institution to another. As mentioned previously, in general we do not allow for the PIP and PEEP to be higher than 30 and 5 cm H₂O, respectively; it should be possible to gradually lower the FiO₂ to 60% or less in no more than 72 hours, and the base RR on the ventilator should not exceed 40 breaths/min, although a much higher RR from the child is tolerated, when he or she is under flow synchronization on the ventilator. The ventilation parameters are controlled mostly by preductal blood gases. In case the patient cannot be maintained under these guidelines, the use of HFOV and/or NO may be considered in select cases. However, extracorporeal bypass is usually indicated immediately. A potential benefit of placing infants with severe pulmonary hypoplasia on bypass already in the delivery room, the so-called *ex utero* intrapartum (EXIT)-to-ECMO procedure has been evaluated at select referral centers more recently. Our own experience with EXIT-to-ECMO in neonates with less than 15% predicted lung volume does not support an indication for this procedure, at this time.²⁵² Whenever possible, venovenous ECMO is preferred over the venoarterial mode.^{16,246} In case ECMO is initiated preoperatively, we perform the repair on bypass; however there are no data to indicate that the timing of surgery has any effect on survival.

Surgery

If the patient is on ECMO, we begin a continuous infusion of aminocaproic acid (AMICAR), an inhibitor of fibrinolysis, approximately 2 hours before the operation, concomitantly with reductions of the activated clotting time (ACT).^{248,250} If the patient is on HFOV and/or NO administration, they need not be discontinued during the procedure; they can be useful in select cases. If ECMO, HFOV, or NO are not being used, the best form of intraoperative ventilation is one at low pressures and high respiratory rates, with a dedicated infant or pediatric ventilator. Conventional anesthesia ventilators are excessively compliant and have too much dead space, and they are not suitable for these children.

In addition to general inhaled anesthesia, we recommend the routine introduction of a catheter for continuous epidural anesthesia, which allows for early withdrawal of curare in the postoperative period, as well as for maintenance of abdominal wall relaxation.¹⁶ All these effects, in turn, facilitate early postoperative resumption of flow synchronization and minimize volume retention, commonly associated with the continued use of curare. NO should not be used, because it tends to cause bowel distention, which can hinder hernia reduction and abdominal closure.

The patient is positioned supine and slightly tilted to the side contralateral to the hernia by a small support placed under the ipsilateral thoracoabdominal transition. An abdominal access is preferred over a thoracic one, usually through a subcostal laparotomy.¹⁷ After careful reduction of the herniated content, one should always

inspect the ipsilateral lung. Should it not be visible, the presence of a hernia sac, which is not always easily identifiable, must be investigated. If present, the hernia sac should be separated from the diaphragm and at least partially resected. Frequently, it is necessary to detach the posterior aspect of the residual diaphragm from the posterior abdominal wall, after opening the peritoneum and the pleura, which usually cover that area.

Whenever possible, a primary repair of the hernia is performed, with nonabsorbable sutures (Fig. 33-6). Yet, one should not force a primary repair under tension, because of the following potentially harmful consequences: the diaphragm will become flat and tense, minimizing, if not eliminating its functionality; there will be an excessive enlargement of the thoracic cavity, which may lead to alveolar hyperextension in the ipsilateral lung and consequent worsening of the pulmonary hypertension and barotrauma; the tension exerted on the diaphragm may be transmitted to the rib cage, resulting in chest wall deformities; and, finally, there will be further decrease of the abdominal cavity volume, hampering closure of the laparotomy.²⁵³ According to the Congenital Diaphragmatic Hernia Registry, approximately half of the patients receive a “patch” of some kind to have the diaphragm closed.^{17,35} In case a tension-free primary repair is not possible, several alternative techniques have been proposed, including abdominal or thoracic muscle flaps, free fascia lata grafts, and a myriad of prostheses, such as lyophilized dura mater, silicone, Dacron, polypropylene (Marlex, C. R. Bard, Inc., Murray Hill, NJ), polytetrafluoroethylene (PTFE, or Teflon; DuPont, Wilmington, DE), composite prosthesis, and others.^{17,215,254-260} Regardless of the technique used, care should be taken not to leave the diaphragm too flat, but with a slight to moderately sized dome, so that the same problems associated with primary closure under tension can be avoided.²⁵³ The dome should not be too pronounced, otherwise local paradoxical respiration can ensue. We and many others do not favor muscle flaps because of the residual defects left in the abdominal or thoracic walls, as well as the increased risk for local hemorrhage, particularly if ECMO is or may be used; however, this form of repair does have a sizeable following. At most



FIGURE 33-6 ■ Primary repair of a diaphragmatic defect in a newborn with congenital diaphragmatic hernia.

U.S. centers, pediatric surgeons favor the use of either a prosthesis made of expanded Teflon (Fig. 33-7) or a Teflon–Marlex composite. At least part of the reasons for such a preference for Teflon derive from a study showing improved incorporation by the host and a better motility pattern of this prosthesis in the short term, when compared with silicone prosthesis and muscle flaps.²⁶¹ A number of acellular biological prostheses, including acellular human dermis, cross-linked porcine dermal collagen, and porcine small intestinal submucosa, have also been studied experimentally, with conflicting results.²⁶²⁻²⁶⁶ Among these results, small intestinal submucosa and acellular human dermis have mostly led to disappointing results, whereas cross-linked porcine dermal collagen (Permacol) may hold some promise, albeit yet to be confirmed by more than one center.²⁶⁶ When the posterior residual diaphragm is not large enough for proper suturing, one option is to pass the suture around the subjacent rib, after gentle anterior traction of the rib with a clamp, to avoid injury to its neurovascular bundle.

Soon before completion of the diaphragmatic closure, a multiperforated tube is placed into the pleural cavity, exteriorized through the chest, and typically just placed under water seal. Continuous suction through the chest is usually avoided, because of the possibility of pulmonary overdistention, which is highly detrimental in CDH. Many authors even recommend that a chest tube not be placed at all.^{22,267} In a review by the Congenital Diaphragmatic Hernia Registry, 24% of the patients did not receive a chest tube.¹⁷

We prefer to correct the intestinal malrotation, almost always present; however, most centers do not perform this maneuver.¹⁷ In most institutions, including ours, an appendectomy is not routinely done, in order to minimize morbidity.¹⁷ Given the reduced abdominal volume, difficulty closing the abdominal wall is not uncommon. Should there be excessive intra-abdominal tension after abdominal wall closure, a syndrome of compression of the inferior vena cava may develop, along with a decrease in thoracic expansibility and tidal volume. To prevent



FIGURE 33-7 ■ Prosthetic repair of a diaphragmatic defect with expanded Teflon (DuPont, Wilmington, DE) in a newborn with congenital diaphragmatic hernia.

this, repeated digital distention of the abdominal wall and evacuation of intestinal gas may be of help. Some have suggested a routine gastrotomy as an additional means to decompress the stomach, facilitate abdominal closure, and minimize postoperative respiratory complications, but there has been no evidence-based support for this idea.^{247,268} When tension-free closure of the abdominal wall is not possible, the use of an abdominal silo should be considered, followed by postoperative serial reductions and definitive primary closure.^{22,215,269} Another option is simply to close the skin, leaving the proper, definitive closure for a later date.²⁴⁸ The need for either of these maneuvers, however, should be extremely rare.

In children on ECMO, a few technical precautions should be taken to prevent excessive bleeding: the skin should be open with needle-tip electrocautery; when primary diaphragmatic closure is unlikely, one should not dissect the posterior residual diaphragm, if it is adhered to the posterior abdominal wall, but pass the stitches around the subjacent rib, as described above; finally, fibrin glue should be applied to the diaphragmatic suture line and other raw surfaces.²⁴⁸ We do not leave a drain in the abdomen. If the abdominal wall cannot be closed primarily and a silo is implanted, serial reductions should commence only after the child comes off bypass.

Thoracoscopic and laparoscopic repairs of CDH have been used increasingly.²⁷⁰⁻²⁷² During thoracoscopy, reduction of the hernia can even be facilitated by the mild positive intrathoracic pressure often applied intraoperatively. These procedures have also proved viable in the presence of associated cardiac anomalies, as well as for the placement of prosthetic patches. On the other hand, a recent randomized controlled trial has shown that thoracoscopic repair of CDH is associated with prolonged and severe intraoperative hypercapnia and acidosis, compared with open surgery, calling into question the safety of thoracoscopy with CO₂ insufflation and conventional ventilation for the repair of CDH.²⁷³ That study was preceded by another one from the same group showing decreased cerebral oxygen saturation during thoracoscopic repair of CDH.²⁷⁴ The precise indications, pros and cons of the so-called minimally invasive repair of CDH are yet to be fully clarified. A possible beneficial role for intratracheal pulmonary ventilation during the procedure in severe cases has been proposed in an animal model.²⁷⁵

Postoperative Care

If the patient was not on ECMO during surgery, mild ventilatory support under flow synchronization, as described above, should resume as soon as possible, if necessary with pharmacologic reversal of the muscle paralysis, in case it had to be used. This transition can be tremendously facilitated if the child was placed under continuous epidural anesthesia intraoperatively.¹⁶ The principles guiding mechanical ventilation described for the preoperative period also apply to the postoperative period. The same is true for the criteria to go on ECMO.

Although some children improve after repair of the hernia, frequently there is (at least temporary) deterioration of the respiratory mechanics in the immediate

postoperative period.^{213,276} This phenomenon is thought to be due to anatomic distortions on the diaphragm and thoracic cavity, to hyperinflation of both lungs, and to an increase of the intra-abdominal pressure.²⁷⁶ Under these circumstances, the ventilator parameters may need to be temporarily "increased," sometimes to the point that alternative modes of ventilation and even ECMO may have to be used. Occasionally, children that had been on bypass preoperatively and were decannulated before the operation may need to go back on ECMO (this also is one of the reasons why we prefer to perform the repair on bypass).

Another potential complicating factor is the administration of intravenous fluids, which must be controlled carefully. Concomitantly to the common risk of hypovolemia, related to surgical trauma and bleeding, neonates with CDH, more so than newborns with other surgical diseases, initially behave as if with inappropriate secretion of antidiuretic hormone and may tend to retain excessive amounts of water.²⁶⁹ The explanation for this phenomenon is not yet clear. This predisposition must be recognized early, otherwise patients can be overloaded with fluids, with harmful consequences to their respiratory and cardiac status.

Sometimes, intra-abdominal pressure rises significantly in the immediate postoperative period. One should be attentive to signs of inferior vena cava syndrome, which can lead to a decrease in the venous return to the heart, impairment of renal blood flow, or a reduction in tidal volume. Should there be any evidence of renal insufficiency or major worsening of the respiratory or cardiac status, one must consider muscle paralysis, which may lower the intra-abdominal pressure. In the more severe cases, it may be necessary to take the child back to the operating room for placement of an abdominal silo.

Whenever the chest tube is used, it is not continuously aspirated, but only placed under a passive water seal to avoid pulmonary hyperdistention, which can occur on both lungs because of the large empty residual space within the ipsilateral pleural cavity.^{22,276} The chest tube should be removed only after the patient is extubated, usually after liquid drainage ceases. Not infrequently, liquid drainage lasts for a long period of time, until the lung can occupy the whole pleural space. In these circumstances, one may consider removing the chest tube while it is still draining fluid and tolerate a temporary pleural collection.

Children on ECMO should continue to receive AMICAR, in parallel to the maintenance of ACT levels lower than usual for bypass.²⁴⁸ When AMICAR is not used, or the technical precautions described above are not duly followed, the incidence and severity of hemorrhagic complications tend to be high.^{215,277} Should there be bleeding, surgical dressings must be regularly weighed and the losses through the chest tube and abdominal drain (if present) must be quantified. In our service, blood losses equal to or higher than 20% of a patient's total blood content in 8 hours or less, or progressive abdominal distention, is a criterion for surgical re-exploration. Frequently, one cannot find specific areas of bleeding during reoperation, but a diffuse oozing throughout the operative field. In these cases, more aggressive

pharmacologic management related to AMICAR and ACT levels must be pondered. In addition to these potential surgical complications related to ECMO, the common risks associated with extracorporeal bypass itself are, obviously, also a possibility.

More rarely, GI obstruction resulting from adhesions, gastric volvulus, or midgut volvulus can occur even in the immediate postoperative period.²⁷⁸ Other rare complications are chylothorax and chylous ascites.²⁷⁹⁻²⁸¹ In the few cases reported to date, the causes for these chylous collections have not been clearly determined. Their treatment should be based on parenteral nutrition, feedings with middle chain triglycerides and, if necessary, occasional needle drainages.²⁷⁹⁻²⁸¹

Late-Presentation Congenital Diaphragmatic Hernia

Regardless of its initial clinical presentation, including cases of purely incidental findings, late-presentation CDH should be repaired as soon as possible because of the risks of incarceration and strangulation of the herniated content, and even sudden death.²⁸²⁻²⁸⁴ In these cases, a laparotomy is still the preferred access; however, a thoracotomy can be considered much more frequently than in neonates whenever the presence of firm adhesions within the herniated content into the chest is suspected. Frequently, one cannot determine preoperatively whether a laparotomy or a thoracotomy would be the best access and personal, somewhat subjective preferences may play a role in the decision process. Minimally invasive access can be justified in select cases.

RESULTS

Even at referral centers with all known therapeutic options for treatment of CDH available, there may be a sizeable variability of the survival rates associated with this disease. These differences are due to several reasons. On one hand, patient population profiles can vary in regard to the proportion of high-risk neonates from one institution to another. In addition, patients may die before reaching a center and thus not be included in the final numbers; it is the so-called hidden mortality originally described by Harrison and colleagues.²⁸⁵ At the same time, a few authors deliberately exclude children considered to have pulmonary hypoplasia incompatible with life, often based on arguable criteria, which artificially improve survival rates.^{190,194} The same is true for the inclusion, or not, of children bearing other congenital anomalies associated with CDH.^{117,187} In addition, there are still major differences among institutions related to therapeutic protocols/strategies. Such heterogeneities, combined with the different sizes of the review series and the constant evolution of the treatment options for CDH, can limit one's interpretation of the results.

Bearing in mind the limitations described above, the latest meaningful reviews have shown that overall survival for isolated CDH at many referral centers has been close to 80%, a sharp increase from the depressing figures of a little over 20 years ago, when ECMO was not widely

available and aggressive hyperventilation was still the norm.^{24,35,127,194} At our institution, more than 80% of the diagnoses are prenatal. As a consequence, their delivery can be planned, usually at one of two sister institutions linked to our hospital. The few cases diagnosed only after birth within our referral base are rapidly transferred to us, consequently our "hidden mortality" is practically zero and our patient population is large and illustrative. In accordance with the data from other referral centers, our survival rates for high risk neonates ($\approx 90\%$ of our cases) had varied between approximately 85% and 90% for isolated CDH and had been approximately 70% when all cases, including those with other associated anomalies, were considered.^{16,127,286} These numbers were intimately related to the application of the principle of gentle ventilation and permissive hypercapnia, as well to the liberal and early indication for ECMO. In the past several years, our overall survival has surpassed 80%, by adding careful attention to the right heart to the management principles outlined earlier.²⁸⁷ Among the several other anomalies that can be associated with CDH, the most common of them, cardiac defects, deserve special consideration as to their effect on outcome. Not long ago, cardiac anomalies were a virtual harbinger of a death; now they are associated with a highly variable overall prognosis, regardless of type.¹⁸⁷ In non-high-risk patients (i.e., when an isolated CDH becomes symptomatic after 6 hours of life), survival is close to 100%.^{127,194}

LONG-TERM FOLLOW-UP

At the same time that CDH survival rates have almost skyrocketed lately, perhaps predictably so, morbidity rates have worsened. High-risk children who would otherwise have died not long ago, now survive often with multiple problems, in various systems, and they need to be followed by a dedicated, multidisciplinary team.^{281,286,288-291} Although this seems to be somewhat more evident in patients who had to go on ECMO, it is currently a universal trend, which also applies to those who did not need bypass.^{281,286,290,291} In many series, including ours, there is a direct relationship between the need for prosthetic diaphragmatic repair and the incidence and severity of late complications.^{286,288,290,291}

One of the most common problems in CDH survivors is gastroesophageal reflux (GER).^{*} In our experience, virtually every child has some manifestation of GER, but only approximately 20% of them need to undergo a fundoplication.²⁹¹ It has been suggested that, in addition to GER, esophageal motility is often abnormal, not infrequently with concurrent esophageal dilation, hindering management of the GER itself.²⁹² In addition to the expected and well-documented adverse effects of CDH in esophageal topography and in the angle of His, at least in experimental CDH, abnormalities in intrinsic esophageal innervation have also been demonstrated, which may correspond to an unrecognized equivalent in humans, possibly contributing to this common clinical scenario.²⁹³

*References 215, 247, 281, 286, 288, 289, 291, 292.

In comparable manner, deficient enteric innervation and impaired gastrointestinal motility have been described in the nitrofen model of CDH, the clinical significance of which remains to be determined.²⁹⁴ In our series, more than half of the children stayed below the 25th percentile for weight during the first year of life, despite a higher than normal caloric intake.²⁹¹ Up to two thirds of the children may need a gastric tube or gastrostomy to be fed adequately, usually because of oral feeding difficulties.^{281,288,292} Prolonged endotracheal intubation is predictive for severe oral aversion, which was found in one quarter of our patients during the first year of life.²⁹¹ Most of these gastrointestinal and nutritional complications tend to improve with age.²⁹¹

Bronchopulmonary dysplasia, or “chronic lung disease,” is present in one to two thirds of patients.^{288,295} The need for continuous oxygen delivery through a nasal catheter after hospital discharge is not uncommon (16% of the cases, in our experience), in some patients for more than 2 years.^{159,281,288,290} Volume restrictions, usually through diet based on hyperosmolar formula, may help minimize pulmonary complications.²⁸¹ Diuretics, sometimes in association with bronchodilators or steroids, may also be useful.^{288,290} In our patients, prophylaxis against respiratory syncytial virus has been proposed as a means to decrease both the incidence and severity of acute respiratory failure related to this disease.²⁹⁰

Although the alveoli continue to multiply during the first 8 years of life,^{120,296} their total numbers do not reach normal values in CDH.^{113,115,116,297} Emphysematous changes may occasionally be seen on plain chest radiographs, especially in the more caudal portions of the lungs.²⁹⁸ Radioisotopic pulmonary scans usually show reductions on both ventilation and perfusion, which are also typically disproportionate to each other.^{290,298} Interestingly, despite all these initial disturbances, pulmonary function seems to normalize in the long term.^{134,299,300} Pulmonary artery pressure, estimated by Doppler echocardiogram, tends to normalize with time in most children. However, deaths from right cardiac failure have been reported as late as 18 months of age.²¹⁵

Different factors, including hypoxemia, ventilation strategy, and ECMO, can affect the neurodevelopmental outcome. Furthermore, fetal cerebral blood flow velocities have been shown to be decreased in fetuses with CDH, although overall cranial and cerebral growths tend not to be conserved.³⁰¹ In general, the overall incidence of neurologic complications in patients that received ECMO for CDH is comparable to that found in infants who required bypass because of other diseases.^{302,303} There is some controversy, however, regarding purely cognitive development. Although a few authors have found cognition problems to be more frequent in CDH children than in those who went on ECMO for other reasons, others have not confirmed such findings.^{286,302,303} In most cases, such impairment is mild or moderate.^{281,286,288,302,303} Children with continued need for oxygen therapy and/or failure to thrive seem more susceptible to neurodevelopmental complications.³⁰⁴ Otherwise, neurodevelopmental delays tend to disappear, or at least improve with age, with patients typically functioning within the average range as early as preschool ages.^{281,286,304}

Hearing deficits and need for hearing aids have been noticed in up to one fifth of the children, for reasons yet to be completely clarified.^{281,286,288,289} Putative causes include prolonged alkalosis, the use of aminoglycoside antibiotics, and the administration of high doses of furosemide.²⁸¹ ECMO is also a risk factor.³⁰⁵ Every child with CDH, particularly those with speech delays, must undergo screening audiometry and brain-stem auditory evoked response testing periodically, given that hearing deficits may have a delayed onset.^{281,286}

Chest wall development can be affected by the disease itself and its treatment. The volume of the ipsilateral thoracic cavity may be reduced, apparently as a consequence of the reduced size of the lungs.³⁰⁶ Overall, up to one third of the children have some degree of chest wall deformity, more commonly pectus excavatum and thoracic scoliosis; the latter is a risk factor for hernia recurrence in children who receive a diaphragmatic prosthesis.^{281,286} In general, chest wall deformities associated with CDH are mild and rarely need surgical repair.^{281,286}

Several other complications have been reported in different systems. Intestinal obstruction is the most frequent reason for reoperation in our experience, occurring in less than 20% of cases.²⁸¹ Its most common causes are adhesions, followed by midgut volvulus and gastric volvulus.^{281,286,288} A number of other ailments have also been reported in association with CDH, albeit much less frequently, including vesicoureteral reflux, cholelithiasis, asymptomatic renal calculi, chylothorax, hypertrophic pyloric stenosis, retinal vasculopathy without functional visual deficit, and chronic superior vena cava syndrome (the latter two complications were likely related to ECMO).^{281,286,288}

Diaphragmatic Hernia Recurrence

Overall postoperative recurrence rates have been reported to be between 6% and 80%.[†] Recurrence rates constitute a moving target, given the not uncommon introduction of new materials and/or techniques over time. Hernia recurrence is more common within the first 18 months of age, but it can happen at any age.³⁰⁷ The vast majority of the cases occur in children in whom a prosthetic patch was used for repair of the hernia, with approximately half of them progressing with a recurrence in the larger and longer series.^{247,281,302,307} Diaphragmatic repair with a prosthesis has also been associated with higher rates of infection, adhesions, and both thoracic and spinal column deformities, when compared with primary repair.^{288,309,310} There are conflicting data as to whether split abdominal wall flap repairs are associated with higher rates of recurrence than that of prosthetic patches, or not.^{308,311,312} Either way, these types of repair also fail more often than primary repairs and of course leave a residual abdominal defect. It remains unclear whether minimally invasive approaches have an effect on recurrence rates, or not.

The main mechanism behind hernia recurrence is believed to be related to normal growth, which is supposed to lead to traction and eventual detachment of the

[†]References 215, 247, 281, 302, 307, 308.

prosthesis, usually at its posterior-medial aspect.²⁴⁷ The most common clinical manifestations of hernia recurrence are intestinal obstruction and respiratory distress, in that order.^{286,307} Asymptomatic recurrences are not uncommon,^{281,307} nor are patients with multiple recurrences.³⁰⁷ Diagnosis is usually made with a plain chest radiograph; however, sometimes a contrast GI radiograph is necessary. Occasionally, depending on the herniated content, ultrasound, CT, or, more rarely, a contrast enema, may be of help. Hernia recurrence should be surgically repaired, because of the risk for incarceration or strangulation. In select cases of short-term, “small” and stable recurrences, reoperation may be postponed, depending on the patients’ overall condition.³¹³ Given that hernia recurrence is frequently asymptomatic at first, a plain chest radiograph should be performed at least once per year postoperatively in every patient who underwent prosthetic repair.²⁸¹

FUTURE PERSPECTIVES

Since the mid-1990s, much progress has been made on the treatment of CDH. Survival rates consistently hovering around 90% are now commonplace at major referral centers. At the same time, one could say that a formerly fatal illness has been turned into a chronic disease, as morbidity rates have increased in parallel to survival. The challenges ahead relate to both minimizing morbidity and rescuing the cases with extreme pulmonary hypoplasia, which remain the leading cause of death in this disease. These challenges have been the stimuli for some of the most fertile research efforts in pediatric surgery lately. Summarized accounts of some of these efforts will follow, along with a few brief historical notes.

Despite a few anecdotal successes, the results of the actual repair of the hernia in the fetus were disappointing.^{19,20} One of the reasons for the bad results was the fact that the reduction of the hernia increased intra-abdominal pressure, hampering umbilical blood flow, and frequently lead to kinking of the umbilical vein and of the ductus venosus.^{20,314} Wilson and colleagues^{28,315,316} first showed that a complete occlusion of the fetal trachea drastically accelerated fetal lung growth, reversing both the pulmonary hypoplasia and its associated pulmonary vascular abnormalities in experimental CDH, resulting in marked improvements of lung function at birth (Fig. 33-8).^{28,315,316} This led almost immediately to clinical trials, in which fetal tracheal occlusion was accomplished first through open surgery, then videofetoscopically, and then percutaneously.^{31,32,317-320} The tracheal occlusion device is typically removed at birth before occluding the umbilical cord, during an EXIT procedure. Once again, despite successes, at major referral centers results have been significantly worse than that of postnatal care, mostly because of shifting patient selection, postoperative preterm labor, dislodgment of the tracheal occlusion device, erratic secretion of the pulmonary liquid by the fetus, and pulmonary dysfunction in a few patients in whom there was reversal of the lung hypoplasia (the cause of which remains to be determined).^{30-32,318,320} Even so, experimental developments can contribute to refine and

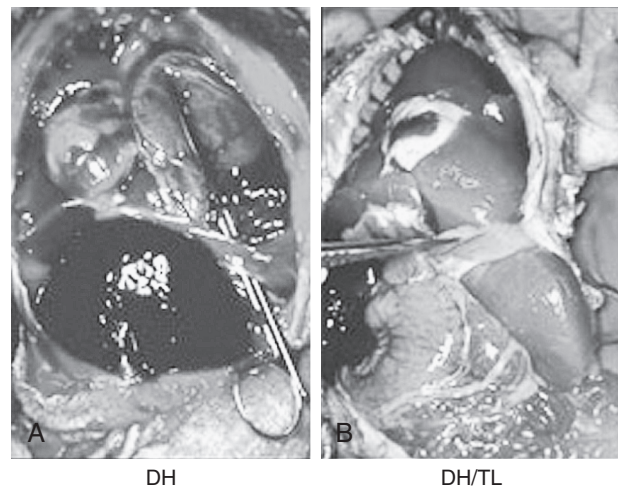


FIGURE 33-8 ■ **A**, Gross necropsy finding in a newborn lamb with experimental congenital diaphragmatic hernia (CDH). The scissors are placed through a defect on the left diaphragm. Abdominal viscera are present in the left hemithorax. The lungs are small and not visible. **B**, Gross necropsy finding in a newborn lamb with experimental CDH and complete tracheal occlusion. The forceps are holding the left diaphragm. Both lungs are markedly enlarged. The left lung has completely reduced the herniated abdominal viscera and has grown into the abdomen, through the diaphragmatic defect. *DH*, Diaphragmatic hernia; *TL*, tracheal ligation. (Reproduced with permission from DiFiore JW, Fauza DO, Slavin R, et al: Experimental fetal tracheal ligation reverses the structural and physiological effects of pulmonary hypoplasia in congenital diaphragmatic hernia. *J Pediatr Surg* 29:248-256, 1994.)

optimize fetal tracheal occlusion in the future—for example, via improvements in patient selection, less invasive methods such as ultrasound-guided or dynamic or reversible techniques, the intrapulmonary delivery of select oncotic agents, and the development of nonhuman primate models.³²¹⁻³²⁶

The acceleration of pulmonary growth observed after fetal tracheal occlusion depends on sustained intrapulmonary distention by retained lung liquid, which is actively secreted by the alveolar-capillary membrane.^{28,315,316} One development of this finding was our demonstration that lung growth can also be accelerated after birth by continuous intrapulmonary distention with a liquid medium, namely PFC, which is bioinert and nonabsorbable by the alveolar-capillary membrane.³⁶ This phenomenon cannot be reproduced in the lungs of adult individuals.³⁷ Apparently, liquid-based pulmonary distention simply accelerates normal growth and cannot induce hyperplasia in mature, developed lungs. Long-term studies in animal models have revealed no deleterious effects of PFC-based lung distention.³²⁷ The first series of neonates to undergo pulmonary distention with PFC under extracorporeal support was presented in 2000, with encouraging results (Fig. 33-9).³⁸ A larger, multicenter study with longer distention times than those allowed by the U.S. Food and Drug Administration in the first series is being pursued.

The concept of lung transplantation in CDH involves the notion that the transplanted lung (or lobe) should maintain the patient only until the native lung

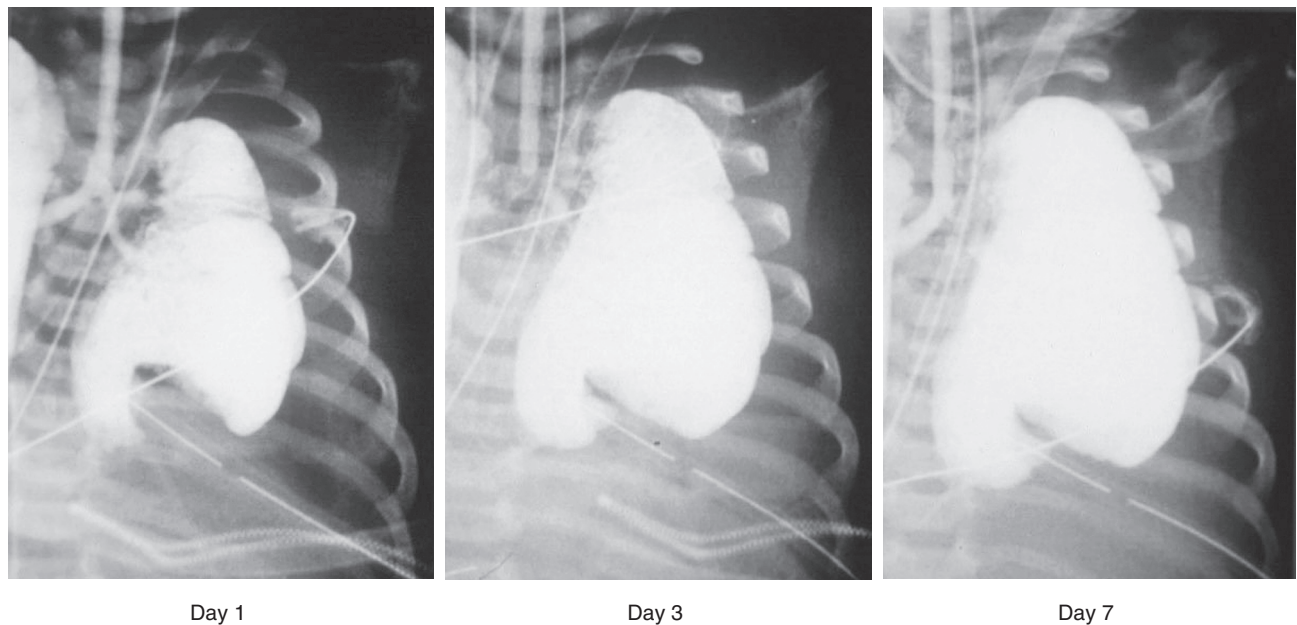


FIGURE 33-9 ■ Plain chest radiographs from a neonate with congenital diaphragmatic hernia, showing the progress of the ipsilateral lung during intrapulmonary distention with a perfluorocarbon (radiopaque) for 7 days. Notice its obvious increase in size, which did not happen in the contralateral lung. (Reproduced with permission from Fauza DO, Hirschl RB, Wilson JM: Continuous intrapulmonary distention with perfluorocarbon accelerates lung growth in infants with congenital diaphragmatic hernia: initial experience. *J Pediatr Surg* 36:1237–1240, 2001.)

contralateral to the hernia develops enough to allow for resection of the graft, so that immunosuppression is no longer necessary. Successful conventional lung transplantations have been performed in CDH in few cases.²⁶ Survival after living donor, reduced lung transplantations has been achieved as well, albeit only experimentally.³²⁸ Chronic donor shortage and the many difficulties yet to be overcome in reduced lung transplantation to newborns render these options of limited, if any, value, at least for the foreseeable future.

Diaphragmatic reconstruction with an autologous engineered construct was first proposed in 2000, and it has since continued to develop experimentally as a viable and potentially improved alternative for diaphragmatic replacement in the neonatal period.^{39,40} Recent data have shown that diaphragmatic repair with an autologous tendon engineered from mesenchymal cells isolated from the amniotic fluid leads to improved mechanical and functional outcomes when compared with an equivalent acellular bioprosthetic repair, or with myogenic cell-based grafts, given a suitable scaffold environment.^{40,41} Cell manufacturing for engineered diaphragmatic replacement has recently proven viable under guidelines mandated by the U.S. Food and Drug Administration.^{42,43} Translation of these findings into clinical practice is hoped for the not too distant future, pending the generation of additional animal safety data as part of the prerequisites for regulatory approval, some of which have already been produced.⁴⁴

Fundamental knowledge and basic aspects of the management of CDH should also continue to improve. A better understanding of the pathogenesis and pathophysiology of this disease is expected. A large, detailed

multicenter study sponsored by the National Institutes of Health aimed at uncovering genetic aspects of CDH has been leading to new germane insights.⁷² The notion of prenatal gene therapy for CDH has started to be explored experimentally in rodent models.³²⁹ The contemporary addition of computer simulation models, including cell-based simulation, could shed additional light on the pathogenesis of CDH.^{330,331} The search for prognostic markers will continue through ever-improving imaging methods such as three-dimensional anatomic measurements via MRI. The role of so-called adjunct therapies and alternative ventilation methods should be better defined.

The role of the Congenital Diaphragmatic Hernia Registry is as important as any of the above mentioned initiatives. Like its pediatric oncology counterparts, this organization, now embracing several tens of centers, has had a significant effect on the understanding and treatment of this disease, and its influence should only continue to grow. The most recent demonstration of the power of such a registry has been the development of a staging system based on defect size measured at the time of repair. It was noted that primary repairs and small patches (types A and B, respectively) were associated with a low incidence of other anomalies and a survival exceeding 96%. Conversely, large patch repairs and diaphragmatic agenesis (type C and D, respectively) had a higher incidence of associated anomalies and lower survival (76% and 58%). Diaphragmatic agenesis associated with a cardiac anomaly had the lowest survival of all at 38%.^{331a} It is hoped that future reports will use this system so that relative severity of different populations can finally be compared.

OTHER DIAPHRAGMATIC ANOMALIES

In addition to “classical” CDH, many other congenital diaphragmatic anomalies have been described. An overview of their location and frequency at different ages can be seen in [Figure 33-10](#).¹⁵⁸ Classical CDH is, by far, the most common diaphragmatic anomaly of the neonatal period. Hiatal hernia seldom manifests prior to adulthood. In this section, only general aspects of these other diaphragmatic anomalies will be briefly discussed.

Diaphragmatic Eventration

The term *eventration* is used to describe an abnormal elevation of the diaphragm. It can be congenital or acquired. Acquired cases, also known as *diaphragmatic paralysis* or *paresis*, usually result from damage to the phrenic nerve, which in turn may be due to traumatic delivery, thoracic surgery, tumors, inflammation, or central nervous system conditions, such as poliomyelitis and Werdnig-Hoffmann disease.³³²⁻³³⁴ In congenital cases, the phrenic nerve is almost always normal. It is often difficult to differentiate a congenital case from one caused by obstetric trauma. Acquired eventration should be suspected whenever there is a history of complications at delivery and/or concomitant signs of injury to the brachial plexus.

In congenital eventration, either the whole diaphragm may be affected or only part of it, usually its dome, which is not a meeting point of embryonic components. Indeed, it is thought that diaphragmatic eventration represents a failure of muscularization of the diaphragm, not a failed fusion of all its embryonic components. Its cause is unknown. It can be present on either side, but is more

frequent on the left. Bilateral cases have been reported.³³⁵ Diaphragmatic thickness and its muscle fiber density vary within a broad spectrum in the eventrated area, going from normal, with practically all fibers present, to very thin, without any fibers. The eventrated portion of the diaphragm does not function. In certain cases, the differentiation with CDH containing a hernia sac is purely arbitrary. Like in CDH, there may be associated pulmonary hypoplasia, intestinal malrotation, and other anomalies in various systems.³³⁶⁻³³⁸

Clinical manifestations also vary within an ample spectrum which, to a certain extent, is analogous to that of CDH. However, presentation after the neonatal period is much more common, and symptoms are usually much less exuberant than in CDH. In older children, (often recurrent) pneumonia may be the first manifestation. Gastrointestinal symptoms, usually obstructive in nature, and failure to thrive are not uncommon. In cases linked to Werdnig-Hoffmann, respiratory distress owing to the eventration may be the initial manifestation of disease.³³³ The patient may also be completely asymptomatic. The diagnosis is typically made with a plain chest radiograph, although sometimes it may have to be confirmed with ultrasonography or fluoroscopy, both of which can also be helpful in an eventual differential with CDH. In the latter two examinations, one should be able to notice paradoxical respiration on the affected area, as long as the patient is not being artificially ventilated.

Symptomatic patients should undergo surgical repair. In asymptomatic patients, surgery is recommended when there is a large eventration or pulmonary function test results are abnormal, given that lung growth may be compromised if the eventration is not treated. In a few patients with an asymptomatic acquired eventration,

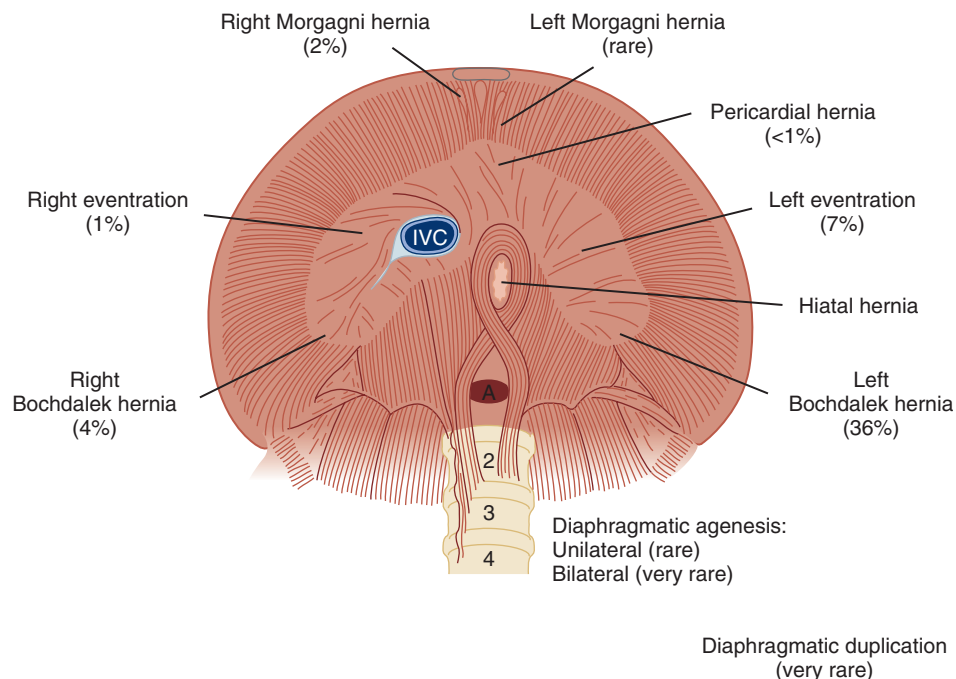


FIGURE 33-10 ■ Overall relative incidence and location of different diaphragmatic anomalies at all ages, including children and adults. Bochdalek hernia is, by far, the most common in infants. Hiatal hernia rarely manifests before adulthood. IVC, Inferior vena cava.

there may be variable degrees of recovery of the diaphragmatic function with time and spontaneous reversal of the eventration, so that a so-called conservative treatment may be initially justified, but not for long.

At surgery, plication of the diaphragm with nonabsorbable sutures is usually preferred, but, in select patients, partial resection followed by overlapped reconstruction of the residual diaphragm may be the best option (simple end-to-end suturing commonly leads to recurrence). In right eventrations, most authors prefer to perform the repair through a thoracotomy. In left eventrations, there is some controversy as to whether a thoracotomy or a laparotomy would be the most suitable access. We favor the thoracic access, mostly because it allows for visualization of the branches of the phrenic nerve, which thus can be preserved during diaphragmatic plication. This is particularly relevant in view of the fact that, after plication, there may be at least partial recovery of diaphragmatic function.³³⁹ When a thoracotomy is used, regardless of the side, usually the seventh intercostal space is the one to be opened. An abdominal access may be preferred in certain bilateral cases. Over the last decade or so, thoracoscopic repair has been increasingly favored by most centers, having become the method of choice for many patients; however, it is still unclear whether recurrence rates are comparable to those for open repair, and such techniques are still evolving.³⁴⁰⁻³⁴²

Morgagni Hernia

Morgagni hernia is also known as *retrosternal* or *parasternal hernia*. This kind of diaphragmatic hernia occurs through the parasternal spaces, also called *Morgagni foramina*, or Larrey clefts, which are small, triangular portions of the diaphragm on each side of the inferior limit of the sternum that form as a result of the union between the transverse septum and the thoracic wall. This hernia can occur on both sides, but is more common on the right. Bilateral cases have been reported.^{343,344} If a hernia sac is present, the superior epigastric artery normally stays lateral to it. This hernia is more frequent in adults and in older children. In childhood, this hernia occurs in a proportion of approximately 1:20 in relation to classic CDH.³⁴⁴⁻³⁴⁶ Predisposing factors include obesity and a history of trauma. The hernia is usually asymptomatic. Occasionally, it leads to mild symptoms such as respiratory discomfort, vague gastrointestinal manifestations, or epigastric tenderness. It tends to be symptomatic more often in children than in adults.³⁴⁴ Most of the time, this hernia is diagnosed as an incidental finding of a chest roentgenogram. A lateral radiograph is usually more helpful than an anterior-posterior image, sometimes after a barium swallow, or, more rarely, after contrast enema. Occasionally, ultrasound or CT can be valuable to confirm the diagnosis as well.³⁴⁴

Incarceration of the herniated content is rare. Open repair is frequently performed through a supraumbilical, usually subcostal laparotomy. After hernia reduction and resection of the hernia sac (if present), the diaphragm is sutured to the posterior sheath of the rectus abdominis muscle. A prosthesis is typically not necessary for

diaphragmatic repair. In addition, the laparoscopic approach has been increasingly favored, although it is still unclear how it compares with open repair in the long term.^{347,348}

Various other anomalies can be associated with Morgagni hernia, more frequently cardiac.^{344,346} Intestinal malrotation is somewhat common.³⁴⁴ A Morgagni hernia may be part of the pentalogy of Cantrell, if associated with defects of the inferior aspect of the sternum, of the supraumbilical abdominal wall, and of the pericardium (all of which lead to cardiac ectopia), in addition to a cardiac anomaly.³⁴⁹ In these cases, one usually tries to suture the diaphragm to the sternum and may need to use a prosthesis more frequently than in isolated hernias.

Hiatal Hernia

Hernias through the esophageal hiatus can be divided into four main types: (1) sliding esophageal hernia, the most common, in which the esophagus moves freely through the hiatus, so that the esophagogastric junction may be either in the chest or in the abdomen at different times; (2) paraesophageal hernia, in which the esophagogastric junction remains below the diaphragm and the stomach rolls up into the chest parallel to the esophagus; (3) combined hernia, in which the two previous types coexist; and (4) the controversial congenital short esophagus. Hiatal hernia can manifest as early as the neonatal period; however, most cases first present in adulthood. Vomiting is the most common manifestation, yet patients may often be asymptomatic. The diagnosis is usually made through a contrast upper GI. An upper GI endoscopy is frequently part of the diagnostic evaluation as well. Surgical treatment is the norm, particularly because of the risks of incarceration and strangulation. Through a laparoscopy or a laparotomy, the hernia is reduced, the diameter of the esophageal hiatus is normalized, and a gastroesophageal fundoplication is performed. The treatment of choice for certain cases of short esophagus remains a subject of much debate.

Pericardial Hernia

Pericardial hernia, also known as *hernia of the central diaphragmatic tendon*, is the rarest and least understood of the diaphragmatic defects that can lead to a hernia. In this defect, there is a communication between the peritoneal and pericardial cavities, with or without herniation.³⁵⁰ In general, there is no hernia sac.³⁵⁰⁻³⁵² It has been identified from soon after birth up to late adulthood, with most of the cases diagnosed in neonates.³⁵²⁻³⁵⁴ It is thought that the primary defect affects the transverse septum directly.¹⁵⁸ There are not enough data for typical clinical manifestations to be described. The hernia can be asymptomatic and only incidentally suspected on a plain chest radiograph.^{353,354} Surgical repair through the abdomen is recommended.³⁵³

Diaphragmatic Agenesis

Diaphragmatic agenesis is customarily confused with CDH in which the diaphragmatic defect is particularly

large, especially if the residual posterior diaphragm is not dissected from the abdominal wall. True diaphragmatic agenesis is rare. It is usually unilateral, more common on the left, and rarely bilateral.³⁵⁵⁻³⁵⁷ It is generally identified in the neonatal period, but cases uncovered only in adulthood have been described.^{358,359} It can be associated with multiple other anomalies, especially if bilateral.^{356,360} Clinical manifestations, diagnosis, and treatment are analogous to those of CDH, with the exception of the fact that a prosthesis is always necessary for diaphragmatic closure.³⁵⁹ Survival data are unreliable because in many studies the differentiation with classical CDH is not clear. In general, it is thought that the prognosis is worse than that for classical CDH, given the dimensions of the diaphragmatic defect.

Diaphragmatic Duplication

Diaphragmatic duplication, be it partial or complete, is exceedingly rare.^{361,362} It consists of a fibromuscular membrane that separates the affected hemithorax in two cavities and represents a duplication of the pleuroperitoneal membrane. In most cases, the accessory diaphragm is not innervated by the phrenic nerve. The accessory diaphragm may be eminently muscular and the orthopic diaphragm fibrous, or vice versa.^{363,364} The accessory diaphragm may be in such a location within the chest that the ipsilateral lung is divided in two compartments; it may also be associated with anomalous airways or pulmonary vessels, as well as with partial pulmonary agenesis.³⁶⁴⁻³⁶⁷ Clinically, duplication can cause respiratory distress in the neonatal period, recurring airway infections during childhood, and chronic pulmonary inflammation in adulthood, occasionally with bronchiectasis.^{361,366} Apparently, it can also be asymptomatic.^{365,368} Given that symptoms are non-specific when present, the diagnosis is commonly confirmed only intraoperatively. In the rare cases in which a diaphragmatic duplication was resected, it resulted in improvement of respiratory symptoms. At least one case of association between (right-sided) CDH and diaphragmatic duplication in a neonate has been reported.³⁶⁹

Cribriform Diaphragm

A case of incidental intraoperative finding of a cribriform aspect of the right diaphragm, with several portions of the liver protruding to the chest through the many diaphragmatic defects, has been described in an older patient.³⁷⁰ It is not yet possible to know whether this is another diaphragmatic anomaly, with a distinct embryonic pathogenesis, or an extremely rare variant of CDH, or even simply an acquired diaphragmatic defect.

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PART K

ESOPHAGUS—BENIGN DISEASE

PART OUTLINE

- | | | | |
|-----------|--|-----------|---|
| 34 | ESOPHAGEAL ANATOMY AND FUNCTION | 36 | SURGICAL TREATMENT OF BENIGN
ESOPHAGEAL DISEASES |
| 35 | SURGERY FOR CONGENITAL LESIONS OF THE
ESOPHAGUS | | |

ESOPHAGEAL ANATOMY AND FUNCTION

Daniel S. Oh • Tom R. DeMeester

CHAPTER OUTLINE

EMBRYOLOGY

ANATOMY

Cervical Esophagus
Thoracic Esophagus
Abdominal Esophagus
Structure of the Esophageal Wall
Blood Supply, Lymphatics, and Innervation

PHYSIOLOGY

The Swallowing Mechanism
Lower Esophageal Sphincter
Causes and Consequences of the Failure of the Gastroesophageal Barrier

EVALUATION OF ESOPHAGEAL FUNCTION

Radiographic Evaluation
Endoscopic Examination
Esophageal Manometry
Lower Esophageal Sphincter
Lower Esophageal Sphincter Relaxation
Esophageal Body Motility
Upper Esophageal Sphincter
High-Resolution Impedance
Ambulatory pH Monitoring

The esophagus is a muscular tube that starts as the continuation of the pharynx with the upper esophageal sphincter (UES), or cricopharyngeus, and ends with the lower esophageal sphincter at the fundus of the stomach. Knowledge of the anatomy of the esophagus and its relationship with other organs and structures is essential for the surgeon to evaluate the location of lesions seen through use of endoscopy, barium swallow study, or computed tomography; to interpret esophageal function studies; and to safely expose the esophagus during surgery (Fig. 34-1). Similarly, knowledge of foregut embryology is key to the understanding of the pathogenesis of both congenital malformations and acquired diseases of the esophagus.

EMBRYOLOGY

The embryonic esophagus forms when paired longitudinal grooves appear on each side of the laryngotracheal diverticulum. These grooves subsequently grow medially and fuse to form the tracheoesophageal septum. This septum divides the foregut into the ventral laryngotracheal tube and the dorsal esophagus. Incomplete fusion of the two lateral grooves was formerly thought to be the major factor in the pathogenesis of congenital tracheoesophageal fistula, but the anomaly is now attributed to abnormal growth and differentiation of the lung buds. The esophagus is initially short, but it rapidly elongates; the relative final length is attained by the seventh week

of gestation.¹ This is followed by endodermal proliferation, which nearly obliterates the esophageal lumen. Subsequent recanalization occurs by the development of large vacuoles that coalesce. The adult position of the vagal nerves on the lower third of the esophagus results from the unequal growth of the greater and lesser curvature of the stomach, so the left vagus rotates anteriorly and the right vagus posteriorly.

The UES and the most proximal 1 to 2 cm of the cervical esophagus are primarily striated muscle. The striated muscle is derived from the caudal branchial arches and innervated by the vagus nerve and its recurrent laryngeal branches. The UES is made up primarily of the cricopharyngeus muscle, but it is also aided by the inferior pharyngeal constrictors and the circular muscles of the upper esophagus. Studies have indicated that the transition from predominantly striated to predominantly smooth muscle occurs in the proximal 4 to 5 cm of the esophagus and that only 1 cm of the proximal esophagus below the cricopharyngeal sphincter is entirely striated muscle.² In contrast with the proximal portion of the cervical esophagus, the thoracic and abdominal esophagus and the lower esophageal sphincter (LES) consist entirely of smooth muscle and are composed of an inner circular and outer longitudinal layer. A transition zone exists between the smooth and striated muscle components 4 to 8 cm below the cricopharyngeus. The smooth muscle of the lower esophagus arises from the splanchnic mesenchyme and is supplied by nerves of the esophageal plexus derived from neural crest cells.¹

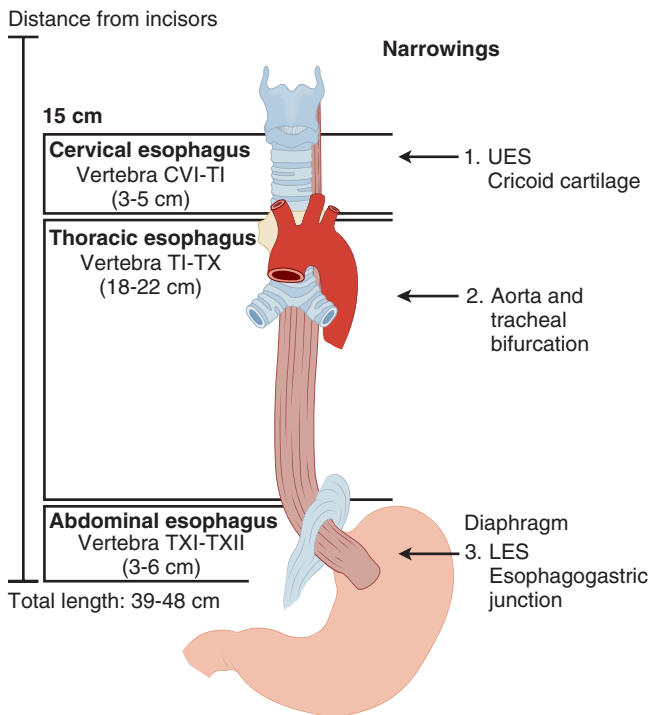


FIGURE 34-1 ■ Classic division of the esophagus and relationships to the cervical and thoracic vertebrae as radiologic landmarks. The approximate lengths and narrowings (arrows) of the esophagus are shown. LES, Lower esophageal sphincter; UES, upper esophageal sphincter.

Esophageal mucosal development in the fetus is complex and undergoes several stages of transformation before birth.³ In early development, the esophagus is lined by a stratified columnar epithelium, which then becomes ciliated; however, at the upper and lower ends of the esophagus a simple columnar epithelium remains. By the third trimester, all the columnar mucosa is subsequently replaced by stratified squamous epithelium throughout the esophagus. By birth, the entire esophagus appears to be completely lined by stratified squamous epithelium and directly abuts the oxyntic mucosa of the stomach below the LES. Any changes to this mucosa in future life are thought to represent acquired metaplasia of the esophageal squamous mucosa, with transformation into cardiac mucosa or intestinal metaplasia as a result of mucosal injury from exposure to gastric juice.

ANATOMY

Cervical Esophagus

The cervical portion of the esophagus is approximately 3 to 5 cm long. It starts below the cricopharyngeus muscle and appears as a continuation of the inferior constrictor muscle of the pharynx. A space between the right and left inferior constrictor muscles posteriorly just above the cricopharyngeus muscle is an area of natural weakening and referred to as Killian triangle, the site where a Zenker diverticulum develops (Fig. 34-2). The beginning of the cervical esophagus is marked by the level of C6, and

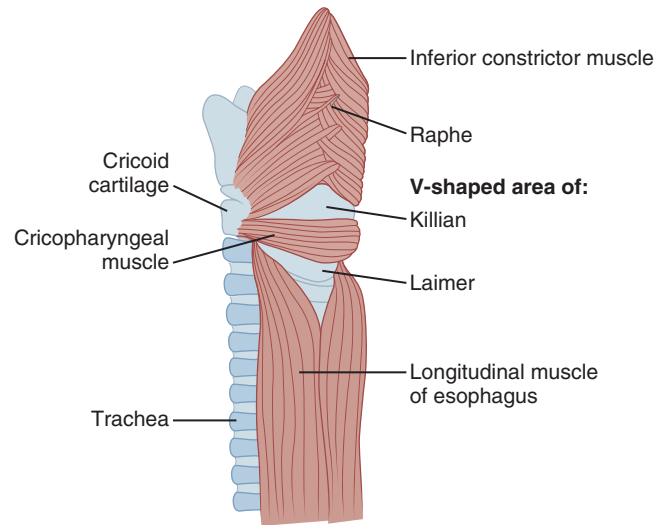


FIGURE 34-2 ■ Muscular architecture of the pharyngoesophageal junction, which is the region of the upper esophageal sphincter. The triangular areas of the sparse muscle cover are shown in the scheme. Zenker diverticulum arises from Killian triangle. (Modified from Liebermann-Meffert D: Anatomy, embryology, and histology. In Pearson FG, Deslauriers J, Ginsberg RJ, et al, editors: *Esophageal surgery*, New York, 1995, Churchill Livingstone, pp 1–25.)

the end by the lower border of T1. The cervical esophagus curves slightly to the left as it descends. Anteriorly, it abuts the trachea and larynx and can be dissected off both organs. Posteriorly, the cervical esophagus lies on the vertebral bodies in a prevertebral or retroesophageal space. This space is continuous with the retropharyngeal space superiorly and the posterior mediastinum inferiorly, which is the primary route of descending mediastinitis from oropharyngeal infections. Laterally, the omohyoid muscle crosses the cervical esophagus obliquely, and it is usually necessary to divide this to expose that portion of the esophagus. The carotid sheaths lie laterally, and the lobes of the thyroid and the strap muscles lie anteriorly. The recurrent laryngeal nerves lie in the grooves between the esophagus and the trachea. The right recurrent nerve runs a more lateral and oblique course to reach the groove and is more prone to anatomic variation. Although the surgical approach to the cervical esophagus may be from either side of the neck through an incision along the medial border of the sternocleidomastoid muscle, the left-sided approach is preferred to avoid injury to the more variable course of the right recurrent nerve.

Thoracic Esophagus

The thoracic portion of the esophagus is approximately 18 to 20 cm long (see Fig. 34-1) and starts at the thoracic inlet. In the upper portion of the thorax, it is closely related to the posterior membranous wall of the trachea. This close relationship is responsible for the early spread of cancer of the upper esophagus into the trachea, and it may limit the surgeon's ability to resect such a tumor. Above the level of the tracheal bifurcation, the esophagus courses to the right of the aortic arch and the descending

aorta and then deviates to the left, passing behind the tracheal bifurcation and the left main bronchus. In the lower portion of the thorax, the esophagus remains deviated to the left and passes anteriorly through the diaphragmatic hiatus. There are three natural areas of constriction in the thoracic esophagus: the cricopharyngeus, or UES; the bronchoaortic constriction as it crosses behind the aortic arch and left mainstem bronchus; and the LES.

Unlike the remainder of the gastrointestinal tract, the esophagus does not have a serosal layer and its strength is derived from its mucosa. The thoracic esophagus is covered only by parietal pleura, making this portion the weakest and the most common site of perforation in Boerhaave syndrome, usually on the left side where there is a lack of support from adjacent structures.

The azygos vein is closely related to the right of the esophagus as it ascends from the abdomen and then arches from its paraspinal position over the esophagus and the right main bronchus to enter the superior vena cava.

The thoracic duct ascends behind and to the right of the distal thoracic esophagus between the azygos vein and aorta. At approximately the level of T5, it passes alongside the aorta and ascends on the left side of the esophagus to enter behind the junction of the left internal jugular and subclavian veins. Because of the possibility of disrupting the thoracic duct during its course across the mediastinum during an esophagectomy, ligation of the duct is generally performed low in the chest where it comes through the aortic hiatus.

Abdominal Esophagus

The abdominal portion of the esophagus is approximately 3 to 6 cm long and includes the abdominal portion of the LES. It begins where the esophagus passes through the diaphragmatic hiatus, and it is surrounded by the phrenoesophageal membrane, a fibroelastic ligament that arises from the subdiaphragmatic fascia as a continuation of the transversalis fascia lining the abdomen (Fig. 34-3). The upper leaf of the membrane attaches in a circumferential fashion around the esophagus approximately 1 to 2 cm above the level of the hiatus. The lower leaf of the phrenoesophageal membrane blends with the serosa of the stomach, and its end is marked anteriorly by a prominent fat pad, which corresponds approximately with the

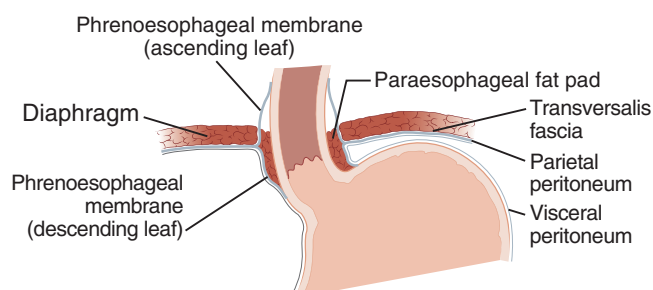


FIGURE 34-3 ■ Attachments of the phrenoesophageal membrane.

gastroesophageal junction. The LES is a zone of high pressure 3 to 4 cm long at the lower end of the esophagus⁴ and does not correspond to any visible macroscopic anatomic landmark either on the external surface of the esophagus or in the endoscopic appearance of the mucosa. Its function is derived from the microscopic architecture of the muscle fibers. The esophageal hiatus is surrounded by the right and left crura, which together form a sling of diaphragmatic skeletal muscle around the esophagus that originates from tendinous bands attached to the anterolateral surface of the first lumbar vertebra (Fig. 34-4). The relative contribution of the right and left crura to this sling is variable. Posterior to the esophagus, the crura are united by a tendinous arch, the median arcuate ligament, which lies just anterior to the aorta.

Structure of the Esophageal Wall

The esophagus is composed of three primary layers: mucosa, submucosa, and muscularis propria. The mucosal layer is normally made of nonkeratinized stratified squamous epithelium. In the distal aspect of the esophagus within the LES, repeated exposure of the squamous epithelium to gastric contents can result in metaplasia to a columnar epithelium known as cardiac mucosa. With further injury and exposure to a specific component of refluxed gastric juice such as bile acids, cardiac mucosa may transform into intestinal metaplasia or Barrett esophagus.

A critical layer within the mucosa for determining the biological behavior of superficial cancers is the muscularis mucosa. This thin, poorly developed layer lies below the basement membrane and above the submucosa. Early tumors that are restricted to the muscularis mucosa are usually confined to the mucosal layer and have little risk of gaining entry into the lymphatics for metastatic spread. When intestinal metaplasia does occur, it is common that the muscularis mucosa is splintered into two separate layers, which can complicate determining the depth of invasion of a superficial tumor.⁵

The submucosa is characterized by a rich lymphatic plexus that extends throughout the esophagus. Lymphatic

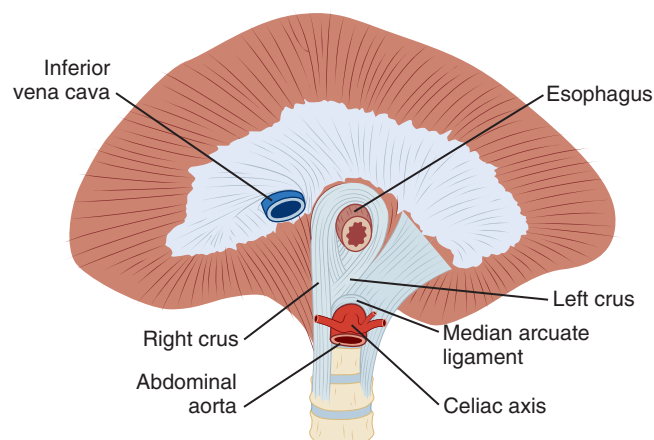


FIGURE 34-4 ■ Diaphragm and esophageal hiatus viewed from the abdomen.

collecting branches arise from within the submucosa and pierce the muscularis propria to communicate with regional lymph nodes and the thoracic duct outside of the esophagus. This network of lymphatics allows for significant longitudinal spread of esophageal cancers and a high rate of skip metastases. Clinically, tumor invasion beyond the muscularis mucosa into the submucosa is significant as a result of this lymphatic system, with the rate of regional lymph node metastases increasing from less than 5% with intramucosal tumors up to approximately 50% for submucosal tumors.⁶ Finally, the submucosa of the esophagus also harbors mucous glands that drain into the lumen. These glands are helpful for determining the true extent of the esophagus when metaplasia of the mucosa occurs.

The muscularis propria has an inner circular layer and an outer longitudinal layer. The muscles are striated in the upper portion and transition to completely smooth muscle near the upper third of the esophagus. The longitudinal muscle layer courses down in an elongated spiral pattern, turning approximately 90 degrees as it descends to the stomach. The circular muscle layer is thicker than the longitudinal layer, which also takes on an elliptical or spiral orientation. This arrangement of muscle is responsible for the wormlike drive of peristalsis.

Blood Supply, Lymphatics, and Innervation

The cervical portion of the esophagus receives its main blood supply from the inferior thyroid artery. The thoracic portion receives blood from the bronchial and esophageal arteries. Seventy-five percent of individuals have one right-sided and two left-sided bronchial arteries, and usually two esophageal branches arise directly from the aorta. The blood supply of the abdominal portion of the esophagus comes from the ascending branch of the left gastric artery and from the right and left inferior phrenic arteries (Fig. 34-5). After the vessels have entered the muscular wall of the esophagus, branching occurs at right angles to provide an extensive longitudinal vascular plexus. The rich blood supply provided by this vascular plexus allows mobilization of the esophagus from the stomach to the aortic arch without causing ischemic injury.⁷

The capillaries of the esophagus drain into a submucosal and periesophageal venous plexus, from which the esophageal veins originate. In the cervical region, the esophageal veins empty into the inferior thyroid vein; in the thoracic region, they empty into the bronchial, azygos, or hemiazygos veins; and in the abdominal region, they empty into the coronary vein (Fig. 34-6).

The lymphatic channels are located almost exclusively below the muscularis mucosa in the submucosa of the esophagus, constituting a dense and interconnected plexus with more lymph vessels than blood capillaries (Fig. 34-7). Lymph flow in the submucosal plexus runs in a longitudinal direction, and after the injection of a contrast medium, the longitudinal spread is six times that of the transverse spread. In the upper two thirds of the esophagus, the lymphatic flow is mostly cephalad; in the

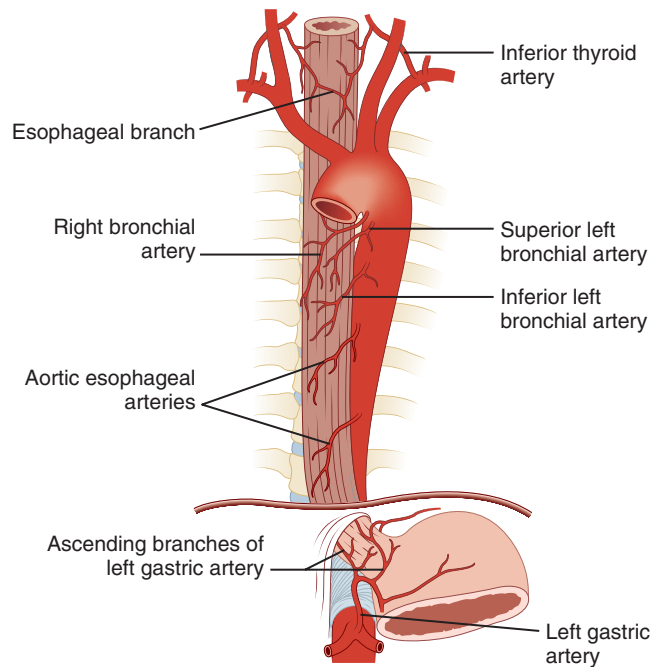


FIGURE 34-5 ■ Arterial blood supply of the esophagus. (Modified from Rothberg M, DeMeester TR: Surgical anatomy of the esophagus. In Shields TW, editor: *General thoracic surgery*, ed 3, Philadelphia, 1989, Lea & Febiger, p 84.)

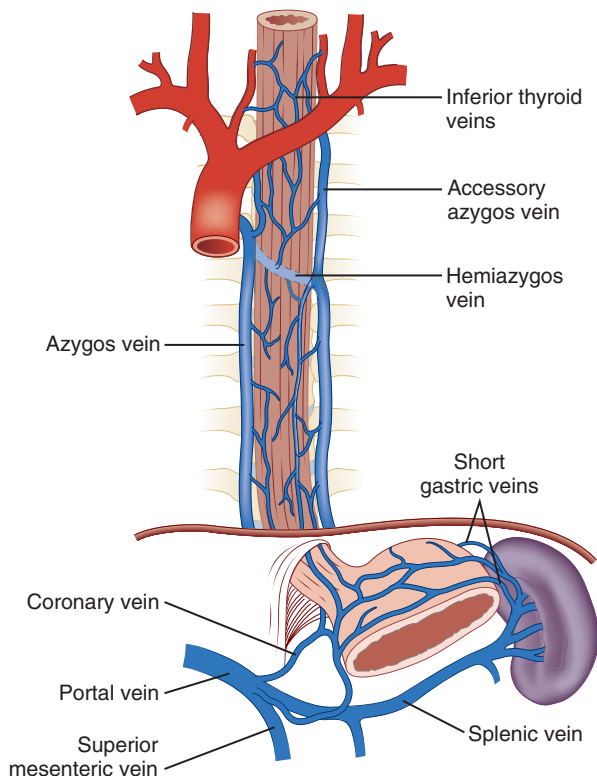


FIGURE 34-6 ■ Venous drainage of the esophagus. (Modified from Rothberg M, DeMeester TR: Surgical anatomy of the esophagus. In Shields TW, editor: *General thoracic surgery*, ed 3, Philadelphia, 1989, Lea & Febiger, p 85.)

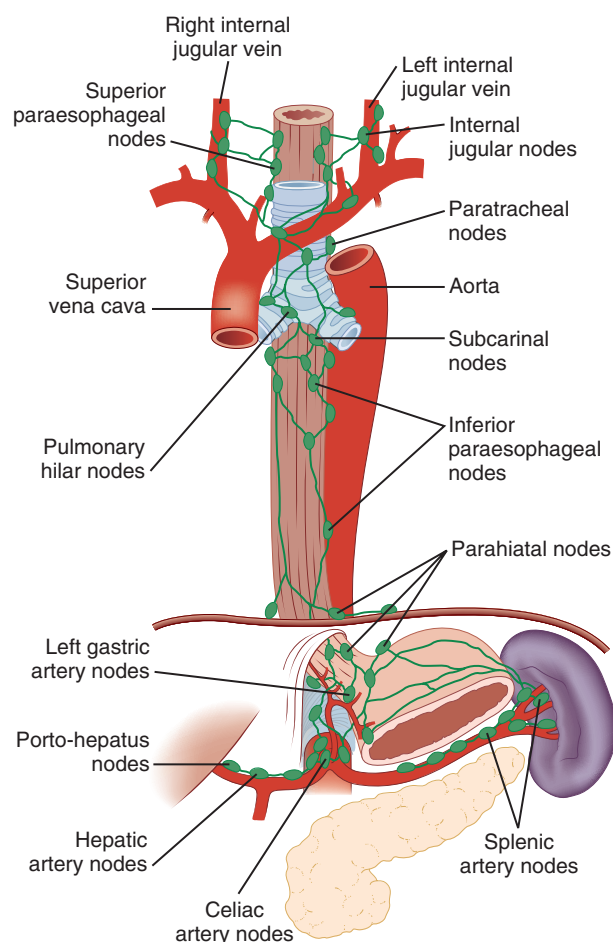


FIGURE 34-7 ■ Lymphatic drainage of the esophagus. (From DeMeester TR, Barlow AP: Surgery and current management for cancer of the esophagus and cardia: Part 1. *Curr Probl Surg* 25:475–531, 1988.)

lower third, it is mostly caudad. In the thoracic portion of the esophagus, the submucosal lymph plexus extends over a long distance in a longitudinal direction before penetrating the muscle layer to enter lymph vessels in the adventitia. As a consequence of this nonsegmental lymph drainage, the lymphatic spread of tumor cells can extend for a considerable distance superiorly and inferiorly within the submucosal lymphatics before the cells pass through lymphatic channels in the muscularis and into the regional lymph nodes. There is a high rate of skip metastases in esophageal cancer because of this arrangement. By contrast, the cervical esophagus has a more segmental lymph drainage into the regional lymph nodes, and as a result, tumors in this portion of the esophagus have less submucosal extension.

Lymph from the cervical esophagus drains into the paratracheal and deep cervical lymph nodes, whereas lymph from the upper thoracic esophagus flows mainly into the paratracheal lymph nodes. The lymph from the lower thoracic esophagus drains into the subcarinal and inferior pulmonary nodes. Lymph from the distal thoracic and abdominal portion of the esophagus drains into the parahiatal and perigastric nodes.¹

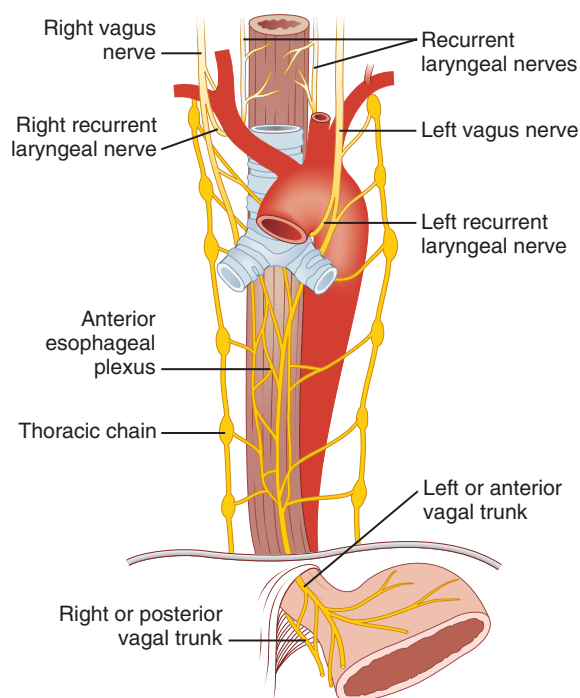


FIGURE 34-8 ■ Innervation of the esophagus. (Modified from Rothberg M, DeMeester TR: Surgical anatomy of the esophagus. In Shields TW, editor: *General thoracic surgery*, ed 3, Philadelphia, 1989, Lea & Febiger, p 85.)

The parasympathetic innervation of the pharynx and esophagus is provided mainly by cranial nerve X or the vagus nerves. The constrictor muscles of the pharynx receive branches from the pharyngeal plexus, which is located on the posterior lateral surface of the middle constrictor muscle and is formed by pharyngeal branches of the vagus nerve, with a small contribution from cranial nerves IX and XI. The cricopharyngeal sphincter and the cervical portion of the esophagus receive branches from both right and left recurrent laryngeal nerves originating from the vagus nerves (Fig. 34-8). Damage to these recurrent nerves interferes not only with the movement of the vocal cords but also with the function of the cricopharyngeal sphincter and the motility of the cervical esophagus, predisposing the patient to pulmonary aspiration on swallowing. The upper thoracic esophagus receives innervation from the left recurrent laryngeal nerve and both vagus nerves. As the right and left vagus nerves descend into the mediastinum, they join the outer surface of the esophagus. The esophageal plexus, which is formed by the branches of the right and left vagus nerves and thoracic sympathetic chain, lies on the anterior and posterior walls of the esophagus and innervates the lower thoracic portion.⁸ The branches of the plexus coalesce into the left (anterior) and right (posterior) vagal trunks.

Afferent visceral sensory fibers from the esophagus end without synapse in the first four segments of the thoracic spinal cord by a combination of sympathetic and vagal pathways. These pathways are also occupied by afferent visceral sensory fibers from the heart, which explains the similarity of symptoms in esophageal and cardiac diseases.

PHYSIOLOGY

To comprehend the mechanics of alimentation, it is useful to visualize the gullet as a series of pumps and valves. In the pharyngeal segment, the tongue and pharyngeal muscle function as pumps, whereas the soft palate, the epiglottis, and the cricopharyngeus serve as the valves that regulate flow. In the esophageal segment, the esophageal body functions as the pump to propel the food bolus, whereas the LES serves as a valve to allow transport into the stomach and to prevent the flow of gastric contents back into the esophagus.

The Swallowing Mechanism

Swallowing can be started at will, or it can be reflexively elicited by the stimulation of the anterior and posterior tonsillar pillars or the posterior lateral walls of the hypopharynx. The afferent sensory nerves of the pharynx are the glossopharyngeal nerves and the superior laryngeal branches of the vagal nerves. Once it is aroused by stimuli entering through these nerves, the swallowing center in the medulla coordinates the complete act of swallowing by discharging impulses through cranial nerves V, VII, X, XI, and XII and the motor neurons of C1 through C3. Discharges through these nerves always occur in a specific pattern and last for approximately 0.5 second. Little is known about the swallowing center except that it can trigger swallowing after a variety of different inputs. Once it is triggered, the swallow response is always a rigidly ordered pattern of outflow neurogenic impulses.

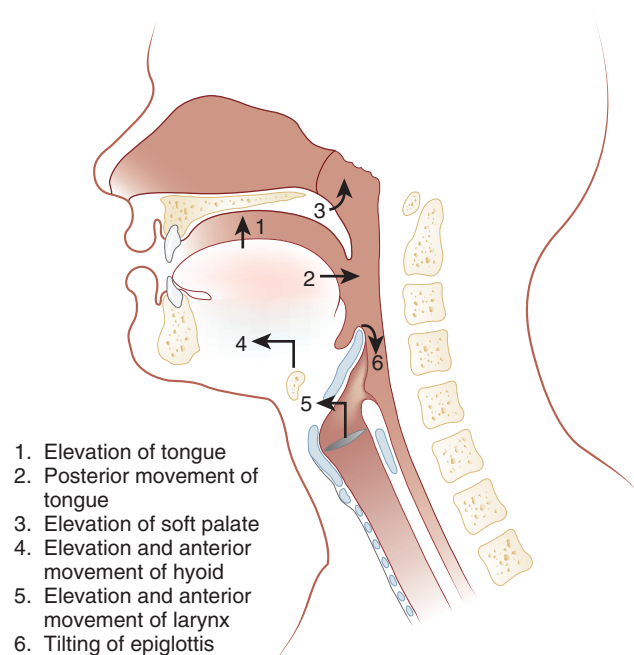


FIGURE 34-9 ■ Sequence of events during the oropharyngeal phase of swallowing. (From DeMeester TR, Stein HJ, Fuchs KH: Physiologic diagnostic studies. In Zuidema GD, Orringer MB, editors: *Shackelford's surgery of the alimentary tract*, ed 3, vol 1, Philadelphia, 1991, Saunders, p 95.)

The act of alimentation requires the passage of food and drink from the mouth into the stomach. Food is taken into the mouth in a variety of bite sizes, after which it is broken up by the teeth, mixed with saliva, and lubricated. When food is ready for swallowing, the tongue, acting as a pump, moves the bolus into the posterior oropharynx and forces it into the hypopharynx (Fig. 34-9). Concomitantly with the posterior movement of the tongue, the soft palate is elevated, thereby closing the passage between the oropharynx and nasopharynx. With the initiation of the swallow, the hyoid moves superiorly and anteriorly, thereby elevating the larynx and enlarging the retropharyngeal space. At the same time, the epiglottis covers the laryngeal inlet to prevent aspiration.

During swallowing, the pressure in the hypopharynx rises abruptly to 60 mm Hg as a result of the backward movement of the tongue and contraction of the posterior pharyngeal constrictors. A sizable pressure difference develops between the hypopharyngeal pressure and the subatmospheric midesophageal or intrathoracic pressure (Fig. 34-10). This pressure gradient speeds the movement of food from the hypopharynx into the esophagus when the cricopharyngeus or UES relaxes. The bolus is both propelled by the peristaltic contraction of the posterior pharyngeal constrictors and sucked into the thoracic esophagus by this pressure gradient.

Critical to receiving the bolus is the compliance of the cervical esophageal muscle and the timing and degree of relaxation of the UES. Abnormalities of compliance and UES opening can result in pharyngeal dysphagia. During the transfer of the bolus from the mouth into the esophagus, the UES is mechanically pulled open. Elevation of

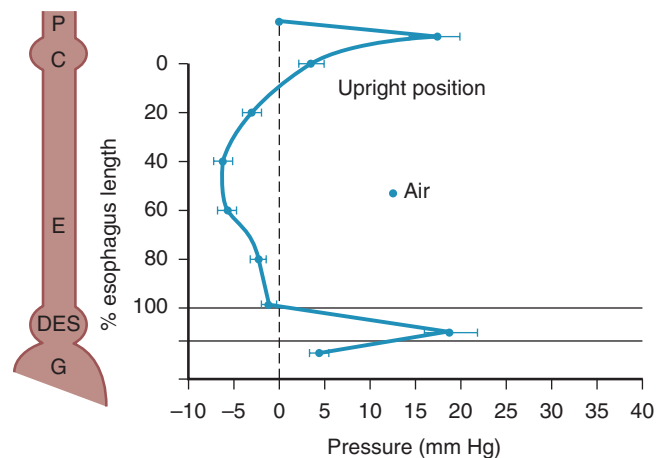


FIGURE 34-10 ■ Resting pressure profile of the foregut showing the pressure differential between the atmospheric pharyngeal pressure (P) and the less-than-atmospheric midesophageal pressure (E) and the greater-than-atmospheric intragastric pressure (G), with the interposed high-pressure zones of the cricopharyngeus (C) and the distal esophageal sphincter (DES). The necessity for relaxation of the cricopharyngeus and DES pressure to move a bolus into the stomach is apparent. Esophageal work occurs when a bolus is pushed from the midesophageal area with a pressure that is less than atmospheric (E) and into the stomach, which has a pressure that is greater than atmospheric (G). (From Waters PF, DeMeester TR: Foregut motor disorders and their surgical management. *Med Clin North Am* 65:1235-1268, 1981.)

the larynx by muscles attached to the hyoid bone pulls the UES open at the time muscle relaxation of the UES occurs. This is an active relaxation caused by a reduction in the tone of the tonic cricopharyngeus muscle, and it is dependent on a neurologically mediated reflex. This is an all-or-nothing event; partial relaxation does not normally occur. The UES closes within 0.5 second of the initiation of the swallow, with a postrelaxation contraction pressure that is approximately twice the resting pressure of 30 mm Hg. The postrelaxation contraction continues down the esophagus as a peristaltic wave (Fig. 34-11). The high closing pressure and the initiation of the peristaltic wave prevent reflux of the bolus from the esophagus into the pharynx. After completion of the swallow, the pressure of the UES returns to its normal resting pressure.

The pharyngeal activity in swallowing initiates the esophageal phase of swallowing. Because of the helical arrangement of its circular muscles, the body of the esophagus functions as a worm-drive propulsive pump,

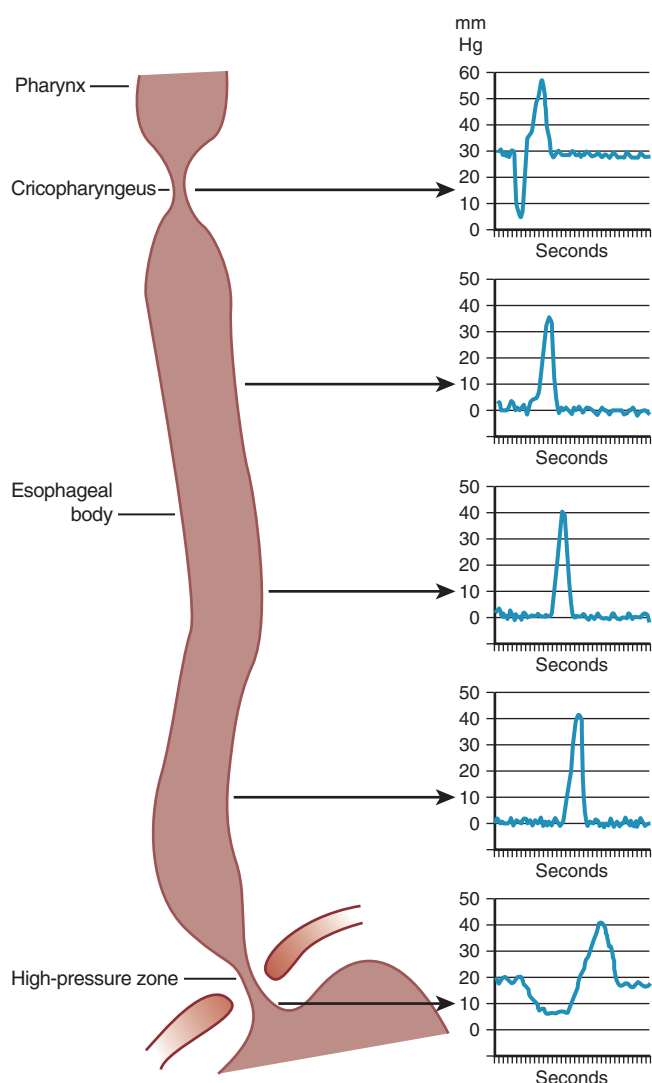


FIGURE 34-11 ■ Intraluminal esophageal pressures in response to swallowing. (From Waters PF, DeMeester TR: Foregut motor disorders and their surgical management. *Med Clin North Am* 65:1235-1268, 1981.)

and it is responsible for transmitting a bolus of food into the stomach. With the act of swallowing, the longitudinal muscle of the esophageal body shortens, thus enlarging the lumen to accept the bolus (the “on response”), after which the circular smooth muscle contraction forms the peristaltic wave (the “off response”). During the esophageal phase of swallowing, the bolus is moved into the stomach over a gradient of 12 mm Hg (i.e., from a negative intrathoracic pressure environment of -6 mm Hg to a positive intra-abdominal pressure environment of $+6$ mm Hg). Effective and coordinated smooth muscle function in the lower two thirds of the esophageal body is important to allow this movement to occur.

The peristaltic wave generates an occlusive pressure that varies from 30 to 120 mm Hg. The wave rises to a peak in 1 second, remains at the peak for approximately 0.5 second, and then subsides in approximately 1.5 seconds. The whole course of the rise and fall of an occlusive contraction may occupy one point in the esophagus for 3 to 5 seconds.^{9,10} The peak of the primary peristaltic contraction moves down the esophagus at a rate of 2 to 4 cm per second and reaches the distal esophagus approximately 9 seconds after swallowing starts. A consecutive swallow after 20 seconds produces a similar primary peristaltic wave; however, if repetitive swallowing occurs sooner, the esophagus becomes unresponsive (*deglutitive inhibition*).

To be effective, peristaltic contractions must be of sufficient amplitude to occlude the esophageal lumen and sufficiently organized in a peristaltic waveform to propel a bolus toward the stomach. Low-amplitude contractions that do not occlude the lumen merely indent a semisolid bolus rather than propel it, and simultaneous contractions throughout the body of the esophagus result in splitting the bolus or even propelling it orally, which can be observed on a barium esophagram as bolus segmentation or cephalic escape.

Clinically, defects in peristalsis occur in three broad categories, depending on which major feature is the most impaired. First, there is a neural abnormality that results in the defective organization of the peristaltic wave; this is recognized by the presence of simultaneous contractions with a loss of the peristaltic sequence and results in typical primary motility disorders (e.g., diffuse esophageal spasm). The second category defect is evident when there is a reduction of the amplitude of the contraction but the peristaltic sequence remains; this is usually the result of muscle damage and the formation of fibrous tissue within the muscle. Examples include end-stage gastroesophageal reflux disease and connective tissue disorders such as scleroderma. The third category defect results from altered anatomy of the esophageal body. A loss in the efficiency of the peristaltic sequence can result when the esophagus is not anchored distally (as occurs with a large paraesophageal hernia), which can result in the appearance of an accordion esophagus on a barium swallow esophagram with ineffective clearance of barium.

Lower Esophageal Sphincter

The LES represents the barrier that confines the gastric juice to the stomach and protects the acid-sensitive

squamous esophageal mucosa from injury by refluxed gastric juice. As is true for any valve, failure of the LES can occur in two completely opposite ways, which lead to two distinct clinical disease entities. Regardless of the type of LES failure, the secondary effects are produced proximally in the esophagus. Failure of the LES to relax or to open appropriately leads to the inability of the esophagus to propel food into the stomach, esophageal distention, and the condition known as *achalasia*. On the other hand, failure of the LES to remain closed leads to an increased exposure of the squamous epithelium to gastric juice and the condition known as *gastroesophageal reflux disease* (GERD).

The LES has no anatomic landmarks and cannot be seen endoscopically; it is identified on manometry as a rise in pressure over gastric baseline pressure. This high-pressure zone is normally present except in two situations: (1) after a swallow, when it is momentarily dissipated or relaxes to allow passage of food into the stomach; and (2) during a belch, when it allows gas to be vented from a distended fundus. The common denominator for virtually all episodes of gastroesophageal reflux is the loss of this normal high-pressure zone or barrier. When the barrier is absent, resistance to the flow of gastric juice from an environment of higher pressure (the stomach) to an environment of lower pressure (the esophagus) is lost. In early GERD, this is usually caused by a transient loss of the barrier. In advanced GERD, there is usually a permanent loss of the barrier.¹¹

Three characteristics of the LES or high-pressure zone maintain its function as a barrier to intragastric and intra-abdominal pressure challenges. Two of these characteristics—the overall length and pressure of the LES—work together and depend on each other to provide resistance to the flow of gastric juice from the stomach into the esophagus.¹² The shorter the overall length is, the higher the pressure must be for the LES to maintain sufficient resistance to remain competent (Fig. 34-12). Consequently, the effect of a normal LES pressure can be nullified by a short overall LES length, and the effect of a normal overall LES length can be nullified by a low LES pressure. For practical purposes, the

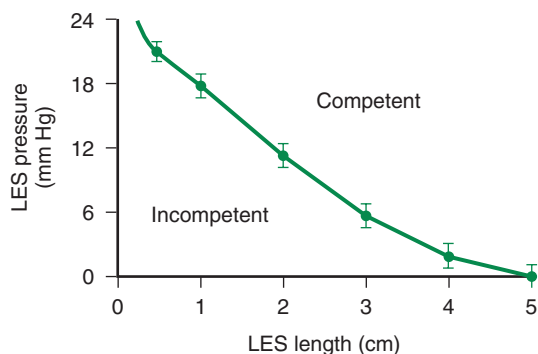


FIGURE 34-12 ■ The relationship of the lower esophageal sphincter (LES) pressure (measured at the respiratory inversion point) and overall LES length with the resistance to the flow of fluid through the barrier. Note that the shorter the overall length of the high-pressure zone is, the higher the pressures must be to maintain sufficient resistance to remain competent. *Competent*, No flow; *incompetent*, flow of varied volumes.

pressure of the LES is measured at a single point, but in actuality, pressure is applied over the entire length of the LES; this allows the computer formation of a three-dimensional image of the LES or barrier (Fig. 34-13). The volume of this image reflects the resistance of the LES to the flow of fluid through it, which is called the *sphincter pressure vector volume*. A calculated volume below that of the fifth percentile of normal resting subjects indicates a permanently defective LES.¹³ A fundamental principle for surgeons to understand is that the length of the barrier or LES is critical to its function.

Foreshortening of LES length occurs naturally with gastric filling as the terminal esophagus is “taken up” by the expanding fundus (Fig. 34-14)¹⁴; this is similar to the shortening of the neck of a balloon as it is inflated. With excessive gastric distention (e.g., with overeating), the length of the LES shortens to a critical point at which it gives way, the pressure drops precipitously, and reflux

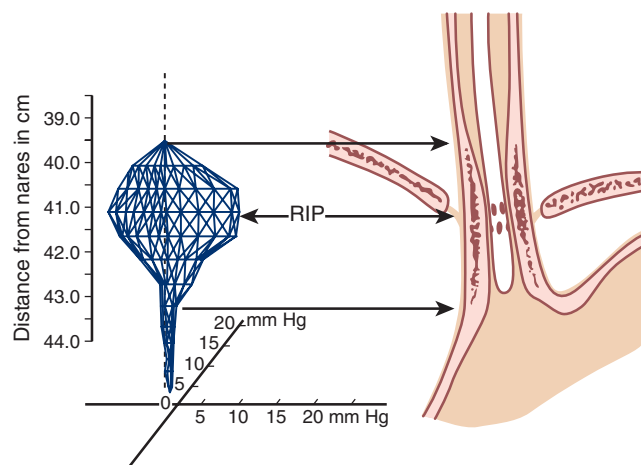


FIGURE 34-13 ■ A graphic illustration of how a three-dimensional computerized image of the lower esophageal sphincter can be constructed by measuring the pressure of the high-pressure zone in four quadrants at 0.5-cm intervals over the entire length of the zone. *RIP*, Respiratory inversion point. (From Stein HJ, DeMeester TR, Naspetti R, et al: Three-dimensional imaging of the lower esophageal sphincter in gastroesophageal reflux disease. *Ann Surg* 214:374–384, 1991.)

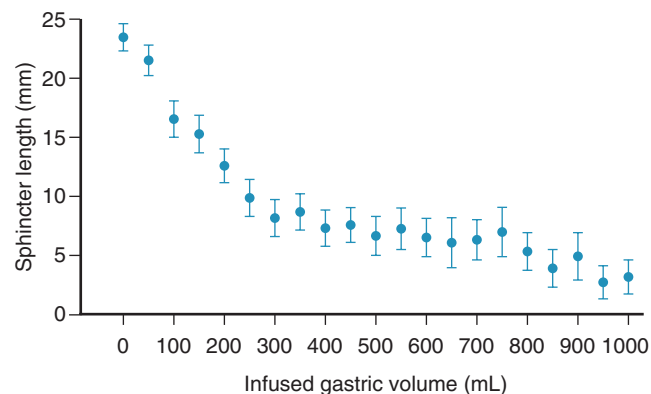


FIGURE 34-14 ■ The relationship between overall sphincter length and gastric distention with increasing volumes of water. (From Mason RJ, Lund RJ, DeMeester TR, et al: Nissen fundoplication prevents shortening of the sphincter during gastric distention. *Arch Surg* 132:719–726, 1997.)

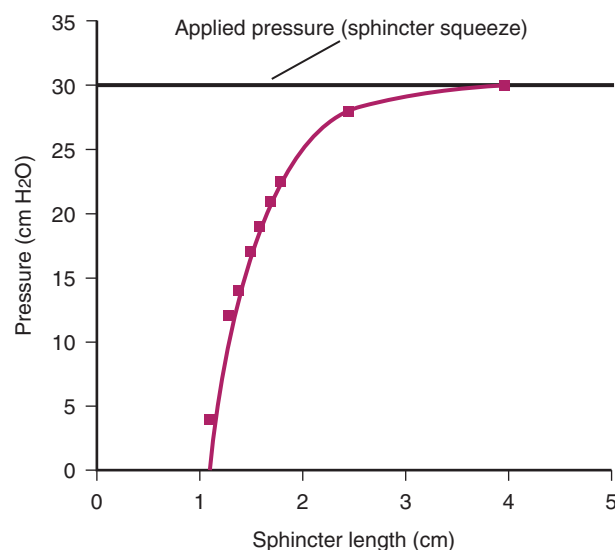


FIGURE 34-15 ■ The relationship between resting lower esophageal sphincter (LES) pressure measured by manometry and LES length when applied pressure or “sphincter squeeze” is kept constant. Analysis was made with a model of the LES high-pressure zone. Note that as the LES length decreases, the pressure recorded within the LES decreases only slightly until a length of 2 cm is reached, when LES pressure drops precipitously and its competency is lost. (From Pettersson GB, Bombeck CT, Nyhus LM: The lower esophageal sphincter: mechanisms of opening and closure. *Surgery* 88:307–314, 1980.)

occurs (Fig. 34-15).¹⁵ If the length of the LES is permanently shortened, then further shortening caused by the normal gastric distention with normal-volume meals results in postprandial reflux. In this situation, competency of the barrier is an ever-constant clinical problem. The observation that gastric distention results in shortening of the LES down to a critical length so that the pressure dissipates, the lumen opens, and reflux occurs provides a mechanical explanation for transient LES relaxations without invoking a neuromuscular reflex. If only the LES pressure and not its length is measured (e.g., with a Dent sleeve), the event appears as a spontaneous relaxation of LES pressure.¹⁶ In reality, it is the progressive shortening of the LES rather than the transient LES relaxations that results in the loss of LES pressure.

Variations in the anatomy of the cardia, from a normal acute angle of His to an abnormal dome architecture of a sliding hiatal hernia, influence the ease with which the sphincter is shortened by gastric distention. A hernia can result from the pulsion force of abdominal pressure on the esophageal hiatus or from the traction produced by inflammatory fibrosis of the esophageal body. The resulting alteration in the geometry of the cardia places the sphincter at a mechanical disadvantage in maintaining its length with progressive degrees of gastric distention. Greater gastric distention is necessary to open the barrier in patients with an intact angle of His than in those with a hiatal hernia.¹⁷ The reason is that the dome or funnel shape of a hiatal hernia allows the wall tension forces that pull open the barrier with gastric distention to be more effectively applied to the gastroesophageal junction,¹⁸ and it accounts for the common association of a hiatal hernia with GERD. Kahrilas and colleagues¹⁹ demonstrated this

mechanical disadvantage by studying the effect of intra-gastric air infusion on the number of transient LES relaxations or “shortenings” per hour. Patients with hiatal hernias had significantly more transient LES relaxations per hour than did control subjects without hernias. The reduction in length became significant 20 to 30 minutes after the beginning of air infusion and occurred in a distal to cephalad direction before a loss of LES pressure was observed.

The third characteristic of the LES high-pressure zone is its position. A portion of the overall length of the high-pressure zone is normally exposed to the positive intra-abdominal pressure environment and is commonly referred to as the abdominal length of the LES.²⁰ During periods of increased intra-abdominal pressure, the resistance of the LES would easily be overcome if its position were such that abdominal pressure is unable to be applied equally to the LES and the stomach.^{21–23} This is analogous to sucking on a soft soda straw immersed in a bottle of liquid; the positive hydrostatic pressure of the fluid and the negative pressure inside the straw from sucking cause the straw to collapse instead of allowing the liquid to flow up the straw in the direction of the negative pressure. If the LES is positioned so that the abdominal length is inadequate, it cannot collapse in response to applied positive intra-abdominal pressure. On the other hand, intra-gastric pressure would be augmented by the applied positive intra-abdominal pressure, and the sphincter pressure would be easily overcome; the negative intrathoracic pressure will encourage reflux to occur. More than 1 cm of the LES needs to be exposed to the abdominal pressure environment for it to respond effectively to changes in intra-abdominal pressure.

If, in the fasting state, the LES has an abnormally low pressure, a short overall length, or a minimal length exposure to the abdominal pressure environment, the result is a permanent loss of resistance with unhampered reflux of gastric contents into the esophagus; this is known as a permanently defective barrier or LES. The most common consequence of a permanently defective LES is increased esophageal exposure to gastric juice, which results in inflammatory injury to the mucosa and ultimately to the muscularis propria of the esophageal body, thereby causing a reduced contraction amplitude of the esophageal body and interrupted or dropped peristaltic sequences. If the reflux is not brought under control, the progressive loss of effective esophageal clearance results in an ever-increasing esophageal exposure to gastric juice, with further organ injury (Fig. 34-16).^{24,25}

Causes and Consequences of the Failure of the Gastroesophageal Barrier

Early GERD is initiated by increased transient losses of the barrier as a result of gastric overdistention from excessive air and food ingestion.^{11,26} The tension vectors produced by gastric wall distention pull on the gastroesophageal junction, which results in the terminal esophagus being “taken up” into the stretched fundus, thereby reducing the length of the LES. With overeating, a critical length is reached (usually approximately 1 to 2 cm) at which the sphincter gives way; its pressure drops

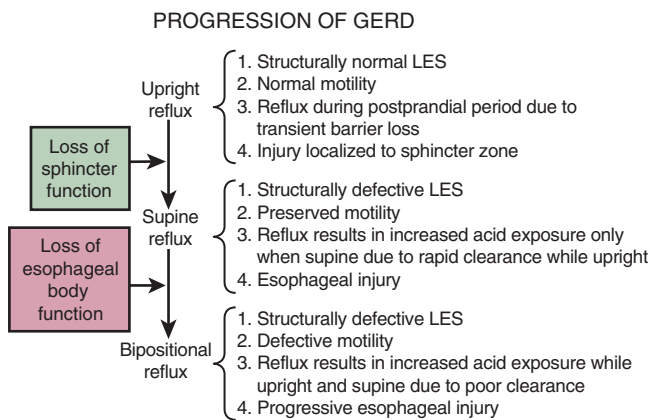


FIGURE 34-16 ■ Schema of the progression of gastroesophageal reflux disease (GERD). Initially, esophageal acid exposure occurs only after meals and when the patient is in the upright, awake position, as a result of the transient losses of the barrier. With inflammatory injury to the lower esophageal sphincter (LES), the barrier becomes permanently defective, and an increase in the esophageal acid exposure occurs with the patient in the supine position, whereas gravity and the esophageal body effectively clear the refluxed acid during the day when the patient is upright. Inflammatory injury to the esophageal body from supine acid exposure results in the loss of esophageal body clearance function and increased esophageal acid exposure during the day and night; this is known as bipositional reflux.

precipitously, and reflux occurs (see Fig. 34-14). If the swallowed air is vented, gastric distention is reduced, the length of the LES is restored, and competency returns until subsequent distention again shortens it and further reflux occurs. Aerophagia is common in patients with GERD because they swallow their saliva more frequently to neutralize the acidic gastric juice that is refluxed into the esophagus.²⁷ Together, the actions of overeating and air swallowing result in the common complaint of postprandial bloating, repetitive belching, and heartburn in patients with early GERD. The high prevalence of the disease in the Western world is thought to be a result of the eating habits of Western society. Gastric distention from overeating, along with delayed gastric emptying resulting from the increased ingestion of fatty foods, leads to prolonged periods of postprandial gastric distention with shortening of the LES and repetitive transient loss of the barrier. Surgical correction with a fundoplication prevents the shortening of the barrier with progressive degrees of gastric distention by diverting the forces produced by gastric wall tension that pull on the gastroesophageal junction.¹⁵

In advanced GERD, permanent loss of sphincter length occurs from inflammatory injury that extends from the mucosa into the muscular layers of the LES. Fletcher and colleagues²⁸ showed that in the fasting state, there is a persistent region of high acidity in the area of the gastroesophageal junction and this region of acidity migrates 2 cm proximally after meals.²⁹ This migration occurs from distention of the stomach with eating and pulling apart of the distal high-pressure zone or LES, thus allowing the area of high acidity to move proximal to the squamocolumnar junction. This proximal movement exposes the distal esophageal squamous mucosa to acid and results in the formation of cardiac mucosa.

Cardiac mucosa is an acquired mucosa that replaces chronically injured squamous mucosa in the terminal esophagus.³⁰ The inflammatory process can extend into the muscular layer of the LES, thereby resulting in muscle cell injury with permanent shortening of the high-pressure zone or LES and a concomitant reduction in the amplitude of the high-pressure zone or barrier pressure.³⁰⁻³² A defective barrier is recognized when the length or pressure of the LES measured during the fasting state is below the 2.5 percentile of normal.³³

For clinicians, the finding of a permanently defective LES has several implications. First, symptoms in patients with a defective LES can be difficult to manage, and mucosal damage may persist with medical therapy.³⁴ Surgery is usually required to achieve consistent long-term symptom relief in these patients to restore a gastroesophageal barrier and interrupt the natural history of the disease. It has been shown repeatedly that a laparoscopic Nissen fundoplication can consistently restore the length and pressure of the LES to normal parameters.³⁵ Newer techniques of sphincter augmentation such as with a magnetic bracelet is an alternative means of restoring the LES that is gaining in popularity.³⁶ Second, a permanently defective LES is commonly associated with reduced contractility and abnormal wave progression of the esophageal body³⁷; this makes the clearance of reflux acid difficult and leads to excessive esophageal exposure to acid. For this reason, careful evaluation of the esophageal body is critical in the evaluation for antireflux surgery for potential tailoring of the operation with a partial fundoplication. Third, a permanently defective LES and the loss of effective esophageal clearance lead to increased esophageal exposure to gastric juice with mucosal injury and the potential for Barrett metaplasia, repetitive regurgitation, aspiration, and pulmonary fibrosis. Without reestablishing a barrier, chronic use of acid suppression therapy may simply mask the symptoms due to modification of the pH; however, in the setting of a structurally defective LES, reflux will continue unabated.³⁸

EVALUATION OF ESOPHAGEAL FUNCTION

A thorough understanding of the patient's underlying anatomic and functional deficits is fundamental to the successful treatment of esophageal disease. The diagnostic tests used to evaluate the esophagus are those used to visualize structural abnormalities, to detect functional abnormalities, and to measure esophageal exposure to gastric juice. At the authors' center, a panel of four diagnostic tests is used routinely in the evaluation of known or suspected reflux disease: barium esophagram, upper endoscopy, high-resolution esophageal manometry, and ambulatory pH monitoring.

Radiographic Evaluation

Radiographic assessment of the anatomy and function of the esophagus and stomach is one of the more important aspects of the esophageal evaluation, provided the surgeon has a working knowledge of esophageal physiology. Classically, the barium esophagram has been described as a

road map for the esophagus. The first diagnostic test in patients with suspected esophageal disease should be a barium swallow that includes a full assessment of the stomach and the duodenum.³⁹ Video recording of the study greatly aids in the evaluation by providing the surgeon with a real-time visualization of bolus transport and the size and reducibility of the hiatal hernia. The study also provides anatomic information, such as the presence of obstructing lesions and structural abnormalities of the foregut.

The pharynx and the UES are evaluated in the upright position, with the performance of an assessment of the relative timing and coordination of the events of pharyngeal transit.⁴⁰ This includes oropharyngeal bolus transport, pharyngeal contraction, opening of the pharyngoesophageal segment, and degree of airway protection during swallowing. It readily identifies a diverticulum, stasis of the contrast medium in the valleculae, cricopharyngeal bar, or narrowing of the pharyngoesophageal segment. These are anatomic manifestations of neuromuscular disease and result from the loss of muscle compliance from the deinnervation of the skeletal muscle of the pharynx and the cervical esophagus.⁴¹

The assessment of peristalsis on video esophagography often adds to or complements the information obtained by esophageal manometry. Esophageal clearance is optimally assessed by observing several individual swallows of barium with the patient in both upright and supine positions; the study can be performed with both liquid and solid bolus material. During normal swallowing, a primary peristaltic wave is generated that completely strips the bolus out of the esophagus and into the stomach. Residual material rarely stimulates a secondary peristaltic wave; rather, an additional pharyngeal swallow is usually required.

The protocol developed and used at the authors' institution has previously been reported.⁴² Normal subjects in the prone position can clear at least three of five 10-mL liquid barium boluses with one swallow and have only one episode of proximal escape or distal retention of a barium bolus with the five swallows. Normal subjects can clear a solid barium bolus with four or fewer swallows in the upright position. Motility disorders with disorganized or simultaneous esophageal contraction give a segmented appearance to the barium column. This can often give a beading or corkscrew appearance to the barium within the esophagus. In patients with dysphagia, the use of a barium-impregnated marshmallow, piece of bread, or hamburger can identify an esophageal transport disturbance that is not evident on the liquid barium study.

A hiatal hernia is present in a high percentage of patients with gastroesophageal reflux.¹¹ A hiatal hernia is best demonstrated with the patient in the prone position; the increased intra-abdominal pressure produced in this position promotes displacement of the hernia above the diaphragm. The hiatal hernia is an important component of the underlying pathophysiology of reflux. A large (>5 cm) or irreducible hiatal hernia suggests a shortening of the esophagus, and a paraesophageal hernia can result in dysphagia. Reflux is not easily seen on video esophagography, and spontaneous reflux of contrast from the stomach to the esophagus does not necessarily predict abnormal acid exposure on pH monitoring. Moreover,

failure to observe reflux during a video esophagram does not indicate the absence of disease.

A full-column technique with distention of the esophageal wall can discern extrinsic compression of the esophagus, and a fully distended esophagogastric region is necessary to identify narrowing from a Schatzki ring, stricture, or obstructing lesion. Mucosal relief or double-contrast films can be obtained to enhance the detection of small neoplasms, esophagitis, and varices. Assessment of the stomach and duodenum during the barium study is helpful for the evaluation of the patient with esophageal symptoms. A gastric or duodenal ulcer, a neoplasm, or poor gastroduodenal transit can mimic many of the symptoms that are suggestive of an esophageal disorder.

Endoscopic Examination

Endoscopic evaluation of the esophagus is essentially the physical examination of the foregut. It is a critical part of the assessment of a patient with esophageal disease and is indicated even if the video esophagogram is normal. A barium study obtained before esophagoscopy is helpful to the endoscopist by directing attention to locations of subtle change and alerting the examiner to such potential danger spots as a cervical vertebral osteophyte, an esophageal diverticulum, a deeply penetrating ulcer, or a carcinoma. Regardless of the radiologist's interpretation of an abnormal finding, each structural abnormality of the esophagus should be examined visually with an endoscope.

During every endoscopic examination, the locations of three specific landmarks are routinely obtained relative to the front incisors: the squamocolumnar junction, gastroesophageal junction, and the diaphragmatic crura. The crura are usually evident, and their location can be confirmed by having the patient sniff. The gastroesophageal junction is the location at which the gastric rugal folds meet the tubular esophagus; it is normally aligned with the squamocolumnar junction. The squamocolumnar junction is the location at which the velvet and darker rose-colored columnar epithelium changes to the lighter squamous epithelium. When this junction is not clear, narrow band imaging is extremely helpful in distinguishing columnar from squamous mucosa, a feature that is standard on all modern endoscopic systems. Particular effort should be made to detect esophagitis and Barrett columnar epithelium-lined esophagus when GERD is suspected.

Barrett esophagus is a condition in which the tubular esophagus is lined with columnar epithelium as opposed to the normal squamous epithelium. On histologic examination, it appears as columnar mucosa with goblet cells and is called intestinal metaplasia. It is suspected at endoscopy when there has been separation of the squamocolumnar junction from the gastroesophageal junction. When columnar metaplasia is observed, it must be biopsied to confirm the presence of intestinal metaplasia to make the diagnosis of Barrett esophagus; the finding of cardiac metaplasia without goblet cells does not meet this criterion. Early metaplasia is often manifested as an irregular or eccentric squamocolumnar junction. Routine four-quadrant biopsies with jumbo forceps are necessary

every 2 cm of columnar metaplasia. In addition, the likelihood of identifying goblet cells is greatest at the cephalad portion of a columnar segment, especially at the squamocolumnar junction.⁴³ Barrett esophagus is susceptible to ulceration, bleeding, stricture formation, and malignant degeneration. The earliest histologic sign of malignant degeneration is high-grade dysplasia or intramucosal adenocarcinoma. These dysplastic changes have a patchy distribution, so a minimum of four biopsy specimens every 2 cm should be taken from the Barrett mucosa-lined portion of the esophagus. A study of intramucosal adenocarcinomas arising in patients with Barrett esophagus showed that most of the tumors arose in the distal Barrett segment, closer to the stomach.⁴⁴

Abnormalities of the cardia or gastroesophageal junction can be visualized by retroflexion of the endoscope and provide a complementary assessment regarding the competency of the gastroesophageal barrier. Hill and colleagues⁴⁵ have graded the appearance of the gastroesophageal valve from I to IV according to the degree of unfolding or deterioration of the normal architecture (Fig. 34-17). This is a commonly used grading system that has allowed endoscopists to maintain uniformity in their reporting. The Hill grade correlates well with the competence of the gastroesophageal barrier; that is, increasing acid exposure is prevalent in patients with a worsening Hill grade.⁴⁶

A hiatal hernia is diagnosed by observing separation of the gastroesophageal junction from the crura. By definition, a hiatal hernia is present when at least 2 cm of the top of the rugal folds has migrated above the margins of the diaphragmatic crura. A prominent sliding hiatal hernia is frequently associated with GERD. When a hernia is observed, particular care is taken to exclude a gastric Cameron ulcer or gastritis within the herniated stomach.

As the endoscope is slowly withdrawn, the esophagus is examined again, and biopsy samples are taken. The location of the cricopharyngeus is identified, and the larynx and vocal cords are visualized. Acid reflux may result in inflammation of the larynx. Vocal cord movement should also be recorded, both as a reference for subsequent surgery and as an assessment of the patient's ability to protect the airway.

Esophageal Manometry

Fundamental to the evaluation of a patient with benign esophageal disease is the assessment of esophageal contractility and sphincter function. Manometry is indicated whenever an abnormality of the esophagus is suggested by the symptoms of dysphagia, odynophagia, chest pain, heartburn, and regurgitation. It is particularly necessary to confirm the diagnosis of specific primary esophageal motility disorders, such as achalasia, diffuse esophageal spasm, nutcracker esophagus, or hypertensive LES. It can also identify ineffective esophageal motility abnormalities that result from GERD and systemic disease, such as scleroderma, dermatomyositis, polymyositis, or mixed connective tissue disease. In patients with symptomatic GERD, esophageal manometry can identify a mechanically defective LES and evaluate the adequacy of the esophageal body contraction amplitudes and waveform. Finally, manometry is mandatory for accurate placement of an ambulatory pH monitor in relationship to the upper border of the LES.

High-resolution esophageal manometry has become standard technology and represents an improvement in methodology that leads to a more detailed data collection and simpler data interpretation. The concept behind this technology is that by vastly increasing the number of sensors and reducing the space between the sensors, it

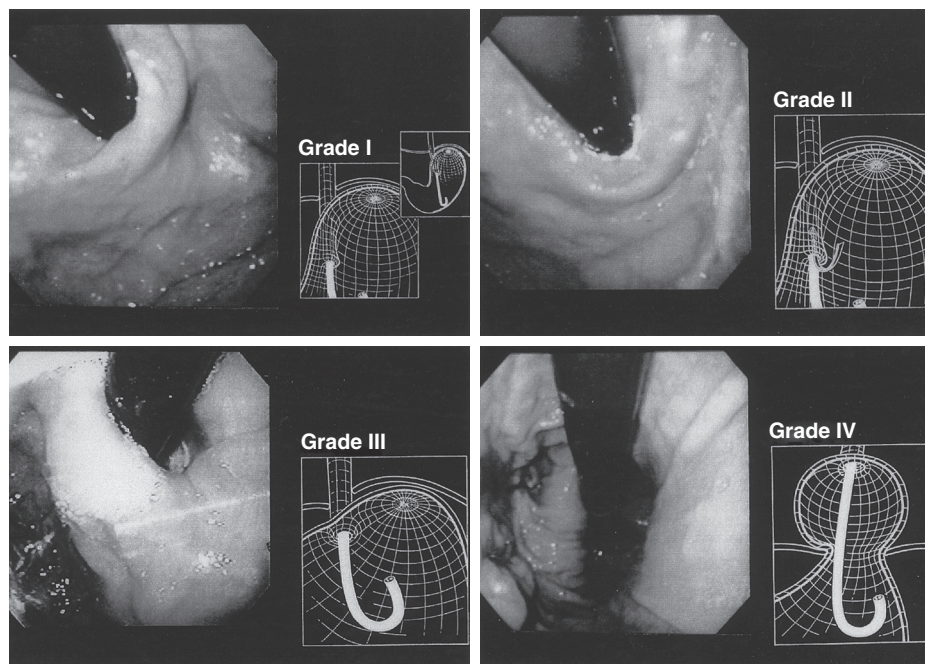


FIGURE 34-17 ■ Endoscopic Hill grading of the gastroesophageal valve. (From Hill LD, Kozarek RA: The gastroesophageal flap valve. *J Clin Gastroenterol* 28:194–197, 1999.)

can provide representation of the entire pressure profile along the esophagus from the pharynx to the proximal stomach without the need to reposition or to pull back the catheter as in conventional manometry.

The most commonly used high-resolution system is a solid-state manometric assembly with 36 circumferential sensors spaced at 1-cm intervals (ManoScan, Covidien). These transducers detect the pressure over a length of 25 mm in each of 12 radially dispersed sectors. The recorded pressure at each sector is then averaged, making each of the 36 sensors a circumferential pressure detector with the extended frequency response characteristic of solid-state manometric systems and free of the hydrostatic influence characteristic of water-perfused systems. The increased number of circumferential pressure sensors results in a vastly greater amount of data and detail.

Interpretation of the data has been simplified by a sophisticated topographic plotting algorithm that converts the traditional linear waveform tracings into an esophageal pressure topography or Clouse plot (Fig. 34-18). Sphincter characteristics and esophageal motor function are represented by isocontour manometric plots, eliminating the need for the tedious analysis of the increased waveform data that are generated by the 36 sensors.

The test is performed by passing the catheter into the stomach and esophagus to measure contraction pressures and waveform in the esophageal body and the sphincters' resting pressure and response to swallowing. The lubricated catheter is passed through the nostril and into the esophagus. The catheter is advanced until a portion of the sensors are in the stomach. In patients who have a dilated or tortuous esophagus, such as in cases of suspected achalasia or a large paraesophageal hernia, it is recommended that the catheter be passed endoscopically to ensure that it is properly positioned into the stomach and not coiled in the esophagus. The pressure topogram is assessed to ensure that the catheter is completely

traversing the UES and the LES. Unlike with traditional manometry, a HRM study can be performed with 10 swallows without the need to repeatedly move the catheter back and forth for different portions of the exam. The patient is then asked to refrain from swallowing for 30 seconds with quiet breathing, which allows the capture of a landmark frame for assessment of the resting UES and LES. The patient is positioned supine with the head elevated and is asked to swallow 5-mL aliquots of water separated by a minimum of 30 seconds to prevent deglutitive inhibition. A complete manometric study includes the assessment of the structural characteristics of the LES, the degree of LES relaxation, the esophageal body coordination, contraction amplitude and waveform, and the UES function.

Lower Esophageal Sphincter

The resting LES is assessed during the landmark frame (Fig. 34-19). The lower (distal) border of the LES is the point at which the resting pressure rises above the gastric baseline; the upper border is the point at which sphincter pressure reaches the esophageal baseline. The respiratory inversion point is identified when the positive excursions that occur with breathing in the abdominal environment change to negative deflections in the thoracic environment. The respiratory inversion point is the functional division between the abdomen and thorax. The resting pressure of the LES is the pressure above gastric baseline measured during mid-respiration at the respiratory inversion point. The overall length of the sphincter is the distance from the distal border to the proximal border. The abdominal length is the distance from the distal border to the respiratory inversion point and represents the portion of the LES that is subject to fluctuations in intra-abdominal pressure. The measurements for each of these components from each transducer are expressed as an average during the landmark frame, which extends for 30 seconds.

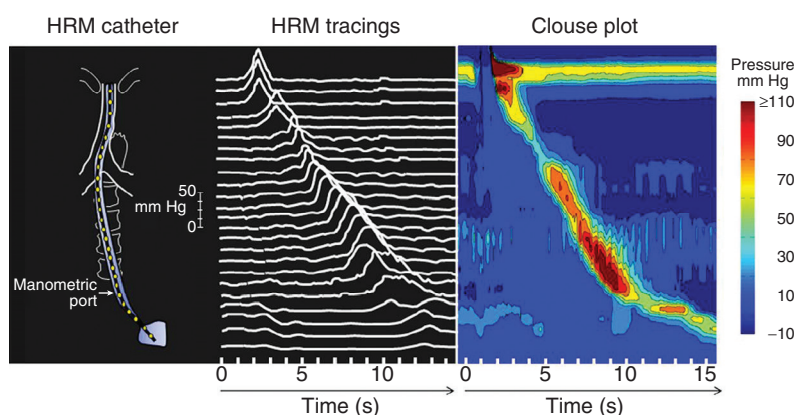


FIGURE 34-18 ■ The distinction between high-resolution manometry (HRM) and esophageal pressure topography (EPT). The HRM catheter consists of 21 to 36 closely spaced pressure sensors. The position of pressure sensors in the esophagus is indicated in the anatomic drawing on the left. In the middle panel, the data from HRM records are displayed as tracings for each pressure sensor, similar to conventional manometry. EPT is illustrated on the right. EPT is distinct from HRM in that it is purely a data analysis method, whereas HRM is a data acquisition method. The Clouse plots (EPT plots) are derived from the data acquired from HRM and are displayed using a color code to describe peristaltic amplitude in a space-time continuum. A technique of interpolating between the recording sensors allows one to obtain a seamless representation of the pressure activity through the entire swallow. Note the tremendously enhanced detail provided by the Clouse plot, especially in the area of the esophagogastric junction. (From Pandolfino JE, Roman S: High-resolution manometry: an atlas of esophageal motility disorders and findings of GERD using esophageal pressure topography. *Thorac Surg Clin* 21(4):465–475, 2011.)

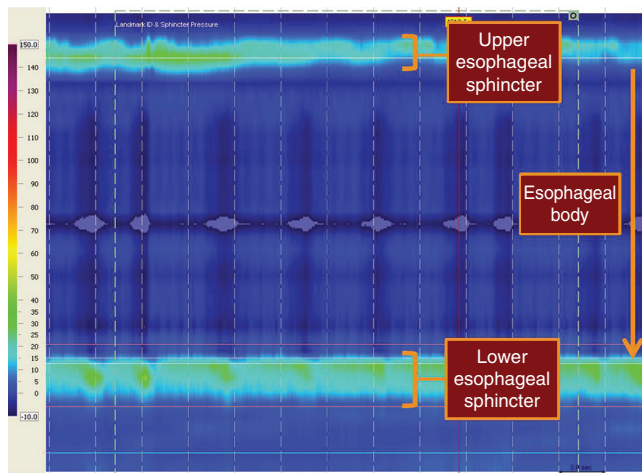


FIGURE 34-19 ■ High-resolution esophageal manometry showing the landmark frame. The upper and lower esophageal sphincters are observed at the top and bottom of the frame, respectively. Resting pressure and length measurements of the sphincters can be determined in this portion of the study while the patient is refraining from any swallowing.

A structurally defective sphincter is identified as one that has low resting pressure or short length. Based on conventional manometry in normal volunteers, the following characteristics have traditionally been used to identify a structurally defective LES: (1) an average LES pressure of less than 6 mm Hg, (2) an average abdominal length of less than 1 cm, and (3) an average overall length of less than 2 cm. Based on normative data, these values are below the 2.5 percentile. A defect in one or even two components of the LES may be compensated by good esophageal body function, but when all three components are defective, excessive esophageal acid exposure is inevitable.

It should be noted that whereas HRM has revolutionized the assessment of the esophageal body as a result of improved resolution of contraction waves, the assessment of the LES has been less than optimal. This is primarily because of the nature of the HRM catheter, which functions as a sleeve manometry catheter and results in circumferential averaging of pressure data. For this reason, length assessment of the LES and UES is believed to be suboptimal compared with that obtained with conventional manometry with a manually pulled through catheter.⁴⁶ It is hoped that the newly developed three-dimensional HRM catheter will allow more precise or detailed evaluation of the LES structure, but clinical experience is necessary to fully evaluate its additive value.

Lower Esophageal Sphincter Relaxation

The LES pressure normally drops to gastric baseline immediately after initiation of a swallow and remains open until the oncoming peristaltic wave reaches the stomach (Fig. 34-20). A characteristic postrelaxation contraction of the LES is subsequently observed as the LES closes with passage of the bolus. Using HRM, relaxation is assessed during a 4-second integrated relaxation

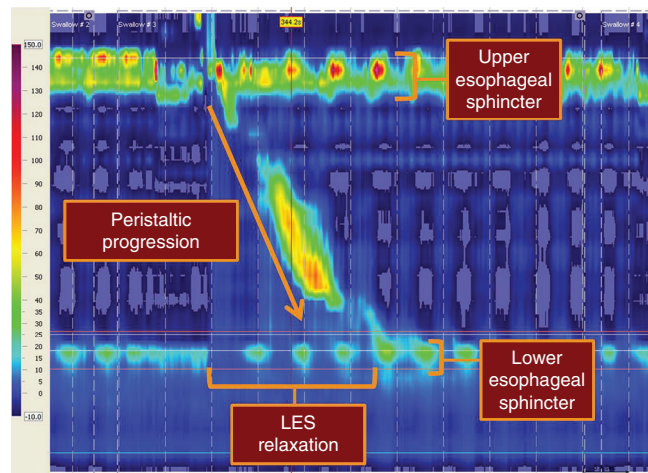


FIGURE 34-20 ■ High-resolution esophageal manometry during a swallow. The initiation of swallowing is reflected by transient relaxation of the upper esophageal sphincter followed by a peristaltic pressure wave progressing down the esophageal body. Note the lower esophageal sphincter (LES) relaxes at the initiation of swallowing. A characteristic peristaltic break is observed in the upper third of the esophageal body at the transition zone between the striated and smooth muscle.

pressure (IRP). This 4-second window is often captured in a noncontiguous manner during the swallow to eliminate the effect of respiratory variation from the crura. A residual pressure of greater than 15 mm Hg is considered elevated and may result in clinically significant outflow resistance of bolus transport through the esophagus.

Esophageal Body Motility

The esophageal body is evaluated by assessing its contraction amplitude, duration, slope, velocity, and morphology (i.e., single, double, or triple peaked) (see Fig. 34-20). A physiologic gap in contraction or proximal peristaltic break typically occurs in the upper one third of the esophagus and corresponds to the transition zone between the striated muscle above and smooth muscle below. Pathologic breaks are those that are longer than 2 cm or if a break occurs in the distal esophagus. HRM has had its greatest improvement in the assessment of esophageal body function. It is important to allow 30 seconds between swallows to prevent deglutitive inhibition of the body, a physiologic dampening or absence of peristalsis with repetitive swallowing.

Further improvement in assessing esophageal body function with HRM has been the use of the distal contractile integral (DCI), which gives a global assessment of esophageal contractile function. This is an integrated summation of the contractile pressures generated between the proximal peristaltic break and the upper border of the LES and is calculated as the product of amplitude (mm Hg) $\times$ duration (seconds) $\times$ length (cm), with normal values ranging from 500 to 4300 (Fig. 34-21). Based on conventional manometry, it was believed that a minimum of distal contraction amplitude of greater than 20 mm Hg at one level 5 cm above the LES was necessary to overcome the resistance of an antireflux procedure. With HRM, it is currently believed that a DCI greater than

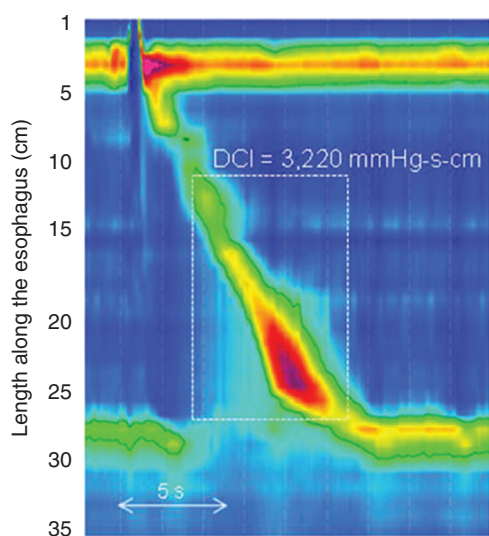


FIGURE 34-21 ■ The distal contractile integral (DCI) is measured from the proximal peristaltic break to the top of the lower esophageal sphincter. It provides a more global assessment of esophageal body contractility. (From Pandolfino JE, Roman S: High-resolution manometry: an atlas of esophageal motility disorders and findings of GERD using esophageal pressure topography. *Thorac Surg Clin* 21:465–475, 2011.)

500 mm Hg/sec/cm is necessary to minimize the possibility of postoperative dysphagia; however, clinical validation of this cutoff has not been performed.

Upper Esophageal Sphincter

The position, length, and resting pressure of the UES and its relaxation with swallowing are assessed with a technique similar to that used for the LES. The key features to be assessed are the adequacy of pharyngeal contraction and the timing and extent of UES relaxation. An indirect measure of UES stiffness or loss of compliance is the intrabolus pressure, which appears as a pressure rise or shoulder on the upstroke of the pharyngeal contraction.

High-Resolution Impedance

Even with the addition of high-resolution topography, manometric data often do not exactly correlate with the effective passage of the swallowed bolus. The barium video esophagram has been used to complement this shortcoming of manometry; one drawback, however, is that these tests cannot be performed simultaneously. Not infrequently, a discrepancy may exist between these studies with a normal video esophagram but poor esophageal body manometry characteristics, or vice versa. Currently, the authors are using combined high-resolution manometry with high-resolution impedance to gain additional information on bolus transport.

Ambulatory pH Monitoring

The development of ambulatory pH monitoring was a major advance in the unraveling of the pathophysiology of GERD. All previous tests had relied on the

identification of reflux by a provocative maneuver, which had little relevance to the patient's daily activities. The 24-hour pH monitoring test made it possible to determine if the time of esophageal exposure to gastric juice in a patient during a 24-hour period was greater than what was found in normal subjects.

The 24-hour pH monitoring test is considered by many to be the gold standard for the diagnosis of GERD because it has the highest sensitivity and specificity of all tests currently available. It is indicated in any patient with symptoms suggestive of GERD, unless the symptoms are trivial or permanently abolished by a short course of acid suppression therapy. The need for continued acid suppression should stimulate objective study. A 24-hour pH monitoring study is especially important in patients who are being considered for antireflux surgery. Atypical presentations of GERD are also a common indication; they include such symptoms as noncardiac chest pain (i.e., pain despite a normal cardiac evaluation) and respiratory symptoms such as shortness of breath, cough, nocturnal wheezing, and chronic hoarseness. In such patients, 24-hour pH monitoring allows confirmation of the diagnosis of GERD and can relate the occurrence of the symptoms to an episode of reflux.

To perform the test, a thin catheter containing a pH electrode is passed transnasally into the esophagus and placed 5 cm above the upper border of the LES, a position that has been previously determined by manometry. Different probes are available, but bipolar glass electrodes are preferred for their greater reliability and their elimination of the need for an external reference electrode. The electrode is connected to an external portable digital storage device that is kept at the patient's side, and pH values are continuously recorded at 6-second intervals for 24 hours (i.e., a complete circadian cycle). Precalibration and postcalibration of the system to pH levels of 1 and 7 is important to exclude electrode drift. A gastric "dipstick" maneuver is performed prior to securing the location of the catheter to confirm acid in the stomach and to ensure that the patient does not have atrophic gastritis. The patient is then instructed to carry out normal daily activities but to avoid strenuous exertion. He or she is asked to remain in the upright position while awake during the day, lying down supine only at night while sleeping, and to ingest two meals at the usual time. The diet is standardized only by its absence of food and beverages with a pH value of less than 5.0 and greater than 6.0. The patient notes in a diary the times of meals, retiring for sleep, and rising the following morning as well as the presence and duration of any symptoms. At the authors' institution, patients are also asked to consume a challenge meal consisting of a hamburger, French fries, and a milk shake. It has been found that a refluxogenic meal can often uncover early acid reflux disease that would not ordinarily be detected during a typical 24-hour period.⁴⁷ Figure 34-22 shows typical 24-hour pH tracings from a healthy subject and from a patient with GERD. Medications such as H₂ blockers and prokinetics should be discontinued for 48 hours before the testing begins. Proton pump inhibitors (e.g., omeprazole) should be stopped for 2 weeks before pH monitoring because of their long-lasting action.

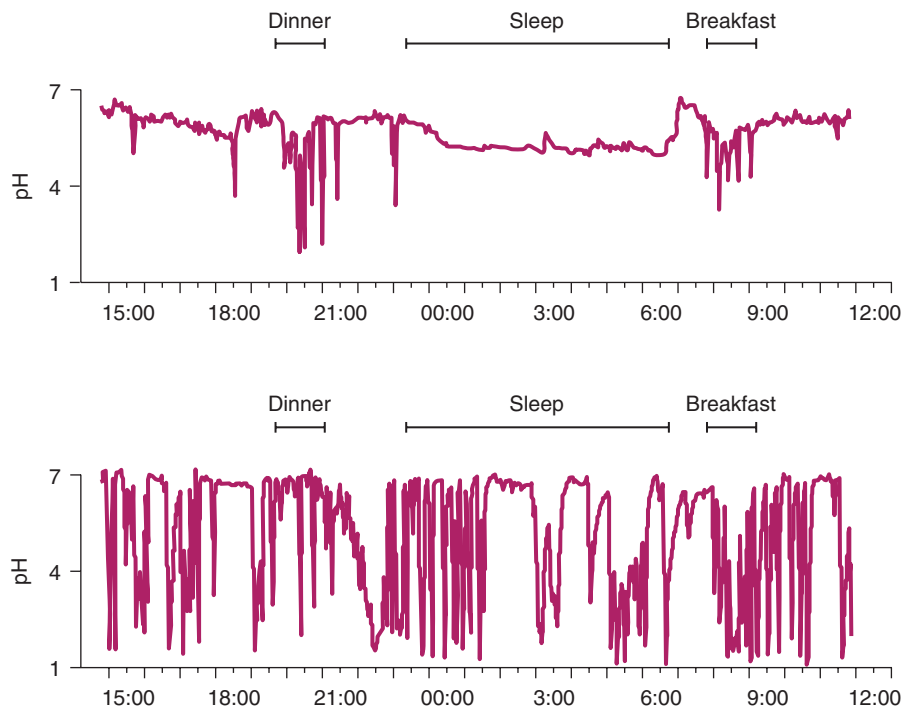


FIGURE 34-22 ■ Tracings of 24-hour pH monitoring of the distal esophagus in a healthy subject (*top*) and in a patient with gastroesophageal reflux disease (*bottom*). Physiologic reflux occurs in the normal subject, mainly in the upright position after meals. The patient's record shows an increased number of reflux episodes in both upright and supine positions, some of them with prolonged clearing time.

It is important to emphasize that 24-hour esophageal pH monitoring should not be considered a test for reflux; rather, it is a measurement of the esophageal exposure to gastric juice. The measurement is expressed as the percentage of time that the esophageal pH was below 4 during the 24-hour period. Just measuring the percentage of time that the pH is less than 4, although concise, does not reflect how the exposure has occurred; for example, it may have occurred in a few long or several short reflux episodes. Consequently, two other assessments are necessary: (1) the frequency of the reflux episodes and (2) their duration. For this reason, esophageal exposure to gastric juice is best assessed by the following measurements⁴⁷:

- The cumulative time that the esophageal pH is below 4 expressed as the percentage of the total, upright, and supine monitored times;
- The frequency of reflux episodes, when the pH drops below 4, expressed as the number of episodes per 24 hours;
- The number of episodes during which the pH remained below 4 for longer than 5 minutes per 24 hours; and
- The time in minutes of the longest recorded reflux episode, the longest time the pH consistently remained below 4.

Normal values for these six components of the 24-hour record were derived from 50 asymptomatic control subjects. The upper limits of normal were established at the 95th percentile.⁴⁷ If the values of symptomatic patients are outside of the 95th percentile of normal subjects, they are considered to be abnormal for the component measured. There is a uniformity of normal values for these

six components as reported by centers throughout the world. The normal values for the six components obtained from 50 healthy volunteers are shown in [Table 34-1](#). A composite scoring system has been derived that integrates the different components of the pH record into a single measurement of esophageal acid exposure. This composite score is calculated from the six parameters with use of their standard deviations as weighing factors.⁴⁷

Advances in technology have made pH testing more comfortable for the patient. The development of a catheter-free miniaturized pH electrode has revolutionized the way that standard ambulatory pH testing is performed. The Bravo system (Medtronic, Minneapolis, MN) allows the transnasal or transoral deployment of a small capsule attached to the esophageal mucosa that is capable of transmitting pH data by radiotelemetry to a pager-sized receiver, thus eliminating the need for an unpleasant catheter. It may also provide a more accurate physiologic picture by allowing patients to perform their normal daily activities without the social and behavioral restrictions imposed by the catheter. Another major advantage of the Bravo capsule is the ability to record for prolonged periods, and routine monitoring of 48 hours is now performed with improved diagnostic capabilities.⁴⁸ New normal thresholds have been defined and validated for the 48-hour Bravo pH test, with the normal composite score for the first 24 hours being 14.0, the second 24 hours being 14.0, and the combined 48-hour score being 16.0.⁴⁸

In patients with symptoms of chronic cough, hoarseness, or pulmonary aspiration, placement of an additional pH electrode in the proximal part of the esophagus or pharynx can be helpful.⁴⁹ Such dual probe catheters are

TABLE 34-1 Esophageal Acid Exposure 5 cm above the Upper Border of the LES during 24 Hours of Ambulatory pH Monitoring in 50 Healthy Volunteers

Component	95th Percentile
% Total time pH < 4	4.5%
% Upright time pH < 4	8.4%
% Supine time pH < 4	3.5%
Number of episodes	46.9
Number of episodes ≥ 5 min	3.5
Longest episode	19.8 min
24-hr DeMeester composite score	14.7

LES, Lower esophageal sphincter.

From Johnson LF, DeMeester TR: Twenty-four-hour pH monitoring of the distal esophagus: a quantitative measure of gastroesophageal reflux. *Am J Gastroenterol* 62:325–332, 1974.

particularly helpful in determining if gastroesophageal reflux events extend proximally, which could give indirect evidence of acid exposure into the pharyngeal area and subsequent irritation. If the accumulated acid exposure in the proximal esophagus is greater than 1% or the number of reflux episodes is more than 24 (particularly if there is a temporal relationship between the reflux episodes and the onset of the symptoms), reflux can be documented and assumed to be the cause of the patient's respiratory symptoms.⁴⁹ A composite score has been developed for proximal pH monitoring, analogous to that developed for the distal probe, with the normal threshold composite score being 16.4.⁴⁹

Additional testing is sometimes necessary if the standard methods of assessing esophageal function fail to yield conclusive results, particularly when investigating the relationship of acid reflux and extraesophageal symptoms. A novel pharyngeal pH system has been developed that allows a pH probe to be positioned directly into the pharynx just below the uvula (Restech pH probe, Respiratory Technology Corp, San Diego, CA).⁵⁰ This probe uses a novel antimony sensor that allows measurement of pH within the humidified air of that environment without drying out and creating artifacts. Early clinical experience with this technique indicates that it is a useful adjunct diagnostic test in patients suspected of having laryngo-pharyngeal reflux.

Testing for reflux that is nonacidic or weakly acidic can be gained by multichannel intraluminal esophageal impedance monitoring. This type of measurement determines the resistance to the flow of current through a given medium (impedance). The impedance to current changes as the composition of the medium in which the current is traveling changes (i.e., air, liquids, or solids). Coupled with a pH probe, it can differentiate acid reflux from nonacid reflux, which may be particularly important in patients who remain symptomatic on acid suppression therapy.

Lastly, the assessment of gastric function can be important in many patients with esophageal symptoms. Disorders of gastric emptying frequently can contribute to, or be confused with, esophageal disease, especially GERD. Nuclear medicine radioisotope with solid food

matter such as scrambled eggs has been used for this purpose and is indicated in any patient being evaluated for GERD who also has a history of nausea, early satiety, and vomiting. Such information may be invaluable to prevent performing an antireflux operation in the setting of gastroparesis.

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SURGERY FOR CONGENITAL LESIONS OF THE ESOPHAGUS

A. Alfred Chahine • David Spurlock • Kurt D. Newman

CHAPTER OUTLINE

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LARYNGOTRACHEOESOPHAGEAL CLEFT

Anatomy

Presentation

Diagnosis

Treatment

EMBRYOLOGY

At approximately the 18th or 19th day of fetal life, the notochord, the anlage of the vertebral column, starts to form, first in close association with endodermal cells and then separating from them. The foregut develops from the endodermal cells as they are separating from the notochord. At approximately 3 weeks of embryonic development, the tracheal primordium appears as a ventral diverticulum in the cephalad portion of the foregut. Over the next few weeks, growth and elongation of the diverticulum and the foregut along the tracheoesophageal groove contribute to the separation of the esophagus and the trachea, which is complete by approximately 5 to 6 weeks of fetal life. During the seventh and eighth weeks, the esophageal epithelium proliferates and fills the lumen almost completely. Vacuoles appear in the lumen and eventually coalesce to recanalize it by the 10th week.¹

The major anomalies of the esophagus are a result of some aberration in the orderly development of the organ. Failure of separation of the trachea and esophagus may result in esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF) and laryngotracheoesophageal clefts. Tracheobronchial elements including cartilage can be left behind in the distal esophagus and cause congenital esophageal stenosis. Failure of recanalization of the esophageal lumen may contribute to the pathogenesis

of EA and esophageal webs. Intramural esophageal duplication cysts may result from failure of the esophageal vacuoles to completely coalesce and disappear. Aberrations in the orderly separation of endodermal cells and the notochord may explain the formation of duplication cysts in the posterior mediastinum and vertebral defects associated with EA.

An Adriamycin-induced murine model of EA was described.² Using this model, investigators are studying the role that patterning genes and proteins like Sonic hedgehog (*Shh*) might play in the morphogenesis of EA.^{3,4} Using the same rat model as well as neonates with EA/TEF, Spilde and coworkers have studied the molecular expression of foregut-patterning genes to shed a light on the origin of the TEF. The distal esophagus seems to arise as a diverticulum of the trachea, which elongates and joins the stomach, rather than from the foregut itself.^{2,5,6} They speculate that this might explain the well-known poor motility of the esophagus.

ESOPHAGEAL ATRESIA

Historical Aspects

The historical background relevant to EA is thoroughly reviewed by Harmon and Coran.⁷ Durston in 1670 and Gibson in 1697 described the first cases of EA. It took

approximately 250 years before the first cases of survivors were reported by Leven and Ladd independently in 1939. Both were able to achieve success by performing a series of operations, including gastrostomy, ligation of fistula, marsupialization of the upper pouch, and final reconstruction with an antethoracic skin tube. The early attempts at primary repair were all unsuccessful. It was not until 1941 that Haight reported the first survivor of a primary repair. In the decade that followed, it became evident that the mortality in infants of lower birth weights, those with severe associated anomalies, and those critically ill from aspiration pneumonia was very high.⁸⁻¹⁰ There followed a shift toward staging the operation for sick babies, with a gastrostomy, followed by division of the TEF and the esophageal reconstruction performed as a third stage.⁸⁻¹⁰ In 1962, Waterston proposed a classification based on birth weight, presence of pneumonia and associated anomalies.⁹ The 1970s and 1980 witnessed major advances in respiratory, neonatal, anesthetic, and surgical care, as well as introduction of more effective antibiotics. These advances included endotracheal intubation, which made it easier to prevent aspiration from the esophageal pouch and to deal with its sequelae. As a result, multiple groups started recommending either direct primary anastomosis (anastomosis shortly after birth) or delayed primary anastomosis (anastomosis delayed for the treatment of other life-threatening anomalies or stabilization of the patient) regardless of the patient's weight but based on physiologic criteria.¹¹⁻¹⁹ The end of the 20th century ushered in the application of thoracoscopy to the repair of EA/TEF and other congenital anomalies of the esophagus.²⁰⁻²⁷

Epidemiology

The average rate of EA is reported to be approximately 2.4 per 10,000 births.²⁸ There is no significant described sex predilection. Other congenital anomalies occur in patients with EA frequently, ranging from 30% to 76%.²⁹⁻³³ This might be because the malformation in EA occurs early in the first trimester when there is active organogenesis. As a result, the developmental cause of EA/TEF might also affect other organ systems at the same time. The number of associated anomalies occurring in each patient increases with decreasing birth weight.^{29,34,35} With the improvement in anesthetic, respiratory, and neonatal techniques over the past few decades, the associated anomalies are now the major contributor to mortality in patients with EA.³¹ The most common associated anomaly is congenital heart disease, present in some form in approximately one fifth of patients.^{29,33-37}

Approximately 20% of patients will have some combination of the constellation of anomalies referred to as VATER or VACTERL association: *v*ertebral, *a*norectal, *c*ardiac, *t*racheo*e*sophageal, *r*enal or *r*adial, and *l*imb anomalies.^{36,37}

Babies born with EA often have low birth weight and are premature.^{35,38} In one study, 90% of the patients with EA were below the 50th percentile for gestational age, and 40% were below the 10th percentile or small for gestational age (SGA).³⁹ The growth retardation might be secondary to decreased absorption of the amniotic fluid protein or from a mechanical factor.³⁹ Severe intra-uterine growth retardation increases the mortality rate of the SGA neonate by 5 to 20 times that of appropriate-for-gestational age neonates of the same gestational age.⁴⁰

Anatomy

There are five types of EA with or without TEF. The types of EA are numbered differently depending on the classification scheme, so it is preferable to describe the actual anomaly rather than assign it a number or a letter: EA with distal TEF, EA without TEF, EA with proximal TEF, EA with proximal and distal fistula, and isolated TEF (H-type TEF) (Fig. 35-1). The distribution of the different types in large series has been relatively uniform across decades and countries with the most common being EA with distal TEF (Table 35-1).^{11,29,41-43} The fistula is usually small and most of the time arises from the midline of the membranous portion of the trachea just above the bifurcation; however, significant variations exist.

Presentation

A significant number of cases of EA are now suspected on prenatal ultrasonography, with polyhydramnios, absent or small stomach bubble, and visualization of an

TABLE 35-1 Distribution of Types of Esophageal Atresia

Type of Anomaly	Number	Percentage
EA with distal TEF	1024	87.1
EA	82	7.0
H-type TEF	37	3.1
EA with proximal TEF	11	0.9
EA with double TEF	22	1.9

EA, Esophageal atresia; TEF, tracheoesophageal fistula. Data from references 11, 29, 41-43.

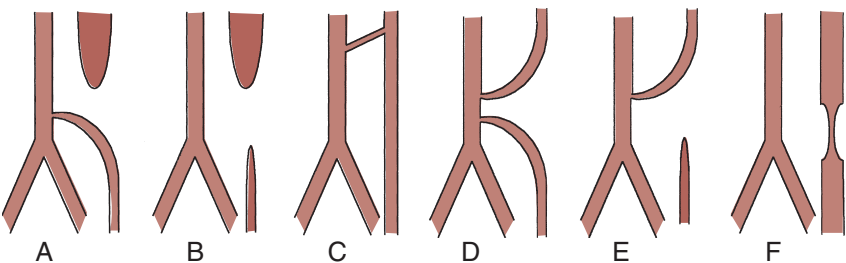


FIGURE 35-1 ■ Classification of types of esophageal anomalies. A, Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF). B, EA without TEF. C, TEF without EA (H-type fistula). D, EA with proximal and distal TEF. E, EA with proximal TEF. F, Esophageal stenosis.

esophageal pouch in the neck being the most prominent features.^{44,45} Suspecting the diagnosis prenatally is invaluable in preparing the family. Prenatal counseling with a pediatric surgeon and a neonatologist and planning for appropriate delivery arrangements are extremely helpful. Postnatally, most patients with EA are diagnosed in the first few hours after birth. Choking with feeding, regurgitation of saliva and feeds, respiratory distress from aspiration of saliva or gastric contents through the TEF are the most common signs and symptoms. Inability to pass a feeding tube confirms the diagnosis.

Patients with isolated TEF (H-type TEF) may not be diagnosed until later in life. Recurrent episodes of aspiration pneumonia and choking and coughing with feedings should raise the suspicion. Contrast esophagram and rigid bronchoscopy are complementary in making the diagnosis, which is often very difficult to make.⁴⁶

Patients with isolated EA often have a scaphoid abdomen because of the absence of gas in the intestines. If EA is suspected, one should always look for other physical signs of the VATER association: anorectal malformations, limb anomalies, and vertebral defects (Fig. 35-2).

Workup

A chest radiograph showing a curved catheter in the proximal esophageal pouch is often all that is required to make the diagnosis (Fig. 35-3). In patients with isolated EA, the radiograph reveals absence of intestinal air (Fig. 35-4). If still in doubt, a small amount of air injected into the pouch accentuates it on a plain radiograph and confirms the presence of EA (Fig. 35-5). The use of barium to look for an upper pouch fistula should be discouraged because it may potentially lead to aspiration. Upper pouch fistulae are rare and are usually found at the time of repair by either bronchoscopy or a careful dissection of the proximal pouch. An esophagram performed via a catheter being pulled up along the esophagus while the patient is prone is invaluable in making the diagnosis of H-type fistula (Fig. 35-6).



FIGURE 35-2 ■ Radial aplasia, one component of the VATER association.

An echocardiogram, renal ultrasound, and vertebral films are often performed to rule out major cardiac, renal, and vertebral anomalies as part of the VATER association. The echocardiogram is also helpful in determining the location of the aortic arch and of any aberrant central vessels, which might alter the surgical approach. Recently,

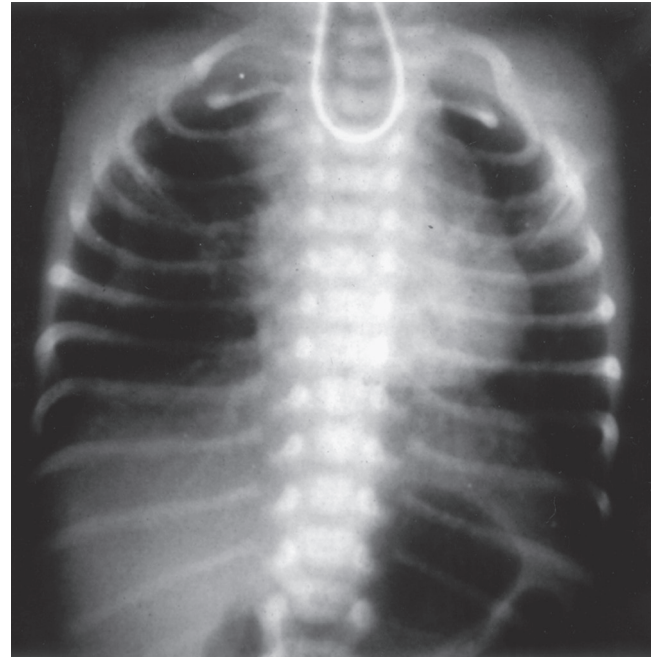


FIGURE 35-3 ■ Chest radiograph of a patient with esophageal atresia and tracheoesophageal fistula. Note the catheter curved in the upper pouch and the presence of air in the intestinal tract. (Courtesy Dr. R. Ricketts, Emory University Medical Center.)

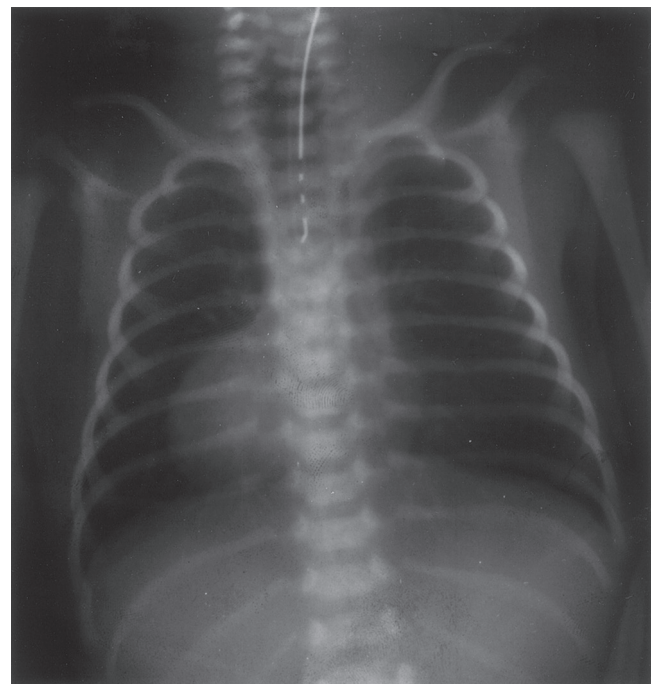


FIGURE 35-4 ■ Chest radiograph of a patient with isolated esophageal atresia. Note the absence of air in the intestinal tract. (Courtesy Dr. C. Leftridge, Georgetown University Medical Center.)

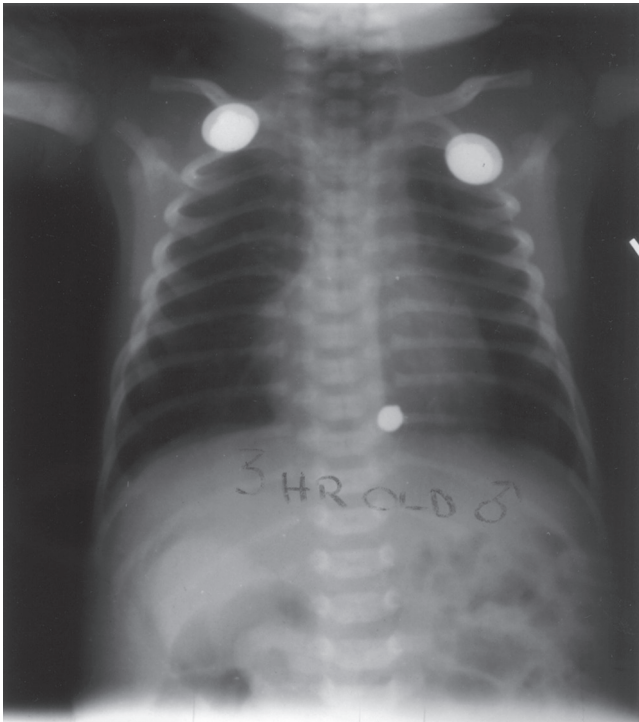


FIGURE 35-5 ■ Air contrast esophagram in patient with esophageal atresia showing the distended proximal pouch. (Courtesy Dr. C. Leftridge, Georgetown University Medical Center.)

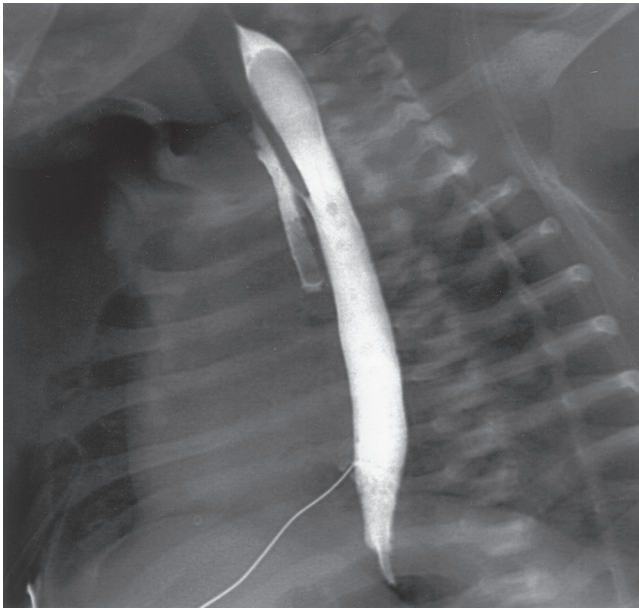


FIGURE 35-6 ■ Contrast esophagram showing an isolated tracheoesophageal fistula (H-type) with contrast delineating the trachea. (Courtesy Dr. C. Leftridge, Georgetown University Medical Center.)

the need for a preoperative echocardiogram in asymptomatic patients has been questioned.⁴⁷

Initial Management

Patients born with EA are at risk for aspiration of saliva or gastric contents into the tracheobronchial tree. A

Replogle-type soft sump suction catheter with the holes close to the tip should be placed in the upper pouch and put on continuous suction. In the presence of a TEF, the patient should be placed in the reverse Trendelenburg position with the head up to minimize reflux of gastric contents into the trachea. Having the patient prone might also help to keep the gastroesophageal junction at a less dependent position and decrease gastric reflux. With isolated EA, the Trendelenburg position facilitates the passive drainage of the hypopharynx and complements the active suction of the catheter. Even with a drainage catheter in place, frequent suctioning of the hypopharynx helps in decreasing the risk of aspiration. If there is any evidence of aspiration pneumonitis on a radiograph, broad-spectrum antibiotics should be started.

If possible, positive-pressure ventilation should be avoided in a patient with a TEF to minimize shunting through the TEF and abdominal distention. Because most fistulae are located just proximal to the carina, the tip of the tube should be kept high in the trachea to prevent the tip of the tube from becoming lodged in the TEF. Sometimes, the TEF is significant enough that adequate ventilation cannot be maintained, especially in the presence of respiratory distress syndrome (RDS), in premature patients, with its attendant high intraparenchymal pressures. In these cases, emergent ligation of the TEF or division of the esophagus might be warranted.^{48,49} A more difficult way to control the TEF emergently is obliteration of the TEF with a Fogarty balloon introduced via bronchoscopy.⁵⁰ A hazardous situation can occur when a patient with significant steal through a TEF also has a very high intestinal obstruction, such as duodenal atresia. The massive gastric distention exacerbates the respiratory compromise and could lead to perforation of the stomach. Emergent gastric decompression has to be performed, sometimes at the bedside with a needle.

The timing of surgery is of particular interest. The key issues affecting the timing include severity of the infant's condition, associated abnormalities, and birth weight. The Spitz classification identified low birth weight (<1500 g) and major congenital heart disease as two major risk factors associated with EA.⁵¹ This system stratifies patients into groups. Survival was estimated at 97% for group I (weight > 1500 g with no major congenital cardiac defect), 59% for group II (birth weight < 1500 g or major congenital cardiac defect), and 22% for group III (birth weight < 1500 g and major congenital cardiac defect). In 2006, Lopez validated the original Spitz classification in a series of 188 neonates.⁵² Weight-based classification systems such as the Spitz and Waterston classifications have traditionally been used to assess prognostic outcomes with surgical intervention. However, others have not found weight to be an independent predictor of survival.^{53,54}

Several groups investigated the issue of operating on extremely low-birth-weight (ELBW, weight < 1000g) infants and very low-birth-weight (VLBW, weight < 1500 g) infants and the ideal surgical management of these patients is still controversial. In 2006, Seitz and colleagues published their data of four children who underwent open primary repair of EA/TEF whose weight

ranged from 780 to 1120 grams.⁵⁵ Their postoperative complications included one patient with anastomotic leak and a separate patient with esophageal stenosis requiring dilation. They concluded that a one-stage approach is a good option in ELBW children. In 2009, Petrosyan and colleagues published a retrospective review of 25 VLBW infants with EA/TEF who underwent open operative repair between the years of 1987 and 2008.⁵⁶ The researchers divided these patients into two groups: 16 of these patients underwent primary repair and 9 underwent staged repair. There was no difference in patient characteristics, including weight or mean gestational age. However, there was a significantly higher rate of anastomotic leak (50% versus 0%), strictures (81% versus 33%), and sepsis/pneumonia (81% versus 66%) in the primary repair versus staged repair groups, respectively. They concluded that there are increased risks of postoperative complications in premature VLBW infants with EA/TEF and recommended a staged surgical approach in these patients, which is consistent with the series of Chahine and Ricketts.³⁵

Operative Principles

Rigid bronchoscopy is helpful at the beginning of the procedure to identify the exact location of the TEF, recognize rare variants like double fistulae or H-type fistula and laryngotracheoesophageal clefts, identify the presence of tracheomalacia, and help in placement of the endotracheal tube to avoid dislodgement into the TEF (Fig. 35-7).⁵⁷⁻⁵⁹

Primary repair of EA with division of the TEF and end-to-end anastomosis is the ideal goal (Fig. 35-8). The standard approach is a right posterolateral thoracotomy. If the patient has a right-sided aortic arch, it might be easier to approach the esophagus from the left thorax.

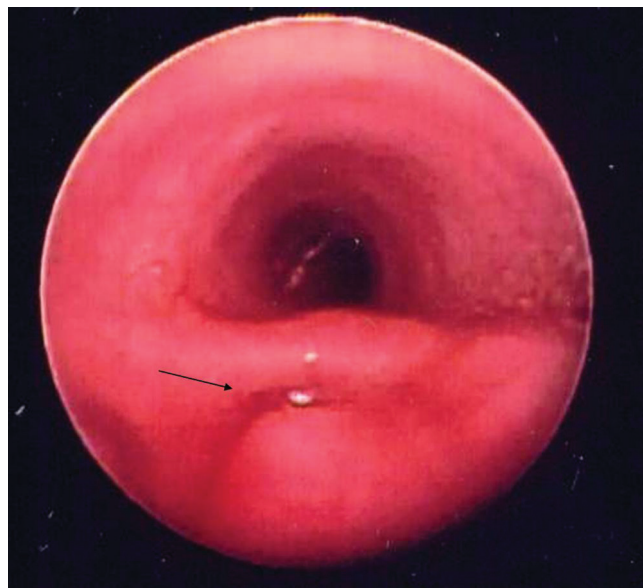


FIGURE 35-7 ■ Bronchoscopic appearance of a tracheoesophageal fistula (arrow) in the membranous portion of the trachea proximal to the carina.

Having the patient tilted forward in the near prone position facilitates access to the posterior mediastinum. To minimize some of the complications reported with thoracotomy in neonates, namely winged scapula and scoliosis, an axillary skin crease thoracotomy (reported by Bianchi⁶⁰ and used with good results⁶¹) may be considered. Traditionally, an extrapleural approach has been advocated to decrease the risk of empyema if an esophageal leak occurs. With the introduction of more powerful antibiotics in the 1970s and 1980s, the importance of a retropleural approach with the potential increase in operative time has been questioned.^{41,62}

The posterior mediastinum is exposed by dividing the parietal pleura. The azygous vein is divided to allow access to the TEF, which is usually located behind it. The fistula is circumferentially controlled and occluded. The fistula is divided leaving approximately 1 mm of esophageal tissue on the tracheal side to avoid narrowing the tracheal lumen. Leaving more than a minimal amount of esophageal rim might create a pouch, which could accumulate secretions and cause repeated aspirations. The tracheal defect is closed in an airtight manner, usually with an absorbable monofilament suture.

Gentle pressure by the anesthesiologist on the pouch catheter helps to identify the upper pouch, which is usually high in the thoracic inlet. A transmural suture placed through the fistula and incorporating the catheter makes the manipulation of the upper esophagus less traumatic. The upper pouch and the trachea are intimately juxtaposed, often sharing a common wall. The dissection between the esophageal pouch and the trachea is delicate. Extreme caution should be applied to avoiding injury to both vagus and recurrent laryngeal nerves. The pouch is mobilized as high as possible to minimize the tension of the anastomosis. The blood supply of the upper esophagus is intramural, allowing for minimal ischemia even after extensive mobilization. In contradistinction, the lower esophagus is supplied by segmental branches from the aorta; therefore, its mobilization should be minimized to prevent ischemia. The ends of the esophagus are trimmed, and an end-to-end anastomosis is built in a single-layer fashion with fine monofilament absorbable sutures. The knots are tied extraluminally if possible. It is crucial to identify the mucosa of both the upper and the lower esophagus and incorporate it in the sutures. If there is significant tension, it is helpful to leave the sutures untied and approximate all at the same time because the knots are tied to take some of the tension off. The esophageal and tracheal suture lines must be separated to avoid fistula formation. This is usually accomplished by the interposition of a pleural flap, but sometimes a pericardial flap is required. The routine use of transanastomotic feeding tubes remains controversial.⁷ Before constructing the anastomosis, the surgeon needs to rule out congenital esophageal stenosis by passing a tube through the distal esophagus into the stomach.⁶³ At the completion of the procedure, a small chest tube is placed and secured to the endothoracic fascia away from the anastomosis. At approximately 5 or 7 days postoperatively, a contrast study is obtained to assess the anastomosis. The disparity in size between the distended proximal pouch and the small distal esophagus gives the

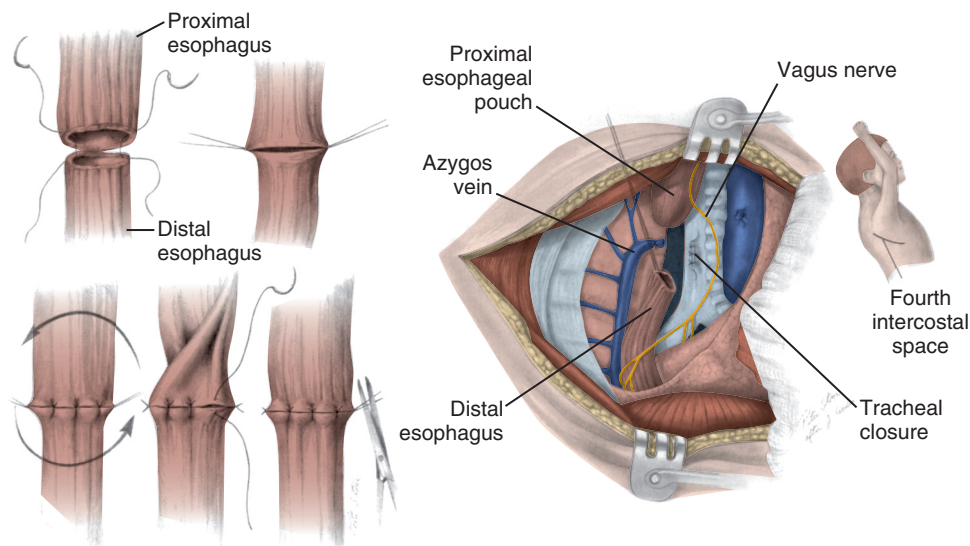


FIGURE 35-8 ■ Construction of the anastomosis in a patient with esophageal atresia and tracheoesophageal fistula. End sutures are placed to draw the ends of the esophageal segments together. A single row of simple sutures completes the front-presenting portions of the anastomosis, with the knots tied on the outside. One of the corner sutures is passed behind the esophagus, which is then rotated 180 degrees. The anastomosis is completed with simple sutures in the presenting posterior surface, which has been rotated into view. It is essential that the sutures are full thickness because the mucosa has a tendency to retract.

appearance of a narrowing, but usually prompt emptying of contrast attests to the wide patency of the anastomosis (Fig. 35-9A). With time, the size discrepancy becomes less pronounced (see Fig. 35-9B). If there is no leak, the chest tube is removed and feedings are started. Because of the frequent occurrence of gastroesophageal reflux (GER) and the deleterious effects acid can have on a fresh anastomosis, serious consideration should be made to keep the patient on acid suppressing and promotility drugs until the anastomosis is well healed.

Repair of EA in patients with significant gaps between the two ends of the esophagus can be challenging. The magnitude of the challenge is reflected in the number of innovative techniques described to save the native esophagus. Rehbein and Schweder proposed approximating the two ends as much as possible and waiting for a fistula to develop around the sutures then dilating that fistula.⁶⁴ Staging the operation with initial ligation of the TEF and delayed primary anastomosis has been advocated.⁶⁵ The growth of the esophagus can be spontaneous or active with serial bougienage of the upper pouch. Delayed primary anastomosis is certainly a safe and effective strategy in patients with very low birth weight in whom the tissues are friable or in patients who are unstable.^{13,35} Livaditis and Eklof described performing a circular myotomy on the upper esophagus to gain length.¹⁹ This has been used with good results by multiple groups.⁶⁶⁻⁶⁸ Delayed ballooning and diverticulum formation are two described long-term complications of circular myotomy.^{69,70} A second circular myotomy can be added via a cervical incision if more length is still needed. Kimura and colleagues advocate elongating the esophagus by performing a series of cervical esophagostomies with gradual elongation.⁷¹ Foker et al proposed the application of tension on the two ends through sutures brought out of the skin and tightened sequentially.⁷² Elongating the distal esophagus by performing a Collis-Nissen

fundoplication at the time of repair of EA has been described.⁷³ Schärli advocates division of the lesser curvature of the stomach to elongate it and partial gastric transfer to gain as much as 6 cm in length in the treatment of long-gap atresia and pure EA.⁷⁴ Tubularization of the upper pouch after creation of a U-shaped flap is an attractive technique described by Bar-Maor et al.⁷⁵

The repair of pure EA without a TEF is even more challenging. The distal esophagus is usually very short and the gap significant. All of the previously described techniques can be tried in this situation. Traditionally, the most common approaches were delayed primary anastomosis or esophageal replacement.⁷⁶ Colonic interposition, jejunal interposition, creation of a gastric tube, and gastric transposition are well-established techniques for esophageal replacement in children.⁷⁷⁻⁸⁰ More recently, the Foker technique of esophageal elongation with traction and delayed primary anastomosis has become a popular approach in the surgical treatment of these difficult patients. In 2013, Nasr and Langer performed a systematic review and cumulative meta-analysis that included articles describing the Foker technique or delayed primary anastomosis in patients with long gap EA.⁸¹ They compared 71 patients undergoing the Foker technique to 451 children undergoing delayed primary anastomosis with a primary outcome of postoperative complications and secondary outcome of time to definitive anastomosis. Their data showed a significantly lower rate of postoperative complications in the Foker group, including GER, anastomotic leak rate, and postoperative stricture rate. Additionally, there was a significant decreased time to definitive anastomosis between the Foker group and delayed anastomosis group at 14 ± 8.2 days versus 83 ± 62 days, respectively. They concluded that the use of mechanical traction is at least as effective as delayed primary anastomosis in this patient population.

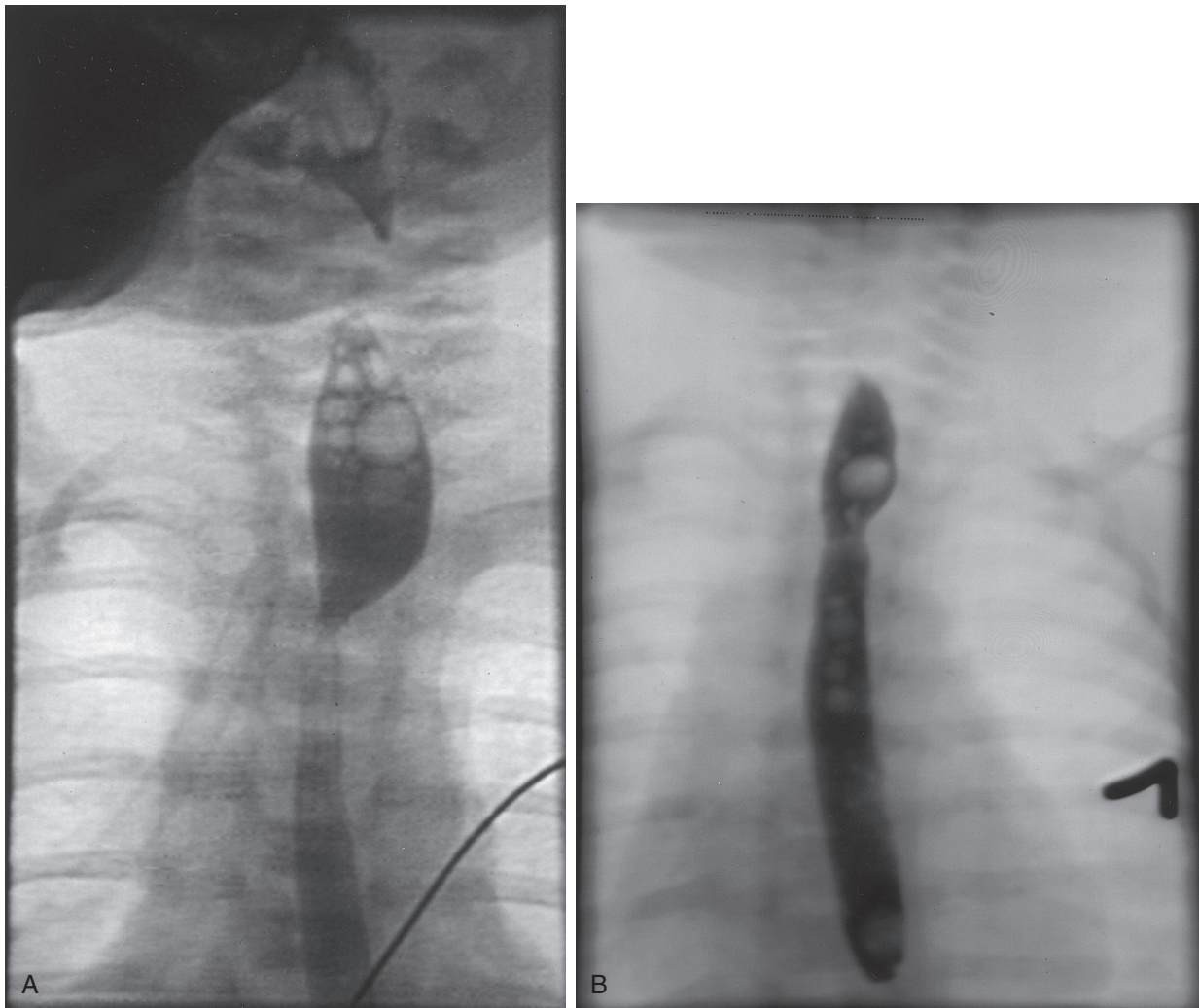


FIGURE 35-9 ■ **A**, Postoperative esophagram at 1 week revealing a patent anastomosis and a size discrepancy between the proximal and distal esophagus. **B**, Esophagram at 2 months postoperatively showing a decrease in the size discrepancy.

The approach to an H-type fistula is usually through a right cervical incision because most of these fistulae are in the neck. Direct division of the fistula and repair of the esophagus and tracheal components are the goal (Fig. 35-10). Placing a wire through the fistula via bronchoscopy and retrieving it from the mouth aid in the identification of the fistula and offer the opportunity to apply cephalad traction on the fistula to bring it up from the thorax if it is more distal than usual.⁸²

In 1999, Lobe and colleagues performed the first thoracoscopic repair of isolated EA.²¹ Since then, multiple groups have reported the successful thoracoscopic repair of EA with TEF (Fig. 35-11).^{24,25,83-85} This method of repair has become more widely practiced. In 2005, Holcomb et al performed a multi-institutional retrospective review of 104 newborns with EA/TEF undergoing thoracoscopic repair.⁸⁶ Their results demonstrated advantages such as superior visualization of the anatomy within the thoracic cage and decreased musculoskeletal deformities (i.e., winged scapula, thoracic wall asymmetry, serratus anterior muscle atrophy, thoracic scoliosis). In comparison to open repair, operative time was slightly

shorter at approximately 2 hours and time on the ventilator was slightly longer at 3.5 days. Time at discharge (18 days) was comparable between the two techniques. However, this is a phase I study and does not answer the question if the thoracoscopic technique is superior to the open approach.

Several articles have been published since Holcomb's publication comparing the minimally invasive and open approaches. However, none of these comparisons involved prospective randomized trials. In 2012, Burruto and colleagues published a meta-analysis of several retrospective reviews ultimately comparing 69 thoracoscopic to 97 thoracotomy approaches to EA/TEF.⁸⁷ Their primary endpoints were intraoperative and postoperative complications. They found no statistically significant difference in intraoperative complications in either group. Additionally, they did not find a difference in postoperative complications, including leak rate and stricture rate, between these groups. They concluded that the outcome of thoracoscopic technique is no different from that of the open technique but that a randomized controlled trial was necessary to determine which procedure is superior.

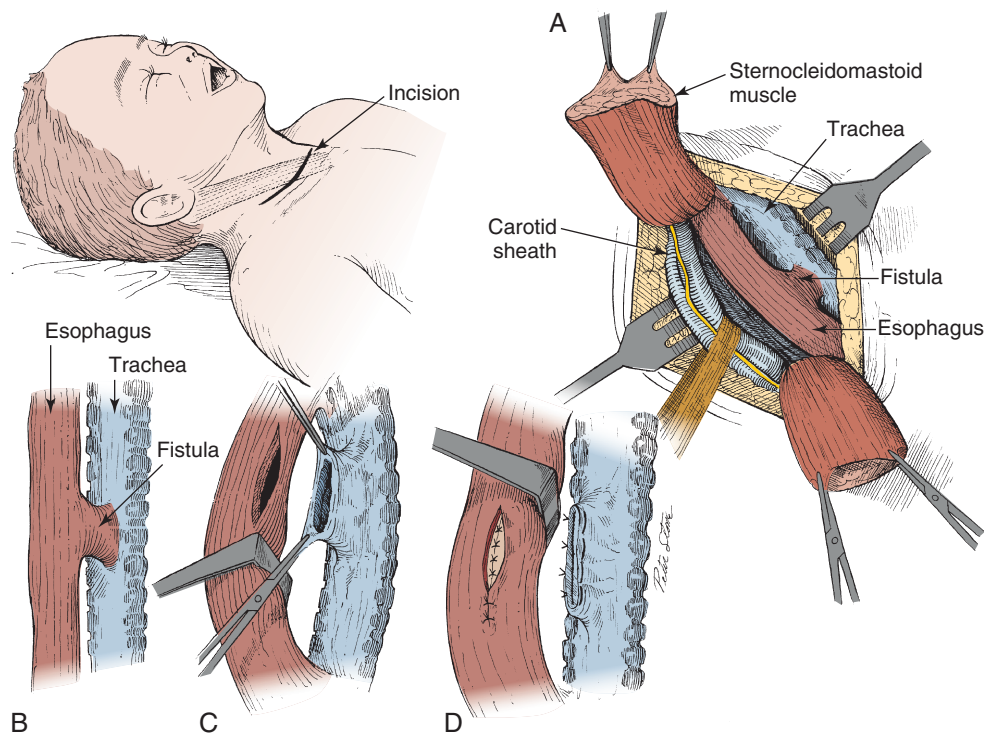


FIGURE 35-10 ■ Repair of H-type fistula. An incision is made in the neck. The sternocleidomastoid is retracted or severed. The fistula is divided flush with the esophagus to ensure closure of the trachea without narrowing the lumen.

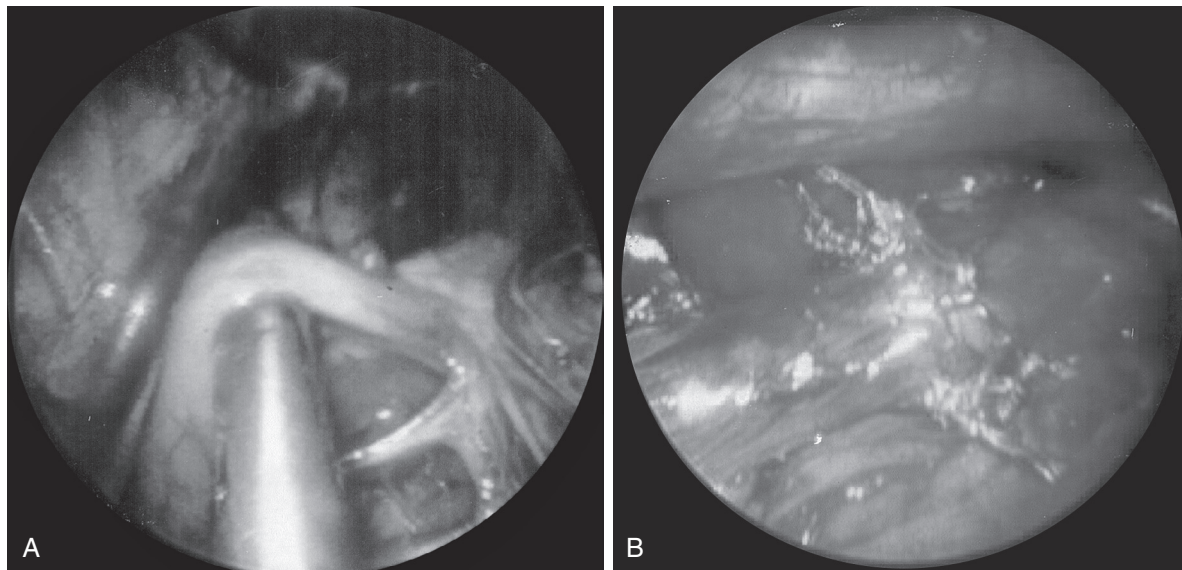


FIGURE 35-11 ■ **A**, Thoracoscopic mobilization of the tracheoesophageal fistula. **B**, Thoracoscopic view of completed esophageal anastomosis. (Courtesy Dr. C. Albanese, Stanford University Medical Center.)

Complications and Long-Term Effects

Complications of EA repair can be thought of as short term (leak, stricture) and long term (tracheomalacia, GER, nutritional, recurrent fistula, foreign body impaction).

Most large series report the rate of anastomotic leak to be between 15% and 20%.^{36,41,88} Most leaks are small and can be managed nonoperatively with broad-spectrum

antibiotics and thoracic drainage. Very rarely, suture repair or cervical diversion is required for a major leak.

The rate of esophageal stricture following repair is variable, ranging from 4% to approximately 50%.^{36,41,88} The wide range probably reflects the variability in the criteria for defining the stenosis (whether it requires dilations, the number of dilations, and the need for resection). Singh and Shun have proposed to spatulate the distal esophagus, creating a wider anastomosis, as a way

to decrease the rate of stricture formation.⁸⁹ Symptoms include choking, apnea, near-death spells, and food impaction. Most strictures are adequately treated with dilations. Strictures that are refractory to dilations should prompt a diligent search for, and control of, GER, often with a fundoplication. Recalcitrant strictures can also be secondary to the occurrence of ectopic tissues, tumors or tracheobronchial remnants near the anastomosis.^{63,90,91} The standard approach to refractory strictures has been resection and reanastomosis. Recently, the application of interventional radiological techniques has allowed the recanalization of impassable strictures that could not be dilated using standard techniques.^{92,93}

GER is a major concern in patients with EA, occurring in as many as 54% of patients.^{36,88} It is a significant contributor to the rate of occurrence of leaks and strictures as well as to respiratory complications, including aspiration pneumonia and cyanotic, near-death spells.⁸⁸ Most patients with significant GER eventually require a fundoplication to control their symptoms. The short-term morbidity of fundoplication in patients with EA is higher than in the general population, perhaps because of the dysmotility of the distal esophagus. A partial fundoplication, such as the Toupet 270-degree wrap, could be considered in patients with severe dysmotility or small stomachs.

With the significantly increased rate of GER in this patient population, there is a concern for metaplasia of the esophageal mucosa and eventual development of esophageal cancer. Sistonen and colleagues studied 502 patients who had surgery for EA at the University of Helsinki between the years 1949 and 1978. A chart review of these patients was performed with a primary focus of the development of cancer until the patient's death or December 2004, whichever came first.^{94,95} None of these patients developed esophageal cancer. They found that the statistical risk of EA patients' developing esophageal cancer postoperatively is less than 500-fold that of the general population. Additionally, the overall cancer incidence was similar to that of the general population. This group did, however, recommend long-term endoscopic surveillance. Since then, several authors have published case reports about adult patients with repaired EA/TEF and GER developing esophageal cancer squamous cell cancer or adenocarcinoma.⁹⁶ In 2010, Burjonrappa et al published an article describing endoscopic results of 51 patients who previously underwent EA/TEF correction.⁹⁷ Endoscopies with biopsies were performed every 3 years beginning at the age of 3. The authors reported that 15% of patients developed metaplasia (gastric metaplasia or Barrett esophagus) with an average lag time of 10 years to develop metaplasia after the initial operation. In 2013 Rintala and Pakarinen updated their recommendation for a surveillance protocol with the initial endoscopy and pH measurement being performed at 1 year of age and follow-up endoscopies continued until 15 years of age.⁹⁸ At that time, patients undergo surveillance endoscopies at 15, 30, 40, 50 and 60 years of age. However, these intervals are shortened to every 5 years if pathologic findings such as erosive esophagitis, esophageal stricture requiring dilation, or columnar metaplasia are noted.

Recurrent TEF occurs in as many as 10% of the patients following EA repair.^{36,41,88,99} Symptoms include coughing, gagging, cyanotic and apneic spells, and recurrent respiratory infections. The diagnosis is difficult to make and relies heavily on contrast studies. Most will require a repeat resection, but a few reports of bronchoscopic obliteration with fibrin glue, laser, or tissue adhesives have been published.¹⁰⁰⁻¹⁰⁴

Tracheomalacia is common in patients with EA and is thought to be secondary to the prolonged compression of the developing trachea by the enlarged esophageal pouch. Patients with EA and severe tracheomalacia often have a characteristic barking cough. Severe symptoms include stridor, choking, apnea, and near-death spells. The diagnosis is confirmed by bronchoscopy performed while the patient is spontaneously breathing and more recently by cinecomputed tomography and magnetic resonance imaging.^{105,106} Symptomatic patients usually benefit from aortosternotomy. Sutures are placed in the adventitia of the aorta and fixed anteriorly to the sternum, therefore suspending the trachea and increasing its diameter. The improvement in diameter is monitored bronchoscopically (Fig. 35-12). This can be accomplished via a left thoracotomy, an anterior thoracotomy, or thoracoscopically.¹⁰⁵⁻¹⁰⁷

Andrassy et al have studied the long-term nutritional status of patients with EA.¹⁰⁸ They found that even though the patients suffered from malnutrition in the first few years after repair, they seem to "catch up" in the later years, especially after the age of 13 years.

Foreign body impaction in the esophagus after EA repair occurs in at least 13% of patients.¹⁰⁹ Often esophagoscopy is needed to clear the esophagus, evaluate for a stricture, and potentially dilate the esophagus. No specific predisposing factors were identified, but the incidence of food impaction decreases after age 5 years.

With the increase in experience with repairing EA, more studies have surfaced discussing the long-term effects of EA repair.^{98,110-115} These studies show an increase in restrictive ventilator defects, bronchial hyper-responsiveness, and asthma, and a 13-fold increase in scoliosis thought to be secondary to thoracotomy-induced rib fusion. Several studies have investigated the quality of life in adults who have undergone EA repair. In 2005, Deurloo et al reported on these quality-of-life issues in 97 patients 16 years and older who had undergone EA repair.¹¹⁶ A questionnaire was sent that included questions from the Gastrointestinal Quality of Life Index, the Illness Cognition Questionnaire, and three open-ended questions. The results to the open-ended questions included 8% who responded in the affirmative to a question asking if there were things that the patient would like to do but could not do because of their EA repair. Limitations that study participants mentioned included inability to play certain sports, inability to lift heavy objects, and dysphagia. Of the participants, 33% answered yes to the question that asked if there are negative consequences of EA; gastrointestinal symptoms were the most common responses. Fourteen percent of patients stated they have positive experiences of EA in their daily life, and 50% of these responders stated they were grateful to be alive. In 2008, Deurloo et al updated their

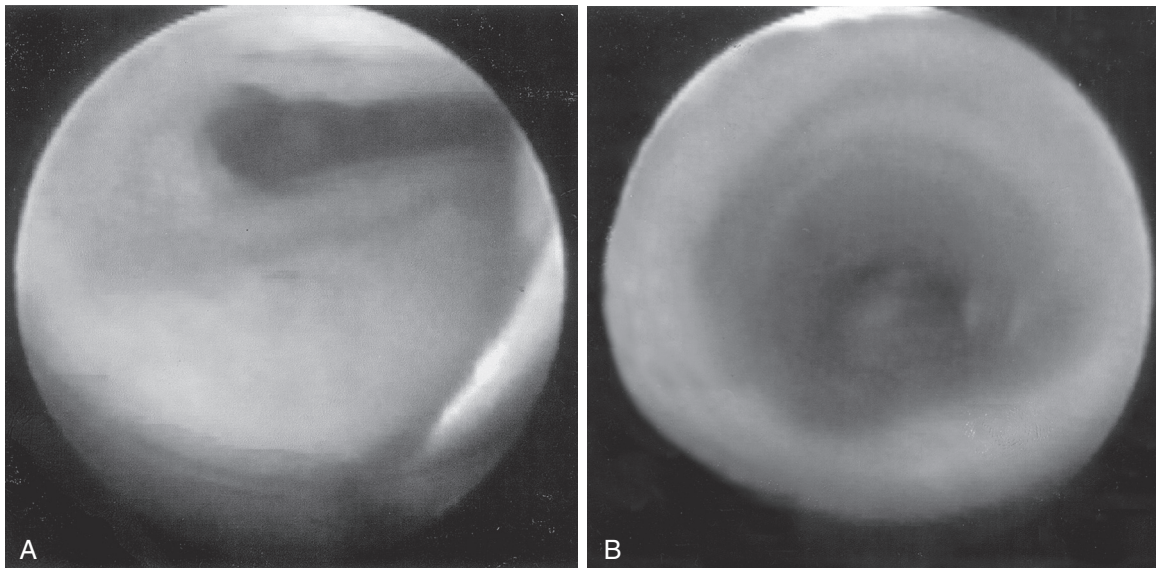


FIGURE 35-12 ■ **A**, Bronchoscopic appearance of tracheomalacia in a patient with esophageal atresia with tracheoesophageal fistula. Note that the anterior and posterior walls of the trachea are almost touching. **B**, Bronchoscopic appearance of the same patient after aortosternotomy. The anterior wall is now stented open by the suspension of the aorta. (Courtesy Dr. D. Powell, Children's National Medical Center.)

results on the long-term effects of GER, esophageal function, and quality of life in 25 patients older than age 18 after EA repair.¹¹⁷ Manometry, pH measurement, and patient's subjective feeling of dysphagia or heartburn were used to evaluate esophageal function. The study found that 70% of patients met manometric criteria for "ineffective esophageal motility." In this study, 20% of patients showed minor or pathologic reflux based on pH measurements. Interestingly, when these symptoms are compared to their effect on quality of life, dysphagia had a negative effect on quality of life but GER did not.

ESOPHAGEAL DUPLICATIONS

Anatomy and Embryology

The nomenclature of esophageal duplications is confusing. They have been referred to as *enterogenous cysts*, *esophageal duplication cysts*, *neuroenteric cysts*, and *gastrocystomas*, among other terms. In addition, there has been some confusion about bronchogenic cysts when they occur in the mediastinum between the esophagus and the trachea. Because the foregut and the notochord originate in direct continuity to each other and because both trachea and esophagus arise from the primitive foregut, it is helpful to view all these cysts as part of a continuum of foregut duplication cysts.¹¹⁸ The duplications can be lined by alimentary or tracheobronchial mucosa, regardless of where they are located. Approximately 50% of the cysts will contain ectopic gastric mucosa. They can be located in the posterior mediastinum or between the trachea and the esophagus. Cysts located in the posterior mediastinum are often associated with vertebral defects. Intramural duplications probably originate from a failure of vacuolization of the esophageal lumen.¹

Most esophageal duplications do not communicate with the lumen, but they can be tubular with one or more

openings into the lumen. They can be localized to the chest or extend into the abdomen with extensive thoracoabdominal components. Most are located in the distal esophagus, but they can occur anywhere along the length of the esophagus.^{119,120}

Incidence

Esophageal duplications are rare, with an incidence of 1 in 8200.¹¹⁹ Only 10% to 22% of alimentary duplications are esophageal.¹²⁰

Presentation

Approximately one third of patients with esophageal duplications are asymptomatic. Symptomatic patients have a variety of respiratory and intestinal symptoms: dyspnea, wheezing, recurrent infections and pneumonias, dysphagia, anorexia, and bleeding if they have ectopic gastric mucosa.¹¹⁸ If the cyst has a fistula to the spinal canal, meningitis can be the presenting symptom.

Diagnosis

Plain chest radiographs often show a mediastinal mass and aid in the detection of any associated vertebral anomalies. A CT scan will delineate the mass further and allow an exact anatomic localization. If there are any vertebral anomalies, MRI is helpful to rule out intraspinal pathology. Contrast esophagram can show extrinsic or intrinsic compression.

Treatment

Complete resection is the preferred method of treatment, traditionally via a thoracotomy or, more recently, via thoracoscopy.^{20,22,23,26,121} Marsupialization and simple aspiration have a high recurrence rate. If the cyst shares a

common wall with either the tracheobronchial tree or the esophagus, part of the wall can be left behind, but the mucosa has to be stripped to prevent recurrence. Intramural cysts are enucleated without violating the esophageal lumen. A bougie inserted into the esophagus might make the dissection easier. Posterior mediastinal cysts are usually easily excised unless they have an intraspinal component. Cysts located between the esophagus and the trachea can be challenging to remove because of the close association with the trachea. Long tubular thoracoabdominal duplications might require a combined thoracoabdominal approach.

CONGENITAL ESOPHAGEAL STENOSIS

Congenital esophageal stenosis (CES) is a rare anomaly.

Anatomy

Three types of CES have been described: fibromuscular, membranous, and those secondary to tracheobronchial remnants. The latter two are usually refractory to dilations and require surgical relief. These lesions can coexist with EA and should be ruled out at the time of EA repair by inserting a catheter into the distal esophagus.⁶³

Presentation

Patients with CES usually display progressive feeding intolerance and regurgitation. Often the symptoms do not manifest themselves until the patient starts to eat solid foods.

Diagnosis

An esophagram is frequently diagnostic, showing the tapered narrowing in the distal esophagus similar to achalasia. Endoscopic ultrasonography has been used to differentiate stenosis secondary to tracheobronchial remnants from those associated with fibromuscular hyperplasia.^{122,123}

Treatment

Stenosis caused by tracheobronchial remnants and intraluminal membranes do not respond to dilation and require resection with end-to-end anastomosis. One of the complications is esophageal shortening and GER. Nihoul-Fékété et al have recommended the addition of a Nissen fundoplication to the management of distal esophageal stenosis to prevent this complication.¹²⁴ The combined Collis gastropasty and Nissen fundoplication has been proposed to prevent both the shortening and the reflux.¹²⁵

LARYNGOTRACHEOESOPHAGEAL CLEFT

Laryngotracheoesophageal cleft (LTEC) is a rare anomaly arising from the failure of orderly separation of the trachea and esophagus.

Anatomy

There are four subtypes of LTEC¹²⁶:

- Type I: cleft present to, but not below, the vocal cords
- Type II: cleft extends into, but not through, the posterior cricoid cartilage
- Type III: cleft extends through the cricoid cartilage
- Type IV: cleft extends to the trachea

Presentation

LTEC has a wide spectrum of presenting symptoms. Patients with types I to III can have subtle symptoms: chronic cough, wheezing, repeated chest infections. Patients with type IV often have severe symptoms similar to those of patients with TEF: choking with feeding, severe aspiration pneumonia, and respiratory distress.

Diagnosis

Rigid bronchoscopy and esophagoscopy are essential to making the diagnosis. Other associated anomalies, including TEF, GER, congenital heart disease, and cleft lip and palate, should be sought.

Treatment

Observation of asymptomatic patients with type I clefts is often warranted. If they are symptomatic, they could be repaired endoscopically or open. Types II to IV clefts need to be repaired. The lateral pharyngotomy approach has been abandoned because of the high risk of recurrent laryngeal nerve injury and poor access to longer defects. The standard method is a transtracheal approach splitting the airway and trachea in the midline to expose the LTEC, which is then repaired. Long type IV clefts can be challenging to repair and might require cardiopulmonary bypass or extracorporeal membrane oxygenation. A multidisciplinary collaboration between pediatric surgeons, otorhinolaryngologists, and cardiac surgeons is often required.

If GER is significant, aggressive therapy with fundoplication enhances the chances of success of LTEC repair.

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SURGICAL TREATMENT OF BENIGN ESOPHAGEAL DISEASES

Thomas W. Rice • Steven S. Shay • Sigurbjorn Birgisson

It is preferable to bring your own esophagus to dinner.

LUCIUS D. HILL

CHAPTER OUTLINE

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CONCLUSION

The esophagus actively transports solids and liquids from the pharynx to the stomach. It has no digestive, absorptive, metabolic, or endocrine functions. A muscular tube subtended by two sphincters performs this rudimentary transfer task. Despite simplicity in esophageal function and form, surgical treatment of benign esophageal disorders is challenging. Few options are available to repair damaged sphincters; disorders of the esophageal body are rarely amenable to surgical correction. Often, progressive disease and/or failed surgical therapy result in a nonreparable esophagus. The only treatment option is resection and replacement. Successful surgical therapy requires a sound understanding of esophageal anatomy, physiology, investigative techniques, and disease processes.

THE ESOPHAGUS AND ITS SURROUNDINGS

Esophageal Wall

The esophagus is lined with stratified, nonkeratinizing squamous epithelium (Fig. 36-1), isolated from the remainder of the esophageal wall by a basement membrane. Immediately beneath the basement membrane is the lamina propria, a thin layer of loose connective tissue with a complex of collagen and elastic fibers. It contains a network of endothelium-lined channels, both capillaries and lymphatics. The muscularis mucosae supports the lamina propria and is composed of a longitudinal layer of

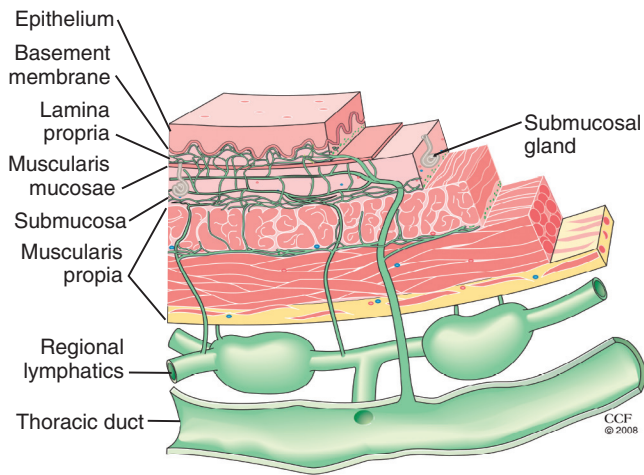


FIGURE 36-1 ■ Esophageal wall and its unique lymphatic drainage. (The Cleveland Clinic Center for Medical Art and Photography © 2009. All rights reserved.)

smooth muscle. This continuous muscle layer pleats the inner layers of the esophagus into a series of folds that disappear with distention. The epithelium, lamina propria, and muscularis mucosae comprise the esophageal mucosa.

The submucosa is composed of connective tissue that contains a network of blood vessels and lymphatics. Elastic fibers and collagen combine to make this the strongest esophageal layer. Submucosal glands are mixed types, producing a combination of serous and mucous secretions. These submucosal glands are unique to the esophagus and allow differentiation of the esophagus from the stomach in instances of glandular epithelial metaplasia. Ducts from these glands pierce the mucosa to drain into the esophageal lumen.

The muscularis propria is the muscular sleeve that provides the propulsive force necessary for swallowing. There are two layers of muscle: an inner circular layer and an outer longitudinal layer. The proximal 4% to 5% of the esophagus is composed completely of striated muscle and the distal 54% to 62% completely of smooth muscle.¹ Smooth muscle first appears in the anterior circular layer. The transition from striated to smooth muscle in the circular muscle layer is gradual, and the 50/50 point is approximately 5 cm from the cricopharyngeus muscle.

The cricopharyngeus (upper esophageal sphincter [UES]) is a continuous transverse band of muscle originating from the cricoid cartilage (Fig. 36-2). Superiorly, the muscle of the cricopharyngeus blends with the inferior pharyngeal constrictor muscle. A posterior defect, Killian triangle, is an inverted fan-shaped weakness in the inferior constrictor at the superior border of the cricopharyngeus. Inferiorly, the cricopharyngeus merges with the inner, circular layer of the muscularis propria. The longitudinal muscle layer of the muscularis propria originates from the lateral aspect of the cricoesophageal tendon. Posteriorly, these anterior and lateral components converge to meet at the midline. Thus, the proximal 1 to 2 cm of the posterior cervical esophagus is

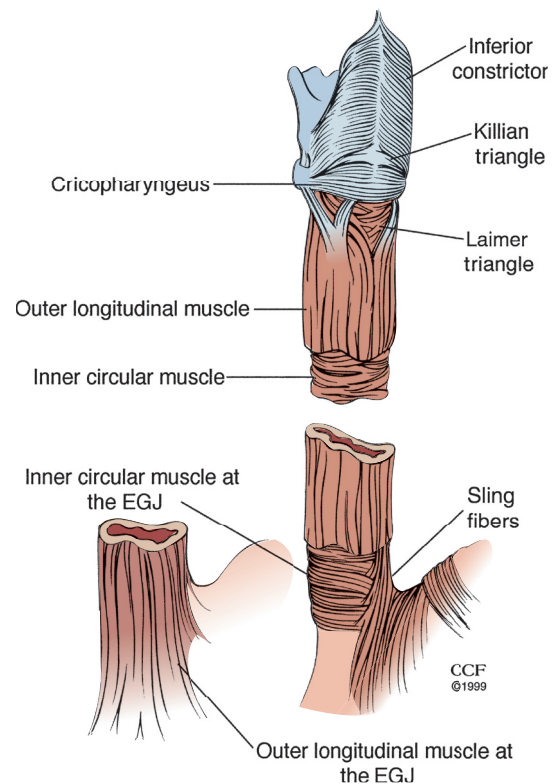


FIGURE 36-2 ■ Esophageal musculature. EGJ, Esophagogastric junction.

composed only of inner circular muscle, creating a potential for a mirror-image triangular area of weakness called Laimer triangle.

Contraction of the longitudinal muscle fibers of the esophageal body produces esophageal shortening. The inner circular muscle is arranged in incomplete rings producing a helical pattern. Muscle layers are equal and uniform in thickness until the distal 3 to 4 cm of the esophagus. Here, the inner circular layer thickens and divides into incomplete horizontal muscular clasp on the lesser curve aspect of the distal esophagus and oblique sling fibers on the greater curve aspect. These become gastric sling fibers (see Fig. 36-2). Although no complete circular bands exist at the lower esophageal sphincter (LES), this area of rearranged circular fibers corresponds to the high-pressure zone of the LES.

The esophagus lies in a bed of fat, neurovascular, and connective tissue and elastic fibers termed the *adventitia*. This layer of loose connective tissue surrounding the esophagus contains lymphatics and regional lymph nodes, blood vessels, and nerves. Unlike the stomach, small bowel, and colon, it has no serosa, except in its short abdominal segment.

Lymphatics begin as blind endothelium-lined saccules in the lamina propria just below the epithelium and basement membrane. An immunohistochemical study of the esophageal wall using lymphatic endothelial marker D2-40 has provided insight into the lymphatic anatomy of the esophageal wall (see Fig. 36-1).² The lamina propria contains a dense longitudinal plexus of lymphatic vessels. Rare perforating lymphatics have been found

draining into a sparse circumferential lymphatic network in the outer margin of the submucosa. Perforating lymphatics from the submucosal plexus, usually running with an artery and vein, penetrate the inner circular layer of the muscularis propria. Here, they drain into a circumferential intramuscular plexus that accompanies the artery, vein, and nerves of this space. Afferent lymphatics, usually accompanied by an artery and vein, drain the intramuscular plexus into the lymphatic channels in the adventitia. No direct connection from the lamina propria network and the thoracic duct has been identified.² Existence of direct routes from mural lymphatics to the thoracic duct, without a relay through regional lymphatics and lymph nodes, has been documented by many authors; however, the exact patterns and occurrence of these pathways are highly variable.³⁻⁵

The arterial supply of the esophagus is parasitic. It is derived from blood vessels supplying other organs in the neck, chest, and abdomen. Generally, these vessels divide at a distance from the esophagus and send small segmental branches to that segment of the esophagus. Esophageal blood supply has three principal sources. The superior and inferior thyroid arteries supply the cervical esophagus. The proximal and middle thoracic esophagus receives blood from branches of the bronchial arteries. The only dedicated esophageal arteries are one or two branches that arise from the anterior aspect of the aorta below the tracheal carina. In one third of autopsy specimens, no esophageal artery could be identified.⁶ These esophageal arteries directly supply the lower thoracic esophagus. The lower thoracic esophagus and abdominal esophagus receive arterial branches from the left gastric and, occasionally, the splenic arteries. The combination of a segmented arterial supply derived from multiple sources and a rich intramural vascular plexus ensures an excellent esophageal blood flow and permits extensive esophageal mobilization without esophageal arterial insufficiency or ischemia. Because esophageal arteries branch from larger arteries some distance from the esophagus, stripping of the esophagus from its bed during transhiatal (blunt) esophagectomy is possible without direct ligation of the esophageal arterial supply. Arterial spasm provides adequate hemostasis; thus, significant bleeding does not complicate this procedure.

Subepithelial esophageal venules drain into a substantial submucosal venous plexus that extends the length of the esophagus.⁷ There are venous connections between the lower thoracic and abdominal esophagus and the portal venous system. Venules then pierce the muscularis propria to drain into veins on the surface of the esophagus. Regional drainage is directed to the inferior thyroid and brachiocephalic veins in the neck, the azygous and hemiazygous veins in the chest, and the left gastric and splenic veins in the abdomen.

Both parasympathetic and sympathetic nerves innervate the esophagus. Branches of the vagus nerve supply parasympathetic fibers that are motor to the muscle coat and secretomotor to the submucosal glands. The cervical and thoracic sympathetic chain and the celiac plexus provide sympathetic fibers that promote contraction of sphincters and relaxation of the esophageal body muscle, increase peristaltic and glandular activity, and cause

vasoconstriction. These fibers enter the esophageal wall with the blood supply and form fibers and ganglia within it. The myenteric (Auerbach) plexus is positioned between the longitudinal and circular layers of the muscularis propria and controls these muscles. The submucosal (Meissner) plexus controls the muscularis mucosa and submucosal glands.

Regional Anatomy

The esophagus spans the lower neck, thoracic cavity, and upper abdomen (Fig. 36-3). The anatomy of the esophagus is best divided into fifths: cervical, upper thoracic, middle thoracic, lower thoracic, and abdominal esophagus. The anterior wall of the cervical esophagus is in intimate contact with the posterior membranous trachea. The recurrent laryngeal nerves course anteriorly and laterally in the tracheoesophageal groove. The carotid sheaths bind the cervical esophagus laterally. The posterior wall of the cervical esophagus lies on the vertebral bodies.

The thoracic esophagus occupies the posterior mediastinum and passes anteriorly to the vertebral bodies. The upper thoracic esophagus lies posteriorly to the trachea and is bound laterally by the mediastinal pleura. In its lower left aspect, it is sandwiched between the azygous vein on the right and the aortic arch on the left. The middle thoracic esophagus lies behind the pulmonary hilum and between the azygous vein and descending aorta. The lower thoracic esophagus has the same lateral and posterior boundaries but lies behind the pericardium. The thoracic duct is situated between the azygous vein and descending thoracic aorta and posteriorly and to the right of the lower and midthoracic esophagus. At approximately the level of the fourth thoracic vertebra, it crosses the midline to become a left-sided structure.

The abdominal esophagus is cradled in the muscular esophageal hiatus. The inferior vena cava is on the right posterolateral aspect; the abdominal aorta is on the left posterolateral aspect. Superiorly, the left lateral segment of the liver overlies the esophagus and esophagogastric junction (EGJ).

ESOPHAGEAL FUNCTION

Swallowing has three phases: oral, pharyngeal, and esophageal. The action of swallowing is voluntarily initiated and is followed by a cascade of involuntary muscle activities that propels the swallowed bolus aborally. The esophageal phase of swallowing commences with the relaxation of the UES during the initiation of pharyngeal contraction. Food is pushed by pharyngeal contraction, and its transit is facilitated by negative intrathoracic pressure. Duration of UES relaxation is between 0.5 second and 1 second. After passage of the bolus, the UES contracts, reaching twice resting pressure.

A primary wave begins after a swallow stimulus and results first in immediate smooth muscle relaxation without increasing intraluminal pressure. Then, the contraction front begins and propagates antegrade at a speed

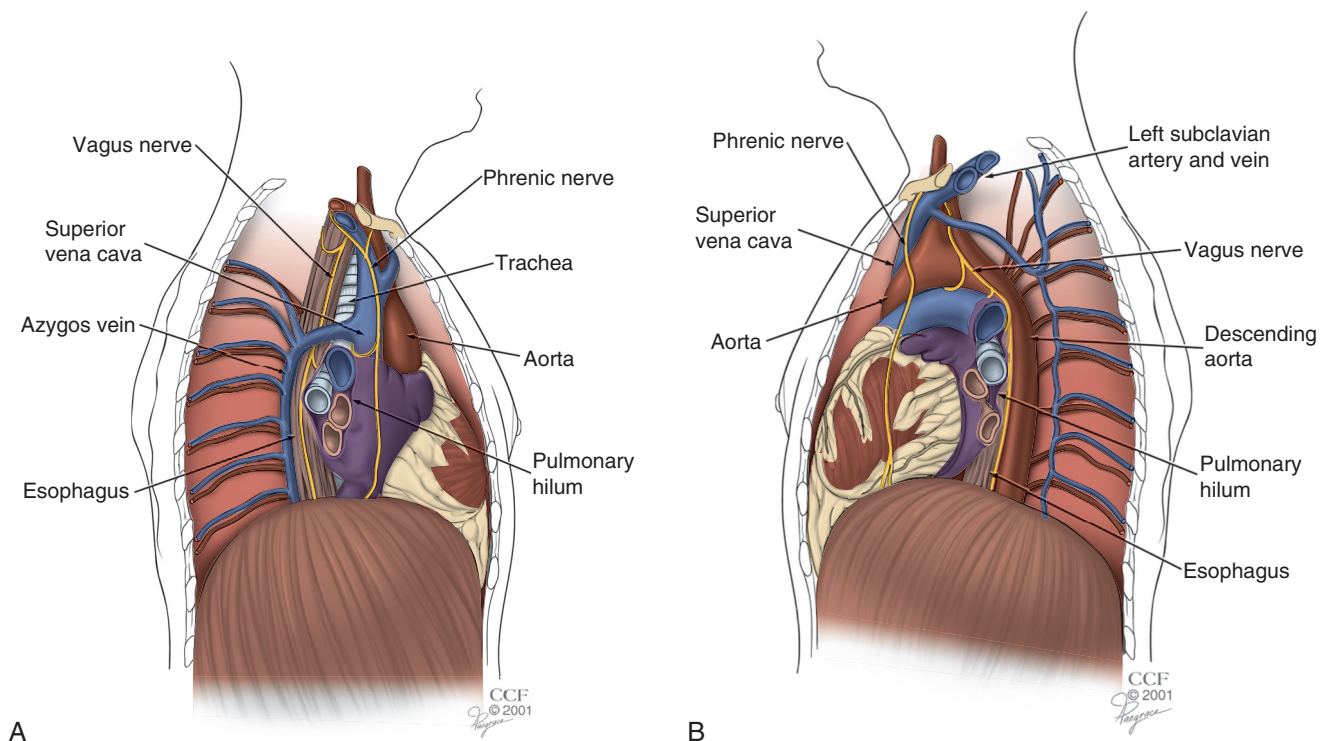


FIGURE 36-3 ■ Regional anatomy. **A**, Right mediastinal view. **B**, Left mediastinal view.

of 7 cm/sec in the proximal esophagus. However, the contraction front progressively slows to 2 cm/sec in the distal esophagus. This slowing is because latency until muscle contraction increases down the esophagus. The strength of the contraction increases with propagation along the esophagus. If impaction occurs, esophageal distention produces closure of the UES, and a secondary peristaltic wave begins at the site of obstruction and passes distally. Tertiary contractions are nonperistaltic contractions occurring spontaneously between swallows that are ineffective in antegrade bolus transit.

Resting pressure of the LES exceeds intragastric pressure and prevents reflux of gastric contents into the distal esophagus. Within 2 seconds of pharyngeal contraction, the LES relaxes to near intragastric pressure for 7 to 10 seconds. The LES then contracts to above resting pressure for 8 to 12 seconds before returning to resting pressure.

EVALUATION OF THE ESOPHAGUS

History and Physical Examination

The symptoms most commonly associated with esophageal diseases are heartburn, regurgitation, dysphagia, and odynophagia. Other symptoms that may be associated with esophageal disease are sore throat, hoarseness, cough, bad taste, globus, hiccup, aspiration, wheezing, chest pain, nausea, vomiting, choking, hematemesis, and melena. Symptom composition depends on the esophageal disorder and is discussed in various sections of this chapter. Physical examination of the esophagus is indirect

and focuses on head and neck, thoracic, and abdominal findings.

Box 36-1 lists systemic diseases with esophageal manifestations. Some are discussed later in this chapter. These potential underlying disorders should be considered during the history and physical examination.

Investigations

Patients with suspected esophageal disease will typically undergo barium esophagram and/or esophagoscopy as their initial diagnostic tests.

Barium Esophagram

A three-phase study assessing mucosa, contour, and function of the esophagus is optimal.⁸ In the double-contrast phase, conducted with the patient ingesting high-density barium and CO₂ tablets in the upright position, the mucosa is examined (**Fig. 36-4**). Next, esophageal function is assessed in the right anterior oblique (RAO) position with the ingestion of low-density barium in single swallows at 20- to 30-second intervals (**Fig. 36-5**). The examination is videotaped. The value of attempting to elicit reflux in this phase is questionable because 20% of normal individuals have radiologic reflux.⁹ Barium tablets or barium-coated marshmallows or solids may demonstrate abnormalities not visualized by liquid barium studies. The final phase, the full-column technique, is performed with the patient in a semiprone RAO position and low-density barium. Multiple quick swallows produce a column of barium that fully distends the esophagus. This optimizes imaging of the distal esophagus and can

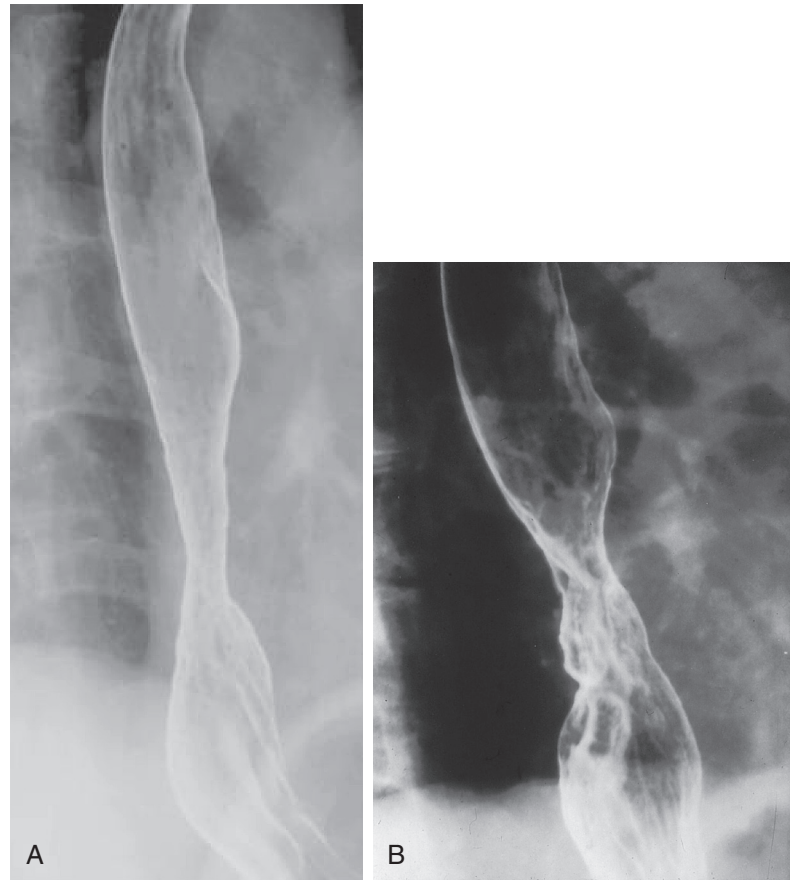


FIGURE 36-4 ■ Barium esophagram: mucosa. Double-contrast phase of the barium esophagram provides mucosal definition. **A**, Patient with a hiatal hernia and peptic stricture; no significant ulceration is seen. **B**, Patient with a columnar-lined esophagus, distal peptic stricture, ulcers, and nodules.

BOX 36-1 Systemic Diseases of the Esophagus

CONNECTIVE TISSUE DISORDERS

Scleroderma
Systemic lupus erythematosus
Polymyositis
Dermatomyositis
Mixed connective tissue disorder
Raynaud disease

ALLERGIC DISEASE

Eosinophilic esophagitis

METABOLIC DISEASES

Amyloidosis
Diabetes mellitus
Hypothyroidism
Hyperthyroidism

DERMATOLOGIC DISEASES

Epidermolysis bullosa
Pemphigus vulgaris
Pemphigoid

Erythema multiforme
Lichen planus
Behçet disease

INFECTIOUS DISEASES

Histoplasmosis
Tuberculosis
Actinomycosis
Immunocompromised host
Fungal: *Candida* species
Viral: herpes simplex, cytomegalovirus
Mycobacterial
Bacterial: *Streptococcus viridans*, *Staphylococcus*, bacilli,
Treponema pallidum
Protozoal

MISCELLANEOUS DISORDERS

Sarcoidosis
Crohn disease

demonstrate small hiatal hernias, subtle strictures, or distal rings (Fig. 36-6). The esophagus is allowed to empty, and the remaining barium coating the esophageal wall provides a mucosal relief study, now rarely performed.

The timed barium esophagogram is a simple test of esophageal emptying (Fig. 36-7). After the patient ingests

a premeasured amount of barium, usually 250 mL, spot films are taken at 1-, 2- and 5-minute intervals and, if necessary, at 10 minutes and 20 minutes after barium ingestion. This allows simple quantification of esophageal emptying and is useful for evaluations of both motility disorders and the results of therapy.^{10,11}

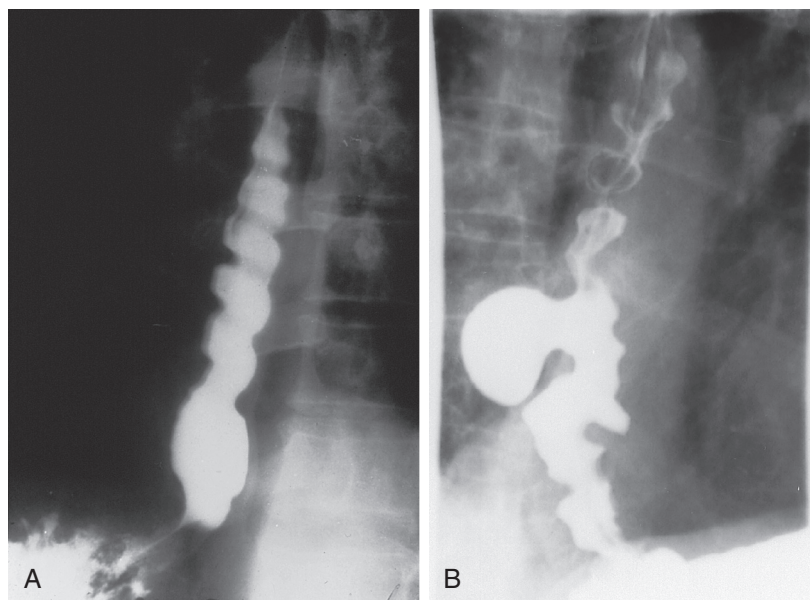


FIGURE 36-5 ■ Barium esophagram: function. Single swallows every 20 to 30 seconds in the right anterior oblique semiprone position assesses esophageal function. **A**, Patient with diffuse esophageal spasm (corkscrew esophagus). **B**, Patient with abnormal motility and a midthoracic diverticulum.

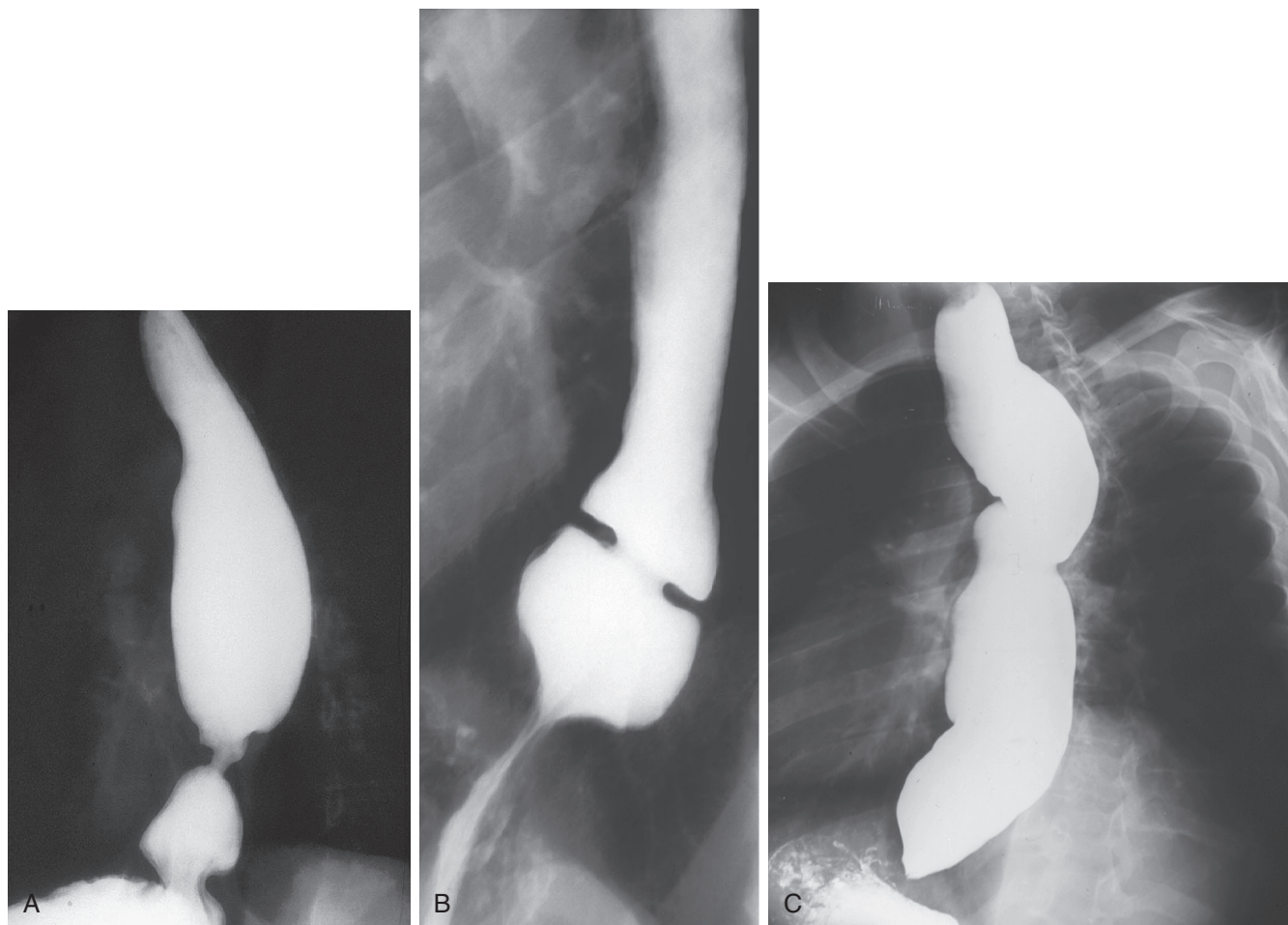


FIGURE 36-6 ■ Barium esophagram: contour. The full column phase of the barium esophagram fills and fully distends the esophagus, providing an examination of esophageal contour. **A**, Patient with an obstructed esophagus caused by a peptic stricture and associated nonreducible hiatal hernia. **B**, Patient with a Schatzki ring. **C**, Patient with achalasia.

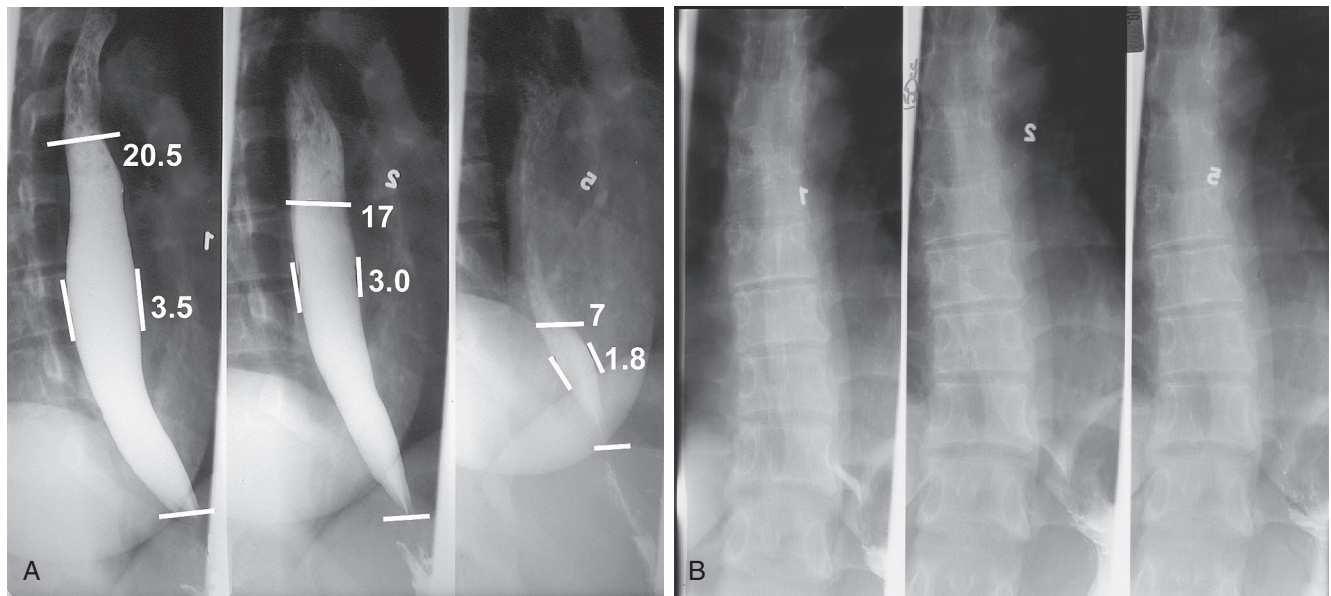


FIGURE 36-7 ■ Timed-barium esophagram. **A**, Before Heller myotomy, patient was able to ingest only 70 mL of the requested 250 mL barium. Height (barium-coated saliva not included) and width of the column are measured at 1, 2, and 5 minutes after ingestion. Note markedly delayed esophageal emptying and incomplete emptying at 5 minutes. **B**, After Heller myotomy, ingestion of 70 mL of barium resulted in trace barium in the esophagus at 1 and 2 minutes and clearance by 5 minutes.

Esophagoscopy

Esophagoscopy is used to visually assess mucosal and structural esophageal abnormalities. Biopsies of epithelial abnormalities such as esophagitis, mucosal nodules, columnar cell-lined segments, and strictures are an integral part of flexible fiberoptic esophagoscopy. However, the biopsies are limited to the mucosa. Indirect evidence of deeper mural abnormalities or extraesophageal lesions may be appreciated by extrinsic compression or displacement of the overlying epithelium. Endoscopic resection, either mucosal resection (EMR) or submucosal dissection (ESD), is an endoscopic alternative to surgical resection in the diagnosis and management of some esophageal lesions. In benign esophageal diseases, endoscopic resection is used most commonly in evaluating lesions in patients with Barrett esophagus.¹²

Esophageal Manometry

Esophageal manometry is indicated (1) to establish the diagnosis of dysphagia when obstruction and eosinophilic esophagitis have been excluded, (2) for placement of intraluminal devices such as a pH probe, and (3) before antireflux surgery. It is possibly indicated for dysphagia after antireflux surgery or therapy for achalasia.¹³ High-resolution manometry (HRM) is a major advance over traditional low-resolution manometry in that it has increased the number of pressure sensors from 5 to 36, has decreased the distance between sensors from 5 to 1 cm, and includes sensors in the pharynx and proximal stomach (Fig. 36-8). Sophisticated computer algorithms extrapolate between these sensors, permitting a continuous, seamless assessment of intraluminal esophageal pressure from pharynx to stomach. The display of intraluminal pressure as a color spectrum on a plot of esophageal

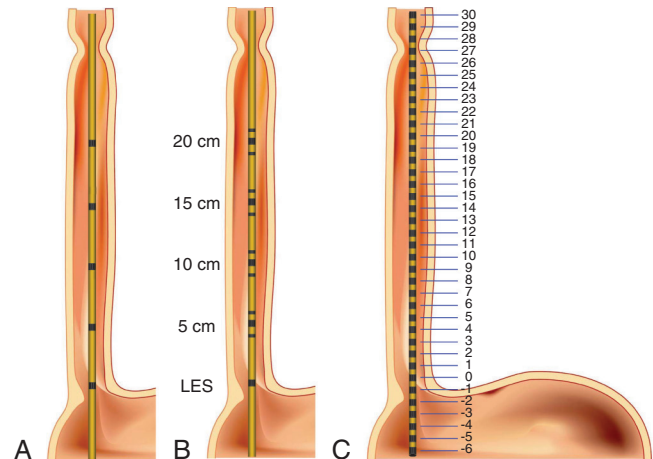


FIGURE 36-8 ■ Manometry catheter types. **A**, The traditional low-resolution manometry catheter has five pressure sites located in the lower esophageal sphincter (LES) and 5, 10, 15, and 20 cm above the LES. **B**, Impedance manometry has impedance pairs at the four esophageal pressure sites of the low-resolution manometry catheter. **C**, The high-resolution manometry catheter has 36 pressure sites 1 cm apart that extend from pharynx to stomach.

position (y axis) against time (x axis) produces a pressure topography of swallowing (Fig. 36-9). Catheter placement is easier, and study duration is markedly shorter by eliminating the LES pull-through. As a result of these features, this technology has had widespread adoption into clinical practice.

HRM accurately measures LES relaxation by compensating for LES movement with swallows. HRM also determines latency until esophageal contraction after a swallow stimulus to assess for premature contractions, as well as multiple smooth muscle contraction parameters

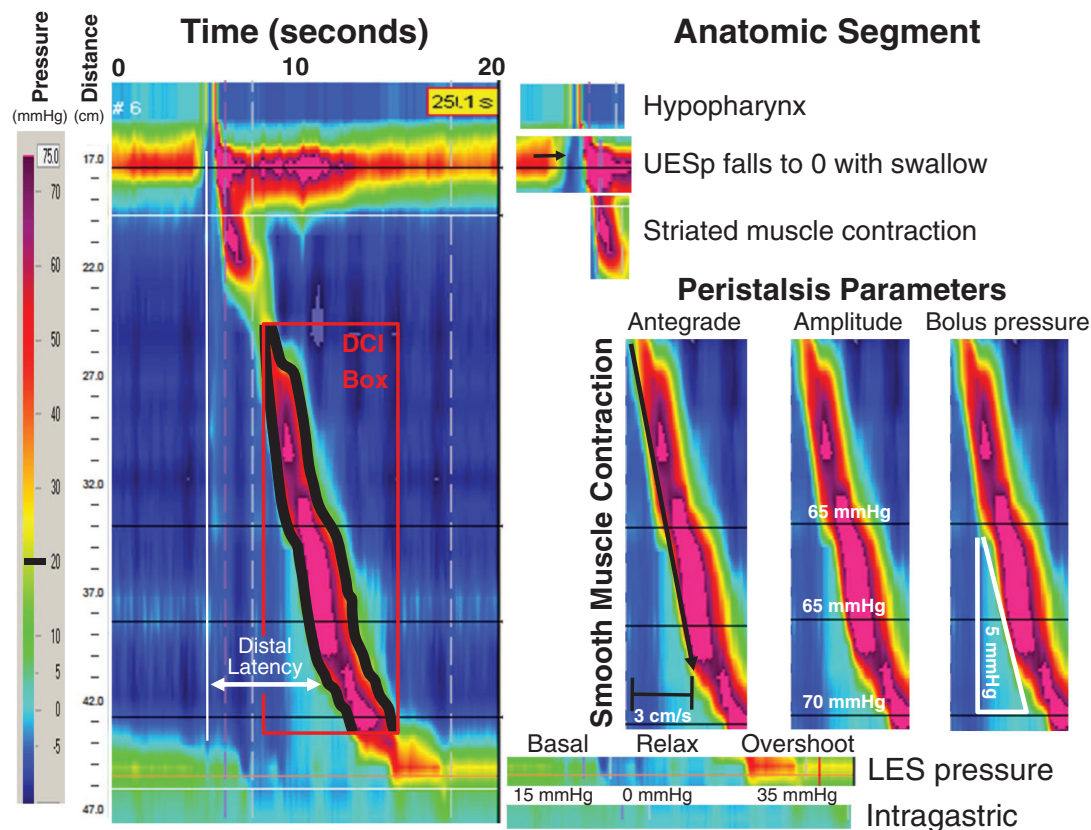


FIGURE 36-9 ■ High-resolution manometry topograph derived from 36 pressure sites 1 cm apart. The left side of the figure shows several topographic metrics. Distal latency (white arrow) is the duration from swallow onset (vertical white line) to where peristalsis decelerates (5 sec; normal, >4.5 sec). Contractile vigor (DCI [distal contractile integral] box) is average pressure (mm Hg) × duration (sec) × height (cm) (2650; normal, 450-5000 mm Hg/sec/cm). Isobaric contour at 20 mm Hg (black curved line) shows no large (>5 cm) or small (2-5 cm) waveform defects. The right side of the figure divides the tracing into anatomic segments from pharynx to stomach. The pharynx is from 16 to 18 cm, and pharyngeal contraction (black arrow) occurs as the upper esophageal sphincter (UES) (18-20 cm) relaxes after a 5-mL swallow, and the UES pressure falls from 50 to 0 mm Hg. The striated muscle contraction wave begins as the UES recovers, and advances from 21 to 24 cm, where a transition zone (24-26 cm) of lower pressure occurs. The smooth muscle peristaltic contraction wave extends from 26 to 44 cm, is antegrade (3 cm/sec; normal, <9), and normal in amplitude (50-75 mm Hg; normal, <180), duration, and intrabolus pressure. The lower esophageal sphincter (LES) extends from 44 to 47 cm, relaxes just after a swallow occurs from 15 mm Hg to near 0, and then overshoots to 30 mm Hg.

(antegrade peristalsis, amplitude, intrabolus pressure). These and other topographic metrics are shown in Figure 36-9. Table 36-1 lists the Chicago Classification Criteria of Esophageal Motility Disorders based on these topographic metrics and agreed on by an international panel of experts.¹⁴ More extensive discussion of HRM (e.g., detailed assessment of EG junction morphology allowing separation of LES and diaphragm [for detecting hiatal hernia, etc.]), other metrics, and use in lap band surgery is available elsewhere.¹⁴⁻¹⁶ Continued experience with HRM and especially outcome data should allow refinements in the classification scheme in the future.

Impedance Manometry

The traditional impedance manometry catheter adds an impedance pair at each of the four esophageal pressure sites of the low-resolution manometry catheter (see Fig. 36-8). This catheter allows bolus transit to be compared with simultaneous esophageal peristalsis and contraction amplitude and is termed the *esophageal function test* (Fig. 36-10).¹⁷ In 350 patients studied at a single

center, all with achalasia and scleroderma had abnormal bolus transit and more than 95% of those with normal manometry, nutcracker esophagus, and LES dysfunction (high or low) had normal bolus transit.¹⁸ Recently, a catheter with both high-resolution manometry (36 sites, 1 cm apart) and high-resolution impedance (18 impedance pairs) capability was developed to improve on the low resolution of the esophageal function test catheter. A classification of weak peristalsis has been proposed based on this newly developed catheter's ability to correlate abnormalities in peristaltic integrity with failed bolus clearing.¹⁹

Ambulatory Conventional and Wireless pH Monitoring

Ambulatory pH monitoring detects and quantifies acid gastroesophageal reflux. Because this test is typically performed without acid suppression medication, proton pump inhibitors (PPIs) should be discontinued for 1 week, H₂ blockers for 24 hours and antacids for 8 hours. Conventional transnasal monitoring is done for 24 hours

with the thin pH catheter placed 5 cm above the LES, located by manometry. Patients are instructed to have a “typical day” regarding activity and eating. Because symptom correlation is an important component of this test, the patient presses a symptom button when symptoms occur.

TABLE 36-1 Chicago Classification Criteria of Esophageal Motility Disorders

Diagnosis Criteria

Achalasia

- Type I achalasia—Mean IRP > 15 mm Hg, 100% failed peristalsis
- Type II achalasia—Mean IRP $\geq$ 15 mm Hg, aperistalsis, panesophageal pressurization $\geq$ 20%
- Type III achalasia—Mean IRP $\geq$ 15 mm Hg, aperistalsis, spastic contractions $\geq$ 20% swallows
- EGJ outflow obstruction—Mean IRP $\geq$ 15 mm Hg, some normal or weak peristalsis

Motility Disorders (Defined as Pattern not Seen in Normal Individuals)

- Distal esophageal spasm—Normal mean IRP, $\geq$ 20% premature contractions (DL < 4.5 sec)
- Jackhammer esophagus—At least one swallow DCI > 8000 with single or multi-peaked contraction
- Absent peristalsis—Normal mean IRP, 100% swallows with failed peristalsis

Peristaltic Abnormalities (Defined by Exceeding Statistical Limits of Normal)

- Weak peristalsis:
 - Large peristaltic defects—Mean IRP < 15 mm Hg and >20% swallows with >5-cm breaks in 20-mm isobar
 - Small peristaltic defects—Mean IRP < 15 mm Hg and >30% swallows with 2- to 5-cm breaks in 20-mm isobar
- Frequent failed peristalsis—>30%, but <100% of swallows with failed peristalsis
- Rapid contractions with normal latency—Rapid contractions > 20% swallows, DL > 4.5 sec
- Hypertensive peristalsis—Mean DCI > 5000, but lacks hypercontractile (jackhammer) criteria (also termed *nutcracker*)

Normal (Not Achieving any of the above Diagnostic Criteria)

DCI, Distal contractile integral; DL, distal latency; EGJ, esophagogastric junction; IRP, integrated relaxation pressure; LES, lower esophageal sphincter.

IRP: Lowest average pressure of 4 seconds within the LES window. Modified from Bredenoord A, Fox M, et al: *Chicago classification criteria of esophageal motility disorders defined in HRM esophageal pressure topography*. *Neurogastroenterol Motil* 24(Suppl 1):57–65, 2012.

A pH less than 4 has arbitrarily been chosen to define an acid reflux episode. The normal parameters for 24-hour pH monitoring have been defined (Table 36-2). Total acid exposure time, expressed as a percentage of study time, is the best discriminator between normal and abnormal values.²⁰ Composite scores, such as the DeMeester score and frequency-duration index, are no better than simple measured parameters in identifying abnormal reflux. The symptom index relates symptoms to reflux events and is calculated by dividing symptom episodes with reflux by the total number of symptom episodes multiplied by 100%; 50% is the optimum threshold.²¹

Wireless pH monitoring is a recent technological advance. The Bravo delivery system “pins” a capsule measuring $6 \times 5.5 \times 25$ mm to the esophagus 6 cm above the squamocolumnar junction, identified by endoscopy. Manometry is not required. Improved patient tolerance allows increased activities and improved food intake; moreover, monitoring is traditionally extended to 48 hours (Fig. 36-11).²² Wireless pH monitoring has an increased diagnostic yield compared with transnasal monitoring because of higher sensitivity for both abnormal acid exposure and positive symptom-reflux association.²³ Drawbacks are cost, occasional premature detachment, and severe pain requiring endoscopic removal in less than 2% of cases. Similar to nasal pH monitoring, wireless pH monitoring is unable to detect nonacid reflux.

Impedance-pH Monitoring

When an ionic fluid bolus traverses an electrode pair, impedance to current flow decreases. Impedance pairs placed on a pH catheter at multiple sites can detect retrograde fluid flow throughout the esophagus as acid reflux if the pH is less than 4 or as nonacid reflux if pH is greater than 4.²⁴ An expert panel concluded that impedance-pH monitoring off PPI therapy is the best test to detect all reflux episodes in a patient,²⁵ and thus is the best test for symptom association in patients with gastroesophageal reflux disease (GERD). The test has limitations, such as the necessity of a nasal catheter, and low baselines in esophagitis or Barrett esophagus make interpretation difficult. Moreover, currently available software for automated detection of reflux episodes is sensitive but not very specific, and manual editing is recommended at this time.²⁶

TABLE 36-2 Normal Distal Values for 24-hour pH Monitoring

Parameter	Johnson ³¹³ 95th Percentile	Richter ³¹⁴ 95th Percentile	Jamieson ³¹⁵	
			Mean	Percentile
Total time (%)	4.45	5.78	4.5	95
Upright time (%)	8.42	8.15	7.1	93
Supine time (%)	3.45	3.45	1.5	86
No. of episodes	47	46	56	98
No. >5 min	3	4	3	94
Longest episode (min)	19.8	18.5	12	84
Composite score	14.7	—	16.7	96

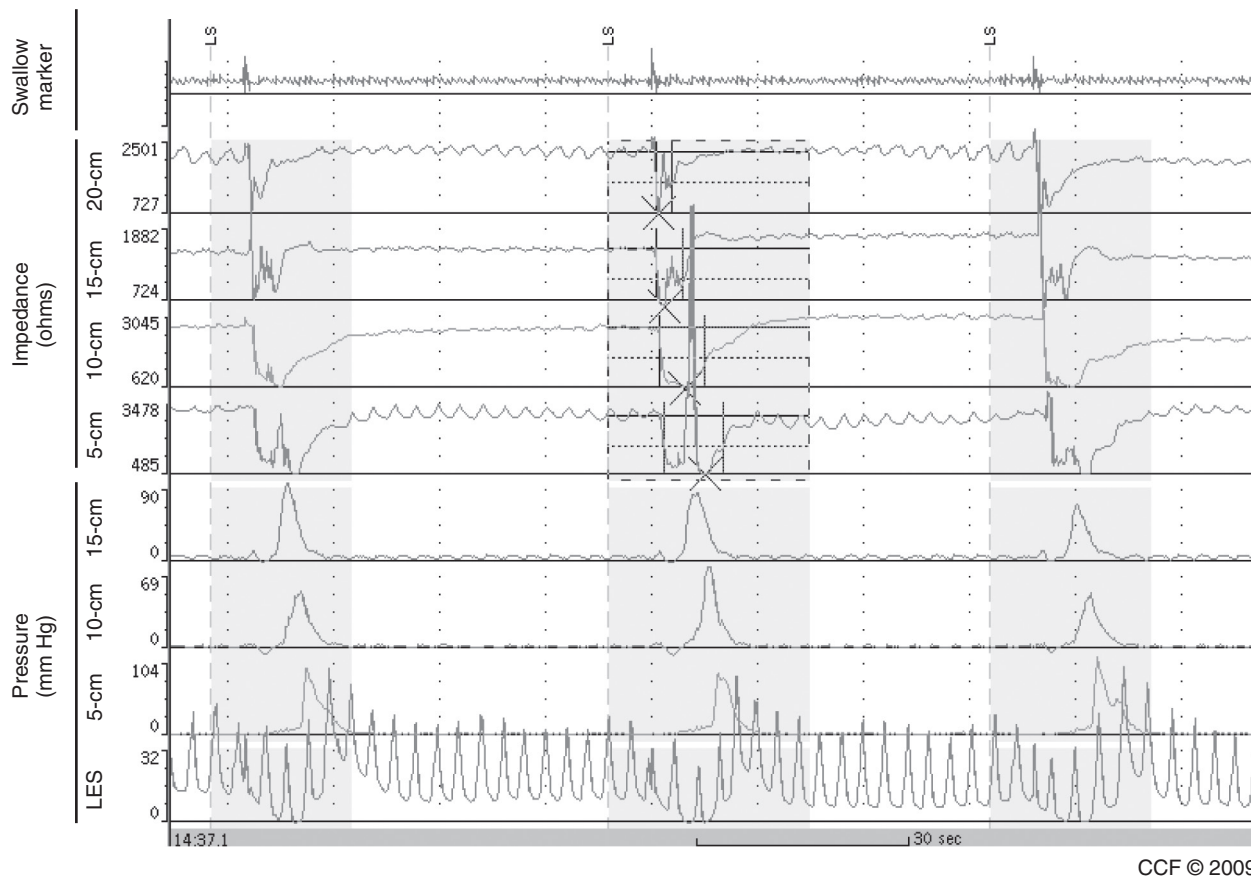


FIGURE 36-10 ■ Simultaneous impedance and manometry showing normal bolus transit after each of three 5-mL saline swallows. Bolus entry occurs at each of four impedance sites as impedance decreases (see first vertical line in second swallow). Antegrade decrease in impedance in the four sites shows normal bolus advance through the esophagus. After bolus persistence with a low impedance value, a rise in impedance toward baseline occurs at each site from bolus clearing (see second vertical line in second swallow) as a result of simultaneous esophageal contraction at the same level. Antegrade increase in the four impedance sites shows normal bolus clearing from the esophagus. Normal lower esophageal sphincter (LES) relaxation and overshoot is seen.

Impedance-pH monitoring on PPI therapy has been used when suspected esophageal and/or extraesophageal reflux symptoms persist despite PPIs (Fig. 36-12). Small case series in patients with a positive symptom index have shown good results after fundoplication.²⁷ However, we believe long-term controlled studies first performed in centers with experience in impedance-pH monitoring are needed to identify the role of such monitoring when only symptom association and nonacid reflux are found.

Endoscopic Esophageal Ultrasound

Endoscopic esophageal ultrasound (EUS) provides definition of the esophageal wall and periesophageal tissue not possible to obtain with routine fiberoptic esophagoscopy. It is indispensable in evaluating abnormalities of the esophageal wall and diagnosing nonmucosal esophageal tumors. Ultrasound endoscopes scan the wall with ultrasound waves of 5 to 12 MHz. Probes, which can be passed through the biopsy channel of flexible endoscopes, can evaluate esophageal strictures that prevent passage of standard ultrasound equipment. The esophagus and periesophageal tissues are viewed as five alternating layers of different echogenicity (Fig. 36-13). This examination also provides images of periesophageal structures, includ-

ing regional lymph nodes. Both the layer of origin and ultrasound characteristics of a mass are critical in diagnosing benign esophageal tumors. Periesophageal masses and regional lymph nodes can also be studied. EUS-directed fine-needle aspiration (FNA) provides cytologic and pathologic assessment of esophageal tumors, periesophageal masses, and regional lymph nodes.

BENIGN ESOPHAGEAL DISEASES AND THEIR TREATMENT

Hiatal Hernia

Herniation of abdominal contents through the esophageal hiatus is a common occurrence. With provocative maneuvers that increase intra-abdominal pressure, 55% of patients undergoing barium esophagram were found to have herniation of the stomach into the chest.²⁸ Symptoms are secondary to reflux, incarceration or strangulation of herniated organs, or compression of thoracic structures. There are four types of hiatal hernia, each with its own symptom presentation. Type I, or sliding hiatal hernia, is the most common (see Figs. 36-6A and



FIGURE 36-11 ■ Example of 48-hour Bravo pH monitoring in a symptomatic patient with suspected GERD. Severe (day 1) and moderate (day 2) bipositional acid exposure is present, as well as positive symptom index (>50%) for heartburn and regurgitation.

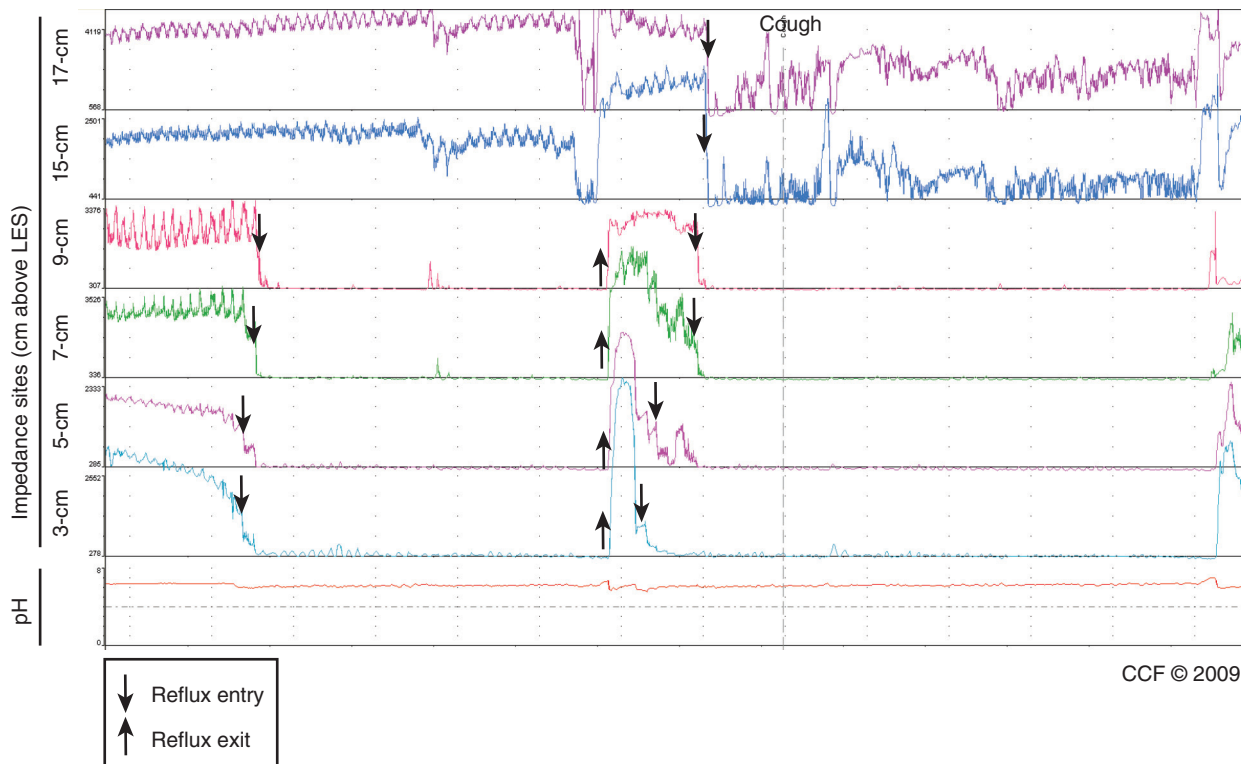


FIGURE 36-12 ■ Simultaneous impedance and pH monitoring shows two nonacid liquid reflux episodes in patient receiving acid suppression. The first shows retrograde liquid reflux to 9 cm above the lower esophageal sphincter (LES) (down arrows), and subsequent clearance after 2 minutes at all sites (up arrows). The second shows retrograde liquid reflux to the most proximal site, and cough occurs 40 seconds later.

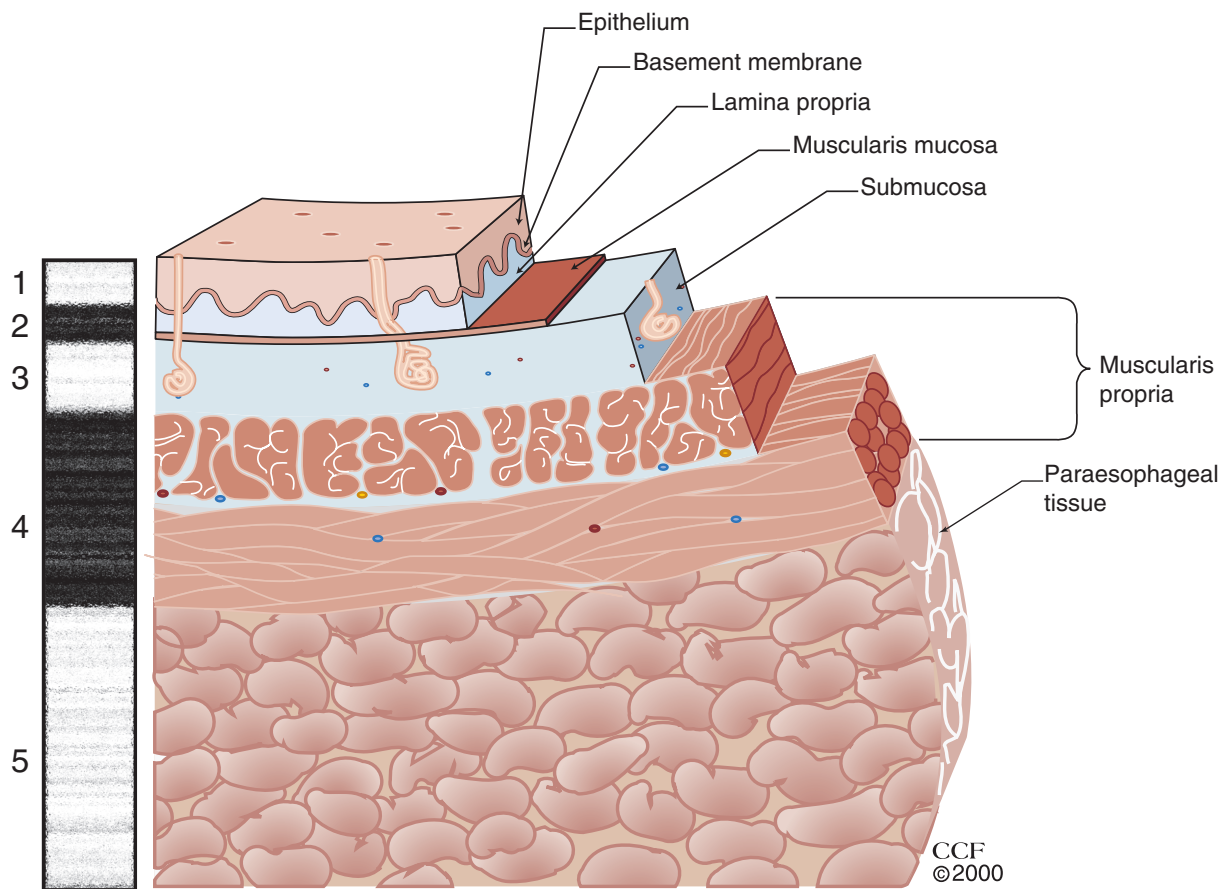


FIGURE 36-13 ■ Esophageal wall is visualized as five alternating layers of differing echogenicity by esophageal ultrasound. The first (inner) layer is hyperechoic (*white*) and represents the superficial mucosa (epithelium and lamina propria). The second layer is hypoechoic (*black*) and represents the deep mucosa (muscularis mucosae). The third layer is hyperechoic and represents the submucosa. The fourth layer is hypoechoic and represents the muscularis propria. The fifth layer is hyperechoic and represents the paraesophageal tissue. The thickness of ultrasound layers does not equal the actual thickness of the anatomic layers.

36-14). Herniation of the EGJ into the posterior mediastinum occurs because of thinning and elongation of the phrenoesophageal ligament. There is no potential for incarceration. Most patients with type I hiatal hernias are asymptomatic. If symptoms occur, they are GERD related. Type II, or rolling, hiatal hernias are uncommon (Fig. 36-15). They result from a defect in or isolated weakness of the phrenoesophageal ligament, allowing a portion of the stomach to herniate through the hiatus while the EGJ remains anchored in the abdomen. Symptoms of gastric obstruction, strangulation, anemia, and, less commonly, shortness of breath and arrhythmia result from gastric herniation through the hiatus and presence of the stomach in the chest. Type III, or mixed, hiatal hernias are the second most common type (Fig. 36-16). Patients may present with reflux, symptoms of type II hernias, or both. As type III hernias increase in size, there may be organoaxial volvulus with the potential for strangulation. In many patients, these hernias may be a progression of type I hernias.²⁹ Type IV hiatal hernias contain the stomach and other abdominal contents such as colon, spleen, small bowel, and pancreas (Fig. 36-17). The term *paraesophageal hernia* is sometimes used to describe any type II, III, or IV hiatal hernia.

Symptomatic hiatal hernias should be repaired. Repair of asymptomatic types II and III hernias is controversial. The potential for strangulation and gastric necrosis has been advocated as the primary reason to repair paraesophageal hernias in all patients, particularly because a 50% mortality rate was initially reported when this complication occurred.³⁰ However, strangulation is an uncommon occurrence without antecedent symptoms; therefore, this is an overestimate, and careful follow-up of asymptomatic patients is a viable alternative to repair in all patients.

Repair follows the principles of surgical treatment of GERD. Addition of a fundoplication is controversial but is definitely indicated if symptomatic GERD is present. Laparoscopic repairs have been reported to have an earlier and increased rate of failure.³¹ A meta-analysis showed this to be 25% at variable follow-up.³² This high incidence of recurrence has prompted the use of various types of mesh reinforcement of laparoscopic hiatal reconstruction. Although mesh has been reported to decrease recurrence at 6 months but not at 5 years,^{33,34} the clinical significance of these early findings³⁵ and long-term durability^{36,37} are in question. In most patients, addition of a gastrostomy or gastropexy is not required. Compared

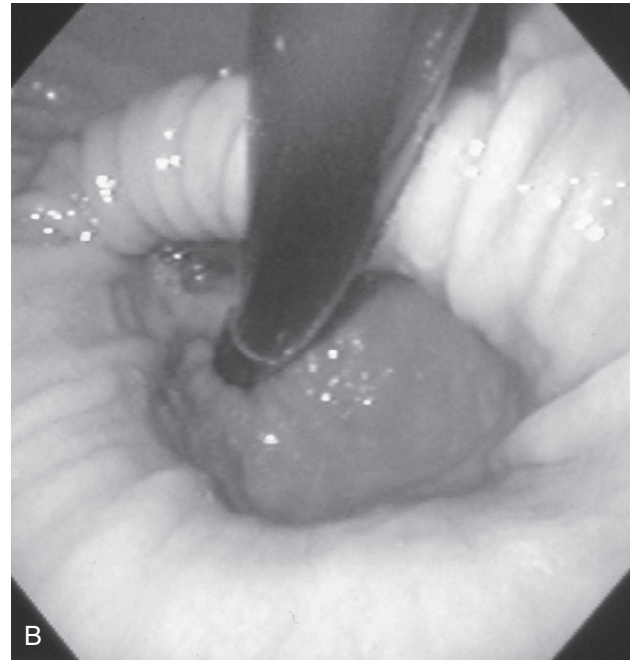
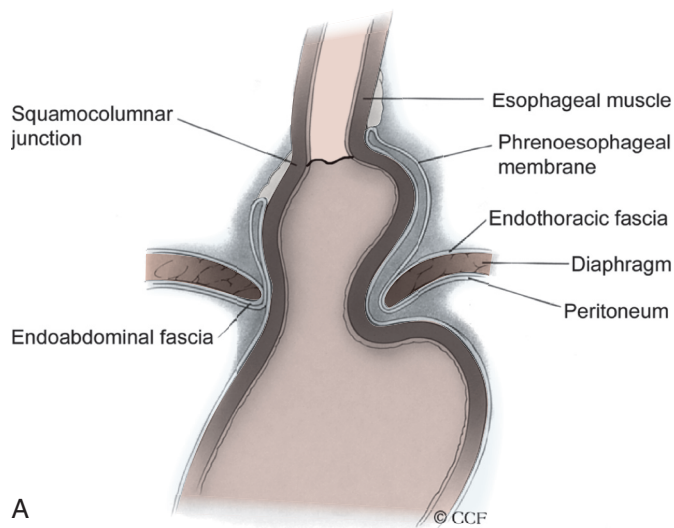


FIGURE 36-14 ■ Type I hiatal hernia. **A**, Pictorial presentation. **B**, Retroflexed view from the intra-abdominal stomach at esophagoscopy. Diaphragmatic impression and intrathoracic stomach can be seen.

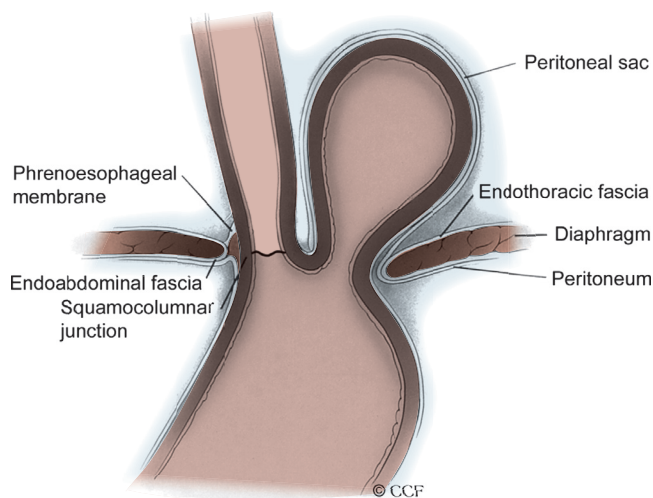


FIGURE 36-15 ■ Type II hiatal hernia.

with GERD patients, patients with type III hiatal hernias are older and have more comorbidities. Adjusting for these factors demonstrates that patients with type III hernias are more likely to have pulmonary, thromboembolic, and bleeding complications in their postoperative course than those with type I hiatal hernias.³⁸

Gastroesophageal Reflux Disease

GERD was defined at the Montreal consensus conference as “a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.”³⁹ The diagnosis is made through some combination of symptom presentation, objective testing

with endoscopy, ambulatory reflux monitoring, and response to antireflux therapy.

Typical symptoms of GERD are heartburn, regurgitation, and dysphagia. Patients with noncardiac chest pain suspected to be caused by GERD should have a cardiac cause excluded before starting a gastrointestinal evaluation. Extraesophageal symptoms/disorders of which GERD is a potential co-factor are asthma, chronic cough, and laryngitis, although a diagnosis of reflux laryngitis should not be made solely based on laryngoscopic findings.⁴⁰ Other atypical symptoms/disorders (pulmonary fibrosis, pharyngitis, otitis media, and sinusitis) are often linked to reflux and are proposed associations, but data are insufficient to establish causation.³⁹ It is important that abdominal pain, gas, and bloating not be misinterpreted as GERD symptoms.

Complicated GERD includes reflux esophagitis, esophageal stricture, and Barrett esophagus. The mucosal response to acid may produce intestinal metaplasia (Barrett esophagus), and damage to the submucosa and muscularis propria can result in a short esophagus (see Fig. 36-4 and 36-6A). Peptic stricture and high-grade dysplasia or intramucosal carcinoma developing in Barrett epithelium are the most feared complications of GERD.

The LES and diaphragmatic hiatal mechanism are the major components of the reflux barrier.^{41,42} A hiatal hernia is seen in 50% to 90% of patients with GERD.⁴³⁻⁴⁶ However, reflux events are most commonly the result of transient LES relaxations, although reflux over a low basal LES is also important.⁴⁷ Poor acid clearance from peristaltic dysfunction and delayed gastric emptying contribute to prolonged acid exposure in some patients.

The mainstay of therapy for GERD is medical management. Randomized studies do not demonstrate a superiority of surgery over medical therapy.⁴⁸⁻⁵⁰ Weight

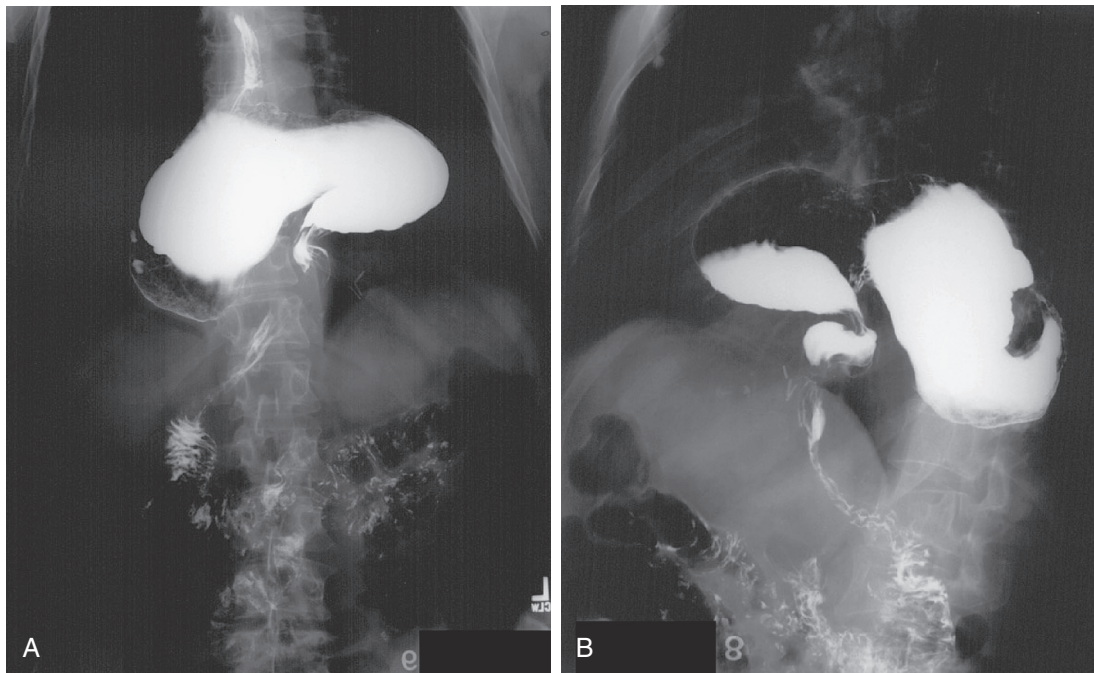


FIGURE 36-16 ■ Type III hiatal hernia. A barium esophagram demonstrates a type III hiatal hernia with organoaxial rotation. **A**, Posteroanterior view. **B**, Lateral view.

loss for those who are overweight, head of bed elevation for recumbent symptoms, and other lifestyle modifications tailored to the individual are suggested.⁵¹ An 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis. PPIs can heal esophagitis in more than 90% of patients. Maintenance PPI therapy is appropriate for GERD patients with continued symptoms after PPI is stopped and in patients with complications such as Barrett esophagus and erosive esophagitis,⁴² because most with Los Angeles (LA) grade B-C esophagitis will relapse by 6 months.⁵² There is insufficient evidence to recommend for or against endoluminal antireflux procedures⁵¹ or transoral incisionless fundoplication as an alternative to medical or traditional surgical therapy.⁴⁰ However, sphincter augmentation with the LINX management system for selected patients is promising and more data are eagerly awaited.^{53,54}

Atypical symptoms/disorders respond less predictably to PPIs, especially in the absence of typical symptoms. Patients with extraesophageal symptoms who have concomitant typical symptoms, moderate-sized hiatal hernias, and moderate reflux on pH testing may respond better to acid suppression. PPI failures usually have causes other than GERD.⁵⁵ The increased incrimination of GERD as a causative factor for extraesophageal syndromes along with the lack of accurate confirmatory diagnostic tests has resulted in widespread overdiagnosis and overtreatment of these conditions.⁵¹

Surgical management of GERD is a treatment option for long-term therapy in GERD patients. It should be considered in patients who are noncompliant, experience side effects from medical therapy, or have esophagitis refractory to medical therapy.⁴⁰ Surgical therapy is generally not recommended in patients who do not respond to PPI therapy⁴⁰ except for highly selected patients,

especially those with persistent and severe “volume regurgitation.”⁵¹

The following preoperative GERD evaluation is suggested. First, endoscopy should be performed to assess for presence of esophagitis, Barrett mucosa, stricture, hiatal hernia, and alternative upper GI diagnoses such as ulcer disease. Second, manometry should be performed to locate and measure LES, exclude another diagnosis such as esophageal spasm, and assess peristalsis. Third, ambulatory pH monitoring off therapy should be performed to confirm excessive acid exposure in those patients without LA class C-D erosive esophagitis or Barrett esophagus. Typical symptoms that respond to PPI therapy and abnormal acid exposure as determined by pH monitoring are reliable predictors of successful surgical treatment of GERD.^{56,57} We typically also do barium esophagram to assess anatomy of the esophagus and EGJ, mucosal changes, and esophageal function. In patients with suspected gastric drainage abnormalities, a nuclear medicine gastric emptying study is required.

Surgical management is less likely to be effective in patients with persistent atypical symptoms/disorders. Recent guidelines suggest surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with optimal use of PPIs.⁴⁰ Instead, non-GERD causes should be pursued. Although small case series have shown good results for antireflux surgery in patients with persistent cough on PPIs and a positive symptom index for cough and nonacid reflux by impedance-pH monitoring,⁵⁸ long-term controlled studies are needed to validate this approach.⁵⁹

Complicated GERD is first managed with aggressive medical therapy; however, peptic esophageal stricture and chronic Barrett ulcer may require surgery. The

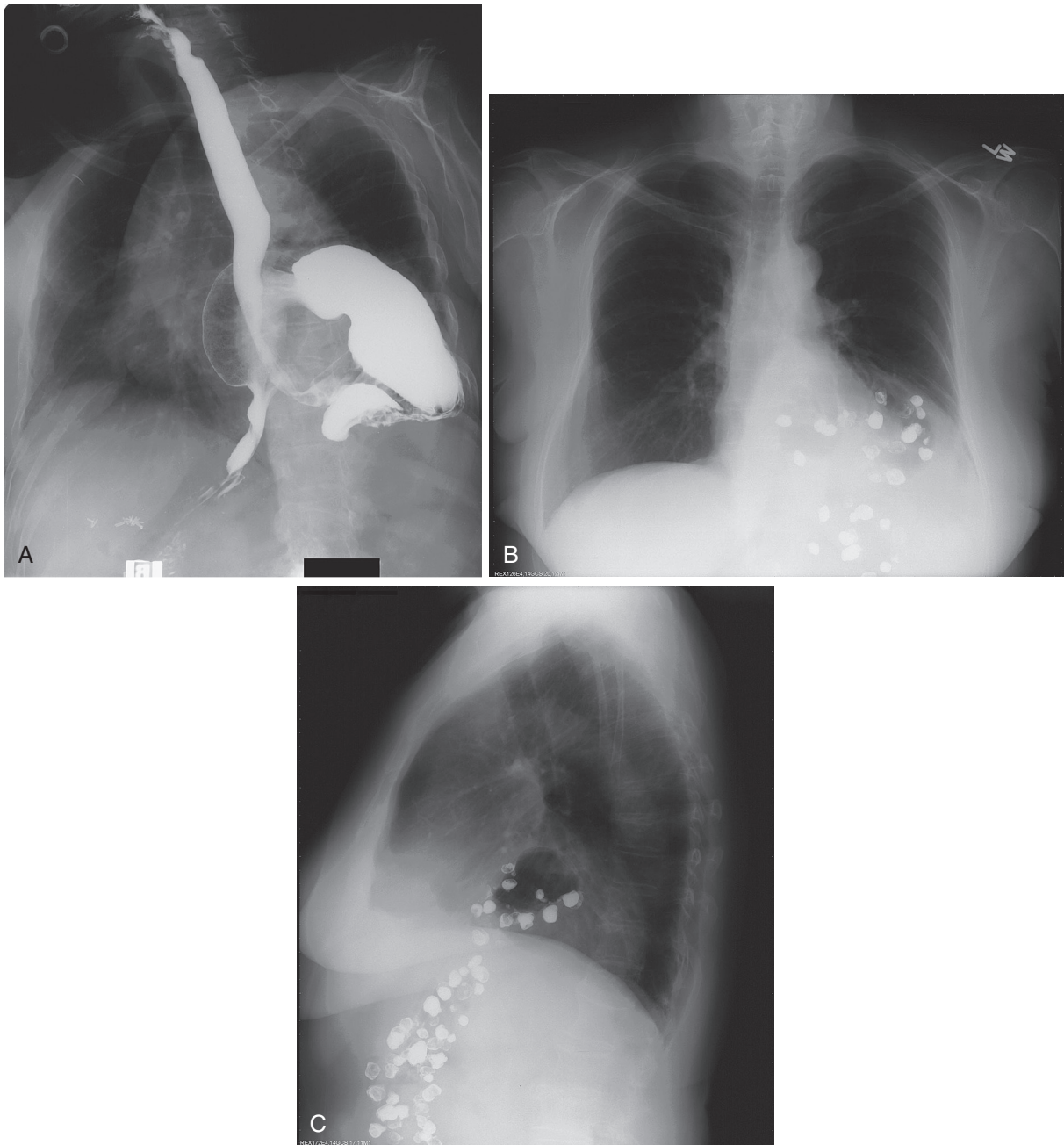


FIGURE 36-17 ■ Type IV hiatal hernia. **A**, Barium esophagram demonstrates a type III hiatal hernia with organoaxial rotation. Three days later, barium is seen in colonic diverticulum on preoperative chest radiograph. **B**, Posteroanterior view. **C**, Lateral view. Therefore, this is a type IV hiatal hernia.

columnar cell-lined esophagus is not in itself an indication for surgery. However, patients with Barrett esophagus should have endoscopic surveillance for detection of dysplasia.⁶⁰ It is debatable that surgery can reverse the changes of columnar lining. Partial reversal, although interesting, is not a compelling argument for surgical correction of GERD.⁶¹ Therefore, either prevention of or halting malignant degeneration in a columnar cell-lined esophagus is not an indication for surgery. If a patient with a columnar cell-lined esophagus has antireflux surgery, the need for endoscopic surveillance is not eliminated. Therefore, the patient with a columnar cell-lined esophagus has the same indications for surgery as

the patient with a squamous-lined esophagus, although they often have the most disordered physiology, largest hernias, and most disrupted hiatal mechanisms.⁶²

The principles of antireflux surgery are restoration of the intra-abdominal length of esophagus, reconstruction of the esophageal hiatus, and reinforcement of the LES.⁶³ These can be accomplished by a number of approaches and techniques. Possible approaches, in descending order of morbidity, are thoracoabdominal, thoracotomy, laparotomy, and laparoscopy. Facility with all of these approaches is necessary.

Restoration of the intra-abdominal esophagus requires reducing the hiatal hernia and mobilizing the esophagus.

This portion of the operation necessitates recognition of the short esophagus.⁶⁴ Failure to lengthen the short esophagus by extensive esophageal mobilization to the aortic arch or by addition of a Collis gastropasty will result in a repair under tension and early failure. The short esophagus should be suspected by history of a stricture or previous dilation or findings of a long segment columnar cell-lined esophagus, a large type I hiatal hernia (>4 cm), a type III hiatal hernia, or failure of the hernia to reduce below the diaphragm on upright barium esophagram.

The importance of reconstruction of the hiatus cannot be underestimated. It plays a role in reflux prevention equal to that of the LES.⁶⁵ The recent addition of mesh reinforcement of the hiatal closure ignores the past history of antireflux surgery and the dynamic nature of this structure. Complete mobilization of the hiatal crura and careful removal of the hernia sac will allow primary suture reconstruction of the hiatus. Failure to reconstruct the hiatus is a common cause of failure of laparoscopic antireflux surgery.⁶⁶ The principal reason for reherniation after an otherwise adequate repair is usually tension on the repair (because the short esophagus was either ignored or not recognized) and not an unbuttressed reconstruction of the hiatus.

The final step in the surgical correction of GERD is reinforcing the LES by constructing a fundoplication, which may be either total or partial. The Nissen fundoplication, which is a 360-degree total fundoplication, completely encircles the esophagus. Partial fundoplication is typically 270 degrees and is either anteriorly placed (Belsey Mark IV repair) or posteriorly placed (Toupet repair). Theoretically, the trade-off is between better reflux control with a total fundoplication or less dysphagia with a partial fundoplication. Some surgeons tailor the fundoplication to suit the peristaltic activity of the esophageal body.⁶⁷ HRM and concomitant high-resolution impedance to assess bolus transport should allow a more precise cutoff at which the severity of peristaltic dysfunction requires partial fundoplication.¹⁹ Until this can be accomplished, we consider total fundoplication to be appropriate for all except the patient with an aperistaltic esophagus.⁶⁸⁻⁷² Use of a partial fundoplication in the presence of complicated GERD is associated with increased incidence of failed repairs.⁷³ Dysphagia following surgery for GERD is usually transient with a properly constructed fundoplication. Prolonged dysphagia is indicative of a malformed fundoplication—long, tight, or twisted. Return of normal esophageal motility with resolution of GERD following fundoplication is hypothetically possible. It is more likely that the amplitude of the peristaltic wave will increase than failure of propagation will be corrected. Therefore, any fundoplication should be constructed assuming the peristaltic abnormalities will not improve. Finally, the potential for postprandial symptoms of gas bloat and early satiety must be mentioned to any patient being considered for fundoplication.

An ignored but essential part of physical examination is measuring and recording weight and height and calculating body mass index (BMI). Overweight (BMI, 25 to 29) and obese (BMI, 30 to 34) patients with GERD should be counseled on weight loss and encouraged to

reach their ideal weight before elective surgery. Because obesity and GERD are interrelated,^{74,75} successful and sustained weight loss may eliminate the need for surgery. Although there is disagreement concerning the impact of obesity on the outcome of antireflux surgery,⁷⁶⁻⁸¹ health benefits of weight loss in severely (BMI, 35 to 39) and morbidly (BMI, ≥40) obese GERD patients should make weight loss surgery the operation of choice in these patients.

Antireflux operations are not infinitely durable. It is important that all patients be instructed to avoid activities that excessively increase intra-abdominal pressure and to maintain their ideal weight.⁸² Unrealistic patient expectations and widespread application of laparoscopic fundoplication without careful patient selection in low-volume centers by inexperienced surgical teams have produced poor results and have had a negative impact on this operative approach.⁸³⁻⁸⁵

Motility Disorders

Achalasia

Achalasia is an uncommon and incurable neurodegenerative esophageal motility disorder of unknown cause, which affects both sexes and all races equally.^{86,87} Achalasia results from damage to the myenteric plexus with selective destruction of inhibitory neurons in the myenteric plexus by cytotoxic T lymphocytes.⁸⁸⁻⁹² The inflammatory neurodegenerative insult causes an imbalance between excitatory and inhibitory neurons, cumulating in aperistalsis of the esophageal body and failure of LES relaxation.⁹³ Most patients complain of progressive dysphagia to solids and liquids and regurgitation. Weight loss is a common sequel, depending on the disease duration.⁹⁴ Retrosternal discomfort is common; significant chest pain affects some patients and may persist although other symptoms improve after successful therapy. Recurrent respiratory infection, aspiration pneumonia, and lung abscess may be initial presentations and often herald advanced disease. Most patients seek medical attention only after significant and irreversible damage to the esophageal myenteric neural plexus has occurred.

Barium esophagram and esophagoscopy are usually the first diagnostic tests performed because the usual symptoms are dysphagia and regurgitation. Classic findings on esophagram are esophageal dilation, aperistalsis, impaired esophageal emptying, and symmetrical tapering at the EGJ (bird's beak or ace of spades appearance) (see Fig. 36-6C). Timed barium esophagram allows quantification of esophageal obstruction and emptying (see Fig. 36-7). Esophagoscopy usually shows some degree of food or fluid retention (occasionally only saliva), chronic stasis changes, and a tight, spastic or puckered EGJ, not restricting endoscope passage. When achalasia is suspected, endoscopy is essential to exclude benign or malignant strictures, particularly pseudoachalasia (esophageal obstruction secondary to malignancy), which may be clinically and manometrically indistinguishable from primary achalasia.⁹⁵

Esophageal manometry confirms achalasia when suggested by symptoms and other studies mentioned earlier.

Manometrically, achalasia is defined by incomplete or failed relaxation of the LES and aperistalsis of the esophageal body.^{14,96} Resting LES pressure can be normal in up to 50% of patients; therefore, elevated LES pressure is not required for diagnosis.^{14,97,98} HRM has recently identified three subtypes of achalasia based on different biomechanics and treatment responses (Fig. 36-18). Type I (classic) has minimal or no esophageal pressurization or peristaltic activity; type II demonstrates panesophageal pressurization, greater than 30 mm Hg, throughout the entire esophagus in at least 20% of sequences; and type III (spastic, vigorous) is associated with 20% or more swallows associated with premature contractions.^{14,99,100} Type II achalasia has been reported to be a predictor of an excellent outcome after all available treatment modalities. Type I patients do significantly better with Heller myotomy than with pneumatic dilation. Type III and pretreatment esophageal dilation were predictive of poorer outcomes.¹⁰¹⁻¹⁰⁴ Although retrospective studies show that these subtypes can predict clinical outcome, it is unclear if the subtyping has clinical impact such as for clinical decision making.^{99,105}

Treatment of achalasia is palliative, aimed at reducing the esophageal outflow obstruction caused by the nonrelaxing LES to improve esophageal emptying. Goals of therapy are symptom relief, improving esophageal emptying by barium radiographs,¹⁰⁶ and preventing progression to megaesophagus. To accomplish this, achalasia patients require follow-up by their gastroenterologist or surgeon every 1 to 2 years for subjective and objective evaluation. Variable emptying in patients with achalasia is possible,¹⁰⁷ but repeated studies in the long-term follow-up are valuable.

Available treatment options include pharmacologic, endoscopic, and surgical means tailored to each patient.

Oral pharmacologic options are the least effective. Calcium channel blockers, long-acting nitrates, and phosphodiesterase-5-inhibitors transiently relax the LES pressures and may provide short-acting but incomplete relief of symptoms. Frequent and unpleasant side effects along with development of tolerance are the major limiting factors for their use.¹⁰⁸⁻¹¹⁰

Endoscopic injection of botulinum toxin (a potent inhibitor of acetylcholine release from nerve endings) has been used to treat achalasia with approximately 50% reduction in LES pressure.^{108,111} Palliation is temporary, lasting a mean of 6 months, with recurrent symptoms in more than 50% of patients.^{112,113} Resistance to repeat injections is thought to result from antibody production against botulinum toxin. Use of botulinum toxin may complicate future surgery because it causes inflammation and fibrosis in the plane between the submucosa and the muscularis propria, resulting in difficulty in the dissection of the submucosal plane.¹¹⁴⁻¹¹⁶ Although this may result in increased intraoperative mucosal perforation rate, there does not seem to be an increase in length of hospital stay or postoperative symptoms. This therapy is reserved for patients who cannot tolerate more aggressive forms of treatment, as a bridge to more definitive treatment or for intractable achalasia-associated chest pain.

Pneumatic dilation and surgical myotomy are the two most effective treatment modalities for achalasia. Pneumatic dilation with the modern Rigidflex balloon dilator (balloon diameters of 3.0, 3.5, and 4.0 cm) is successful in controlling symptoms in 50% to 93% of patients.¹¹⁵ A graded dilator approach with 3.0 cm, 3.5 cm, and 4.0 cm results in good-to-excellent response rates of 74%, 86%, and 90%, respectively, with an average follow-up of 1.6 years (range, 0.1 to 6 years).¹¹⁰ A recent summary of 22 studies with 1212 patients treated with

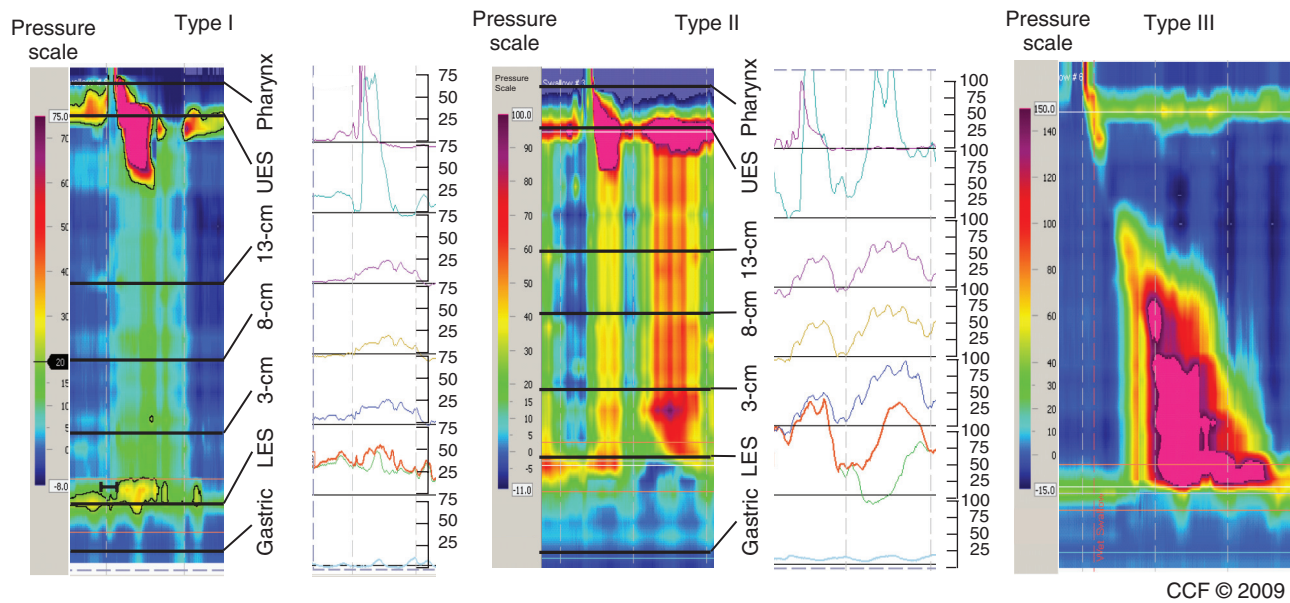


FIGURE 36-18 ■ Three achalasia subtypes. *Type I* has no contraction identified in the smooth muscle portion of the esophagus. Lower esophageal sphincter pressure (LESp) is greater than 30 mm Hg, and LES relaxation is never less than 20 mm Hg (normal, <15). *Type II* has esophageal pressurization greater than 40 mm Hg extending from upper esophageal sphincter (UES) to the LES that is simultaneous and repetitive. *Type III* has a prolonged, simultaneous, high-amplitude contraction characteristic of “vigorous achalasia.” The contraction does not extend from UES to LES as in type II.

Rigiflex balloon dilation reported a 2.0% perforation rate and 78% good or excellent results at 3-year follow-up. More than a third of patients will have symptom recurrence during a 4-year period, but they may respond to repeat dilation.¹¹⁷

Open modified Heller myotomy performed transabdominally or transthoracically has been successful in treating achalasia. Two prospective studies have been reported comparing pneumatic dilation to myotomy.^{118,119} After 4.8 years of follow-up, laparotomy and myotomy provided symptom control in 95% of patients, whereas pneumatic dilation with the Mosher system provided symptom control in 65%.¹¹⁸ In a small randomized study of 40 patients, no difference was observed between modalities, except that myotomy was associated with a lower LES pressure and less reflux.¹¹⁹

Development of laparoscopic Heller myotomy has resulted in more patients being referred for surgery and fewer for pneumatic dilation.¹²⁰ Laparoscopic Heller myotomy results in a shorter hospital stay.¹²¹ Improved outcome is associated with increased surgical volume. With short follow-up (mean, 1 year), good to excellent symptom control is seen in 94% of patients, but 11% report reflux.¹¹⁶ A recent review of 33 published studies of laparoscopic Heller myotomy reported that 85% of 1812 patients had a good to excellent response at a mean follow-up of 32 months, and 17% reported GERD as a postoperative complication.¹¹⁷ Preoperative pneumatic dilation has been reported to increase the risk of intraoperative esophageal perforation during laparoscopic Heller myotomy.¹²²

Regardless of surgical approach, the extent of myotomy is critical to good long-term outcome. A 3-cm extension of the myotomy onto the stomach is superior to a lesser myotomy for symptomatic and physiologic effects.¹²³ Controversy continues regarding the need for fundoplication added to myotomy. A fundoplication has been reported to be less essential when a thoracotomy is used. This finding most likely reflects a lesser myotomy. However, with the adoption of longer extensions of the myotomy onto the stomach, it is prudent to add a partial fundoplication to reduce reflux. The addition of a partial fundoplication has been demonstrated to reduce reflux¹²⁴ without impairing esophageal emptying.¹²⁵

A systematic review comparing the outcomes of 3086 patients who had laparoscopic myotomy to 1065 patients who had pneumatic dilation showed that symptom relief was significantly higher in the myotomy group at 12 and more than 36 months after treatment (89.3% vs. 68.2% and 89.3% vs. 56.3%, respectively).¹²⁶ However, in this study the myotomy outcome was compared with the result of the first pneumatic dilation, and the need for repeat pneumatic dilation was considered a failure. Currently, graded pneumatic dilation is considered as an accepted treatment approach.^{105,127} According to a Canadian study of 1181 patients initially treated with pneumatic dilation, the need for subsequent treatment, most often “touch up” dilation, at 1, 5, and 10 years was 36.8%, 56.2%, and 63.5%, respectively.¹²⁸ Recently, a multicentric European prospective trial randomized 200 achalasia patients to laparoscopic myotomy with Dor fundoplication or graded pneumatic dilation. After 2 years follow-up,

there was no statistical difference in success rates: 87% versus 92%, respectively.¹²⁹

Whereas laparoscopic myotomy with partial fundoplication and graded pneumatic dilation seem to be equally effective initial treatment options for achalasia patients, the choice of therapy should be guided by patients’ age, preference, and local institutional expertise.¹⁰⁵

Failure to reduce LES pressure may produce an “end-stage” dilated sigmoid esophagus, which may require esophagectomy.¹³⁰⁻¹³⁴ Although pneumatic dilation may be less effective in patients with megaesophagus, surgical myotomy may be a reasonable alternative before considering esophagectomy. Two studies showed 72% and 92% symptomatic improvement in this group of patients after myotomy.^{135,136} Despite treatment with pneumatic dilation or surgical myotomy, 10% to 15% will develop progressive deterioration of their esophageal function and up to 5% may eventually require an esophagectomy.¹³⁷ Esophagectomy is reserved for patients who fail pneumatic dilation and/or myotomy. Symptomatic improvement after esophagectomy can be expected in 80% with a mortality rate of up to 5.4%.¹³⁸⁻¹⁴⁰

Recently, a novel endoscopic myotomy technique has emerged as a minimally invasive alternative to the laparoscopic myotomy. The per-oral endoscopic myotomy (POEM) procedure was initially developed in Japan.¹⁴¹ Using a regular endoscope with a transparent cap, an endoluminal submucosal plane is created to gain access to the circular esophageal muscle for endoscopic myotomy with a dissection knife.¹⁴² The endoscopic myotomy is usually started 10 cm above and extended 2 cm below the gastroesophageal junction. The procedure time is approximately 2 hours. Short-term success rate of higher than 90% is reported in several studies.¹⁴²⁻¹⁴⁸ Symptomatic reflux and/or reflux esophagitis occurs frequently after POEM. POEM has been applied to all categories of achalasia, including end-stage disease, and to treatment failures from pneumatic dilation and laparoscopic myotomy. Nonrandomized comparison between POEM and laparoscopic myotomy indicate similar perioperative short-term outcomes.^{146,147,149} Wider use of POEM requires prospective randomized trials demonstrating the safety and long-term efficacy of this procedure compared with other effective treatment modalities for achalasia.^{105,150}

Hypercontractile and Spastic Disorders

Since the initial description of hypertensive and spastic motility disorders was realized with conventional manometry, substantial refinements and definition changes have been made with the invention and evolution of HRM.^{14,16,96,151-154} By analyzing esophageal contractile patterns in terms of esophageal pressure topography (EPT), rather than as line tracings, the conventional manometric criteria for hypercontractile and spastic disorders have changed significantly. Additionally, the EGJ morphology and dynamics can now be assessed in more detail for non-achalasia-related causes of EGJ outflow obstruction.^{155,156}

Diffuse (distal) esophageal spasm (DES) is a motility disorder of unknown etiology. The characteristic

pathophysiologic finding is impairment of deglutitive neural inhibition in the distal esophagus.¹⁵⁷⁻¹⁵⁹ Patients typically present with dysphagia and/or chest pain, and most patients have had extensive but negative cardiac evaluation for chest pain. Barium esophagram classically demonstrates a normal upper esophagus with a corkscrew or rosary bead pattern in the smooth muscle (distal two-thirds) portion (see Fig. 36-5A). DES is defined by manometric criteria rather than by clinical, functional, or pathologic criteria.⁹⁶ The diagnosis is therefore made by esophageal manometry. Traditionally, simultaneous contractions of normal (>30 mm Hg) or increased amplitude occurring after more than 20% of swallows were required for diagnosis, as was the presence of intermittent normal peristaltic contractions. Other findings that may be present are repetitive or prolonged contractions and elevated LES pressure.¹⁵¹ HRM has demonstrated that simultaneous contractions by traditional manometry are not true spasms; as a result, the conventional manometric definition may lead to overdiagnosis of DES, related to clinically irrelevant cases.^{96,160} DES was rare (1.5%) in a 400 consecutive patients study population.¹⁵⁴ The early Chicago classification interpreted “simultaneous contractions,” as described in conventional manometry schemes, as rapid contractions, defined by a contractile front velocity (CFV) greater than 8 mm/sec. DES was redefined by HRM as rapid contractions occurring with more than 20% of swallows.¹⁵⁴ The most recent Chicago classification proposed distal latency (DL) of less than 4.5 seconds (premature contractions) as an improved measure to represent simultaneous contractions.¹⁴ Reduced DL is thought to be indicative of a defect in distal neuromuscular inhibition.¹⁶¹ A recent study suggested that the diagnosis of DES based on an abnormal DL defines a more distinct clinical phenotype, whereas simultaneous contractions identify a large heterogeneous population, most of which do not have a clinical syndrome suggestive of esophageal spasm.¹⁶² Patients with premature contractions defined by a DL of less than 4.5 seconds were uniformly diagnosed clinically with a spastic disorder of the distal esophagus.¹⁶² The DL has therefore been adapted into the most recent Chicago classification to define DES.^{14,156,158,162} DES may progress to achalasia or be an atypical achalasia variant.^{158,163,164}

Because DES is poorly understood and there are most likely subgroups, including patients with predominant dysphagia or chest pain, multiple therapies have been tried with variable success.¹⁶⁵ Medical therapy includes PPIs, calcium channel blockers, nitrates, and sildenafil.¹⁶⁶⁻¹⁶⁹ Endoscopic therapy with botulinum toxin injection into the LES and the distal esophageal muscle has successfully controlled symptoms in selected patients.¹⁷⁰ Balloon or pneumatic dilation has been used for the subgroup of DES patients with poor relaxation of the LES.^{171,172}

An excellent review emphasizes the need for careful selection of patients for DES surgery and points out that surgery is rarely indicated.¹⁷³ For patients with severe DES refractory to medical therapy, a long myotomy extending from the aortic arch to the proximal stomach has been reported to provide good to excellent symptom control in 70%^{174,175} and to provide excellent medium-term control of dysphagia and chest pain.

However, 10% of patients have been reported to experience postoperative reflux.¹⁷⁶ Recent reports suggest that the recently developed endoscopic technique POEM might become an alternative treatment modality.^{177,178} Future studies are necessary to assess the efficacy of tailoring therapy for different DES subgroups.

Esophageal hypertensive peristaltic disorders, including nutcracker esophagus, spastic nutcracker or jackhammer esophagus, and hypertensive LES, represent a spectrum of abnormal esophageal vigor on esophageal manometry.^{14,152} Nutcracker esophagus is characterized by high-amplitude contractions of the distal esophagus (average peristaltic amplitude >180 mm Hg over pressure sensors 3 and 8 cm above LES by conventional manometry or as mean DCI >5000 and <8000 mm Hg/sec/cm by HRM), but esophageal peristalsis is normal. In 400 patient series, hypertensive peristalsis (mean DCI >5000 mm Hg/sec/cm) was found in 9% and nutcracker in 4% of patients.¹⁵⁴ By its definition, nutcracker can be seen in healthy volunteers and asymptomatic patients.^{95,154} Nutcracker has been reported in association with chest pain, dysphagia, and heartburn. It can be found in approximately up to 48% of patients with noncardiac chest pain undergoing esophageal manometry and in 10% with dysphagia.¹⁷⁹ Jackhammer esophagus (Fig.

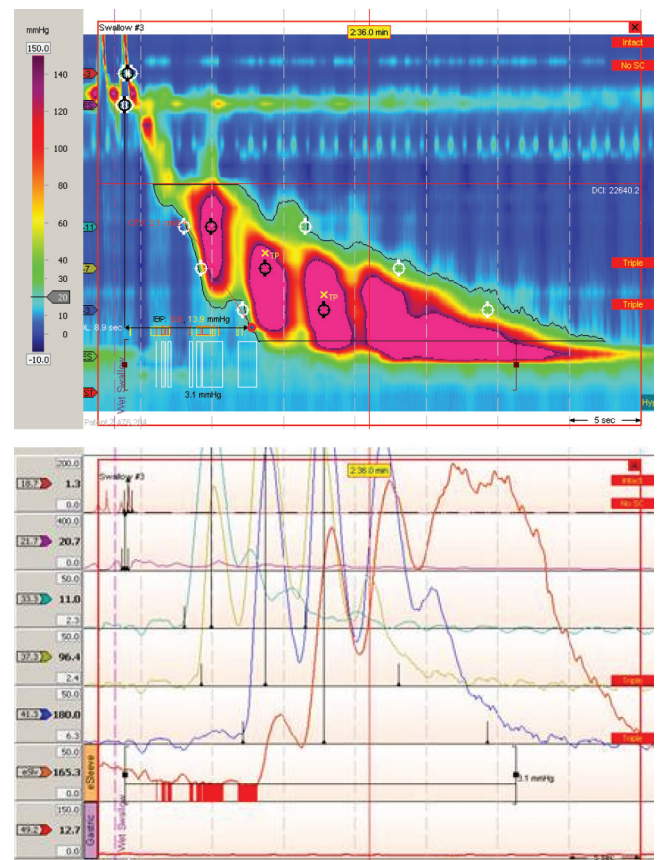


FIGURE 36-19 ■ High-resolution manometry and traditional manometry in a patient with jackhammer esophagus show esophageal pressure topography and line tracings of a swallow with extreme distal contractile integral (DCI = 22,640) and multi-peaked contractions. Esophageal peristalsis and the esophago-gastric junction relaxation are normal.

36-19) refers to a hypercontractile disorder where at least one propagated swallow-induced contraction has a DCI greater than 8000 mm Hg/sec/cm by HRM in the context of normal EGJ relaxation. The contraction is usually multipeaked, associated with repetitive prolonged contractions evoking the action of the jackhammer.¹⁵² This disorder is rarely seen in asymptomatic subjects and is found in only 4% of manometries.¹⁵³ Most patients are symptomatic, most often with dysphagia and/or chest pain or reflux symptoms. The pathophysiology is largely unknown but patients with hypertensive contractions have been noted to have increased esophageal muscle thickness on endoscopic ultrasound.¹⁸⁰ Hypercontractile esophagus may be attributable not only to primary esophageal muscle hypercontractility but also secondary to reflux disease or mechanical obstruction at the gastroesophageal junction.^{152,153,181} Treatment is medical; however, it remains to be determined if medical treatment is associated with reduction of symptoms. GERD is often present, and these patients should be treated with a PPI. Calcium channel blockers have not been found to be consistently effective. Trazodone and imipramine reduced chest pain in some patients.¹⁶⁸ Botulinum toxin injection in esophageal muscle has also been used.¹⁸² Surgery should be avoided.

Hypomotility Disorders

Hypocontractile motility disorders are nonspecific esophageal motor abnormalities that are frequently encountered.¹⁸³ They have been classified as ineffective esophageal motility (IEM), mild to severe peristaltic dysfunction or, most recently, as weak peristalsis with small or large peristaltic defects (breaks) and/or frequent failed peristalsis.^{14,151,154,184} IEM is most frequently associated with GERD, especially erosive esophagitis, and can be found in over 30% of GERD patients. Hypotensive LES pressure is commonly observed in patients with severe GERD and a large hiatal hernia. Hypomotility is also observed in approximately 30% of patients presenting with nonobstructive dysphagia without GERD.¹⁸⁴⁻¹⁸⁶ Therapeutic options to restore contractility are limited, but patients with borderline esophageal motor function have a good long-term outcome.¹⁸¹ Empiric therapy with PPIs is a reasonable approach because of the frequent association of IEM with GERD. In patients with predominant dysphagia despite PPI treatment, empiric dilation can be done; however, this is controversial.¹⁸⁷

Absent peristalsis or severe hypomotility can cause dysphagia after complete fundoplication. The degree of hypomotility needed to result in post-fundoplication dysphagia is unclear; patients with complete aperistalsis (such as achalasia or scleroderma) will harbor a high prevalence of dysphagia. Patients who have preoperative dysphagia along with hypomotility are more likely to develop worsening dysphagia postoperatively.¹⁸⁸ Incomplete fundoplication should be considered in these patients. On the other hand, some patients with preoperative dysphagia and IEM may have improvement of the esophageal body function and/or the dysphagia postoperatively.^{188,189} Impedance manometry can assess which patients with IEM have abnormal bolus transport,¹⁹⁰ and,

as with standard manometry, HRM can assess the entire peristaltic wave-front rather than just three to four pressure sites. Few studies have related the risk of dysphagia after fundoplication using impedance manometry.¹⁸¹ One study showed that impedance manometry could not predict dysphagia in patients with GERD or its occurrence after laparoscopic Nissen fundoplication.¹⁸⁸ However, patients who had worsened postoperative dysphagia had preoperative lower liquid bolus clearance rates and longer liquid bolus transit times, compared with patients who did not have worsening of dysphagia.

Secondary Esophageal Motility Disorders

Scleroderma, or progressive systemic sclerosis, is a systemic disease that commonly results in esophageal dysfunction. Fibrosis, collagen deposition, and patchy smooth muscle atrophy are histologic hallmarks of esophageal involvement. The esophageal skeletal muscle is unaffected. Destruction of esophageal smooth muscle results in diminished or absent peristalsis of the lower esophagus and hypotensive LES in scleroderma esophagus (Fig. 36-20).¹⁹¹ Reflux and dysphagia are common complaints. Therapy includes aggressive acid suppression with potent PPIs and dilation of strictures.¹⁹² Surgery

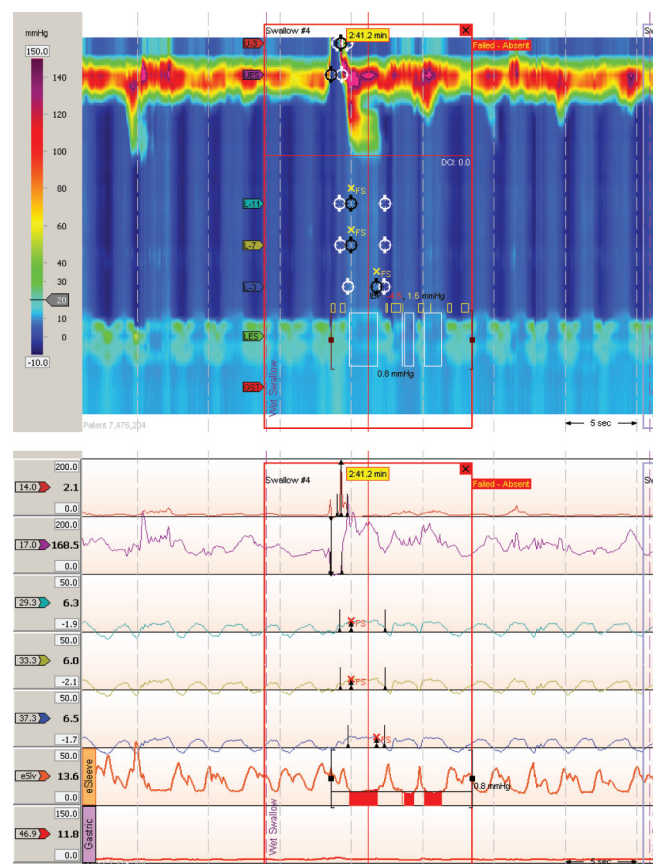


FIGURE 36-20 ■ High-resolution manometry and traditional manometry in a patient with scleroderma. There is a complete absence of smooth muscle contraction in the distal 75% of the esophagus. However, there is preserved striated muscle contraction in proximal 25% of esophagus. Lower esophageal sphincter pressure is less than 5 mm Hg.

should be avoided if possible, especially if aperistalsis is present. When surgery is performed, it usually requires esophageal lengthening (Collis gastroplasty) and a partial fundoplication.¹⁹³ For extensive, repairable esophageal damage, resection may be required.

Neurologic and muscular disorders such as stroke, amyotrophic lateral sclerosis, and muscular dystrophies may be accompanied by esophageal dysfunction. Esophageal involvement is also seen in patients with diabetes or alcoholic neuropathy.

Diverticula

A diverticulum is an outpouching that protrudes from the gastrointestinal wall. True diverticula contain all layers of the gastrointestinal wall and are uncommon in the esophagus. Most esophageal diverticula consist of mucosa, submucosa, and strands of muscle fibers and are, therefore, false diverticula. The mechanisms by which diverticula develop are not completely understood. However, diverticula are categorized as pulsion, traction, or congenital, according to the suspected mechanism of formation. A pulsion diverticulum usually occurs at or proximal to an esophageal sphincter or proximal to areas of prolonged or increased pressure. They are assumed to be the result of excessive outward pressure on the gastrointestinal wall. Generally, these are false diverticula. Traction diverticula result from forces arising outside the gastrointestinal wall and are usually true diverticula. They are far less common and are found adjacent to regions of periesophageal inflammation, such as chronic lymphadenitis.

Diverticula of the esophagus are most commonly acquired. Pulsion diverticula can be located anywhere along the esophagus. Traction and congenital diverticula are rare. Focal diverticula occur in three common anatomic sites. Proximally, they occur in the hypopharyngeal or pharyngoesophageal region. Mid-esophageal diverticula are seen near the tracheal carina. Distal or epiphrenic diverticula appear within a few centimeters of the gastroesophageal junction.

Zenker Diverticulum

Zenker diverticulum is the most common esophageal diverticulum and occurs above the cricopharynx at the Killian triangle. Typically, it is located opposite the C6 or C7 vertebral body (Fig. 36-21). Incomplete UES opening is reported in patients with Zenker diverticula.¹⁹⁴ Over time, a permanent narrow-mouthed outpouching of the posterior pharynx and esophagus develops and enlarges inferiorly. As a result, saliva and ingested food-stuffs pool dependently in the sac and cannot empty easily into the esophagus.

Early on, patients may complain of a vague sensation or sticking in their throat, intermittent cough, excessive salivation, and intermittent solid food dysphagia. These minor symptoms may be dismissed as globus hystericus. As the sac enlarges, symptoms worsen as dysphagia becomes more frequent. This usually occurs in patients who are older than 50 years. Gurgling sounds during swallowing, regurgitation of undigested food ingested, halitosis, voice change, retrosternal pain, and respiratory

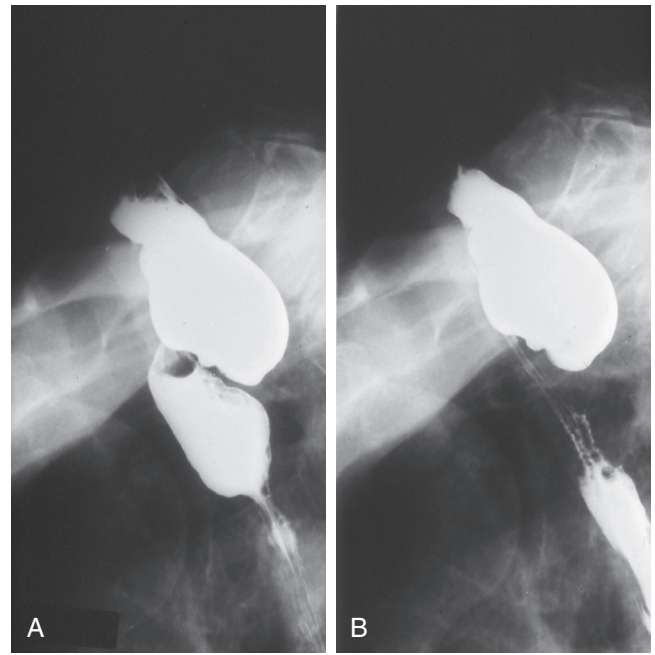


FIGURE 36-21 ■ Zenker diverticulum. Lateral view during barium esophagram shows a large diverticulum (A) that does not clear with repeated swallowing (B).

problems may be accompanying symptoms. To aid swallowing, patients use unusual maneuvers such as throat clearing, coughing, or placing manual pressure on the neck. In rare cases, the diverticulum can become large enough to obstruct the esophagus. A neck mass may be observed in these patients. The most serious complication associated with a Zenker diverticulum is aspiration, which can lead to pneumonia or lung abscess. Perforation, hemorrhage, or carcinoma may complicate Zenker diverticula.

A Zenker diverticulum is best identified and evaluated by barium esophagram, which can also evaluate the esophagus, as described earlier. Endoscopy is not required in all cases, but it is indicated when abnormal esophagram or concomitant esophageal or gastric symptoms exist. Experience is necessary to safely navigate past large diverticula. Manometric testing of the cricopharyngeal area is not clinically useful. Esophageal manometry is performed when symptoms or esophagram findings warrant it, and it usually requires endoscopic placement.

Treatment goals of Zenker diverticula are to increase UES compliance and reduce resting pressure in the cricopharynx. This can be accomplished endoscopically by creating an esophagodiverticulostomy with an endoscopic stapler.¹⁹⁵ Mid-term results with this technique are excellent.¹⁹⁶ Large diverticula and redundant mucosa are reported as risk factors for failure of endoscopic transoral stapling.¹⁹⁷ An open surgical myotomy is adequate treatment for small diverticula. For large diverticula, a myotomy with suspension or excision of the diverticulum is indicated.¹⁹⁸ Both endoscopic and open procedures provide similar outcomes with the same incidence of complications.¹⁹⁹⁻²⁰¹ The use of a traction suture to ensure complete incorporation of the diverticulum within the

stapler has been reported to reduce recurrent diverticula in patients undergoing endoscopic therapy.²⁰²

Midthoracic Diverticulum

Midthoracic diverticula usually develop within 4 cm to 5 cm of the tracheal carina. Until recently, these diverticula were commonly caused by traction secondary to mediastinal fibrosis and/or chronic lymphadenopathy from pulmonary tuberculosis or histoplasmosis. Many patients with these diverticula are found to have abnormal peristaltic waves from achalasia, DES, or other non-specific esophageal motor disorders (see Fig. 36-5B).^{203,204}

Patients with mid-esophageal diverticula may be asymptomatic; however, a history of dysphagia, retrosternal pain, regurgitation, belching, epigastric pain, heartburn, and weight loss may be elicited. Although attributed to the diverticulum, these symptoms may be the result of the associated motor disorder. Complications are unusual, but spontaneous rupture, hemorrhage, aspiration, esophagobronchial fistula, and carcinoma have been reported.

Most patients with midthoracic diverticula require no treatment. It has been reported that although 80% of patients had a proven motility disorder, only 20% required surgery.²⁰⁵ Diverticulectomy with esophageal myotomy is the preferred treatment for midthoracic diverticula associated with esophageal motility disorders. Right thoracotomy provides excellent exposure of the esophagus and airway at the tracheal bifurcation. Placing a bougie in the esophagus avoids compromise of the esophageal lumen and helps guide diverticulectomy. The mural defect should be repaired in two layers: the mucosal and submucosal layers closed with a continuous absorbable suture and the muscularis propria reapproximated with

interrupted absorbable sutures. The esophageal repair may be buttressed with pleura, pleuropericardial fat pad, or omentum. A myotomy can be carried out on the esophageal wall opposite the diverticulectomy. Diverticulectomy with suspension of the diverticulum superiorly from the prevertebral fascia,²⁰⁶ a myotomy alone,²⁰⁷ and diverticulectomy alone²⁰⁸ have been successfully applied in treating midthoracic esophageal diverticula. Treatment of true traction diverticulum, secondary to periesophageal inflammation, is often in the setting of an esophagobronchial fistula. Excision of the diverticulum, repair of the esophagus, removal of inflammatory nodes, closure of the airway fistula, and interposition of muscle are required.

Epiphrenic Diverticulum

Epiphrenic diverticula occur in the distal third of the esophagus, and the distal margin of the diverticulum is less than 4 cm from the gastroesophageal junction. There is usually an associated esophageal motor disorder or hiatal hernia.²⁰⁹ Epiphrenic diverticula may be asymptomatic, but patients typically present with dysphagia and regurgitation. They may also complain of vomiting, chest and epigastric pain, anorexia, weight loss, cough, halitosis, and/or noisy swallowing. There is no apparent relationship between symptoms and the size of the diverticulum. Symptoms may be attributable more to the underlying motility abnormality than to the diverticulum.

Barium esophagogram best identifies epiphrenic diverticula and often characterizes the underlying motility disorder (Fig. 36-22). Many patients show bizarre, nonpropulsive tertiary contractions during examination.

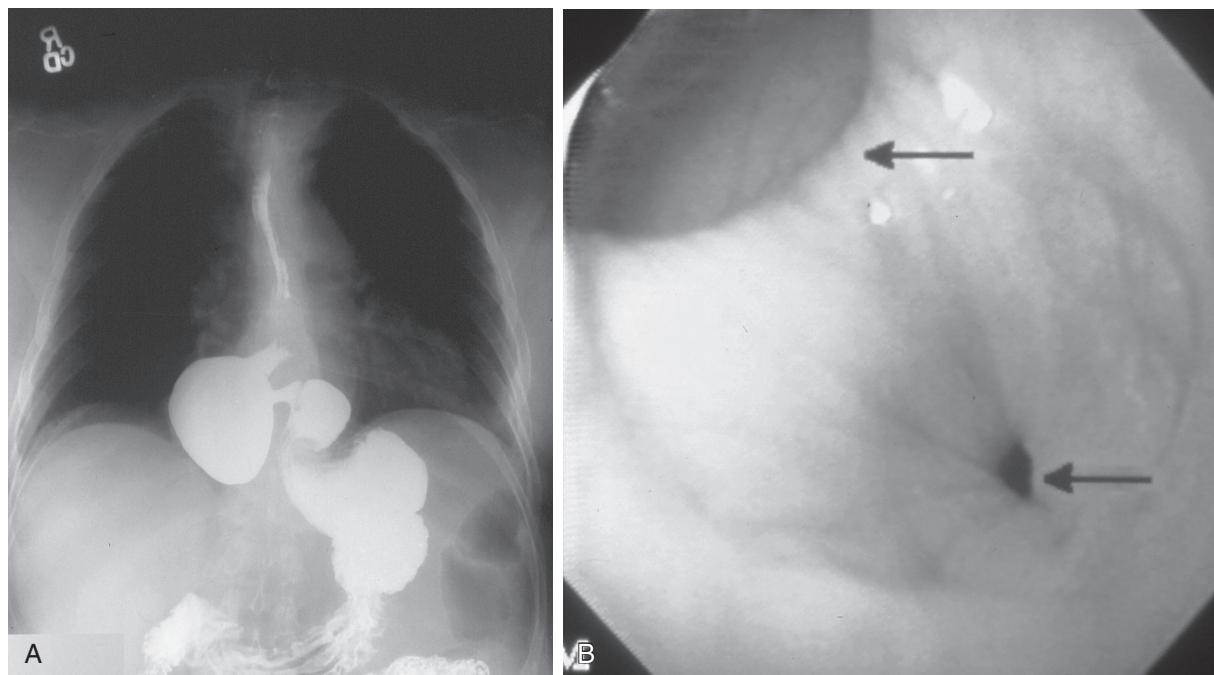


FIGURE 36-22 ■ Epiphrenic diverticulum. **A**, Barium esophagogram shows a large diverticulum. **B**, At esophagoscopy, the wide mouth diverticulum (upper arrow) and deviated distal esophageal lumen (lower arrow) are seen. Preferential filling of the diverticulum with swallowing can be appreciated from this examination.

In addition to fixed, wide-mouthed diverticula, transient outpouchings can occur proximally in segments where peristalsis is absent. Timed barium esophagogram may be used in any patient in whom an emptying disorder is suspected, particularly in patients with achalasia (see Fig. 36-7). Esophagoscopy generally yields little information about diverticula but may rule out malignancy and assess associated esophageal problems. Esophageal motility is essential before surgery. Esophagoscopy may be required to pass the manometry catheter past the diverticulum into the stomach.

Most authors agree that a diverticulectomy alone may result in a recurrence and advocate adding a myotomy.²¹⁰⁻²¹² Addition of an antireflux procedure to diverticulectomy and myotomy is controversial. However, if added, a partial (nonobstructing) wrap, such as a Belsey, Toupet, or Dor fundoplication, may minimize postoperative dysphagia.

Because epiphrenic diverticula are rare, most literature reports case series from single institutions. The optimal approach and the components of the operation remain controversial. A recent literature review of minimally invasive surgery for epiphrenic diverticulum identified 25 publications and 133 patients treated.²¹³ Most of these patients had both a myotomy (83%) and a fundoplication (85%). The operative mortality was 2%, morbidity was 21%, and 15% of complications were esophageal leaks.

Benign Esophageal Tumors and Cysts

Benign esophageal tumors are uncommon and represent less than 1% of esophageal neoplasms. EUS is essential in the diagnosis. Thus, classification by layer of origin in the esophageal wall is the most clinically useful categorization of benign esophageal tumors (Box 36-2).

BOX 36-2 Classification of Benign Esophageal Tumors

MUCOSA (FIRST AND SECOND ESOPHAGEAL ULTRASOUND [EUS] LAYERS)

- Squamous papilloma
- Fibrovascular polyp
- Retention cyst

SUBMUCOSA (THIRD EUS LAYER)

- Lipoma
- Fibroma
- Neurofibroma
- Granular cell tumor
- Hemangiomas
- Salivary gland-type tumor

MUSCULARIS PROPRIA (FOURTH EUS LAYER)

- Leiomyoma
- Duplication cyst

PERIESOPHAGEAL TISSUE (FIFTH EUS LAYER)

- Foregut cyst

Tumors of the Mucosa

Squamous papillomas are small (<1 cm), solitary, sessile projections in the distal esophagus and are usually found incidentally.^{214,215} They are uncommon, detected in 0.01% of 7618 esophagoscopies.²¹⁶ Histologic evaluation shows vascularized projections of the lamina propria covered by hyperplastic squamous epithelium. Biopsy differentiates squamous papillomas from small superficial squamous cell carcinomas. Because progression to malignancy is rare, asymptomatic patients require no follow-up. Symptomatic papillomas or those with atypical histologic features require excision, usually endoscopic. Although the cause of squamous papillomas is unknown, associations with human papillomavirus and GERD have been reported.^{215,217}

Fibrovascular polyps are collections of fibrous, vascular, and adipose tissue lined by normal squamous epithelium. Although fibrovascular polyps of the esophagus are uncommon in any one practice, the literature is replete with individual case reports. These polyps, which usually arise in the cervical esophagus and extend into the esophageal lumen, may reach into the stomach. Most patients complain of dysphagia and respiratory symptoms.²¹⁸ Regurgitation into the hypopharynx with subsequent aspiration and asphyxia is possible. These lesions can be detected by either barium esophagogram or esophagoscopy (Fig. 36-23). Because fibrovascular polyps fill the esophageal lumen and have a composition similar to that of the mucosa, diagnosis by esophagoscopy or EUS may be difficult or impossible.²¹⁹ Most polyps are surgically treated, although some have been removed endoscopically. Recurrence after resection is rare.²²⁰

Tumors of the Submucosa

At esophagoscopy, lipomas are noted as a bulging of the overlying esophageal mucosa. They have a pale yellow appearance and soft or pillow-like texture when probed endoscopically. Esophagoscopy biopsies demonstrate only normal squamous epithelium because forceps rarely penetrate the submucosa. EUS demonstrates a hyperechoic homogeneous lesion that originates in and is confined to the submucosal layer. If the patient is asymptomatic, only observation is required. Typically the lesions must reach an extremely large size before the patient becomes symptomatic. Rarely has malignant degeneration been reported.²²¹ Fibromas and neurofibromas are rare. At endoscopy, unlike lipomas, they are firm to the touch. These lesions, which arise from the submucosa, are less hyperechoic by EUS than are lipomas. Symptomatic submucosal tumors have been enucleated with minimally invasive techniques.²²²

Granular cell tumors are of neural origin and arise from Schwann cells. Most patients with granular cell tumors are asymptomatic and rarely require surgery.²²³ At esophagoscopy, these lesions are yellow, firm nodules, which can be diagnosed by routine endoscopic biopsies (Fig. 36-24). On EUS, granular cell tumors arise from the submucosa and are hyperechoic, but less so than lipomas.²²⁴ Nests of cells with pyknotic nuclei, abundant granular cytoplasm, absence of mitotic figures, and strong

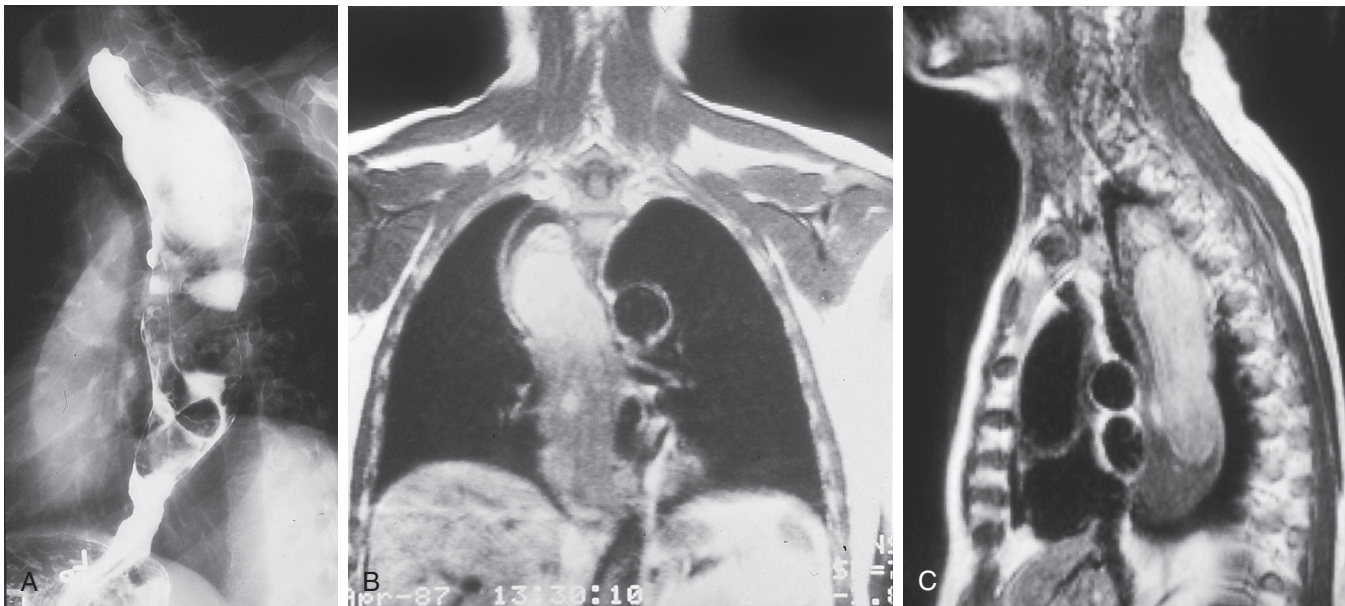


FIGURE 36-23 ■ Fibrovascular polyp. **A**, A large polypoid filling defect of the intrathoracic esophagus is seen. **B** and **C**, Magnetic resonance image of tumor shows a large soft tissue mass filling the esophagus.

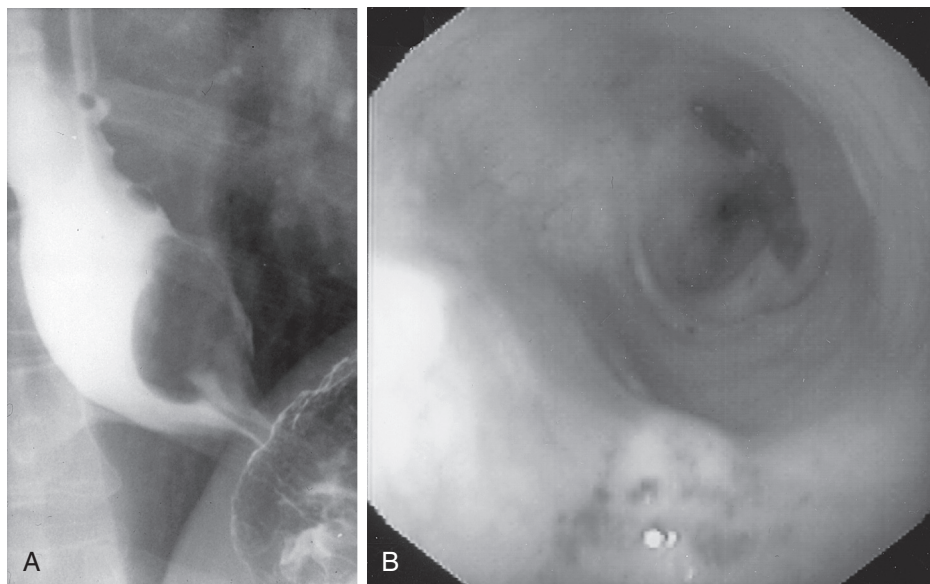


FIGURE 36-24 ■ Granular cell tumor. **A**, In a patient with dysphagia and acid reflux symptoms, barium esophagram shows a polypoid filling defect in distal esophagus. **B**, Esophagoscopy of another patient with a granular cell tumor shows a tumor that is extra-epithelial. Biopsy of this tumor was diagnostic for granular cell tumor.

S-100 protein expression characterize these tumors. Malignant variants have been reported.^{223,224}

Hemangiomas can present with dysphagia and bleeding. Most are found in the lower esophagus, where they may be mistaken for esophageal varices. EUS examination reveals a hypoechoic mass with sharp margins arising from the second or third EUS layer.^{225,226} Treatment options include observation, simple excision, fulguration, or radiotherapy.²²⁷ Salivary gland-type tumors have been rarely reported in the esophagus and probably arise from submucosal esophageal glands.

Tumors of the Muscularis Propria

Leiomyomas are benign smooth muscle tumors of the muscularis propria. They are the most common benign esophageal tumor and account for more than 70% of these neoplasms. Most arise from the inner circular muscle layer of the distal and midthoracic esophagus. There is no sex predominance. Leiomyomas typically occur in younger patients. Although frequently asymptomatic and discovered incidentally,²²⁸ leiomyomas can cause dysphagia, pain, or bleeding. In addition, distal

esophageal leiomyomas are often associated with symptoms of GERD. Barium esophagogram demonstrates smooth-contoured filling defects. At esophagoscopy and EUS, a normal overlying mucosa is seen over a hypoechoic tumor arising from the fourth ultrasound layer (Fig. 36-25). Atypical EUS findings are a tumor 4 cm or larger, irregular margins, mixed internal echo characteristics, and associated regional lymphadenopathy. Definitive diagnosis is difficult to obtain, because endoscopic biopsies do not reach the muscularis propria, and EUS-directed FNA does not provide enough information to differentiate leiomyomas from leiomyosarcomas.

Symptomatic neoplasms should be resected. For asymptomatic tumors with typical EUS features, expectant therapy and EUS observation are indicated. Leiomyosarcomas are exceedingly rare,²²⁹ and malignant transformation of benign leiomyomas has been infrequently reported.²³⁰ Gastrointestinal stromal tumors (GISTs) rarely occur in the esophagus and must be differentiated from leiomyomas. These tumors, which originate from the gastrointestinal pacemaker cells of Cajal, stain positively for tyrosine kinase and should be excised by esophagectomy.²³¹

Esophageal Cysts

Esophageal cysts are the second most common benign esophageal tumor, accounting for 20% of these lesions. The minority are acquired epithelial cysts, arising in the

lamina propria.²³² Submucosal glandular inflammation is the suspected cause. Most esophageal cysts are congenital foregut cysts.²³³ They are lined with squamous, respiratory, or columnar epithelium and may contain smooth muscle, cartilage, or fat. An esophageal duplication is a type of foregut cyst; it is lined with squamous epithelium, and its submucosal and muscularis elements interdigitate with the muscularis propria of the esophagus. Duplication cysts may be associated with vertebral and spinal cord abnormalities. Many patients with foregut cysts present in the first year of life with life-threatening respiratory compromise resulting from mass effect. EUS can clearly define the intramural or extraesophageal nature of these tumors and further determine their anechoic, cystic nature (Fig. 36-26).²³⁴⁻²³⁷ Regardless, removal of all discovered cysts is suggested because most become symptomatic by adulthood.²³⁸ In addition, trans-esophageal drainage has also been reported, but drainage of the cyst without destroying its lining often results in recurrence.²³⁹

Esophageal Injuries

Strictures

Various benign congenital and acquired disorders as well as malignant lesions can result in esophageal stricture. Congenital esophageal strictures, although rare, occur in the distal esophagus. They may result from the same

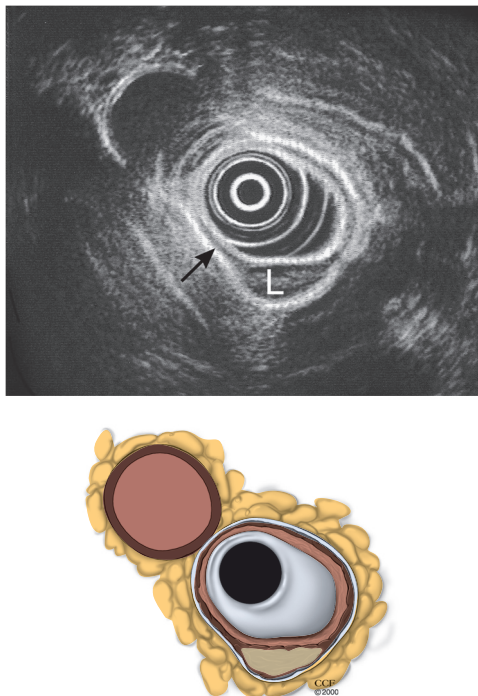


FIGURE 36-25 ■ An esophageal leiomyoma (L). *Top*: Esophageal ultrasound (EUS) of this most common benign tumor demonstrates a hypoechoic, homogeneous, well-demarcated tumor with no associated lymphadenopathy. EUS balloon overdistention blends the first three ultrasound layers into one hyperechoic layer. Tumor arises from and is confined to the fourth ultrasound layer (arrow). *Bottom*: A benign leiomyoma arises from and is confined to the muscularis propria.

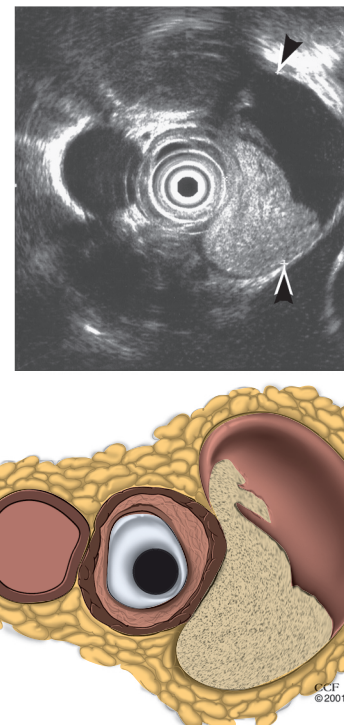


FIGURE 36-26 ■ Foregut cyst. *Top*: Esophageal ultrasound demonstrates a mass (arrowheads) adjacent to the trachea and esophagus. The cyst has two components, one hyperechoic (white) representing proteinaceous material and one hypoechoic (black) representing fluid. *Bottom*: Foregut cyst in close proximity to esophagus and trachea.

developmental abnormalities that produce tracheoesophageal fistula or esophageal atresia.²⁴⁰ Acquired esophageal strictures can be benign or malignant (Box 36-3). Although most benign strictures result from chronic injury and resultant fibrous repair, they can occur after a single injury. Malignant strictures are usually primary esophageal adenocarcinomas or squamous cell carcinomas. Local invasion of a bronchogenic carcinoma or secondary involvement from breast, lung, or renal primary sites can produce a malignant stricture.

Causes of Esophageal Strictures

The patient typically does not perceive difficulty swallowing until the esophageal lumen is half its normal diameter. Because the obstruction is structural, dysphagia associated with esophageal stricture is unremitting and reproducible. Dysphagia from strictures can often be distinguished from other causes by history. Dysphagia in esophageal motility disorders is typically intermittent, with both liquids and solids. Chest pain is often present. Oropharyngeal dysphagia is suggested by choking, aspiration, drooling, or nasal regurgitation, in addition to a sense of solid bolus retention in the neck, resulting in repeated swallowing.

Barium esophagram is usually the first test in evaluation of dysphagia and suspected esophageal stricture. Subtle strictures may be found with a barium tablet (13 mm). Once the stricture anatomy is defined, esophagoscopy is crucial to characterize, biopsy, and dilate the stricture. EUS is an important diagnostic adjunct after successful dilation in strictures with submucosal or extrinsic features at esophagoscopy or esophagram.

A treatment algorithm for esophageal stricture is given in Figure 36-27. For benign dilatable strictures, the inciting agent must be identified and removed and the stricture treated by dilation as necessary. Simple benign strictures can usually be treated with bougie or through-the-scope balloon dilators. More complex strictures typically need wire-guided dilation, which is best done with fluoroscopy. Longer, more complex, and tight strictures are typically from corrosive ingestion, radiation, nasogastric tubes, eosinophilic esophagitis, or congenital esophageal stenosis; these are particularly challenging to dilate. Reported perforation rate is 0.1% to 0.4% and is seen mainly with complex strictures.²⁴¹ Frequent dilation may

BOX 36-3 Esophageal Strictures

BENIGN

Congenital

- Esophageal atresia
- Tracheoesophageal fistula
- Web

Acquired

- Peptic
 - Gastroesophageal reflux
 - Scleroderma
- Schatzki ring
- Caustic ingestion
- Drug induced
 - Anticholinergic medications
 - Aspirin
 - Ferrous sulfate
 - Fosamax
 - Nonsteroidal anti-inflammatory
 - Quinidine
 - Potassium supplements
 - Tetracycline
 - Vitamin C
- Eosinophilic esophagitis
- Iatrogenic
 - Variceal ligation/injection
 - Endoscopic mucosal resection
 - Ablation therapy (cryotherapy/radiofrequency)
 - Postoperative (anastomotic)
 - Radiation
 - Instrumentation
 - Nasogastric tube
- Infections
 - Fungal: moniliasis
 - Bacterial: syphilis
 - Mycobacterial: tuberculosis
- Granulomatous
 - Crohn disease
- Dermatosis
 - Epidermolysis bullosa dystrophica
 - Pemphigoid
 - Behçet disease

MALIGNANT

- Primary
- Secondary

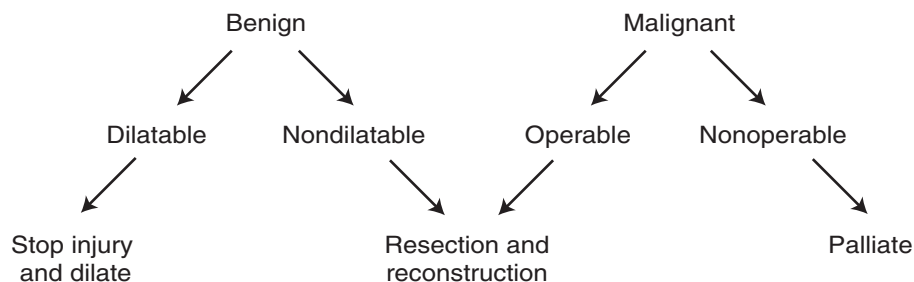


FIGURE 36-27 ■ Treatment algorithm for esophageal strictures.

be necessary, and stricture injection with steroids should be considered.^{242,243} Temporary stent placement has been increasingly used for refractory benign esophageal strictures, particularly plastic stents.²⁴¹ However, a recent pooled-data analysis on the use of self-expanding plastic stents for this indication suggested it was only moderately effective, with high early migration and complication rate.^{244,245} A recent preliminary study indicated that a biodegradable stent was safe and relatively effective for treating refractory benign strictures.²⁴⁶ Nondilatable benign strictures and resectable malignant strictures are treated by excision and reconstruction. Inoperable malignant strictures are palliated.

Peptic esophageal stricture is a late complication of severe, poorly controlled GERD and accounts for most benign esophageal strictures. Fortunately, peptic stricture is much less common since the widespread use of PPIs.²⁴⁷ Although initial damage is confined to the epithelium, with continued exposure to refluxed gastric contents, the injury progresses to involve the submucosa, the esophageal musculature, and, eventually, periesophageal tissue. The components of this injury are spasm, inflammation, and fibrosis. Eventually, the injury-repair cycle ends in cicatricial fibrosis and obstructive physiology of the distal esophagus. Most patients with peptic strictures present with dysphagia. It is less common for a patient to develop a symptomatic stricture during the treatment and follow-up of GERD. Although patients often do not have a prior diagnosis of GERD, more than 75% have symptoms of reflux.²⁴⁸

Most peptic strictures are located in the distal esophagus, usually above a hiatal hernia (see Figs. 36-4 and 36-6A). They are smooth, tapered areas of concentric narrowing. Occasionally, asymmetrical peptic scarring produces an eccentric stricture mimicking carcinoma. Symptomatic peptic strictures are usually 1 to 4 cm in length and 2 to 15 mm in diameter. They may be difficult to dilate, and they often recur, although aggressive PPI therapy makes this uncommon. Most peptic strictures occur at the squamocolumnar junction. Occurrence of the stricture well above the EGJ is suggestive of Barrett mucosa, which has been reported in 44% of patients with peptic esophageal strictures.²⁴⁹

Surgery should be considered for young patients who would require lifelong medication and for those who cannot tolerate medication. Early surgical correction provides better long-term results than late intervention, because the esophageal injury is more likely to be reversible.

Scleroderma should be suspected in patients with refractory and complicated GERD. The disease affects the smooth muscle of the esophagus and results in an incompetent LES and poor motility of the esophageal body. Massive reflux and insufficient esophageal clearance causes severe GERD and peptic complications that are difficult to treat. The mainstay of treatment is acid suppression and repeated dilation. Antireflux surgery should be avoided if possible because of poor or absent peristalsis. If required, an esophageal lengthening procedure and partial fundoplication are indicated. Total fundoplication may worsen the dysphagia because inadequate peristalsis and poor clearance may not overcome a

reconstructed LES. Peptic damage may be so severe that it requires resecting the amotile strictured esophagus.

Schatzki ring occurs precisely at the squamocolumnar junction (see Fig. 36-6B). These ringlike narrowings involve the mucosa and submucosa. They are thin, web-like constrictions, usually associated with small hiatal hernia, and are best seen radiographically. These rings may be missed at esophagoscopy because of incomplete distention of the esophagus. The most common symptom is intermittent solid food dysphagia when the internal ring diameter becomes 13 mm or less. Schatzki rings, thought to be reflux related, are amenable to dilation. Single large-bore bougie dilation may give long-lasting results, especially if PPI maintenance therapy is given after the dilation.²⁵⁰

Patients with pill-induced esophageal injury generally have no previous esophageal disease history. The initial injury is an ulcer, and patients typically present with chest pain and odynophagia.^{251,252} Then, painless dysphagia heralds the onset of a pill-induced stricture. Many patients recall the initial episode of pill lodging, typically a rushed ingestion done without caution, often without liquids and in a recumbent position. Pill injury is more common in women than in men.

Common locations of pill injury are in the cervical esophagus and the thoracic esophagus at the aortic arch, but other areas of anatomic or pathologic narrowing may trap a pill. Most medications produce superficial injuries that usually heal spontaneously. However, quinidine, potassium chloride, and Fosamax can produce severe esophagitis, and transmural injury may occur, leading to scarring and a stricture requiring dilation. Hemorrhage, mediastinitis, and free esophageal perforation have been reported.²⁵³

In rare cases, an esophageal stricture can be caused by a nasogastric tube in place for days to weeks. Patients develop symptoms weeks to months after tube removal. The mechanism of injury is unknown but is postulated to be trauma from tube insertion, chronic irritation by the tube, uncontrolled gastroesophageal reflux from an indwelling tube stenting the LES open, or impaired esophageal clearance secondary to the tube. Typically, barium esophagram demonstrates a long stricture with extensive ulceration in the mid and distal esophagus (Fig. 36-28). Initially, the strictures are smooth, tapered concentric narrowings that mimic peptic strictures. Progression can be rapid, with increased stricture length and severity resembling caustic strictures. Treatment includes dilation, avoidance of esophageal intubation, and aggressive antireflux medication.

Eosinophilic esophagitis (EE) has been recognized as a common cause of dysphagia and esophageal food bolus obstruction.²⁵⁴ EE is defined as a pathologic disorder characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant esophageal inflammation (peak value of ≥ 15 eosinophils per high-power field) despite PPI treatment.²⁵⁵ Endoscopic findings suggestive of EE are multiple rings (corrugated rings or trachealization), linear furrowing, and a diffuse esophageal narrowing or narrow-caliber esophagus. Barium esophagram seems to be of low sensitivity to diagnose EE. Although EE can occur

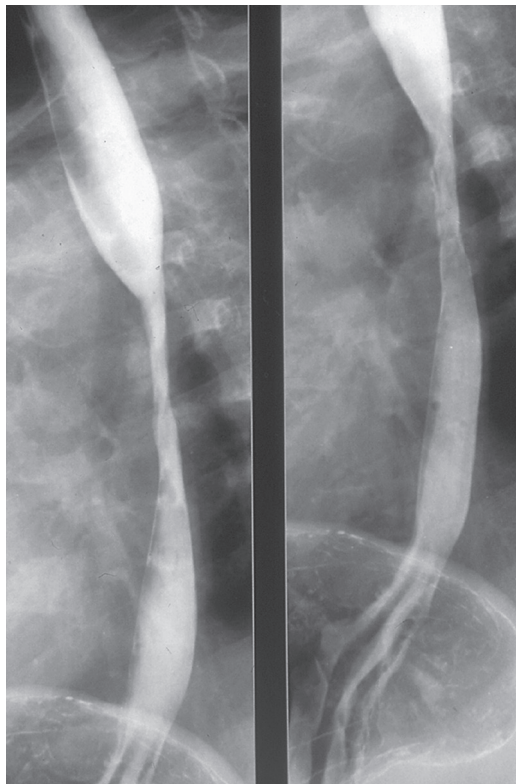


FIGURE 36-28 ■ Nasogastric tube stricture. In a patient with prolonged intensive care unit stay and protracted period of nasogastric tube drainage, a barium esophagram 1 month after discharge demonstrates a long smooth benign-appearing stricture of the midthoracic esophagus.

at any age, it predominantly presents in childhood or during the third or fourth decade of life; it is more common in males than in females.²⁵⁶ Three main treatment modalities are used for EE, the three Ds: diet, drug therapy, and dilation.²⁵⁷ Whereas EE is believed to be an immune/antigen-mediated esophageal disease, particularly food allergy related, topical swallowed steroids are often recommended. Elimination diets have been particularly beneficial in children, but also in adult patients with EE.^{258,259} For persistent dysphagia related to fibrostenotic disease, esophageal dilation alone can result in long-lasting (>1 year) relief of the dysphagia in most patients.^{257,260,261} Recent studies have indicated that the esophageal perforation rate from dilation in EE is similar to that seen for esophageal dilation for other benign esophageal diseases.^{262,263} When a long tight stricture is present, multiple dilation sessions may be necessary, and a goal diameter of 14 to 15 mm is suggested.²⁶⁴

Radiation strictures can occur as early as 3 to 8 months after radiation dosages between 30 and 60 Gy.^{265,266} They are smooth, concentric, and tapered, and they lie in the radiation portals. Low-dose radiotherapy and concurrent doxorubicin administration can also produce esophageal strictures. Other esophageal complications attributed to these therapies include esophagotracheal and esophagobronchial fistulae.

Anastomotic strictures complicate as many as a third of reconstructions after esophagectomy. Factors that produce these strictures include anastomotic

tension, ischemia, infection, and radiation. Strictures are more common after anastomotic leaks, local infection, and adjuvant radiotherapy. Treatment is usually repeated dilation. Recurrent carcinoma may be difficult to detect by esophagoscopy and may require endoscopic ultrasound.^{267,268}

Corrosive Injuries

Corrosive injuries of the esophagus are caused by the ingestion of strong acid or alkali. There is a bimodal distribution of age and causes. In children younger than 5 years, ingestion is usually accidental—the result of an inquisitive toddler ingesting improperly stored corrosive agents. The first swallow of the noxious substance usually stops further ingestion and injury. In adults, ingestion of large volumes of caustic agents is usually a suicide attempt.²⁶⁹

Early Management. Obtaining a history of the estimated amount and nature of the ingested agent is critical to directing treatment.²⁷⁰ Bleach and phosphate detergents are irritants that rarely produce significant injury. Ingestion of strong acid produces coagulation necrosis, which may limit the depth of injury. However, rapid passage and pooling in the stomach can promote gastric injury.²⁷¹ Ingesting viscous alkali produces liquefaction necrosis and increases the depth of injury. Historically, most alkali agents were solids, generally restricting injuries to the mouth, oropharynx, hypopharynx, esophagus, and trachea. Significant solid corrosive ingestion may produce oral pain, drooling, excessive salivation, inability or refusal to swallow or drink, hoarseness, aphonia, dyspnea, stridor, and ulceration of the mouth, pharynx, or larynx. Currently, the availability of liquid alkali has altered the pattern of injury. These agents pass rapidly through the upper gastrointestinal tract, producing severe injury to the esophagus at physiologic points of narrowing (cricopharyngeus, upper thoracic esophagus at the tracheal bifurcation, and the distal thoracic esophagus) as well as to the stomach and adjacent intra-abdominal organs. Significant liquid caustic ingestion typically produces dysphagia, odynophagia, chest and abdominal pain, and signs of mediastinitis or peritonitis.

Patients should be admitted to the hospital and given orders not to receive anything by mouth. Because the injury is immediate, dilution or induction of emesis is not helpful. In fact, regurgitation of the alkali may worsen the injury by repeat exposure of the injured area to the agent. Fluid resuscitation and broad-spectrum antibiotic therapy are essential. Early administration of corticosteroids does not limit the depth of injury or reduce the incidence of late strictures.^{272,273} Intubation or tracheostomy and ventilation may be urgently required if there is significant laryngotracheal injury. Rapid evaluation of the upper gastrointestinal tract with flexible fiberoptic esophagogastroduodenoscopy is important to identify location and extent of injury. This is facilitated by the smallest esophagoscope available with limited use of insufflation. Grading of caustic injury is similar to that of cutaneous burns.²⁷⁴ First-degree injuries exhibit only mucosal edema and hyperemia. Second-degree injuries demonstrate

blisters with vesicle and pseudomembrane formation. Third-degree injuries produce deep ulcers with eschar formation.

Patients with first-degree injuries require no specific treatment; the incidence of stricture is low. Patients with second- and third-degree burns are at increased risk of early mortality and late complications. The esophagus should be allowed to reepithelialize; early dilation may increase stricture formation and risk for perforation.²⁷⁵ Frequent clinical assessment is necessary to detect and treat necrosis of the esophagus or stomach. Resection of the involved organ or organs with delayed reconstruction is recommended for transmural necrosis with mediastinitis or peritonitis. Tracheoesophageal fistula complicating caustic injury should be managed with esophageal resection and exclusion and tracheostomy.²⁷⁶ Reconstruction is delayed for several months. Patients without acute complications should be placed on a bland liquid or mechanical soft diet and prophylactic acid-suppression medication.

Ingestion of small alkali disc batteries presents a particular threat to small children. Severe esophageal injury may result within hours of ingestion, as a result of current generation, seepage of extremely corrosive contents from damaged cases, and pressure necrosis. Careful endoscopic removal is aimed at preserving the integrity of the battery case.²⁷⁷ Passage of batteries through the stomach or lower gastrointestinal tract is uneventful.

Late Management. Dilation of caustic strictures should begin a few weeks after injury if the patient is symptomatic or a stricture is demonstrated radiographically. Although retrograde dilation has been proposed as the safest dilation technique, it requires gastrostomy. Prograde guided bougienage or balloon dilation has been successful.²⁷⁸ Short strictures not responding to initial dilation may benefit from local steroid injection followed by repeat dilation.²⁷⁹ A biodegradable stent for palliation of dysphagia from caustic esophageal stricture has also been applied as an alternative new treatment modality.²⁸⁰ Axial shortening of the esophagus results in hiatal hernia and GERD and may worsen the original corrosive injury. Need for excessive dilation and inability to dilate to a sufficient diameter are indications for resection and reconstruction. Colonic interposition used to be preferred for replacement after resection of corrosive esophageal injuries, but the stomach, if not injured by the ingestion, is now the organ of choice.²⁸¹ Lye ingestion places patients at 1000 times the cancer risk of the general population.^{282,283}

Perforation

Perforation of the esophagus results in chemical and infectious mediastinitis, which is lethal unless treated early and effectively. Iatrogenic injury is the most common cause of perforation.²⁸¹ The incidence of this complication is less than 0.05% during diagnostic endoscopy, but it increases with the complexity of the procedure and the underlying esophageal pathology. A perforation rate up to 17% has been documented after dilation of caustic strictures and in approximately 2% (median rate, up to

16%) of patients with achalasia treated with pneumatic dilation.^{105,278,284,285} The esophagus may be injured not only by instrumentation but during any procedure performed in the vicinity of the esophagus. Trauma and spontaneous (barogenic) rupture are the next most common causes of perforation. The esophagus is normal in approximately 50% of perforations. Pathologic changes in the remaining cases include benign strictures in 25% of patients, diverticula in 15%, carcinoma in 10%, and achalasia in 5%.^{281,286}

A high index of suspicion is important for early recognition of injury. Symptoms of spontaneous rupture are often nonspecific and include acute chest and abdominal pain, odynophagia, dyspnea, and fever. A catastrophic presentation with acute sepsis may be seen. Any patient reporting symptoms after instrumentation of the esophagus should be considered to have a perforation until proved otherwise. Pleural effusion, pneumothorax, pneumomediastinum, and subcutaneous emphysema are nonspecific chest radiograph findings. However, chest radiographs are diagnostic in only 15% of patients and may be normal in 10%.²⁸⁷ Clinical diagnosis of esophageal perforation is confirmed by esophagram (Fig. 36-29). This is first performed with Gastrografin aqueous contrast material and, if that is negative, repeated with barium. Up to 22% of perforations are missed if only aqueous contrast is used.²⁸⁸ Computed tomographic scanning with ingestion of oral contrast has replaced barium esophagram in many institutions.

Some injuries may be contained within the wall of the esophagus. When the laceration is limited to the esophageal wall or when contrast material drains freely into the esophagus without distal esophageal obstruction, patients

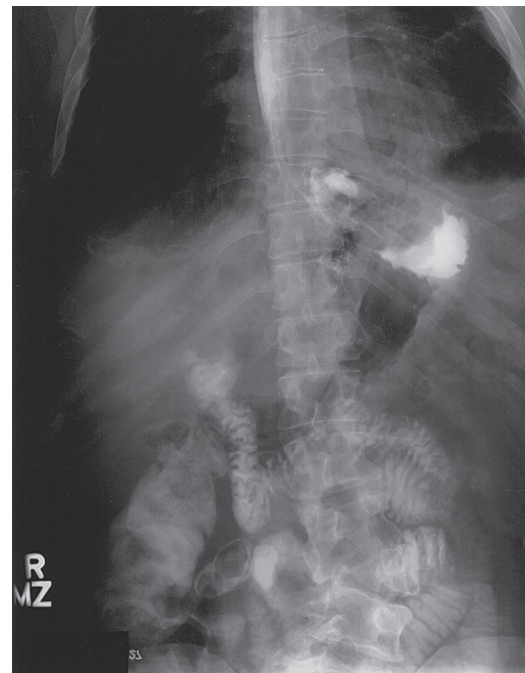


FIGURE 36-29 ■ Perforation. Barium esophagram in a patient who has just undergone unguided esophageal dilation of a distal esophageal stricture shows extravasation of barium into the mediastinum.

without fever or elevated white blood cell count can be followed by observation.^{289,290} However, if a transmural injury with mediastinal soiling is identified, definitive management is required after fluid resuscitation and administration of intravenous antibiotics. The principles of surgical treatment are débridement of infected or necrotic tissue, closure of the perforation, treatment of underlying esophageal pathology (if present), and drainage of the mediastinum. A myotomy at the site of perforation allows the full extent of damage to the mucosa to be recognized and repaired. Reinforcement of the repair results in decreased mortality rate and decreased incidence of fistula formation.²⁹¹ Delayed recognition of a perforation makes successful primary repair less likely. Therapy should be directed toward defunctioning, débridement, drainage, and resection.²⁹²⁻²⁹⁴ Surgical drainage without repair is possible for most cervical perforations. Descending mediastinitis requires prompt treatment of the mediastinal component of a cervical perforation and may necessitate addition of a right thoracotomy to the cervical incision.²⁹⁵ Palliation of perforated esophageal carcinoma has been successful with self-expanding, covered metallic stents.²⁹⁶ One third of patients experience dysphagia after repair of esophageal perforations and require either dilation or further surgery.²⁹⁷ The best results are seen in patients with achalasia and other motor disorders who undergo a myotomy during perforation repair. In patients with strictures or diffuse esophageal disease, esophagectomy may produce the best long-term results.

Endoscopic stenting to obliterate perforations, preventing further soiling, has been rapidly accepted and is increasingly used.²⁹⁸⁻³⁰³ Ongoing drainage of the soiled area has been provided with percutaneous or minimally invasive approaches, obviating the need for open surgery.³⁰⁴ Esophageal stenting does not necessarily spare patients from undergoing additional surgical intervention for esophageal perforation, but it offers the advantages of esophageal salvage and earlier return to an oral diet. Esophageal stenting is likely to be unsuccessful in the cervical esophagus, at the EGJ, or in perforations longer than 6 cm.³⁰⁵

Multiple case reports and small series have used endoscopic clips to manage esophageal perforations. The inability to obtain durable, full-thickness closure has hindered their use. However, the newly introduced Over-the-Scope Clip has recently been reported to be highly successful in closure of esophageal perforations.^{306,307} Equally promising and extremely innovative is the use of intraluminal vacuum therapy.^{308,309} The apparatus is applied endoscopically and changed every 3 to 4 days until the perforation is closed.

Esophageal Foreign Bodies

Most ingested foreign bodies are seen in toddlers.³¹⁰ In younger adults, ingested foreign bodies are usually associated with drug or alcohol use or psychiatric illness. In older adults, with either dentures or esophageal pathology, a food bolus may be the impacted foreign body. Food bolus impaction is a common presentation in patients with EE and can lead to Boerhaave syndrome.^{311,312} The

site of impaction is invariably at a physiologic or pathologic area of narrowing. Plain film and contrast radiography are diagnostic for most patients. Most small blunt objects pass into the distal gastrointestinal tract without difficulty. Blunt impacted foreign bodies may be removed with a flexible esophagoscope and balloon catheters or baskets. Sharp or pointed objects, if the sharp edge is directed aborally, may be removed with flexible esophagoscopy; little damage is incurred from the sharp trailing edge. However, if the leading edge is sharp, rigid esophagoscopy with retraction of the sharp edge into the barrel of the rigid esophagoscope may be necessary. Surgical removal is rarely required for impacted foreign objects or those complicated by lacerations and mediastinitis.

CONCLUSION

The understanding of esophageal anatomy, function, and physiology is essential to correctly diagnose and successfully treat benign esophageal diseases. Except for hiatal hernia and GERD, esophageal conditions amenable to surgery are uncommon. Restoration of esophageal function and the ability to swallow are essential. It is imperative that the first operation be successful, or the patient is started down the path of multiple reoperations that will ultimately end in esophagectomy for benign disease.

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ESOPHAGUS—CANCER

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STAGING TECHNIQUES FOR CARCINOMA OF THE ESOPHAGUS

Virginia R. Little

CHAPTER OUTLINE

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SUMMARY

There were 17,460 estimated new cases of esophageal cancer diagnosed in the United States in 2012 and 15,070 estimated deaths.¹ The overall survival from esophageal cancer remains dismal at less than 17% at 5 years in the United States.² The poor prognosis can be attributed to advanced stage at diagnosis and biological characteristics of the cancer. Less than 50% of the patients will be eligible for potentially curative resection at time of presentation, but because cure is uncommon without surgical resection, the importance of complete staging of the patient to determine if he or she is a surgical candidate is in the patient's best interest. Eighty percent of the esophageal deaths in the United States are in men, and esophageal adenocarcinoma (EAC) continues to increase in incidence in non-Hispanic white men and women older than 55, whereas the incidence in African Americans is declining.

Although the prognosis of patients with EAC remains poor overall, there have been improvements in the 5-year overall survival rates for patients with local or regionally advanced disease. The prognosis for those with distant disease remains low at less than 3% at 5 years.² Improvements in staging modalities and appropriate selection of treatment for patients, as well as the endoscopic treatment of Barrett-associated superficial cancers, have contributed to the small improvement in survival. Significant advances have been made in less invasive therapeutic modalities from endoscopic mucosal resection (EMR) of in situ and intramucosal cancers to minimally invasive approaches for esophagogastrectomy. As the therapeutic management of esophageal cancer continues to evolve, EMR has joined the staging modalities for superficial lesions.³ Improvements in early detection of the disease,

selection of appropriate treatment for patients, and surgical approaches may eventually translate into improved overall survival rates. For superficial early T1a cancers, treatments with EMR, ablative therapy, and salvage esophagectomy have resulted in cure rates of 100%.⁴ For low-risk T1b tumors, 84% are without evidence of disease at a mean follow-up of 4 years.⁵ An esophagectomy provides the best chance of cure for a completely staged patient with esophageal cancer. Historically high perioperative mortality rates of 20% dissuaded many oncologists from referring patients for resection with curative intent.⁶ With modernization of approaches and improved perioperative care, the surgical mortality rates after esophagectomy have improved to less than 4%.⁷⁻⁹ Esophagectomy, however, should be considered a potentially curative option and not a palliative modality because of the negative impact on quality of life after such resection.¹⁰ There are more palliative options currently available in the form of stents, laser, and cryotherapy,¹¹ and resection may be reserved for the significantly bleeding or complicated perforated tumor. Accurate staging is also important for determining the best mode of palliation for stage IV patients and for carrying out a realistic discussion with the patient and family.

In addition to early detection of this disease, identification of early-stage patients with accurate staging tests allows optimal selection of surgical candidates. Routine noninvasive preoperative staging modalities available at most institutions include endoscopic ultrasound (EUS) and positron emission tomography–computed tomography (PET-CT) scans. Early-stage patients benefit from endoscopic or surgical resection, whereas

advanced-stage patients benefit from palliative procedures like ablation, dilation, stents, chemotherapy, or radiation to improve quality of life. Intermediate-stage patients can benefit from neoadjuvant therapy followed by restaging and surgical resection with curative intent.

Although clinical trials of neoadjuvant chemotherapy or chemoradiation previously have not shown a consistent survival benefit,¹²⁻¹⁵ a few recent individual studies and a meta-analysis have shown some benefit.¹⁶⁻¹⁹ With the completion of the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS), however, neoadjuvant chemoradiation has become the standard of care at most centers for patients with clinical stage T3 or node-positive (cT3 or cN1/2/3) esophageal squamous carcinoma or adenocarcinoma.²⁰ Although this study included T2N0 cancers, the role of neoadjuvant therapy for such patients remains controversial.

This chapter will outline what is available now for staging the patient with endoscopic confirmation of a thoracic esophageal cancer.

ESOPHAGEAL CANCER TNM STAGING

The current staging system for esophageal cancer follows the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, 7th edition, which uses the TNM system of T for tumor, N for regional nodal status, and M for presence or absence of distant metastases (Table 37-1).²¹ The TNM staging system was recently revised, and significant changes included modifying the T stage, incorporating the grade of the tumor into the stage, subdividing the N stage based on the number of involved lymph nodes, and separating adenocarcinoma from squamous cell carcinoma (SCC). There is also only one class for metastatic lesions. M1a and M1b, separating distant nodal and distant organ metastases, have been removed. High-grade dysplasia is now T in situ (Tis), and T4 has been divided into T4a and T4b. T4a cancers are locally invasive but are still deemed potentially resectable albeit with a portion of pericardium, pleura, or diaphragm. T4b tumors invade the trachea, aorta, or vertebral bodies and deem the tumors unresectable.

Another major modification in the staging system is the subset of nodal stage. As has been modified for gastric, colon, melanoma, and other malignancies, the number of lymph nodes involved has become a prognostic marker and thus incorporated into the formal staging system. Accurate clinical nodal staging of esophageal cancer is challenging, and typically the patient is clinically staged as either node-positive or node-negative; however, this change in nodal staging is an important prognostic adaptation. Multiple studies from different esophageal groups have found significant survival differences based on absolute number of positive lymph nodes,²²⁻²⁶ absolute number of negative lymph nodes,²⁷ and ratio of positive to negative lymph nodes.^{25,28,29}

The grade of the tumor is also now a part of the staging classification as poorer differentiation corresponds with worse prognosis.³⁰ T1 is divided into T1a for intramucosal cancers and T1b for submucosal lesions. This T stage modification is based on the incidence of

lymph node involvement and subsequent survival differences for tumors of increasing depth. Other changes include the addition of tumor location to the SCC staging and the staging of tumors of mixed histology as per the SCC group.

ENDOSCOPIC ULTRASONOGRAPHY

EUS staging of esophageal cancers was first advanced in the literature by Lightdale in 1992,³¹ and in the next decade the modality became a standard part of staging newly diagnosed esophageal cancer patients.³² Before EUS, CT scan was the primary modality available to decide whether to proceed with an esophagectomy on an otherwise medically fit patient presenting with esophagus cancer, although MRI and bone scans were sometimes indicated by clinical presentation. Now EUS is available to help determine locoregional stage of esophagus cancer as well as distant disease by providing cytology of liver and adrenal or celiac lymph node metastases.

For patients without evidence of distant disease on PET-CT, EUS is used for T and N stages to allow referral for neoadjuvant therapy. It is most often performed by the gastroenterologists; however, some surgical groups are experienced and it would behoove thoracic surgeons to be proficient so that they can offer one-stop shopping for staging esophageal and lung cancer patients.³³

Conventional EUS is carried out with conscious sedation using the 360-degree radial mechanical echoendoscope with a 7.5-MHz ultrasound probe. Conventional radial EUS is the best approach for assessing depth of primary tumor into the esophageal wall. For EUS-guided fine-needle aspiration (FNA) of suspicious lymph nodes, a curved linear array echoendoscope is used with a 22- or 25-gauge needle. A 7.5-MHz or lower frequency endoscope is better than the high frequency endoscope for assessing regional lymph nodes because of the greater depth of visualization. Endoscopic criteria for potentially malignant lymph nodes include at least two of the following characteristics: round, discrete, hypoechoic, or a dimension greater than 1 cm.^{34,35} EUS imaging of nodes alone is not specific enough, but FNA of the suspicious nodes can result in a specificity rate of up to 95%.³⁶

EUS remains the most accurate modality for determining T stage with accuracy rates ranging from 64% to 80% for the low-frequency probe³⁷⁻⁴⁰ and up to 85% to 92% for the high-frequency probe.^{35,38,41} Accuracy can only be calculated when patients have undergone histologic confirmation of their tumor and nodal status. The accuracy of EUS for staging of T and N in the most recent series of patients in the past 15 years is summarized in Table 37-2. As summarized, EUS staging is indicated before initiation of neoadjuvant therapy.

EUS has an accuracy range of 80% to 90% for T3 and T4 stages^{38,39} but for T1 and T2 the rate drops to 74%.³⁹ In a large series of more than 200 patients with pathologic confirmation of their tumor and nodal stages, most EUS staging errors were understaging of T0 and T1 and overstaging of T2.⁴² The reliability of EUS for accurately staging T2N0 tumors was examined by Crabtree and colleagues, who retrospectively studied the Society of

TABLE 37-1 American Joint Committee on Cancer (AJCC) TNM Classification of Esophageal and Esophagogastric Junction Cancer

T	Primary Tumor	N	Regional Nodes
X	Tumor cannot be assessed	X	Regional nodes cannot be assessed
0	No primary tumor	0	No regional nodes
is	High-grade dysplasia	1	1-2 Regional nodes involved
1a	Tumor invades lamina propria or muscularis mucosae	2	3-6 Regional nodes involved
1b	Tumor invades submucosa	3	≥7 Regional nodes involved
2	Tumor invades muscularis propria		
3	Tumor invades adventitia	M	Distant metastases
4a	Resectable tumor invading pleura, pericardium, or diaphragm	0	No distant metastases
4b	Unresectable tumor invading other structures, including aorta, vertebral body, trachea	1	Distant metastases

SCC Stage Group	T	N	M	Grade	Tumor Location
0	Tis	N0	M0	1, X	Any
IA	T1	N0	M0	1, X	Any
IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
IIA	T2-3	N0	M0	1, X	Upper, middle
	T2-3	N0	M0	2-3	Lower, X
IIB	T2-3	N0	M0	2-3	Upper, middle
	T1-2	N1	M0	Any	Any
IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

Adenocarcinoma Stage Group	T	N	M	Grade
0	Tis	N0	M0	1, X
IA	T1	N0	M0	1-2, X
IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

SCC, Squamous cell carcinoma.

Thoracic Surgeons (STS) General Thoracic Surgery Database (GTDB) and concluded that clinical staging of T2N0 tumors is unreliable.⁴³ They reported a 26% downstaging and 47% upstaging of clinical T2N0 (cT2N0) patients treated with primary esophagectomy. EUS accurately staged T3 and T4 lesions in 85% of cases.³⁷ In another series, of 47 patients undergoing surgical resection for adenocarcinoma or SCC, EUS overstaged T stage in 19% of patients and understaged it in 17%.⁴⁴

In studies with pathologic confirmation, the accuracy rates for N stage range from 70% to 86%.^{34,37-39,45} Before FNA-guided biopsies of lymph nodes by EUS was applied, the false-negative rate of EUS for nodal stage exceeded 33%.⁴⁶ Endobronchial ultrasound (EBUS) has also been combined with EUS to improve the staging

precision of ultrasound modalities. As demonstrated in a prospective clinical trial (NCT01038544), patients with newly diagnosed esophageal cancer underwent radial and convex EUS followed by convex EBUS to evaluate the standard nodal stations.⁴⁷ EBUS complemented the examination of stations 2, 4, and 7 by EUS but also provided access to lymph node level 10R. EBUS added to the sensitivity of the EUS by upstaging 12% of the patients and contributing to the EUS stage in 69% of the patients. The EBUS scope also could be passed across tight malignant strictures, which precluded staging with the EUS but allowed for a clinical T and N stage of tumors that could not otherwise have been staged.

Although EUS has added much to the clinical staging and management of esophageal cancer patients, it still is limited by malignant stenoses preventing staging of the

TABLE 37-2 Accuracy of Endoscopic Ultrasound (EUS) Staging in Various Series with Pathologic Stage Available

Author (year) (ref)	Neoadjuvant Treatment (n)	pT Stage (%)	pN Stage (%)
Pech et al (2010) ⁴⁰	No (179)	74	73
O'Farrell et al (2013) ¹²⁷	No (163)	71	65
Barbour et al (2007) ³⁷	No (209)	61	75
Davies et al (2006) ³⁹	No (94)	78	70
Larghi et al (2005) with miniprobe (15-20 MHz) ⁴¹	No	85	NA
Cen et al (2008) ³⁴	No (87)	NA	81
Vickers and Alderson (1998) ⁴⁵	No (50)	92	86
Zhang et al (2005) ⁵³	No (34)	79	74
	Yes (39)	51	54
Zuccaro et al (1999) ³⁵	Yes (59)	37	38

NA, Not available; p, pathologic.

primary tumor. In these cases, however, tumor obstruction almost always represents T3 or T4Nx.⁴⁵ In addition, the probability of a T3 or T4 tumor being N1 exceeds 80%.⁴⁸

With the continued expansion of endoscopic therapy for patients with early esophageal cancers, accurate staging of T1 adenocarcinoma with EUS will be important to determine which patients may be offered endoscopic therapy with potential cure and which patients should undergo esophagectomy. From *experienced* EUS groups, the accuracy of staging an intramucosal (T1a) cancer was 82% to 94%.^{34,38,49} A T1b cancer has about a 20% likelihood of lymph node metastases versus the intramucosal lesion, which is less than 5%; thus, the EUS T stage may help in choosing between endoscopic and surgical resection.⁵⁰ EUS before endoscopic resection of T1 tumors remains controversial, however, because it is not highly accurate and the patient should probably just have the EMR for staging the superficial lesion.

For the patient initially presenting with a localized cancer, conventional EUS with a 7.5- to 12-MHz radial ultrasound probe is good for initial assessment of tumor infiltration and looking for suspicious lymph nodes (hypoechoic, >1 cm). The higher frequency 12- to 20-MHz probe may provide the most accurate staging for the T1 or T2 suspicious tumors,⁴³ but generally with EUS, pT1 tumors are understaged by 18% and pT2 tumors are overstaged by 47%.⁴⁰ The exam should include a full evaluation of the liver and lymph nodes in the paragastric, subhepatic, and celiac stations. If a suspicious node is identified, a curvilinear echoendoscope allows FNA of the suspicious node.

EUS and Neoadjuvant Therapy

Although EUS is feasible in 70% of patients after neoadjuvant chemoradiation,⁵¹ its accuracy rate with current neoadjuvant modalities drops below 50%.^{35,52} It over-stages the tumor depth in more than 49% of cases and over-stages the nodal status in more than 38% of cases.⁵³ The accuracy for T stage after chemoradiation at current radiation doses of 45 Gy ranges from 37% to 43%.^{35,52} Radiation fibrosis causes overstaging or understaging of T stage about 40% of the time^{51,54} because of radiation fibrosis. T stage by EUS after chemotherapy may be accurate only when the tumors don't respond to the chemotherapy.³⁵ EUS essentially is not recommended after neoadjuvant chemotherapy or chemoradiation because of the low accuracy rate⁵² secondary to the postinflammatory changes.^{35,55} Post-chemoradiation CT scan or endoscopy alone, however, is not as good as EUS in assessing treatment response.⁵⁸

Metastatic Disease

EUS is useful for confirming metastases to celiac lymph nodes (CLNs), which portend a worse prognosis.⁵⁷ CLNs were evaluated in 95% of 62 patients in Reed's series from 1999. In this group, EUS sensitivity was 72% and specificity 97%.⁵⁸ The presence of CLN metastases as detected by EUS has also been associated with a worse survival for all T stages. In another study, from Medical University of South Carolina, the authors concluded the 5-year survival rate of patients without celiac nodal involvement, as detected by EUS, was three times better than patients with CLN involvement (39.8 versus 13.8 months).⁵⁹ EUS can also be helpful in obtaining and evaluating biopsy of liver metastases.⁶⁰ In a recent study of 132 patients, EUS-FNA on noncystic liver lesions confirmed liver metastases in 20% of the cases and EUS was superior to CT in quantifying liver metastases, especially in cases where the metastases were too small to be characterized by CT scan.⁶⁰

ENDOSCOPIC MUCOSAL RESECTION

Aside from the number of involved lymph nodes and the grade of the primary esophageal tumor in the new TNM staging system, the subclassification of T1 into T1a and T1b reflects the acceptance of EMR for diagnosis, staging, and treatment of superficial esophageal cancers. The pioneers of this technique for superficial EACs, May and colleagues, initially reported that in 50 patients, endoscopic resection was a therapeutic alternative to esophagectomy for high-grade dysplasia (now known as Tis) and early adenocarcinomas in patients with Barrett esophagus.⁶¹ The technique was adapted from the Japanese approach to treating superficial gastric cancers and essentially involves identifying the mucosal abnormality and either cutting and coagulating it or using a suction, banding, and ligating method as one might use for a polypectomy. For EMR, the depth of resection is the submucosa. If the muscularis propria is involved, the EMR cannot be completed, at least not with the suction

banding technique. After the lesion is removed, it is carefully oriented by the operator and fixed and examined by a gastroenterology pathologist to classify it as a Tis, T1a, or T1b tumor. There are more specific depth classifications for T1b lesions depending on the level of involvement of the submucosa. Submucosal (sm) 1-3 categorization correlates with frequency of nodal involvement^{5,62}; however, T1b substaging is not part of the seventh edition of TNM staging. The risk of occult nodal involvement in T1a tumors is considered very low, ranging from 0% to 7% in 79 esophagectomy patients.⁶³⁻⁶⁵ Any potential for lymph node involvement dissuades some surgeons from recommending endoscopic therapy except when patients are at high surgical risk.^{63,64} Grade of tumor and lymphovascular invasion are established negative prognostic markers. In future validation studies, molecular staging of the primary tumor will help surgeons decide which patients need an esophagectomy and which can be treated endoscopically.

For T1b tumors, nodal involvement increases significantly, ranging from 21% to 50%⁶⁵; thus surgical resection is indicated. The addition of this modality has significantly and safely impacted the management of patients with mucosal esophageal cancers, who can then be spared a potentially morbid esophagectomy.⁴

COMPUTED TOMOGRAPHY

Accuracy rates of CT scanning for assessing depth of esophageal cancer and gastroesophageal junction (GEJ) cancer are notoriously poor, ranging from 33% for T2, 0% for T3, and 50% for T4 for an overall rate of 15%, and CT tends to understage tumor depth.⁶⁶ Although in more recent series the overall accuracy of CT for T stage was 59%,^{38,46,66,67} CT is used more for identifying distant metastases and suspicious regional nodes than for assessing tumor depth. Historically, nodal staging by CT averaged 50% for node-positive patients,⁶⁶ and the combination of EUS and CT for detecting regional nodal involvement accurately was 82% in a series of 42 patients undergoing surgical resection.⁴⁸ The sensitivity of CT staging of CLNs was only 8% in slightly older series, although the specificity was 100%,⁵⁸ but only 64% accurate for diagnosing stage IV disease by solid organ metastases or distant lymph node metastases in 74 Belgian patients.⁴⁴

Routine CT scans have improved the detection of distant metastases, but they have generally been replaced by the more sensitive PET-CT. Certainly it remains common for patients to have a staging CT scan of the chest and abdomen before they are referred to the surgeon for evaluation. CT scan may still have a role in evaluating chemoradiation response, however. Some groups have suggested that a reduction in maximal cross-sectional area of the tumor on CT scan may be helpful in assessing chemoradiation response preoperatively.^{52,68} Similarly, earlier studies suggested that preoperative CT width of the cancer may be a prognostic factor⁵⁶ even without neoadjuvant downstaging.⁶⁹ This staging of tumor measurements on radiographics is developing new interest with assessment of treatment response based on tumor length.⁷⁰

POSITRON EMISSION TOMOGRAPHY—COMPUTED TOMOGRAPHY

Just as EUS contributes to the preoperative evaluation and management of patients newly diagnosed with esophagus cancer, PET-CT adds biological information about the primary tumor and is standard for identifying distant disease.

Before the wider availability of PET-CT, the usefulness of PET alone was investigated for staging esophagus cancer patients. Flanagan et al at Washington University found that in 29 patients who underwent curative surgery (19 with adenocarcinoma), PET scan accurately detected regional nodal disease in 76% of patients and distant metastases in 93% of the patients. PET identified regional nodal involvement twice as often as CT in 21 patients undergoing esophagectomy for adenocarcinoma or SCC and improved detection of metastatic disease by 80% (45% by CT and 82% by PET-CT).⁷¹ For detecting stage IV disease in patients with EAC or SCC, PET alone had sensitivity, specificity, and accuracy rates of 74%, 90%, and 82% when compared with rates of 41%, 83%, and 64%, respectively, for CT scan.⁴⁴ Small (<1 cm) hepatic metastases were missed by both PET and CT scan in one patient, and in another patient a pancreatic metastasis was missed.⁷² The authors concluded that PET changed clinical management in 17% of 36 patients with adenocarcinoma or SCC.⁷² False-positive results on PET alone can result from granulomatous disease, reactive hyperplasia, or local extension of tumor misinterpreted as regional nodal involvement.^{44,72} False-negative regional lymph node involvement can result from occult, micrometastatic disease in normal-sized nodes and in nodes adjacent to the primary tumor where the PET uptake of the primary tumor obscures the nodal uptake. False-negative findings of stage IV disease by PET can result from peritoneal metastases, small (<1 cm) or superficial hepatic metastases, and small lung lesions.⁴⁴

Results of the ACOSOG Z0060 trial of PET staging in esophagus cancer were published in 2007.⁷³ In this intergroup trial, PET alone and not PET-CT was used to determine whether PET could improve on an acceptable 5% rate of metastasis detection and hence prevent unnecessary surgery for esophageal cancer patients with metastatic disease. All patients underwent a CT of chest and abdomen first; then, if that was negative, they had a PET scan to look for stage IV disease. Although tissue confirmation of PET-positive, suspicious lesions was part of the study algorithm, not all patients were able to undergo confirmatory biopsies of PET-positive areas. Indeed two patients who underwent procedures sustained complications after biopsy or after an adrenalectomy, procedures performed based on a false-positive PET result. Of the 145 patients who had a PET scan negative for metastases and who underwent potentially surgical resection, 5.6% developed recurrent cancer (location not otherwise specified) within 6 months of surgery. The group concluded that confirmed metastatic disease was detected in 4.8% of patients otherwise potentially eligible for curative surgery after body CT staging and as needed brain or bone imaging and that tissue confirmation is

important for avoiding the 3.7% false-positive rate resulting from PET scanning of these patients.

Initial Staging

With the advent of PET-CT more than 15 years ago,^{44,74,75} this modality has replaced PET alone at most institutions. One of the big advantages of PET scan over CT scan alone is the three-dimensional imaging with PET. This modality also identifies second primary tumors more than CT scans.⁷¹ PET is not used to diagnose esophageal cancer but instead to evaluate regional nodal disease and distant metastases. Lymph node status is the most important prognostic predictor for patients with potentially resectable disease,⁷⁶ and clinical staging of positive lymph nodes triages the patient to induction therapy. Ideally the patient should have histologic confirmation of PET-positive nodes before neoadjuvant therapy is initiated, but such stringent management is not routine.

The minimum lesion size that can be detected with PET scan alone is 5 mm.⁷⁷ PET-CT improves the accuracy of PET alone for identifying malignant lymph nodes, as demonstrated in a series of 39 patients, because the CT improved the localization of the PET tracer.⁷⁸ In this particular study, small lymph nodes (6 to 11 mm) that were negative on PET were detected with PET-CT. PET findings for detecting or eliminating metastatic disease have been shown to change patient management in about 20% of patients staged by CT initially.⁷⁷ PET alone is very sensitive for the primary tumor being hypermetabolic in more than 95% of cases.^{44,71,79}

The PET-CT is carried out in similar fashion to PET with the patient fasting for at least 4 hours before scan so that they are normoglycemic at time of the study. The radiopharmaceutical is ¹⁸F-2-fluoro-2-deoxy-D-glucose (¹⁸F-FDG), the tracer for glucose metabolism. ¹⁸F-FDG is taken up into the cell and phosphorylated but cannot be metabolized as glucose-6-phosphate and instead is trapped within cells using high rates of glucose. The patient receives the ¹⁸F-FDG, then a CT scan followed by the capture of the PET images within 45-60 minutes of injection of the radiotracer. The PET and CT images are fused and both PET and PET-CT images are analyzed. The accuracy of lymph node staging in EAC has increased from 78% with PET alone to 83% with fused PET-CT.⁷⁸ The authors of this study found the staging accuracy increased to 95% when they included the diameter of the primary tumor. In a meta-analysis of 12 studies, PET-CT had a sensitivity and specificity of 55% to 62% and 76% to 96%, respectively, for nodal staging; however, the authors concluded that the accuracy was no better than PET alone.⁸⁰ Manabe and colleagues supported some of these findings when they found that PET-CT has a sensitivity range of 29% to 53% for nodal metastases in thoracic SCCs, but the specificity of the study was 90% in regional thoracic nodes.⁸¹ They also found that, as is seen for some primary lung cancers, a low standard uptake value (SUV) of the primary tumor correlated with limited detection of nodal metastases because of low avidity for the radiopharmaceutical tracer.

PET-CT is the standard test for detecting stage IV disease. In a diagnostic imaging study from M. D.

Anderson Cancer Center, PET-CT was used to detect distant metastases in 22% of esophageal cancer patients undergoing initial staging.⁸² The most common sites of metastases were liver (10%), bone (9%), lung (9%), adrenal glands (2%), and peritoneum (1.4%). In addition, "atypical" metastases were found in the skeletal muscle, brain, and thyroid in 0.3% to 1.7% of the patients. One patient (0.5%) was found to have a synchronous colon cancer after colonoscopy for focal uptake by PET-CT. Although some authors have suggested it is not ethically possible to always confirm histologically metastatic disease,⁷⁷ the counterargument is that it is ethically right to proceed with a biopsy if possible and if potentially curative options are available.

Patients who respond to chemotherapy or chemoradiation therapy have a better prognosis after surgical resection,^{13,15,83-86} and some groups have suggested only the complete responders have survival benefit.⁸⁷ Complete pathologic response occurs in approximately 25% of cases.^{79,88}

Interval Staging

What is the role of a PET scan in assessing response to the neoadjuvant treatment? Historically an interval PET or PET-CT scan was done after two cycles of chemotherapy⁸⁸ to select out the responders and the nonresponders. The Metabolic response evaluation for Individualization of neoadjuvant Chemotherapy in esophageal and esophagogastric adenocarcinoma (MUNICON) I and II trials investigated locally advanced distal esophageal and GEJ adenocarcinomas, in which interval metabolic response evaluation was used to classify patients as nonresponders or responders.^{89,90} In the MUNICON I trial, responders were deemed those who had a greater than 35% decrease in the SUV of the primary tumor after 2 weeks of induction chemotherapy. Nonresponders went to surgery and had a worse median overall survival of 25.8 months compared with the responders, who received a complete course of neoadjuvant chemotherapy. In MUNICON II, PET nonresponders received neoadjuvant chemoradiation resulting in an increased histopathologic response but still with a significantly lower 2-year overall survival.⁹⁰ As based on the MUNICON II trial,⁹¹ this approach is helpful for patients treated with neoadjuvant chemotherapy.

Because the standard of care, since the CROSS trial particularly, has become neoadjuvant concurrent chemoradiation, interval staging with PET-CT is not feasible. In MUNICON II, Lordick summarized that interval staging is less common as most patients are treated with neoadjuvant chemoradiation and the radiation can show misleading persistently positive disease with little response.

Restaging

A metabolic response by PET or PET-CT scan is increasingly being shown to correlate with histologic response to induction therapy with a sensitivity of 89%.^{91,92} In one study of 37 patients with GEJ adenocarcinomas (98% clinical stage T3Nx, 2% T4Nx), those with a significant

decrease in SUV also were able to undergo complete surgical resection.⁹¹ In addition, a significant decrease from maximum SUV on repeat PET images after induction therapy predicts a lower likelihood of disease recurrence⁹¹ and improved disease-free and overall survival.^{79,91-94} The optimal timing of the repeat PET-CT after neoadjuvant chemotherapy or chemoradiation therapy is typically 3 to 4 weeks after completion of treatment. Metastatic disease is identified in 8% to 17% in posttreatment PET-CT.^{79,88,95} Additional distant metastases can be found intraoperatively, in an additional 2% to 6% of patients,^{79,88} and in one series 29% of patients had pathologic N1 nodes despite a negative PET-CT before esophagectomy.⁸⁸

An interesting aspect of restaging with PET-CT scans is the potential prognostic information from the decrease in SUV as was suggested initially by Downey et al, who stratified 17 patients after induction therapy into those with a greater or less than 60% change in SUV pre- and post-chemoradiation.⁹³ Of the eight surgically resected patients who had a greater than 60% decrease in SUV peritreatment, 67% were disease-free at 2 years postoperatively. The 2-year overall survival rate difference was 89% versus 63% for the two groups with the 60% SUV cutoff. Other studies support using a relative decrease in SUV as a predictor of histologic response to induction chemotherapy, and the sensitivity from Roedl et al was 86% for identifying responders.⁷⁰ The correlation of change in primary tumor SUV and histologic response to chemoradiation is controversial though.^{79,88} In a set of 55 patients who underwent esophagectomy, PET-CT had only a 39% positive predictive value for differentiating patients with a pathologic response.⁸⁸ In another study the positive predictive value of PET for determining pathologic complete response was only 50%.⁷⁹ The optimal cutoff point of what is considered significant is not known. Some groups use higher than 35% for a sensitivity and specificity of 75%, and a greater than 45% decrease in SUV for a specificity of 86%,⁹¹ while greater than 60% was used for predicting improved survival. Finally, the Massachusetts General group concluded in their 47 patients with esophageal or GEJ cancers that decrease in tumor length as assessed by PET-CT was a better predictor of treatment response than was change in SUV.⁷⁰

The standard interval for the restaging PET-CT after completion of neoadjuvant chemotherapy or chemoradiation therapy is about 21 to 40 days.^{79,88} At most institutions it is not yet standard to forego an esophagectomy in patients without a significant decrease in SUV of the primary tumor.⁸⁸ Although it is not the standard to repeat the EUS, the M. D. Anderson group gave it a positive predictive value of 88% for evaluating tumor response to neoadjuvant therapy.⁸⁸ Also they have found that adding PET-CT to a postinduction repeat endoscopy improved significantly the ability to detect residual tumor compared with repeat endoscopy alone.⁹⁶

Although change in SUV on pretreatment and posttreatment PET-CT has prognostic significance, the primary role for the postinduction PET-CT is to rule out metastatic disease that would preclude the patient from benefitting from a surgical resection.

SURGICAL STAGING

What is the role of staging the newly diagnosed esophageal cancer patient surgically? That question was examined by a few groups and then the feasibility evaluated in a multicenter trial led by Krasna.⁹⁷ Early results of surgical staging for esophageal cancer entered the literature in 1995, when Krasna et al reported the CALGB pilot study findings of video-assisted thoracoscopic surgery (VATS) staging.^{98,99} The three institutions involved concluded that VATS staging of patients with thoracic esophageal cancer was feasible in 95% of patients enrolled and that 88% of the patients undergoing esophagectomy with confirmatory pathologic stage were correctly staged. Then Luketich et al and Bonavina et al separately reported the use of laparoscopy.^{100,101} In the study by Bonavina and colleagues, 50 patients with distal EAC or SCC underwent CT scan, EUS, and laparoscopy. The investigators concluded that laparoscopy was safe, was quick (mean time 20 minutes), and changed the therapeutic approach in 10% of patients.¹⁰¹ Luketich and colleagues at the same time published results of minimally invasive staging of 26 patients with EAC (92%) or SCC and compared laparoscopic/right VATS staging to EUS staging. They concluded that surgical staging improved the accuracy of lymph node staging by 16%.¹⁰⁰

Krasna led the CALGB 9380 prospective trial looking at the feasibility of surgical staging with laparoscopy and right VATS and found that the approach was feasible and that the number of positive lymph nodes doubled when compared to those detected by less invasive staging modalities.⁹⁷ An unanswered question, as it was not an endpoint of the study, is what is the cost-effectiveness of surgical staging? Since these earlier studies were carried out, PET-CT and EUS techniques have improved staging enough to conclude that surgical staging is not considered the standard of care mostly because the added costs and patient morbidity do not outweigh the small potential benefit. Given the controversy of managing cT2N0 patients, however, perhaps there may be a role for surgical staging of this subset of patients as minimally invasive surgical staging is superior to EUS staging alone for assessing N status.¹⁰⁰

BRAIN IMAGING

Brain metastases from esophageal cancer are rare. Brain metastases were detected at initial diagnosis of esophagus cancer in 1.7% to 5% of patients in large series of patients with adenocarcinoma or SCC.¹⁰²⁻¹⁰⁴ Brain metastases in a recent series of 27 patients with esophageal cancer (82% adenocarcinoma) was associated with a median survival of 3.8 months.¹⁰⁴ After potentially curative esophagectomy, intracranial metastases occur in an estimated 2% of patients in multiple series.¹⁰⁵ Esophageal metastases are typically to liver, lung, bone, and, in rare cases, adrenal gland and kidney. In a series of 27 (1.7% of all esophagus cancer patients) patients with esophageal brain metastases over an 8-year period, only one presented with the brain metastasis as the index sign of his esophagus cancer.¹⁰⁵ Of

916 patients presenting for whole brain irradiation for brain metastases, only 6% originated from the gastrointestinal malignancies and none from the esophagus.¹⁰⁶ In a high-volume esophageal cancer center, however, 28% of patients presenting for stereotactic radiosurgery for gastrointestinal tract brain metastases had esophageal primaries.¹⁰⁷ Most reports of patients developing brain metastases identify stage IV disease after potentially curative resection.¹⁰⁸⁻¹¹⁰ In one Japanese study of 803 patients treated for brain metastases, 2% originated from primary esophageal cancer (52% SCC).¹⁰⁹ The authors recommended whole brain irradiation to improve median survival from 18 to 66 months in patients who underwent metastasectomy or stereotactic radiosurgery.¹⁰⁹ Other Japanese groups have found the brain as sole site of recurrent disease in 2% of patients and a median survival of 17 months post craniotomy and resection.^{108,111}

Currently the indications for a brain scan (either CT or MRI) for a patient initially presenting with esophagus cancer are similar as for other patients with solid tumors, which would be new-onset headaches or neurologic complaints, including ataxia, paresthesias, or weakness. As routine CT scanning of the brain was not cost effective at the University of Michigan, the authors did note that risk factors for brain metastases included large, locally and regionally advanced primary cancers.¹⁰²

What about restage scanning after neoadjuvant treatment and before potential resection? There is evidence from the Cleveland Clinic that there is a higher occurrence of brain metastases in esophageal cancer patients treated with neoadjuvant or adjuvant chemotherapy and that the adjuvant treatment itself may facilitate development of brain metastases.¹⁰⁵ The significance of this concept is that we may not yet know the role of routine brain MRI or CT in patients treated with neoadjuvant therapy prior to esophagectomy. Although the incidence is low and guidelines of neuropathy or headache should dictate evaluation for brain metastases, in standard practice most patients get a brain MRI before a potentially morbid esophagectomy.

MOLECULAR STAGING: PROGNOSTIC BIOMARKERS

Clinical staging techniques have advanced with the addition of EMR for Tis and T1a tumors; however, solutions are still needed to address controversial areas such as the cT2N0 tumors. Because of weaknesses of EUS with inaccurate T staging and inadequate N sensitivity, initial treatment for these patients is either an esophagectomy or neoadjuvant therapy, most commonly as chemoradiation. Certain tumor characteristics in a cT2N0 patient such as poor differentiation or lymphovascular invasion may sway an esophagectomy-inclined tumor board to refer a patient for induction therapy.

The literature on molecular profiling of esophageal cancers is slowly growing. Some early prognostic predictors of survival include distinct microRNA (miRNA) profiles¹¹² and gene expression variants of cyclin D1 gene expression.¹¹³ Given the 30% to 40% overall response rate of esophageal cancers to induction chemotherapy,

molecular analysis of esophageal tumors could allow for targeted, smart induction therapy. Pretreatment gene expression profiles to predict response to chemoradiation therapy has been shown to be significant in several studies in both SCC and EAC,¹¹⁴⁻¹¹⁶ and there's increasing evidence that gene expression profiling of tumors may help predict an individual patient's response to chemotherapy.¹¹⁷ Microarray analysis of gene expression profiles also should help identify targeted therapy tailored to an individual patient's tumor.^{118,119} Although pathologic response to chemoradiation has been associated with molecular subtypes of endoscopic biopsies in preliminary studies,¹¹⁵ the significant genes and proteins have not been validated through prospective studies.

Molecular studies to date on gene expression profiling as a prognostic marker and not a predictive marker of treatment response include integrated array comparative genomic hybridization (a-CGH) and gene expression to find a prognostic signature based on aberrant regions of interest and worse patient survival.¹²⁰ Chromosomal aberrations correlated with patient survival in a pathology study by Pasello and coworkers,¹²¹ in which multiplex ligation-dependent probe amplification (MLPA) technique was used on 33 resected EACs. With this technique, which is robustly similar to a-CGH, the total number of genomic aberrations correlated with significantly worse survival. Applying these techniques to primary tumors may allow stratification of early-stage patients to induction therapy.

Another approach for early-stage, cT1/2N0 tumors is to use gene signature profiling to classify the tumors as being more likely to have nodal involvement. Although such results have not been reported, there are several gene and protein signature studies that support incorporating molecular staging into the current TNM stage and again supporting stratification to induction or post-resection therapy. A four-gene signature was reported by the Esophageal Cancer Clinical And Molecular Stratification (OCCAMS) study group, to correlate with survival in node-positive patients and was an independent prognostic factor over TNM staging alone.¹²² More recently the same investigators collaborated with esophageal centers and found that a three-gene immunohistochemical panel of EGFR, TRIM44, and SIRT2 portended a worse survival.¹²³ Expression of miRNA, the ubiquitous regulators of gene translation, have also been shown in several studies to associate with survival in both adenocarcinoma and SCC.¹²⁴⁻¹²⁶

We can begin however to envision a future staging system of genomic profiling esophageal cancers where the easily accessible endoscopic biopsies of esophageal cancer would allow for molecular staging. Integrated genetic profiling of primary tumors includes gene and protein expression and, with validation trials, molecular staging could be complementary to current staging modalities with their inherent weaknesses. Therapeutic stratification of patients would include endoscopic mucosal resectional therapy, targeted induction therapy, traditional neoadjuvant therapy, minimally invasive esophagectomy, en bloc esophagectomy, palliative therapy, definitive chemoradiation therapy or perhaps no therapy.

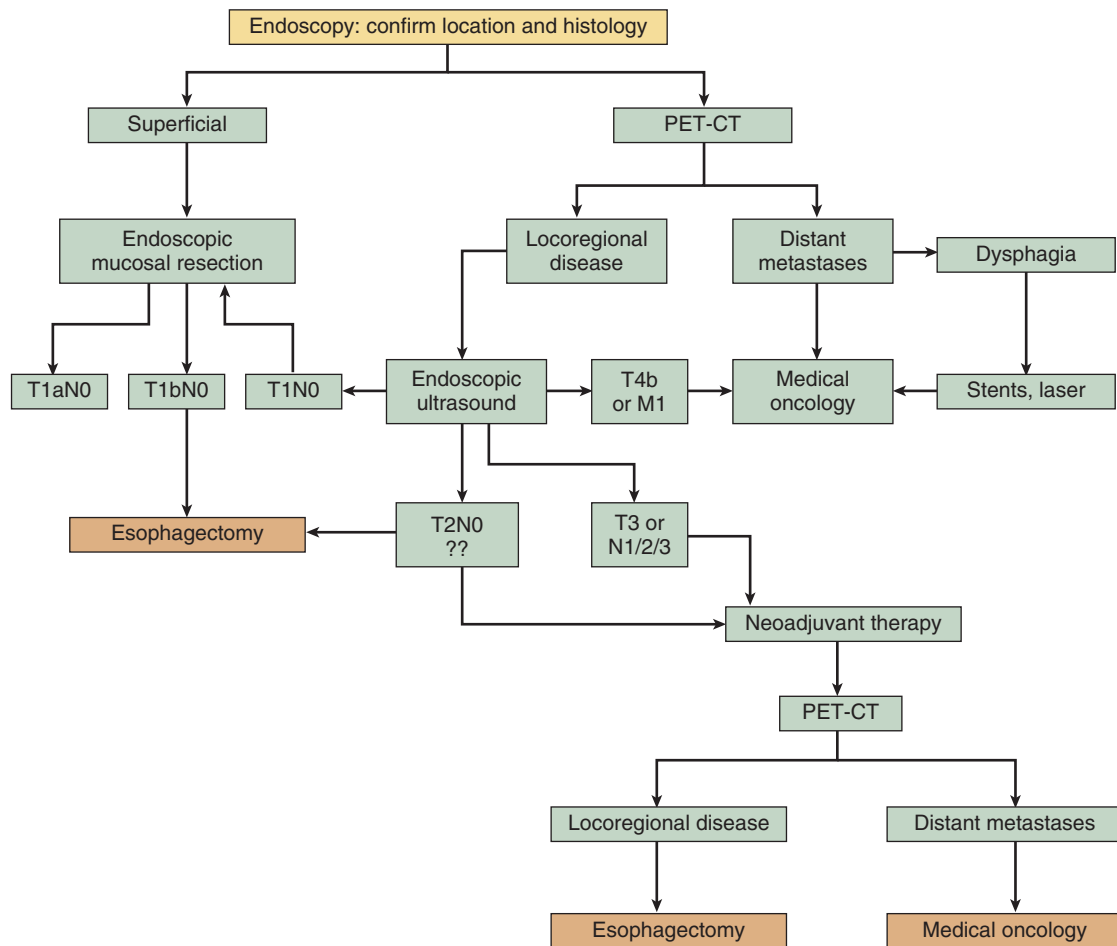


FIGURE 37-1 ■ An algorithm for staging a thoracic esophageal cancer patient. Metastatic disease must always be confirmed by pathologic evaluation of the tissue in question. *PET-CT*, Positron emission tomography-computed tomography.

SUMMARY

The incidence of EAC is on the rise in the United States, and treatment and staging modalities are evolving to translate into a much needed improvement in survival rates. Appropriate staging of the patient with a newly diagnosed esophageal cancer will translate into appropriate triage of patients for esophagectomy, thus contributing to best outcomes in survival rates after resection. Complete clinical staging with EUS, PET-CT, and, in early cancer cases, EMR, and discussion of the results at a multidisciplinary team meeting improve patient selection for induction therapy and esophagectomy.³⁹ The staging algorithm outlined in Figure 37-1 applies to most patients with thoracic EAC and SCC under the recently revised TNM staging system.

Molecular staging of tumors is still not ready for inclusion in the staging system; however, we are getting closer. Our energy should be directed at improving esophageal biomarkers for prognostic and therapeutic management. We look forward to advances in this area so we may optimize clinical staging and targeted treatment to improve patient survival.

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ESOPHAGEAL RESECTION AND REPLACEMENT

Cynthia S. Chin • Philip A. Linden • Ali Al-Dameh • Scott J. Swanson

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SUMMARY

The prevalence of esophageal adenocarcinoma has risen dramatically over the past three decades. Esophageal cancer is the eighth most common cancer worldwide, and more than 480,000 new cases were diagnosed in 2008. The documented increase is approximately six- to seven-fold,¹ with adenocarcinoma now contributing to approximately 80% of the esophageal cancer surgical workload in many surgical units. This increase is unprecedented

and has occurred at a faster rate than for any other cancer.²

Treatment of this disease continues to represent a formidable challenge. According to American Cancer Society's *Cancer Facts & Figures, 2013*, the overall 5-year survival rate for all patients is 19%. Despite the common practice of incorporating chemotherapy or chemoradiotherapy into the treatment paradigm, surgical resection

remains the cornerstone of most treatment protocols for early-stage and locally advanced disease.³ Today patients treated with an esophagectomy have a 5-year survival rate close to 35%.⁴

HISTORY OF ESOPHAGEAL RESECTION

The first esophageal resection was performed more than 125 years ago, yet it remains one of the most formidable operations, carrying the highest morbidity rate of any commonly performed resection. The perioperative mortality rate has decreased from 40% to less than 3% in selected academic centers, largely because of advances in surgical and anesthetic technique, intensive care, and management of complications. The rate of morbidity for this surgery has not decreased as dramatically as has the rate for mortality. With average mortality rates at 10% and complication rates exceeding 50%, careful selection of patients, thoughtful surgical planning, meticulous technique, and timely management of complications are essential to ensure good outcome for the patient.

In general, the principle objective for the surgeon is to balance oncologic principles of clear surgical margins and adequacy of lymphadenectomy with the risks associated with the planned operative approach on a case-by-case basis. Patient and tumor-related characteristics should play a pivotal role in the surgical decision making rather than individual or institutional practice patterns.

The esophageal surgeon must be familiar with the anatomy of the neck, chest, and abdomen and be skilled in surgery of the entire alimentary tract to provide complete care of the patient requiring esophageal resection. Only with this knowledge can the surgeon fit the operation to the patient, not the patient to the operation. These issues are detailed in this chapter.

Ivor Lewis, writing in 1946, is credited with popularizing transthoracic resection of the esophagus. He initially performed the operation in two stages, first mobilizing the stomach through a laparotomy and second, several days later, resecting the esophagus and performing an intrathoracic anastomosis through a right thoracotomy. Lewis showed a sophisticated understanding of the challenges involved in esophageal surgery when he stated that “the oesophagus is a difficult surgical field for three reasons: its inaccessibility; its lack of a serous coat, and its enclosure in structures where infection is especially dangerous and rapid.”⁵ The Ivor Lewis and transhiatal approaches are the most commonly used techniques of esophageal resection today. In 1962, McKeown described a three-stage esophagectomy, with the addition of a cervical incision and anastomosis to allow better margins for proximal tumors.⁶ It is now called the three-hole or tri-incisional esophagectomy.

Open esophagectomy has up to 60% reported morbidity.^{7,8} For this reason, several approaches have been supplemented with thoracoscopic or laparoscopic modifications. Since Cuschieri and colleagues first introduced the concept of a minimally invasive approach to esophagectomy in 1992,⁹ there have been numerous descriptions in the literature.¹⁰⁻¹⁵

TECHNIQUES OF ESOPHAGEAL RESECTION

Modified McKeown or Tri-incisional Technique

Indications

The tri-incisional esophagectomy (modified McKeown) is a versatile technique that can be used for tumors at any level and for various benign and malignant conditions. It combines the advantages of the Ivor Lewis approach with those of a transhiatal technique. These include complete lymph node dissection in the chest, direct visualization of the intrathoracic dissection, avoidance of an intrathoracic anastomosis, maximal margins, and diminution of chances for postoperative gastroesophageal reflux disease. It is especially useful for tumors of the mid and upper esophagus and for tumors arising in a long Barrett segment where almost total excision of the esophagus is required.

Contraindications

Fusion of the right pleural space or inability to support ventilation with the left lung would make an approach through a right thoracotomy difficult. Relative contraindications include small gastric conduits secondary to tumor or limited vascular supply. Patients with tumor extending onto the stomach require more gastric resection than do those with tumor isolated to the esophagus. These patients are most suited for an Ivor Lewis or a jejunal reconstruction if there is not enough stomach.

Preparation

A detailed history and physical examination are necessary to evaluate for coexistent comorbid disease. Computed tomography and positron emission tomography of the chest and abdomen should be performed to evaluate for metastatic disease, anatomic abnormalities, and location of the tumor adjacent to vital structures. Pulmonary function tests should be obtained. Poor forced expiratory volume in 1 second (FEV₁) is not a contraindication to a muscle-sparing limited thoracotomy, although increased risk of pulmonary complications may be expected. Computed tomography and positron emission tomography of the head are useful in ruling out metastatic disease. Preoperative bowel preparation is generally done in the rare and unfortunate case in which there needs to be a change in conduit.

Technique

Esophagogastroduodenoscopy is performed to identify the location of the tumor and to rule out disease of the stomach or duodenum. Retroflexion of the esophagogastroduodenoscopy is important for proper evaluation of the gastroesophageal junction. The carina is at the level of 25 cm from the incisor on esophagogastroduodenoscopy. Tumors in this area should be carefully evaluated by bronchoscopy for tumor invasion of the trachea. A double-lumen tube is placed, and the patient is positioned

in a left lateral decubitus position. A right posterolateral thoracotomy incision is made wide enough to insert the surgeon's hand (approximately 10 cm). A portion of the latissimus is divided; the serratus is spared (Fig. 38-1). Division of the intercostal muscle from the vertebral bodies posteriorly to the mammary vessels anteriorly usually provides enough working space without division of a rib. The chest is entered through the fifth or sixth interspace, depending on the location of the tumor.

The lung is retracted anteriorly, and the inferior pulmonary ligament is divided with use of cautery. In a region away from the tumor and away from any scarring, the pleura overlying the esophagus is incised anteriorly and posteriorly and the esophagus is surrounded with a Penrose drain. With traction on the Penrose drain, the esophagus is retracted both anteriorly and posteriorly and is dissected by electrocautery, including all adjacent lymph node tissue. Arterial branches supplying the esophagus from the aorta are clipped before being divided. Any cautery performed in the region of the

carina must be at low settings to avoid thermal injury to the trachea. The azygos vein is typically divided. At the level of the azygos vein, the vagus nerves are identified on the esophagus and divided between clips. Division of the vagal nerve is important because an intact vagus nerve can lead to a traction injury of the recurrent laryngeal nerve. Further cranial dissection proceeds with the vagus nerves away from the esophagus to avoid recurrent nerve injury. Blunt dissection is useful high in the right chest (Fig. 38-2). Most dissection should be in the posterior plane to avoid injury to the recurrent laryngeal nerve, which is in the groove between the esophagus and trachea. A knotted Penrose drain is placed around the cervical esophagus and pushed into the posterior neck for retrieval during the cervical portion of the case (Fig. 38-3). This Penrose drain, positioned inside the vagus nerves relative to the esophagus, permits isolation of the cervical esophagus without traction on the recurrent nerve. A sponge is packed high in the chest to assist in hemostasis and is removed before closure. The lower portion of the esophagus is encircled with a second Penrose drain and the remaining distal esophagus is dissected, including in the specimen all tissue lateral to the pericardium and medial to the aorta and spine.

If the tumor is near the gastroesophageal junction, a 2-cm rim of diaphragm is resected with the esophagus (Fig. 38-4). The Penrose drain is knotted and left in the abdomen for retrieval during the abdominal portion of the operation. Mass ligation of the thoracic duct at the level of the hiatus is performed by encircling all tissue between the aorta and spine with a 0 silk suture. The chest is inspected for hemostasis, the sponge previously

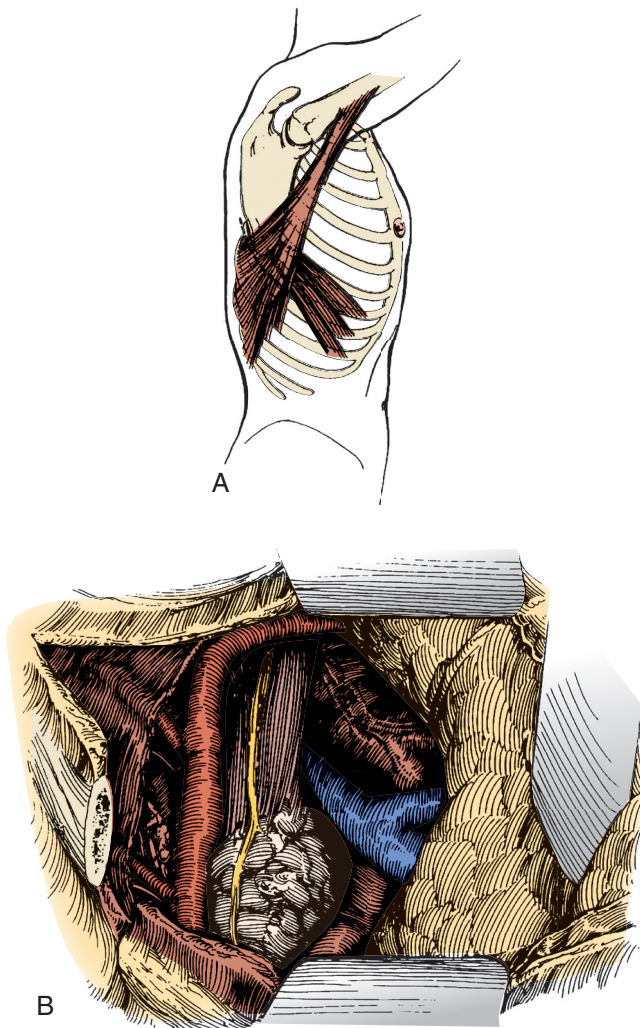


FIGURE 38-1 ■ **A**, A limited right posterolateral thoracotomy is performed, dividing the latissimus. **B**, View of the esophagus with tumor through the incision. (From Swanson S, Grondin S, Sugarbaker D: Total esophagectomy: the Brigham and Women's Hospital approach. *Oper Tech Thorac Cardiovasc Surg* 4:197-209, 1999.)

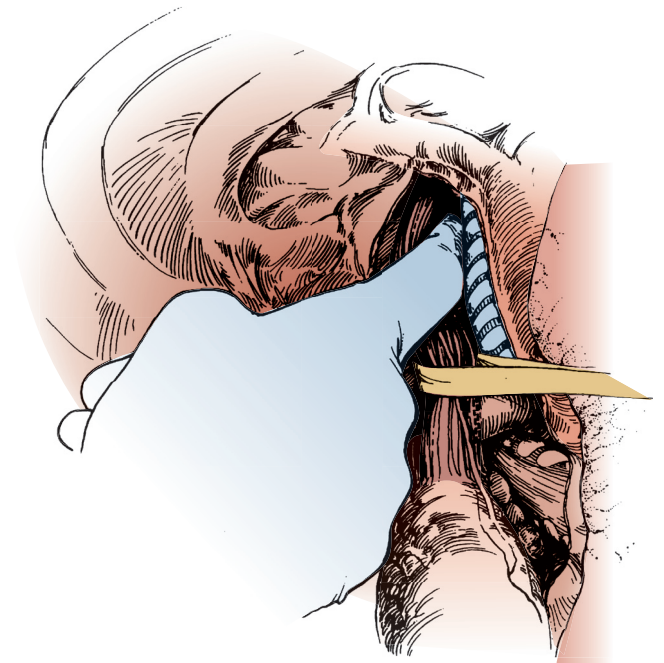


FIGURE 38-2 ■ Blunt finger dissection close to the esophagus is used to free the esophagus up into the neck. (From Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885-910.)

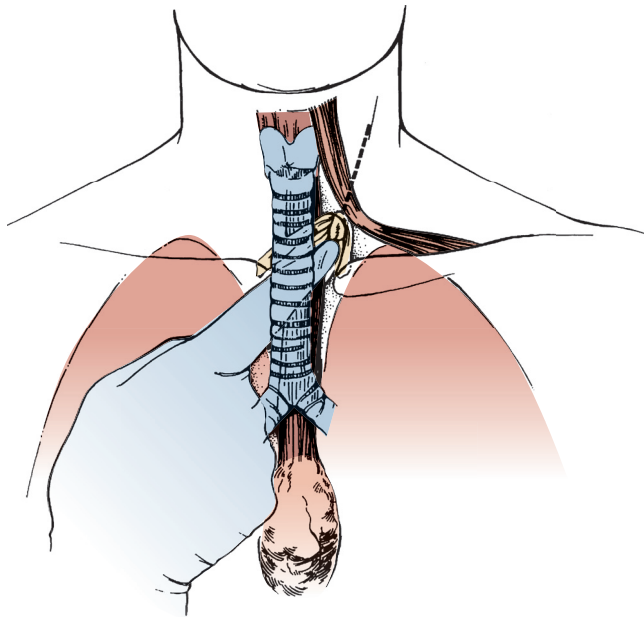


FIGURE 38-3 ■ A knotted Penrose drain is placed into the left side of the neck for later retrieval during the cervical dissection. This helps ensure isolation of the esophagus without injury to the recurrent nerves. (From Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885–910.)

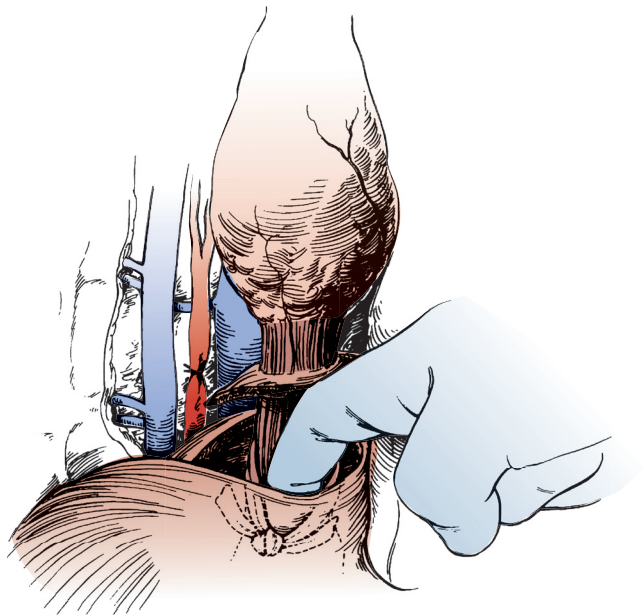


FIGURE 38-4 ■ A rim of diaphragm is incorporated into the specimen for all gastroesophageal junction tumors. A knotted Penrose drain is placed into the abdomen to aid dissection of the esophagus at the gastroesophageal junction during the abdominal phase of the operation. (From Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885–910.)

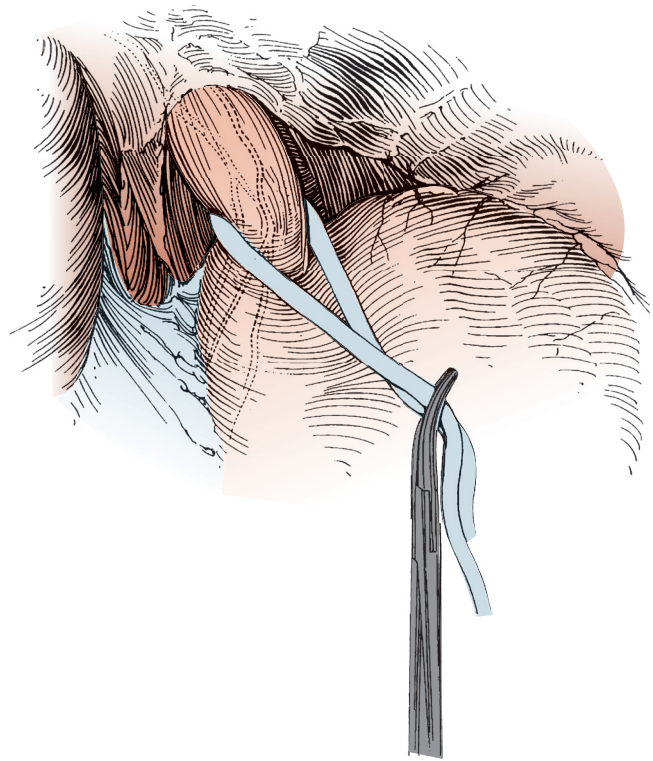


FIGURE 38-5 ■ The phrenoesophageal ligament is divided fully after retrieval of the Penrose drain. (From Swanson S, Grondin S, Sugarbaker D: Total esophagectomy: the Brigham and Women's Hospital approach. *Oper Tech Thorac Cardiovasc Surg* 4:197–209, 1999.)

placed is removed, and a 28 Fr straight chest tube is inserted through a separate stab incision and directed to the apex of the chest. The ribs are approximated with interrupted #2 Vicryl sutures. The latissimus is closed with running 0 Vicryl suture. The subdermal fascia is closed with a running 2-0 Vicryl suture. The skin is closed with staples or suture. The patient is repositioned in the supine position and is reintubated with a single-lumen tube. A transverse roll is placed under the scapula, and the head is turned 45 degrees to the right. An upper midline laparotomy is performed from the umbilicus to the junction of the costal margin and the left side of the xiphoid; the xiphoid is occasionally resected for better visualization. The abdomen is explored for metastatic disease, which includes inspection of the liver, omentum, and peritoneal surfaces. The left lobe of the liver is mobilized by dividing the triangular ligament. Close to the triangular ligament are large diaphragmatic veins that should be avoided during this dissection. The Penrose drain surrounding the gastroesophageal junction is grasped, and the remaining phrenoesophageal ligament is divided (Fig. 38-5). The gastroepiploic pulse is palpated. At a point 2 cm away from the gastroepiploic artery on the greater curvature of the stomach, the lesser sac is entered. Dissection along the greater curvature of the stomach toward the spleen proceeds with division of vascular branches by use of double clips, silk ties, or the harmonic scalpel. Short gastric vessels are taken in identical fashion. Displacement of the spleen anteriorly by placement of lap pads behind the spleen may aid in

dissection of the short gastric vessels. Once the short gastric arteries are divided, additional dissection toward the pylorus is performed. The gastroduodenal artery travels behind the pylorus before branching into the right gastric epiploic and superior pancreaticoduodenal arteries. The duodenum is mobilized from its retroperitoneum connections by a Kocher maneuver. The duodenum is adequately mobilized when the pylorus can reach the esophageal hiatus.

The stomach is then lifted anteriorly, and any adhesions between the stomach and pancreas are divided with electrocautery. The left gastric artery is identified and skeletonized, sweeping lymph node tissue onto the specimen. With a 30-mm vascular stapler, the base of the left gastric artery is clamped. A continued strong pulse in the gastroepiploic artery is confirmed, and the left gastric artery is divided (Fig. 38-6). The gastrohepatic ligament is divided by a combination of cautery and the stapler. Either a pyloromyotomy or a pyloroplasty may be performed. If a pyloroplasty is performed, it should be a single layer with interrupted 3-0 silk sutures, carefully incorporating mucosa and muscular wall.

Attention is then turned to the neck, and a 6-cm incision is made from the sternal notch along the anterior border of the sternocleidomastoid muscle. The platysma is divided, and dissection proceeds between the carotid sheath laterally and the strap muscles medially. The omohyoid muscle may be divided. The knot of the Penrose drain should be palpable on the spine. The Penrose drain is grasped, and the esophagus is gently mobilized. The nasogastric tube is partially withdrawn, and the cervical esophagus is divided with a 75-mm linear stapler (Fig. 38-7). A #2 silk suture ligature is fastened to the distal end of the divided esophagus, and the specimen is drawn

into the abdomen with the attached silk suture. The cervical end of the silk suture is fastened to a clamp.

A gastric tube is fashioned by resecting the gastroesophageal junction and the lesser curve of the stomach with a series of 75-mm-thick tissue staples (Fig. 38-8). A narrow gastric tube aids in gastric emptying. A diameter

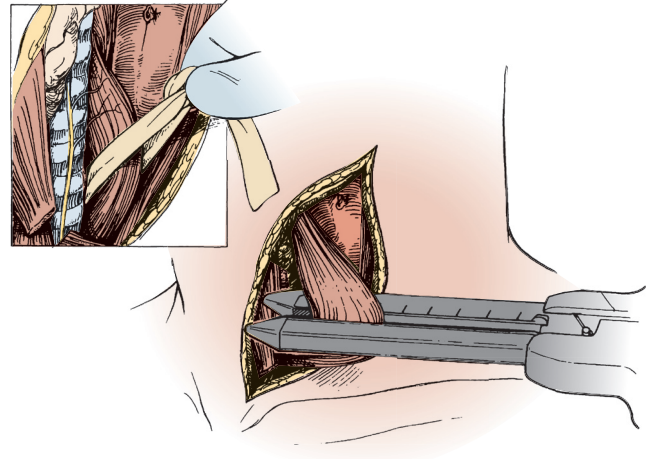


FIGURE 38-7 ■ Retrieval of the Penrose drain placed around the esophagus inside the recurrent nerves during chest dissection. This aids in the prevention of recurrent nerve injury. The esophagus is divided after removal of the nasogastric tube. (From Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885-910.)

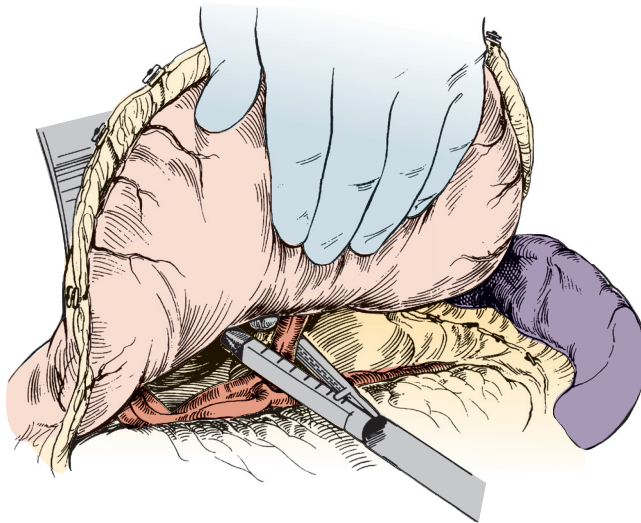


FIGURE 38-6 ■ After complete mobilization of the greater curvature of the stomach and division of the gastrohepatic ligament, the left gastric vessels are identified. An endoscopic vascular stapler is used to divide these vessels, with care taken not to impinge on the celiac axis. (From Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885-910.)

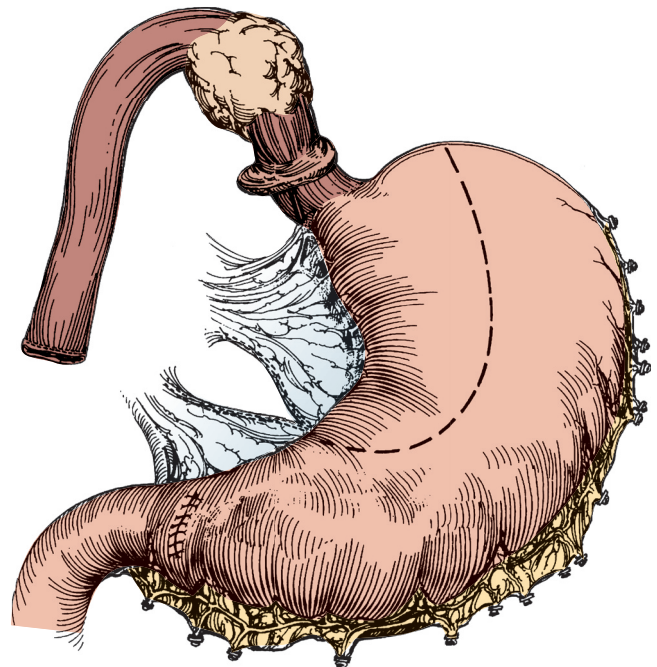


FIGURE 38-8 ■ The gastric tube is created after complete dissection of the stomach and after the cervical esophagus is divided and brought into the abdomen. The gastric tube should be kept at least 5 cm in diameter. This also allows longer margins for gastroesophageal junction tumors. A pyloroplasty has been performed. (From Swanson S, Grondin S, Sugarbaker D: Total esophagectomy: the Brigham and Women's Hospital approach. *Oper Tech Thorac Cardiovasc Surg* 4:197-209, 1999.)

of less than 6 cm, however, can compromise venous and arterial blood supply. The line of division ends at a point on the lesser curve near the crow's-feet of veins. At this point along the lesser curve, the right gastric artery and associated tissue can be divided to maximize conduit length.

With the specimen removed, a final check for hemostasis is made in the bed of the stomach and spleen. Before the conduit is pulled into the neck, the esophageal hiatus should be dilated to four fingers. The gastric conduit may be pulled to the neck in relatively atraumatic fashion by the use of an endoscopic camera bag attached to a Foley catheter. The heavy silk tie that traverses the mediastinum from the neck is tied to the valved end of a 30-cm three-way Foley urinary catheter.⁶ The endoscopic bag is secured to the Foley balloon. The conduit is placed in the bag, and the valved end is drawn into the neck (Fig. 38-9). The assistant must guide the conduit through the hiatus and up the lower mediastinum, ensuring that there is no torsion. The bag is cut away from the conduit in the neck, and the conduit is grasped with a Babcock instrument. The pylorus should sit at the hiatus. A side-to-side, functional end-to-end stapled anastomosis may be performed. The anastomosis is created with a 75-mm linear stapler followed by a 30-mm endoscopic

stapler. Alternatively, the neck anastomosis can be hand sewn with interrupted circumferential full-thickness 3-0 silk sutures (Fig. 38-10). The nasogastric tube is advanced across the anastomosis and positioned just proximal to the pylorus before closure of the remaining anastomotic defect (Fig. 38-11). A drain is placed along the spine posterior to the anastomosis, and the platysma is run closed with 2-0 Vicryl sutures. The skin is closed with staples. A feeding tube is inserted in the jejunum at a point 40 cm distal to the ligament of Treitz. The abdominal fascia is closed with a running #2 monofilament suture, and the skin is closed with staples.

Ivor Lewis Esophagectomy

Indications

The indications are similar to those for a tri-incisional approach.

Contraindications

Tumors located in the upper third of the thoracic esophagus, above the carina, are better approached with resection of the cervical esophagus and anastomosis in the neck to ensure adequate margins. Long-segment Barrett esophagus with extension into the cervical esophagus is also a contraindication to an anastomosis in the right chest. A fused pleural space or severely compromised lung function should lead to reconsideration of a thoracotomy.

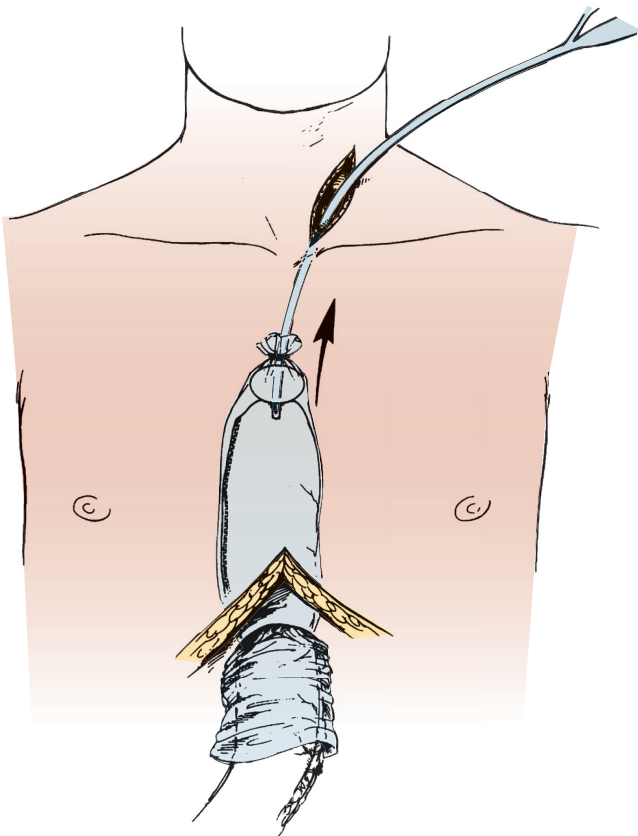


FIGURE 38-9 ■ An endoscopic camera bag is used as an atraumatic means of drawing the conduit into the neck for anastomosis. Suction is applied to the Foley catheter as it is pulled into the neck. (From Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885-910.)

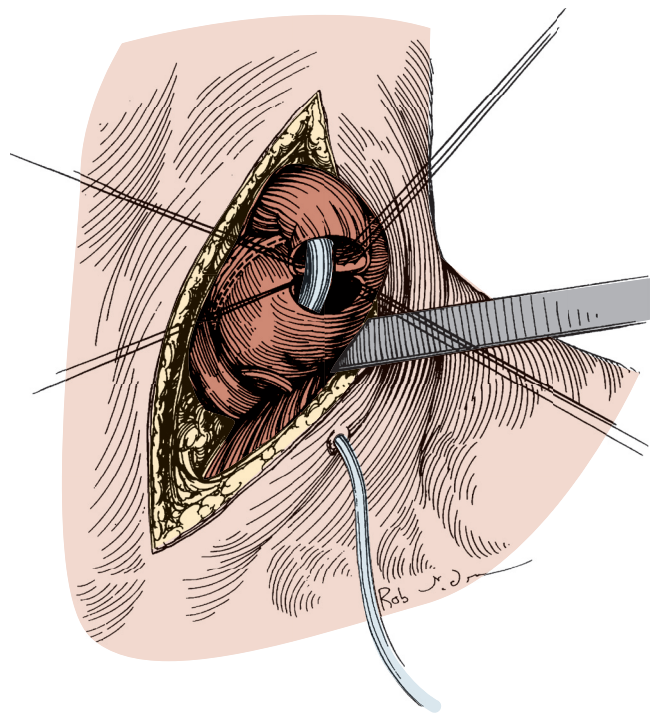


FIGURE 38-10 ■ The cervical anastomosis may be hand sewn with interrupted silk sutures over a nasogastric tube. (From Swanson S, Grondin S, Sugarbaker D: Total esophagectomy: the Brigham and Women's Hospital approach. *Oper Tech Thorac Cardiovasc Surg* 4:197-209, 1999.)

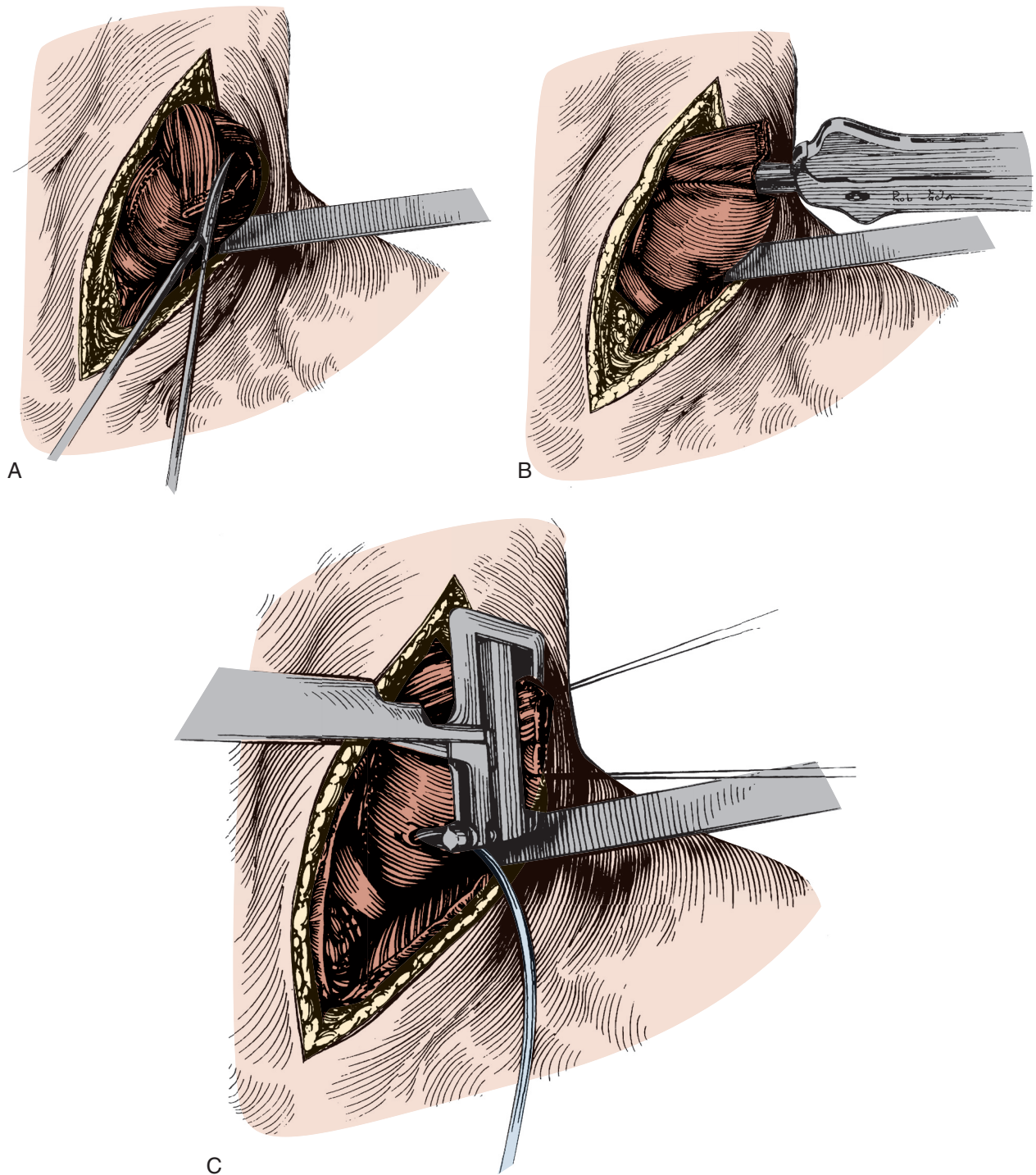


FIGURE 38-11 ■ **A**, A corner of the proximal esophageal staple line is trimmed, and an enterotomy is made in the proximal gastric conduit away from the staple line. **B**, A gastrointestinal anastomosis stapler is used to create the back wall of the cervical anastomosis. Additional length may be obtained with an additional fire of an endoscopic 30-mm stapler. **C**, The anterior wall of the anastomosis is closed with a thoracoabdominal stapler. In this illustration, a gastric drainage tube exits through the neck. These tubes can be used in place of a nasogastric tube and are more comfortable for the patient. (From Swanson S, Grondin S, Sugarbaker D: Total esophagectomy: the Brigham and Women's Hospital approach. *Oper Tech Thorac Cardiovasc Surg* 4:197-209, 1999.)

Technique

The patient is positioned supine. Preoperative bronchoscopy and esophagogastroduodenoscopy are performed. An upper midline incision is made extending from the umbilicus to the xiphoid. The abdominal portion of the

operation is identical to that described for a tri-incisional esophagectomy, with complete mobilization of the stomach, kocherization of the duodenum, pyloroplasty, construction of the gastric tube, and placement of a J tube. The conduit is advanced into the chest as far as possible before the abdomen is closed. After placement

of a double-lumen endotracheal tube, the patient is repositioned in the left lateral decubitus position, and a standard right posterolateral thoracotomy is performed. Entry into the chest is through the fourth or fifth interspace. The azygos vein is divided and the intrathoracic esophagus is dissected, including all adjacent areolar and lymphatic tissue. A margin of at least 5 cm and ideally 10 cm is desirable, and thus the anastomosis is usually performed high in the right chest. The esophagus is dissected free to a point only several centimeters above the proposed line of transection to preserve blood supply to the anastomosis. The esophagus is divided and the stomach is pulled up, and the gastric conduit is fashioned with a gastrointestinal anastomosis (GIA) stapler. Various techniques may be used to perform the anastomosis, including single-layer hand sewn, double-layer hand sewn, end-to-end stapled, and side-to-side functional end-to-end stapled.

With all techniques, wrapping of the anastomosis with omentum and passage of the nasogastric tube before completion of the final portion of the anastomosis are advised. A stapled anastomosis may be performed in a side-to-side, functional end-to-end manner with creation of the anastomosis by a GIA 75-mm or sequential 30-mm endoscopic stapler and closure of the defect with a thoracoabdominal (TA) 30-mm or 60-mm stapler. A similar technique involves lining up the gastric conduit and esophagus in a linear fashion and stapling the back wall of the anastomosis with a linear stapler or endostapler and sewing the front wall by either a one- or a two-layer technique. This type of approach is used in the neck as described by Orringer. The anastomosis can also be performed with an end-to-end anastomosis (EEA) stapler, although anastomoses created with EEA staplers smaller than 33 mm carry a significant risk of stricture.¹⁶ With the EEA stapler, passage of the nasogastric tube is, of course, performed after completion of the anastomosis.

If a hand-sewn anastomosis is to be performed, the proximal esophagus is divided with a knife after clamping the esophagus proximally with a noncrushing bowel clamp. A single-layer anastomosis is performed with interrupted 3-0 silk stitches with full-thickness bites of the mucosa and muscularis and careful approximation of tissues. Knots on the posterior row may be tied inside the

lumen (Fig. 38-12).¹⁷ A double-layer anastomosis was described by Churchill and Sweet in 1942.^{18,19} At a point at least 2 cm beyond the staple line, a 2-cm-diameter area of gastric serosa is scored. Underlying vessels are ligated with interrupted silk sutures. The posterior layer of the anastomosis is created with interrupted 3-0 silk stitches. An inner, full-thickness layer is performed with a fine 4-0 absorbable suture, either catgut or Monocryl, by a running Connell stitch to invert the mucosa. Before completion of the inner layer, the nasogastric tube is passed to the hiatus. An anterior outer layer is then performed with interrupted 3-0 silk. Omentum is used to wrap the anastomosis. The distal portion of the stomach is reduced into the abdomen to avoid excess redundancy of the stomach in the chest, which might impair conduit emptying. Stitches are placed anchoring the conduit to the diaphragmatic hiatus. Some surgeons use additional stitches anchoring the intrathoracic conduit to the pleura, although the effectiveness of these stitches is debated.

Transhiatal Esophagectomy

Indications

Some physicians believe that transhiatal esophagectomy is ideally suited for benign esophageal disease and possibly Barrett esophagus with high-grade dysplasia, for which complete lymphadenectomy may not be necessary. Other factors, such as poor pulmonary function (FEV_1 <800 mL or <35% predicted) and pleural symphysis, would favor a technique that avoids a thoracotomy.

Contraindications

Bulky tumors of the midthoracic esophagus are difficult to visualize from the transhiatal approach, and injury to adjacent structures may occur. Scarring after neoadjuvant treatment of esophageal tumors may also make the transhiatal approach difficult. The need to perform a complete lymphadenectomy is a contraindication to this approach.

The presence of severe coronary or valvular disease makes the episodic drops in blood pressure associated with blunt dissection behind the heart especially

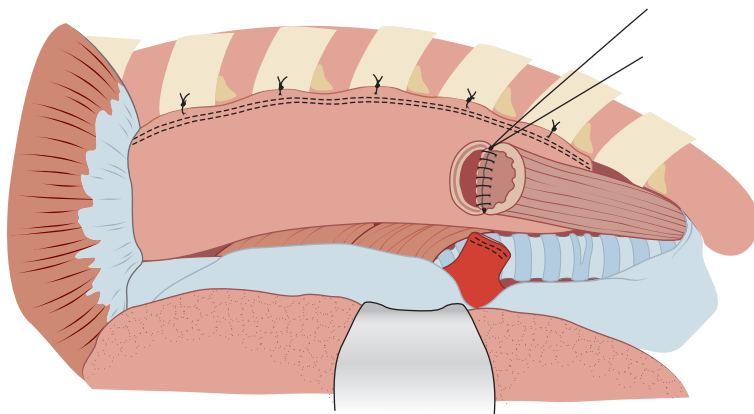


FIGURE 38-12 ■ The Ivor Lewis anastomosis is performed at the level of the azygos vein, in two layers, after creation of a circular enterotomy in the proximal conduit. The edges of the conduit are shown here tacked to the pleura, although it is debatable whether this effectively reduces tension on the anastomosis. (Adapted from Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885–910.)

treacherous. A transthoracic approach may be preferable in these cases.

Preparation

The preparation is identical to preparation for a trincisional esophagectomy.

Technique

Bronchoscopy and esophagogastroduodenoscopy are performed as previously described. The abdominal portion of the procedure is performed as described in the previous section. An upper hand retractor aids in raising the xiphoid and sternum for visualization of the mediastinum. The esophagophrenic attachments are divided with cautery, the gastroesophageal junction is separated from the crura, and the distal esophagus is encircled with a Penrose drain. The hiatus is dilated to allow entry of the surgeon's hand. Various hand-held malleable retractors may be used in dissection of the mediastinum through the hiatus. With the use of the Penrose drain to retract the lower esophagus, the lower esophagus is dissected through the hiatus. Arterial branches supplying the lower esophagus from the aorta are clipped under direct vision. With the fingertips against the esophagus, the esophagus is dissected off the vertebral plane bluntly into the upper chest. The palmar aspect of the fingertips is kept directly against the esophagus. Arteries supplying the esophagus branch approximately 1 cm away from the esophagus, and dissection close to the esophagus disrupts only the smaller arterial branches directly entering the esophagus. Close dissection of the esophagus also avoids injury to adjacent structures. A cervical incision is made along the lower border of the left sternocleidomastoid muscle. Dissection proceeds as described in the previous section with the exception that the esophagus must be identified and encircled from the neck. An approach from the left side of the neck aids in avoiding injury to the right recurrent laryngeal nerve, which is farther from the esophagus than the left recurrent nerve at this level. Dissection is kept immediately on the esophagus to avoid recurrent nerve injury. Metal retractors should not be placed near the tracheoesophageal groove. A Penrose drain is placed around the cervical esophagus.

Dissection caudally is performed with two fingers against the esophagus in the posterior plane. Depending on the length of the surgeon's fingers and the width of the abdominal surgeon's hand, it should be possible for the two hands to contact directly. A thin plane of tissue remains, which must be torn for the two hands to touch. Alternatively, a sponge stick can be advanced posteriorly from the neck to touch the dissecting hand from the abdomen (Fig. 38-13). Dissection then proceeds in a similar fashion on the anterior surface of the esophagus. Extreme care must be taken in the region of the trachea and especially the carina to avoid injury to the membranous trachea. (At this point in the operation, any difficulty in dissecting the esophagus from the trachea or any concern of adhesion to, or invasion of, the trachea should result in repositioning of the patient in the left lateral decubitus position, and a right thoracotomy should be

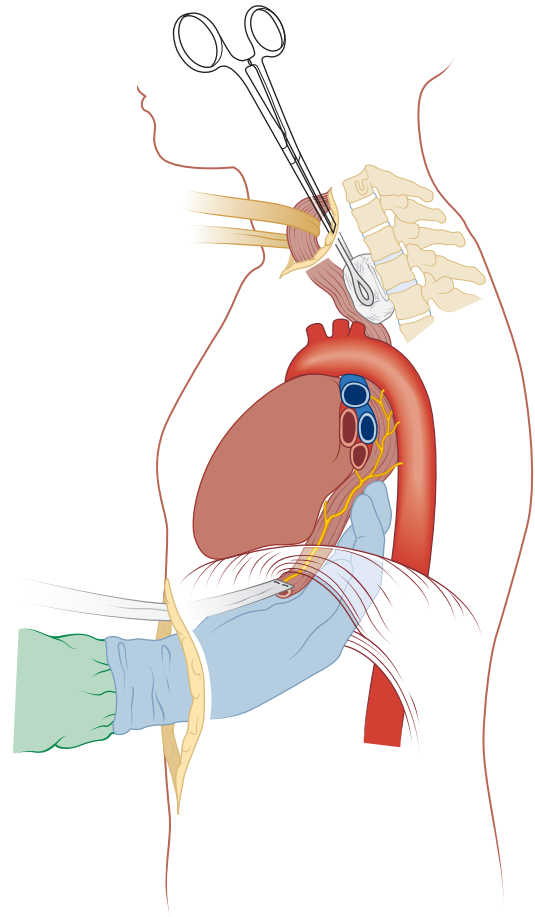


FIGURE 38-13 ■ Posterior dissection is performed with the fingertips adjacent to the esophagus. Dissection from the cranial aspect may be performed with a sponge stick if the surgeon's upper hand cannot reach the lower hand. (Adapted from Orringer MB, Sloan H: Esophagectomy without thoracotomy. *J Thorac Cardiovasc Surg* 76:643–654, 1978.)

performed for direct visualization and dissection.) The fingers from above and below should meet in the region of the carina (Fig. 38-14).

As much dissection as possible should be performed under direct vision from the neck and from the abdomen. Portions of the lateral dissection near the lower aspect of the trachea often cannot be visualized, and lateral dissection must be performed bluntly. The surgeon's right hand is advanced from the abdomen high up in the chest to the point where circumferential dissection has been completed from the neck. The first and second fingers surround the esophagus, and with a raking motion, the lateral attachments are avulsed as the hand is drawn back into the abdomen. Care must be taken near the region of the azygos vein (Fig. 38-15). After complete mobilization of the esophagus, it is divided in the neck, and the specimen is brought out into the abdomen. The mediastinum is packed for hemostasis. Before the gastric tube is drawn up into the neck, the mediastinal packing is removed and both pleural spaces are inspected for integrity. Entry into the pleural space is managed by chest tube placement before removal of the drapes.

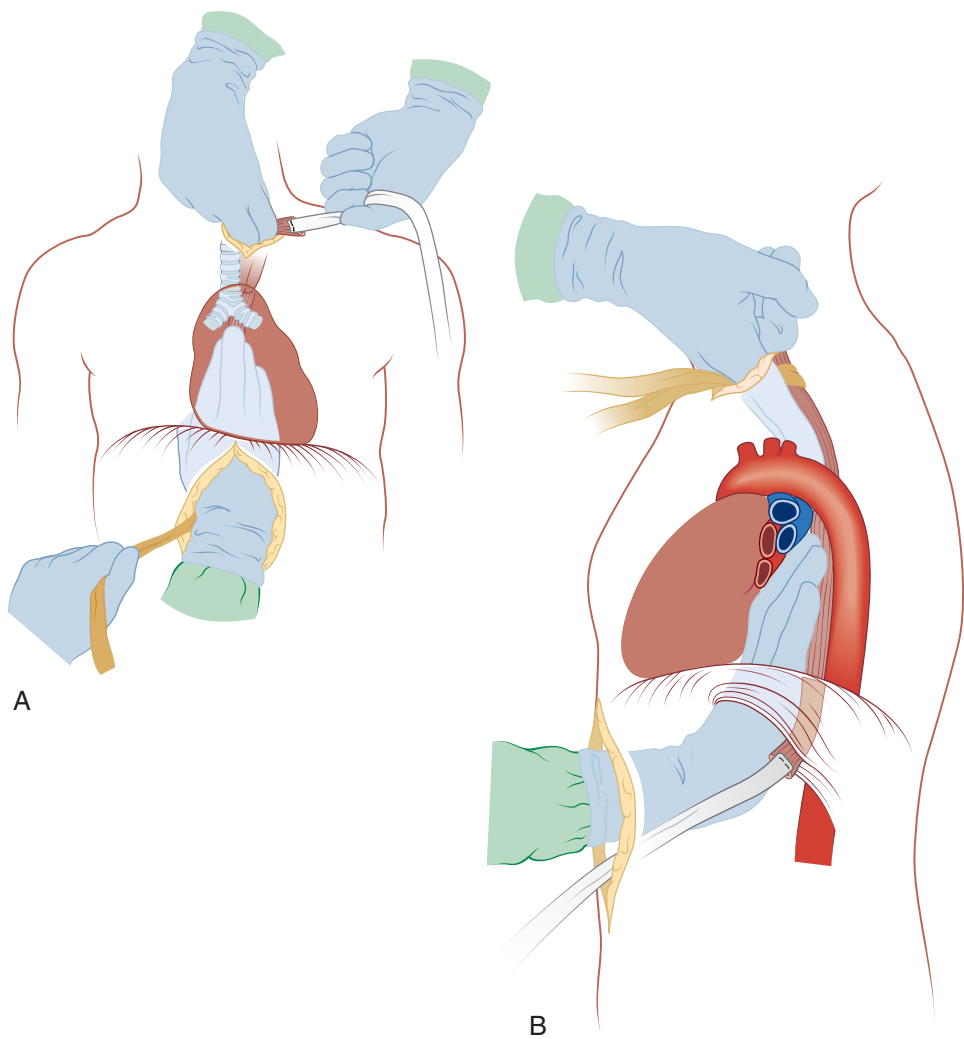


FIGURE 38-14 ■ **A**, Blunt dissection of the esophagus off of the trachea is performed with the fingertips immediately against the esophagus. **B**, The fingertips are united. The fingertips from above should be able to reach near the carina, as they do during cervical mediastinoscopy. (Adapted from Orringer MB: Transhiatal esophagectomy without thoracotomy. In Cohn LH, editor: *Modern techniques in surgery*, New York, 1983, Futura Publishing.)

Trials Comparing Transhiatal with Transthoracic Resection

Numerous nonrandomized, retrospective trials have been performed in an attempt to define differences in either perioperative complication rate or long-term survival between the transhiatal and transthoracic approaches (Table 38-1).²⁰⁻²² Most of these were limited by small study size and selection bias. A large meta-analysis review was performed by Rindani and coworkers²³ in 1999. Forty-four trials published in the English literature between 1986 and 1996 consisting of 5483 patients undergoing either Ivor Lewis or transhiatal esophagectomy were reviewed. The overall incidence of pneumonia was 25%, and it was not appreciably different between the two techniques. The incidence of bleeding and cardiac complications was also not different. The most significant differences were seen in the anastomotic leak rate (16% transhiatal vs. 10% Ivor Lewis), stricture (28% transhiatal vs. 16% Ivor Lewis), and recurrent nerve injury (11% transhiatal vs. 5% Ivor Lewis). Perioperative

TABLE 38-1 Comparison of Transthoracic and Transhiatal Approaches to Esophagectomy: Perioperative Complications

Complication	Transthoracic	Transhiatal
Blood loss (mL)	1001	728
Operative time (hours)	5.6	4.0
Cardiac complications (%)	6.6	19.5
Pulmonary complications (%)	18.7	12.7
Anastomotic leak (%)	7.2	13.6
Vocal cord paralysis (%)	3.5	9.5
Chyle leak (%)	2.4	1.4
In-hospital mortality (%)	9.2	5.7

Adapted from Hulscher JB, Tijssen JG, Obertop H, et al: Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. *Ann Thorac Surg* 72:306-313, 2001.

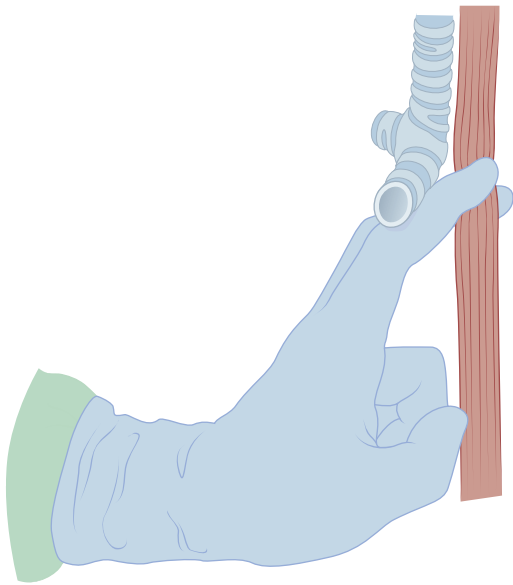


FIGURE 38-15 ■ After dissection of the anterior and posterior planes, the lateral stalks can be torn between the first and second fingers in a “raking” motion. (Adapted from Orringer MB: Transhiatal esophagectomy without thoracotomy. In Cohn LH, editor: *Modern techniques in surgery*, New York, 1983, Futura Publishing.)

mortality was higher in the Ivor Lewis population (9.5%) than in the transhiatal population (6.3%). Overall long-term (5-year) survival was similar in the two groups, 25%. Hulscher and colleagues²⁴ also performed a meta-analysis of trials between 1990 and 1999 published in English language journals. Fifty publications were identified, some randomized, some comparing transthoracic with transhiatal approaches, and some evaluating only one technique. Overall, cardiac complications (20% vs. 7%), anastomotic leakage (14% vs. 7%), and vocal cord paralysis (10% vs. 4%) were higher in the transhiatal versus the transthoracic groups. Pulmonary complications (19% vs. 13%), in-hospital mortality (9% vs. 6%), and operative time (5.6 vs. 4.0 hours) were higher in the transthoracic versus the transhiatal group. Overall 5-year survival was similar among all the studies and patients evaluated (23% for transthoracic resections and 21.7% for transhiatal resections). These reviews are of historical and factual interest only, and little can be concluded about the relative merits of each technique in matched populations.

Orringer and colleagues²⁵ reviewed their 30-year experience with transhiatal esophagectomies in 2007 patients. The patients were divided into two groups: group I, those operated on between 1976 and 1998; and group II, those operated on from 1998 to 2006. Postoperative mediastinal bleeding requiring reoperation occurred in less than 1%. The incidence of recurrent laryngeal nerve injury was significantly lower in group II (2%) compared with group I (7%; $P < 0.0001$). They believed that this decrease in injury was secondary to an increase in operative volume. Chylothorax was seen in 1%. The incidence of respiratory complications that required a hospital stay beyond 10 days was 2%. They also reported that the routine use of side-to-side stapled cervical esophagogastric anastomosis after 1997 has led

to a notable decrease in leak rate and need for postoperative dilation. The overall hospital mortality was 3%. The hospital mortality fell with increased volume (group I, 4%; group II, 1%). It is clear that the high volume at this center has produced impressive results with regard to transhiatal esophagectomy.

Wolff and associates²⁶ retrospectively reviewed all esophagectomies at the Mayo Clinic between 1994 and 2004. Of the 517 esophagectomies performed, the type of surgery was as follows: transhiatal (68), Ivor Lewis (392), and extended Ivor Lewis (57). The mean lymph nodes retrieved for the Ivor Lewis and extended Ivor Lewis were 18.7 and 17.4, respectively. This was not statistically different. The transhiatal patients had a mean of 8.99 lymph nodes in the specimen. They found that the combined Ivor Lewis group and the transhiatal group were significantly different, showing on average 9.5 lymph nodes in the surgical specimen ($P < 0.001$). The importance of the number of lymph nodes harvested at the time of surgery is discussed in a later section.

Orringer and associates²⁷ reviewed outcomes after transhiatal and transthoracic surgery using the Surveillance, Epidemiology, and End Results (SEER) cancer registry. They identified patients between 1992 and 2002 undergoing esophagectomy. Of the 868 patients studied, 643 had a transthoracic approach and 225 underwent a transhiatal esophagectomy. They concluded that patients undergoing a transhiatal esophagectomy had a lower operative mortality rate than did those undergoing transthoracic operations (6.7% vs. 13.1%; $P = 0.009$). The need for anastomotic dilation was higher in the transhiatal group (43.1%) compared with the transthoracic patients (34.5%; $P = 0.02$). The 5-year survival rate was significantly higher in the transhiatal group; however, this benefit over the transthoracic group was diminished after adjustments were made for patient and hospital or provider characteristics, such as volume performed at the center and involvement of trainees.

Three randomized, prospective trials comparing transhiatal resection with transthoracic resection demonstrated that either technique can be performed safely in skilled hands and no clear differences have been shown between the two techniques, in large part because of an inadequate number of patients enrolled in the trials. Extrapolating from their retrospective meta-analysis, Rindani and colleagues²³ estimated that 2360 patients would have to be randomized for a significant difference to be shown in perioperative mortality, and 6400 patients would be needed for a difference to be shown in long-term survival. Clearly, this is beyond the capacity of any prospective esophagectomy trial.

The first randomized, prospective trial was published in 1993 by Goldmine and coworkers.²⁸ They randomized 67 patients younger than 70 years with squamous cell cancer of the esophagus to Ivor Lewis esophagectomy or transhiatal esophagectomy. Operative time was longer (6 vs. 4 hours) in the transthoracic group. No difference was found in incidence of pneumonia (20%), anastomotic leak, recurrent nerve injury, bleeding, perioperative mortality, or length of hospitalization. At a mean follow-up of 3 years, survival was not statistically different between the two groups. For those patients with nodal disease,

however, none of the transhiatal patients was alive at 18 months, whereas 30% of the transthoracic patients were alive at 18 months.

Wong and colleagues reported a prospective, randomized series of 39 patients with lower third esophageal cancers treated with either an Ivor Lewis resection or a transhiatal resection.²⁹ Patients undergoing neoadjuvant therapy or those with an FEV₁ below 70% were excluded from the study. There were no perioperative (30-day) deaths in either group, although the in-hospital mortality rate was 15% for the transhiatal group and 0% for the transthoracic group (not significantly different). Intraoperative hypotension occurred in 60% of transhiatal patients but in only 5% of transthoracic patients. There was no difference in blood loss, pneumonia, or recurrent nerve injury. Operating time was longer for the transthoracic group. The mean proximal margin was 3 cm longer in the transhiatal group. No significant difference was seen in tumor recurrence or survival. This group recently published their 5-year results from this study.³⁰ After a complete 5-year follow-up, they concluded that overall survival rate was not significantly different between the two groups. However, they reported a trend toward improved survival in the extended transthoracic group over the transhiatal group in the patients with a type I esophageal cancer.

More recently, a randomized study was completed in the Netherlands comparing transhiatal resection with extended transthoracic en bloc resection for distal adenocarcinomas of the esophagus or cardia³¹; 106 patients had a transhiatal resection, and 114 patients had a transthoracic resection. The median follow-up was 4.7 years. The in-hospital mortality rate was 2% to 4% in each group. The incidence of respiratory complications, including atelectasis and pneumonia, was higher in the transthoracic group (57% vs. 27%), as was the incidence of chyle leak (10% vs. 2%). The high incidence of respiratory complications in the transthoracic group (57%) should be questioned, because it is much higher than that quoted in many previous transthoracic resection series.²³ Although statistical significance was not reached, there was a trend toward improved survival at 5 years in the transthoracic group (39% vs. 29%).

Minimally Invasive Esophagectomy

Cuschieri is credited with first applying minimally invasive techniques to an esophagectomy. Since his initial description of subtotal endoscopic esophagectomy using thoracoscopic techniques for mobilization of the esophagus, there have been numerous descriptions with varying degrees of endoscopic involvement. The three most widely performed open procedures for esophageal resection—tri-incisional, Ivor Lewis, and transhiatal esophagectomy—have endoscopic counterparts. These are discussed.

Minimally Invasive Tri-incisional Esophagectomy

Minimally invasive techniques can be used to perform a modified McKeown esophagectomy. All or part of the

procedure may be replaced with thoracoscopic or laparoscopic dissection.

Indications. There are no finite indications for minimally invasive esophagectomy (MIE). There are relative indications advocated by those who specialize in this surgery. These reported benefits of MIE are discussed in a later section.

Contraindications. Fusion of the right pleural space or inability to maintain isolated lung ventilation is a contraindication to the approach. Unlike its open counterpart, video-assisted thoracoscopic esophagectomy requires almost perfect lung isolation to allow adequate room to thoracoscopically maneuver within the thoracic cavity. On occasion, continuous positive airway pressure to the right lung will aid in achieving adequate ventilation and oxygenation with minimal effect on exposure. Relative contraindications with respect to minimally invasive surgery are the same as those in the open sections. As with any endoscopically assisted surgery, the surgeon's comfort is a strong determining factor in use of this technology. Those not trained in minimally invasive surgery should consider performing this highly technical surgery with a surgeon who is facile with this procedure.

Technique

Video-Assisted Thoracoscopic Mobilization of the Thoracic Esophagus. Video-assisted thoracoscopic esophageal mobilization uses four thoracoscopic incisions. After the patient is prepared and draped in the left lateral decubitus position, a 1-cm incision is made in the eighth intercostal space at the posterior axillary line. Ideally, the camera needs to be as posterior as possible for optimal visualization. However, this port will be used for the chest tube, and any position farther posterior will result in an ineffective chest tube because the patient will be lying on it.

With the thoracoscope, the right hemithorax is examined for pleural disease that may prohibit further surgery. Three access incisions are placed next, with two of the ports in line with the tip of the scapula, at the level of the sixth and ninth intercostal spaces. The final access incision will be in the fourth intercostal space in line with the camera. This is used mainly for lung retraction and suctioning of the operative field.

Most surgeons use a port only for the camera. Standard open instruments, such as a ring forceps, are passed through the other incisions without a port. Some surgeons prefer laparoscopic instruments, so they use 5-mm and 10-mm ports to allow easy passage of these surgical tools.

Some surgeons place a stitch in the central tendon of the diaphragm and bring it out through a separate intercostal space to retract the diaphragm. The authors of this chapter place an endoscopic Kittner (Ethicon, Somerville, NJ) alongside the camera to provide gentle caudal retraction on the diaphragm.

Through the posterior ports, the surgeon uses an ultrasonic scalpel, the harmonic scalpel (Ethicon, Somerville, NJ), to divide the inferior pulmonary ligament. The posterior mediastinal pleura is opened, and the lymph nodes are swept off the pericardium toward the

esophagus. This dissection is carried to the azygos vein. The pleura above the azygos vein is opened close to the esophagus. An endovascular stapler is used to ligate the azygos vein. Once this is achieved, the pleura on the posterior aspect of the esophagus is opened at an area away from the tumor and carina. Once circumferentially around the esophagus, a Penrose drain is placed. The Penrose drain is stapled together with an endovascular stapling device. This Penrose drain can be used as a handle to hold the esophagus during dissection. The vagus is divided just above the azygos vein to prevent traction injury to the recurrent laryngeal nerve. The thoracic esophagus is circumferentially dissected for its entire length. The diaphragmatic hiatus is not opened in the chest to allow adequate pneumoperitoneum during the laparoscopic portion. After adequate mobilization, the Penrose drain is placed into the apex of the thoracic cavity to allow retrieval from the neck. A complete thoracic lymphadenectomy is an important aspect of this component of the operation and should be performed routinely. The chest tube is placed, and all thoracic incisions are closed. The patient is turned supine, and the double-lumen endotracheal tube is changed to a single-lumen tube. The patient is prepared and draped for laparoscopic surgery.

Laparoscopic Mobilization of the Gastric Conduit, Pyloroplasty, and Formation of a Jejunostomy Tube. Four 5-mm ports and one 10-mm port are placed as they would be in preparation for a laparoscopic Nissen fundoplication. The liver retractor is used to retract the left lobe of the liver so the underlying esophageal hiatus is visualized. The assistant standing to the patient's left will maintain the camera and provide countertraction for the surgeon. The harmonic scalpel is used to open the gastrocolic ligament. Great care is taken to maintain a 2-cm distance from the gastroepiploic arcade. The short gastric arteries can be divided with the harmonic scalpel. The gastric hepatic ligament is opened to allow access to the right crus of the diaphragm. The lymph nodes along the celiac and left gastric are swept toward the stomach. The left gastric artery is ligated. A gastric tube is created by dividing the stomach starting at the distal lesser curve with use of a 3.5- or 4.8-mm endovascular stapler. The conduit is formed with several firings of the endovascular stapler until this area on the lesser curve is connected with the cardia-fundus of the greater curvature. Once achieved, the proximal gastric tube is attached to the gastric remnant with several Endo Stitch sutures (U.S. Surgical Corp., Norwalk, CT).

A pyloroplasty could be performed with use of the harmonic scalpel to open the pylorus in a longitudinal fashion and placement of interrupted Endo Stitch sutures to close the opening in a transverse manner.³² Recent analysis of literature demonstrated that pyloric drainage procedure was associated with a nonsignificant trend for delayed gastric emptying and biliary reflux, while not affecting the incidence of dumping, and it is not performed routinely by the authors of this chapter.³³

Before a neck dissection is performed, a jejunostomy is created. The ligament of Treitz is identified by elevating the transverse colon. A place on the jejunum, approximately 40 cm from the ligament of Treitz, is attached to

the anterior abdominal wall with the Endo Stitch. A needle catheter kit (Compat Biosystems, Minneapolis, MN) is placed percutaneously into the jejunal loop. The Seldinger technique is used to guide a catheter into the jejunum. The placement is visually confirmed by injecting air into the catheter and watching for jejunal distention.

Finally, a neck incision and dissection are performed as described earlier. The esophagus is pulled out of the neck while an assistant laparoscopically guides the conduit through the hiatus, ensuring proper alignment. The specimen is sent for pathologic examination, and the anastomosis is performed as previously described.

Of interest, Fabian and coworkers³⁴ published a report of 21 patients who had a thoracoscopic mobilization of the esophagus in the prone position. They thought the prone position for thoracoscopic esophageal mobilization to be equivalent to lateral decubitus position with respect to blood loss, number of lymph nodes dissected, and complications. The operative time, however, was significantly reduced in the group of prone patients.

Minimally Invasive Ivor Lewis Esophagectomy

Indications, contraindications, and preparation for this procedure are identical to those for open surgery. After esophagogastroduodenoscopy and bronchoscopy, the patient is prepared and draped in the supine position. The laparoscopic portion of this surgery, including jejunostomy tube formation and pyloroplasty, is almost identical to that for minimally invasive tri-incisional surgery.

After gastric conduit formation and completion of the laparoscopic surgery, a double-lumen endotracheal tube is placed. The patient is prepared and draped in the lateral decubitus position. The thoracoscopic incisions are identical to those described in the minimally invasive tri-incisional section with one exception. The posterior eighth intercostal access incision is 3 to 4 cm to allow placement of a laparoscopic wound protector.³⁵ A combination of the wound protector and lubrication allows easy introduction of the EEA stapler through this port. The esophagus is mobilized to a few centimeters above the azygos vein. The gastroesophageal junction and conduit are then delivered through the hiatus. The proximal esophagus is divided above the azygos vein, and the specimen is brought out the protected port. The anvil of the EEA stapler is secured in the proximal esophagus with an Endo Stitch. The EEA stapler is then maneuvered into the proximal gastric conduit. An end-to-side (esophagus to stomach) circular anastomosis is formed. A linear stapler is used to close the gastric conduit. Chest tubes and standard closure are performed.

Minimally Invasive Transhiatal Esophagectomy

Laparoscopic transhiatal surgery has been described by various centers.³⁶⁻³⁸ The procedure has the same preparation and positioning as a transhiatal esophagectomy. Laparoscopic instruments are used for mediastinal dissection, thus avoiding the blind, blunt dissection done in

open transhiatal surgery. The esophagogastric anastomosis is made in the left neck. Limited visualization of the middle and upper third of the mediastinum and incomplete mediastinal lymphadenectomy are the main criticisms of this surgery. A mediastinoscope placed in the superior mediastinum has been used to help address this concern.³⁹

Results of Minimally Invasive Esophagectomy

Regardless of surgical approach and the use of minimally invasive techniques, esophageal surgery for malignant disease must adhere to certain principles. The procedure must ensure safe and complete resection of the tumor with adequate margins and provide restoration of gastrointestinal continuity. The literature contains numerous descriptions and outcome data of MIE. However, the publications at present are almost entirely composed of case series.

Luketich and associates⁴⁰ at the University of Pittsburgh Medical Center published their results of 222 consecutive minimally invasive esophagectomies performed between 1996 and 2002. The median age was 66.5 years. The indications for surgery were carcinoma (78%) and high-grade dysplasia (21.2%). Of the patients with invasive esophageal cancer, 31 were assigned to stage I, 71 to stage II, and 81 to stage III. Neoadjuvant chemotherapy was given to 78 patients (35.1%) and radiation therapy to 36 patients (16.2%). Fifty-five patients had previous abdominal surgery. A pyloromyotomy was performed in 28 patients and a pyloroplasty in 136 patients. Luketich and coworkers abandoned the pyloroplasty mid series when they made a narrower gastric conduit (4 cm). The leak rate increased, and the pyloroplasty was reinstituted as part of a MIE. A laparoscopic jejunostomy tube was placed in 202 patients. The surgeons completed a MIE in 206 patients (92.8%). Twelve patients required a thoracotomy, and four patients needed a laparotomy to complete the esophagectomy. Patients were given oral intake by postoperative day 4. Median intensive care stay was 1 day (range, 1 to 30 days), with an average hospital stay of 7 days (range, 3 to 75 days). The mean follow-up was 19 months (range, 1 to 68 months). Dysphagia scores were assigned during follow-up. The mean Health-Related Quality of Life score was 4.6, which represented a normal score. Significant reflux (score of >15) was reported by 4% of the patients. The 30-day operative mortality was 1.4% (three patients). The first death was related to development of pneumonia. The second and third deaths were secondary to a myocardial infarct and pericardial tamponade, respectively. The minor and major complications were 23.9% and 32%, respectively. The most common complications in this series were atrial fibrillation (11.7%) and pleural effusions requiring a chest tube (6.3%). Interestingly, patients with 6-cm conduits had an anastomotic leak rate of 6.1%, and patients with a smaller conduit had a significantly increased leak rate (27.6%; $P < 0.001$). Luketich and associates compared their results with those published in a prospective U.S. Department of Veterans Affairs (VA) database of 1777 patients undergoing esophagectomy.⁴¹ They considered that their 1.3%

mortality rate compared well with the results of the VA study, which reported a 10% perioperative mortality rate. The incidence of complications in the VA database was reported at 50%, with the most frequent complications being pneumonia (21%), respiratory failure (16%), and prolonged ventilatory support (22%). Of the 222 studied cases of MIE, pneumonia was reported in 7.6% and acute respiratory distress syndrome in 5%. It was thought that this suggested an advantage for MIE.

This large series also compared its results with the single-institution report by Swanson and coworkers.¹⁷ In their series of 250 patients undergoing a modified McKeown esophagectomy, the reported 3-year survival rates for their patients assigned to stages I, IIa, IIb, and III were 65%, 41%, 45%, and 17%, respectively. Luketich and associates noted similar survival rates. The higher percentage of induction therapy might be the reason for increased mortality (3.9%) and length of stay (13 days) in the open series compared with that reported by the MIE group. Berrisford and colleagues⁴² found that the operating time for a total MIE decreased significantly ($P < 0.001$) as experience with the procedure increased.

One study evaluated MIE in 41 older adult patients (range, 75 to 89 years).⁴³ In this cohort of patients, the mean intensive care unit (ICU) time was 1 day, and the median hospital stay was 7 days. Major morbidity was reported as 19%, and there was no perioperative mortality.

There are a handful of case-controlled studies. Nguyen and colleagues⁴⁴ reported on a direct comparison of open esophagectomy (OE) and MIE. There was a trend toward shorter operating times, less blood loss, and lower intensive care and hospital stays for this group. However, it has been noted that the MIE group had less advanced stage cancers and the technique was performed by one surgeon, whereas the OE cases were performed by one of four surgeons. Law and coworkers⁴⁵ compared 22 patients who underwent thoracoscopic esophageal mobilization with 63 OE patients. Blood loss was significantly lower in the thoracoscopic group; however, there was no significant difference in morbidity or mortality. Laparoscopically assisted transhiatal surgery in 17 patients was compared with open transhiatal esophagectomy in 14 patients.⁴⁶ This published series also reported shorter operative times and decreased blood loss in the minimally invasive group. In a series of 166 patients, 47 MIE patients were compared with 60 open transthoracic patients and 59 open transhiatal patients.⁸ A lower mortality and reduced morbidity were noted in the MIE group.

The largest series to date comparing minimally invasive surgery with open surgery is that published by Smithers and associates.⁴⁷ This group compared open (114) with thoracoscopically assisted (309) and total minimally invasive (23) esophagectomy. Decreased blood loss in the thoracoscopically assisted (400 mL) and minimally invasive (300 mL) esophagectomy was noted compared with the open surgery (600 mL). Open surgery had shorter operative times (300 minutes) compared with total MIE (330 minutes) but longer times compared with thoracoscopically assisted surgery (285 minutes). MIE patients had the shortest reported hospital stay (11 days),

followed by thoracoscopically assisted patients (13 days) and the open surgical patients (14 days). Stage for stage, there was no difference in overall median or 3-year survival rates among the three groups.

Gemmill and McCulloch⁴⁸ performed a systematic review of minimally invasive surgery for gastric and esophageal surgery spanning 1997 to 2007. Of the 46 articles that met criteria, 23 pertained to esophageal surgery. Most studies reviewed from that period were case series. There were no randomized controlled studies of MIE published during that time. There were 1398 patients in the combined papers. A completely endoscopic surgery was performed in 405 patients; 103 patients had laparoscopic mobilization and a thoracotomy; 561 patients had the reverse, thoracoscopic mobilization and laparotomy. The 30-day in-hospital mortality was 2.3%, and the morbidity was 46.2%. The incidence of anastomotic leak was 7.7%. Respiratory complications at a rate of 13.2% were reported in 1268 patients. Mean operating room time reported for 981 patients was 281 minutes. One group noted that the operating time for a total MIE decreased significantly ($P < 0.001$) as experience with the procedure increased.⁴² Hospital stay was 2 to 195 days, with a mean of 11 days. The average number of lymph nodes retrieved in 607 patients was 17.6. Interestingly, length of stay and overall morbidity rates were not different from those of their open counterparts.

In a recent update Watanabe and colleagues reported acceptable short-term outcomes of video-assisted thoracoscopic esophagectomy for thoracic esophageal cancer in terms of operating time, blood loss, and postoperative complications; these outcomes are comparable with those of conventional open surgery.⁴⁹ With regard to the number of total retrieved mediastinal lymph nodes, most studies have demonstrated that video-assisted thoracoscopic esophagectomy is almost equivalent to open surgery.⁵⁰⁻⁵² Furthermore, a meta-analysis by Dantoc and colleagues emphasized that the number of retrieved lymph nodes was significantly greater with video-assisted thoracoscopic esophagectomy than with OE.⁵³

Uttley and coworkers recently published a systemic review comparing MIE and open surgery. In their review, 28 studies were included. No randomized controlled trials were available. Mean length follow-up was 30 months. Mortality was recorded at 2.4% in the MIE group versus 3.8% in the open group. Recurrence rates were 23.4% in the MIE group and 24.8% in the open group. Tracheal perforation rates were 2.3% in the MIE group versus 6.5% in the open group. Vocal cord injury rates were 12.7% in the MIE group and 9.6% in the open group.⁵⁴

In 2012 Mamidanna and coworkers⁵⁵ published a large United Kingdom population-based study that analyzed the hospital data from April 2005 to March 2010 and included 7502 esophagectomies, 1155 (15.4%) of which were MIE. There was no difference between open and MIE groups, respectively, in 30-day mortality (4.3% vs. 4.0%) and overall morbidity (38.0% vs. 39.2%). However, reintervention rate was higher with MIE compared to open surgery (21% vs. 17.6%; $P = 0.006$). Further editorials pointed to the significant limitations of this population-based study based on an administrative data-

base, as commented by Rice and Blackstone⁵⁶ and Penathur and Luketich.⁵⁷

In 2009, the Eastern Cooperative Oncology Group (ECOG) conducted a prospective, multi-institutional (ECOG 2202) phase II study, evaluating MIE. A total of 106 patients were enrolled. The preliminary results showed that the mortality was low (2%), and at a mean follow-up of 19 months, the estimated 3-year overall survival for the entire cohort was 50%. Stage-specific survival was comparable to that of the open series.⁵⁸

To date, there have been three meta-analyses that examined short-term outcomes of MIE with comparisons with the traditional open technique.⁵⁹⁻⁶¹ There were essentially no marked differences in postoperative major morbidity and mortality rates between the two groups in these meta-analyses. However, Biere and colleagues⁵⁹ demonstrated that there was considerably less incidence of anastomotic leakage in hybrid (thoracoscopy and laparotomy) MIE compared with open surgery. Nagpal and coworkers⁶¹ compared 672 patients for total MIE and hybrid MIE and 612 for open surgery from 12 studies. There were no marked differences in the operating time, number of retrieved lymph nodes, incidence of anastomotic leak, or 30-day mortality between the MIE and OE groups, but MIE had significantly lower blood loss, reduced total morbidity and respiratory complications, and shorter ICU and hospital stay compared with OE.⁶¹ In these meta-analyses, the authors emphasized that several limitations should be considered when referring to the results. Biases may have been introduced by not only the study design but also volume, learning curves, surgeon experience, and publication bias, and it can be difficult to adjust for these factors in meta-analyses.

In terms of cancer outcomes, long-term studies have shown statistical equivalency in long-term survival between MIE and OE. Sgourakis and colleagues⁶⁰ and Dantoc and coworkers⁵³ found no significant differences in 3-year survival rate between the two groups in their meta-analyses.

A randomized controlled trial in this field would be helpful in understanding any benefit that minimally invasive surgery may have over an OE. The time and power that would be required to complete such study are considerable. Surgical skills, specific training in thoracic and upper gastrointestinal surgery, and learning curves are imperative factors to the choice and success of surgery type and are not captured by most available studies. Quality and transparent comparative studies and long-term follow-up of these patients also need to be reported to assess whether smaller access surgery provides equal oncologic outcomes.

A study group in Europe has recently reported the results of the first multicenter randomized controlled trial (TIME trial) that compared MIE and OE.⁶² Patients were randomized to 56 patients in the OE group and 59 to the MIE group. The incidence of pulmonary infection was considerably lower in the MIE group than in the OE group, both within the first 2 weeks after surgery and during the entire hospital stay. MIE patients overall had less operative blood loss, better postoperative quality of life, and shorter hospital stay; however, the 30-day and in-hospital mortality rates did not differ significantly

between the groups. Oncologic parameters, including number of lymph nodes retrieved, did not differ markedly between the two groups. Despite mounting evidence for the safety and benefits of MIE, additional prospective multicenter trials are warranted to further evaluate the long-term outcome of MIE compared with OE.

Left Thoracoabdominal Approach

Indications

The indications for a left thoracoabdominal approach are limited. A distal esophageal tumor beyond 30 to 35 cm in a patient with compromised physiologic status may be a suitable candidate, although some would argue that a transhiatal approach is preferable.

Contraindications

The presence of a tumor that is 30 cm or larger makes an approach from the left chest much more difficult, as the anastomosis must be placed above the aortic arch or in the neck. A distal esophageal peptic stricture is considered by many to be a contraindication to limited distal esophagectomy because gastroesophageal reflux is often a severe problem after distal esophagectomy and placement of the anastomosis low in the chest.

Technique

The left thoracoabdominal approach can be performed in a variety of ways. Isolation with a double-lumen tube is necessary in all the approaches. In the supine position, an upper midline laparotomy can be extended across the costal margin into the left chest through the seventh interspace and the diaphragm taken down in circumferential fashion. This position is least versatile and is generally used only when extension into the chest is unanticipated, as with proximal extension of certain tumors of the gastric cardia. Conversely, the patient may be placed in the full lateral position, and a complete esophagectomy may be performed through a thoracic incision. Abdominal dissection can be performed, although with some difficulty, through an enlarged hiatus or through a circumferential peripheral incision in the diaphragm (Fig. 38-16).

The most versatile thoracoabdominal approach involves placement of the patient in the right lateral decubitus position with the abdomen rolled back 45 degrees. The abdomen is readily accessible for extension of the distal aspect of the thoracotomy across the costal margin and across the rectus muscle. The neck is prepared in the field if extension to the cervical esophagus is a possibility. An incision is made from a point behind the tip of the scapula along the seventh interspace across the costal margin to the middle of the abdomen. The inferior pulmonary ligament is divided with cautery. The esophagus is encircled with a Penrose drain at a point away from the tumor where there is minimal scarring. Complete dissection of the esophagus and all surrounding lymphatic and connective tissue is performed up, including all tissue in between the aorta and

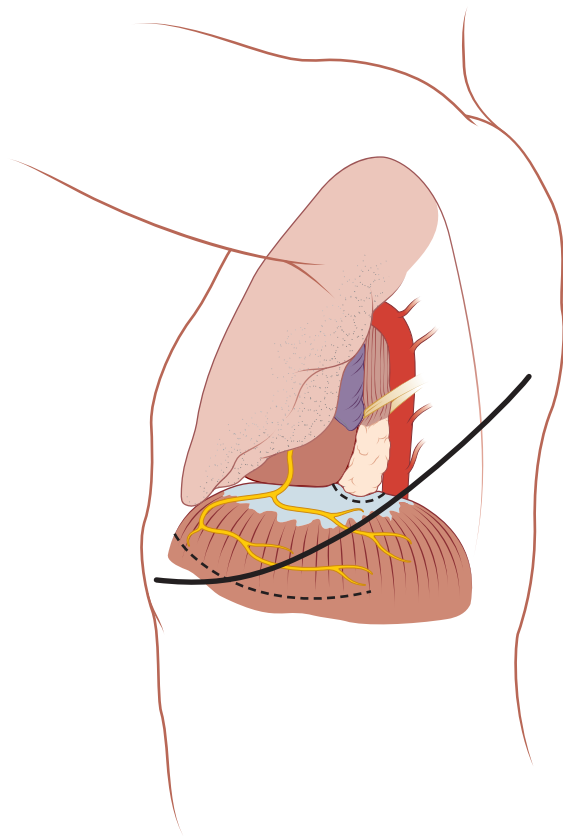


FIGURE 38-16 ■ The left thoracoabdominal approach. The abdomen can be entered through incisions in the diaphragm as delineated by the *dotted lines*. Alternatively, the incision can be taken across the costal margin onto the abdomen and the diaphragm taken down circumferentially from the costal margin incision. (Adapted from Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885–910.)

the pericardium in the specimen. Dissection proceeds cranially posterior to the left pulmonary veins. Cranial dissection should be performed only to a point approximately 3 cm above the proposed line of transection to preserve blood supply to the anastomosis.

At the diaphragmatic hiatus, a 2-cm rim of diaphragm is included with the specimen. Although it is at times possible to continue dissection of the short gastric vessels and gastrohepatic ligament through the hiatus, exposure is improved by taking the diaphragm down circumferentially at a point 2 to 3 cm away from its insertion on the chest wall. Dissection proceeds from the gastroesophageal junction along the greater curvature, dividing all short gastric vessels. Dissection of the remainder of the gastric conduit is performed as detailed in the section on tri-incisional esophagectomy. Complete dissection of the stomach may not be required if only a very limited portion of distal esophagus is resected. Minimizing dissection at the expense of an entirely tension-free anastomosis, however, is unwise. Kocherization of the duodenum and either pyloroplasty or pyloromyotomy are performed. The conduit is lifted into the chest. The anastomosis can be hand sewn in either a single layer or a double layer. It may also be performed with a large (33-mm) EEA stapler

or as a side-to-side, functional end-to-end anastomosis. A nasogastric tube is positioned before completion of the anastomosis. The conduit should be tacked to the diaphragm and may also be tacked to the adjacent pleura. Buttressing of the anastomosis with available omentum is recommended. The diaphragmatic rim is reattached to the chest wall with interrupted horizontal mattress 0 silk stitches. The costal margin is reattached with a single figure-of-eight wire or heavy Prolene stitch. The abdominal fascia is closed in layers. Before closure of the thoracotomy, a soft drain may be inserted dependently near the anastomosis, and an apical chest tube should be placed, each through separate stab incisions. The thoracotomy incision is closed with #2 Vicryl paracostal sutures, a 0 Vicryl latissimus layer, a 2-0 subdermal layer, and a 3-0 subcuticular stitch.

En Bloc Resection

The long-term survival rate after esophagectomy for esophageal cancer remains approximately 20% despite recent advances in surgical technique, instrumentation, and perioperative care. A large percentage of esophageal cancers manifest with invasion through the esophageal wall (T3) or nodal involvement (N1 or N2). Because radial margins are difficult to assess grossly and even microscopically, it is difficult to ensure complete removal of all invasive and nodal disease. To ensure complete margins and removal of all adjacent nodal tissue, several surgeons have advocated en bloc resection of the esophagus, including all adjacent tissues in the resected specimen. DeMeester and Skinner recommend en bloc esophagectomy for all patients in whom the cardiopulmonary morbidity is not prohibitive.^{63,64} In one of these studies, an FEV₁ of less than 1.5 liters was considered prohibitive. In their nonrandomized series, long-term survival was significantly better in the en bloc resection group versus the conventional approach.

Technique

Although an en bloc resection may be performed through either the left or the right side of the chest, only very distal esophageal tumors may be resected with ease and with adequate margins through a left thoracotomy. Because of the high incidence of postoperative reflux esophagitis, an approach through a right thoracotomy is advised. Entry into the chest is through the right sixth interspace. Two parallel incisions are made in the pleura. An incision is made anteriorly, entering the pericardium, and posteriorly, behind the azygos vein. Intercostal veins draining into the azygos are ligated individually, and the thoracic duct and azygos vein are included in the specimen. Some surgeons do not resect the azygos vein. The left pleura bordering the specimen is harvested and included in the specimen. This plane of dissection is continued cranially to the carina. Above the carina, the margins are limited by the proximity of the trachea anteriorly and the spine posteriorly.

At the hiatus, a 2-cm rim of diaphragm is included with the specimen. In the abdomen, the lesser curvature of the stomach and all nodal tissue along the left gastric

artery are taken. All tissue posterior to the stomach and superior to the border of the pancreas is removed. Nodes along the celiac axis, splenic artery, and superior mesenteric artery are dissected. The gastric tube is then pulled up to the neck for esophageal replacement. DeMeester and his group routinely resect the proximal two thirds of stomach, the greater omentum, and the spleen and its associated nodes. They replace the esophagus with isoperistaltic colon.

Results

Retrospective trials comparing en bloc resection with conventional resection have been associated with heavy selection and staging bias. Patients with poor cardiopulmonary reserve are typically excluded from en bloc resection. Moreover, in conventional resection, the disease is commonly understaged as a limited nodal dissection is performed. Both factors would favor stage per stage improved survival in the en bloc group. In Skinner's series of 128 patients, 78 underwent en bloc resection and the remainder underwent a simpler resection, most through the transthoracic route. Perioperative mortality was similar at 4% to 5% in each group. The incidence of pneumonia, leak, and recurrent nerve injury was similar. Four-year survival in patients assigned to stage III was 37% after en bloc resection and 0% after transhiatal resection. Survival was also better in patients with early-stage disease after en bloc resection compared with non-en bloc resection. In DeMeester's series, 69 patients with gastroesophageal junction tumors were studied. Patients in good health with resectable disease underwent en bloc resection, whereas those in poor health or with apparently unresectable disease underwent a transhiatal resection. Five-year survival was significantly better in the en bloc resection group (41%) compared with the transhiatal group (14%). The complication rate was not mentioned in this study.

Three-Field Lymph Node Dissection

Three-field lymph node dissection is a term applied to the addition of a cervical nodal dissection to the traditional thoracic and abdominal nodal dissections that are performed during esophagectomy for cancer. Ten percent to 30% of patients with lower esophageal cancers have cancers that spread to cervical nodal areas, and the same is true of celiac nodes in patients with cervical esophageal cancers.⁶⁵⁻⁶⁷ Proponents of this technique argue that cervical nodes should be considered resectable even in patients with lower esophageal cancers and should routinely be resected with the specimen.

The abdominal and thoracic phases of the operation are almost identical to those performed during a tri-incisional en bloc resection of the esophagus. Attention is paid to dissection of the recurrent nerve lymph node chain in the thorax. The neck is incised bilaterally with a U-shaped incision. The sternocleidomastoid muscles are divided. The deep cervical nodes deep and lateral to the jugular vein are dissected, dissection of the recurrent nerve nodes in the neck is continued, and the supraclavicular nodes are also removed.

In experienced hands, the incidence of recurrent nerve injury is no higher than with any other esophagectomy requiring a cervical incision. Altorki and Skinner⁶⁶ described a recurrent nerve injury rate of 6%. In their series, there was only one perioperative death, which was from the only case of pneumonia. Although the benefit of three-field lymph node dissections is not clear, several older studies suggested an improved survival.^{65,68} A Japanese study by Ando and coworkers⁶⁷ and a U.S. study by Altorki and coworkers⁶⁹ showed 5-year survival rates in the range of 40% to 50% after en bloc esophagectomy with three-field lymph node dissection. The study of Ando and coworkers was limited to patients with squamous carcinoma; the U.S. study included patients with adenocarcinoma and squamous cell carcinoma. The perioperative mortality rate was 5% to 8% in both studies. There was a 20% to 25% pulmonary complication rate in each study. The recurrent nerve injury rate was 9% in the study of Altorki and coworkers; it was not mentioned in the study by Ando and coworkers. In these selected studies, the perioperative morbidity rate is comparable to that in other studies, although perioperative mortality in the Ando study is higher than the quoted rate of 3% to 4% from several large academic studies of esophagectomy without en bloc or three-field dissections.^{17,70} Long-term survival is impressive, although it is not clear if selection factors or differences in tumor biology between the Japanese and U.S. populations might account for some of the difference.

Surgical Variations

Minimally Invasive Esophagectomy in the Prone Position. A number of surgeons have advocated thoracoscopic mobilization of the esophagus in prone position as a potentially ergonomic approach with the advantage of less pulmonary morbidity. Noshiro and colleagues published their experience with prone positioning during MIE.⁷¹ Compared with left lateral decubitus positioning, prone positioning was associated with lower blood loss and better exposure of the operative field around the left recurrent laryngeal nerve. However, recurrent laryngeal nerve injury rates were not significantly different between prone and left lateral decubitus-positioned patients.

Palanivelu and coworkers published their series of 130 patients who underwent MIE with thoracoscopic esophageal mobilization in prone position using a right prone posterior approach. This approach allows left lung ventilation with possible intermittent ventilation of the right lung. Mean operative time was 220 minutes (range 160 to 450 minutes) and median ICU stay was 1 day (range, 1 to 32 days). Postoperative pneumonia rate was only 1.54%. The authors have advocated prone positioning, allowing partial intermittent right lung ventilation and possibly prevention of postoperative atelectasis.⁷² Surgeons who advocate the prone position argue that functional residual capacity and ventilation-perfusion matching, ventilation in the dorsal lung areas, tidal volume in relation to modulated chest wall movement, and alveolar recruitment are improved in prone, compared with supine, position. Further comparison of the left lateral decubitus position with the prone position has

recently been published.⁷³ Twelve articles reporting the outcomes following prone thoracoscopic esophagectomy were analyzed. All 12 studies were nonrandomized single-center prospective or retrospective studies of which four compared the technique with traditional minimally invasive surgery. The prone esophagectomy has been demonstrated as being both feasible and safe; however, there is no convincing evidence that it is superior to other forms of esophageal surgery. Additional comparison studies are needed to confirm the superiority of the prone position over the left lateral decubitus position in MIE.

Robotic Esophagectomy. Robot-assisted esophagectomies have been described with a wide variety of reported outcomes. Recent review articles of robotic-assisted MIE have concluded that the data regarding robotic-assisted MIE indicate safety, feasibility, and equivalent outcomes compared with open surgery or MIE. However, there are no available data to suggest improved outcomes with robotic-assisted MIE in terms of operative morbidity, pain, length of stay, operative time, or total costs.⁷⁴

Weksler and colleagues performed a retrospective comparison of 11 patients who underwent thoracoscopic robot-assisted MIE versus 26 who underwent MIE. No significant differences were seen in operative time, blood loss, postoperative complications, or length of stay.⁷⁵

Galvani and coworkers at the University of Illinois reported on 18 patients who underwent robotic-assisted transhiatal esophagectomy. Although anastomotic leak occurred in 6 (33%) patients, other parameters such as mean estimated blood loss of 54 mL and low cardiopulmonary morbidity (1 pleural effusion and 2 cases of atrial fibrillation) suggested safety and feasibility of robotic-assisted transhiatal esophagectomy.⁷⁶

Rusch and associates⁷⁷ recently reported their series of 21 patients who underwent four-arm robotic esophagectomy (17 with the Ivor Lewis technique and 4 with the McKeown technique). The median operative time was 556 minutes (range, 395 to 807 minutes); this reduced to 414 minutes (range, 405 to 543 minutes) for the last 5 cases in the series. The median length of hospital stay was 10 days (range, 7 to 70 days). The median number of lymph nodes resected was 20 (range, 10 to 49). Five (24%) patients were converted to open procedures. Five patients (24%) had major complications. One (5%) died of complications on postoperative day 70, and 3 (14%) had clinically significant anastomotic leaks.

The ROBOT trial, currently under way, is the first randomized controlled trial designed to compare robotic esophagectomy with open transthoracic esophagectomy; the trial started in January 2012.⁷⁸ Until further results are available, the superiority of robot-assisted thoracoscopic esophagectomy compared with conventional thoracoscopic esophagectomy without robot assistance should be carefully evaluated.

Prognostic Significance of Number of Lymph Nodes Resected

Any assessment of the benefits of extended lymphadenectomy must consider the potential morbidity of the procedure. Until an improvement in survival can be

demonstrated, the potential morbidity of this procedure has heightened significance.

Rizk and colleagues⁷⁹ reported the prognostic significance of the number of involved lymph nodes in patients with esophageal cancer. This retrospective review examined the records of 336 patients operated on between January 1996 and September 2003. The patients studied received surgery as their only treatment. Recursive partitioning analysis using lymph nodes as a variable in addition to T, N, and M status showed that the presence of more than four positive lymph nodes was the most important prognostic factor. This group also reported that the likelihood of finding positive N1 nodes increased when more than 18 nodes were present in the specimen. They concluded that when the appropriate number of lymph nodes is obtained, depth of invasion of the tumor is not a prognostic indicator because survival assessment will be based on lymph node involvement. Since this landmark article was published, several published articles have confirmed that the number of lymph nodes removed has prognostic significance.

Greenstein and associates⁸⁰ evaluated 972 patients in the SEER cancer registry treated with an esophagectomy for esophageal malignant disease diagnosed between 1988 and 2003. Interestingly, on multivariate regression controlling for age, race or ethnicity, sex, histology, tumor status, and postoperative radiotherapy, patients with pathologic node-negative disease in 18 lymph nodes or more were found to have a higher disease-specific survival.

Another group, also using the SEER database, reported that the number of lymph nodes removed is an independent predictor of survival after an esophagectomy for malignant disease.⁸¹ Of the 2303 patients studied, 1700 patients had an esophagectomy with a thoracotomy and 603 patients had an esophagectomy without a thoracotomy. The Cox regression analysis showed that the number of lymph nodes removed was an independent factor for survival. They concluded that it was necessary to have 23 to 29 lymph nodes in the specimen to provide optimal survival.

Altorki and coworkers⁸² retrospectively reviewed their single-institution experience with 264 patients with esophageal cancer treated with esophagectomy between 1988 and 2006. They also concluded that increased nodal resection is an independent factor that favorably influences survival. The survival advantage is most apparent in the subgroup of patients with distal esophageal cancers with limited lymph nodes metastasis who have had a more extensive lymph node dissection. A recent review concluded that a radical lymph node dissection is beneficial and provides better survival advantage in patients with resectable esophageal cancer.⁸³

Techniques of Alternative Conduits: Colon and Jejunum

Colon

Indications. The stomach is the preferred conduit for esophageal replacement. It has several advantages over the colon, including a reliable blood supply that is usually

free of atherosclerotic disease, a low intraluminal bacterial burden, and the need for only a single anastomosis. In those cases when the stomach is not available, usually because of previous abdominal or gastric surgery or involvement of the stomach with tumor, the colon becomes the preferred conduit. The left colon differs from the right in that its lumen is smaller and more closely approximates that of the esophagus. Its usable length is usually greater than that of the right colon. The vascular anatomy on the left is more consistent than on the right; however, involvement by atherosclerotic disease of the inferior mesenteric artery is more common than in any other mesenteric vessel. In general, isoperistaltic orientation is preferred and can be achieved without tension.

Contraindications. Intrinsic disease of the colon by neoplasia, stricture, or extensive diverticulosis precludes its use as an esophageal replacement. In addition, prior abdominal surgery that may have interrupted either the arterial blood supply or the venous drainage of the colon may render a segment of the colon unusable. The inferior mesenteric vein drains into the splenic vein, and prior severe pancreatitis or other causes of splenic vein thrombosis may render the left colon unusable as a conduit because of inferior mesenteric vein thrombosis.

Preparation. The patient should be screened for cardiopulmonary disease as for esophagectomy with gastric reconstruction. In addition, preoperative mesenteric angiography should be performed for any patient older than 40 years or otherwise with risk factors for atherosclerotic disease. A barium enema study or colonoscopy should be performed to rule out a coexistent neoplasia or extensive diverticular disease. Mechanical and antibiotic bowel preparation is administered.

Left Colon

As stated previously, the left colon has several advantages over the right, including a longer length, a less vascular anatomic variation, and a caliber more similar to that of the esophagus. A midline laparotomy is performed, and the abdomen is explored. The peritoneal attachments of the left colon to the retroperitoneum are divided along the white line of Toldt. The length of the conduit that is needed should be estimated by passing an umbilical tape from the proposed proximal line of transection of the esophagus through the proposed route of placement of the conduit to the point of proposed anastomosis to the stomach. The umbilical tape can then be used to measure an appropriate length of colon.

The vessels supplying the left colon are visualized by transillumination. The middle colic artery should be test clamped with a noncrushing bulldog clamp. A palpable pulse should still be present in the marginal artery. If there is any question, a Doppler probe may be used, or the bulldog clamp should be left in place and the conduit inspected for adequate perfusion. Only after it is determined that the conduit is of satisfactory quality should the esophagectomy be completed. The left colon should then be prepared. The omentum is separated from the

left colon and splenic flexure that is to be used as a conduit. The middle colic artery is divided, and the mesentery is divided near its root, away from the marginal artery of Drummond (Fig. 38-17). The colon is reanastomosed, and the mesenteric defect is closed.

Either the proximal or the distal anastomosis may be done first; however, we believe that construction of the proximal anastomosis first allows better determination of conduit length and ensures that the conduit will sit properly in the neck. The proximal end of the conduit may be drawn up into the neck by use of an atraumatic method,

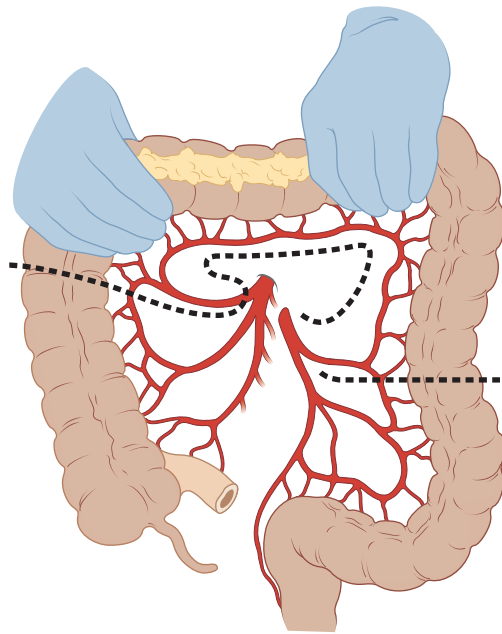


FIGURE 38-17 ■ The mesentery of the mobilized colon is transilluminated, revealing the mesenteric vessels. The *dotted lines* are the lines of division for a conduit based on the left colic artery. (Adapted from Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885–910.)

such as an endoscopic camera bag (see tri-incisional technique). The posterior mediastinal (in situ) route is preferred as this is the shortest route between the stomach and esophagus (Fig. 38-18). If the posterior mediastinal route is unavailable because of prior infection or scarring, as occurs with a prior gastric conduit leak, the substernal or transpleural route is an option. These routes, however, result in more conduit angulation and may impair emptying. Routine resection of the manubrium or a portion of the manubrium is necessary to prevent obstruction and to allow adequate space for the colon if the substernal route is used. Excess length is taken out of the conduit. If there is significant excess length, the proximal end may be trimmed as needed. The proximal anastomosis is typically constructed with a single- or two-layer hand-sewn anastomosis of the end of the esophagus to the side of the antimesenteric taenia. A stapled technique may also be used as detailed in the section on tri-incisional esophagectomy. The anastomosis should be constructed over a nasogastric tube with its tip positioned in the center of the stomach. The conduit should be monitored for arterial insufficiency or venous engorgement. The gastrocolic anastomosis is performed with a large EEA stapler or in a side-to-side functional end-to-end stapled manner. Before closure, the conduit should be sutured to the crus to prevent migration of the colon into the chest or herniation of abdominal viscera into the chest.

Right Colon

Various conditions may make the left colon unusable as a conduit. These include extensive diverticular disease, stricture secondary to ischemia or prior diverticular infection, atherosclerotic occlusion of the inferior mesenteric artery, and splenic vein thrombosis with thrombosis of the inferior mesenteric vein. The right colon is an acceptable conduit and will readily reach the esophagus in the neck.

The right colon is inspected for any disease, and its retroperitoneal attachments are lysed. The mesentery of the right colon may be transilluminated, showing the ileocolic, right colic, marginal, and middle colic arteries.

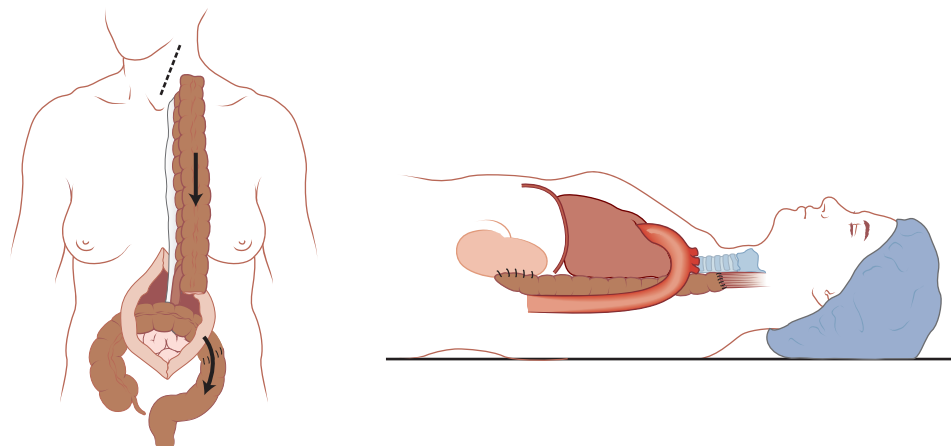


FIGURE 38-18 ■ The posterior mediastinal (in situ) route is the shortest route between the stomach and esophagus. (Adapted from Sugarbaker D, DeCamp M, Liptay M: Surgical procedures to resect and replace the esophagus. In Zinner M, Schwartz S, Ellis H, et al, editors: *Maingot's abdominal operations*, Stamford, CT, 1997, Appleton & Lange, pp 885–910.)

Soft clamps are placed on the ileocolic and right colic arteries, and the right colon is inspected for adequate perfusion through the marginal artery. The right colon is then harvested, leaving the marginal artery intact. An appendectomy is performed. Whether the ileocecal valve and short segment of ileum should be included in the conduit for esophageal anastomosis is controversial. The ileum provides a better size match for anastomosis with the esophagus, and in theory, the ileocecal valve should guard against reflux in the neck. Opponents argue that despite the size mismatch, a hand-sewn anastomosis of the end of the esophagus to the side of the colon is easy, reflux esophagitis is rare high in the neck, and the ileocecal valve may contribute to antegrade obstruction.

Appropriate lengths of right colon are divided with a GIA 75-mm stapler, and the colocolonic anastomosis is performed. From the surgeon's perspective, the right colon conduit is rotated counterclockwise, and the proximal end is drawn up into the neck in atraumatic fashion. The proximal anastomosis is created most easily by a single-layer end of esophagus to the side of the colon along a taenia. Excess length is brought out into the abdomen, and the conduit is tacked to the hiatus. At this point, excess length in the distal conduit can be managed by excising colon at the end of the vascular conduit. The cologastric anastomosis is usually constructed with either EEA staplers or a side-to-side stapled technique. The colon may be brought into the anterior aspect or posterior aspect of the stomach.

Jejunum

Indications. Jejunum may be used to replace a portion of the esophagus as a free graft, pedicled graft, or Roux-en-Y replacement.^{84,85} Replacement of the esophagus with jejunum is indicated when the stomach is not available because of prior surgery or intrinsic disease. When limited distal esophagectomy is planned, jejunum or colon is preferred to stomach as these two conduits are more resistant to the effects of gastroesophageal reflux. Replacement of a distal esophageal peptic stricture should be performed with colon or jejunum in preference to stomach. Interposition of an isoperistaltic segment of intestine is preferable to gastric pull-up, which has a very high incidence of recurrent severe reflux. Free jejunal graft is indicated in limited reconstruction of the cervical esophagus. Roux-en-Y jejunal replacement may be used to replace the stomach and distal esophagus after total gastrectomy including distal esophagectomy.

Contraindications. Intrinsic disease of the small bowel, whether it is a result of inflammatory bowel disease or previous surgery, may prevent use of the small bowel as a conduit. In general, total esophageal replacement cannot be accomplished with jejunum alone because the length is insufficient to reach the neck.

Preparation. Although mechanical bowel preparation is not necessary for jejunal interposition, it is advisable so that colon is available if the jejunum is found to be unacceptable as a conduit or if the blood supply to the jejunum is damaged during harvest, rendering it unusable as a

conduit. Antibiotics (a cephalosporin and an anaerobic antibiotic) should be administered preoperatively.

Roux-en-Y Replacement. Roux-en-Y replacement (Fig. 38-19) may be used for reconstruction after total gastrectomy and distal esophageal resection as indicated in proximal gastric tumors or for esophageal resection into the upper chest. On occasion, a Roux-en-Y replacement may reach the neck, but this is variable, and unlike the stomach, it will not reliably reach the cervical esophagus. When it is used after total gastrectomy, jejunum is divided approximately 20 to 30 cm beyond the ligament of Treitz. The jejunum is elevated outside the abdomen, and the vascular arcade is transilluminated. The proposed point of division is identified, and the line of division of the mesentery is also identified along with the proposed division of several vessels of the mesentery, which will allow movement of the jejunum up into the chest. The proposed feeder vessel is identified and preserved. The serosal surface of the mesentery is scored, and the vessels to be transected are clamped with a soft bulldog clamp. The conduit is observed for several minutes for evidence of ischemia or congestion. By this technique, 60 cm of jejunal conduit can be mobilized. A hole in the transverse mesocolon is made to the left of the middle colic vessels large enough for the jejunum and its mesentery to pass through. For replacement after total gastrectomy, the proximal anastomosis is to the very distal esophagus in the upper abdomen. If distal esophagectomy is also performed as for a malignant lesion of the cardia extending

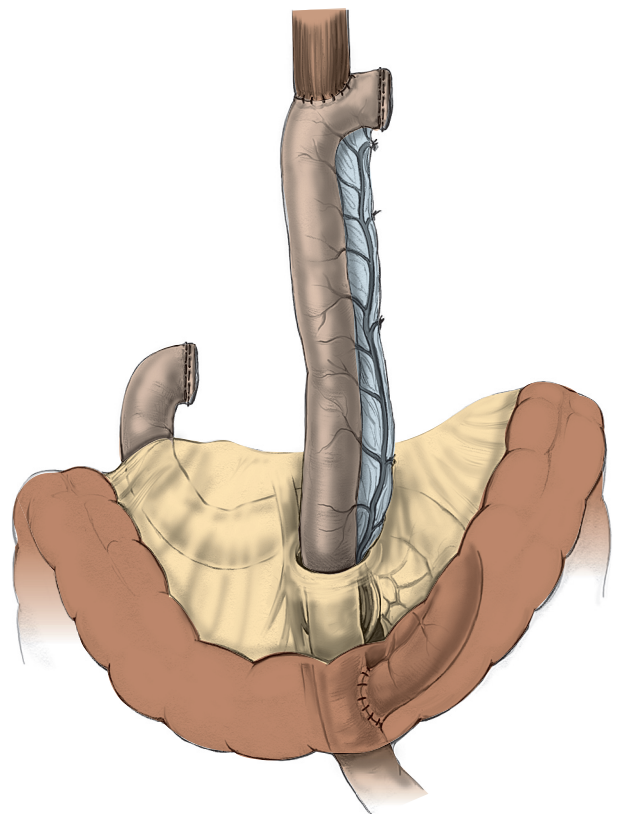


FIGURE 38-19 ■ Roux-en-Y replacement with jejunum is useful for reconstruction after esophagectomy with gastrectomy, as with proximal gastric tumors.

to the gastroesophageal junction, the abdominal incision must be brought across the costal margin into the left sixth or seventh interspace. If, after division of the esophagus and mobilization of the Roux-en-Y limb into the lower chest, additional length of jejunum is needed, the next vessel in the mesenteric arcade is test clamped and then divided.

The esophagojejunal anastomosis can be performed by stapled or hand-sewn techniques. The stapled anastomosis is most easily performed with an EEA stapler. Ideally, a size 33-mm EEA stapler should be used to protect against the development of strictures. The distal esophagus may be gently dilated with a lubricated dilator. A full-thickness 2-0 Prolene suture is used to create a purse-string in the distal esophagus. The shaft of the EEA stapler can be introduced through the stapled end of the proximal jejunum. Care must be taken not to occlude the ongoing lumen of the jejunum with the stapler. Two full-thickness anastomotic doughnuts should be verified. After removal of the EEA stapler, the jejunal end can be closed with a TA 60-mm stapler. A hand-sewn anastomosis in two layers may also be performed. The outer layer is seromuscular on the jejunum to muscular esophagus with 3-0 silk, and the inner layer is full thickness with interrupted 3-0 or 4-0 chromic gut.

The jejunum should be tacked to the hiatus at several points with interrupted silk sutures. This prevents herniation of abdominal contents into the chest and limits tension on the esophagojejunal anastomosis. Similarly, the defect in the colonic mesentery should be closed to prevent an internal hernia. The distal anastomosis can be hand sewn or performed by a side-to-side functional end-to-end stapled technique.

Pediced Jejunal Interposition. A left thoracoabdominal incision is used with a left seventh interspace incision extended across the costal margin and across the rectus muscle. As with the harvest of a Roux-en-Y loop, the jejunum is transilluminated, and an appropriate length of jejunum is selected from a point 20 cm distal to the ligament of Treitz. A single large vessel is used as a feeding vessel for the conduit. The jejunum is transected proximally and distally with a GIA stapler, and the mesentery is divided down each side to the origin of the vessel. The remaining jejunum is reconnected by a side-to-side functional end-to-end stapled technique. The pediced jejunum is tunneled through the mesocolon and brought into the left chest. The proximal anastomosis is constructed like the Roux-en-Y esophagojejunal anastomosis. The jejunogastric anastomosis may be hand sewn in two layers or stapled with an EEA stapler (Fig. 38-20).

Free Jejunal Interposition. Free jejunal graft may reach portions of the upper esophagus that pediced grafts may not. It is not clear whether the use of a short jejunal interposition is preferable to total esophageal replacement with a normal gastric conduit. The use of jejunum carries a lower incidence of gastroesophageal reflux; however, the increased risk of life-threatening graft ischemia and necrosis is significant. Moreover, two anastomoses are required, increasing the risk of anastomotic leak.

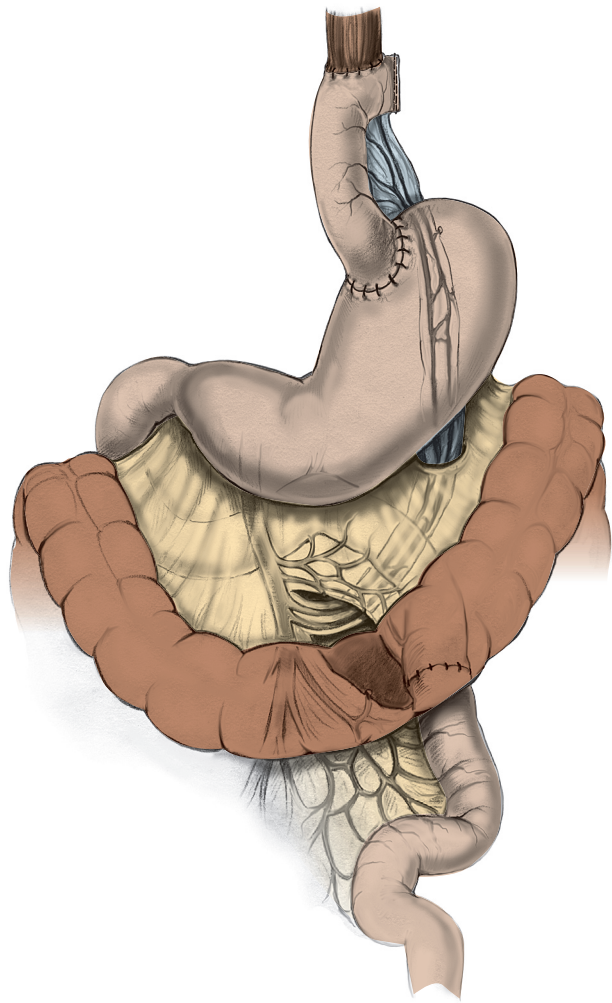


FIGURE 38-20 ■ Pediced jejunum is ideally suited for distal esophageal replacement. An appropriate length of jejunum is harvested beginning 20 cm beyond the ligament of Treitz.

As with the pediced jejunal graft, a short segment of jejunum is chosen for harvest. A left cervical incision is made, and the esophagus and carotid and jugular vessels are isolated. Soon after division of the jejunal vessels with a scalpel, the artery and vein are flushed with heparinized saline. The proximal hand-sewn anastomosis is constructed first, an operating microscope and fine 9-0 or 10-0 suture are used to anastomose the jejunal vessels to the carotid and jugular vessels, and the distal anastomosis is then constructed (Fig. 38-21). The graft is covered with a meshed split-thickness skin graft to monitor graft viability in the postoperative period.

CONSIDERATIONS IN ESOPHAGEAL RESECTION

Perioperative Mortality

Historically, esophagectomy has been associated with the highest perioperative mortality rate of any commonly performed resection. The combination of a long

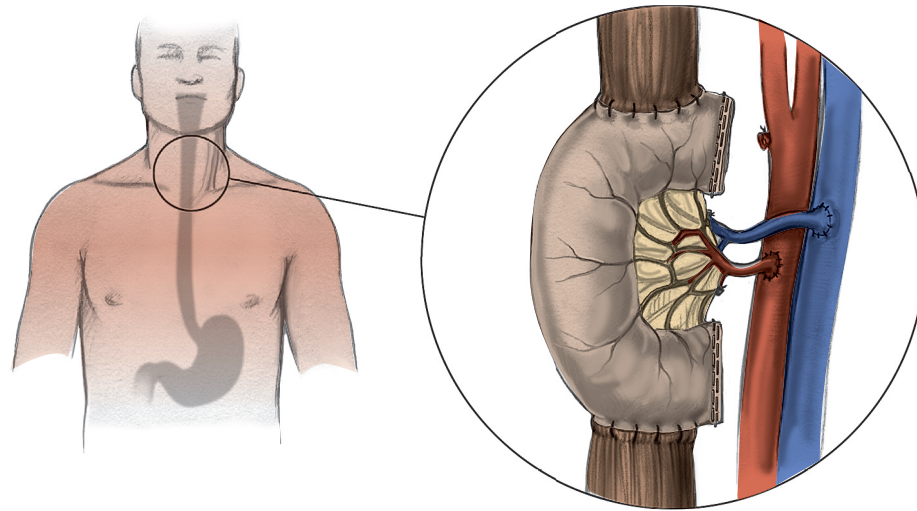


FIGURE 38-21 ■ Free jejunal interposition may be used where pedicled graft will not reach, such as in the proximal esophagus. The arterial and venous supplies are anastomosed to the carotid and jugular vessels under the operating microscope. A split-thickness skin graft covers the graft to allow inspection of graft viability in the perioperative period.

operation traversing three body compartments in an older, potentially malnourished adult with the potential for overwhelming mediastinal sepsis has produced perioperative mortality rates that were initially quoted at 15% to 40%.^{86,87} Reports published after 1980 showed improvement in the mortality rates to approximately 15%, with a large meta-analysis of papers published between 1986 and 1996 showing mortality rates averaging 6% to 10%.^{23,88} Several large academic centers have published large series with mortality rates ranging from 3% to 4%.^{17,70,89}

A relationship between esophagectomy and hospital volume and outcome has been reported, beginning in the late 1970s.⁹⁰ In a review of this topic for the journal *Thoracic Surgery Clinics*, Chang and Birkmeyer⁹¹ noted 11 of 12 studies publishing statistically significant volume-outcome relationships pertaining to esophagectomy. One of the authors had used the Medicare database to produce the largest study to date evaluating mortality and esophagectomy.⁹² His analysis showed that 6337 patients underwent an esophagectomy at 1575 hospitals. Low-volume hospitals were defined as those with fewer than two operations per year. Higher volume hospitals performed more than 19 such operations per year. The in-hospital mortality rate of the high-volume center was considerably lower (8.1%) than that of the low-volume hospital (23.1%). A second report from this same group examined surgeon volume and outcomes.⁹³ Using the Medicare database from 1998 to 1999, they reported that surgical outcome with regard to operative mortality was inversely related to surgeon volume. They found the surgeon volume and hospital volume to be independent factors in outcomes. A low-volume surgeon at a high-volume center has higher mortality rates than does a high-volume surgeon at a high-volume center. The application of this information to policy and certification of hospitals and surgeons for this highly technical operation is beyond the scope of this chapter.

Several studies have identified age as a risk factor for increased morbidity and mortality after an esophagectomy. An analysis of the Nationwide Inpatient Sample

database revealed a 19.9% perioperative mortality rate in octogenarians after esophagectomy. This is significantly different from the 8.8% perioperative mortality after similar surgery in patients 65 to 69 years old ($P < 0.0001$).⁹⁴ It is clear that advances in surgical technique, anesthesia, and intensive care have markedly improved the safety of esophagectomy during the past several decades. In older series, the greatest contributor to perioperative mortality was intrathoracic sepsis caused by either an anastomotic or a conduit leak. The mortality rate from a clinically overt intrathoracic leak may be greater than 50%.⁹⁵ Aggressive, early management of an intrathoracic esophageal leak is essential in limiting its possible fatal effects.

In the more recent, larger series published with mortality rates less than 5%, the most common cause of perioperative death is not conduit leak; rather, it is pulmonary causes: respiratory insufficiency, pneumonia, or pulmonary embolus.^{17,70,89} The combination of a low incidence of leak with early, aggressive management has made the intrathoracic enteric leak less of a factor in perioperative mortality.

Early Perioperative Complications

Anastomotic Leak

The incidence of intrathoracic leak after Ivor Lewis esophagectomy is typically 5% to 10%.^{19,23} The incidence of leak after a cervical anastomosis is higher, generally in the 10% to 15% range.^{23,70} Older studies have quoted cervical leak rates at 25% to 26%, whereas a recent large study described a leak rate of 8%.^{17,87,96} A retrospective evaluation of anastomotic leaks revealed that albumin level below 3 g/dL, positive margins, and cervical anastomosis were risk factors for anastomotic leak after esophagectomy.⁹⁶ Several factors are believed to be responsible for the increased incidence of leak in the cervical position. The increase in length needed may cause increased tension on the anastomosis. Blood supply to the anastomosis may be compromised because it is

farther away from the origin of the gastroepiploic artery, and arterial inflow and venous drainage may be compromised by a tight thoracic inlet. In a randomized trial of hand-sewn versus stapled anastomosis in 102 patients undergoing Ivor Lewis esophagectomy, no significant difference was seen in the incidence of leaks between the two groups. The incidence of leak was 5% after a single hand-sewn monofilament anastomosis and 2% after stapled anastomosis.⁹⁷

The Mayo Clinic published its retrospective review of stapled versus hand-sewn esophagogastric anastomosis.⁹⁸ Hand-sewn esophagogastric anastomosis was performed at the Mayo Clinic only until 2002, when stapling devices were used to resume gastrointestinal continuity. Around this time, 280 patients who underwent an esophagectomy by the transhiatal, transthoracic, or tri-incisional approach were evaluated. It was found that the method of stapling of the anastomosis was safe and associated with a lower leak rate and need for dilation compared with the hand-sewn group. Clearly, the incidence of leak after hand-sewn anastomosis is more operator dependent than with stapled anastomosis, and the reproducibility of the stapled anastomosis is its main advantage.

An intrathoracic leak is a life-threatening event that usually requires immediate operative intervention. Although the mortality rate from this complication has been lowered at large centers during the past few decades, the cost in ICU and hospital stay and delayed recovery remains high. The intervention required ranges from repair and drainage of a limited leak, to placement of a T tube, to complete diversion by split fistula and reduction of viable gastric conduit into the abdomen. The more critically ill the patient is as a result of the leak, the more aggressive and definitive the treatment required. In rare cases (a clinically silent, small contained leak draining back into the conduit not near vital structures such as the trachea or aorta), such a leak may be treated conservatively with antibiotics and maintenance of strict NPO status.

Historically, a thoracic leak is associated with a higher mortality rate than a cervical anastomotic leak is. With adequate drainage, some authors are questioning this belief.^{99,100} As stent technology has developed, there have been reports of its use for control of an anastomotic leak.¹⁰¹⁻¹⁰⁴ Siewert and coworkers¹⁰¹ inserted a self-expanding covered metal stent at the site of intrathoracic leak in 10 patients. Radiologic methods confirmed closure of anastomotic leak in all but one patient. In this patient the stent was adjusted, and closure of the leak was confirmed. Stent migration requiring new stents and adjustment occurred in four patients. The authors found that in all but one patient, complete leak closure was achieved. Two patients died of reasons not related to stent placement, but further details were missing from the report. Stent technology continues to develop new indications for its use; however, indications for control of an anastomotic leak have not been confirmed by large randomized trials.

Leak after a cervical anastomosis, although more frequent, is uncommonly a life-threatening event. Older series have described mortality from a cervical leak as high as 20%, although recent series have described mortality rates that are much lower.^{17,95} Cervical anastomotic leak occurs, in general, later than intrathoracic leaks do,

with many diagnosed only on routine postoperative barium swallow study or on commencement of oral feeds after a normal barium swallow study.¹⁰⁵ Patients with cervical leaks can develop low-grade fevers, localized redness, or wound discharge. Treatment usually entails limited opening of the neck incision and placement of a wick. Larger leaks resulting from anastomotic necrosis may be treated with a Silastic stent or T tube. Leaks into the chest after cervical anastomosis, resulting from either retraction of the anastomosis into the chest or dependent drainage of enteric contents into the chest, must be treated in the same manner as any intrathoracic leak. The main long-term sequela of a cervical anastomotic leak without signs of systemic sepsis is an increased incidence of delayed stricture formation.

Respiratory Complications

Pneumonia, atelectasis, and respiratory failure, in the modern era, are probably the most serious complications after esophagectomy given their relatively high incidence and potentially life-threatening consequences. The incidence of pneumonia after esophagectomy ranges from 2% to 47%.^{31,95} Respiratory failure after esophagectomy occurs in 4% of patients.²³ The assumption that avoidance of thoracotomy results in fewer pulmonary complications than with a transthoracic esophagectomy has not conclusively been supported by the literature. In the randomized trial of Goldmine and associates²⁸ comparing transhiatal with Ivor Lewis esophagectomy, the incidence of pneumonia was 20% for both groups. In the randomized trial of Chu and coworkers³⁹ comparing transhiatal with Ivor Lewis esophagectomy in 39 patients, the incidence of pneumonia was 10% after transhiatal and 0% after Ivor Lewis resection (no significant difference). A European randomized trial comparing transhiatal with en bloc tri-incisional esophagectomy showed a difference in the rate of pulmonary complications (pneumonia or lobar atelectasis) in the tri-incisional (57%) versus the transhiatal group (27%).³² The unusually high incidence of pulmonary complications in both groups of this series should be questioned. Typically, rates of pulmonary complications are in the 20% range.²⁴ Previous series involving en bloc resections have described pneumonia rates of 5%.⁶³

A muscle-sparing, limited thoracotomy, epidural anesthesia, and early ambulation are essential in limiting post-thoracotomy respiratory complications. A multivariate analysis showed that age and decreased FEV₁ are predictive of postoperative respiratory failure.¹⁰⁶ Age, preoperative chemoradiation, and decreased FEV₁ have also been identified as risk factors for respiratory compromise after an esophagectomy.¹⁰⁷

As discussed in the earlier section on MIE, many proponents of smaller access surgery have reported fewer pulmonary complications with this approach to an esophagectomy.

Recurrent Laryngeal Nerve Injury

The incidence of recurrent nerve injury and vocal cord dysfunction after esophagectomy is higher with a cervical anastomosis than with an intrathoracic anastomosis.

Malfunction of a single vocal cord, although seemingly a minor complication resulting in hoarseness, can lead to a series of life-threatening complications if it is not recognized early and treated. The lack of vocal cord apposition makes an effective cough and clearance of pulmonary secretions difficult. This is exacerbated by the loss of airway protection during swallowing and repeated episodes of overt aspiration or microaspiration.

As expected, the incidence of recurrent nerve injury is higher with a cervical anastomosis (11%) than with an intrathoracic anastomosis (5%).²³ In the right thorax, the recurrent nerve may be injured by traction on the vagus nerves or by cautery near the nerve as it recurs around the subclavian artery. In addition, a neck dissection may result in direct injury to the recurrent nerves as the esophagus is dissected away from the tracheoesophageal groove. In the neck, dissection must be performed immediately against the esophagus, with care taken to recognize and avoid the recurrent nerve. Dissection close to the recurrent nerves does not necessarily place them at risk; one series of three-field lymph node dissection with direct dissection of all lymph nodes adjacent to both recurrent nerves resulted in a recurrent nerve injury rate of only 6%.⁶⁶

Early recognition and treatment of a recurrent nerve injury (in itself a non-life-threatening condition unless both cords are simultaneously injured) are essential in preventing the potentially lethal complications of aspiration and pneumonia. Any patient who presents with hoarseness and an ineffective cough after esophagectomy should undergo fiberoptic laryngoscopy. Unilateral paralyzed vocal cords should be medialized by either injection or prosthesis implantation. Early intervention can lead to a low incidence of pulmonary complications.¹⁷

Bleeding

The incidence of bleeding after esophagectomy is approximately 5% and does not vary according to the techniques used.²³ In a meta-analysis, average blood loss was slightly higher for the transthoracic approach, averaging 1000 mL, than for the transhiatal approach, averaging 728 mL.²⁴ Anticoagulants and antiplatelet agents should be stopped before esophagectomy is performed. Low-dose subcutaneous heparin does not increase the incidence of bleeding after esophagectomy. Direct arterial branches from the aorta to the esophagus usually found in the lower thorax should be clipped, not simply cauterized. Larger arteries supplying the esophagus branch into a fine plexus of arterioles at a point 1 to 2 cm away from the esophagus. If blunt dissection of the esophagus is used, it should be kept immediately adjacent to the esophagus with disruption of only the smaller arterioles.

Chyle Leak

The thoracic duct drains the cisterna chyli in the abdomen beginning at the L2 level. It enters the chest through the aortic hiatus and ascends through the right chest behind the esophagus along the vertebral bodies between the azygos vein and the aorta. On occasion, more than one

channel exists in the lower chest at the level of the hiatus. At approximately the T6 level, it crosses to the left side behind the aorta and ascends along the left side of the esophagus posterior to the left subclavian artery. Above the clavicle, the duct descends behind the carotid sheath and anterior to the anterior scalene muscle and phrenic nerve to empty into the junction of the left internal jugular and subclavian vein. The duct can be injured at any point along dissection of the esophagus. The incidence of chyle leak after esophagectomy ranges from 2% to 10%.^{23,31} The incidence is higher after transthoracic resection, probably as a result of an extended radial dissection of the esophagus and associated nodal tissue. Prophylactic mass ligation of the duct at the hiatus may help decrease the incidence of postoperative leak. If chest tube output is 1000 mL/day or more 48 hours after esophagectomy, chylothorax should be suspected. Diagnosis can be difficult because the classic milky appearance of chyle is apparent only in a fed patient. Gram stain will exclude polymorphonuclear cells. Fluid should be sent for determination of triglyceride level, cholesterol level, and cell count. A triglyceride level of greater than 1 mmol/liter is highly suggestive of a chyle leak, as is a lymphocyte count of greater than 90%. A cholesterol-to-triglyceride ratio of less than 1 and confirmation of chylomicrons on electrophoresis have also been suggested to be diagnostic of a chyle leak. Perhaps the best and simplest test is feeding cream at 30 mL/hr through the J tube for 3 to 4 hours, watching for a change from serous pleural fluid to a milky fluid.

There is no role for conservative management of a high-output chyle leak after esophagectomy. Continued loss of lymphocytes, protein, fats, and fluid at a rate of 1 liter/day or more in a malnourished patient healing from a major operation invites disaster. Once the diagnosis is confirmed, or even if the diagnosis is highly suspected, the patient should be brought back to the operating room for ligation of the duct at the level of the hiatus. Cream should be instilled through the J tube for several hours before reoperation. The approach to ligation of the duct should be through a right thoracotomy or thoracoscopy. The exact site of injury can often be located after the patient has been given cream enterally. It may be repaired with pledgeted 4-0 or 5-0 monofilament sutures. If there is any doubt about the integrity of the repair, the duct should be mass ligated at the level of the hiatus. The pleura is incised, and a 0 silk mass ligature is used to encompass all tissue between the azygos vein and aorta along the spine. A pledgeted suture should be used if tissue integrity is poor. A careful search to confirm cessation of the leak should be performed before closure.

Noninvasive methods for closure of thoracic duct leaks have been proposed. The thoracic duct can be cannulated percutaneously by puncture into the cisterna chyli and embolized with coils or fibrin glue. In a trial of 42 patients (9 of whom were postesophagectomy patients), the thoracic duct could be embolized in 26 patients, and 16 of these were cured.¹⁰⁸ This technology is in evolution and at this point should be reserved for complex patients for whom surgical repair has failed or for patients who are not candidates for surgical repair.

Cardiovascular Morbidity

Perioperative arrhythmias after esophagectomies have a reported incidence of 20% to 60%.¹⁰⁹⁻¹¹⁴ The development of new-onset perioperative atrial fibrillation has been linked to anastomotic leaks and pulmonary complications.¹¹¹ Although arrhythmias can be treated effectively with calcium channel blockers and beta blockers,¹¹⁵ patients given prophylactic digoxin did not have a reduced incidence of cardiac arrhythmias.¹¹⁰

The incidence of myocardial infarction after esophageal resection is 1% to 2%.¹⁰⁹ Currently, a double-blinded, randomized trial is under way in 182 centers in 21 countries to evaluate the benefit of perioperative beta blockage in patients undergoing noncardiac thoracic surgery. The study has entered 6400 patients and is set to accrue 10,000 patients.¹¹⁶

Late Perioperative Complications

Anastomotic Stricture

Although anastomotic stricture is never life-threatening, it is not uncommon and, if severe, negates the primary benefit of intestinal continuity after esophageal replacement. A large retrospective meta-analysis concluded that the incidence of symptomatic stricture is somewhat higher after anastomosis in the cervical position (28%) than after Ivor Lewis resection (16%).²³ This is in part because of the higher incidence of leak after cervical anastomosis. In an examination of risk factors of benign stricture after transhiatal esophagectomy, the use of a stapled anastomosis, an anastomotic leak, and the presence of cardiac disease were the only risk factors identified for the development of stricture.¹¹⁷ Earlier studies had identified intraoperative blood loss and poor vascularization of the gastric conduit as risk factors.^{118,119} From these studies, it is apparent that three factors influence the development of postoperative stricture: infection, ischemia, and mechanical issues.

Anastomotic leak is a well-known risk factor for the development of a delayed stricture. It is curious that Honkoop and associates¹¹⁷ found no difference in the incidence of delayed stricture between clinically overt leaks and those detected by swallow only. Preemptive bougienage dilation (7 to 10 days after operation) has been advocated by some physicians to prevent the development of stricture after cervical leak.¹²⁰ Ischemia is one of the major contributors to anastomotic leak, and it is difficult to determine what effect this alone has on the development of postoperative stricture. All efforts to avoid ischemia (adequate blood supply, systemic oxygen delivery, avoidance of congestion) should certainly be made to prevent both leak and stricture. It is also evident that mechanical factors influence the development of stricture. Law and colleagues⁹⁷ performed a randomized trial of hand-sewn versus EEA-stapled Ivor Lewis anastomosis. The incidence of stricture after the hand-sewn anastomosis was 9%, whereas that after stapled anastomosis was 40%. Strictures were not seen with the 33-mm EEA stapler but had a 12.5% incidence with the 29-mm stapler and a 43% incidence when a 25-mm stapler was

used. Not every esophagus will allow a 33-mm stapler, but it should be used whenever possible. Otherwise, a hand-sewn anastomosis or a different stapling technique should be considered. A retrospective study performed at the University of Texas MD Anderson Cancer Center indicated that side-to-side stapled esophagogastric anastomosis represented a trend in which this technique had lower associated postoperative dysphagia and need for stricture dilation compared with its hand-sewn counterparts.¹²¹

Postoperative stricture is usually managed by repeated bougie dilation. In Honkoop's study, three dilations, on average, were needed to achieve normal swallowing. Perforation occurred in 2 of 519 episodes of dilation. Both of these perforations resulted in death of the patient. In the study by Law and colleagues, 53% were treated by one dilation, 20% by two, 12% by three, and 8% by four. No patient in either study was treated by reoperation.

Martin and coworkers¹²² reported that most postesophagectomy patients will have some degree of dysphagia. Some have advocated early dilation of the anastomosis and conduit in patients with dysphagia even if there is no anatomic reason for the dysphagia.¹²³

Barthel and colleagues¹²⁴ advocate the use of a silicone stent as an alternative to serial dilations. They evaluated eight patients who had persistent anastomotic strictures after a transhiatal esophagectomy. They placed 13 stents in eight patients with strictures between 20 and 23 cm from the incisors. All strictures were less than 2 cm and had a predilation luminal diameter of 2 to 5 mm. The authors concluded that stent placement significantly prolonged the interval between endoscopic interventions that are necessary for management of strictures. However, their data did not show permanent resolution of the stricture after the stent was removed.

Postresection Reflux

Reflux of duodenal contents into the conduit occurs to some degree after esophagectomy in virtually all patients. It is not clear that preservation of the integrity of the pylorus protects against bile reflux. In fact, a study by Romagnoli and colleagues¹²⁵ involving 24-hour bile monitoring of the denervated gastric conduit in 16 patients showed elevated concentrations of bile in the stomach irrespective of the presence or absence of a drainage procedure.

The incidence of severe postoperative reflux requiring intervention after distal esophagectomy with esophagogastric anastomosis low in the chest approaches 20%.¹²⁶ For this reason, when esophageal replacement is contemplated for a distal peptic stricture, colon or jejunal interposition should be used. These conduits, in the isoperistaltic position, are more resistant to the effects of gastric reflux and provide active peristalsis that allows clearance of bile.

Impaired Conduit Emptying

Several factors have been implicated in delayed conduit emptying after esophagectomy; these factors include truncal vagotomy, absence of pyloric drainage procedure,

swelling at the pyloroplasty site, kinking of redundant conduit in the lower chest, and conduit that is too wide and patulous. Some of these variables are difficult to assess, whereas others have been carefully studied. After truncal vagotomy for ulcer disease, there is a 25% incidence of impaired gastric emptying.¹²⁷ Whether this applies to transposed stomach after esophagectomy is not clear. One study showed that delayed emptying after esophagectomy with gastric replacement was less in those undergoing pyloroplasty (the time of emptying of radio-labeled water was 378 minutes with no pyloroplasty versus 161 minutes in patients undergoing pyloroplasty).¹²⁸ Other studies showed no objective difference in gastric conduit emptying.¹²⁹ In any event, there is often poor correlation between gastric emptying tests and symptoms.

Fok and associates¹³⁰ conducted a prospective randomized trial of pyloroplasty versus no pyloroplasty in 200 patients undergoing Ivor Lewis esophagectomy with gastric reconstruction. There were no complications from the pyloroplasty procedure. Of the 100 patients who had no drainage procedure, 13 patients had symptoms of delayed gastric emptying. Two of these patients died as a result of aspiration pneumonia, one required reoperation, and three others had prolonged symptoms. The daily postoperative nasogastric drainage was not significantly different between the two groups. Gastric emptying measured at 6 months was 6 minutes in the pyloroplasty group and 24 minutes in the patients without pyloroplasty. The patients without pyloroplasty also had more symptoms attributable to impaired gastric emptying at 6 months than the pyloroplasty patients did. The authors strongly advocate a routine pyloric drainage procedure. The same group conducted a randomized trial of pyloroplasty compared with pyloromyotomy and found both to be effective and safe procedures.¹³¹ Six months after the procedure, gastric emptying was twice as fast in the pyloroplasty groups versus the pyloromyotomy group; however, the incidence of symptoms appeared to be no different.

Kim and associates¹³² reported on balloon dilation in 21 patients who had delayed gastric emptying after an esophagectomy. Gastric emptying before and after dilation was measured by radioisotope imaging. Single dilation was performed in 19 patients. Two patients required a second dilation. Gastric emptying improved after dilation in 67% of the patients; seven patients were greatly improved and six patients were slightly improved, whereas six patients showed no improvement. There were no complications. This is clearly a small case report, and larger studies need to be performed to observe any benefit from balloon dilation.

The width of the gastric conduit is also believed to influence the rate of emptying. The gastric tube should be kept narrow, with the width not significantly exceeding that of the antrum. A retrospective study examined the relationship between conduit emptying and size and found that patients with a narrow gastric tube had a far lower incidence of symptoms attributable to delayed gastric emptying (3%) than did patients with whole stomach (38%) or distal two-thirds stomach (14%) conduits.¹³³ A conduit that is too narrow, however, may become ischemic from a compromised arterial inflow and

venous congestion. In the authors' opinion, conduit diameter should not be less than 5 cm. Proper length of the gastric conduit is also important because excess conduit can fold over into the right chest and has been associated with impaired emptying.

Local Recurrence

Factors involved in local recurrence include resection margins and clearance of adjacent nodal disease. Tam and coworkers¹³⁴ found a correlation between the incidence of local recurrence and the lateral spread of tumor outside the esophageal wall (T3) but no correlation with tumor differentiation or lymph node metastasis. As discussed earlier, the importance of complete clearance of nodal tissue is debated among proponents of complete lymphadenectomy (by transthoracic or en bloc dissection) and proponents of simple transhiatal dissection.

The issue of recurrence with an incomplete linear margin is better understood. The palpable intraoperative *in situ* resection margin will be larger than the contracted gross postresection margin, which in turn is longer than the final fixed margin. Siu and colleagues¹³⁵ estimated that margins after removal of the esophagus were approximately 50% of the *in situ* margin. Descriptions of margin length must take this factor into account. Tam and coworkers¹³⁴ examined the *in situ* resection margins of 100 patients with squamous cell carcinoma of the esophagus. When the *in situ* margin was less than 5 cm, there was a 20% incidence of anastomotic recurrence; between 5 and 10 cm, there was an 8% chance; and when the margin was greater than 10 cm, there were no anastomotic recurrences. Wong¹⁶ further pointed out that it is difficult to obtain a 10-cm margin, because the length of the average esophageal tumor is 6 cm. Assuming the average esophagus is 25 cm in length, only distal esophageal tumors can, on average, be resected with a 10-cm margin if the larynx is to be conserved. Another author suggested that an adequate distal margin after resection of adenocarcinoma of the gastroesophageal junction should be 6 cm.¹³⁶

Long-Term (5-Year) Survival

Long-term survival remains an elusive goal for the medical and surgical oncologist caring for a patient with esophageal cancer. Despite advances in perioperative care that have reduced the perioperative mortality rate to 7% and less, 5-year survival has changed marginally during the past 2 decades. The 5-year survival described by Cunha-Melo and associates⁸⁶ in their analysis of cases reported between 1953 and 1978 (18%) is similar to that described in the meta-analysis by Hulscher and coworkers³¹ covering the years 1990 to 1999 (22%). It remains to be seen whether the introduction of neoadjuvant treatment for advanced esophageal cancers (invading through the esophageal wall or with positive nodes) will change the overall survival of patients with esophageal cancer. Three randomized trials using neoadjuvant chemoradiation before esophagectomy have been performed. A trial randomizing 100 esophageal cancer patients to preoperative chemoradiation followed by

transhiatal esophagectomy versus transhiatal esophagectomy alone showed that survival in the neoadjuvant group was 30% at 3 years versus 16% in the surgery-alone group; the difference was not statistically significant.¹³⁷ A European study randomizing 282 patients with squamous cell cancer to neoadjuvant chemoradiation followed by en bloc transthoracic esophagectomy and to esophagectomy alone found no difference in 5-year survival.¹³⁸ Walsh and coworkers¹³⁹ randomized 113 patients with adenocarcinoma to surgery alone versus chemoradiation followed by surgery. Five-year survival was approximately 50% in the neoadjuvant group and unusually poor in the surgery-alone group (8%); the difference was statistically significant. Larger trials have been attempted; however, they have encountered difficulty in enrolling patients in a randomized fashion, and the true benefit of neoadjuvant chemoradiation may never be measured.

A few isolated series in selected centers using radical en bloc dissection of the esophagus with three-field lymph node dissection have described 5-year survival rates in the 40% to 50% range.^{67,69} These results are discussed in the sections on en bloc resection and three-field lymph node dissection.

SUMMARY

The reduction in perioperative mortality of esophagectomy from more than 40% during the past 50 years to as low as 3% as described in several large academic centers is attributable to improvements in selection of patients, operative technique, and intensive care and early recognition and aggressive management of perioperative complications. Minimizing complications and optimizing chances of cure require that the skilled esophageal surgeon be familiar with the anatomy of the neck, chest, and abdomen and be well trained in and ready to use a variety of routes of esophageal resection and methods of reconstruction. As MIE has become more prominent, numerous institutions have reported their experience, suggesting an advantage to MIE over open surgery. However, randomized controlled trials need to be performed to affirm these claims.

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MULTIMODALITY THERAPY FOR ESOPHAGEAL CANCER

Wayne L. Hofstetter • Boris Sepesi

CHAPTER OUTLINE

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OVERVIEW: PRINCIPLES OF MULTIMODALITY THERAPY

Achieving real improvement in the treatment outcomes for esophageal cancer has been a slow process. Arguably, the major hurdles impeding our ability to diagnose and treat the disease were, for the most part, overcome in the last century. Establishing reliable and safe anesthetic techniques for thoracic surgery and minimizing mortality from an esophageal resection while maximizing local/regional control (to the extent that radical surgery is capable) had significant impact in placing surgery at the forefront of esophageal cancer therapy. Yet, the breakthrough discovery that would allow us to cure a significant percentage of people with this diagnosis eludes us. Radical surgery reached a ceiling of effectiveness, and the field is now in the process of backing away from larger resections in favor of minimizing trauma and operative morbidity. Nominal improvements in survival outcomes have been made by avoiding mortality rather than salvaging sicker patients, by focusing on more appropriate patient selection by avoiding those that are at high risk for perioperative mortality or distant failure. Whereas this gives the impression that we are improving, it leaves behind the patients who are not salvageable with existing local/regional therapies. Even though resection has been considered the backbone of esophageal cancer treatment, we have learned that radical resections with or without other forms of local/regional therapy are not adequate to cure advanced disease in most cases. Distant recurrence

continues to be the main cause of death in patients with esophageal cancer.

As long as we lack truly effective methods of screening, most patients with esophageal cancer will present with locally advanced disease. Strategies that address both local/regional as well as distant disease have the most potential to realize real gains in survival outcomes for patients who have esophageal cancer. The early evolution of a multimodality treatment paradigm started decades ago, first with the recognition that a cure could be obtained in some patients without the use of surgery. But the relatively poor local/regional control attained with (nonoperative) medical therapy led to the concept that multimodality therapy that involved surgery could be feasible and could more effectively address both compartments of disease, local and lymphatic. The combination of local and systemic therapies has become the focus of many clinical trials investigating the role and timing of each method.

Preoperative (neoadjuvant) combination therapy is based on principles of patient tolerance and compliance with therapy compared to postoperative therapy (adjuvant). What became apparent in early trials of multimodality therapy was that patients were more frequently able to receive all of their therapy if it was administered before surgery. Also of interest is that when patients receive therapy while tumor is *in vivo*, therapy response can be directly observed via imaging and later pathologically assessed after resection. These clinical findings amount to surrogate endpoints of efficacy. In contrast, advocates of adjuvant therapy administer therapy only to

patients with indications based on final pathologic analysis, thus sparing some patients the unnecessary toxic effects of treatment.

RADIATION THERAPY

Before the surgical era, radiation was considered the primary treatment modality for esophageal cancer. Early experience with radium bougies demonstrated esophageal tumor regression but rarely complete cure. With the evolution of surgical care, external beam radiation became a component of a multidisciplinary approach to esophageal cancer therapy with the goal of sterilizing areas within or around the operative field.¹

Preoperative Radiation Therapy and Surgery

Randomized trials of preoperative radiation therapy for esophageal cancer focused on administering intermediate radiation doses of 20 to 40 Gy for the purpose of decreasing local recurrences (Table 39-1). The lower dose of radiation was given in an attempt to avoid surgical/treatment toxicity. These trials included primarily patients with squamous cell carcinoma (SCC), and none of the trials demonstrated significant benefits of adding radiation therapy to resection.²⁻⁵ A meta-analysis of 1147 patients by Arnott et al (1998) reiterated that preoperative radiation alone does not improve survival in resectable esophageal cancer.⁶ However, lumping patients with different tumor histology and location into one group for the analysis may have confounded the results. Another potential criticism of these studies is that modern forms of radiation therapy are more precise, effective, and less toxic, allowing for higher dose administration to achieve a desired effect.

Surgery and Adjuvant Radiation Therapy

The patients that surgeons were faced with decades ago were different than patients we commonly see today. Squamous cell cancer, with its inherent comorbidities, was the dominant histology. Tumors were large, often involving surrounding structures, and patients were often sick with malnutrition, cirrhosis, and/or lung disease. Preoperative staging was limited to barium swallow and very low resolution computed tomography imaging, yielding

very inaccurate results. Attaining complete surgical margins (R0) was frequently difficult, and failure within or around the surgical field was common. The issue of local/regional recurrences following resection led to the consideration of postoperative radiation therapy (PORT) for esophageal cancer. The rationale for this approach was the ability to deliver a higher dose (40 to 60 Gy) of radiation postoperatively without worsening perioperative complications. Although PORT was described in the 1960s, it was in the 1980s that some prospective trials demonstrated that PORT could achieve better local control and perhaps improve survival compared with surgery alone. In fact, PORT for esophageal cancer appeared to be potentially beneficial in some of the phase III trials (Table 39-2).⁷⁻¹⁰ However, the results from the four published randomized trials are conflicting: some were positive, whereas others showed no benefit. Those that showed a benefit have been criticized for selection bias. Notably, none of these trials used newer radiation techniques such as intensity-modulated radiation therapy and proton therapy, which have become more widely available than they were at the time of these studies.

CHEMOTHERAPY

There are several reasons that chemotherapy would seem to be an attractive treatment modality for esophageal cancer. The most frequent mode of death from esophageal cancer is attributed to metastatic disease. Naturally, the concept of delivering systemic chemotherapy to treat hematogenous disease would seem advantageous. Chemotherapy is also capable of downstaging larger, marginally resectable tumors, which could allow for an improvement in complete (R0) resection rates and decrease the incidence of local/regional recurrence.¹¹ Shrinking tumors also allows patients to become nutritionally replete and independent from supplements as dysphagia resolves. Finally, chemotherapy acts synergistically with radiation as a local/regional therapy, further strengthening arguments for its use.

Current chemotherapeutic regimens are typically delivered as a doublet or triplet combination based on platinum compounds given in concert with 5-fluorouracil (5-FU) or a taxane.¹² This approach has had encouraging results in early phase II trials, in some cases producing clinical responses in up to 50% of patients with the occasional complete pathologic response.

TABLE 39-1 Randomized Trials of Preoperative Radiation Therapy for Esophageal Cancer

Investigators	Year	Histology	Total Number of Patients	Treatment	5-Year Survival Rate (%)	P
Launois et al ²	1981	SCC	124	XRT (40 Gy) + surgery	12	NS
				Surgery alone	10	
Wang et al ³	1989	SCC	206	XRT (40 Gy) + surgery	35	NS
				Surgery alone	30	
Gignoux et al ⁴ (EORTC)	1987	SCC	208	XRT (30 Gy) + surgery	10	NS
				Surgery alone	10	
Arnott et al ⁵	1992	SCC/EAC	176	XRT (20 Gy) + surgery	17	NS
				Surgery alone	9	

EAC, Esophageal adenocarcinoma; EORTC, European Organisation for Research and Treatment of Cancer; NS, not significant; SCC, squamous cell carcinoma; XRT, radiation therapy.

TABLE 39-2 Randomized Trials of PORT (40-60 Gy) for Esophageal Cancer

Authors	Year	Histology	Total Number of Patients	Treatment	Median Survival Duration (months)	3-Year Survival Rate (%)	P
Ténière et al ⁷	1991	SCC	221	Surgery + XRT	18.0	26.0	NS
Fok et al ⁸	1993	SCC	130	Surgery alone	18.0	24.0	0.0200
				Surgery + XRT	8.7	11.0	
				Surgery alone	15.0	22.0	
				Surgery + XRT (curative)	15.0	24.0	
				Surgery alone (curative)	21.0	28.0	
Zieran et al ⁹	1995	SCC	68	Surgery + XRT (palliative)	7.0	0	0.0900
				Surgery alone (palliative)	12.0	15.0	
				Surgery alone	—	22.0	
Xiao et al ¹⁰	2003	SCC/EAC	495	Surgery + XRT	—	43.5	NS
				Surgery alone	—	50.9	
				Surgery + XRT (subset analysis)	—	43.2	
			272	Surgery alone	—	23.3	0.0027

EAC, Esophageal adenocarcinoma; NS, not significant; PORT, postoperative radiation therapy; SCC, squamous cell carcinoma; XRT, radiation therapy.

TABLE 39-3 Randomized Trials of Preoperative Chemotherapy for Esophageal Cancer

Investigators	Year	Histology	Total Number of Patients	Agents	3-Year Survival Rate (%)	Median Survival Duration (months)	P
Roth et al ¹³	1988	SCC	36	Cis, Vb, Bleo	25	10	NS
Schlag et al ¹⁴	1992	SCC	69	None	5	10	NS
				Cis, 5-FU	—	8	
Law et al ¹⁵	1997	SCC	147	None	—	9	NS
				Cis, 5-FU	44	17	
Ancona et al ¹⁶	2001	SCC	96	None	31	13	NS
				Cis, 5-FU	44	24	
Kelsen et al ^{17,18} (RTOG 8911)	1998/2007	SCC + EAC	440	None	41	15	NS
				Cis, 5-FU	23	15	
MRC ¹⁹	2002	SCC + EAC + UD	802	None	26	16	<0.005
				Cis, 5-FU	43*	16.8	
Allum et al ²⁰ (OEO2)	2009	SCC + EAC + UD	802	None	34*	13.3	0.030
				Cis, 5-FU	23	—	
Cunningham et al ²¹ (MAGIC)	2006	EAC	503	None	17	—	0.009
				ECF (before and after surgery)	36	—	
Ychou et al ²²	2011		224	None	23	—	0.02
				Cis, 5-FU	—	—	

*Two-year survival rates.

Bleo, Bleomycin; Cis, cisplatin; EAC, esophageal adenocarcinoma; ECF, epirubicin, cisplatin, and 5-FU; 5-FU, 5-fluorouracil; MRC, Medical Research Council; NS, not significant; SCC, squamous cell carcinoma; UD, undifferentiated carcinoma; Vb, vinblastine.

Preoperative Chemotherapy and Surgery

There are several prospective randomized trials comparing chemotherapy followed by surgery with surgery alone (Table 39-3).¹³⁻²² A landmark trial by Roth and colleagues compared esophagectomy against cisplatin-based chemotherapy followed by esophagectomy in patients with mid-distal esophageal SCC.¹³ The major contribution of this study was the observation that patients who achieved a major or complete response to chemotherapy (47% and 5%, respectively) reached a significantly longer median survival compared with nonresponders (20 months versus 6 months; $P = 0.008$). This study demonstrated that within populations of similar tumors there is biological

heterogeneity leading to variable susceptibility to therapy, and treatment response translated to survival outcome benefits.

One of the largest randomized trials of combined preoperative and postoperative chemotherapy versus surgery alone in esophageal cancer patients was the North American Intergroup trial (INT 0113).^{17,18} The addition of chemotherapy to surgery in this trial failed to demonstrate a significant survival advantage. One of the notable drawbacks of the trial included a low compliance with therapy in both the preoperative (66%) and postoperative (38%) chemotherapy regimens, and outdated staging and response evaluation based on the use of barium swallow. The observed local/regional recurrence rate in this trial

was 30%. These results became one of the motivating influences to perform more radical surgery and perhaps to include radiation therapy to the multimodality treatment regimen in future trials. Ultimately, the 3-year survival rate in this trial did not reach its goals (23% for chemotherapy plus surgery versus 26% for surgery alone; $P = 0.74$).

In contrast to the Intergroup 0113 trial, the Medical Research Counsel (MRC) trial, a large prospective, randomized trial that also evaluated the benefit of chemotherapy plus surgery versus surgery alone in locally advanced esophageal cancer, demonstrated significant survival improvement with additional therapy.¹⁹ This trial included 802 patients randomized to receive chemotherapy followed by esophagectomy versus esophagectomy alone. The chemotherapy that was administered in this trial (cisplatin + 5-FU) was tolerated far better than the treatment in the Intergroup trial, with the MRC trial showing an 86% compliance rate with therapy. The additional treatment resulted in a survival benefit compared to surgery alone. This advantage persisted after a median follow-up duration of 6 years when the long-term results of the trial were published in 2009; the 5-year survival rates of patients treated with chemotherapy plus surgery were 23% compared to 17% with surgery alone ($P = 0.03$). Patients with either adenocarcinoma or SCC experienced a survival benefit.²⁰

The 2006 MRC Adjuvant Gastric Infusion Chemotherapy (MAGIC) trial also demonstrated a survival advantage using preoperative chemotherapy.²¹ In this randomized trial, patients received perioperative treatment with cisplatin, 5-FU, and epirubicin in three cycles before and after surgery. Patients in the treatment arm had better overall (hazard ratio [HR], 0.75 [95% confidence interval (CI), 0.60-0.93]; $P = 0.009$) and progression-free (HR, 0.66 [95% CI, 0.53-0.80]; $P < 0.001$) survival compared to those in the surgery-alone arm. Note that most enrolled patients in this trial had gastric carcinoma, with only a subgroup having esophageal or gastroesophageal junction (GEJ) tumors.

Overall, trials of preoperative chemotherapy have reported a mixture of efficacy. The MRC and MAGIC trials indicate that the addition of chemotherapy to esophagectomy for resectable esophageal cancer is beneficial. However, completeness of resection in these trials is also clinically relevant. The Intergroup trial had a very

low R0 resection rate (partially because of poor compliance with surgery). Considering that R0 resection is a significant predictor of survival in most patients with solid organ malignancies, the question arises whether chemotherapy combined with radical en bloc surgery or chemoradiotherapy and surgery would achieve better R0 resection rates and better overall outcomes.

Surgery and Adjuvant Chemotherapy

Achieving accurate clinical staging of esophageal cancer is a challenge that frequently results in the under- or overstaging of patients.²³ A more accurate method of determining the disease stage is the assessment of a surgical specimen in a previously untreated patient.²⁴ Clinicians who advocate for adjuvant chemotherapy favor its use because theoretically, one could spare the inappropriate use of additional therapy in clinically overstaged patients by examining the surgical specimen. This tactic reserves therapy only for patients who have pathologic stage characteristics associated with a high recurrence rate (e.g., lymph node involvement).

Summarizing the available data (Table 39-4), there are no phase III data supporting adjuvant chemotherapy alone for patients with esophageal adenocarcinoma.²⁵⁻²⁸ This is a bit distressing for clinicians who prefer to resect prior to any therapy. If the resection was complete and radical, those patients who show nodal involvement on pathologic analysis are faced with a high risk of distant failure, but the only trial with data supporting postoperative therapy used chemotherapy *and* radiation.²⁹ Regarding SCC histology, the results were mixed, with some trials showing benefit and others none. Those that have shown benefit have been criticized for selection bias and early study termination. Nonetheless, chemotherapy is often offered to SCC patients with nodal involvement on pathology.

CHEMORADIATION

Definitive Combined Chemoradiation

Both chemotherapy and radiation have demonstrated cytotoxic effects on esophageal cancer when given as individual therapy. When these two therapies are

TABLE 39-4 Randomized Trials of Postoperative Chemotherapy for Esophageal Cancer

Investigators	Year	Histology	Total Number of Patients	Treatment	5-Year Survival Rate (%)	Median Survival Duration (months)	P
Pouliquen et al ²⁵	1996	SCC	120	Cisplatin + 5-FU	—	13	—
Ando et al ²⁶ (JCOG 9204)	2003	SCC	222	Surgery alone	—	14	0.037
				Cisplatin + 5-FU	55*	—	
Armanios et al ²⁷ (phase II)	2004	EAC	58	Surgery alone	45*	—	N/A
				Cisplatin and paclitaxel	60†	30	

*Five-year disease-free survival rate.

†Two-year survival rate.

EAC, Esophageal adenocarcinoma; 5-FU, 5-fluorouracil; N/A, not available; SCC, squamous cell carcinoma.

TABLE 39-5 Studies of Definitive Chemoradiation versus Radiation Therapy Alone for Esophageal Cancer

Investigators	Year	Histology	Total Number of Patients	Treatment	Median Survival Duration (months)	2-Year Survival Rate (%)	P
Herskovic et al ²⁸ (RTOG 85-01)	1992	SCC + EAC	121	Cisplatin + 5-FU + 50.4 Gy	12.5	38	0.001
Cooper et al ^{30*}	1999	SCC + EAC	129	64.8 Gy alone Cisplatin + 5-FU + 50.4 Gy	8.9 —	10 26 [†]	<0.001
Minsky et al ³¹ (RTOG 94-05/INT 0123)	2002	SCC + EAC	236	64.8 Gy alone Cisplatin + 5-FU + 50.4 Gy	— 18.0	0 [†] 40	NS
				Cisplatin + 5-FU + 64.8 Gy	13.0	31	

*Long-term follow-up to the RTOG 85-01 trial.

[†]Five-year survival rate.

EAC, Esophageal adenocarcinoma; 5-FU, 5-fluorouracil; NS, not significant; SCC, squamous cell carcinoma.

administered concurrently, there is a synergistic effect, with increased tumor cytotoxicity at lower doses. The rationale for using chemoradiation for GEJ and thoracic esophageal cancers was based on results of definitive chemoradiation for cervical esophageal squamous tumors. This was later translated to use in the thoracic esophagus. Table 39-5 summarizes the initial studies on definitive chemoradiation for the thoracic esophagus that have helped to shape current therapeutic algorithms.

Radiation Therapy Oncology Group (RTOG) 85-01 is the landmark definitive concurrent chemoradiation trial on thoracic esophageal cancer.²⁸ This was a nonoperative randomized prospective multi-institutional trial comparing chemoradiation with radiation alone in 121 patients with esophageal SCC or adenocarcinoma (T1-3N0-1M0). Sixty-one patients received cisplatin and 5-FU with a radiation dose of 50.4 Gy, and 60 patients received a radiation dose of 64.8 Gy alone (see Table 39-5). At a median follow-up duration of 17.9 months, both survival and local/regional recurrence rates favored chemoradiation over radiation alone. The 2-year survival rate was 38% in the chemoradiation group versus 10% in the radiation therapy-only group ($P < 0.001$). The study terminated prematurely when early analysis revealed that statistical stopping points as a result of treatment superiority were reached. Grade 4 toxicity was much higher in the chemoradiation group (20% versus 3%), but the authors accepted the toxicity of chemoradiation as a tradeoff for improved overall survival.

In the long-term follow-up for the RTOG 85-01 trial, coupled with the addition of 73 nonrandomized patients who received chemoradiation, survival advantages persisted in the treatment arm.³⁰ At a minimum follow-up duration of 5 years, none of the patients in the radiation therapy-only group was alive, whereas 26% of the randomized and 14% of the nonrandomized patients who received definitive chemoradiation were alive ($P < 0.001$). Moreover, 22% of the patients in the randomized group survived for at least 8 years. Survival in patients with SCC was better than that of patients with adenocarcinoma (21% versus 13%), although not significantly. Some patients died as a direct result of chemoradiation toxicity (2%). However, the toxic effects in patients in the

chemoradiation group who survived for more than 90 days did not differ from those in the patients in the radiation therapy-only group. This was the first randomized study to establish that both esophageal SCC and adenocarcinoma could be cured in some patients without performing resection.

A major issue with definitive chemoradiation is very high rates of local/regional therapy failure, reported in up to 60% of patients in trials omitting surgery. Improving nonoperative control of the primary disease site became the focus of subsequent esophageal cancer trials. The Intergroup 0123/RTOG 94-05 trial modified the intensity of radiation therapy given concurrently with chemotherapy in an attempt to improve local/regional disease control.³¹ The investigators randomized 218 eligible patients with esophageal SCC ($N = 187$) or adenocarcinoma ($N = 31$) having T1-4N0-1M0 disease. Half of the patients (109) received induction chemotherapy followed by concurrent chemoradiation with a higher radiation dose (64.8 Gy); the other half was treated with the same chemotherapy but with a radiation dose of 50.4 Gy. The compliance rate for this aggressive regimen was 69% in the induction phase but only 48% in the chemoradiation phase. The radiologic complete response rate was 47%. At a median follow-up duration of 16 months, the survival and local/regional disease control rates did not differ significantly from those in the RTOG 85-01 trial. Importantly, the toxicity in RTOG 94-05 was worse, with excess treatment-related deaths occurring in the high-dose radiation therapy group. Notwithstanding the nuances of radiation therapy administration, for which the Intergroup 0123/RTOG 94-05 trial has received criticism, the study established the currently used radiation dose of 50.4 Gy.³¹

Selective Surgery

Randomized trials comparing chemoradiation with or without surgery have illustrated that cure is possible without surgical resection. We know that after chemoradiation, patients belong to one of three groups: those who are already cured by the chemoradiation therapy, those who would currently be considered incurable because of

systemic disease (ultimately leading to distant failure), and those who require further local/regional therapy (resection) to effect a cure. Selecting patients who would benefit from surgery after chemoradiation and identifying those who would not benefit compels the possibility of reserving surgical resection for those who are appropriate risks and require resection for cure. Incomplete responders would go for surgery, and patients who are complete responders or who will progress to distant disease would avoid resection. The problem is knowing to which group an individual patient belongs.

Two randomized trials have sought to evaluate a selective surgical approach as an adjunct to definitive medical therapy in patients with squamous histology.^{32,33} Both show high clinical response rates to therapy, suggesting that a selective surgical approach using chemoradiotherapy represents an equivalent outcome to using surgery for every patient who receives chemoradiation therapy. Similarly, a phase II study including patients with adenocarcinoma was completed by the RTOG (protocol 0246) showing feasibility of this approach in a multi-institutional study albeit with high medical mortality (5/41).³⁴ None of these studies was designed to show superiority over a planned trimodality chemoradiotherapy + surgery approach and therefore conclusions cannot be reached on that question. What the RTOG 0246 study did show is that among the patients taken selectively to resection, 17 of 18 patients had disease in the pathologic specimen. The only patient in the study that was resected to a pathologic complete response had insisted on surgical therapy. These results underscore the positive predictive value of surgeons who are experienced in multimodality therapy to predict when viable tumor will be present in the specimen. Several patients in that series

also presented for later salvage resection, indicating that accuracy is incomplete. It seems that it is easier to derive when a patient has had an incomplete response than to accurately recognize a complete response.

Preoperative Chemoradiation and Surgery

The paradigm of chemoradiation followed by resection is the current treatment of choice because this maximizes local/regional control with the potential to treat early invisible metastatic disease. But the effect on systemic disease should not be overstated. This treatment is really focused on local/regional control, and the record of curing distant disease with this regimen is not optimal.

Over a 2-decade period from 1992 to 2012, there have been nine randomized trials of trimodality treatment for esophageal cancer. Table 39-6 reviews the doses of radiation and types of chemotherapy used in these trials.³⁵⁻⁴³ The mixture of histology, mainly SCC and adenocarcinoma, varied significantly between trials. Many of the trials were underpowered and failed to reach the accrual goals or statistical endpoints. Only three of the nine trials favored therapy over surgery alone. Two of the positive trials, Walsh et al (1996)³⁸ and the Cancer and Leukemia Group B 9781 study by Tepper et al,⁴² were heavily criticized. The Walsh trial had statistical errors and unusually poor surgical outcomes in the surgery arm. The Tepper trial accrued a tenth of their patient goal.

The most recent randomized trial comparing chemoradiation followed by surgery with surgery alone for esophageal and GEJ cancer was the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS) reported by van Hagen et al (2012).⁴³ The trial

TABLE 39-6 Randomized Trials of Preoperative Chemoradiation for Esophageal Cancer

Investigator	Year	Histology	Total Number of Patients	Treatment	Median Survival Duration (months)	3-Year Survival Rate (%)	P
Nygaard et al ³⁵	1992	SCC	88	Surgery	7.5	9.0	NS
Le Prise et al ³⁶	1994	SCC	86	Cisplatin/Bleo + 35 Gy	7.5	17.0	NS
				Surgery	10.0	13.8	
Apinop et al ³⁷	1994	SCC	69	Cisplatin/5-FU + 20 Gy	10.0	19.2	NS
				Surgery	7.4	10.0*	
Walsh et al ³⁸	1996	EAC	113	Cisplatin/5-FU + 40 Gy	9.4	24.0*	0.010
				Surgery	11.0	6.0	
Bosset et al ³⁹	1997	SCC	282	Cisplatin/5-FU + 40 Gy	16.0	32.0	NS
				Surgery	18.6	—	
Urba et al ⁴⁰	2001	SCC + EAC	100	Cisplatin + 37 Gy	18.6	—	NS
				Surgery	17.6	16.0	
Burmeister et al ⁴¹	2005	SCC + EAC	256	Cisplatin/Vb/5-FU + 37 Gy	16.9	30.0	NS
				Surgery	19.0	—	
Tepper et al ⁴² (CALGB 9781)	2009	SCC + EAC	56	Cisplatin/5-FU + 35 Gy	22.0	—	0.002
				Surgery	21.5	16.0*	
van Hagen ⁴³ (CROSS)	2012	SCC + EAC	366	Cisplatin/5-FU + 50.4 Gy	53.8	39.0*	0.003
				Surgery	24.0	34.0*	
				Carboplatin/paclitaxel + 41.4 Gy	49.4	47.0*	

*Five-year survival rate.

Bleo, Bleomycin; EAC, esophageal adenocarcinoma; 5-FU, 5-fluorouracil; NS, not significant; SCC, squamous cell carcinoma; Vb, vinblastine.

reported on 368 patients with surgically resectable (T1N1-T2,3N0,1) disease. Of the 366 patients included in their analysis, 188 underwent surgery alone, whereas 178 underwent chemoradiation followed by surgery. Seventy-five percent of the patients had adenocarcinoma, whereas 23% had SCC. The chemotherapy regimen consisted of carboplatin and paclitaxel given for 5 weeks with concurrent three-dimensional conformal radiation therapy at a dose of 41.4 Gy given in 23 fractions 5 days a week. Physicians performed resection within 4 to 6 weeks in the treatment group and immediately after randomization in the control group. The toxicity of chemoradiation was relatively low, and the toxic effects included leukopenia (6%), neutropenia (2%), anorexia (5%), and fatigue (3%). The R0 resection rate was much higher in the trimodality group (92%) than in the surgery-alone group (69%; $P < 0.001$). Complete pathologic response (ypT0N0M0) was significantly more prevalent in the SCC patients (49%) than in the adenocarcinoma patients (29%). After similar surgical node harvest in both groups, pathologic analysis revealed N1 disease in 75% of the patients in the surgery-alone group and 31% of those in the chemoradiation plus surgery group ($P < 0.001$). At a median follow-up of 45 months, patients receiving trimodality therapy had a significantly longer median overall survival (49.4 months) compared to patients undergoing surgery alone (24 months; HR, 0.65 [95% CI, 0.49-0.87]; $P = 0.003$). The estimated 5-year survival rate in the trimodality therapy group was 47%, compared to 34% in the surgery-alone group (HR, 0.65 [95% CI, 0.49-0.87]; $P = 0.003$). Likewise, the median disease-free survival duration was better in the trimodality group (duration not reached in the trimodality therapy group versus 24.2 months in the surgery-alone group; HR, 0.49 [95% CI, 0.35-0.69]). Subgroup analysis according to histology demonstrated that the trimodality approach was beneficial in both SCC ($P = 0.01$) and adenocarcinoma ($P = 0.049$) patients, although the benefit was clearly more pronounced in SCC patients. Interestingly, in a hazard ratio analysis, trimodality therapy favored males, SCC, and clinically node-negative disease (HR, 0.42 [95% CI, 0.23-0.74]; $P = 0.003$) but not those with node-positive disease (HR, 0.80 [95% CI, 0.57-1.13]; $P = 0.21$).⁴³

The Role of Surgery in Trimodality Therapy for Esophageal Cancer

Preoperative chemoradiation improves R0 resection and local/regional recurrence rates and results in pathologic complete responses in some patients, but other subgroups of esophageal cancer patients clearly derive no benefit from neoadjuvant therapy over surgery alone. Likewise, patients whose cancer is cured by chemoradiation may not derive additional benefits from surgery. The problem is, we are currently unable to accurately select those groups of patients and thus must search for surrogate markers predictive of treatment outcome. A simple, reproducible, validated molecular marker has yet to be identified for clinical decision making regarding therapy. Pathologic specimen analysis for evaluation of tumor histoviability after preoperative therapy has emerged as a predictor of survival in esophageal cancer patients.⁴⁴ Histoviability is a

short-term surrogate endpoint for survival. Above and beyond the potential for surgical cure, pathologic specimens provide answers necessary for the development of novel treatment strategies.

With respect to survival, how much does esophageal resection contribute to overall and disease-free survival over definitive chemoradiotherapy? This question has been the focus of two European trials. In the Fédération Francophone de Cancérologie Digestive (FFCD) 9102 trial, the researchers randomized 259 patients with operable T3N0-1M0 esophageal cancer (88% with SCC) that responded to initial chemoradiation to undergo more chemoradiation followed by observation or resection (nonresponders received off-protocol treatment).³² The 2-year survival rate was 34% in the chemoradiation-only arm versus 40% in the chemoradiation plus surgery arm ($P = 0.44$), with median survival durations of 17.7 months and 19.3 months, respectively. The trend in local control rates favored surgery, but not significantly (57% for chemoradiation only versus 66% for chemoradiation plus surgery). Most notably, the investigators observed an initial toxicity cost in terms of a higher mortality rate in the chemoradiation plus surgery group, which likely negated any benefit that may have been derived from the surgery. The 90-day mortality rate was 9.3% in the chemoradiation plus surgery group and only 0.8% in the chemoradiation group.

A German trial reported by Stahl et al (2005) was a multi-institutional phase III trial with 172 patients who received preoperative induction chemotherapy followed by concurrent chemoradiation.³³ All patients received chemotherapy plus chemoradiation therapy but were randomized to observation or surgery. They limited the study to patients with locally advanced (T3-4N0-1M0) upper to middle esophageal SCC, but in contrast with the FFCD 9102 trial, they included both responders and nonresponders. At a median follow-up duration of 6 years (range, 1.4 to 9.3 years), the authors reported that local/regional control was markedly better with surgery than with observation, but this failed to translate into a statistically significant survival advantage. Similarly to the French trial, they concluded that even though patients in the surgery arm were less likely to die of their cancer, they had a much higher risk of treatment-related deaths than did the patients in the nonsurgical arm. Specifically, the mortality rate was 12.8% in the surgery arm versus 3.5% in the nonsurgical arm. Both this trial and the French study consisted predominantly of SCC patients who consistently had better responses to concurrent chemoradiation than did adenocarcinoma patients. Both trials are criticized for excess mortality in surgical patients.

Murphy and colleagues set out to answer the question about the additional role of surgery after chemoradiation in a retrospective review of 143 patients with clinical stage III esophageal adenocarcinoma eligible for trimodality therapy.⁴⁵ They included only the patients deemed to be appropriate candidates for surgery after completion of preoperative chemoradiation; 114 patients underwent resection, whereas 29 did not because they refused surgery or their physicians chose observation over resection. The demographics of the groups who did and did not undergo resection were similar. Survival analysis

demonstrated that the patients who underwent surgery had overall and disease-specific mortality rates of 50% and 54%, respectively. Multivariable analysis identified only poor tumor differentiation (HR, 2.04 [95% CI, 1.23–3.37]) and resection (HR, 0.504 [95% CI, 0.28–0.89]) to be independently associated with overall survival. This study suggests that resection is an integral component of trimodality therapy for locally advanced esophageal adenocarcinoma.⁴⁵

Chemoradiation with Surgery versus Chemotherapy with Surgery

Currently, chemotherapy is truncated when given concomitantly with radiation therapy. Therefore, its effect is sensitizing rather than systemic; treatment is focused on the area of radiation. If true systemic doses of chemotherapy were added to the treatment, would this improve the outcomes in esophageal cancer patients? Two randomized trials compared chemotherapy versus chemoradiation followed by surgery.^{46,47} Stahl and coworkers (2009)⁴⁶ addressed this question in a phase III study in which they randomized patients with resectable but locally advanced type I–III GEJ adenocarcinoma to undergo either 15 weeks of chemotherapy followed by surgery or 12 weeks of chemotherapy followed by 3 weeks of concurrent chemoradiation (30 Gy) and subsequent surgery. At a median follow-up duration of 45 months, they demonstrated both a 3-year survival and local control advantage with chemoradiation plus surgery. These advantages were not statistically significant, however ($P = 0.07$ and $P = 0.06$, respectively), likely because of a type II error, given the accrual of only 126 patients in the trial. Notably, the hospital mortality rate differed markedly in the two groups: 3.8% for the chemotherapy plus surgery group and 10.2% for the chemoradiation plus surgery group ($P = 0.26$). A randomized phase II trial by Burmeister and colleagues⁴⁷ also failed to show a benefit to chemoradiation therapy over chemotherapy followed by surgery, but they noted that the R0 resection rate was higher when radiation was added to the therapy, especially in bulky tumors. One should note that the comparison in the Stahl et al trial really involved induction therapy (albeit shorter), which is not the standard for concurrent chemoradiation.

Postoperative Chemoradiation

Investigators have demonstrated the feasibility of postoperative chemoradiation in multiple trials, the largest of which was reported by MacDonald et al (2001).²⁹ This study mainly included gastric cancer patients but also included cardia cancer patients. It demonstrated better survival with surgery and adjuvant chemoradiation than with surgery alone. The main limitation of this adjuvant approach is the administration of chemoradiation in patients who are already somewhat weakened from surgery. Also, irradiation of tissue conduits used to reconstruct intestinal continuity may have short- and long-term side effects. There has never been a trial evaluating the benefit of adjuvant therapy after radical surgery (en bloc and D2 lymphadenectomy).

META-ANALYSIS

A meta-analysis by Sjöquist et al⁴⁸ of 24 trials and 4188 patients focusing on survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable esophageal carcinoma provided evidence for survival benefit of multimodality therapy versus surgery alone. The clear benefit of neoadjuvant chemoradiation over chemotherapy was not demonstrated, however.

SUMMARY

Multimodality therapy for esophageal cancer will continue to evolve. Very soon, molecular predictors will shed light on which patients to treat with surgery versus those who will benefit entirely from chemoradiation alone. Clearly the tumor biology/susceptibility is present; it is only a matter of identifying the appropriate patients to focus on. Targeted therapies for this cancer are limited to trastuzumab, but only 10% to 15% of advanced patients are eligible for this therapy at this time. Our hope is to evolve that type of treatment into potentially curable patients as well. Finally, the accuracy of pretreatment disease staging is not fully addressed in this chapter but is known to be suboptimal. Too much heterogeneity exists within the spectrum of cTNM, mostly because imaging techniques are just not sensitive enough to deliver the necessary information with accurate results. This will become even more important as alternative treatment strategies emerge.

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MEDIASTINUM

PART OUTLINE

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MEDIASTINAL ANATOMY AND MEDIASTINOSCOPY

Pamela P. Samson • Bryan Fitch Meyers

CHAPTER OUTLINE

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MEDIASTINAL ANATOMY

The anatomic boundaries of the mediastinum include the thoracic inlet superiorly, the diaphragm inferiorly, the sternum anteriorly, the spine posteriorly, and the pleural spaces bilaterally. It is convenient to divide the mediastinum into anatomic compartments that provide a method for classification of disease processes.

A classic description divides the mediastinum into four compartments: superior, anterior, middle, and posterior (Fig. 40-1). The superior mediastinum includes all structures from the thoracic inlet superiorly to an imaginary plane that includes the lower edge of the manubrium and the lower edge of the fourth thoracic vertebra. The inferior mediastinum, which lies below this boundary, is further divided into the anterior, middle, and posterior compartments. The boundary between the anterior and middle compartments is the anterior pericardium, whereas the border between the middle and posterior compartments is the posterior aspect of the tracheal bifurcation, pulmonary vessels, and pericardium. In this four-compartment model, the upper portions of the trachea and esophagus are contained within the superior mediastinum; the lower portions are contained within the middle and posterior mediastinum.

Shields proposed a simpler three-compartment model consisting of an anterior compartment, a middle (or

visceral) compartment, and a posterior compartment (paravertebral sulcus; Fig. 40-2).¹ All three compartments are bounded inferiorly by the diaphragm, laterally by the pleural space, and superiorly by the thoracic inlet. The anterior compartment is contained anteriorly by the sternum and posteriorly by the great vessels and pericardium and this compartment contains the thymus, internal mammary vessels, areolar and adipose tissue, and potentially pathologic structures such as ectopic parathyroid tissue or a retrosternal goiter. The middle mediastinum is bordered posteriorly by the ventral surface of the thoracic spine; it occupies the entire thoracic inlet and contains the majority of mediastinal structures, namely, the great vessels, heart, pericardium, trachea, proximal mainstem bronchi, vagus nerves, phrenic nerves, esophagus, thoracic duct, descending aorta, and azygos venous system. The posterior compartment (paravertebral sulcus or sulci) consists of potential spaces along the thoracic vertebrae that contain the sympathetic chain, proximal portions of the intercostal neurovascular bundles, thoracic spinal ganglia, and distal azygos vein. Whereas some anatomists may argue that the paravertebral sulci are not truly a mediastinal space, they often harbor disease processes that are classically considered in the posterior mediastinum (i.e. neurogenic tumors). Detailed sagittal views of mediastinal anatomy are depicted in Figures 40-3 and 40-4.

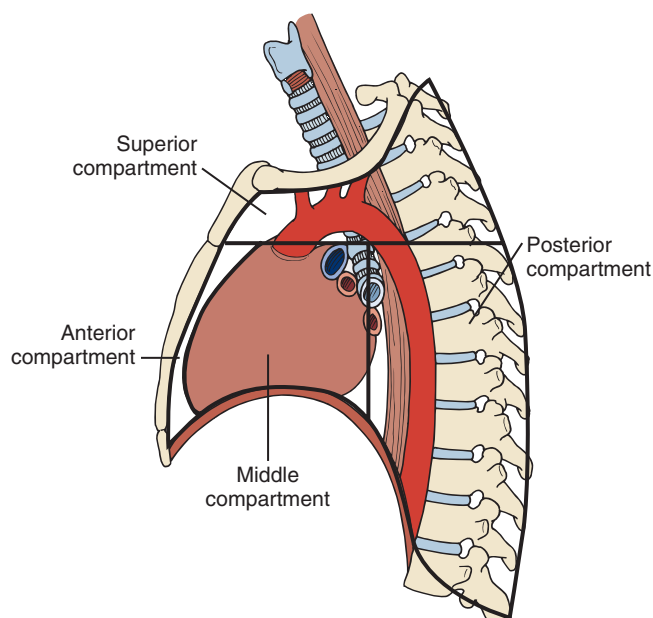


FIGURE 40-1 ■ Four-compartment model of the mediastinum.

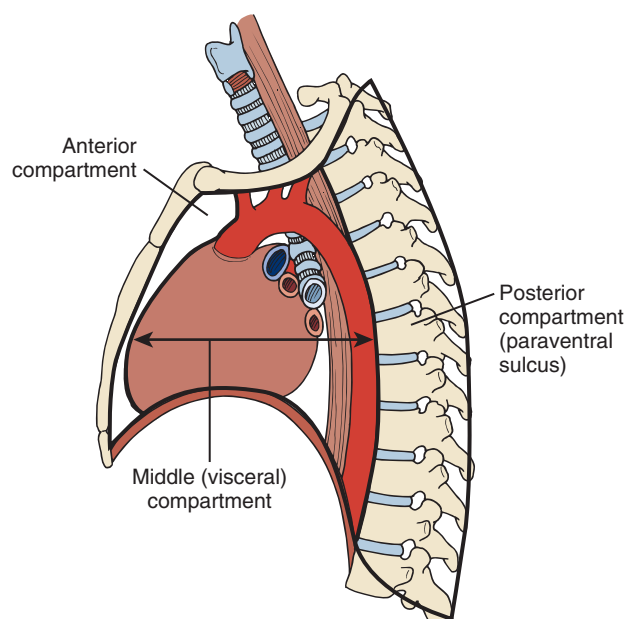


FIGURE 40-2 ■ Three-compartment model of the mediastinum.

POTENTIAL SPACES IN THE MEDIASTINUM

For ease and accuracy of communication in describing pathologic abnormalities (most commonly lymph node enlargement), several potential mediastinal spaces are described. The pretracheal space is a triangular space bounded anterolaterally by the superior vena cava and right brachiocephalic vein on the right, the aorta and pericardium on the left, and the trachea posteriorly. Continuing inferiorly from the pretracheal space is the subcarinal space. This location is bounded superiorly by the carina, laterally by the two main-stem bronchi, anteriorly by the back of the right pulmonary artery, and posteriorly

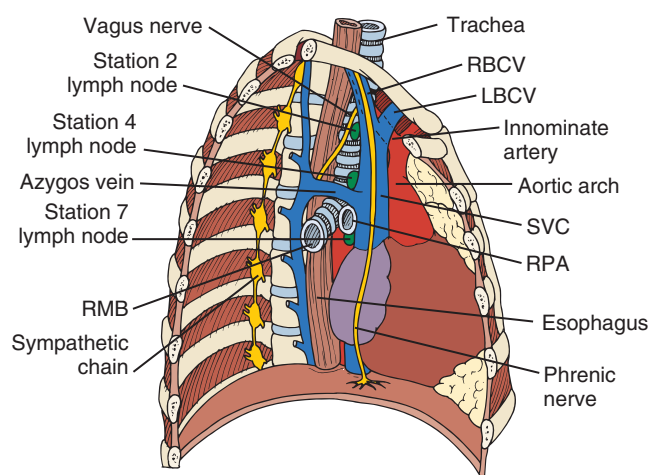


FIGURE 40-3 ■ Right mediastinal view. *LBCV*, Left brachiocephalic vein; *RBCV*, right brachiocephalic vein; *RMB*, right main bronchus; *RPA*, right pulmonary artery; *SVC*, superior vena cava.

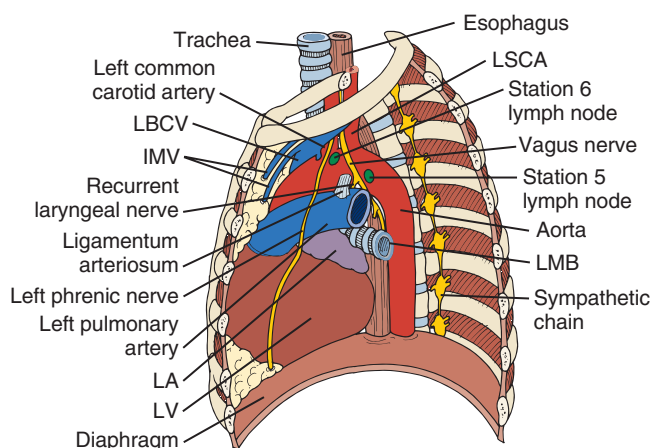


FIGURE 40-4 ■ Left mediastinal view. *IMV*, Internal mammary vessels; *LA*, left atrium; *LBCV*, left brachiocephalic vein; *LMB*, left main bronchus; *LSCA*, left subclavian artery; *LV*, left ventricle.

by the esophagus (see Fig. 40-3). The pretracheal and subcarinal spaces are routinely explored in mediastinoscopy and endobronchial ultrasound. The aortopulmonary window is the space bounded superiorly by the aortic arch, medially by the trachea and esophagus, inferiorly by the pulmonary artery, and laterally by the pleura. This space contains lymph nodes, the ligamentum arteriosum, and the left recurrent laryngeal nerve (see Fig. 40-4). Routine cervical mediastinoscopy does not fully access this space, but anterior mediastinotomy (Chamberlain procedure), extended cervical mediastinoscopy, and thoracoscopy or thoracotomy can all provide access to the aortopulmonary window.

MEDIASTINAL LYMPH NODE ANATOMY

The adoption of a common thoracic regional lymph node classification by the American Joint Committee on Cancer and the Union for International Cancer Control in 1997,

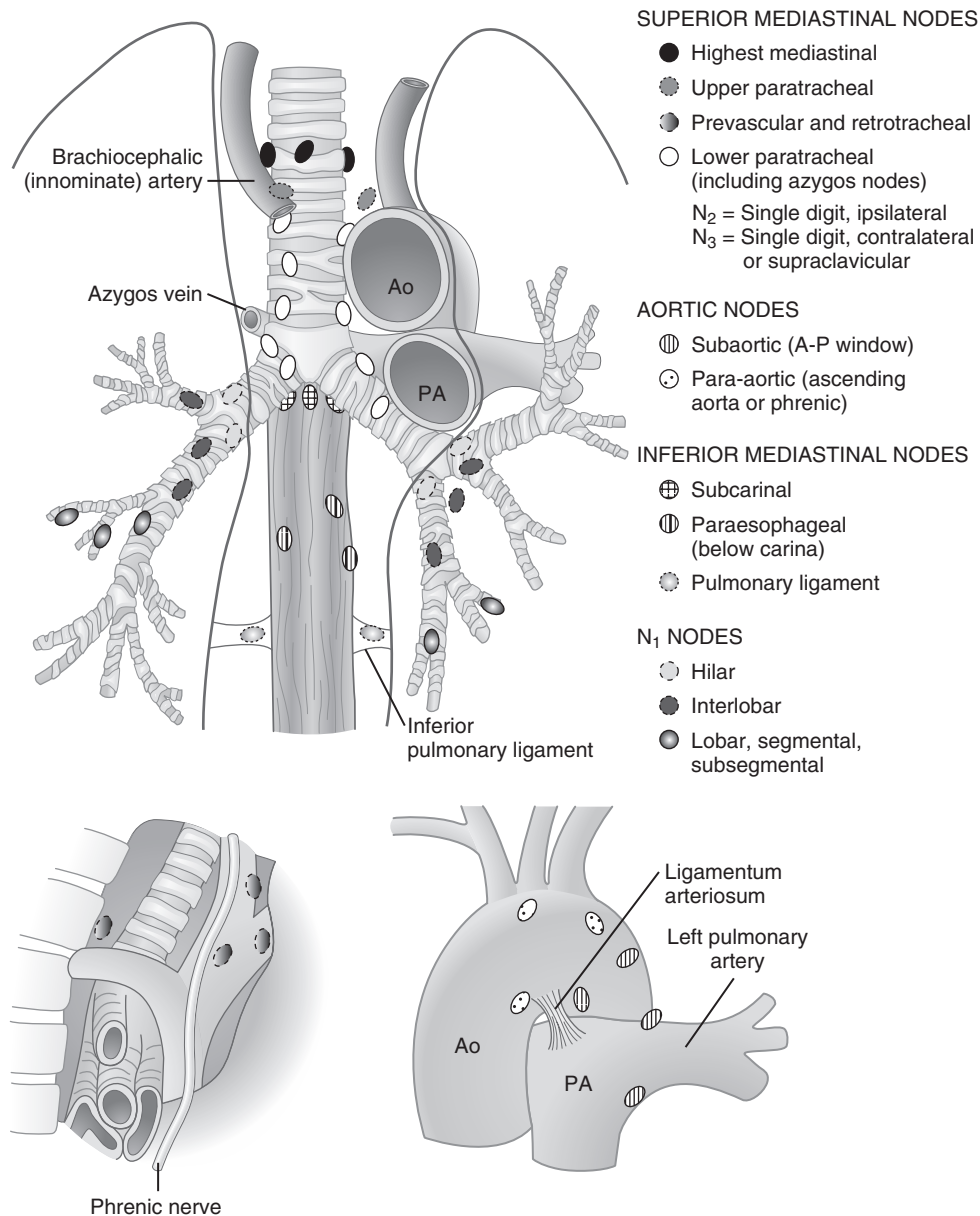


FIGURE 40-5 ■ Regional lymph node stations for lung cancer staging. Ao, Aorta; A-P, aortopulmonary; PA, pulmonary artery. (From Mountain CF, Dresler CM: Regional lymph node classification for lung cancer staging. *Chest* 111:1718–1723, 1997.)

known as the Mountain-Dresler chart, has found widespread acceptance (Fig. 40-5).² This system classifies lymph nodes into 14 stations, of which stations 1 through 9 are contained within the mediastinal pleura and are considered to be mediastinal lymph nodes. The highest mediastinal station (level 1), upper right and left paratracheal nodes (level 2R, 2L), lower right and left paratracheal nodes (level 4R, 4L), and the subcarinal nodes (level 7; see Fig. 40-3) are the only mediastinal nodal stations accessible by standard cervical mediastinoscopy, while stations 5 (subaortic nodes) and 6 (para-aortic nodes; see Fig. 40-4) require an alternative approach such as extended mediastinoscopy or anterior mediastinotomy (Chamberlain procedure) or, rarely, endoscopic ultrasound (EUS).

INDICATIONS FOR MEDIASTINAL LYMPH NODE ASSESSMENT

The most common indication for surgical assessment of mediastinal lymph nodes is non-small cell lung cancer (NSCLC). Other indications include mediastinal lymphadenopathy of unknown etiology, mediastinal masses, primary tracheal tumors, and occasional esophageal tumors. Rare indications for mediastinoscopy include drainage of bronchogenic cysts, abscess drainage, identification of ectopic parathyroid tissue, and tissue sampling for causes of superior vena cava syndrome.

EFFICACY AND UTILITY OF MEDIASTINOSCOPY

Ideally, levels 2R, 2L, 4R, 4L, and 7 should be sampled (with at least one specimen from each level) during mediastinoscopy, though this ideal is seldom achieved. It is estimated that approximately half of false-negative mediastinoscopy results were due to pathologically positive mediastinal nodes not accessible by the mediastinoscope.³ A retrospective series comparing conventional mediastinoscopy to video-assisted mediastinoscopy has demonstrated a significantly lower complication rate (3.6 versus 1.6; $P = 0.03$), higher number of sampled lymph nodes, and lower number of missed positive lymph nodes after definitive lung resection with the use of video mediastinoscopy at the time of staging.⁴ Another retrospective series also showed a higher average number of lymph node samples (7 versus 5; $P < 0.001$) and number of lymph node stations sampled (3.6 versus 2.6; $P < 0.01$) with video mediastinoscopy, but in contrast to the previous study, there was a higher complication rate with video assistance (3.8% with versus 0.8% without; $P = 0.04$), which was attributed to a more aggressive dissection.⁵ The most frequent nodal station to be implicated in a false-negative result at time of eventual pulmonary resection was level 7 (approximately 70% of surprise N2 cases found at thoracotomy).⁵ However, almost 90% of these false-negative cases at level 7 were in the conventional mediastinoscopy group, only one false-negative level 7 case resulted after video mediastinoscopy.⁵

The use of modern imaging techniques, including high-resolution computed tomography (CT) and positron emission tomography (PET), has led to an appropriately selective strategy for invasive mediastinal lymph node assessment, especially for patients with stage I NSCLC. Some series have shown that the sensitivity and negative predictive value of positron emission tomography–computed tomography (PET/CT) approaches levels achieved with cervical mediastinoscopy (Table 40-1).^{6,7} However, reviews of large series have reminded surgeons to interpret PET results with caution. In one such study in which preoperative PET (alone) was followed by mediastinoscopy, the sensitivity of PET was 64.4%, specificity was 77.1%, positive predictive value was 44.6%, negative predictive value was 88.3%, and accuracy was 74.3%.⁸ In a similarly sized series that evaluated

combined PET-CT in patients who subsequently underwent mediastinoscopy, these values improved with a sensitivity of 70%, specificity of 94%, positive predictive value of 64%, and negative predictive value of 95%.⁹ However, both studies demonstrate a clinically important number of false-positive results with PET or PET/CT that, if accepted without confirmation, would result in unnecessary induction therapy or, in some practices, the possibility of the patient not being offered surgical management at all. These results suggest the continued need for pathologic confirmation of mediastinal lymph node staging before definitive management.

The European Society of Cardiothoracic Surgery has provided recommendations for mediastinal lymph node assessment in preoperative staging of NSCLC (Fig. 40-6).⁷ Similarly, the National Comprehensive Cancer Network guidelines currently recommend preoperative PET/CT scanning and pathologic mediastinal lymph node evaluation (either mediastinoscopy or endobronchial ultrasound-transbronchial needle aspiration [EBUS-TBNA]), EUS, or CT-guided biopsy for clinical stage IA–IIIB NSCLC disease.¹⁰ However, a cost-effectiveness analysis found that patients with clinical stage I lung cancer staged by PET/CT benefit little from mediastinoscopy.¹¹ In this series of stage I NSCLC patients who underwent mediastinoscopy, only 3% demonstrated N2 disease, with an additional 3.6% found to have occult N2 disease after their definitive surgery.¹¹ With this rate of N2 disease, mediastinoscopy added 0.008 years of life expectancy, costing more than \$250,000 per life-year gained.¹¹ Many practitioners do not routinely perform mediastinoscopy for patients with clinical stage IA or IB disease after CT and PET screening. Exceptions may include patients with central tumors, bronchoalveolar cell carcinoma, or in situations in which the primary tumor has low fluorodeoxyglucose uptake and there are enlarged, but PET-negative, mediastinal nodes.⁷ Any patient with suspected N1 disease after CT or PET scan should undergo mediastinal evaluation.

PREOPERATIVE EVALUATION

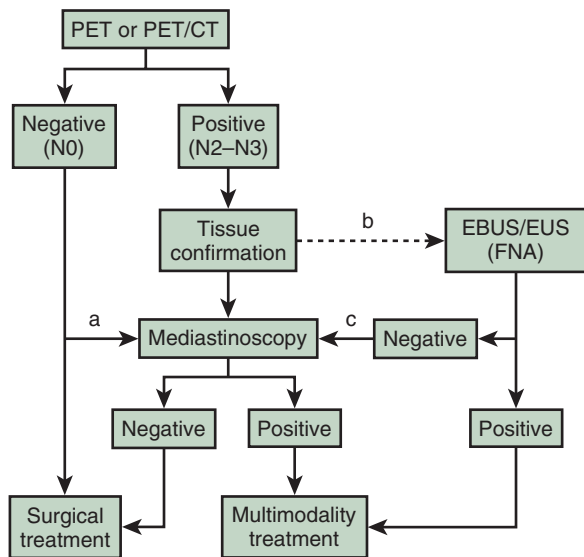
Standard preoperative evaluation in a patient undergoing mediastinoscopy includes a history and physical examination with a special focus on any history of neck or chest surgery, or a coexistent pathologic process such as a

TABLE 40-1 Relative Performance of Various Modalities of Mediastinal Lymph Node Assessment

Modality	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Prevalence (%)
CT	57	82	83	56	28
PET	84	89	93	79	32
Blind TBNA	76	96	71	100	70
EUS-FNA	88	91	77	98	69
Mediastinoscopy	81	100	91	100	37

CT, Computed tomography; EUS-FNA, endoscopic ultrasound–fine needle aspiration; NPV, negative predictive value; PPV, positive predictive value; TBNA, transbronchial needle aspiration.

From De Leyn, Lardinois D, Van Schil PE, et al: ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. *Eur J Cardiothorac Surg* 32:1–8, 2007.



- a: In central tumors, tumors with low FDG uptake, tumors with LNs ≥ 1.6 cm and/or PET N1 disease invasive staging remains indicated
- b: Endoscopic techniques are minimally invasive and can be the first choice
- c: Due to its higher NPV mediastinoscopy remains indicated

EUS: endoscopic esophageal ultrasound
 EBUS: endobronchial ultrasound
 NPV: negative predictive value
 N0: LN < 1 cm

FIGURE 40-6 ■ The proposed algorithm to follow for primary mediastinal staging when positron emission tomography (PET) or positron emission tomography–computed tomography (PET/CT) is available. *FDG*, Fluorodeoxyglucose; *FNA*, fine needle aspiration; *LN*, lymph node. (From De Leyn P, Lardinois D, Van Schil PE, et al: ESTS guidelines for preoperative lymph node staging for non–small cell lung cancer. *Eur J Cardiothorac Surg* 32:1–8, 2007.)

goiter or aneurysms of the aortic arch or innominate artery that may prevent safe access to the pretracheal space. Prior neck or sternal incisions, including prior mediastinoscopy, can complicate the initial dissection, but they are not absolute contraindications to the procedure. A retrospective series of patients undergoing both cervical mediastinoscopy and left anterior mediastinotomy with a history of sternotomy (half with left internal mammary artery coronary grafts) over two decades showed no differences in the efficacy or safety of these two procedures.¹²

Significant vascular calcification in the innominate artery can increase the risk of embolic events as this vessel is manipulated during the procedure. In addition, total atherosclerotic occlusion of the left common carotid artery can predispose a patient for stroke if the innominate artery supplying the right common carotid artery is compressed by the mediastinoscope. The evaluation should also note cervical spine arthritis because moderate neck extension is required for the procedure. Severe cervical kyphosis can make insertion of the mediastinoscope impossible. Patients should undergo laboratory workup as they might for any general anesthetic and should have

typical preparations for the small possibility of a blood transfusion.

POTENTIAL COMPLICATIONS OF MEDIASTINOSCOPY

Mediastinoscopy is a safe procedure when it is performed by experienced surgeons with knowledge of the surrounding mediastinal structures and a systematic deliberate method of tissue biopsy. Meticulous attention to hemostasis of minor bleeding can help to prevent subsequent bigger problems. A large series of more than 2000 procedures described a morbidity rate of 0.6% and a mortality rate of 0.2%.¹³ Possible major complications include major vessel hemorrhage (aorta, innominate artery, pulmonary artery, bronchial artery, vena cava, azygos vein), esophageal perforation, and stroke secondary to innominate artery compression in the setting of severe atherosclerosis. Other potential complications include left (and rarely right) recurrent laryngeal nerve injury, pneumothorax, wound infection, and tumor seeding of the neck incision.

For lung cancer patients undergoing restaging after induction chemoradiation therapy for N2 disease and without a history of prior mediastinoscopy (i.e., EBUS-TBNA determined N2 positivity before induction treatment), mediastinal changes from the treatment may be present. In one series that examined 51 patients who had mediastinoscopy after radiation therapy, approximately 10% of these patients had complications including two permanent recurrent laryngeal nerve injuries, an azygos injury that resulted in emergent right thoracotomy, and two aborted procedures that were truncated for safety.¹⁴ All but one of these patients experiencing complications had received levels of radiation therapy greater than or equal to 60 Gy. However, the overall performance of mediastinoscopy in terms of sensitivity, specificity, and negative predictive value were similar to metrics for mediastinoscopy done without prior therapy. Although this complication rate is higher than in other reported experience, it seems prudent to say that extra care should be taken when the patient has a known history of mediastinal radiation.

Reoperative mediastinoscopy for evaluating mediastinal nodes after induction therapy, inadequate first mediastinoscopy, or recurrent lung cancer can also be perilous, even among experienced surgeons. Although a series of almost 100 patients had a complication rate of 4%, the severity of these complications were higher than those seen in primary procedures, including biopsy of lung tissue, bronchial injury requiring patch repair, superior vena cava puncture requiring emergent right thoracotomy, and proximal innominate artery hemorrhage resulting in cardiac tamponade and death.¹⁵ Furthermore, in a review of patients undergoing restaging after induction therapy for stage IIIA NSCLC, the safer and less invasive alternatives offered with EBUS-TBNA and endoscopic ultrasound–fine needle aspiration (EUS-FNA; procedures to be discussed later in this chapter), demonstrated a lower false-negative rate and higher sensitivity than redo mediastinoscopy did.¹⁶ Reoperative

mediastinoscopy seems unnecessary given these safer alternatives.

SURGICAL TECHNIQUE

Standard cervical mediastinoscopy involves access of the middle mediastinal structures through a lighted, hollow, metal mediastinoscope introduced through a cervical incision. Large-bore venous access is warranted, and many anesthesiologists routinely place a right radial arterial catheter to monitor blood pressure and to watch for innominate artery compression during the procedure. Alternatively, some centers use a pulse oximeter probe on the right hand. Once patients are intubated, they are placed in the supine position with the neck gently hyperextended and supported with an inflatable bag or rolled blanket placed behind the shoulders (Fig. 40-7).

The endotracheal tube is brought out to the patient's right and kept as lateral and low in profile as possible to allow the surgeon to insert the mediastinoscope directly over the patient's chin in the midline. Care must be taken to avoid turning the patient's chin to the side as this can result in an off-center incision, which makes subsequent dissection more difficult and produces a suboptimal cosmetic result.

The entire sternum and anterior cervical areas are typically prepared and draped to facilitate a sternotomy for the rare event that massive bleeding is encountered.

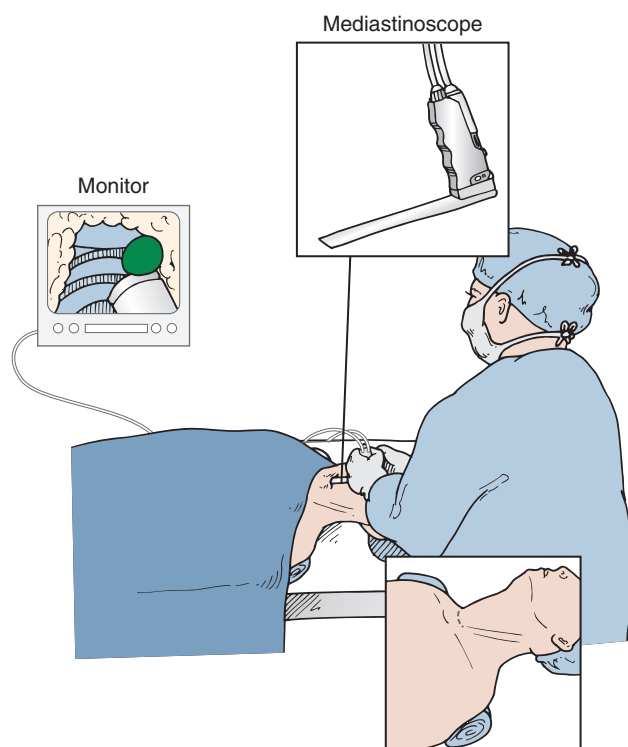


FIGURE 40-7 ■ Patient and equipment positioning for video mediastinoscopy. The surgeon is shown looking across the operative field at the video monitor. *Top inset*, Diagram of a video mediastinoscope. *Bottom inset*, View of the patient's neck in extension, the incision site, and the support behind the patient's shoulders.

A 2.5-cm transverse incision is made one fingerbreadth above the sternal notch, and the platysma is divided in the line of the skin incision. The midline raphe between the strap muscles is opened vertically, and dissection is carried down to the trachea. On occasion, it is necessary to divide a low-lying thyroid isthmus or a thyroidea ima artery to reach the trachea. The pretracheal fascia is divided, and blunt finger dissection is undertaken to develop a plane anterior to the trachea in a caudal direction. A high-riding innominate artery can be seen in aneurysmal disease, in the setting of an enlarged station 2 (right) lymph node, or as an anatomic variant. The preoperative CT scan can provide a clue to this situation and help to avoid injury to the vessel during the initial dissection. The surgeon can obtain useful information during initial finger dissection of the pretracheal space, including the exact location of the ascending aorta and the angle and level at which the innominate artery crosses the field. In addition, firm pathologic lymph nodes alongside the distal trachea can be palpated and partially dissected free of surrounding tissue with the surgeon's fingertip.

The mediastinoscope is then inserted into the pretracheal plane that has been created (see Fig. 40-7). A standard mediastinoscope is a hollow, lighted, metal tube that permits only one individual to visualize the operative field. The introduction of video mediastinoscopy (Fig. 40-8; see also Fig. 40-7) has permitted all members of the team to visualize the operative field. This provides educational benefit for trainees, improves participation in the procedure (including the anticipation of the surgeon's needs), and allows better supervision during training. In addition, magnification, improved optics, and superior lighting have improved anatomic visualization (see Fig. 40-8). With a first assistant stabilizing the scope, the video mediastinoscope can be used by the surgeon to introduce two instruments into the field for bimanual dissection and hemostasis.

HIGH PARATRACHEAL DISSECTION

The major anatomic landmark of the high paratracheal level is the innominate artery (Figs. 40-9 and 40-10), which is seen as a pulsatile structure crossing anterior to the trachea. Station 2 lymph nodes lie to the left and right of the trachea at this level and above. Correlation of the endoscopic view at the station 2 lymph node level with sagittal anatomic structures as seen from the right chest is shown in Figure 40-11. Correlation of the endoscopic view with a transverse view of the mediastinal structures at this high paratracheal level is seen in Figure 40-12.

The operator's initial view of the paratracheal tissue often shows no obvious nodal tissue. Subsequent blunt dissection through the pretracheal tissue plane, assisted by careful use of the suction cautery tip, usually exposes the underlying lymph nodes. Dark pigmentation facilitates recognition of lymph nodes. It is recommended by the authors that blunt lymph node dissection be carried out to the point that the node bulges into the operative field (see Fig. 40-10). This technique helps to prevent inadvertent biopsy of other "dark" paratracheal

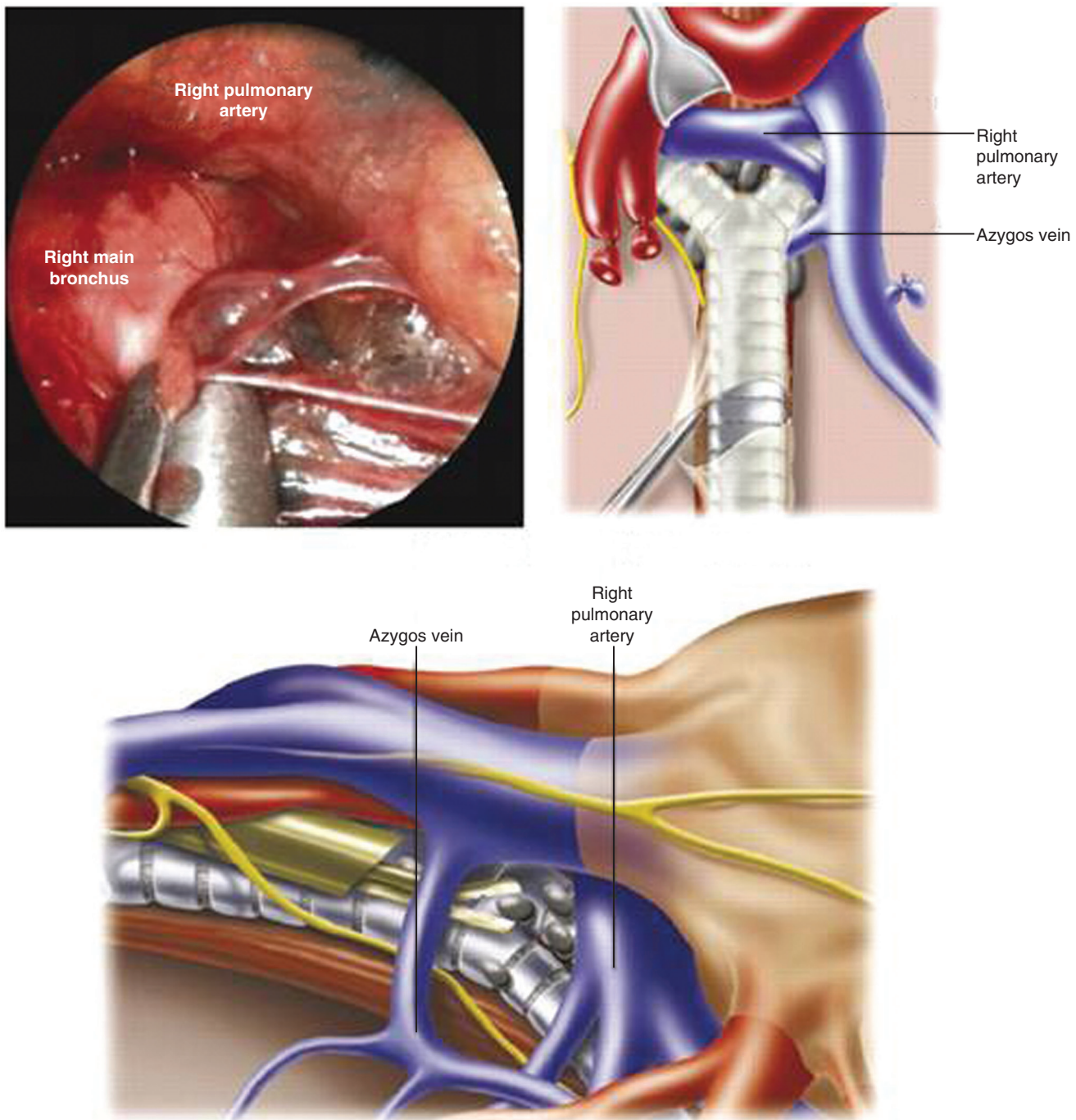


FIGURE 40-8 ■ Enhanced visualization with cervical video mediastinoscopy. (From De Leyn P, Lardinois D, Van Schil PE, et al: ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. *Eur J Cardiothorac Surg* 32:1–8, 2007.)

structures, such as the vena cava or the right brachiocephalic vein, which do not bulge into the field. In other words, lymph nodes should be recognized as three-dimensional structures; major veins remain two-dimensional dark surfaces after the dissection.

LOWER PARATRACHEAL DISSECTION

Dissection inferior to the innominate artery reaches the lower paratracheal area and station 4 lymph nodes, which

lie to the right and left of the trachea cephalad to the carina (Fig. 40-13). After blunt dissection of the paratracheal tissue permitting the nodes to bulge into the operative field, if there is any question about whether the tissue considered for biopsy is a lymph node, it is wise to aspirate the tissue first with a small-bore needle to rule out a vascular structure (Fig. 40-14). This maneuver, which can be used at any level, may also alert the operator to the presence of a major blood vessel lying immediately beneath the node to be sampled. This is important because inflammatory or malignant adhesions between

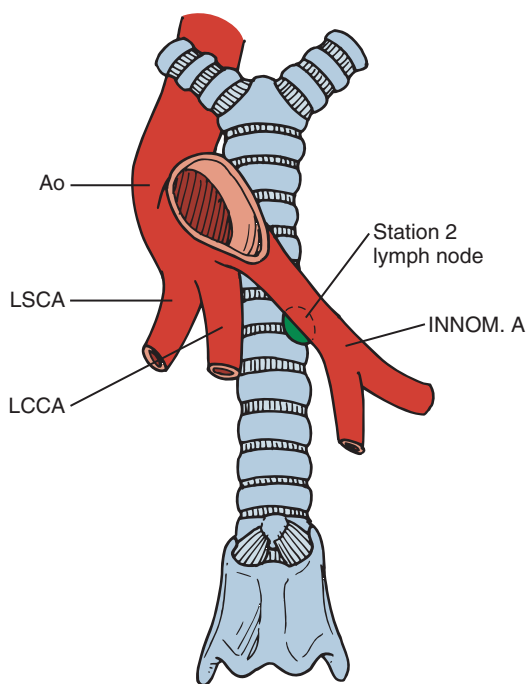


FIGURE 40-9 ■ Anatomic structures at the high paratracheal level as seen from the surgeon's position standing at the patient's head. *Ao*, Aorta; *INNOM. A*, innominate artery; *LCCA*, left common carotid artery; *LSCA*, left subclavian artery.

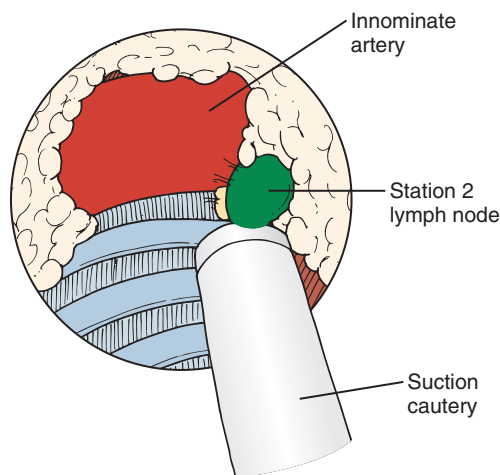


FIGURE 40-10 ■ View through the mediastinoscope at the high paratracheal level. Note the tracheal rings posteriorly and the innominate artery anteriorly. Also note the suction cautery dissection through the pretracheal fascia to allow the underlying station 2 lymph node located to the right of the trachea to bulge into the operative field.

the lymph node and the underlying major vessel can lead to avulsion injury to the vessel during vigorous lymph node biopsy. The non-lymph node structures lying to the right of the trachea at this level include the azygos vein, the superior vena cava, the mediastinal pleura, and the adjacent right upper lobe of the lung. The visceral pleura can appear darkly pigmented like a node, but the lung is characteristically seen to move behind the pleura with respiration. Structures lying to the left of the trachea at this level are the aortic arch, the left recurrent laryngeal

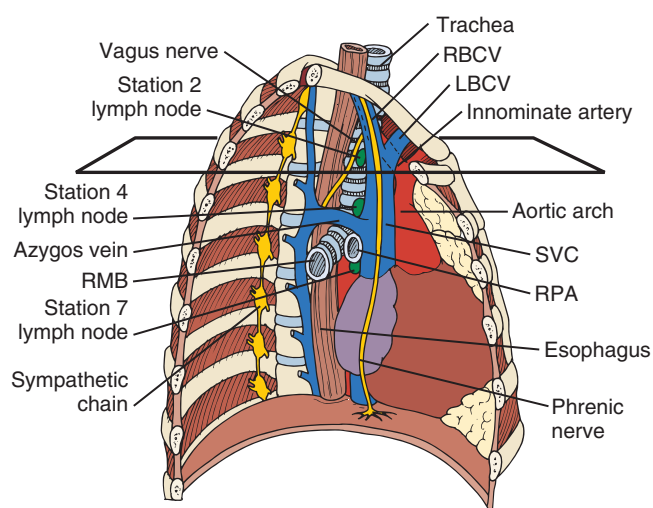


FIGURE 40-11 ■ Right mediastinal view. The plane traverses the mediastinal structures at the high paratracheal station 2 lymph node level. *LBCV*, Left brachiocephalic vein; *RBCV*, right brachiocephalic vein; *RMB*, right main bronchus; *RPA*, right pulmonary artery; *SVC*, superior vena cava.

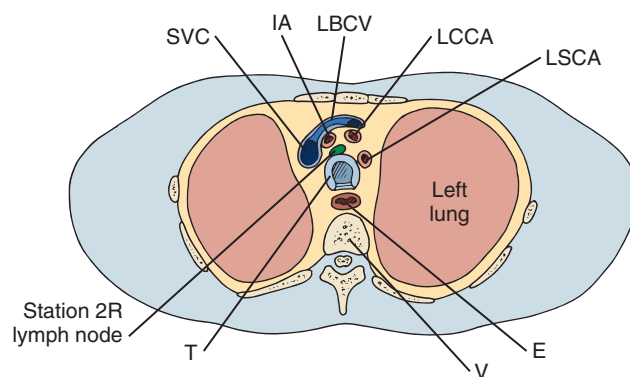


FIGURE 40-12 ■ Transverse view of mediastinal structures at the high paratracheal level. *E*, Esophagus; *IA*, innominate artery; *LBCV*, left brachiocephalic vein; *LCCA*, left common carotid artery; *LSCA*, left subclavian artery; *SVC*, superior vena cava; *T*, trachea; *V*, vertebra.

nerve, a bronchial artery branch from the aorta, and the esophagus. The esophagus lies posterior and to the left of the trachea at this level and can be mistaken for a white tumor-filled lymph node. It can be recognized by the longitudinal muscle fibers of its outer muscular layer.

The use of electrocautery should be avoided in the left lower paratracheal region to prevent inadvertent injury to the esophagus or paresis of the rarely visualized left recurrent laryngeal nerve lying in the tracheoesophageal groove. If esophageal injury is identified, the esophagus should immediately be repaired through a right or left thoracotomy. Most surgeons would prefer a right thoracotomy to repair the esophagus at this level. However, if there is preexisting lung disease in the left chest, a left thoracotomy may be used to address both. The site of esophageal injury usually lies directly medial to the aortic arch. With appropriate care, most surgeons will never face this rare complication. Correlation of the sagittal

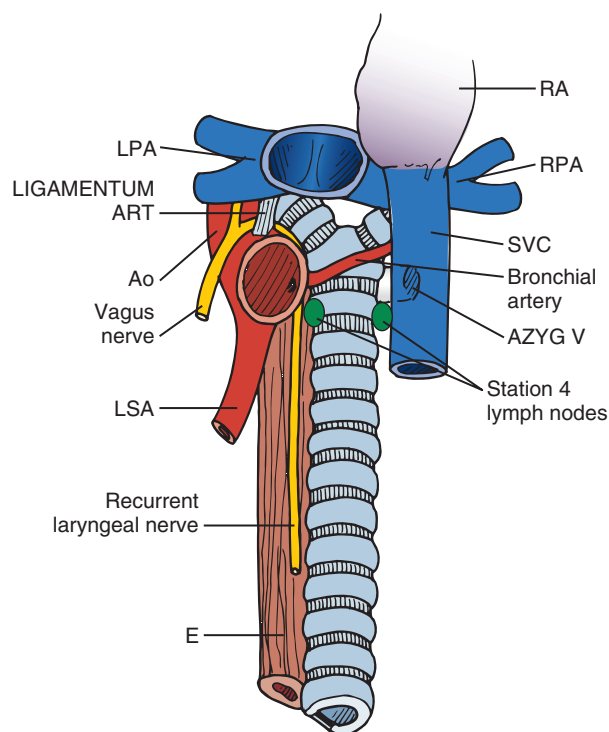


FIGURE 40-13 ■ Anatomic structures at the lower paratracheal level as seen from the surgeon's position standing at the patient's head. Ao, Aorta; AZYG V, azygos vein; E, esophagus; LIGAMENTUM ART, ligamentum arteriosum; LPA, left pulmonary artery; LSA, left subclavian artery; RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava.

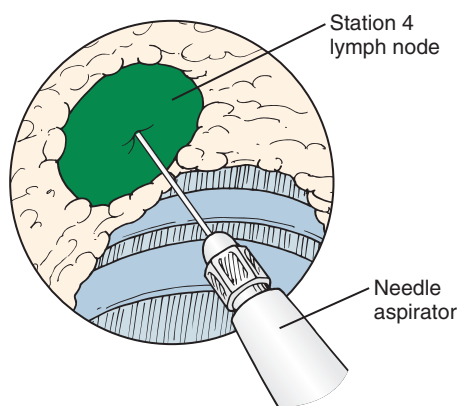


FIGURE 40-14 ■ View through the mediastinoscope at the lower paratracheal level. Note the use of an aspirating needle to rule out a vascular structure before biopsy of the suspected lymph node.

and transverse anatomy at the station 4 lymph node level is shown in Figures 40-15 and 40-16, respectively.

CARINAL DISSECTION

The major anatomic landmarks of carinal dissection are widening of the trachea, the triangular tracheal cartilage

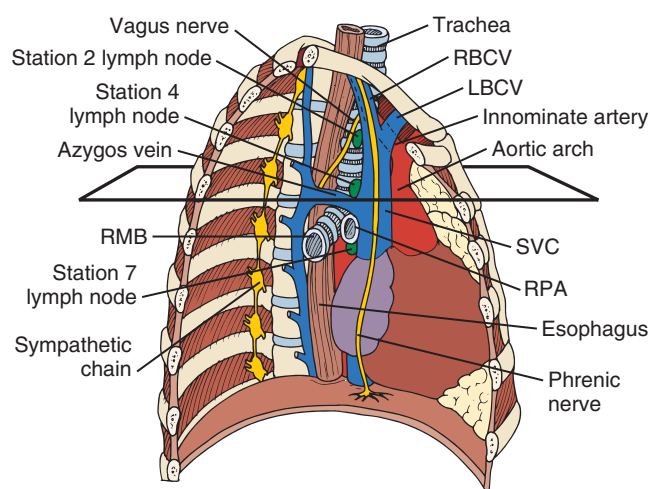


FIGURE 40-15 ■ Right mediastinoscopic view with plane passing through the mediastinal structures located at the lower paratracheal level. LBCV, Left brachiocephalic vein; RBCV, right brachiocephalic vein; RMB, right main bronchus; RPA, right pulmonary artery; SVC, superior vena cava.

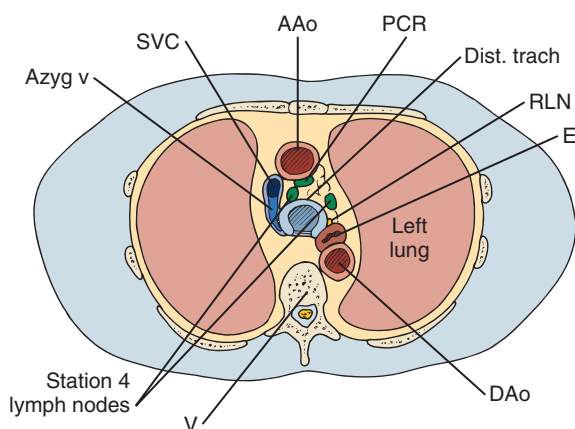


FIGURE 40-16 ■ Transverse view of mediastinal structures at the lower paratracheal level. The pericardial recess (PCR) is a fluid-containing structure often mistaken for a lower mediastinal lymph node. The attenuated conformation of the structure along the outer wall of the ascending aorta (AAo) is a clue to its being a fluid-filled structure and not a node. Azyg v, Azygos vein; DAo, descending aorta; Dist. trach, distal trachea; E, esophagus; RLN, recurrent laryngeal nerve; SVC, superior vena cava; V, vertebra.

at the carina, the proximal left main bronchus, and the right pulmonary artery crossing anteriorly (Fig. 40-17). Because of its more posterior takeoff from the trachea, the proximal right main bronchus may be difficult to identify. The mediastinoscopic view of structures at the carinal level is depicted in Figure 40-18.

Identification of the triangular cartilage of the distal trachea helps to identify the level and prevents misidentification of the proximal left main bronchus as the trachea. Dissection at the carinal level must be performed with meticulous attention paid to the location of the right pulmonary artery. This pulsatile structure passes transversely across the field anterior to the airway.

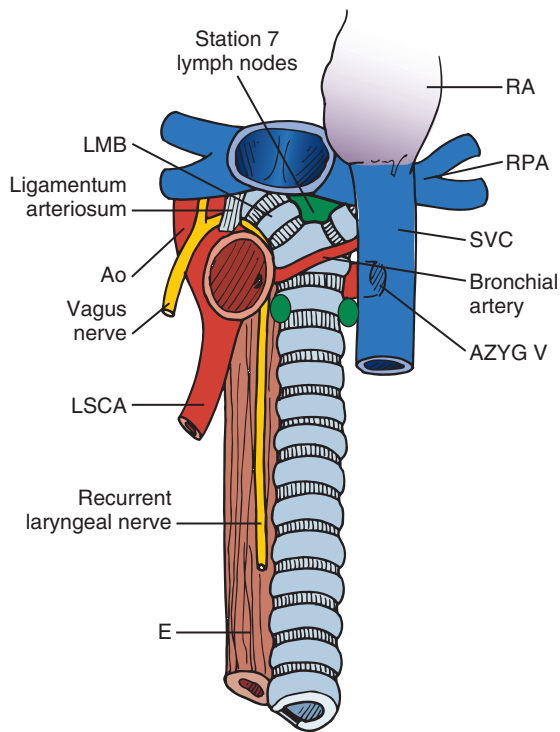


FIGURE 40-17 ■ Anatomic structures at the carinal level as seen from the surgeon's perspective standing at the patient's head. Ao, Aorta; AZYG V, azygos vein; E, esophagus; LMB, left main bronchus; LSCA, left subclavian artery; RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava.

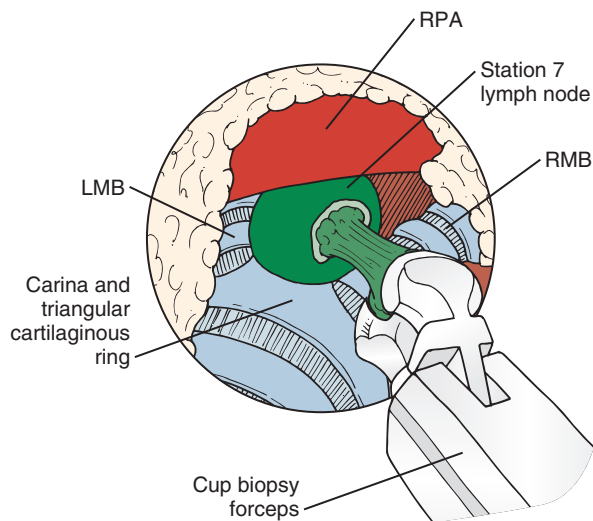


FIGURE 40-18 ■ View through the mediastinoscope at the carinal level. Note the widened tracheal diameter and the triangular tracheal cartilage just proximal to the subcarinal tissue containing station 7 lymph nodes. After blunt dissection and needle aspiration, as described earlier, a nodal biopsy is illustrated with a cup biopsy forceps. LMB, Left main bronchus; RMB, right main bronchus; RPA, right pulmonary artery.

Extensive blunt dissection of any suspected nodal tissue followed by needle aspiration before biopsy is vital (see Fig. 40-18).

Correlation of the endoscopic view at the carinal station 7 lymph node level with anatomic structures as

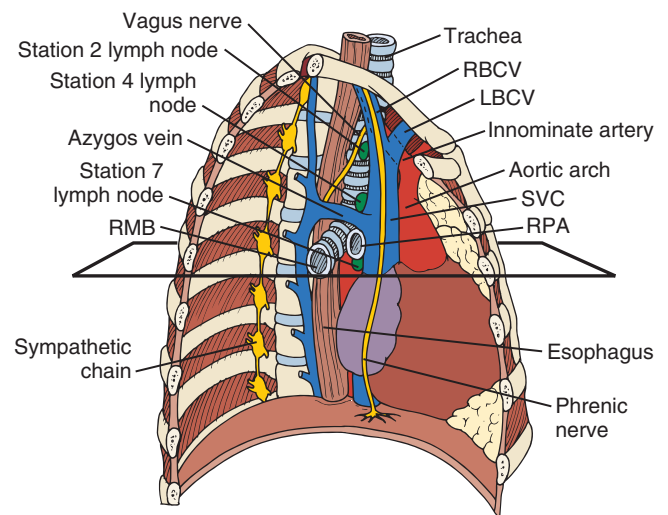


FIGURE 40-19 ■ Right mediastinal view with a plane passing through the structures located at the subcarinal level. LBCV, Left brachiocephalic vein; RBCV, right brachiocephalic vein; RMB, right main bronchus; RPA, right pulmonary artery; SVC, superior vena cava.

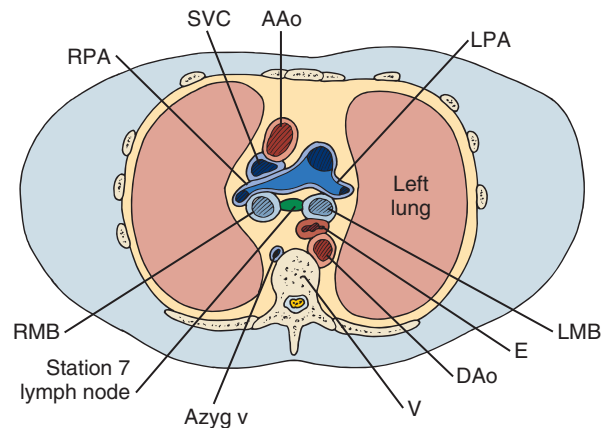


FIGURE 40-20 ■ Transverse view of mediastinal structures at the subcarinal level. AAo, Ascending aorta; Azyg v, azygos vein; DAO, descending aorta; E, esophagus; LMB, left main bronchus; LPA, left pulmonary artery; RMB, right main bronchus; RPA, right pulmonary artery; SVC, superior vena cava; V, vertebra.

seen sagittally from the right chest is shown in Figure 40-19. The transverse sectional anatomy at this level is shown in Figure 40-20.

NODE BIOPSY TECHNIQUE AND CLOSURE OF THE INCISION

As discussed previously, mediastinal node biopsy is initiated by dissection through the pretracheal fascia with a blunt suction cautery instrument (see Fig. 40-10). Next, the suspected lymph node is aspirated with a needle to confirm that it is not a vascular structure (see Fig. 40-14). Finally, a biopsy specimen is taken with a biopsy forceps

(see Fig. 40-18). Often, the first biopsy removes only the outer capsule of the node and exposes the underlying parenchyma, which can then be further sampled. If no node is seen at the desired station, it is often helpful to withdraw the mediastinoscope slightly and even to rotate it to see tissue lying more anterior or anterolateral to the trachea. These areas may reveal nodal tissue with further dissection. After biopsy, hemostasis is achieved with electrocautery or with temporary packing with long length gauze that is marked with a radiopaque thread (often described as a Vag Pack). Close attention must be paid to hemostasis throughout the procedure to maintain a clear field of vision. For a mild, persistent ooze of blood, withdrawal of the mediastinoscope a short distance and patient waiting will often achieve hemostasis because of simple tissue apposition. Rarely, an endoscopic clip applicator has been described as helpful to address a visible bleeding vessel. It is likely that many unsuccessful applications of endoscopic clips have been attempted and will never be reported; therefore, caution and careful consideration are strongly advised before resorting to such a strategy. Once hemostasis has been achieved at all levels, the mediastinoscope is removed and the wound is closed in several layers. The strap muscles are reapproximated with interrupted sutures vertically in the midline and the platysma muscle transversely; the skin is closed with a subcuticular suture. We obtain postprocedure chest radiographs of all patients to ensure the absence of a pneumothorax, a retained pack, or other visible abnormality. The patient can subsequently be discharged to home after standard postanesthesia care. Alternatively, after mediastinoscopy, the patient may be repositioned for pulmonary resection under the same anesthesia after frozen section evaluation of the lymph nodes by a pathologist.

MANAGEMENT OF MAJOR BLEEDING

A well-organized plan helps to address the possibility of major bleeding during mediastinoscopy. The first thing that is likely to happen is a complete loss of visualization. We recommend leaving the mediastinoscope in place and immediately packing the operative field with long gauze or a Vag Pack. This maneuver will temporarily contain most hemorrhage except that from systemic arteries. Attention is then turned to volume resuscitation and blood replacement if necessary. Waiting several minutes and then removing the packing often accomplishes hemostasis. If not, repeated packing preceded by a topical hemostatic agent such as oxidized cellulose can control venous and minor arterial bleeding without having to resort to median sternotomy or thoracotomy. Aortic, innominate artery, and bronchial artery injury adjacent to the aorta and major pulmonary artery injuries will not be contained with packing. Management should start with compression of the vessel with the mediastinoscope or removal of the mediastinoscope and compression of the vessel against the sternum with one's finger until either a median sternotomy (preferable in most situations) or a thoracotomy can be performed to allow direct vascular control.

EXTENDED MEDIASTINOSCOPY

We use the term *extended mediastinoscopy* to encompass techniques that go beyond the routine assessment of station 2, 4, and 7 lymph nodes in the mediastinum. A common misconception is that routine mediastinoscopy permits evaluation of the anterior mediastinum. However, a variation of mediastinoscopy known as *extended cervical mediastinoscopy* has been described that can access the anterior mediastinum as well as station 5 and 6 nodes in the aortopulmonary window (see Fig. 40-5). This procedure is started through the same cervical incision, but the surgeon subsequently creates a plane anterior to the innominate artery and posterior to the left brachiocephalic vein. Although the procedure has been described, it is rarely done, because of the inherent difficulty of the procedure involving dissection of major vessels in a confined anatomic space and the easy accessibility to the aortopulmonary window by an anterior mediastinotomy or thoracoscopy. In addition, the belief among many thoracic surgeons is that tumors of the left upper lobe with involvement of nodes in stations 5 and 6 (if limited to intracapsular spread and in the absence of other mediastinal node involvement) have a better prognosis with surgical resection than do tumors in other lobes with mediastinal node involvement and therefore do not have to be staged before lung resection.

Transcervical extended mediastinal lymphadenectomy (TEMLA) is also a mediastinal staging option for NSCLC and is performed through a 5- to 8-cm collar incision in the neck, enabling complete removal of all mediastinal nodal stations except for the pulmonary ligament nodes (station 9) and the most distal left paratracheal nodes (station 4L).¹⁷ In general, TEMLA is an open procedure performed partly with mediastinoscopy-assisted and video thoracoscopy-assisted techniques. The operative technique of TEMLA includes the elevation of the sternal manubrium with a special retractor and bilateral visualization of the laryngeal recurrent and vagus nerves. The stated benefits include a higher sensitivity and specificity compared with standard mediastinoscopy or video mediastinoscopy.

Video-assisted mediastinoscopic lymphadenectomy (VAMLA) is a mediastinoscopic dissection technique proposed for a radical mediastinal assessment and as an adjunct to open lymphadenectomy at the time of pulmonary resection.¹⁸ VAMLA dissection includes the en bloc resection of the subcarinal, right paratracheal, right tracheobronchial, and pretracheal compartments and dissection and lymphadenectomy of the left-sided tracheobronchial and paratracheal compartments. A specialized mediastinoscope with spreadable blades is used. A retrospective series comparing conventional mediastinoscopy to VAMLA demonstrated significantly increased mean number of lymph nodes sampled, improved sensitivity and negative predictive value, and even improved 5-year survival rates with VAMLA, presumably from improved detection and triaging of N2 disease.¹⁹ At this time, VAMLA also has a significantly higher complication rate (9.0% versus 4.1% in the conventional mediastinoscopy group), with the most common complication being dysphonia.¹⁹

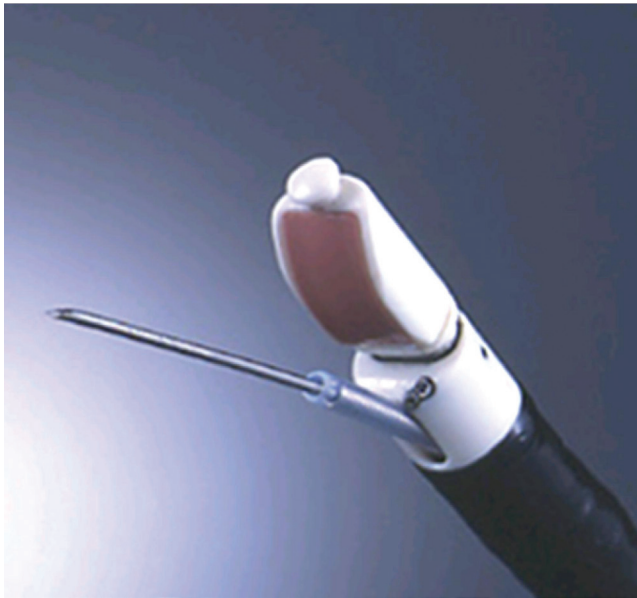


FIGURE 40-21 ■ Image of the distal tip of a dedicated endobronchial ultrasound-transbronchial needle aspiration bronchoscope. The needle exits obliquely so the puncture site can be within the EBUS view. (From Ernst A, Feller-Kopman D, Herth FJ: Endobronchial ultrasound in the diagnosis and staging of lung cancer and other thoracic tumors. *Semin Thorac Cardiovasc Surg* 19:201–205, 2007.)

ENDOSCOPIC TECHNIQUES FOR MEDIASTINAL LYMPH NODE ASSESSMENT

Of recent significance has been the increasing use of EBUS-TBNA by surgeons and pulmonologists in the pathologic staging of the mediastinum. EBUS-TBNA can access mediastinal lymph node levels 1, 2R and 2L, 3, 4R and 4L, and 7. It can additionally sample hilar lymph nodes at levels 10R and 10L and 11 bilaterally, and part of level 12. EBUS uses an integrated, curvilinear ultrasound scanner at 7.5 MHz that produces a view through the bronchial wall into the mediastinal structures (Fig. 40-21).²⁰ A dedicated needle system is attached to the bronchoscope and advanced through the working channel. The needle, when advanced, can be seen in real time (Fig. 40-22).²⁰ The EBUS-TBNA bronchoscope handles differently from a conventional bronchoscope as the distal end is thicker and stiffer. The forward view is oblique instead of a straight ahead viewing angle. Once it is mastered, this endoscope allows lymph node biopsies under real-time ultrasound guidance. EUS-FNA can additionally provide access to level 8 and 9 lymph nodes (providing better posterior and inferior mediastinal lymph node access), leaving only the lateral aspects of levels 5 and 6 unreachable by either EBUS or EUS.^{21,22}

Although the option of an even less invasive method of mediastinal testing is attractive, especially in patients with bulky and suspicious mediastinal targets, there are still important gaps for optimal mediastinal staging with this technique. Although some studies have reported comparable results of EBUS-TBNA to mediastinoscopy

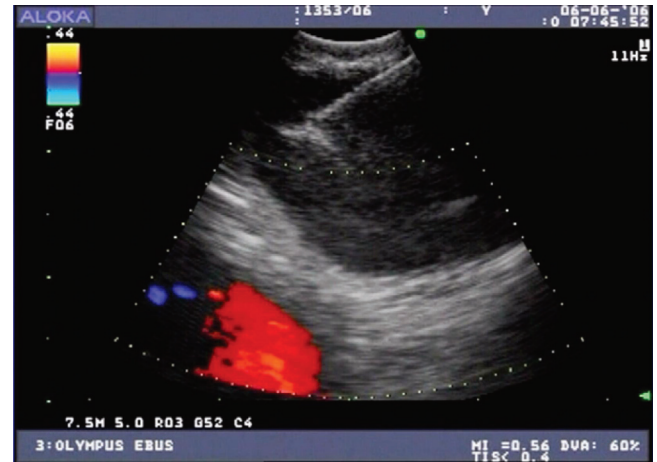


FIGURE 40-22 ■ Endobronchial ultrasound-guided puncture of a node in 10R position. The needle is clearly visible within the lesion. The system also allows color Doppler assessment of unclear structures. (From Ernst A, Feller-Kopman D, Herth FJ: Endobronchial ultrasound in the diagnosis and staging of lung cancer and other thoracic tumors. *Semin Thorac Cardiovasc Surg* 19:201–205, 2007.)

in determining final pathologic N staging, there are also some important exceptions that make this conclusion controversial.²³ While mediastinoscopy provides actual lymph node tissue for analysis, EBUS can only provide needle aspirates, raising the concern for higher false-negative rates, especially in marginally suspicious lymph nodes where micrometastases may be an issue. New techniques, such as EBUS-guided mini forceps biopsy, have been developed but are used for patients with concern for mediastinal diseases other than NSCLC.²⁴ One review of eight studies of EBUS-TBNA showed a similar sensitivity to video mediastinoscopy, but a clinically important average false-negative rate of 24% (range, 1%–37%).³ The average false-negative rate of mediastinoscopy in the same review was 10%.³ One series that examined EBUS-TBNA–negative patients with continued clinical suspicion of mediastinal nodal involvement based on CT or PET imaging found that subsequent mediastinoscopy revealed positive N2 disease in 28% of these patients.²⁵

Also of concern is the fact that many studies of EBUS-TBNA were performed on patients with discrete, enlarged mediastinal lymph nodes who represent a population with more obvious targets, thus artificially raising the EBUS-TBNA sensitivity.^{3,26} As an extension of the concern for the false-negative rate and unclear performance data in patients of advanced T stage (T2–T4) without obvious mediastinal lymph node involvement with EBUS-TBNA, the current recommendation by the American College of Chest Physicians is that when EBUS-TBNA provides a negative result in a setting of clinical suspicion, these findings should be confirmed by mediastinoscopy before definitive treatment.³ In prospective randomized trials comparing mediastinoscopy alone with EBUS-TBNA and EUS-FNA (followed by intraoperative surgical staging if no nodal metastases were detected by endosonography), it was found that the greatest sensitivity for mediastinal nodal metastasis and prevention of proceeding to inappropriate thoracotomy

was a *combined strategy* of endosonographic and surgical staging.^{27,28}

An additional role for these endosonographic techniques is in the setting of mediastinal reassessment after induction therapy when the initial diagnosis of N2 disease was made at mediastinoscopy. As mentioned earlier, redo mediastinoscopy remains a technically difficult and potentially dangerous procedure. Our preference is to establish the initial diagnosis of histologic N2 disease by EBUS-TBNA (where there are more likely to be larger targets that can be easily accessible) and limit video mediastinoscopy for restaging after induction chemoradiation therapy. Furthermore, it is strongly recommended that thoracic surgeons gain expertise in the endosonographic assessment of mediastinal lymphadenopathy, as these procedures can be performed sequentially in the operating room with the assistance of pathology interpreting the initial EBUS-TBNA findings.

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ANTERIOR MEDIASTINAL MASSES

Chuong D. Hoang • Joseph B. Shrager

CHAPTER OUTLINE

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Thymoma

Pathology

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Thymolipoma

Thymic Cysts

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Benign Mediastinal Teratoma

Malignant Mediastinal Germ Cell Tumors

LYMPHOMAS

SUBSTERNAL THYROID

HYPERFUNCTIONING MEDIASTINAL PARATHYROID ADENOMA

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Transcervical Biopsy (Cervical Mediastinotomy)

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Transcervical Thymectomy

Maximal Thymectomy: Trans-sternal and Transcervical

Thoracoscopic Thymectomy

Robotic Thymectomy

SUMMARY

Although the anatomy of the mediastinum is presented in detail elsewhere in this book, it is reviewed here from a thoracic surgical perspective to highlight the radiographic and surgical anatomic subdivisions of the mediastinum that have been proposed. The simplest and most commonly used description is the three-compartment model proposed by Shields.¹ He divided the mediastinum into the anterior compartment, the middle (or visceral) compartment, and the posterior (or paravertebral) compartment. The anatomic limits of each compartment are shown in [Figure 41-1](#), and the structures contained within each compartment are listed in [Table 41-1](#). Locating a mass in the anterior mediastinum allows a differential diagnosis to be generated that is based on the knowledge of the normal structures in that compartment. From the perspective of thoracic surgery, this approach best allows the appropriate diagnostic and therapeutic procedures to be selected.

[Box 41-1](#) contains an extensive list of the pathologic conditions that can appear as a mass in the anterior mediastinal compartment. By far, the three most common of

these are thymoma, lymphoma, and teratoma (and other germ cell tumors).

THYMIC TUMORS

Lesions of the thymus account for approximately 50% of anterior mediastinal masses in adults and are thus of great importance. Although lymphomas and germ cell tumors of the anterior mediastinum often involve the thymus or actually arise from cells within the thymus (or both), these are most appropriately discussed as a group separate from thymic tumors and are usually classified separately. The thymic masses discussed in this section are listed in [Box 41-2](#).

Thymoma

Thymomas are the most common thymic tumor, and approximately 95% are located in the anterior mediastinum. They are of surgical interest both because excision is

TABLE 41-1 Components of Mediastinal Compartments*

Anterior	Visceral (Middle)	Paravertebral (Posterior)
Thymus	Pericardium/heart	Sympathetic chain
Internal thoracic vessels	Great vessels	Proximal intercostals: nerve, artery, and vein
Internal thoracic lymph nodes	Trachea	Posterior paraesophageal lymph nodes
Prevascular lymph nodes	Proximal right and left main-stem	Intercostal lymph nodes
Fat and connective tissue	Esophagus	
	Phrenic nerve	
	Thoracic duct	
	Proximal azygos vein	
	Pretracheal lymph nodes (levels 2, 4, and 7)	
	Pleuropericardial lymph nodes	
	Fat and connective tissue	

*The nodal basin draining the anterior chest wall, and the female breast lie in the anterior compartment, whereas the majority of those draining the lung that are important in lung cancer staging lie in the visceral compartment.

From Shields TW: *General thoracic surgery*, ed 2, Philadelphia, 1983, Lea & Febiger, with permission.

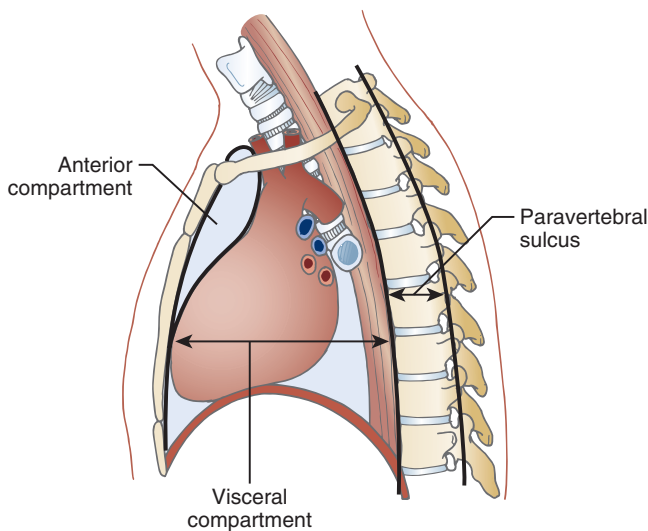


FIGURE 41-1 ■ Three-compartment division of the mediastinum as proposed by Shields. (From Shields TW: *General thoracic surgery*, ed 2, Philadelphia, 1983, Lea & Febiger, with permission.)

the primary therapy and because of their interesting association with myasthenia gravis (MG), the clinical course of which can be favorably influenced by thymectomy.

Thymomas may be completely encapsulated or invasive. Large series have demonstrated the incidence of encapsulated lesions to be between 40% and 70%, and that of microscopic or grossly invasive lesions to be between 30% and 60%. Although local invasion is usually limited to the capsule or to immediately adjacent structures, spread to more distant sites within the chest does occur, particularly to the pleura, diaphragm, and mediastinal lymph nodes. Aggressive thymomas have been reported to be associated with distant metastases in as many as 30% of patients at high-level referral centers,² but most broad studies report distant metastasis to be rare (<5%).

Pathology

Thymomas are derived from thymic epithelial cells, but most contain varying mixes of epithelial cells and

lymphocytes.³ Traditional histologic classifications have therefore grouped thymomas according to cytologic make-up: (1) predominantly lymphocytic, (2) predominantly epithelial, and (3) mixed.⁴ There is also a recognized spindle-cell variant of the epithelial subtype. Approximately 50% of the tumors are of the mixed variety, with the remainder split between the epithelial and lymphocytic subtypes. Unfortunately, these subtypes have little prognostic significance aside from the generally better prognosis of the spindle-cell variant, and thus more recent investigators have proposed alternative histologic classification schemes (discussed later).

Of clinical significance is the fact that it may be more difficult to establish the diagnosis of thymoma from a small sample (e.g., by needle biopsy) of a lymphocyte-predominant thymoma versus the other subtypes because of its microscopic similarity to lymphoma. Immunohistochemical staining for cytokeratin often aids in making the diagnosis, because antibodies to this protein are present in 95% to 100% of thymomas.⁵ Chromogranin staining allows for differentiation between thymoma and thymic carcinoid (the former being negative and the latter being positive for chromogranin).

Classification

No tumor-nodes-metastasis (TNM) classification has been found to be of value for staging thymomas.

The most widely used clinical classification scheme is that proposed by Masaoka and colleagues in 1981⁶ (Table 41-2). This scheme takes into account the gross presence or absence of encapsulation, and fixation or invasion, into adjacent structures as identified at the time of surgery. It also recognizes that a grossly well-encapsulated tumor may be found to have invasion through the capsule at microscopic examination. In the years since it was originally proposed, the Masaoka system, or later variations of it, have been found by numerous authors to have prognostic significance.

In 1985, Marino and Müller-Hermelink⁷ proposed a histologic classification that has come to be known as the Müller-Hermelink (MH) classification. This scheme divides thymomas into cortical, medullary, and mixed types. The cortical type contains medium to large

BOX 41-1 Mass Lesion in the Anterior Mediastinal Compartment: Differential Diagnosis

NEOPLASTIC

Thyroid
Substernal goiter
Ectopic thyroid tissue
Thymus
Thymic hyperplasia
Thymoma
Thymic carcinoma
Thymic carcinoid
Thymic small-cell carcinoma
Thymic cysts
Thymolipoma
Teratoma
Mature teratoma
Immature teratoma
Teratoma with malignant component
Lymphoma
Ectopic parathyroid with adenoma
Germ cell tumors
Seminoma
Nonseminomatous
Yolk sac tumors
Embryonal carcinoma
Choriocarcinoma lymphangioma
Hemangioma
Lipoma
Liposarcoma
Fibroma
Fibrosarcoma
Cervicomedial hyroma

INFECTIOUS

Acute descending necrotizing mediastinitis
Extension of deep cervical bacterial infection into the anterior compartment, with abscess formation and sepsis
Subacute mediastinitis
Fungal, mycobacterial, actinomycotic, or histoplasma infection causing an inflammatory mass in the anterior mediastinum

VASCULAR

Aneurysm of the aortic arch with projection into the anterior mediastinum
Innominate vein aneurysm
Superior vena cava aneurysm
Dilation of the superior vena cava (with anomalous pulmonary venous return)
Persistent left superior vena cava

BOX 41-2 Thymic Masses

- Thymic hyperplasia
- Thymoma
- Thymic carcinoma
- Thymic neuroendocrine tumors
 - Carcinoid
 - Small-cell carcinoma
- Thymic cysts (not rhizomatous)
- Thymolipoma
- Metastases to the thymus

TABLE 41-2 Classification Schemes for Thymoma

Stage	Masaoka	WHO*
I	Encapsulated; tumor may invade into, but not through, capsule microscopically	Type A (spindle cell, medullary)
II		
IIA	Microscopic invasion into thymus or fat or adherent to, but not through, pleura or pericardium	Type AB (mixed) Type B
IIB	Macroscopic transcapsular invasion	B1 (lymphocyte-rich, predominantly cortical) B2 (cortical)
III	Macroscopic invasion of neighboring organs (pericardium, great vessels, lung)	B3 (epithelial, well-differentiated thymic carcinoma)
IV		
IVA	Pleural or pericardial dissemination	Type C (thymic carcinoma)
IVB	Lymphogenous or hematogenous metastasis	

*In the World Health Organization (WHO) column, terms in parentheses represent nomenclature from previous histologic classifications that most closely approximate the current classification category.

Health Organization (WHO) has adopted a classification system based on the MH criteria (see Table 41-2).¹² Currently the state of the art is to use a combination of the WHO histologic systems in combination with the Masaoka staging system to provide the most precise prognostic information.

Presentation

Most patients with thymomas present at an age older than 40 years. There is no major predominance in men or women. Approximately 50% of patients are asymptomatic; the remaining patients have either local symptoms (e.g., pain, dyspnea, cough, hoarseness) resulting from locally invasive tumors or systemic symptoms of one of the associated systemic diseases.

epithelial cells of characteristic appearance, and usually abundant lymphocytes. The medullary type contains small to medium cells with different features and fewer lymphocytes. The former tend to be of higher clinical stage, whereas the latter tend to be of lower invasiveness. Many investigators have generated data in support of the prognostic significance of the MH classification,⁸⁻¹¹ showing that the medullary type has the best and the cortical type the least favorable prognosis. The World

Association with Myasthenia Gravis

Patients with thymomas may present with a number of associated diseases, largely autoimmune in etiology, but the most common associated illness is MG. Accumulated experience suggests that 5% to 15% of patients with MG are found to have thymomas, and that 30% to 50% of thymomas are associated with clinical MG. Notably, the disease may develop later, even after thymoma resection, if it is not present at the time of discovery of the thymic tumor. For this reason, it is essential that a complete thymectomy be performed as part of the resection of any anterior mediastinal tumor that may be a thymoma. Because MG is an autoimmune disease caused by anti-acetylcholine receptor (anti-AChR) antibodies, its relationship to thymoma and treatment by thymectomy appears to be related to the role of the thymus in the creation of these antibodies.^{13,14}

This association has a long and very interesting history that is beyond the scope of this chapter. Highlights, however, include the first description by Schumacher and Roth in 1912 of improvement in MG after thymectomy,¹⁵ the more systematic evaluation of this concept by Blalock and coworkers in the late 1930s,¹⁶ and the subsequent controversy over whether the morbidity and rare mortality rates associated with the procedure justified the chances of a remission from MG. Only in the late 1960s and 1970s did thymectomy for MG in the absence of thymoma gain wide acceptance, because improvements in perioperative care reduced the morbidity of the procedure and the benefits became clearer. Convincing data suggest that patients with MG who are treated with thymectomy have a higher remission rate than historical controls treated by medication alone. A multinational randomized study sponsored by the National Institute of Neurological Disorders and Stroke to definitively establish this concept is currently ongoing.¹⁷ Results are eagerly awaited in the coming years.

Association with Other Diseases

Box 41-3 lists MG and the other systemic, autoimmune disorders most commonly associated with thymoma. Two percent to 15% of patients with thymoma have some type of cytopenia. The most common type is pure red-cell aplasia thought to result from an abnormal IgG antibody that inhibits red-cell synthesis. Most patients with this

disease have the favorable, spindle-cell type of thymoma.¹⁸ Approximately one-third of patients with aplasia demonstrate improvement after thymectomy.¹⁹ Hypogammaglobulinemia occurs in less than 5% of patients with thymoma, those being principally older patients. This disease generally does not respond to thymectomy and the prognosis is poor. Of the other autoimmune disorders that occur in association with thymoma in lower frequencies, lupus appears to be the most common; again, resection does not appear to have an impact on the clinical course.

The Anterior Mediastinal Mass That Might Be Thymoma

Imaging. Radiologic studies play a central role in the evaluation of thymoma. Because many patients are asymptomatic at presentation, a widened mediastinum or loss of the normal anterior clear space on the lateral film of a routine chest radiograph may be the first sign of disease. In such a patient, a computed tomography (CT) scan of the chest with intravenous contrast medium should be obtained as the next step. Patients who present with MG or another of the disorders that may be associated with thymoma should also have a chest CT scan.

Although no appearance on CT scan is definitively diagnostic of thymoma, a well-circumscribed, solid anterior mediastinal mass in an adult older than 40 years, without low-density areas that suggest the cystic and fatty components of a teratoma, is very likely to be a thymoma (Figs. 41-2 and 41-3). The presence of calcification is not particularly helpful, because both thymomas and teratomas may contain calcium. In some cases, lymphoma will be the obvious diagnosis on the basis of adenopathy outside of the anterior mediastinum or “B” symptoms, but in the absence of these findings, differentiating a thymoma from a lymphoma may be difficult. It is often possible to suspect one over the other only on the basis of the thymoma patient’s typically more advanced age. Magnetic resonance imaging (MRI) provides useful additional information only when the fluid or fatty nature of

BOX 41-3 Systemic Diseases Most Commonly Associated with Thymoma

- Myasthenia gravis
- Cytopenias (most commonly red cell hypoplasia)
- Nonthymic malignancies
- Hypogammaglobulinemia
- Systemic lupus erythematosus
- Polymyositis
- Rheumatoid arthritis
- Thyroiditis
- Sjögren syndrome
- Ulcerative colitis

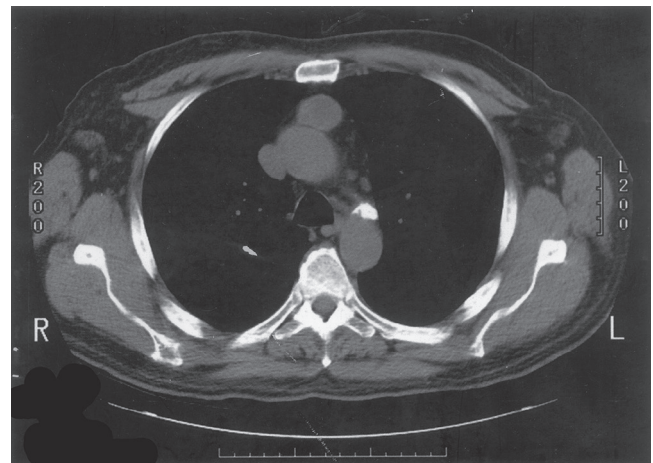


FIGURE 41-2 ■ Characteristic CT appearance of a noninvasive thymoma: a well-circumscribed, solid anterior mediastinal mass.

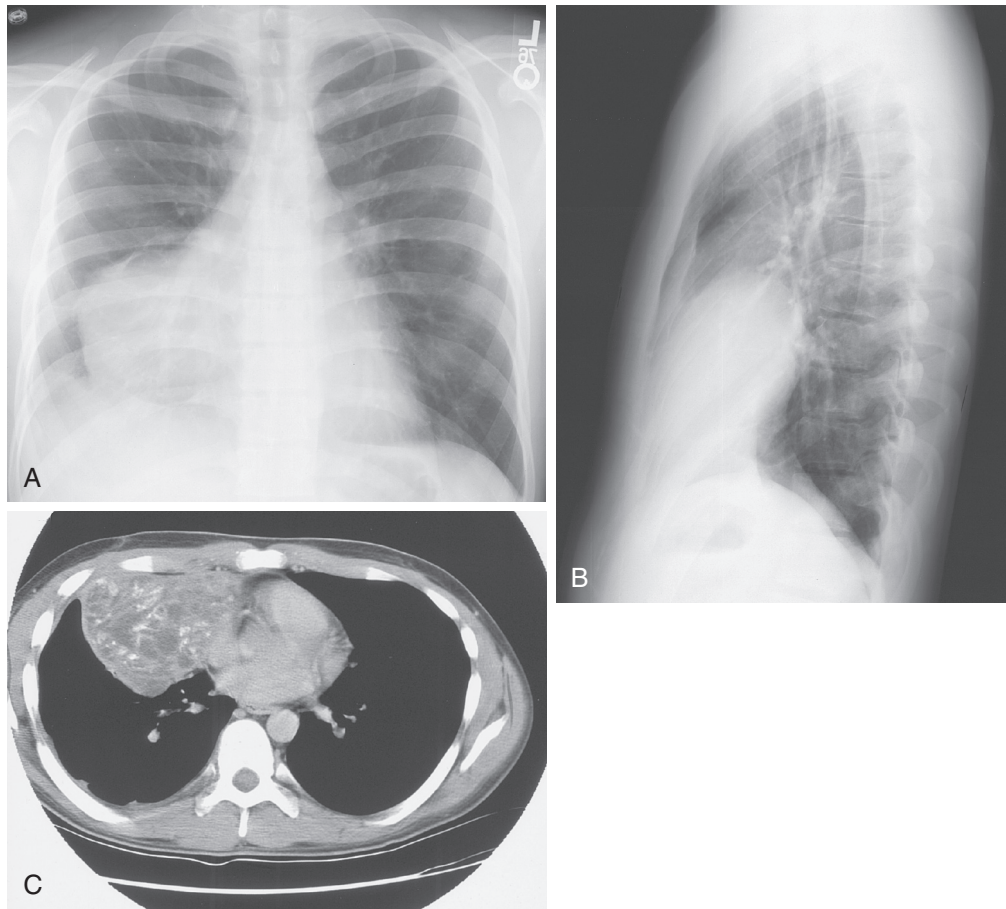


FIGURE 41-3 ■ (A) Posteroanterior and (B) lateral chest radiographs from a 21-year-old man showing a large mediastinal mass adjacent to the right cardiac border. This appearance is characteristic of a mediastinal teratoma. The CT scan (C) shows a complex cystic mass with solid components, including fat and calcification consistent with a diagnosis of teratoma. In the absence of metastatic disease, the final differentiation between teratoma and teratocarcinoma can be made only by pathologic review. (A and B, Courtesy Wallace T. Miller, Jr., Hospital of the University of Pennsylvania, Philadelphia.)

a component of the tumor is not clearly defined by CT scan or when a vascular structure (e.g., an aneurysm) is suspected and has not been clearly ruled out by the contrast CT study.

The chest CT scan also provides information about a putative thymoma's local and regional spread. Loss of planes between the tumor and normal structures may suggest direct invasion, and visceral or parietal pleural deposits may be visible as well. The presence of such signs of local aggressiveness should steer the surgeon toward biopsy rather than primary resection, given the recent data suggesting improved results with neoadjuvant chemoradiotherapy before operation in aggressive thymoma and thymic carcinoma.²⁰⁻²² The role of positron emission tomography (PET) in thymic tumors is not well-defined. It has been shown that PET may be useful for predicting the grade of malignancy according to histologic subtype.²³

Serum Studies. All male patients with an anterior mediastinal mass should have serum testing for α -fetoprotein (AFP), β -human chorionic gonadotropin (β -hCG), and lactic dehydrogenase. Although these levels are normal in patients with mature teratoma, those with malignant germ cell tumors have significant elevations; thus, the

clinician should establish this diagnosis and rule out thymoma.

Evaluation for Myasthenia Gravis. All patients with suspected thymoma should be carefully questioned about muscle weakness or ocular or bulbar signs of MG. The diagnosis of MG classically requires a characteristic history or physical findings, or both, as well as two positive diagnostic tests. Diagnostic testing for MG includes pharmacologic, serologic, and electrodiagnostic studies. Unfortunately, no single diagnostic test can rule out MG with certainty in patients with thymoma. If there is the slightest suggestion of MG at a patient's initial presentation, the patient should undergo additional testing preoperatively under the direction of an experienced neurologist.

Depending on the disease severity, patients with MG may require medical optimization before surgery by some combination of cholinesterase inhibitors, steroids, gamma globulin, and plasmapheresis. In addition, drugs that may exacerbate the symptoms of MG must be avoided (e.g., aminoglycosides, certain inhalation anesthetics, iodinated radiographic contrast). Establishing the preoperative forced vital capacity for comparison with values obtained serially postoperatively can be useful for

determining the appropriateness of extubation in patients with MG after general anesthesia and as an early sign of postoperative deterioration that can then be rapidly addressed.

Biopsy. Typically, the clinician proceeds directly to resection of a discrete anterior mediastinal mass in any of the following situations: (1) the CT or MRI shows features pathognomonic of teratoma; (2) the patient is older than 40 years, without clinical signs or symptoms of lymphoma and with normal AFP and β -hCG; or (3) the mass is associated with MG. In most other instances, biopsy is indicated because, despite the history, physical examination, imaging, and serum studies, a mass still remains that could represent thymoma, lymphoma, or teratoma.

There is controversy regarding whether the biopsy should be done by core-needle biopsy,²⁴ anterior mediastinotomy (Chamberlain procedure), transcervical mediastinotomy, or video-assisted thoracoscopic surgery (VATS) (see Surgical Approaches to Biopsy, discussed later). Needle biopsy has the disadvantage that optimal tissue may not be obtained, and the availability of pathologists adept at differentiating lymphoma from thymoma and among the various types of lymphoma by cytology and flow cytometry is required. Although mediastinotomy almost always provides adequate tissue for diagnosis, there is a theoretical risk (unproven) that thymoma cells may be spread, rendering a previously contained tumor less clearly resectable (an even greater concern for VATS). We favor mediastinotomy when lymphoma is the leading clinical diagnosis, but we believe that core-needle biopsy is required for tumors that are more likely to be thymoma or germ cell tumor (e.g., radiographically aggressive thymoma in which neoadjuvant protocols might be considered).

Treatment

Surgery. Complete surgical resection along with complete thymectomy is the optimal management for thymoma that is not known preoperatively to be invasive. The technique is detailed later in this chapter.

Adjuvant Therapies. For aggressive thymomas, neoadjuvant chemotherapy before resection should be considered because thymomas are chemotherapy-sensitive malignancies. The response rate to these regimens, which generally contain cisplatin, is high, and the rate of complete resection appears likely to be improved by such an approach. These patients should probably also receive postoperative radiotherapy. Some neoadjuvant protocols have included radiotherapy.

Postoperative radiation therapy is certainly indicated in cases of incomplete resection and likely after complete resection of Masaoka stage III thymomas. Because the rate of recurrence of completely resected stage I tumors is less than 5%, these patients are generally not considered for adjuvant radiation. Adjuvant radiotherapy for completely resected stage II thymoma is more controversial. We²⁵ and others²⁶ have presented data that strongly suggest that postoperative radiotherapy is not indicated

in stage II disease, where the surgeon has no uncertainty about resection margins.

Outcome

The outcome for patients with thymoma is stage specific. Patients with completely resected Masaoka stage I thymomas have an excellent prognosis, with an expected recurrence rate of less than 5%. The 10- and 20-year survival rates are 99% and 90%, respectively.²⁷ As the stage increases, the recurrence rates increase and the survival rates decrease. Patients with stage II thymomas treated by complete resection with or without postoperative radiation therapy have recurrence rates as high as 20%.^{26,28} The 5- and 10-year survival rates are 70% to 90% and 55% to 85%, respectively.^{28,29} Long-term data from Japan show better 10- and 20-year survival rates of 94% and 90%, respectively.²⁷ The 5-year survival rates for patients with resected stage III tumors decreases to approximately 50%.³⁰ It is clear that patients with stage III disease who are able to undergo complete resection—even if that requires resection of great vessels or contiguous lung—have substantial cure rates.

What is less clear is whether patients with advanced stage III and IV disease who undergo a marginally complete resection have an improved prognosis compared with those who undergo biopsy alone. The MD Anderson Cancer Center (Houston, Tex.) reported their results in a patient cohort ($N = 22$) of this sort with advanced-stage thymoma in a recent phase 2 study evaluating tumor resectability after induction chemotherapy followed by surgical resection, radiation therapy, and consolidation chemotherapy.³¹ Ten patients had stage IVA disease, and the results are encouraging. With a median follow-up time of 50 months, 18 of 19 patients who completed the multidisciplinary approach were disease-free. The progression-free survival rates were 77% at 5 years and 77% at 7 years. Comparisons of the results of this study with other studies of multimodality therapy of advanced thymoma that did not include surgical resection strongly indicate that surgical resection should be included if there is any chance for a complete resection.

Historically, the presence of thymoma was believed to affect the outcome adversely after thymectomy for MG. Several modern studies, however, suggest that this is not the case. A review from the Toronto General Hospital revealed no significant difference in the complete response rate or postoperative Osserman grade of patients with MG undergoing thymectomy, with or without thymoma.³² The complete remission rate of MG at 5 years after thymectomy was 36% with or without thymoma.

Thymic Carcinoma

Thymic carcinomas are rare invasive epithelial malignancies. A clinicopathologic study of 60 cases of thymic carcinoma revealed an overall 5-year survival of 33%.³³ Histologically, this group consists of a number of different cell types. They are unified, however, by their unequivocal malignant appearance on light microscopy. Although there is no formalized staging system, division

of patients into those with low-grade histology and those with high-grade histology does have prognostic significance. Low-grade tumors include squamous, mucoepidermoid, and basaloid carcinomas. The high-grade tumors include sarcomatoid and clear-cell carcinoma. The median survival time for patients with low-grade histology is 29 months, compared with 11 months for patients with high-grade histology.³⁴ Effective therapy of thymic carcinoma requires a multimodality approach, which typically includes induction therapy followed by resection (if possible), with postoperative radiation therapy if it was not included preoperatively. Unfortunately, most patients have recurrence, either locally or at distant sites, and die of their disease. Multiple neoadjuvant chemotherapy protocols have been proposed for patients presenting with clearly unresectable disease. To date, the numbers are too small and the results too variable to determine whether this approach converts these patients into operative candidates or affects their overall outcome.³⁵

Neuroendocrine Tumors of the Thymus

Neuroendocrine tumors of the thymus include thymic carcinoid and small cell carcinoma of the thymus. These tumors are related biochemically by the presence of amine precursor uptake and decarboxylation cells and may actually represent a spectrum of the same abnormality.

Thymic carcinoid occurs more frequently in men than in women. One-third of patients present with Cushing syndrome because of ectopic adrenocorticotrophic hormone production. This portends a very poor prognosis. The treatment of thymic carcinoid is complete excision, and the overall cure rate is very low. The role of multimodality therapy is undefined.

Small cell carcinoma of the thymus is very uncommon. A 20-year review of extrapulmonary small cell carcinoma at the Mayo Clinic revealed only three cases of a total 54 patients.³⁶ This tumor, however, is extremely aggressive. It is treated with chemotherapy alone or in combination with radiation. Like small cell carcinoma of the lung, it is usually responsive to initial chemotherapy, but the response is often not durable.

Other Abnormalities of the Thymus

Hyperplasia

The infant thymus is a large, pyramid-shaped gland that occupies a significant portion of the anterior mediastinum. In contrast, the adult thymus is an involuted organ consisting mostly of adipose tissue surrounded by a capsule. The gland shrinks slowly over the years. In true thymic hyperplasia, the gland is generally enlarged in both size and weight (for the patient's age), but the key feature is that histologically the gland is hyperplastic, with more cellularity and less adipose tissue. The presentation of thymic hyperplasia is along a spectrum ranging from usual adult presentation of an incidentally discovered, asymptomatic mass to the giant mass in an infant causing respiratory compromise due to tracheal

compression. Thymic hyperplasia can certainly be seen in association with MG, and it is believed likely to be causally related to MG, but it is also commonly seen in association with Graves disease and after a severe illness or a course of steroid therapy—so-called “thymic rebound.” All of these must be considered before recommending surgical intervention for someone with an “enlarged” thymus.

Unfortunately, no one has ever carried out a definitive study establishing what constitutes “normal” thymic size at various ages. The thoracic surgeon is therefore typically left to use judgment and experience to decide whether a given referred patient's thymus is “normal” or “enlarged.” A study from the senior author has shown that an asymptomatic patient with diffuse thymic enlargement and no discrete mass can be safely observed without resection.³⁷ Others have also suggested that normal thymuses are perhaps too often removed when a patient presents with no other problem than a gland that is felt to be modestly enlarged.³⁸

Thymolipoma

Thymolipomas are distinguished from simple mediastinal lipomas by their location in the thymic capsule. Histologically, these neoplasms contain mature adipose cells as well as normal thymic components. Interestingly, thymolipomas can be associated with thymic paraneoplastic syndromes such as red-cell aplasia, aplastic anemia, and hypogammaglobulinemia like thymuses (see previous discussion). The treatment of thymolipoma is excision.

Thymic Cysts

Mediastinal thymic cysts account for less than 0.2% of anterior mediastinal masses.³⁹ They are often asymptomatic and are usually discovered incidentally. Most are unilocular, and they must contain thymic tissue within the cyst wall to confirm the diagnosis. As a unique entity, they are inconsequential and completely benign. Removal is only indicated when it is necessary to rule out other entities, such as thymoma with cystic components (i.e., cystic thymoma). Unfortunately, these diagnoses are not easily differentiated on radiographic grounds. Excision may be required; it yields a definitive diagnosis and completes treatment.

GERM CELL TUMORS

Germ cell tumors (GCTs) comprise a group of neoplasms that usually arise in gonadal tissue. The anterior mediastinum is the most common extragonadal location for GCTs, which account for 15% to 20% of all anterior mediastinal masses. These tumors are divided into benign and malignant lesions.

Benign Mediastinal Teratoma

Benign mediastinal teratoma accounts for 60% of mediastinal GCTs. It is usually asymptomatic in the adult but can cause cough or discomfort/pain when large. Children

are more likely to present with symptoms caused by airway compression. On CT scan, the mass is well-circumscribed and may contain calcification. It usually shows variable enhancement because of the presence of different tissue types including fat, muscle, bone, and cystic components (see Fig. 41-3). Curative treatment consists of complete excision, classically via median sternotomy, but now probably more commonly by VATS or robotic approaches. Thoracosternotomy may be required for giant tumors.

Malignant Mediastinal Germ Cell Tumors

The malignant mediastinal GCTs are divided into seminomatous and nonseminomatous tumors. Seminomas account for 40% of these tumors, and nonseminomas account for 60%. The nonseminomas include embryonal cell carcinoma, choriocarcinoma, yolk sac tumors, and teratocarcinomas. These tumors are generally diffuse—not discrete—anterior mediastinal masses, and they frequently invade surrounding structure, causing symptoms.

The malignant GCTs are much more common in males, but they have been reported in females.⁴⁰ The preoperative evaluation of these patients includes a complete physical examination, including testicular examination in male patients to be certain these are primary mediastinal tumors and not metastases. Radiographic studies should include a CT scan of the chest, abdomen, and pelvis. Serum AFP, β -hCG, and lactate dehydrogenase levels should be obtained.

Patients with pure seminoma have normal AFP and usually a mild elevation of β -hCG. A pure nonseminomatous GCT may have elevated AFP (in 50%) and/or β -hCG (also in approximately 50%). Elevated AFP is most closely associated with yolk sac tumors, whereas elevation of hCG is more closely associated with choriocarcinomas. The differentiation between the seminomatous and nonseminomatous germ cell tumors has important prognostic and therapeutic implications. Like testicular seminomas, the pure mediastinal seminomas are extremely radiosensitive, but today the primary treatment is more commonly cisplatin-based chemotherapy alone, which also yields very high response rates, and about 80% of patients with pure seminomas are cured.⁴¹ Residual masses with PET activity and histopathologic residual cancer after treatment of seminoma may be resected if possible in preference to adding radiation. Alternatively, chemotherapy can be used. The optimal treatment of a residual mass remains debatable.⁴²

After confirmation by needle biopsy, nonseminomas are usually treated with three-drug chemotherapy (etoposide, ifosfamide, and cisplatin). Traditionally, surgical resection was reserved for a residual mass after treatment that was associated with normalization of serum markers (this indirectly suggesting a strong response to treatment, translating to a greater chance of complete resectability). This approach, however, has been changing. Researchers at Indiana University reviewed their 25-year experience with treated mediastinal nonseminomatous germ cell tumors in 158 patients.⁴³ With a median follow-up of 34

months, they reported a 62% overall survival. Multivariate analysis revealed that, among other variables, pathologically identified complete tumor necrosis after chemotherapy was an independent predictor of survival. Operative risks for nonseminomatous germ cell tumors appear to be improved with the use of chemotherapy regimens that did not contain bleomycin. Data from Memorial Sloan-Kettering⁴⁴ and other institutions⁴⁵ suggest that all patients with a residual mass after chemotherapy should undergo resection even if their markers remain elevated. These studies revealed that postchemotherapy serum marker levels correlated poorly with pathologic evidence of disease. Further, there were no effective second-line chemotherapy regimens, and long-term survival differences did not exist in patients with presurgical elevated markers versus patients with normal markers.

LYMPHOMAS

Both Hodgkin disease and non-Hodgkin lymphomas can appear as anterior mediastinal masses. The diagnosis is usually suspected on clinical history and CT scan. We recommend surgical biopsy over needle biopsy as the most efficient method of obtaining a precise diagnosis when lymphoma is suspected (see previous discussion), although in many institutions now there is sufficient expertise with flow cytometry to obtain a diagnosis in most cases with a core-needle biopsy specimen only. Surgical approaches to biopsy include cervical mediastinoscopy, anterior mediastinotomy, and, less commonly, thoracoscopy. It is imperative that the surgeon work in conjunction with the pathologist at the time of surgery to ensure that adequate tissue is obtained. The diagnosis of Hodgkin disease is confirmed by the presence of Reed-Sternberg cells. The diagnosis and characterization of the non-Hodgkin lymphoma rely on both light microscopy and cell-surface markers. Flow cytometry requires fresh (unfixed) tissue, so the surgeon must ensure that not all of the biopsy tissue is placed in formalin.

Controversy persists over the sensitivity and specificity of the CT scan and PET scan in determining the composition of residual masses after chemotherapy and radiotherapy for lymphoma. Some clinicians advocate multiple core-needle biopsies in this setting, but this is subject to sampling error. Surgical biopsy clearly is more sensitive and is indicated commonly.

SUBSTERNAL THYROID

Substernal thyroid and ectopic thyroid tissue can appear as an anterior mediastinal mass. In most cases of substernal thyroid, an enlarged thyroid gland is palpable in the neck. Often, a chest radiograph shows deviation of the trachea. We have found that a CT scan without contrast is the single most useful test in differentiating substernal thyroid from other mediastinal masses. Because of its iodine content, substernal thyroid tissue shows enhancement on a noncontrast CT scan, and this usually confirms the diagnosis. The majority of substernal thyroids are

goiters, but a benign process versus a malignant process cannot be differentiated radiographically. The vast majority of substernal goiters are able to be removed via a cervical approach. This is possible because the blood supply of the superior and inferior thyroid arteries originate in the neck. In some instances, a partial sternal split is required to provide adequate room for delivery of the gland from its substernal location. Infrequently, tracheal stenting, or even resection with primary anastomosis, is required to correct tracheomalacia caused by compression, or for direct tracheal invasion in the case of malignant substernal thyroid neoplasms. This should be performed as a single-stage operation at the time of thyroid resection.

HYPERFUNCTIONING MEDIASTINAL PARATHYROID ADENOMA

Ectopic parathyroid glands are not infrequently located in the mediastinum—typically embedded with the thymus gland. These patients exhibit primary hyperparathyroidism after unsuccessful neck exploration. Before mediastinal exploration is undertaken, localizing studies should be performed. Nonfunctional anatomic studies such as CT and MRI may reveal a well-defined mass. Technetium-99m-sestamibiscintigraphy, however, is the most useful study to localize hyperfunctioning ectopic parathyroid adenomas. In rare cases, no clear ectopic gland is identified, and “blind” resection of the thymus may be indicated. The treatment for an ectopic mediastinal parathyroid adenoma is resection. This is performed via a transcervical approach (i.e., a transcervical thymectomy [TCT]) via a median sternotomy or by thoracoscopy. Resection involves removal of the thymus and surrounding fat to include the adenoma. Intraoperative use of rapid parathyroid hormone levels can be used to confirm the successful localization and removal of the adenoma. The presence of parathyroid tissue should be at a minimum confirmed by frozen section examination. If the transcervical or VATS approach is selected and there is no normalization of intraoperative parathyroid hormone, or if parathyroid tissue cannot be confirmed pathologically, the surgeon should convert to a median sternotomy.

SURGICAL APPROACHES TO BIOPSY

Chamberlain Procedure (Anterior Mediastinotomy)

This procedure is usually performed under general anesthesia, but it can be performed under local anesthesia if required. The patient is placed in the supine position with arms tucked. A 5-cm, horizontally oriented incision is made just lateral to the sternomanubrial joint over the second costal cartilage. The pectoralis muscle fibers are split from the sternochondral to the costochondral junction. The second cartilage is removed subperichondrially, and the pleura is gently swept laterally to avoid inadvertent pneumothorax. Care is taken to avoid injury to the internal thoracic artery and vein, but sometimes they

must be divided to gain sufficient exposure. Biopsy is performed under direct vision with a scalpel or biopsy forceps. During closure, the perichondrium should be reapproximated to promote regrowth of normally shaped cartilage.

Transcervical Biopsy (Cervical Mediastinotomy)

Transcervical biopsy is performed through a transcervical collar-type incision. The exposure is identical to that described later for TCT, and it is facilitated by use of the Cooper retractor. Once exposure is obtained, tissue can be procured directly with biopsy forceps or scalpel. We have found this approach to be particularly useful to biopsy lesions directly beneath the sternum that would be difficult to reach by a Chamberlain procedure and thus might otherwise require a sternotomy.⁴⁶

Thoracoscopic Biopsy

VATS can be used for biopsy of anterior mediastinal masses, but in most situations there are simpler and more direct approaches. The anterior mediastinum can be reached from either the left or the right hemithorax, and the side should be selected on the basis of the predominant location of the mass. A 30-degree thoracoscope facilitates visualization of the anterior mediastinum. The thoracoscope is introduced generally through the fourth intercostal space at approximately the anterior axillary line. A simple biopsy can often be performed through this single port, extended to about 2 cm in length, by placing the biopsy forceps adjacent to and parallel with the camera. Sometimes one additional working port is needed. The anterior compartment is accessed by incising the pleura anterior to the phrenic nerve. The connective tissue is gently swept away and the lesion identified and biopsied—typically with mediastinoscopic biopsy forceps.

It is our opinion that the VATS approach is more cumbersome and associated with greater risks than either the anterior mediastinotomy or the transcervical approach. Injury to a phrenic nerve, though rare, is a catastrophe. Spillage of tumor during biopsy (which is probably impossible to avoid using the VATS approach) may cause contamination of the pleural space, facilitating, in the case of thymoma, its natural means of spreading. Finally, this approach requires single-lung ventilation, which adds an additional level of complexity to the anesthetic management, especially in patients with large masses and tracheal compression.

Extended Mediastinoscopy

In 1987, Ginsberg and colleagues reported the use of extended cervical mediastinoscopy in the staging of lung cancer.⁴⁷ This advanced technique allows placement of a mediastinoscope into the anterior compartment through a standard cervical mediastinoscopy incision. This involves the creation of a tunnel between the origin of the innominate artery and the left carotid artery. The tunnel is created by careful digital dissection, the mediastinoscope is then reinserted and advanced anteriorly

toward the left into the tunnel, and the target lesion is identified and biopsied. This technique requires considerable experience and carries the risk of significant bleeding because of the proximity of the aorta and pulmonary artery. Unless the surgeon has been specifically trained in this technique, most anterior mediastinal masses are more safely and easily approached via anterior or cervical mediastinotomy, as described previously.

THERAPEUTIC SURGICAL PROCEDURES: TECHNIQUES OF THYMECTOMY

The main surgical procedure carried out for tumors of the anterior mediastinum is thymectomy, because thymoma is the most common tumor in this area and demands complete extirpation of the gland. Only if there is certainty preoperatively that the tumor is other than thymoma (generally a teratoma) should the surgeon attempt to explore the anterior mediastinum and resect the tumor alone without the entire adjoining thymus. In this circumstance, a frozen section should always be obtained to confirm the preoperative diagnosis so as not to inadvertently perform less than a complete thymectomy for thymoma.

The reasons for performing a total thymectomy in patients with thymoma include that:

- It promises the widest possible resection margin through a natural anatomic plane, and
- Patients with thymoma may develop MG well after their operation. Because total thymectomy appears to improve the course of MG, it should be performed during all thymoma operations.

Thymectomy by Median Sternotomy

Median sternotomy is still likely the most widely used approach to thymectomy. Although a full sternotomy is

typical, partial upper sternotomy with extension of the bony incision into the third or fourth intercostal space also has its advocates.⁴⁸ We find that this is no less painful than sternotomy and substantially limits exposure. Adjacent structures to which the tumor is adherent must be resected en bloc. This often includes pleura, pericardium, and, in more aggressive tumors, the innominate vein (which may be resected without reconstruction), the superior vena cava (requiring reconstruction), and/or the lung. Both pleural spaces should be widely opened by two incisions in the mediastinal pleura on each side: one just anterior to the phrenic nerve and one just posterior to the chest wall. In all procedures, the upper thymic poles are identified and are traced all the way to the thyrothymic ligament to ensure complete resection, and all fatty tissue between the phrenic nerves and all the way down to the diaphragm is included in the resection. This description implies a “T3b” thymectomy according to the MGFA classification.⁴⁹ More or less extensive thymectomies are carried out by some surgeons, but these have largely fallen from favor.

Transcervical Thymectomy

We have reported that noninvasive thymomas less than 4 cm in diameter may be completely resected along with the thymus by a transcervical approach (we would go only as far as 3 cm currently).⁴⁶ However, when using this approach, the surgeon must have a low threshold for conversion to sternotomy if any suggestion of gross invasion is encountered. Strong evidence exists, conversely, that in the absence of thymoma, TCT provides results very similar to more aggressive thymectomy approaches in the treatment of MG.⁵⁰ Table 41-3 lists results of large modern studies of the various approaches to thymectomy for MG. Note that there is no dramatic difference in complete MG remission rates between the proposed approaches to thymectomy.

TABLE 41-3 Large Studies of Myasthenia Gravis Response Rates after Thymectomy by Three Surgical Approaches*

	References	Crude Complete Remission Rate (%)	Mean Follow-Up (yr)	Kaplan-Meier 5-Year Remission Rate (%)
Maximal transcervical and trans-sternal	Ashour et al ⁵¹	35	1.7	NA
	Jaretzki et al ⁵²	46	3.4	50
	Busch et al ⁵³	19	7.7	NA
	Klein et al ⁵⁴	40	5.0	NA
Trans-sternal	Budde et al ⁵⁵	21	4.3	NA
	Durelli et al ⁵⁶	NA	5.0	30
	Masaoka et al ⁵⁷	40/45	5.0/20.0	NA
	Mulder et al ⁵⁸	36	3.6	NA
	Stern et al ⁵⁹	50	6.8	NA
	Huang et al ⁶⁰	58	8.5	NA
	Kattach et al ⁶¹	17	4.5	NA
	Bril et al ⁶²	44	8.4	NA
Extended transcervical†	Calhoun et al ⁶³	35	5.0	NA
	de Perrot et al ⁶⁴	41	4.1	30
	Shrager et al ⁵⁰	37 (29)‡	4.4	43 (33)‡

*Includes only studies in the past 20 years in the English-language literature that represent a pure series of one type of procedure with at least 48 adult patients and that report complete remission rates and mean follow-up.

†Includes only studies representing pure series of extended transcervical thymectomy using the Cooper thymectomy retractor.

‡Values in parentheses represent the most restrictive definition of a complete response.

NA, Data not available.

TCT and transcervical approaches to other masses in the anterior mediastinum are performed through a 5-cm curvilinear incision in the jugular notch. Details of the procedure have been described elsewhere.⁶⁵ In brief, after dissection of the two cervical poles, each is tied with a silk suture and used for traction to aid in dissection of the remainder of the gland. After, or just before, branches from the innominate vein to the gland are ligated and divided, and a Cooper thymectomy retractor (Pilling Co., Fort Washington, PA) is inserted and positioned to maximally lift the sternum as an inflatable bag beneath the shoulders is deflated. Extracapsular removal of the entire gland then proceeds by primarily blunt dissection within the mediastinum by the operator, seated at the head of the table and using a headlight (Fig. 41-4). The resection includes the bulk of the extra-thymic mediastinal fat between the phrenic nerves and down to the diaphragm. The procedure does not remove the pleurae or the fat directly apposed to the pleurae (which are generally removed during sternotomy), tissue posterior to the phrenic nerves, or other areas where ectopic thymic tissue has been described. No drains are left in place. Patients are generally discharged late on the same day of surgery.

Maximal Thymectomy: Trans-sternal and Transcervical

Jaretzki and a few others have for many years advocated “maximal” thymectomy for MG patients, involving a cervical incision in addition to median sternotomy and requiring extensive neck and mediastinal dissection to

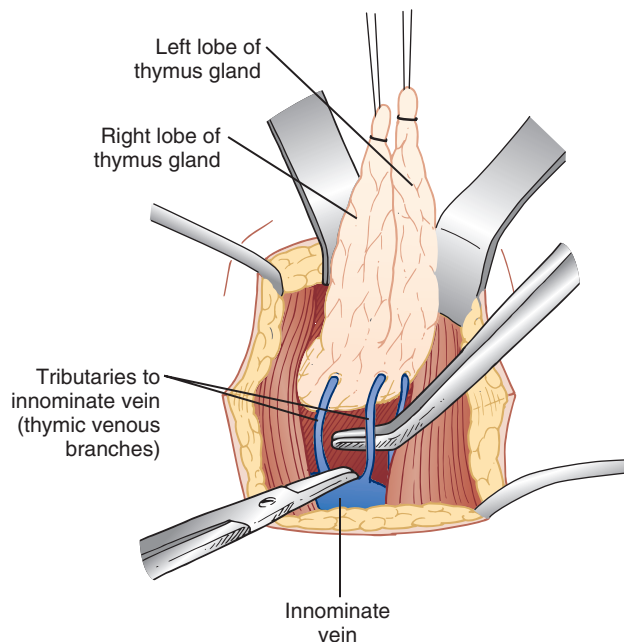


FIGURE 41-4 ■ Technique of transcervical thymectomy. The surgeon's view from the head of the table shows the ligated upper thymic poles retracted anteriorly while the branches into the thymus from the innominate vein are controlled. (From Kaiser LR: *Atlas of general thoracic surgery*, St. Louis, 1997, Mosby-Year Book, with permission.)

investigate all areas where aberrant thymic tissue has been described.⁶⁶ Although Jaretzki has argued in favor of this approach, the evidence that this extensive operation provides better control of MG than even the least invasive transcervical approach is controversial (see Table 41-3) and has not convinced many to adopt this procedure.

Thoracoscopic Thymectomy

A number of thoracoscopic approaches to thymectomy have been described that appear to allow complete thymectomy to be performed.^{67,68} Approaches that combine the thoracoscopic and transcervical techniques with sternal lifting have also been reported.⁶⁹ However, there is no doubt that intercostal, thoracoscopic port incisions are more painful than a small incision in the jugular notch as performed for TCT. Thus, there would appear to be little reason to use thoracoscopy in lieu of or in addition to the transcervical approach for nonthymomatous MG unless it can be demonstrated that this allows more complete resection of thymic tissue and results in higher complete responses. This is very unlikely when even “maximal” thymectomy does not result in markedly higher response rates than TCT. Shigemura and colleagues⁷⁰ performed a prospective trial on 20 patients to compare the efficacy of various thoracoscopic approaches with and without an open transcervical approach, and they concluded that a strictly VATS approach resulted in incomplete gland removal.

For smaller, noninvasive thymomas, thoracoscopic approaches have also gained favor. However, concern that inadvertent breaching of the tumor capsule at the time of thoracoscopy would facilitate spread of thymoma by the route that it follows by nature—directly into the pleural space—has led many experienced surgeons to adopt VATS approaches cautiously, if at all. Nevertheless, it has been demonstrated in several series that stage I and II thymomas, generally with a size limit of approximately 4 cm, can likely be safely resected by VATS. One must be concerned, however, that follow-up time is limited in currently published studies, given the known propensity of thymoma to recur even up to 10 years postoperatively.

Robotic Thymectomy

Although conceptually and anatomically little different than a VATS thymectomy, robotic system removal of the thymus can have certain advantages over the VATS approach, and it too is being increasingly applied. Resection of mediastinal masses is probably the ideal intrathoracic application of robotic technology—the robot tends to be the most useful in procedures that require manipulation in smaller, remote spaces where the fully articulating “wrists” provide maximal advantage. In MG, early adopters have presented medium-term experience showing complete stable remission rates at least as good as those reported after VATS thymectomy.^{71,72} For thymoma, although the concern raised just previously for VATS approaches regarding spillage into the pleural space remains relevant, a multicenter European study has

suggested safety and efficacy for stage I-II thymoma.⁷³ Of 79 cases carried out at four centers for tumors with a median 3-cm diameter (mainly from a left-sided approach), one conversion to open surgery was required, no vascular or nerve injuries occurred, and median hospital stay was 3 days. Most importantly, 5-year disease-specific survival was 97%—one patient had diffuse pleural recurrence. A right-sided robotic approach, sometimes with an additional single-port VATS on the left to clearly identify the left phrenic nerve, is advocated by some. Certainly, additional series and longer interval follow-up data will be important as this technology is increasingly applied.

SUMMARY

We have reviewed the various anterior mediastinal masses, paying particular attention to their presentation, diagnosis, and management. The association of thymic disease and MG has been emphasized. Surgical approaches to biopsy and resection of anterior mediastinal masses, including their respective advantages and disadvantages, have been described. The appropriate management of anterior mediastinal masses requires flexibility and versatility on the part of the surgeon with regard to the method selected in each patient for biopsy or resection.

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THE MIDDLE MEDIASTINUM

Christopher W. Seder • Michael J. Liptay

CHAPTER OUTLINE

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ANATOMY

Using the traditional “three-compartment” classification, the middle mediastinum is bounded anteriorly by the pericardium and posteriorly by the pericardium and membranous wall of the trachea (Fig. 42-1). The lateral borders are composed of the mediastinal pleura, while the superior margin is the thoracic inlet and the inferior margin is the diaphragm. Contained within this space are portions of the airway, the pericardial contents, lymphatics, and nervous structures. The intrathoracic trachea, proximal main-stem bronchi, pericardium, phrenic nerves, heart, ascending aorta, and proximal arch are all located within the middle mediastinum. It also contains a rich network of lymphatic channels and lymph nodes that primarily drain the lungs and esophagus, such as lymph nodes in the paratracheal and subcarinal positions.

The structures located within the middle mediastinum can be the site of neoplastic, inflammatory, degenerative, or infectious pathologic conditions. In addition, the superior aspect of the middle mediastinum is in communication with the inferior aspect of the neck; thus, disorders involving the neck can also involve the mediastinum. Therefore, a thorough understanding of the middle mediastinum and its contents is required of any surgeon who treats conditions that involve the structures located within this space.

DIAGNOSTIC MODALITIES

Signs and Symptoms

Although often asymptomatic, a variety of signs and symptoms may be present in patients with diseases of the

middle mediastinum. Individual presentation depends on the size and location of the lesion and whether it is benign, malignant, inflammatory, or infectious. The most common symptoms include cough, dyspnea, and chest pain. In the presence of malignancy, direct invasion can lead to diaphragmatic paralysis or chylothorax. Compression of the superior vena cava can obstruct blood return from the upper body. Rarely, hormonal or endocrine substrates lead to systemic manifestations, leading to workup and diagnosis of middle mediastinal pathology.

Imaging

The conventional chest radiograph often provides the first indication of an abnormality in the middle mediastinum. Narrowing or deviation of the tracheobronchial tree, enlargement of the pericardial silhouette, and calcification or enlargement of the great vessels are detectable radiographically (Fig. 42-2A). The right paratracheal stripe is formed by the lateral trachea, mediastinal tissue, and paratracheal pleura, and it should be visible on posterior-anterior chest radiograph (CXR). Obliteration of this stripe can indicate the presence of lymphadenopathy in station 4R, a right-sided aortic arch, or a paratracheal mass. Similarly, the aortopulmonary window should appear as a concavity at the interface between the aortic knob and left pulmonary artery on CXR. Fullness in this region is considered abnormal and may reflect lymphadenopathy in the aortopulmonary window. However, because of its limited resolution, CXR often does not provide adequate information about specific mediastinal pathology. Further radiographic assessment by other modalities is necessary for a more accurate assessment.

Computed tomography (CT), often with intravenous or oral contrast, is indicated when mediastinal pathology

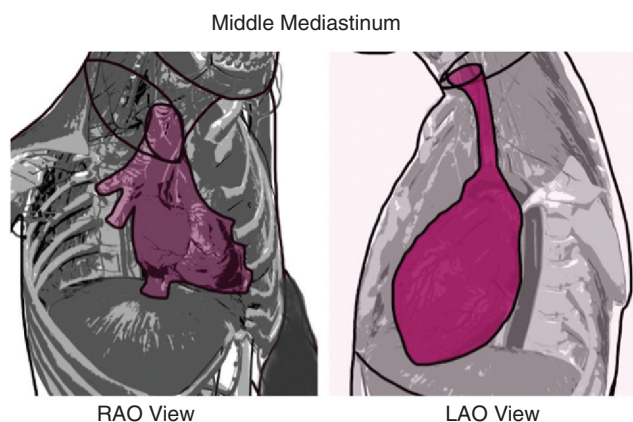


FIGURE 42-1 ■ Traditional three-compartment classification of the mediastinum. (Courtesy Gary Chmielewski, MD.)

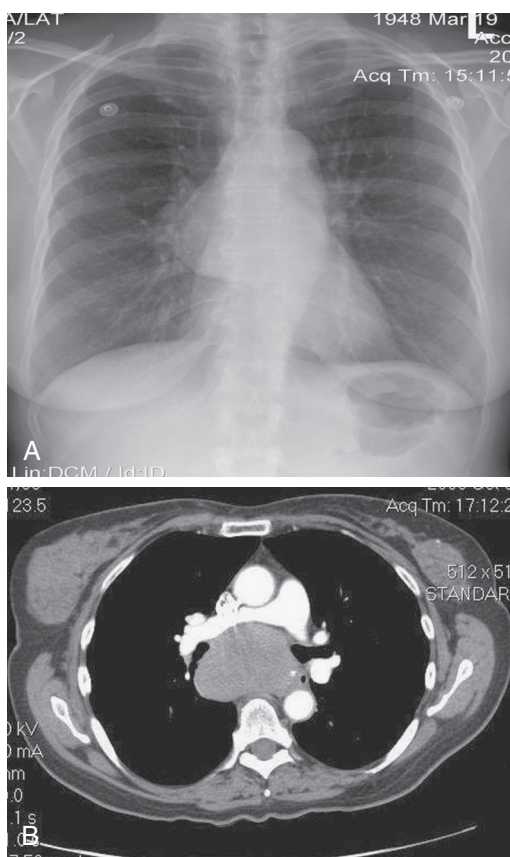


FIGURE 42-2 ■ **A**, Posteroanterior chest radiograph of a 55-year-old woman with chest heaviness and mild dysphagia to solids. A large middle mediastinal mass is noted. **B**, Computed tomographic scan demonstrates a subcarinal mass. Differential diagnosis includes adenopathy (lymphoma) and bronchogenic or esophageal duplication cyst. Resection revealed a plasmacytoma.

is suspected (see Fig. 42-2B). High-resolution spiral CT, with cross-sectional imaging of structures at intervals as narrow as 1 mm, is the radiologic modality of choice for imaging the middle mediastinum. All structures of the middle mediastinum are visible on CT scan, and their relationship to adjacent structures is often easily delineated. Three-dimensional reconstructions can be created,

and they are particularly useful for detailed assessment of structures, such as the trachea and aortic arch. The presence of calcified mediastinal lymph nodes and pulmonary granulomas may suggest a subacute, benign process, such as mediastinal histoplasmosis.

Magnetic resonance imaging (MRI) may provide additional information in the assessment of middle mediastinal pathology. Advantages of MRI include its ability to differentiate between vascular, solid, and fluid elements in a given mass. MRI has been shown to be superior to CT for assessing tumor invasion into vascular structures.¹ T1-weighted images are preferable for delineating anatomy, whereas T2-weighted images are preferable for characterizing solid from cystic structures.

Positron emission tomography (PET) using fluorine-18 fluorodeoxyglucose (FDG) is a valuable tool for evaluating middle mediastinal pathology. It has become an integral component in the clinical staging of lung and esophageal cancers, as well as in the follow-up of mediastinal lymphomas.^{2,3} The fusion of PET and CT technology increases diagnostic accuracy by allowing precise localization of hypermetabolism.⁴ The degree of FDG uptake is used as a surrogate marker for the degree of metabolic activity in a given tissue. Areas of increased activity are often targeted for biopsy to provide the most high yield results. However, the utility of PET scanning is limited because it is difficult to distinguish between hypermetabolism caused by malignancy and that caused by inflammation. For example, acute mediastinal lymphadenopathy related to pneumonia commonly demonstrates FDG avidity.

Outside of echocardiography, transthoracic ultrasonography is of limited value in the evaluation of the middle mediastinum. However, endobronchial ultrasonography (EBUS) and transesophageal ultrasonography (EUS) have emerged as valuable tools for the evaluation of the mediastinum. Both techniques can be performed using moderate sedation on an outpatient basis. Using EBUS, lymph nodes in stations 2, 4, 7, 10, and 11 can be visualized and sampled. The addition of EUS allows access to lymph nodes in stations 8 and 9. Both modalities can differentiate solid from cystic masses, detect lymph nodes as small as 3 × 5 mm, and allow for reliable ultrasound-guided fine-needle aspiration.⁵

Other modalities, such as leukocyte scintigraphy, lymphoscintigraphy, and metaiodobenzylguanidine (MIBG) scanning, have limited and very specific indications in the evaluation of pathology in the middle mediastinum.

Invasive Techniques

CT-Guided Percutaneous Biopsy

Tissue from masses in the middle mediastinum can be obtained with CT-guided percutaneous biopsy. Both fine-needle biopsy and core needle biopsy can be performed using CT guidance. This technique offers the advantage of obtaining tissue for diagnosis using only local anesthesia on an outpatient basis. Success rates, particularly with core needle biopsy, are excellent in experienced hands. The disadvantage of these techniques is the possibility of obtaining an inadequate amount of

tissue for diagnosis or failure to make a diagnosis in relatively small masses.

Endoscopic Ultrasound and Endobronchial Ultrasound-Guided Biopsy

EBUS and EUS are being used with increasing frequency to obtain tissue from the mediastinum. With EUS, both fine-needle and core biopsy specimens may be obtained with minimal morbidity. EBUS-guided fine-needle aspiration can be used to obtain tissue from masses located near the trachea and mainstem bronchi. These modalities are increasingly used in the staging of lung cancer, but can also be used to obtain tissue from other middle mediastinal masses. Pathologic lymph nodes are often homogeneous, hypoechoic, round, and larger than 1 cm in diameter. Several studies have suggested that combining EBUS- and EUS-guided biopsy has a higher accuracy than either procedure alone and has a diagnostic accuracy comparable to mediastinoscopy in the staging of patients with suspected lung cancer.⁶⁻¹⁰ Additional benefits of endoscopic ultrasound-guided biopsy are that it carries a low morbidity profile, usually does not require a general anesthetic, is preferred by patients,¹¹ and is cost-effective¹² compared with surgical staging.

Cervical Mediastinoscopy and Anterior Mediastinotomy

Cervical mediastinoscopy has been traditionally considered the gold standard for evaluation of mediastinal pathology. In experienced hands, the procedure can be performed with less than 2% morbidity and less than 0.1% mortality. It offers the advantage of obtaining a large amount of tissue from mediastinal lymph nodes in the pretracheal, paratracheal, and subcarinal regions, but the surgeon cannot access the inferior or posterior mediastinum or the aortopulmonary window.

On occasion, a 3- to 4-cm parasternal anterior mediastinotomy (Chamberlain procedure) may be necessary to obtain tissue for diagnosis. Under direct visualization, anterior mediastinal masses, aortopulmonary window lymph nodes, and para-aortic masses can be accessed for sampling. The primary disadvantages of cervical mediastinoscopy and anterior mediastinotomy are that they require an incision and general anesthesia. However, with either technique, a histologic diagnosis can be obtained in a majority of cases.

Video-Assisted Thoracoscopic Surgery

The use of video-assisted thoracoscopic surgery (VATS) in the diagnosis and management of thoracic conditions has gained widespread acceptance. VATS allows the surgeon to visualize the entire pleural space and ipsilateral mediastinum. Using VATS and dedicated instruments, tissue can be obtained from nearly all mediastinal compartments. In addition, many middle mediastinal masses can be managed effectively with VATS techniques. A VATS approach is particularly useful in the evaluation and treatment of lesions that require direct visualization, such as those in close proximity to the heart and great

vessels. The principal disadvantages of VATS are that it requires general anesthesia and split-lung ventilation, and the surgeon risks seeding the pleural space if a malignant tumor is disrupted during dissection. However, VATS has emerged as a powerful tool in the armamentarium of the thoracic surgeon.¹³

Other Techniques

Rarely, other attempts fail, or the preceding procedures cannot be used in a specific instance. Then, a thoracotomy or sternotomy may be necessary to obtain tissue to establish a histologic diagnosis of a middle mediastinal mass.

DISEASES OF THE MIDDLE MEDIASTINUM

Mediastinal Lymphadenopathy

Enlargement of middle mediastinal lymph nodes is seen in a wide variety of disorders. Metastasis from lung cancer is the most common cause of malignant mediastinal lymphadenopathy. Lymph nodes located in the paratracheal region, tracheobronchial angle, and subcarinal space are often involved. When infiltrated by malignancy, these lymph nodes can appear enlarged on imaging studies or demonstrate hypermetabolism on PET scan. Esophageal and tracheal malignancies, mesothelioma, and extrathoracic tumors with metastases to the lungs can subsequently spread to mediastinal lymph nodes. Extrathoracic malignancies can also metastasize directly to mediastinal lymph nodes, without the development of pulmonary metastases. The middle mediastinum may be the primary site of disease in Hodgkin lymphoma and primary mediastinal B cell lymphoma. Typically, however, mediastinal lymphomas occur with anterior mediastinal masses. Lymphangiomas are another rare cause of middle mediastinal lymphadenopathy.

Among the benign disorders that manifest with middle mediastinal lymphadenopathy, inflammatory and infectious causes predominate (Table 42-1). Sarcoidosis is one of the most common causes of benign mediastinal lymphadenopathy. Most commonly, this is seen on CT scan as hilar or as mediastinal lymphadenopathy. Sarcoidosis can create a confusing picture in the setting of a known malignancy. Histologic confirmation demonstrating non-necrotizing granulomas and elevated levels of angiotensin-converting enzyme are required for diagnosis. Although PET scan cannot make a diagnosis of sarcoidosis, some authors have reported using FDG uptake as a marker for response to therapy.¹⁴

Histoplasmosis is a common cause of mediastinal lymphadenopathy, particularly in the Mississippi, Ohio, and Missouri River valleys. This fungal infection has a spectrum of disease manifestations in the thoracic cavity, including benign lymphadenopathy (with characteristic calcification), broncholithiasis, granuloma formation, and mediastinal fibrosis. Other fungal infections that might be seen in specific regions include cryptococcosis and coccidioidomycosis. Mycobacterial infections, both

TABLE 42-1 Histologic Diagnoses of Patients with Benign Mediastinal Adenopathy

Diagnosis	Patients (n)	Patients (%)
Noncaseating granuloma	130	63
Follicular reactive hyperplasia	20	10
Caseating granuloma	16	8
Anthracois	11	5
Other	29	14
Total	206	100

From Hammoud ZT, Anderson RC, Meyers BF, et al: *The current role of mediastinoscopy in the evaluation of thoracic disease. J Thorac Cardiovasc Surg* 118:894–899, 1999.

tuberculous and nontuberculous, may present with hilar and mediastinal lymphadenopathy as well. As in malignant disease, involvement of mediastinal lymph nodes can occur secondary to a primarily parenchymal process, such as bacterial or viral pneumonia.

Other rare causes of middle mediastinal lymphadenopathy include congestive heart failure, which can lead to engorgement of lymph nodes in the mediastinum. Giant lymph node hyperplasia, or Castleman disease, commonly manifests as a solitary lesion but may have a multicentric appearance. Although this disease can be found anywhere, the majority (70%) of cases originate in the thorax.¹⁵ The etiology of giant lymph node hyperplasia is unknown, and patients are typically asymptomatic.

Tracheal Disorders

The trachea is a tubular structure that connects the larynx with the mainstem bronchi. In the average adult, it measures 11 to 13 cm in length. The trachea begins at the cricoid, the only circumferential cartilaginous ring, and ends at the bifurcation into the right and left mainstem bronchi. The intrathoracic portion of the trachea and both mainstem bronchi course through the middle mediastinum and may be involved in a variety of disorders. Primary tumors of the trachea, such as squamous cell carcinoma and adenoid cystic carcinoma, can involve any portion of the airway, but they are usually seen in the intrathoracic portions. Other diseases, such as amyloidosis and Wegener granulomatosis, can also involve the trachea. Tracheomalacia, which may be congenital or secondary to other disorders, such as chronic obstructive pulmonary disease, can involve the intrathoracic trachea as well as the mainstem bronchi.

Bronchogenic cysts are the most common congenital foregut cysts, resulting from abnormal budding of the tracheolaryngeal groove.¹⁶ Unlike esophageal duplication cysts, there is no association with congenital spinal and skeletal abnormalities. Approximately 80% of bronchogenic cysts are located in the middle mediastinum, most commonly in close proximity to the carina and right mainstem bronchus. Bronchogenic cysts are lined with ciliated, columnar respiratory epithelium or cuboid epithelium containing mucous glands. Mucous production typically leads to gradual cyst enlargement over

time. The presence of an air-fluid level suggests a communication with the airway. These cysts may be incidentally found, or patients may exhibit symptoms such as cough, dyspnea, or dysphagia owing to compression from the cyst. The risk of infection is great enough that routine resection is recommended in those who will tolerate surgery. This can usually be performed in a minimally invasive fashion; however, if a cyst is actively infected, surgery should be delayed until a course of antibiotics is administered.

Pericardial Disorders

The pericardial sac serves multiple purposes, including mechanical protection of the heart and lubrication of cardiac movement. It also has an influence on the mechanical properties of cardiac function. The most common condition affecting the pericardium is an effusion. The presence of a pericardial effusion can lead to compromised diastolic filling. The most common cause of pericardial effusion is malignancy, which accounts for more than 75% of cases, with lung and breast cancer predominating.¹⁷ Other causes of pericardial effusion include myocardial infarction, cardiac surgery, and trauma. Treatment, when indicated, involves drainage by either pericardiocentesis or the creation of a pericardial window.

Acute pericarditis can be caused by a wide variety of disorders, including connective tissue disorders, uremia, infection, malignancy, and cardiac surgery. However, most cases are considered idiopathic because of the inability to identify a clear etiology. Patients typically present with fevers, malaise, chest pain, and leukocytosis. The pleuritic chest pain is often increased with deep inspiration, and a friction rub may be heard on physical examination. Electrocardiography may reveal diffuse PR depression and ST segment elevations, without Q waves or T wave inversions. CXR may demonstrate cardiomegaly, reflecting a pericardial effusion. Echocardiogram is indicated to assess the volume of pericardial fluid and to rule out other pathology, such as an intrapericardial neoplasm. Treatment generally consists of management of the underlying condition, nonsteroidal anti-inflammatory medication, colchicine, with or without steroids.¹⁸ When pericarditis is severe or recurrent, the condition can progress to a chronically diseased pericardium that constricts cardiac function by impairing diastolic filling. Constrictive pericarditis must be differentiated from restrictive cardiomyopathy, and it may require surgical resection of the pericardium for cure.

Pericardial cysts occur in approximately 1 in 100,000 persons, and they are thought to arise during embryonic development. They are most commonly found in the right cardiophrenic angle. Pericardial cysts are usually asymptomatic; however, approximately 20% of patients will present with shortness of breath, cardiac compression, or infection. They are often first identified on routine CXR. CT scan and echocardiography can help to differentiate pericardial cysts from foramen of Morgagni hernias or other mediastinal pathology. Treatment consists of percutaneous drainage or surgical resection.

Pericardial neoplasms are rare—mesothelioma is the most common primary pericardial neoplasm. Metastatic neoplasms to the pericardium (e.g., from lung, breast, prostate, and lymphoma) are far more common than primary tumors.

Mediastinal Infections

Acute mediastinal infection is relatively rare. Most instances result from processes that involve the mediastinum secondarily, such as esophageal perforation, sternal infections after sternotomy, and tonsillar or odontogenic abscess. The most common cause of esophageal perforation is iatrogenic, occurring during endoscopic procedures in the cervical esophagus. However, spontaneous perforation or iatrogenic injury during intrathoracic procedures may occur. Esophageal perforation leads to contamination of the middle mediastinum by oropharyngeal secretions, which results in a spectrum of clinical presentations such as abscess formation or sepsis syndrome secondary to mediastinitis. Treatment depends on the location of the perforation, the timing of presentation, and the clinical condition of the patient. General principles of treatment include wide drainage, débridement of necrotic tissue, and closure of the perforation, either primarily or with endoluminal stenting.

Infections after sternotomy can contaminate the middle mediastinum with skin flora. Most commonly, such infections occur after cardiac surgical procedures. Risk factors include diabetes mellitus, redo sternotomy, and harvesting of bilateral internal mammary arteries. Treatment includes antibiotics, removal of any foreign material, prompt surgical débridement of devitalized tissue and bone, and possible muscle flap coverage.

Acute necrotizing mediastinitis is a life-threatening condition that occurs when oropharyngeal bacterial flora gain access to the middle mediastinum by following the perivascular, pretracheal, or retrovisceral planes. It is most commonly seen in men in their fourth decade of life. Necrotizing mediastinitis typically occurs secondary to odontogenic abscesses, and it is the result of a polymicrobial mix of aerobes and anaerobes. CT scan of the neck and chest is key in determining the extent of mediastinal involvement. Treatment generally consists of broad-spectrum antibiotics and early surgical drainage through the neck, chest, or both. Complete débridement is paramount for survival, and a surgeon's threshold to perform a transthoracic drainage in addition to cervical drainage should be low. The underlying cause must be treated promptly.

Fibrosing mediastinitis is a rare disorder characterized by the proliferation of acellular collagen and fibrous tissue within the mediastinum. This proliferation is thought to be caused by an immune-mediated hypersensitivity response to *Histoplasma capsulatum* infection.¹⁹ There are two forms: focal and diffuse. In its most severe form, the fibrotic process encases mediastinal structures including the airway, superior vena cava, and pulmonary arterial and venous branches, leading to compression of these structures with resultant symptoms. Antifungal

therapies generally provide little benefit, and treatment, when necessary, centers on relief of symptoms. Surgical and nonsurgical vascular interventions often provide some symptomatic relief; however, the benefit is often of limited duration.²⁰

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THE POSTERIOR MEDIASTINUM

Larry R. Kaiser

CHAPTER OUTLINE

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EPIDEMIOLOGY

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Other Masses of the Posterior Mediastinum

INFECTIONS OF THE MEDIASTINUM

SUMMARY

The posterior mediastinum is an anatomically diverse region that includes visceral organs, major vascular structures, large neural structures, and important lymphatic vessels. Lesions that originate in the mediastinum are relatively rare compared with the diverse pathology that can involve the mediastinum secondarily, although metastatic disease appearing in the posterior mediastinum, excluding the spine, is unusual. The most common lesions arising within the posterior mediastinum are primarily tumors of neurogenic origin. Less common is a potpourri of lesions including vascular tumors, mesenchymal tumors, and lymphatic lesions.

ANATOMY

The posterior mediastinum, also called the *paravertebral compartment*, is a defined space between the posterior pericardium and the anterior spinal ligament including the paravertebral gutters. According to the traditional four-compartment model, the mediastinum is divided into anterior, middle, posterior, and superior compartments. The posterior mediastinum is bounded superiorly by the inferior border of the T4 vertebral body.^{1,2}

In the traditional three-compartment model without a superior division, the entire length of the spine is included in the posterior mediastinum.² The diaphragm is the common inferior border for all three compartments. Within these boundaries, the posterior mediastinum contains the esophagus, descending aorta, sympathetic chain and vagus nerves, thoracic duct, azygos and hemiazygos veins, fat, and lymph nodes (Fig. 43-1).¹ Recently, Fujimoto and colleagues³ proposed a new mediastinal compartment classification based on transverse axial computed tomographic (CT) imaging. Because of the routine use of CT scanning in the diagnosis and

management of these lesions this classification appears to be more user-friendly and clinically applicable. The authors proposed the division of the mediastinum into four compartments that are visible on CT axial images: superior portion, anterior mediastinum (prevascular zone), middle mediastinum (peri-tracheoesophageal zone), and posterior mediastinum (paravertebral zone). The authors validated their classification by retrospectively analyzing 445 pathologically proven mediastinal tumors (Fig. 43-2).

EPIDEMIOLOGY

Significant differences exist between children and adults with respect to the location of mediastinal masses.⁴ In adults, 65% of the lesions arise in the anterosuperior, 10% in the middle, and 25% in the posterior compartments; this distribution is reversed in children, in whom 25% of lesions arise in the anterosuperior, 10% in the middle, and 65% in the posterior compartments. In general, the incidence of posterior mediastinal lesions is higher in children, whereas anterior lesions predominate in adults.

DIAGNOSIS

Approximately 50% of posterior mediastinal lesions are asymptomatic and are detected on chest radiographs or CT scans taken for unrelated reasons. As a rough guideline, the absence of symptoms is more commonly associated with a lesion that likely is benign, whereas the presence of symptoms suggests malignancy. The percentage of patients with symptoms arising from a mediastinal mass precisely parallels or equals the incidence of

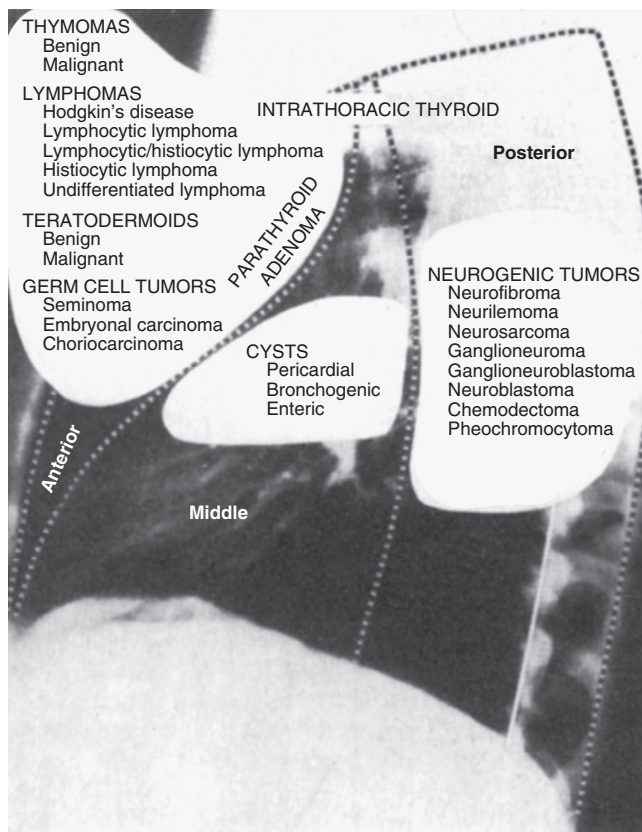


FIGURE 43-1 ■ Lateral chest film divided into three anatomic subdivisions with the most common location of the tumors and cysts. (From Davis RD Jr, Sabiston DC Jr: Primary mediastinal cysts and neoplasms. In Sabiston DC Jr, editor: *Essentials of surgery*, Philadelphia, 1987, WB Saunders.)

malignant lesions. In adults, 50% to 60% of lesions are symptomatic, whereas the percentage of symptomatic lesions is higher in children, ranging from 60% to 80%. Because the incidence of symptoms parallels the incidence of malignant lesions, a child with a mediastinal mass is considerably more likely to have a malignant neoplasm than is an adult with a mediastinal mass. When a posterior mediastinal mass is discovered, a detailed history and physical examination should be obtained, looking particularly for signs such as hoarseness or Horner syndrome. The age of the patient also significantly narrows the diagnostic possibilities.

Computed tomography (CT) is the imaging modality of choice for the posterior mediastinum because of its ability to visualize a mass on an axial cut and to provide some idea as to the extent of invasion, although distinguishing abutment from invasion remains difficult. CT often can distinguish among the various lesions and identify the origin, allowing a correct diagnosis often based strictly on radiographic imaging.⁵ Magnetic resonance imaging (MRI) has been useful in certain circumstances, specifically with dumbbell tumors to assess the presence and extent of invasion within the spinal canal, but also for cysts, and extramedullary hematopoiesis. CT scanning, however, remains the better imaging modality for most posterior mediastinal masses.⁶ Mediastinal sonography, although less expensive and comparable to CT in

the diagnosis of many mediastinal masses, is not useful in the posterior mediastinum.⁷

The decision to sample a mediastinal mass is not straightforward. Obtaining a biopsy before proceeding with resection is not necessary in some cases and potentially harmful in others. The likelihood of a positive finding in a biopsy specimen depends on the presence of local symptoms in addition to the location and extent of the lesion. Lesions in the posterior mediastinum require either fine-needle aspiration (CT guided) or a thoracoscopic approach.^{8,9} If these procedures are not possible because of location in the paravertebral gutters, a limited posterolateral thoracotomy should be used to obtain adequate tissue for diagnosis or, alternatively, simply to resect the lesion in its entirety.^{10,11}

SURGICAL APPROACHES TO THE POSTERIOR MEDIASTINUM

Multiple standard approaches have been described to access the posterior mediastinum depending upon the location relative to the particular aspect of the spine. These include an anterior transcervical approach, a posterior paravertebral approach, posterolateral thoracotomy or video-assisted thoracoscopy¹³ or via a transabdominal incision (Fig. 43-3).

The transcervical approach is accomplished through an incision along the anterior border of the sternocleidomastoid muscle. The region that is most difficult to access is at the level of the T1 vertebral body, because transthoracic and transcervical approaches are not ideal. For a lesion at this location, an extension of the incision along the anterior border of the sternocleidomastoid muscles down to the manubrium and then out along the infraclavicular region allows the manubrium to be divided and retracted upward, giving access to the region of the T1 vertebral body. We have used this approach for a number of lesions with great success. Di Rienzo and colleagues¹² have described a modified transmanubrial osteomuscular sparing approach for resection of lesions between C7 and T2, recognizing that either a right-sided or left-sided approach can be used because the vascular dissection is similar on both sides.¹²

When more inferior posterior mediastinal masses need to be accessed, the paravertebral approach can be used by resecting posterior segments of one or more ribs and entering the retropleural plane that leads to the posterior mediastinum. Standard posterolateral thoracotomy, the most commonly used approach, provides excellent access to the posterior mediastinum; the location of the lesion determines the intercostal space to be entered.

The posterior mediastinum can also be accessed transabdominally through the esophageal hiatus, important in various antireflux procedures or hiatal hernia repairs, and for mobilization of the mediastinal esophagus when performing a transhiatal esophagectomy.¹³ A combined cervical approach with transabdominal mobilization allows for the removal of the esophagus extrapleurally ideally without entering either the right or left pleural reflection. A transabdominal approach at the level of the hiatus also

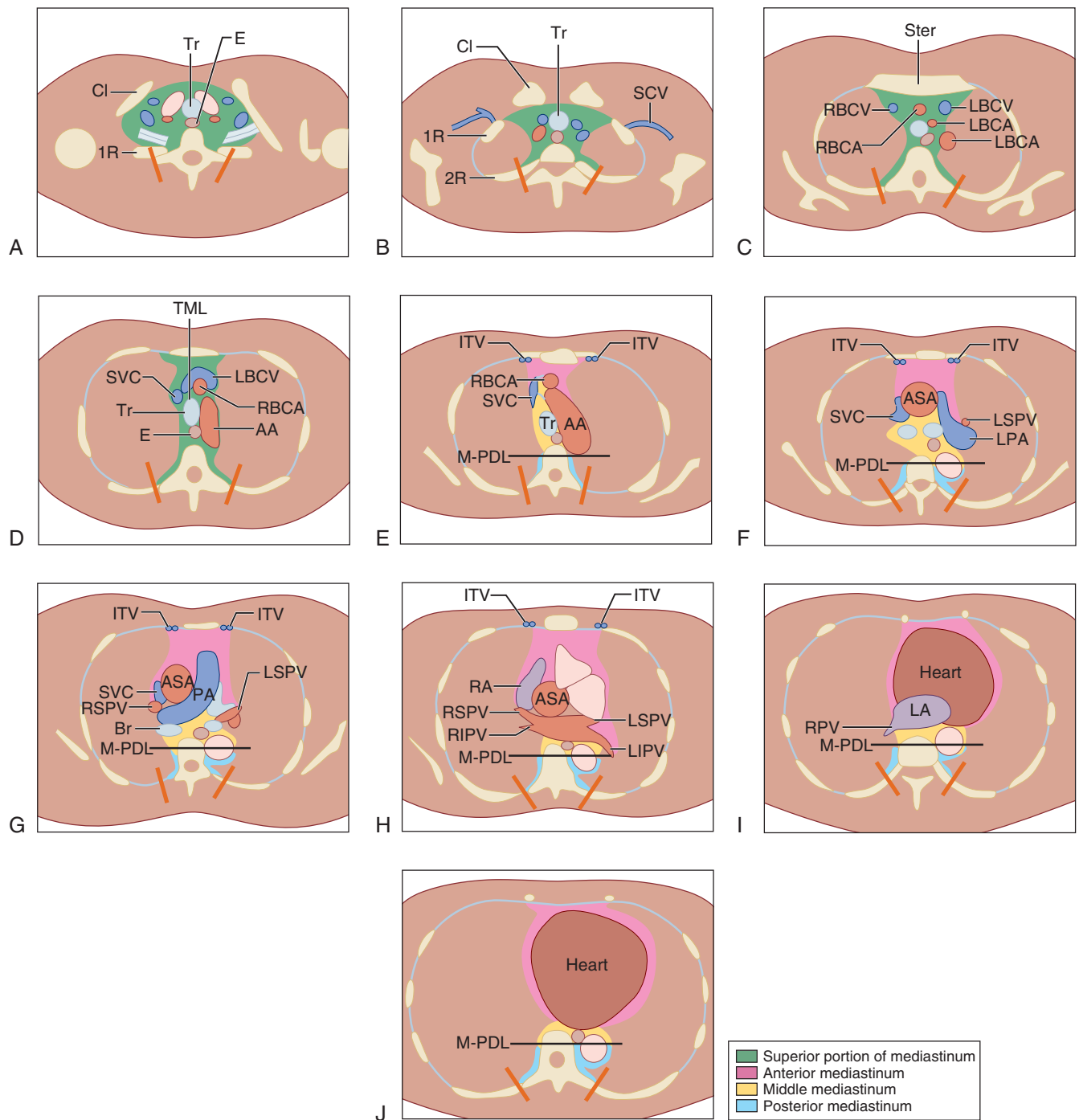


FIGURE 43-2 ■ Mediastinal compartment classification according to the General Rules for Study of Mediastinal Tumors of the Japan Association for Research on the Thymus. **A**, Thoracic inlet. **B**, Upper rim of clavicle. **C**, Sternoclavicular joint. **D**, Left brachiocephalic vein across TML. **E**, Aortic arch. **F**, Tracheal carina. **G**, Right main pulmonary artery. **H**, Pulmonary trunk. **I**, Left atrium. **J**, Tricuspid valve. 1R, First rib; 2R, second rib; AA, aortic arch; AsA, ascending aorta; Br, bronchus; CL, clavicle; E, esophagus; ITV, internal thoracic vessels; LA, left atrium; LBCV, left brachiocephalic vein; LCCA, left common carotid artery; LIPV, left inferior pulmonary vein; LPA, left pulmonary artery; LSCA, left subclavian artery; LSPV, left superior pulmonary vein; M-PBL, middle-posterior boundary line; PA, pulmonary artery; RA, right atrium; RBCA, right brachiocephalic artery; RBCV, right brachiocephalic vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SCA, subclavian artery; SCV, subclavian vein; Ster, sternum; SVC, superior vena cava; TML, tracheal mid-line; Tr, trachea. (From Fijimoto K, Hara M, Tomiyama N, et al: Proposal for a new mediastinal compartment classification of transverse plane images according to the Japanese Association for Research on the Thymus (JART) General Rules for the Study of Mediastinal Tumors. *Oncology Reports* 31:565–572, 2014, with permission.)

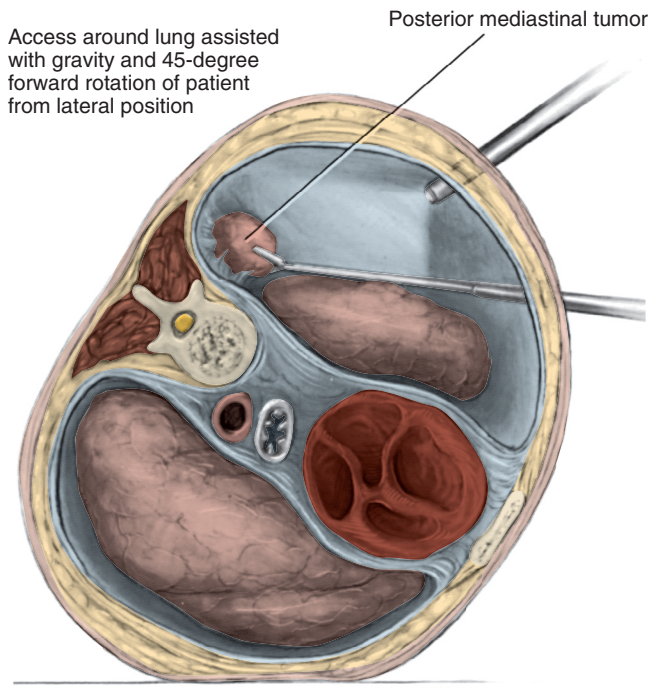


FIGURE 43-3 ■ Thoracoscopic resection of a posterior mediastinal tumor. (Reprinted with permission from Davis RD Jr, Sabiston DC Jr: *Textbook of surgery*, Philadelphia, 1997, WB Saunders, p 1915.)

allows access to the cisterna chyli, which may need to be ligated when dealing with a chylothorax when ligation of the thoracic duct in the chest has been unsuccessful.

Currently it is the preference of most surgeons to access lesions of the posterior mediastinum using a video-assisted thoracic surgical (VATS) approach,¹³ but this depends on the surgeon's experience and comfort with video-assisted procedures. If the intent is strictly to secure material for histologic study, then VATS clearly should be the procedure of choice.^{9,14,15} Zierold and Halow¹⁶ conducted a retrospective review that described the use of a VATS approach for posterior mediastinal neurogenic lesions. Twenty-nine patients (13 men, 16 women; 26 to 68 years old) who underwent a thoracoscopic resection were identified. Preoperative imaging included chest radiography and CT in all patients and MRI in 15 of 29 patients (52%). All tumors were located in the posterior mediastinum and in none was there preoperative evidence of invasion or malignancy. Conversion to an open procedure was required in 12 of 29 (41%) patients (minithoracotomy in 11, posterolateral thoracotomy in 1). Tumor size necessitating conversion to an open procedure (mean = 4.79 cm) and tumor size amenable to thoracoscopy alone (mean = 3.84 cm) were not significantly different ($P < 0.09$). They concluded that thoracoscopic resection could be performed successfully, regardless of tumor type or size; however, malignant lesions, local invasion, and tumors larger than 5 cm may require an open procedure. Cardillo and associates¹⁷ detailed their experience with 93 patients who underwent resection of a posterior mediastinal neurogenic tumor. The tumor was resected with a videothoracoscopic approach in 57

patients; 44 underwent VATS only, and 13 required conversion to an open approach. Mean operative time was significantly shorter in the VATS group, as was the median postoperative hospital stay and postoperative pain. No recurrences were noted at a mean follow-up of 73 months.

More recently, robotic surgery has been used for the resection of mediastinal lesions, including those in the posterior mediastinum. Melfi and colleagues¹⁸ recently reported on a 10-year experience of mediastinal robotic surgery in a single referral center. Sixty-nine patients were resected using the da Vinci robotic system, including 13 paravertebral neurogenic tumors. Patients were positioned in the lateral decubitus position, and the robotic arms were located based on the site of the lesion generally at the fourth intercostal space. Lesions were removed through the anterior port, where the intercostal space is widest, and the largest incision used was 3 cm. No additional utility incision was performed. The authors noted significant progression on the learning curve, especially related to the resection of anterior mediastinal lesions where the mean operative time between the first 10 resections and the second 10 decreased significantly from a mean of 194 minutes to 97.5 minutes. The authors confirmed the safety and feasibility of the robotic approach for different mediastinal lesions, but they point out that cost may be an important limitation.

LESIONS OF THE MEDIASTINUM

Neurogenic Tumors

Neurogenic tumors of the thorax commonly occur in the posterior mediastinum and primarily affect young adults and children.¹⁹ In recent decades, although these tumors continue to be the most common malignant neoplasm in children, they have become less common than tumors of the anterior mediastinum (thymomas or lymphomas) in adults. Neurogenic tumors currently represent approximately 15% of all mediastinal masses in adults. Furthermore, in adults the malignancy rate of neurogenic tumors is less than 10%. In children, 50% of these lesions are malignant.¹⁹ Takeda and colleagues reviewed their experience with 146 patients with intrathoracic neurogenic tumors treated during a 50-year period. In this series of 60 pediatric and 86 adult patients, there were 51 gangliogliomas, 37 schwannomas, 30 neurofibromas, 18 neuroblastomas, 5 ganglioblastomas, and 5 lesions classified as "other."²⁰ Of these lesions, 136 were located in the posterior mediastinum, but only 13 patients (8.9%) had extension of tumor into the spinal canal; 84% of adults and 60% of children were asymptomatic at the time of presentation, and 20.5% of the lesions were malignant, with these occurring predominantly in the first 5 years of life.

Neurogenic tumors originate from embryonic neural crest cells located near the spinal ganglia and from either sympathetic or parasympathetic components (Box 43-1). The differential diagnosis for neurogenic tumors arising from intercostal nerves includes neurofibroma, neurilemmoma, and neurogenic sarcoma. Tumors arising from

BOX 43-1 Origin of Neurogenic Tumors in the Posterior Mediastinum

INTERCOSTAL NERVE TUMORS

- Neurofibroma
- Neurilemoma
- Neurofibrosarcoma
- Neurosarcoma

SYMPATHETIC GANGLIA TUMORS

- Ganglioma
- Ganglioneuroblastoma
- Neuroblastoma

PARAGANGLIA CELL TUMORS

- Paraganglioma (pheochromocytoma)

sympathetic ganglia include ganglioneuroma, ganglioneuroblastoma, and neuroblastoma. Pheochromocytomas arising from paraganglion cells also may be seen in the posterior mediastinum. Neurogenic tumors rarely arise from the phrenic or vagus nerves.

Neurogenic tumors may be benign or malignant, with benign lesions classified as either neurilemoma (schwannoma) or neurofibroma. Neurilemmas are more common than neurofibromas. Of patients presenting with nerve sheath tumors, 25% to 40% have neurofibromatosis type 1 (NF1; von Recklinghausen disease), an autosomal dominant disorder caused by mutation in the neurofibromin gene found on chromosome 17q11.2. The worldwide incidence of NF1 is 1 in 2500 to 1 in 3000 individuals. Malignant tumors (neurogenic sarcomas or malignant schwannomas) are unusual with the incidence of malignancy greater in tumors found in patients with NF1 (10% to 20%).

Patients with benign lesions most often are asymptomatic as opposed to patients with malignant tumors, who frequently manifest symptoms of spinal cord compression or have cough, dyspnea, chest wall pain, or hoarseness. Horner's syndrome caused by involvement of the superior cervical ganglion of the sympathetic chain is an unusual, but not unheard of, presenting sign. Because most patients with neurogenic tumors are asymptomatic, the initial diagnosis usually is made on the basis of findings noted on a chest radiograph or CT scan performed for a different reason. Rarely, a patient might have a pheochromocytoma or a chemically active neuroblastoma or ganglioneuroma. In all symptomatic patients, especially those with a history of significant hypertension or hypermetabolism, serum catecholamine levels and 24-hour urine levels of homovanillic acid and vanillylmandelic acid should be obtained. If these levels are elevated, suggesting pheochromocytoma, preoperative α -adrenergic blockade along with a β -blocker need to be administered to avoid intraoperative complications owing to episodic catecholamine release during tumor manipulation.

Neurogenic tumors that arise from intercostal nerves typically prove to be neurilemmas or neurofibromas.²¹ Neurilemmas (schwannomas) are the most common neurogenic tumors.^{22,23} On histologic examination, they appear as well-encapsulated, firm, gray-tan masses.²⁴

They tend to occur in one of two morphologic patterns: either with an organized architecture with a cellular palisading pattern of growth (Antoni type A) or a loose reticular pattern (Antoni type B²⁵; Fig. 43-4). Neurofibromas are poorly encapsulated, with a random arrangement of spindle-shaped cells.²⁶ Associated with neurofibromatosis type 1, these tumors tend to form in the paravertebral gutters and have the potential to degenerate into neurosarcoma, a major indication for their surgical excision.

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma are tumors of the sympathetic nervous system that arise from primitive sympathetic ganglia and are referred to collectively as *neuroblastic tumors*.²⁷ These tumors can arise from wherever sympathetic nerves exist, and they are seen in the neck, posterior mediastinum, adrenal gland, retroperitoneum, and pelvis. The three tumors differ in their degree of cellular and extracellular maturation and represent a continuum of maturation and differentiation. Immature, highly malignant tumors tend to be aggressive and occur in younger patients (median age, just under 2 years), whereas mature tumors, specifically ganglioneuromas, occur in older children (median age, approximately 7 years) and tend to behave in a benign fashion.²⁷

Ganglioneuromas usually manifest as a benign tumor composed of ganglion cells and nerve fibers. These are the most common neurogenic tumors in children and usually appear at an early age located in the paravertebral region; most commonly, they are an incidental finding on a routine chest radiograph. These tumors are fully differentiated and appear as well-encapsulated lesions on cross-sectional imaging and often exhibit areas of cystic degeneration. Surgical resection is the definitive treatment for these lesions and is curative (Fig. 43-5).

Ganglioneuroblastomas are composed of both mature and immature ganglion cells and have intermediate malignant potential somewhere between ganglioneuromas and neuroblastoma.²⁸ These malignant tumors possess a recognizable capsule and most commonly manifest with symptoms. Of the two categories of ganglioneuroblastoma, the composite type presents with evidence of metastatic disease in 65% to 70% of patients while in the so-called diffuse type fewer than 5% of patients develop metastatic disease.

Neuroblastomas are highly malignant tumors that occur in young children and infants. The majority of these tumors, more than 75% of them, occur in children younger than 4 years of age. These tumors account for greater than 50% of the neurogenic tumors of the mediastinum in children, although intrathoracic lesions account for only approximately 20% of neuroblastomas. On histologic examination, these tumors are composed of small, round immature cells organized in a rosette pattern. The tumors are highly invasive, and by the time the diagnosis is made, they have often metastasized to the regional lymph nodes, bone, brain, liver, and lung. Interestingly, in certain patients, they have a relatively benign course, even when metastatic. Symptoms at the time of diagnosis typically include cough, fever, dysphagia, chest pain, and occasionally paraplegia. At times, the patient may have paraneoplastic syndromes such as profuse

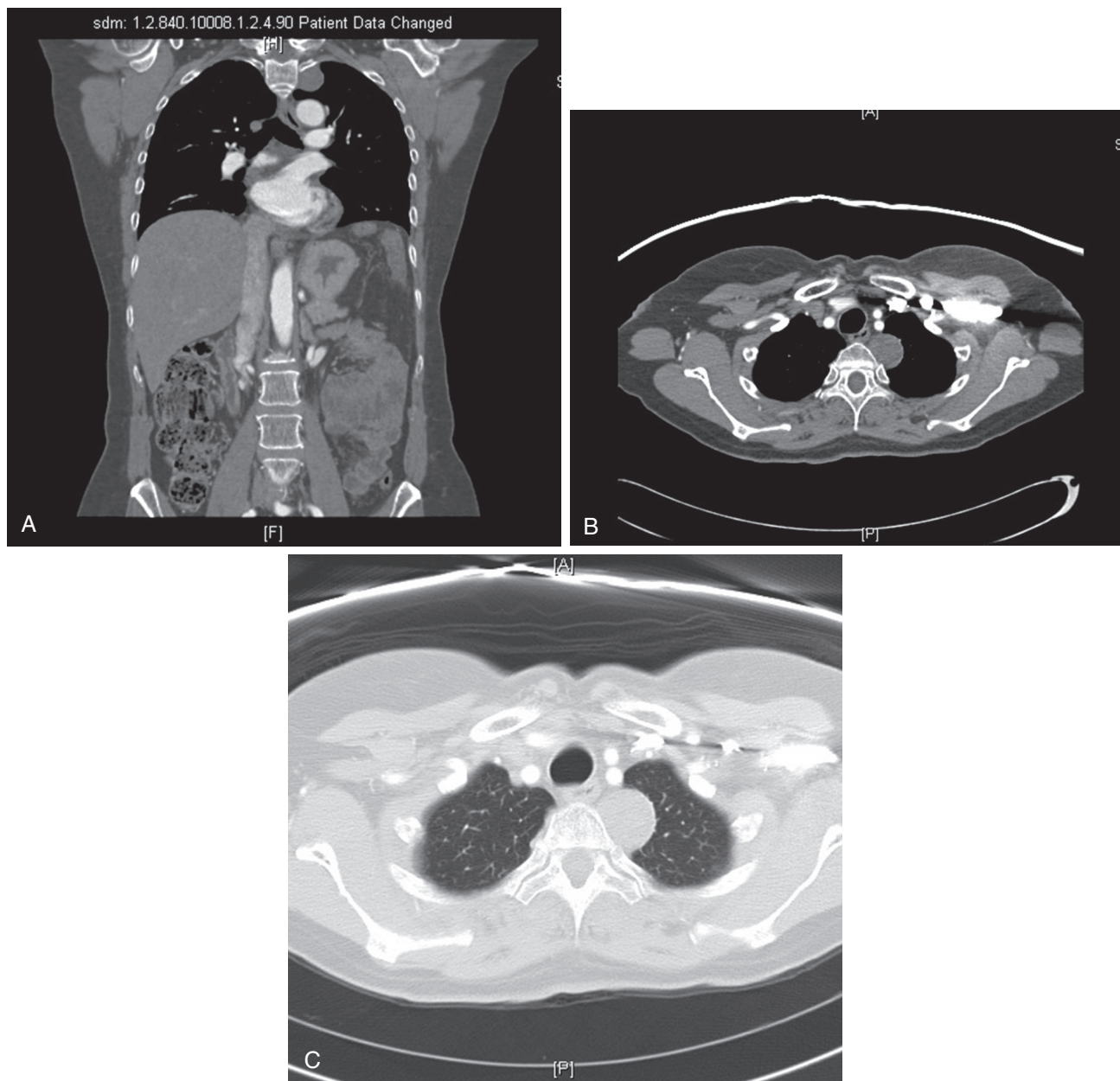


FIGURE 43-4 ■ **A**, Schwannoma presenting at the T1-T2 level as seen on **(A)** coronal CT image. **B**, Note the proximity to the vertebral body also well seen on the axial image. **C**, The relationship between the lesion and the lung parenchyma is well demonstrated.

watery diarrhea secondary to vasoactive intestinal protein syndrome, opsoclonus-polymyoclonus syndrome, and pheochromocytoma-like syndrome. Features such as DNA content, the presence of tumor proto-oncogenes, and catecholamine synthesis correlate with prognosis, and their presence or absence aids in stratifying patients as high, intermediate, or low risk. Ganglioneuroblastomas and neuroblastomas are staged from stage I, a well-circumscribed noninvasive tumor to stage IV-S, where disseminated disease is present. Treatment consists of a multimodality approach including surgical debulking, systemic chemotherapy, and radiation therapy. Overall 5-year survival rate for neuroblastoma is slightly greater than 20%. Despite recent advances in treatment, including bone marrow transplantation, neuroblastoma in most patients remains a relatively lethal tumor, accounting for

10% of pediatric cancers but 15% of cancer deaths in children.²⁹ Because of the rarity of these lesions children with these tumors should be, and usually are, managed in specialized centers with most being entered on cooperative group treatment protocols.

A CT scan can help to elucidate the tumor type and extent of tumor involvement (Fig. 43-6).^{6,27} Neurogenic tumors from peripheral nerves appear as well-defined, round or oval masses in the paravertebral gutter that are noncalcified. Neurilemmomas have variable enhancement with either homogeneity or heterogeneity.³⁰ With enhanced CT, these tumors demonstrate variable attenuation, depending on their histology. Neurofibromas are usually homogeneous, low-attenuation lesions when visualized on unenhanced CT. Enhanced CT demonstrates homogeneous enhancement or early central

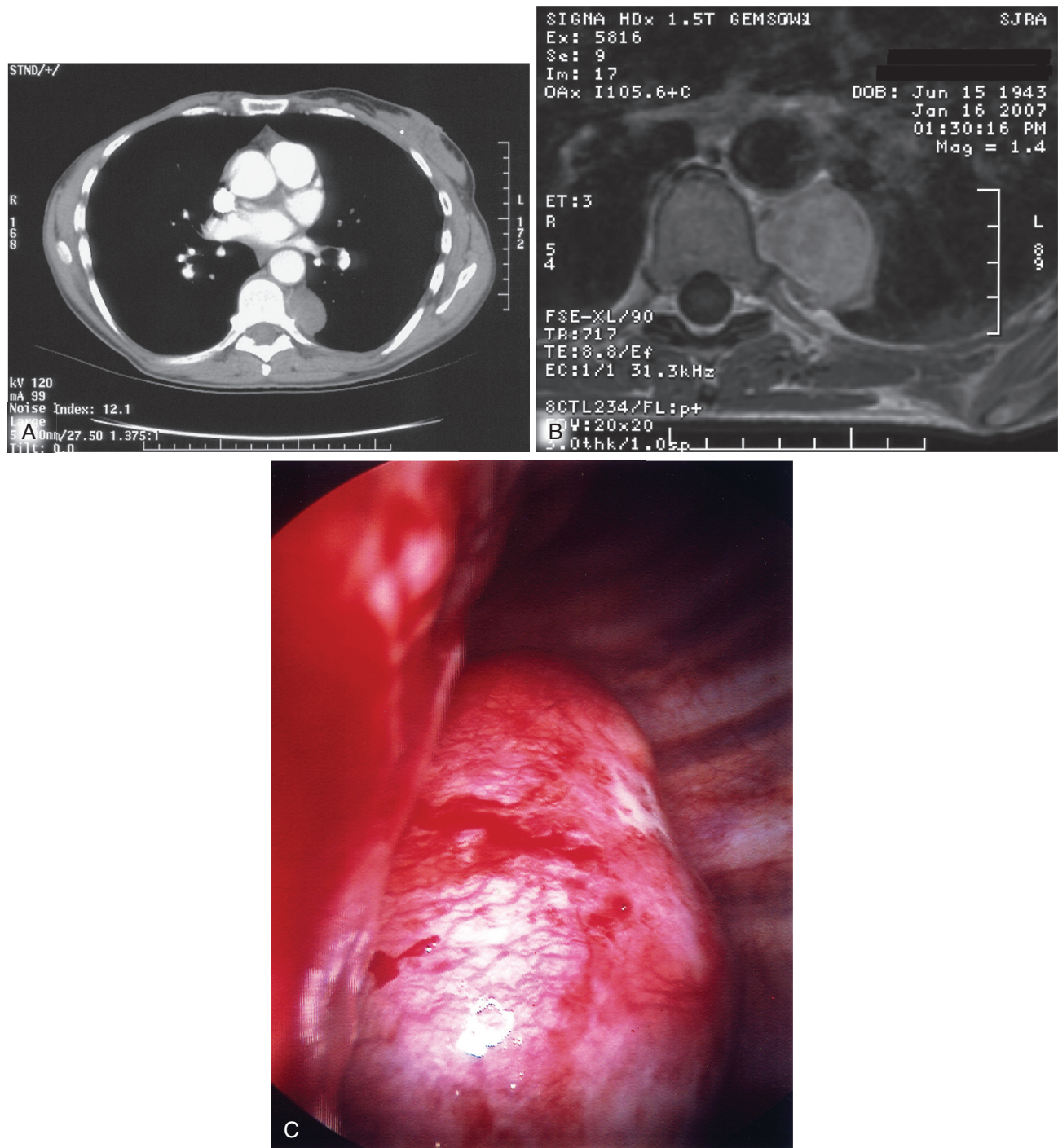


FIGURE 43-5 ■ **A**, Axial CT image demonstrating a ganglioneuroma. **B**, The same lesion as seen on MRI. **C**, Intraoperative photograph of a ganglioneuroma as seen through the thoracoscope. (Courtesy Dr. John Kucharczuk.)

blush. Malignant nerve sheath tumors show variable attenuation.²³

Tumors arising from the sympathetic chain expand along the spinal axis, making them difficult to detect on a lateral view. Sympathetic chain tumors do not demonstrate calcification or bone changes. Characteristic radiographic findings of ganglioneuromas include oblong, homogeneous low-attenuation lesions on both enhanced and unenhanced CT. Neuroblastomas appear as aggressive soft tissue lesions commonly with

calcification. Ganglioneuroblastomas appear with combined radiographic features of both ganglioneuromas and neuroblastomas. On CT scans, paragangliomas characteristically appear in the aortopulmonary window with significant enhancement following administration of contrast medium.²⁵ MRI is useful in further delineating the relationship of neurogenic tumors to adjacent structures such as the spinal cord, aorta, and esophagus, although differentiating between abutment and invasion remains difficult.

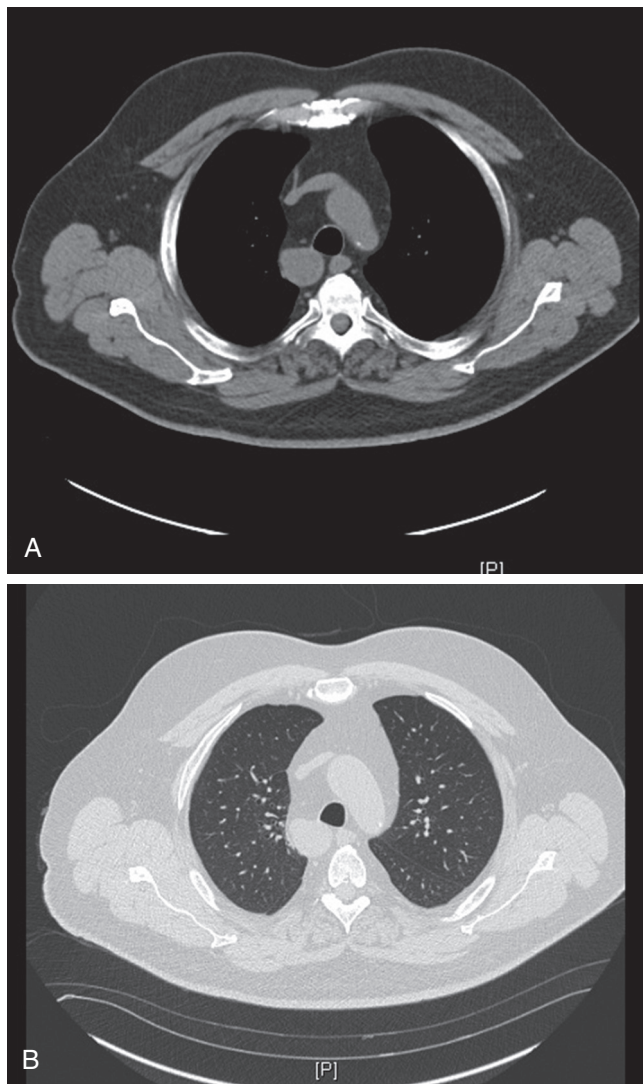


FIGURE 43-6 ■ CT scan of a schwannoma showing the proximity to the vertebral body and the trachea seen on both the mediastinal window (A) and parenchymal window (B). (Courtesy Dr. John Kucharczuk.)

Tumors located in the posterior mediastinum that extend into the spinal canal through the intervertebral foramen are referred to as *dumbbell tumors*. Preoperative determination of intraspinal involvement of a neurogenic tumor is critical as surgical intervention mandates a combined thoracic surgical-neurosurgical procedure to avoid bleeding within the spinal canal that could lead to spinal cord compression.³¹⁻³⁴ This can be addressed by obtaining an MRI study looking for tumor within the spinal canal. These patients rarely exhibit symptoms of spinal cord compression. Approximately 10% of patients with neurogenic tumors have extension through a vertebral foramen. Although most of these lesions are benign, approximately 1% to 2% are malignant. MRI typically shows a smoothly rounded, homogeneous density abutting the vertebral column.

If a decision is made to obtain tissue, percutaneous fine-needle aspiration biopsy is an appropriate modality to confirm a diagnosis of a neurogenic tumor. A biopsy specimen that reveals a spindle cell

neoplasm with characteristic radiographic findings is diagnostic of a neurogenic tumor. Biopsy specimens that demonstrate a combination of spindle cells and ganglion cells are diagnostic of ganglioneuromas. Immunohistochemical analysis can clinch the diagnosis, particularly with molecular markers such as S-100 tumor antigen.^{35,36}

Surgical intervention is the standard of care for neurogenic tumors; thus, biopsy should be performed only if the results will alter therapy. Traditionally, surgical resection of a posterior mediastinal neurogenic tumor was accomplished through a posterolateral thoracotomy, and this remains an excellent and safe approach. Recent improvements in video-assisted thoracoscopic surgery have allowed minimally invasive approaches to diagnosis and treatment of many tumors in the posterior mediastinum.³⁷ Advantages of thoracoscopic surgery compared with the classic thoracotomy operation include decreased operative time, decreased average length of postoperative hospitalization, and in many patients less postoperative pain.³⁸ Benign intrathoracic tumors are ideal lesions for resection by a video-assisted technique.

Thoracoscopic resection of posterior mediastinal neurogenic tumors can be performed successfully regardless of tumor type or size. However, malignant transformation, local invasion, and tumors larger than 5 cm are characteristics that increase the likelihood of requiring conversion to an open procedure.¹⁶

The standard surgical approach involves a posterolateral thoracotomy incision and exposure of the posterior mediastinum (Fig. 43-7). The tumor is always found in a paravertebral location, and the resection is begun first by incising the overlying pleura and then, with a combination of sharp and blunt dissection, removal of the lesion from the underlying vertebral bodies. Rarely is there any invasion of the bony vertebral body, but it is important to recognize any involvement of a neural foramen. If, in dissecting at the origin of the involved nerve root, it appears that the neural foramen is widened, this may indicate that the tumor is present within the spinal canal. If the foramen is widened, it is best to have a neurosurgeon perform a foraminotomy to ensure complete excision of the lesion and to ensure that tumor is either not left in the canal or divided, causing bleeding within the canal. The involved nerve root itself is routinely taken as part of the resection, although at times a portion of the root may be spared as long as the tumor is completely resected. Some of these tumors arise from the sympathetic chain, and it is important to recognize this and to resect that portion of the sympathetic chain. Care should be taken to avoid resection of segmental vessels, if possible.

Once the pleura has been incised, it usually is straightforward to mobilize these lesions with a combination of sharp and blunt dissection. Complete resection can be accomplished in essentially all cases. The procedure often starts with videothoracoscopic visualization of the tumor and mobilization with the tumor removed through a small incision in the skin. However, if mobilization proves difficult by the videothoracoscopic approach, there should be no hesitation about converting to an open procedure. This is especially important with lesions at the thoracic inlet.

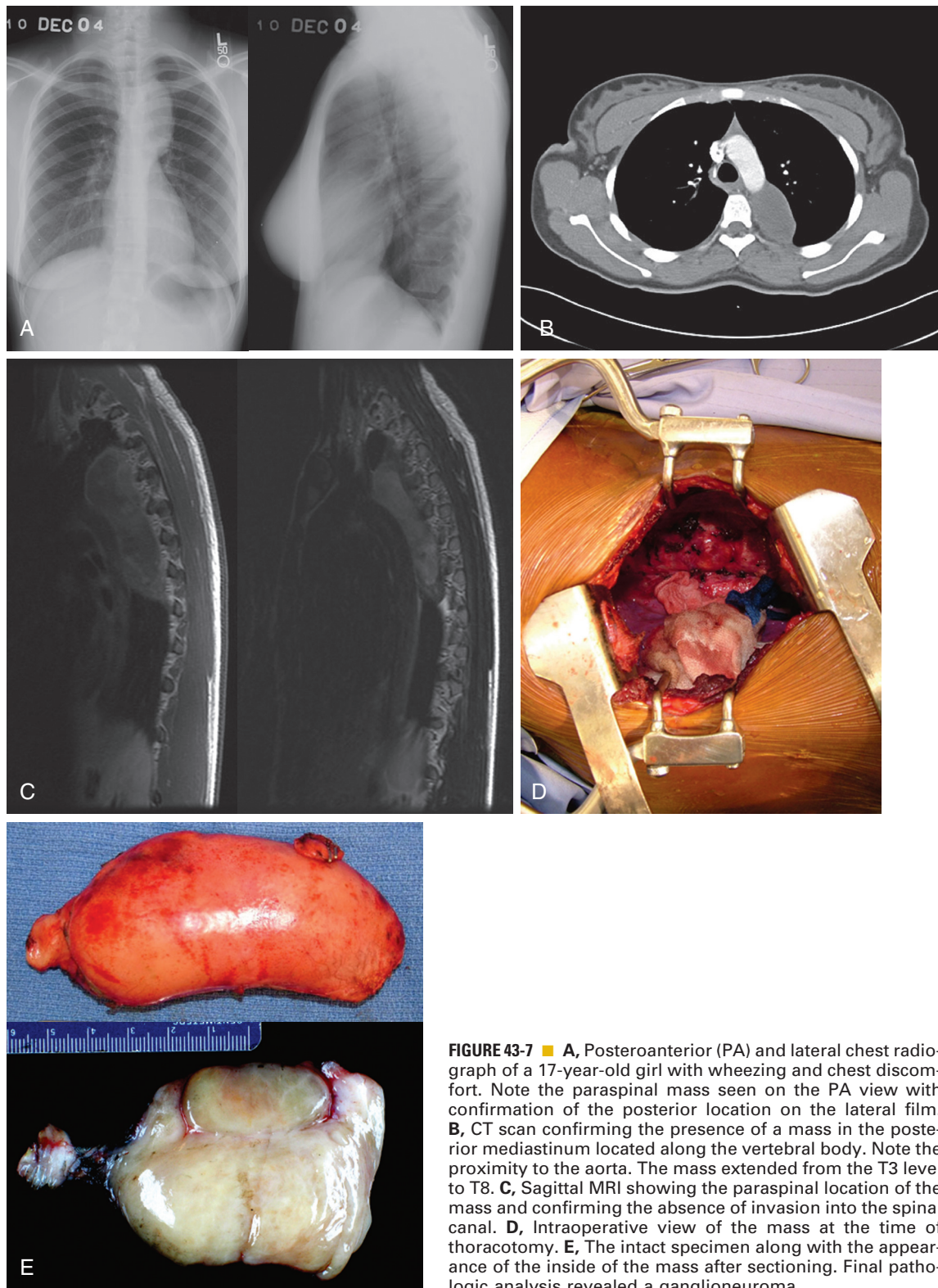


FIGURE 43-7 ■ **A**, Posteroanterior (PA) and lateral chest radiograph of a 17-year-old girl with wheezing and chest discomfort. Note the paraspinal mass seen on the PA view with confirmation of the posterior location on the lateral film. **B**, CT scan confirming the presence of a mass in the posterior mediastinum located along the vertebral body. Note the proximity to the aorta. The mass extended from the T3 level to T8. **C**, Sagittal MRI showing the paraspinal location of the mass and confirming the absence of invasion into the spinal canal. **D**, Intraoperative view of the mass at the time of thoracotomy. **E**, The intact specimen along with the appearance of the inside of the mass after sectioning. Final pathologic analysis revealed a ganglioneuroma.

When it is known that there is tumor involvement within the spinal canal, a well-described approach is the one-stage removal of the tumor performed through a posterolateral thoracotomy combined with transthoracic partial laminectomy.³⁹ This surgical approach avoids two incisions and limits traction on the spinal cord.⁴⁰

Alternatively, an initial posterior approach to the spine with laminectomy and removal of that portion of tumor within the canal is immediately followed by thoracotomy with resection of the intrathoracic paravertebral tumor.

A more recently described procedure avoids a thoracotomy and invasion of the parietal pleura and uses a

dorsal approach to perform a laminectomy with resection of a small portion of the neighboring rib head and neck.⁴¹ In either case, once a dumbbell tumor has been recognized, a combined two-team approach with thoracic surgeons and neurosurgeons working together to perform a one-stage removal is the procedure of choice.^{34,42}

The prognosis of primary neurogenic mediastinal tumors varies with their histopathology. Patients with benign neurogenic tumors have an excellent prognosis with complete surgical excision; patients with malignant neurogenic tumors still have poor long-term survival prospects.¹⁹ Recurrence of a benign lesion is unusual.⁴³ Kang and colleagues⁴⁴ reviewed the results of surgical treatment of 38 children with malignant mediastinal neurogenic tumors seen during an 18-year period. There were 23 (60.5%) neuroblastomas, 14 (36.8%) ganglioneuroblastomas, and 1 malignant neuroepithelioma. The mean age for the series was 3.4 ± 3.0 years, and 26 of the patients were symptomatic at presentation. Complete gross resection was possible in 30 patients, with 5-year survival of 95.2% for localized tumors and 52.5% for stage IV tumors.

Spontaneous regression of neuroblastomas, though rare, has been reported. Stage I (noninvasive) neuroblastomas are managed by resection alone, whereas stage II lesions (locally invasive on same side of midline) require postoperative irradiation. Stage III lesions (invasive across the midline) and stage IV lesions (systemic metastasis) require multimodality treatment including debulking, radiation therapy, chemotherapy, and a second-look operation. Children younger than 1 year tend to have an excellent prognosis; in older children, poorer prognosis is directly proportional to age.

Esophageal Masses

Esophagus-related posterior mediastinal lesions include neoplasm, esophageal cysts,⁴⁵ diverticula, hiatal hernias, megaesophagus, and esophageal varices.⁴⁶ Esophageal disease rarely is seen on chest radiographs. Plain chest radiography usually is normal in patients with esophageal carcinoma though subtle abnormalities sometimes are present, including a retrocardiac mass, abnormal azygos-esophageal recess interface, widened mediastinum, widened retrotracheal stripe, and esophageal air-fluid level. Often these abnormalities are recognized in retrospect once the pathology has been identified by other modalities. Hiatal hernia, seen often in the adult population, is the most common esophageal pathologic process detected on the chest radiograph, although it is only pathologic when accompanied by symptoms such as severe gastroesophageal reflux. As with other posterior mediastinal pathology, CT is reliable in establishing tumor size and assessing invasion of the mediastinum and tracheobronchial tree as well as spread of esophageal carcinoma to the liver, adrenals, and upper abdominal lymph nodes.

Endoscopic ultrasonography (EUS) has become the most accurate imaging modality for locoregional staging in cancer of the esophagus. Fine-needle aspiration capabilities have added an entirely new level of accuracy in regional lymph node staging, with reported accuracy in

the 90% range.⁴⁷ Transesophageal echocardiography (TEE) may be an adjunct in assessing a mediastinal mass, although it should be used in conjunction with CT or MRI for more thorough evaluation. TEE nicely demonstrates impingement of the left atrium or ventricle, which is a common occurrence with posterior masses. Echocardiographers need to be aware of a type of posterior mediastinal encroachment that is common with gastric or esophageal disease, specifically the two-dimensional echo features that may simulate a left atrial mass.⁴⁸

A barium swallow definitively identifies a hiatal hernia, usually a sliding type, that occurs in as many as 15% of symptomatic patients.⁴⁹ An air fluid level seen in a retrocardiac location on a plain chest radiograph often is enough evidence to diagnose a hiatal hernia. This is discussed in detail in the following chapters. The barium swallow also remains the most useful study to clarify the nature of a retrocardiac mass, such as a pseudotumoral venous collateral.⁵⁰ A complete discussion of esophageal cancer can be found in [Chapters 37 to 39](#).

Cysts of the Posterior Mediastinum

Mediastinal cysts form a group of uncommon benign lesions of congenital origin. Cystic lesions of the posterior mediastinum are relatively rare and include bronchogenic, hydatid,⁵¹ enteric, intramural esophageal, and neuroenteric cysts. Thoracic CT is the most effective method for the diagnosis of posterior mediastinal cysts ([Fig. 43-8](#)).⁵²

The significant controversy regarding these cysts is whether to manage them with observation or surgical resection. They are benign lesions in which operation can be performed with a low morbidity and mortality, enabling the surgeon to rule out malignant transformation and to offer a definitive cure.⁵² Reports of uneventful operative courses without recurrence for mediastinal cysts are readily available.^{53,54} Alternatively, many of these cysts may be “treated” by observation only with serial chest radiographs or CT scans.

Bronchogenic Cysts

Mediastinal cysts constitute 20% of all mediastinal masses, and bronchogenic cysts represent 60% of all mediastinal cysts.^{10,55-57} These cysts are part of the spectrum of bronchopulmonary foregut abnormalities that include extralobar and intralobar sequestration and congenital cystic adenomatoid malformations of the lung.

Cystic lesions can be located in the lung parenchyma or mediastinum. On histologic examination, bronchogenic cysts demonstrate a lining composed of ciliated columnar epithelium. The cyst wall may be composed of cartilage, mucus glands, and smooth muscle. They rarely communicate with the tracheobronchial tree.

Symptoms are present in the occasional patient, usually from compression of adjacent structures or recurrent infection. Paraesophageal bronchogenic cysts often are noted incidentally in the posterior mediastinum during routine chest radiography. If the diagnosis of a bronchogenic cyst is made preoperatively and patients are asymptomatic, observation is an appropriate course. If there is

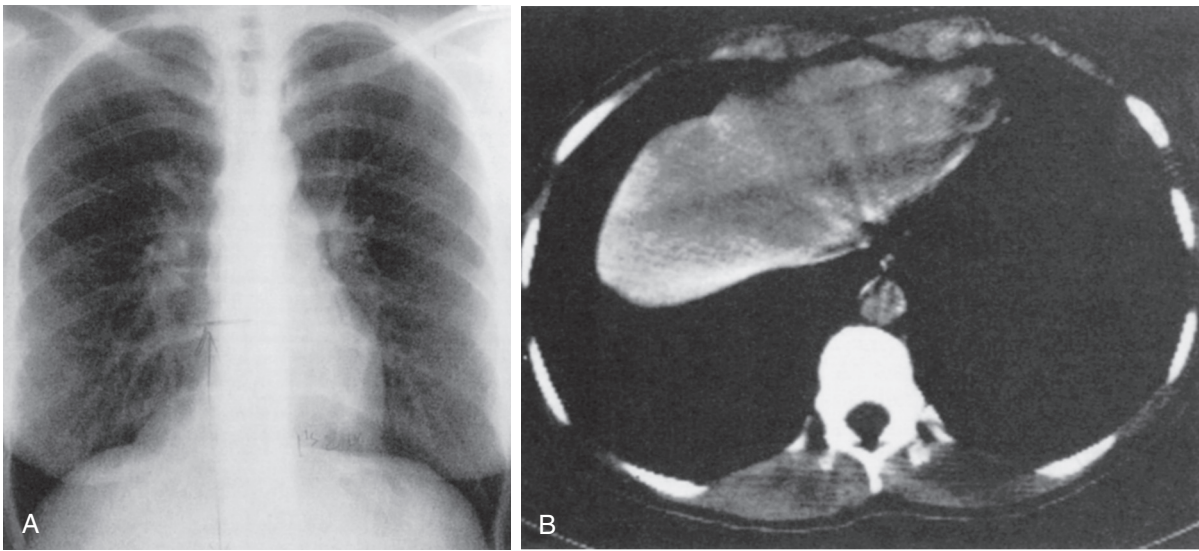


FIGURE 43-8 ■ **A**, Chest film of a pericardial cyst in the right pericardiophrenic angle. **B**, CT image shows the characteristic nearer attenuation of the mass and the typical anatomic location.

any question of malignant transformation based on radiographic appearance, positive results of cytology, or evidence of enlargement or recurrence, the lesion should be resected. The presence of symptoms—especially pain, cough, or hemoptysis—suggests the advisability of resection. Barium swallow study may identify the source of dysphagia due to external compression. The presence of an air–fluid level may indicate communication with the bronchopulmonary tree (rare) and the likelihood of recurrent infection and indicates that resection is in order. Once a bronchogenic cyst has become infected, the infection is difficult to eradicate, and the lesion should be resected.⁵⁸

Symptoms tend to develop with time, and resection at an asymptomatic stage may be best in healthy subjects. A VATS approach provides an ideal method for resection of these benign lesions. Depending on location, specifically if they are in the superior mediastinum, many of these may be resected through the mediastinoscope.⁵⁹ Martinod and coworkers⁵⁶ reported their 3- to 7-year experience with thoracoscopic resection in 10 patients with posterior mediastinal bronchogenic cysts. The average cyst size was 4.9 cm, and the largest diameter was 10 cm. There were no operative deaths and no postoperative complications. Long-term follow-up (range, 4.5 to 7.5 years) showed no late complications and no recurrence.

Gastroenteric Cysts

Gastroenteric or esophageal duplication cysts are peri-esophageal lesions that form from the posterior division of the primitive foregut. They can cause a middle or posterior mediastinal mass, particularly seen in the younger patient. They occur within or adjacent to the wall of the esophagus and rarely communicate with the upper gastrointestinal tract.

On histologic examination, duplication cysts are lined by nonkeratinizing squamous, ciliated columnar, gastric, or small intestinal epithelium. In distinguishing

a bronchogenic cyst from esophageal cysts, the lining epithelium is not helpful, but the presence of two muscle layers in esophageal cysts and bronchial glands or bronchial cartilage in bronchogenic cysts enables categorization in the majority of cases.⁵⁴

Patients can have a variety of symptoms, but these lesions usually are asymptomatic. Respiratory compromise with cough, dyspnea, recurrent pulmonary infections, and chest pain are uncommon. If gastric mucosa is present, perforation into the esophagus can cause hematemesis, or erosion into the adjacent lung parenchyma can develop into an abscess. These complications are exceedingly rare with these lesions.

Diagnosis is facilitated by the use of esophageal ultrasonography, chest CT, or contrast studies of the upper gastrointestinal tract.⁴⁵ Technetium-99m scanning can be used to look for ectopic gastric mucosa. Resection is the therapy of choice, whether by thoracoscopic or open technique. Many of these lesions are amenable to a minimally invasive thoracoscopic approach that still allows complete resection. Posterolateral thoracotomy is the procedure of choice when greater exposure is required. The question always arises as to whether it is necessary to resect these benign lesions. Certainly, resection is indicated if the lesion is producing compressive symptoms or is infected; it is the asymptomatic lesion discovered incidentally that poses the question of whether resection is indicated. It is often unclear whether the lesion is truly cystic because the cyst contents become so inspissated as to appear solid. When the cystic nature of the lesion is unclear, a case can be made for resection, especially through a minimally invasive approach. Observation may be the best approach for asymptomatic lesions that are clearly cystic.

Neuroenteric Cysts

Neuroenteric cysts make up 5% to 10% of foregut lesions. They occur in infants younger than 1 year and

are uncommon in adults.⁵³ They have a connection to the meninges, usually by a stalk, and are associated with congenital defects of the thoracic spine. Neuroenteric cysts possess endodermal and ectodermal or neurogenic elements. They develop because of failure of separation of the notochord from the primitive gut. A CT scan showing a cystic mediastinal lesion associated with a vertebral abnormality such as congenital scoliosis, hemivertebrae, or spina bifida should prompt consideration of a diagnosis of neuroenteric cyst.

Other Masses of the Posterior Mediastinum

Primary or metastatic tumors of the thoracic spine may also appear as a posterior mediastinal paravertebral mass. Lymphomas, particularly Hodgkin disease, can involve the posterior parietal group of lymph nodes and produce a fusiform paravertebral soft tissue mass. Infections such as tuberculosis can result in a paravertebral mass, as can a post-traumatic hematoma. A descending thoracic aortic aneurysm is an important lesion that can masquerade as a mediastinal neoplasm.

Extramedullary hematopoiesis, a compensatory response to insufficient bone marrow blood cell production, is a rare cause of a paravertebral mass.⁶⁰ The preferred sites of extramedullary hematopoietic involvement are the spleen, liver, and lymph nodes. However, in hereditary spherocytosis, for example, the posterior paravertebral mediastinum is also commonly involved. Extramedullary hematopoietic tumors can occur without severe chronic hemolytic anemia. Therefore, this lesion must be considered in the differential diagnosis of a posterior mediastinal mass in patients even without clinical evidence of anemia.⁶¹ Earlier reports demonstrated the utility of a conventional chest radiograph and CT scan of the thorax for diagnosis without biopsy or thoracotomy.⁶² Later reports clarify the superiority of MRI in identifying intrathoracic extramedullary hematopoiesis, although it usually is used in conjunction with CT because of specific limitations.^{60,63}

Castleman disease (giant lymph node hyperplasia) is characterized by mass lesions that are vascular tumors often surrounded by lymphadenopathy (Fig. 43-9).^{64,65} This arrangement makes lymph CT useful diagnostically because CT can reveal lymphadenopathy surrounding an encapsulated mass that enhances brightly and is distinct from the aorta. The term is applied to three lesions that are histologically distinct: hyaline vascular, plasma cell, and generalized. The first two represent localized disease, whereas the third refers to multicentric (generalized) disease.

Hyaline vascular Castleman disease accounts for 90% of cases; it is a localized lesion usually found incidentally in asymptomatic patients. Castleman disease manifesting as a spinal epidural mass lesion with cord compression has been reported.⁶⁶ Surgical excision is the treatment of choice; radiotherapy has not been effective. The plasma cell variant, also localized, is much less common. Patients are much more likely to have symptoms and to exhibit fever, fatigue, weight loss, and hemolytic anemia. The sedimentation rate is often high and is associated with

hypergammaglobulinemia, which results from the production of interleukin-6 by the hyperplastic lymph nodes. Resection is the treatment of choice.

Generalized or multicentric Castleman disease has the histologic features of both localized forms. The disease occurs in older patients, who typically present with severe systemic symptoms, generalized lymphadenopathy, and hepatosplenomegaly. The mortality from this disease is 50%, and the median survival is 27 months. Progression to lymphoma is common (see Fig. 43-8). The diagnosis of lymphoma is made from a sample of the lesion and treatment is directed at management of the lymphoma.

Other rare causes of a primary posterior mediastinal mass most commonly occurring in the paravertebral sulcus include angiomyolipoma,^{67,68} extralobar pulmonary sequestration,⁶⁹ neuroendocrine carcinoma,⁷⁰ mediastinal ependymomas,⁷¹ cellular hemangiomas,⁷² melanotic paraganglioma,⁷³ and mediastinal extension of a pancreatic pseudocyst.

INFECTIONS OF THE MEDIASTINUM

Descending necrotizing mediastinitis is a potentially fatal condition in its acute or chronic form that can involve the posterior mediastinum.⁷⁴ Acute mediastinitis most commonly occurs after postoperative infection or esophageal perforation. The organism most commonly isolated is *Staphylococcus* spp. In acute mediastinitis, the patient presents with the typical signs of infection, including fever, tachycardia, and leukocytosis. Subcutaneous emphysema resulting from esophageal perforation may be another clue to an infectious source.^{74,75} In chronic mediastinitis, the etiology is a granulomatous infection. When the granulomas rupture, the contents lead to a fibrotic reaction.

The posterior mediastinum is more susceptible to infection than the other compartments of the thorax. Anatomically, this is explained by the relative accessibility and communication of the posterior mediastinum to the neck and abdomen. Inferiorly, the hiatus for the inferior vena cava and the hiatus for the aorta traversing the diaphragm are well sealed; however, the esophageal hiatus, which is the furthest posterior, is not closed as well, and it provides a track between the posterior mediastinum and the abdominal cavity. Similarly, infections from the head and neck have easy access to the posterior mediastinum. The more anterior fascial planes that arise from the neck terminate before reaching the mediastinal compartments. Two posterior spaces communicate directly with the pharynx, neck, and mediastinum. The first space is located between the visceral fascia and the alar fascia and is termed the *danger space* because of its direct communication with the posterior mediastinum. The second space is located between the prevertebral fascia and the vertebral bodies, allowing communication of vertebral infections.⁷⁴

Not surprisingly, abscesses are more frequent in the posterior mediastinum than in the anterior compartment (Fig. 43-10). Although primary infection is possible, most infections are secondary and the source usually is readily apparent. Most common signs of posterior mediastinal

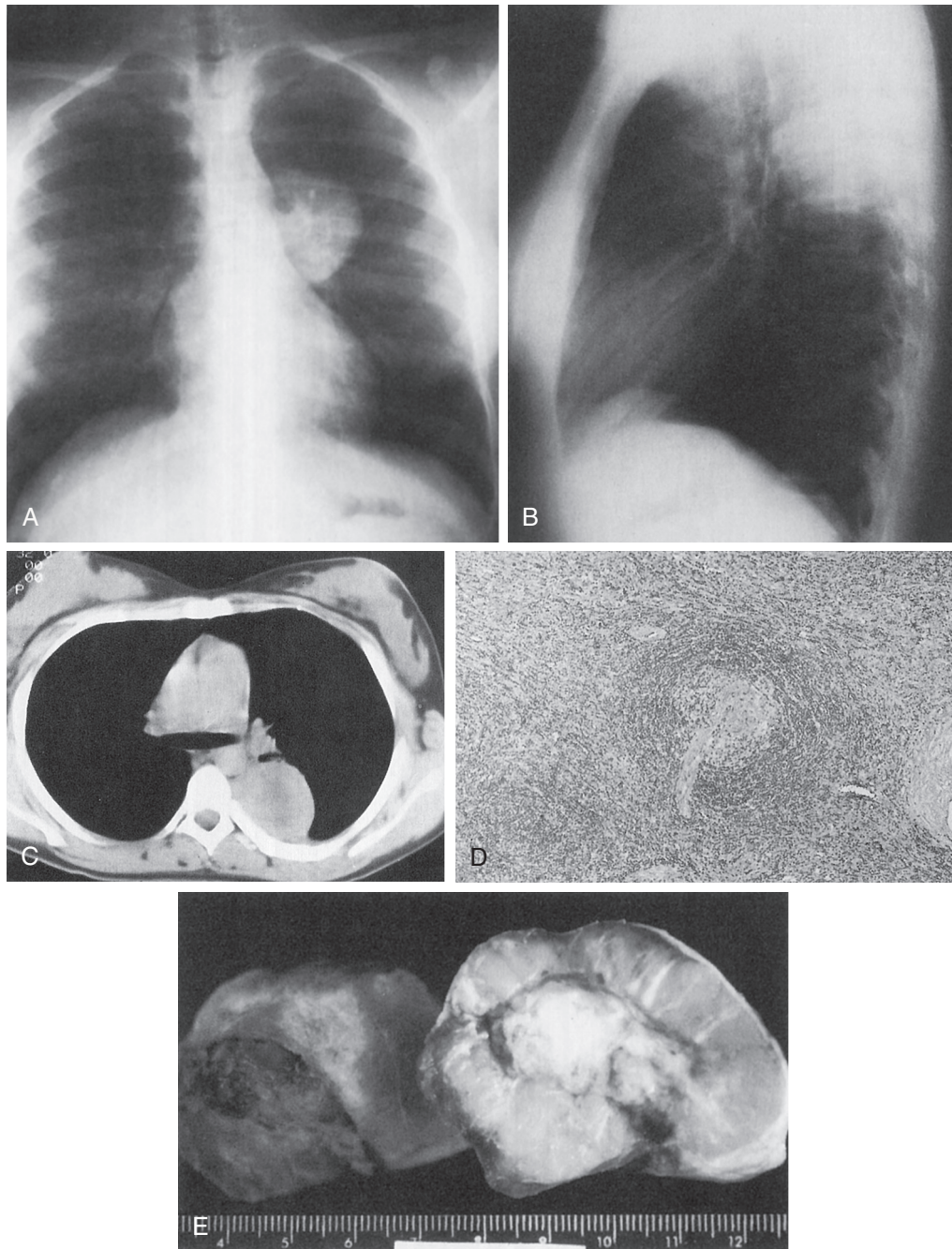


FIGURE 43-9 ■ **A** and **B**, Chest films of a giant lymph node hyperplasia (Castleman's disease) that occurs in the posterior mediastinum. **C**, CT image of the tumor is similar to a neurogenic tumor. **D**, Photomicrograph of the tumor shows the small hyaline follicles and interfollicular capillary proliferation that are characteristic of the hyaline vascular form. **E**, Photograph of a gross specimen.

abscess are pain, dysphagia, cough, and dyspnea. The pain occurs most often on swallowing and coughing, and it is felt posteriorly in the interscapular region or may radiate anteriorly. The symptoms are due to encroachment on the esophagus and trachea in the upper part of the chest. Esophageal perforation is the most common cause of a posterior mediastinal abscess, and it is often fatal if not recognized and treated expeditiously. Another cause of posterior mediastinal abscess is extension of infection from the oropharynx, spine, lung pleura, or abdominal cavity.

CT scan may demonstrate an air–fluid level or mediastinal air as part of an otherwise solid-appearing mass (Fig. 43-11). Nonsurgical management, which occasionally may be appropriate if there is no ongoing leak, includes intravenous antibiotics, but surgical drainage and débridement usually is required on an urgent basis. Surgical intervention includes widely opening the mediastinal compartment by incision of the pleura followed by débridement, irrigation, drainage, and closure of the esophageal perforation with or without a muscle flap. In diffuse mediastinitis involving the posterior

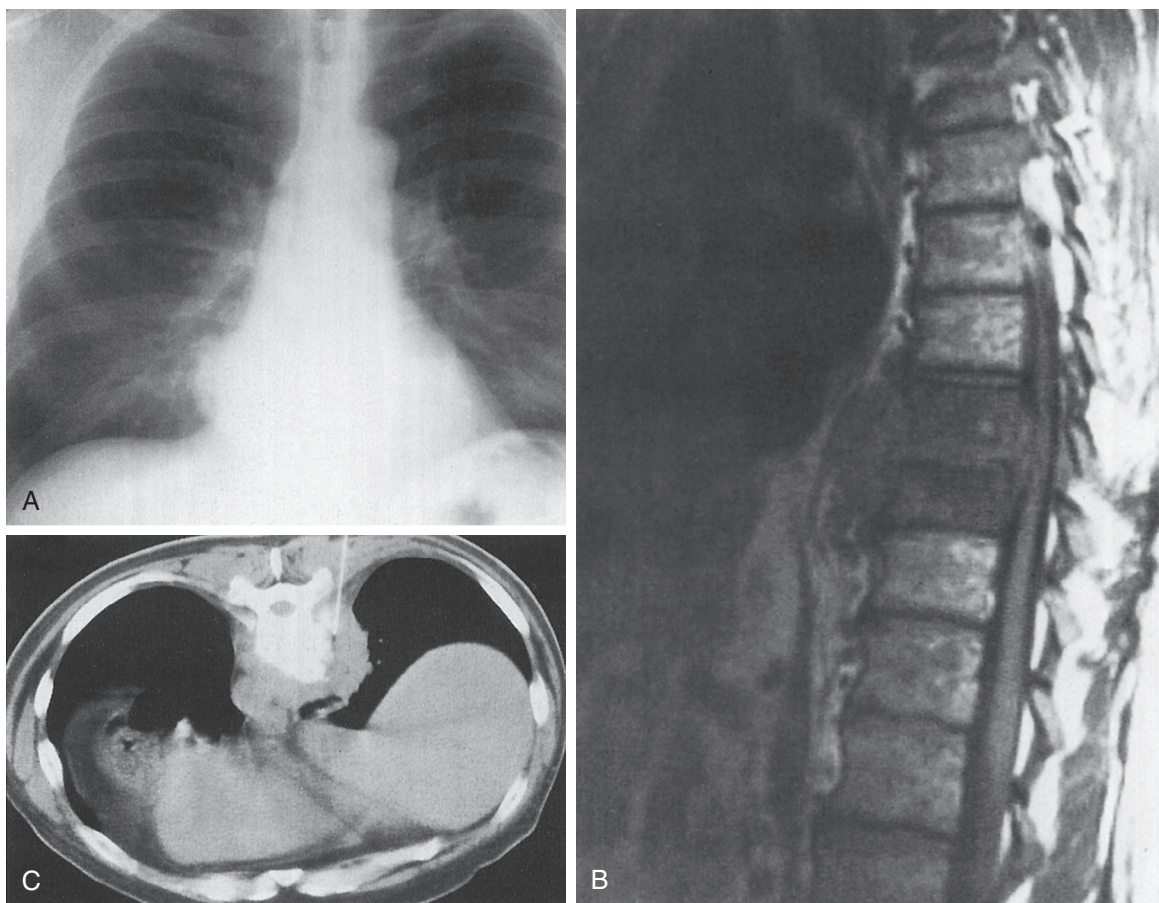


FIGURE 43-10 ■ Paraspinous abscess in a 45-year-old man with AIDS and a systemic infection. **A**, Frontal chest radiograph demonstrates a mass behind the right side of the heart. **B**, Spinal MRI demonstrates reduced intensity in two vertebral bodies with posterior and anterior masses. **C**, CT-guided aspiration of the mass demonstrated a paraspinous *Staphylococcus aureus* infection. (Reprinted with permission from Gamsu G: The mediastinum. In Moss AA, Gamsu G, Genant HK, editors: *Computed tomography of the body*, ed 2, vol 1, Philadelphia, 1992, WB Saunders, p 83.)

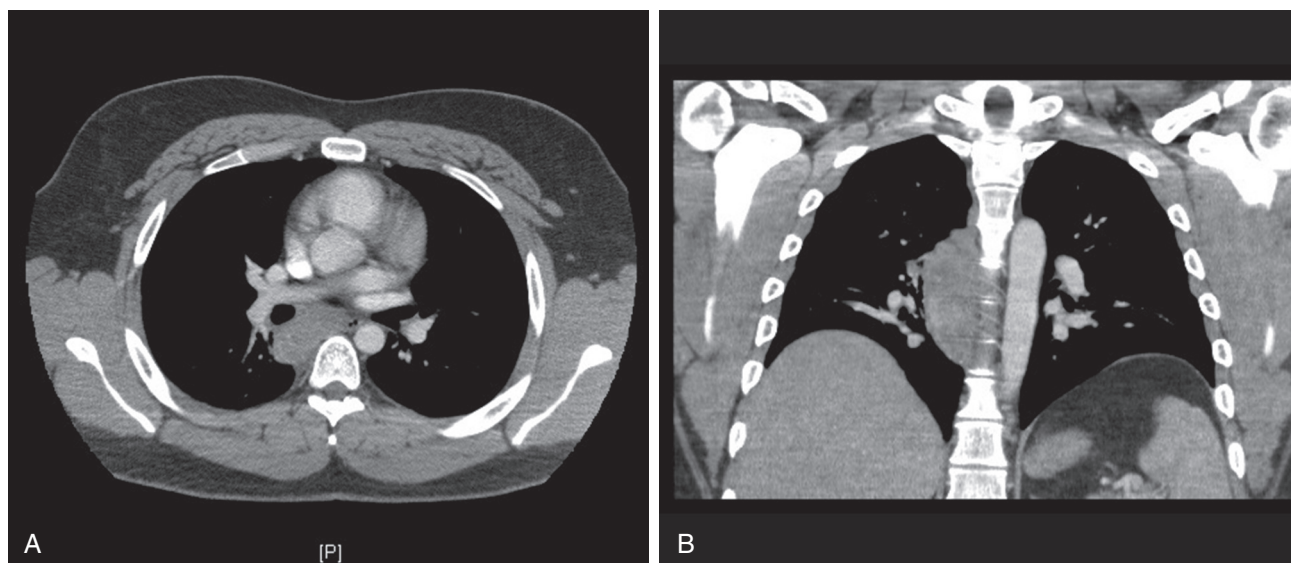


FIGURE 43-11 ■ **A**, CT scan showing necrotizing granulomatous infection of the posterior mediastinum also seen in the coronal reconstruction (**B**).

mediastinum, pericarditis or bilateral exudative pleuritis may be present.

SUMMARY

Lesions of the posterior mediastinum most commonly are neurogenic in origin and usually are benign in adults. Despite this recognition, surgical intervention commonly is required. Minimally invasive surgical approaches can provide additional justification for removal of these lesions before they become symptomatic.

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SURGICAL TREATMENT OF HYPERHIDROSIS

Daniel L. Miller • Meagan M. Miller

CHAPTER OUTLINE

NOMENCLATURE FOR SYMPATHETIC SURGERY

PATIENT SELECTION FOR VATS SYMPATHECTOMY

LOCATION OF INTERRUPTION OF SYMPATHETIC CHAIN

Palmar Hyperhidrosis

Axillary Hyperhidrosis

Craniofacial Hyperhidrosis

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VATS Sympathetic Block

VATS Sympathicotomy

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CONCLUSION

Hyperhidrosis is a pathologic condition characterized by excessive sweating beyond what is required for normal physiologic thermoregulation. This overproduction causes a significant psychosocial affliction that can negatively affect an individual's quality of life. The incidence of hyperhidrosis depends on the culture, on the climate, and on subjective definitions. Hyperhidrosis affects 1% to 3% of the U.S. population, but this percentage is likely underestimated because of infrequent reporting by patients and incorrect diagnosis by physicians.¹ Hyperhidrosis affects both sexes equally, affects predominantly adolescents or young adults, and can affect multiple body sites. Characteristically, the palmar symptoms start in early childhood, axillary symptoms in adolescence, and craniofacial symptoms in adulthood; puberty usually worsens the symptoms.

Hyperhidrosis is a primary (idiopathic) or secondary disorder with localized or generalized sweating. Focal or primary hyperhidrosis is excessive sweating not associated with a systemic process and usually affects the palms, axillae, or feet. Additionally, some patients may have craniofacial hyperhidrosis, or excessive blushing that is associated with severe emotional, occupational, and social distress. Hyperhidrosis can develop secondary to various medical disorders, such as hyperthyroidism, hypertension, diabetes mellitus, systemic infections, brain lesions, and certain medication use. Systemic medical conditions need to be diagnosed correctly and treated medically and should not be treated with surgery. Also, patients who are overweight (a body mass index > 28) may have full-body or secondary hyperhidrosis.²

Eccrine sweat glands are responsible for hyperhidrosis.³ Eccrine glands are innervated by the sympathetic

nervous system but use acetylcholine as the primary neurotransmitter. Thermal sweating is controlled by the hypothalamus, whereas emotional sweating is regulated by the cerebral cortex. A sympathetic signal is carried to sweat glands by cholinergic autonomic neurons. In patients with primary hyperhidrosis, the sweat glands are usually histologically and functionally normal. Although the pathophysiology remains unknown, the cause of hyperhidrosis appears to be an abnormal central response to emotional stress, but it can also occur spontaneously and intermittently. Additionally, there is evidence for a genetic component to hyperhidrosis, and it can be seen in family members.⁴ A genetic analysis suggests that an allele for hyperhidrosis may be present in 5% of the population.

There remains significant controversy concerning the optimal surgical therapy for primary hyperhidrosis. That is partially because of the poor definitions of the terms used for both the diagnosis of the problem and the surgical therapy. For example, video-assisted thoracic surgery (VATS) sympathectomy goes by other names, such as endoscopic thoracic sympathectomy (ETS) or sympathotomy. These terms are not synonymous. Sympathectomy and ganglionectomy refer to total ablation or removal of a segment of the sympathetic chain and ganglia, or both. Sympathicotomy and sympathotomy refer to interruption or simple transection of the sympathetic chain. Sympathetic block refers to a potentially reversible procedure, such as clipping of the sympathetic chain or local anesthetic injections of the nerve. Selective sympathectomy refers to preservation of the sympathetic chain with ramicotomy (division of the rami communicantes). To help clarify these controversies, the Society

of Thoracic Surgeons (STS) Task Force on Hyperhidrosis published an expert's consensus paper for the surgical treatment of hyperhidrosis that suggested the adoption of a standard international nomenclature that refers to the rib level (R) instead of the vertebral level at which the nerve is interrupted, how the chain is interrupted, along with systematic pre- and postoperative assessments of sweating pattern, intensity, and quality of life.⁵ This report also established specific treatment strategies regarding sympathectomy for distinct patterns of hyperhidrosis.

NOMENCLATURE FOR SYMPATHETIC SURGERY

The International Society on Sympathetic Surgery (ISSS) and the STS Task Force on Hyperhidrosis decided that an internationally agreed upon nomenclature was needed. It has often been unclear exactly where and how a surgeon interrupted the chain, which has made it almost impossible to compare techniques and results. The nomenclature needs to include the location where the sympathetic chain is interrupted and the method of how it is interrupted. Various anatomic landmarks exist to guide the surgeon in determining the exact level where to divide or clip the chain or ganglia for a sympathectomy. The ISSS and STS committees' consensus used a rib-oriented nomenclature. This decision was based on too many patients having mediastinal fat that can obscure clear identification of the specific ganglia and on the multitude of anatomic variations in the ganglion anatomy. The surgeon may add the ganglia that are interrupted to the operative note as well. In addition, the committees agreed that a description of the type of interruption is required denoting whether the chain was clipped, cut, or cauterized or whether a segment was removed.

At operation, therefore, the level is abbreviated as an R3 or an R4 (R referring to rib, and the number referring to which rib). If the chain is clipped on top of the second rib, the abbreviation for the operative note would be "clipped R2, top." If the chain is cauterized on the top and bottom of the fourth rib, the operative note would be "cauterized, top R4, bottom R4." Using this standardized nomenclature would allow surgeons worldwide to better communicate with one another.⁵

The literature on sympathectomy for hyperhidrosis must be interpreted cautiously because the definitions can differ from paper to paper. Some studies use objective data such as hand temperature postoperatively to determine success, whereas others simply rely on subjective reporting by the patient. Not all studies assess compensatory hyperhidrosis (CH) similarly, or at the same point postoperatively, or quantify the degree of CH. Standardized preoperative and postoperative questionnaires are needed to objectify the improvement of these patients. One of the best data collection sheets was developed and used by De Campos and associates⁶ in an effort to standardize results. Follow-up is a critical part of hyperhidrosis treatment. It is recommended that patients have follow-up appointments or surveys at 1 month, 6 months, 1 year, and annually for at least 5 years if possible.

PATIENT SELECTION FOR VATS SYMPATHECTOMY

The ideal candidates for VATS sympathectomy are those who have onset of hyperhidrosis at an early age (usually before 16 years of age), are young at the time of surgery (usually younger than 25 years old), have an appropriate body mass index (<28), report no sweating during sleep, are relatively healthy (no other significant comorbidities), do not have bradycardia (resting heart rate < 55 beats/min), and have no associated body sweating.

Only a small percentage of patients should be considered for surgical treatment. Surgical consultation should include the correct diagnosis of primary hyperhidrosis, the anatomic locations involved, the amount of hyperhidrosis, and full discussion of the surgical options and potential complications. The patients should be made aware that the most satisfied patients are those with palmar or palmar-axillary hyperhidrosis, or both. Finally, patients should also be told of the success and failure rates and long-term results. Physicians can offer the patient the option to discuss the procedure and its side effects with a patient who has already undergone the surgery. This can be done by a conference call under the Health Insurance Portability and Accountability Act (HIPAA) guidelines or face to face at the patient's request.

Prior to any surgical procedure, patients must fail conservative medical therapy. Most insurance companies require a patient to fail at least three nonsurgical treatments. First-line treatment is usually prescription-strength antiperspirants, which work by mechanical obstruction of the eccrine sweat gland ducts or by causing atrophy of the secretory cells. These include antiperspirants with 20% aluminum chloride in ethanol (Drysol) or 6.25% aluminum tetrachloride (Xerac). Drawbacks to using these agents include dyspigmentation of skin, contact dermatitis, and necessity for continuous use. Systematic medication may also be used in the treatment of hyperhidrosis. Anticholinergic agents (glycopyrrolate, propantheline, oxybutynin) are the most commonly used, but the dosage required to reduce sweating causes significant side effects such as dry mouth, blurred vision, and urinary retention. In patients with hyperhidrosis triggered by specific emotional events, beta blockers or benzodiazepines may be useful for reducing the emotional stimulus that leads to excessive sweating. Long-term use of these oral agents is not advisable, and rebound sweating may be more severe with withdrawal of the medication than it is with the baseline hyperhidrosis.

Iontophoresis may be used. It is the introduction of ionized substances through the intact skin by the application of a direct electrical current. Iontophoresis is most often used for palmar or plantar hyperhidrosis; a special axillary electrode can also be used but is less effective. There are limited data from randomized trials, but iontophoresis appears to alleviate symptoms in approximately 85% of patients with palmar or plantar hyperhidrosis.⁷ The drawbacks are the upfront machine cost, the labor intensiveness of the treatment, irritation of the skin with scaling and fissuring, and, primarily, the pain associated with the daily treatment sessions.

Botulinum toxin type A (Botox) and type B (Myobloc) have been shown to be effective for axillary and palmar hyperhidrosis, although Botox has not been approved by the Food and Drug Administration (FDA) for palmar treatment. Botox blocks the release of acetylcholine from the presynaptic junction of the autonomic neurons and temporarily reduces sweat production. The effect usually lasts for 3 to 4 months. Long-term results with repeated injections for more than 2 years is infrequent because of antibodies produced against the toxin.⁸ Drawback includes pain at the injection sites, transient hand weakness, and high treatment cost.

Surgical therapy is extremely effective for medical refractory primary hyperhidrosis and is based on the interruption of transmission of impulses from the sympathetic ganglia to the sweat glands. Currently, a VATS approach is preferred. The literature on sympathectomy for hyperhidrosis must be interpreted cautiously because of non-uniform definitions of sympathetic chain levels treated, of successful treatment, and of the incidence of post-sympathectomy CH.

LOCATION OF INTERRUPTION OF SYMPATHETIC CHAIN

Palmar Hyperhidrosis

Opinions differ on how to treat patients who have only palmar hyperhidrosis. For patients who are willing to accept a higher risk of CH because they want their hands to be completely dry, it is suggested that two interruptions in the sympathetic chain be made, at R3 and R4. However, based on a prospective randomized study in 2009 by Liu and associates⁹ and a study in 2007 by Yang and colleagues,¹⁰ an R4 alone interruption may be acceptable for these patients because it limits the degree of CH; however, it may lead to moister hands. The patients should be counseled about these differences and should participate in the decision-making process. For these reasons, the top of R3 sympathectomy alone for patients with isolated palmar hyperhidrosis is recommended.

Patients with palmar and plantar hyperhidrosis represent a different challenge. Again, two operations can be performed. An R4 interruption alone may reduce the incidence of CH. Alternatively, an R4 and R5 intervention is a reasonable option; because this intervention results in drier feet, it is the preferred treatment.

Axillary Hyperhidrosis

VATS sympathectomy for axillary hyperhidrosis is often less successful and has higher “regret rates” than sympathectomy for palmar hyperhidrosis. A qualitative review showed a trend of lower incidence of CH with fewer interruptions, even when the interruptions are fairly low on the chain.^{11,12} In a randomized, prospective study of patients with axillary hyperhidrosis, Munia and colleagues¹³ in 2008 showed that all (100%) patients who underwent R3/R4 ETS experienced greater incidence and severity of CH, 1 year after surgery, compared with patients who underwent R4 ETS alone (42%). Chou and

associates¹⁴ found that patients with axillary hyperhidrosis who underwent R5 clipping alone experienced no CH, and none regretted having the surgery. Therefore, for patients who have palmar-axillary, palmar-axillary-plantar, or pure axillary hyperhidrosis, an R4 and R5 transection is recommended.

Craniofacial Hyperhidrosis

Patients with cranial and facial sweating present a more complicated problem compared with patients who have hyperhidrosis that affects the lower part of their body. Chou and colleagues¹⁴ in 2006 reported an experience with R3 interruption of the chain in 33 patients with craniofacial sweating. They found that only 3 patients (9%) regretted the procedure and 9 (27%) reported CH. In that same series, Chou and colleagues also performed R2 interruption in 54 patients with facial blushing. More than 40% of these patients experienced CH, and 16.7% of patients regretted having the operation. Licht and coworkers¹⁵ in 2006 compared R2 interruption with R2 and R3 interruption in 173 patients with facial blushing. They found a significantly higher CH rate in the group that underwent the R2 and R3 transection (95%) compared with the R2 group (83%). Craniofacial sweating must be distinguished from blushing. Based on the findings of these and other series, an R3 alone interruption is suggested for craniofacial sweating, because it reduces the risk of CH and the risk of Horner syndrome when compared with R2 or an R2 and R3 transection.

TYPE OF INTERRUPTION

Should the sympathetic chain be resected, transected, ablated with cautery, or divided with a harmonic scalpel, or should clips be used? No clear differences have been demonstrated among the different techniques; when the correct level of division is achieved, the results are excellent and reproducible. The most important concept about nerve disruption is that there is enough separation (>1.0 to 1.5 cm) between the ends of the chain so that regrowth is impossible. By just ablating the nerve, it is more than likely to regrow, and symptoms could reoccur. Also, accessory nerves (Kuntz) must also be interrupted to prevent persistent excessive sweating or recurrence. Despite initial enthusiasm, the presumption that the patient can return for “surgical reversal” by removing the clip appears questionable. Clip removal for reversible of postprocedure CH has shown disappointing results at long-term follow-up, which is more than likely because of permanent perineural damage to the sympathetic chain secondary to multiple clips, which is usually irreversible.¹⁶

SURGICAL TECHNIQUE (see Video 44-1)

VATS Sympathetic Block

A temporary VATS sympathetic block is performed as an outpatient procedure within our hospital's main

operating room or in our ambulatory surgical center. The patients are placed in a supine position. General anesthesia is initiated with a single-lumen endotracheal tube, usually 7.0 or 7.5 Fr. After the patient is asleep, the arms are extended laterally to 90 degrees. Excessive abduction of the upper extremities is avoided to prevent injury to the brachial plexus. Temperature probes are placed on each index finger. Each axilla is prepped in standard fashion. Attention is first directed to the right side. A single 4-mm incision is made vertically over the fourth rib along the midaxillary line. Using a mosquito clamp, the chest cavity is entered over the fourth rib during suspension of ventilation. During continued ventilation suspension, a 3-mm 30-degree rigid thoracoscope (Karl Storz, Munich, Germany) is placed. Alongside the thoracoscope, a standard laparoscopic Veress needle (Ethicon, Inc., Cincinnati, OH) is also placed. After the two instruments are placed without difficulty, ventilation is resumed with a decreased tidal volume of 250 mL for women and 300 mL for men. Temporary CO₂ insufflation is carried out to 10 mm Hg for approximately 30 to 90 seconds to allow partial collapse of the lung. The apical and posterior chest is examined in detail to allow accurate identification of the anatomy of the sympathetic chain and its accessory nerves.

Prior to performing the block, a finger temperature is recorded as a baseline measurement. The block is performed by placing a 2-mm hollow semi-rigid catheter alongside the thoracoscope to the apex of the chest under direct visualization. A 22-gauge laparoscopic needle is then placed through the catheter. The sympathetic chain is injected with 2.5 mL of 0.25% Marcaine with epinephrine at each planned sympathectomy site and 1.0 mL at each accessory nerve. After completion of the block of the primary nerve and its accessories, a postblock temperature is taken at 5 minutes. The needle is removed, and the external end of the catheter is placed in a basin of sterile water to create a water seal. The pneumothorax is evacuated by immersing the catheter in sterile water, adjusting positive pressure ventilation to 40 mm Hg, and suctioning. After the pneumothorax is evacuated, the catheter is removed. The skin is reapproximated with a Dermabond adhesive. The left side is completed in a similar fashion. A dose of 15 mL 0.25% Marcaine is injected into each incision prior to making the incision and at the time of closure. Also, 30 mg of ketorolac is given intravenously prior to making the incision. The patient is taken to the recovery room for an upright chest radiograph and subsequent planned dismissal.

VATS Sympathicotomy

The subsequent sympathectomy is usually performed within 4 weeks of the VATS block procedure. Again, the procedure is performed as an outpatient surgery within our hospital's main operating room or in our ambulatory surgical center. Redo single 4-mm bilateral incisions are made, incorporating the previous incisions. Again using a mosquito clamp, the chest cavity is entered over the fourth rib during suspension of ventilation. During continued ventilation suspension, the thoracoscope and Veress needle are placed. After the two instruments are



FIGURE 44-1 ■ Video-assisted thoracic surgery (VATS) scar 4 weeks after surgery.

placed without difficulty, ventilation is resumed. Temporary carbon dioxide insufflation is carried out. The Veress needle is removed, and through the same incision alongside the thoracoscope, a 2-mm-long electrocautery device is placed. Again, a detailed examination is carried out of the apical and posterior chest to accurately identify the anatomy of the sympathetic chain and its accessory nerves. Prior to the sympathectomy, a finger temperature is taken for a baseline measurement. The sympathetic chain is then divided over the second, third, or fourth rib to complete the planned sympathectomy (depending on preoperative indication, T2 only, T3 only, or T3/T4) with a 2-mm-long electrocautery device. All accessory nerves are also divided with electrocautery. The cauterized ends of the nerves are separated from each other to allow at least a 1.0- to 1.5-cm gap to diminish the chance of regrowth and possible recurrence of hyperhidrosis. The external end of the catheter is placed in a basin of sterile water to create a water seal, and the pneumothorax is evacuated as described earlier. After the pneumothorax is evacuated, the catheter is removed. The skin is reapproximated with a Dermabond adhesive. The left side is completed in similar fashion. A dose of 15 mL 0.25% Marcaine is injected into each incision prior to making the incision and at the time of closure. In addition, 1000 mg of acetaminophen and 30 mg of ketorolac are given intravenously prior to making the incision.

In the recovery room, an upright chest radiograph is obtained approximately 30 minutes after completion of the procedure. If the chest radiograph is satisfactory and the patient has minimal discomfort, the patient can be discharged. The patient is asked to return to the clinic within 3 to 4 weeks after the procedure for follow-up. Postoperative scarring is minimal (Fig. 44-1).

COMPLICATIONS AND TREATMENT

Because the goal of the surgery is to improve the patient's quality of life, complications should be minimal and essentially eliminated. The primary side effects of hyperhidrosis surgery include CH, bradycardia, and Horner syndrome. It is important for patients to be aware, however, of all possible complications that can occur.

The most common side effect is CH, which, according to the literature, occurs in 3% to 98% of cases.^{17,18} This wide variability in the incidence of CH may be attributable to heterogeneous patient populations, different surgical procedures, or, more importantly, a variety of definitions of CH. The clinical presentation of CH can be classified as mild, moderate, or severe.⁹ Mild CH is sweating that occurs in small amounts and is triggered by ambient heat, psychological stress, or physical exercise. The sweat that forms does not flow, is tolerable, and does not cause embarrassment or the need to change clothes. Moderate CH is when sweating occurs in moderate amounts and is triggered by ambient heat, psychological stress, or physical exercise. The sweat coalesces into droplets that flow, although not necessitating a change of clothes. Therefore, the sweating, although uncomfortable, does not embarrass the patient. Severe or intense CH is when sweating occurs in large amounts and is triggered by low or no ambient heat, psychological stress, or physical exercise. With severe CH, the sweat droplets form profusely, requiring a change of clothes one or more times a day. If the patient is already experiencing increased sweating in the trunk, groin region, or upper thighs, then the patient should be warned that he or she is at increased risk of developing CH, and the patient should think twice about proceeding with the procedure.

The most common risk factor cited in the literature for moderate to severe CH is interruption of T2 ganglion (R2, R3).^{10,19} The number of levels interrupted has been inconclusive as a risk factor.^{20,21} Some techniques have been described to help predict or minimize the degree of CH. A reversal sympathetic block technique with bupivacaine hydrochloride was developed by Miller and associates in 2007 for patients who are at an increased risk for CH.²² This technique has been useful for predicting which patients may develop severe debilitating CH. If the patient does not have bothersome CH and has cessation of the hyperhidrosis, then nerve transection is performed at a later date. Other options to help treat patients with CH include use of medication (Ditropan or other anticholinergic medications) in escalating doses and liposuction of the axillary sweat glands. Gustatory sweating may also occur, but rarely, in less than 0.1% of patients.

Horner syndrome is another side effect that has been reported to occur at a rate between 0.7% and 3% after VATS sympathectomy. The possibility of Horner syndrome should be addressed in patients with craniofacial hyperhidrosis, as direct injury by cautery, traction, or surrounding inflammation can occur as a result of improper localization of the second rib. In all series, inadequate localization decreases with surgical experience. The risk of this complication may be minimized with procedures performed below the second rib (R2), although indirect injury may still result. Misidentification of the operative level can occur; some recommend that an intraoperative radiograph be performed if the anatomy is uncertain. Anatomically, the stellate ganglion can be lower on the left side down to R3.

Permanent bradycardia has been reported after surgery for hyperhidrosis as well.²³ This issue needs to be fully discussed with patients who come in with a resting heart rate less than 55 or 50 beats/min because there have been

reports of patients who may require a pacemaker. Patients who are highly competitive athletes who may require compensatory increase in heart rate or vascular tone with exercise should be told that their exercise capacity could theoretically be reduced and should be encouraged to drink large quantities of electrolyte-containing fluids while participating in sports.

Other less common complications (1%) include pneumothorax requiring chest tube drainage, pleural effusion, acute bleeding or delayed hemothorax, chylothorax, and persistent intercostal neuralgia. Bleeding and pain complications can be reduced by careful port placement²⁴ or no port placement at all as described by Miller and Force.²⁵ Pneumothorax can also be minimized with careful attention to avoiding parenchymal injury during initial port placement as well as to the technique of reinflation.

Recurrent hyperhidrosis is another potential side effect from hyperhidrosis surgery. Incidence rates vary considerably and have been described as 0% to 65%.²⁶ This wide variability may be a result of the differences in the techniques used, the levels of the sympathetic chain interrupted, the definitions used, and the length of follow-up. The primary reason for failure is inadequate surgery. That can be attributed to an anatomic variation in the sympathetic chain, surgical technique, intense pleural adhesion, presence of vessels overlying the sympathetic chain or aberrant venous arch drainage, abundant adipose tissue, and possible reinnervation, especially in children who grow after the procedure. Resympathectomy has been advocated and successfully performed, mainly for immediate failures. Adhesions from the first operation have been the most frequently reported reason for avoiding resympathectomy.²⁷ Analyzing the previous medical records and operative notes is essential before performing the second operation.

OTHER SURGICAL TREATMENTS FOR HYPERHIDROSIS

Other surgical therapies for axillary hyperhidrosis are the removal of the axillary sweat glands by means of curettage²⁸ or liposuction.²⁹ Complications include wound infection, scar formation, skin necrosis, and skin discolorations. The VASER (Sound Surgical Technologies, Louisville, CO) is a third-generation FDA-approved ultrasound device that allows emulsification of axillary tissue and glands. Primary side effects include transient dysesthesia, indurations, seroma, and ecchymosis.³⁰ All of these procedures take approximately an hour to perform and can be performed in the office.

CONCLUSION

VATS sympathectomy for medical refractory primary hyperhidrosis is extremely successful. Interruption of the chain can be achieved by cauterizing, cutting, or clipping the sympathetic chain. Although the level of interruption, based on the patient's distribution of the hyperhidrosis, remains controversial, standardized

anatomic classifications and careful literature review provide the best framework for treatment strategies. A thorough preoperative workup, attention to detail at the time of the nerve interruption, an understanding of the levels that should be interrupted, and comprehensive education of the patient about treatment options, success rates, and complications will lead to a satisfied patient with a significant improvement in quality of life. These results are also dependent on the weather, the climate, physical and work activities, psychological aspects, and other specific conditions of the patient.

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PART N

THE FUTURE

PART OUTLINE

45 THE MOLECULAR BIOLOGY OF
THORACIC MALIGNANCIES

46 INNOVATIVE THERAPY AND TECHNOLOGY

THE MOLECULAR BIOLOGY OF THORACIC MALIGNANCIES

Shawn S. Groth • Jonathan D'Cunha

CHAPTER OUTLINE

MECHANISMS OF ONCOGENESIS AND METASTASIS

Environmental Exposure
Genetic Mutations
Heterogeneity of Mutations
DNA Aneuploidy
Dysregulation of Cellular Proliferation
Cancer Stem Cells

EPIGENETICS

PROTEOMICS

METABOLOMICS

CLINICAL APPLICATION OF NUCLEIC ACID AND PROTEIN BIOMARKERS

Detection in Tumor Tissue
Lung Cancer
Esophageal Cancer
Mesothelioma

Detection in Lymph Node Tissue

Lung Cancer
Esophageal Cancer

Detection in Blood

Lung Cancer
Esophageal Cancer

Detection in Bone Marrow

Lung Cancer

Detection in Sputum

Lung Cancer

NEXT-GENERATION DNA SEQUENCING IN CLINICAL CARE

PERSONALIZED ONCOLOGY

Customized Chemotherapy
Targeted Therapies

SUMMARY

As Dr. Blake Cady eloquently stated, tumor biology is the principle determinant of outcome in surgical oncology.

“Biology is King, Selection is Queen, and the technical details of surgical procedures are the Princes and Princesses of the realm who frequently try to overthrow the powerful forces of the King and Queen, usually to no long-term avail, although with some temporary apparent victories.”¹

Reflections such as this and our clinical experience highlight that our ability to make a significant, lasting impact on the outcomes of most cancer patients rests in our capacity to understand and influence tumor biology.

A revolution in the care of patients with thoracic malignancies is upon us. The clinical application of molecular diagnostic and analytic technologies is growing rapidly, and recent studies have begun to unfold their true potential for thoracic oncology patients. In particular, genetic science has a possible role in guiding therapy (based on both an individual's risk of recurrence and death and a tumor's genetic features) and counseling

patients (with regards to risk of recurrence and prognosis). Indeed, as our understanding of tumor biology continues to evolve, effective personalized oncology is becoming a reality. In this chapter, we provide a brief review of our current understanding of the molecular mechanisms underlying oncogenesis and metastases of thoracic malignancies. We also highlight the current role of epigenetics, proteomics, biomarkers, and personalized oncology in the care of patients with thoracic malignancies.

MECHANISMS OF ONCOGENESIS AND METASTASIS

The progression of a cell from normal to overt malignancy is the end result of a complex sequence of genetic events influenced by a number of environmental and biological factors. The precise mechanism of oncogenesis of thoracic malignancies is complex and incompletely understood (Fig. 45-1). However, a few salient points have emerged from the literature.

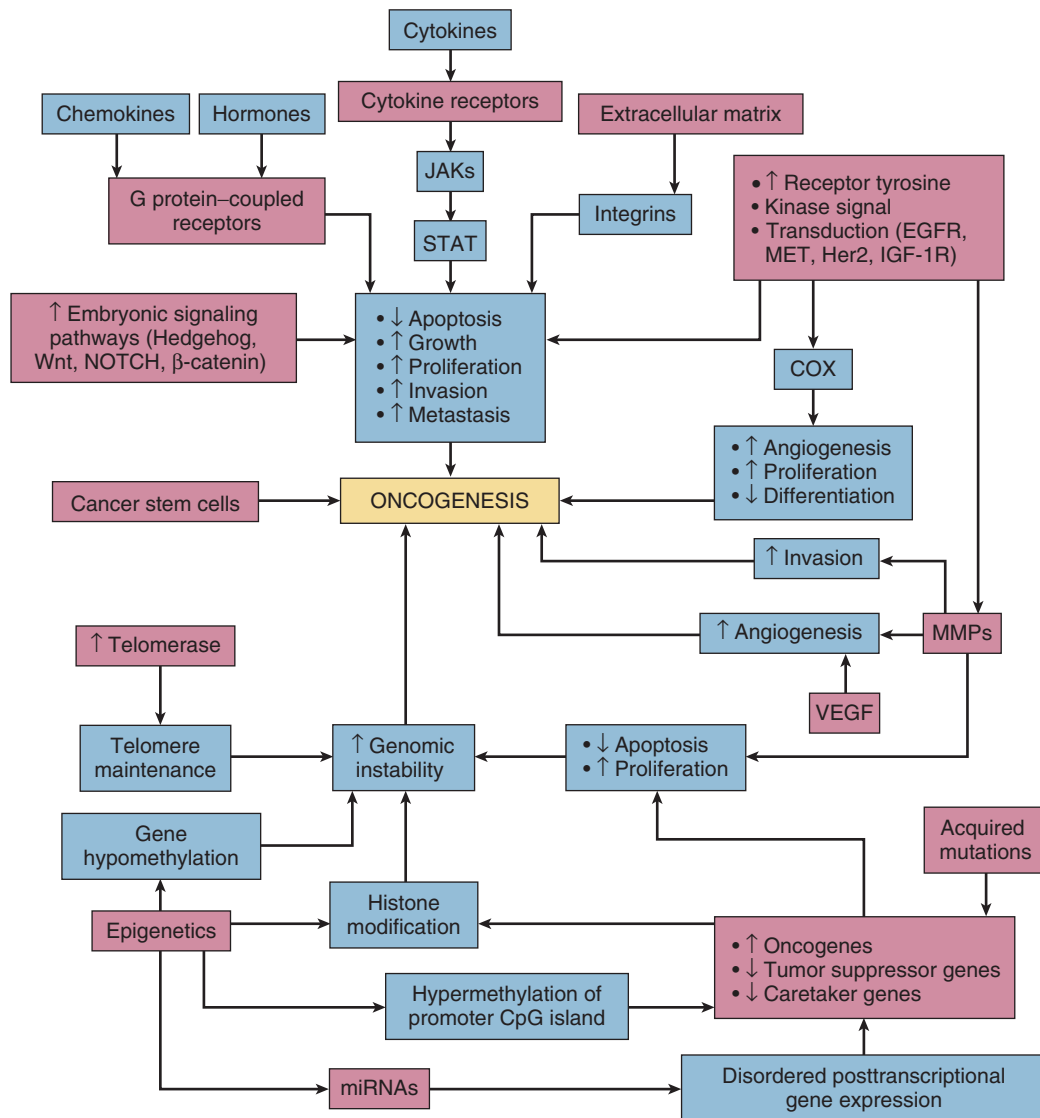


FIGURE 45-1 ■ Overview of the pathways involved in oncogenesis.

Environmental Exposure

First, most thoracic malignancies are the end result of the effect of an environmental exposure (e.g., tobacco smoke, alcohol use, chronic gastroesophageal reflux, asbestos) on a cell's genome. Such exposures can cause alterations in DNA structure (e.g., pyrimidine dimers and double-strand breaks), which can alter DNA replication and transcription. Environmental exposures can also induce mutations if errors are introduced by DNA repair mechanisms while attempting to correct mistakes in DNA structure. Other carcinogens (e.g., asbestos), however, cause chromosomal loss, gain, and/or rearrangements before causing genetic mutations.^{2,3}

Genetic Mutations

Second, mutated genes contribute to oncogenesis by selectively conferring a growth advantage to cancer cells. Such mutations can be either inherited (*germline*)

mutations or acquired (*somatic*) mutations. *Proto-oncogenes* are dominant genes that encode proteins that are responsible for cell-cycle progression, cell differentiation, or regulation of *apoptosis* (programmed cell death). When proto-oncogenes are mutated (by point mutations, translocations, gene amplifications, gene insertions, or gene deletions), they are called *oncogenes*, which are either constitutively active or abnormally active (under conditions that the normal wild-type gene is not).⁴

Tumor-suppressor genes are the genetic brakes on aberrant cell proliferation by regulating cell division, DNA repair, and apoptosis. In contrast to oncogenes, tumor-suppressor genes are recessive genes—both copies need to be inactivated for their effect to be lost. One allele is typically lost through loss of heterozygosity, and the other is typically lost by a mutation or epigenetic modification (discussed later).⁵ Mutations in tumor-suppressor genes confer a growth advantage by removing a normal checkpoint in cellular proliferation.

Mismatch repair genes are recessive genes involved in repairing mistakes occurring primarily during DNA replication. Because microsatellites (tandem repeats in DNA sequences) are especially vulnerable to DNA replication mistakes, *microsatellite instability* is a hallmark of defective DNA repair.^{5,6} To appreciate the interaction among proto-oncogenes, tumor suppressor genes, and mismatch repair genes, these genes have also been subclassified as gatekeepers, caretakers, and landscapers.

Gatekeepers are oncogenes and tumor suppressor genes that control cell growth and differentiation.^{7,8} In contrast, *caretakers* (i.e., tumor suppressor genes and mismatch repair genes) are responsible for maintaining the genomic integrity of the cell. Mutations in caretaker genes promote oncogenesis indirectly by inciting genetic instability, which increases the rate of mutations of other genes (including gatekeepers).^{7,8} If these mutations result in a selective advantage toward cell proliferation (or repression of apoptosis), tumor formation may ensue. Finally, *landscapers* are not directly involved in cellular growth. Rather, they foster a stromal environment conducive to unregulated cell proliferation.^{8,9} Indeed, although normal stroma creates an environment with innate antitumor properties, inherited or acquired mutations in landscaper genes facilitate tumor growth by removing the natural antagonism of the stroma toward oncogenesis (e.g., by altering cell adhesions, cellular signaling, and altered innate immunity) or by altering the microenvironment to a more oncogenic state (e.g., through matrix metalloproteinases and angiogenesis).¹⁰

Heterogeneity of Mutations

Third, not all genetic mutations that accrue during tumorigenesis are equipotent—some mutations involved in cancer progression are more significant than others.¹¹ As oncogenesis progresses, cancer cell proliferation becomes increasingly reliant on these more potent (driver) mutations, a phenomenon known as *oncogene addiction*.^{12,13} Because of a tumor's reliance on the products of these critical oncogenes for growth and survival, this dependence is a point of weakness (an Achilles heel in the seemingly impenetrable armor of unrestrained genetic activity) and, therefore, a potential therapeutic target.^{12,13}

Driver mutations, which comprise a minority of mutations in cancer, are mutations that have been positively selected during oncogenesis by conferring a growth advantage to the cancer cell. They “drive” cancer cell proliferation. In contrast, *passenger mutations*, which comprise the majority of mutations in cancer cells, confer no such advantage. They are simply the expected functional consequence of normal clonal and subclonal expansion.¹⁴ In other words, passenger mutations are simply “along for the ride.” To have a positive therapeutic effect on tumor biology, one must sort through the passenger mutations and devise means to target the driver mutations effectively.

Most genetic mutations found in tumors are clonal (they are present in all cells within the tumor). However, subclonal mutations are an important source of intratumoral, intermetastatic, intrametastatic, and interpatient

tumoral heterogeneity.¹⁵ This source of heterogeneity has significant treatment implications.

Intratumoral heterogeneity refers to heterogeneity of tumor cells within the same tumor.¹⁵⁻¹⁷ Each time a tumor cell divides, the progeny cells acquire new mutations that distinguish them from their common progenitor cells. Therefore, in the process of cell replication down the genetic tree of oncogenesis, cells that are generationally divergent will also be more genetically distinct. From a practical standpoint, this form of heterogeneity is usually not clinically significant in patients with localized disease because the primary tumor is often surgically removed. However, this divergence down the genetic tree of oncogenesis spawns the seeds of intermetastatic heterogeneity.¹⁵

Intermetastatic heterogeneity refers to heterogeneity among spatially distinct metastatic lesions in the same patient.¹⁵ Most patients who die from cancer die from an overwhelming tumor burden in metastatic sites that cannot be removed surgically and that fail systemic chemotherapy or radiation therapy. As such, this form of heterogeneity has significant clinical implications. At one end of the spectrum, if each metastatic site is sufficiently genetically distinct to respond differently to chemotherapeutic agents, then long-term survival is nearly impossible to achieve. Fortunately, most intermetastatic heterogeneity is confined to passenger mutations. The mutations required for metastasis are present in the progenitor cells before the seeds of metastasis are released.¹⁵

Similar to the heterogeneity within the primary tumor that develops during the process of tumor cell propagation (intratumoral heterogeneity), *intrametastatic heterogeneity* is the end result of genetic mutations that occur as a founding cell of a metastatic site divides.¹⁵ Such mutations are the grounds for drug resistance. Metastatic deposits may initially respond to treatment that targets mutations that occurred in progenitor cells before metastases occurred, because many of the cells in a metastatic lesion have the same susceptibility to chemotherapy, evidenced by a decrease in the size (or complete resolution) of the lesion noted on posttreatment medical imaging. However, hundreds or thousands of the cells with acquired drug resistance are likely still present, perhaps below the resolution of medical imaging or clinical examination. Recurrence in such situations is inevitable.

There is also heterogeneity of the same tumor type between different patients (*interpatient heterogeneity*).¹⁵ This form of heterogeneity is responsible for the clinical observation that “no two cancer patients are the same.” As a result, uniformly applying the same systemic treatment to all patients with the same type of tumor does not result in the same response rates for each patient. Even if the end result is the same in two different patients (e.g., a particular driver mutation that leads to lung cancer), the mutations in each patient are likely sufficiently distinct such that they alter the coding sequence of the gene and hence the translated protein product of the gene in unique ways. Even small differences in a protein product can affect the conformation of the protein and hence its susceptibility to treatment. This heterogeneity is likely the result of host factors (e.g., inherited mutations that predispose to developing cancer,

mutations that affect the pharmacokinetics of chemotherapeutic agents, environmental factors within a host that facilitate tumor propagation) and distinct mutations between different tumors that develop during clonal and subclonal expansion.

DNA Aneuploidy

One of the most common observations in solid tumors is *DNA aneuploidy* (abnormal chromosome number and content). Aneuploidy can result from aberrant mitotic divisions, chromosome cohesion defects, improper attachments of chromosomes to microtubules, weakened mitotic checkpoint signaling, or mutated mitotic checkpoint genes.^{18,19} The contribution of aneuploidy to oncogenesis is controversial. Aneuploidy may simply facilitate (rather than directly cause) oncogenesis. For instance, populations of cells that are capable of redistributing chromosomes such that there is an increased probability of loss of heterozygosity (and hence loss of function of tumor-suppressor genes) or duplication of a mutated oncogene allele would confer a growth advantage.¹⁹ Alternatively, aneuploidy (generated either spontaneously or by a carcinogen) could catalyze a chain reaction of genetic instability and therefore initiate carcinogenesis. Regardless of its precise role in oncogenesis, aneuploidy is clinically significant, because it may be a mechanism of acquired resistance to chemotherapy.¹⁹

Dysregulation of Cellular Proliferation

Mutations in proto-oncogenes and tumor-suppressor genes promote uncontrolled cellular growth if they lead to increased cellular proliferation, decreased apoptosis, or both.⁵ Cell proliferation is directly controlled by *cyclins*, a group of proteins that interact with *cyclin-dependent kinases* (CDKs) and are controlled by *cyclin-dependent kinase inhibitors* (CDKIs). Increased expression of cyclins and decreased activity (or loss) of CDKIs contribute to cell cycle dysregulation.

Cell proliferation is also controlled by *telomeres*, non-coding, tandemly repeated DNA sequences at the ends of chromosomes that allow DNA to be completely replicated all the way to the end of the coding sequence, thereby preventing enzymatic degradation and stabilizing the chromosome. A small amount of telomeric DNA is lost with cell cycle. Once this DNA reaches a critical point, a signal prevents further cell division.²⁰ *Telomerase* is a ribonucleoprotein enzyme complex (containing a reverse transcriptase subunit and an RNA subunit) that maintains telomere length and hence evades replicative senescence.^{5,20} In contrast to most somatic cells (which have no telomerase activity), many cancer cells have increased telomerase activity. Consequently, telomerase activity may be a marker of progression for a benign to malignant process and may be a therapeutic target.

There are multiple interconnected complex pathways of cell-cycle control. Noncoding ribonucleic acids (ncRNA) are functional RNA molecules that are not translated into proteins and are important mediators of these pathways. One such ncRNA is microRNA (miRNA), single-stranded, short (about 22-nucleotide) ncRNAs that are important

regulators of mRNA translation and degradation by binding at partially complementary sites in the untranslated regions of target mRNAs.²¹ miRNAs contribute to tumorigenesis by directly and indirectly (through epigenetic regulation) influencing translation of tumor-suppressor genes and oncogenes and by triggering a toll-like receptor-mediated tumorigenesis inflammatory response.²¹ miRNAs are in turn regulated by endogenous RNAs, which share miRNA response elements with mRNA, thereby vying for miRNA binding.^{22,23} As such, endogenous RNAs can remove the repressive effect of miRNAs on gene expression. The result is a complex network of classic genetic and epigenetic regulation of gene expression by miRNAs and endogenous RNAs. Dysfunctional endogenous RNAs can promote oncogenesis by removing the inhibitory effect of miRNA on oncogenes.^{22,23}

Cancer Stem Cells

Most cancers arise from a single cell that has undergone genetic mutations.²⁴ Such cells, known as *cancer stem cells*, have the ability to self-renew, proliferate, and produce the heterogeneous lineages of cancer cells within a tumor.²⁵ It is unclear whether cancer stem cells are true pluripotent stem cells, adult tissue-specific stem cells that acquire oncogenic mutations, or mature cells influenced by their microenvironment to undergo de-differentiation.² The process of tumor progression from cancer stem cells is also unclear. It may involve aberrant differentiation of cancer stem cells or it may involve cell-cell fusion between cancer stem cells and differentiated heterogeneous somatic cells, which can then undergo further cell division into various permutations of phenotypically unique cancer stem cells, mutated differentiated cells, or fused cells. Both pathways account for cellular heterogeneity and aneuploidy noted in tumors.²

There is growing evidence of lung cancer stem cells. Normal stem cells and lung cancer cells share several proliferative cell signaling pathways (e.g., K-ras, hedgehog, phosphate and tensin homolog [PTEN], Akt, and phosphoinositide 3-kinase [PI3K]).²⁶ Furthermore, lung cancers often share cell-surface markers with lung stem cells, which may explain the distribution of lung cancer histologies along the tracheal-bronchiole-alveoli axis.²⁶ For instance, squamous cell carcinomas, which tend to occur in the central airways, and stem cells of the pseudostratified epithelium of the central airways both contain keratin-expressing basal cells.²⁷

There is also growing evidence of esophageal cancer stem cells. Several studies on murine models demonstrated evidence of phenotypic stem-cell surface markers (e.g., α -6 integrin,²⁸ p75^{ntr},²⁹ and CD44³⁰). Based on evidence found in murine models, pluripotent bone marrow progenitor cells contribute to Barrett esophagus.³¹ Given the relative low turnover of lung and esophageal epithelial tissue compared with hematopoietic cells and keratinocytes, stem cells research in lung and esophageal basic science research has been somewhat limited.

The cancer stem cell theory has important therapeutic implications. The success of existing systemic chemotherapy relies on a stochastic model in which all cells in a tumor have the same oncogenic potential.³² However,

if there is only a small subset of cells with proliferative potential (i.e., cancer stem cells), treatment failure is likely. In fact, non-small-cell lung cancer (NSCLC) patients with CD133⁺ lung cancer stem cells are less responsive to platinum treatment.³³ Potential mechanisms for resistance of cancer stem cells to chemoradiation therapy include their relative dormant nature compared with nontumorigenic cancer cells (which tend to replicate more rapidly), ability to survive in hypoxic microenvironments, upregulation of chemotherapy efflux mechanisms, and upregulation of DNA repair pathways.^{32,34}

EPIGENETICS

In basic genetics, the expression of a gene (the *phenotype*) is directly associated with the DNA sequence of the gene (the *genotype*). However, this seemingly simple association between phenotype and genotype is often more complex. There are other heritable changes in gene expression not accompanied by alterations in the DNA sequence. These processes, known as *epigenetics*, provide insight into the complex link between the genotype and expressed phenotype, which may differ from the phenotype anticipated by basic genetics. Epigenetic changes may explain why cells in the human body share the same genome yet have vast (yet stable) differences in gene expression.³⁵

The most studied area of epigenetics is DNA methylation. DNA methylation occurs in normal cells, predominantly on cytosines, which are adjacent to guanines and separated by only a phosphodiester bond. This dinucleotide sequence (*CpG*, shorthand for 5' cytosine-phosphate-guanine) is distinct from cytosine-guanine DNA base pairing.³⁶ High-density *CpG* regions (known as *CpG islands*) span the promoter region of many (approximately 40%) genes and are often constitutively unmethylated in normal tissues.^{36,37} When these islands are methylated by DNA methyltransferases, transcription is repressed.³⁸ During the process of tumorigenesis and the resultant accumulation of genetic defects, there is a progressive loss of total genomic methylation, an increased frequency of hypermethylation at *CpG* islands, and an increase in histone modification.³⁶

One of the epigenetic hallmarks of cancer cells is global genomic hypomethylation compared with the methylation content in normal cells.^{39,40} Hypomethylation occurs at highly repeated, interspersed DNA sequences (which results in transcriptional interference of neighboring genes and cancer-associated gene insertions)^{41,42}; centromeric satellite DNA^{43,44}; and single-copy transcriptional control sequences.^{45,46} The contribution of DNA hypomethylation to tumorigenesis is independent of effects of DNA hypermethylation at *CpG* islands. It is neither a prelude nor a consequence of DNA hypermethylation.⁴⁷

The mechanistic basis for the contribution of hypomethylation to tumorigenesis is poorly understood but may include genomic instability (thereby facilitating genetic recombination) and dysfunctional transcriptional control elements (thereby increasing oncogene expression).⁴⁷

DNA hypermethylation in tumorigenesis usually affects the *CpG* islands at the promoter regions of tumor suppressor genes (upwards of 80% of patients with lung cancer) and transcription factors, which can upregulate expression of oncogenes or downregulate expression of tumor suppressor genes.^{48,49} Although it is less well understood, hypermethylation may also affect non-*CpG* island promoters and gene target sites.⁵⁰ In general, promoters with hypermethylated *CpG* islands cannot initiate transcription unless it is overridden by alternative signals (e.g., demethylation or chromatin modulation).⁵⁰ Consequently, epigenetic silencing of tumor-suppressor genes leads to upregulation of cell survival and proliferation pathways. In contrast to genetic mutations, which often affect proliferation pathways at a single foci,⁵¹ multiple epigenetic events can affect a single signaling pathway and in turn affect other pathways, thereby promoting tumorigenesis in a more integrated manner.⁵⁰

Histones, the major protein component of chromatin, also undergo epigenetic modification, predominately through changes in lysine acetylation (via histone acetyltransferases and deacetylases), arginine and lysine methylation (via histone methyltransferases), and serine phosphorylation (via histone kinases).³⁶ Such covalent modifications can alter the physical properties of chromatin, thereby influencing its interactions with catalytic enzymes and hence its control of gene activity.^{35,52} There are also noncovalent modifications that contribute to chromatin variation, including chromatin-remodeling complexes, variations in histone proteins, and nucleosome (segments of DNA wound around histone proteins) remodeling.^{35,50,53} Epigenetic chromatin modifiers such as the polycomb complexes of proteins, which are important for long-term transcriptional repression, may link epigenetic gene silencing with cancer stem cells.^{50,54}

DNA hypomethylation, DNA hypermethylation, histone modification, and likely undiscovered epigenetic pathways are not mutually exclusive. There is significant functional crosstalk among these pathways, producing an intricate network of signals that influence gene expression.⁵⁵⁻⁵⁸ Epigenetic changes in cancer may serve as biomarkers and potential therapeutic targets.

PROTEOMICS

As a result of posttranslational modifications, genomic studies of DNA and RNA often poorly correlate with protein expression and hence the phenotype of the cell or tissue.⁵⁹ The *proteome* is the protein complement of the genome. Hence, *proteomics* is the study of the structure and function of proteins expressed by the genome of a biological system.⁶⁰ Because of posttranslational modifications and the resultant heterogeneous nature of proteins, human proteomics is more complex than human genomics.

Most proteomic approaches involve homogenization of a particular sample of interest followed by separation of the proteins in the sample of two-dimensional polyacrylamide gel electrophoresis (2D-PAGE).^{60,61} The samples are first separated by their isoelectric point and then by their molecular weight (hence, "2D" PAGE).

The proteins on these gels are displayed as spots, which can be identified by Western blot analysis and comparing the results with protein databases or by digesting the gel spots with trypsin and then performing mass spectrometry on the sample.⁵⁹ Alternative techniques to 2D-PAGE include high-performance liquid chromatography and gel-free isotope-labeling techniques to separate peptides from a sample.⁵⁹

Regardless of the separation technique, mass spectrometry is the primary technique used in proteomics to identify proteins and peptides in a sample. Protein identification is based on measurement of their molecular weight and charge (m/z ratio). To obtain these measurements, samples are ionized (i.e., by matrix-assisted laser desorption ionization or by electrospray ionization), travel through a mass analyzer that separates ions based on their m/z ratio (e.g., using time-of-flight, Fourier transformation, or ion traps), and then are processed by a mass detector.^{59,60,62,63} A second mass spectrometer can be added to this sequence (known as *tandem mass spectrometry*) to identify the amino acid sequence of a peptide. The resultant data are compared against protein databases to identify the protein in the sample.^{59,60} As an alternative to performing proteomic analysis in two steps, multidimensional protein identification technology uses high-performance liquid chromatography in-line with tandem mass spectrometry.⁶⁴

Understanding the proteome will provide tremendous insight into the downstream cellular response to perturbations in the genome of thoracic malignancies.

METABOLOMICS

Metabolomics is the quantitative description of all endogenous metabolites in a biological sample (e.g., tissue, blood, urine) simultaneously.^{65,66} It allows for a global assessment of changes in phenotype in the context of the immediate environment of the cell by reflecting changes in enzymatic gene regulation and altered kinetics of metabolic enzymes.⁶⁵ Metabolites include those involved in cellular respiration (e.g., metabolic intermediates of glycolysis, anaerobic metabolism, the citric acid cycle), amino acid metabolism (i.e., alterations in the levels of essential and nonessential fatty acids and their metabolites), fatty acid metabolism (i.e., the relative abundance of unsaturated and saturated fatty acids), and nucleotide metabolism.^{66,67} Most metabolomic platforms are based on spectroscopic techniques (e.g., nuclear magnetic resonance and mass spectroscopy).⁶⁶ Multivariate metabolomic analyses are performed in three major steps. First, pattern recognition (also known as *group clustering*) is used to decipher differences in spectral patterns between two groups (e.g., cancer and normal specimens). Next, the spectral region of interest identified in the first step of the analysis is linked to a specific metabolite based on its nuclear magnetic resonance chemical shift. The final step involves ascertaining associations between the metabolite of interest and a particular clinical outcome.⁶⁵ Although studies on cancer metabolomics are still in the preclinical exploratory phase, metabolomics have a potential role in cancer diagnosis and assessment of response to therapy by providing relatively inexpensive,

rapid, and automated methods to assay biomarkers in biological samples.⁶⁵⁻⁶⁷

CLINICAL APPLICATION OF NUCLEIC ACID AND PROTEIN BIOMARKERS

A *biomarker* is a surrogate indicator of a biological process that can be measured qualitatively or quantitatively. DNA biomarkers include mutations (in oncogenes, tumor-suppressor genes, and mismatch repair genes), single nucleotide polymorphisms, DNA copy number changes, chromosomal translocations, microsatellite instability, and epigenetic changes (e.g., differential promoter methylation). RNA biomarkers include messenger RNA (mRNA) and miRNA. Protein biomarkers include proteins that are expressed on cell surfaces or shed into serum. For patients with thoracic malignancies, nucleic acid and protein biomarkers may have diagnostic, prognostic, and predictive roles in patient care and may serve as therapeutic targets.

In general, detection of nucleic acid and protein biomarkers in tumor tissue primarily has prognostic, predictive, and therapeutic implications. In contrast, detection of these biomarkers in other tissues and body fluids primarily has diagnostic implications for cancer screening and for detection of occult malignancy.

Detection in Tumor Tissue

Lung Cancer

p53. p53 is a tumor-suppressor gene that plays a central role in cell-cycle regulation, apoptosis, and DNA repair. As such, inactivation of (or mutations in) p53 lead to derangements in cell-cycle progression, evasion of apoptosis, and genomic instability due to impaired DNA repair mechanisms. Given its vital role in controlling cellular proliferation, it is not surprising that p53 mutations are among the most common mutations in all human malignancies.⁶⁸ As much as 50% of NSCLCs and 90% of small-cell lung cancers contain p53 mutations or deletions.^{68,69} A systematic review of 56 studies found that p53 mutations in NSCLC are associated with worse overall survival for all stages and for both adenocarcinoma and squamous cell carcinoma histologies. In that study, there were insufficient data to determine the prognostic significance of p53 mutations in small-cell lung cancer.⁷⁰

ERCC1. Platinum-based chemotherapy is the gold standard for neoadjuvant and adjuvant chemotherapy for patients with resectable NSCLC and for treating patients with unresectable NSCLC.⁷¹⁻⁷³ The mechanism of action of platinum chemotherapeutic agents (i.e., cisplatin, carboplatin, and oxaliplatin) is formation of DNA adducts.^{74,75} These adducts disrupt DNA replication.

Excision repair cross-complementing group 1 (ERCC1) is part of a DNA repair pathway that recognizes and removes platinum-induced DNA adducts, therefore conferring resistance to platinum-based chemotherapy.⁶⁸ ERCC1 expression is common (present in

44% of tumors in one study⁷⁶) and is an important prognostic factor (independent of treatment). Low ERCC1 levels are associated with a worse prognosis and identify patients who may benefit from platinum-based chemotherapy.⁷⁷ In contrast, high ERCC1 levels are associated with a better prognosis and identify patients who are less likely to benefit from platinum-based chemotherapy.^{76,78} One possible explanation is that high levels of ERCC1 indicate intact DNA repair pathways and hence greater genomic stability.⁷⁸ In one study of 51 NSCLC patients who underwent resection for cure, high-level ERCC1 expression was associated with an absolute improvement in median overall survival of 60 months.⁷⁸

***k-ras*.** The *k-ras* gene encodes a G protein involved in signal transductions in cellular growth, differentiation, and apoptosis. Among patients with NSCLC, mutations in *k-ras* are more common in white smokers (26%), as compared with nonsmokers (6%). It is also more common in adenocarcinoma (30%), as compared with squamous cell carcinoma (5%).⁷⁹⁻⁸² It is important to note that *k-ras* mutations are mutually exclusive of *EGFR* mutations. Consequently, patients with *k-ras* mutations may be intrinsically resistant to *EGFR*-targeted therapies.⁸³

The gold standard for detecting *k-ras* mutations is DNA sequencing.⁸⁴ Currently, there is no effective therapy specifically targeting *k-ras* mutations; promising small-molecule inhibitors are under preclinical investigation.

Epidermal Growth Factor Receptor. Epidermal growth factor receptor is a member of the human *EGFR* (HER) family of transmembrane tyrosine kinase receptors that promotes cellular proliferation, impairs apoptosis, and increases angiogenesis.^{68,84} *EGFR* overexpression and mutations are rare in small-cell lung cancer.⁶⁸ In contrast, *EGFR* overexpression is seen in as much as 80% of NSCLCs.⁸⁵ *EGFR* mutations occur in as much as 22% of NSCLCs and are most common among women, patients of East Asian descent, nonsmokers, and patients with adenocarcinomas.^{84,85} It has important therapeutic implications because select NSCLC patients with *EGFR* mutations have a survival benefit when treated with *EGFR* tyrosine kinase inhibitors.

EML4-ALK. Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase. As such, it plays a role in cellular signal transduction.^{86,87} In approximately 3% to 13% of NSCLC patients, the 5' end of echinoderm microtubule-associated protein-like 4 (EML4) gene binds with the 3' end of the ALK gene, resulting in a fusion oncogene (EML4-ALK) that tends to occur in younger patients, women, light or never-smokers, and adenocarcinomas (specifically those with acinar histologies).⁸⁸ EML4-ALK results in constitutive activity of ALK that results in downstream activation of several signaling pathways important in cellular proliferation (e.g., Ras, JAK3-STAT3, PI3K), inhibition of apoptosis, and cell migration.⁸⁶ The EML4-ALK oncogene has therapeutic implications; crizotinib is a TKI that targets it. It is important to note that EML4-ALK mutations are mutually exclusive with *k-ras* and *EGFR* mutations.

Vascular Endothelial Growth Factor. Vascular endothelial growth factor (VEGF) binds to a group of receptor tyrosine kinases (VEGF receptors) that stimulate angiogenesis. VEGF expression in NSCLC is associated with a worse overall survival rate.⁸⁹ In one study of resectable NSCLC, VEGF expression was associated with a sevenfold increased risk of all-cause mortality.⁹⁰ VEGF also has therapeutic implications; bevacizumab is a monoclonal antibody against VEGF that is effective in select patients with NSCLC.

Tumor Panels. Lung cancer, like all thoracic malignancies, cannot be fully characterized by a single biomarker. Each tumor has its own unique "molecular fingerprint." As such, tumor marker panels may be more useful rather than detection of a single tumor biomarker. D'Amico and colleagues examined the tumors of 408 stage I NSCLC patients. They identified five biomarkers by immunohistochemistry (IHC) that were associated with the risk of recurrence and death. Each marker was associated with a different oncogenic pathway: apoptosis (p53), angiogenesis (factor VIII), growth regulation (erb-b2), cell adhesion (CD-44), and cell cycle regulation (Rb).⁹¹ Using this model, patients were substratified by survival rates: zero to one marker (5-year survival, 77%), two markers (5-year survival, 62%), and three to five markers (5-year survival, 62%).

Microarray Analysis. Oncogenesis and metastasis are largely controlled at the level of transcription. Consequently, significant insight can be gained by globally assessing gene expression. The workhorse for such analyses is DNA microarray. A DNA microarray comprises multiple, gene-specific polynucleotides (probes) arranged along exact coordinates of a two-dimensional grid (array).⁹² Total RNA from experimental and reference specimens is reverse-transcribed to fluorescence-labeled complementary DNA (cDNA) before incubation with the microarray. This process allows for simultaneous quantification of the relative (experimental vs. reference) amount of mRNA transcripts. The number of immobilized microarray probes, which may number in the hundreds of thousands, is reflective of the relative degree of gene expression. This method depends on the highly sensitive and specific hybridization between complementary strands of nucleic acids.

Data analysis revolves around four common themes: detection of differential gene expression, pattern discovery, prediction of specimen characteristics, and inference of molecular pathways and networks. Microarray studies generate a vast amount of data, which is one of the major challenges of this technology.

A number of microarray studies have used differential gene expression to predict survival and identify potential novel therapeutic targets.⁹³⁻⁹⁵ Beer and colleagues examined 86 early-stage adenocarcinomas and constructed a 50-gene risk index based on hierarchical clustering.⁹⁵ Members of this 50-gene set included genes that had not been previously associated with survival, suggesting potential novel therapeutic targets. Using this gene set, the investigators were able to predict survival.

Other microarray studies have used pattern discovery to segregate NSCLC histologies based on gene

expression profiles. Bhattacharjee and colleagues⁹⁶ studied 186 NSCLC tumors. They used a specialized clustering technique for pattern discovery to identify four distinct adenocarcinoma subgroups based on gene expression profiles.

To date, there have been numerous studies that have expanded on the potential prognostic significance of miRNAs in NSCLC tissue. Raponi and colleagues⁹⁷ reported the robust predictive ability of miRNA-146b in the overall survival in squamous cell carcinoma. Landi and colleagues⁹⁸ identified another miRNA expression profile that strongly differentiated 165 adenocarcinomas from 125 squamous cell carcinomas based on decreased expression of miRNAs let-7e and miR-34a, -34c-5p, -25, and -191. This panel was associated with worse survival among male smokers with stages I to IIIA squamous cell carcinoma.⁹⁸

In addition to the prognostic significance of miRNA in tumor tissue, miRNAs from the adjacent nontumor microenvironment have been investigated with interesting results. Boeri and colleagues⁹⁹ have explored miRNA expression profiles of lung tumors and normal lung tissues and noted that miRNA expression patterns significantly distinguished tumors from normal lung tissues, tumor histology and growth rate, and clinical outcome. These findings strengthen the growing evidence that the normal lung microenvironment potentially influences tumor growth and proliferation.

Finally, microarray studies have also shown promise as a potential indicator of risk of lymph node metastasis and responsiveness to chemotherapy. Kikuchi and colleagues microdissected individual cancer cells from 37 NSCLC tumors before performing microarray analysis to identify novel genes involved in oncogenesis, using a clustering algorithm to distinguish adenocarcinomas from squamous cell carcinomas. A separate analysis of the 18 adenocarcinomas identified 40 genes whose expression profiles could reliably distinguish tumors with lymph node metastasis from those tumors without metastasis. Finally, they were able to predict chemosensitivity based on expression profiles.¹⁰⁰ This study highlights the potential utility of gene-expression profiles of NSCLC patients to guide personalized cancer therapy.

Proteomic Analysis. Proteomic analysis of lung cancer specimens has demonstrated the utility of protein signatures in the diagnosis and histologic classification of lung cancer.¹⁰¹⁻¹⁰³ Protein signatures also have potential prognostic significance. Yanagisawa and colleagues¹⁰⁴ examined the protein signatures in stage I NSCLC patients and internally validated a 25-protein signature panel. A high-risk signature was identified that was significantly predictive of overall and relapse-free survival. These studies highlight the potential role of proteomics in counseling patients and identifying those patients at high risk for recurrence, which could be used to guide therapy.

Esophageal Cancer

Her2. Her2/neu (also known as ErbB2) is a receptor tyrosine kinase that inhibits apoptosis and promotes cellular proliferation through PI3K pathways.¹⁰⁵ In

adenocarcinomas, Her2/neu is overexpressed in 10% to 80% of tumor specimens, and gene amplification is found in 15% to 100%.^{105,106} Her2/neu overexpression is associated with depth of invasion, lymph node metastases, distant metastases, and poor prognosis.^{105,107,108} As compared with adenocarcinomas, Her2/neu overexpression (0%-56% of tumors) and gene amplification (0%-25% of tumors) is lower in squamous cell carcinomas.^{105,109} Although Her2/neu overexpression may also be associated with stage and prognosis in squamous cell carcinomas, its independent prognostic value is controversial.¹⁰⁵ Her2/neu expression has important therapeutic implications because of the availability of a humanized monoclonal antibody (trastuzumab).

VEGF. As with lung cancer patients, VEGF expression has significant prognostic and therapeutic implications for esophageal cancer patients. Based on a recent meta-analysis, high VEGF expression in esophageal cancer is associated with a nearly twofold increase in the risk of death.¹¹⁰ Bevacizumab is a monoclonal antibody that binds to VEGF, thereby impairing its ability to activate the VEGF receptor.

Microarray Analysis. Microarray studies on esophageal tumors have also provided insight into its potential role in treating patients with esophageal cancer. Microarrays are able to distinguish between tissues at various stages of disease progression. Zhou and colleagues were able to identify differential expression of genes in normal esophageal mucosa, basal cell hyperplasia, high-grade dysplasia, carcinoma in situ, and overt cancer.¹¹¹ Microarray studies have also led to the discovery of gene expression profiles that can also distinguish between Barrett esophagus and adenocarcinoma^{112,113} and between adenocarcinoma and squamous cell carcinoma.¹¹¹ In addition, these analyses demonstrated the prognostic importance of gene expression profiles in esophageal cancer patients who have undergone surgical resection. In one such study of 64 esophagectomy patients, Luketich and colleagues demonstrated the ability to prospectively place patients in high-risk and low-risk groups according to their tumor's genetic signature. In their multivariate analysis, only the gene signature was independently associated with survival.¹¹⁴

Microarray analyses have also led to the identification of novel oncogenic genes that improves our understanding of oncogenesis and treatment of esophageal cancer. Zhou and colleagues¹¹¹ identified a gene (*PI60ROCK*, a rho-associated serine/threonine kinase isoenzyme that regulates cell motility and morphologic changes) that plays an important role in carcinogenesis. This gene was dramatically upregulated in tissues with high-grade dysplasia compared with normal tissues. As such, its activation is likely one of the early events in esophageal carcinogenesis and may be a potential therapeutic target.

Finally, microarray analysis can be used to predict response to therapy. In a study of 20 resected esophageal tumors in patients who underwent adjuvant therapy, Kihara and colleagues¹¹⁵ identified a 52-gene profile that accurately predicted prognosis and chemosensitivity and chemoresistance to various agents. Prospective studies

validating these gene sets and predictive models have not been performed.

Mesothelioma

Microarray Analyses. Because malignant pleural mesothelioma (MPM) is a relatively rare tumor, few studies have evaluated the use of microarrays in patients with mesothelioma. Similar to microarray analyses of other malignancies, studies on MPM have unfolded mechanisms of oncogenesis and tumor dissemination. Hoang and colleagues noted overexpression of matriptase (a membrane protease involved in the activation of other proteases, tumor invasion, and metastases).¹¹⁶

Similar to other malignancies, microarrays provide prognostic information for MPM patients. Researchers at Brigham and Women's Hospital examined specimens from 17 MPM patients with different overall survival times to identify a four-gene expression ratio test that reliably predicted treatment-related outcomes, independent of histologic subtype.¹¹⁷

Detection in Lymph Node Tissue

Lung Cancer

Regional lymph node metastasis assessed by routine histologic analysis is associated with a marked decreased survival rate compared with node-negative disease.¹¹⁸ However, even with completely resected node-negative T1 or T2 tumors, 5-year cancer-specific survival rates are only 60% to 90%, possibly owing to undetected occult micrometastases.^{119,120} Two techniques are primarily used to detect occult micrometastases: IHC and reverse-transcriptase polymerase chain reaction (RT-PCR). Both techniques rely on the identification of an appropriate tumor marker.

Cancer and Leukemia Group B (CALGB) 9761 was a prospective, multi-institutional study that assessed the prognostic implications of occult mediastinal lymph node metastasis in patients who underwent curative resections of early stage (T1-2N0M0) NSCLC. As part of the study, IHC against cytokeratin (AE1/3, an epithelial tumor marker) was assessed in mediastinal lymph nodes.¹²¹ In the first 193 patients in the study, cytokeratin IHC upstaged 11% of patients to N2 disease.¹²¹ Use of IHC to detect occult micrometastases has two main drawbacks: (1) the need for visual detection (and hence the risk of human error), and (2) the inability to test the entire nodal specimen. RT-PCR overcomes these shortcomings.

Based on a number of RT-PCR-based studies, carcinoembryonic antigen (CEA, an embryonic epithelial surface glycoprotein) is another potentially suitable NSCLC tumor marker.¹²²⁻¹²⁴ Collectively, those studies demonstrated that CEA has a relatively high sensitivity (it can detect 1 malignant cell in as many as 10⁶ normal cells) and high specificity (because it is detected in almost all epithelial cells but not in nonepithelial cells). Consequently, detection of CEA (an epithelial protein) in mediastinal lymph nodes (which derive from embryonic mesenchymal tissue) is a sensitive and specific marker of occult metastases. CALGB 9761 used standard RT-PCR

for CEA; 43% of patients were upstaged based on RT-PCR analysis of mediastinal lymph nodes.¹²⁵

A potential shortcoming of occult micrometastasis detection by IHC and standard RT-PCR is the binary (yes/no) result regarding the presence or absence of occult metastases. In fact, the amount of micrometastatic burden may be important. Quantitative real-time RT-PCR (QRT-PCR) is a possible solution to this problem.

QRT-PCR uses a target molecule-specific oligonucleotide probe (e.g., CEA mRNA) with a covalently attached fluorescent reporter and quencher dye. If the target module of interest is present, the oligonucleotide probe will anneal to it. During the PCR extension phase, the fluorescent probe is cleaved by the exonuclease activity of Taq DNA polymerase, thus increasing the reporter dye's emission. Curves plotting the relative fluorescence change against the PCR cycle number are constructed, and the point of increase in fluorescence above the background (the threshold cycle [C_T]) is calculated. Because C_T values decrease linearly with increasing target molecule quantity, they provide a quantitative measurement.

QRT-PCR for CEA from samples from 53 patients enrolled in CALGB 9761 demonstrated the feasibility of QRT-PCR to detect occult micrometastases. This resulted in an estimated median of 7190 tumor cells per lymph node harboring occult micrometastases.¹²⁵ Several retrospective studies confirmed these findings and suggested a prognostic relationship between occult metastases detected by QRT-PCR for CEA.^{126,127} The prognostic importance of occult metastases in NSCLC patients awaits the final analysis of CALGB 9761, which is currently being finalized.

In addition to CEA, there are many other tumor markers (e.g., cytokeratin 7, cytokeratin 19, apomucin 1, KS1/4, LUNX, and PDEF).¹²⁸⁻¹³¹ KS1/4 is especially intriguing because it has very high specificity for lung cancer, and it is recognized by the monoclonal antibody Ber-EP4.¹³¹ Furthermore, there are monoclonal antibodies to Ber-EP4 (e.g., edrecolomab), which may be a therapeutic target. Its utility in treating lung cancer is yet to be determined.

Esophageal Cancer

Lymph node involvement is a strong predictor of recurrence and poor survival rates in esophageal cancer patients.¹¹⁸ Similar to studies evaluating the prognostic importance of IHC-detected NSCLC micrometastases, studies on esophageal cancer have produced mixed results, underscoring one of the potential pitfalls of IHC: sampling error because only a limited number of lymph node sections are examined.¹³²⁻¹³⁶

Luketich and colleagues used QRT-PCR to detect occult micrometastases in 387 lymph nodes from 30 histologically node-negative esophageal adenocarcinoma cancer patients.¹³⁷ Based on CEA expression, 11 patients were found to have occult metastases. Of those 11 patients, 9 developed recurrent disease. Kaplan-Meier analysis demonstrated that QRT-PCR-positive lymph nodes correlated with significantly lower disease-free and

overall survival rates.¹³⁷ These studies highlight the potential role of using QRT-PCR to identify patients with a high risk of recurrence to guide use of adjuvant chemotherapy.

Detection in Blood

Use of genetic science to detect circulating tumor cells (CTCs) in peripheral blood has a potential role in cancer screening, risk stratification, assessing response to therapy, and individualizing treatment. Because peripheral blood acquisition is safe and easily accessible, this approach is appealing. However, there are several challenges. First, a sensitive and specific marker needs to be identified. Second, one CTC must be detected among 10⁶ background circulating tumor cells. Consequently, most approaches use an enrichment step from peripheral blood followed by RT-PCR. Nonetheless, there can be significant signal-to-noise ratio, making it difficult to differentiate meaningful information from background gene expression.

Lung Cancer

Nucleic Acids. Although CTCs are detectable in patients with early-stage NSCLC, detection is more frequent in patients with advanced disease.¹³⁸ Several investigators have used RT-PCR to detect circulating tumor cells in patients with NSCLC. Such assays focused on a limited number of mRNA tumor markers, such as EGFR¹³⁹ and CEA.¹²⁴ These studies highlighted several important findings: (1) There is a clear correlation between a positive preoperative blood test and a postoperative pathological stage; (2) A significant number of patients with “early” stage NSCLC (based on radiographic studies and routine histologic analysis of tumor and lymph nodes) developed recurrent disease after surgery; and (3) There was a correlation between persistently positive postoperative blood samples and stage, suggesting occult systemic disease.

Several investigators have attempted to evaluate circulating miRNAs as a biomarker for cancer detection. In 2008, Mitchell and colleagues were the first to demonstrate that clinical samples of plasma and serum had measurable amounts of miRNAs and existed in a stable form through repeated freeze-thaw cycles.¹⁴⁰ Further investigation has validated that circulating miRNAs hold promise as diagnostic and prognostic biomarkers; many studies have demonstrated an association between circulating miRNAs and stage and survival. Not surprisingly, most of the studies on individual miRNA expression and miRNA panels have had inconsistent results, likely because of selection bias and lack of data normalization methods. The lack of a reliable housekeeping miRNA in serum to compare against is one such issue that complicates the significance of these studies.¹⁴¹

Because no single tumor marker will provide adequate sensitivity, tumor marker combinations may be preferable.¹⁴² Although these studies are promising, there are no prospective studies that have validated the prognostic implication of using nucleic acid tumor markers to detect CTCs.

Proteins. For several years, there has been interest in identifying peptide, protein, and autoantibody tumor biomarkers.¹⁴³⁻¹⁴⁶ Efforts to detect serum autoantibodies appear to be most promising. Abnormally expressed or structurally altered proteins may elicit the production of autoantibodies. A number of studies have demonstrated the feasibility of detecting such antibodies¹⁴⁷⁻¹⁴⁹ and serve as the basis for the development of biochips that provide molecular profiles of the antibody response to tumor antigens.¹⁵⁰

Esophageal Cancer

The presence of CTCs has important prognostic implications. For patients with metastatic esophageal cancer, two or more CTCs (per 7.5 mL of peripheral blood) is associated with lower progression-free¹⁵¹ and overall survival rates.^{151,152} The presence of CTCs also has important therapeutic implications, because it is associated with lower response rates to chemotherapy¹⁵¹ and lower response to radiotherapy.¹⁵³

Detection in Bone Marrow

Lung Cancer

Using IHC, several groups have demonstrated a 22% to 59% incidence of bone marrow micrometastases in NSCLC patients, which have potential prognostic implications.¹⁵⁴⁻¹⁵⁸

Detection in Sputum

Lung Cancer

Sputum analysis for the early detection of lung cancer has been studied for decades. In the 1980s, several lung cancer screening trials examined the role of sputum cytology and chest radiographs in the early diagnosis of lung cancer, which demonstrated that standard sputum cytology has a relatively low sensitivity for detecting lung cancers.¹⁵⁹⁻¹⁶¹ Still, sputum specimens are readily accessible from patients, making sputum cytology an appealing method for lung cancer screening and surveillance. Consequently, there has been growing interest since those initial screening trials in using molecular techniques to augment the sensitivity of sputum analysis.

There is a relatively low amount of tumor DNA (about 1%) in a background of normal DNA.¹⁶² As such, crude DNA and RNA (analyzed through gene sequencing or mutation-specific oligonucleotide hybridization) has no utility in lung cancer screening.¹⁶² However, PCR mutation analysis of p53,¹⁶³ *k-ras*,¹⁶⁴ EGFR,¹⁶⁵ EML4-ALK,¹⁶⁶ and other markers may be helpful. Other potential biomarkers include heterogeneous nuclear riboprotein A2/B1,¹⁶⁷ hypermethylated promoters,¹⁶⁸ and microRNA.¹⁶⁹ Given the heterogeneous nature of lung cancer and the absence of a tumor marker with 100% sensitivity, tumor marker panels are likely needed for lung cancer screening. Such panels may be especially useful as an adjunct to low-dose computed tomography screening programs.

NEXT-GENERATION DNA SEQUENCING IN CLINICAL CARE

For nearly 30 years, the most common method of DNA sequencing was the capillary electrophoresis–based Sanger (chain termination) method.¹⁷⁰ This method involves the denaturation of DNA into two strands. DNA replication is then performed in vitro with polymerase and nucleotides that have been chemically altered. Once the altered nucleotides are incorporated into the DNA sequence that is being replicated, DNA replication is terminated. This process is performed for each of the four nucleotides, thereby generating strands of DNA of various lengths, which are overlaid with one another to decipher the code. Recently, the Sanger technique has been largely supplanted by next-generation (also known as second-generation) sequencing.

Similar to Sanger-based methods, next-generation sequencing methods entail the sequential detection of nucleotides from signals emitted from fragments of DNA as they are being replicated from a template DNA strand. In contrast to Sanger methods, however, this process occurs in a digital, massively parallel fashion, enabling higher throughput DNA sequencing at a fraction of the cost per base. Currently available next-generation platforms include Illumina, Helicos, 454 Pyrosequencing, SOLiD, and Ion Torrent. Next-generation sequencing includes a number of whole-exome (sequences of exons, the DNA sequences that encode proteins), whole-transcriptome (the sequence of expressed genes), whole-genome, epigenome, and location-based approaches (which map the location of nucleic acid–nucleic acid and nucleic acid–protein interactions).^{171–173} It has allowed cancer genetics to move from focused approaches (e.g., single-gene sequencing) to more comprehensive approaches.¹⁷² The “depth” of a sequencing process refers to the number of times a single nucleotide is read, hence the terms *deep* and *ultra-deep sequencing*. Next-generation methods allow a much greater depth (also known as *coverage*) of sequencing, thereby allowing sequencing to be performed with greater sensitivity and to provide a more unbiased assessment of the heterogeneity of specimens. As described earlier in this chapter, tumors are a heterogeneous group of cells.

Next-generation techniques have a number of potential roles in oncology, including cancer gene discovery, chromosomal rearrangement discovery, characterization of clonal and subclonal cell populations in tumors, and integrated biomarker analysis to longitudinally track adoptive changes in signaling pathways during the course of treatment.^{174–176} For instance, next-generation sequencing could be used to track circulating tumor markers during the course of treatment and screen for adoptive changes by the tumor, thereby facilitating appropriate treatment changes to be made during the course of therapy. As such, next-generation sequencing has tremendous potential in personalized oncology as it becomes more widely available. The human genome project took more than 12 years to complete and cost \$2.7 billion. With next-generation sequencing, the entire genome of an individual can be sequenced in less than a week for

\$5000 to \$10,000. As the cost of these techniques continue to decline, next-generation sequencing will likely emerge into the clinical care of cancer patients.¹⁷¹

PERSONALIZED ONCOLOGY

Even histologically similar tumors are heterogeneous diseases—no two tumors and their biological milieu are the same. As such, a “one-size-fits-all” approach to oncology is fraught with frequent treatment failures. As our understanding of the molecular biology of thoracic malignancies continues to evolve and becomes increasingly more sophisticated, personalized oncology is becoming a reality. Many techniques (e.g., assessment of differential gene expression profiles, protein expression profiles, and detection of occult metastasis) are promising but are largely unproven and have not been introduced into mainstream clinical care. Other techniques (e.g., detection of gene overexpression and gene mutations) are being actively used in practice and have led to rational use of targeted therapies (Table 45-1). The use of molecular diagnostics to risk-stratify patients (and hence guide therapy), as well as the use of targeted therapies, has developed furthest in the treatment of NSCLC.

Customized Chemotherapy

For instance, ERCC1 overexpression is associated with poor response to platinum-based chemotherapy. Furthermore, ERCC1-negative tumors are associated with lower survival rates.⁷⁶ As such, adjuvant cisplatin-based chemotherapy may benefit patients with ERCC1-negative tumors.⁶⁸ Currently, there are several clinical trials exploring the use of personalized chemotherapy based on ERCC1 status, including adjuvant therapy for resected stage I NSCLC (NCT00792701), adjuvant therapy for resected stage II to III (non-N2) NSCLC (NCT00775385), and therapy for advanced (stage IIIB [malignant effusion] and IV) NSCLC (NCT00499109).

In a recent landmark trial, the BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial enrolled 255 patients with chemorefractory stage IV NSCLC and used molecular biomarkers analyzed in real-time core biopsies to adaptively randomize patients to one of four treatment arms (erlotinib, vandetanib, erlotinib plus bexarotene, or sorafenib) based on their molecular profile.¹⁷⁷ At eight weeks, there was a 46% control rate, establishing a potential new paradigm in NSCLC treatment.

Targeted Therapies

Targeted therapies are largely limited to patients with advanced (stage IIIB and IV) disease. In particular, all patients with advanced disease should be tested for EGFR and ALK mutations. For patients with nonsquamous stage IIIB and IV NSCLC and EGFR mutations, use of tyrosine kinase inhibitors (i.e., erlotinib, gefitinib, and afatinib) has a significantly improved overall survival (median, 6.7 months vs. 4.7 months; $P < 0.001$),¹⁷⁸ progression-free survival (median, 10.8 months vs. 5.4

TABLE 45-1 Selected Non–Small-Cell Lung Cancer Oncogenes and Targeted Therapy

Oncogene Alteration	Incidence (%)	Clinical Relevance	Treatment
<i>BRAF</i> Mutation	1-5	V600E mutation: most common, equal association with smokers and nonsmokers May be mechanism of acquired EGFR TKI resistance	V600E mutation: dabrafenib vemurafenib
<i>EGFR (ErbB1, HER1)</i> Mutation	13-50	Exon 19 deletion and Exon 21 point mutation are the most common Predominately adenocarcinoma and nonsmokers Up to 50% frequency in Asian	TKI: gefitinib, erlotinib Monoclonal antibodies: cetuximab
<i>EML4-ALK</i> Fusion	3-13	Most frequent in adenocarcinomas, nonsmokers, men, and younger patients	Nonspecific TKI: crizotinib Monoclonal antibodies: trastuzumab
<i>Her2/neu (ErbB2)</i> Mutation	2-6	Mostly adenocarcinomas and nonsmokers	
Amplification	23	Mechanism of resistance to EGFR TKI	
<i>KRAS</i> Mutation	5-30	Mostly adenocarcinomas and smokers May contribute to resistance to ALF, BRAF, and PI3K inhibitors	No approved therapy Small-molecule inhibitors in preclinical trials Nonspecific TKI: crizotinib
<i>MET</i> Mutation	<5		
Amplification	21	Mechanism of resistance to EGFR TKI	
<i>PIK3CA</i> Mutation	<10	Frequently occurs in association with other mutations; more common in squamous cell	Nonspecific TKI: crizotinib
Amplification	5-43	Mechanism of resistance to EGFR TKI	
<i>PTEN</i> Mutation	1.7-10	Associated with PI3K activation, resistance to EGFR TKI, and sensitivity to PI3K inhibitors	Nonspecific TKI: crizotinib
Loss of function	4-21	More frequent in squamous cell Associated with PI3K activation, resistance to EGFR TKI, and sensitivity to PI3K inhibitors	
<i>RET</i> fusion gene	1-2	More frequent in squamous cell Mostly adenocarcinomas and nonsmokers	RET inhibitors: cabozantinib
<i>ROS1</i> fusion gene	2	Mostly adenocarcinomas, nonsmokers, and younger patients	ALK inhibitor: crizotinib
<i>VEGF</i>			Monoclonal antibodies: bevacizumab VEGFR TKI

BRAF, v-raf murine sarcoma viral oncogene homolog B1; *EGFR*, epidermal growth factor receptor; *EML4-ALK*, echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase; *ERBB*, avian erythroblastosis oncogene B; *Her2*, human epidermal growth factor receptor 2; *KRAS*, Kirsten Rat sarcoma viral oncogene homolog; *MET*, mesenchymal-epithelial transition; *PIK3CA*, phosphoinositide-3-kinase catalytic alpha polypeptide; *PTEH*, phosphatase and tensin homolog; *RET*, rearranged during transfection; *ROS1*, reactive oxygen species 1; *TKI*, tyrosine kinase inhibitor; *VEGF*, vascular endothelial growth factor; *VEGFR*, vascular endothelial growth factor receptor.

Data from references 79-82, 84, 85, 88, and 186.

months; $P < 0.001$),¹⁷⁹ and objective response rates (73.7% vs. 30.7%; $P < 0.001$)¹⁷⁹ compared with placebo. Unfortunately, long-term results with TKIs are disappointing. Most tumors develop resistance to TKIs¹⁸⁰ because of crosstalk between signaling pathways and rewiring of feedback loops.¹⁷⁵ This highlights the need to target cancer cells at multiple cellular growth and proliferation pathways.

Cetuximab is a monoclonal antibody that targets the extracellular domain of EGFR and is an alternative to oral TKIs. However, for patients with advanced NSCLC, the addition of cetuximab offers only a slight increase in overall survival (11.3 months vs. 10.1 months; $P = 0.044$),

is harder to administer, and is associated with high rates of toxicities.¹⁸¹

For patients with EML4-ALK mutations, there is no benefit to treatment with TKIs because ALK mutations are mutually exclusive with EGFR mutations.¹⁸² However, for patients with EML4-ALK, crizotinib (an ALK inhibitor) has a potential benefit. Based on preliminary data of a phase 1 trial, the overall response rate was 57%, and 33% had stable disease at a median follow-up of 6.4 months.¹⁸³ A phase 3 trial is underway.

Other potential therapeutic targets have been identified. Targetable oncogenes in adenocarcinomas include tyrosine kinase inhibitors toward BRAF mutations,

HER2 insertions, MET mutations, PIK3CA mutations, RET rearrangements, and ROS1 rearrangements.¹⁸⁴ Targetable oncogenes in squamous cell carcinomas include tyrosine kinase inhibitors toward DDR2 mutations, FGFR1 amplification, and PIK3CA mutations.¹⁸⁴ Telomerase inhibitors may also have a role in treating NSCLC, including treating cancer stem cells.¹⁸⁵

In contrast to gene mutations, DNA methylation and histone deacetylation are reversible processes. Consequently, DNA demethylating drugs and histone deacetylase inhibitors have a theoretical benefit of altering the epigenetic changes involved in oncogenesis and, as a result, target multiple pathways simultaneously.³⁶ Unfortunately, these epigenetic agents have no proven benefit in solid tumors and could have a paradoxical result of promoting tumor growth through nonspecific effects on gene expression.³⁶

SUMMARY

Over the last 50 years, there have been significant advances in systemic chemotherapy, radiation therapy, perioperative patient care, and surgical techniques, including the emergence and development of minimally invasive techniques. During this same time period, there has also been a revolution in our understanding of biology, including the characterization of the structure of DNA, the discovery of oncogenes, and the development of targeted therapy against those oncogenes. As our understanding of the complex interwoven pathways of oncogenesis continues to evolve, our ability to make a significant impact on tumor biology through personalized oncology will lead to improvements in our patients' outcomes. The challenges that lie ahead are both stimulating and remarkable because the closer we think we are to understanding thoracic malignancies, the more we realize that "Biology is King."

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INNOVATIVE THERAPY AND TECHNOLOGY

Valentino J. Bianco • Arjun Pennathur • James D. Luketich

CHAPTER OUTLINE

RADIOFREQUENCY ABLATION

Patient Selection
Operative Technique
Treatment Response
Clinical Results

STEREOTACTIC RADIOSURGERY

Techniques
Patient Selection
Results
Summary

MICROWAVE ABLATION

CRYOABLATION

CHEMOPERFUSION OF THE PLEURAL CAVITY

MODALITIES CURRENTLY UNDER INVESTIGATION

IMPLICATIONS FOR THORACIC SURGICAL ONCOLOGISTS

SUMMARY

Lung cancer remains the number one cause of cancer-related deaths in men and women, and the incidence continues to rise with approximately 175,000 new cases diagnosed annually in the United States.¹ In this chapter, we review several innovative therapies for patients who are at high risk for primary and metastatic lung tumors. Application of these new therapies continues to evolve, and in most cases, surgical resection remains the mainstay of therapy. Lobectomy has been considered the standard treatment modality for early-stage non-small cell lung cancer (NSCLC) for years, with sublobar resection being suboptimal because of an increased potential for recurrent disease.² More recent data on small tumors (less than 2 cm) with good margins (with margin distance at least the diameter of the tumor) show the local recurrence rate has lowered to near that of lobectomy.³ However, most patients with NSCLC present with advanced disease, and a significant number of patients with early-stage disease are unable to undergo pulmonary resection because of compromised cardiopulmonary function or other reasons.⁴ The new alternatives to traditional surgical treatment allow additional options when surgery is not clearly of benefit or when the patient is not a candidate for traditional resection. As with other recent advances, such as video-assisted thoracoscopic surgery (VATS), these newer, less invasive approaches may allow surgeons to treat patients with thoracic malignancies even in the setting of marginal pulmonary reserve.⁵

The two principal ablative modalities discussed in this chapter for inoperable or high-risk patients are radiofrequency ablation and stereotactic radiosurgery. Another

ablative modality, microwave ablation, is also being evaluated, although current clinical experience with this novel approach is limited. We also briefly discuss some newer technologies for ablation, including irreversible electroporation. The main goal of these less invasive therapies is to locally destroy the pulmonary or thoracic neoplasm while preserving the surrounding normal tissues. In addition, we discuss intrathoracic chemoperfusion for pleural malignancies.

It is important that thoracic surgical oncologists stay abreast of new therapies, design clinical trials, and critically evaluate and report the results. The introduction of new technology should not change the paradigm of who treats thoracic malignancies. Failure of surgeons to adapt to new technology will lead to fragmentation in the care of the patient with a thoracic malignancy. However, for the time being, the current evaluable data support the concept that most localized thoracic malignancies should ideally still be treated by minimally invasive surgical resection. Thus, failure to involve an experienced thoracic surgical oncologist in the design of clinical trials will increase the risk of compromising patient care.

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) is a thermal ablative modality, which uses high-frequency alternating current to generate heat and coagulate tissue. RFA systems typically have three components: (1) a generator, (2) an active electrode that is placed within the tumor, and (3) a

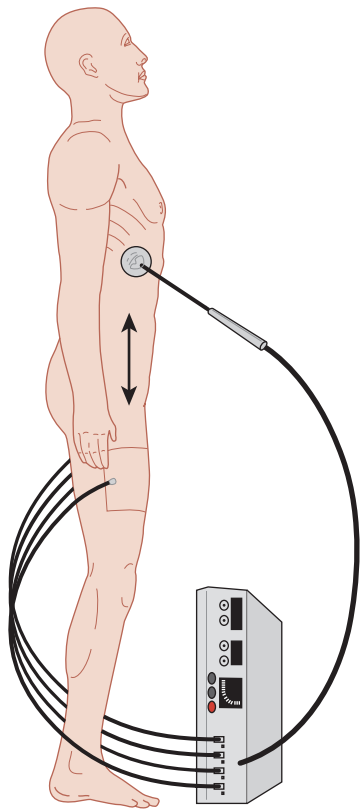


FIGURE 46-1 ■ The radiofrequency ablation system.

dispersive electrode (Bovie pad) placed on the thighs of the patient (Fig. 46-1). As the radiofrequency energy moves from the active electrode to the dispersive electrode and back, ions within the tissue oscillate with the changing direction of the current, resulting in frictional heating of the tissue. As the temperature within the tissue rises to greater than 60° C, cell death occurs as a result of protein denaturation and coagulation necrosis. Moreover, the dispersion of energy beyond the vicinity of the active electrode is minimal, allowing for focused delivery of energy to the target lesion with minimal injury to the surrounding normal tissue. The advantages of this minimally invasive ablative approach include lower morbidity and mortality in comparison with the more invasive approaches, lower costs per treatment, lower costs to set up a program and the associated technology, reduced hospital stay, and the ability to complete treatment without multiple sessions.^{6,7} The goal of RFA in the treatment of lung tumors is complete coagulation necrosis of the lesion with a small margin of extension into adjacent normal pulmonary parenchyma.

Initial experience with RFA has been primarily in the treatment of liver tumors, both as an adjunct to resection and as primary therapy. Due to low complication rates, RFA may supplant other thermal ablative modalities (e.g., cryotherapy).^{8,9} Pulmonary RFA also has a low rate of major complications, which include sepsis, respiratory infection, bleeding, infection at the operative puncture site, and prolonged air leak.⁶ In a large international, multicenter study of 2320 patients who underwent percutaneous RFA for liver malignancies, the mortality

rate was 0.3%, and the overall complication rate was 7.1%.¹⁰

Several centers around the world have published reports demonstrating the safety and feasibility of RFA for lung tumors.^{11,12} Animal models, to investigate the feasibility of RFA for the treatment of lung tumors, have been used to develop treatment algorithms for humans. In a study by Goldberg and colleagues¹³ using a rabbit model of lung sarcoma, seven lesions were treated with RFA for 6 minutes at 90° C, and the remaining four tumors were left untreated as controls. The authors noted computed tomography (CT) evidence of coagulation necrosis surrounding the tumor, manifested radiographically by increased opacity enveloping the lesion. This was followed temporally by the development of central tissue attenuation consistent with cavitation. Histologic analysis revealed that at least 95% of the tumor nodules were necrotic, although some rabbits (43%) had residual tumor nests at the periphery of the tumor. Pneumothorax was the only procedure-related complication, occurring in 29% of treated rabbits and 25% of controls. In another study, Miao and colleagues¹⁴ implanted VX2 sarcomas into the lungs of 18 rabbits (12 treated and 6 controls). The lesions were then treated with RFA using a cooled-tip electrode. Absolute tumor eradication was achieved in 33% of the rabbits. A partial response was observed in 41.6% of rabbits that survived longer than 3 months. On histopathologic evaluation, the ablated lesions retained their fundamental tissue architecture with evidence of coagulation necrosis. Surrounding edema and inflammation were noted in the normal adjacent pulmonary parenchyma. One to 3 months after treatment, the ablated tumor became an atrophied nodule of coagulation necrosis within a fibrotic capsule.

The timing and progression of these postablation changes becomes an important issue when evaluating postprocedure treatment response in patients with pulmonary tumors. Some investigators have performed RFA followed by resection to evaluate the efficacy of the ablation procedure. In one multicenter study of 15 patients, ablation was possible in 13 cases.¹⁵ In these 13 patients, median tumor kill was 70%, with seven patients achieving 100% ablation. Five of the final six cases exhibited 100% ablation. Nguyen and colleagues¹⁶ published the results of an ablate-and-resect study in which vital immunohistochemical stains were used to assess tumor cell viability. In seven tumors studied with this technique, more than 80% nonviability was documented. Three patients (38%) demonstrated 100% nonviability. All three tumors were less than 2 cm in diameter. A single ablation with a 3- or 3.5-cm active electrode was performed, such that the larger tumors may have been inadequately ablated. Schneider and colleagues¹⁷ reported their series of ablate-and-resect pulmonary metastasectomies. Eighteen patients underwent RFA and subsequent thoracotomy and resection for 18 diverse solid tumor metastases. Lesion size ranged 0.7 to 2.5 cm. The resected specimens were evaluated for tumor viability with immunohistochemistry. Complete ablation was achieved in 39%. More than 90% ablation was achieved in 50% of the resected lesions, and the authors considered this to be a successful ablation, asserting that subsequent growth

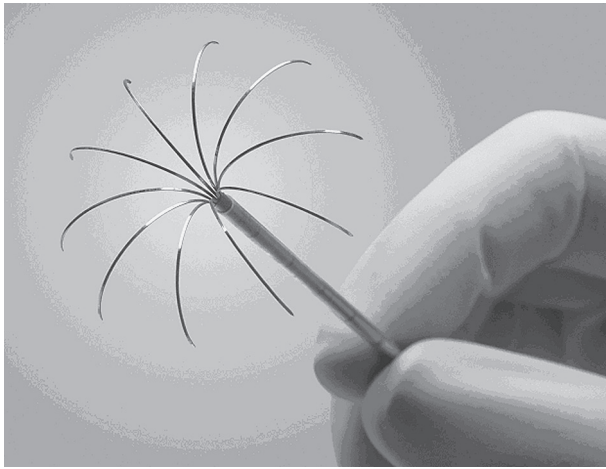


FIGURE 46-2 ■ The LeVein (Boston Scientific, Boston, MA) needle electrode.

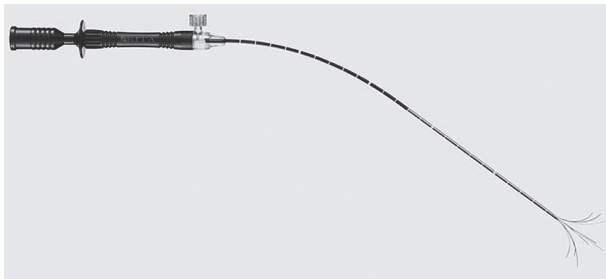


FIGURE 46-3 ■ The RITA (AngioDynamics, Latham, NY) electrode.

of the residual lesion (had it not been resected) was unlikely. An incomplete ablation (with less than 90% ablation) was documented in the remaining 11%. In another study, by Ambroggi and colleagues, a total of nine patients underwent RFA either by the CT-guided approach or by thoracotomy followed by resection.¹⁸ Complete ablation was noted in six of the nine patients (67%). These studies demonstrate that although RFA can produce effective ablation, 100% tumor cell death is not universally achieved and resection remains the treatment of choice for those able to tolerate surgical intervention.

Several U.S. Food and Drug Administration–approved devices are available for the performance of RFA, including (1) LeVein (Boston Scientific, Boston, MA), (2) RITA (AngioDynamics, Latham, NY), and (3) Valleylab (Covidien, Boulder, CO). The Boston Scientific and Covidien devices are impedance-based systems in which the end-point of treatment is determined by a significant rise in tissue impedance, indicating an inability of the target lesion to maintain further conduction and, therefore, ablation. The RITA system is a temperature-based device, which elevates the tumor temperature to predetermined lethal levels for a designated period of time. The Boston Scientific and AngioDynamics (Figs. 46-2 and 46-3) active probes consist of an expandable needle system, whereas the Covidien system consists of either a single needle or three parallel needles (Fig. 46-4) that are placed

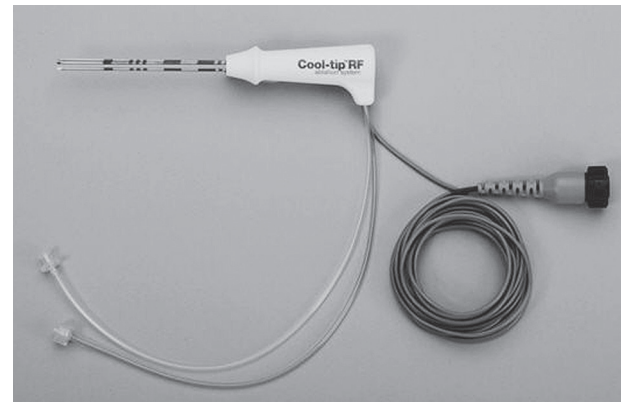


FIGURE 46-4 ■ The Valleylab probe (Covidien, Boulder, CO).

within the tumor. The Covidien electrode consists of a proximal insulated portion and a distal uninsulated active tip. The electrode is irrigated with a continuous infusion of cold saline and for this reason is sometimes referred to as a “cool-tip” electrode. The dissolved saline ions enhance conduction and therefore theoretically decrease the required time to achieve effective ablation.

Two animal studies compared the relative efficacy of the various probes by assessing the region of ablation in a liver model.^{19,20} A recent Japanese report of RFA for treatment of 342 pulmonary tumors in 128 patients cites tumor size greater than 2 cm and use of the single-needle VL probe to be associated with local progression on multivariate analysis. Further analyses comparing the array probe and the internally cooled electrode for tumors showed that the use of the internally cooled electrode was an independent risk factor for local progression (hazard ratio [HR] 3.39; 95% confidence interval [CI], 1.56-7.38).²¹

Patient Selection

For stage I NSCLC, RFA should be reserved for those patients who are believed to be at increased risk for pulmonary resection and for those who refuse surgery. Occasionally, RFA may be a reasonable therapy for a medically inoperable patient with more advanced cancer (e.g., satellite nodules) localized to the lung.²² The efficacy of RFA is low for nodules greater than 5 cm in diameter. RFA is also not recommended for central lesions or those abutting the mediastinum.²³ Other patients who may be considered for treatment with RFA include those with advanced-stage disease who have responded to definitive radiation and chemotherapy but have a persistent solitary peripheral focus of cancer, and for those who present with a recurrent isolated cancer after previous lung resection. Leung and colleagues demonstrated that thermally ablative techniques, including RFA, applied to a previously irradiated field have the potential to enhance survival in patients with recurrent NSCLC.²⁴

RFA is also a suitable option for some patients with limited peripheral pulmonary metastases. Similar to resection, this treatment should be reserved for those patients with a limited number of metastases, disease localized to the chest, controlled or controllable primary

TABLE 46-1 Selection Criteria for Radiofrequency Ablation

Inclusion Criteria	Exclusion Criteria
NSCLC stage I or II*; poor surgical candidate	Tumor abutting hilum or large pulmonary vessel
NSCLC stage II (satellite nodule same lobe) or stage III/IV (nodule in another lobe or lung); poor surgical candidate	Malignant effusion
Stage IIIa or IV with solitary pulmonary nodule remaining after standard therapies	Pulmonary hypertension
Limited pulmonary metastases and recurrent disease; primary disease controlled or controllable; poor surgical candidate	More than three tumors in one lung
Target lesion ≤ 5 cm	Target lesion > 5 cm

*Patients with stage II should receive additional therapy because N1 disease will not be treated with radiofrequency ablation.
NSCLC, Non-small cell lung cancer.

sites, and for those patients who are believed to be at increased operative risk for resection of their pulmonary metastases. In some situations, complete resection of all pulmonary metastases is not possible, and RFA can be used as an adjunct intraoperatively. We have found RFA to be of use when a wedge resection of a peripheral nodule was performed and resection of other deeper nodules would have required a lobectomy or pneumonectomy. To preserve pulmonary parenchyma, some of these tumors were treated with intraoperative RFA via open thoracotomy. We recently reported the outcomes of RFA therapy for high-risk patients with pulmonary metastasis. Although surgical resection still remains the standard of care, we find RFA to be safe and feasible in selected patients or as a parenchymal-sparing approach in combination with surgical resection.²⁵ Table 46-1 outlines suggested selection criteria for the use of RFA.

Operative Technique

In our initial experience, RFA was performed via an open thoracotomy in some patients. This approach provides the most controlled method for RFA application but negates the most attractive attribute of the technology, that is, its nonoperative applicability. Surgical resection remains the standard of care for early-stage NSCLC. RFA should be used as an adjunct to surgery or as a sub-optimal substitute in patients unable or unwilling to undergo resection. Situations may arise, such as that described previously, in which a patient presents with two or more tumors, some amenable to resection and others to RFA. Although VATS has been postulated to be an attractive approach for the application of RFA, optimal needle deployment within the tumor in the setting of a collapsed lung is often difficult.

The most common method of pulmonary RFA entails percutaneous CT-guided administration. Either general or local anesthesia can be used when performing

CT-guided RFA. Our preference is to use general anesthesia.²⁶ This allows needle deployment, ablation, and biopsies (if required) to be performed in a more controlled manner. Additionally, some patients with cardiopulmonary compromise may have difficulty maintaining optimal body position if awake or sedated. Patient positioning is extremely important during CT-guided RFA. It is advantageous to position the patient in such a way that the target lesion is accessed with minimal penetration of normal lung parenchyma. This decreases the risks of hemorrhage and prolonged air leak. Positioning is also important to ensure adequate clearance of the RFA probe within the scanner. The maximum number of lesions that can be ablated in a single setting is debatable. As a general rule, however, ablation of more than three lesions in one setting is not recommended.

Treatment Response

RFA incites an inflammatory response that can persist for up to 3 months, making it difficult to determine radiographically whether the mass represents scar or viable cancer. The mass may initially appear larger on radiographic imaging and subsequently decrease in size. Ablated lesions may demonstrate central cavitation (Fig. 46-5) or develop bubble lucencies, both of which are radiographic indicators of effective ablation. Other centers have used CT densitometry protocols to evaluate for persistent or recurrent disease.²⁷ Densitometry involves the injection of contrast and subsequent CT images of the ablated nodule at 45, 180, and 300 seconds after the injection of contrast material. These densitometry techniques are time consuming and typically valuable only for those patients with single tumor nodules. The Response Evaluation Criteria in Solid Tumors has been modified to evaluate treatment responses objectively (Table 46-2).²⁵ CT scans are obtained at 3-month intervals to assess lesion size and characteristics. Whenever possible, positron emission tomography (PET) scans are also obtained to aid in the determination of tumor response. The American College of Surgeons Oncology Group (ACOSOG) completed a multicenter study evaluating RFA in high-risk patients with stage IA NSCLC. This study (Z4033) addresses such issues as response assessment by standardizing the follow-up protocol. The preliminary results have been presented, and final results are awaited.²⁸

Clinical Results

In our initial experience with RFA at the University of Pittsburgh, we treated 33 tumors in 18 patients.²³ Tumor pathologies included metastatic carcinoma ($n = 8$), sarcoma ($n = 5$), and NSCLC ($n = 5$). The mean age was 60 (range, 27 to 95) years. Our principal finding was the lack of effectiveness in treating tumors greater than 5 cm in size. Using the Response Evaluation Criteria in Solid Tumors, we found a radiographically determined response rate of 66% for tumors less than or equal to 5 cm in size, compared with only 33% in patients with tumors greater than 5 cm. A multicenter study summarizing the results of 493 percutaneous RFA procedures for pulmonary

nodules concluded that RFA was safe, with negligible morbidity and mortality (0.4%), and is associated with a gain in quality of life.²⁹

We reported our experience with RFA for the treatment of stage I NSCLC.³⁰ Nineteen patients underwent RFA over a 3-year period. Median age was 78 years

(range, 68 to 88). An initial complete response was observed in two patients (10.5%), partial response in 10 (53%), and stable disease in 5 (26%). Early progression occurred in two patients (10.5%). During follow-up, local progression occurred in eight nodules (42%), and the median time to progression was 27 months. There was no procedure-related mortality, although six deaths occurred during follow-up. The median follow-up in the remaining patients was 28 (range, 9-52) months. The probability of survival at 1 year was estimated to be 95% (95% CI, 0.85-1.0), and the median survival was not reached.

We have published a study of 100 patients who underwent image-guided RFA for lung malignancy.³¹ The median age was 73.5 years (range, 26 to 95 years), and there were 46 patients with primary lung cancer, 25 patients with recurrent lung cancer, and 29 patients with metastatic disease. The median hospital stay was 2 days (range, 1 to 33 days), and the most common complication was pneumothorax. Local progression occurred in the treated lesions in 35 patients, and median time to local progression was 15 months. The mean follow-up time was 17 months, and the median overall survival for the entire group was 23 months.

Lanuti and colleagues³² published their mid-term results of a series of 31 nonsurgical patients with NSCLC who underwent a total of 38 percutaneous RFA treatments. There were no 30-day mortalities. Five treatments resulted in pneumothoraces, and three required chest tubes. Six patients developed pneumonia within 4 weeks of treatment; all were resolved with oral antibiotics. There were eight cases of postprocedure pleural effusion. These are typical morbidities. The authors report that one patient developed transient laryngeal nerve injury following ablation of a right upper lobe lesion abutting the mediastinum. We reiterate that RFA should not be applied to central lesions. Tumor size ranged from 0.8 to 4.4 cm. Local recurrence was assessed via CT and PET and found in 31.5% of all treated tumors but in 50% of tumors greater than 3.0 cm, 44.4% in tumors 2.0 to 3.0 cm, and 21.7% in tumors less than 2.0 cm. Survival at median follow-up of 17.3 months was 74%, and overall survival was 30 months. Lanuti and associates recently published the results of a study assessing the management of locoregional recurrence in NSCLC.³³ From 2003 to 2010, 55 ablations were performed in 45 patients with a total of 21 locoregional recurrences following treatment.

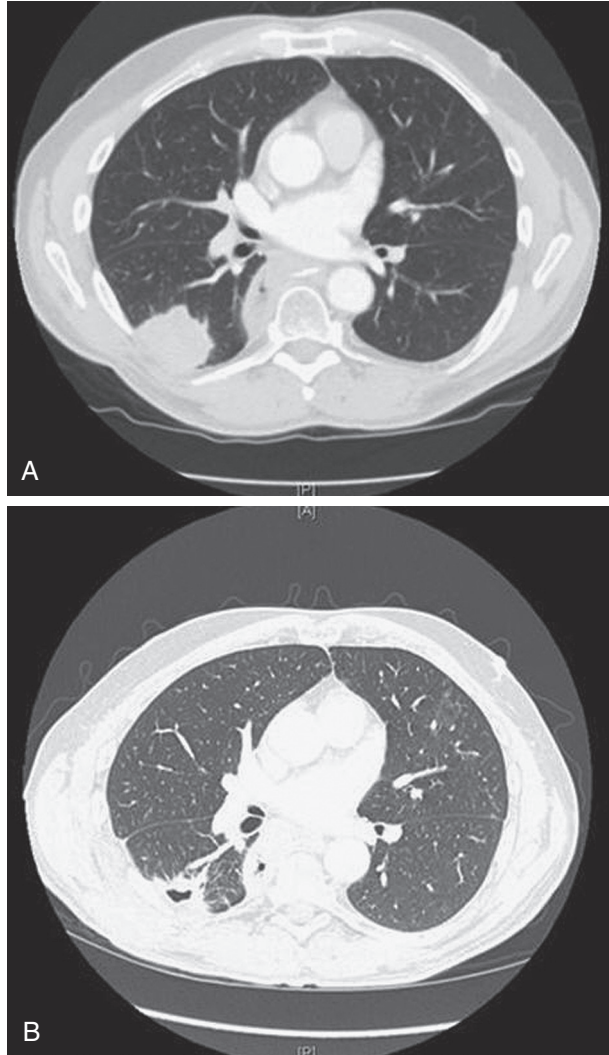


FIGURE 46-5 ■ Radiographic evidence of tumor ablation: **A**, Before ablation. **B**, Three months after ablation; note central cavitation and overall decrease in size.

TABLE 46-2 Modified RECIST

Response	CT Mass Size	CT Mass Quality	PET
Complete (Two of the following)	Lesion disappearance (scar) less than 25% of original size	Cyst/cavity formation Low density of entire lesion	SUV < 2.5
Partial (One of the following)	More than 30% decrease in the LD of target lesion	Central necrosis or central cavitation with liquid density	Decreased SUV or area of FDG uptake
Stable lesion (One of the following)	Less than 30% decrease in the LD of target lesion	Mass solid appearance, no central necrosis or cavitation	Unchanged SUV or area of FDG uptake
Progression (Two of the following)	Increase of more than 20% in the LD of target lesion	Solid mass, invasion of adjacent structures	Higher SUV or larger area of FDG uptake

CT, Computed tomography; FDG, fluorodeoxyglucose; LD, largest diameter of lesion; PET, positron emission tomography; RECIST, Response Evaluation Criteria in Solid Tumors; SUV, standard uptake value of ¹⁸F-FDG on PET scan.

Mean tumor diameter was 2.3 cm (range, 0.7 to 4.5). Eighty percent of tumors that exceeded 3 cm in diameter were associated with locoregional recurrences. Overall survival was similar for patients who had locoregional recurrences compared with those who did not.

The RAPTURE study³⁴ was a prospective, intention-to-treat, single-arm, multicenter, international clinical trial designed to validate the feasibility and safety of RFA for pulmonary tumors as well as to assess efficacy. A total of 105 patients with 183 tumors were treated with 137 RFA treatments. All patients were deemed to be nonsurgical candidates. There were no mortalities. Twenty-seven patients developed a pneumothorax requiring chest tube evacuation. Pleural effusions occurred in 15 patients, 4 requiring drainage. Tumor sizes ranged 0.5 to 3.4 cm. Pulmonary function was assessed before the procedure and 1, 3, 6, and 12 months after the procedure and no significant change was found. Of the 85 patients who could be assessed for tumor response, 88% exhibited complete response to treatment at 1 year. Local progression was noted in 12%. Overall survival was 70%, and cancer-specific survival was 92% at 1 year.

Huang and associates³⁵ performed a study assessing the safety and efficacy of RFA for the treatment of pulmonary malignancy. Over a 7-year period, 329 patients (237 NSCLC and 92 metastasis) were treated with CT-guided RFA. The 30-day mortality rate was 0.6%, including 2 patients (one death from pericardial tamponade and another from hemoptysis), and there were postoperative complications in 113 of 329 (34.3%) patients. Complications included 63 (19.1%) pneumothorax, 15 (4.5%) pneumonia, 14 (4.2%) hemoptysis, 10 (3%) hemothorax, and 3 (0.9%) pericardial tamponade. Lesions greater than 4 cm were associated with a significantly increased risk of local progression. The median progression-free interval was 21.6 months, and 1-, 2-, and 5-year survival rates were 68.2%, 35.3%, and 20.1%, respectively. In conclusion, the authors deemed RFA to be a safe and effective procedure for the treatment of pulmonary malignancy but noted that it requires proper training and patient selection to limit complications.

ACOSOG completed a multicenter study (Z4033) that included 54 patients from 16 centers evaluating RFA in high-risk patients with stage IA NSCLC.²⁸ The preliminary results of this trial have been presented. The overall survival at 1 and 2 years was 87% and 70%, respectively. One-year local recurrence-free rate was 70%, and the 2-year rate was 61%. Change in the FEV₁ and diffusion of carbon monoxide in the lung (DLCO) at 24 months was not clinically significant. The final results of this trial are awaited.

These results demonstrate feasibility, safety, and intermediate-term results of RFA for pulmonary tumors not amenable to surgical resection. Techniques to more precisely localize the lesion under image guidance for ablative therapy are evolving; one such technique is electromagnetic navigation to aid RFA.³⁶ These technologies may improve the local progression rates after RFA. Further critical evaluation of ongoing clinical trials will aid in defining the impact of RFA on long-term tumor control and its potential applicability for larger tumors and more advanced disease.

STEREOTACTIC RADIOSURGERY

Conventional external beam radiation therapy is commonly used to primarily treat NSCLC when surgical resection is not possible. Unfortunately, cure is rare, local progression is common, and morbidity can be significant. Qiao and associates³⁷ summarized results from 18 studies reporting external beam radiation for stage I NSCLC. The mean 3- and 5-year survival rates were 34% and 21%, respectively. In one study of 71 node-negative patients who received at least 60 Gy of external beam radiation to their primary tumors, 3- and 5-year survival rates were only 19% and 12%.³⁸ In another study of radiation therapy in 60 patients with stage I or II NSCLC, local progression was documented in 53% of patients with a median progression-free survival of 18 months and an overall median survival of only 20.5 months.^{38a}

Higher radiation doses seem to enhance local tumor control.³⁹ Bradley and colleagues⁴⁰ showed that patients receiving greater than 70 Gy of radiation had better local control and cause-specific survival than those treated with lower doses. Increased doses of radiation, however, result in increased toxicity and damage to the surrounding pulmonary parenchyma. Radiation fibrosis seems to depend on the volume of lung radiated above a threshold of 20 to 30 Gy.⁴¹ Pulmonary toxicity is the major morbidity associated with external beam radiation treatment of NSCLC. Radiation pneumonitis is a potentially life-threatening sequela and occurred in 8.3% of patients treated with definitive radiotherapy.^{38a} Heightened toxicity, poor survival outcomes, and frequent local progression have prompted a growing interest in alternative means of irradiating pulmonary malignancy.

Techniques

Stereotactic radiosurgery (SRS; also referred to as stereotactic body radiotherapy [SBRT] or stereotactic ablative body radiotherapy [SABR]) is a relatively new approach that enables the selective delivery of an intense dose of high-energy radiation to a precise target volume. The improved accuracy is achieved through computer-controlled spatial localization of the tumor and delivery of multiple cross-fired beams of radiation that converge on the tumor, minimizing injury to surrounding normal tissue. In many centers, this technology has become standard treatment for intracranial tumors (gamma knife). Unlike in the brain, however, respiratory motion imposes technical difficulties for the precise delivery of radiation to lung tumors. Respiratory displacement is greatest near the diaphragm and less significant near the lung apices and adjacent to the carina. Several techniques are available to minimize the effects of respiratory motion on the precise delivery of the concentrated radiation. One approach is to use breath-holding techniques, often in combination with an abdominal compression device, to limit the ability of the diaphragm to move caudally.⁴²

At the University of Pittsburgh, we published the results of SRS using the CyberKnife stereotactic radiosurgery system (Accuray, Sunnyvale, California), a frameless SRS.⁴³ The Cyberknife system consists of a linear

accelerator radiation source that is mounted on a robotic arm (Fig. 46-6). Before initiating treatment, two to four small gold fiducials are implanted in the pulmonary parenchyma around the periphery of the tumor. This is accomplished either percutaneously via CT guidance or transbronchially under fluoroscopic guidance. At the time of therapy, cameras on the Cyberknife system use these markers to localize the tumor in space. The CyberKnife synchrony option records respiratory motion and combines this information with the fiducial images to optimize precise radiation delivery for any point of the respiratory cycle. A major advantage with this system

over those involving breath-holding and immobilization techniques is that the treatment times are shorter and therefore better tolerated by patients, who often have some degree of cardiopulmonary compromise (Fig. 46-7).

Patient Selection

Patient selection for SRS is similar to that for RFA, with some notable differences. One advantage of SRS is that central tumors can be safely treated, although dose-dependent toxicity still remains a concern. Therefore, we used a modified dose schema with a decreased dose (typically 12 Gy in 4 fractions) to treat central tumors. Additionally, we have found that osteosarcomas can be extremely difficult to penetrate with the RFA needle. Because SRS requires fiducials to be positioned close to a tumor rather than within it, SRS may be a better option for the treatment of metastatic osteosarcomas.

Results

Whyte and coworkers⁴⁴ published the first results of SRS for the treatment of lung tumors using the Cyberknife system. This study included 23 patients from two institutions. Respiratory gating was used in 14 patients and breath-holding in 9 patients. A single fraction of 15 Gy was used. Three patients developed pneumothoraces following fiducial placement. There was no radiation esophagitis or clinically apparent radiation pneumonitis. At a mean follow-up of 7 months, 2 patients (8.6%) had a complete response, 15 (65.2%) had a partial response, 4

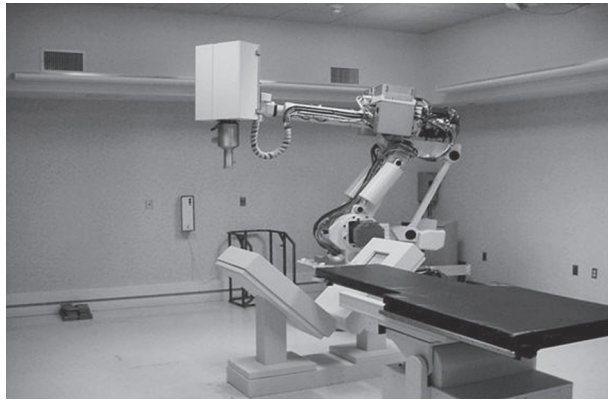


FIGURE 46-6 ■ CyberKnife (Accuray) stereotactic robotic radio-surgery system.

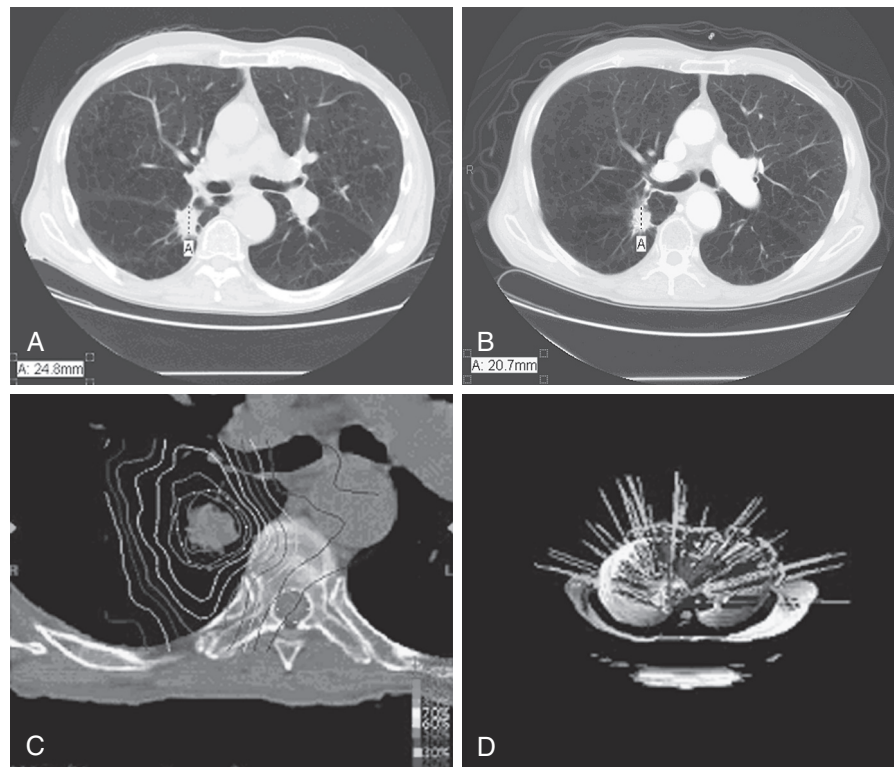


FIGURE 46-7 ■ Computed tomographic scans of right lung squamous carcinoma treated with CyberKnife stereotactic radiosurgery (SRS). **A**, Before SRS treatment. **B**, Three months after treatment. **C**, Radiation plan with isodose mapping. **D**, Radiation paths.

(17.4%) had stable disease, and 2 (8.7%) had evidence of progression.

In our initial experience at the University of Pittsburgh, 32 patients (27 with NSCLC and 5 with pulmonary metastases) were treated with SRS using the Cyberknife system.⁴³ Patients were treated with 20 Gy in a single fraction. It should be noted that the radiobiology of SRS (by virtue of a high single focused dose) is different from that of external beam radiation. The biologically effective dose is much higher for SRS.⁴⁵ Biologic effective dose (BED) is based on the linear-quadratic equation and allows dose comparison among different institutions. $BED = nd(1 + d/[\alpha/\beta])$; where n = number of fractions, d = dose per fraction, and the α/β ratio value is unique to each tissue type ($\alpha/\beta = 3$ for normal lung parenchyma, $\alpha/\beta = 10$ for tumors).⁴⁶ It has been shown that higher biologically effective doses improve local progression-free survival.^{47,48} In our initial protocol, the 20-Gy dose was equivalent to a BED of 60 to 70 Gy with standard techniques.⁴³ Following SRS in the 32 patients, an initial complete response was seen in 7 (22%), partial response in 10 (31%), stable disease in 9 (28%), and progression in 5 (16%). The probability of 1-year overall survival for the entire group and stage I patients was 78% (95% CI, 0.65-0.94) and 91% (95% CI, 0.75-1), respectively.

We reported the results of 100 patients who underwent treatment with SRS for various pulmonary malignancies, including 46 patients with primary lung neoplasm, 35 with recurrent cancer, and 19 with pulmonary metastasis.⁴⁹ Patients were initially treated with a median dose of 20 Gy in a single fraction, which was later increased to 60 Gy in three fractions for peripheral lesions. Complications included pneumothorax in 26 patients (26%) following percutaneous fiducial placement, chronic obstructive pulmonary disease exacerbation in 1 patient, and 1 death a month after the initial SRS treatment. The initial response to treatment was measured using the modified RECIST criteria in 90 evaluable patients. Complete response was achieved in 20%, partial response was found in 29%, stable disease was observed in 22%, and progressive disease was noted in 29% of patients. Local progression, at the treated nodule, occurred in 25 patients with a median time to local progression of 22 months. The median follow-up time was 20 months, and the median overall survival of the entire group was 24 months, with an estimated 2-year overall survival of 50%. Increased SRS dose (60 Gy) was associated with lengthened time to local progression. With an increase in local progression, with a single fraction of 20 Gy for peripheral tumors, we have increased the dose to 60 Gy in three fractions for peripheral tumors.

The impact of SRS dose escalation on oncologic patient outcomes has been investigated. Timmerman and colleagues⁴² previously reported the results of a dose escalation study in 37 patients with stage I NSCLC. A breath-holding technique with abdominal compression was used. In this series, the dose was escalated from 20 to 60 Gy in three fractions. Complete response was seen in 27% of patients and a partial response in 60%. At a median follow-up of 15 months, six patients (16.2%) had experienced local failure and all six received fractions lower than 18 Gy, supporting the concept of dose escalation.

The same group published a follow-up study 2 years later.⁵⁰ Stage I NSCLC patients were stratified into T1 and T2 tumors. Dose-limiting toxicity included bronchitis, pericardial effusion, hypoxia, and pneumonitis. Local failure occurred in four (21%) of the T1 tumors and six (21%) of the T2 tumors. In the T1 tumors, eight (42%) patients had regional or distant recurrences (or both). In the T2 tumors, six (21%) had regional or distant recurrence.

Although an increased dose delivered during SRS may improve local control, an increased dose is also associated with increased toxicity, when treating central lesions.⁵¹⁻⁵³ In a phase II study of 70 medically inoperable stage I NSCLC patients treated with SRS using 60 to 66 Gy in three fractions, local control was found in 95% of the patients, and the estimated 2-year overall survival rate was 54.7%.⁵² However, increased toxicity was noted in central tumors, with a 2-year freedom from severe toxicity of 54% in central lesions compared with 83% in peripheral lesions. During a median follow-up of 17.5 months, 6 of the 70 patients (8.6%) died of treatment-related causes. These results led the authors to conclude that this regimen should not be used for patients with tumors near central airways. In view of these data, we use a dose of 60 Gy in three fractions for peripheral lesions, and we currently use a modified dose schema with 48 Gy in four fractions for central tumors.

Dose escalation for locally advanced cancer with a SBRT "boost" in addition to conventional chemoradiotherapy is also a current treatment modality being investigated. Karam and colleagues⁵⁴ reported the results of a study including 16 patients with locally advanced NSCLC who were treated with an average dose of 25 Gy (range, 20 to 30 Gy) with SBRT. The SBRT was in addition to a median dose of 50.4 Gy of conventional chemoradiotherapy. One-year overall survival for the patient group was 78% with a median time to cancer progression of 10 months. The authors concluded that dose elevation using SBRT in addition to conventional external beam radiotherapy is a feasible option for locally advanced NSCLC.

Several additional case series have also been published.⁵⁵⁻⁵⁸ A review by Nguyen and colleagues⁴⁶ compared effectiveness and morbidity of the published VATS lobectomy data (19 studies, 3988 patients) with the published SRS data (24 studies, 1485 patients) for early-stage NSCLC. The SRS data were further subgrouped into studies that reported a BED of at least 100 Gy (14 studies) and those that reported a BED of less than 100 Gy (10 studies). Local control and survival rates were comparable for studies that used a BED of 100 Gy or more. The mortality rate was 1% for the VATS group and 0.4% for the SRS group that received more than 100 Gy. All of the SRS deaths (6 patients) were noted to be from a single study that used a BED of >180 Gy to centrally located tumors. Morbidity was a mean of 16% for the VATS group (prolonged air leak, arrhythmia, pneumonia, stroke, pulmonary embolism) versus a mean of 4% for the entire SRS group (grade 3-4 pneumonitis, rib fractures, pleural effusion). VATS 2- to 5-year survival ranged from 60% to 96%. Actuarial survival for the SRS group that received more than 100 Gy ranged from 42% to 91%, and that for the SRS group that received less than 100 Gy

ranged from 24% to 90%. Local control, although not reported in all studies, ranged from 88% to 100% for the VATS group, 74% to 100% for the SRS group that received more than 100 Gy, and 57% to 91% for the SRS group that received less than 100 Gy. The authors note that SRS is feasible and associated with minimal morbidity, and delivery of more than 100 Gy appears comparable with VATS lobectomy with respect to local control.⁴⁶ We have modified our initial protocol of delivering a single 20-Gy fraction to now include a total of three fractions for peripheral lesions and four fractions for central lesions to achieve a BED of more than 100 Gy.

Onishi and associates⁵⁹ reported the Japanese multi-institutional SBRT data. Ninety-nine patients who were surgical candidates but refused surgery underwent SRS. The 5-year overall survival for operable patients was 70.8% for those patients treated with BED more than 100 Gy and 30.2% for those treated with BED less than 100 Gy. Multi-institutional phase II studies of SRS have been reported for the treatment of potentially resectable stage I NSCLC in Japan (JCOG 0403) and the United States (RTOG 0236). Another phase II multi-institutional study (NCT00643318) investigating Cyberknife SRS for medically inoperable stage I NSCLC, led by the University of Pittsburgh, is in progress. There are two randomized multi-institutional studies on surgical resection with SRS in operable patients with stage I NSCLC that were initiated; however, they were terminated due to low accrual. One study (STARS; NCT00840749) was led by MD Anderson Cancer Center group, and another study (ROSEL; NCT00687986) was based in the Netherlands. The Netherlands study did not require tissue confirmation of lung cancer, which will impact the interpretation of the results.

Timmerman and colleagues⁶⁰ recently reported the 3-year results of a prospective phase II multicenter study (RTOG 0236) including 59 (55 evaluable) patients who underwent SBRT for inoperable early-stage lung cancer. The median follow-up time for the 55 evaluable patients was 34.4 months (range, 4.8 to 49.9). A complete response to SBRT was achieved in 28 patients, a partial response was reported in 21 patients, and the combined sum of complete and partial responses accounted for 89% of patient responses to treatment. The 3-year primary tumor control rate was 97.6%, with only one patient having a recurrence or progression at the primary tumor site. The 3-year disease free survival and overall survival rates were 48.3% and 55.8%, respectively. For the entire group of patients, the median disease-free survival and overall survival rates were 34.4 and 48.1 months, respectively. The initial results of a large phase II multicenter trial of Cyberknife SRS for medically inoperable patients, led by investigators from the University of Pittsburgh, has been presented.⁶¹ In this large multicenter trial, 78 patients with stage I NSCLC were treated with SRS (60 Gy in three fractions). The median follow-up was 26 months. The probability of 2-year cancer-specific survival was 79%. During follow-up, 3.8% of patients had local progression only. The authors concluded that the intermediate-term results of SRS are promising. Additional follow-up is currently ongoing to fully evaluate the results of SRS in this trial.

Fakiris and coworkers reported the updated results of a prospective phase II study assessing the outcomes of 70 medically inoperable patients who underwent SBRT for stage T1 ($n = 34$) and T2 ($n = 36$) NSCLC.⁶² Treatment was delivered at 80% isodose volume and consisted of total doses of 60 Gy (three fractions of 20 Gy) for patients with T1 tumors and 66 Gy (three fractions of 22) for patients with T2 tumors.

Median follow-up was 50.2 months (range, 1.4 to 64.8), which consisted of the results for all 70 patients who completed SBRT as initially planned. The 3-year overall survival rate was 42.7% (95% CI, 31.1%-54.3%), and the median survival rate was 32.4 months. Patients with T1 tumors had a median survival rate of 38.7 months, and patients with T2 tumors had a median survival rate of 24.5 months.

Summary

Neither of the aforementioned novel treatment modalities is as effective as surgical resection. RFA ablates lesions from the inside-out, with treatment failures typically seen at the periphery of the lesion. SRS, on the other hand, can be configured to deliver a concentrated dose to the entire target volume, usually encompassing a small amount of normal lung parenchyma surrounding the lesion. At the University of Pittsburgh, we typically place fiducial markers during RFA for lesions greater than 3 cm or for asymmetrical lesions in which a uniform ablation is not likely to be achieved. During follow-up, if persistent tumor is suspected, it can be retreated with either another RFA application or SRS. We use SRS more often than RFA for such scenarios.

MICROWAVE ABLATION

Microwave ablation (MWA) is a relatively recent promising tumor ablation modality. Microwaves comprise the zone of electromagnetic radiation between 900 and 2450 MHz. The waves possess electrical properties, with the charge changing from positive to negative as the wave travels from peak to trough. As microwave radiation interacts with water, the individual polar molecules oscillate, flipping back and forth with the changing charge of the microwave. Because of the high frequency, the water molecules change direction 2 to 5 billion times per second. The resulting friction produces heat. This dielectric heating can be of sufficient magnitude to coagulate protein and cause cell death.^{63,64}

Like RFA, MWA is amenable to percutaneous and open approaches. In general, a microwave antenna is inserted into a target lesion via CT guidance in much the same way as is an RFA probe. The antenna is insulated throughout most of its length, with a variable length of exposed tip. The antenna is connected to a microwave generator, which emits an electromagnetic wave. This leads to excitation of water molecules, subsequent friction and heat generation, and, ultimately, coagulation necrosis. Unlike RFA, a dispersive electrode is not necessary. Moreover, multiple antennae can be activated simultaneously (multiple active antennae per lesion and/or

treatment of multiple lesions simultaneously). MWA may allow temperatures within the targeted lesions to be driven higher, resulting in a larger ablation zone in a shorter period of time.⁶⁴ As with RFA, the initial clinical experience with MWA has been in the treatment of liver tumors.⁶⁴⁻⁶⁶

Clinical experience with MWA for the treatment of lung tumors is relatively limited but there are few studies evaluating the use of MWA for lung malignancy. Feng and coworkers⁶⁷ reported the application of MWA to 28 lung tumors in 20 patients. A response of 50% or more was noted in 13 (46.4%) of the nodules and a complete response in 3 (10.7%). No significant complications were noted. An ablate-and-resect study was performed by Simon and colleagues.⁶⁴ Patients underwent MWA prior to planned resection. The mean tumor diameter was 3 cm (range, 2 to 5.5 cm), with an average tumor volume of 7.1 cm³. The maximum ablation achieved was 4 cm (3 to 5 cm), with an ablation zone volume of 23.4 cm³.

Belfiore and associates⁶⁸ reported the results of a study that included MWA treatment of 69 separate lung lesions in 56 patients (44 patients with lung cancer lesion, 12 patients with metastatic disease). Complications included pneumothorax in 18 patients with chest tubes being required in 8 patients, 10 patients had pain (mild to moderate) at the site of needle insertion, and fever occurred in 4 patients. The overall survival rates at 12, 24, and 36 months were 69%, 54%, and 49%, respectively. The estimated mean survival time was 27.8 months.

Lu and colleagues⁶⁹ performed a study of 69 patients who underwent percutaneous MWA therapy for pulmonary malignancy. The entire group consisted of varying stages of cancer, including 22 patients with recurrent cancer, 21 patients with metastases, and 26 patients with primary lung malignancies. For patients with NSCLC, the cancer stages included 7 (14.58%) stage I, 10 (20.83%) stage II, 22 (45.84%) stage III, and 9 (18.75%) stage IV. The most common complication was pneumothorax, which varied in severity and occurred in 13 (18.84%) patients. Local tumor progression rate based on a 3-year analysis was 16.13%, occurring in 15 patients. The 1-, 2-, and 3-year overall survival rates for patients with NSCLC were 75%, 54.2%, and 29.2%, respectively. Patients with metastatic lung tumors had 1-, 2-, and 3-year survival rates of 47.6%, 23.8%, and 14.3%, respectively.

Wolf and coworkers⁷⁰ published their retrospective experience using CT-guided MWA to treat 82 lung tumors (primary NSCLC and metastases) in 50 patients. Tumor size was a mean of 3.5 cm $\pm$ 1.6 cm. A single antenna was used for lesions 2 cm in size or less; multiple antennae were used to treat lesions greater than 2 cm. Follow-up evaluation consisted of CT and PET imaging. The 30-day mortality rate was 0.0%. Morbidities included acute respiratory distress syndrome (1 patient, 2% of ablations), cutaneous burns (2 patients, 3%), pneumothorax (26 patients, 39%; 8 patients required chest tube), minor hemoptysis (4 patients, 6%), pain (1 patient, 2%), postablation syndrome (1 patient, 2%), and infection (2 patients, 3%). At mean follow-up of 10 months, 48% had residual or recurrent disease. Local control at 1 year was 67%, and mean time to first recurrence was 16.2 months.

Actuarial survival was 65%, 55%, and 45% at 1, 2, and 3 years, respectively. Cancer-specific survival was 83%, 73%, and 61% at 1, 2, and 3 years respectively. Tumor size larger than 3 cm was not significantly associated with decreased local control or survival. Radiographic evidence of postablation lesion cavitation was associated with reduced cancer-specific mortality.

Wolf and associates⁷¹ recently published a prospective ablation and resection study including 10 patients who underwent intraoperative MWA for pulmonary malignancies. Tumor histology varied and included 3 patients with squamous cell carcinoma, 5 patients with adenocarcinoma, and 2 with metastatic tumors. The maximal tumor diameter was a mean of 2.4 cm, and the maximum diameter of the ablation zone (based on five tumor specimens) was 4.8 cm. Postoperative histologic characteristics of the ablation zones included coagulation necrosis, amorphous cytoplasm, no discernible cellular membrane, and a loss of cell structure. On further examination of the ablation zones using vital histochemical nicotinamide adenine dinucleotide staining, it was confirmed that six specimens had coagulation necrosis extending into the peritumoral parenchyma, and cellular death was noted beyond demarcated transition zones between viable and unviable ablated cells. Five of the six ablation zones were deemed a complete ablation. Other than minor air leak, no complications were identified strictly for the MWA, although there was one postoperative death from pneumonia and respiratory failure attributed to surgical resection. It was concluded that the peritumoral ablation zone could potentially be considered the equivalent of an oncologic resection margin. Although this study has encouraging results, we believe that a cautionary note should be taken with the understanding that only 50% of patients (5 of 10) had verification of complete cellular death in ablation zones. Further studies are needed to support MWA as a treatment modality capable of providing consistent microscopically negative tumor margins.

MWA potentially results in higher intratumoral temperatures, potentially larger ablation zones, and faster treatment times. Additional experience with this modality, along with refinements in equipment and techniques, is necessary before the role of MWA can be established in the treatment of early-stage lung cancer.

CRYOABLATION

Cryotherapy is another ablative modality for the treatment of pulmonary malignancy and is essentially a method for inducing tumor death by cellular freezing. Cryosurgery has been used for several other cancers.⁷²⁻⁷⁵ Similar to RFA, cryoablation is best suited for patients who are not candidates for resection.⁷² Cryotherapy can be performed through various routes, including endobronchially and percutaneously. There are few reports of cryotherapy for lung tumors.

Wang and coworkers⁷⁶ reported the results in 187 patients who underwent CT-guided percutaneous cryotherapy for thoracic cancer masses. CT imaging was used to compare low-attenuation ice formation with the size and location of the initial tumor that was treated. Mean

tumor coverage with low-attenuated ice formation was 99% for peripheral lesions 4 cm or less ($n = 101$) and 80% for centrally located ($n = 58$) masses greater than 4 cm. Kawamura and associates⁷⁷ applied the use of cryotherapy for the treatment of small pulmonary metastases. Cryoablation was performed for 35 tumors in 20 patients. The 1-year survival rate was 89.4%, and 7 (35%) patients had local recurrence during a median follow-up of 21 months.

CHEMOPERFUSION OF THE PLEURAL CAVITY

The results of surgical therapy alone or combined with traditional chemotherapy or radiation therapy have been disappointing for patients with malignant pleural mesothelioma or patients with diffuse pleural disease from thymic malignancies. The standard of care for most of these malignancies continues to evolve. Baldini and colleagues⁷⁸ reviewed a series of patients who underwent multimodal therapy for malignant pleural mesothelioma. In this series, 54% of patients developed recurrences, of which the site of recurrence included the ipsilateral hemithorax in 35% of patients. Several strategies have been investigated to improve the local control of disease, after macroscopic complete resection (MCR). One method for the treatment of malignant pleural mesothelioma is to surgically remove all gross disease (complete macroscopic resection) and then bathe the hemithorax with cytotoxic agents (chemoperfusion) with or without hyperthermia. The advantage of this approach is the direct exposure of any residual microscopic disease to higher drug concentrations than that achievable via conventional (systemic) chemotherapy, while also minimizing the toxic systemic side effects. Adding hyperthermia to this strategy has been shown in some studies to increase the local tissue and cellular concentrations of the chemotherapeutic agent compared with normothermic perfusion.⁷⁹ The drug most commonly reported for use in intrapleural hyperthermic chemoperfusion is cisplatin. Early experience with “chemothermotherapy,” using intrathoracic bolus injection of cisplatin, suggested the potential efficacy of using postoperative hyperthermic chemotherapy for the treatment of carcinomatous pleuritis.⁸⁰

Most of the experience with hyperthermic intraoperative chemoperfusion (HIOC) has been in the treatment of intraperitoneal malignancies.⁷⁹⁻⁸¹ A few centers have published results of nonrandomized trials of cytoreductive surgery followed by intraoperative hyperthermic intrathoracic perfusion chemotherapy. In most centers, this application is limited to clinical trials, with most of the experience being reported for patients with malignant mesothelioma and, to a lesser degree, thymic malignancies. Relatively few data exist for the application of chemoperfusion for the treatment of stage IIIB NSCLC. Although a cautionary note must be added regarding efficacy, these reports have demonstrated feasibility and some optimism that local control and, in some cases, survival may be better in comparison with historical controls.

The optimal temperature of the perfusate is unknown, but temperatures higher than 43° C may be associated

with an increased risk of pulmonary edema if the ipsilateral lung remains in situ, for example, after pleurectomy alone. One of the main concerns of HIOC is renal toxicity. In the case of extrapleural pneumonectomy, perfusion at the same operative setting as the resection may lead to an increased risk of postpneumonectomy pulmonary edema as a result of the aggressive hydration that is routinely administered to minimize the renal toxicity of cisplatin. In our experience, if extrapleural pneumonectomy is performed, we may consider delay of hyperthermic chemoperfusion with cisplatin for a few days. If the contralateral lung is functioning well at that point, and there is minimal oxygen requirement, we return to the operating room and hydrate the patient aggressively for renal protection. We then perform the hyperthermic chemoperfusion using videothoroscopic access. Several adjuncts have been proposed to reduce the renal toxicity in these patients. These include admission of the patient a day before surgery and administration of intravenous hydration overnight, prior to resection and HIOC. In addition, there have been clinical investigations with pharmacologic cytoprotection with amifostine and sodium thiosulfate.^{84,85} In general, the technique involves MCR, followed by amifostine infusion. After hemostasis is achieved, HIOC is performed with cisplatin at a temperature of 42° C. At the conclusion of the intrapleural lavage, intravenous sodium thiosulfate is administered to bind and inactivate residual circulating cisplatin. Some of the clinical trials on chemoperfusion are summarized next.^{82,83}

Zellos and colleagues⁸⁴ performed a study of 42 patients in a prospectively enrolled protocol for treatment with intraoperative hyperthermic cisplatin for malignant pleural mesothelioma. In this study, amifostine was used in an attempt to decrease the renal toxicity of cisplatin. Amifostine was administered before hyperthermic chemoperfusion. Twenty-nine patients underwent extrapleural pneumonectomy followed by intraoperative hyperthermic cisplatin perfusion in the abdomen and chest for 1 hour at 42° C. Median postoperative hospital stay was 15 days, and the most common complications were atrial fibrillation in 19 patients (66%) and deep venous thrombosis in 9 patients (31%). Fifteen patients received elevated doses of cisplatin (175 to 200 mg/m²) and had improved survival at 26 months compared with the 14 patients who received lower doses (75 to 150 mg/m²) of cisplatin, who had a median survival of 16 months.

Tilleman and associates⁸⁵ reported the results of a phase II prospective study of 121 patients who were enrolled to undergo extrapleural pneumonectomy followed by intraoperative intracavitary hyperthermic cisplatin therapy (dose of 225 mg/m²) for malignant pleural mesothelioma. In this study, intravenous amifostine was administered before the cisplatin lavage, and intravenous sodium thiosulfate was administered immediately after chemoperfusion to enhance the renal protection. Of the 121 patients initially enrolled, 96 patients underwent extrapleural pneumonectomy. Of these 96 patients, 92 had cisplatin perfusion following extrapleural pneumonectomy. There was a reduction in renal toxicity for the amifostine and sodium thiosulfate group (1 of 27) when compared to the sodium thiosulfate group alone (7 of 65).

Disease recurrence occurred in 47 of 92 (51.1%) patients with a mean disease-free interval of 15.3 months. Median follow-up was 31.2 months (range, 16.7 to 45.8 months), and median overall survival (121 patients) was 12.8 months. Median survival was 11 months for those patients who did not undergo treatment based on the HIOC protocol compared with a median survival of 13.1 months for the treatment group (92 patients). Patients with early-stage disease (stage I or II) had a statistically significant ($P = 0.0071$) improved median survival (21.3 months) in comparison with patients with stage III disease (11.5 months). The overall cancer-specific survival for the treatment group was 16.9 months.

In one report, Yellin and colleagues⁸¹ described the results of hyperthermic pleural perfusion with cisplatin in a heterogeneous group of patients with malignant pleural involvement. This group of 26 patients included 7 with malignant mesothelioma, 7 with stage IVA thymoma, 4 with thymic carcinoma, 1 with chest wall sarcoma, 3 with NSCLC, 2 with metastatic sarcoma, and 2 with metastatic carcinoma (1 ovarian, 1 squamous of unknown origin). Surgical resection of all gross disease was attempted with resection and pleurectomy in 10, extrapleural pneumonectomy in 8, and incomplete resections in the other patients. Hyperthermic chemoperfusion was performed with cisplatin at various concentrations at an infusion temperature of 42° C for 1 hour. Intrapleural temperatures ranged from 40.1° C to 41.5° C with a maximal systemic temperature of 38° C. Creatinine clearance remained unchanged in all patients, and no significant hematologic toxicities were reported, except for a single patient with thrombocytopenia following chemotherapy. The most notable postoperative complication was empyema, which occurred in 4 of 26 patients (15%). There was one postoperative death from a gastric herniation. Complete ipsilateral pleuropulmonary control of disease was reported in 17 of 24 (71%) evaluable patients. Overall 3-year survival was 44% in this group of patients.

In a report by de Bree and associates from the Netherlands Cancer Institute,⁸⁶ cytoreductive surgery was performed for 11 patients with malignant mesothelioma and 3 patients with pleural thymoma metastases. This was followed by hyperthermic chemoperfusion of the pleural cavity with a combination of Adriamycin and cisplatin. In the thymoma group, four perfusions were performed for three patients (one patient with a second operation for contralateral pleural metastases discovered on follow-up). Complications included one grade 2 nephrotoxicity and one wound dehiscence. At an early follow-up of 18 months, all three patients were alive and free of disease. In a follow-up comment, however, two of the patients suffered disease recurrence.⁸⁷ In the mesothelioma group, at a mean follow-up of 7.4 months, there were three recurrences with two of the patients dying of contralateral pleural and peritoneal disease.

The same group⁸⁸ more recently reported a comparison of 20 patients with mesothelioma treated with cytoreductive surgery and hyperthermic chemoperfusion with another 15 mesothelioma patients treated with extrapleural pneumonectomy and postoperative hemithoracic radiation to 54 Gy (no chemoperfusion). The

chemoperfusion group suffered the only postoperative mortalities (two [10%]), more complications (70% vs. 53%), and shorter survival (11 months vs. 29 months; $P = \text{ns}$). Local control was 67% versus 20% for the extrapleural pneumonectomy/radiation therapy group and hyperthermic chemoperfusion group, respectively. Median time to local recurrence was not reached in the extrapleural pneumonectomy/radiation therapy group and was 9 months in the chemoperfusion group ($P = 0.003$). Although feasible, and with results not unlike historical controls, hyperthermic chemoperfusion was associated with significant morbidity and a relatively short term of local control.

Richards and colleagues⁸⁹ reported their experience of 44 patients with malignant pleural mesothelioma who underwent resection followed by intraoperative intracavitary chemoperfusion with escalating doses of cisplatin. They report an 11% mortality rate, dose-limiting renal toxicity with a cisplatin dose of 250 mg/m², atrial fibrillation (32%), acute respiratory distress syndrome (11%), pneumonia (9%), and deep venous thrombosis (9%). A significant difference in survival was seen between those patients receiving low-dose hyperthermic chemoperfusion (50 to 150 mg/m²; median survival, 6 months) and those receiving higher, but not toxic, doses (175 to 250 mg/m²; median survival, 18 months).

Recently Sugarbaker and colleagues⁸³ studied a cohort of 103 patients with malignant pleural mesothelioma undergoing surgical MCR. Of the 103 patients, 72 underwent hyperthermic intraoperative cisplatin chemotherapy. The 72 patients treated with HIOC had a significantly lengthened interval (27.1 months) until recurrence compared with the 31 patients who did not have hyperthermic cisplatin (12.8 months). Furthermore, the overall survival for the HIOC group (35.3 months) was improved compared with the group not treated with hyperthermic cisplatin (22.8 months).

Although some encouraging results of chemoperfusion have emerged from selected centers, the precise role of intracavitary chemotherapy with or without hyperthermia for thoracic malignancies with extensive pleural involvement is not clear. Further clinical trials are required to determine the ideal candidates, optimal chemotherapeutic agent(s), and the timing and temperature of the perfusate. Logical inclusion criteria would consist of patients with disease confined to one pleural cavity, ability for gross tumor removal of all local disease, and lack of distant extrathoracic metastasis.

MODALITIES CURRENTLY UNDER INVESTIGATION

Recent modalities under investigation for the treatment of lung tumors include bronchoscopy-guided RFA, high-intensity focused ultrasound, and irreversible electroporation. Results of both animal and human studies have demonstrated bronchoscopy-guided internally cooled RFA as a potentially "safe and feasible" procedure for the treatment of lung tumors.^{90,91} High-intensity focused ultrasound has been shown to target cancerous lesions with highly precise ablation. However, most clinical trials

evaluating the efficacy of high-intensity focused ultrasound are for malignancies other than lung cancer because of the inherent limitations (unfavorable environment for ultrasound application) of the ventilated lung. A recent study using *in vivo* porcine tumors and an *ex vivo* human lung model have proposed “lung flooding,” whereby the lung is filled with isotonic saline until functional residual capacity is reached, as a potential solution to the problems with the lung environment as a result of lung ventilation.⁹² Irreversible electroporation functions by the proposed mechanism of generating electrical pulses that affect the cellular membrane by the formation of pores (electroporation) causing irreversible cell death and tumor ablation.⁹³ Irreversible electroporation is different from other ablative techniques in that it causes tumor cell death with a nonthermal mechanism, which serves as the primary impetus for the application of this modality to tumor ablation. It is believed that irreversible electroporation is not susceptible to the “heat sink effect” caused by thermal ablation (RFA, MWA) and can therefore be used more efficiently adjacent to large vessels.⁹³⁻⁹⁶ Preliminary results of a recent porcine study indicate that irreversible electroporation has both a nonthermal and an “extracellular matrix sparing” mechanism of action for tumor ablation.⁹⁷

IMPLICATIONS FOR THORACIC SURGICAL ONCOLOGISTS

With the advent of percutaneous ablation techniques for the treatment of early-stage lung cancer, controversy has emerged regarding the optimal approach to treating these patients. Furthermore, with the National Lung Screening Trial (NLST) showing benefits of early detection of lung cancer in selected patients^{98,99} and with the increasing use of CT screening, many small lung lesions are being discovered, some of which are found in older adult and high-risk patients. Controversy with regard to percutaneous ablation techniques is driven by the emergence of novel technology that spans the practice venues of several disciplines, including interventional radiologists, pulmonologists, and thoracic surgical oncologists. Some are eager to proceed, but a careful comparison with surgery makes others wary to relinquish surgical management of patients with lung cancer. However, as patients’ natural tendency to seek out less invasive interventions continues, the detection of smaller, earlier, and more easily treatable lesions is becoming more commonplace, and we are seeing many patients choose the least invasive option. Thus, the question remains regarding which patients should be referred for these new, less invasive but potentially less effective treatments. Another remaining question is who should be performing these procedures—should it be experienced interventional radiologists with surgical backup, or thoracic surgeons with extensive experience in open and minimally invasive resection techniques who now have training in percutaneous CT-guided techniques, or a combined team approach whereby the radiologist performs the biopsy and the surgeon performs the ablation? A variety of scenarios have occurred at different centers,

based on institutional and departmental biases and the available expertise and interest of the surgical and radiology staff.

A similar procedural evolution occurred with the implementation of VATS techniques. The Society of Thoracic Surgeons/American Association for Thoracic Surgery position statement on VATS recommends that such procedures be performed by surgeons familiar with open thoracic surgical approaches and the management of their complications. The surgeon must have the judgment, training, and capability to proceed to an open thoracic procedure if necessary and should personally guide the preoperative and postoperative care of the patient.¹⁰⁰ Although some interventional radiologists may have the experience and ability to perform difficult percutaneous interventions, there is great variability in their clinical training, and many may have never studied or treated patients with lung cancer. Conversely, many thoracic surgeons have dedicated their entire training and career to treating lung cancer and perform minimally invasive and percutaneous procedures on a routine basis. Thoracic surgeons are specifically trained in the areas of pulmonary physiology, thoracic oncology, pulmonary surgery, and lymph node evaluation and are personally capable of managing procedure-related complications. In addition, they have been, and continue to be, involved in the primary workup and follow-up care of patients with lung cancer and have developed a historical association with consultants in the management of this disease.

There is no doubt, however, that complacency of thoracic surgical leadership can lead to a critical deficiency in embracing and incorporating these new techniques in a timely manner, resulting in a loss of thoracic surgeons trained in the appropriate application of these modalities. Credentialing is also an important and controversial issue. Hospital administration and departmental guidelines have to be established to identify those physicians approved to conduct these procedures. Surgeons need to complete a dedicated didactic session covering the basic knowledge base and techniques, in conjunction with a period of proctorship until proficiency is demonstrated after performing a prescribed number of supervised interventions. Currently, there are no nationally accepted standards for the credentialing of surgeons to perform RFA within the chest.

Gaining access to a CT scanner can also be a complicated process. Operating rooms with built-in CT scanners offer the ideal environment for performing these procedures but are not yet available in many centers. However, in the operating room setting, the necessary surgical equipment and staff are on hand, making the procedure and any complications safer and more efficient to manage. If the procedures must be performed in the radiology suite, thoracic surgeons should work in a collaborative fashion with the interventional radiology colleagues. The room must be capable of supporting an anesthesia circuit, with built-in oxygen and suction. All supplies related to the procedure must be stored on-site or in a portable cart. Quality assurance programs must be implemented to ensure optimal patient outcomes, with a database monitoring treatment morbidity and mortality profiles. Thoracic surgeons are best suited to

make the decision as to which surgical or ablative modality to use in any given clinical setting. Whether to use an open, thorascopic, percutaneous technique or SRS to manage a patient with a small pulmonary nodule requires careful judgment and expertise with each technique to ensure an optimal oncologic outcome. Certainly, percutaneous and other ablative therapeutic modalities will ultimately have a role in high-risk patients with compromised lung function.

Decision making can be even more complex in managing patients with difficult lesions, such as ground glass opacities. These lesions tend to be small and slow-growing and have a more indolent natural history. Some of these lesions may represent carcinoma in situ or minimally invasive cancers in which case anatomic resection with or without lymph node dissection may not always be necessary.¹⁰¹ The use of percutaneous ablative techniques in this setting may represent an ideal utilization of the technology.

As these innovative techniques are developed and refined, careful attention must be paid to several important pitfalls, including overapplication in the setting of indeterminate solitary pulmonary nodules, inappropriate or inadequate management of small to medium-sized lung tumors, inappropriate interventions directed toward metastatic disease, and the risk of inadequately staging patients prior to intervention. To avoid these pitfalls, thoracic surgeons should maintain a leadership position in the deployment of these techniques for the treatment of patients with thoracic malignancies.

SUMMARY

RFA and SRS have been demonstrated to be safe with reasonable efficacy in the treatment of small lung tumors. RFA appears to have a higher rate of local progression when compared with SRS; however, with evolving techniques of tumor localization for image-guided ablation of tumors, these results may improve with more precise image-guided percutaneous ablation.²⁹ RFA can be performed in one treatment session, whereas it now appears that SRS is more effective if larger doses of radiation over three to four fractions are performed. RFA is not recommended for centrally based tumors. In addition, for some tumors (e.g., small apical tumors, posteriorly positioned tumors close to the diaphragm, and tumors close to the scapula) it may be difficult to accurately place the probe percutaneously. Patients with these types of tumors are more optimally treated with SRS. SRS with a high BED appears to be an effective modality for patients who are not operable candidates. As a result of the increased toxicity of a 60-Gy dose (in three fractions) for central tumors, a modified dose schema with a lower dose is required for patients with central tumors. We use a dose of 60 Gy in three fractions for peripheral lesions, and we use a modified dose schema with 48 Gy in four fractions for central tumors. In certain circumstances, a combined approach (RFA and SRS) may be beneficial.

Experience with MWA and cryotherapy is currently too limited to assess its value in the armamentarium against lung cancer; further investigations are ongoing.

MWA treatment times and heat-sink effect may be less with respect to RFA. This may prove to be protective, minimizing the necrosis of large blood vessels and reducing the risk of fatal hemoptysis. Future studies need to address long-term outcomes using standardized assessments of treatment response between centers. Comparisons among different RFA and SRS systems must be undertaken to delineate the optimal use of these strategies in the treatment of early-stage lung cancer. Until long-term data with these ablative techniques become available, surgical resection should be performed when clinically possible.

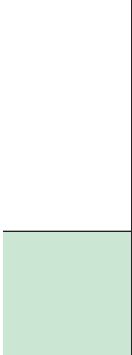
Although surgical resection remains the gold standard for local control of pulmonary malignancies, newer technologies such as RFA and SRS hold the potential for less invasive treatment in the future. We anticipate that these newer, less invasive techniques will complement existing minimally invasive surgical treatments, which may further ease the burden of treatment and ultimately improve the survival in selected high-risk patients with pulmonary tumors. Critical appraisal of these techniques over the next decade will establish their role, and the thoracic surgical oncologist must remain abreast of the evolving technology, playing an active leadership role in its evaluation.

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SECTION 2

ADULT CARDIAC SURGERY

SECTION OUTLINE

PART A	BASIC SCIENCE	PART F	SURGICAL MANAGEMENT OF VALVULAR HEART DISEASE
PART B	DIAGNOSTIC PROCEDURES	PART G	MANAGEMENT OF CARDIAC ARRHYTHMIAS
PART C	MEDICAL- AND CATHETER-BASED TREATMENT OF CARDIOVASCULAR DISEASE	PART H	SURGICAL MANAGEMENT OF CORONARY ARTERY DISEASE AND ITS COMPLICATIONS
PART D	PERIOPERATIVE AND INTRAOPERATIVE CARE OF THE CARDIAC SURGICAL PATIENT	PART I	SURGICAL MANAGEMENT OF HEART FAILURE
PART E	SURGICAL MANAGEMENT OF AORTIC DISEASE		

PART A

BASIC SCIENCE

PART OUTLINE

47 SURGICAL ANATOMY OF THE HEART
48 VASCULAR PHYSIOLOGY
49 PHYSIOLOGY OF THE MYOCARDIUM

50 VENTRICULAR MECHANICS
51 BLOOD COAGULATION, TRANSFUSION, AND
CONSERVATION

SURGICAL ANATOMY OF THE HEART

Andrew C. Cook • Benson R. Wilcox[†] • Robert H. Anderson

CHAPTER OUTLINE

LOCATION OF THE HEART

MORPHOLOGICALLY RIGHT ATRIUM

MORPHOLOGICALLY LEFT ATRIUM

MORPHOLOGICALLY RIGHT VENTRICLE

MORPHOLOGICALLY LEFT VENTRICLE

AORTA

PULMONARY TRUNK AND BRANCH PULMONARY ARTERIES

CORONARY ARTERIES AND VEINS

In this chapter, we provide a brief overview of cardiac structure as it is relevant for the cardiac surgeon. We describe the heart as it is located in the body in its anatomic, or attitudinally correct, position.¹ Whenever possible, however, we illustrate the cardiac components as they would be viewed by the surgeon during an operative procedure, whether the pictures were taken in the operating room or are of anatomic specimens.² In some instances, information is best presented with the heart photographed in a nonsurgical orientation. When this occurs, it is clearly stated.

LOCATION OF THE HEART

Regardless of the surgical approach, the surgeon who enters the mediastinum is confronted by the heart enclosed in its pericardial sac. The sac is freestanding around the atrial chambers and the ventricles, but it becomes adherent to the adventitial coverings of the great arteries and veins at their entrances to and exits from the heart, where these attachments close the pericardial cavity. The pericardial cavity is contained between the two layers of the serous pericardium, a thin-walled sac folded on itself within the fibrous cavity. The inner layer, or epicardium, is firmly attached to the myocardium, whereas the outer layer is adherent to the fibrous pericardium. The pericardial cavity, therefore, is the space between the inner lining of the fibrous pericardium and the surface of the heart (Fig. 47-1). By virtue of the shape of the cardiac chambers and the great arteries, there are two recesses within this cavity that are lined by serous pericardium. The first is the transverse sinus, a horseshoe-shaped space behind the great arteries and in front of the atria (Fig. 47-2). Laterally on each side, the ends of the transverse sinus are in free communication

with the rest of the pericardial cavity. The second pericardial recess is the oblique sinus, a blind-ending cavity behind the left atrium (Fig. 47-3).

Most of the cardiac surface facing the surgeon is occupied by the so-called right heart, which in reality is anterior. Thus, the surgeon is confronted by the extensive appendage of the right atrium, receiving the superior caval vein at its superior border. To the left are the aorta and the pulmonary trunk, exiting from the base of the heart and extending in a superior direction, with the aortic root in an inferior and rightward position. When the aortic root is not in this “normal” relationship, the ventriculoarterial connections are almost always abnormal. The morphologically right appendage has a characteristic shape, being triangular and possessing a broad junction with its venous component (Fig. 47-4). The morphologically left appendage might not be seen immediately. If searched for, it is found as a tubular, meandering structure at the left border of the pulmonary trunk (Fig. 47-5), having a narrow junction with the rest of the atrium.

The ventricular mass then extends to the cardiac apex, which normally reaches into the left hemithorax. The overall cardiac silhouette is usually positioned with one third of its bulk to the right and two thirds to the left of the midline (Fig. 47-6). An anomalous position of either the ventricular mass or the apex is highly suggestive of the presence of congenital cardiac malformations, although not always. In shape, the ventricular mass is a three-sided pyramid, having (1) diaphragmatic, (2) anterior or sternocostal, and (3) left or pulmonary surfaces. The margin between the first two surfaces is sharp; therefore, it is called the acute margin. The transition between the sternocostal and pulmonary surfaces is more gradual and rounded. For the surgeon, it is the pulmonary surface that is considered to be the obtuse margin, as it is irrigated by the obtuse marginal arteries (Fig. 47-7). The greater part of the anterior surface of the ventricular mass

[†]Deceased.

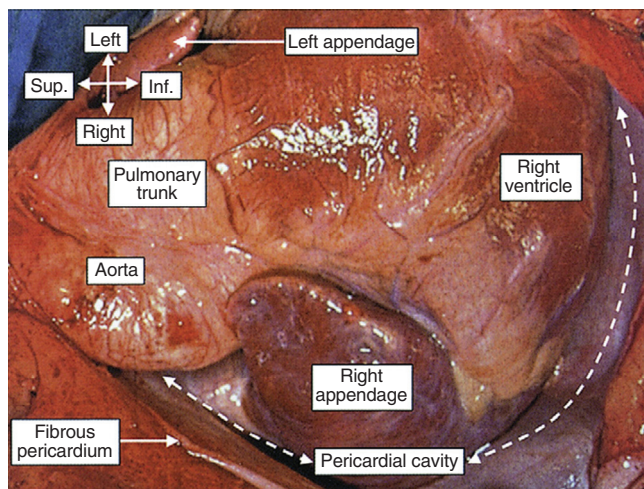


FIGURE 47-1 ■ The heart is shown as seen by the surgeon through a median sternotomy. The pericardial cavity has been opened and is between the fibrous pericardium and the epicardium. The compass shows the orientation. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

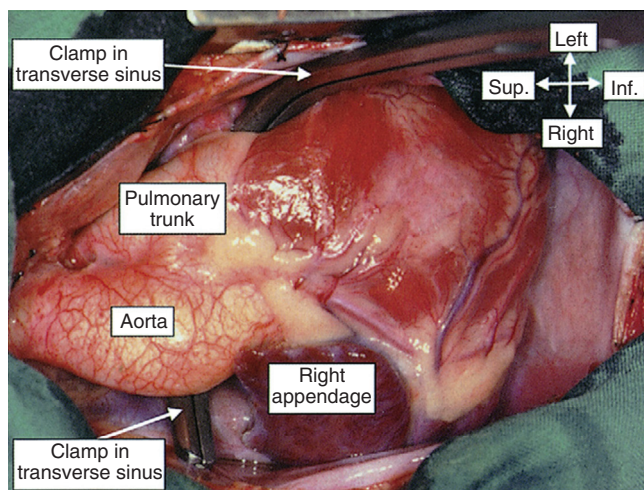


FIGURE 47-2 ■ With the pericardium opened in the operating room, the surgical clamp has been passed through the transverse sinus of the pericardium, which is between the back of the arterial trunks and the front of the atrial chambers. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

is occupied by the morphologically right ventricle. Its left border is marked by the anterior interventricular, or descending, branch of the left coronary artery, and its right border is marked by the right coronary artery, which runs obliquely in the atrioventricular groove.

Appreciating the surface anatomy of the heart is helpful in determining the most appropriate site for an incision to gain access to a given cardiac chamber.² For example, the relatively bloodless outlet portion of the right ventricle just beneath the origin of the pulmonary trunk affords ready access to the ventricular cavity. The important landmark for the right atrium is the terminal groove, or sulcus terminalis, which marks the border

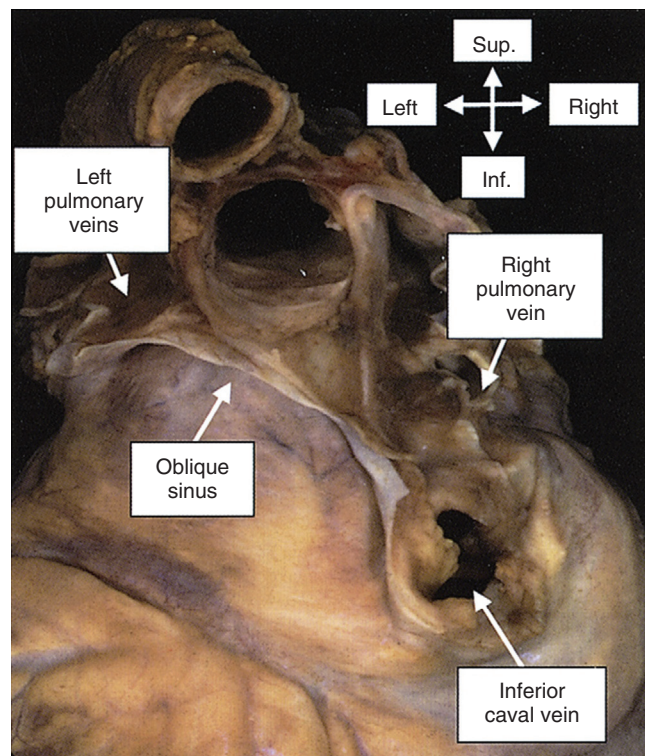


FIGURE 47-3 ■ This anatomic specimen has been removed from the body and is viewed from behind, with the apex pointing downward. The oblique sinus of the pericardium is seen between the pericardial reflections around the pulmonary veins and the inferior caval vein. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

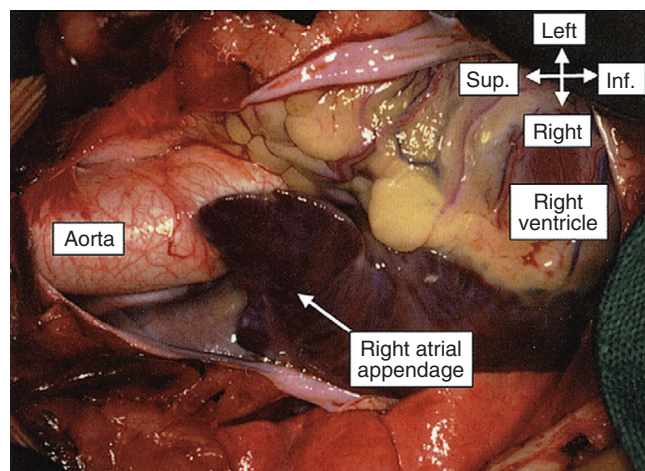


FIGURE 47-4 ■ This picture of the heart, as seen in the operating room through a median sternotomy, shows the typical triangular appearance of the morphologically right atrial appendage. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

between the appendage and the venous component (Fig. 47-8). The sinus node is typically located in this groove, usually laterally in the superior cavoatrial junction inferior to the crest of the appendage. Posterior and parallel to the terminal groove is a second, deeper groove between

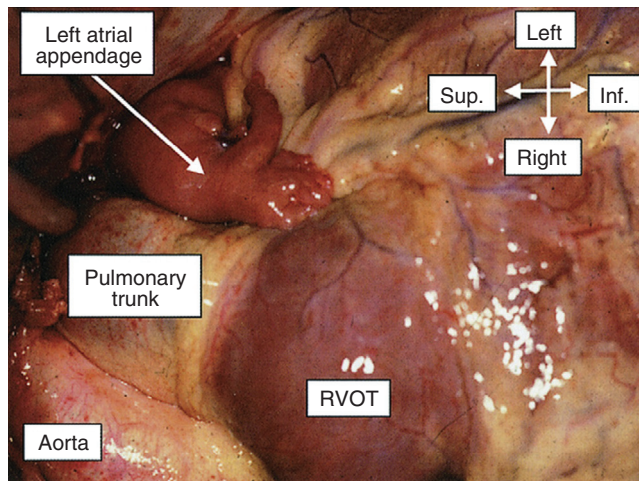


FIGURE 47-5 ■ With the pericardium opened through a median sternotomy, the heart is rotated slightly to show the typical tubular configuration of the morphologically left atrial appendage. *Inf.*, Inferior; *RVOT*, right ventricular outflow tract; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

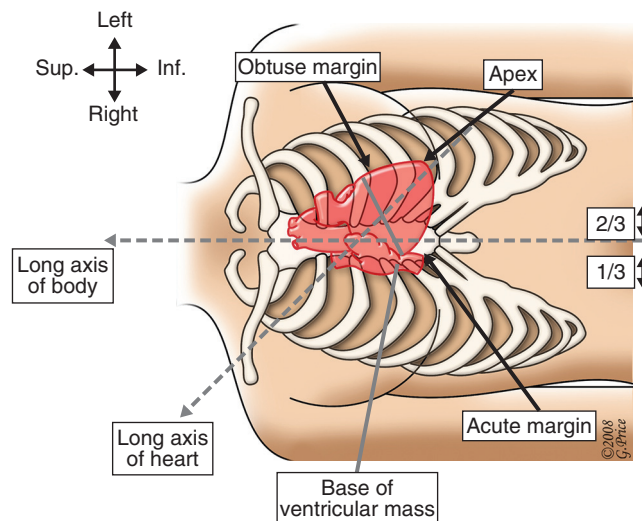


FIGURE 47-6 ■ The cardiac structure placed in the context of the chest as would be seen by a surgeon standing on the right side of the operating table. Note that in the usual situation, two thirds of the cardiac silhouette are positioned to the left of the midline. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original diagram from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

the right atrium and the right pulmonary veins. Dissections into this deep interatrial groove, also known as Waterston or Sondergaard groove, permit incisions to be made into the left atrium (Fig. 47-9).

MORPHOLOGICALLY RIGHT ATRIUM

The right atrium has three components: the appendage, the venous sinus receiving the systemic venous return, and the vestibule. It is separated from the left atrium by the septum. As mentioned, the junction between the

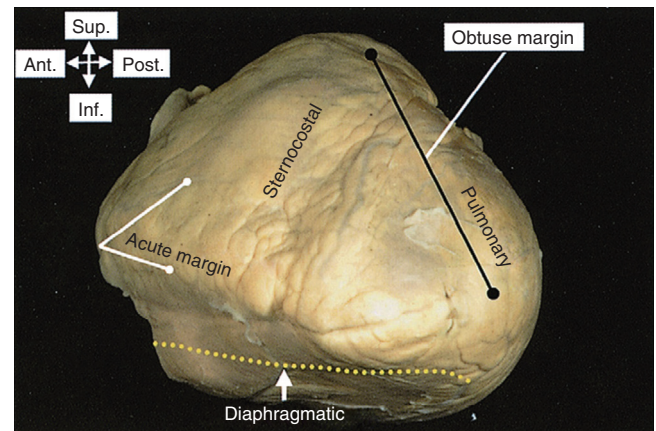


FIGURE 47-7 ■ This heart has been removed from the thorax and is viewed from the apex, looking toward the base of the ventricular mass. It shows the surfaces of the ventricular mass and the locations of the acute and obtuse margins. *Ant.*, Anterior, *Inf.*, inferior; *Post.*, posterior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

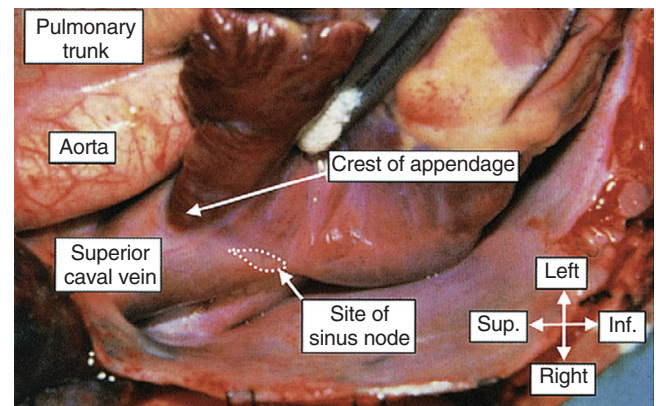


FIGURE 47-8 ■ In this picture, taken in the operating room, the surgeon has reflected the atrial appendage to show the location of the terminal groove and the crest of the appendage. Note the site of the sinus node (*dotted lines*). *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

appendage and the venous sinus is marked externally by the prominent terminal groove. Internally, the groove corresponds with the position of the terminal crest (*crista terminalis*), which gives origin to the pectinate muscles of the appendage (Fig. 47-10). Significantly, the pectinate muscles within the appendage encircle the full extent of the third component, the vestibule, which is the smooth muscle encircling the orifice of the tricuspid valve (Fig. 47-11). This extensive array of pectinate muscles serves to identify an atrium as being morphologically right even when abnormally located, or when duplicated as seen in isomerism.³ Superiorly and anteriorly, the appendage terminates in a prominent crest that forms the summit of the terminal groove and continues in the transverse sinus behind the aorta across the interatrial groove as Bachmann bundle (Fig. 47-12). The sinus node lies in the terminal groove in an immediately subepicardial position. It is a spindle-shaped structure that usually lies to

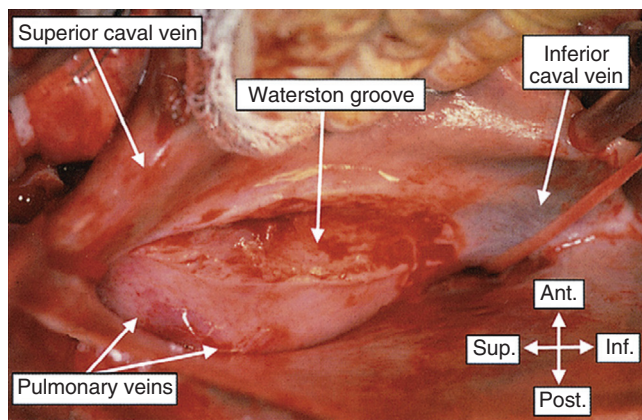


FIGURE 47-9 ■ In this view through a median sternotomy, the surgeon has incised through the epicardium covering Waterston groove, showing the base of the deep fold between the systemic venous tributaries and the right pulmonary veins. *Ant.*, Anterior; *Inf.*, inferior; *Post.*, posterior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

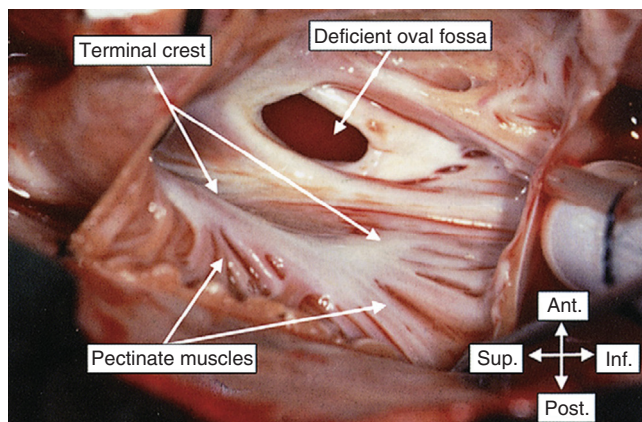


FIGURE 47-10 ■ Opening the right atrial appendage in this patient with a defect in the oval fossa reveals the markedly different configuration of the endocardial surfaces of the pectinate appendage as opposed to the smooth-walled systemic sinus. The pectinate muscles originate from the terminal crest, marked externally by the terminal groove (see Fig. 47-7). *Ant.*, Anterior; *Inf.*, inferior; *Post.*, posterior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

the right of the crest—that is, lateral to the superior cavoatrial junction. In approximately one tenth of cases, the node extends across the crest into the interatrial groove, draping itself across the cavoatrial junction in horseshoe fashion.⁴ For the surgeon, the artery to the sinus node is also of significance. It is a branch of the right coronary artery in approximately 55% of individuals and a branch of the circumflex artery in the remainder.⁵ Regardless of its origin, it usually courses through the anterior interatrial groove toward the superior cavoatrial junction, frequently running within the atrial myocardium. Having reached the cavoatrial junction, the artery may cross the crest of the appendage, course

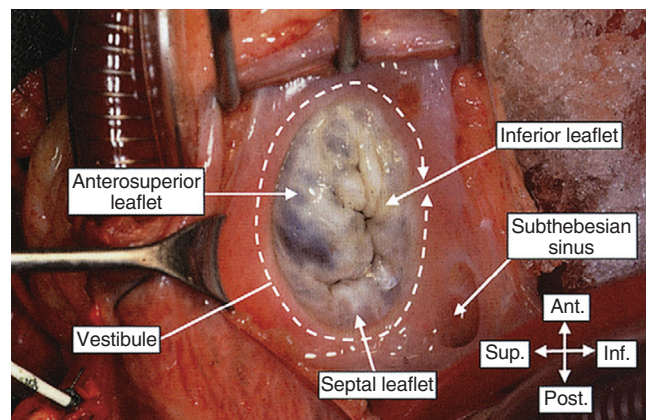


FIGURE 47-11 ■ The right atrium has been opened to show the smooth vestibule of the tricuspid valve. The three leaflets of the valve are positioned septally, anterosuperiorly, and inferiorly. Note the extensive subthebesian sinus, often described as subeustachian when the heart is viewed in attitudinally incorrect fashion. *Ant.*, Anterior; *Inf.*, inferior; *Post.*, posterior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

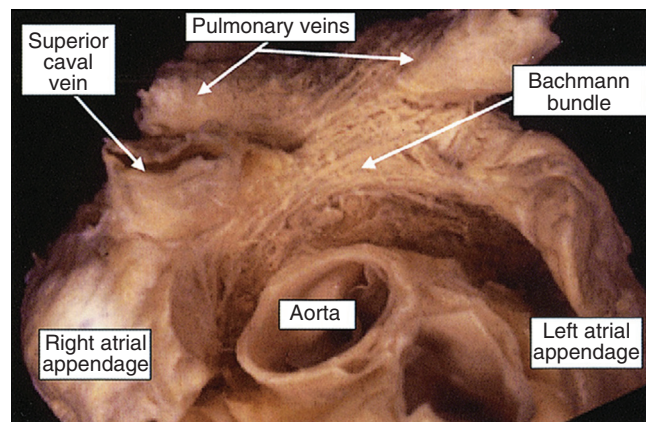


FIGURE 47-12 ■ The heart has been photographed from in front, after the epicardium has been removed from the surface of the anterosuperior interatrial groove. Note the broad sweep of parallel fibers that extend from the crest of the atrial appendage in front of the superior caval vein toward the left atrial appendage. This is Bachmann bundle. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

retrocavally, or even divide to form an arterial circle around the junction.

On first sight, when inspecting the internal morphology of the right atrium, there appears to be an extensive septal surface between the orifices of the caval veins and the orifice of the tricuspid valve. The apparent extent of this septum is spurious.^{6,7} The true septum between the right and left atrial chambers is formed by the floor of the oval fossa (derived from the fetal flap valve), and its adjacent anteroinferior muscular rim.⁶ The extensive superior rim, or the so-called septum secundum, is formed by a deep interatrial fold extending between the systemic and the pulmonary veins (Fig. 47-13). The larger part of the anterior atrial wall is folded around the aortic root. That the margins of the true atrial septum

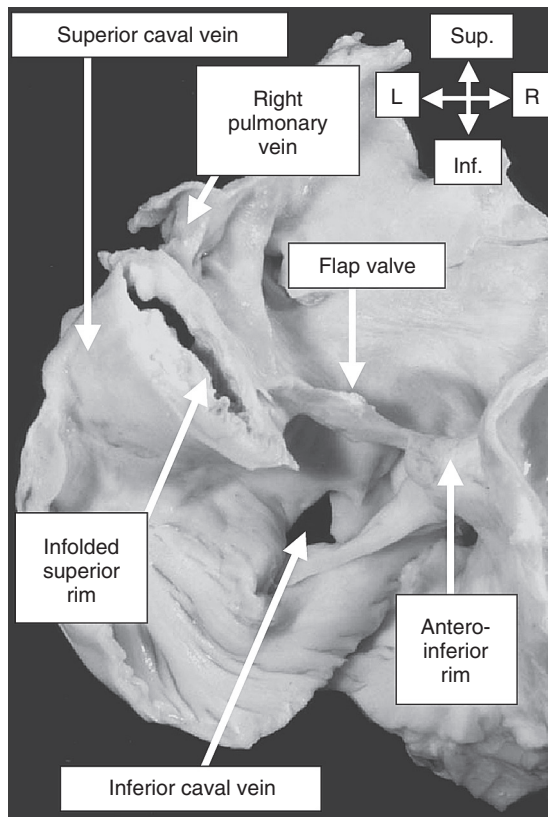


FIGURE 47-13 ■ This heart has been sectioned in four-chamber fashion through the oval fossa. The section shows that the so-called septum secundum is no more than the infolded atrial walls between the tributaries of the systemic venous sinus and the right pulmonary veins. The true septal structures are the floor of the oval fossa (flap valve) and its hinge point from the antero-inferior rim. *Inf.*, Inferior; *L*, left; *R*, right; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

are limited is of major surgical importance, as it is easy to pass outside the heart when attempting to gain access to the left atrium through a right atrial approach.

In addition to the position of the sinus node, and the extent of the atrial septum, the other major area of surgical significance in the right atrium is the site of the atrioventricular node. This is contained within the triangle of Koch (Fig. 47-14). This important landmark is demarcated by the tendon of Todaro, the attachment of the septal leaflet of the tricuspid valve, and the orifice of the coronary sinus.⁸ The tendon of Todaro is a fibrous structure formed by the union of the eustachian and thebesian valves. The fibrous extension of these two valvar remnants buries itself in the tissue separating the oval fossa from the mouth of the coronary sinus, and it runs medially as the tendon of Todaro, which inserts into the central fibrous body. The entire atrial component of the axis of atrioventricular conduction tissues is contained within the confines of the triangle of Koch. If, in hearts with normal segmental connections, this area is scrupulously avoided during surgical procedures, the atrioventricular conduction tissues will not be damaged. The node itself, located in the smooth atrial musculature of the triangle, is some distance above the hinge point of

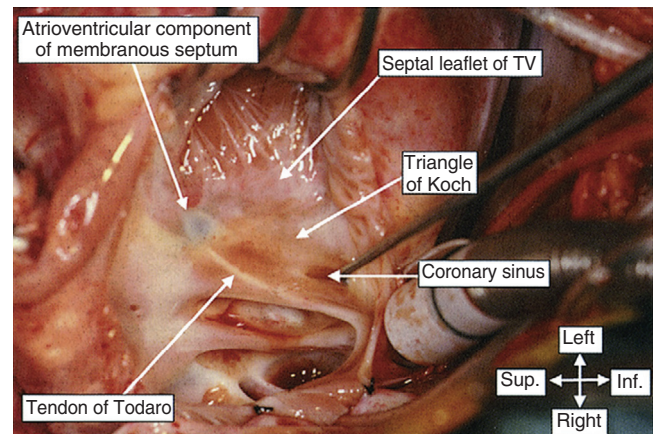


FIGURE 47-14 ■ The right atrium has been opened through a median sternotomy to show the landmarks of the triangle of Koch. In this patient, the continuation of the eustachian valve through the tendon of Todaro is clearly seen, with the tendon inserting into the atrioventricular component of the central fibrous body. *Inf.*, Inferior; *Sup.*, superior; *TV*, tricuspid valve. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

the septal leaflet of the tricuspid valve. The atrioventricular bundle, however, penetrates more or less directly at the apex of the triangle of Koch.

Much has been written in recent years about the role of “specialized” pathways of tissue in conduction of the sinus impulse to the atrioventricular node.^{9,10} It can now be stated with certainty that there are no insulated or isolated tracts of specialized conduction tissue extending between the nodes that can be avoided surgically, as is possible with the penetrating and branching atrioventricular bundles.¹¹ The major muscle bundles of the atrial chambers serve as preferential pathways of conduction, but the course of these preferential pathways is dictated by the overall geometry of the chambers. Ideally, prominent muscle bundles, such as the terminal crest or the superior rim of the oval fossa, should be preserved during atrial surgery. But even if they cannot be preserved, the surgeon can be sure that internodal conduction will continue as long as some strand of atrial myocardium connects the nodes, provided that the arterial supply to the nodes, or the nodes themselves, are not traumatized. The key to avoidance of postoperative atrial arrhythmias, therefore, is the fastidious preservation of the sinus and atrioventricular nodes and their arteries.²

The central fibrous body touches on three of the four cardiac chambers, but it is in the right atrium that it becomes first, and perhaps most clearly, evident to the surgeon (see Fig. 47-14). Rather than being a specific body, it is better conceptualized as an area in the heart where the membranous septum and the leaflets of the atrioventricular and aortic valves join in fibrous continuity. When viewed from the left heart (Fig. 47-15), it is possible to assess its proximity to the aortic and mitral valves and to the left bundle branch of the conduction axis. Because of this intimate relationship to so many important structures in the heart, the central fibrous body acts as an anatomic focal point for the cardiac surgeon.²

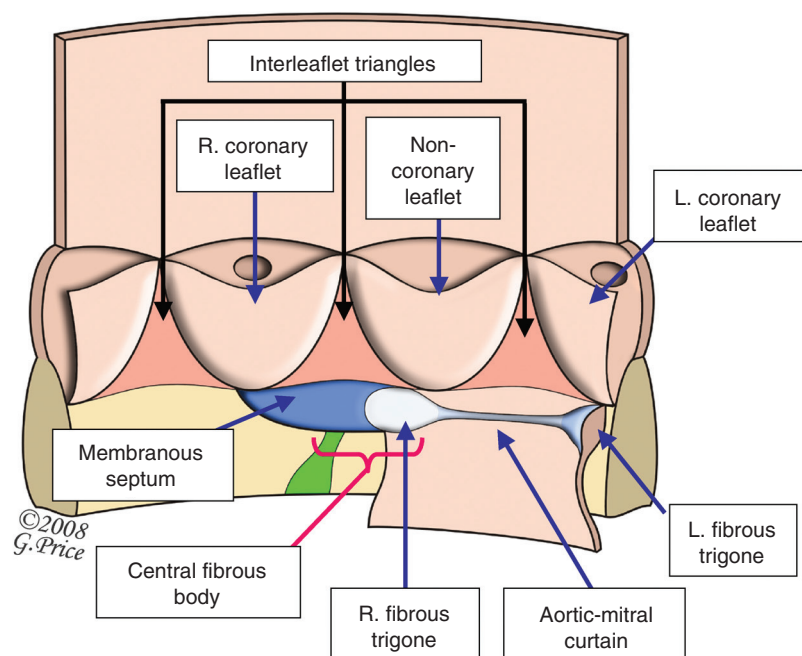


FIGURE 47-15 ■ The left ventricular aspect of the aortic root, illustrating the various components of the fibrous skeleton. The area of fibrous continuity between the leaflets of the aortic and mitral valves is thickened at both ends to form the so-called fibrous trigones. As can be seen, the right trigone is then continuous with the membranous septum, with these structures forming the central fibrous body. Note that the membranous septum itself continues upward to the sinotubular junction as one of the fibrous interleaflet triangles of the aortic root. Note also the location of the left bundle branch (see Fig. 47-26). *L*, Left; *R*, right. (Copyright for the original diagram from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

The vestibule of the atrium, surrounding the orifice of the tricuspid valve, is continuous with both the venous component and the appendage of the right atrium. Its anterosuperior part overlies the anteroseptal commissure of the tricuspid valve and continues along the supraventricular crest of the right ventricle. The posteroinferior component extends beneath the orifice of the coronary sinus, where there is usually an extensive trabeculated diverticulum found behind the sinus, the so-called post-eustachian sinus of Keith.

MORPHOLOGICALLY LEFT ATRIUM

Because of its position, only the appendage of the left atrium may be immediately evident to a surgeon upon exposing the heart. Like the right atrium, the left atrium has a venous component, an appendage, and a vestibule, and it is separated from its partner by the septum. In addition, the left atrium possesses a well-formed body, forming the dome of the atrium when the veins are connected anomalously, as in totally anomalous pulmonary venous connection. Unlike that of the right atrium, however, the venous component of the left atrium is considerably larger than the appendage, and the narrow junction between these two parts is not marked by either a terminal groove or a crest (Fig. 47-16). The pectinate muscles are confined within the appendage, and again, unlike on the right side, they do not extend around the vestibule.³ This difference in the extent of the pectinate muscles always permits the morphologically right appendage to be distinguished from the morphologically left structure. Because of its posterior position and its firm anchorage by the four pulmonary veins, direct access to the left atrium can be difficult; therefore, surgeons must use their knowledge of anatomy to gain the best exposure of the cavity. Probably the most popular route is an

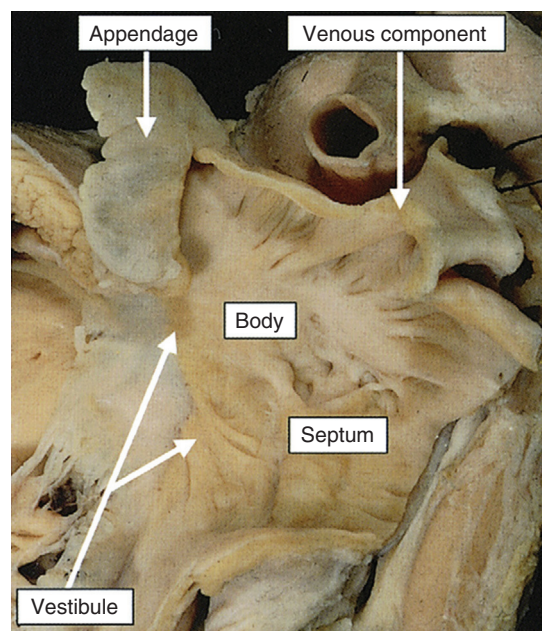


FIGURE 47-16 ■ The morphologically left atrium is photographed from its left side to show the component parts. Note the extensive body, which also receives the septal aspect of the chamber. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

incision made just posterior to the interatrial groove. As described, this extensive infolding between the right pulmonary veins and the systemic veins produces the superior rim of the oval fossa. A posteriorly directed incision along this groove takes the surgeon directly into the left atrium. Because the infolding of the interatrial groove also forms the superior border of the oval fossa, much the same access can be gained by approaching through the

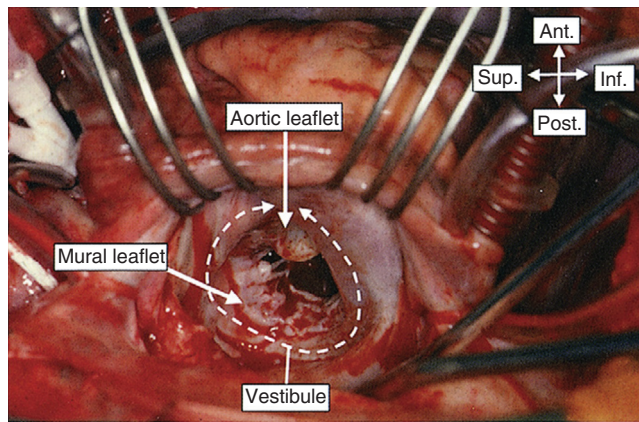


FIGURE 47-17 ■ The left atrium is photographed in the operating room through an incision made in the dome. Note the vestibule of the mitral valve, which has aortic and mural leaflets. *Ant.*, Anterior; *Inf.*, inferior; *Post.*, posterior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

right atrium and incising just superiorly within the fossa. A further approach to the left atrium is the so-called superior approach, incising directly through the roof.

Once access is gained to the left atrium, the small size of the opening of the appendage is apparent, lying to the left of the mitral orifice as viewed by the surgeon. The greater part of the pulmonary venous atrium is usually located inferiorly, away from the operative field, and the vestibule of the mitral orifice dominates the picture (Fig. 47-17). The septal aspect is anterior, exhibiting the typically roughened flap-valve aspect of its left side (see Fig. 47-16). The large sweep of tissue between the flap-valve of the septum and the opening of the appendage is the internal aspect of the deep anterior interatrial groove.

MORPHOLOGICALLY RIGHT VENTRICLE

Understanding of ventricular morphology is greatly aided by considering the ventricles in terms of three components (Fig. 47-18), rather than in terms of the traditional sinus and conus parts.¹² The inlet portion of the right ventricle contains, and is limited by, the tricuspid valve and its tension apparatus. The leaflets of the valve are positioned septally, inferiorly (or murally), and anterosuperiorly. The most constant distinguishing feature of the valve is the direct attachments to the septum of the cords of its septal leaflet (Fig. 47-19). The trabecular component of the right ventricle extends out to the apex, where its wall is particularly thin and is especially vulnerable to perforation by cardiac catheters and pacemaker electrodes. The outlet component of the right ventricle is a complete muscular structure, the infundibulum, which supports the pulmonary valve. The three leaflets of the pulmonary valve do not have a ring or an annulus. Instead, they are attached to the infundibular musculature in semilunar fashion (Fig. 47-20), the semilunar hinge-points crossing the anatomic ventriculoarterial junction, which does form a complete ring, as does

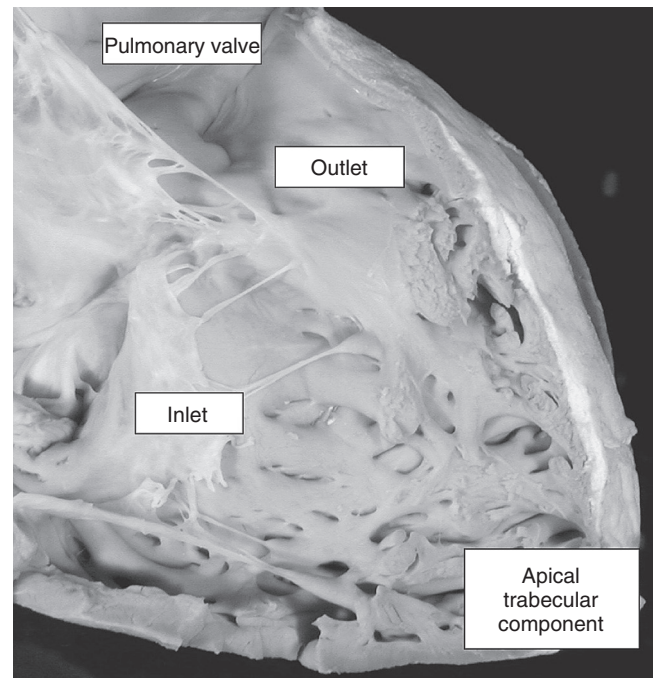


FIGURE 47-18 ■ The morphologically right ventricle is opened in a clamlike fashion and the septal surface is photographed to show its three component parts. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

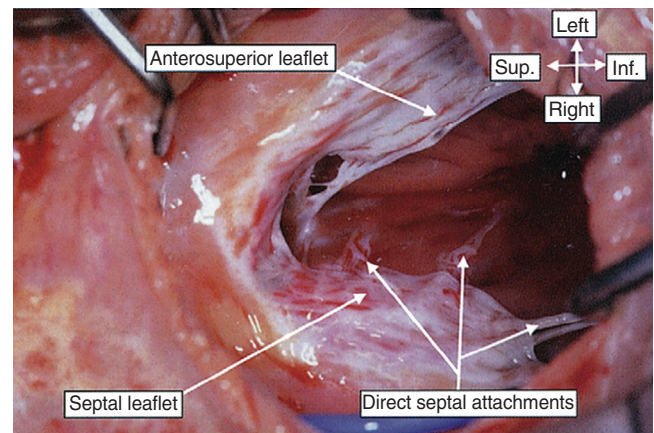


FIGURE 47-19 ■ The tricuspid valve is seen through the right atrium in the operating room. Note the tendinous cords that attach the septal leaflet directly to the septum. This is the most characteristic morphologic feature of the tricuspid valve. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

the sinotubular junction.¹³ The basal attachments of the leaflets are attached in the ventricle, upstream relative to the anatomic ventriculoarterial junction, whereas the peripheral attachments are to the arterial sinotubular junction. The overall valvar structure, therefore, takes the form of a three-pointed coronet (Fig. 47-21).

A distinguishing feature of the right ventricle is the prominent muscular shelf separating the tricuspid and pulmonary valves: the supraventricular crest. Although at first sight it looks like a large muscle bundle, much of the

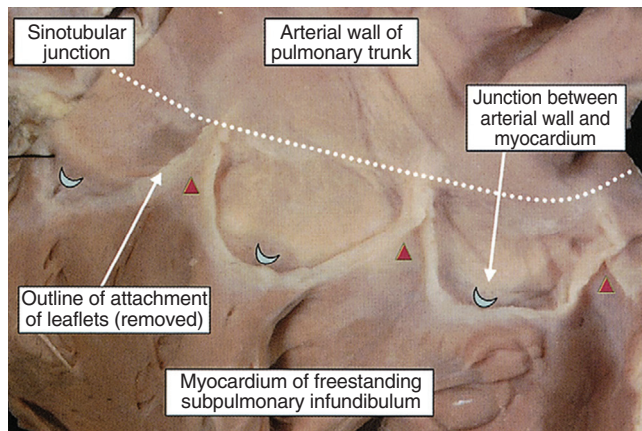


FIGURE 47-20 ■ The pulmonary outflow tract has been opened, and the leaflets of the pulmonary valve have been removed, showing their initial semilunar attachment. The most distal attachment is to the sinotubular junction (*dotted line*). Proximally, the hinge point incorporates right ventricular musculature into the base of each pulmonary valvar sinus (*gray crescents*). Fibrous triangles composing the wall of the pulmonary trunk (*red triangles*) are incorporated into the ventricular outflow tract. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

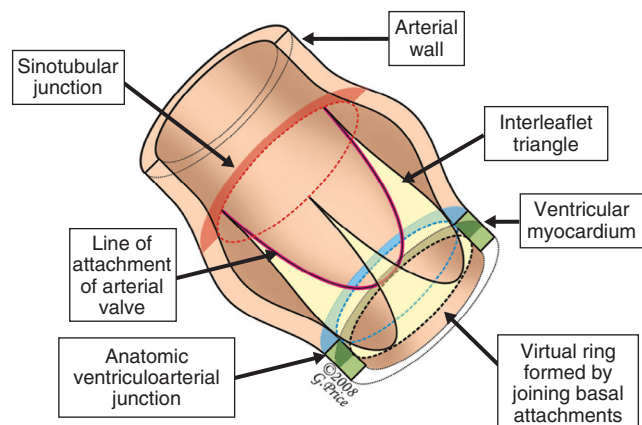


FIGURE 47-21 ■ The idealized three-dimensional arrangement of the arterial valves. There is no ringlike annulus supporting the valvar leaflets. Instead, the leaflets are attached within the arterial root in crownlike fashion. (Copyright for the original diagram from which this figure was prepared belongs to Robert H. Anderson, Benson R. Wilcox, and Andrew C. Cook.)

crest is no more than the infolded inner heart curve. Incisions, or deep sutures through this part, run into the transverse sinus and right atrioventricular groove and can jeopardize the right coronary artery.¹⁴ The distal part of the crest is continuous with the freestanding subpulmonary infundibulum, the presence of this muscular sleeve permitting the valve to be removed and used as an autograft in the Ross procedure (Fig. 47-22). The body of the supraventricular crest inserts between the limbs of a prominent and important right ventricular septal trabeculation. This structure, called the *septomarginal trabeculation*, has superior and inferior limbs that clasp the crest. The superior limb runs up to the attachment of the

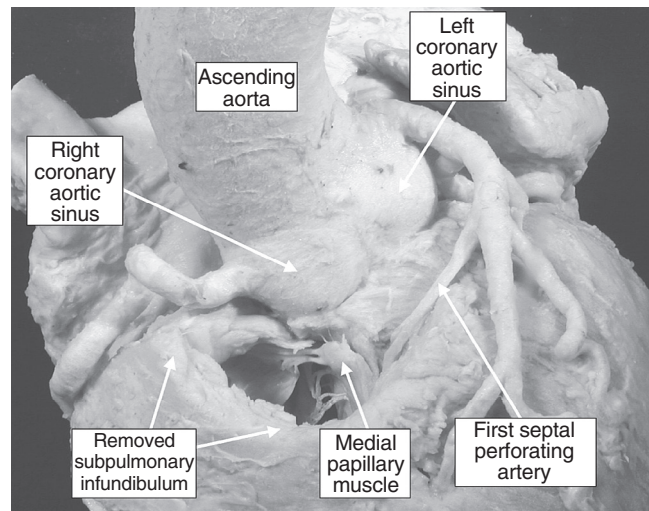


FIGURE 47-22 ■ The freestanding sleeve of subpulmonary infundibular musculature has been removed in this anatomic specimen, as the surgeon would remove the pulmonary valve during the Ross procedure. The dissection has not impinged on the cavity of the left ventricle. Note the location of the medial papillary muscle and the first septal perforating artery. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

leaflets of the pulmonary valve, whereas the inferior limb extends backward inferior to the interventricular component of the membranous septum. The characteristic medial papillary muscle (see Fig. 47-22) usually arises from this inferior limb, and a line extending from the muscle to the apex of the triangle of Koch marks the location of the atrioventricular conduction axis. The body of the septomarginal trabeculation runs to the apex of the ventricle, where it breaks up into a sheath of smaller trabeculations. Some of these mingle into the trabecular portion, and some support the tension apparatus of the tricuspid valve. Two trabeculations may be particularly prominent. One becomes the anterior papillary muscle of the tricuspid valve, and the other extends from the septomarginal trabeculation to the papillary muscle, forming the moderator band. Other significant right ventricular trabeculations are usually found in the transitional zone to the infundibulum. Variable in number, these are the septoparietal trabeculations (Fig. 47-23).

It is the coarseness of the apical trabeculations that is the most constant feature of the morphologically right ventricle when the chamber is malformed. In the normal heart, a number of morphologic differences exist between the two ventricles, including the arrangement of the leaflets of the atrioventricular valves and their tension apparatus, their shape, the thickness of their walls, and the configuration of the outflow tracts. These features, however, can be altered or lacking in the congenitally abnormal heart. When making the final arbitration, therefore, it is important to follow the “morphological method” introduced by Van Praagh and colleagues,¹⁵ which states that one variable feature should not be defined on the basis of another feature that is itself variable. When distinguishing ventricular morphology, therefore, it is necessary to rely on the contrast between

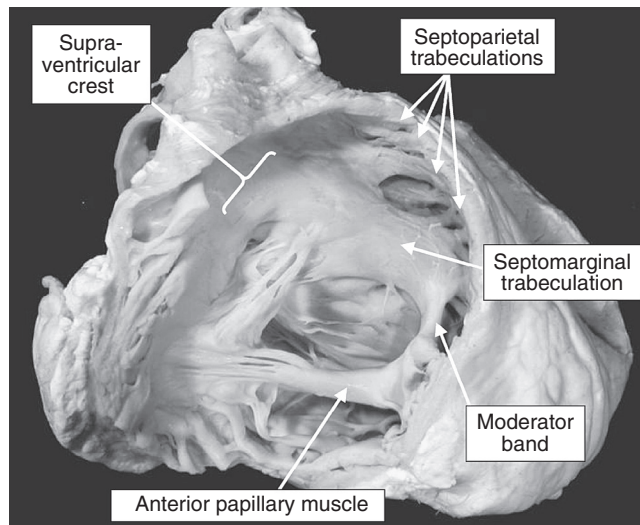


FIGURE 47-23 ■ This heart, seen in anatomic orientation, has been prepared by windowing the anterior wall of the right ventricle. The dissection reveals the continuation of the septomarginal trabeculation through the moderator band to the anterior papillary muscle, and shows well the multiple septoparietal trabeculations. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

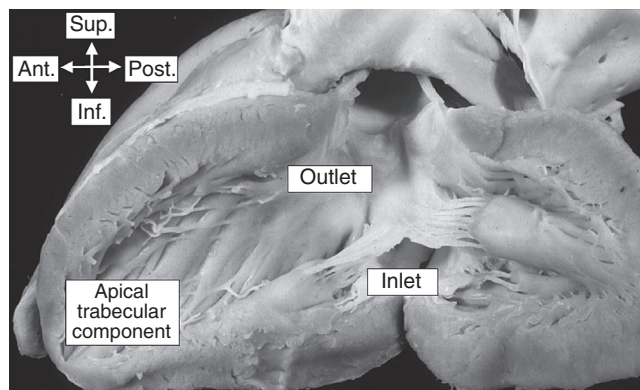


FIGURE 47-24 ■ The morphologically left ventricle is opened in clamlike fashion to show its three component parts. *Ant.*, Anterior; *Inf.*, inferior; *Post.*, posterior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

the coarse trabeculations of the right ventricle and those that are much finer in the apical part of the left ventricle.

MORPHOLOGICALLY LEFT VENTRICLE

The left ventricle is also conveniently considered in terms of inlet, trabecular, and outlet components (Fig. 47-24), although in contrast to the right ventricle, the inlet and outlet components overlap considerably in the morphologically left ventricle. The inlet component surrounds, and is limited by, the mitral valve and its tension apparatus. The two leaflets of the mitral valve, supported by two prominent papillary muscle groups and their

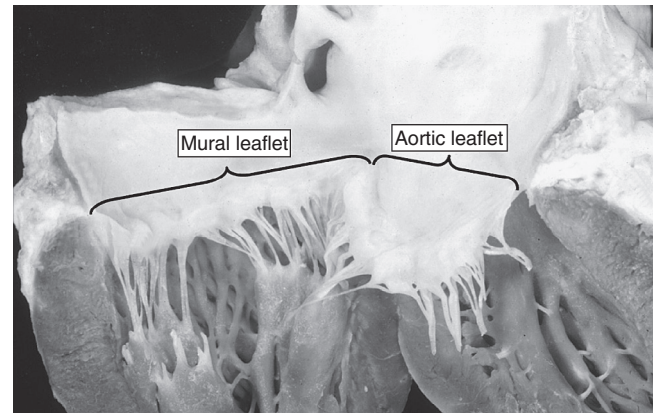


FIGURE 47-25 ■ The heart has been opened through the left atrioventricular junction, and it has been spread to show the difference in structure between the aortic and mural leaflets of the mitral valve. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

commissural cords and closing along a solitary zone of apposition, have widely different appearances (Fig. 47-25). The aortic leaflet is short, squat, and relatively square. This leaflet, which is in fibrous continuity with two of the leaflets of the aortic valve, is best termed the *aortic leaflet*, because it is not strictly in either an anterior or a superior position. The other leaflet is much shallower, and its junctional attachment is more extensive, being connected to the parietal part of the left atrioventricular junction; it is accurately termed the *mural leaflet*. Because the aortic leaflet of the mitral valve also forms part of the outlet of the left ventricle (Fig. 47-26), the distinction between inlet and outlet is somewhat blurred. The papillary muscles of the valve, located in anteroinferior and posterosuperior positions, are close to each other at their origin. The muscles are usually described as being posteromedial and anterolateral, but this is wrong, reflecting the penchant of previous anatomists, and others, to describe the heart as though positioned on its apex.¹ Unlike those of the tricuspid valve, the leaflets of the mitral valve have no direct septal attachments. The deep posterior diverticulum of the subaortic outflow tract displaces the aortic leaflet of the mitral valve away from the septum (see Fig. 47-26). The trabecular component of the left ventricle extends to the ventricular apex and has characteristically fine trabeculations (see Fig. 47-24).

As in the right ventricle, the apical myocardium is surprisingly thin. This feature is important to the cardiac surgeon who has reason to place catheters and electrodes in the right ventricle or drainage tubes in the left side.² Immediate perforation, or delayed rupture, can occur. The outlet component of the left ventricle supports the aortic valve. Unlike its right ventricular counterpart, it is not a complete muscular structure. The septal wall is largely composed of muscle, but the membranous septum forms part of the subaortic outflow tract. The posterior portion of the outflow tract is composed of the fibrous curtain joining the apparatus of the aortic valve to the aortic leaflet of the mitral valve (see Fig. 47-26). As with the pulmonary valve, the leaflets of the aortic valve are hinged in semilunar fashion, with the peripheral

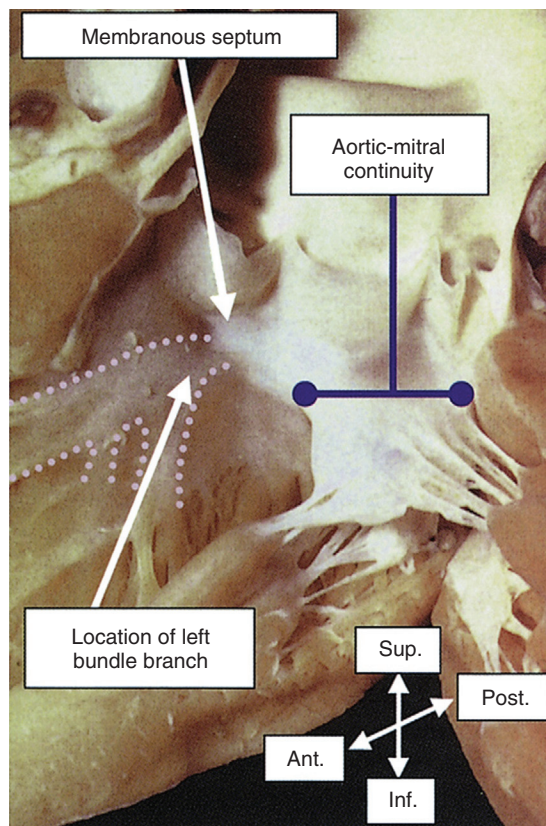


FIGURE 47-26 ■ The specimen is opened through the left ventricular outflow tract, showing the relationship of the left bundle branch to the membranous septum and the aortic root. Note the region of aortic to mitral valvar fibrous continuity. *Ant.*, Anterior; *Inf.*, inferior; *Post.*, posterior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

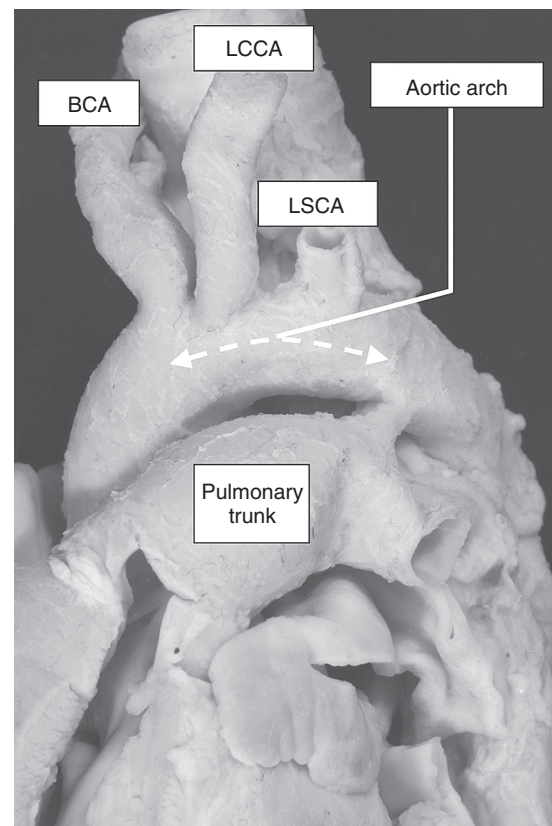


FIGURE 47-27 ■ The heart has been photographed from the left side in anatomic position to show the normal structure of the great arteries and the arterial duct. *BCA*, Brachiocephalic artery; *LCCA*, left common carotid artery; *LSCA*, left subclavian artery. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

attachments supported at the sinotubular junction, whereas the most basal parts take origin from ventricular structures. The overall arrangement is crownlike (see Fig. 47-21), rather than forming an annulus.^{13,16}

The muscular septal surface of the outflow tract is characteristically smooth, and down this surface cascades the fanlike left bundle branch. The landmark of the descent of the left bundle branch is the membranous septum immediately beneath the zone of apposition between the right coronary and noncoronary leaflets of the aortic valve (see Fig. 47-15). The bundle descends, initially, as a relatively narrow solitary fascicle, but soon it divides into three interconnected fascicles that radiate into anterior, septal, and posterior divisions. The interconnecting radiations do not fan out to any degree until the bundle itself has descended to between one third and one half the length of the septum.

AORTA

The ascending aorta begins at the distal extremity of the three aortic sinuses, the sinotubular junction, which lies at the line of opening of the free edge of the leaflets of the aortic valve. It runs its short course passing superiorly,

obliquely to the right, and slightly forward toward the sternum. It is contained within the fibrous pericardial sac, so its surface is covered with serous pericardium. Its anterior surface abuts directly on the pulmonary trunk, which is also covered with serous pericardium. The two vessels together compose the vascular pedicle of the heart. The ascending aorta is related anterolaterally to the right atrial appendage, and posterolaterally to the right ventricular outflow tract and the pulmonary trunk. Extrapericardially, the thymus gland lies between it and the sternum. The medial wall of the right atrium, the superior caval vein, and the right pleura relate to its right side. On the left, its principal relationship is with the pulmonary trunk. Posterior to the ascending aorta is the transverse sinus of the pericardium, which separates it from the roof of the left atrium and the right pulmonary artery.

The arch of the aorta begins at the superior attachment of the pericardial reflection just proximal to the origin of the brachiocephalic artery (Fig. 47-27). It continues superiorly briefly before coursing posteriorly and to the left, crossing the lateral aspect of the distal trachea and finally terminating on the lateral aspect of the vertebral column. Here it is tethered by the parietal pleura and the arterial ligament. During its course, it gives off the brachiocephalic, the left common carotid, and the left

subclavian arteries. Bronchial arteries can arise from the arch and can be particularly troublesome if not carefully identified in the presence of aortic coarctation. The left phrenic and vagus nerves run over the anterolateral aspect of the arch just beneath the mediastinal pleura. The left recurrent laryngeal nerve takes origin from the vagus and curls superiorly around the arterial ligament before passing on to the posteromedial side of the arch. Here, the arch relates to the tracheal bifurcation and esophagus on its medial border, but also to the left main bronchus and the left pulmonary artery inferiorly.

The descending, or thoracic, aorta continues from the arch, running an initial course lateral to the vertebral bodies and reaching an anterior position at its termination. It gives off many branches to the organs of the thorax throughout its course, as well as the prominent lower nine pairs of intercostal arteries. These latter vessels are of critical concern for the cardiac surgeon. In coarctation of the aorta, they serve as primary collateral vessels to bypass the obstructed aorta, accounting for the rib notching seen in older children with this lesion. These vessels, and their branches to the chest wall, can be a source of troublesome bleeding if not properly secured when operating on such patients. In addition, the surgeon must remember that the dorsal branches of the intercostal vessels contribute a spinal branch that is important in supplying blood to the spinal cord. Because it is difficult to predict exactly from where these vital branches will arise, the surgeon must make every attempt to protect their origin from permanent occlusion. The important bronchial arteries (Fig. 47-28) also arise from the descending segment of the thoracic aorta. These vessels can become dilated in the presence of pulmonary atresia, when they serve as a source of pulmonary vascular supply.

PULMONARY TRUNK AND BRANCH PULMONARY ARTERIES

The pulmonary trunk is a short vessel, usually less than 5 cm in length in the adult (Fig. 47-29). It is completely contained within the pericardium and, like its running mate, the ascending aorta, is covered with a layer of serous pericardium except where the two vessels abut each other in the vascular pedicle. It takes origin from the most anterior aspect of the heart, lying just behind the lateral edge of the sternum and the second left intercostal space, superior and to the left of the aortic root. Initially, the pulmonary trunk overlies the aorta and the left coronary artery, but it soon moves to a side-by-side relationship with the ascending aorta. The left coronary artery turns abruptly anteriorly to lie between the left atrial appendage and the pulmonary trunk. The arterial ligament extends from the aortic arch to the very end of the pulmonary trunk as the latter divides into left and right pulmonary arteries. The left pulmonary artery courses superior to the left main-stem bronchus and laterally in front of the descending aorta before it sends branches to the hilum of the lung. The right pulmonary artery is somewhat longer than the left, having to traverse the mediastinum beneath the aortic arch, and then behind the superior caval vein, to reach the hilum of the lung. It

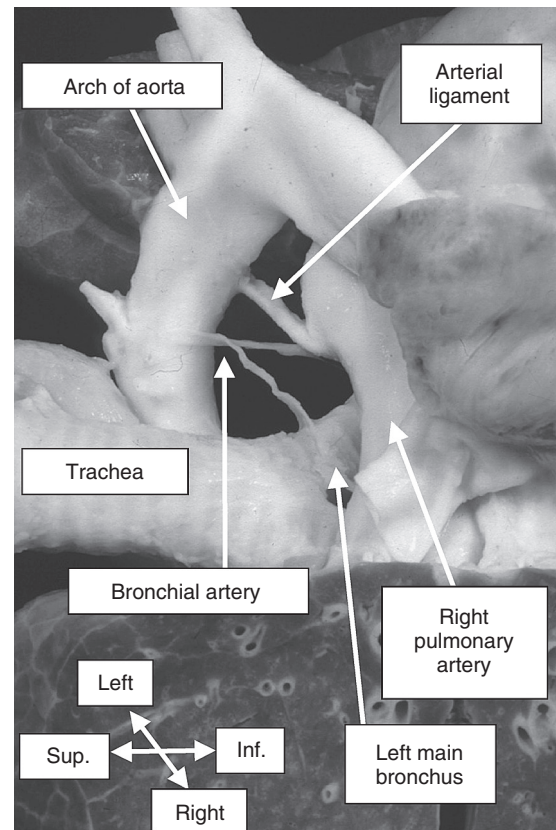


FIGURE 47-28 ■ This heart is positioned as it might be seen by the surgeon working through a median sternotomy. The aortic arch is deflected forward and has been dissected to show the origin of the bronchial arteries. Note that the arterial duct in this specimen has become ligamentous. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

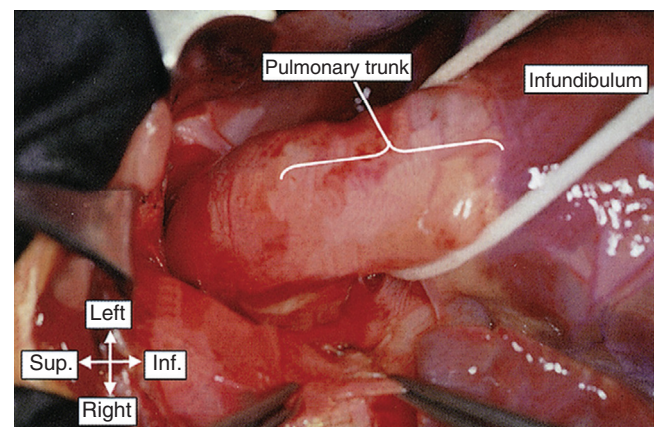


FIGURE 47-29 ■ This view of the heart through a median sternotomy shows the extent of the pulmonary trunk, the surgeon having encircled the trunk with a tape. Note the circular ventriculoarterial junction. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

lies in a posteroinferior position relative to the azygos vein, and is anterior to the left main bronchus. The right pulmonary artery often branches before reaching the lateral wall of the superior caval vein posterior to the transverse sinus of the pericardium. In this situation, a large upper lobar branch may be mistaken for the right pulmonary artery itself.

CORONARY ARTERIES AND VEINS

The coronary circulation is composed of the coronary arteries and veins together with the lymphatics of the heart. Because the lymphatics are of limited significance to operative anatomy, they are not discussed further. The coronary arteries are the first branches of the ascending portion of the aorta, arising from the aortic root immediately above its attachment to the heart. Normally, there are three sinuses at the aortic root, but only two coronary arteries. The sinuses can be named, therefore, according to whether they give rise to an artery, the normal arrangement being a right coronary, left coronary, and noncoronary sinus (Fig. 47-30). In this respect, the terms *right* and *left* refer to the coronary sinuses giving rise to the

right and left coronary arteries, rather than to the position of the sinuses relative to the right-left coordinates of the body. This is important because in the normal heart, the aortic root is obliquely situated, whereas in malformed hearts, the root is frequently abnormally situated. Whatever the position of the aortic root, however, the two coronary arteries, when two are present, almost always take origin from those aortic sinuses that face the sinuses of the pulmonary trunk. Because of this, it is more convenient and more accurate to term these sinuses the *left-hand-* and *right-hand-facing sinuses*, taking as the point of reference the observer standing within the nonfacing sinus and looking toward the pulmonary trunk (Fig. 47-31). This convention, introduced by the group from Leiden,¹⁷ holds true regardless of the relationships of the arterial trunks.

The coronary arteries usually arise from the aortic sinuses beneath the sinotubular junction. Deviations of origins relative to the junction are not uncommon and are considered abnormal only when they deviate by a distance greater than 1 cm. According to Bader,¹⁸ this occurs in 3.5% of hearts. The arterial opening can be deviated either toward the ventricle, so that the artery arises deep within the aortic sinus, or toward the aortic arch, so that the origin is outside the sinus. Such displacement can lead to the artery's taking an oblique course through the aortic wall, thus called an *intramural course*, which introduces the potential for luminal narrowing and

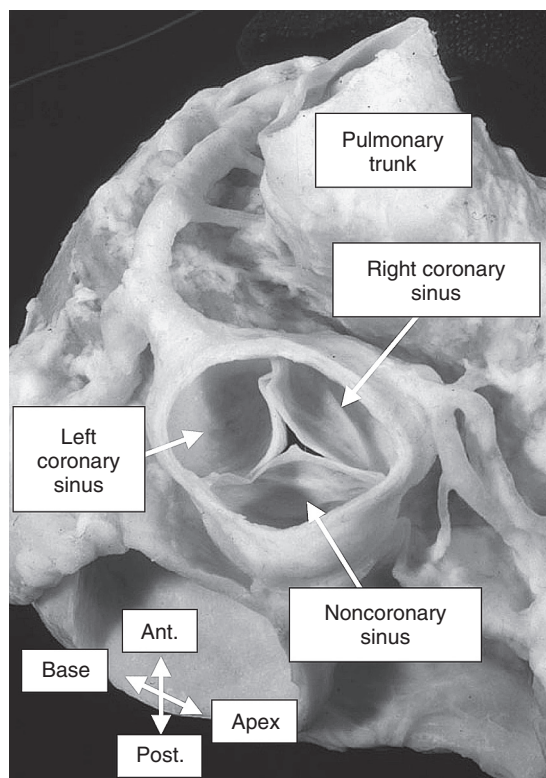


FIGURE 47-30 ■ The aorta has been removed at the level of the sinotubular junction, and the heart is photographed from above and from the right. The dissection shows the origin of the coronary arteries from the two aortic sinuses adjacent to the pulmonary trunk. Note again the circular anatomic ventriculoarterial junction between the pulmonary trunk and the right ventricular infundibular musculature (compare with Fig. 47-29). *Ant.*, Anterior; *Post.*, posterior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

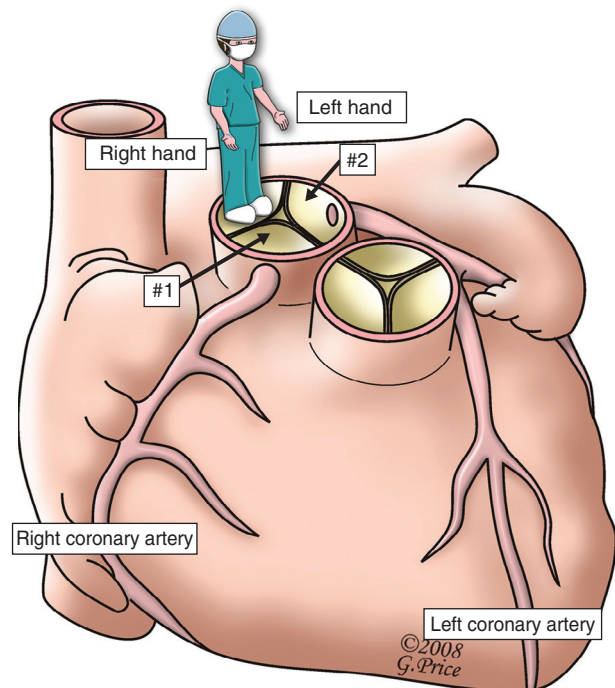


FIGURE 47-31 ■ From the stance of the surgeon, the two aortic sinuses supporting the coronary arteries are to the right- and left-hand sides. Conventionally, the right-hand sinus is considered sinus #1. In the normal heart, this sinus gives rise to the right coronary artery. The convention of naming the sinuses holds, regardless of the interrelationships of the arterial trunks. (Copyright for the original diagram from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

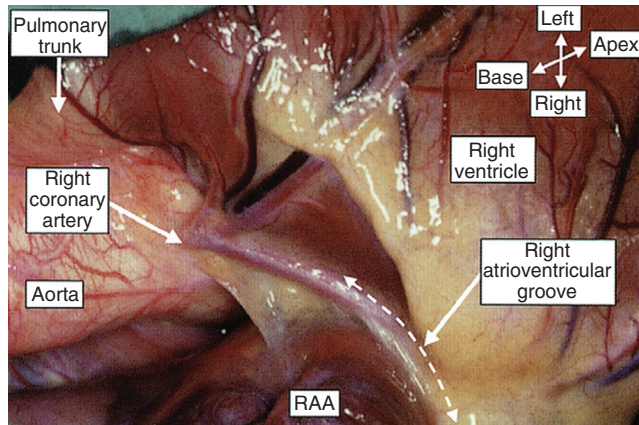


FIGURE 47-32 ■ This photograph, taken in the operating room through a median sternotomy, shows the aortic origin of the right coronary artery. RAA, Right atrial appendage. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

disturbances in myocardial perfusion, particularly when the deviated origin is intimately related to a valvar commissure.¹⁹

The left coronary artery almost always takes origin from a single orifice in the left-hand-facing sinus. In contrast, in about half of all hearts, there are two orifices in the right-hand-facing sinus. In such instances, the orifices are unequal in size, the larger giving rise to the main trunk of the right coronary artery, whereas the considerably smaller second orifice usually gives rise to an infundibular artery, or rarely to the artery supplying the sinus node. The coronary arteries can also arise, though rarely, from a solitary orifice, usually within the right-hand-facing sinus.

The epicardial course of the major coronary arteries follows the atrioventricular and interventricular grooves. The right coronary artery emerges from the right-hand-facing aortic sinus and immediately enters the right atrioventricular groove (Fig. 47-32). In approximately 90% of cases, this artery gives rise to the so-called posterior descending artery at the crux, the artery in reality being positioned inferiorly rather than posteriorly. In a good proportion of these cases, the artery then continues beyond the crux, and it supplies downgoing branches to the diaphragmatic surface of the left ventricle; this is called *right coronary arterial dominance* (Fig. 47-33). As the artery encircles the tricuspid orifice, it is most closely related to the origin of the valvar attachments near the takeoff of its acute marginal branch. Other important branches also take origin from this encircling segment of the artery. Immediately after its origin, the artery gives rise to downgoing infundibular branches, one of which may also arise by a separate orifice. In just over half the cases, the right coronary artery also gives rise to the artery to the sinus node. Rarely, but of major significance when present, the nodal artery can arise laterally from the right coronary artery, coursing over the lateral margin of the appendage to reach the terminal groove.²

The main stem of the left coronary artery emerges from the left-hand-facing sinus between the pulmonary

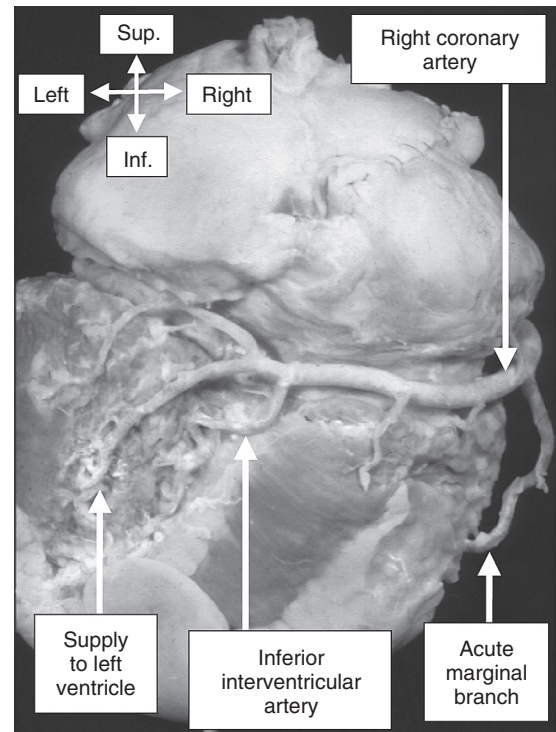


FIGURE 47-33 ■ The heart has been removed from the thorax and is positioned on its apex. The dissection shows a right dominant coronary artery. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

trunk and the left atrial appendage. It is a short structure, rarely extending beyond 1 cm before branching into its anterior interventricular and circumflex branches (Fig. 47-34). In some hearts, the main stem trifurcates, with an intermediate branch present between the two main branches. The intermediate branch supplies the obtuse margin of the left ventricle. The anterior interventricular artery runs within the anterior interventricular groove, giving off diagonal branches to the obtuse margin, and the important perforating branches that pass inferiorly into the septum. The first major septal perforating branch is particularly important (see Fig. 47-22), as it is at major risk when the pulmonary valve is removed for use as a homograft.²⁰ The interventricular artery then continues toward the apex, and it frequently curves under the apex onto the diaphragmatic surface of the ventricles. The circumflex branch of the left coronary artery passes backward to run in relationship with the mitral orifice. It is most closely related to the orifice when it gives rise to the inferior interventricular artery at the crux, a so-called dominant left coronary artery (Fig. 47-35). A dominant left coronary artery, however, is found in only approximately 10% of cases. When the left coronary is not dominant, the circumflex artery usually terminates by supplying downgoing branches to the pulmonary surface of the left ventricle. In approximately 45% of normal individuals, the circumflex artery also gives rise to the artery that supplies the sinus node.

Throughout much of their epicardial course, the arteries and their accompanying veins are encased in

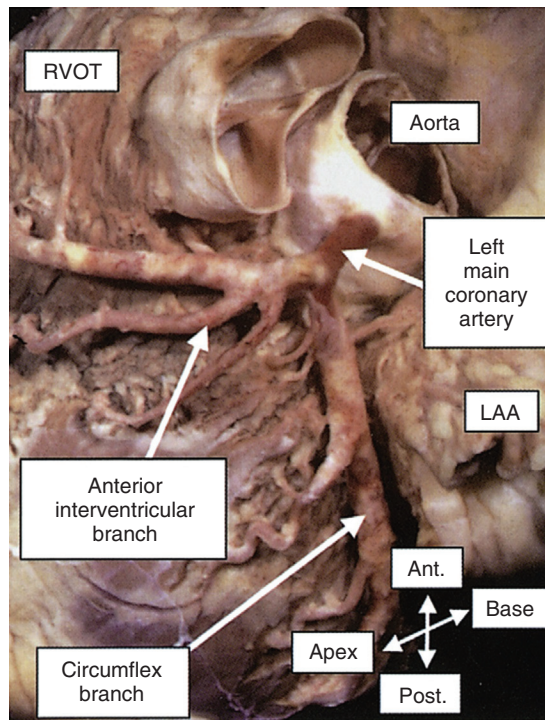


FIGURE 47-34 ■ This dissection, with the heart positioned in anatomic position and photographed from the left side, shows the branches of the main stem of the left coronary artery. *Ant.*, Anterior; *LAA*, left atrial appendage; *Post.*, posterior; *RVOT*, right ventricular outflow tract. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

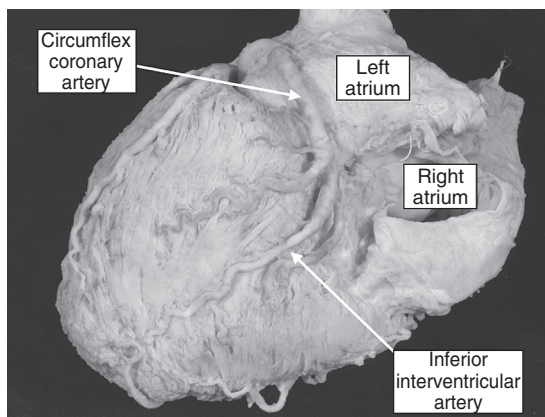


FIGURE 47-35 ■ In this heart, which is positioned in anatomic orientation but photographed from its diaphragmatic aspect, the circumflex coronary artery is dominant (compare with Fig. 47-33). (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

epicardial adipose tissue. In some hearts, the myocardium itself may form a “bridge” over segments of the artery. The role of these bridges in the development of coronary arterial disease is not clear. They can certainly be an impediment to surgeons in their effort to isolate the artery.

The coronary veins drain blood from the myocardium to the right atrium. The smaller veins—namely, the

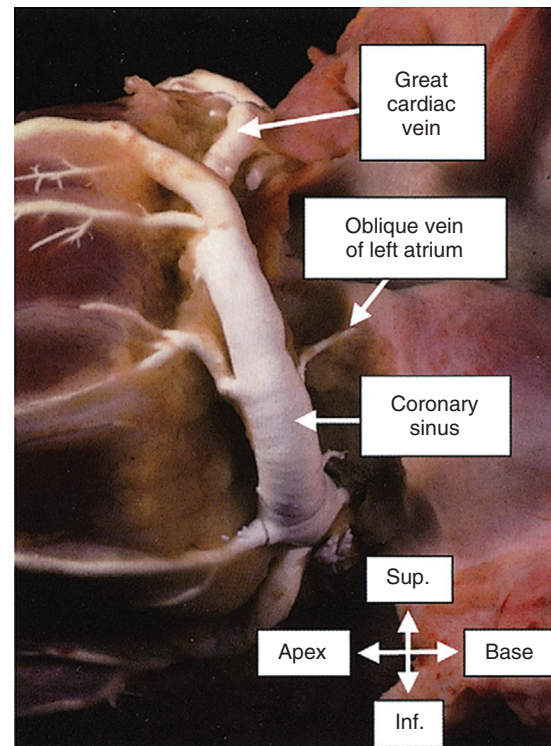


FIGURE 47-36 ■ This specimen has been prepared by filling the coronary sinus with silastic polymer. The heart is positioned to show its diaphragmatic aspect. The coronary sinus is formed at the union of the great cardiac vein with the oblique vein of the left atrium. *Inf.*, Inferior; *Sup.*, superior. (Copyright for the original illustration from which this figure was prepared belongs to Benson R. Wilcox, Andrew C. Cook, and Robert H. Anderson.)

anterior and the so-called small cardiac veins—drain directly to the cavity of the atrium. They are not of surgical significance. The larger veins accompany the major arteries and are the tributaries of the coronary sinus. The great cardiac vein runs alongside the anterior interventricular (left anterior descending) artery. It encircles the mitral orifice to enter the posterior and leftward margin of the atrioventricular groove, becoming the coronary sinus as it receives the oblique vein of the left atrium (Fig. 47-36). The coronary sinus then runs within the groove, lying between the left atrial wall and the ventricular myocardium, before draining into the right atrium. At the crux, the sinus receives the middle cardiac vein, which has ascended with the inferior interventricular (posterior descending) artery, and the small cardiac vein, which has encircled the tricuspid orifice in company with the right coronary artery. Occasionally, these latter two veins drain directly to the right atrium. The orifice of the coronary sinus is guarded by the thebesian valve, which on rare occasions is imperforate. Valves are also found in the cardiac veins. That found in the great cardiac vein where it turns around the pulmonary surface is most constant and is called the *valve of Vieussens*.

Acknowledgments

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VASCULAR PHYSIOLOGY

Ashraf A. Sabe • David G. Harrison • Frank W. Sellke

CHAPTER OUTLINE

VASCULAR RESISTANCE**REGULATION OF VASCULAR TONE**

Intrinsic and Extrinsic Vasomotor Control
 Role of the Endothelium
 Role of Metabolism and Autoregulation
 Flow-Induced Dilation
 Neurohumoral Influence on Microcirculation
 Intrinsic Myogenic Tone
 Impact of Extravascular and Humoral Forces
 on the Microcirculation
 Role of Venules in Vascular Resistance

**ENDOTHELIAL FACTORS IN VASCULAR GROWTH
AND RESPONSE TO INJURY****EFFECT OF DISEASE STATES ON CORONARY
CIRCULATION****PULMONARY VASCULAR PHYSIOLOGY****IMPROVING MYOCARDIAL PERFUSION**

Angiogenesis
 Challenges and Future Directions

SUMMARY

Myocardial and pulmonary perfusion is regulated by a complex array of influences intrinsic and extrinsic to the vasculature. Surgical decisions are generally based on the anatomy of large arteries, where the presence of obstructive lesions and vasomotor state of these vessels can affect myocardial, pulmonary, or other organ perfusion. Under normal circumstances, the microcirculation actually plays a more significant role in the regulation of blood flow. A basic understanding of vascular tone and vasomotor regulation, and the influence of various disease states, is necessary to optimize patient care. Over the past four decades, a great deal has been learned, and this has promoted the understanding of blood vessel regulation and organ perfusion in healthy and in diseased states.

The blood vessel wall is organized in three layers: the intima, media, and adventitia. The innermost, or intimal, layer is made of endothelial cells. Initially, the endothelium was thought to serve mainly as a barrier to the diffusion of macromolecules, but it is now known that the endothelium plays a pivotal role in vascular function, regulation of vascular tone, and control of local blood flow.¹ The medial layer surrounds this intimal endothelial layer, and it is composed of a variable number of smooth muscle cells. Smooth muscle cells also control vascular tone via humoral vasoactive factors, neural mediators, or local paracrine factors (Fig. 48-1). The outermost, adventitial, layer surrounds these vascular smooth muscle cells and provides structural integrity to the blood vessel, particularly larger arteries.

The classification of microvessels based on structural characteristics is rather arbitrary, and there is a lack of uniformity in the definitions of microvascular segments such as small arteries, arterioles, and venules.

Furthermore, the transition between these segments is gradual, and there is no clear demarcation between them. In general, microvessels are defined as vessels less than 300 μm in internal diameter. Capillaries are the smallest blood vessels, defined as vessels whose walls are composed of only endothelial tubes. The microvessels through which blood flows toward capillaries are arterial microvessels, and those that drain from capillaries are venous microvessels.² Arterial microvessels usually have three coats: (1) a thin tunica intima; (2) a relatively thick tunica media, composed of one to several layers of smooth muscle cells disposed circumferentially; and (3) tunica adventitia, composed of fibrous elements and fibroblasts. Venous microvessels collect the blood from capillaries and have thinner vascular walls than arterial microvessels do. Venules (50 μm in diameter) do not possess smooth muscle cell layers. Smaller venules are composed of only endothelial cells and pericytes. Venules are highly permeable and have an important role in nutrient exchange.

The regulation of myocardial perfusion depends on many intrinsic and extrinsic factors that might be affected by atherosclerotic lesions. In the coronary circulation, it has been shown that vasomotor regulation of vessels, in addition to the actual anatomy, plays an important role in coronary perfusion and operative decision making. Blood flow is also largely dependent on the resistance generated by the microcirculation. Although early studies on vasomotor regulation consisted of indirect assessments using measurements of flow and calculations of resistance, recent investigations into the properties of the intact coronary circulation have yielded much information, as have modern methods of analysis for interpretation of physiologic data.³⁻⁶

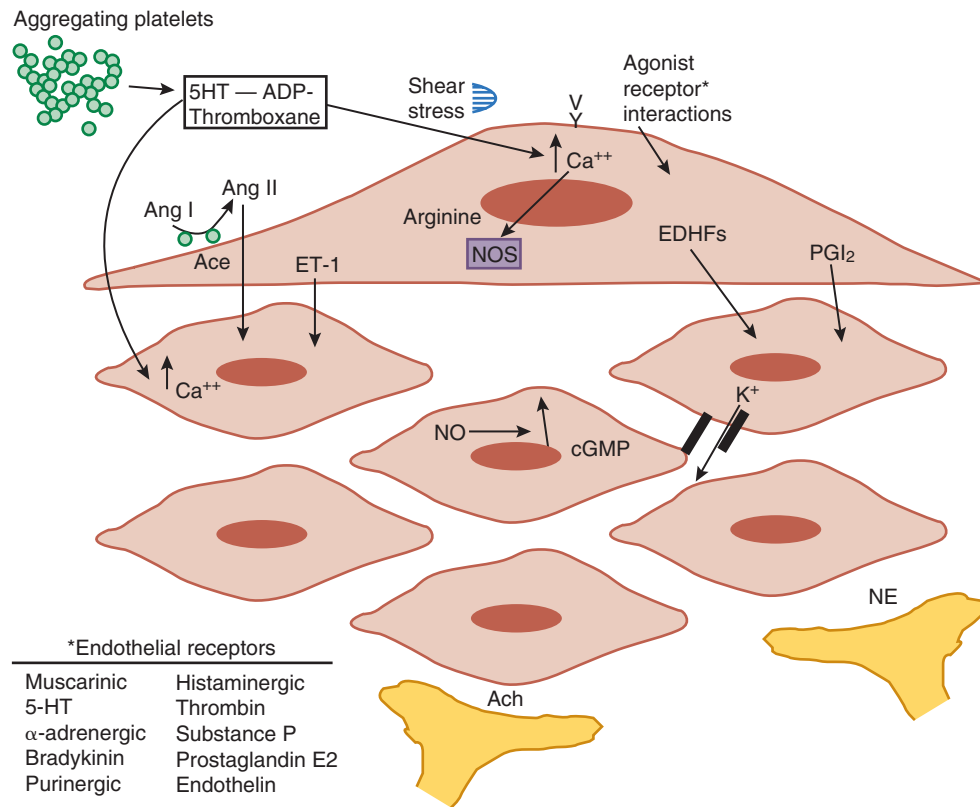


FIGURE 48-1 ■ Regulation of vascular tone by factors released from the endothelium, activated platelets and leukocytes, neuronally released factors, and circulating substances. *Ace*, Angiotensin-converting enzyme; *Ach*, acetylcholine; *ADP*, adenosine diphosphate; *Ang*, angiotensin; *cGMP*, cyclic guanosine monophosphate; *EDHF*, endothelium-derived hyperpolarizing factor; *ET*, endothelin; *5HT*, 5-hydroxytryptamine (serotonin); *NE*, norepinephrine; *NO*, nitric oxide; *NOS*, nitric oxide synthase; *PGI₂*, prostaglandin I₂.

The microcirculation possesses unique features that allow it to respond to the dynamic changes in nutrient requirements and to interact with surrounding tissue. It is important to note that although the various vascular beds in the body possess many similarities, there are also subtle differences. This chapter will discuss regulation of vascular tone, with an emphasis on coronary and pulmonary circulation, and will review the physiologic and molecular basis of recent advances in ischemic cardiac disease.

VASCULAR RESISTANCE

An understanding of vascular resistance is important, because these resistance vessels cause pressure losses and are responsible for regulation of perfusion. Initially, it was thought that the precapillary arterioles were responsible for vascular resistance, with little resistance involvement by the vessels larger than 25 to 50 μm in diameter. However, subsequent work revealed that over half of total vascular resistance is caused by vessels with diameters larger than 100 μm , even including vessels up to 300 μm .^{7,8} Contrary to previous belief, the venous circulation, under conditions of vasodilation, may account for up to 30% of vascular resistance. Figure 48-2 shows that after vasodilation with dipyridamole, larger arteries and veins assume a greater role in resistance.^{8,9} Similarly, ischemia results in a significant redistribution of vascular

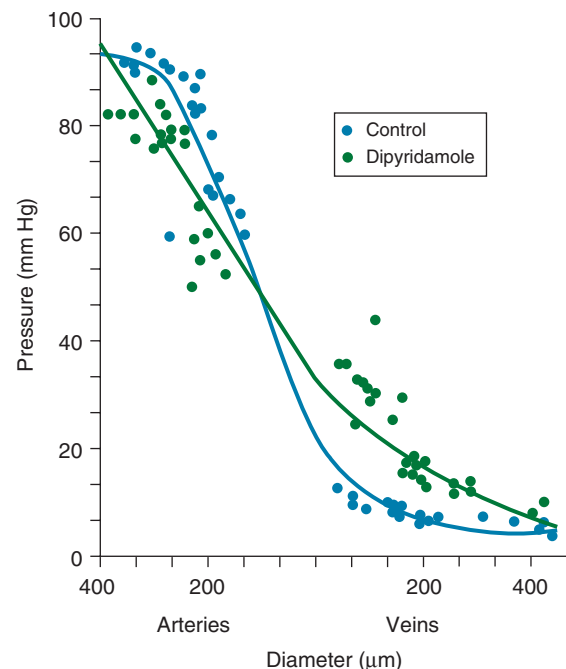


FIGURE 48-2 ■ Intravascular pressures in the coronary microcirculation under basal conditions and during vasodilation with dipyridamole. The distribution of vascular resistance is not static. Instead, the size of the vessels regulating vascular tone depends on the tone of the vasculature. (Adapted from Chilian WM, Layne SM, Klausner EC, et al: Redistribution of coronary microvascular resistance produced by dipyridamole. *Am J Physiol* 256:H383–H390, 1989.)

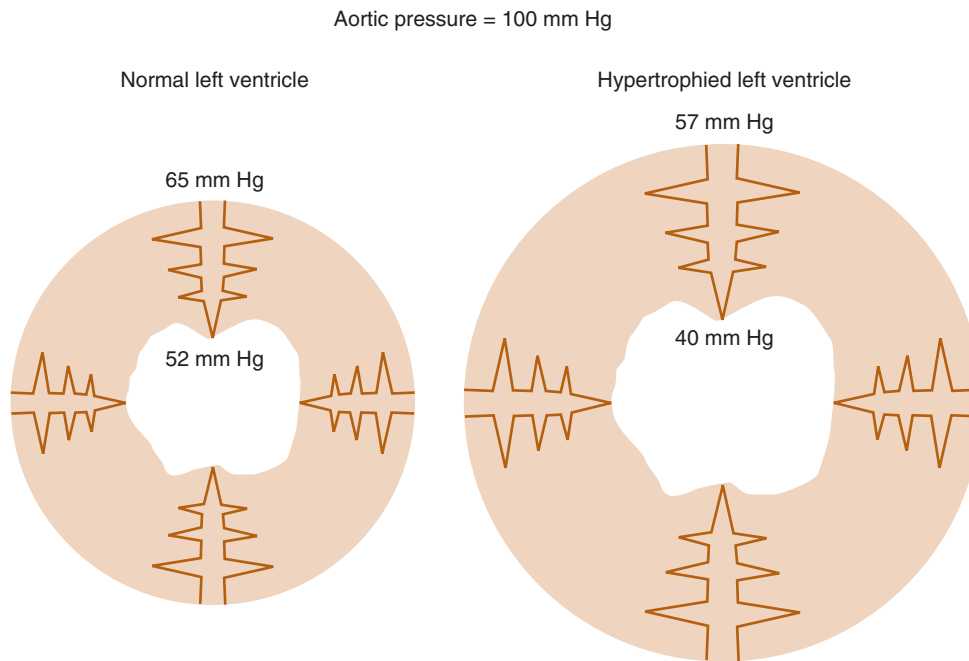


FIGURE 48-3 ■ Transmural losses of coronary perfusion pressure in normal and hypertrophied hearts. Pressures were measured using micropuncture–servo null techniques in hearts perfused via the left main coronary artery at 100 mm Hg. (Adapted from Fujii M, Nuno DW, Lamping KG, et al: Effect of hypertension and hypertrophy on coronary microvascular pressure. *Circ Res* 71:120–126, 1992.)

resistance⁹; this reveals that the distribution of vascular resistance is dynamic and is also largely dependent on vascular tone.

The redistribution of microvascular resistance can change the myogenic tone in each microvascular segment because the luminal pressure in a certain vascular segment is determined by the systemic pressure and the upstream distribution of vascular resistance. For example, when resistance is shifted upstream by the dilation of small arterioles, the luminal pressure in the upstream microvessels decreases, resulting in myogenic dilation. Changes in the venular pressure caused by the resistance redistribution can also affect the capacity for substance exchange and lead to edema formation.

In the coronary circulation, pressure losses also occur as vessels course from the epicardium through the myocardium¹⁰; this is accentuated further in the setting of cardiac hypertrophy. Such a phenomenon is particularly relevant clinically, as it in part explains the propensity of the subendocardium to develop ischemia in hypertrophied hearts (Fig. 48-3). The hypertrophied pathologic state causes a decrease in the perfusion pressure of the subendocardium, predisposing it to ischemia and infarction.¹¹

REGULATION OF VASCULAR TONE

Intrinsic and Extrinsic Vasomotor Control

Vasomotor tone is influenced by the intrinsic properties of the vessel wall, by local innervation, and by substances from surrounding parenchymal tissue. This regulation of

vasomotor tone is critically involved in organ perfusion. Vascular responses to endogenous substances are summarized in Figure 48-4. All these factors have an especially significant role in the setting of microvascular tone.²

Based on in vitro observations, Jones and colleagues¹² found that larger arterioles are more sensitive to shear stress than myogenic factors, whereas small microvessels are more sensitive to metabolic factors. They organized arterial microvessels into three microdomains as governed by distinct forms of regulation based on vessel size: (1) small arterioles (<50 μ m), most sensitive to metabolic mediators; (2) intermediate arterioles (50 to 80 μ m), most sensitive to myogenic mechanisms; and (3) large arterioles (80 to 150 μ m), most sensitive to flow-induced dilation. Undoubtedly, there is overlap among these three components; however, this model provides a framework for understanding the regulation of microvessels.

Jones and colleagues¹² hypothesized that the longitudinal disposition of these three microdomains enables integrated adjustment of flow conductance in the face of various influences, such as increased metabolism or a reduction in perfusion pressure. For example, dilation of small arterioles by augmented metabolism produces a decrease in luminal pressure in upstream microvessels, leading to the dilation of intermediate arterioles by decreasing the myogenic tone. These microvascular dilations could also produce an increase in shear stress and result in enhanced flow-induced dilation in large arterioles. As a result, all sizes, or domains, of arterial microvessels dilate in response to the metabolic stimulation. The marked longitudinal heterogeneity of microvascular responses may be at least partly explained by this microdomain hypothesis.

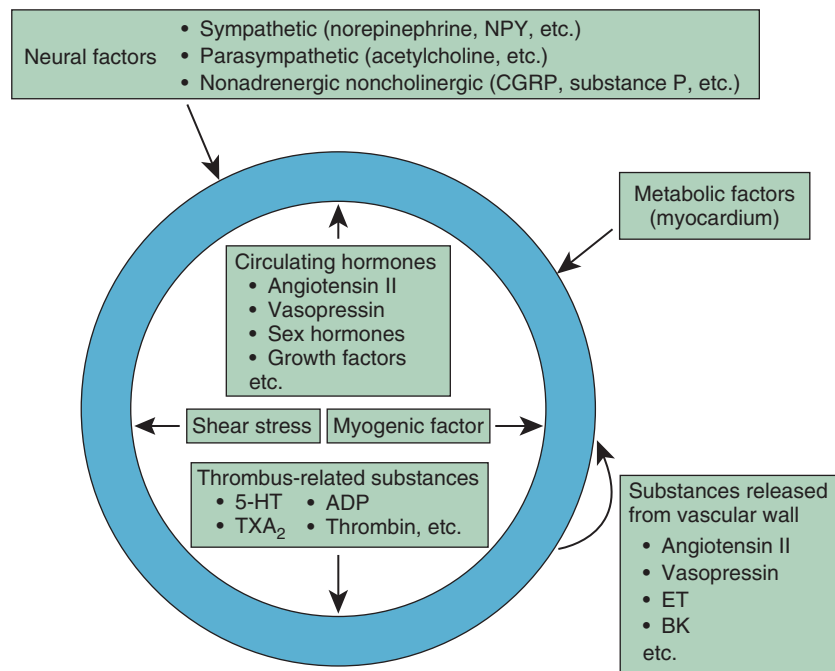


FIGURE 48-4 ■ Factors that influence microvascular tone. *ADP*, Adenosine diphosphate; *BK*, Ca²⁺-activated K⁺; *CGRP*, calcitonin gene-related peptide; *ET*, endothelin; *5HT*, 5-hydroxytryptamine (serotonin); *NPY*, neuropeptide Y; *TXA₂*, thromboxane A₂. (Adapted from Komaru T, Kanatsuka H, Shirato K: Coronary microcirculation: physiology and pharmacology. *Pharmacol Ther* 86:217–261, 2000.)

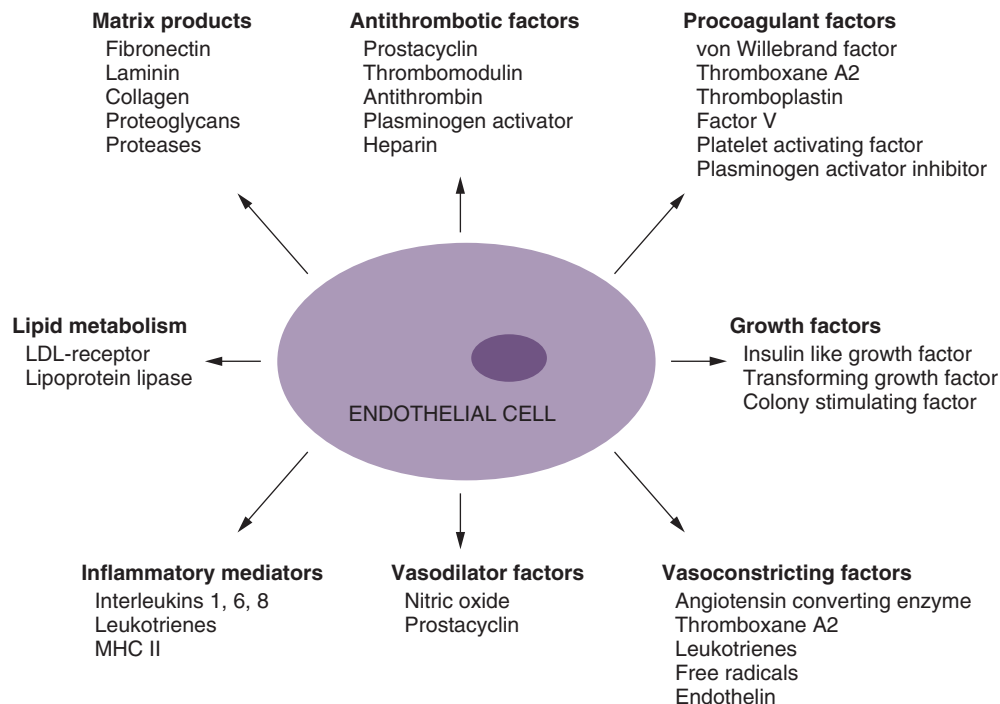


FIGURE 48-5 ■ Endothelial cells have both metabolic and synthetic functions. Through the secretion of a large variety of mediators, these cells are able to influence cellular function throughout the body. *LDL*, Low-density lipoprotein; *MHC*, major histocompatibility complex. (Adapted from Galley HF, Webster NR: Physiology of the endothelium. *Br J Anaesth* 93:105–113, 2004.)

Role of the Endothelium

The endothelium plays a pivotal role in vasomotor tone regulation. Many substances affect tone via endothelium-mediated mechanisms. Endothelial cells also release several substances that affect coronary

resistance, including vasodilators such as nitric oxide (NO•), prostaglandins, and vasoconstrictors including angiotensin converting enzyme endothelin, and reactive oxygen species (summarized in Fig. 48-5). As the major regulatory molecule, NO• is produced by a constitutively expressed enzyme known as *endothelial nitric oxide synthase*

(eNOS or NOS-3). NO• is formed as a result of a series of electron transfers from reduced nicotinamide adenine dinucleotide phosphate (i.e., NADPH) to flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) on the reductase domain, and electron transfer to a prosthetic heme group in the oxygenase domain. When heme reduction occurs, arginine is catalyzed to citrulline and NO•. The NO• formed diffuses to underlying vascular smooth muscle, where its actions include stimulation of soluble guanylate cyclase, increasing the level of cyclic guanosine monophosphate (cGMP) and prompting vasodilation via activation of cGMP-dependent protein kinase.¹³ Although binding of calcium and calmodulin is a prerequisite for activity of eNOS, other events, such as phosphorylation,¹⁴ membrane binding,¹⁵ binding of eNOS with heat-shock protein 90, and association with the integral membrane protein caveolin¹⁶ can also modulate NOS activity. In addition, NO• can undergo reactions with thiol-containing compounds to form biologically active nitroso molecules.¹⁷

Although eNOS is expressed constitutively, it undergoes important gene expression regulation by factors such as shear stress, endothelial cell growth, hypoxia, exposure to oxidized low-density lipoprotein, and

exposure to cytokines.¹⁸⁻²⁰ In the coronary circulation, the release of NO• confers a state of basal vasodilation; therefore, administration of NO• synthase antagonists increases resting coronary resistance. However, when substances such as acetylcholine and bradykinin are administered, coronary microvessels of all sizes dilate, resulting in decreased coronary resistance. Endothelial NO• production is affected by a variety of mechanisms in many disease states. The signal transduction pathways through which NO• acts are summarized in Figure 48-6. It is likely that the most important pathway involves activation of soluble guanylate cyclase, which catalyzes the formation of cGMP from guanine triphosphate. The cGMP serves as an allosteric regulator of the enzyme cGMP-dependent protein kinase, which phosphorylates contractile proteins and ion channels, decreasing intracellular calcium and the sensitivity of contractile proteins to intracellular calcium. The binding of NO• to cytochrome oxidase in the mitochondria alters oxygen consumption and in turn can affect oxygen demand. Similarly, receptors for atrial natriuretic peptide and brain natriuretic peptide are also the particulate forms of guanylate cyclases, and these signal vasodilation via similar pathways. NO• is also released in response to sodium nitroprusside and organic nitrates.

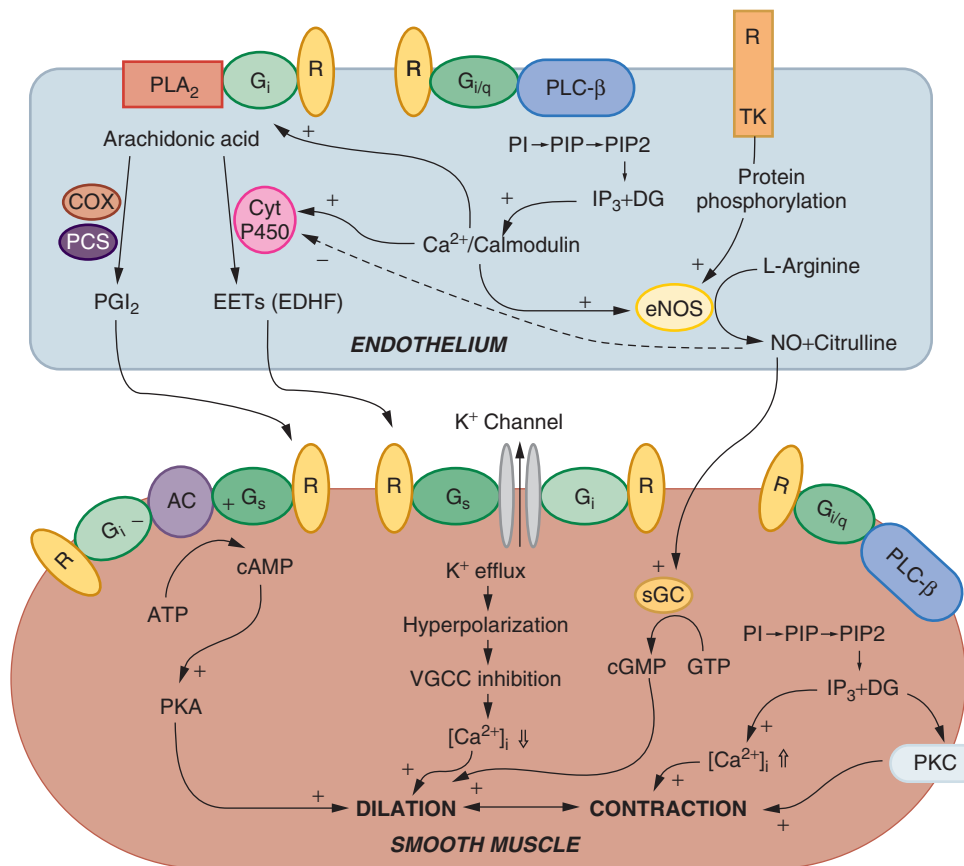


FIGURE 48-6 ■ Signal transduction pathways for the vascular responses to agonists. Nitric oxide (NO), prostaglandin I₂ (PGI₂), and endothelium-derived hyperpolarizing factor (EDHF) are important for the cross-talk between the endothelium and the vascular smooth muscle. AC, Adenyl cyclase; COX, cyclooxygenase; Cyt P450, cytochrome P450; DG, diacylglycerol; eNOS, endothelial nitric oxide synthase; G_i, G_i-protein; G_q, G_q protein; PCS, prostacyclin synthase; PI, phosphatidylinositol; PIP, phosphatidylinositol 4-phosphate; PIP₂, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PLA₂, phospholipase A₂; PLC, phospholipase C; R, receptors; TK, tyrosine kinase; VGCC, voltage-gated Ca²⁺ channel. (Adapted from Komaru T, Kanatsuka H, Shirato K: Coronary microcirculation: physiology and pharmacology. *Pharmacol Ther* 86:217-261, 2000.)

Although $\text{NO}^\bullet$ is the major regulator of vascular tone, there are other factors that modulate endothelium-dependent vascular tone in coronary, pulmonary, and peripheral circulations. Endothelium-derived hyperpolarizing factor (EDHF) is an example. The endothelium-dependent hyperpolarization of vascular smooth muscle is mediated by the opening of a calcium-dependent potassium channel, leading to K^+ exit from the cell. When the vascular smooth muscle is hyperpolarized, voltage-sensitive calcium channels are closed, leading to a reduction in intracellular calcium. The role of the various EDHFs probably varies depending on the vessel size, the species, and the vascular bed under consideration. It is likely that several EDHFs exist, but current evidence suggests that hydrogen peroxide and epoxyeicosatrienoic acid, a cytochrome p450 metabolite of arachidonic acid, play major roles. Hydrogen peroxide is formed by the mitochondria in response to shear stress and acetylcholine. The hydrogen peroxide not only opens large conductance potassium channels; it also activates protein kinase G, causing oxidation and dimerization.²¹ Prostaglandin synthesis by the endothelium also modulates tone in the microcirculation. The predominant prostaglandin produced by endothelial cells is prostacyclin. There is substantial interaction between $\text{NO}^\bullet$, EDHF, and prostacyclin. A major stimulus for release of these factors is shear stress, or the tangential force of fluid as it flows over the endothelium, resulting in flow-dependent vasodilation. Interestingly, the importance of $\text{NO}^\bullet$ seems to decline and the role of the EDHF increases as blood vessels decrease in size. In addition, the production of EDHF may increase when $\text{NO}^\bullet$ is low. The interaction

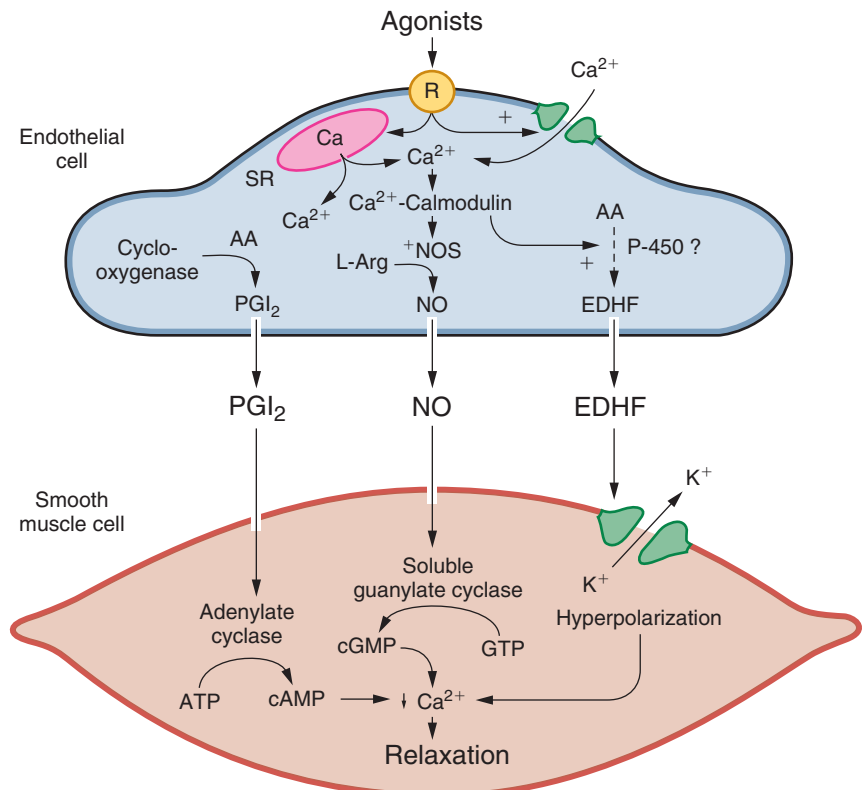
of endothelial cells with vascular smooth muscle cells and the intermediates involved is outlined in Figure 48-7.

Role of Metabolism and Autoregulation

The ability of a vascular bed to adjust its tone to maintain a constant flow during changes in perfusion pressure is termed autoregulation.²² This process is most effective in the coronary circulation when pressure is between 40 and 160 mm Hg. The subendocardium and subepicardium differ in the range of pressures over which autoregulation can be observed. In the subendocardium flow begins to decrease at pressures of less than 60 to 70 mm Hg, whereas in the subepicardium these decreases in flow occur at significantly lower pressures.²³ Clinically, systemic arterial hypertension affects the range over which autoregulation occurs in the subendocardium, such that flow begins to decline at even higher pressures. Such a change in subendocardial perfusion pressure in the setting of hypertrophic myocardium increases the likelihood of subendocardial ischemia. Patients with systemic hypertension may have an increased lower limit of autoregulation and may be more likely to suffer brain ischemia during surgery, or other times, even at pressures sufficient to sustain adequate perfusion in patients with normal blood pressure.

The predominant changes in vasomotor tone, concerning both autoregulation and metabolic vascular regulation, occur in vessels smaller than 100 μm in diameter. The rate of oxygen consumption in the myocardium is closely related to myocardial perfusion via coronary microvascular tone. The ability of the myocardium to

FIGURE 48-7 ■ Role of the increase in cytosolic calcium concentration in the release of endothelium-derived relaxing factors (EDRF). Endothelial receptor activation induces an influx of calcium into the cytoplasm of the endothelial cell. After interaction with calmodulin, NO-synthase and cyclooxygenase are activated, leading to the release of endothelium-derived hyperpolarizing factor (EDHF). NO causes relaxation by activating the formation of cyclic GMP (cGMP) from GTP. EDHF causes hyperpolarization and relaxation by opening K^+ channels. Prostacyclin (PGI_2) causes relaxation by activating adenylate cyclase (AC), which leads to the formation of cyclic AMP (cAMP). Any increase in cytosolic calcium (including that induced by the calcium ionophore A23187) causes the release of relaxing factors. When agonists activate the endothelial cells, an increase in inositol phosphate may contribute to the increase in cytoplasmic Ca^{2+} by releasing it from the sarcoplasmic reticulum (SR). (Adapted with permission from Vanhoutte PM, Boulanger CM, Vidal M, et al: Endothelium-derived mediators and the renin-angiotensin system. In Robertson JIS, Nicholls MG, editors: *The renin-angiotensin system*, London, 1993, Gower Medical.)



extract additional oxygen to meet increased demand is limited because myocardial oxygen extraction is already near its maximal threshold under resting conditions. To account for this limitation, coronary flow rises in response to increased myocardial oxygen requirements.

Flow-Induced Dilation

Flow-induced dilation is a ubiquitous phenomenon of blood vessels in various organs of animals, including humans.^{2,24,25} Flow-induced dilation plays important physiologic roles by: (1) protecting the vessel wall against friction induced injury, (2) preventing vascular steal phenomenon by dilating upstream vessels when there is focal hyperemia, (3) reducing the heterogeneity of flow distribution, and (4) buffering the pressure distribution in response to rapid pressure changes.

The mechanism by which endothelial cells sense flow has been a focus of substantial investigation. Studies by Tzima and colleagues²⁶ have defined a mechanosensory complex composed of VE cadherin, the platelet endothelial cell adhesion molecule (PECAM-1), and the vascular endothelial growth factor receptor-2 (VEGFR-2) that is critical in this process. Shear seems to stimulate PECAM-1 and VE-cadherin, which in turn transactivate VEGFR2, leading to downstream signaling events. In contrast to the myogenic response, the endothelium is required for flow-induced dilation. Regulation of flow-mediated vasodilation is controversial, and both NO• and prostaglandins

have been shown to be involved, at least in porcine coronary arterioles.^{27,28} The exact mechanism of regulation can depend on age, vessel size, and the vascular bed under consideration. A possible flow-induced arteriolar dilation mechanism is summarized in Figure 48-8.

Autoregulation is mediated by the actions of several factors such as NO•, EDHF, and adenosine. Removal of a particular factor does not prevent autoregulation, because the other factors seem to take over its function. Adenosine and hydrogen peroxide also cause hyperpolarization of vascular smooth muscle. From the work of Duncker and colleagues,²² and others, we now know that several factors work together to influence metabolic regulation and autoregulation, leading to adequate regulation of coronary vascular tone despite interruption of any particular pathway.²²

Neurohumoral Influence on Microcirculation

The coronary arterial system is densely innervated with sympathetic and parasympathetic nerves.²⁹ Neurotransmitters released from these, and a wide variety of humoral substances, significantly affect the microvascular tone. Neurohumoral factors affect coronary microvascular tone, and together with myogenic, flow-induced, and local metabolic controls, they participate in determining the coronary vascular resistance necessary for oxygen and nutrition supply to the myocardium (see Fig. 48-4).

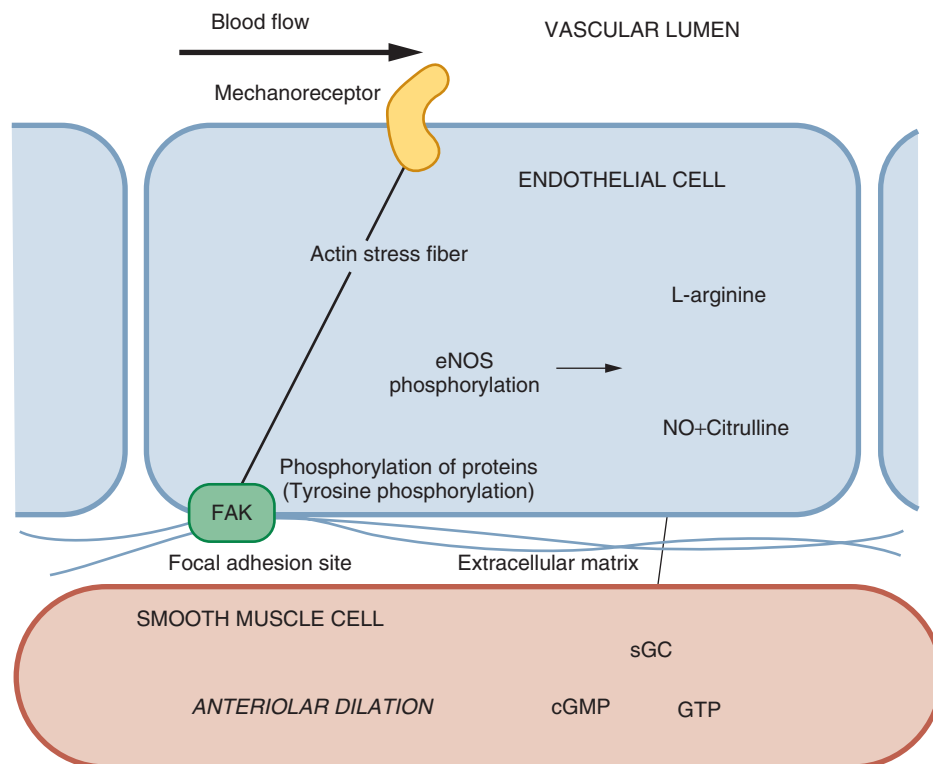


FIGURE 48-8 ■ Possible signal transduction pathway for the flow-induced arteriolar dilation, which is mediated by mechanotransduction via actin stress fibers, and the subsequent activation of the focal adhesion kinase and endothelial nitric oxide synthase (eNOS) phosphorylation. cGMP, Cyclic guanosine monophosphate; FAK, focal adhesion kinase; GTP, guanosine triphosphate; NO, nitric oxide; sGC, soluble guanylyl cyclase. (Adapted from Komaru T, Kanatsuka H, Shirato K: Coronary microcirculation: physiology and pharmacology. *Pharmacol Ther* 86:217–261, 2000.)

The role of the autonomic sympathetic and parasympathetic nervous systems is important in regulation of coronary perfusion. In vivo, the vascular response to sympathetic stimulation is mediated by both α -adrenergic and β -adrenergic receptors. In the coronary circulation, the predominant receptor subtype is the β -adrenergic receptor.³⁰ For example, direct sympathetic nerve stimulation evokes coronary vasodilation and an increase in coronary flow. If β -adrenergic antagonists are administered, a transient vasoconstriction can be observed.³⁰ When coronary microvessels are studied in vitro, α -adrenergic stimulation has minimal contractile effects. When selective α_2 -adrenergic stimulation is applied using pharmacologic stimuli, there is rather potent vasodilation of all sizes of coronary microvessels, predominantly the result of the release of endothelium-derived NO•. β -Adrenergic stimulation produces a potent relaxation of all coronary arteries, but especially of small-resistance vessels.³⁰ In addition, β_2 -adrenergic receptor subtype predominates in vessels smaller than 10 μ m in diameter in in vitro studies, whereas a mixed β_1 - and β_2 -adrenergic receptor population controls vascular resistance in in vivo studies.³⁰ On the other hand, larger coronary vessels are regulated by a mixed β_1 - and β_2 -adrenoceptor subtype population. Activation of cholinergic receptors by either vagal stimulation or the infusion of acetylcholine produces uniform vasodilation of coronary vessels.³¹ This vasodilation is predominantly mediated by endothelium-derived NO•, although release of EDHF³² and release of prostaglandin substances may contribute.³³ The coronary flow increase by vagal stimulation could be blunted by a metabolically mediated flow decrease caused by a decrease in the heart rate and myocardial contractility.³⁴

Other neurotransmitters that act on the coronary circulation include neuropeptide Y, which is mainly released with norepinephrine as a co-transmitter from sympathetic postganglionic nerve terminals upon intense sympathetic activation.^{2,35} Intracoronary application of neuropeptide Y markedly decreases coronary flow, producing myocardial ischemia without large coronary artery constriction.^{36,37} These results point to its potent and specific constrictor effects on coronary microvessels. Substance P, a potent vasodilator whose effect is dependent on the endothelium, is contained in perivascular nerve fibers and sensory ganglia.³⁸

Intrinsic Myogenic Tone

Myogenic contraction is observed when applying luminal pressure to microvessels, which causes development of intrinsic vascular tone, as shown by elevated wall tension or a decrease in vessel diameter. The microcirculation possesses this intrinsic myogenic tone response, which also contributes to maintaining basal vascular tone and autoregulation.³⁹ Recent evidence has shown that in the microcirculation, fenestrations in the internal elastic lamina allow communications between the endothelium and vascular smooth muscle. Lowering pressure activates endothelial TRPV4 channels in this microdomain, promoting endothelial cell calcium sparklets, vascular smooth muscle hyperpolarization, and vasodilation.⁴⁰ Responses

such as these play a critical role in determining the basal tone and in maintaining the intraluminal pressure of the downstream exchange vessels within a physiologic level.^{41,42} In the myocardium, myogenic responses to increases in pressure are greater in subepicardial microvessels than in vessels from the subendocardium. In addition, myogenic tone can be reduced during inflammatory states when increased expression of inducible nitric oxide synthase (iNOS) causes altered myocardial perfusion. Increases in myogenic tone, which occur during stretch of vascular smooth muscle, are associated with an increase in inositol 1,4,5-trisphosphate, presumably because of activation of phospholipase C.^{39,43,44} In addition, the myogenic tone mediator 20-HETE produces constriction of vascular smooth muscle by promoting Ca^{2+} -activated K^+ (BK) channel inhibition. This induces depolarization and increases levels of $[\text{Ca}^{2+}]_i$. This effect is most likely caused by activation of L-type Ca^{2+} channels or the activation of protein kinase C and inhibition of the Na/K-ATPase.⁴⁵ Other mediators probably involved in the myogenic tone response include mitogen-activated protein kinases and Rho protein. The downstream mediator Rho kinase can modulate myogenic tone by regulation of the actin cytoskeleton. One potential therapeutic agent for treatment of hypertension and coronary spasm is the use of Rho kinase inhibitors. A summary of possible mechanisms of myogenic tone is shown in Figure 48-9.

Impact of Extravascular and Humoral Forces on the Microcirculation

In the setting of pathologic processes such as ischemia leading to decreased tissue compliance or increased tissue edema, extravascular forces have an especially important role. For example, collateral perfusion is particularly sensitive to changes in heart rate (more frequent extravascular compression) and ventricular diameter (stretch).^{6,46} The coronary circulation is particularly unique in that it is exposed to a large number of extravascular forces produced by contraction of adjacent myocardium and intraventricular pressures. Of relevance to the concept of extravascular forces is the idea that these might collapse coronary vessels under certain circumstances. Of note, flow through the epicardial coronary arteries halted when aortic pressure fell to levels ranging from 25 to 50 mm Hg, raising the possibility that extravascular forces might be sufficiently high to collapse vessels when intraluminal pressures declined to values below this critical value.⁴⁷ Flow in the coronary microcirculation continued even when the arterial driving pressure was minimally higher than coronary venous pressure. Based on modeling and various experimental interventions, it has been determined that the decrease of antegrade blood flow in larger upstream vessels is associated with continued forward flow in microvessels and that this is due to capacitance in the coronary circulation.⁴⁸ Kanatsuka and colleagues⁴⁹ used a floating microscope to visualize epicardial capillaries and were able to show that red cells continued to flow, even after perfusion had stopped in the more proximal vessels.⁴⁹ Using this approach, they showed that the pressure at which flow stops in the epicardial coronary

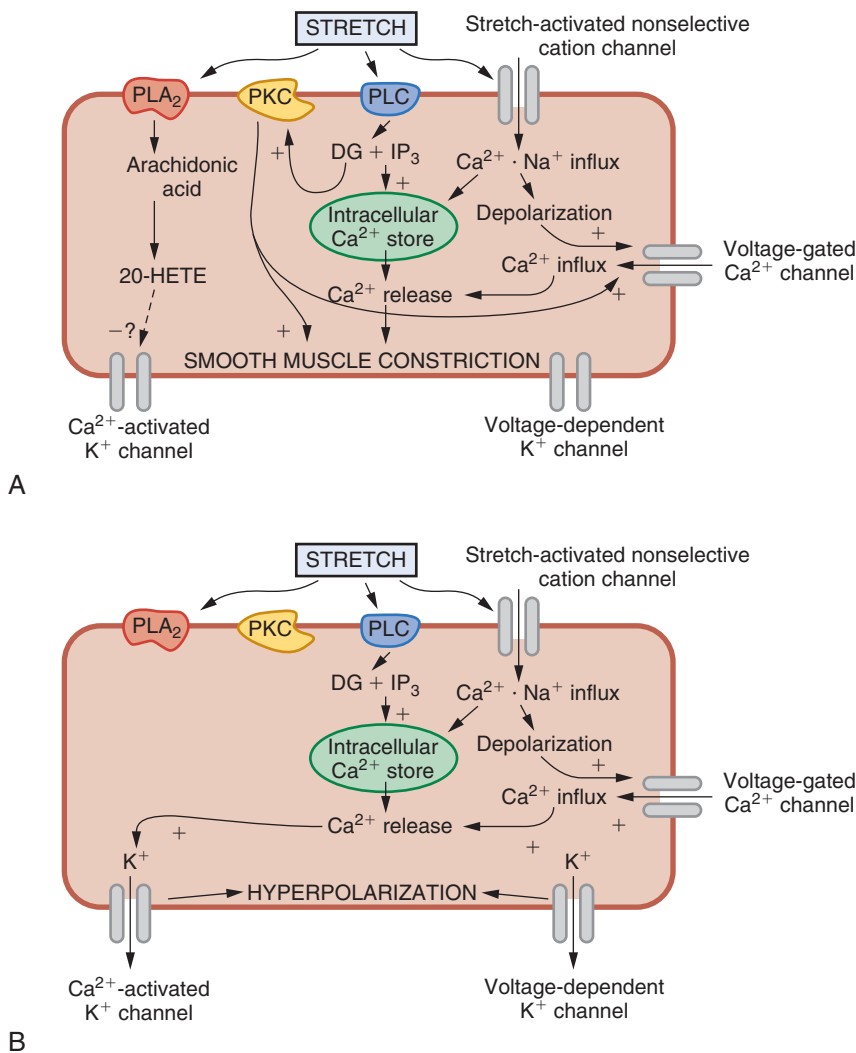


FIGURE 48-9 ■ Schematic illustrations for the possible mechanisms of (A) the myogenic constriction and (B) its compensatory mechanisms. *DG*, Diacylglycerol; *20-HETE*, 20-hydroxyeicosatetraenoic acid; *IP₃*, inositol 1,4,5-trisphosphate; *PKC*, protein kinase C; *PLA₂*, phospholipase A₂; *PLC*, phospholipase C. (Adapted from Komaru T, Kanatsuka H, Shirato K: Coronary microcirculation: physiology and pharmacology. *Pharmacol Ther* 86:217–261, 2000.)

microvessels was only a few millimeters of mercury higher than right atrial pressure.⁴⁹ In addition, when ventricular diastolic pressure is high, vessels deeper in the subendocardium might be made to collapse by pressure transmitted from the ventricular chamber. In contrast, coronary epicardial vessels do not close at any pressure. It therefore seems likely that the concept of “critical closing pressure” is not applicable to all vessels in the coronary circulation.

The response of the coronary microcirculation to humoral agents differs with vessel size and location. Endothelin-1 produces vasoconstriction when administered to the adventitial surfaces of coronary microvessels. The degree of constriction produced by endothelin-1 is inversely related to the size of the vessels. In contrast, when endothelin-1 is administered intra-arterially, vasodilation occurs, presumably via release of NO•.^{31,33} Serotonin constricts vessels less than 100 μ m in diameter, whereas it causes vasodilation of smaller arteries.⁵⁰ Vasopressin, on the other hand, produces greater constriction of microvessels less than 100 μ m in diameter than it produces in larger microvessels.^{51,52} In the larger epicardial coronary arteries, vasopressin predominantly causes vasodilation.

Role of Venules in Vascular Resistance

Control of vasomotor regulation differs between the venous and arterial microcirculations, and certain reactions to pathologic stimuli occur preferentially on one side of the capillary bed. Therefore, consideration of the venous circulation apart from the arterial circulation is needed. Venules have considerable importance under conditions of vascular dilation, such as during exercise, metabolic stress, or reperfusion after myocardial ischemia.⁹ The venous circulation can influence myocardial stiffness and relaxation properties of the heart. Veins also respond differently to agonists and neuronal stimulation compared with arteries in the same vascular bed.^{33,52} Venules are also the initiating site of neutrophil adherence and transmigration, whereas arterioles seldom manifest these initial changes in the inflammatory response.⁵³ Ischemia-reperfusion has been determined to cause endothelial dysfunction in veins but, under similar conditions, arterioles appear to be more susceptible to a reduction in endothelium-dependent relaxation than are coronary venules, despite the fact that leukocytes preferentially adhere to venular rather than to arterial endothelial cells.⁵⁴ In addition, complement fragment C5a causes

neutrophil adherence in venules but not in arterioles, suggesting that different mechanisms mediate neutrophil-endothelial adherence in the two vessel types.⁵⁵

ENDOTHELIAL FACTORS IN VASCULAR GROWTH AND RESPONSE TO INJURY

It is important to identify the role of NO• and NO•-related factors in vascular development (Fig. 48-10). Nitric oxide inhibits vascular smooth muscle proliferation via apoptosis. Animal models have shown that treatment with L-nitroarginine methyl ester, an inhibitor of NO• formation, markedly increases neointimal development after vascular injury.⁵⁶ Local transfection with the eNOS cDNA also reduces the intimal proliferation that follows balloon injury.⁵⁷ The vascular response to injury is enhanced in mice deficient in eNOS.^{58,59} Thus, NO• and cGMP-elevating agents inhibit the growth of fibroblasts and vascular smooth muscle. This effect of NO• on vascular smooth muscle growth is mediated by cGMP and can be mimicked by cGMP analogs such as atrial natriuretic factor.^{59,60}

NO• plays an important role in the process of angiogenesis, and endothelial cells do not seem to be sensitive to the growth-inhibitory effects of NO•. In fact, vascular endothelial growth factor (VEGF)-1 actions during angiogenesis are mediated by NO•. Endothelial cells in the proliferative phase have a sixfold increase in eNOS expression compared with confluent ones, and eNOS knockout mice have little VEGF activity.¹⁹ During the vascular injury response, this feed-forward condition

promotes vascular growth, because while endothelial cells are proliferating to form new blood vessels, the high levels of NO• promote tube formation. Similarly, in response to the denudation injury, proliferating endothelial cells increase NO• production during the growth period to compensate for the lack of endothelial cells in the denuded area while also decreasing platelet adhesion and vascular smooth muscle proliferation in that same area. Moreover, endothelial progenitor cells (EPCs) from the bone marrow have a role in repair of denuded vessels as well as angiogenesis. Although not completely elucidated, circulating EPCs seem to vary in quantity from one patient to the next. Common risk factors such as diabetes and hypercholesterolemia decrease these cells, whereas lipid-lowering drugs such as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors increase them.

EFFECT OF DISEASE STATES ON CORONARY CIRCULATION

Coronary microvascular homeostasis can be adversely affected in disease states by altering vascular diameter, quantity, or response to humoral factors. The contribution of the endothelium to vascular regulation is particularly vulnerable to pathologies such as atherosclerosis, hyperlipidemia, diabetes, and the aging process. This mechanism is highlighted in Figure 48-11. The mechanisms underlying these abnormal endothelium-dependent responses are most likely multifactorial. Factors responsible include abnormalities of G-protein signaling,

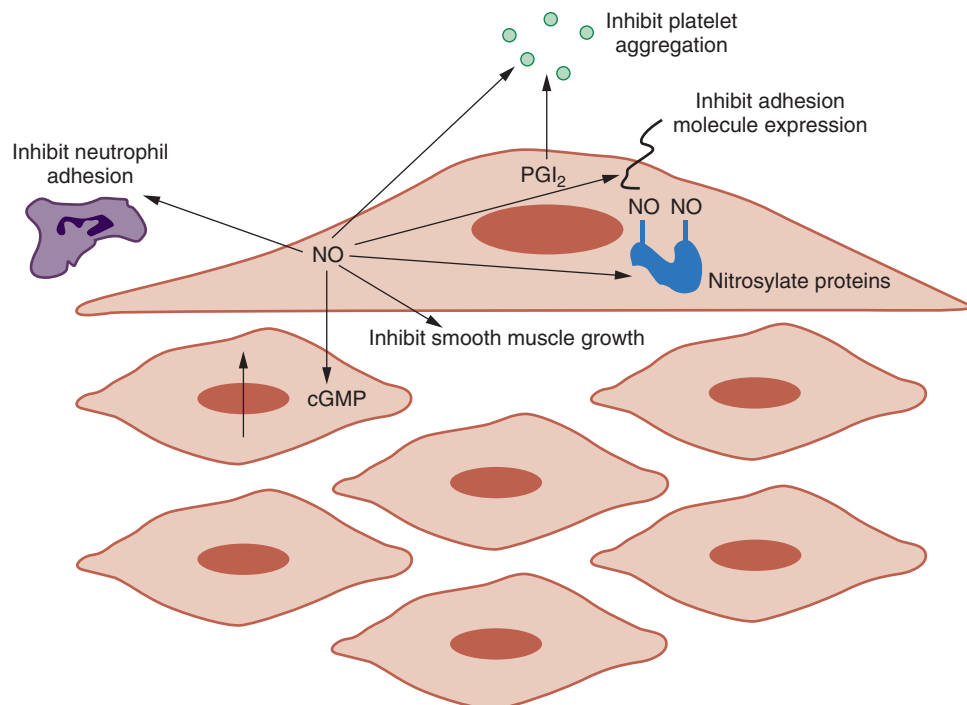


FIGURE 48-10 ■ Schematic representation of endothelium and vascular smooth muscle, demonstrating the multifaceted roles of nitric oxide released from the endothelium in the modulation of vascular function, structure, and the response to injury. cGMP, Cyclic guanine monophosphate; PGI₂, prostacyclin.

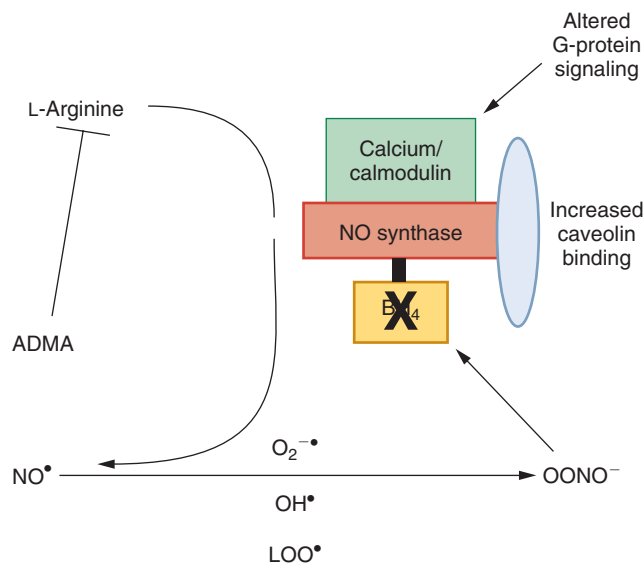


FIGURE 48-11 ■ Reduced production and bioreactivity of endothelium-derived nitric oxide (NO•) in the setting of atherosclerosis, diabetes, and many other pathologic conditions. Asymmetric dimethylarginine (ADMA) acts as an antagonist of L-arginine. Superoxide and other oxygen free radicals may interfere with NO• availability in conditions of increased oxidant stress. The peroxynitrite radical (OONO•) can inhibit tetrahydrobiopterin (BH₄), a cofactor for nitric oxide synthase (NOS). LOO•, Peroxyl radical.

resulting in reduced activation of eNOS in response to endothelial cell receptor activation; an alteration of levels of the critical cofactor for eNOS tetrahydrobiopterin; and an overproduction of asymmetric dimethylarginine, which acts as an antagonist for the eNOS substrate L-arginine. It has been shown that oxidative stress (via increased production of vascular superoxide O₂•⁻) is particularly increased in the presence of common risk factors. Such an increase in oxidative stress will cause a reduction in endothelium-dependent vasodilation.

It is accepted that diseases that affect endothelium-dependent vascular dilation affect the coronary microcirculation as well as the larger vessels. Endothelium-dependent vasodilation acetylcholine and bradykinin is dramatically impaired in coronary microvessels from monkeys fed a high-cholesterol diet for 18 months, and sometimes paradoxical constrictions can be observed.⁶¹ Similar findings have been made in other animal models. Subsequent studies performed using *in vivo* techniques showed that vasoconstriction caused by serotonin and ergonovine (both known to be modulated by the endothelium) is markedly enhanced in the coronary microcirculation of hypercholesterolemic monkeys.⁶² These findings are impressive because the coronary microcirculation is spared from the development of overt atherosclerosis. Therefore, in the setting of a risk factor for atherosclerosis, endothelial dysfunction occurs, leading to abnormal vascular responses. In humans with hypercholesterolemia, diminished flow responses to acetylcholine are restored by cholesterol lowering.⁶³ Similar observations have been made either in humans or in experimental models of hypertension,⁶⁴ ischemia-reperfusion,^{55,65} and diabetes.⁶⁶ It has been suggested that this endothelial dysfunction plays a role in the

development of clinical symptoms despite normal coronary anatomy.

Impaired endothelium-dependent vasodilation has also been linked to increased cardiovascular events. The loss of NO• in cardiovascular disease not only leads to a decrease in vasodilation; it also predisposes to atherosclerotic lesion formation and vascular smooth muscle proliferation. NO• also has antioxidant properties and prevents adhesion molecule expression by endothelial cells. An example of relevance to the clinical setting is the endothelial changes in the coronary microcirculation after cardioplegic arrest and cardiopulmonary bypass during cardiac surgery.⁶⁷ In this setting, endothelial dysfunction persists for some time after cardiopulmonary bypass, and it normalizes thereafter. This result has important clinical implications, because it is common for patients undergoing coronary artery bypass grafting, with seemingly complete coronary revascularization, to exhibit signs of myocardial ischemia during the hours after surgery—most likely caused by endothelial dysfunction.

Collateral vessels in the coronary circulation are particularly important in coronary disease. These allow for normal resting perfusion to a region of the myocardium that is served by an occluded vessel, albeit at a lower perfusion pressure; however, the coronary arterioles nourished by collaterals develop markedly abnormal vascular reactivity—for example, impaired endothelium-dependent vascular relaxations and enhanced constrictions to vasopressin.⁵¹ Possible mechanisms of this impaired microvascular endothelium-dependent relaxation in the collateral-dependent region can involve changes in shear stress, pulsatile flow in the collateral-dependent microvasculature, or intracellular calcium levels. Such changes can cause disturbance in microvascular tone during a disease state.¹⁸

Clinically, patients suffering from ventricular hypertrophy often complain of angina-like symptoms. Animal and human studies have demonstrated that cardiac hypertrophy causes a reduction in the maximal capacity of the coronary circulation to dilate in response to either reactive hyperemia or pharmacologic stimuli.^{5,64,68} One possible cause for this abnormal response may be a mismatch between the elevated myocardial mass and the relatively reduced coronary microcirculation. Peak flow normalized to myocardial mass may be reduced because of this relative paucity of coronary arterioles, because as the myocardium hypertrophies, the coronary resistance circulation might not increase enough to keep pace with the larger muscle mass. Another possible mechanism of impaired vasodilator responses may be explained by endothelial dysfunction, because many of the diseases associated with myocardial hypertrophy are also associated with a loss of endothelial NO• production.

In normal hearts, there is a linear relationship between the diameter of an epicardial coronary artery and the mass of myocardium perfused. Interestingly, epicardial coronary arteries do not enlarge to the same extent as the myocardium hypertrophies, so that for any diameter coronary artery, the amount of myocardium perfused is increased twofold. This phenomenon is particularly

relevant in the presence of a coronary stenosis, where a small lesion that is otherwise considered minimal becomes flow limiting in a hypertrophic state.

PULMONARY VASCULAR PHYSIOLOGY

The pulmonary vascular response has unique characteristics that distinguish it from other vascular beds. The normal pulmonary circulation is a low-pressure, low-resistance circuit with little or no resting tone. In contrast to the systemic circulation, where neural and humoral mechanisms predominate, the pulmonary circulation is under the control of both active factors that affect vascular smooth muscle tone (e.g., autonomic nerves, humoral factors, gasses), and passive factors (e.g., cardiac output, left atrial pressure, airway pressure).⁶⁹

In a normal state, unlike systemic arteries, pulmonary arteries have a much thinner smooth muscle layer, which is consistent with a low-pressure system. Small pulmonary arteries are the main effectors of pulmonary vascular resistance, such as hypoxic pulmonary vasoconstriction. In addition, the pulmonary capillary bed and the systemic capillary bed respond differently. Pulmonary veins are similar in structure to pulmonary arteries, but have less smooth muscle and may be regulated differently. Constriction of pulmonary arteries results in elevated pulmonary artery pressure, which increases the pressure on the right side of the heart, whereas constriction of pulmonary veins increases pulmonary capillary pressure, and this could result in pulmonary edema. With disease, the structure of pulmonary vessels can change significantly. With a chronic increase in pulmonary vascular pressure, there is a structural remodeling, with fibrosis, particularly in the intimal layer, and increased size of the smooth muscle layer, which results in a marked alteration in control mechanisms.⁶⁹

A unique characteristic of the pulmonary circulation is its response to hypoxia. Pulmonary arteries contract when oxygen tension is acutely decreased (Fig. 48-12), unlike systemic vessels, which dilate in response to hypoxia. This phenomenon, called *hypoxia-induced pulmonary vasoconstriction* (HPV) is an important mechanism that aids in matching ventilation with perfusion by directing blood flow from poorly ventilated regions of the lung to areas with normal or relatively high ventilation.⁷⁰ Although acute HPV benefits gas exchange and maximizes oxygenation of venous blood in the pulmonary artery, sustained HPV or chronic exposure to hypoxia is a major cause of the elevated pulmonary vascular resistance and pulmonary arterial pressure in patients with pulmonary arterial hypertension associated with hypoxic cardiopulmonary diseases.⁷¹ Chronic vasoconstriction leads to vascular remodeling, pulmonary hypertension, and possibly cor pulmonale. Patients with chronic obstructive pulmonary disease, for example, are usually hypoxemic and may fall into this category. Similarly, pulmonary vasoconstriction presents a challenge in pediatric patients with congenital heart disease, as they are particularly susceptible to developing pulmonary hypertensive crises after cardiac interventions.⁷² Pulmonary vascular resistance is often increased after lung transplantation.⁷³

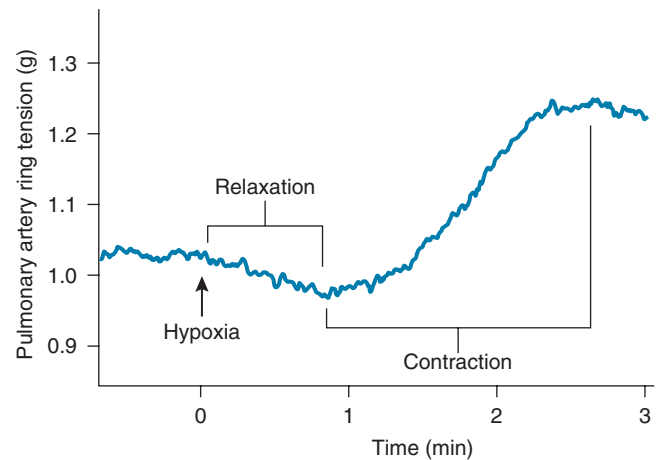


FIGURE 48-12 ■ Actual tracing of isolated pulmonary artery response to hypoxia. Isolated rat pulmonary artery, supported between steel wires in a 37° C organ bath containing modified Henseleit solution and connected to a force transducer, was contracted with phenylephrine (10^{-7} M) and gassed with 95% oxygen, 5% carbon dioxide (hypoxia). The resulting tension tracing exhibits relaxation preceding a transient vascular contraction. (Adapted from Tsai BM, Wang M, Turrentine MW, et al: Hypoxic pulmonary vasoconstriction in cardiothoracic surgery: basic mechanisms to potential therapies. *Ann Thorac Surg* 78:360–368, 2004.)

Hypoxia is a potent vasoconstrictive stimulus in these patients.⁷⁴

Although the exact mechanism of HPV remains unclear, many believe that it is related to the inhibition of calcium channels in the pulmonary vascular smooth muscle that leads to contraction.⁷⁵⁻⁷⁸ This hypothesis is supported by increasing evidence that an increase in cytosolic calcium appears to be an important factor in HPV development.^{77,79} Hypoxia has also been shown to promote membrane depolarization.⁷⁹ Alternatively, HPV might also be related to the inhibition or secretion of an unknown endogenous mediator that results in vasoconstriction.⁷¹ Pulmonary venous hypertension causes pulmonary endothelial dysfunction characterized by reduced bioavailability of NO• and increased formation of vasoconstrictors such as endothelin 1 and thromboxane A₂.^{80,81} Pulmonary venous hypertension may therefore increase pulmonary vasoconstriction and remodeling and cause an increase in pulmonary vascular resistance.^{82,83} Lung vascular responses may further increase pulmonary arterial pressure in congestive heart failure and augment the risk for right ventricular failure.

Aside from oxygen, agents used as potential therapies for HPV have included inhaled NO•, prostaglandins, endothelin receptor antagonists, protein kinase C inhibitors, and potassium channel activators (Fig. 48-13). Currently, advanced therapies are more likely to include combination treatments, and often incorporate endothelin receptor antagonists or cyclic GMP phosphodiesterase-5 inhibitors.⁸⁴ Inhaled vasodilators are thought to circumvent potentially deleterious systemic side effects by acting predominantly on the pulmonary circulation (e.g., epoprostenol or the phosphodiesterase-3 inhibitor milrinone).^{85,86}

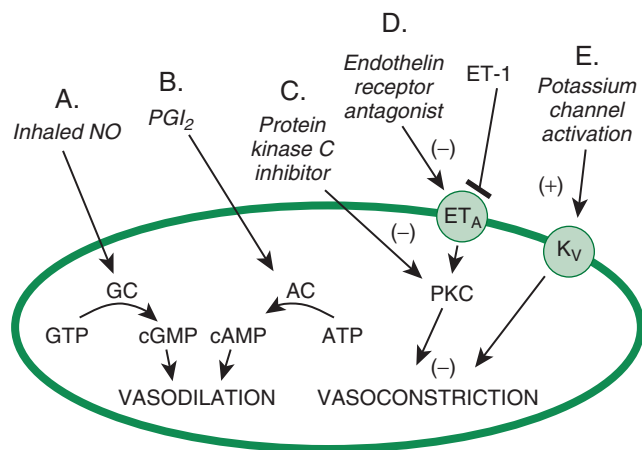


FIGURE 48-13 ■ Therapeutic strategies for blocking hypoxic pulmonary vasoconstriction. (A) Inhaled nitric oxide (NO) and (B) prostacyclin (PGI_2) activate guanylate cyclase (GC) and adenylate cyclase (AC), respectively, to cause vasodilation. (C) Protein kinase C (PKC) inhibitors prevent protein kinase C-mediated vasoconstriction. (D) Endothelin receptor (ET_A , ET_B) antagonists prevent endothelin-1 (ET-1) from binding to ET_A , thus inhibiting vasoconstriction. (E) Potassium channel activation prevents calcium-dependent vasoconstriction. ATP, Adenosine triphosphate; cAMP, adenosine 3',5'-cyclic monophosphate; cGMP, guanosine 3',5'-cyclic monophosphate; GTP, guanosine triphosphate; K_v , voltage-gated potassium channel. (Adapted from Tsai BM, Wang M, Turrentine MW, et al: Hypoxic pulmonary vasoconstriction in cardiothoracic surgery: basic mechanisms to potential therapies. *Ann Thorac Surg* 78:360–368, 2004.)

IMPROVING MYOCARDIAL PERFUSION

Despite improvement in catheter-based interventions and the use of coronary artery bypass grafting, a number of patients present with such diffuse coronary artery disease (CAD) that these interventions result in incomplete or failed revascularization. These patients have poor clinical outcomes associated with decreased survival and decreased angina free survival. We will briefly discuss alternative and theoretical approaches to improve collateral formation for patients suffering from CAD not amenable to current interventions. These therapies include growth factor therapy, gene therapy, cell therapy, and adjuvant drug treatment.

It is important to note that collateral formation resulting from the generic term *angiogenesis* actually encompasses three distinct modes of vessel formation with differential regulation and developmental processes. These modes of vessel formation include “true angiogenesis,” arteriogenesis, and vasculogenesis. True angiogenesis is the growth of vessels from pre-existing vessels; arteriogenesis is the growth of large muscular arteries from existing vessels; and vasculogenesis is de novo blood vessel formation from progenitor cells. These three entities have differential regulatory and developmental processes. Of these processes, arteriogenesis most effectively improves collateral dependent myocardial perfusion.

Angiogenesis

It has also been found that treatment of collateral-dependent vessels with angiogenic growth factors and

gene therapy may enhance endothelium-dependent relaxation, in addition to improving other aspects of cardiac performance. Several animal studies have demonstrated that therapeutic angiogenic interventions, in the setting of chronic ischemia, are associated with an improvement in myocardial perfusion and endothelium-dependent vasodilation in the area supplied by collaterals.⁸⁷⁻⁸⁹ These studies used growth factors such as VEGF, fibroblast growth factor (FGF)-1, or FGF-2 placed in the perivascular area. Possible mechanisms through which these factors act include FGF-2- and VEGF-induced release of NO , which improves collateral perfusion and decreases tissue ischemia.⁹⁰ In addition, it has been shown that during periods of chronic ischemia there occurs an upregulation of FGF-2 and VEGF receptors. This finding is consistent with results showing that after administration of growth factors, endothelium-dependent relaxation occurs in the collateral-dependent region, but not in myocardium perfused via the original vessels.⁹¹ In addition, these growth factors can stimulate the release of bone marrow-derived endothelial progenitor cells that promote collateral growth and endothelial function at the treated sites. Unfortunately, clinical trials to date have not demonstrated much benefit with growth factor and gene therapy in patients. Similarly, in clinical trials cell therapy has largely failed to enhance collateral formation to provide sufficient perfusion in the setting of myocardial ischemia. A number of clinical studies have been performed in which patients received bone marrow-derived mononuclear cells or endothelial progenitor cells by infusion several days after myocardial infarction. Other clinical trials have similarly found clinically insignificant benefits or no benefit to cell therapy.⁹² These studies demonstrate that cell therapy is safe in the short and long term. Differences in study outcomes are likely related to patient selection, comorbidities, and method of delivery.

Challenges and Future Directions

Multiple factors may explain the failure to reproduce the multiple effective preclinical trials with growth factors, genes or cell therapy on vascular regeneration. Patients with end-stage CAD often have significant comorbid conditions, including diabetes and hypercholesterolemia, resulting in aberrant vascular signaling and endothelial dysfunction.⁹³ These conditions result in hostile local environments with increased oxidative stress and increased expression of anti-angiogenic proteins.⁹⁴ Technical issues may contribute to failure in growth factor therapy, including incomplete or nonsustained drug delivery. Similarly, cell-based therapies are fraught with biological and technical failures. Issues include technical failure during injection resulting in “washout,” or “leak out” of cells from injection sites in the heart, lack of homing and incorporation of cells, and cell death.⁹⁵ Potential approaches to improve homing and survival of the cells include heat shock treatment and incorporation of bioactive matrices. Another effort to improve functionality is the coadministration of growth factors with cell-based therapy. Gene-based therapies may hold the greatest promise for improving angiogenesis and myocardial perfusion, yet are the least studied and most

poorly understood. Gene-based therapies result in overexpression of survival proteins, use of genetically engineered bone marrow cells, and embryonic stem cells.⁹⁵⁻⁹⁷

In addition, investigators have also searched for adjuvant drugs to improve regenerative therapies. Commonly prescribed drugs like statins, cyclo-oxygenase inhibitors, and metformin, as well as naturally occurring substances like resveratrol have demonstrated a number of pleiotropic effects in preclinical and clinical studies.⁹⁸⁻¹⁰⁴ The direct and indirect effects of these and other drugs on hyperglycemia, hypercholesterolemia, and oxidative stress can act synergistically with other therapies to improve collateral formation.⁹⁸⁻¹⁰⁴ Despite the overall lack of clinical efficacy to date, the future of regenerative treatments holds much promise. Improvements in treating patient comorbidities along with continued advances in understanding the basic science of angiogenesis, pharmacology, genetic engineering, and more procedure based interventions will be required to demonstrate successful clinical application of regenerative therapies.

SUMMARY

This chapter provided an overview of some of the newer concepts regarding physiologic and pathophysiologic control of vascular tone. Properties of peripheral vessels cannot be extrapolated to the coronary or pulmonary circulation. Similarly, properties of one size or class of coronary microvasculature cannot be generalized. Certainly, the technology used in recent studies is dramatically changed from that of older ones. Although we attempted to focus on studies that directly examined the microvasculature using the newer technology (in vitro preparations or in situ observations), it was also important to present classical studies of the intact circulation performed in intact animals or isolated hearts. Newer research questions have necessitated the use of more basic techniques, including cell culture and molecular biological approaches. A more recent development has been the ability to make many in vivo hemodynamic measurements in human subjects in the catheterization laboratory, thus obviating the need and the expenses of flow studies in large animals. As the field of vascular biology grows, we will continue to validate our observations in the intact circulation of our patients and to translate this basic science to the clinical setting.

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PHYSIOLOGY OF THE MYOCARDIUM

R. John Solaro • Margaret V. Westfall

CHAPTER OUTLINE

INTEGRATIVE BIOLOGY OF THE MYOCARDIUM
CARDIAC DYNAMICS IN EXERCISE
MOLECULAR CELLULAR BIOLOGY
SARCOMERE MECHANICS
EXCITATION–CONTRACTION COUPLING
MODULATION OF EXCITATION–CONTRACTION COUPLING BY PHOSPHORYLATION

CROSS-BRIDGES AND STROKE VOLUME
CELLULAR BIOLOGY OF CONTRACTILITY
CELLULAR BIOLOGY OF AFTERLOAD
CELLULAR BIOLOGY OF CELL LENGTH
CARDIAC FUNCTION CURVES

INTEGRATIVE BIOLOGY OF THE MYOCARDIUM

The essential function of the muscles that make up the myocardium is to transfer to the arteries the volume of blood added to the ventricular chambers during diastole.¹ This transfer must occur within the narrow limits of end-diastolic pressures and must produce a flow of materials to the organs that matches the needs of the cells. The term *needs* means “matching the flow of oxygen,” which is consumed by the cells at a rate greater than all other materials, to the demand for oxygen. By supplying the tissues’ oxygen needs, the demand for all other substances in blood is met. An inevitable consequence of the work done during exercise is an increase in oxygen consumption, and with linear incremental increases in oxygen consumption there are linear incremental increases in cardiac output (CO) to match the increases in venous return (VR). The tight coupling of oxygen demand to CO and VR indicates a regulatory system that is able to sense the tissue oxygen needs, and to engage control mechanisms that adjust the CO. In this chapter, we are concerned with the role of the myocardium in the task of the cardiovascular system to couple oxygen demand to oxygen supply.

In accomplishing this task, the activity of the myocardium must vary over a wide range of short-term regulation (seconds, minutes, and hours) and of long-term regulation (days, weeks, and years). In the short term, during the course of a normal day as tissue oxygen demands and hence cardiac output changes from sleep to strong exercise, variations in activity of the myocardium occur by both intrinsic and extrinsic control mechanisms. The major intrinsic regulator is the Frank-Starling mechanism, in which the pressure developed by the

ventricle increases as the end-diastolic volume increases. Extrinsic regulators of the myocardium include the autonomic nerves of the sympathetic and parasympathetic systems, and humoral factors including catecholamines, thyroid hormone, and insulin. In long-term regulation, the activity of the myocardium is more permanently changed in response to chronic changes in oxygen demand associated with frequent bouts of chronic exercise and altered states of the pump and vascular system associated with aging and various long-standing pathologies. In this long-term regulation, the size of the cells composing the ventricular myocardium changes (i.e., hypertrophy or atrophy, without a change in cell number). The cells are remodeled by alterations in subcellular mechanisms regulating contraction and relaxation. This long-term regulation occurs physiologically with normal development of the heart from the immature to the mature myocardium, with normal physiologic aging, and with acquired or inherited pathologies that directly or indirectly affect the function of the myocardium.^{2,3} In this chapter, we focus on current concepts and theories of the cellular, subcellular, and molecular mechanisms for short-term regulation of the myocardium. These mechanisms are constrained to account for the dynamic and steady-state functional properties of the heart. Changes in flow and ventricular volumes during an episode of exercise reveal these functional properties.

CARDIAC DYNAMICS IN EXERCISE

Figure 49-1 displays changes in heart rate (HR), CO, stroke volume (SV), and ventricular volumes of a young healthy adult during a bout of exercise on a stationary bike. The measurements were made before and after administration of propranolol, a β -adrenergic blocking

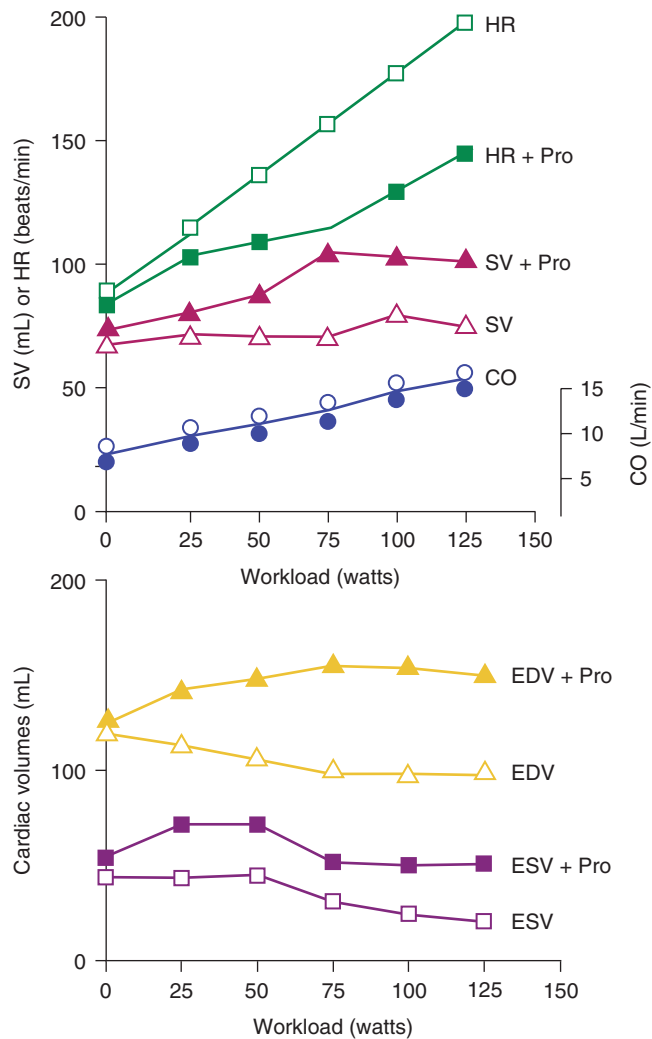


FIGURE 49-1 ■ Dependence of heart rate (HR), cardiac output (CO), and left ventricular volumes on workload in a bout of exercise. The experiments were performed on a healthy young man before and after the administration of propranolol, a β -adrenergic blocking agent. EDV, End-diastolic volume; ESV, end-systolic volume; Pro, propranolol; SV, stroke volume. (Data courtesy Dr. Edward Lakatta.)

agent. Note that in the control condition, CO increased with workload, but end-diastolic volume (EDV) remained rather constant even though CO nearly tripled. SV increased and end-systolic volume (ESV) decreased. These data show that the increased VR that occurs in exercise is handled by the heart largely by increases in HR and decreases in ESV. Elevations in EDV as a mechanism to increase CO are not favorable because of the increased energy cost according to Laplace's law.¹ A decrease in ESV provides an important mechanism for matching CO to increased VR without increases in EDV. As we will show, this reduction in ESV at constant EDV can be one measure of the contractile ability of the cells of the heart—that is, the contractility or inotropic state of the heart. After blockade of adrenergic β -receptors with propranolol, there is a blunting of the ability of the sympathetic nervous system to influence the heart; however, CO still increased approximately threefold. This result demonstrates the ability of the cardiovascular

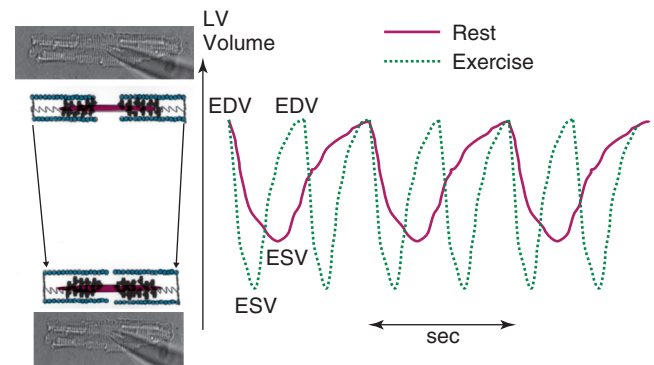


FIGURE 49-2 ■ Time dependence of left ventricular (LV) volume before and during exercise. Note the reduction in cycle time associated with the increased heart rate. The left panel depicts how the change in volume reflects a change in sarcomere length and cell length of ventricular myocytes composing the ventricular chamber. EDV, End-diastolic volume; ESV, end-systolic volume.

system to match the CO to the increased tissue oxygen needs without sympathetic nervous system control mechanisms. However, the increase in CO in the presence of propranolol did not occur without cost. One cost was that the increase in HR was reduced. With a decrease in HR and a constant CO, the SV had to be elevated ($CO = SV \times HR$). The increase in SV occurred largely because of an increase in EDV. Increases in EDV present a threat to the economy of contraction, and they can also stimulate hypertrophic signaling pathways as a result of cell stretch.^{2,3} These effects of propranolol indicate an important role of the β -receptors and the sympathetic nervous system in regulation of the ability of the heart to maintain CO with little or no change in EDV. Figure 49-2 depicts the dynamics of cardiac function with data relating time dependence of left ventricular volume before and after an episode of exercise. These data demonstrate the decrease in ESV with little change in EDV and enhanced dynamics and abbreviation of the contraction-relaxation cycle. The abbreviation of cardiac cycle time is critical for the maintenance of cardiac filling during the fast HR that occurs with exercise. Figure 49-2 also illustrates that the volume changes are associated with shortening of the cells composing the left ventricular chamber, and that the changes in cell length reflect changes in sarcomere length. Next, we discuss the molecular and cellular mechanisms responsible for maintenance of CO with elevations of VR with minimal change in EDV.

MOLECULAR CELLULAR BIOLOGY

Figure 49-3 depicts cellular structures involved in excitation, contraction, and relaxation. Tight junctions of low electrical resistance connect heart cells.^{4,5} When one cell is activated (depolarized), all cells become activated. Therefore, unlike skeletal muscle, the heart does not recruit motor units to regulate contraction. Instead, regulation is at the level of the cells themselves. There are mechanisms that permit regulation of the activity of each cell to meet varying demands on the circulation. We will therefore concentrate now on understanding overt left

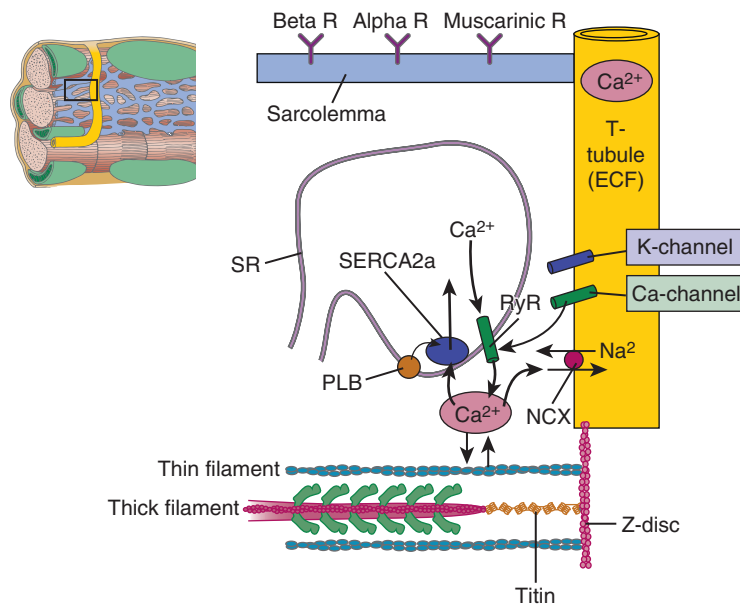


FIGURE 49-3 ■ Microscopic view of a portion of a myocardial cell illustrating structures critical to excitation–contraction coupling. The T-tubule—containing channels and transporters—are shown as an invagination of the surface membrane (or sarcolemma), which contains surface α - and β -receptors for norepinephrine, epinephrine, and muscarinic receptors for acetylcholine. Also shown is the sarcoplasmic reticulum (SR), an internally enclosed network of tubules in which high concentrations of Ca^{2+} are stored in diastole. With electrical excitation of the cell, Ca^{2+} channels open and the small release of Ca^{2+} into the cytoplasm induces Ca^{2+} release from the SR through ryanodine receptors (RyR2; SR Ca^{2+} release channels). Ca^{2+} moves to the myofilaments (shown as a half-sarcomere; see Fig. 49-4) and activates contraction. Ca^{2+} is removed from the cytoplasm by an SR Ca^{2+} -activated Mg-ATPase (SERCA2a) and exchanged for Na^+ by the action of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) in the sarcolemma. Phospholamban (PLB) inhibits transport of Ca^{2+} by SERCA2a, and the inhibition is released when PLB becomes phosphorylated. ECF, Extracellular fluid.

ventricular cardiac function in terms of the properties of the cardiac myocytes. The objectives are to understand the following:

- The molecular and cellular mechanisms responsible for the changes in wall tension and ventricular volume that occur in the transition from diastole to systole
- The regulatory devices used by the heart to ensure ejection of an SV equal to the LV at optimal EDV during basal physiologic states and during exercise
- The mechanisms that ensure that dynamics of the heart beat are tuned to match the prevailing frequency (i.e., the HR)

SARCOMERE MECHANICS

Sarcomeres are the fundamental structural units responsible for the ability of myocardial cells to shorten and generate forces (Fig. 49-4, and see Fig. 49-3). Side arms of the myosin molecules (cross-bridges) that compose the thick filament are molecular motors that also hydrolyze adenosine triphosphate (ATP). Light chains on the myosin head, which are different in ventricles and atria, appear to regulate the rate of the ATP hydrolysis. A thick filament-associated protein (called myosin-binding protein C, or C-protein) may be important in regulating the radial movement of the cross-bridge. C-protein also binds to titin, a long structural protein that extends from the center of the sarcomere to the Z-disc. This interaction is of significance in cross-bridge function and in the

generation of passive tension. The reaction of the myosin cross-bridges with the actins of the thin filaments generates active cellular force, shortening, and power.^{6,7} The basic reaction cycle includes an attachment step; a movement of the lever arm of the myosin head, which impels the thin filament in each half-sarcomere to slide toward the center; and a detachment step, which completes the cycle.⁶ Figure 49-4 displays the cross-bridge in diastole (left) and at the end of the power stroke (right). The energy for these movements comes from the hydrolysis of one molecule of Mg-ATP during each cycle. In diastole, the cross-bridges contain bound Mg-ADP and inorganic phosphate (P_i), which has been generated from the splitting of Mg-ATP on the surface of the myosin head, poising it for reaction with actin. As actin sites become available, the cross-bridge attaches and enters into a catalytic cycle in which the release of P_i and Mg-ADP, together with isomerization of the cross-bridge, induces a progressive change in mechanical state of the cross-bridge, leading to thin-filament sliding. The terminal state is a strongly bound, so-called rigor cross-bridge that is free of P_i and nucleotide. Detachment requires binding of Mg-ATP, which is quickly split, without release of products, so that the cycle can begin again if actins remain accessible. Each actin–cross-bridge reaction cycle is therefore powered by the hydrolysis of Mg-ATP.

Ca^{2+} binding triggers conformational changes and movements of the thin-filament proteins troponin (Tn, a heterotrimeric protein complex) and tropomyosin (Tm) that switch on the actin–cross-bridge reaction.^{3,8} Figures 49-4 and 49-5 illustrate the steps in this process. In

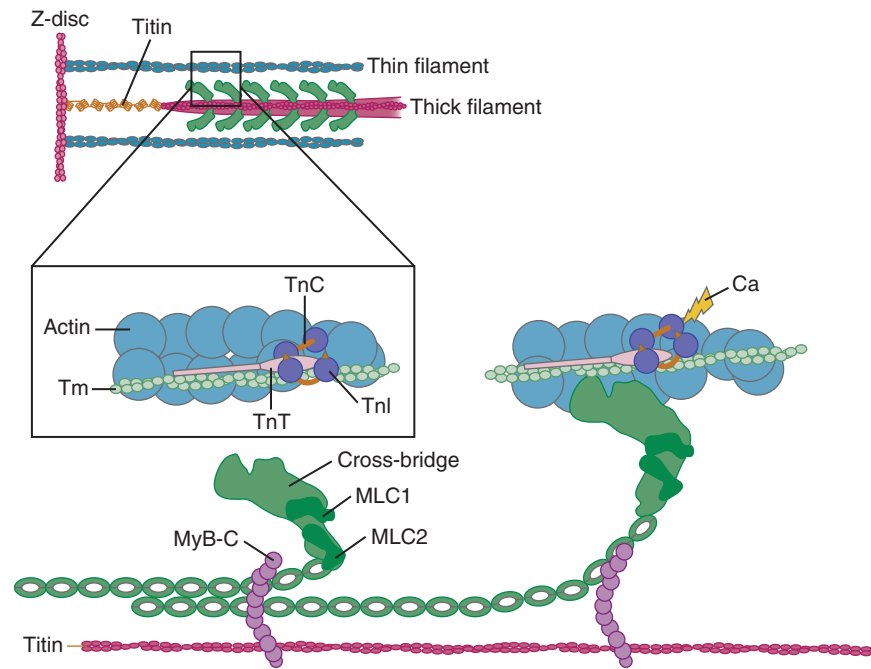


FIGURE 49-4 ■ Illustration of a cardiac myocyte half-sarcomere showing a regulatory unit in diastole and systole. Microscopic view shows that the regulatory unit consists of seven actins, one tropomyosin (Tm), and one heterotrimeric troponin complex, which consists of a Ca^{2+} -binding protein (TnC), an inhibitory protein (TnI), and a Tm-binding protein (TnT). Although not shown here, the thin filament in a half-sarcomere contains approximately 30 regulatory units. The action of cross-bridges, discussed further in the text, in each half-sarcomere impels the thin filaments toward the center of the sarcomere by a reaction with actin powered by ATP hydrolysis. Cross-bridges are impeded from reacting with the thin filament by tropomyosin and troponin. Ca^{2+} binding to a regulatory lobe of troponin C releases the thin filament from this inhibition. Myosin-binding protein C (MyB-C) and myosin light chains (MLC1 and MLC2) modulate cross-bridge activity. Titin is a major structural protein responsible for passive tension.

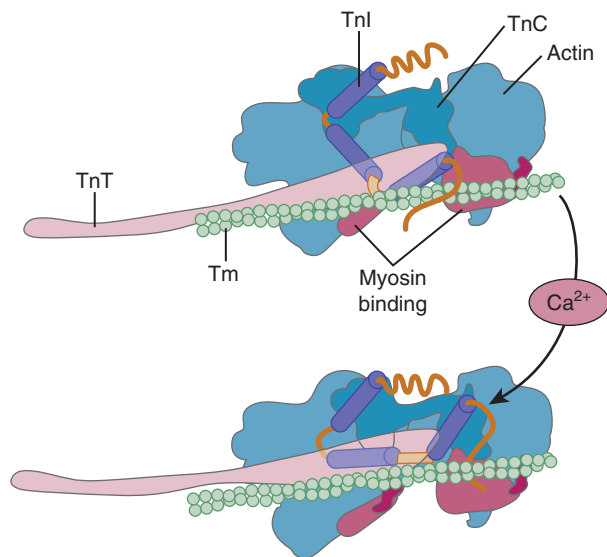


FIGURE 49-5 ■ Molecular mechanism of thin filament activation by Ca^{2+} . In diastole, tropomyosin (Tm) and troponin (Tn) act to impede the thin filament-cross-bridge reaction by steric and allosteric effects on the actin sites that react with myosin. TnI, the inhibitory protein, binds tightly to actin through an inhibitory peptide (Ip). With Ca^{2+} binding to troponin C (TnC), a strong attraction between the Ip and C-terminal regions of Tn is promoted, resulting in movement of the Ip of TnI away from the actin-binding site, a release of TnT, and a movement of Tm, exposing regions of actin that react with myosin cross-bridges also.

diastole, Tn and Tm are situated on the thin filament in positions that hinder the actin-cross-bridge reaction. Tn and Tm are held in this position largely through the tethering action of troponin I (TnI). TnI is an inhibitory protein of the Tn complex, which binds tightly to actin through a highly basic peptide, to the C-terminal end of TnT, the Tm binding unit of Tn, and the C-terminal lobe of troponin C (TnC), the Ca^{2+} receptor protein. This inhibitory property of TnI is amplified by virtue of these multiple protein-protein interactions to immobilize the long α -helical Tm in a blocking position that encompasses many actins along the thin filament. When released into the myofilament space by mechanisms summarized later, Ca^{2+} binds to a single regulatory site on the N-terminal lobe of TnC, the Ca^{2+} receptor protein in the heterotrimeric Tn complex. Ca^{2+} binding to the C-lobe exposes a “sticky patch” of hydrophobic amino acids that promotes binding of TnC to the inhibitory peptide and C-terminal regions of TnI. This reaction releases the inhibitory peptide from actin and leads to a pivoting of the Tn complex on the thin filament, with TnT acting as a lever to move Tm from its blocking position on the thin filament. An important aspect of the transition from diastole to systole is that the reaction of cross-bridges with the thin filament can itself promote more actin-cross-bridge reactions by cooperative feedback mechanisms. It is apparent that cross-bridge binding can enhance the affinity of TnC for Ca^{2+} and move Tm farther away from the region of actin that reacts with the cross-bridges.

At this stage, it is important to understand that the number of cross-bridges reacting with the thin filaments determines the force generated by the sarcomere. An important determinant of the number of cross-bridges reacting with the thin filaments is the amount of Ca^{2+} released to the myofilaments and, thus, the relative occupation of sarcomeric TnC proteins with Ca^{2+} (in the basal state, this is about 20% to 25% of the total TnC).⁸ Other important determinants of the number of cross-bridges reacting with the thin filaments are the sarcomere length⁹ and the load (velocity of shortening).⁶ We will discuss the mechanisms by which each of these variables affects the number of cycling cross-bridges.

Molecular springs interlaced with the thin and thick filaments form elastic elements in the sarcomere that determine passive elastic properties of the cell and have a possible role in active contraction of the cells.¹⁰ A major elastic element is the giant protein titin (see Fig. 49-3), which is a long and flexible protein extending from the Z-disc to the midline of the sarcomere. As illustrated in Figure 49-3, titin has a region near the Z-disc that is coiled much like a spring. There is accumulating and solid evidence that when the sarcomere is stretched, titin elongates, giving rise to passive tension. Moreover, there is evidence that when the sarcomere shortens, the titin spring imposes a restoring force that is likely to be important in early diastole. Regions of titin in the thin filament–thick filament overlap zone also interact with myosin-binding protein C, a thick filament–associated

protein that binds to the head–neck region of myosin. Thus, the conformational changes in titin can also affect cross-bridge disposition. Although not depicted in Figure 48-3, the Z-disc of the sarcomere not only anchors the thin filaments; it also links sarcomeres in series by interactions between titin and the thin filaments. There are also lateral connections linking the sarcomere to the surface membrane. In addition to its role in force transmission, the Z-disc is emerging as a locus of communication in the cells. The Z-disc appears as a crossroad for interactions among many diverse proteins including channels, kinases, phosphatases, and cytoskeletal elements that connect to the nucleus and to a network of cytoskeletal proteins and membrane proteins at focal adhesion complexes.¹⁰

We will use Figure 49-6, which relates the circumferential shortening associated with the heartbeat to sarcomeric activity, to discuss the cellular and sarcomeric correlates of preload, afterload, and contractility. In Figure 49-6, we relate the contraction–relaxation cycle of the heart beat to events in a single sarcomere; mechanical changes that occur in the active and passive elements of the sarcomere are related to the beat of the heart. The sarcomere is depicted as a contractile element in series with a passive spring that is a lumped elastic element (collagen, titin, and cytoskeletal proteins). A load attached to the end of the sarcomere establishes the sarcomere length before activation and is termed the *preload*. The preload stretches the sarcomere to its diastolic length; the

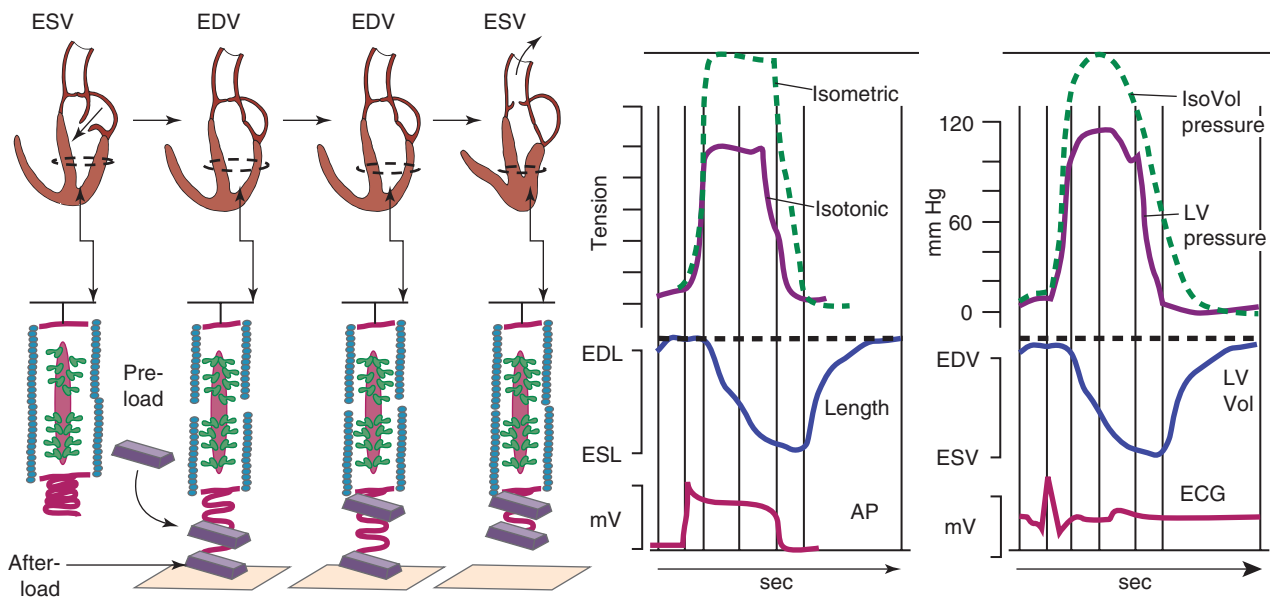


FIGURE 49-6 ■ Relationships between ventricular states in the cardiac cycle and the mechanics of isolated muscle preparations. The cycle begins on the left at an end-systolic volume (ESV) and end-systolic (ES) sarcomere length. In the linear muscle setup, the analog of end-diastolic volume (EDV) is a weight—the preload—added before activation. The addition of the preload establishes sarcomere length. The load that the sarcomere discovers it must lift is not seen until after activation, and the afterload is supported on the platform. With activation as triggered by the action potential (AP) and measured as the electrocardiogram (ECG), force-generating cross-bridges react with actin; this develops tension isometrically until the tension developed matches the afterload. At that point, the sarcomere shortens with a velocity appropriate to the number of reacting cross-bridges to the load. This sarcomeric activity is reflected in the ventricle as an increase in wall tension, isovolumic (IsoVol) pressure development followed by opening of the aortic valve, and ejection of blood against the rising pressure in the aorta. Dashed lines represent measurements in which muscle length was held constant, or in which the aorta was clamped to produce an isovolumic beat. The peak amplitude of pressure or tension provides a measure of contractility. EDL, End-diastolic length; ESL, end-systolic length; LV, left ventricular.

correlate of the preload in the ventricle is the EDV. In the ventricle, an end-diastolic pressure (EDP) develops as the passive springs are stretched.

Figure 49-6 also illustrates the sarcomere with an attached afterload. The sarcomere does not “see” this load until after activation. The correlate of afterload in the ventricle is the aortic pressure. With cellular excitation, Ca^{2+} is released into the myofilament space, the cross-bridges in the sarcomere react with actin sites on thin filaments, and the cell develops tension, shortens, and stretches the elastic element. As tension increases, the afterload is lifted, and the muscle cell shortens. The sarcomere will shorten as long as it can develop tension equal to the afterload. As excitation wanes, the cell returns to the diastolic state, ready for another cycle. Figure 49-6 also shows records of the isotonic twitch (the load is constant) and the ventricular pressure. The correlate of cellular tension is the pressure (by Laplace’s law, where $\text{Wall tension} = \text{Pressure} \times \text{Radius of curvature} \div [2 \times \text{Wall thickness}]$), and the correlate of cellular length is the ventricular volume. In fact, the aortic pressure is increasing during ejection, and, thus, strictly speaking, afterload is not constant. This is referred to as an *auxotonic twitch*.

The concept of contractility is illuminated by repeating this sequence of events, but with the sarcomere held isometric (dashed lines in Fig. 49-6). In this case, the sarcomere cannot lift the load and develops the maximum isometric tension possible at the particular length, established by the preload and the extent of availability of thin filament sites for reaction with cross-bridges. The peak amplitude of isometric tension is a measure of contractility, one definition of which is maximum tension when the sarcomeres are neither lengthening nor shortening. The peak tension in the isometric twitch reflects in part the amount of Ca^{2+} delivered to the myofilaments, and in part the sarcomere length. As we will see, the amount of Ca^{2+} is a regulated variable in heart muscle cells; thus, peak tension or contractility in the isometric twitch could increase or decrease. In animal experiments, this measure of contractility can be determined in beating hearts as well.¹ The approach is to cross-clamp the aorta transiently, which creates resistance and therefore infinite afterload. Dashed lines in the right panel of Figure 49-6 show an isovolumic beat of the ventricle. The peak pressure in this isovolumic beat is a measure of the contractility in the same way that peak tension is a measure of contractility in the sarcomere.

How can contractility be measured in humans without the drastic invasive procedure of clamping the aorta? And how does this present definition of contractility relate to the previous indication that contractility is related to end-systolic length and thus end-systolic pressure (ESP) of the sarcomeres? The answers to both these questions are couched in terms of the pressure-volume loop of the left ventricular beat. Figure 49-7 shows the dependence of ventricular pressure on ventricular volume during cardiac cycles occurring at three different afterloads. The figure also illustrates that the cross-sectional area of the ventricles at the ESV and the EDV is associated with changes in sarcomere length of the cells. In a beat, the volume added during diastole (loading volume) stretches the sarcomeres from the ESV to establish the

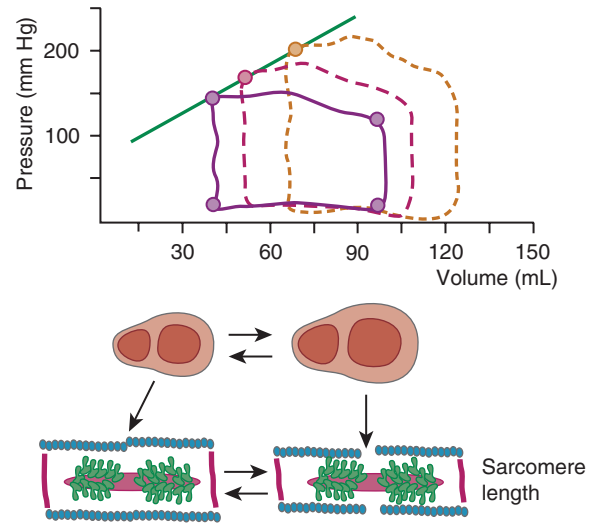


FIGURE 49-7 ■ Pressure–volume (P–V) relationships of the left ventricle at varying end-diastolic volumes generated by infusion of blood or saline into the circulation. The P–V loops represent data obtained in human subjects in a resting condition. End-systolic pressure (ESP) points are shown as filled circles. These points represent a state in which the ventricle is neither lengthening nor shortening, and is developing the peak pressure (tension) at that particular ventricular volume (sarcomere length). Thus, points on the volume–ESP relationship reflect the length–tension properties of the muscle cells. The relationship between these points and a circumferential array of ventricular cells and the length of the sarcomere is schematically shown to illustrate that the P–V loop is rooted in a complex relationship between sarcomere length and ventricular geometry. See the text and Covell and Ross¹ for further discussion.

end-diastolic cell length and EDV. With electrical activation, Ca^{2+} is released into the myofilament space. The sarcomeres develop tension isometrically (isovolumic pressure development) until the cell tension produces a pressure greater than the aortic pressure (the afterload); the valve opens and blood is ejected from the ventricle. The ejection continues with shortening of the sarcomeres to a point at which the pressure developed in the ventricle no longer exceeds the afterload. At this ESP point, the valve closes with the waning of electrical activation and restoration of diastolic Ca^{2+} , and pressure falls isovolumically. The ESP is thus a point in which the sarcomeres are no longer shortening or lengthening. ESP is, in effect, a point essentially reflecting isometric tension—that is, a measure of contractility. The ESP points can be varied by varying afterload, as displayed in Figure 49-7 with the dashed pressure–volume loops. Afterload was increased in this example by rapidly increasing the loading volume through an increase in VR. As discussed later, these ESP points reflect isovolumic pressure or isometric cellular tension and are points on the sarcomere length–tension relationship. A line connecting these points represents a constant state of contractility. The pressure or tension is different at each of the points because the muscle and sarcomere length has changed, not because the contractility has changed. Each beat depicted in Figure 49-7 thus occurred with essentially the same amount of Ca^{2+} released to the myofilaments. The increase in ESP with increases in ventricular volume is the essence of Starling’s

law of the heart, also known as the *Frank-Starling relationship*.^{1,9}

The ESP also reflects the extent of shortening, as previously discussed. Imagine, as we will consider later, that the contractility increases. The ESP–volume relationship will shift upward and to the left, and thus at a given afterload the sarcomere will be able to shorten farther than at the previous level. Circumferential shortening will occur to a greater extent, and the SV will be increased for a given afterload. We address this concept again after describing the cellular mechanisms by which contractility can be altered.

EXCITATION–CONTRACTION COUPLING

With the realization that Ca^{2+} ions trigger and regulate the number of actin–cross-bridge reactions, it is easy to understand that switching the heart beat on and off must involve cellular mechanisms that provide and remove Ca^{2+} ions to and from troponin C. Figure 49-8 shows evidence that during a beat of the cells, there is transient increase in intracellular Ca^{2+} . Adult mammalian myocardial cells have evolved elaborate membranous structures and membrane proteins to keep Ca^{2+} away from the myofilaments during diastole, and to provide Ca^{2+} to the myofilaments during systole.^{4,11,12} The myofilaments are surrounded by a reticulum of tubular membranes, called the *sarcoplasmic reticulum* (SR). These tubules form an internally enclosed compartment that is not contiguous with the extracellular fluid and that contains a number of proteins that regulate the storage, release, and reuptake of Ca^{2+} . As illustrated in Figure 49-3, the surface membrane or sarcolemma of ventricular myocytes plunges

into the cellular interior and forms the T-tubules. These invaginations occur along the length of the cell in register with each of the sarcomeres. The T-tubules serve to bring the extracellular fluid, as well as membrane ion channels, transporters, and exchangers, into the depths of the cell interior. The T-tubules are in proximity to the terminal swellings of the SR that are the main storage depots for Ca^{2+} during diastole.

Integrated activity of proteins and protein complexes in the sarcolemma (SL), the T-tubules, the SR, and the myofilaments compose the essential elements of a process known as *excitation–contraction coupling*, whereby electrical impulses arriving at the cell are coupled to a release of Ca^{2+} and to the promotion of the actin–cross-bridge reaction.^{4,11,12} Measurements of cellular processes of membrane potential, intracellular Ca^{2+} , and tension are displayed in Figure 49-8. The triggering event is action potential depolarization of the SL and the ensuing depolarization of the sarcolemmal T-tubule. This excitatory process initiates activation of voltage-dependent, L-type Ca^{2+} channels (also known as *dihydropyridine receptors*), which are primarily clustered within the T-tubules at the sarcolemmal–SR junction. The transverse tubules of the SR contain Ca^{2+} release channels. These channels are also known as *ryanodine receptors* (RyR2, cardiac isoform) because of their ability to bind this alkaloid. Depolarization-induced influx of Ca^{2+} current (I_{Ca}) through the L-type channels contributes approximately 20% to 25% of the free Ca^{2+} in a cardiac twitch. Equally important, I_{Ca} is proposed to act locally to trigger the release of SR Ca^{2+} via the SR Ca^{2+} release channels. The release of Ca^{2+} through the RyRs contributes the remaining 75% to 80% of Ca^{2+} necessary for cardiac contraction. The process of coupling between the influx of Ca^{2+} via I_{Ca} and Ca^{2+} release from the RyR2 is known as Ca^{2+} -induced Ca^{2+} release (CICR). The gating of the RyR2 by I_{Ca} is the essence of CICR. Experiments employing fluorescent indicators that sense Ca^{2+} have revealed the activity of local clusters of RyR receptors. These experiments demonstrate elementary events known as Ca^{2+} sparks that reflect the activity of small groups of RyRs. Enhanced I_{Ca} increases localized Ca^{2+} accumulation, which increases Ca^{2+} spark frequency and produces a graded stimulation of RyR Ca^{2+} release from the SR. Release into the cytosol increases the local concentration of Ca^{2+} surrounding the myofilaments and promotes Ca^{2+} binding to TnC on the thin filaments. The reaction of Ca^{2+} with TnC triggers the protein–protein interactions that release regulatory units of the thin filament from an inhibited state (see Figs. 49-4 and 49-5). During a beat of the heart in a basal physiologic state, the amount of Ca^{2+} delivered to the myofilaments is sufficient to activate only about 20% to 25% of the regulatory units. The 75% of actin–cross-bridge reactions that remains available for increases in contractility form a molecular basis for what is commonly referred to as *cardiac reserve*.

As illustrated in Figure 49-8, the elevation in Ca^{2+} levels observed during systole is transient, with SL and SR proteins working to sequester Ca^{2+} and return it to baseline levels in the return to diastole.^{4,11,12} In the steady-state contraction–relaxation cycle, an equal efflux must match the influx of Ca^{2+} . In human hearts, this

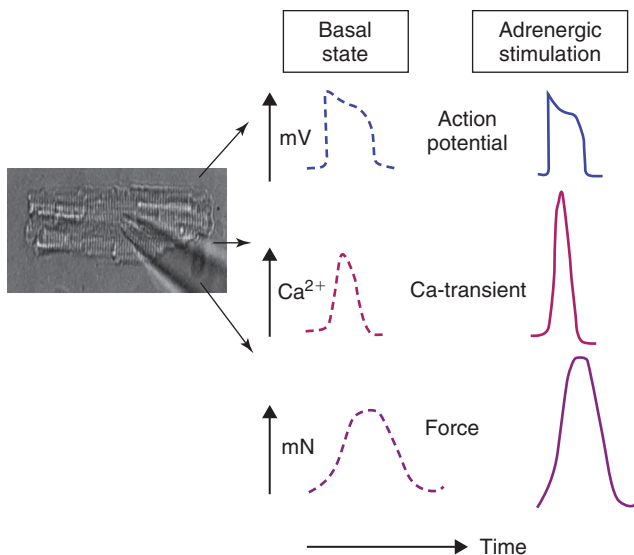


FIGURE 49-8 ■ Schematic of action potential, intracellular transient change in Ca^{2+} , and isometric tension of a single cardiac myocyte in a basal state and during stimulation with an adrenergic agonist. The effects of adrenergic stimulation are an abbreviation of the action potential and an increase in the amplitude and dynamics of both the Ca^{2+} transient and the twitch tensions.

sequestration process involves two major cellular pumps. The majority of Ca^{2+} (70%) is re-sequestered into the SR via Ca^{2+} pumps (sarcoendoplasmic reticulum Ca^{2+} pump; SERCA2a isoform) present on the longitudinal tubules of the SR. SERCA2a is a Ca^{2+} -activated Mg-ATPase that couples Mg-ATP hydrolysis to the active transport of Ca^{2+} from the cytoplasmic space into the SR. A high-capacity, low-affinity Ca^{2+} binding protein, known as *calsequestrin*, serves as a sink for Ca^{2+} in the interior of the SR. Most of the remaining Ca^{2+} is removed from the cell via the SL $\text{Na}^+/\text{Ca}^{2+}$ exchanger operating in the inward mode (inward $\text{I}_{\text{Na}/\text{Ca}}$). Relatively small and slow processes for Ca^{2+} efflux from the cytosol include transport via a sarcolemmal Ca^{2+} pump and transport into the mitochondrial space.⁹ The proportion of Ca^{2+} flux through the $\text{Na}^+/\text{Ca}^{2+}$ exchanger and these slow processes is species dependent, with a lower proportion of Ca^{2+} handled by these mechanisms in rodents than in humans. This species difference requires consideration when applying results obtained in rodent studies to human cardiac function.⁴

MODULATION OF EXCITATION–CONTRACTION COUPLING BY PHOSPHORYLATION

The autonomic nervous system is the major regulator of the amount of Ca^{2+} delivered to the myofilaments.^{4,11,12} The myocardium has evolved an elaborate signaling cascade to link adrenergic and cholinergic neural activity as well as blood levels of neurohumors such as epinephrine and acetylcholine to modulation of cellular Ca^{2+} fluxes. As illustrated in Figure 49-9, binding of neurotransmitters, neurohumors, or pharmacologic agonists to adrenergic or cholinergic receptors triggers the cascade. GTP-binding proteins, known collectively as *G-proteins*, transduce receptor binding to an alteration of the enzyme activity of adenylyl cyclase, which is responsible for the generation of cyclic adenosine monophosphate (cAMP) from ATP. Stimulatory G-proteins (G_s) linked to adrenergic β -receptors promote the formation of cAMP, whereas inhibitory G-proteins (G_i) inhibit adenylyl cyclase and can activate phosphatases. cAMP activates protein kinase A (PKA), which phosphorylates key proteins that regulate the entry and exit of Ca^{2+} from the myofilament space. In the case of SR, the PKA substrate is phospholamban (PLB), a small proteolipid that, when dephosphorylated, inhibits the activity of SERCA2a (see Figs. 49-3 and 49-9). PLB is also a substrate for Ca^{2+} -activated calmodulin-dependent kinase (CAMK).^{4,11} This Ca^{2+} -dependent phosphorylation appears important in a “staircase” effect, in which force generated by the myocardium increases with HR. With the increased frequency, there is a higher Ca^{2+} influx because of increased amplitude and delayed inactivation of I_{Ca} . Phosphorylation of PLB by either PKA or CAMK depresses the PLB-SERCA2a interaction and releases Ca^{2+} pumping activity from inhibition; Ca^{2+} affinity of the pump increases, without changes in the maximal Ca^{2+} transport velocity. This increase in Ca^{2+} uptake increases Ca^{2+}

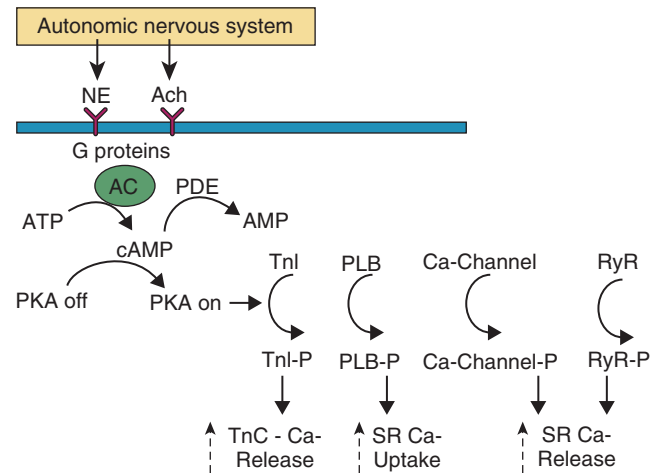


FIGURE 49-9 ■ Schematic representation of autonomic signal transduction and signaling in cardiac muscle cells. With binding of neurotransmitters acetylcholine (ACh) and norepinephrine (NE) to the receptors indicated, there is an activation of adenylyl cyclase (AC), elaboration of cyclic adenosine monophosphate (cAMP), and activation of protein kinase A (PKA). Levels of cAMP are also regulated by the activity of phosphodiesterases (PDE) that convert cAMP to AMP. PKA phosphorylates troponin I (TnI), phospholamban (PLB), Ca^{2+} channel subunits, and ryanodine receptors (RyR), as well as K channels (not shown). These phosphorylations elicit effects on Ca^{2+} uptake and release into the cytoplasmic space, resulting in increased contractility and dynamics of contraction and relaxation. Separate enzymes called phosphatases catalyze dephosphorylation.

loaded into the SR and induces an accelerated relaxation of the myocytes. This increase in rate of Ca^{2+} removal from the cytoplasm and myofilaments accounts in large part for the enhanced relaxation and abbreviated contraction–relaxation cycle during adrenergic stimulation. The enhanced relaxation also depends on PKA-dependent phosphorylation of TnI.^{3,8,13} The phosphorylation of TnI at PKA sites enhances Ca^{2+} release from TnC and speeds up cross-bridge cycling rate.⁸ These consequences of PLB and TnI phosphorylation are critical to the ability of the heart to tune its activity cycle to the fast heart rates during adrenergic stimulation and to accommodate the increasing VR without a significant change in EDV (see Figs. 49-1 and 49-2). A subunit in the oligomeric assembly of proteins that makes up the L-type Ca^{2+} channel of the heart is also a substrate for PKA.⁴ Phosphorylation enhances the probability that the channel will open upon depolarization, but it does not affect the unitary conductance. This increase in the trigger for Ca^{2+} release, together with the increased Ca^{2+} loading associated with PLB phosphorylation, essentially accounts for the increase in the systolic Ca^{2+} transient (see Fig. 49-8). Regulation of the release of Ca^{2+} through SR RyRs by PKA and by CAMK also provides a mechanism to control delivery of Ca^{2+} to the myofilaments and thus to control contractility by an increase in the open probability of the Ca^{2+} release channel. The amount of Ca^{2+} loaded within the SR lumen is a critical factor influencing RyR Ca^{2+} release. Increases in SR Ca^{2+} content generally stimulate the frequency and amplitude of Ca^{2+} sparks, and decreases in content reverse these trends. The duration

of the cardiac action potential is also abbreviated with adrenergic stimulation (see Fig. 49-8). This appears because of PKA-dependent phosphorylation of one form of the K channel important in determination of the duration of the action potential.¹⁴ Separate enzymes called phosphatases, which are controlled by a poorly understood regulatory pathway, catalyze dephosphorylation and restoration of the basal state.

CROSS-BRIDGES AND STROKE VOLUME

In connecting the molecular and cellular properties of the heart to cardiac output, we use the premise that the stroke volume ultimately depends on the actin–myosin interaction. Up to now, we have discussed the determinants of SV in terms of contractility, afterload, and preload. We now discuss the relationships between contractility, afterload, and preload as determinants of the number and rate of cycling of force-generating cross-bridges reacting with the thin filaments. The following equation serves to illustrate the progression of this analysis from active cross-bridges, which determine the systolic change in cell length and tension, to SV and to CO:

$$CO = HR \times SV \begin{cases} \text{(Change in LV volume and pressure)} \\ \text{(Change in cell tension and length)} \end{cases}$$

The cellular properties of length and tension are related in a highly complex manner to LV pressure and volume.¹ However, an understanding of how systolic cross-bridges determine cell tension and shortening sets the stage for understanding the geometric considerations that relate these properties to the ventricular chamber.^{1,15}

CELLULAR BIOLOGY OF CONTRACTILITY

Changes in the amount of Ca^{2+} delivered to the myofilaments, which recruit spare actin–cross-bridge reactions, can occur by the following:

- Changes in the intracellular Ca^{2+} and activity of the autonomic nervous system release neurohumors, which alter the state of phosphorylation of the regulatory proteins in the cells as described earlier.
- Changes in the chemical environment of the cells occur, such as the accumulation of metabolic wastes that occurs during a reduction in coronary flow and that results in acidosis.
- Changes in HR occur. With increases in HR, the SR fills to a greater extent with Ca^{2+} , through phosphorylations involving Ca^{2+} calmodulin-dependent kinases.
- Administration of pharmacologic agents can cause changes. Drugs that affect contractility are known as *inotropic agents*. Some agents such as dobutamine mimic adrenergic neurotransmitters, and some agents such as digitalis indirectly increase Ca^{2+} loading into the SR by inhibiting Na^+/K^+ -ATPase, reducing the Na gradient, and thus inhibiting Ca^{2+} extrusion through the Na^+/Ca^{2+} exchanger. Some inotropic agents inhibit breakdown of cAMP by an inhibition of phosphodiesterase activity, whereas other agents, known as *Ca^{2+} sensitizers*, activate the sarcomere directly.¹⁶

Figure 49-10 shows a recording of ventricular pressure and of tension developed by ventricular papillary muscles. In precise determinations of contractility, it is important that afterload and preload remain constant. Both of these constraints are met if the pressure is developed at constant LV volume or the tension is developed at constant muscle length. In this case, peak pressure or tension

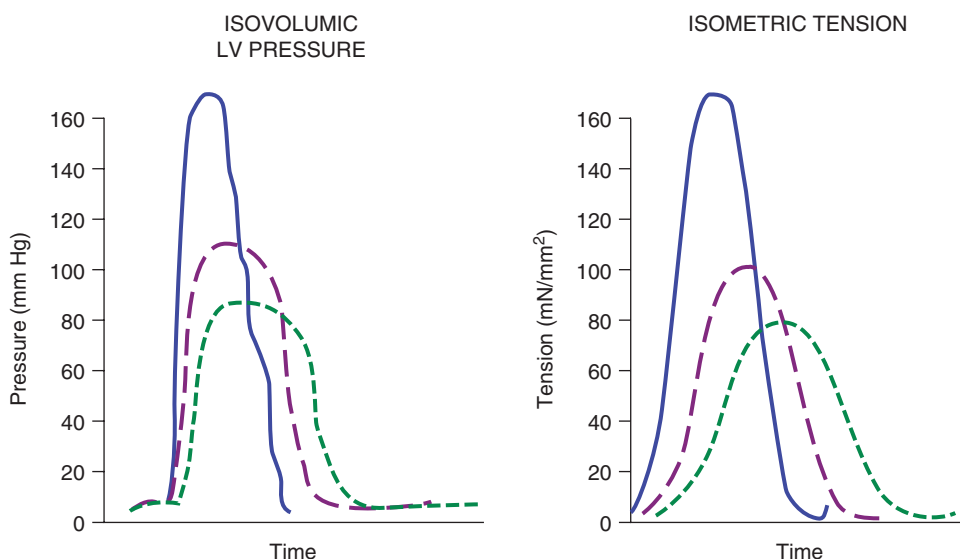


FIGURE 49-10 ■ Comparison of isovolumic beats and isometric twitches at three levels of contractility. Peak amplitude of tension or pressure under these conditions provides a measure of contractility or inotropic state of the heart. Maximum rates of pressure development ($+dp/dt_{max}$) also provide a measure of contractility. Even though pressures are not developed isovolumically during normal beats, $+dp/dt_{max}$ remains a useful index of contractility. LV, Left ventricular.

would be expected to vary with the amount of Ca^{2+} delivered to the myofilaments, as would occur with variations in sympathetic nervous system stimulation, for example. Note that the rate of increase in the pressure also varies with contractility. The time derivative of the pressure trace gives the maximum rate of pressure rise ($+dp/dt$) and fall ($-dp/dt$), both of which are useful indices of contractility in the clinic, even though afterload and preload are not strictly controlled. Ejection fraction (SV/EDV) is also an index of contractility, as is the ratio of end-systolic to end-diastolic dimensions obtained from echocardiographic assessment of cardiac function.

CELLULAR BIOLOGY OF AFTERLOAD

Cardiac muscle cells lift light loads faster than heavier loads, according to a general characteristic property of striated muscle known as the force-velocity relationship.⁶ The velocity of shortening approaches a maximum value (V_{max}) as the load approaches zero, velocity is zero at the maximum load, and the cells develop maximum isometric tension under the particular conditions. As load increases between these extremes, the rate of thin-filament sliding decreases, permitting a longer time for the cross-bridges to react. By this mechanism, the number of cycling cross-bridges is matched to the load that the muscle discovers it must lift. As discussed in the context of Figure 49-6, at the isometric extreme (zero velocity), the level of Ca^{2+} activation determines maximum tension. It is also apparent that Ca^{2+} also increases V_{max} by increasing the rate that the cross-bridges enter the force-generating state. Thus, the force-velocity relationship shifts with increases or decreases in contractility.

CELLULAR BIOLOGY OF CELL LENGTH

We now explicitly relate the sarcomere length tension properties of the cardiac muscle cells to the pressure-volume relationship. Figure 49-11 displays the entire relationship between sarcomere length and the active and passive (resting) tension. Active tension rises and falls from an optimal value, whereas passive tension rises exponentially. The rise in passive tension, which would elevate diastolic LV pressure, is so steep in heart cells as to disallow filling of the ventricle to sarcomere lengths greater than 2.2 μm . In other words, during diastole, atrial pressures cannot increase enough to fill the ventricles to a volume that produces sarcomere lengths exceeding 2.2 μm . Thus, in the physiologic state, considerations of the length-tension relationships, and therefore the volume-pressure relationships of the heart, are restricted to the operating range illustrated in Figure 49-11. To measure the length-tension relationship, the muscle cells are stretched at rest to various sarcomere lengths and held isometric. The cells develop a passive tension as they are stretched. At each length, the cells are stimulated to give a measure of the total isometric tension at that particular sarcomere length. Two such lengths are illustrated in Figure 49-11. At the shorter length, there is no passive tension and maximum developed tension is

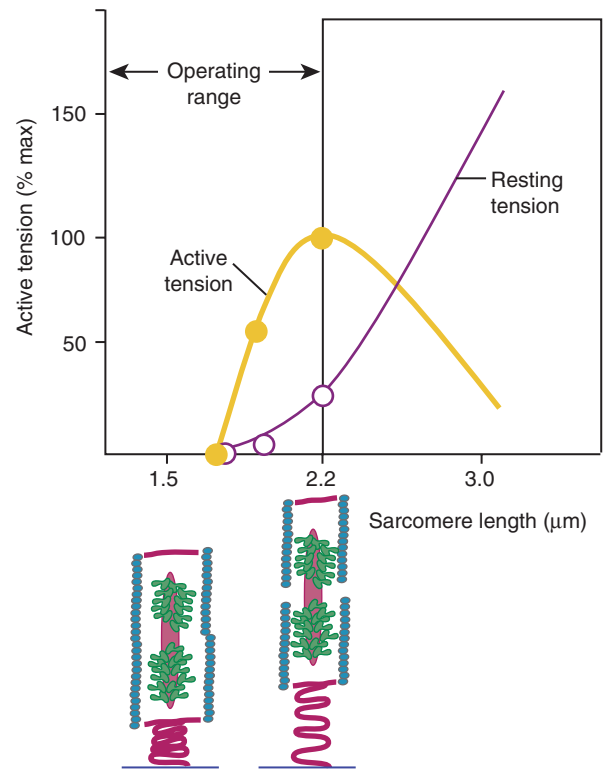


FIGURE 49-11 ■ Dependence of tension on sarcomere length. Three measurements are shown in which a linear muscle preparation (papillary muscle or trabecula) was stretched from its equilibrium length, and determinations of resting (passive) and total active force were made. Active tension is the difference between total tension and passive tension. Beyond a sarcomere length of 2.2 μm , resting tension rises to high levels that are nonphysiologic. Thus, the cells never operate beyond the working range into the *panel*. Two sarcomeres, depicted at the extreme ends of the length-tension relationship, illustrate the stretching of passive springs in titin and the change in overlap of the thin and thick filaments.

essentially zero because of the double overlap of thin filaments. At the optimal sarcomere length, active tension (the difference between total and passive tension) is at an optimum. Some resting tension exists at this sarcomere length as passive elements (notably titin) in the sarcomere and extracellular matrix are stretched. At the optimal sarcomere length of 2.2 μm , there is maximal overlap between the thick filament cross-bridges and the thin filaments.

In Figure 49-12, we show how the working range of the length-tension relationship relates to the pressure-volume relationship of the left ventricle. The basic premise is that cell and sarcomere lengths track the change in ventricular volumes, and ventricular pressure tracks changes in cell tension. Thus, one can imagine the generation of the volume-pressure relationship by an approach similar to that for generation of the length-tension relationship. In this case, although EDV is increased incrementally, EDP is measured at each volume, as is peak systolic isovolumic pressure. Figure 49-12 indicates an association of each ventricular volume with a particular sarcomere length. Important points are the following:

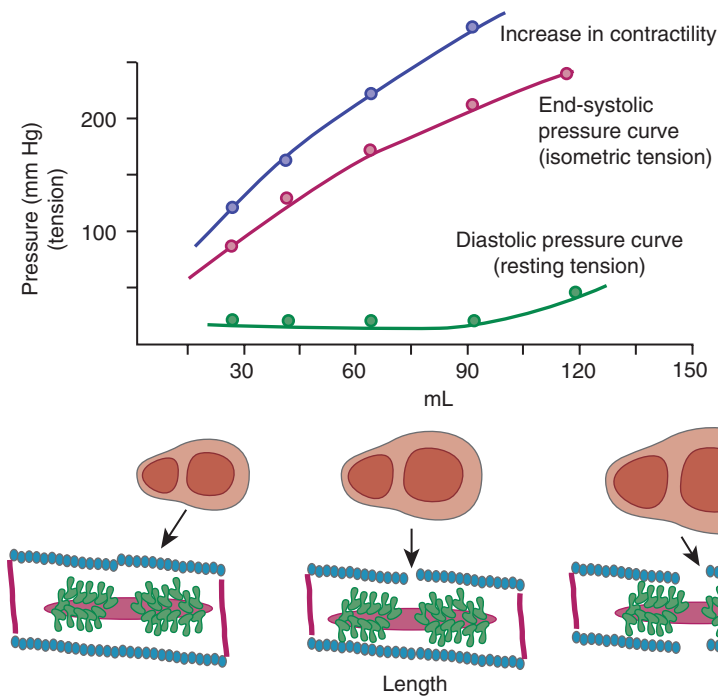


FIGURE 49-12 ■ Generation of systolic and diastolic pressure curves from steady-state measurements of isovolumic pressure development over a range of end-diastolic volumes. Points on the curves were generated by plotting the peak diastolic and systolic pressures at each ventricular volume in hearts with cross-clamped aortas (as in Fig. 49-6). The correlation of ventricular volume with sarcomere length and of ventricular pressure with tension emphasizes that the dependence of pressure on volume is rooted in the length–tension relationship of cardiac sarcomeres.

- Measurements of the relationship between, on the one hand, cell length and tension and, on the other, ventricular volume and isovolumic peak systolic pressure, are made at constant contractility. The basal inotropic state represents 20% to 25% of the maximal inotropic state.
- A line connecting the peak systolic pressure points determined at constant volumes is a measure of contractility. These systolic pressure points are essentially the same ESP points inscribed by variations in afterload (see Fig. 49-7). As mentioned earlier, the ESP represents a point at which the cells are neither lengthening nor shortening.
- The position of the ESP–volume relationship is a critical determinant of ESV and thus of the ability of the ventricle to eject blood.
- Figure 49-12 indicates that this position changes with an increase in contractility, which we now picture as an increase in Ca^{2+} activation of the cells that results in an increase in peak systolic pressure at a particular ventricular volume. This relationship between ventricular volume and pressure was recognized by Otto Frank and Ernest Starling over 100 years ago and is commonly referred to as the *Frank-Starling relationship* or *Starling's law of the heart*.

Despite this long-standing knowledge of Starling's law, the molecular mechanism responsible for the shape of the ESP–volume relationship remains unclear.⁹ The relationship is steeper than one would expect from simple geometric considerations of filament overlap. There is excellent evidence that this relatively steep relationship is the result of a length dependence of Ca^{2+} activation.⁹ Measurement of myofilament response to Ca^{2+} demonstrated a decrease in Ca^{2+} sensitivity as the sarcomere becomes shorter. Thus, at a constant level of systolic Ca^{2+} , we would expect the sarcomeres to be more

sensitive to Ca^{2+} as their length increases. This results in a steeper length–tension relationship that would occur with no change in Ca^{2+} sensitivity. Length-dependent changes in interfilament spacing, radial movements of cross-bridges away from the thick filament proper, and cross-bridge–dependent activation of the myofilaments have all been invoked as mechanisms for length-dependent activation.⁹

CARDIAC FUNCTION CURVES

So far, we have depicted the regulation of CO as relationships among workload, HR, and ventricular volumes (see Fig. 49-1), as relationships between time and ventricular volume changes (see Fig. 49-2), and as a relationship between ventricular volume and ventricular pressure (see Fig. 49-7). We now consider another view of regulation of cardiac output as so-called Starling curves or the Starling relationship, or simply cardiac function curves. These curves relate some measure of ventricular filling, such as EDV or EDP, to some measure of ejection, SV, or CO. Figure 49-13A depicts the transition from determinations of SV from pressure–volume loops at constant contractility and afterload to a relationship between EDV and SV. Three beats are shown at different preloads. The function curve thus provides a relationship between EDV and SV at constant afterload and contractility. Figure 49-13B indicates the shift in the cardiac function curve resulting from an elevated afterload. In this case, the pressure–volume loops show the same SV, which is achieved at an elevated EDV. Figure 49-13C indicates the shift in the cardiac function curve resulting from increased contractility. The pressure–volume loops show the same SV, which is achieved at a lower EDV and ESV. One imagines the same shift for all the preloads indicated in

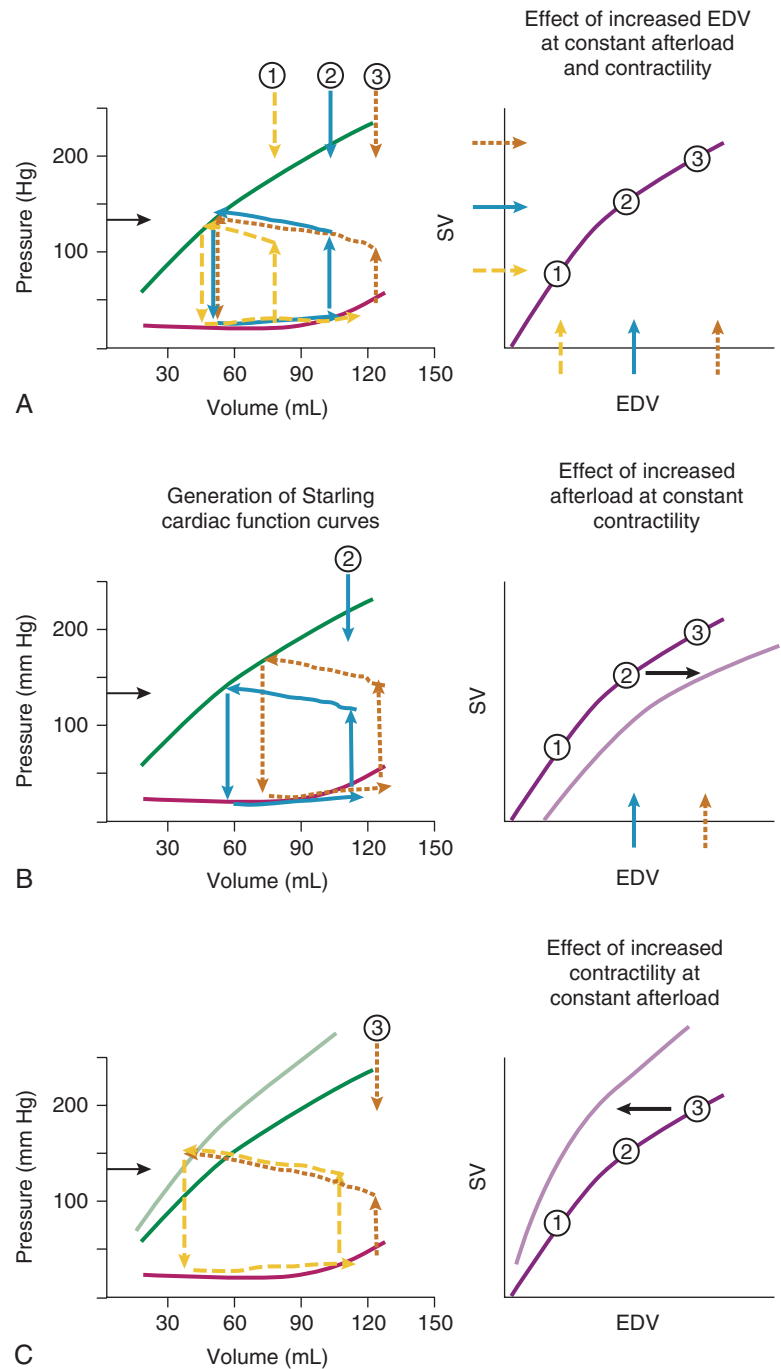


FIGURE 49-13 ■ Generation of Starling cardiac function curves from pressure-volume relationships. **A**, Three beats (1, 2, 3) are shown with increases in preload at constant contractility and afterload. A plot of stroke volume (SV) at each of the end-diastolic volumes (EDV) associated with each beat generates a common form of the cardiac function curve or Starling relationship. **B**, Change in steady-state pressure-volume loop after an increase in afterload. Only beat 2 from **A** is shown for illustrative purposes, but a similar shift in the cardiac function would occur at all EDVs. **C**, Change in steady-state pressure-volume loop after an increase in contractility. Only beat 3 from **A** is shown for illustrative purposes, but a similar shift in the cardiac function would occur at all EDVs.

Figure 49-13A. With knowledge of the HR, it is possible to convert the EDV-SV relationship to a relationship between EDV and CO. Effects of increases and decreases in afterload and contractility on the relationship between EDV and CO and SV are illustrated in **Figure 49-14**.

The exact cardiac function that is operative in the heart at any particular time reflects the integrated effects of many factors. These factors include the determinants of afterload (blood pressure) and of contractility, changes in HR, levels of autonomic nervous system activity and circulating neurohumors, the intracellular and cellular chemical environment (anoxia, hypoxia, acidosis, hypercapnia, metabolites), and the presence of pharmacologic

agents that affect afterload or contractility. The EDV is determined by the flow of blood back to the heart, which in turn is determined by the total blood volume, the venous tone, resistance to flow, the pumping actions of muscle, and the intrathoracic pressure. The integrated effects of these determinants of cardiac function in the physiologic state are revealed in the exercise episode depicted in **Figure 49-1**. Pathophysiologic states can be understood in terms of a breakdown of these physiologic control mechanisms.^{16,17} For example, in heart failure, the SR Ca^{2+} load may be diminished by reduced expression of SERCA2a. There may also be alterations in myofilament response to Ca^{2+} . The ultimate effect of these

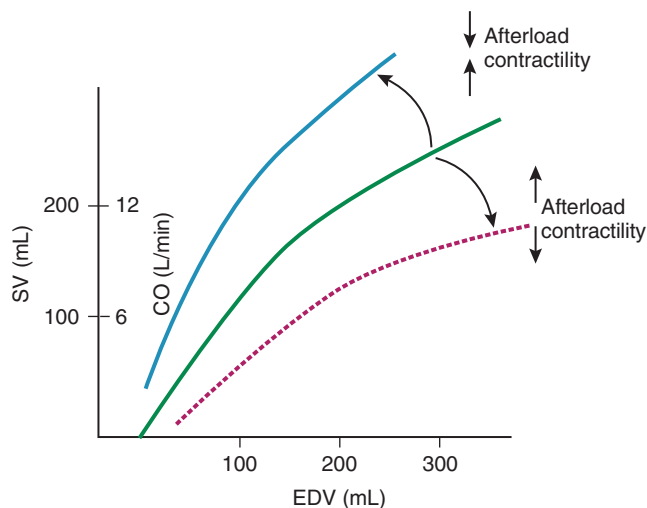


FIGURE 49-14 ■ Effect of alterations in afterload and contractility on the cardiac function curve. Each curve represents a state of constant contractility and afterload. Shifts in the cardiac function curve from a physiologic basal state (central solid line) occur with changes in afterload and contractility. CO, Cardiac output; EDV, end-diastolic volume; SV, stroke volume.

changes is a reduction in contractility, much like that simulated by β -adrenergic blockade in the data shown in Figure 49-1. With elevations in EDV, heart cells are stimulated to grow, but the growth becomes maladaptive and failure ensues as remodeling occurs. Detailed discussion of these events is beyond the scope of this chapter, but it is clear that an understanding of cardiac pathophysiology begins with an understanding of the physiology of the myocardium.^{16,17}

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VENTRICULAR MECHANICS

Mark Ratcliffe • Liang Ge • Julius Guccione

CHAPTER OUTLINE

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Laminar Organization of Myocardium
Extracellular Matrix

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Finite Element Method
Calculation of Stress
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Multiscale Modeling

VENTRICULAR INTERACTION AND PERICARDIUM

Pericardium

In this chapter, we will examine the mechanics of the heart at the tissue and organ level. The chapter will focus primarily on the left ventricle (LV), but short discussions of left atrial function as it relates to LV filling and ventricular interaction will be included. First, we will review several important myocardial structural elements, an understanding of which is necessary for the understanding of function during active contraction (systole) and relaxation and filling (diastole). Next, we will review the cardiac mechanical and flow events that comprise the cardiac cycle. We will then cover diastolic and systolic function with an emphasis on pressure-volume analysis. A discussion of pump function, myocardial energy expenditure, and myocardial efficiency will follow. The finite

element method will be discussed briefly as a means to calculate regional contractility and stress. In each section, we will consider the effect that common clinical conditions such as ventricular hypertrophy and myocardial ischemia have on ventricular function. Where appropriate, we will briefly describe state of the art methods used to measure regional and global LV function.

STRUCTURE OF VENTRICULAR TISSUE

The tissue level structure of the myocardium is intimately related to systolic and diastolic function. For example, myocyte orientation determines the LV torsion

that occurs during active contraction and the subsequent untwisting that occurs during relaxation and filling. The extracellular matrix (ECM) is an important determinant of LV diastolic compliance.

Myocyte Orientation

The orientation of myofibers is complex, with variation across both the LV wall and in different LV regions. The orientation of myofibers was first quantified by Streeter and colleagues,¹ who measured myocyte orientation in tangential sections obtained across the LV wall of the dog heart and found a smooth transition in the helix angle (in the tangential plane relative to the horizontal) from the epicardium (−60 degrees) to the endocardium (+60 degrees). Myofiber orientation data collected by Streeter is seen in Figure 50-1.¹ Other studies using this histologic sampling confirmed these results in different species.

Recent advances in magnetic resonance imaging allow rapid, nondestructive assessment of muscle fibers in the entire heart. Magnetic resonance diffusion tensor imaging exploits the anisotropic diffusion of water through ordered tissues. This method has been correlated with histologically measured fiber angles² and has been used to map the fiber orientation thoroughly in the entire left ventricle of a normal rabbit, goat, sheep, and human.

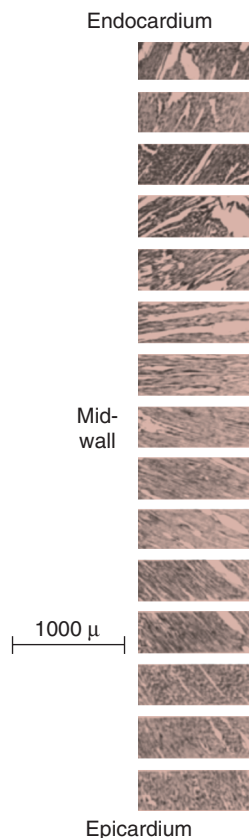


FIGURE 50-1 ■ Photomicrographs of myocardial fiber orientation. (From Streeter DD Jr, Hanna WT: Engineering mechanics for successive states in canine left ventricular myocardium. II. Fiber angle and sarcomere length. *Circ Res* 33:656–664, 1973.)

Laminar Organization of Myocardium

The laminar nature of the myocardium has been appreciated since the 1800s.³ Adjacent myocytes are organized into sheets or lamina that are three to four cells thick.^{4,5} Furthermore, there are extensive cleavage planes between sheets^{4,5} that are most apparent in the midwall of the LV where the planes are radially oriented. The laminar organization of the LV has been recently championed by Torrent-Guasp,⁴ who suggested that the LV consisted of a single, folded myocardial band. Alternatively, Lagrèce and colleagues proposed a finite element–based mathematical model that represents sheet geometry.⁵ A diagram of laminar architecture of the myocardium is seen in Figure 50-2.⁵

Extracellular Matrix

The ECM is an important determinant of LV diastolic compliance. Scanning electron microscopy of the ECM demonstrates an extensive network of collagen fibers that are organized into three primary components.⁶ Briefly, the endomysium surrounds individual cells and groups of cells and the epimysium surrounds entire muscle groups.⁷ Perimysial fibers connect groups of cells. Perimysial fibers can be seen in Figure 50-2A. Of note, perimysial fibers associated with papillary muscle myocardium have a coiled shape with a potentially important role in papillary muscle strength and stiffness.⁸

THE CARDIAC CYCLE

Electromechanical Activation

The rhythmic electrical activation of the heart normally begins at the sinoatrial (SA) node. Electrical activation spreads rapidly over the atria, initiating atrial contraction. There is a delay while electrical activation moves slowly through the atrioventricular (AV) node. The electrical activation then propagates rapidly along the bundle of His, the right and left bundle branches and sub branches (Purkinje fibers) before initiating a coordinated ventricular contraction. The excitation of the ventricles results in the QRS complex of the electrocardiogram.

Cardiac Cycle

A plot of the ECG and left atrial, LV, and aortic pressures during the cardiac cycle is schematically illustrated in Figure 50-3. Depolarization and contraction of the LV raises intracavitary LV pressure. First, this causes the mitral valve to close. When LV pressure exceeds the pressure in the aorta, the aortic valve opens and pressurized blood is ejected into the aorta.

At the end of ejection, LV pressure falls below aortic pressure and the aortic valve closes. Relaxation of the myocytes is locally initiated and not directly coordinated by the conduction system. As the myocytes relax, the pressure drops in the ventricle. When LV pressure falls below the pressure in the atria, the mitral valve opens and filling begins.

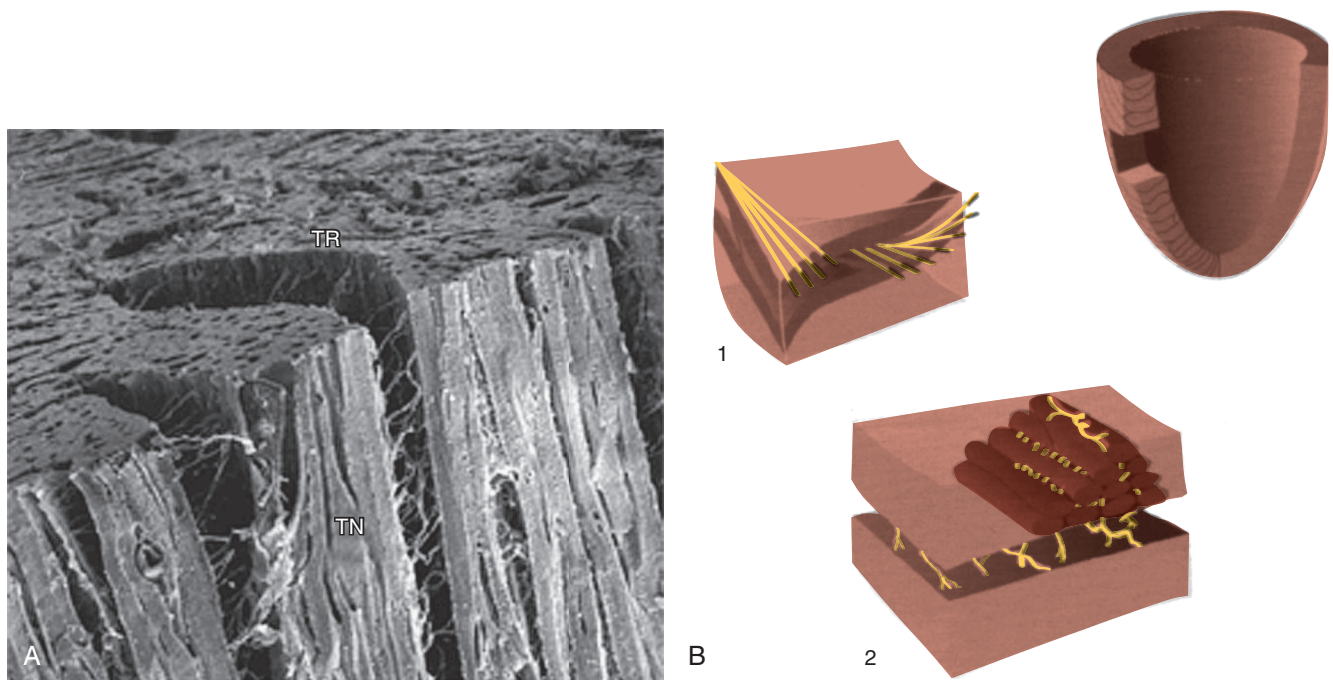


FIGURE 50-2 ■ **A**, Scanning electron microscope image of a left ventricular, midanterior midwall. Tangential (TN) and transverse (TR) surfaces are shown. **B**, Schematic of cardiac microstructure. Transmural segment (1) contains layers of tightly coupled myocytes. These layers run in an approximately radial direction, and there are circumferential and tangential muscle branches between adjacent layers. Orientations of muscle fiber axes are indicated. (2), Cellular arrangement. Fine lines, components of extracellular collagen matrix. (From Legrice IJ, Hunter PJ, Smaill BH: Laminar structure of the heart: a mathematical model. *Am J Physiol* 272[5 Pt 2]:H2466–2476, 1997.)

Pressure-Volume Loop

Pressure and volume of the left ventricle are plotted as shown in [Figure 50-4](#). Active contraction (systole) begins at the bottom right corner of the loop. Contraction is isovolumic until the aortic valve opens at the top right corner and the ventricle ejects. The end of systole is the upper left hand corner of the loop. Diastole is initially isovolumic until the mitral valve opens at the bottom left corner and ventricular filling begins. Ventricular filling begins at the bottom left hand corner of the loop. Ventricular filling is broken into a period of early, rapid filling, a period of slow filling (diastasis), and filling associated with atrial systole. The end of filling is the end of diastole (bottom right corner of the loop).

DETERMINANTS OF LEFT VENTRICULAR FILLING

Pressure-Volume Analysis

Pressure-volume analysis of the cardiac cycle is a cornerstone of LV mechanics. Pressure-volume analysis of cardiac function was initially described by Otto Frank,⁹ but was initially limited by the lack of suitable methods to measure LV pressure and volume. With the development of methods including cineangiography¹⁰ and echocardiography¹¹ in 1960s that could measure ventricular volume in vivo, there was a renewed interest in the use of pressure-volume analysis to measure diastolic and systolic function.¹²

Since that time, cardiac imaging methods have advanced substantially. The imaging method most widely used for studying the heart is still echocardiography.¹³ An additional kind of data that can be obtained with echocardiography is the measurement of flow velocities (or at least the component of velocity along the line of the ultrasound beam), through the Doppler effect.¹³ Magnetic resonance imaging (MRI) with cardiac synchronization of the imaging can provide high-quality spatially registered images that can be used to calculate volumes; MRI is the current “gold standard” method for cardiac global function volume measurements.¹⁴ Computed tomography (CT) has made recent advances in imaging quality and speed, and it can also provide global functional volume measures, although it is still poorer in temporal resolution than MRI and has the additional disadvantages of involving radiation exposure and the use of potentially harmful contrast agents.¹⁴ Because CT, MRI, and three-dimensional (3D) echocardiography build collated data sets from multiple cardiac cycles, they can be used only when hemodynamics are at steady state.

The conductance catheter is best for real-time volume measurement during changes in LV preload or afterload.¹⁵ However, the inability of the conductance catheter to measure absolute ventricular volume because of parallel conductance is a limitation of the method.¹⁵

Pressure-volume loops remain similar unless loading or the strength of contraction (contractility) are changed. If preload or afterload are changed, such as by clamping the vena cava or aorta, and, while contractility remains the same, a family of curves are generated. The end-diastolic and end-systolic points subtend two lines. The

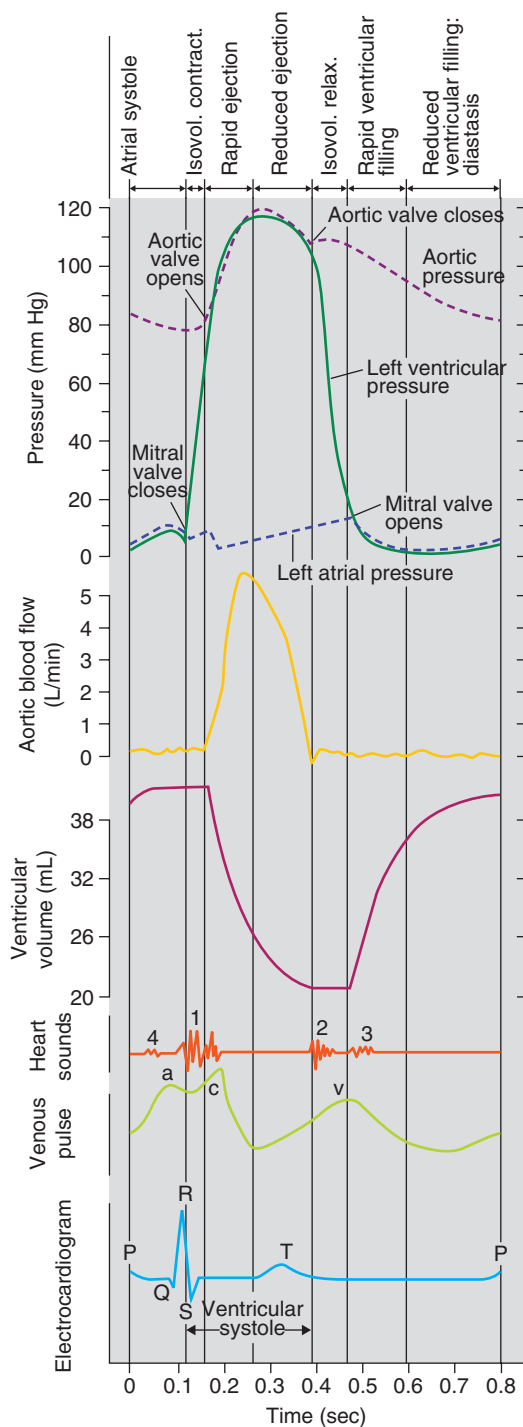


FIGURE 50-3 ■ The cardiac cycle. The time course of pressure in the pulmonary artery and right ventricle is similar to that in the aorta and left ventricle, but at a smaller scale. (Adapted from Hurst JW, Logue RB: *The Heart*, ed 2, New York, 1970, McGraw-Hill, p 76.)

end-diastolic line, referred to as the *end-diastolic pressure-volume relationship* (EDPVR) or ventricular compliance curve, is typically curvilinear. A typical EDPVR relationship is seen in [Figure 50-5A](#). The end-systolic line, referred to as the *end-systolic pressure-volume relationship* (ESPVR) or end-systolic elastance, is nearly straight. The ESPVR relationship is discussed further later.

BOX 50-1 End-Diastolic Pressure-Volume Relationship

The EDPVR is affected by:

- Myocardial (myocyte and extracellular matrix) passive stiffness
- Myocyte relaxation
- Ventricular suction
- Ventricular interaction
- Pericardium

End-Diastolic Pressure-Volume Relationship (Left Ventricular Compliance)

The EDPVR is typically described by an exponential relationship¹²:

$$P_{ED} = A + Be^{\alpha V_{ED}}, \quad (1)$$

where P is left ventricular pressure, V is left ventricular volume, ED is end-diastole, A is an offset in left ventricular pressure, and B and α are diastolic stiffness constants. Note that a shift of the EDPVR curve upward and to the left represents an increase in diastolic chamber stiffness (decrease in compliance). A shift of the curve downward or to the right means that diastolic chamber stiffness is decreased (increase in compliance).

Of note, statistical comparison of EDPVR between subjects before and after interventions is an issue. A t test is not appropriate because it fails to take colinearity into account.^{16,17} A log transform allows the use of multiple linear regression, but the offset term (A) must be removed.^{16,17}

$$\ln(P_{ED}) = \ln(B) + \alpha(V_{ED}), \quad (2)$$

where P is left ventricular pressure, V is left ventricular volume, ED is end-diastole, A is an offset in left ventricular pressure, and B and α are diastolic stiffness constants. A short list of mechanical factors that combine to determine the EDPVR is seen in [Box 50-1](#).

Myocardial Stiffness

Myocyte and ECM stiffness (discussed earlier) are determinants of global LV diastolic function. It is now appreciated that the passive stiffness of the myocyte is dependent on the giant intracellular protein titin. As discussed previously (see [Fig. 49-3](#)), the Z line or disc is the center point of the I band and the attachment point of actin (thin filament). The M line is the center point of the A band (myosin; thick filaments). Titin molecules extend from the Z line to the M line.¹⁸ Successive titin molecules are arranged head-to-head and tail-to-tail, creating a continuous protein structure that extends the entire length of the myocyte. The majority of the titin I band region is extensible and functions as a molecular spring that develops a restoring force when the cell is stretched¹⁸ or compressed.¹⁹ Titin acts as a spring that when compressed

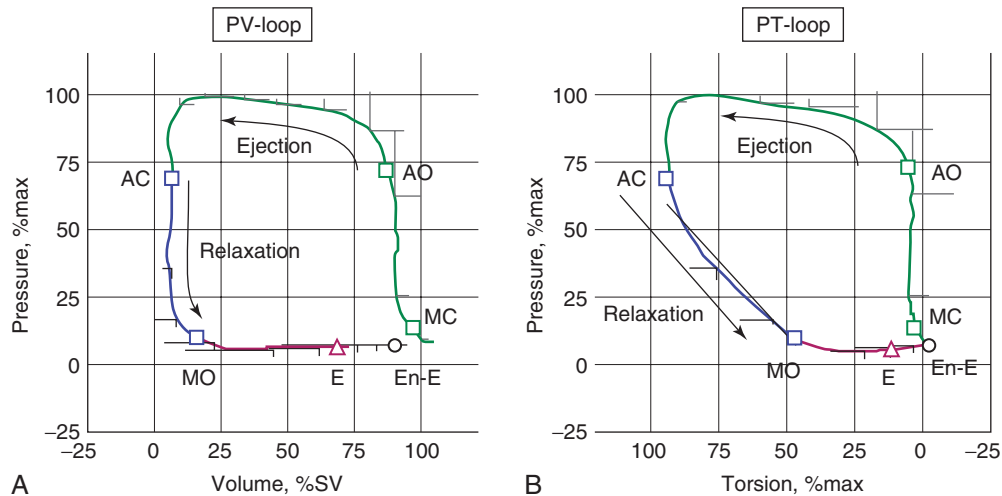


FIGURE 50-4 ■ **A**, The pressure-volume (PV) (work) loop of the left ventricle. **B**, The pressure-torsion (PT) loop of the left ventricle. Loops during variable load (vena caval occlusion) and associated systolic and diastolic chamber stiffness curves. *Ac/Ao*, Aortic valve closing/opening; *E*, peak; *En-E*, end of filling; *MC/MO*, mitral valve closing/opening; *SV*, stroke volume. (From Notomi Y, Martin-Miklovic MG, Oryszak SJ, et al: Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 113[21]:2524–2533, 2006.)

or stretched generates a restoring force.¹⁹ A diagram showing the structure of titin is seen in Figure 50-6.¹⁹

Myocyte Relaxation

Left ventricular relaxation is a component of early diastolic filling. LV relaxation is an energy-dependent process involving the removal of Ca^{2+} from troponin-C, followed by the dissociation of actin and myosin cross bridges, thus allowing the myofibrils to relax and to return to their original end-diastolic length.²⁰ A typical LV relaxation curve is seen in Figure 50-5B.²¹

LV relaxation is classically evaluated by the exponential time constant of isovolumic relaxation (T), requiring cardiac catheterization to measure LV pressure.

$$P(t) = P_0 e^{-\frac{t}{T}}, \quad (3)$$

where $P(t)$ is left ventricular pressure as a function of time, P_0 is the pressure at the time of $dP/dt_{\min}$, t is time after $dP/dt_{\min}$, and T is the time constant of isovolumic pressure fall.²² Figure 50-5B demonstrates how relaxation pressure (Equation 3) can be subtracted from actual diastolic pressure data to obtain a corrected pressure.²¹

Left Ventricular Torsion and Recoil

The myofiber architecture described earlier (Structure of Ventricular Tissue) causes the LV to undergo torsion during systole. The magnitude of torsion is a function of myocyte contractility.²³ As myocyte contraction and torsion occurs, extracellular collagen matrix,²⁴ and intracellular titin are compressed.¹⁸ Untwisting occurs in early diastole. Forty percent of the LV untwisting occurs during isovolumic relaxation.²⁵

LV untwist continues during ventricular filling. Mitral valve opening is immediately followed by the development of a pressure gradient between the LV apex and

base,²⁶ which determines early LV filling.²⁷ The rate of untwisting is a predictor of the pressure gradient between the LV apex and base as well as the time constant of diastolic relaxation.²⁸ Finally, the rate of recoil is a preload-independent assessment of LV relaxation.²⁹

Ventricular Suction

The presence of negative intracavitary LV pressure in early diastole was shown in a series of experiments^{30,31} in which a Starr Edwards mitral prosthesis was modified to close during diastolic filling. Data from one of Yellin's experiments in which mitral valve occlusion caused a negative LV pressure (to the right of the gray bar) is seen in Figure 50-7.³¹

It is now thought that ventricular suction is caused by LV untwisting and elastic recoil of the compressed myocytes in early diastole. The concept is that end-systolic volume is lower than the diastolic equilibrium volume.³² Consequently, and depending on the time course of myocyte relaxation, the LV generates the negative intracavitary pressure described earlier. In short, ventricular suction helps to draw blood into the chamber across the mitral valve.

Echocardiographic Measures of Diastolic Function

Most clinical measurements of diastolic function focus on echocardiographic Doppler transmitral blood flow patterns. Normally, early flow (E wave) is higher than that associated with atrial contraction (A wave). Mitral flow patterns are seen in Figure 50-8.³³ Diastolic dysfunction is typically associated with a reversal of the E/A ratio.³⁴ However, the E/A ratio in dilated cardiomyopathy can range between complete A wave dominance that suggests decreased ventricular compliance and a pseudo-normalized pattern (E wave dominance).³⁵ Mitral flow patterns are difficult to interpret, however, because of

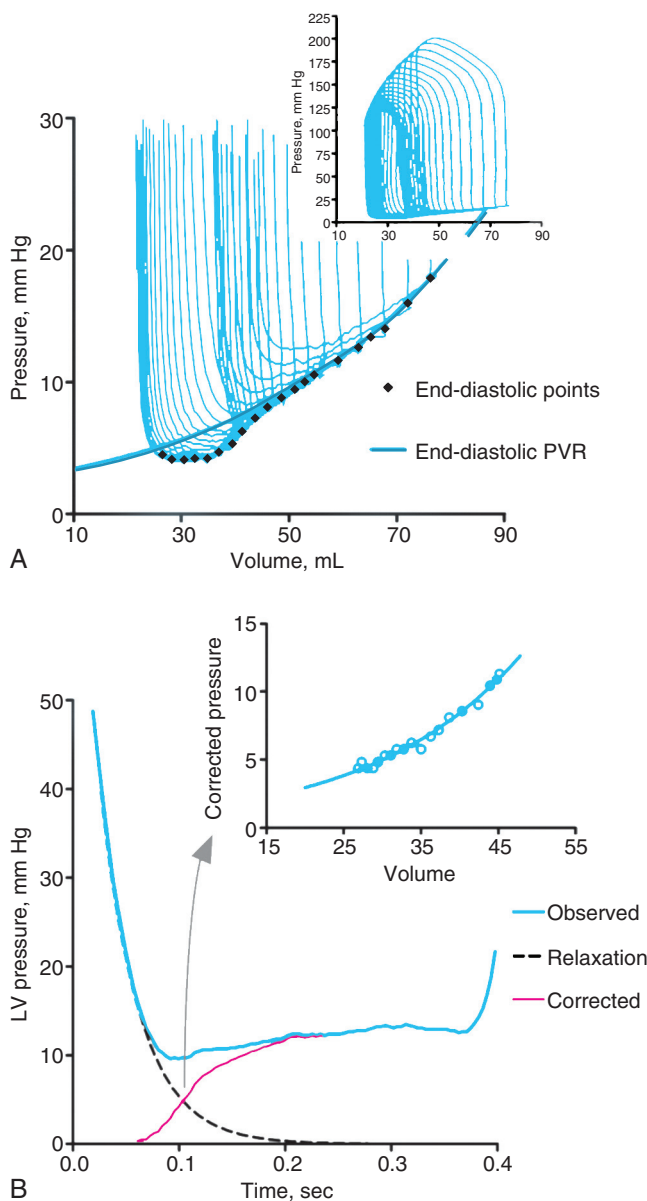


FIGURE 50-5 ■ Characterization of end-diastolic pressure-volume relationship (EDPVR) by multiple-beat (A) and relaxation-corrected single-beat (B) methods. Note that the graph in A is expanded from the complete pressure-volume loop data (insert). LV, Left ventricular. (From Jaber WA, Lam CS, Meyer DM, et al: Revisiting methods for assessing and comparing left ventricular diastolic stiffness: impact of relaxation, external forces, hypertrophy, and comparators. *Am J Physiol Heart Circ Physiol* 293[5]: H2738–2746, 2007.)

confounding factors including atrial pressure, ventricular relaxation time, and mitral regurgitation.³⁶ In addition, aging is associated with a decrease in the E/A ratio, possibly related to increasing myocardial fibrosis with age.³⁷ Abnormal mitral flow patterns are seen in Figure 50-8.³³

Atrial Contraction

The atrial contraction near the end of ventricular diastole augments the final filling of the ventricle before the next ventricular contraction.³⁸

Diastolic Dysfunction from Myocardial Ischemia

Acute coronary occlusion causes the EDPVR to shift upward and to the left.³⁹ It was initially thought that the change in EDPVR was due to an increase in myocardial passive stiffness. However, it is now thought that the change in EDPVR is secondary to increased right ventricular pressure mediated by an intact pericardium.⁴⁰ Anterior myocardial ischemia is also associated with a decrease in the pressure gradient between the LV apex and base that normally occurs during the rapid filling phase of diastole. The mechanism is thought to be a loss of myocardial contractility and LV torsion and subsequent inability to store energy that would be released during elastic recoil.²⁶ Of note, patients with DCM show abnormally low diastolic suction.⁴¹ The mechanism may be similar.

Diastolic Dysfunction from Hypertrophy

Concentric hypertrophy is hypertrophy of the LV in which the ratio of wall thickness to ventricular radius is increased.⁴² It is commonly caused by hypertension and aortic stenosis. The cause of diastolic dysfunction in concentric hypertrophy is thought to be an increase in myocardial stiffness rather than a change in myocardial relaxation or recoil.⁴³ In patients with aortic stenosis, diastolic dysfunction is found in approximately 50% of the patients with normal systolic ejection performance and in 100% of the patients with depressed function.⁴⁴

SYSTOLIC FUNCTION AND END-SYSTOLIC ELASTANCE

Cardiac Output and Cardiac Index

The simplest and most common measures of systolic function are cardiac output (CO) and ejection fraction. The difference between the volume at end diastole (ED) and end systole (ES) is the stroke volume (SV):

$$SV = V_{ED} - V_{ES}, \quad (4)$$

and the cardiac output is the stroke volume multiplied by the heart rate (HR).

$$CO = HR \times SV \quad (5)$$

To account for the differences to be expected in the values of the cardiac output for differently sized subjects, we can use the cardiac index (CI), which scales the cardiac output for body surface area:

$$CI = \frac{CO}{BSA} \quad (6)$$

Swan-Ganz Catheter

The indicator dilution technique is widely used to estimate cardiac output and thermodilution using a Swan-Ganz catheter is the most common method of indicator

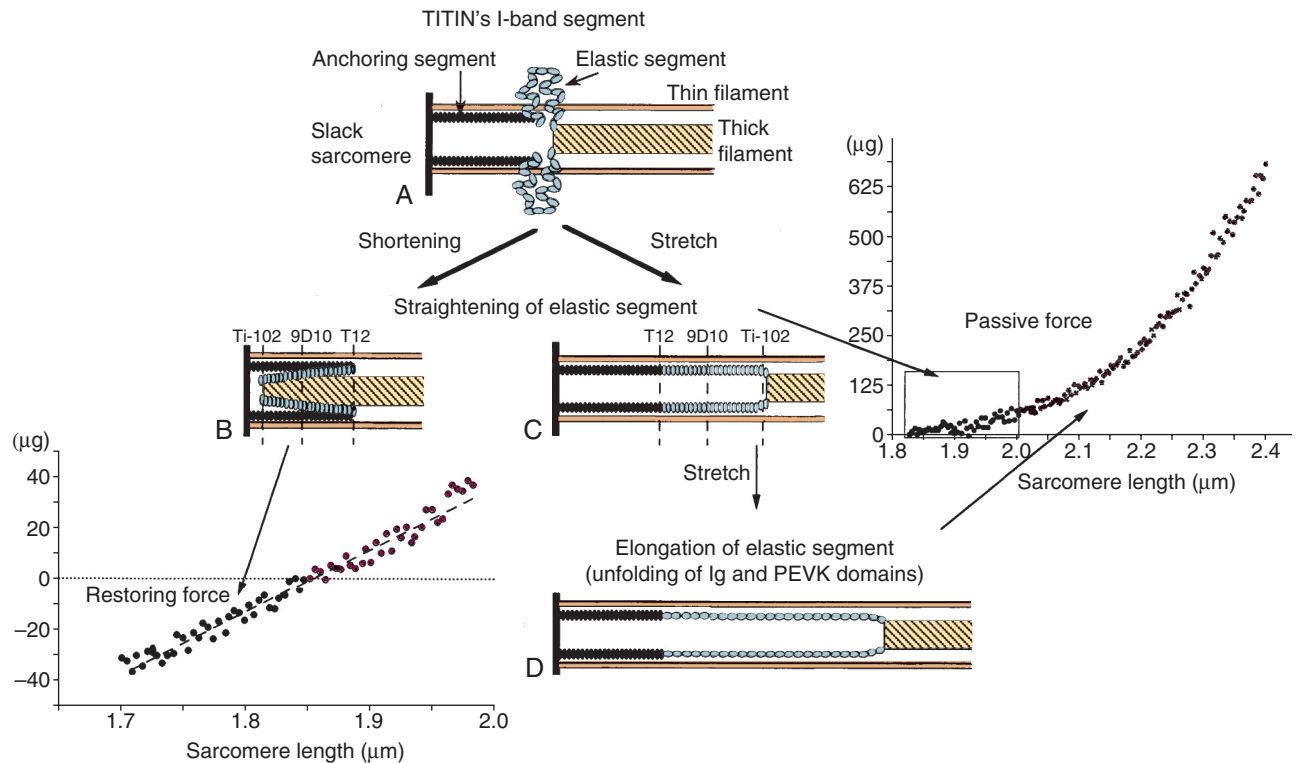


FIGURE 50-6 ■ Working hypothesis of how titin generates both passive and restoring forces. *Ig*, Immunoglobulin; *PEVK*, proline, glutamate, valine, and lysine. (From Helmes M, Trombitas K, Granzier H: Titin develops restoring force in rat cardiac myocytes. *Circ Res* 79[3]:619–626, 1996.)

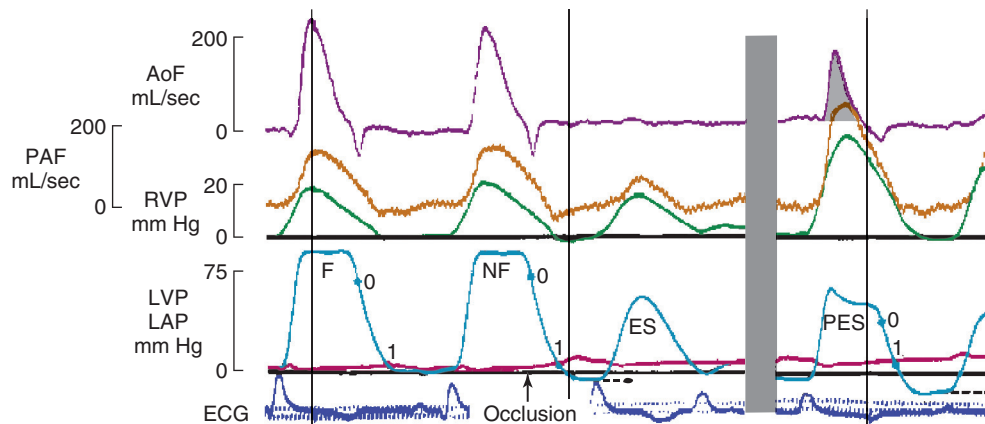


FIGURE 50-7 ■ Oscillographic record of hemodynamic response to mitral valve occlusion. Note that left ventricular pressure (LVP) during diastole is negative after occlusion of the mitral valve (gray bar). AoF, Aortic flow; ES, extrasystolic beats; F, filling beats; LAP, left atrial pressure; NF, nonfilling beats; PAF, pulmonary artery flow; PES, postextrasystolic beats; RVP, right ventricular pressure. (From Yellin EL, Hori M, Yoran C, et al: Left ventricular relaxation in the filling and nonfilling intact canine heart. *Am J Physiol* 250[4 Pt 2]:H620–629, 1986.)

dilution.⁴⁵ A room temperature bolus of saline is injected into the right atrium through the proximal port of the Swan-Ganz catheter. A thermistor in the tip of the catheter measures the change in temperature as the bolus of saline is carried through the pulmonary artery.⁴⁵ Thermodilution cardiac output compares favorably with measurement of cardiac output using the Fick principle.⁴⁶

The Swan-Ganz catheter is used by many cardiac surgery units; however, there has been recent controversy over the risk benefit of the device.⁴⁷ Complications including right ventricular perforation and pulmonary artery rupture occur in 0.1% of patients.⁴⁸ A recent meta-analysis found the odds ratio to be 1.0.⁴⁹

Ejection Fraction

The ratio of the SV to the ED volume is the ejection fraction (EF):

$$EF = \frac{SV}{V_{ED}} \quad (7)$$

Both cardiac output and ejection fraction are sensitive to afterload. Specifically, the greater the afterload (resistance to flow), the lower the cardiac output and ejection fraction will be. In addition, procedures and operations

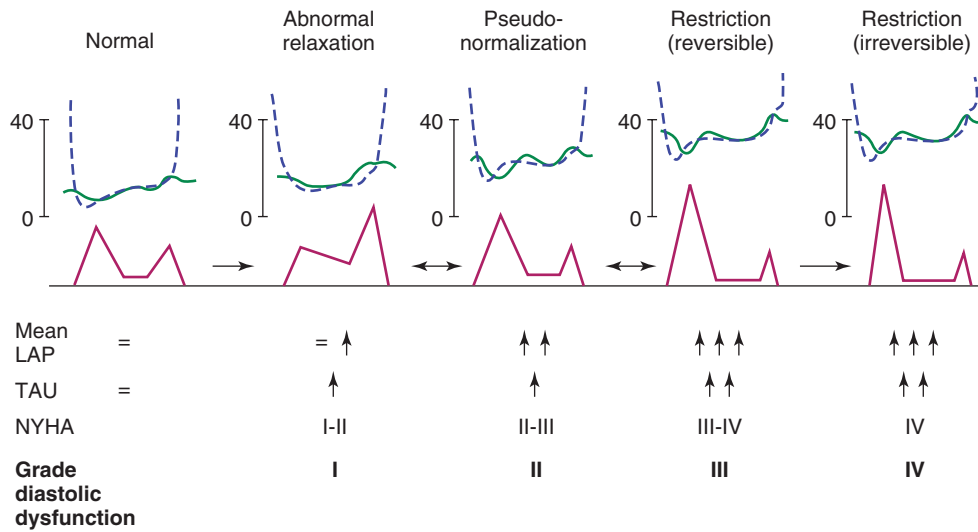


FIGURE 50-8 ■ Diagram of a proposed grading system for diastolic dysfunction based on the progression of disease patterns in patients with cardiac disease. *LAP*, Left atrial pressure; *NYHA*, New York Heart Association class; *TAU*, time constant of left ventricular relaxation (see Equation 3). (From Nishimura RA, Tajik AJ: Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol* 30[1]:8-18, 1997.)

that alter ventricular size and material properties can cause an increase in ejection fraction that does not represent a true increase in ventricular pump function. This point has been previously made by Dickstein and colleagues⁵⁰ in regard to Batista's operation and by Wall and colleagues⁵¹ in regard to cell transplantation. It is therefore incorrect to conclude that if a surgical procedure increases ejection fraction then that pump function has improved.

End-Systolic Pressure-Volume Relationship

Several authors developed the concept of the ESPVR and suggested that it could be used as an index of global ventricular contractility.⁵²⁻⁵⁷ In principle, the measurement of ESPVR is straightforward. It requires only the acquisition of ventricular pressure-volume (PV) loops at two or more preload or afterload conditions. The end-systolic points on these PV loops are identified, and a line is drawn through them; the slope of this line is the end-systolic (peak) elastance or $E_{\max}$.⁵²⁻⁵⁷ A typical ESPVR relationship with and without catecholamine effect is shown in Figure 50-9.⁵⁷

The ESPVR is of great value because it is inherently load independent; however, it must be recognized that the ESPVR is not pump function per se because it does not take diastolic function into consideration. As with EF, this point has been previously made by Dickstein and colleagues⁵⁰ concerning the Batista operation.

$E_{\max}$ is typically described with the following equation:

$$P_{ES} = E_{ES}(V_{ES} - V_0), \quad (8)$$

where *ES* is end systole, and E_{ES} and V_0 are the slope and volume intercept of the ESPVR curve, respectively.⁵⁵ Note that a shift of the ESPVR curve upward and to the left represents an improvement in systolic chamber

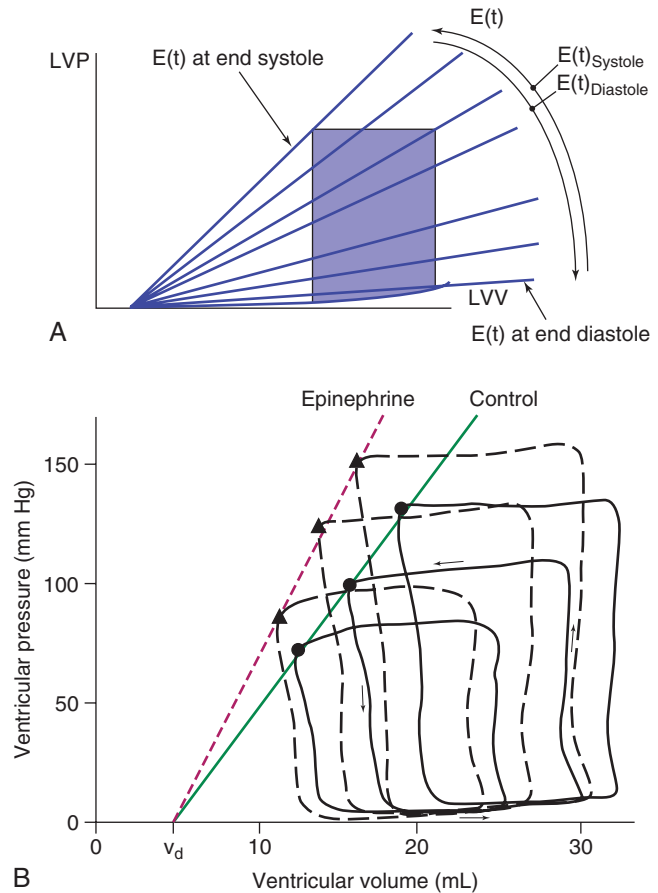


FIGURE 50-9 ■ **A**, The time varying elastance ($E(t)$) concept and graph of the end-systolic pressure-volume relationship (ESPVR), with and without catecholamine effect. **B**, A graph of left ventricular pressure-volume loops of a denervated heart. *LVP*, Left ventricular pressure; *LVV*, left ventricular volume. (From Suga H, Sagawa K, Shoukas AA: Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res* 32[3]:314-322, 1973.)

stiffness. A shift of the curve downward or to the right means that systolic function is worse. Note that both the slope and intercept can change.¹²

Systolic Dysfunction from Myocardial Ischemia

Myocardial ischemia and infarction results in loss of contractile function of the involved myocytes. As a result, the ESPVR curve moves to the right.⁵⁸

PUMP FUNCTION

Frank-Starling Relationship

Cardiac output is regulated by intrinsic cardiac and extrinsic mechanisms. The Frank-Starling relationship is the principal intrinsic cardiac regulatory mechanism. In 1914, Patterson and Starling described the stroke volume–end diastolic pressure and the stroke volume–end diastolic pressure relationships.^{59,60} Starling's work was remarkable given that he did not possess cardiac imaging and relied on the displacement of water in a cylindrical container surrounding the heart as a measure of left ventricular volume. The stroke volume–end diastolic pressure is typically referred to as the *Frank-Starling relationship* or *Starling's law*.

The molecular determinants of the Frank-Starling relationship are discussed in Chapter 48. Briefly, the magnitude of the force generated by the myocytes is dependent on their initial length at the time of initiation of the contraction, as described by the Frank-Starling law. The general shape of the Frank-Starling relationship is seen in Figure 50-10.⁶¹ No specific mathematical relationship exists although a quadratic polynomial function has been used to approximate the relationship.⁶² Note that a shift of the Frank-Starling curve upward and to the left reflects an improvement in pump function. A shift of the curve downward and to the right implies that pump function is worse.

Recently, the stroke work–end diastolic volume relationship has been recommended by Glower and colleagues⁶¹ because of its linear nature (see Fig. 50-10).

$$SW = M_W(V_{ED} - V_W), \quad (9)$$

where M_W and V_W are the slope and intercept respectively of the preload recruitable stroke work (PRSW) relationship.⁶¹ Stroke work is defined as follows:

$$SW = \int_{ED}^{ES} P(V) dV - \int_{ES}^{ED} P(V) dV \approx P_{Max} SV, \quad (10)$$

where SW is stroke work, ED is end diastole, ES is end systole, P is left ventricular pressure, V is left ventricular volume, and SV is stroke volume. Note that two types of work must be considered. The integral from end diastole to end systole gives the work performed by the heart during ventricular ejection. Once the mitral valve opens, the vasculature then performs work on the ventricle during ventricular filling. The integral of the

pressure-volume plot under the end-diastolic pressure-volume relationship gives the work performed by the vasculature on the ventricle.

Force Frequency Relationship

The effect of contraction frequency on myocardial force generation is known as the *force frequency relationship* or as the *staircase* or *treppe phenomenon*.^{63,64} Specifically, in isolated cat papillary muscle, developed force increases substantially when contraction is increased from 20 to 200 beats/min.⁶⁵ The effect is thought to be secondary to an increase in intracellular Ca^{2+} concentration.

The force frequency relationship is operative in normal human hearts.⁶⁶ However, the effect of heart rate on E_{ES} in patients with hypertrophic cardiomyopathy⁶⁷ and on tension development in muscle strips from patients with dilated cardiomyopathy⁶⁶ is absent.

NON-STARLING REGULATION OF BLOOD PRESSURE AND CARDIAC OUTPUT

Extrinsic regulatory mechanisms of cardiac output are mediated by the autonomic nervous system and include effects on heart rate and ventricular contractility. Efferent sympathetic fibers that originate in the upper thoracic and lower cervical segments of the spinal cord synapse with postganglionic fibers in the stellate and middle cervical ganglia. Postganglionic sympathetic fibers join parasympathetic fibers to form the cardiac plexus before they course to the heart. Preganglionic parasympathetic fibers course in the vagus nerves to synapse with postganglionic fibers from cells in the epicardium of the heart.⁴⁴ Sympathetic activity increases heart rate while parasympathetic decreases heart rate. Of note, parasympathetic activity usually predominates.

Pressure and volume receptors provide input to two important heart rate regulatory mechanisms: the baroreceptor¹⁴ and Bainbridge reflexes.¹³ An increase in systemic blood pressure stimulates baroreceptors in the carotid sinus and aortic arch and increases parasympathetic tone, causing heart rate to decrease¹⁴; this is called the *baroreceptor reflex*. Conversely, an increase in circulating blood volume stimulates stretch receptors in the atria and increases sympathetic tone, causing heart rate to increase (i.e., the Bainbridge reflex).¹³ The resultant change in heart rate is the sum of the competing reflexes.

In addition, the autonomic nervous system alters atrial and ventricular contractility. Stimulation of cardiac sympathetic fibers have been shown to double LV pressure and the rate of pressure change in the isolated dog heart.⁶⁸ In contrast to the effect on heart rate, the effect of sympathetic output on contractility is stronger than parasympathetic activity.

A variety of circulating hormones effects cardiac contractility. The most obvious hormone is epinephrine, which is released from the adrenal medulla into the circulation as part of the body's fight-or-flight acute reaction to danger or other stress. Other circulating hormones that increase contractility include thyroid hormone,⁴⁰ insulin,⁴³ and glucagon.⁶⁹

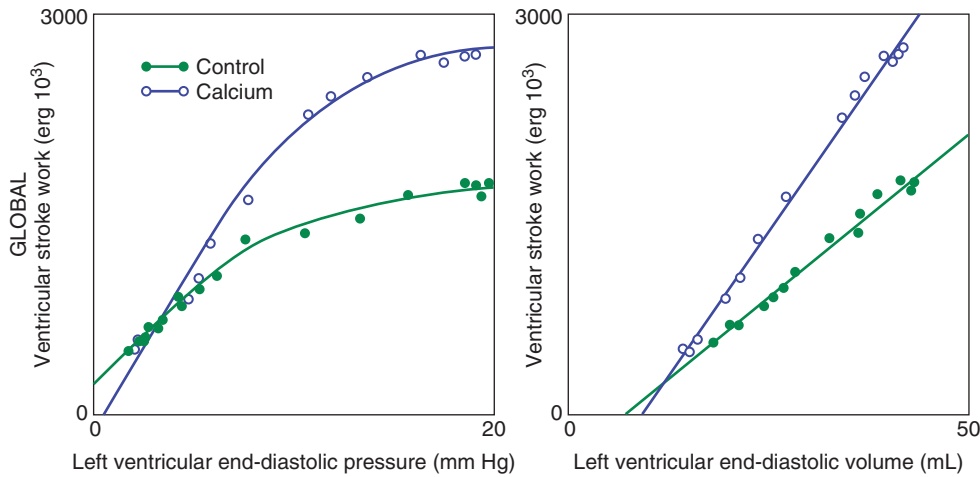


FIGURE 50-10 ■ Effects of calcium infusion on stroke work versus end-diastolic pressure (*left*) and stroke work versus end-diastolic volume (*right*). (From Glover DD, Spratt JA, Snow ND, et al: Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation* 71:944–1009, 1985.)

MYOCARDIAL ENERGY EXPENDITURE AND EFFICIENCY

Determinants of Myocardial Energy Consumption

Since cardiac energy metabolism is aerobic, myocardial oxygen consumption (MVO_2) should be proportional to myocardial energy expenditure. A number of investigators have proposed models that explain the energy expenditure of the ventricle.^{70–72} Braunwald, in pioneering work that began in the 1950s, found that wall tension⁷⁰ and contractility⁷¹ were determinants of MVO_2 . The tension time index concept of Braunwald has been expanded by Weber and others to become the integral of systolic stress.⁶⁸ It should be noted that the work of Braunwald in this area is the cornerstone of our treatment of myocardial ischemia with afterload reduction and reduction of heart rate with β -blockers.

Suga and colleagues⁷³ proposed a model of myocardial energy expenditure based on pressure-volume analysis; they used an isolated heart preparation that allowed ejecting beats with a variable afterload to study the relationship between stroke work, potential energy, and myocardial oxygen consumption. Interestingly, they found a close relationship between ventricular energetics described by the pressure-volume analysis and the oxygen consumption. Specifically, they found that total oxygen consumption per beat was proportional to the sum of the potential energy (Fig. 50-11, *purple triangle*) and stroke work (see Fig. 50-11, *gold*).

$$\text{PVA} = (\text{SW} + \text{PE}) \propto \text{MVO}_2, \quad (11)$$

where *PVA* is the pressure-volume area, *SW* is the stroke work, and *PE* is potential energy.⁷³

The efficiency of ventricular function can be calculated by the ratio of external work divided by the total energy consumed per beat. Total work is equal to the total energy consumed per beat. The total energy consumed per beat is equal to the sum of the external work and the potential energy per beat. The efficiency can

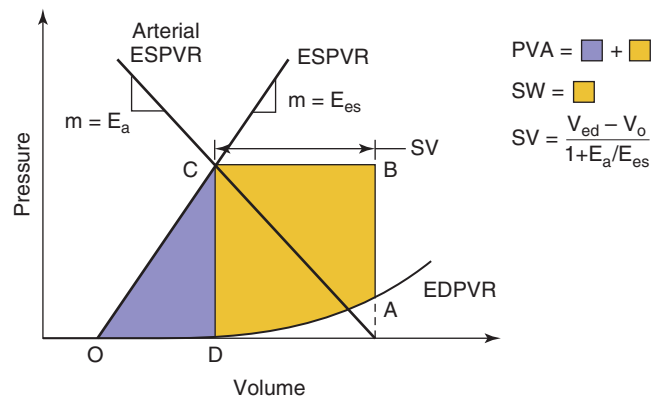


FIGURE 50-11 ■ Model of myocardial energy expenditure based on pressure-volume analysis. *Gray triangle*, Potential energy. A is the end of diastole; B, the start of ejection; C, the end of systole; and D, the end of isovolumic relaxation. Please see the section on afterload and ventriculoarterial coupling for an explanation of the arterial ESPVR and E_a . *EDPVR*, End-diastolic pressure-volume relationship; *ESPVR*, end-systolic pressure-volume relationship; *PVA*, pressure-volume area; *SV*, stroke volume; *SW*, stroke work. (From Suga H: Total mechanical energy of a ventricle model and cardiac oxygen consumption. *Am J Physiol* 236[3]:H498–505, 1979.)

therefore be derived from the oxygen consumed to pump divided by the total oxygen consumed per beat.

$$\text{Efficiency} = \frac{\text{SW}}{\text{MVO}_2} \quad (12)$$

It is possible to account for all changes in SW/MVO_2 efficiency by the relative changes in E_{es} and E_a in the LV pressure-volume diagram.⁷⁴

AFTERLOAD AND VENTRICULOARTERIAL COUPLING

Optimal vascular function is essential to optimal ventricular performance. Impedance is the opposition of a system to a driving function. Maximal energy transfer of

a system is achieved when the output impedance of the source equals the input impedance of the load.

The impedance of the heart can be described by the pressure-volume relationship. The end-systolic pressure-volume relationship describes the output impedance of the heart. Sunagawa and colleagues⁷⁵ developed a formula that gives the SV for a given preload as a function of systolic ventricular properties (E_{ES} , V_0) and the arterial elastance (E_A).⁷⁵ The model included the vascular system as a modified Windkessel element, and E_A is a lumped parameter characterization of the impedance of the Windkessel element.⁷⁶ The equation is as follows:

$$SV = \frac{V_{ED} - V_0}{1 + \frac{E_A}{E_{ES}}}, \quad (13)$$

where SV is stroke volume, V is LV volume, ED is end diastole, V_0 and E_{ES} are the intercept and slope of the ESPVR relationship, respectively, and E_A is the arterial elastance.

Burkoff and Sagawa⁷⁶ extended the SV/E_A relationship (Equation 13)⁷⁵ to include SW , MVO_2 , and ventricular efficiency. The model predicted that SW would be maximum when $E_A = E_{ES}$ ($E_A/E_{ES} = 1$).⁷⁶ Of note, the afterload that resulted in the greatest efficiency was always less than that which provided the maximum SW .⁷⁶ Because of concern that the optimal E_A/E_{ES} for stroke volume and efficiency occurred at different points, De Tombe and colleagues measured stroke work in isolated hearts and found that maximal stroke work occurred at $E_A/E_{ES} = 0.80$, but that efficiency was maximal at $E_A/E_{ES} = 0.70$. However, there was a significant range of E_A/E_{ES} values where both stroke work and efficiency were greater than 90% of their maximum values (Fig. 50-12).⁷⁷ Thus, impedance matching between the LV and arterial system does seem to be important.

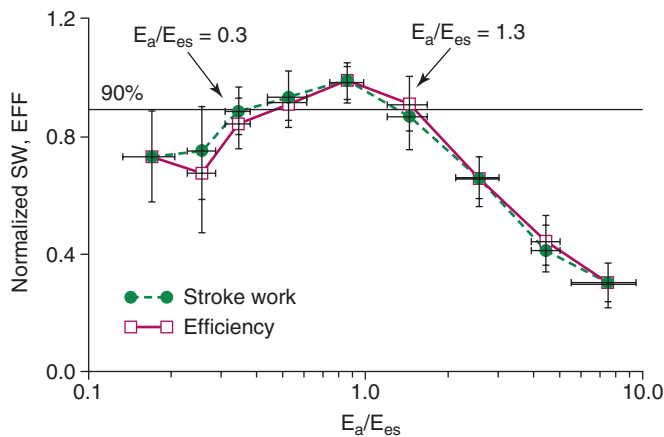


FIGURE 50-12 ■ Average normalized stroke work (SW) and SW per myocardial oxygen consumption (MVO_2) as a function of the curve from graphing arterial elastance (E_A) against the slope of the end-systolic pressure-volume relationship (E_{ES}). *EFF*, Efficiency. (From De Tombe PP, Jones S, Burkoff D, et al: Ventricular stroke work and efficiency both remain nearly optimal despite altered vascular loading. *Am J Physiol* 264[6 Pt 2]:H1817–1824, 1993.)

E_A/E_{ES} has subsequently been measured in patients with dilated cardiomyopathy. E_A/E_{ES} was 3.24, but was decreased to 1.86 when the patients were given dobutamine and to 1.78 with afterload reduction.⁷⁸ This study shows that impedance matching in the hypertrophied and failing heart is far from optimal and lays the ground work for afterload reduction therapy.

REGIONAL STRAIN

Strain is the normalized deformation of a body in regard to its reference configuration. For a one-dimensional rod, for example, strain is defined as:

$$\epsilon = \frac{l - l_0}{l_0}, \quad (14)$$

where ϵ is the strain, l is the deformed length, and l_0 is the initial length.

Extending one-dimensional strain to 3D requires mathematical representation as a second-order tensor defined as:

$$\epsilon = \begin{bmatrix} \epsilon_{xx} & \epsilon_{xy} & \epsilon_{xz} \\ \epsilon_{yx} & \epsilon_{yy} & \epsilon_{yz} \\ \epsilon_{zx} & \epsilon_{zy} & \epsilon_{zz} \end{bmatrix}, \quad (15)$$

where ϵ_{xx} is the normal strain in the x direction and ϵ_{xy} is shear strain on the x face in the y direction. Note that the strain tensor is symmetric with $\epsilon_{xy} = \epsilon_{yx}$ and therefore has only six independent variables. Graphic representation of normal and shear strain is illustrated in Figure 50-13.

Furthermore, the normal and shear strain values are dependent on the choice of reference frame. For instance, a reference frame in which ϵ_{xx} is oriented in the local muscle fiber direction will be different than a reference frame where ϵ_{xx} is oriented in the circumferential or hoop direction. In addition, there will always be a set of three mutually orthogonal initial directions in the tissue at each location that will remain orthogonal after motion, the “eigenvectors,” or principal directions of the deformation. One of these directions will lie along the direction of the greatest lengthening and another will lie along the direction of the smallest lengthening or greatest shortening; the strain components along these directions of the eigenvectors are called the *principal strains*. The principal strains and their directions provide a description of the deformation that is independent of the choice of reference frame.

Implanted Markers

Regional cardiac strain measurement is widely used to assess regional myocardial function. It is obvious from Equation 14 that, to measure cardiac strain, one needs to track the deformation of a specific area of tissue over time. One approach is to track implanted radiographic markers.^{79–81} A second is to use sonomicrometry to measure one-dimensional or 3D cardiac locations and strain.^{82–84} However, the invasive nature of this approach limits this approach primarily to animal research.

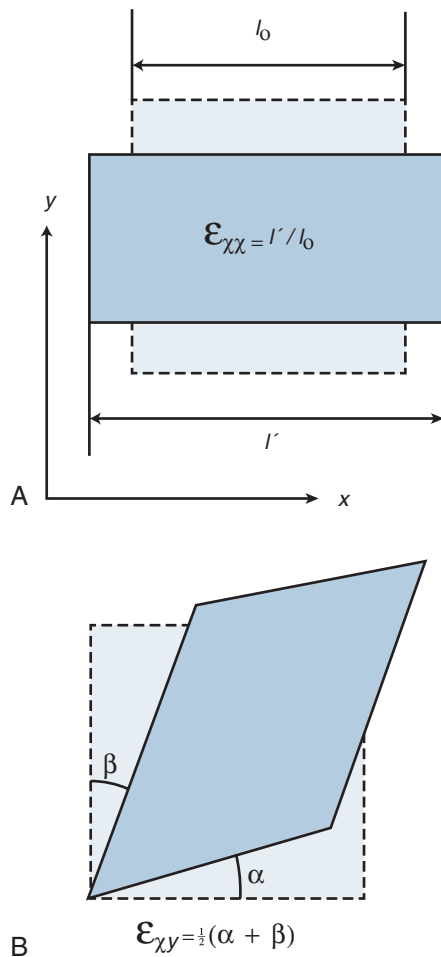


FIGURE 50-13 ■ Graphic representation of normal (A) and shear (B) strain.

Echocardiography

The rapid development of modern imaging techniques in recent decades, however, has made it possible to measure cardiac strain in vivo noninvasively in human subjects. Currently there are two echocardiographic methods available to measure cardiac strain. The first method is tissue Doppler imaging,⁸⁵ which uses echo Doppler to measure the velocity of myocardium in the proximal LV wall. The gradient of the velocity gives the one-dimensional rate of tissue deformation (also called *strain rate*, $e = \frac{d\epsilon}{dt}$) in the ultrasound beam direction.

Cardiac strain is then calculated by integration of the strain rate over the cardiac cycle.⁸⁵

The second echocardiographic method of strain measurement is speckle tracking echocardiography.⁸⁵ Speckles are regions of echocardiographic nonhomogeneity that appear on B-mode echocardiographic images. These regions are randomly generated artifacts caused by the reflection, refraction, and scattering of the ultrasound beam by the heart walls.⁸⁵ Speckles that remain stable can be used as markers to track cardiac motion. Typically, an image correlation method is applied offline to follow the speckles frame-by-frame. Full two-dimensional motion of the cardiac wall can be tracked and two-dimensional

cardiac strain can be subsequently calculated from these motion data. Recently, speckle tracking techniques have been extended to 3D.

Magnetic Resonance Imaging

Magnetic resonance image has several advantages as a method for noninvasive assessment of cardiac motion, including the potential to recover the full 3D motion pattern within the heart wall. Two approaches have been used to study myocardial motion with MRI. The first approach is magnetization tagging, which uses the ability of modified, noninvasive MRI techniques to create localized perturbations of the tissue magnetization (e.g., with spatial modulation of magnetization [SPAMM])⁸⁶⁻⁸⁸ noninvasively to produce MRI-visible landmarks within the heart wall. These markers move along the underlying tissue and will persist for times on the order of the tissue T_1 relaxation time (see Bernstein and colleagues⁸⁹ for references of T_1 and T_2 relaxation time), so that they can be tracked over the cardiac cycle. The second approach is the so-called displacement encoding method.⁹⁰ MRI creates images of the measured subject using magnetic fields with strong spatial gradients along three perpendicular directions. Moving objects within such magnetic field gradients cause a phase shift, which creates artifacts in the acquired image. The amount of phase-shift is known to be related linearly to the degree of motion. This property has been used in MRI noninvasively to measure in vivo blood flow velocity.⁹¹⁻⁹³ Straightforward phase shift approaches, however, are restricted by the tissue T_2 relaxation time, which is much shorter than T_1 relaxation time, and are not suitable for full cycle cardiac motion measurement.⁹⁰ The displacement encoding stimulated echo technique addressed this issue by creatively combining SPAMM and phase shift techniques together.⁹⁰ The displacement encoded phase information is stored along the direction of the static magnetic field, thus resulting in encoding duration comparable to T_1 relaxation time.

REGIONAL STRESS AND THE FINITE ELEMENT METHOD

The distributions of stress in the atrial and ventricular myocardium, valves, and fibrous structures of the heart are determined by (1) the three-dimensional geometry and tissue structure of the walls, (2) the boundary conditions imposed by the ventricular cavity and pericardial pressures and structures like the fibrous valve ring skeleton at the base of the ventricles, and (3) the three-dimensional mechanical properties of the myofibers and their collagen interconnections in the relaxed and actively contracting states. To formulate a mathematical model for predicting the distributions of wall stress in such a complex and constantly changing mechanical system is clearly difficult, but there are important reasons to attempt it. An accurate model of the mechanics of the ventricular myocardium would provide a sound basis for interpreting the complex regional changes in cardiac function that occur in pathologic conditions, such as ischemic heart disease,^{94,95} in terms of changes in the local

properties of the tissue. Knowledge of the stress distributions in the intact myocardium would also provide valuable insight into normal ventricular function because regional coronary blood flow,⁹⁶ myocardial oxygen consumption,⁷⁰ hypertrophy, and remodeling^{97,98} are all influenced by ventricular wall stress.⁹⁹

To keep the problem mathematically tractable, many workers have developed models of left ventricular mechanics using simple geometric approximations such as thin-walled spheres,¹⁰⁰ thin-walled ellipsoids,¹⁰¹⁻¹⁰⁵ thick-walled ellipsoids,^{101-104,106,107} thick-walled spheres,¹⁰⁸⁻¹¹³ thick-walled cylinders,^{96,114-121} solids of revolution,¹²² and noncircular cylinders.¹²³

The most common thin walled model is Laplace's law:

$$P = \frac{T_1}{r_1} + \frac{T_2}{r_2}, \quad (16)$$

where P is intracavitary pressure, r_1 and r_2 are the greatest and least (principal) radii of curvature of the membrane, and T_1 and T_2 are the tensions in the membrane along the corresponding directions.¹²⁴ Of note, the Laplace stress law assumes a thin-walled sphere (i.e., the ratio of wall thickness to radius is small); therefore, tension is calculated, not stress.

Such approximations generally neglect the anisotropy of the material properties of the heart wall. In addition, they generally neglect the presence of significant residual stresses in the wall even in the absence of pressure differences (the unloaded state), as manifested experimentally by the springing open of an incision into the heart wall, even in the absence of contraction or pressurized blood within the chamber.^{122,125}

Despite those limitations, stress predicted with Laplace's law is accurate in normal and globally deformed LV.¹²⁶ However, Laplace's law is not accurate in the LV after myocardial infarction (MI). For instance, Zhang and colleagues¹²⁷ found pronounced differences between modified Laplace and the finite element method in the endocardium and epicardium of the infarct border zone (BZ).¹²⁷

Formulas that are more sophisticated try to take the finite thickness of the wall into explicit account. One of the most common is the following equation developed by Janz:

$$\bar{\sigma}_{\theta\alpha} = P \frac{\Delta A_C}{\Delta A_W}, \quad (17)$$

where $\bar{\sigma}_{\theta\alpha}$ is average circumferential stress, A_C is the area of the cavity, and A_W is the area of the wall (Fig. 50-14).¹²²

Finite Element Method

As early as 1906, researchers first began suggesting the solution of continuum mechanics problems by modeling the body with a lattice of elastic bars and using frame analysis methods.¹²⁸ In 1941, Courant recognized piecewise polynomial interpolation over triangular subregions as a Rayleigh-Ritz solution of a variational problem. Neither approach was practical because there were no computers at the time, and Courant's work was

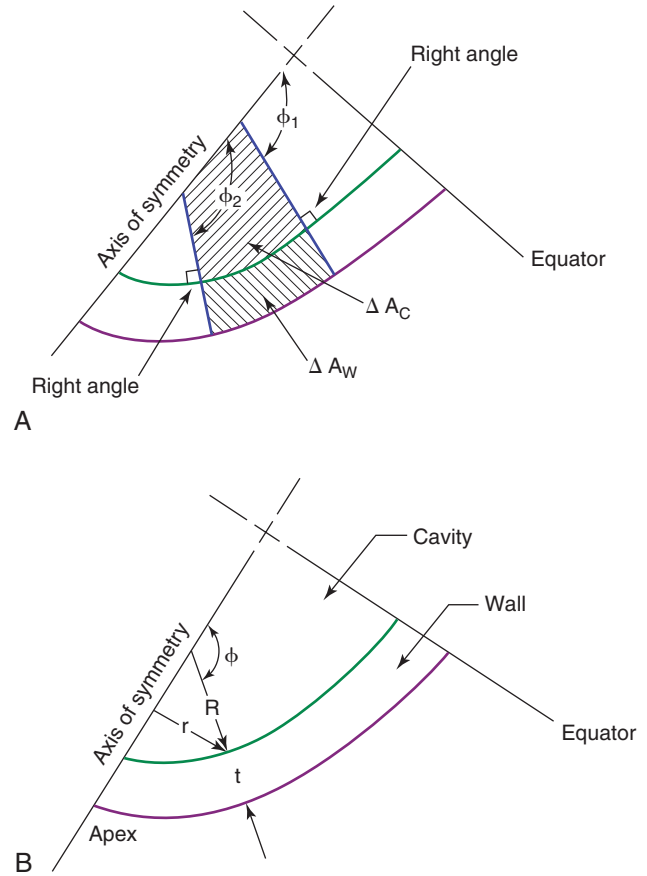


FIGURE 50-14 ■ Estimation of local myocardial stress using geometric approximations. A_C , Area of the cavity; A_W , area of the wall; r , circumferential radius of curvature at the cavity surface; R , meridional radius of curvature at the cavity surface; t , wall thickness. (From Janz RF: Estimation of local myocardial stress. *Am J Physiol* 242[5]:H875–881, 1982.)

largely forgotten until engineers had independently developed it. By 1953, structural engineers were solving matrix stiffness equations with digital computers. The widespread use of finite element methods in engineering began with the classic papers by Turner and colleagues¹²⁹ and Argyris and Kelsey.¹³⁰ The term *finite element* was coined in 1960, and the method began to be recognized as mathematically rigorous by 1963.

Many finite element models of ventricular mechanics have been proposed, although most of them did not include the nonlinear kinematic terms associated with large deformations because iterative solution of the nonlinear governing equations at each load step is required. The importance of adopting nonlinear finite deformation theory for the analysis was demonstrated by Janz and colleagues.¹³¹

A few finite element modeling studies of the left ventricle have validated stress calculations by showing good agreement with myocardial strain measured with implanted markers.^{107,120,125,132} However, this technique is invasive and is limited to few simultaneous LV locations (usually only two). With advancements in MRI, myocardial strain can be quantified noninvasively throughout the LV with tagged MRI.^{133,134} In a pioneering study, Moulton

and colleagues¹³⁵ used tagged MRI to determine isotropic, diastolic material properties in a two-dimensional finite element analysis of beating canine hearts. Using a more realistic material law, Okamoto and colleagues¹³⁶ determine anisotropic myocardial material properties in a three-dimensional finite element model using tagged MRI. However, the experimental preparation and loading conditions were not physiologic, to create significant transverse shear strain. Since then, Guccione and colleagues¹³⁷ have successfully modeled end-isovolumic systole in an ovine model of myocardial infarction (see [Inverse Calculation of Myocardial Material Properties](#)).

Our state-of-the-art finite element model is built on the laws of large deformation continuum mechanics and has been described previously.^{137,138} In short, the passive myocardium is modeled by a strain energy function, W , that is anisotropic relative to the local fiber direction:

$$W = 0.5C(e^Q - 1), \quad (18)$$

where

$$Q = [b_f E_{11}^2 + b_t (E_{22}^2 + E_{33}^2 + E_{23}^2 + E_{32}^2) + b_s (E_{12}^2 + E_{21}^2 + E_{13}^2 + E_{31}^2)], \quad (19)$$

where E_{11} is fiber strain, E_{22} is cross-fiber in-plane strain, E_{33} is radial strain, E_{23} is shear in the transverse plane, and E_{12} and E_{13} are shear strain in the fiber-cross fiber and fiber-radial coordinate planes, respectively, and where $C = 0.88$ kPa, $b_f = 18.48$, $b_t = 3.58$, and $b_s = 1.627$.¹³⁹

We have been using a time-varying elastance model in our research work to simulate the active contraction of cardiac muscles.¹³⁷ The time-varying elastance model has the following form:

$$T_0 = T_{\max} \frac{Ca_0^2}{Ca_0^2 + E C a_{50}^2} C_t, \quad (20)$$

where $T_{\max}$ is the maximum isometric tension achieved at the longest sarcomere length and maximum peak intracellular calcium concentration $(Ca_0)_{\max}$, Ca_0 is the intracellular calcium concentration and $E C a_{50}$ is length-independent calcium sensitivity. C_t is the time-varying variable that reads

$$C_t = \frac{1}{2} [1 - \cos(\bar{\omega})], \quad (21)$$

where $\bar{\omega}$ is a time and sarcomere length dependent variable that increases from 0 at the start of contraction to π during peak contraction and then decreases to 0 during diastole. This model is a purely phenomenological model, but it can provide reasonable prediction of cardiac contraction.

Calculation of Stress

Finite element modeling can be used to calculate stress in the atrial and ventricular myocardium, valves, and fibrous structures of the heart. Moreover, finite element

modeling can also predict the end-systolic and end-diastolic pressure-volume relationship, thus predicting the pump function of hearts.

One example is finite element based analysis of the Acorn CorCap Cardiac Support Device (Acorn CSD).¹⁴⁰ The Acorn CSD is a bidirectional woven polyester yarn jacket that is placed around the ventricles of the heart. It is hypothesized that Acorn CSD can reduce the ventricular wall stress, halt, or even reverse the adverse ventricular remodeling process and improve heart function.^{141,142} To study the effect of Acorn CSD on the heart, a biventricular finite element model of a dog with induced dilated cardiomyopathy from rapid pacing was created. The Acorn CSD was modeled as a thin shell layer attached to the epicardium. Prestretching of the device (slack, stretched, strained) was also modeled to study the effects of device implantation on wall stress and heart function ([Fig. 50-15A](#)). The simulations show that Acorn CSD can reduce the end-diastolic myofiber stress substantially (by as much as 78%). The stress-reduction, however, was always accompanied by a decrease in diastolic compliance; LV ED pressure-volume relationship was shifted to the left by 7% without prestretching and 11% with prestretching. End-systolic pressure-volume relationship, however, was not affected by the presence of Acorn CSD. As a result, the Starling's relationship became more depressed, and stroke volume was reduced by 23% without prestretching and 30% with prestretching (see [Fig. 50-15B](#)).¹⁴⁰

Inverse Calculation of Myocardial Material Parameters

Finite element modeling can also be used to calculate diastolic and systolic myocardial material parameters by comparing experimentally measured myocardial strain with strains calculated by the finite element program. The nonischemic BZ surrounding a MI is illustrative. It has been known since the mid-1980s that systolic shortening is depressed in the nonischemic BZ after anteroapical MI,¹⁴³ and Jackson and colleagues⁸³ described infarct extension after anteroapical myocardial infarction in sheep that surprisingly occurs in the face of normal BZ blood flow.⁸³ Guccione and colleagues¹³⁷ performed inverse calculation of the regional systolic contractility parameter, $T_{\max}$, by manually adjusting the regional myocardial contractility until finite element calculated BZ strain was similar to strain measured with MRI and found that regional contractility in the normally perfused BZ is reduced by more than 50%.¹³⁷ More recently, optimization of myocardial material properties by automatic optimization programs has been performed.^{144,145}

Virtual Surgery

Cardiac surgeries often involve tissue resection, suturing, or mechanical device implantation. A unique advantage of finite element modeling over traditional animal experiments is its capability in conducting repeated virtual experiments.

One example is the simulation of mitral annuloplasty performed using a finite element model based on a sheep

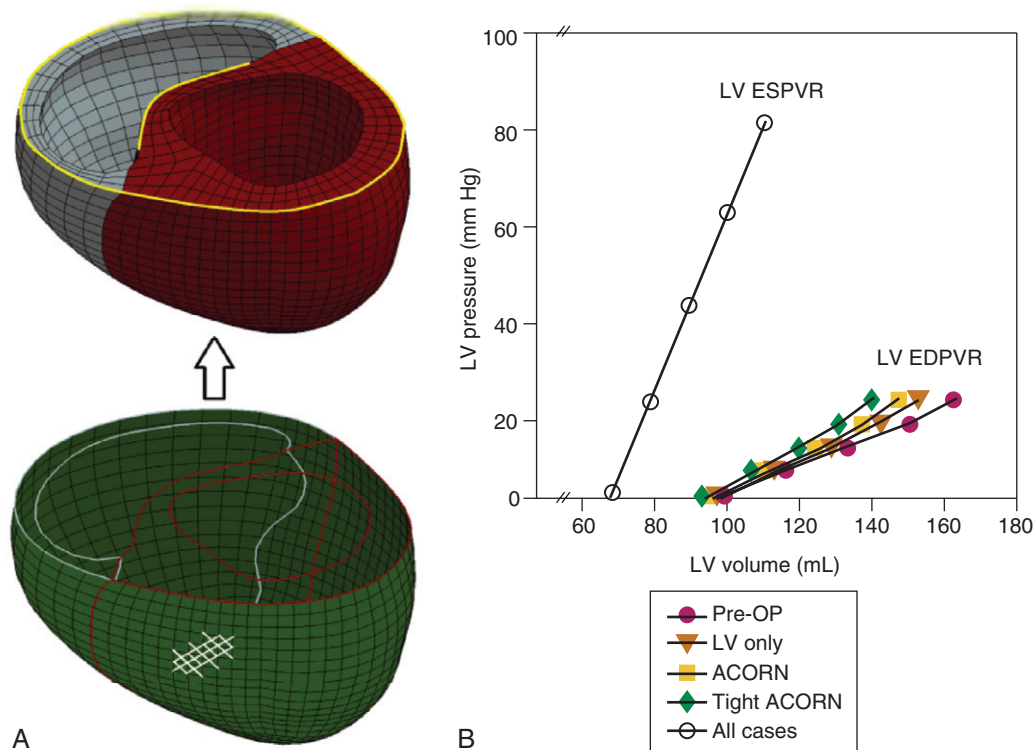


FIGURE 50-15 ■ **A**, A biventricular finite element model created for a dog heart with cardiomyopathy induced by rapid pacing. **B**, Left ventricular end-systolic (LV ESPVR) and end-diastolic (LV EDPVR) pressure-volume relationship before (Pre-OP) and after (with different device implantation: LV Only—device wrapped around left ventricle only; ACORN—slack Acorn implantation; Tight ACORN—device was stretched before implantation).

with moderate ischemic mitral regurgitation that was 8 weeks after posterolateral MI.¹⁴⁶ Cardiac MRI was used to measure the heart geometry and systolic cardiac motion. A finite element model that included the left ventricle and the mitral valve was created. Finite element models of saddle shape (Physio II; Edwards Lifesciences, Irvine, Calif.) and asymmetric (IMR ETLogix; Edwards Lifesciences) annuloplasty rings were created and implanted using the so-called virtual suture technique using these two rings (Fig. 50-16). Although both rings were shown to reduce the LV end-systolic myofiber stress in the basal region, the ETLogix ring was found to have a slightly greater ventricular wall-stress reduction effect.¹⁴⁶

Multiscale Modeling

The cardiovascular system is an inherently multiphysics, multiscale system. It involves electrophysiology, cardiac mechanics, and hemodynamics and cover scales including molecular, cell, tissue, organ, and whole body. There are ongoing research efforts to develop multiscale, multiphysics simulation tools that can ultimately simulate the complicated cardiovascular system in an integrated fashion.¹⁴⁷ Potential applications include predicting effects of cardiac surgery (e.g., cardiac resynchronization therapy,¹⁴⁸ passive cardiac constraint¹⁴⁹), studying effects of new drug on the cardiovascular system,¹⁴⁹ revealing mechanisms of cardiac disease,¹⁵⁰ among many others.

One key component in such a multiphysics model is the myofilament active contraction model, which con-

nects electrophysiology to cardiac mechanics. The active contraction model listed in Equations 19 and 20 are not sophisticated enough for such a task. Increasingly sophisticated models are needed; over the years, a number of such models have been developed.¹⁵¹⁻¹⁵⁵ These models often seek to model the cross-bridge directly, the underlying contraction machinery in myocytes, and cycling dynamics through a set of mathematical equations. These models have their roots in the cross-bridge model originally developed by Huxley.¹⁵¹ The original Huxley type models, however, require a set of partial differential equations (PDEs) to model the probability density function of the fractions of attached cross-bridges as a function of cardiac strain. Incorporating these PDE-based cell or tissue level active-contraction models into the organ-level finite element simulations would make the computations prohibitively expensive. To alleviate this problem, ordinary differential equation-based models have been developed. The model developed by Rice and colleagues¹⁵⁴ represents the state-of-the-art. Their model uses a set of ordinary differential equations to approximate the cooperative binding of calcium to troponin and the mean strain of cross-bridges. Their model is able to reproduce many myocyte contraction experiments, including steady-state force-sarcomere length relations, steady-state force-calcium relations, isometric twitches including Ca activation and sarcomere length effects, and cell shortening twitches as a function of activator Ca, among others. The model has been incorporated successfully into large-scale, finite element models to

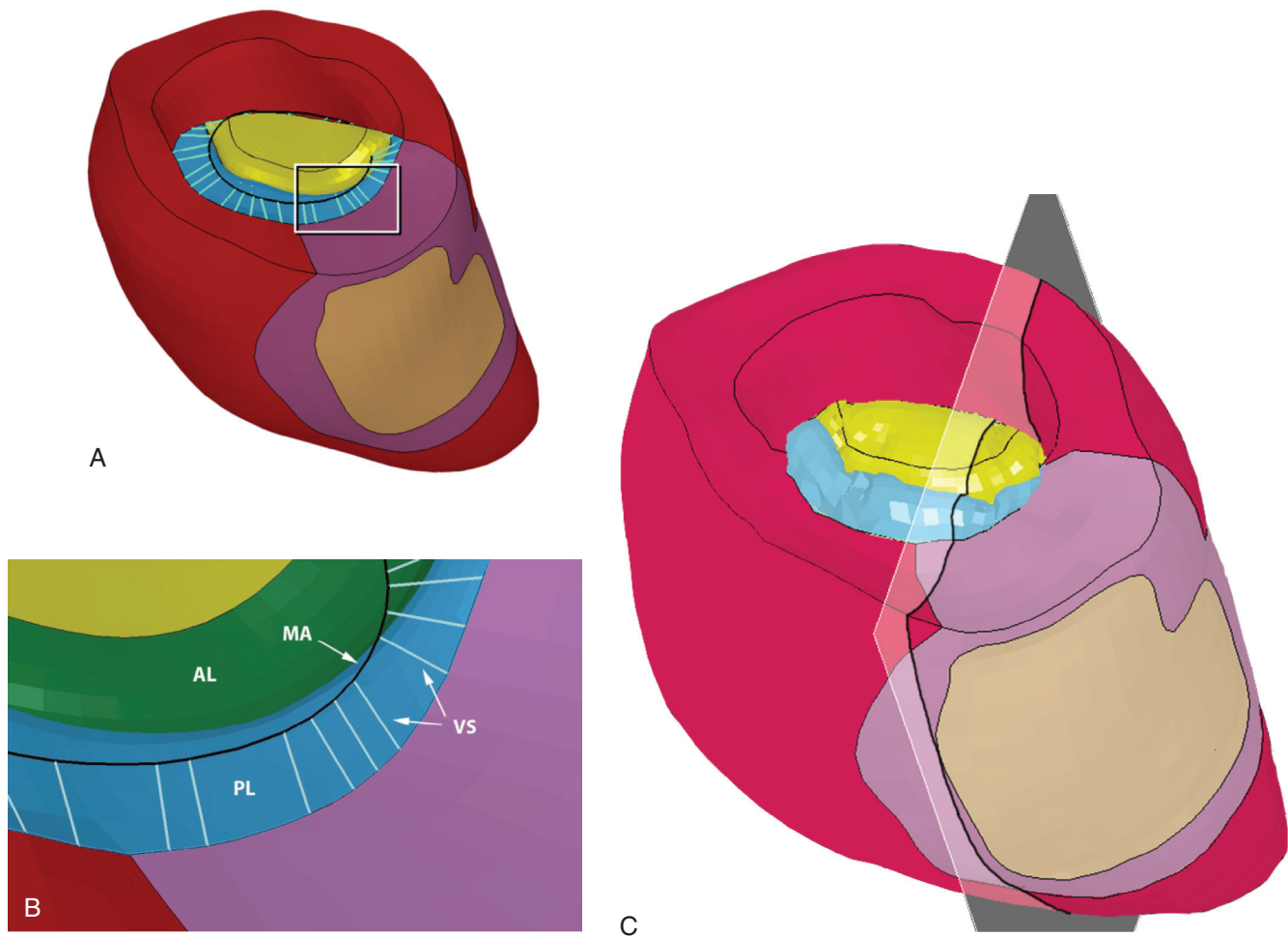


FIGURE 50-16 ■ Virtual mitral annuloplasty with a Physio II ring (black). **A**, Virtual sutures (cyan) are about to attach a Physio II ring. **B**, Expanded view of region in **A**. **C**, At end-systole after virtual Physio II attachment. A white shaded plane is added to reveal the leaflet coaptation profile. AL, Anterior leaflet; MA, mitral annuloplasty, PL, posterior leaflet; VS, virtual suture. (From Wong VM, Wenk JF, Zhang Z, et al: The effect of mitral annuloplasty shape in ischemic mitral regurgitation: a finite element simulation. *Ann Thorac Surg* 93(3):776–782, 2012.)

analyze the interaction between heart electrophysiology and mechanics.¹⁵⁶

VENTRICULAR INTERACTION AND PERICARDIUM

The right ventricle can affect or interact with the performance of the left ventricle and vice versa.^{157,158} Interaction occurs in two ways. First, the ventricles are connected in series, and a change in output of one will affect the other (series interaction). In addition, direct ventricular interaction occurs because the right and left ventricles are mechanically connected throughout the interventricular septum. Determination of the relative effects of series and direct interaction can be difficult. Slinker and Glantz used a statistical approach,¹⁵⁹ Baker used right heart bypass,¹⁶⁰ and Slater and colleagues¹⁶¹ used an isolated heart preparation to determine the relative contribution of series and direct ventricular interaction.

Ventricular interaction analysis is broken into diastolic¹⁵⁹ and systolic interactions.^{161–163} With an intact

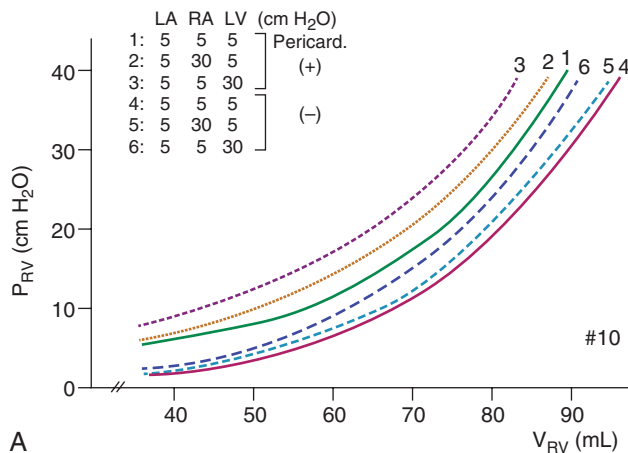
pericardium, Slinker and Glantz¹⁵⁹ determined that direct ventricular interaction is half as important as series interaction at end diastole.⁹ Concentric hypertrophy reduces the effect of direct diastolic interaction further, presumably because the septum is thicker.¹⁶⁴

Ventricular interaction during systole has been measured by causing abrupt changes in right or left ventricular load and measuring the performance of the other ventricle. The ratio of pressure change or gain is usually reported. Typical right-to-left gain is 10%.¹⁶³ Typical left-to-right gain is 4%.¹⁶³ Systolic interaction is increased substantially in dilated cardiomyopathy, with a right-to-left gain of 22% in isolated perfused heart excised at heart transplantation.¹⁶¹

Pericardium

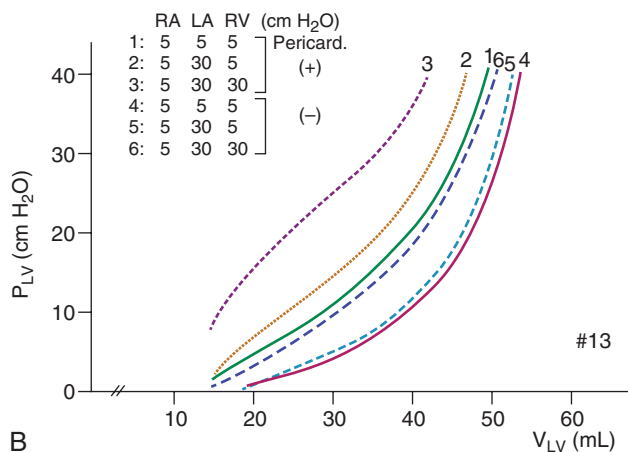
The heart is invested by the pericardium. This double-layered fibrous sac is flexible but not stretchable. The inner (visceral) layer is effectively part of the epicardial aspect of the heart, whereas the outer (parietal) layer fits closely around the heart with a potential space between.

RIGHT VENTRICULAR PRESSURE-VOLUME RELATIONSHIP



A

LEFT VENTRICULAR PRESSURE-VOLUME RELATIONSHIP



B

FIGURE 50-17 ■ The representative data of right ventricle (A) and left ventricle (B) pressure-volume curves obtained during the inflation in various conditions of other heart chambers with and without the pericardium. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Maruyama Y, Ashikawa K, Itoyama S, et al: Mechanical interactions between four heart chambers with and without the pericardium in canine hearts. *Circ Res* 50(1):86–100, 1982.)

Normally, the layers are separated by only a thin film of fluid that acts as a lubricant so that the two surfaces can slide freely. The pericardium is, in turn, surrounded by the intrathoracic cavity, which is normally at subatmospheric pressure, which might help with venous return to the right side of the heart. When discussing the effect of myocardial ischemia on diastolic dysfunction,⁴⁰ the pericardium plays an important role in mediating mechanical effect between ventricles and between atria and ventricles (Fig. 50-17).¹⁶⁵

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BLOOD COAGULATION, TRANSFUSION, AND CONSERVATION

Jerrold H. Levy • Ian J. Welsby • Charles E. Murphy

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SUMMARY

Following cardiac surgery, multiple quantitative and qualitative hemostatic abnormalities have been described. Preexisting and acquired defects contribute to bleeding. The increasing use of anticoagulants, including antiplatelet agents (clopidogrel, prasugrel, ticagrelor) and new oral anticoagulation (NOAC) agents (dabigatran, rivaroxaban and apixaban), contributes to a preoperative hemostatic defect.¹ These events produce a complex hemostatic alteration that is further complicated by heparin and cardiopulmonary bypass, which cause additional acquired defects in hemostatic mechanisms.² With massive bleeding, dilutional hemostatic changes and hypothermia contribute to coagulopathy.

The management of bleeding following cardiac surgery requires a multimodal approach based on both prevention and therapy.^{3,4} In high-risk patients, intraoperative measures to prevent bleeding can be used to

ameliorate the coagulopathic effects of cardiopulmonary bypass (CPB) and mediastinal suctioning.¹ Tissue injury and stress response can also activate fibrinolysis that produces hemostatic defects. Pharmacologic therapies to treat bleeding and to reduce the need for allogeneic transfusions have been studied extensively in cardiac surgery and will be reviewed.

Multiple preoperative and perioperative interventions can reduce bleeding and postoperative blood transfusion. Preoperative interventions that are likely to reduce blood transfusion include identification of high-risk patients, who should receive available preoperative and perioperative blood conservation interventions, and cessation of antithrombotic drugs (Box 51-1). Perioperative blood conservation interventions include the use of antifibrinolytic drugs, selective use of off-pump coronary artery bypass graft surgery, routine use of a cell-saving device,

BOX 51-1 Predictors of Postoperative Bleeding: Computed Tomographic Surgery

- Advanced age
- Small body size or preoperative anemia (low RBC volume)
- Antiplatelet, antithrombotic drugs
- Prolonged operation (CPB time)—high correlation with OR type.
- Emergency operation
- Other comorbidities (CHF, COPD, HTN, PVD, renal failure)

CHF, Congestive heart failure; COPD, chronic obstructive pulmonary disease; CPB, coronary bypass; HTN, hypertension; OR, operating room; PVD, peripheral vascular disease; RBC, red blood cell.

From Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, et al: Perioperative blood transfusion and blood conservation in cardiac surgery: The STS and The SCA Clinical Practice Guideline. *Ann Thorac Surg* 83(Suppl 5):S27–S86, 2007.

and implementation of appropriate transfusion indications. An important intervention is the application of a multimodality blood conservation program that is institution-based, accepted by all health care providers, and that involves well-planned transfusion algorithms to guide transfusion decisions. This chapter will focus on the spectrum of coagulation changes that occur in cardiac surgery, discuss therapies to prevent and treat bleeding when it occurs, and review blood conservation strategies. Recent concepts in understanding pharmacologic agents will also be reviewed.

NORMAL HEMOSTATIC MECHANISMS

In patients, the vascular endothelium plays a major role in preventing clotting. The vascular endothelium is a nonthrombogenic surface that secretes various substances to prevent coagulation from occurring (Fig. 51-1). Prostacyclin, tissue plasminogen activator, heparan sulfate, antithrombin III, protein C, and endothelium-derived relaxing factor are expressed or secreted to inhibit platelet activation and fibrin formation and to provide vascular patency.⁵ However, if a blood vessel is cut or otherwise damaged, tissue factor and other molecular promoters are released or exposed to provide a thrombotic surface. Exposure of subendothelial vascular basement membrane will activate platelets, and expression of tissue factor will also activate thrombin generation and cellular amplification.⁶ An important additional mechanism for the initiation of the coagulation cascade is platelet activation. Receptors on platelets bind to the damaged blood vessel by forming a bridge with von Willebrand factor (VWF) to initiate platelet adhesion.⁷ Once platelets adhere, they undergo surface receptor changes that cause platelets to aggregate. Once platelets aggregate, they expose factors on their surfaces that provide a template for additional initiation of the coagulation cascade and formation of the early hemostatic plug. Platelets play vital roles in maintaining vascular hemostasis. Any abnormality in platelet

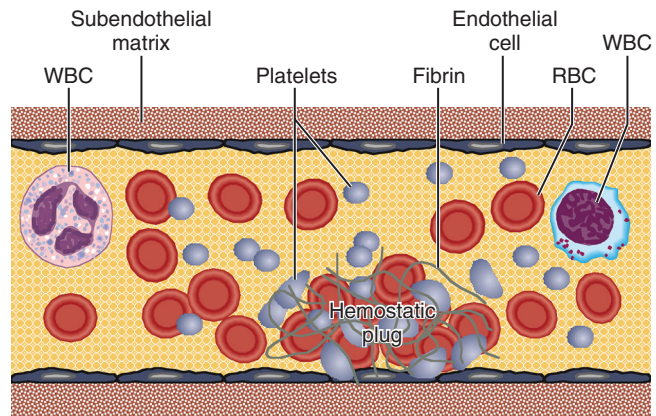


FIGURE 51-1 ■ Hemostasis is the prevention of blood loss; it is accomplished by vasoconstriction and coagulation by cellular and coagulation factors. Undue bleeding is controlled, and the fluidity of the blood is maintained by counterbalances within the coagulation and fibrinolytic systems. Blood vessel injury or disruption, platelet defects, abnormalities of the normally circulating anticoagulants, and fibrinolytic mechanisms can upset the balance between fibrinolysis and coagulation. Blood normally circulates through endothelium-lined vessels without coagulation or platelet activation occurring and without appreciable hemorrhage. Injury to the endothelial cells triggers the hemostatic process, which begins with tissue factor liberation, exposed subendothelial proteins such as collagen, the attachment of platelets (adhesion) to the damaged endothelium or via a von Willebrand factor bridge to allow platelet attachment. The platelets then change form (i.e., activate) and release factors that stimulate the clotting process. They also bind together (i.e., aggregate). At the same time, plasma proteins can react with elements in the subendothelium, activating the contact phase of coagulation. Exposed fibroblasts and macrophages present tissue factor, a membrane protein, to the blood at the injured site, thereby triggering the extrinsic phase of blood coagulation. Under normal conditions, hemostasis protects the individual from massive bleeding secondary to trauma. In abnormal states, life-threatening bleeding can occur or thrombosis can occlude the vascular tree. Hemostasis is influenced by a number of different factors including: (a) vascular extracellular matrix and alterations in endothelial reactivity, (b) platelets, (c) coagulation proteins, (d) inhibitors of coagulation, and (e) fibrinolysis. RBC, Red blood cell; WBC, white blood cell. (From BleedingWeb.com, with permission.)

number or function poses significant risk for postoperative coagulopathy and bleeding.

INHIBITING HEMOSTASIS: ANTICOAGULATION

Heparin

Heparin is the mainstay agent used to prevent clotting during cardiovascular surgery. Heparin is isolated from porcine intestine and previously from beef lung, where it is bound to histamine and stored in the mast cell granules. When heparin is isolated, the purification leads to a heterogeneous mixture of molecules. Heparin is an acidic molecule with side groups, either sulfates or *N*-acetyl groups, attached to individual sugar groups. These structural characteristics are important for producing its anticoagulant activity.^{8,9} Heparin acts as an anticoagulant by binding to antithrombin III (AT), which enhances the rate of thrombin-AT complex formation by

1000- to 10,000-fold. Other factors in the clotting cascade, including factor Xa, are also inhibited by AT.⁹ Anticoagulation thus depends on the presence of adequate amounts of circulating AT.

Heparin anticoagulation can be reversed immediately by removing heparin from AT with the highly basic molecule protamine. Heparin also binds to a number of other blood and endothelial proteins.⁸ Each of these proteins can influence the ability of heparin to act as an anticoagulant, and may, along with AT levels, affect heparin dose responses in patients. Heparin can also produce platelet dysfunction following acute or constant administration, especially with high-dose administration during cardiac surgery. Severe adverse reactions to heparin can also occur because of immune-related causes, including hypersensitivity (allergic) and heparin-induced thrombocytopenia (discussed later).

In January 2008, the U.S. Food and Drug Administration (FDA) received reports of clusters of acute hypersensitivity reactions in patients undergoing dialysis. The Centers for Disease Control and Prevention identified heparin as a common feature of the cases, leading to a recall of affected lots. After the initial recall, there were continuing reports of allergic-type reactions from patients in other clinical settings. The contaminant was recently identified as an unusual, oversulfated form of chondroitin sulfate.¹⁰ Highly charged molecules like this can activate enzymatic cascades in plasma. Activation of kinin pathways produced vasodilation via contact activation, the mechanism of the reported adverse reactions.¹⁰

Protamine Administration and Heparin Reversal

Protamine, the mainstay neutralizing agent, is a basic polypeptide isolated from salmon sperm. Composed mostly of arginine, protamine reverses heparin by a non-specific acid-base interaction (polyanionic-polycationic). Protamine can immediately reverse the anticoagulation effect of unfractionated heparin by nonspecific polyionic-polycationic (acid-base) interactions. Different methods can be used to calculate the reversal dose of protamine, but using a ratio of 1.0 to 1.3 mg protamine to 100 units of the initial dose of unfractionated heparin administered is a useful estimate.⁸ Protamine has the potential to function as an anticoagulant when excessive doses have been administered (Fig. 51-2).¹¹ Additional considerations about protamine and potential adverse effects will be considered later.

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) is a derivative of unfractionated heparin producing fragments with a mean molecular weight of approximately 5000 daltons. LMWH fragments of fewer than 18 saccharides retain the critical pentasaccharide sequence needed for formation of a Xa:antithrombin complex.¹² The LMWHs have been suggested to provide a therapeutic benefit because factor Xa generation occurs several steps earlier in the coagulation cascade than thrombin generation; inhibition of Xa has a marked effect on the later steps in

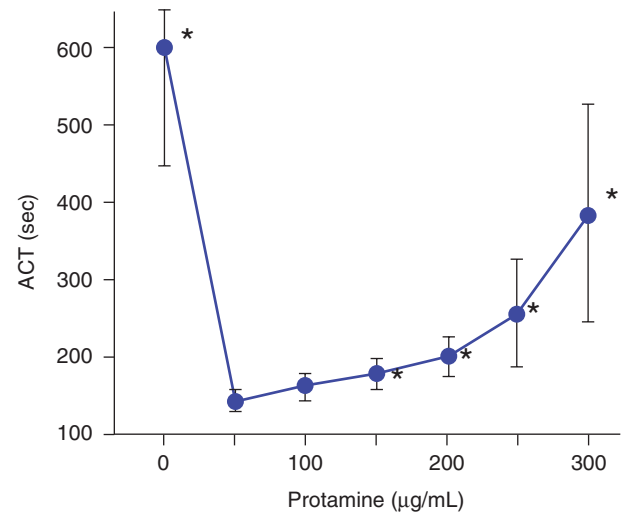


FIGURE 51-2 ■ Excess protamine causes hemostatic dysfunction. Excess protamine contributes to elevations in the activated clotting time (ACT), at greater than the exact dose required to reverse systemic anticoagulation. Overdose of protamine should be strictly avoided. (From Mochizuki T, Olson PJ, Szlam F, et al: Protamine reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. *Anesth Analg* 87:781-785, 1998.)

coagulation. LMWH use is rapidly growing and evolving in cardiovascular medicine because of its long half-life and ease of dosing; however, it can pose a potential problem for cardiac surgical patients because commonly used hemostatic tests are not affected by LMWH. In addition, because these agents are not readily reversed by protamine, they are not suitable anticoagulants for CPB.

Fondaparinux

Fondaparinux (Arixtra), a synthetic pentasaccharide with a duration of action longer than LMWH, selectively binds antithrombin and causes rapid and predictable inhibition of factor Xa.¹³ Fondaparinux is more effective than enoxaparin in preventing venous thrombosis in patients undergoing orthopedic surgery, and it is similar in effectiveness to enoxaparin or unfractionated heparin in patients with pulmonary embolism.¹⁴ Pilot trials involving patients with acute coronary syndromes and those undergoing percutaneous coronary intervention suggest that fondaparinux may be as effective as enoxaparin or safer than unfractionated heparin.¹⁵ The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5; NCT00139815) trial compared the efficacy and safety of fondaparinux and enoxaparin (Lovenox, Sanofi-Aventis) in high-risk patients with unstable angina or myocardial infarction without ST-segment elevation.¹⁵ The result of this study indicated that fondaparinux reduces the risk of ischemic events similar to enoxaparin, but with less risk of major bleeding.

Warfarin

Warfarin is the most commonly used oral anticoagulant; it is a member of the family of drugs known as *vitamin K antagonists*. Warfarin has major limitations, including slow onset and offset, a narrow therapeutic window, and

metabolism affected by diet, concomitant drug therapy, and genetic polymorphisms. Warfarin also requires careful monitoring.¹⁶ Warfarin is a vitamin K analog that interferes with the transformation of coagulation factors to an active form. Vitamin K is required in the posttranslational carboxylation required for the synthesis of active coagulation factors II, VII, IX, and X. Without vitamin K, these coagulation factors are incapable of chelating calcium that is required for their binding to phospholipid membranes during the normal clotting process, thereby decreasing prothrombin activation. Warfarin also inhibits the carboxylation of protein C and protein S, thus impairing the function of the anticoagulant proteins. Warfarin is often a mainstay in preventing thromboembolic complication in patients with prosthetic heart valves, atrial fibrillation, atrial mural thrombi, deep vein thrombosis, or prior pulmonary embolic problems. Warfarin is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached 1 to 4 hours after ingestion; its anticoagulant effect occurs only after a significant decrease in the concentration of normal vitamin K-dependent clotting factors.⁸

The NOAC agent ximelagatran was the first oral anticoagulant, but it was withdrawn from the market in Europe because of hepatic toxicity. A next-generation direct thrombin inhibitor, dabigatran (Pradaxa), is now recommended for atrial fibrillation and VTE prophylaxis.¹⁷ Additional agents include rivaroxaban and apixaban, also approved for paroxysmal atrial fibrillation and VTE prophylaxis. Rivaroxaban and apixaban target factor Xa, whereas dabigatran etexilate inhibits thrombin. Rivaroxaban is a small molecule directed against the active site of factor Xa. After oral administration, all the agents have a rapid onset of action within a few hours. Although monitoring is not required for the NOAC agents, their effects can be determined using readily available coagulation assays.¹⁷ For dabigatran, this includes thrombin times and partial thromboplastin times, and if possible a dabigatran-specific assay that is a diluted thrombin time (HemoClot assay). For rivaroxaban and apixaban, an antiXa assay, similar to LMWH assay but calibrated for the specific drug, is the assay used to measure levels of the Xa inhibitors including edoxaban. All the agents have some renal elimination, but dabigatran is the agent most dependent on renal function, and for all of the NOAC agents dose alterations must be made with renal dysfunction.¹⁷ For more information about the NOAC agents and bleeding, a recent review has discussed this as therapeutic modalities continue to evolve.¹⁷

Heparin-Induced Thrombocytopenia and New Anticoagulants

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening, adverse effect of heparin produced by antibodies (IgG) induced to the composite antigen of heparin-platelet factor 4 (PF4). Later exposure of seropositive patients to heparin risks forming the heparin-PF4 antigen and immune complexes.¹⁸ These immune complexes bind to platelets via platelet Fc-receptors (CD 32); this produces intravascular platelet activation, thrombocytopenia, and platelet activation with potential

thromboembolic complications that can result in limb loss or death.¹⁸ HIT can occur after 5 to 10 days of heparin therapy, but can occur earlier because of occult heparin exposure from prior hospitalizations or in the cardiac catheterization laboratory.

This serious, yet treatable, prothrombotic disease develops in 1% to 3% of heparin-treated patients and dramatically increases their risk of thrombosis.¹⁹ HIT antibodies (IgM and IgG), occur more often than the overt disease itself. Even without thrombocytopenia, the IgG subclass may be associated with increased thrombotic morbidity and mortality.¹⁹ HIT should be suspected whenever the platelet count drops greater than 50% from baseline more than 4 to 5 days after starting heparin (or sooner if there was prior heparin exposure) or when new thrombosis occurs during, or soon after, heparin treatment, with other causes excluded. When HIT is strongly suspected, with or without complicating thrombosis, heparin should be discontinued and a fast-acting, non-heparin alternative anticoagulant, such as a direct thrombin inhibitor (argatroban or bivalirudin), should be initiated immediately,^{19,20} because HIT is a prothrombotic disease that carries significant morbidity and mortality.

Despite their association with long-term adverse effects, circulating heparin-PF4 antibodies are transient. Should a patient require cardiac surgery and have a history of HIT, antibody titers should be checked. If the patient is currently seronegative, heparin is the anticoagulant of choice.²¹ Bivalirudin has emerged as the agent most studied for use during on- or off-pump surgery in patients with HIT.^{22,23} For prophylaxis in the intensive care unit in patients with HIT, fondaparinux is a potential alternative, but its long duration of effect makes it impractical. Rivaroxaban can have a role for prophylaxis and can be given via a nasogastric tube. Eventually the patient should be switched to warfarin for long-term anticoagulation.¹⁸ Warfarin should not be started until the platelet count has recovered. A minimum of a 5-day overlap of the direct thrombin inhibitor and warfarin should be used before stopping the direct thrombin inhibitor. The role of NOAC agents is yet to be determined.

ACQUIRED PLATELET DYSFUNCTION

Antiplatelet agents are the mainstay therapy for patients with atherosclerotic vascular disease and coronary artery disease. This therapy is based on the role of platelets in causing complications of atherosclerosis.²⁴ Treatment with aspirin reduces the incidence of occlusive arterial vascular events. Aspirin irreversibly acetylates cyclooxygenase and thereby prevents formation of thromboxane A₂, a prostaglandin that mediates activation of more platelets. Clopidogrel is a thienopyridine that inhibits the P2Y₁₂ receptor, and it is widely used in patients with atherosclerotic vascular disease and in patients who do not tolerate aspirin.²⁴ The combination of aspirin plus clopidogrel is recommended after coronary stenting and for up to 9 months after acute coronary syndrome.²⁴ These drugs and other anticoagulant therapies are associated with excessive intraoperative and postoperative bleeding and resultant transfusions in most situations.²⁵⁻²⁷

Patients with thrombocytopenia or with qualitative platelet defects (e.g., renal failure, von Willebrand disease) may represent a group at greater risk for bleeding. Discontinuation of antiplatelet and antithrombotic drugs before cardiac surgery in these high-risk patients should be considered.

Clopidogrel and aspirin therapy result in higher rates of postoperative bleeding, blood product transfusion, and reexploration for mediastinal hemorrhage following emergency coronary artery bypass grafting (CABG).²⁸⁻³⁰ American College of Cardiology/American Heart Association (ACC/AHA) guidelines and the current Society of Thoracic Surgeons (STS) guidelines recommend stopping adenosine diphosphate (ADP) inhibitors 5 to 7 days before cardiac operations, if possible, recognizing that operations sooner than 5 days in patients taking ADP-inhibitors risk increased perioperative bleeding and transfusions.³¹ However, in patients with drug-eluting stents, the abrupt discontinuation of platelet inhibitors may also increase the risk for thrombotic events, and there is little evidence available to guide therapy in this situation. Discussion with all members of the cardiovascular team including cardiologists, cardiac surgeons, and anesthesiologists is recommended. New shorter-acting antiplatelet agents that should soon be available (e.g., cangrelor) might offer an important therapy and a new paradigm for management.³² Changing to a glycoprotein IIb/IIIa inhibitor (GPI) or to a direct thrombin inhibitor might also be an alternative.²⁵

Additional therapeutic agents can produce platelet dysfunction. Platelet glycoprotein (GP) IIb/IIIa complexes are also important in platelet-mediated thrombus formation. GP IIb/IIIa inhibitors have been used less commonly to treat acute coronary thromboses, most likely because of the increasing use of clopidogrel as based on 2013 ST-elevation myocardial infarction (STEMI) guidelines.^{33,34} GP IIb/IIIa (IIb β 3) is a receptor on platelets that binds to key hemostatic proteins, including fibrinogen and VWF, to allow cross-linking of platelets and platelet aggregation. GP IIb/IIIa antagonists block the final common pathway and function as inhibitors of platelet participation in acute thrombosis. Three different agents are available and differ in antagonist affinity, reversibility, and receptor specificity.

The first of these agents, the monoclonal antibody abciximab (ReoPro), was approved for use in percutaneous coronary intervention. Tirofiban (Aggrastat), a nonpeptide, is approved for treatment of acute coronary syndromes (unstable angina or non-Q-wave myocardial infarction). Eptifibatide (Integrilin), a peptide, was approved for use in percutaneous coronary intervention and acute coronary syndromes. The shorter-acting agents tirofiban and eptifibatide are used during coronary intervention. Abciximab, the longer-acting agent, is used with decreasing frequency because of its long half-life and potential for producing thrombocytopenia and bleeding.

HEMOSTATIC TESTING

Hemostatic testing is often used preoperatively to identify patients at risk for bleeding and to define the

presence of any specific defect that could produce bleeding. Because platelet dysfunction is a major cause of bleeding following cardiac surgery, laboratory evaluation of platelet function would provide valuable information. However, most platelet function tests available as point-of-care testing or as laboratory-based testing have not been suitably validated in cardiac surgical patients. In addition, dilutional thrombocytopenia can affect the test results. Better tests of platelet function are needed and should be applied in this patient population to allow for accurate diagnosis of underlying disorders.³⁵

Despite the lack of studies supporting platelet function tests in the perioperative management of cardiac surgical patients, multiple studies have showed that using algorithms based on point-of-care coagulation tests can decrease bleeding and transfusion requirements after cardiac surgery. One important caution is that hemostatic test results can also be abnormal in patients who are not bleeding. Transfusion algorithms can prevent or decrease the empirical administration of hemostatic factors.³⁶ Cardiac surgery services should use transfusion guidelines based on laboratory-guided algorithms, and the possible benefits of point-of-care testing should be tested against this standard.

Risk Factors for Bleeding

Ferraris and colleagues²⁵ summarize variables associated with increased transfusion requirements caused by patient-related, procedure-related, and process-related factors in their inclusive review. However, most studies do not distinguish between red blood cell (RBC) transfusion and hemostatic factor transfusion. Ferraris and colleagues²⁵ identified a high-risk profile associated with increased postoperative blood transfusion. Six variables were identified as important indicators of the risk of bleeding: (1) advanced age, (2) low preoperative RBC volume (preoperative anemia or small body size), (3) preoperative antiplatelet or antithrombotic drugs, (4) reoperative or complex procedures, (5) emergency operations, and (6) certain patient comorbidities. The web site of the review can be found at www.sts.org/sites/default/files/documents/pdf/guidelines/BloodConservationUpdate0311.pdf.

Patient-Related Causes of Bleeding

Certain patients are at greater risk for bleeding, such as those with acquired or congenital coagulopathies, patients scheduled for re-do or complex procedures (e.g., combined valve and coronary revascularization, and aortic dissection with deep hypothermic circulatory arrest). There is evidence that certain patients have an accentuated response to antiplatelet drugs.³⁷ Patients with thrombocytopenia from any cause (defined as platelet count less than 50,000) are at a high risk of excessive bleeding after CABG. Patients with preoperative anemia have a lower starting RBC mass. Anemia in complex ways can also contribute to bleeding. Patients with other congenital or acquired qualitative platelet defects, such as von Willebrand disease, Bernard-Soulier syndrome, and Glanzmann thrombasthenia, are at increased risk of bleeding.²⁵

Acquired qualitative defects occur with hepatic and renal failure, as well as following the administration of some drugs.

Physician-Related Causes of Bleeding

One important factor in surgical bleeding and blood transfusion is the surgeon. Surgical practices differ widely and influence morbidity and mortality.³⁸ Cardiopulmonary bypass times influence platelet function and postoperative bleeding. Meticulous attention to surgical technique and to intraoperative hemostasis will affect bleeding and transfusion requirements. Differences in practice patterns relative to the diagnosis and therapy of postoperative hemorrhage also contribute to variability in transfusion practices.³⁹ Transfusion practices also vary among centers.^{25,40,41}

Procedure-Related Causes of Bleeding

Certain procedure-related factors increase risk for bleeding and perioperative morbidity and mortality. Repeated procedures have higher transfusion rates. The type and urgency of operation are independent predictors for transfusion.⁴²⁻⁴⁵ Cardiopulmonary bypass also influences platelet function and coagulation.⁴⁵ Off-pump cardiac surgery can be associated with an overall reduction in transfusion requirements.^{46,47} Complex, long procedures including those using bilateral internal mammary artery grafts, aortic valve replacement with a pulmonary autograft (Ross procedure), and implantation of ventricular assist devices or artificial hearts, are examples of complex surgeries associated with greater risk of bleeding.²⁵

Drug-Related Causes of Bleeding

Therapy for the prevention and treatment of cardiovascular disease is based on inhibiting clot formation, platelet function, or by causing clot lysis, as previously reviewed.⁴⁸ Patients who are taking these agents and who need surgery are at a greater risk of bleeding as described by Ferraris and colleagues.²⁵ However, in patients undergoing cardiopulmonary bypass while taking warfarin, this might not be the case because of better thrombin inhibition.⁴⁹ Ferraris notes that preoperative antiplatelet and anticoagulant treatment as prophylaxis for coronary occlusive disease is associated with excessive intraoperative and postoperative bleeding as well as resultant transfusion. Therefore, this aspect of patients' preoperative medication regimens must be managed for maximum cardioprotective benefit while minimizing the risk of hemorrhagic complications.²⁵ As noted previously, clopidogrel and aspirin therapy result in higher levels of postoperative bleeding, more transfused blood products, and a higher rate of reexploration for mediastinal hemorrhage following emergency CABG.²⁸⁻³⁰ ACC/AHA guidelines and the current STS guidelines recommend stopping ADP-inhibitors 5 to 7 days before cardiac operations, if possible, recognizing that operations sooner than 5 days in patients taking ADP inhibitors risk increased perioperative bleeding and transfusions.^{31,48}

TRANSFUSION THERAPY AND TRANSFUSION GUIDELINES

The appropriate use of RBC or platelet transfusions continues to be defined in cardiac surgical patients. Guidelines and transfusion algorithms for the management of bleeding in cardiac surgical patients have been reported.^{43,50} Bleeding and reexploration in cardiac surgery are consistently associated with adverse outcomes.⁵¹⁻⁵³ As a result, patients often undergo transfusion in the setting of perioperative bleeding; however, the lack of consistent evidence-based medicine supporting the transfusion decision is illustrated by the wide range of blood product use in CABG surgery. These rates range from 3% to 83% for RBCs and from 0% to 40% for platelets.^{40,41}

Transfusion algorithms have been developed using institution-derived transfusion practices with point-of-care testing to guide therapeutic approaches to bleeding and transfusion. In most studies, point-of-care testing and transfusion algorithms decrease transfusions and improve hemostasis in randomized studies.⁵⁴⁻⁵⁷ It is not certain whether the algorithms, the multidisciplinary approach, or the point-of-care testing are more important in reducing blood product utilization. Ferraris notes that the importance of a multimodality approach is the most important factor rather than the individual components of the process.

The American Society of Anesthesiologists established the Task Force on Blood Component Therapy to develop evidence-based indications for transfusing RBCs, platelets, fresh-frozen plasma, and cryoprecipitate in perioperative settings. Specific guidelines were developed according to an exact methodology.⁵⁸ The recommendations of the task force were reported and can be found at www.asahq.org/For-Members/Practice-Management/Practice-Parameters.aspx and are listed in Box 51-2. Although these guidelines are reported as recommendations, there are also other important considerations regarding the use of specific blood products in cardiac surgical patients. The rationale for transfusion of individual blood components will be presented.

Red Blood Cells

Unfortunately, there is no single minimum acceptable hemoglobin level for all patients. Chronic anemia is better tolerated than acute anemia. With acute anemia, compensatory mechanisms that increase cardiac output and improve oxygen transport depend on the patient's cardiovascular reserve. This may be a problem in cardiac surgical patients with heart failure or flow-restricting lesions. Multiple factors should be considered, including intravascular volume, the presence of active bleeding, and the need for oxygen transport. The anemic cardiac surgery patient who is receiving multiple inotropes and who has an intraaortic balloon pump may require RBCs, although the definition of *anemia* is contentious. The need for transfusion must balance the risks versus the need for oxygen-carrying capacity in recovery from trauma, surgery, or illness as noted in the American Society of Anesthesiologists practice guidelines for

BOX 51-2**Evidence-Based Indications for Transfusing Red Blood Cells, Platelets, Fresh Frozen Plasma, and Cryoprecipitate in Perioperative Settings**

- The risks of bleeding in surgical patients are determined by the extent and surgery, the capacity to control bleeding, the expected rate of bleeding and the outcomes of uncontrolled bleeding.
- RBC transfusions should not be dictated by a single hemoglobin “trigger,” but instead should be based on the patient’s risks of developing complications of inadequate oxygenation. RBC transfusions are suggested to be indicated rarely when the hemoglobin concentration is greater than 10 g/dL and are almost always indicated when it is less than 6 g/dL. The indications for autologous transfusion may be more liberal than for allogeneic transfusion.
- Prophylactic platelet transfusion is ineffective when thrombocytopenia is due to increased platelet destruction. Surgical patients with microvascular bleeding usually need platelet transfusion if the platelet count is less than 50×10^9 cells/L and rarely if it is greater than 100×10^9 cells/L.
- Fresh frozen plasma is indicated for urgent reversal of warfarin therapy, correction of known coagulation factor deficiencies for which specific concentrates are unavailable, and correction of microvascular bleeding when prothrombin and partial thromboplastin times are greater than 1.5 times normal. It is contraindicated for increase of plasma volume or albumin concentration.
- Cryoprecipitate should be considered for patients with von Willebrand disease that is unresponsive to desmopressin, bleeding patients with von Willebrand disease, and bleeding patients with fibrinogen levels less than 80 to 100 mg/dL.

RBC, Red blood cell.

Modified from Practice Guidelines for Blood Component Therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology* 84:732–747, 1994.

perioperative blood transfusion and adjuvant therapies.⁵⁹ The task force noted in its recommendations that⁵⁹:

[transfusion of] red blood cells should usually be administered when the hemoglobin concentration is low (e.g., less than 6 g/dL in a young, healthy patient), especially when the anemia is acute. Red blood cells are usually unnecessary when the hemoglobin concentration is more than 10 g/dL. These conclusions may be altered in the presence of anticipated blood loss or active critical (i.e., myocardium, central nervous system or renal) or target organ ischemia. Determining whether intermediate hemoglobin concentrations (i.e., 6–10 g/dL) justify or require RBC transfusion should be based on ongoing indications of organ ischemia, potential or actual ongoing bleeding (rate and magnitude), the patient’s intravascular volume status, and the patient’s risk factors for complications of inadequate oxygenation. These risk factors include a low cardiopulmonary reserve and high oxygen consumption.

Hemoglobin triggers for transfusion are not to be taken as absolute indications, and cardiac patients should

be transfused if signs or symptoms of inadequate myocardial oxygen delivery are present.

Blood transfusions are associated with a significant increase in morbidity and mortality. An observational cohort study from the Cleveland Clinic included more than 11,000 patients. This study demonstrated a dose-dependent increase in mortality and morbidity, including renal failure, serious infection, and stroke, in patients receiving RBC transfusions. They concluded that perioperative RBC transfusion is the single factor most reliably associated with increased risk of postoperative morbid events after isolated CABG. These findings were reinforced by a study from the Cardiothoracic Surgical Trials Network. This prospective observational trial of more than 5000 patients found that each RBC transfusion was associated with a 29% increase in the risk of a major infection ($P < 0.001$). An additional retrospective cohort study from a single center including more than 8000 patients found a strong association between RBC transfusion and mortality, infection, length of stay, and cost.⁶⁰ One important aspect of adverse events associated with RBC transfusions relates to the age of RBCs transfused.^{61–63} Prolonged storage is associated with an increased occurrence of complications, and a current National Heart, Lung, and Blood Institute study is underway to investigate this issue in cardiac surgery.

Plasma and Fresh Frozen Plasma

Following collection of a unit of blood, plasma remains after RBC and platelet removal. Plasma contains blood coagulation factors, fibrinogen and other plasma proteins in a volume of 170 to 250 mL that is then frozen and can be stored for up to 1 year. Fresh frozen plasma (FFP) is rarely available; most transfusable plasma is designated FP24, frozen within 24 hours of collection. Before administration, the plasma must be thawed in a waterbath at 37°C, which takes approximately 30 minutes. After thawing, plasma units are stored at 1° to 6° C and are transfused within 24 hours. Plasma should be administered through a component administration set with a 170-µm filter; if not used within 24 hours, it can be relabeled as “thawed plasma” and stored at 1° to 6° C for an additional 4 days. Thawed plasma maintains normal levels of all factors except factor V, which falls to 80% of normal, and factor VIII, which falls to 60% of normal.⁶⁴ Because these levels are above the in vivo threshold for normal hemostatic function for these factors and because FVIII is an acute phase reactant, FP24 or thawed plasma can be used as an acceptable substitute for FFP.⁶⁴

Plasma is used for treating bleeding caused by coagulopathies with a prolongation of either the activated partial thromboplastin time or the prothrombin time (PT)/international normalized ratio (INR) greater than 1.5 times normal, or a coagulation factor assay of less than 25%,⁵⁹ where a factor concentrate is not available or is not indicated. Plasma is often used to reverse the effect of warfarin before surgery or during active bleeding episodes (see following discussion of anticoagulation reversal). When plasma is indicated, it should be administered in a dose calculated to achieve a minimum of 30% of plasma factor concentration. Ten to 15 mL/kg of plasma will generally

result in a rise of most coagulation proteins by 25%–30% (or increases in 0.25 to 0.3 U/mL). A dose of 5 to 8 mL/kg may be adequate to only partially reverse warfarin anticoagulation urgently, because the lowest INR obtainable with plasma is 1.4–1.5.⁵⁹ Plasma is also part of a 1:1 ratio RBC:plasma transfusion algorithm for massive bleeding.

Plasma is overused in cardiac surgery, often because of empiric therapy. A major cause of bleeding after cardiac surgery is platelet dysfunction. Furthermore, the PT and partial thromboplastin times (PTT), which are widely used to evaluate bleeding, have never been demonstrated to reflect bleeding in cardiac surgical patients, and can be abnormal in patients who are not bleeding. These facts would support a restrictive use of plasma in the setting of heart surgery, based on laboratory testing documenting significant abnormalities in appropriate coagulation studies.

Cryoprecipitate

Cryoprecipitate is the insoluble proteins that precipitate when plasma is thawed at 1° to 6° C, and it is named for the process. The residual volume of cryoprecipitate (approximately 15 mL) is refrozen and stored. Cryoprecipitate contains therapeutic amounts of factor VIII:C, factor XIII, VWF, and fibrinogen. Each bag of cryoprecipitate contains 80 to 100 units of factor VIII:C, 150 to 200 mg of fibrinogen, significant amounts of factor XIII, and VWF, including the important high molecular weight multimers. Cryoprecipitate is used to increase fibrinogen levels depleted because of massive hemorrhage or coagulopathy, but also for the treatment of congenital or acquired Factor XIII deficiency.

In Europe, specific fibrinogen concentrates are available for fibrinogen replacement therapy. However, one unit of cryoprecipitate per 10 kg body weight (10 units is a typical adult dose) increases plasma fibrinogen by approximately 50 to 70 mg/dL in the absence of continuing consumption or massive bleeding.⁶⁵ The minimum hemostatic level of fibrinogen is traditionally suggested to be approximately 100 mg/dL. Normal fibrinogen levels are 200 mg/dL and greater, and higher levels of fibrinogen may be important for clot formation (see fibrinogen section). Because cryoprecipitate does not contain factor V, it should not be the sole replacement therapy for disseminated intravascular coagulopathy, which is almost always associated with various factor deficiencies and thrombocytopenia as noted in the guidelines from the American Association of Blood Banks (AABB). Because fibrinogen is an important determinant of hemostatic function and clot strength, fibrinogen levels should be routinely evaluated in bleeding patients, especially after multiple transfusions. Hypofibrinogenemia itself can cause a prolonged PT and PTT, and plasma transfusion alone might not provide sufficient repletion. Cryoprecipitate is likely underused in cardiac surgical patients who are bleeding and refractory to standard plasma and platelets.

Massive Transfusion

Massive transfusion is the acute replacement of more than one blood volume or more than 10 units of packed

RBCs within several hours. In the acute clinical setting, the transfusion of four or more red cell concentrates within 1 hour, when ongoing need is foreseeable, or replacing 50% of the total blood volume within 3 hours may be a more appropriate definition.^{66,67} The most common clinical situation leading to massive transfusion is extensive trauma; however, it also can occur in non-trauma settings during surgical procedures, such as cardiothoracic procedures, associated with large blood loss.^{66,67} Extensive information in this area has been learned from the war in Iraq.^{68–70} Blood transfusion is a main therapy option for treating acute hemorrhage; however, in trauma patients, the ideal solution is fresh whole blood that is not widely available. The etiology of coagulopathy during massive transfusion is complex and it includes dilution, hypothermia, tissue hypoperfusion and ischemia, acidosis, and disseminated intravascular coagulation. Disseminated intravascular coagulopathy can also occur in the setting of cardiac surgery. Treatment of the coagulopathy should include volume replacement including targeted blood component therapy, reestablishment of normothermia, and the correction of acid-base abnormalities. Because of fibrinolysis, an antifibrinolytic should be considered in all cardiac surgical patients. The role of off-label use of prothrombin complex concentrates and recombinant activated factor VII (rFVIIa section) to manage bleeding that cannot be controlled by conventional measures is still evolving⁷¹; however there are interesting studies in cardiac surgical patients supporting its efficacy.⁷²

ADVERSE EFFECTS OF TRANSFUSIONS

The risks of allogeneic transfusion extend beyond viral transmission, and include allergy, alloimmunization, bacterial sepsis, graft versus host disease, transfusion-related acute lung injury (TRALI), renal failure, volume overload, and immunosuppression.^{73–75} Besides possible bacterial contamination, platelet transfusions contain a high concentration of donor white blood cells. Transfusion of donor white blood cells has the potential to produce multiple adverse effects. Cytokines, such as interleukin (IL)-6, IL-8, tissue necrosis factor alpha (TNF- α), and other inflammatory mediators which are concentrated in platelet products could contribute to adverse outcomes.

Platelet concentrates without leukodepletion have been found to be a pro-inflammatory mixture.⁷⁶ Although similar work has not been performed with platelet transfusion, the levels of cytokines, TNF- α , IL-6, and IL-8 are increased 100- to 1000-fold greater than baseline in platelet products.⁷⁶ Since complement and cytokines depress platelet function and increase the release of tissue plasminogen activator, the large influx of proinflammatory mediators from platelet transfusion might mitigate some of the procoagulant function of platelets, increase bleeding, or render platelet transfusions ineffective.⁷⁷

Although active white cells are responsible for producing the high levels of complement and cytokine factors, leukoreduction may be only partially effective in

reducing the immunosuppressive effects of platelets.⁷⁸ In red cell transfusion, leukoreduction can affect T cell activation and expression of key immune molecules on the surface of white cells.⁷⁹ Other mechanisms of immunosuppression not affected by leukoreduction could come into play. The presence of free non-protein-bound iron leads to the activation of white cells (whether allogeneic or autologous).⁸⁰ Furthermore, platelet units treated with leukoreduction and stored at room temperature can increase the number of platelet transfusion units that cause sepsis. The effect of bacterial cell wall material on systemic proinflammatory processes seen during cardiopulmonary bypass is not clear.

Platelet transfusions have long been known to possess a storage lesion leading to decreased effectiveness compared with native circulating platelets.⁸¹ Large percentages of platelets may already be dead and functioning only as cellular shells. This lack of normal cellular activity and regulation may play some role in increasing adverse events. For example, infusion of a platelet product into a patient with an embolic nidus could potentiate thrombus or infarction. Similarly, a prothrombotic potential in a reperfused coronary or cerebral artery could promote thrombus generation if platelet transfusion were additive to thrombotic tendencies. This is best reflected by a study demonstrating platelet transfusions were associated with infection, vasopressor use, respiratory medication use, stroke, and death.⁷⁶

Transfusion-Related Acute Lung Injury

One of the most life-threatening adverse effects of transfusion is TRALI. The incidence of TRALI in cardiac surgical patients may be higher, and a recent report suggests that in-hospital mortality is 13% of patients who develop the complication. TRALI is the leading cause of transfusion-related death via FDA reporting mechanisms.⁸² Clinical presentation of TRALI, in its severe form, is indistinguishable from adult respiratory distress syndrome (ARDS). It is characterized by acute onset (within minutes to 1 to 2 hours after transfusion), bilateral pulmonary infiltrates, and hypoxia without evidence of heart failure.^{73,83,84} TRALI may resolve faster and has a lower mortality rate when compared with ARDS. TRALI usually develops within 6 hours (most often less than 2 hours) of a transfusion, usually resolves within 24 to 72 hours, and has a mortality rate of 5% to 10%. ARDS does not usually develop until at least 24 hours after exposure to one of its risk factors; it often has a duration longer than 72 hours and a mortality approaching 30% to 60%.⁷³ Because of increasing awareness and identification of TRALI and decreases in the incidence of infectious and hemolytic complications of transfusions, TRALI is currently the primary cause of transfusion-associated mortality reported to the FDA and has become a frequent cause of transfusion-related morbidity.⁸⁵ It can occur after the transfusion of various blood components such as RBCs, platelets, and FFP but is most often seen after transfusion of plasma-containing blood components such as FFP and platelets. TRALI can be confused with other transfusion and non-transfusion-related events such as anaphylaxis, hemolysis, circulatory overload, and

cardiac failure. It can manifest with acute shock, florid pulmonary edema, and pulmonary hypertension.^{86,87} Current risk estimates suggest that it occurs in 1 in 8000 to 70,000 units transfused.⁷³

Depending on the causative factor in the transfused component and the inflammatory state of the pulmonary circulation following cardiac surgery, two different but at times complementary and overlapping pathogenic mechanisms are thought to cause TRALI: “the classical-antibody mediated” for most and “the two-hit (inflammatory insult)” for some.^{73,86,88} Most cases of TRALI are due to passive transfer of donor-related antileukocytic antibodies. This occurs far more commonly in multiparous women because of transplacental alloimmunization.⁸⁹ When donor antibodies cross-react with HLA or granulocyte-specific antigens on the patient’s leukocytes,⁷³ priming and activation of granulocytes occur, leading to their pulmonary sequestration and release of proteases, oxidants and leukotrienes. In turn, this causes alveolar epithelial and microvascular endothelial damage resulting in increased permeability and eventual development of noncardiogenic pulmonary edema.

The two-hit model of TRALI is similar to that proposed to cause ARDS. In TRALI, however, the specific causative agent in the blood component is unknown. There is growing evidence associating white cell priming lipids: CD40 ligand released by platelets or several reactive lipid-like substances accumulating in RBCs or platelets during storage. These compounds are referred to as *biological response modifiers* and can be the first pulmonary insult, but are more likely the second. The first insult or hit is generally a systemic inflammatory condition secondary to major surgery, sepsis, trauma, or pulmonary aspiration. The SIRS state causes activation of the pulmonary endothelium and polymorphonuclear lymphocyte (PMN) priming, leading to their sequestration in the pulmonary vasculature. The second hit occurs when the primed PMNs are activated by the biological response modifier in the transfused component. Therapy for TRALI is supportive. Suspected cases of TRALI should be reported to the hospital transfusion service to initiate a suitable investigation. This should include testing of associated donors for antileukocyte and antiplatelet antibodies and typing recipients for HLA antigens (i.e., via leukocytes in a pretransfusion blood specimen or buccal swab technique). If donor leukocyte antibodies that react specifically to the patient’s leukocytes are found, avoiding future transfusion of plasma-containing components from this donor is recommended. The patient, however, is not at an increased risk of TRALI reactions with future transfusion. Recent TRALI mitigation efforts have focused on reducing transfusion of plasma from multiparous donors.⁹⁰

Blood Conservation Strategies

Preoperative Autologous Donation

Preoperative autologous donation is a technique reported in cardiac and noncardiac surgical patients. Because of the urgent need to operate in many patients, the temporal sequence makes this a difficult technique to use in cardiac

surgery. Other questions about the cost-effectiveness of this technique have also been discussed previously. Hospitals and blood banks need specific pathways to isolate and save blood for subsequent operations. Furthermore, in patients with critical cardiac disease, the potential for volume shifts and hemodynamic instability are always concerns. The American Association of Blood Banks guidelines for preoperative autologous donation suggest that no more than 450 mL or 12% of estimated blood volume should be withdrawn at one time, and the patient's hemoglobin concentration should be 11 g/dL or greater at the time of donation. Donations should not be performed more often than every third day. Autologous donation is often performed with preoperative erythropoietin to boost the RBC mass. A recent meta-analysis demonstrated that erythropoietin use with (relative risk [RR] = 0.28; 95% confidence interval [CI], 0.18-0.44; $P < 0.001$) and without autologous donation (RR = 0.53; 95% CI, 0.32-0.88; $P < 0.01$) was associated with a reduction in blood transfusion before cardiac surgery.⁹¹ In addition, a randomized blind control study demonstrated the effectiveness of a very short-term, high-dose erythropoietin protocol in decreasing blood transfusions related to off-pump coronary bypass grafting.⁹¹

Acute Normovolemic Hemodilution

Autologous blood can be collected (15% to 20% of blood volume) in the operating room before operation with accompanying intravascular volume expansion to maintain normovolemia. This technique is often performed in patients with normal to higher red cell masses and calculated intravascular volumes. Reports have showed a 20% to 58% decrease in allogeneic transfusion when autologous blood is retransfused after cardiopulmonary bypass.^{58,109}

Platelet Plasmapheresis

Platelet-rich plasma is harvested using plasmapheresis in the operating room, with RBCs returned through a large-bore central venous access via this catheter. Autologous platelet-rich plasma is retransfused after cardiopulmonary bypass and heparin neutralization. The efficacy of this technique is not well-established and not commonly practiced.^{16,45,52,127}

Red Blood Cell Scavenging Techniques

RBC salvage is commonly used during cardiac surgery.⁹² Shed blood is removed from the surgical field using a specific device and is mixed with an anticoagulant (heparin or citrate). RBCs are separated from plasma and other formed elements by a centrifuge and washed with saline. Salvaged, processed blood is a pure red cell product, diluted with wash solution (typically saline) to a hematocrit between 50% and 60%. Clinicians can also process blood remaining in the extracorporeal circuit in the cell salvage system after separation from cardiopulmonary bypass; however, this technique removes platelets and coagulation factors.

PROHEMOSTATIC AGENTS USED IN SURGERY

Although the standard therapeutic approaches to surgical bleeding are transfusions^{74,76,93}, there are few studies demonstrating their effectiveness.⁹⁴ Bleeding and the need for reexploration can also contribute to mortality.^{44,75} Multiple systemic and topical prohemostatic agents are used during cardiac surgery (Box 51-3). One of the unique aspects in this patient population is the ability to treat preemptively patients for potential causes of bleeding, specifically with antifibrinolytic agents. The multiple agents used will be reviewed in this section.

Antifibrinolytic Agents

Tissue injury during surgery and cardiopulmonary bypass produce direct and indirect activation of complex hemostatic pathways that produce fibrinolysis.^{95,96} There is extensive published research on the use of aprotinin and lysine analogue antifibrinolytics to modify the adverse effects of CPB in adults and pediatric patients.⁹⁷⁻⁹⁹ Efficacy in decreasing bleeding and transfusion is well established, as noted by the recent guidelines published by the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists.²⁵ Although the safety and efficacy of aprotinin has been studied extensively in randomized placebo-controlled studies,⁹⁹ recent reports from observational databases have posed questions, and it has been removed from the market in North America and Europe.^{100,101}

Lysine Analogs: Epsilon Aminocaproic Acid and Tranexamic Acid

The synthetic lysine analogue epsilon aminocaproic acid (EACA or Amicar) and tranexamic acid (TA) inhibit fibrinolysis by attaching to the lysine binding site of the plasmin(ogen) molecule, displacing plasminogen from fibrin.⁵ Levi reported a meta-analysis of all randomized, controlled trials of the three most often used pharmacologic strategies to decrease perioperative blood loss (aprotinin, lysine analogues [EACA and TA], and

BOX 51-3 Pharmacologic Prohemostatic Agents

- Aprotinin
- Lysine analogs
- Protamine
- Desmopressin (DDAVP)
- Recombinant factor VIIa (rFVIIa, NovoSeven)
- Purified prothrombin complex concentrates (PCCs):
 - 3 component: Profilnine, Bebulin
 - 4 component: KCENTRA/Beriplex, Octaplex
- Activated: FEIBA
- Fibrinogen
- Fibrin glue, topical thrombin

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desmopressin). Studies were included if they reported at least one clinically relevant outcome (mortality, re-thoracotomy, proportion of patients receiving a transfusion, or perioperative myocardial infarction) as well as perioperative blood loss. In addition, a separate meta-analysis was performed for studies on complicated cardiac surgery, and 72 trials (8409 patients) met the inclusion criteria.¹⁰² Treatment with aprotinin decreased short-term mortality almost twofold (odds ratio [OR], 0.55; 95% CI, 0.34-0.90) compared with placebo. Treatment with aprotinin and with lysine analogues decreased the frequency of surgical re-exploration (OR, 0.37; 95% CI, 0.25-0.55]; versus OR, 0.44; 95% CI, 0.22-0.90, respectively). These two treatments also significantly decreased the proportion of patients receiving any allogeneic blood transfusion, without increasing the risk of perioperative myocardial infarction.¹⁰²

From the Cochrane database, Henry and colleagues¹⁰³ reported an evaluation of the randomized controlled trials of antifibrinolytic drugs in adults scheduled for nonurgent surgery. Two reviewers independently assessed trial quality and extracted data.¹⁰³ They found 61 trials of aprotinin (7027 participants). Aprotinin reduced the rate of RBC transfusion by a relative 30% (RR = 0.70; 95% CI, 0.64-0.76). The average absolute risk reduction was 20.4% (95% CI, 15.6%-25.3%). On average, aprotinin use saved 1.1 units of RBCs (95% CI, 0.69-1.47) in those needing transfusion. Aprotinin also significantly reduced the need for reoperation for bleeding (RR = 0.40; 95% CI, 0.25-0.66). However, they did not report a decrease in the transfusion of other blood components (i.e., platelets). They also found 18 trials of TA (1342 participants). TA reduced the rate of RBC transfusion by a relative 34% (RR = 0.66; 95% CI, 0.54-0.81). This represented an absolute risk reduction of 17.2% (95% CI, 8.7%-25.7%). TXA use resulted in a saving of 1.03 units of RBCs (95% CI, 0.67-1.39) in those needing transfusion. They found four trials of EACA (208 participants). EACA use resulted in a statistically nonsignificant decrease in RBC transfusion (RR = 0.48; 95% CI, 0.19-1.19). Eight trials made "head-to-head" comparisons between TA and aprotinin. There was no significant difference between the two drugs in the rate of RBC transfusion (RR = 1.21; 95% CI, 0.83-1.76) for TA compared to aprotinin. They also reported that aprotinin did not seem to be associated with an excess risk of adverse effects, including thromboembolic events (thrombosis RR = 0.64; 95% CI, 0.31-1.31) and renal failure (RR = 1.19; 95% CI, 0.79-1.79). The authors infer that aprotinin reduces the need for red cell transfusion and the need for reoperation for bleeding without serious adverse effects. However, the i3 drug study of more than 135,000 patients showed an increased risk of death, renal failure, and heart failure in patients receiving aprotinin. Bayer removed aprotinin from the market in 2008, following the publication of the BART trial.¹⁰⁴ Although fewer studies were reported for TA and EACA, TA appeared to be equally as effective as aprotinin.

Pediatric Patients

Eaton reviews 11 comparative studies of lysine analogues in pediatric heart surgery that included over 1,000

patients.⁹⁷ Most of the studies were prospective, randomized, controlled trials; however, more than half of the studied patients were from a single center (The All India Institute) and included 750 cyanotic patients.⁹³ Two studies involved EACA,^{105,106} three involved TA,¹⁰⁷⁻¹⁰⁹ and one compared both drugs.¹¹⁰ All six studies showed efficacy of antifibrinolytic treatment in decreasing bleeding and transfusion. Twenty-four-hour blood loss was decreased 11% to 44%, and treated patients received 20% to 50% fewer blood transfusions than controls. In addition, sternal closure times were reduced 6 to 25 minutes, and re-exploration rates were improved by 50% to 100%. The benefit of antifibrinolytic treatment is less clear in reoperations. Both EACA and TA appear effective in reducing bleeding and transfusion in cyanotic patients, but the efficacy in other high-risk and mixed populations is not as well proved. A review of antifibrinolytic agents in pediatric patients describes these data in detail.⁹⁷

Protamine

Protamine is a polypeptide composed of approximately 70% arginine residues, and thus has a high pK_a to reverse the acidic molecule heparin by forming a simple acid-base interaction.¹¹¹ Protamine does not reverse low-molecular-weight heparin. Following administration, protamine rapidly reverses heparin as noted by return of activated clotting times, but with marked elevations in plasma concentrations of prothrombin fragment 1.2, thrombin-antithrombin complex, and fibrin monomer.

Protamine can cause adverse reactions including anaphylaxis, acute pulmonary vasoconstriction and right ventricular failure, as well as hypotension.¹¹¹ Different reactions to protamine have been reported ranging from minimal cardiovascular effects to life-threatening cardiovascular collapse. Life-threatening reactions to protamine probably represent true anaphylactic or allergic manifestations, mediated by immunospecific antibodies. Patients with diabetes are at an increased risk for adverse reactions because of the presence of neutral protamine Hagedorn (NPH), which contains insulin and protamine, causing increased protamine sensitization.¹¹¹ Stewart reported a 27% incidence of reactions following cardiac catheterization in insulin-dependent diabetics who were also receiving NPH insulin preparations. Other reports do not corroborate the extreme results of Stewart.¹¹² In a study of 1551 cardiac surgery patients, we reported that the incidence of reactions to protamine was 1 in 50 among patients with NPH-insulin-dependent diabetes, compared with 1 in 1501 among the non-NPH-insulin-dependent patients with diabetes.¹¹³ A subsequent prospective study found that reactions occurred in less than 1% (1/160) of patients with NPH-insulin-dependent diabetes.¹¹⁴ Individuals reported at risk for protamine reactions include patients with vasectomy, multiple drug allergies, and prior protamine exposure.¹¹¹ Levy reported the incidence of life-threatening reactions in cardiac surgical patients ranged from 0.6% to 2% in patients at risk.^{113,114} Currently, there are no clinically available alternatives to protamine.

Desmopressin

Desmopressin (DDAVP) is the V_2 analog of arginine vasopressin that stimulates the release of ultra-large VWF multimers from endothelial cells. DDAVP increases VWF and associated factor VIII levels. In addition, desmopressin induces release of normal VWF from cellular compartments.¹¹⁵⁻¹¹⁸ Von Willebrand disease (VWD) is the most frequent inherited bleeding disorder and is due to quantitative (types 1 and 3) or qualitative (type 2) defects of VWF.¹¹⁹ DDAVP is the treatment for type 1 VWD. DDAVP is not effective in type 3 and in severe forms of types 1 and 2 VWD. Plasma virally inactivated VWF concentrates should be used in bleeding episodes, surgery, and secondary long-term prophylaxis.¹¹⁹

DDAVP should be administered by slow intravenous infusion at a dose of 0.3 μ g per kilogram to avoid hypotension.^{120,121} An initial study reported that desmopressin reduced blood loss and transfusion needs by approximately 30% during complex cardiac surgery.¹²²⁻¹²⁴ Later efforts to reproduce these findings were variable; most did not confirm the marked benefit originally reported.^{121,125} Mannucci noted that there have been 18 trials of desmopressin in 1295 patients undergoing cardiac surgery that show a small effect on perioperative blood loss (median decrease, 115 mL).¹¹⁸ Although DDAVP helps to reduce perioperative bleeding, its effect is too small to influence other, more clinically relevant outcomes such as the need for transfusion and reoperation. Levi noted the rate of myocardial infarctions in patients receiving DDAVP was twice that compared with patients who received placebo, with no improvement in clinical outcomes.¹²⁶ However, another review evaluating 16 trials of DDAVP in cardiac surgery and in other high-risk operations showed that the rate of thrombosis did not differ significantly between patients who received DDAVP and patients who received placebo (3.4% versus 2.7%).¹²⁷

Fibrinogen

Fibrinogen is an important and often neglected coagulation factor that plays a major role in producing effective clot in surgical patients. Fibrinogen levels represent an important predictor of perioperative bleeding.^{94,128} Blome and colleagues¹²⁹ reported that the fibrinogen level after cardiac surgery bypass was inversely correlated with postoperative chest tube drainage volume, but bleeding was not correlated with platelet count, prothrombin time, or activated partial thromboplastin time. Decreased fibrinogen levels are reported to affect the severity of postpartum bleeding adversely. During the third trimester of pregnancy, fibrinogen levels are elevated to greater than 400 mg/dL. For each decrease in fibrinogen level of 100 mg/dL in parturients, odds for bleeding were 2.63-fold higher.¹³⁰ These clinical data highlight critical roles of fibrinogen in the prevention of excessive bleeding. Adequate plasma levels ($\approx$ 200 mg/dL) need to be achieved before administering other procoagulant interventions (e.g., FVIIa). Fibrinogen can be efficiently repleted by human plasma-derived fibrinogen concentrate; otherwise, fibrinogen-rich cryoprecipitate can be given (one

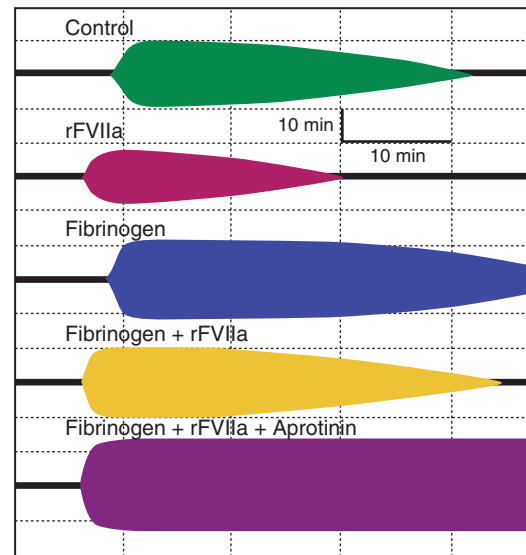


FIGURE 51-3 ■ Thromboelastography recordings obtained with the ROTEM device after the addition of recombinant factor VIIa (rFVIIa), fibrinogen, or both in the presence of tissue-type plasminogen activator in volunteer plasma. Tissue-type plasminogen activator was added to stimulate fibrinolysis. The maximal clot firmness (the width of clot tracing) was only improved after the addition of fibrinogen. The onset of clotting was shorter after the addition of rFVIIa, but the extent of lysis (i.e., decreased clot firmness) was increased in contrast to the samples with fibrinogen. Fibrinolysis was observed after the addition of rFVIIa and fibrinogen, and the clot structure was improved after the addition of an antifibrinolytic aprotinin. rFVIIa was used in a final concentration 1.5 μ g/mL. Fibrinogen was used in a final concentration 100 mg/dL. (From Tanaka KA, Taketomi T, Szlam F, et al: Improved clot formation by combined administration of activated factor VII [NovoSeven] and fibrinogen [Haemocomplettan P]. *Anesth Analg* 106:732-738, 2008.)

unit per 10-kg increases fibrinogen by 50 to 70 mg/dL). In Europe, fibrinogen concentrates are available and cryoprecipitate is not used. Data are accumulating in cardiac surgery demonstrating the effectiveness of fibrinogen in reducing bleeding in cardiac surgical patients as recently reviewed.¹³¹ However, fibrinogen is a critical part of a multimodal therapeutic plan as shown (Fig. 51-3).¹³²

Recombinant Factor VIIa

Recombinant activated factor VII (rFVIIa) is an important example of applying recombinant technology; the ability to synthesize in large quantities specific molecules that are critical for specific biological functions. Although multiple mechanisms for its efficacy have been described, rFVIIa is thought to act locally at the site of tissue and vascular-wall injury by binding to exposed tissue factor, forming small amounts of thrombin that are sufficient to activate platelets.¹³³ The activated platelet surface can then form a template on which rFVIIa directly or indirectly mediates further activation of FXa, eventually forming much more thrombin and leading to the conversion of fibrinogen to fibrin.^{129,130,134,135} In perioperative patients, rFVIIa is an off-label approach to treating refractory bleeding, which is approved in the United States only for treating bleeding in patients with

BOX 51-4 Rescue Therapy with Recombinant Factor VIIa in the Perioperative Setting: Off Label

- Severe (1 L/hr) or life-threatening (central nervous system) bleeding without surgical source of bleeding
- Marginal response to routine hemostatic therapy (i.e., platelets, fresh frozen plasma, cryoprecipitate, desmopressin)
- Judicious use with cardiovascular disease, disseminated intravascular coagulopathy, or ongoing activation (cardiopulmonary bypass)
- Consider lower dose (30 µg/kg)
- Patients with multiple antibodies and platelets or factors not available

Modified from Levy JH: Pharmacologic methods to reduce perioperative bleeding. Transfusion 48:31S–38S, 2008; Goodnough LT, Lublin DM, Zhang L, et al: Transfusion medicine service policies for recombinant factor VIIa administration. Transfusion 44:1325–1331, 2004; and Despotis G, Avidan M, Lublin DM: Off-label use of recombinant factor VIIa concentrates after cardiac surgery. Ann Thorac Surg 80:3–5, 2005.

hemophilia who had antibodies (inhibitors) inactivating infused allogeneic factor VIII or IX concentrates.¹³² Numerous reports described its use in patients following major hemorrhage from surgery, trauma, or spontaneous intracranial hemorrhage.

Initial clinical trials reported that the incidence of thrombotic complications among patients who received rFVIIa was relatively low and similar to that among patients who received placebo.¹³⁶ However, most case reports administering rFVIIa as rescue therapy (Box 51-4) include patients who have impaired coagulation, have received multiple transfusions, and are at a high risk for adverse events. The complex role that transfusion therapy has in producing adverse outcomes is increasingly being noted in the literature. A report using the FDA MedWatch database noted thromboembolic events in patients with diseases other than hemophilia in whom rFVIIa was used on an off-label basis, and included 54% of the events as arterial thrombosis (e.g., stroke, acute myocardial infarction).¹³⁷ Venous thromboembolism (mostly venous thrombosis or pulmonary embolism) occurred in 56% of patients who had thromboembolic events. Thromboembolism was considered the probable cause in 72% of the 50 reported deaths. It is not clear to what extent the clinical conditions requiring the use of rFVIIa may have contributed to the risk of thrombosis.¹¹⁵ Other major issues about rFVIIa include cost and dosing strategies, which are not evidence-based. Randomized studies in cardiac surgery using moderate dosing raised safety concerns; given these and other indications of adverse thrombotic outcomes, further randomized studies are unlikely. However, Mannucci and Levi¹¹⁵ note that rFVIIa has expanded the treatment options for acute hemorrhage in patients with conditions other than hemophilia,¹¹⁵ and use for refractory bleeding continues. In 2009, a phase II dose-escalation trial of activated factor VII was published using 40 µg/kg or 80 µg/kg dosing and a control group. Primary endpoints were adverse events. Secondary events were reoperation rates, blood loss, and

transfusion requirement. While there were more adverse events in the 40-µg/kg group (14%; $P = 0.25$) and the 80 µg/kg arm (12%; $P = 0.11$) versus control (7%), these differences were not statistically significant.

Reversal of Vitamin K Antagonist-Associated Coagulopathy

Older, complex, critically ill patients often receive warfarin and derivative agents for thromboembolic prophylaxis of atrial fibrillation or valvular heart disease. After stopping therapy, the anticoagulant effect of vitamin K antagonists require days to return to baseline, but can be more rapidly reversed by pharmacologic agents such as vitamin K, FFP, and other novel therapies. When warfarin therapy needs to be reversed, patients are given vitamin K at doses of 10 to 20 mg orally or intramuscularly. Although the prothrombin time can reverse in 24 to 48 hours if the patient does not have underlying liver disease, reversal is also dependent on the level of anticoagulation, which affects factor levels. In patients requiring urgent or emergency procedures, the anticoagulation effects cannot be readily reversed by administering FFP. Even after multiple units, the lowest INR to be obtained is approximately 1.5.

Prohemostatic agents are often needed urgently to reverse the anticoagulant effect of these drugs in the perioperative setting. Prothrombin complex concentrates (PCCs) have been originally developed for repleting factor IX in hemophilia B, and they contain a standardized amount of factor IX along with various amounts of other vitamin K-dependent factors (prothrombin, FVII, FX, proteins C and S). PCCs are recommended in guidelines as primary treatment for reversal in patients with life-threatening bleeding and an elevated INR, and rFVIIa may be considered as an alternative.¹³⁸ Evidence suggests that, compared with FFP, PCCs offer quicker INR correction and improved bleeding control; they also have a lower infusion volume and are more readily available without cross matching.^{139–142} Although there are historical concerns regarding potential thrombotic risk with PCCs, present-day PCCs are much improved.¹⁴¹ Although clinicians still use rFVIIa for urgent reversal of warfarin and other vitamin K antagonists, PCCs are more effective in correcting the underlying coagulopathy.^{48,141} Although many patients requiring rapid reversal of warfarin are currently treated with FFP, PCC should be considered as alternative therapy in this setting. A four-component PCC was approved for use in the United States (prothrombin complex concentrate [Kcentra]) in 2013.¹⁴²

Topical Hemostatic Agents

Topical agents are often used as adjunctive measures to promote surgical hemostasis; they include microfibrillar collagen, bovine collagen-based composite mixed with autologous plasma, and fibrin sealants (Box 51-5). Gelatin sponge, or Gelfoam, is purified pork skin gelatin that is intended to augment contact activation and hemostasis. Gelatin substances absorb multiple times their weight in blood. Gelfoam can be applied dry, directly to the

BOX 51-5 Topical Hemostatic Agents

- Gelatin sponge: Gelfoam, purified pork skin gelatin (e.g., Jell-O)
- Oxidized regenerated cellulose: Surgicel or Oxycel, from α -cellulose (plant-based) in knit or microfibrillar form
- Microfibrillar collagen: Avitene (collagen derived from bovine skin)
- Topical thrombin: bovine-derived, human, and human recombinant (Recothrom)
- Fibrin sealants: Tisseal, Crosseal (human fibrinogen, bovine thrombin, aprotinin)

From BleedingWeb.com, with permission.

bleeding surface and pressure applied, or wet in saline. Oxidized regenerated cellulose, also known as Surgicel or Oxycel, is derived from α -cellulose and is plant-based. Surgicel is in “knit form,” and Oxycel comes in a microfibrillar form. These cellulose derivatives are acidic and are thought to cause some small vessel contraction and contact activation. They require an intact hemostatic system to be effective. These agents need to be applied dry, and they absorb within 4 to 8 weeks. Microfibrillar collagen (Avitene) is commonly used in a light flour form, but is also available in a nonwoven web form. This collagen preparation is derived from bovine skin and binds avidly to blood surfaces. A dry field is not necessary to apply the collagen. Avitene causes minimal swelling compared with Gelfoam. Like the other agents, Avitene enhances contact activation. Collagen sponges, derived from bovine Achilles tendon or bovine skin, are similar to Avitene and have the same mechanism of action derived from bovine Achilles tendon or bovine skin, and they work basically the same way.

Other types of hemostatic agents are based on topical thrombin used alone or in combination with other agents. In 1999, Floseal was made available; it consists of bovine thrombin plus cross-linked gelatin granules mixed together. Floseal attained higher rates of hemostasis and shorter times to hemostasis than other hemostatic agents did in a prospective, randomized single-center trial. Fibrin sealants, including Tisseal and CoSeal are combinations of purified human fibrinogen, bovine or human thrombin, with an antifibrinolytic agent to prevent clot lysis.¹⁴³ These agents require a relatively dry field. There are also institutionally based autologous fibrin sealants, in which fibrinogen and thrombin are taken from a patient's plasma or platelet gel from autologous platelets is obtained.

One of the major problems with bovine thrombin is the formation of antibodies that can cross-react with patient thrombin and factor V to produce complications ranging from anaphylaxis to bleeding.¹⁴⁴⁻¹⁵⁰ As a result, both purified and recombinant human thrombin has been developed. Human thrombin is available as Evithrom, and recombinant thrombin is available as Recothrom.¹⁵¹ Human thrombin is purified by extensive means, but it still carries the label “May carry a risk of transmitting infectious agents such as viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent,

despite manufacturing steps designed to reduce the risk of viral transmission.”

Overall, Gelfoam, Surgicel, Avitene, and these collagen sponges can be stored at room temperature, and they are ready to use out of the box. Floseal requires a 2- to 5-minute preparation time. Thrombin is mixed with calcium, and the combination is added to the gelatin granules. Fibrin sealants must be kept in cold storage and thawed before use. The preparation time can be up to 20 to 30 minutes.

SURGICAL APPROACH

Transcatheter approaches to performing cardiac surgical procedures are associated with lower transfusion rates. A study comparing transcatheter versus surgical aortic valve replacement in high-risk patients demonstrated a significant reduction in major bleeding events in the TAVR group (9.3% versus 19.5%; $P < 0.001$). Similarly, a meta-analysis comparing endovascular aortic repair versus open surgical repair of descending thoracic aortic disease demonstrated a significant reduction in transfusion rates and in the incidence of reoperation for bleeding.

BLOOD CONSERVATION PROGRAMS

Evidence is accumulating in support of the efficacy of targeted programs to reduce blood utilization safely. Brevig and colleagues published their experience with the creation of a multidisciplinary program at a community hospital.¹⁵² This retrospective, single-center study included more than 2500 patients with a primary outcome of RBC transfusions. Self-identified essential features of their program included surgeon attention to hemostasis, perfusion strategies to reduce hemodilution, a blood conservation coordinator, a treatment protocol for anemia management, a physician champion, an institutional multidisciplinary commitment to reduce transfusion, and review of provider-specific data. They demonstrated a significant reduction in the percentage of patients receiving transfusions. A recent study from the Virginia Cardiac Surgery Quality group examined the effects of a blood conservation initiative with defined transfusion triggers on risk-adjusted mortality and morbidity. This retrospective, multicenter study involved more than 14,000 CABG patients. Intraoperative (24% versus 18%; $P < 0.001$) and postoperative (39% versus 33%; $P < 0.001$) transfusion rates were reduced in the post-guideline period. In addition, the reduced transfusion rates were associated with lower mortality rates and a lower incidence of pneumonia, prolonged ventilation, and renal failure. In Michigan, a multicenter quality collaborative focused on blood use as a quality metric. In 2008, institutional blood transfusion rates were added to the list of measures. There was also an educational program focused on blood transfusion risks and methods and benefits of blood conservation. The primary outcome was transfusion rates of RBCs, FFP, and platelets. Transfusion rates of all products decreased from 2008 to 2012 ($P < 0.001$ for all). This result was associated with decreased rates of deep sternal

infection, reoperation for bleeding, prolonged ventilation, renal failure, and length of stay in the intensive care unit. There was no change in mortality. Additional evidence in support of the safety of blood conservation programs comes from the Cleveland Clinic experience with Jehovah's Witnesses undergoing cardiac surgery. More than 300 Jehovah's Witnesses underwent cardiac surgery over an 18-year period. When compared with matched patients who received transfusions, Witnesses had fewer complications and a shorter length of stay. Hospital mortality was similar in the two groups (3.1% versus 4.3%; $P=0.4$). The evidence indicates that cardiac surgery with blood conservation is associated with better results than conventional care.

SUMMARY

Cardiac surgical patients are at significant risk for bleeding. Certain patients are at a greater risk for bleeding and a need for transfusions. Variables that are important risk factors include (1) advanced age, (2) low preoperative RBC volume (preoperative anemia or small body size), (3) preoperative antiplatelet or antithrombotic drugs, (4) reoperative or complex procedures, (5) emergency operations, and (6) certain noncardiac patient comorbidities. Perioperative interventions are likely to reduce bleeding and the need for blood transfusion. Blood conservation interventions include use of antifibrinolytic drugs, selective use of off-pump coronary artery bypass graft surgery, routine use of a cell-saving device, and implementation of appropriate transfusion indications. An important intervention is the application of a multimodality blood conservation program that is institution-based and is accepted by all health care providers, and that involves well-planned transfusion algorithms to guide transfusion decisions. Evidence-based blood conservation techniques include (1) drugs that increase preoperative blood volume (e.g., erythropoietin) or decrease postoperative bleeding (e.g., antifibrinolytics), (2) devices that conserve blood (e.g., intraoperative blood salvage and blood-sparing interventions), (3) interventions that protect the patient's own blood from the stress of operation (e.g., autologous predonation and normovolemic hemodilution), (4) consensus, institution-specific blood transfusion algorithms supplemented with point-of-care testing, and most importantly, (5) a multimodality approach to blood conservation combining all the above.

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DIAGNOSTIC PROCEDURES

PART OUTLINE

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| 52 | CORONARY ANGIOGRAPHY: VALVE AND HEMODYNAMIC ASSESSMENT | 54 | NUCLEAR CARDIOLOGY AND POSITRON EMISSION TOMOGRAPHY IN THE ASSESSMENT OF PATIENTS WITH CARDIOVASCULAR DISEASE |
| 53 | APPLICATIONS OF CARDIOVASCULAR MAGNETIC RESONANCE AND COMPUTED TOMOGRAPHY IN CARDIOVASCULAR DIAGNOSIS | 55 | DIAGNOSTIC ECHOCARDIOGRAPHY (ULTRASOUND IMAGING IN CARDIOVASCULAR DIAGNOSIS) |

CORONARY ANGIOGRAPHY: VALVE AND HEMODYNAMIC ASSESSMENT

Alexander G. Truesdell • J. Dawn Abbott

CHAPTER OUTLINE

DIAGNOSTIC CATHETERIZATION TECHNIQUES

Indications
Contraindications
Complications

CORONARY ANGIOGRAPHY

Vascular Access
Left Coronary Angiography
Right Coronary Angiography
Coronary Anomalies
Angiographic Projections
 Left Main Coronary Artery
 Left Anterior Descending Coronary Artery
 Left Circumflex Coronary Artery
 Right Coronary Artery
Bypass Graft Angiography

LESION STRUCTURAL AND FUNCTIONAL ASSESSMENT

Fractional Flow Reserve
Intravascular Ultrasound

HEMODYNAMIC EVALUATION

Principles
Right Heart Catheterization

Pressure Waveforms

Right Atrium
Right Ventricle
Pulmonary Artery
Pulmonary Capillary Wedge Pressure
Systemic Arterial Pressure

Cardiac Output

SHUNTS

Left-to-Right Shunts
Right-to-Left Shunts
Bidirectional Shunts

VASCULAR RESISTANCE

VALVULAR HEART DISEASE

Aortic Stenosis
Aortic Regurgitation
Mitral Stenosis
Mitral Regurgitation

PERICARDIAL DISEASE

Pericarditis
Cardiac Tamponade
Constriction-Restriction

CONCLUSION

Cardiac catheterization and coronary angiography are essential tools in the diagnosis and evaluation of coronary and valvular heart disease, with several million procedures performed annually in the United States. Significant technological advances have occurred since the insertion of the first intravascular catheter by Werner Forsman in the 1920s,¹ the first selective coronary catheterization by F. Mason Sones in 1956,² and the first coronary angioplasty by Andreas Grüntzig in 1977.³ Today, angioplasty and stenting are the predominant modes of catheter-based intervention in all major vascular beds.

Coronary artery disease (CAD) is the leading cause of death in the United States,⁴ a statistic that has remained relatively stable over several decades despite landmark improvements in primary and secondary prevention as well as rapid catheter-based emergency management of acute coronary syndromes.⁵ Morbidity from CAD is

likewise a major public health issue because of increasing numbers of survivors with resultant congestive heart failure (CHF).⁶

DIAGNOSTIC CATHETERIZATION TECHNIQUES

Indications

The most common indications for the performance of diagnostic cardiac catheterization are to assess for the presence, extent, and severity of clinically suspected CAD, or to evaluate the severity of noncoronary valvular or myocardial disorders, particularly when a surgical or percutaneous intervention is contemplated.⁷⁻¹¹ The decision to perform invasive coronary angiography or

BOX 52-1 Relative Contraindications to Cardiac Catheterization and Coronary Angiography

- Active bleeding or severe anemia
- Severe coagulopathy
- Advanced renal dysfunction
- Uncontrolled hypertension
- Significant electrolyte imbalance (e.g., severe hypokalemia)
- Active infection or unexplained fever
- Acute or subacute stroke
- Decompensated heart failure preventing patient positioning or oxygenation

BOX 52-2 Possible Complications of Cardiac Catheterization

- Death: 0.1% to 0.2%
- Myocardial infarction: 0.1%
- Stroke: <0.4%
- Vascular complication: 2% to 5%
- Severe contrast reaction: <0.2%
- Renal failure: 1% to 30%

hemodynamic testing should be based on a careful analysis of the indications, risk-to-benefit ratio, and alternatives, to best identify patients who will benefit most from the procedure.¹²

Contraindications

There are few absolute contraindications to cardiac catheterization other than patient refusal. The principle relative contraindications include active bleeding, severe anemia, coagulopathy, uncontrolled hypertension, significant electrolyte abnormalities, advanced renal dysfunction, active infection, decompensated heart failure precluding adequate patient positioning, and recent stroke (Box 52-1).¹¹

Complications

The overall risk of major complications resulting from diagnostic cardiac catheterization is less than 1%, although non-major vascular access site complications such as non-life-threatening bleeding or pseudoaneurysm formation can be as high as 3% with femoral artery access in patients with peripheral arterial disease.¹³ In addition, catheter manipulation in atherosclerotic vessels can lead to emboli (thrombus, atherosclerotic debris, calcium, or air) or clot formation, potentially leading to stroke, myocardial infarction, worsening renal function, or CHF (Box 52-2).

CORONARY ANGIOGRAPHY

Coronary angiography is performed by selective injection of the coronary arteries. In rare instances, nonselective coronary imaging or aortography can also be performed

to identify ostia of native coronary arteries that are difficult to locate (predominantly those with anomalous origins) or bypass grafts.

Vascular Access

The most common access site for coronary angiography in the United States remains the femoral artery, although axillary, brachial, and radial approaches can also be used.¹⁴ The transradial approach to cardiac catheterization, first introduced by Lucien Campeau in 1989,¹⁵ is being used increasingly for diagnostic coronary angiography and percutaneous coronary interventions, primarily because of its lower bleeding rates, reduced access site complications, improved patient comfort, and reduced length of stay and hospital costs.¹⁶⁻²⁰ Although adoption of radial access in the United States has been slow compared with other parts of the world, the number of procedures performed transradially increased from 3% in 2008 to more than 8% in 2011, and it is predicted to rise to more than 20% in 2015.²¹ Internationally, there are many centers that currently perform more than 95% of procedures via the transradial approach.

Challenges that are unique to the transradial approach include difficulty traversing a spastic radial artery or a tortuous radiobrachial or thoracic artery (Fig. 52-1).^{17,22} Postprocedural permanent radial artery occlusion occurs infrequently,²³ and it is typically clinically silent because of the dual blood supply to the hand. Radial occlusion can, however, affect future use of the radial artery as a bypass conduit.²⁴ Laboratory studies have demonstrated reduced flow-mediated dilation and intimal hyperplasia, which could theoretically reduce radial artery graft patency in the radial arteries of patients who have undergone prior transradial catheterization.²⁵⁻²⁷

The most common method of vessel cannulation is the Seldinger technique.²⁸ In this technique, the vessel of interest is punctured, and a guidewire (usually an 0.035-inch J-tipped wire) is advanced into the vessel.^{29,30} The J-tipped wire then serves as a rail over which a dilator and sheath enter the vessel. For radial artery catheterization, a micropuncture needle with a 0.018-inch wire and a specialized radial sheath with a hydrophilic coating are used instead. Once access is obtained, the sheath acts as an entry point for passage and exchange of all catheters and devices, generally over the 0.035-inch J-tipped wire. After a catheter is advanced into the ascending aorta, the guidewire is withdrawn and the catheter is connected to a manifold system that allows, in a closed system, the ability to simultaneously inject contrast and transduce pressures at the catheter tip. The catheter is then cleared and advanced, with continuous pressure monitoring, into the ostia of the coronary artery. If the pressure waveform dampens or the catheter fails to backbleed, a significant ostial coronary artery lesion, unfavorable catheter engagement angle, catheter kinking, or entrapment of thrombus or atheroma should be suspected. Care should always be taken during engagement and injection of any coronary artery to avoid potentially fatal complications such as introduction of air, vessel dissection, intubation of a critical left main lesion, or disruption of atherosclerotic lesions.

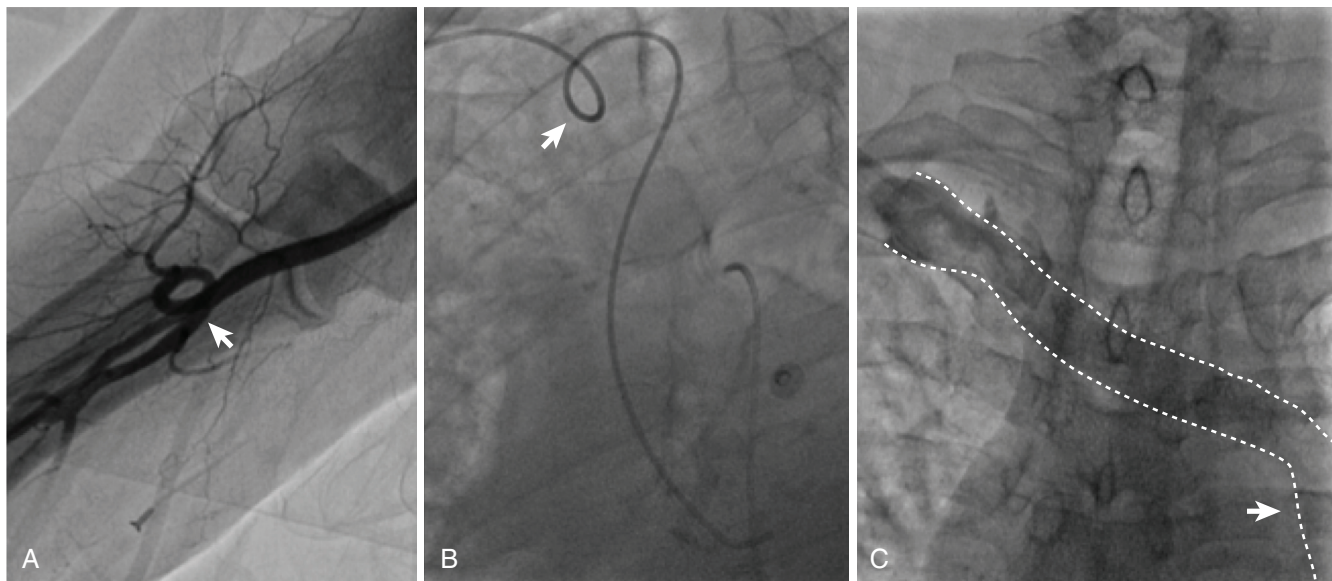


FIGURE 52-1 ■ **A**, Radial artery loop. **B**, Tortuosity of the right subclavian artery. **C**, Venogram of congenitally absent right superior vena cava (SVC) and persistent left SVC (arrow) performed during attempted right heart catheterization via the right antecubital vein.

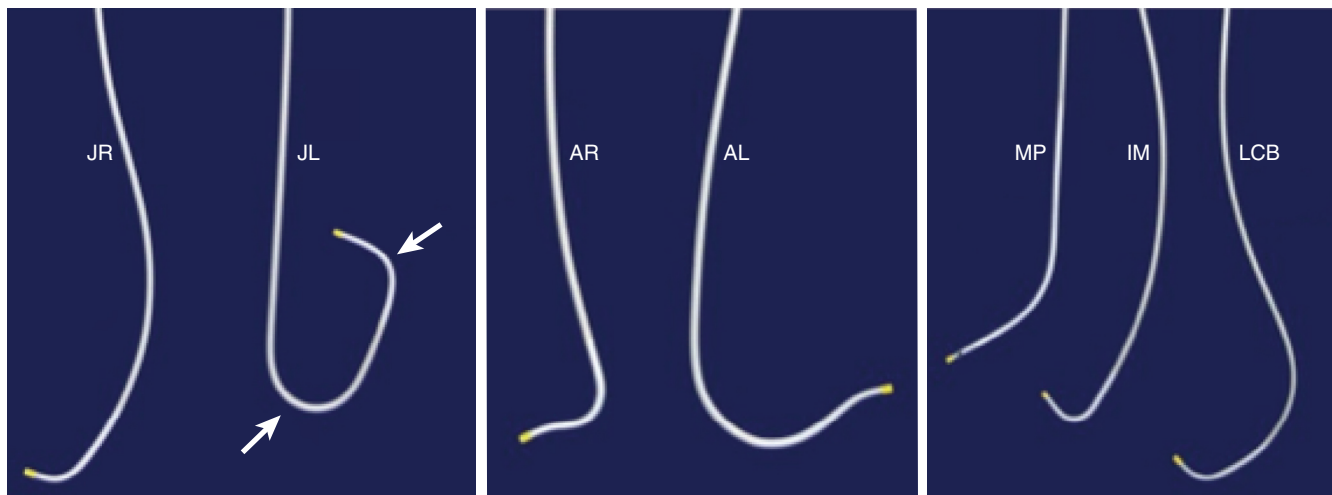


FIGURE 52-2 ■ Representative tip configurations and catheters used in diagnostic coronary angiography: Judkins right (JR) and left (JL) catheters. The primary (*upper arrow*) and secondary (*lower arrow*) curves of the Judkins left catheter are shown; Amplatz right (AR) and left (AL) catheters; multipurpose (MP) catheter; internal mammary (IM) catheter; and left coronary bypass (LCB) catheter.

Accurate delineation of coronary anatomy and identification of coronary stenoses is dependent on the acquisition of multiple orthogonal views to enable full visualization of all coronary segments without foreshortening or overlap. Preshaped coronary catheters are used to engage the left and right coronary arteries selectively. The choice of a specific diagnostic catheter is influenced by the site of arterial access, the size of the aortic root, and the anatomic take-off of the coronary arteries. Typically, a Judkins left 4-cm catheter (JL4) and a Judkins right 4-cm catheter (JR4) are used as the default catheters for left and right coronary angiography, respectively, via the femoral approach (Fig. 52-2). Transradial coronary angiography can generally be performed using femoral catheter curves without difficulty; however, a shorter JL curve and longer JR curve may be required for a proper

fit from the right radial approach. In addition, several universal catheters are also available for transradial use for both right and left coronary angiography, and often left ventriculography as well, such as the Kimny, Jacky, or Tiger catheters.

Left Coronary Angiography

Safe cannulation of the left main (LM) coronary ostium is best ensured by confirming that the pressure tracing is neither dampened nor ventricularized. The default JL4 catheter is successful in engaging the left main ostium approximately 80% of the time. If the aortic root is dilated or unusually narrow, longer or shorter catheters (JL5 or JL3.5) may be required, whereas a posterior origin of the left main is often best imaged using an Amplatz catheter.

Coronary anatomy is defined during angiography with contrast injections of 8 to 10 mL during cineangiography runs. The imaging angles used during angiography permit three-dimensional reconstruction of the coronary anatomy using orthogonal views to visualize each artery and its ostial, proximal, mid, and distal segments in multiple planes.

The left coronary system begins with the left main, which terminally bifurcates into the left anterior descending (LAD) and left circumflex (LCX) coronary arteries. In approximately one third of patients, the LM terminally trifurcates into the LAD, the LCX, and an intermediate branch (the ramus intermedius coronary artery) that supplies much of the left ventricular free wall.³¹ The LAD artery gives off septal branches as it courses down the interventricular groove and diagonal branches, which supply the anterolateral free wall of the left ventricle. The LCX, as it courses in the atrioventricular (AV) groove, gives off obtuse marginal branches that supply the lateral free wall of the left ventricle (Fig. 52-3).

Right Coronary Angiography

The right coronary artery (RCA) is usually engaged with a JR4 catheter. The RCA courses in the interventricular groove and gives off acute marginal and right ventricular branches that supply the right ventricular free wall. The RCA terminally bifurcates at the crux of the heart to form the right posterolateral branch (PLB) and the right posterior descending artery (PDA), which supply the inferolateral segments of the left ventricle, the inferior wall, and posterior interventricular septum (see Fig. 52-3).

The dominance of the coronary circulation depends on which artery supplies the posterior circulation—the PDA or the PLB. Approximately 60% of the population is right-dominant (the RCA provides both of these branches), 25% is codominant (the RCA supplies the PDA and the LCX gives off the PLB), and 15% is left-dominant (the LCX provides both of these branches).³²

Coronary Anomalies

Several coronary anomalies (Fig. 52-4) exist in addition to the typical coronary anatomy described earlier. Most are simple anatomic variants, such as dual ostia for the LAD and LCX, whereas others are congenital abnormalities, such as an anomalous origin of the LCX from the RCA.³³⁻³⁶ Most of these congenital anomalies have little effect on coronary circulation; however, in the case of the LM or LAD originating from the RCA or right coronary cusp and coursing posteriorly between the aorta and pulmonary artery, there is an associated increased mortality, usually secondary to arrhythmias and ischemia.

Angiographic Projections

When performing angiography of the coronary circulation, it is critical to obtain multiple views of each vessel in various orthogonal planes to define all the segments fully and clearly. Methodical, comprehensive angiography with orthogonal angulation prevents an operator missing a significant coronary lesion, which may be evident in only one plane but not another. By convention, all views are reported with left or right angulation first,

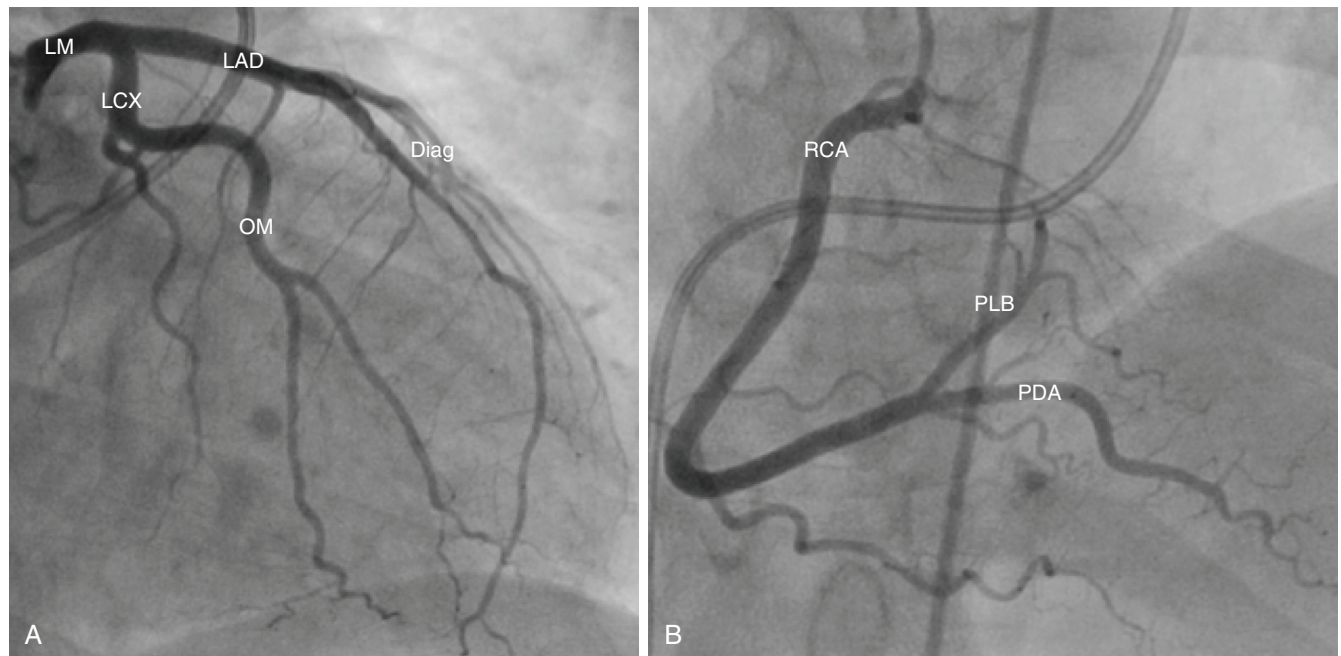


FIGURE 52-3 ■ Coronary angiography of the left (A) and right (B) coronary arteries in the right anterior oblique caudal (A) and left anterior oblique cranial (B) projections. *Diag*, Diagonal artery; *LAD*, left anterior descending artery; *LCX*, left circumflex artery; *LM*, left main artery; *OM*, obtuse marginal artery; *PDA*, posterior descending artery; *PLB*, posterolateral branch artery; *RCA*, right coronary artery.

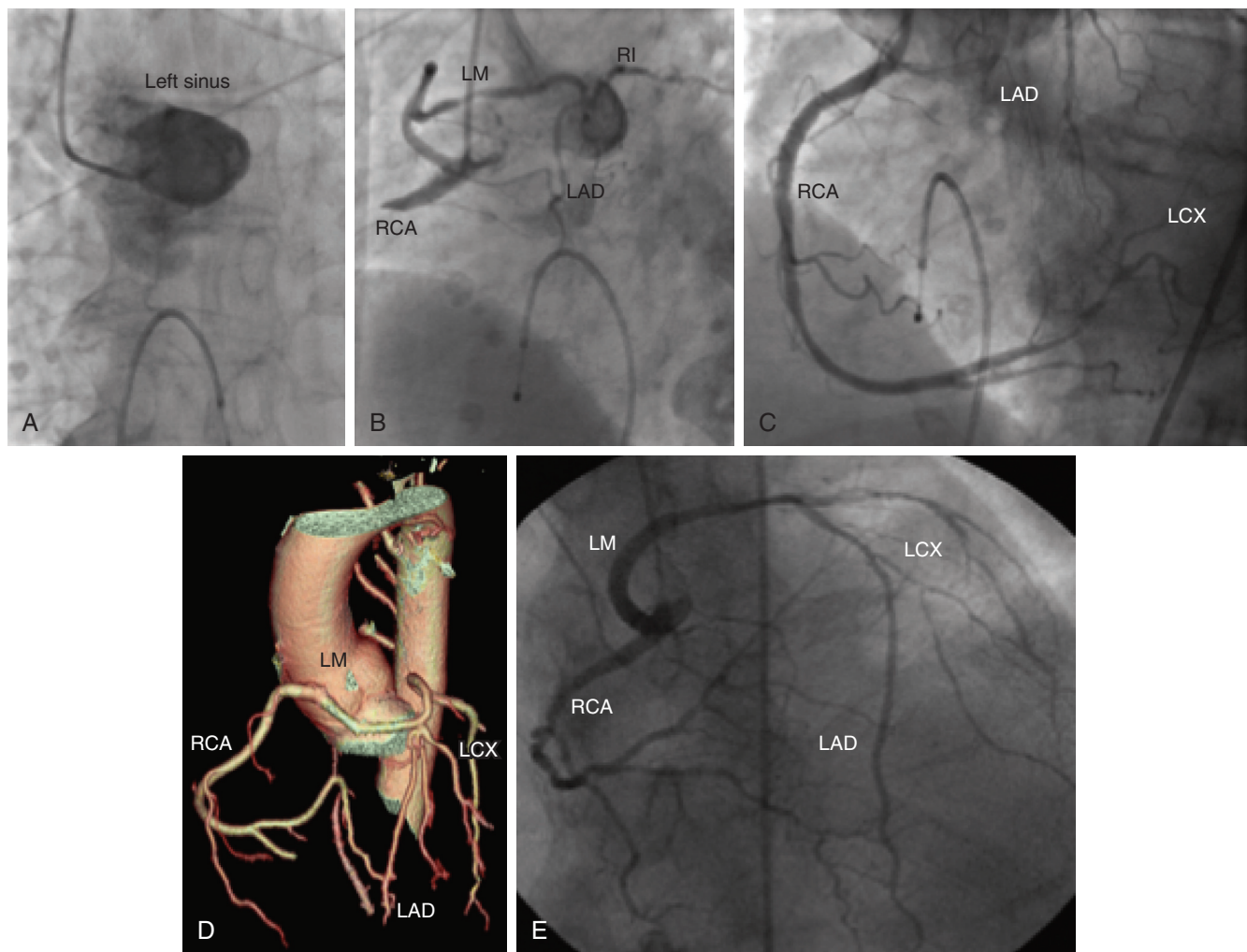


FIGURE 52-4 ■ **A**, Nonselective angiogram of the left coronary sinus in an 81-year-old woman presenting with an acute inferior myocardial infarction and cardiogenic shock, demonstrating absence of coronary arteries arising from the left coronary cusp. **B**, Selective angiogram of the right coronary artery in the same patient revealing an anomalous origin of the left main coronary artery (LM) from the right coronary artery (RCA) and acute thrombotic occlusion of the proximal RCA. **C**, Angiography in the same patient after successful angioplasty of the RCA, now also demonstrating well-established collateral vessels to a severely diseased left circumflex coronary artery (LCX). **D**, Cardiac computed tomography angiogram three-dimensional reconstruction with virtual dissection of a similar anomalous LM arising from the RCA in a 21-year-old woman. **E**, Angiogram from a 54-year-old man with similar anatomy in the left anterior oblique cranial projection. The entire coronary system is visualized from a single ostium located at the right coronary sinus. The RCA and LM trunk arise together, and the LM divides into the left anterior descending (LAD) and LCX branches. *RI*, Ramus intermedius coronary artery.

followed by the degree of cranial or caudal angulation. For example, a 30/25 left anterior oblique (LAO)/cranial view represents 30 degrees of LAO angulation with 25 degrees of cranial angulation.

All major coronary arteries lie in one of two planes: the interventricular septum or the atrioventricular groove (Fig. 52-5). Standard angiographic projections are designed to display the coronary anatomy in profile in these planes. For example, the right PDA in its course along the interventricular septum and the inferior wall is best seen with the interventricular septum in its longest profile—the right anterior oblique (RAO) projection. On the other hand the LCX, which courses along the AV groove, is best visualized in the anteroposterior (AP) or RAO caudal projection, looking at the AV groove in profile.

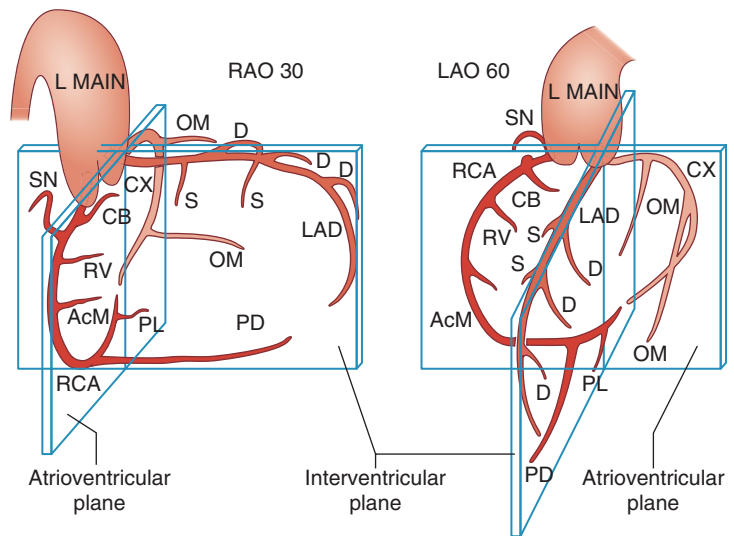
Left Main Coronary Artery

The LM coronary artery is best seen in a shallow LAO projection with slight caudal angulation to visualize its middle and distal segments optimally, and with cranial angulation to improve visualization of its proximal and ostial segments. Another helpful view is the steep LAO caudal (also called the *spider view*) which lays out the terminal left main bifurcation. Unfortunately, this last view is not helpful in the case of a horizontally positioned heart, in which situation a steep RAO caudal view is substituted.

Left Anterior Descending Coronary Artery

The LAD courses anterior and inferior to the LM, enters the interventricular groove, and then travels to the apex

FIGURE 52-5 ■ Representation of coronary anatomy in relationship to the interventricular and atrioventricular valve planes as seen in two views: right anterior oblique (RAO) and left anterior oblique (LAO). Coronary branches are as follows: *AcM*, Acute marginal; *CB*, conus branch; *CX*, circumflex; *D*, diagonal; *L Main*, left main; *LAD*, left anterior descending; *OM*, obtuse marginal; *PD*, posterior descending; *PL*, posterolateral left ventricular; *RCA*, right coronary; *RV*, right ventricular; *S*, septal; *SN*, sinus node. (Reprinted with permission from Baim DS: *Coronary angiography. In Baim DS, Grossman W, editors: Grossman's cardiac catheterization, angiography, and intervention*, ed 6, Philadelphia, 2000, Lippincott Williams and Wilkins.)



of the heart. No single view adequately depicts the entire course of the LAD. The proximal LAD is best visualized in steep LAO projections with cranial angulation, whereas the middle and distal segments are better seen in LAO and RAO views with some caudal angulation. In some cases, when the proximal LAD is not well seen in standard views (e.g., with a horizontally oriented heart), a 30 RAO/30 cranial angle better lays out the proximal LAD and LM bifurcation.

The diagonal arteries, the major branches of the LAD, course off the LAD toward the lateral free wall of the left ventricle. The best view for most of the diagonal arteries, to include their origin and distal segments, is usually a steep LAO (50 degrees) with steep cranial (50 degrees) angulation. In some cases, there is only one diagonal branch off the LAD—sometimes referred to as a *twin LAD* given its large area of subtended myocardium.

Left Circumflex Coronary Artery

The LCX is best seen in caudal projections. The proximal portion of the LCX is usually imaged in the RAO caudal angulation, which also lays out the marginal arteries. An alternative view for the mid segment of the LCX and the marginal arteries is the steep LAO caudal (spider) view. In obese patients, however, this latter view can be challenging, because the x-ray has to penetrate extra tissue, resulting in a distorted, dark, or hazy image.

Right Coronary Artery

The RCA enters the anterior AV groove and courses distally. The proximal segment of the RCA is best seen in the flat LAO angulation. For optimal visualization of the ostium, a steep (50 degrees) LAO projection is preferred. The mid segment of the RCA is best seen in the LAO and flat RAO projections. The crux, or distal RCA, and the proximal portions of the right PDA and PLB arteries are best seen with an AP or slight LAO projection with 20 to 30 degrees of cranial angulation. Finally, the middle and distal segments of the right PDA are best visualized with a flat RAO projection.

Bypass Graft Angiography

Saphenous vein grafts (SVG) to the right and left coronary circulations are commonly sutured onto the anterior surface of the aorta, several centimeters from the sinus of Valsalva (Fig. 52-6). RCA grafts generally arise from the right anterior aorta, whereas left coronary artery grafts usually originate from the left anterior aorta. LAD grafts are conventionally placed below LCX grafts. In some cases, the surgeon can also place a ring at the origin of a graft to facilitate identification of its origin off of the aortic root in the event of future angiography. The optimal views for engaging and imaging bypass grafts are flat LAO and RAO projections, which lay out the grafts in their greatest profile. The distal (native) vessel beyond the anastomosis is best imaged with the addition of cranial or caudal angulation to define all of the vessel segments fully (cranial for the LAD and RCA and caudal for the LCX; see Fig. 52-6).

In recent decades, the internal mammary artery (IMA) has emerged as the conduit of choice for the LAD, and in some cases for the RCA, because of the high patency rates of this conduit.³⁷ During angiography, the IMA is cannulated after engagement of the subclavian artery with the coronary catheter and J wire. The catheter is advanced into the subclavian artery and cleared, the J wire is withdrawn, and gentle counterclockwise torque is applied until the catheter engages the origin of the left IMA (LIMA). Once the vessel is engaged, the catheter is gently torqued clockwise to remove any excess tension.³⁸ Selective cannulation of an IMA graft can be challenging from the femoral approach in patients with peripheral or subclavian tortuosity. In these cases, the ipsilateral radial artery approach may better facilitate selective IMA engagement. Typical views for optimal angiography of the LIMA are AP or slight RAO (0-20 degrees)/cranial (40 degrees) to visualize the proximal and mid segments of the graft, and steep flat LAO or lateral projections to reveal the anastomosis of the LIMA with the native LAD. The right IMA conduit is similarly engaged from the right subclavian artery. The views for the mid-segment, origin, and anastomosis of this graft are typically flat

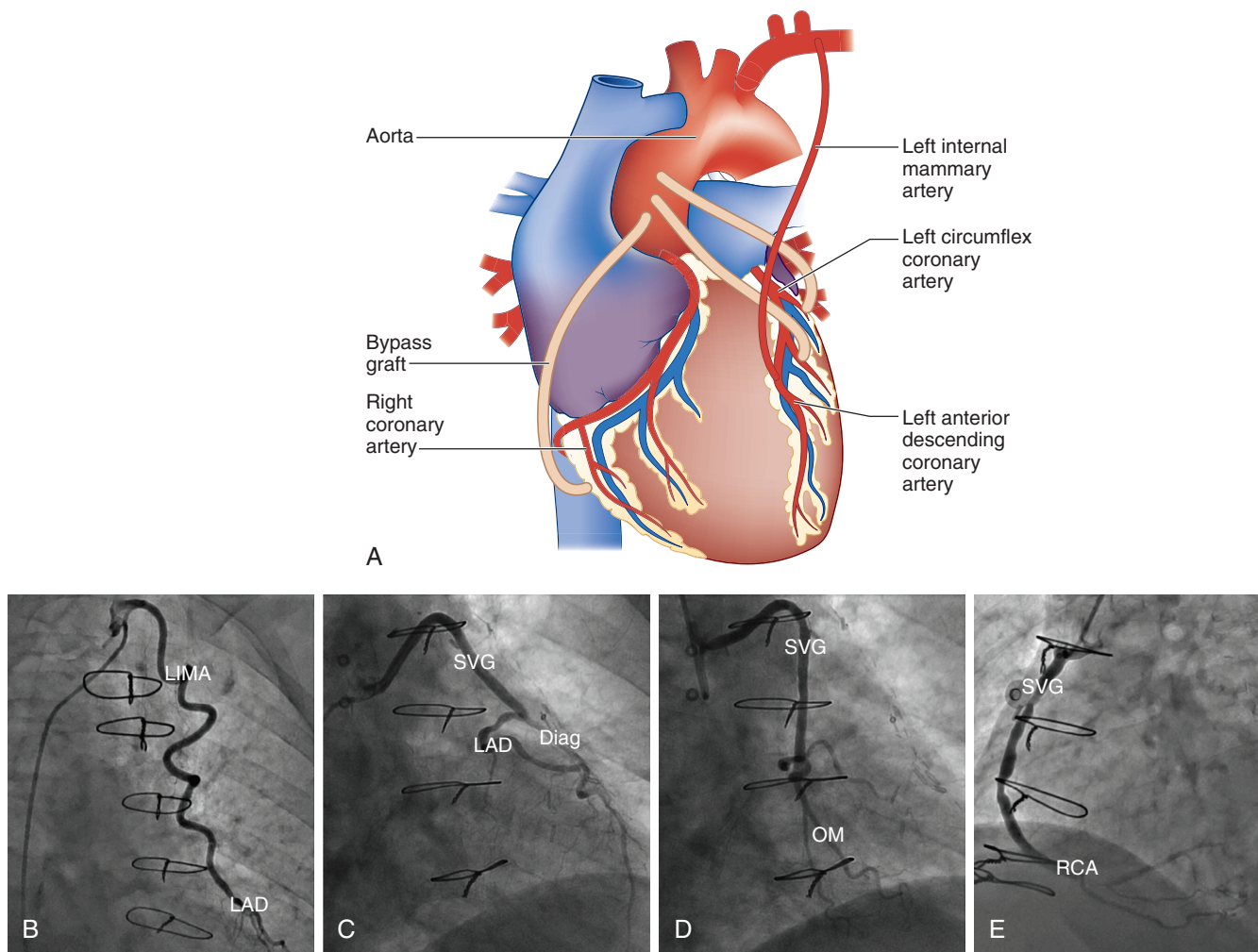


FIGURE 52-6 ■ Graft angiography. **A**, Common location of coronary artery bypass grafts to the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), diagonal branch (Diag), and right coronary artery (RCA). **B**, Angiogram of left internal mammary artery (LIMA) to LAD graft. **C**, Saphenous vein graft (SVG) to Diag. **D**, SVG to obtuse marginal branch (OM). **E**, SVG to the right coronary artery (RCA).

LAO with some cranial angulation and steep AP cranial angulation, respectively.

LESION STRUCTURAL AND FUNCTIONAL ASSESSMENT

Catheter-based invasive modalities are of profound clinical importance in accurately assessing coronary anatomy and physiology.^{39,40} Although coronary angiography provides unsurpassed temporal and spatial resolution compared with noninvasive imaging,⁴¹ it is often confounded by diffuse reference vessel disease, lesion foreshortening, vessel angulation, vascular calcification, lesion eccentricity, vessel overlap, and contrast streaming.⁴² Because of these limitations, the addition of precise morphologic, histologic, and functional information to angiography-only assessment through the use of adjunctive technologies such as fractional flow reserve (FFR) and intravascular ultrasound (IVUS) is indispensable to tailoring the treatment of patients with known or suspected coronary disease.

Fractional Flow Reserve

Inducible myocardial ischemia during functional testing has crucial prognostic significance in determining whether to treat angiographically indeterminate coronary artery lesions (those with an angiographic stenosis of 40% to 70%).⁴³⁻⁴⁶ In real-world practice, however, fewer than half of all patients undergo noninvasive evaluations for myocardial ischemia before coronary angiography.^{43,44} Integrating coronary physiology in the cardiac catheterization laboratory, principally using FFR, provides critical objective and accurate data about the ischemic potential of specific lesions, beyond angiographic anatomic details, and correlates well with noninvasive ischemic stress testing results.^{40,47}

FFR is the ratio of maximal myocardial blood flow in the case of a diseased artery to maximal myocardial blood flow if that same artery were normal.⁴⁸ This ratio of two flows can be accurately derived from the measurement of two pressures, provided they are measured during maximal hyperemia. During the procedure, a 0.014-inch pressure sensor guidewire is advanced beyond a coronary

stenosis and under conditions of pharmacologically induced maximal hyperemia (typically with intravenous adenosine) distal pressure (Pd) is recorded and divided by guiding catheter pressure (Pa), where:

$$FFR = Pd / Pa$$

To assess serial lesions or diffuse CAD, the pressure wire can be pulled back steadily from the distal to proximal vessels during continuous hyperemia, possibly demonstrating either an abrupt change in distal pressure across a focal narrowing or the gradual pressure recovery of diffuse disease without focal obstructions.

FFR is not influenced by systemic hemodynamics or contractile state; it is lesion and vessel specific, takes into account the contribution of collateral circulation, relates stenosis severity to the mass of subtended myocardium, and is highly reproducible.^{47,49} FFR also has a well-defined and validated cutoff value. Coronary stenoses with an

FFR < 0.75 almost uniformly induce myocardial ischemia, whereas stenoses with an FFR > 0.80 are rarely associated with exercise-induced ischemia, with a narrow “gray zone” for values between 0.75 and 0.80.^{41,49} In multiple studies, FFR has demonstrated clear utility in the assessment of angiographically indeterminate lesions,^{50,51} left main stenosis,^{52,53} multivessel disease,^{54,55} sequential stenoses (Fig. 52-7),⁵⁶ diffuse disease,⁵⁷ and bifurcation lesions.⁵⁸

In the setting of multivessel disease, FFR can be used to optimize both percutaneous and surgical revascularization outcomes. In the Fractional Flow Reserve Versus Angiography for Multivessel Disease (FAME) trial, FFR was used to guide multivessel percutaneous coronary intervention (PCI). A physiologically based approach with PCI of lesions with FFR ≤ 0.80 resulted in fewer stents, lower treatment costs, and fewer major adverse cardiac events at 2 years, compared with angiographically guided PCI.⁵⁴ In patients referred for coronary artery

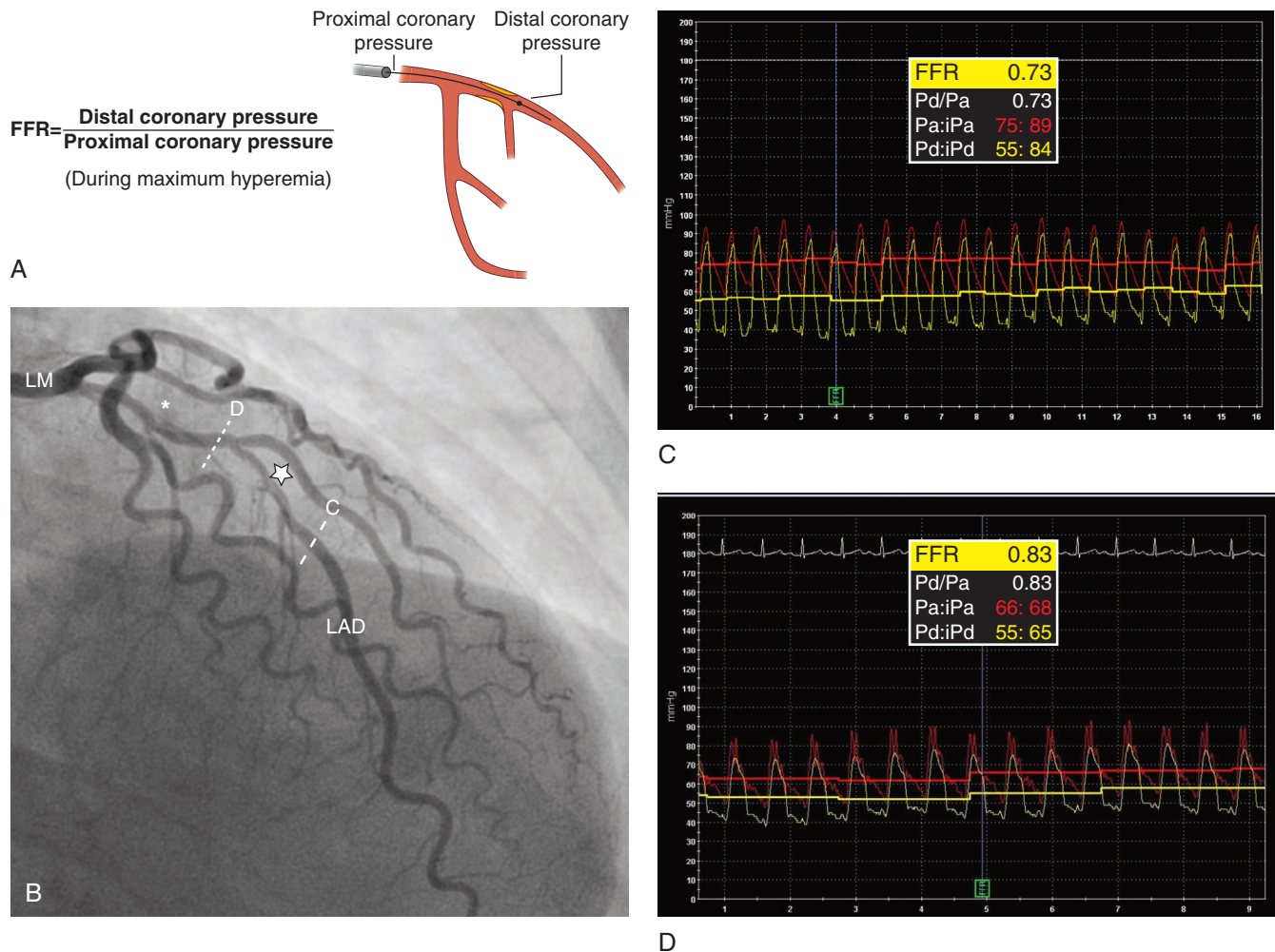


FIGURE 52-7 ■ **A**, Schematic illustrating method of measuring fractional flow reserve (FFR). **B**, Angiogram of a 54-year-old man with serial angiographically intermediate stenoses of the left anterior descending coronary artery (LAD). FFR at dashed line (**C**) was 0.73, denoting a hemodynamically significant stenosis (star) of the mid LAD. Pullback gradient to the dotted line (**D**) demonstrated an FFR value of 0.83, indicating that the stenosis of the proximal LAD (asterisk) was not hemodynamically significant. After this FFR evaluation, only the mid-LAD lesion was stented. Postintervention FFR of the LAD beyond the stented segment was normal (>0.90) (not shown). LM, left main.

bypass grafting that have intermediate stenoses by angiography, a strategy of FFR-guided grafting with deferral of surgical revascularization of lesions with FFR > 0.80 has also been evaluated. Compared with angiographically guided grafting, patients with FFR-guided coronary artery bypass grafting had fewer anastomoses and lower rates of on-pump surgery. Clinical outcomes at 3 years showed similar rates of major adverse cardiac events and lower rates of angina in the FFR-guided group.⁵⁹

Intravascular Ultrasound

Intravascular ultrasound is a catheter-based pullback technique that provides invasive cross-sectional tomographic imaging. The clinical applications of IVUS are numerous and include assessment of plaque volume, stenosis severity, transplant vasculopathy, guidance of coronary stenting, and management of in-stent restenosis. With its excellent imaging quality and spatial resolution, IVUS (Fig. 52-8) provides complementary diagnostic information to traditional angiography and can differentiate atherosclerosis,⁴² coronary dissection,^{60,61} vasospasm,⁶² thrombosis, myocardial bridging,⁶³ fibromuscular dysplasia,⁶⁴ calcification,⁶⁵⁻⁶⁷ and stress cardiomyopathy.^{68,69}

Although IVUS cannot directly estimate the functional significance of coronary stenoses, strong correlations have been observed between IVUS-measured minimal luminal area and inducible ischemia as determined by myocardial perfusion imaging, coronary flow reserve, and FFR.⁷⁰ IVUS is particularly useful in the left main coronary artery segment, which has the greatest amount of interobserver variability when assessed by angiography alone,⁷¹ and has been used widely and successfully to identify patients at low risk for adverse events with deferred revascularization.⁷² Generally accepted criteria for deferral of revascularization in moderate left main disease include an IVUS-derived minimal luminal diameter >3.0 mm or a minimal lumen area >6.0 mm².^{73,74}

Additional modern IVUS modalities such as virtual histology IVUS allow for improved characterization of plaque burden and composition, correlate well with actual histology, and may provide incremental additional prognostic information.^{75,76} Finally, a newer light-based intravascular imaging modality, optical coherence tomography has even better near-field resolution compared with IVUS, thereby permitting better assessment of luminal area, measurement of neointimal volume, determination of patterns of proliferation, and quantification of endothelialization.⁶⁷

HEMODYNAMIC EVALUATION

Principles

Hemodynamic assessments performed alongside coronary angiography are an integral part of cardiac catheterization. The advent of procedures such as balloon valvuloplasty, percutaneous valve implantation, and septal ablation have revived interest in structural heart disease and comprehensive hemodynamic assessment

in the cardiac catheterization laboratory.⁷⁷ At any moment, hemodynamic values reflect the complex interaction between various dynamic processes: CAD, left ventricular function, systemic metabolic needs, and systemic and pulmonary pressures.⁷⁸ Hemodynamic measurements (vessel or ventricular pressures), measurement of cardiac output, and the evaluation of shunts are an essential aspect of diagnostic coronary evaluation. From a technical aspect, all pressures should be measured with a transducer that will allow direct real-time measurements after establishing a zero-reference, which is usually accepted as the mid-chest level in the AP direction.

Right Heart Catheterization

The measurement of right heart (RH) pressures and oxygen saturations is a simple and accurate method of assessing real-time cardiovascular conditions. Cardiac output (CO) is the flow of blood from the heart to the body and is reported in liters per minute; this can be standardized for a patient's size by dividing by the patient's body surface area (BSA) to arrive at the cardiac index (CI), which is reported in liters per minute per meters squared.

During RH catheterization (RHC), oxygen saturations should be obtained from the superior vena cava (SVC), inferior vena cava (IVC), right atrium, right ventricle, pulmonary artery (PA), and pulmonary capillary wedge pressure (PCWP) positions. When obtained with simultaneous arterial saturation measurements, the CO or CI can be calculated, and shunts can be quantified if present.

Pressure tracings are obtained at each level of advancement of the RH catheter. Normal values for the RH and systemic arterial (LV) pressures are shown in Figure 52-9. Since the introduction of the balloon-tipped RH catheter by William Ganz and Jeremy Swan in 1970,⁷⁹ RHC has become a common and essential component of cardiac catheterization.

Pressure Waveforms

Right Atrium

The *a* wave occurs during atrial systole, which follows the *P* wave on the surface electrocardiogram (ECG). During atrial diastole, there is a decline in the pressure waveform, which corresponds to the *x* descent. In the ventricle, as systole begins, the *x* descent may be interrupted by movement of the tricuspid valve, termed the *c* wave, with the remainder of the *x* descent called *x'*. As ventricular systole progresses and forward flow occurs, the tricuspid valve closes, and right atrial filling results in the *v* wave. Ultimately, ventricular relaxation occurs, the tricuspid valve opens, and atrial pressure falls as blood flows from the right atrium to the right ventricle. This corresponds to the *y* descent.

Right Ventricle

Right ventricular pressure rises with ventricular systole. As diastole commences, the pulmonic valve closes and a

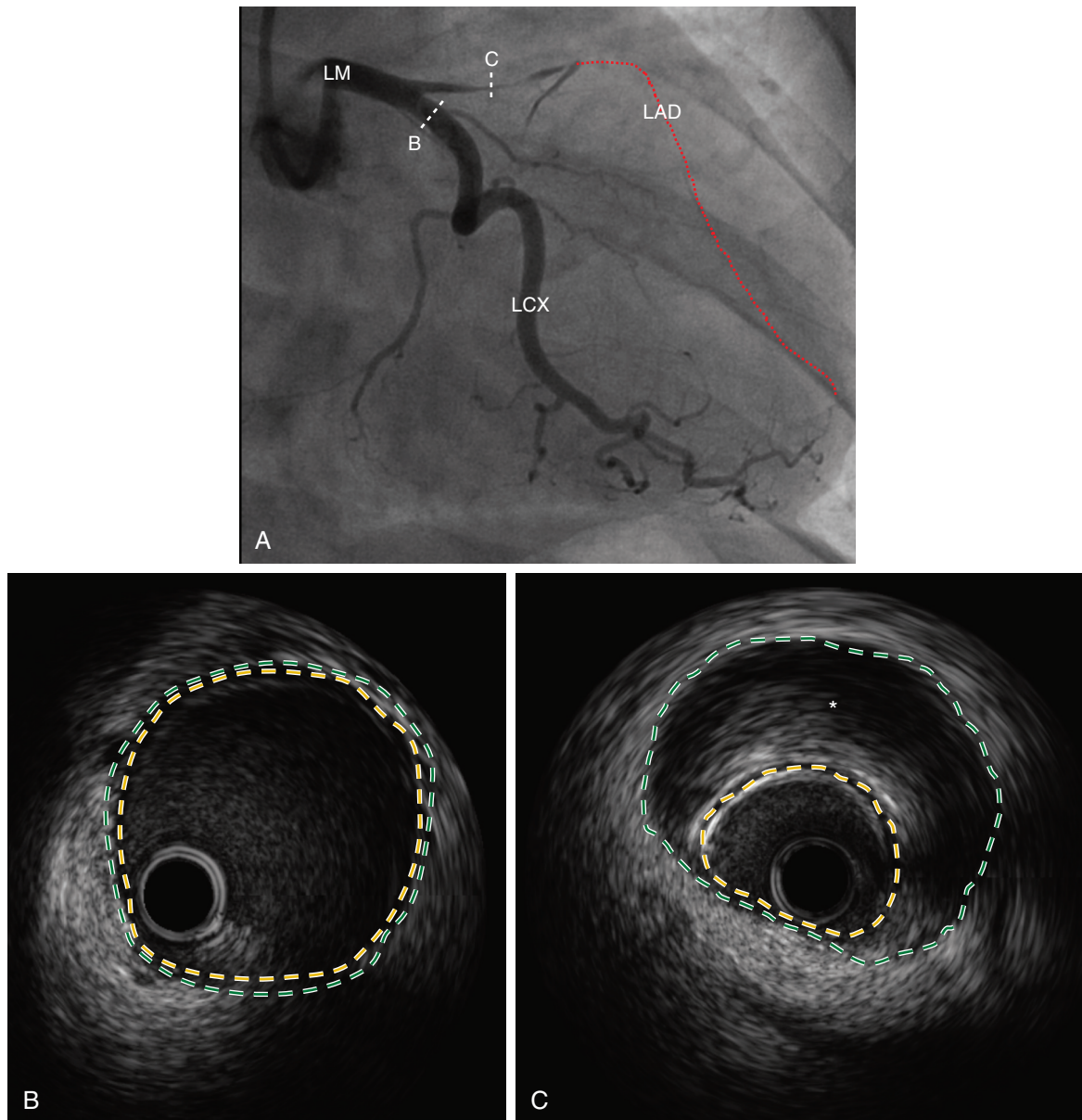


FIGURE 52-8 ■ **A**, Coronary angiography in a 42-year-old postpartum woman in the right anterior oblique caudal projection demonstrating severe spontaneous coronary artery dissection of the left anterior descending coronary artery (LAD). The *dashed line in red* represents the course of the left anterior descending artery. *Dotted lines in white* mark the locations of the accompanying intravascular ultrasound (IVUS) images of the normal left circumflex coronary artery (LCX) and the dissected LAD. **B**, Intravascular ultrasound of the normal LCX. Green dotted line outlines the adventitia; yellow dotted line outlines the intima. **C**, Intravascular ultrasound of the dissected proximal LAD demonstrating large intramural hematoma (*asterisk*) between the intimal (*yellow dotted line*) and the adventitial (*green dotted line*) vessel layers, compressing the vessel lumen. LM, Left main.

rapid decline in pressure ensues. After the tricuspid valve opens, there is rapid filling of the ventricle and a slow increase in its pressure. With atrial systole, the final pressure recorded is the end-diastolic pressure.

Pulmonary Artery

In the pulmonary artery, after the pulmonic valve opens in ventricular systole, there is a rise in the systolic pressure. As diastole commences, the pressure declines. With closure of the pulmonic valve, the diastolic pressure plateaus at a higher level than in the ventricle. Usually, the

diastolic pressure of the PA correlates closely with the left atrial (LA) pressure and PCWP.

Pulmonary Capillary Wedge Pressure

A wedge pressure is obtained using a balloon-tipped catheter “wedged” into a distal pulmonary artery; this transduces pressure from the downstream circulation (i.e., the left atrium).⁸⁰ This simple maneuver allows for indirect measure of LA pressures without the need for trans-septal puncture. Numerous studies have validated PCWP as a surrogate for LA pressure in the

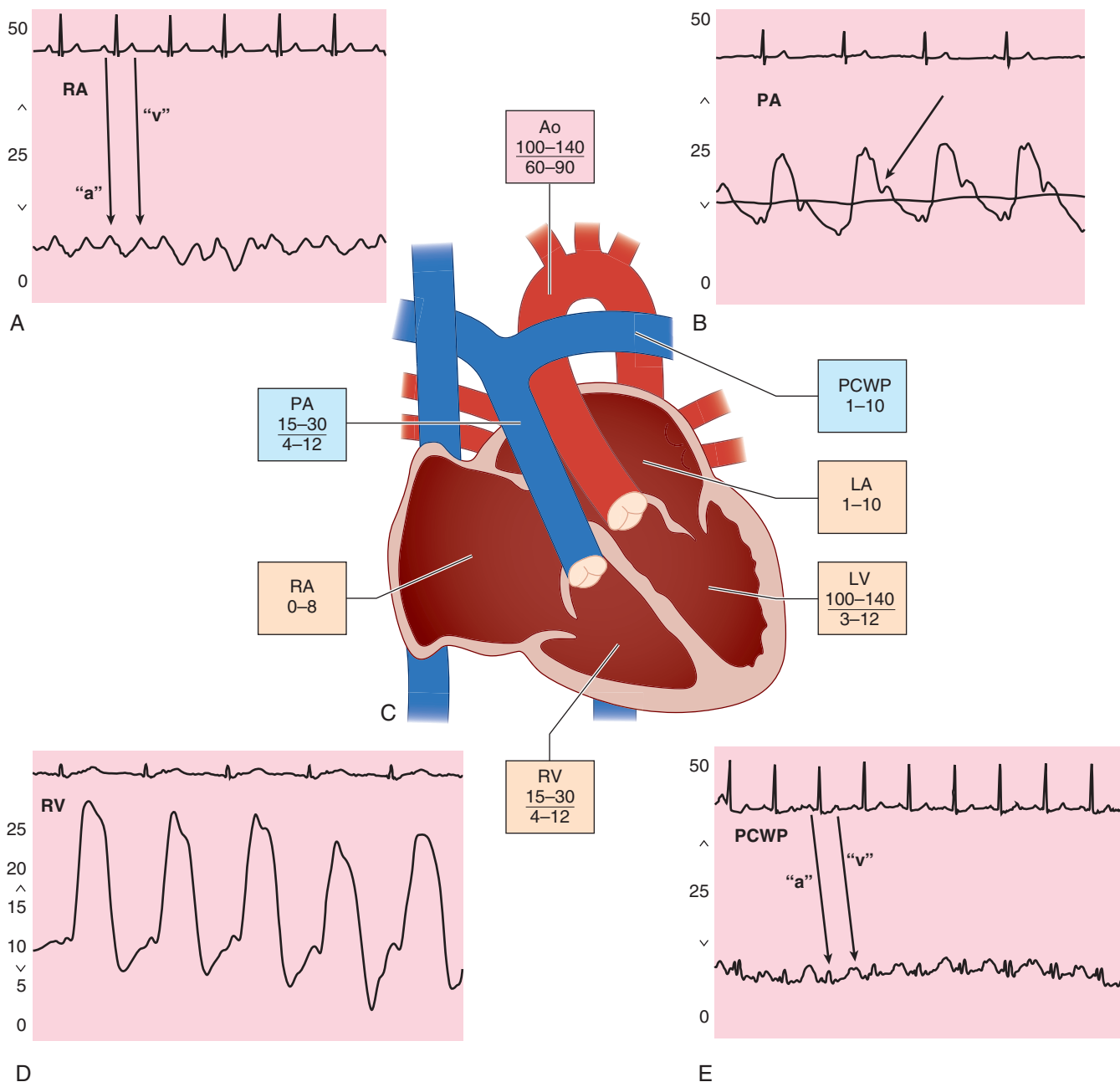


FIGURE 52-9 ■ Normal cardiac chamber pressures and pressure tracings. **A**, Normal right atrial (RA) waveform. Waves: *a*, from atrial systole; *v*, from ventricular systole. Arrows indicate the timing of the *a* and *v* waves relative to the electrocardiogram. **B**, Normal right ventricular (RV) waveform. **C**, Illustration of the cardiac chambers and great vessels with normal pressure ranges in mm Hg. **D**, Normal pulmonary artery (PA) waveform with the arrow depicting the aortic valve closure. **E**, Normal pulmonary capillary wedge pressure (PCWP) waveform showing the timing of the *a* and *v* waves relative to the electrocardiogram. Ao, Aorta; LA, left atrium; LV, left ventricle. (From Ragosta M: Cardiac catheterization. In *An Atlas and DVD*, ed 1, Philadelphia, 2008, Elsevier.)

evaluation of mitral stenosis and other hemodynamic conditions.⁸¹

Systemic Arterial Pressure

The arterial pressure waveform begins with LV systole. Once the aortic valve opens, systolic pressure rises precipitously. As ventricular diastole begins and pressures fall, the aortic valve closes and the aortic pressure declines. An interruption in the pressure tracing corresponds to the aortic valve closure, a phenomenon identified by the

dicotic notch on the arterial waveform. Depending on the patency of the aortic valve and the compliance of the aorta, the usual pulse pressure is 45 to 50 mm Hg. In noncompliant aortic systems, such as in older subjects with calcified vessels or patients with significant aortic regurgitation, there is often a widened pulse pressure.

Cardiac Output

Cardiac output, the amount of blood delivered to provide oxygen, glucose, and nutrients to the body, is expressed

in liters per minute. This measurement can be obtained through several methods, such as the Fick, thermodilution, or dye methods.^{82,83} The Fick method is most commonly used in the cardiac catheterization laboratory. It assumes that the rate at which oxygen is consumed is a function of both the rate of blood flow and the rate of oxygen loading by the red blood cells. By measuring the difference in the oxygen content in the arterial and mixed venous circulations (A-V O₂ difference) and the oxygen consumption, CO can be calculated as follows:

$$\text{CO (L/min)} = \text{O}_2 \text{ consumption (mL/min/m}^2\text{)} \div \text{A-V O}_2 \text{ difference} \times \text{BSA}$$

Normal oxygen consumption indices ranges from 110 to 150 mL/min/m² (see Fig. 52-3). To standardize calculations, oxygen consumption index is commonly assumed to be 125 mL/min/m² (or 110 mL/min/m² for older women). This index is then multiplied by the subject's BSA in meters squared to arrive at the oxygen consumption, and thus the cardiac output. If this value is not multiplied by the BSA, the cardiac index results instead.

A more reliable way to determine O₂ consumption is by direct measurement. This measurement can be accomplished using the Douglas bag, in which the oxygen content of expired air is compared with the oxygen content in the ambient air, and oxygen consumption is calculated. O₂ consumption can also be determined using a metabolic rate meter.⁸⁴ With this method, the patient breathes into a container in which O₂ and CO₂ sensors measure the expired content of O₂ and CO₂, and the oxygen consumption is calculated accordingly. To calculate the A-V O₂ difference, one needs the arterial oxygen

saturation (sat), the mixed venous oxygen saturation, and the hemoglobin (Hgb) concentration:

$$\begin{aligned} \text{A-V O}_2 \text{ difference} &= P_A (\% \text{ sat}) - P_a (\% \text{ sat}) \\ &\times (\text{Hgb in g/dL}) \\ &\times (1.36 \text{ mL O}_2/\text{g Hgb}), \end{aligned}$$

where P_A is the oxygen saturation in the peripheral arterial circulation (assumed to be the same as in the LV or pulmonary vein), P_a is the oxygen saturation in the pulmonary artery, Hgb is the hemoglobin concentration in the blood, and 1.36 is the correction factor for the capacity of fully saturated hemoglobin to carry oxygen.

SHUNTS

When blood flow crosses from one cardiac chamber to another without traversing a valve, a shunt is present. Evaluation, detection, and localization of these intracardiac shunts are integral parts of diagnostic coronary and RH catheterization.^{77,85}

Left-to-Right Shunts

The typical left-to-right shunt seen in the catheterization laboratory is an atrial septal defect (ASD). Other causes of left-to-right shunting are patent foramen ovale (PFO), ventricular septal defect (VSD; Fig. 52-10), and patent ductus arteriosus. In each of these conditions, there is an increase in oxygen saturation at a different level of the RHC. In the case of an ASD, the increase occurs in the right atrium; for a VSD, it is in the right ventricle; for a

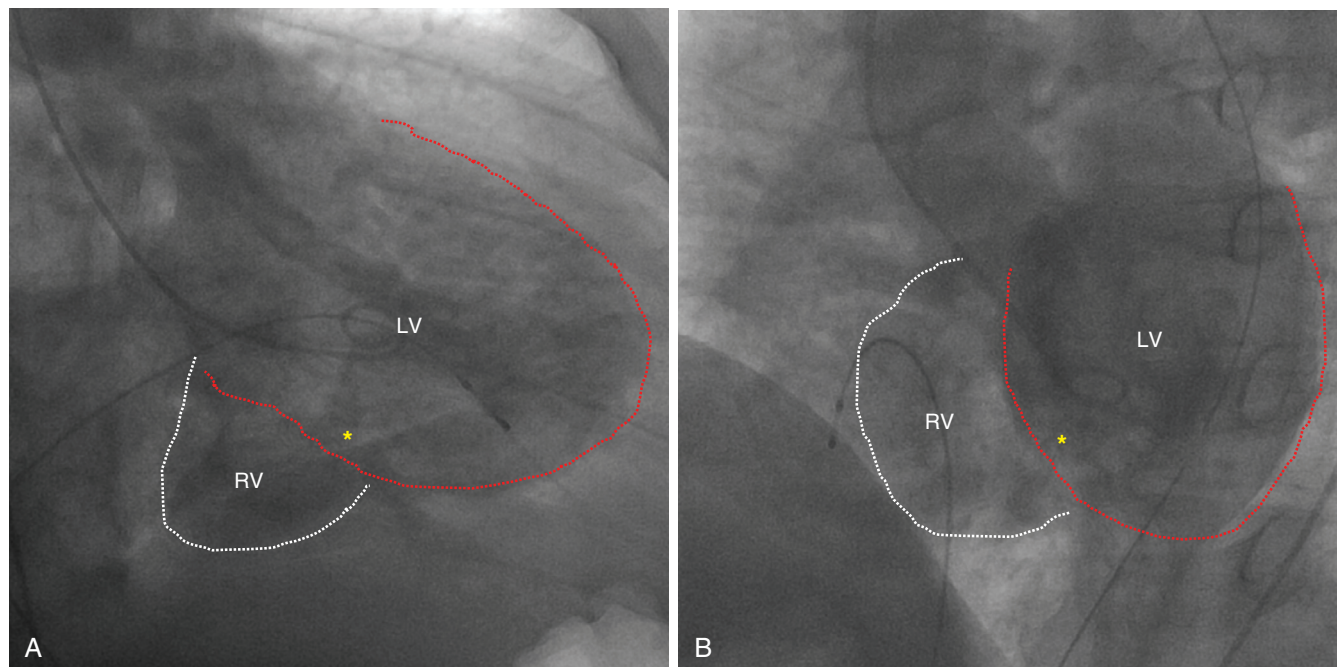


FIGURE 52-10 ■ Ventricular septal defect (VSD; yellow asterisk) with opacification of the right ventricle (RV) via the VSD during left ventriculography from right (A) and left (B) anterior oblique projections. Dashed red lines outline the left ventricle (LV); dashed white lines outline the RV.

patent ductus arteriosus, it is in the PA. The key to understanding and quantifying these shunts is determining where the most-mixed venous sample is obtained. In the case of an ASD, it is a combination of the SVC and the IVC saturations; for a VSD it is the right atrium; for a patent ductus arteriosus, it is the right ventricle.

In a shunt evaluation, oximetry is the method by which the right heart chambers or vessels are evaluated. Early work by Dexter and colleagues⁸⁶ defined the standard range for maximal changes in oxygen saturation while progressing from one RH chamber to another. In general, a maximal change of 8% from the SVC to the PA is considered sufficient to prompt further evaluation to identify the presence and extent of an intracardiac shunt.

If a shunt is suspected, oximetry is performed to identify and then quantify the shunt. Pulmonary and systemic blood flows are first calculated. Next, the magnitude of the left-to-right shunt is derived. Pulmonary blood flow (Q_p) is calculated with the formula:

$$Q_p = \text{O}_2 \text{ consumption (mL/min)} \div [(P_V\text{O}_2) - (P_A\text{O}_2)]$$

and systemic blood flow (Q_s) is calculated with the formula:

$$Q_s = \text{O}_2 \text{ consumption (mL/min)} \div [(S_A\text{O}_2) - (M_V\text{O}_2)],$$

where $M_V\text{O}_2$ denotes the mixed venous oxygen concentration.

The Q_p/Q_s is the ratio of the relative blood flows in the pulmonary and systemic circulations, which can be reduced to:

$$Q_p / Q_s = (S_A\text{O}_2) - (M_V\text{O}_2) \div [(P_V\text{O}_2) - (P_A\text{O}_2)]$$

As mentioned previously, $M_V\text{O}_2$ is a value of the average oxygen concentration from the right atrium for a VSD and from the right ventricle for a patent ductus arteriosus. For an ASD, this value is derived from the Flamm equation,⁴¹ where:

$$M_V\text{O}_2 = [3 (\text{SVC}) + 1 (\text{IVC})] \div 4$$

A Q_p/Q_s value greater than 2.0 is considered abnormal, and it warrants consideration of surgical correction or percutaneous closure of a cardiac shunt. Values between 1.5 and 2.0 are intermediate, for which surgical or percutaneous closure can be pursued if procedural risk is low or if symptoms (e.g., cryptogenic stroke in the case of an ASD) or secondary structural and functional cardiac changes are present. A ratio of less than 1.0 suggests a right-to-left shunt.

Right-to-Left Shunts

A significant right-to-left shunt is generally detected early, without catheterization, as the patient typically manifests cyanosis or arterial hypoxemia. The oximetric evidence is a Q_p/Q_s of less than 1.0. A ratio of less than 0.7 is considered critical, and less than 0.3 is not compatible with life.

Regardless of the cause, the basis for evaluation of the site of a right-to-left shunt may be analyzed by obtaining PV, LA, LV, and aortic saturations. When the shunt is extra-anatomic from the pulmonary circulation, the site of stepdown is the site of the shunt. For example, if the stepdown occurs in the LV, a VSD is present. This evaluation requires direct sampling within the left atrium via trans-septal puncture.

Bidirectional Shunts

If there is evidence of both left-to-right and right-to-left shunting, a formula comparing the effective blood flow (Q_{eff}) is used. This flow rate is the hypothetical flow in the absence of any shunting:

$$Q_{\text{eff}} = \text{O}_2 \text{ consumption (mL/min)} \div [(P_V\text{O}_2) - (M_V\text{O}_2)]$$

Then the left-to-right and right-to-left shunts can be calculated as $Q_p - Q_{\text{eff}}$ and $Q_{\text{eff}} - Q_s$, respectively.

VASCULAR RESISTANCE

Vascular resistance is calculated by dividing the pressure gradient across the vascular bed in question by the blood flow through that same bed. In essence, there are two major vascular beds: systemic and pulmonary. For systemic vascular resistance (SVR):

$$\text{SVR} = (\text{Mean arterial pressure} - \text{Right atrial pressure}) \div \text{CO}$$

For pulmonary vascular resistance (PVR):

$$\text{PVR} = (\text{PA pressure} - \text{PCWP [LA pressure]}) \div \text{CO}$$

Normal values for the SVR and PVR are listed in [Table 52-1](#). A high SVR is seen in patients with systemic hypertension, hypovolemia, significant blood loss, and CHF, whereas a low SVR is seen with high fevers, sepsis, thyrotoxicosis, or arteriovenous fistulae.

VALVULAR HEART DISEASE

The assessment of valvular abnormalities is an integral part of any catheterization. During routine right and left heart catheterization, diagnostic information can be derived for all four valves in the heart. The principal valvular anomalies that require interrogation and potential surgical or catheter-based repair are typically: aortic stenosis (AS), aortic regurgitation (AR), mitral stenosis (MS), mitral regurgitation (MR), pulmonic stenosis, and in some cases, tricuspid regurgitation.

Aortic Stenosis

Hemodynamically significant AS occurs secondary to either primary valve pathology (congenital bicuspid aortic valve) or to valve degeneration (senile calcific AS).⁸⁷⁻⁸⁹ Patients referred for catheterization for evaluation of AS

TABLE 52-1 Normal Values

Reference Point	Value
Oxygen consumption index (mL/min/m ²)	110-150
A-V O ₂ difference (mL/L)	30-50
Cardiac output	2.5-4.2
Cardiac index	2.0-3.0
Resistances	
Pulmonary vascular resistance	20-130
Systemic vascular resistance	700-1600

A-V O₂ difference, Arterial and mixed venous circulations.

generally have one of the following indications for the procedure: syncope, angina, or LV systolic dysfunction. Catheterization is recommended for hemodynamic assessment of the severity of AS if the results of noninvasive tests are equivocal or if there is discordance between the clinical assessment of severity and the results of noninvasive tests.⁹⁰⁻⁹²

To determine the significance of AS, simultaneous measurements of pressure across the aortic valve must be performed. A catheter is passed into the LV cavity, and the systolic pressure in the LV cavity is compared with a simultaneous pressure measurement in the ascending aorta, with either a dual-lumen (preaortic valve and post-aortic valve) catheter across the aortic valve or the use of two separate catheters. Use of the femoral artery sheath pressure is not recommended as a substitute for direct aortic measurements because of pressure augmentation in the periphery.

Traversing the aortic valve in a retrograde fashion can be challenging in patients with severe AS with small aortic valve openings and deformed and calcified valve apparatus. Although one can attempt retrograde crossing of the aortic valve with a pigtail catheter alone, more commonly the valve is probed with a straight wire extended from the tip while changing the orientation of the catheter for serial probing of different regions of the valve orifice. If the pigtail catheter does not provide adequate orientation for crossing, as is often the case, then a JR4 or AL1 catheter can improve the orientation of the wire and more easily allow passage into the LV.

Once the LV is entered, simultaneous pressures should be measured, along with a simultaneous CO. A simultaneous PCWP tracing via the RHC is also obtained at this time to evaluate any mitral valve gradient. Once the CO is determined, the aortic valve area can be calculated using the Gorlin equation,⁹³ as follows:

$$\text{Aortic valve area (cm}^2\text{)} = \frac{\text{CO}}{[(\text{DFP or SEP}) \times \text{HR} \times C \times \sqrt{P}]},$$

where *DFP* or *SEP* is the diastolic filling period or systolic ejection period, *HR* is heart rate in beats per minute, *C* is an empirical constant (44.3 for aortic and tricuspid valves, and 37.7 for the mitral valve), and *P* is the pressure gradient.

In the Gorlin equation, heart rate and systolic ejection periods are generally similar in most patients. Therefore, an alternative (and simpler) equation, the Hakki formula,

is commonly used.⁹⁴ With this equation, the aortic valve area is estimated by dividing *CO* by the square root of the peak-to-peak gradient (*P*) across the aortic valve:

$$\text{Valve area} = \text{CO} \sqrt{P}$$

Aortic stenosis is considered severe when the valve area is less than 1.0 cm², or critical when the valve area is less than 0.7 cm². Indications for aortic valve replacement under such conditions include symptomatic severe AS; severe AS in the setting of coronary artery bypass, aortic root, or other valvular surgery; and severe AS in the setting of a depressed left ventricular ejection (<50%).^{90,92} Aortic valve replacement is also considered reasonable for patients with moderate AS undergoing other planned cardiac or aortic surgery. If aortic valve replacement is contraindicated or carries unacceptable surgical risk because of other medical comorbidities, a temporizing aortic valvuloplasty or more durable transcatheter valve implantation procedure can be considered instead.

Balloon aortic valvuloplasty (BAV) was first developed as a technique to treat aortic stenosis in 1985.⁹⁵ Originally conceived as an alternative to surgical valve replacement, interest waned because the long-term outcomes from aortic valve dilation were poor, with early recurrence of stenosis. BAV was thus relegated to a temporizing role used in palliation or bridge to surgery.⁹⁶ The recent advent of transcatheter aortic valve implantation (TAVI) has brought with it new indications for BAV, which is increasingly being used as a therapeutic trial to assess the potential benefit of definitive aortic valve treatment in patients where alternate assessments are inconclusive, or alternatively as a bridge to TAVI.⁹⁷⁻¹⁰¹

Aortic Regurgitation

Aortic regurgitation (AI) is the result of an incompetent aortic valve. With AI, blood enters the LV cavity in diastole in a retrograde fashion across the aortic valve. The consequence of regurgitation is an increased demand on the LV, which must work harder to maintain adequate forward flow. The magnitude of the regurgitant volume depends on the size of the regurgitant orifice of the valve and on the pressure difference between the aorta and LV in diastole. The principal causes of AR are primary diseases of the valve (rheumatic or endocarditis) and of the aortic root (aneurysm, syphilis, ankylosing spondylitis).¹⁰²⁻¹⁰⁵

Chronic AR is identified by a widened pulse pressure on noninvasive measurements and classic physical examination findings: Quincke pulses (nailbed capillary pulsations), Duroziez sign (systolic murmur over the femoral artery during proximal compression and diastolic murmur during distal compression), Corrigan pulse (water-hammer pulsation with early rise and collapse), Austin-Flint murmur (early closure of the mitral valve from AR, simulating MS), or de Musset sign (head bobbing with each cardiac cycle).

Preoperative evaluation of patients with chronic AR includes coronary angiography and evaluation of LV function. If the patient is mildly symptomatic or

symptomatic with exercise testing, or if there is any deterioration of LV function, aortic valve replacement is warranted.^{90,91,103} Overall, the goal is replacement of the valve before deterioration of LV function.

Mitral Stenosis

Mitral stenosis is almost invariably caused by rheumatic heart disease. The fusion of the mitral apparatus is from the commissure at the cusps, is subvalvular at the cusps, or is a combination of the two.^{106,107} In adults, the normal valve area ranges between 4 and 6 cm². When the valve area is less than 2 cm², mitral stenosis is considered mild; less than 1 cm² is considered critical mitral stenosis. Because the hemodynamic result of chronic mitral stenosis is elevated pulmonary pressure, the typical feature of severe and critical mitral stenosis is dyspnea with exertion.

Determining the gradient across the mitral valve can be accomplished in two ways. LA pressure can be measured directly, through a trans-septal puncture into the left atrium from the right atrium. Although this is the most accurate method of determining the LA pressure, it carries inherent risks, such as aortic puncture or PA puncture. A well-validated and lower-risk approach is to obtain a PCWP via right heart catheterization simultaneously with LV pressure measurements. With either method, reliable mitral valve gradients and valve area measurements can be determined. Along with anatomic valve data, this information helps to guide the decision to perform either valvuloplasty or surgical valve replacement.

Procedurally, access is obtained in both the femoral artery and femoral vein. An RHC is performed, and a “confirmed” PCWP is obtained. Confirming the PCWP position by measuring oxygen saturation ensures the validity of the pulmonary vein samples obtained for the valve area calculation. A pigtail catheter is next placed into the LV cavity, and simultaneous tracings of LV pressure and PCWP are obtained. A normal gradient (<5 mm Hg) at catheterization can be further evaluated by exposing the patient to hemodynamic stress, via exercise, medications, or atrial pacing, to increase the atrial gradient. Once the maximal gradient is confirmed by these methods, and the diastolic filling periods and CO are obtained, the valve area can be calculated with the Gorlin equation. As with AS, the Hakki formula⁹⁴ (if calculated under adequate conditions of heart rate and CO) can also be used to approximate the mitral valve area by dividing the CO by the square root of the transvalvular gradient.

Mitral Regurgitation

Mitral regurgitation can be a consequence of disruption of the mitral leaflets, annulus, or subvalvular apparatus, including the chordae and papillary musculature.¹⁰⁸⁻¹¹⁰ Mitral leaflet abnormalities generally result from rheumatic heart disease, chronic mitral valve prolapse, or bacterial endocarditis. Other causes include systemic diseases such as systemic lupus erythematosus. When the mitral annulus becomes dilated as a secondary consequence of LV dilation, the annulus may no longer permit coaptation of the mitral cusps, with MR as the result. Furthermore,

if the annulus becomes calcified, the ability to constrict with ventricular contraction is impaired, and MR may again result. Lastly, chordal and subchordal structures (papillary muscles) may be congenitally short, long, or fibrotic. They can rupture because of ischemic or infectious myonecrosis, or may become dysfunctional because of ischemia. Any of these clinical scenarios can prevent optimal tethering of the valvular apparatus in systole, resulting in MR.

Ischemic MR is a special case of significant mitral regurgitation.^{111,112} The posterior papillary musculature has a single blood supply (usually via the LCX). Following an acute coronary syndrome involving the obtuse marginal circulation of the LCX, potentially significant and acute MR, often with resultant CHF, can ensue.

In the cardiac catheterization laboratory, significant MR can be assessed with left ventriculography in addition to right heart catheterization. In the RAO projection, the left ventricle and left atrium are both seen in profile, permitting assessment and quantification of MR. Mild MR (1+) promptly clears before the next cardiac cycle; mild-to-moderate MR (2+) clears after the next cycle and does not opacify the left atrium to the same degree as the left ventricle; moderate-to-severe MR (3+) does not clear with subsequent cardiac cycles and opacifies the atrium as much as the left ventricle; and severe MR (4+) does not clear with subsequent cardiac cycles and opacifies the left atrium more than the left ventricle.

Recently, percutaneous clip repair has emerged as a novel endovascular alternative to surgical valve repair.^{113,114} Other percutaneous methods, such as direct and indirect mitral annuloplasty and transcatheter mitral valve replacement, are currently under investigation.¹¹⁵ Overall, clinical indications for surgical or endovascular repair or replacement are based on symptoms, hemodynamic assessment, left ventricular size, and other resultant comorbidities (such as atrial fibrillation).^{90,92}

PERICARDIAL DISEASE

The pericardium forms a cavity that is held firmly in place in the chest by attachments to the sternum, vertebral bodies, and the diaphragm, despite changes in body position.⁷⁰ The pericardium has two layers: an inner (visceral) layer intimately associated with the surface of the heart, and an outer (parietal) layer that is the continuation of the visceral pericardium as it reflects on itself. The parietal pericardium is fibrous, whereas the visceral pericardium is smooth and composed of a single layer of mesothelial cells. Within the pericardial space in a normal state is approximately 50 mL of clear, ultrafiltrate fluid that acts as a lubricant to reduce friction between the heart and the surrounding pericardium.¹¹⁶⁻¹¹⁹

Normal pericardial pressures are zero or negative, and thus have only a small effect on cardiac distending pressures. Several pericardial abnormalities, such as acute pericarditis and pericardial effusion, with or without cardiac tamponade, and constrictive pericarditis, can be evaluated effectively in the cardiac catheterization laboratory.

Pericarditis

Acute pericarditis is caused by inflammation of the pericardium that results in chest pain, possibly a pericardial friction rub, and ECG abnormalities.¹²⁰ Acute pericarditis can be infectious, idiopathic, uremic, neoplastic, or secondary to trauma. The principal indication for evaluating a patient with pericarditis in the catheterization laboratory is the presence of an effusion requiring pericardial drainage or sampling.

ECG signs of acute pericarditis and pericardial effusion include nonspecific ST-segment abnormalities, diffuse ST elevation up to 1 to 2 mm, and PR-segment depression. Because the heart can swing with each cardiac cycle within the fluid space of the effusion, electrical alternans may also be observed in the presence of a large effusion. Once suggested, a pericardial effusion can be readily confirmed with echocardiography.

Cardiac Tamponade

One of the consequences of a large or acute pericardial effusion is cardiac tamponade. In tamponade, an increase in intrapericardial pressure leads to an elevation of intracardiac pressures (with ultimate equalization of chamber pressures), abnormalities of the jugular venous pressures, progressive limitation of ventricular diastolic filling, and finally a reduction of stroke volume and CO.¹²¹ Given this constellation of hemodynamic effects, the clinical findings of a patient with impending or fulminant tamponade are tachycardia, a large pulsus paradoxus, and abnormalities of the jugular venous pulsations. If clinical signs or echocardiographic findings suggest tamponade, a pericardial drain should be placed immediately (Fig. 52-11).

Historically, pericardiocentesis was performed in a blinded or ECG-guided fashion, usually from the subxiphoid approach. Currently, however, pericardiocentesis

is typically performed with echocardiographic or fluoroscopic guidance, or both. In the catheterization laboratory, the pericardial space is usually approached from left of the subxiphoid process, with the needle directed toward the patient's left shoulder.¹²² Often an RHC is performed concurrently via the internal jugular vein, femoral vein, or brachial vein to evaluate PCWP and right atrial pressures. The arterial system is also accessed, via the right femoral artery or right radial artery. Right atrial (central venous) pressures should demonstrate blunted x and prominent y descents. Hypotension and often pulsus paradoxus are observed in the arterial tracing.

Once the pericardial space is entered, confirmation of pericardial position is performed with injection of agitated saline under echocardiography or diluted contrast under fluoroscopy. With the needle in the pericardial space, the pressure is transduced and compared with that of the catheter in the right atrium. If tamponade is present, the pressures should be similar and track each other. A J-tipped wire is then advanced into the pericardial space. A dilator is advanced over this wire, and ultimately a multilumen pigtail catheter is placed. At this time, fluid samples are sent for laboratory evaluation (electrolytes, pH, cultures, hematocrit). Aspiration of the effusion follows, with intermittent hemodynamic assessments and removal of as much fluid as possible to promote reapposition of the parietal and visceral pericardial layers. As the effusion is drained, the pericardial pressure should return to zero or negative, with a resultant decline in right atrial pressure. The drain should be left in place until the drainage falls to less than 25 mL over 24 hours and repeated echocardiography reveals no significant residual effusion.

Constriction-Restriction

Constrictive pericarditis and restrictive cardiomyopathy share similar hemodynamic features and are difficult to

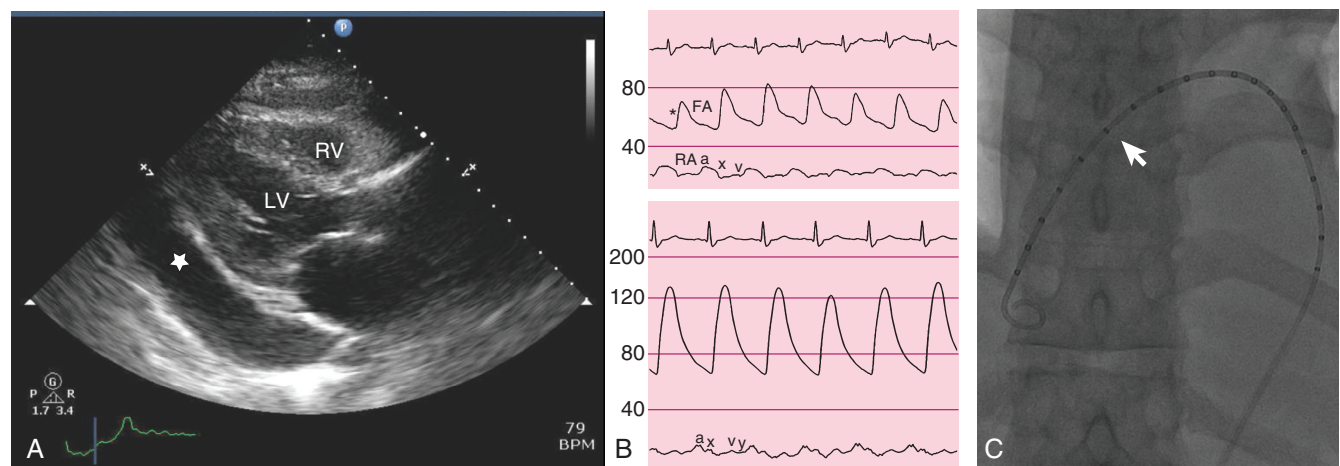


FIGURE 52-11 ■ **A**, Echocardiogram in the parasternal long axis view demonstrating a large circumferential pericardial effusion (*star*). **B**, Hemodynamic tracings demonstrate hypotension and pulsus paradoxus (asterisk) in the femoral artery (FA) pressure tracing and loss of the y descent in the right atrial (RA) pressure tracing (*top*). After pericardiocentesis, there is an increase in arterial pressure and return of the y descent in the RA pressure tracing (*bottom*). **C**, Pericardial drain (*arrow*) in the pericardial space. LV, Left ventricle; RV, right ventricle. (B, From Sorajja P: Invasive hemodynamics of constrictive pericarditis, restrictive cardiomyopathy, and cardiac tamponade. *Cardiol Clin* 29:191–199, 2011.)

differentiate. Thus, the diagnosis can remain equivocal even after extensive noninvasive and invasive evaluations.^{121,123,124} Constriction most commonly follows acute pericarditis with fibrin deposition and scarring of the pericardium, ultimately leading to uniform restriction of diastolic filling.¹²⁵

As in tamponade, there is an elevation and equalization of the diastolic pressure in all four cardiac chambers. The central venous pressure shows a prominent *x* and *y* descent, frequently appearing as a “W” waveform. The right and left ventricular tracings reveal diastolic equalization with the classic “dip and plateau” of ventricular filling: there is rapid ventricular filling in early diastole (dip) and slow or negligible filling in late diastole (plateau). It is important to remember that if ventricular filling is low, such as in hypovolemia, these classic patterns might not be observed. In this instance, a volume load will raise the right atrial pressure and facilitate identification of constrictive pericarditis. Another hemodynamic effect of a uniform constriction to cardiac filling is the absence of transmission of intrathoracic pressures to the pericardium and heart chambers, which results in Kussmaul sign: increases in systemic venous and right atrial pressures with inspiration.¹²⁶

CONCLUSION

Despite significant advances in noninvasive imaging modalities and diagnostic methods, invasive cardiac testing, to include coronary angiography, right and left heart catheterization, and morphologic and physiologic lesion assessment with IVUS and FFR, remain critical components of a complete and thorough diagnostic or preprocedural (whether percutaneous or surgical) cardiac evaluation.

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APPLICATIONS OF CARDIOVASCULAR MAGNETIC RESONANCE AND COMPUTED TOMOGRAPHY IN CARDIOVASCULAR DIAGNOSIS

Murilo Foppa • Thomas H. Hauser • Susan B. Yeon • Warren J. Manning

CHAPTER OUTLINE

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THE FUTURE ROLE OF CMR AND CCT

Cardiovascular magnetic resonance (CMR) and cardiovascular computed tomography (CCT) are increasingly used in the diagnosis and management of cardiovascular disease.^{1,2} Both of these advanced imaging modalities have overcome similar challenges posed by cardiac and respiratory motion and have met the demand for high temporal and spatial resolution to enable noninvasive imaging to aid in the diagnosis and management of a variety of cardiovascular disorders. In addition, CMR and CCT have unique capabilities that permit great flexibility, precision, and reproducibility in the acquisition and display of anatomic and functional data that are useful for surgical diagnosis, planning, and subsequent monitoring.

IMAGING PRINCIPLES AND APPROACHES

CMR imaging is performed using static and dynamic magnetic fields and does not use any ionizing radiation.

Images are generated from induced radiofrequency signals arising from water and fat protons in the body. Differences in proton density, magnetic relaxation times (longitudinal relaxation time [T_1] or transverse relaxation time [T_2]), blood flow, and other parameters produce intrinsic signal contrast among tissues. CMR approaches can be broadly classified into spin-echo (black blood) and gradient-echo (bright blood) and the derived balanced steady-state free-precession (b-SSFP) sequences for cine acquisitions, often modified with prepulses. Spin-echo imaging is particularly useful for defining anatomic structure and tissue characterization (e.g., fat replacement or iron deposition). Gradient-echo techniques can produce single-shot (displaying a single phase during the cardiac cycle) or cine (displaying multiple phases at one level during the cardiac cycle) images, with an improved signal-to-noise ratio (SNR) using b-SSFP sequences. Cine images demonstrate motion of structures (such as cardiac chambers and valves) during the cardiac cycle, permitting qualitative and quantitative assessment of motion. Both spin-echo and gradient-echo CMR

techniques are flow-sensitive. Because of the inherent contrast between the blood pool and surrounding tissue, administration of an exogenous CMR contrast agent is not required for general evaluation of cardiac anatomy. Although the U.S. Food and Drug Administration approved it for angiography (e.g., contrast-enhanced magnetic resonance angiography [CE-MRA]), but not for cardiac applications, the administration of gadolinium chelates as extracellular magnetic resonance (MR)-specific intravenous contrast agent enables certain applications, such as first-pass assessment of myocardial perfusion and late gadolinium enhancement (LGE) for fibrosis and scar identification. Gadolinium induces T_1 shortening, which is detected as an increased signal in T_1 -weighted images, although the signal enhancement is not linearly related to contrast agent concentration. Diverse techniques are under development to quantify magnetization dynamics before and/or after gadolinium administration (T_1 mapping), allowing improved cardiac tissue characterization.³ Flow-velocity encoding (also known as *phase contrast*) is an additional CMR modality that enables volumetric quantitation of blood flow through arteries, veins, conduits, and valves. This method enables determination of regurgitant volumes and shunt flows.

CCT uses ionizing radiation to generate images based on the attenuation of the body's tissues. Today, CCT is typically performed using third-generation multislice scanners. These CCT units are arranged with the radiation tube opposite a series of detectors attached to a gantry that rapidly rotates as the patient is advanced through the scanner. The detector arrays typically obtain 64, dual-64, 256, or 320 axial slices during a single gantry rotation. Higher numbers of slices allow for greater coverage with each gantry rotation, allowing for shorter imaging times, less iodinated contrast, and potentially reduced radiation exposure. In the helical mode, data are acquired in a helical path as the patient is advanced through the scanner. The speed at which the patient is advanced through the scanner is called the *pitch*. A high pitch (faster speed) is associated with a lower radiation exposure, whereas a low pitch (slower speed) is associated with a higher spatial resolution, but also higher radiation exposure. Cardiac imaging is generally performed with a relatively low pitch. The radiation exposure can be reduced by electrocardiogram (ECG) dose modulation, which varies the intensity of radiation exposure during the cardiac cycle.

CHALLENGES OF CARDIAC IMAGING

CMR and CCT have faced similar challenges posed by cardiac and respiratory motion, and requirements for high temporal, spatial, and contrast resolution. The acquisition of most cardiac images requires electrocardiographic gating or triggering during a specific portion of the cardiac cycle with data acquired from successive heartbeats. Thus, imaging is usually best when performed in patients with a regular sinus rhythm. The duration of image acquisition with CCT is generally fewer than 10 to 15 seconds, allowing a single breath-

hold for suppression of respiratory motion. Although breath-holding is used for many CMR acquisitions, free breathing, navigator gating is often used for longer image acquisitions or in situations in which patients cannot sustain a breath-hold. Navigators are a CMR technique that identifies a "signal interface" such as that between the lung and the diaphragm. Most commonly, the dome of the right hemidiaphragm is used for this purpose. Real-time navigator data about the position of the lung/diaphragm interface can then be used for respiratory gating.

High temporal resolution is needed to take advantage of these gating techniques. CMR images can be acquired with a variable temporal resolution at the expense of increased acquisition time. Typical cine temporal resolutions of less than 40 ms are acquired. The temporal resolution of CCT is limited by gantry rotation speed, with typical gantry rotation speeds of 330 to 400 ms per rotation. The use of half-cycle reconstruction allows for an image to be acquired in one half-rotation, with an effective temporal resolution of 165 to 200 ms. Intravenous or oral β -blockers are typically administered for coronary artery CCT to prolong the period of diastasis during which the coronary artery can best be imaged. The temporal resolution of CCT can be improved to approximately 83 ms with dual-source technology, in which two sets of radiation tubes and detectors are mounted on the gantry. Each set acquires data over one quarter-rotation and the data are combined to form a single image. Multicycle reconstruction can also be used to improve the temporal resolution of CCT to approximately 40 ms by acquiring data for a single image over multiple cardiac cycles, but this is infrequently used because of the requirement for a very low pitch and a resultant very high radiation exposure.

The development of high spatial resolution has also been important for CMR and CCT, particularly for coronary artery imaging. Spatial resolution of CMR is also variable, but again at the expense of increased acquisition time and loss of SNR. The latter can be somewhat mitigated by imaging at higher field strengths (e.g., 3 T). Typical in-plane spatial resolutions of 1 to 2 mm are used with 3- to 8-mm slice thickness, whereas the spatial resolution of CCT has improved with the development of smaller detectors. Routine CCT generally has a higher spatial resolution compared with CMR, with CCT isotropic spatial resolution of 0.5 to 0.6 mm. Image contrast for CMR is created using specific imaging sequences and prepulses. The use of an exogenous contrast agent (e.g., gadolinium) is required for specific applications, as noted before. CCT does not have the inherent contrast between tissues of CMR. Thus, iodinated contrast is required for the vast majority of CCT imaging. The timing of iodinated contrast administration relative to image acquisition is critical, with imaging typically performed during passage of iodinated contrast in the ascending aorta and coronary arteries. The correct timing is determined by a small timing bolus or by automated detection of contrast appearance in the ascending or descending aorta. A similar process is used for CE-MRA of the aorta and pulmonary veins. LGE imaging also uses specific timing parameters but is overall less time-sensitive.

IMAGING COMPARISONS

The advantages and limitations of CMR and CCT complement those of other imaging techniques such as echocardiography, fluoroscopic radiographic angiography, and radionuclide imaging. Compared with echocardiography and radionuclide imaging, CMR and CCT offer superior anatomic scope and spatial resolution. CMR is the noninvasive, nonionizing reference standard for evaluation of volumetric left ventricular (LV) and right ventricular (RV) cavity size, systolic function, and LV mass, providing highly reproducible measures for noninvasive follow-up of disease processes. CCT measures of LV cavity size and systolic function compare favorably with CMR.⁴ In contrast to echocardiography and nuclear imaging, CMR permits unrestricted image acquisition orientation, which can be readily adjusted to particular patient and study requirements. Although CCT acquisitions are always in the axial plane, high isotropic spatial resolution facilitates post-processing reconstruction in any desired orientation. There is also relatively advanced post-processing software for CCT. In contrast, echocardiography offers the advantages of portability, lower cost, lack of ionizing radiation (like CMR), widespread availability, greater ease of patient monitoring, and greater sensitivity for structures with chaotic motion, such as vegetations. Further comparisons among CMR, CCT, and other techniques will be made in later sections dealing with specific types of examinations.

IMAGING PRECAUTIONS

Precautions generally applicable to body magnetic resonance imaging (MRI) are applicable to CMR. Before imaging, all patients must undergo detailed screening for any potential contraindications to CMR. In addition to general concerns of metallic implants and severe claustrophobia, patients should be screened for the presence of any incompatible material. Excluded devices include some that are relatively common among those with cardiovascular disease, such as pacemakers, unconnected or retained permanent pacing leads, and implantable cardioverter-defibrillators. Protocols for scanning of non-pacemaker-dependent patients with modern (implanted after 2000) pacemakers or implantable cardioverter-defibrillators have been reported.⁵ In addition, special MR conditional pacemakers are now available and should be considered for patients likely to need future MR studies.^{6,7} Bioprosthetic and mechanical heart valves, sternotomy wires, thoracic vascular clips, and intracoronary stents are generally considered CMR-safe at field strengths up to 3 T (see www.mrisafety.com), although they may produce local artifacts that reduce image quality.⁸ Because of bulk cardiac motion during systole and diastole, most CMR protocols require ECG triggering with images composed from data collected during multiple successive cardiac cycles. Despite this, good functional image quality can usually be obtained among patients with atrial fibrillation, although image quality may be impaired among subjects with frequent

premature beats. Among patients with irregular rhythms, non-ECG gated real-time imaging CMR (which permits real-time image acquisition analogous to two-dimensional echocardiography but at lower spatial and temporal resolutions than that attained with a gated CMR technique) can provide useful information.⁹ Arrhythmias and tachycardia will also lead to suboptimal CCT data image quality.¹⁰ Compared with CMR, where the sequences are adapted for the patient's heart rate, CCT is restricted by gantry rotational speed and often requires β -blockers to slow the heart rate to 60 beats/min or less for coronary studies.² All subjects require appropriate monitoring during their imaging studies. Basic monitoring modalities include ECG monitoring for rate and rhythm (pulsatile blood in the magnetic field distorts the ST segment appearance, rendering the ST wave uninterpretable during CMR), intercom voice contact, and visualization (by direct view, camera, or both). For patients requiring a greater intensity of monitoring, automated cuff blood pressure monitoring and pulse oximetry can be added, especially for hemodynamically unstable patients and for stress CMR.

As noted earlier, CMR often does not require an exogenous contrast agent. When needed, however, gadolinium-containing CMR contrast agents have a much more favorable safety profile in regards to both nephrotoxicity and anaphylaxis compared with the iodinated agents used in CCT.¹¹ Administration of gadolinium contrast to patients with severe renal dysfunction can result in nephrogenic systemic fibrosis, a rare but severe scleroderma-like disorder that can result in death.^{12,13} Patients at high risk of renal dysfunction are screened with a Choyke questionnaire to identify those at increased risk for renal dysfunction.¹⁴ For these patients, a determination of the estimated glomerular filtration rate (eGFR) is required. Patients with mild renal impairment (eGFR 30–60 mL/kg per 1.73m²) can be safely imaged with a reduced dose of contrast agent. Noncontrast CMR or alternative imaging modalities should be considered for patients with severe renal dysfunction (eGFR < 20 mL/kg per 1.73m²), especially those on dialysis.

Because of the general requirement for iodinated contrast, CCT must be performed with caution in patients with renal insufficiency, as in patients with diabetes and use of nonsteroidal antiinflammatory drugs—factors associated with an increased risk of contrast-induced nephropathy.¹⁵ Alternative noninvasive imaging methods are preferable in the setting of moderate or greater renal insufficiency, unless dialysis has already been instituted. Proper hydration with saline solution is recommended, and bicarbonate solution and *N*-acetylcysteine may reduce the incidence of acute renal failure because of iodinated contrast, despite significant heterogeneity among studies.^{16–18}

Radiation exposure is a significant consideration in the use of CCT, especially for younger patients who are more likely to have numerous CT scans during their lifetime and have increased susceptibility to the harmful effects of ionizing radiation. With the technology moving from four-slice to 320-detector scanners, a significant reduction in radiation has been achieved.¹⁹ Dose reduction technologies including lower tube voltage, prospective

gating, and dose modulation permit further reduction in the effective dose from 12 to 20 mSv to 4 to 7 mSv²⁰ without compromising diagnostic accuracy.²¹

CLINICAL APPLICATIONS

Diseases of the Thoracic Aorta

Both CMR and CCT are widely used clinically for the assessment of the thoracic aorta for aneurysms and dissection. With CMR, the structure of the aorta is delineated by a combination of the following protocol components in the transverse, coronal, sagittal, and oblique planes: (1) ECG-gated spin-echo imaging, which reveals the aortic wall with rapidly flowing blood appearing black and thrombuslike, and slowly moving blood appearing gray; (2) ECG-gated SSFP imaging with bright-blood images in single-shot and cine acquisitions; and (3) three-dimensional CE-MRA using a gradient echo acquisition. Temporally resolved CE-MRA is particularly useful to minimize motion artifacts that would otherwise result in nondiagnostic or false-positive results. With CCT, imaging of the aorta involves iodinated contrast with a larger image acquisition volume to include the entire thoracic aorta and can be performed with or without ECG gating. ECG gating is preferred for the CCT evaluation of dissection to avoid motion artifacts that can mimic a dissection flap.

Aortic Aneurysm

Cardiovascular magnetic resonance and CCT are both superior methods for identification of true and false thoracic aortic aneurysms. In true aneurysms, the aneurysmal aortic wall is composed of intima, media, and adventitia. False aneurysms represent a contained rupture of the intima and media, with only the adventitia and periadventitial connective tissue limiting the hemorrhage (Fig. 53-1). False aneurysms generally have a narrow

“neck” or communication with the main aortic lumen. True aneurysms are more commonly fusiform (bulge aligned along the long axis of the aorta; Fig. 53-2) than saccular (sacklike bulge extending from a side of the aortic wall). CE-MRA reveals the presence and extent of these lesions as well as any associated thrombus. CCT is recommended as the imaging modality of choice for most patients in the assessment of acute disease, whereas three-dimensional CE-MRA is preferred for most patients with chronic disease requiring long-term monitoring. As with aortic dissection, advantages of CMR and CCT assessment compared with radiographic angiography include the capability to evaluate for associated complications such as hemopericardium and LV dysfunction. CMR can also assess for the presence of associated aortic regurgitation. After composite graft replacement of the ascending aorta, CMR and CCT are useful for detection of postoperative complications, such as leakage or hematoma

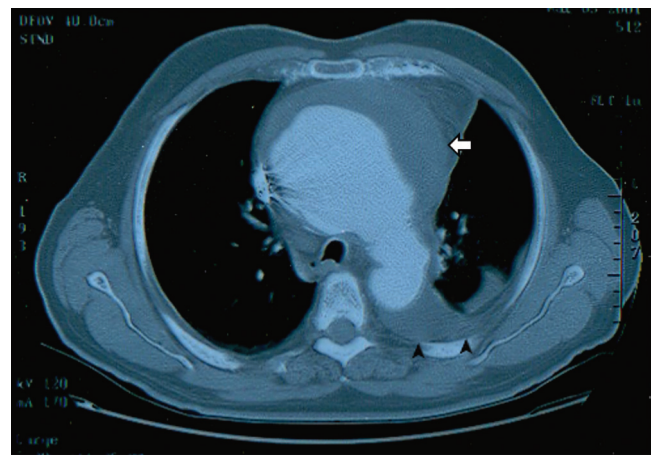


FIGURE 53-1 ■ Ruptured aorta. Non-electrocardiograph-gated contrast-enhanced cardiovascular computed tomography axial image of the aorta at the level of the aortic arch. There is a contained rupture of the ascending aorta, with blood and thrombus filling the mediastinum (white arrow) and a hemorrhagic left pleural effusion (black arrowheads).

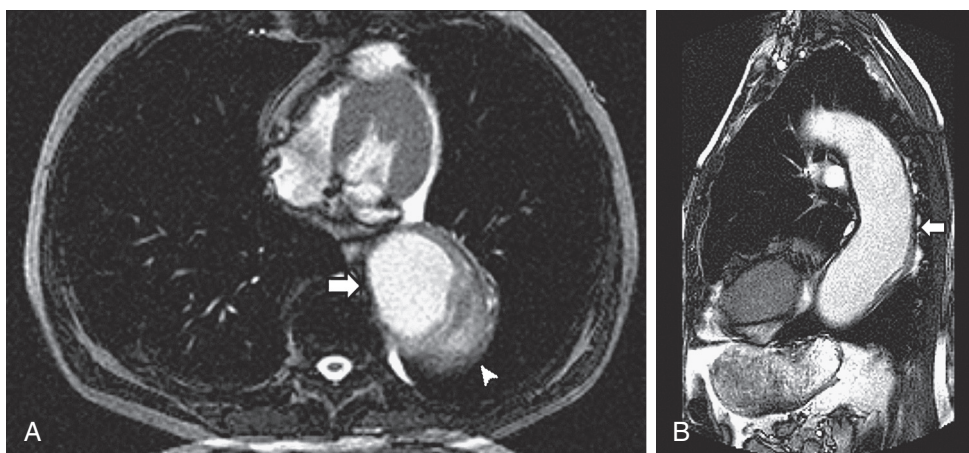


FIGURE 53-2 ■ Aortic aneurysm. Non-contrast-enhanced cardiovascular magnetic resonance in the transverse (A) and oblique sagittal (B) imaging planes of a patient with a descending thoracic aortic aneurysm (arrow) partially filled with thrombus (arrowhead). Each image was acquired in less than 1 second with the steady-state free-precession sequence without the administration of an exogenous contrast agent. (Courtesy Tim Leiner, MD, PhD.)

formation,²² with CMR offering the option for noncontrast methods.

Aortic Dissection

Cardiovascular magnetic resonance and CTT, along with transesophageal echocardiography (TEE), are the primary methods used to diagnose patients with acute aortic dissection. Because each of these imaging modalities has high diagnostic accuracy for dissection, the selection among these methods is generally governed by patient condition, institutional access, and local expertise. In a meta-analysis,²³ the three modalities showed high specificities and sensitivities in a setting of high pretest probability (>40%), but the pooled positive likelihood ratio was highest for MRI. CMR and CCT provide information regarding involvement of major branch vessels and all segments of the aorta, unlike TEE, which is limited to the thoracic aorta and by the adequacy of acoustic windows (particularly for the segment of ascending aorta anterior to the trachea). All three methods provide useful information regarding pericardial involvement. CMR and TEE can also assess aortic valve integrity. The main disadvantages of CMR in the acute setting are potential obstacles to continuous monitoring and care of an unstable patient during transport and performance of the study and the requirement that the patient remain motionless during the examination. CCT is much faster and is frequently available in the emergency department. Thus, CCT is the most common initial imaging modality chosen to diagnose *acute* aortic dissection,²⁴ whereas CMR is considered the imaging procedure of choice for *serial monitoring* of the medically or surgically treated patient with dissection according to the Recommendations of the Task Force on Aortic Dissection of the European Society of Cardiology (which have been endorsed by the American College of Cardiology) because of the lack of radiation exposure.²⁵ Follow-up is recommended after hospital discharge at 1, 3, 6, and 12 months, and yearly thereafter, ideally using the same modality.²⁵ Accurate interpretation of postoperative images requires knowledge of the surgical procedure and the expected range of routine postoperative sequelae including

thickening around the graft and presence of thrombus outside the graft and within the native aortic wrap.^{24,25}

CCT aortic assessment is typically completed in less than 1 minute, and often in less than 30 seconds, whereas CMR aortic assessment may require up to 20 minutes to complete. Both can display the location and extent of dissection identified as an intimal flap separating true and false aortic lumina, along with sites of intraluminal communication, and can readily assess involvement of the aortic root, arch vessels, and renal arteries (Fig. 53-3). CMR spin-echo images may identify relatively bright regions within the true or false lumen attributable to stagnant blood flow or thrombus. Cine SSFP images demonstrate flap motion and blood flow in the true and false lumen. Three-dimensional CE-MRA is highly sensitive for dissection²³ and can be implemented with sub-second temporal resolution to obviate the need for a breath-hold (Fig. 53-4).²⁶ Alternatively, three-dimensional free-breathing SSFP imaging without exogenous contrast can be accomplished with accuracy similar to CE-MRA (see Fig. 53-2).²⁷ LV function and involvement of the proximal coronary arteries can be assessed by CCT with a gated acquisition or using CMR with coronary imaging. Importantly, CMR can also assess the presence of coexistent aortic valve involvement (using cine imaging of the LV outflow tract) and the severity of aortic regurgitation (using a phase velocity-encoding acquisition at the base of the aortic root).

Aortic Intramural Hematoma

Intramural hematoma can be identified by the presence of a localized thickening, frequently crescentic or circular, within the wall of the aorta, interposed between the intima and the media, with characteristics of an acute or subacute collection of blood.²⁸ Although both CMR and CCT can identify intramural hematoma, CMR has been found to be superior to CCT in distinguishing acute intramural hematoma from atherosclerotic plaque and chronic intraluminal thrombus.²⁹ Acute hemorrhage appears as isointense or more intense compared with the aortic wall on T1-weighted images and displays high signal intensity on T2-weighted images. In contrast,

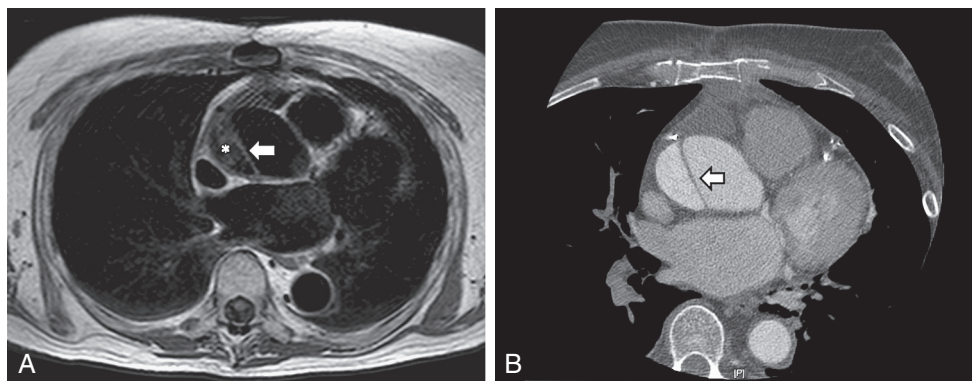


FIGURE 53-3 ■ Aortic dissection. Axial images of aortic dissection from the same patient. **A**, T1-weighted spin-echo cardiovascular magnetic resonance shows a dissection flap (arrow) in the ascending aorta. Note the increased signal in the false lumen (asterisk) caused by slow blood flow. **B**, Electrocardiograph-gated contrast-enhanced cardiovascular computed tomography axial image at the same location as the cardiovascular magnetic resonance image. The dissection flap (arrow) is again identified in the ascending aorta.



FIGURE 53-4 ■ Aortic dissection. The three-dimensional contrast-enhanced cardiovascular magnetic resonance oblique image of the thoracic aorta demonstrates a DeBakey classification type 1 dissection (arrows) involving the ascending and descending thoracic aorta.

subacute hemorrhage displays high signal intensity on T1 images and less signal intensity on T2 images. The layer of displaced calcified intima overlying the hematoma generally produces a relatively smooth surface concave to the lumen (crescentic shape), which may help to distinguish this entity from protuberant, frequently irregularly shaped, atherosclerotic plaque.

Sinus of Valsalva Aneurysm

A sinus of Valsalva aneurysm is often first suggested on transthoracic echocardiography and can be readily visualized by CCT, CMR, and TEE as an enlargement or outpouching (frequently creating a “windsock” appearance) of a sinus of the aortic root. In addition, CMR and echocardiography offer the advantage of providing information regarding blood flow (e.g., rupture of the aneurysmal sinus into an adjacent chamber) in addition to anatomy (Fig. 53-5). Shunt flow through the rupture is generally present in both diastole and systole. The magnitude of the shunt can be calculated using CMR flow velocity-encoding data.

Atherosclerotic Plaque and Aortic Penetrating Ulcer

Cardiovascular magnetic resonance, CCT, and TEE can provide qualitative and quantitative information about the presence, thickness, and distribution of atherosclerotic plaque in the aorta.³⁰⁻³³ Complex plaque is generally defined as protuberant plaque greater than or equal to 4 mm in thickness (or plaque with mobile elements)

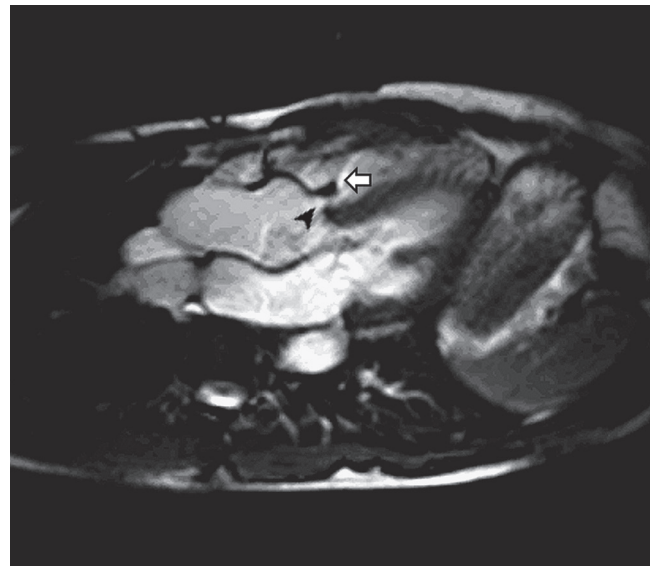


FIGURE 53-5 ■ Sinus of Valsalva aneurysm. Steady-state free-precession cine cardiovascular magnetic resonance image of a ruptured sinus of Valsalva aneurysm (arrowhead) with signal void (arrow) in the right ventricle from associated turbulent flow.

because plaque with these characteristics is associated with increased embolic risk.³⁴ Plaque thickness can readily be ascertained by CMR, CCT, and TEE, although overlying mobile elements are best assessed by TEE because of their chaotic motion and relatively small size.³⁵ Ascending aortic plaque is a predictor of adverse cerebral outcomes after coronary artery bypass grafting. Preoperative (CMR or CCT) or intraoperative (TEE) identification of ascending aortic plaque may prompt alteration in surgical strategy or technique.^{34,36}

Aortic ulceration occurs in regions of atherosclerotic plaque. Penetrating ulcers are described as those breaching the internal elastic lamina, with associated hematoma formation in the media.³⁷ CMR and CCT images visualize the position and shape of such ulcers and accompanying adjacent intramural hematoma.^{29,32,35} Penetrating ulcers are also frequently associated with aortic aneurysm formation.^{38,39} The presence of associated chest or back pain is a significant risk factor for progression to pseudoaneurysm or free rupture.³⁸

Takayasu Arteritis

Takayasu arteritis is a chronic idiopathic vasculitis that primarily affects the aorta and its branches. It is most prevalent among Asian women younger than 40 years of age.^{40,41} The aortic arch (or distal aorta) and its branches, as well as the pulmonary arteries, have characteristically tapered narrowings or occlusions, with areas of dilation. The availability of noninvasive imaging is important among these patients, who require serial long-term follow-up to guide their medical and surgical therapy. These lesions have been traditionally detected by conventional radiographic angiography, but CMR and CCT can accurately display these lesions and also provide information regarding a vessel wall abnormality.^{42,43} CMR is generally preferred to CCT because of the need for repeated imaging in these younger women and the desire

to minimize ionizing radiation exposure. Evidence of vessel wall edema is common but does not correlate well with subsequent lesion development.⁴⁴ Therefore, the current role of imaging in this disease is to identify and monitor the characteristic angiographic lesions.

Congenital Aortic Anomalies

Both CMR and CCT can readily identify and characterize aortic coarctation, patent ductus arteriosus, and other congenital abnormalities involving the great vessels. The choice is based on local expertise/availability and issues related to patient age and renal function. When available, CMR imaging is usually preferred to CCT for evaluation of congenital aortic anomalies because of concerns about radiation exposure in this generally younger population and the likely need for serial lifelong studies.

Aortic coarctation is characterized by a ridge of medial thickening and intimal hyperplasia along the posterolateral aortic wall. Coarctation most commonly presents just distal to the take-off of the left subclavian artery, occurring more rarely just proximal to the left subclavian artery. Anatomic assessment with CMR or CCT reveals the location of the coarctation and associated collaterals, usually assessed in an oblique sagittal view aligned with the descending and ascending thoracic aorta (Fig. 53-6).⁴⁵ Typical CMR protocols use spin-echo, gradient-echo, and CE-MRA techniques.^{46,47} Additional cardiac lesions that frequently accompany coarctation can also be identified, including bicuspid aortic valve (imaged in cross section) and ventricular septal defect (imaged in a horizontal long-axis or four-chamber view). Imaging is also useful for follow-up after surgical repair or balloon angioplasty,^{46,48} and routine CMR follow-up has been recommended.⁴⁹ Potential complications that may be visualized include renarrowing and aneurysm or pseudoaneurysm at the repair site.

Although patent ductus arteriosus can usually be identified by transthoracic echocardiography, CMR or CCT may be useful when echocardiographic images are non-diagnostic because of poor acoustic windows.⁵⁰ For both patent ductus arteriosus and atrial or ventricular septal defect, CMR also provides a quantitative assessment of the pulmonic-to-systemic flow ratio (Qp:Qs) by applying the flow velocity-encoding technique.⁵¹

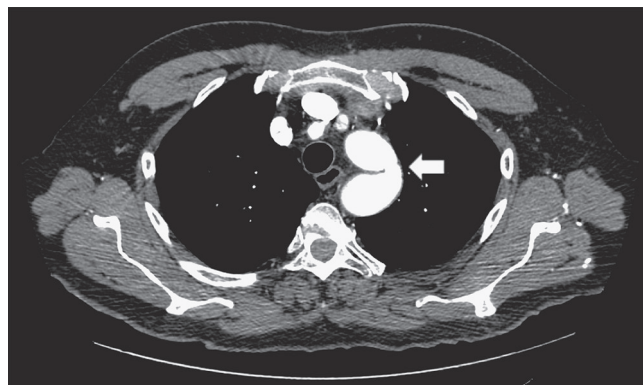


FIGURE 53-6 ■ Aortic coarctation. Non-electrocardiograph-gated contrast-enhanced axial cardiovascular computed tomographic image at the level of the aortic arch shows severe narrowing of the aorta (arrow).

Thoracic Trauma

Aortic trauma is usually related to rapid body deceleration, more frequently at the aortic isthmus, immediately distal to the origin of the left subclavian artery.⁵² Aortic lesions are graded according to lesion extension: intimal tear (Grade I), intramural hematoma (Grade II), pseudoaneurysm (Grade III), and total rupture (Grade IV). Grades II and III lesions may be localized or circumferential, and delayed selective repairs have a relatively good prognosis.⁵³ Chest radiography and emergency department CCT are generally the initial imaging modalities used for the assessment of acute thoracic trauma. In addition to providing information about the thoracic aorta, CCT also provides a comprehensive assessment of the thoracic anatomy, including the chest wall, mediastinum, diaphragm, and vertebrae. CMR may be useful for assessment of diaphragmatic, mediastinal, and aortic injury if CCT results are equivocal, and for characterizing post-traumatic masses such as intramural hematomas and aneurysms.^{54,55}

Preoperative Evaluation for Redo Cardiac Surgery

Revisited cardiac surgery is more frequently related to previous coronary artery bypass grafts and is associated with an almost threefold increase in in-hospital mortality compared with first-time procedures.⁵⁶ Accurate CCT or CMR assessment of mediastinal anatomy, including retrosternal adhesences, distances of the sternum to the aorta, the RV free wall, the left internal mammary artery, and other grafts, may lead to modifications in surgical strategies and reduce surgical complications and mortality.⁵⁷

Cardiac Imaging

Ventricular Structure and Function

CMR is the reference noninvasive, nonionizing radiation modality for the quantitative assessment of the LV and RV chamber sizes, systolic function, and LV mass, with greater reproducibility than that available using other nonvolumetric techniques.⁵⁸ Gender-specific normal reference values for CMR LV mass, volume, and ejection fraction have been defined.^{59,60} A set of breath-hold two-chamber, four-chamber, and short-axis cine SSFP images spanning the ventricles can be acquired within 10 minutes without an exogenous contrast agent. SSFP techniques provide superior endocardial border definition, thereby enabling use of semiautomated techniques for image analysis.⁶¹ Regional systolic function can be assessed by examining segmental wall motion and thickening in the different planes. A 17-segment LV model common to echocardiography and nuclear cardiology is recommended.⁶² Evaluation of LV cavity size and systolic function with CCT requires acquisition of images throughout the cardiac cycle with iodinated contrast and with or without dose modulation. Images are usually reconstructed at 10% intervals over the entire cardiac cycle. The entire three-dimensional volume is reconstructed and displayed as a cine, with most centers evaluating 2D

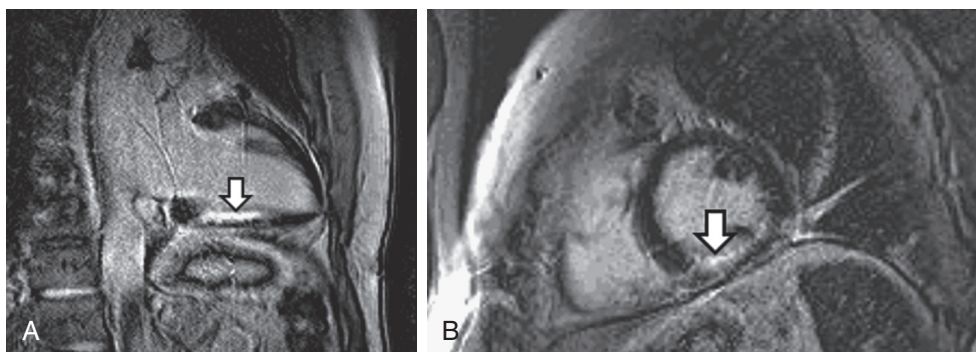


FIGURE 53-7 ■ Late gadolinium enhancement cardiovascular magnetic resonance two-chamber (A) and midventricular short-axis (B) views in a patient with an inferior myocardial infarction. The region of late contrast enhancement (arrows) corresponds to scar.

slices in the two-chamber, four-chamber, and short-axis orientations. Even though assessment of the RV may be impaired because the passage of contrast material through the heart is timed to maximize opacification of the LV, it is possible to obtain accurate and reproducible RV measurements compared with CMR.^{4,63,64} Regional and global LV and RV systolic function is most commonly assessed clinically by transthoracic echocardiography because of its widespread availability, portability, and relative ease of use. Echocardiographic assessment is frequently limited by variability of views and suboptimal image quality. CMR and CCT offer advantages compared with echocardiography in providing superior image quality and more accurate and reproducible volumetric quantification of both systolic function and cavity size.

Identification of Myocardial Scar and Ischemia

The detection of scar using an LGE CMR has proved to be highly sensitive for determining the presence and spatial extent of acute and chronic myocardial infarction identified as regions of subendocardial-based hyperenhancement (Fig. 53-7),⁶⁵ which closely agrees with positron emission tomography data.⁶⁶ Among patients with resting regional LV systolic dysfunction, visualization of the presence and distribution of scar and viable myocardium within dysfunctional regions identifies patients who would benefit from revascularization.⁶⁷ Analogous to transthoracic echocardiographic methods, low-dose dobutamine CMR also provides viability assessment and is especially valuable for those in which there is an intermediate LGE thickness.⁶⁸

Pharmacologic CMR stress testing is useful for assessment of ischemia by induction of either wall motion abnormalities (dobutamine) or perfusion defects (vasodilator with adenosine, dipyridamole, or regadenoson). Although CMR is not as widely used, its accuracy for coronary artery disease surpasses that of myocardial perfusion single photon emission computed tomography imaging⁶⁹ and allows for the identification of patients at low risk for cardiovascular events.⁷⁰ CCT applications for the detection of scar and evaluation of myocardial perfusion are in development^{71,72} but are currently limited because of relatively high radiation exposure and dose of iodinated contrast.

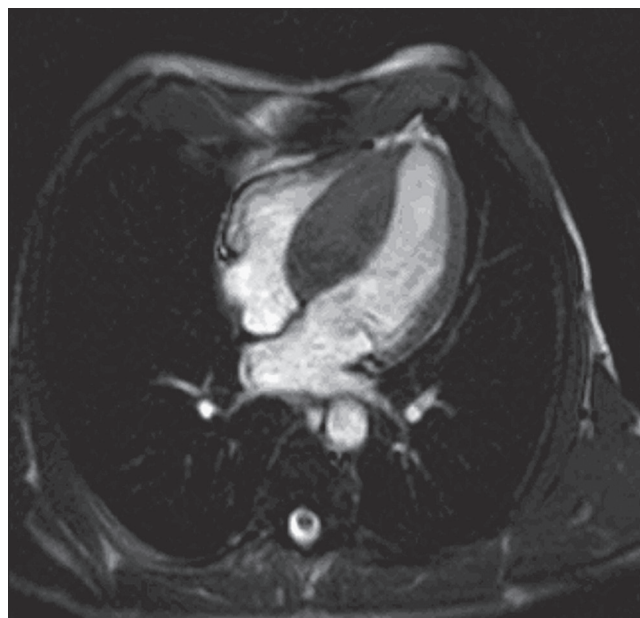


FIGURE 53-8 ■ Hypertrophic cardiomyopathy. Steady-state free-precession cine cardiovascular magnetic resonance four-chamber image in a patient with hypertrophic cardiomyopathy with asymmetrical septal hypertrophy.

Cardiomyopathies

Cardiovascular magnetic resonance and CCT are both useful in characterizing LV and RV structure and function among patients with nonischemic cardiomyopathy. The high reproducibility of these measures of biventricular cavity size and function makes them a valuable tool for quantitative serial assessment among patients with dilated cardiomyopathy, with the favorable advantage of CMR for its nonionizing, noncontrast characteristics.

Among patients with hypertrophic cardiomyopathy, CMR and CCT can accurately delineate the distribution of hypertrophy among ventricular segments free of limitations (such as foreshortening of the apex and off-axis views) encountered by echocardiography. Thus, these imaging modalities are particularly helpful in identifying asymmetric or apical hypertrophy (Fig. 53-8) as well as apical aneurysms.⁷³ Among patients with hypertrophic cardiomyopathy, LGE CMR identifies regions of

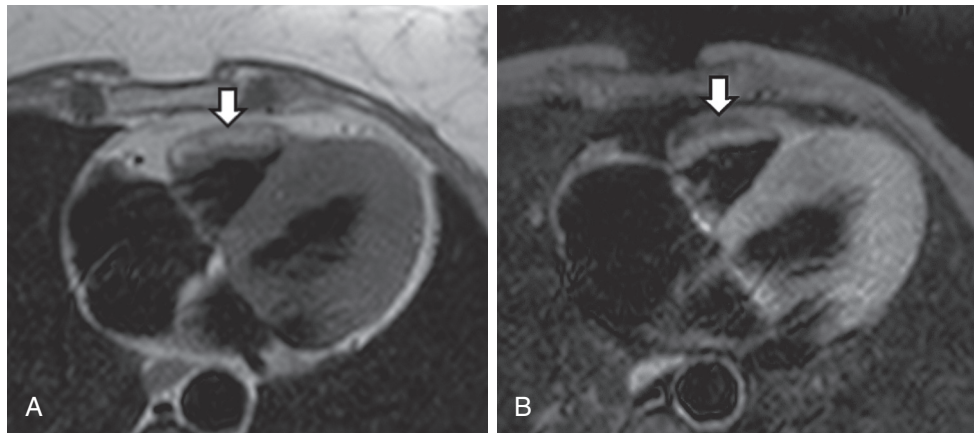


FIGURE 53-9 ■ Arrhythmogenic right ventricular cardiomyopathy. Spin-echo cardiovascular magnetic resonance without (A) and with (B) a fat-suppression prepulse. There is bright signal in the free wall of the right ventricle that suppresses with fat suppression (arrows).

myocardial fibrosis that may be associated with an adverse prognosis.⁷⁴ An LGE pattern at the junction of the interventricular septum with the RV free wall is characteristic in hypertrophic cardiomyopathy.⁷⁵

CMR provides unique information for certain specific types of cardiomyopathy. LGE images may detect focal myocardial abnormalities associated with sarcoidosis.⁷⁶ Hemochromatosis with myocardial iron deposition and LV dysfunction is associated with a depressed T_2^* .^{77,78} CMR serves as a cornerstone for diagnosis of arrhythmogenic RV cardiomyopathy to determine RV cavity size, to evaluate global and regional RV free-wall function, and to detect any fibrofatty infiltration of myocardium,⁷⁹⁻⁸¹ although the specificity and sensitivity of these findings have not been fully defined (Fig. 53-9).⁸²

CMR and CCT can also be useful for discriminating between cardiomyopathy resulting from ischemic and nonischemic causes. CMR can identify the presence of subendocardial LGE suggestive of prior infarction or coronary artery disease,^{83,84} which helps in diagnosing nonischemic cardiomyopathy in new-onset heart failure,⁸⁵ with a high predictive value for excluding the presence of left main or three-vessel coronary disease.⁸⁶ CCT also has excellent accuracy for excluding left main or three-vessel disease.⁸⁷ In nonischemic cardiomyopathy, the detection of midwall and epicardial LGE has been shown to predict events independently of LV ejection fraction.^{88,89}

Congenital Heart Disease

Cardiovascular magnetic resonance plays an important role in the diagnosis and management of simple and complex congenital heart disease.⁹⁰ The lack of ionizing radiation exposure is of particular importance for patients who often undergo numerous monitoring tests during their lifetime. Its capabilities are complementary to those of echocardiography and cardiac catheterization and are particularly useful among children and adults with sub-optimal acoustic windows and those with complex lesions. CMR can effectively identify the location, orientation, and relationships among the vena cavae, cardiac chambers, valves, great vessels, and pulmonary veins. Anatomic structure can be displayed in tomographic views

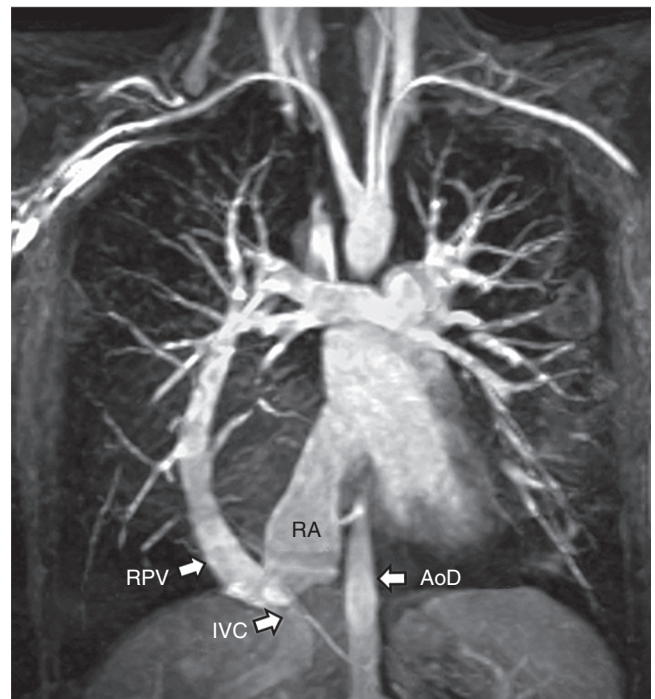


FIGURE 53-10 ■ Scimitar syndrome. Scimitar syndrome is a rare form of partial anomalous pulmonary venous connection in which the entire right lung drains into the inferior vena cava. This contrast-enhanced cardiovascular magnetic resonance coronal maximal intensity projection in the anterior-posterior orientation shows the typical findings of scimitar syndrome. The single right pulmonary vein (RPV) enters the inferior vena cava (IVC). The right atrium (RA) and descending aorta (AoD) are also shown. (Courtesy Andrew Powell, MD.)

and in three-dimensional reconstructions, which delineate complex spatial relationships (Fig. 53-10). In addition, CMR flow velocity-encoding scans can be used for measurement of flow and thus quantify the magnitude of intracardiac shunts associated with atrial and ventricular septal defects (Fig. 53-11) and conduits.⁹¹ Aortic forward and regurgitant volume can be quantified by flow velocity-encoding imaging in an axial (or oblique) plane transverse to the long axis of the ascending aorta.

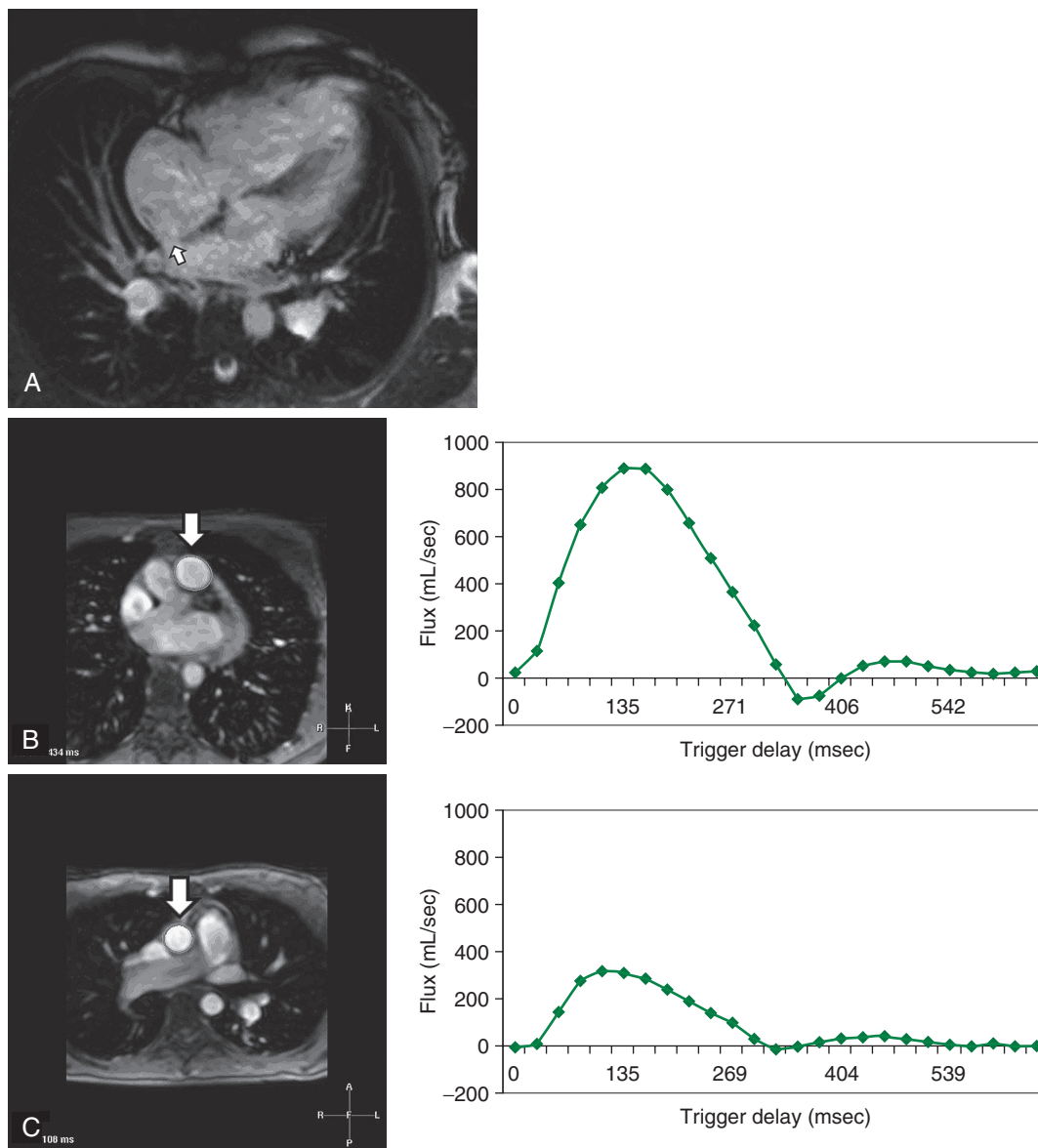


FIGURE 53-11 ■ Sinus venosus atrial septal defect. **A**, Four-chamber steady-state free-precession cine cardiovascular magnetic resonance image of a sinus venosus atrial septal defect (arrow). Phase-velocity cardiovascular magnetic resonance at the level of the pulmonary artery (**B**, arrow) and aortic root (**C**, arrow) and corresponding flux contours indicate a pulmonary-to-systemic shunt ratio ($\dot{Q}_p/\dot{Q}_s$) of 3.0.

Similarly, flow velocity–encoding in a cross-sectional slice of the proximal main pulmonary artery (oblique, generally near the coronal orientation) enables quantification of pulmonary artery forward and regurgitant volume. The ratio of pulmonary and aortic (forward) flows ($\dot{Q}_p/\dot{Q}_s$) can be calculated to identify and quantify a significant ($\dot{Q}_p/\dot{Q}_s > 1.5$) intracardiac shunt.⁹¹ CMR is particularly helpful for volumetric quantitation of RV size and function, which is important for clinical assessment of many types of congenital heart disease.⁹²

CCT has a similar utility in the assessment of the anatomy of the heart and great vessels in congenital heart disease but is less valuable for quantifying blood flow. However, CCT can be helpful in the evaluation or follow-up of congenital heart disease in the adult population and in patients with a contraindication to CMR

imaging.⁹³ Application of CCT in this setting requires careful attention to the reduction of radiation exposure and the timing of contrast administration to delineate the anatomy of interest.

Cardiac and Paracardiac Masses

Cardiovascular magnetic resonance and CCT can readily delineate cardiac and paracardiac masses such as tumors, myxomas, and thrombi.⁹⁴ A particular benefit of both methods is for masses that extend outside of the heart. Intracardiac masses are usually initially detected by transthoracic echocardiography and are frequently effectively characterized by echocardiography alone. When echocardiographic images are suboptimal or do not adequately define the extent of the mass, further imaging with CMR

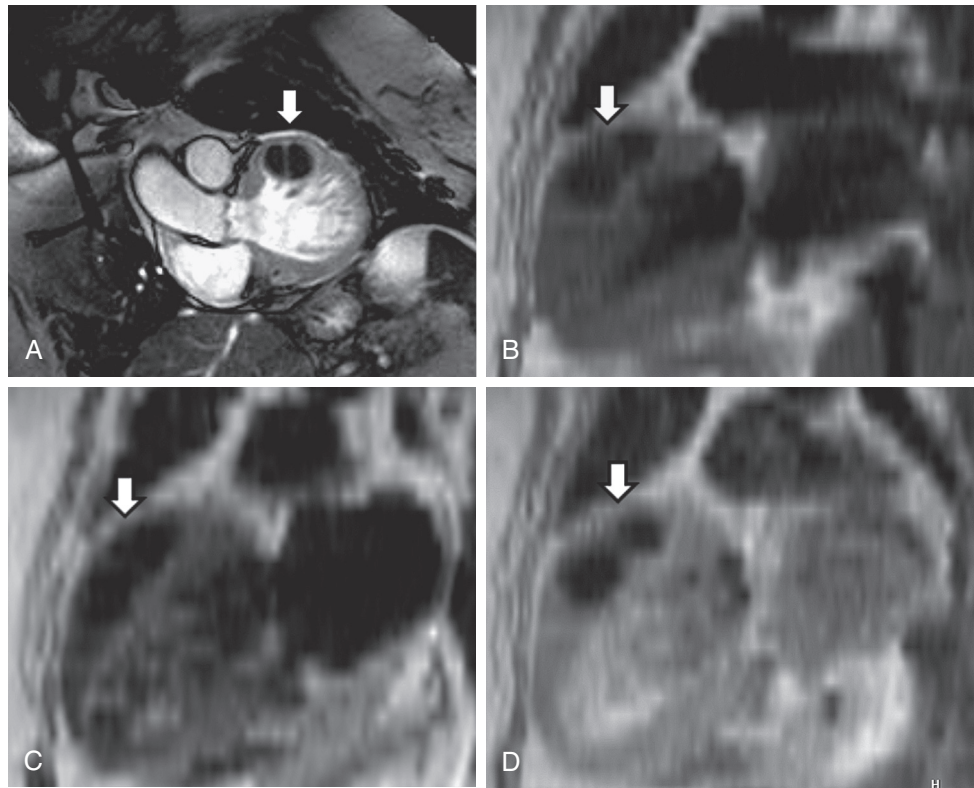


FIGURE 53-12 ■ Myocardial fibroma. **A**, Steady-state free-precession cine cardiovascular magnetic resonance image of the left ventricular outflow tract shows a well-circumscribed intramyocardial mass with low signal (*arrow*). The mass had low signal on T1 weighting (**B**), T2 weighting (**C**), and T1 weighting after administration of contrast material (**D**) on spin-echo imaging in the two-chamber view (*arrows*), indicating calcification of the mass. These findings are consistent with a fibroma.

or CCT will define the characteristics and spatial extent of the mass within and beyond the cardiac borders. The three-dimensional characterization of the mass is often helpful for surgical planning. Characterization of masses based on T1-weighted, T2-weighted, fat-suppression techniques, cine CMR, and postcontrast imaging is useful (Fig. 53-12).⁹⁵

Intracardiac thrombus is generally suspected from the appearance of a mass in a region of blood stasis (such as an aneurysmal or akinetic LV apex) on either CMR or CCT. The appearance of thrombus on CMR varies with the time. Early thrombus is seen as a region of high-signal intensity on T1- and T2-weighted images. After one to two weeks, higher signal intensity may be noted on T1-weighted images and decreased signal intensity on T2-weighted images. Chronic thrombi have low signal intensity, with even greater signal loss in regions of calcification. LGE CMR shows a greater sensitivity than echocardiography to detect a thrombus, particularly mural thrombi in patients with ischemic heart disease (Fig. 53-13).^{96,97}

Pericardial Disease

Echocardiography is frequently the initial modality used in suspected pericardial disease. However, CMR and CCT have superior imaging capabilities, including a wide field of view, and superior identification and characterization of pericardial masses and cysts, effusions (especially

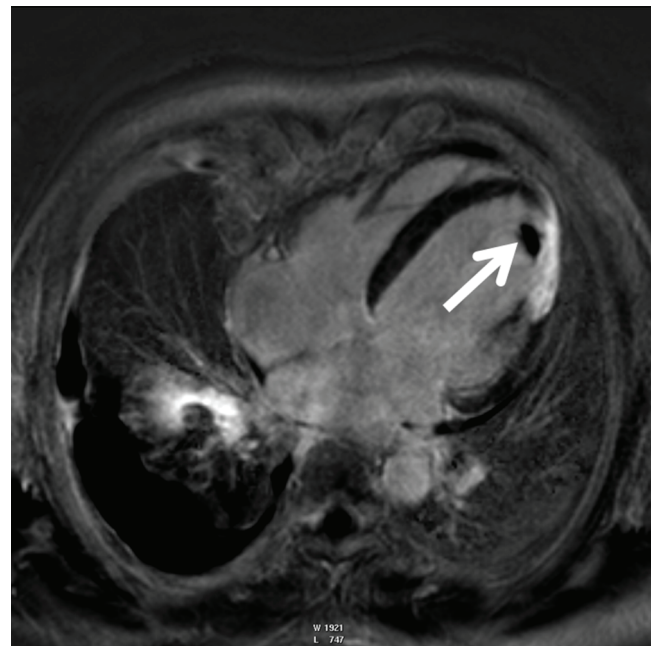


FIGURE 53-13 ■ Late gadolinium-enhancement cardiovascular magnetic resonance in the four-chamber view in a patient with a left ventricular thrombus (*arrow*) adjacent to the bright area of transmural late gadolinium enhancement (scar).

loculated effusions), and pericardial thickening.⁹⁸ With CMR, a pericardial effusion has low signal intensity (relatively dark) on T₁-weighted images and high signal intensity (bright) on T₂-weighted and gradient-echo scans. LGE CMR demonstrates marked enhancement of the pericardium in patients with acute pericarditis⁹⁹ and may help to identify patients who would benefit from medical therapy (Fig. 53-14).¹⁰⁰ With CCT, pericardial effusion has an intermediate attenuation that stands apart from the low-attenuation visceral and parietal pericardial fat (Fig. 53-15). Iodinated contrast is not typically required to assess the pericardium with CCT. Both CCT and CMR are particularly useful for identifying loculated effusions and any accompanying pericardial masses or pericardial thickening.

Although the diagnosis of constrictive pericarditis requires clinical assessment for constrictive physiology, CMR and CCT can effectively identify focal regions of pericardial thickening characteristic of this disorder.^{101,102} CCT is preferred for identification of pericardial calcifications (which lack signal by CMR) (Fig. 53-16).¹⁰¹ On spin-echo CMR images, normal pericardial thickness is less than or equal to 3 mm. Among patients with pericardial constriction, the CMR pericardial thickness is generally greater than 6 mm,^{102,103} with 4 to 6 mm being intermediate. Pericardial thickening associated with constriction is frequently focal, so identifying the location of thickening may be important to the surgical approach. Spin-echo images instead of gradient-echo images should be used to assess pericardial thickness because the latter may overestimate pericardial thickness and fail to distinguish between patients with and without constriction.¹⁰⁴

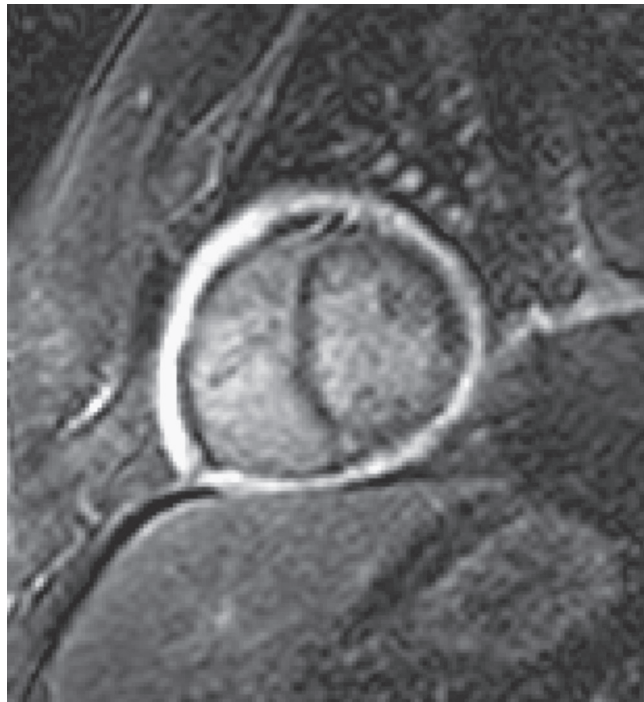


FIGURE 53-14 ■ Pericarditis. Late gadolinium-enhancement cardiovascular magnetic resonance image in the short-axis view at the level of the mid-ventricle shows circumferential enhancement of the pericardium.

ECG-gated acquisitions are useful in demonstrating abnormal early diastolic septal motion characteristic of constriction. CMR tagging methods are also useful in identifying regions of parietal to visceral pericardial adherence (Fig. 53-17).¹⁰⁵ In these areas, lack of free sliding between the pericardial layers during the cardiac cycle is visualized as persistent continuity in tag lines crossing the pericardial interface (lines deform but do not break).

Valvular Heart Disease

Although echocardiography is used most commonly in clinical practice for the assessment of valvular morphology and stenosis, CMR offers specific advantages for the quantitative assessment of valvular regurgitation. Qualitative assessment of valvular regurgitation can be made from the flow disturbance (signal void) on cine images,

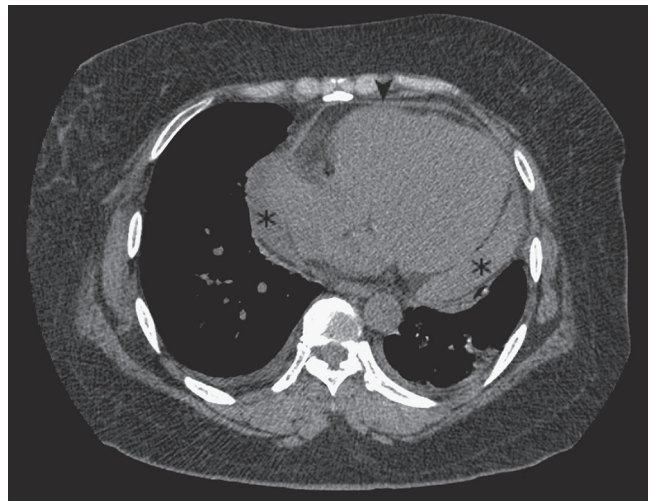


FIGURE 53-15 ■ Pericardial effusion. Nongated cardiovascular computed tomographic image with a moderate pericardial effusion predominantly displayed in the dependent portion of the pericardium (*asterisk*) but also visible as a thin line at the anterior aspect of the heart (*arrowhead*).

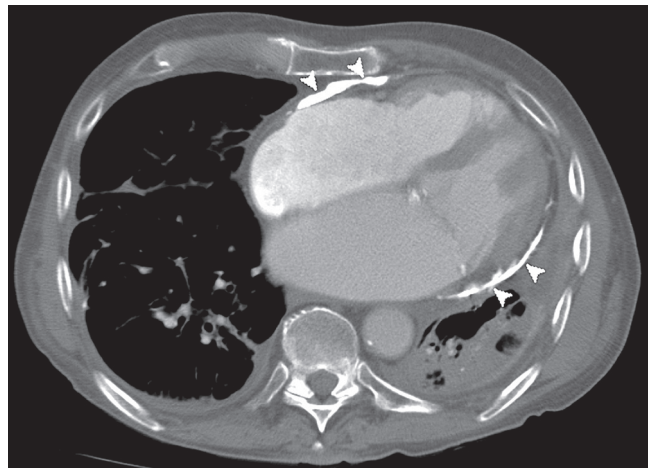


FIGURE 53-16 ■ Non-electrocardiograph-gated contrast-enhanced axial cardiovascular computed tomographic image of a patient with pericardial constriction and pericardial calcification (*arrowheads*).

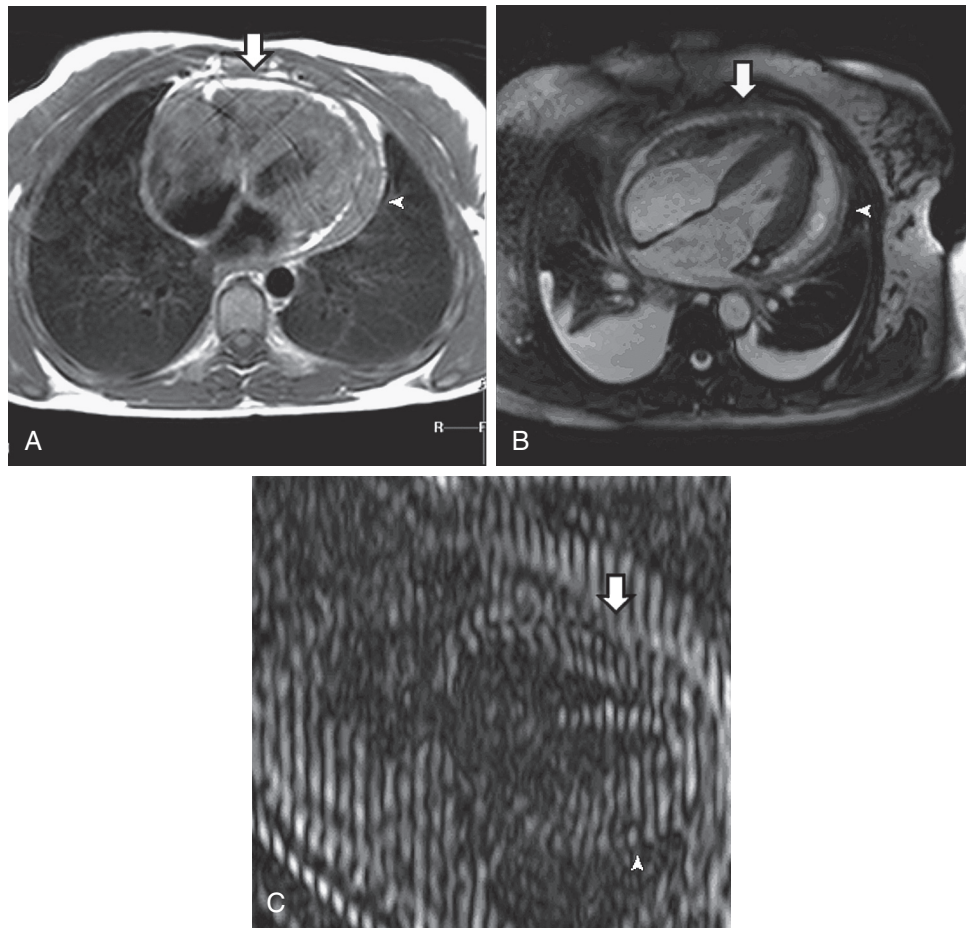


FIGURE 53-17 ■ Effusive-constrictive pericarditis. Axial dual-inversion T1-weighted (**A**) and cine steady-state free-precession (**B**) cardiovascular magnetic resonance images of a patient with effusive-constrictive pericarditis. Pericardial fluid appears relatively bright; pericardium and organized material appear dark. The end-systolic tagged four-chamber image (**C**) demonstrates tethering of pericardial elements to the right ventricular (*arrow*) and left ventricular (*arrowhead*) walls.

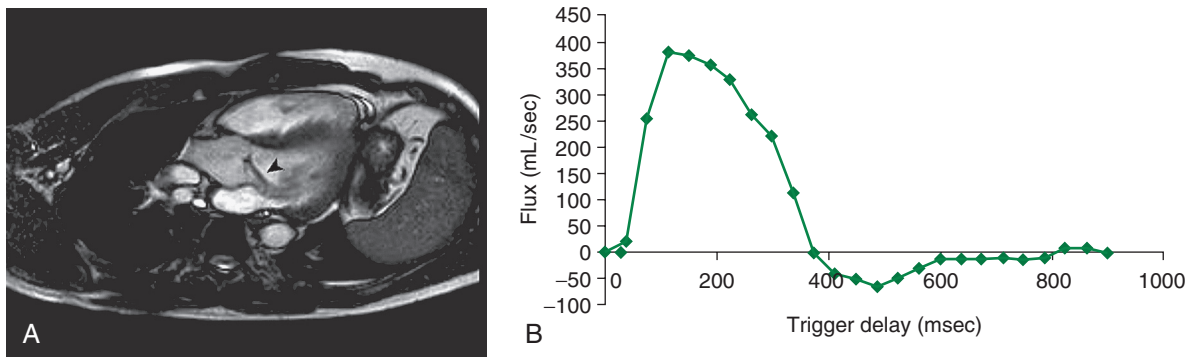


FIGURE 53-18 ■ Aortic regurgitation. **A**, Steady-state free-precession cine cardiovascular magnetic resonance image of the left ventricular outflow tract shows an eccentric jet of turbulent flow indicating aortic regurgitation (*arrowhead*). **B**, Flow contour from a phase-contrast acquisition in the aortic root just above the aortic valve indicates significant negative diastolic flow, which can be quantified.

although the magnitude of the signal void is reduced with SSFP images, which use short echo times. Importantly, flow velocity-encoding is a powerful technique for quantifying the regurgitant volume (Fig. 53-18). Flow velocity-encoding scans of the aortic root in axial or oblique (near axial) cross-sectional views enable quantitation of aortic forward and regurgitant volumes. The difference between LV stroke volume (derived from summation of discs method applied to a contiguous stack of

short-axis images spanning the LV) and forward aortic flow volume is a quantitative measure of mitral regurgitation. The regurgitant fraction can be calculated as the ratio of the regurgitant volume to total stroke volume. Using these techniques, CMR and echocardiography have very good agreement in the assessment of mitral and aortic regurgitation using equivalent severity thresholds.¹⁰⁶ Analogous methodology can be performed for pulmonary and tricuspid regurgitation.

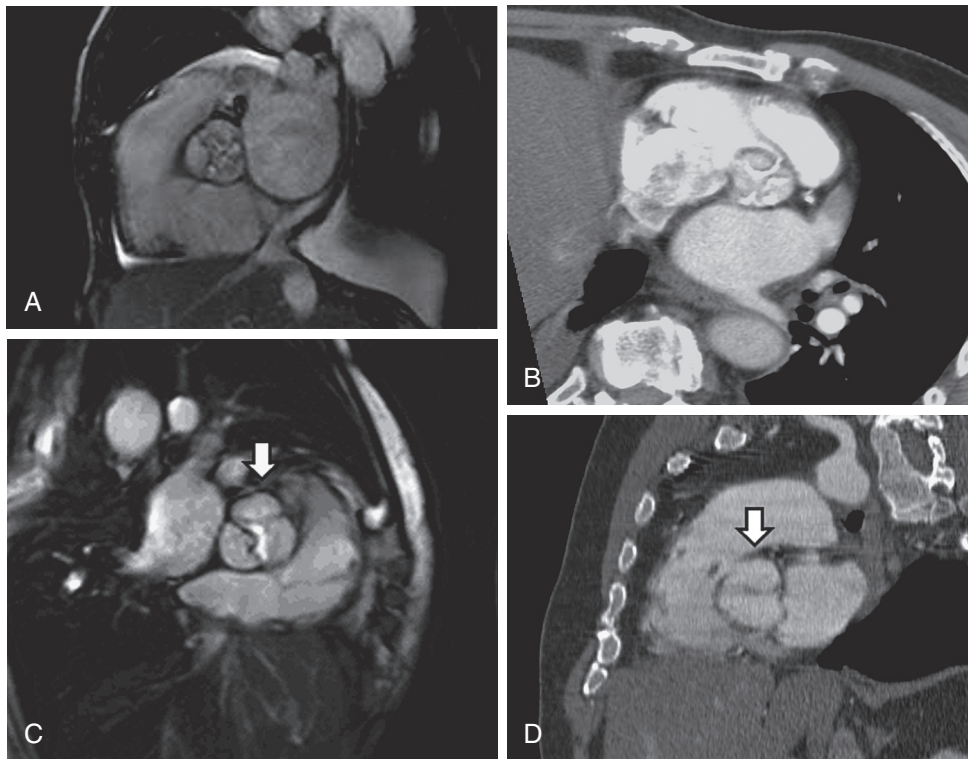


FIGURE 53-19 ■ Aortic valve disease. Steady-state free-precession cine cardiovascular magnetic resonance (CMR) (A) and cardiovascular computed tomography (CCT) (B) images of a trileaflet, calcified, and stenotic aortic valve in short axis. State free-precession CMR (C) and CCT (D) of a stenotic bicuspid aortic valve.

Cross-sectional and longitudinal views of the valves can be used to characterize valve deformities and stenosis (Fig. 53-19). CCT and CMR measures of aortic stenosis agree very closely with both transthoracic and TEE measurements.¹⁰⁷ Flow velocity-encoding techniques¹⁰⁸ may be useful in estimating valve gradients, and four-dimensional CMR flow is a promising technique to evaluate flow patterns.¹⁰⁹

CCT and CMR, as much as TEE, are also recommended for the correct assessment of the aortic root size and anatomy in the planning of transcatheter aortic valve implantation.¹¹⁰ Even though CCT is most frequently used, CMR provides accurate measurements and has a role in patients with restrictions to using iodinated contrast.²¹

Coronary Artery Imaging

Noninvasive coronary artery imaging is technically demanding, with maximal demands on spatial, temporal, and contrast resolution. Current coronary MRA imaging protocols incorporate methodology to suppress the effects of cardiac motion and respiratory motion.¹ Cardiac motion is addressed via robust ECG signal detection to trigger gating and customized adjustment of the acquisition window for patient-specific diastasis periods. Respiratory motion artifacts are suppressed by CMR navigators or prolonged breath-holds.¹¹¹ To enhance contrast between blood in the coronary arteries and the surrounding myocardium and epicardial fat, a T2-weighted preparation prepulse and a frequency-selective fat-saturation prepulse are applied. A three-dimensional acquisition is used to

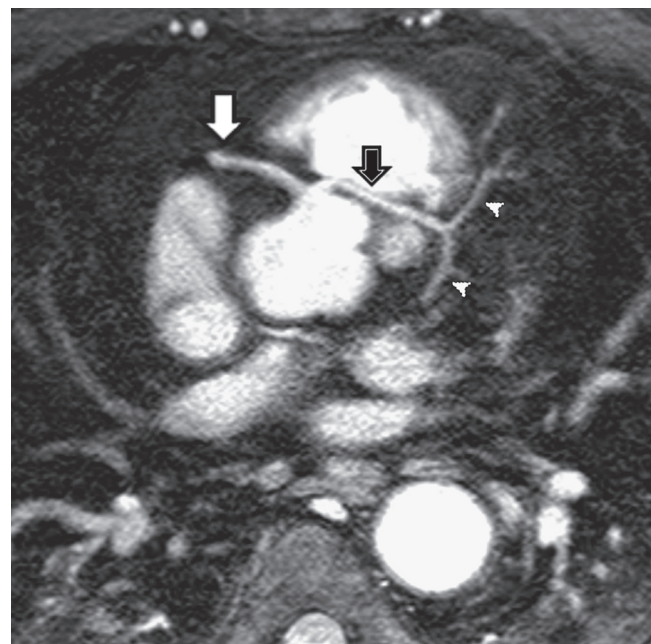


FIGURE 53-20 ■ Anomalous coronary artery. The three-dimensional coronary cardiovascular magnetic resonance image reformatted in the axial plane indicates an anomalous origin of the left main coronary artery (black arrow) from the right sinus of Valsalva. The left coronary artery courses between the aorta and the main pulmonary artery (malignant form) before bifurcating into the left anterior descending and left circumflex arteries (arrowheads). The right coronary artery (white arrow) originates normally from the right sinus of Valsalva.

enhance the SNR, although the SNR is somewhat diminished by the prepulses required to optimize the contrast-to-noise ratio. Three-dimensional images can be prescribed as either two separate volume targeted acquisitions for the left and right coronaries or as a single whole-cardiac volume,¹¹² each with its own advantages but similar quality.¹¹³ High-field (3 T) coronary artery CMR and gadolinium-based contrast agents also appear promising.^{114,115}

The most appropriate clinical use of coronary artery CMR is for the identification and characterization of anomalous coronary arteries. Studies comparing coronary artery CMR with conventional radiographic coronary angiography reveal equivalent to superior accuracy in the identification of anomalous coronary arteries.¹¹⁶⁻¹¹⁸ Because coronary artery CMR demonstrates the origin and course of each coronary artery in three-dimensional relation to the great vessels, it can resolve spatial ambiguity sometimes encountered when interpreting conventional projection radiographic coronary angiographic

images.¹¹⁶⁻¹¹⁸ Coronary artery CMR is particularly helpful in identifying whether the anomalous artery courses between the aorta and the pulmonary artery^{119,120} (Fig. 53-20), a malignant configuration associated with sudden death and myocardial infarction among young adults.¹²¹ In addition, among patients undergoing cardiac surgery for repair or palliation of other congenital defects, it may be important to identify and define any coincident anomalous coronary arteries to avoid inadvertent iatrogenic injury.¹²² Although CCT is also very good at detecting the presence and course of anomalous coronary arteries,¹²³ CMR is typically preferred in this generally younger age population because of its lack of radiation exposure.¹²⁴

CMR effectively identifies significant stenoses in the proximal to mid-native coronary arteries, with an 87% accuracy in diagnosing left main coronary artery disease or three-vessel disease, and a 72% accuracy in diagnosing coronary artery disease (defined as a $\geq 50\%$ diameter stenosis on radiographic angiography; Fig. 53-21).⁸⁶

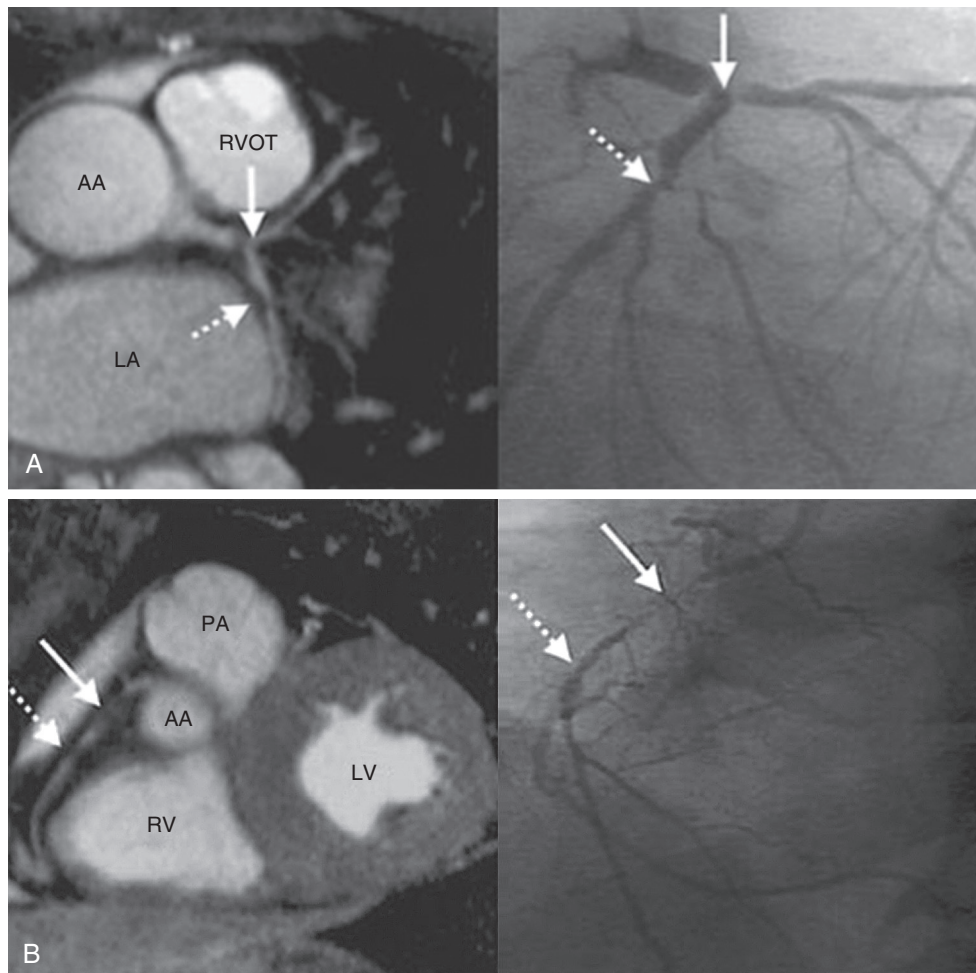


FIGURE 53-21 ■ Coronary artery disease. **A**, Coronary cardiovascular magnetic resonance image with a three-dimensional gradient-echo sequence (left) and a corresponding radiographic coronary angiogram (right) indicate a severe lesion at the bifurcation of the left main coronary artery (solid arrows) and a more distal focal stenosis of the proximal left circumflex coronary artery (broken arrows). **B**, A coronary cardiovascular magnetic resonance image (left) and a corresponding radiographic angiogram (right) indicate two stenoses of the proximal (solid arrows) and middle (broken arrows) right coronary artery. AA, Ascending aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RV, right ventricle; RVOT, right ventricular outflow tract. (From Kim WY, Danias PG, Stuber M, et al: Three-dimensional coronary magnetic resonance angiography for the detection of coronary stenoses. *N Engl J Med* 345:1863-1869, 2001; with permission.)

Remarkably, the negative predictive value of MRA for left main or three-vessel disease was 97% to 100%. A meta-analysis aggregating studies using different CMR sequences showed a subject-level sensitivity of 88% and a specificity of 56% for detection of coronary stenosis,¹²⁵ and a multicenter study using whole-heart 1.5-T CMR showed a subject-level sensitivity of 88% and a specificity of 72% for detection of coronary stenosis greater than 50%.¹²⁶

CCT has shown tremendous progress in the evaluation of native vessel coronary artery disease (Fig. 53-22). Systematic review of studies using 64-slice technology, the current standard, shows a sensitivity of 97% (range, 94-99) and a specificity of 88% (range, 79-97), which is better than that of CMR coronary angiography.¹²⁷ This accuracy was confirmed in recent large studies.^{128,129} Epicardial coronary calcium is associated with the development of coronary atherosclerosis and is a marker of increased risk for adverse events associated with coronary artery disease,¹³⁰ whereas the absence of any significant calcification is associated with a very low risk of future cardiovascular events.¹³¹ The presence of epicardial calcium is a well-recognized limitation for coronary artery CCT, with an exaggerated appearance on imaging (frequently referred to as *blooming*) that interferes with the accurate determination of coronary artery stenosis.¹³²

Available data suggest coronary CMR to be superior to CCT in patients with increased epicardial calcium.¹³³

CCT and CMR are suited for graft vessel disease because accuracy is generally higher than 90%.¹³⁴ Accuracy is superior to that for the detection of native vessel disease because the grafts are larger and move less, thus reducing the technical demands of imaging. However, local image artifacts caused by associated implanted metallic objects (such as hemostatic clips, stainless steel graft markers, and sternal wires) may interfere with adequate graft visualization, causing signal dropout with CMR and beam-hardening artifacts with CCT (Fig. 53-23).¹²⁴ Technical improvement has been achieved with the use of the appropriate CMR sequences.^{135,136}

There are growing data regarding the determination of prognosis in patients with coronary atherosclerosis or obstructive disease. Coronary artery calcification, most commonly quantified with the Agatston score, is predictive of future coronary adverse events and is superior to traditional risk factors alone,^{130,131,137} and it has been proposed as a supplementary stratification tool for assessment of cardiovascular risk.¹³⁸ CCT also has prognostic information: patients with obstructive disease have a worse prognosis compared with those with nonobstructive or no disease, which further worsens with the number of vessels involved.¹³⁹ CT angiography composite scores

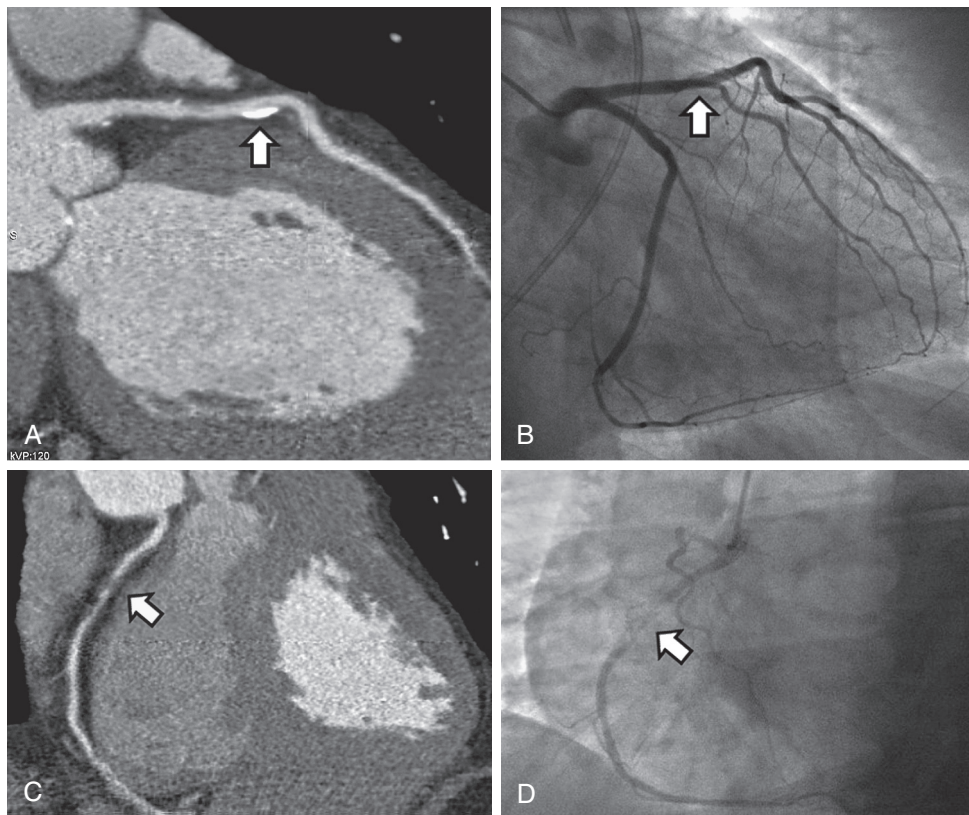


FIGURE 53-22 ■ Coronary artery disease. **A**, Curved multiplanar reformation cardiovascular computed tomographic image of the left anterior descending coronary artery shows a calcified plaque (arrow) without stenosis. **B**, Invasive radiographic angiography confirmed the absence of stenosis, with the plaque present as a subtle indentation of the lumen (arrow). **C**, Curved multiplanar reformation cardiovascular computed tomographic image of the right coronary artery showing a noncalcified plaque with severe stenosis (arrow). **D**, Invasive radiographic angiography confirmed the presence of severe stenosis (arrow).

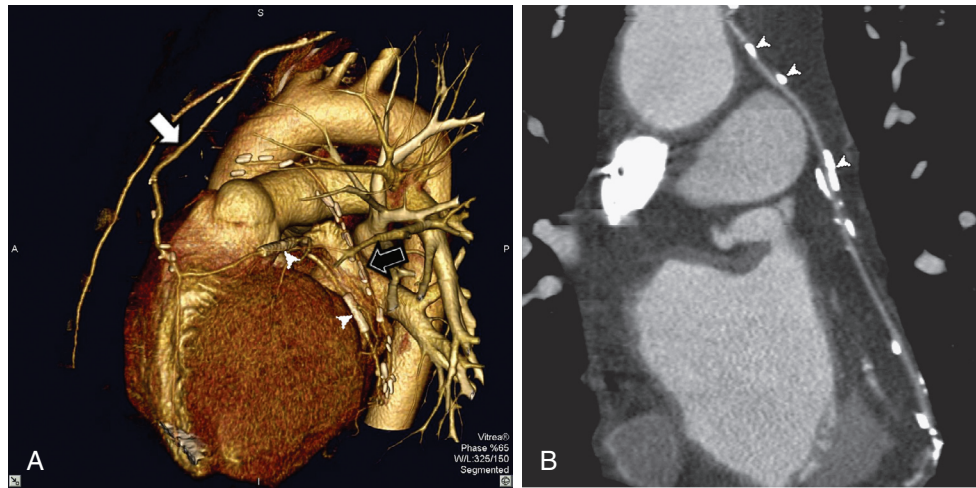


FIGURE 53-23 ■ **A**, A three-dimensional volume-rendered cardiovascular computed tomographic image of a left internal mammary graft to the left anterior descending coronary artery (white arrow) and a reverse saphenous vein graft to an obtuse marginal graft (black arrow). Note the stents in the native coronary vessels (arrowheads). **B**, Curved multiplanar cardiovascular computed tomographic image of the left internal mammary graft to the left anterior descending coronary artery in the same patient, demonstrating multiple surgical clips (arrowheads).

including plaque burden have been proposed for further prognostic improvement.¹⁴⁰

THE FUTURE ROLE OF CMR AND CCT

CMR and CCT technologies continue to evolve both in hardware and software improvements. Advances in CCT have shifted from increasing the number of detectors to algorithms aiming to decrease radiation exposure and to enhance tissue characterization and functional information. Advances in CMR have been focused on higher field strengths, faster imaging, and novel contrast agents. Both technologies are likely to continue to advance quite rapidly with their clinical roles defined by multicenter trials.

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NUCLEAR CARDIOLOGY AND POSITRON EMISSION TOMOGRAPHY IN THE ASSESSMENT OF PATIENTS WITH CARDIOVASCULAR DISEASE

Sunit-Preet Chaudhry • Neil M. Gheewala • Brian G. Abbott

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INTRODUCTION TO NUCLEAR CARDIOLOGY

Nuclear cardiology involves the imaging of cardiac radio-pharmaceutical distribution to characterize physiologic and pathophysiologic processes in the heart. The ability to image myocardial perfusion, function, and metabolism noninvasively with nuclear techniques has led to the development of a field that has been validated extensively and provides powerful diagnostic and prognostic information in the management of patients with known or suspected coronary artery disease (CAD). Moreover, nuclear cardiology procedures have been used widely in the evaluation of patients before cardiac and noncardiac surgery. This chapter provides an overview of the concepts and techniques used in nuclear cardiology and

summarizes its role in the assessment of patients with stable coronary disease and acute coronary syndromes and in the determination of myocardial viability in patients considered for revascularization. A complete discussion of the technical and procedural aspects of nuclear cardiology is beyond the scope of this chapter; therefore, the central focus will be on the use of nuclear cardiology in patients with known or suspected CAD, with an emphasis on patients undergoing cardiac surgery. For a more detailed discussion, the reader is referred to other more comprehensive reviews.^{1,2}

General Principles

Nuclear cardiology has been dominated by radionuclide myocardial perfusion imaging (MPI) as a means to evaluate patients with known or suspected coronary disease.

MPI is performed for diagnostic evaluation of patients with symptoms suggestive of myocardial ischemia and for risk stratification of patients with known CAD. Radionuclide MPI plays a central role in the evaluation of the cardiac patient, and it is in widespread clinical use, with more than 7 million MPI procedures performed in the United States annually.³

Myocardial perfusion is governed during resting conditions by the coronary resistance vessels. During periods of increased work, such as during exercise, flow is increased to balance the metabolic demands of the myocardium. This is achieved by vasodilation of resistance vessels, which reduces vascular resistance in the coronary arterial bed. In stenotic, atherosclerotic coronary arteries, resting flow is maintained by decreasing downstream vascular resistance. Although this compensation maintains flow under resting conditions, a critical stenosis (>50% to 70% narrowing of the lumen) impairs coronary flow reserve or the ability of the artery to increase flow appropriately during periods of increased demand.

Radioactive Tracers

Myocardial perfusion is imaged with the use of radiopharmaceuticals that accumulate rapidly in the myocardium in proportion to myocardial blood flow. The most commonly used radiotracers currently are the ^{99m}Tc-labeled compounds sestamibi and tetrofosmin and, to a lesser extent, thallium (²⁰¹Tl). When injected intravenously, these tracers are extracted from the blood pool and accumulate in cells, including myocytes, which have an intact cell membrane and are metabolically active. ^{99m}Tc-sestamibi and tetrofosmin are lipophilic cationic complexes that are taken up by myocytes across mitochondrial membranes, but at equilibrium are retained within the mitochondria because of a large negative transmembrane potential. ²⁰¹Tl is transported like potassium across the myocyte sarcolemmal membrane, via the Na-K adenosine triphosphatase transport system. Because the retention of radiotracer is proportional to myocardial flow, the amount of tracer uptake is a surrogate visualized representation of regional myocardial perfusion. The tracers used are radioactive isotopes that undergo radioactive decay over a short period of time.

Equipment and Procedures

As the accumulated radiotracer decays, photons are emitted that exit the body and can be detected using a specialized gamma camera. MPI uses single photon emission computed tomography (SPECT) techniques to acquire and ultimately display the perfusion distribution obtained from the radiotracer uptake. After the radiopharmaceutical is injected, the patient lies supine on the SPECT camera table and is positioned in the gantry of the camera. The photons emitted from the heart are then detected via large crystals or solid state detectors in the SPECT camera as it revolves around the patient.

As the camera detector moves around the patient, emitted photons interact with the camera's crystal and produce scintillations of light that represent the spatial

distribution of radioactivity in the patient. The emitted "counts" localized to each region of the myocardium are then stored digitally. This three-dimensional representation of the myocardial perfusion is then processed and reconstructed using computer algorithms to display the acquired information in a series of slices, oriented in the short axis and the horizontal and vertical long axes of the left ventricle. The slices are then displayed on a computer screen for visual inspection of regional myocardial perfusion and computer quantification of tracer uptake. The stress images, acquired after injection of radiotracer during exercise or pharmacologic stress (described later in detail) are displayed adjacent to images acquired at rest, permitting direct comparison of perfusion in the two imaging states. The maximum uptake of radiotracer in the heart is used to represent normal perfusion, and the rest of the counts are considered as relative uptake to this maximum. As shown in Figure 54-1, a regional perfusion defect on the stress images that is not present on the resting study is considered to be *reversible* and consistent with stress-induced ischemia in that vascular territory. A defect that persists on stress and rest is deemed *fixed* and representative of scar from prior myocardial infarction. Quantitative programs are commonly used to assess the extent and severity of each defect, which is then incorporated into the final interpretation of regional myocardial perfusion. The perfusion images are also obtained in concert with electrocardiographic (ECG) gating, which stores the counts with respect to the timing of the cardiac cycle. By gating the acquisition to the R-R interval of the ECG, images from each frame can be summed and displayed as a cine movie of the left ventricle contracting from diastole to systole. Performing gated SPECT facilitates measurement of left ventricular ejection fraction (LVEF) and left ventricle (LV) volumes by automated computer algorithms, as well as visual inspection of the movie for regional wall motion and thickening (Fig. 54-2).⁴

A typical SPECT MPI protocol involves the performance of exercise, typically on a treadmill or bicycle, or with a pharmacologic stressor, such as adenosine, dipyridamole, regadenoson, or dobutamine in patients who are unable to perform physical exercise. The radiotracer is injected at peak stress and the stressor is then continued for an additional 1 to 2 minutes to maximize myocardial extraction of the circulating tracer. Imaging is performed 30 to 60 minutes later for sestamibi or tetrofosmin, because these agents have only minimal redistribution, or washout from the myocardium. The initial imaging can be either at rest or at stress, and both studies can be performed on the same day depending on the patient's weight. While ²⁰¹Tl is used less commonly for stress MPI, it can be used for rest imaging in a "dual isotope" protocol. In this protocol ²⁰¹Tl is injected for resting imaging, which is then followed immediately by stress perfusion imaging with ^{99m}Tc agent, thus obviating the need to wait 2 to 3 hours for the first dose to decay.⁵ As such, imaging time is reduced and patient throughput is increased; however, the radiation dose the patient receives is greater. Recent advances in camera technology and processing have facilitated faster image acquisition and the use of lower doses of radiopharmaceuticals.

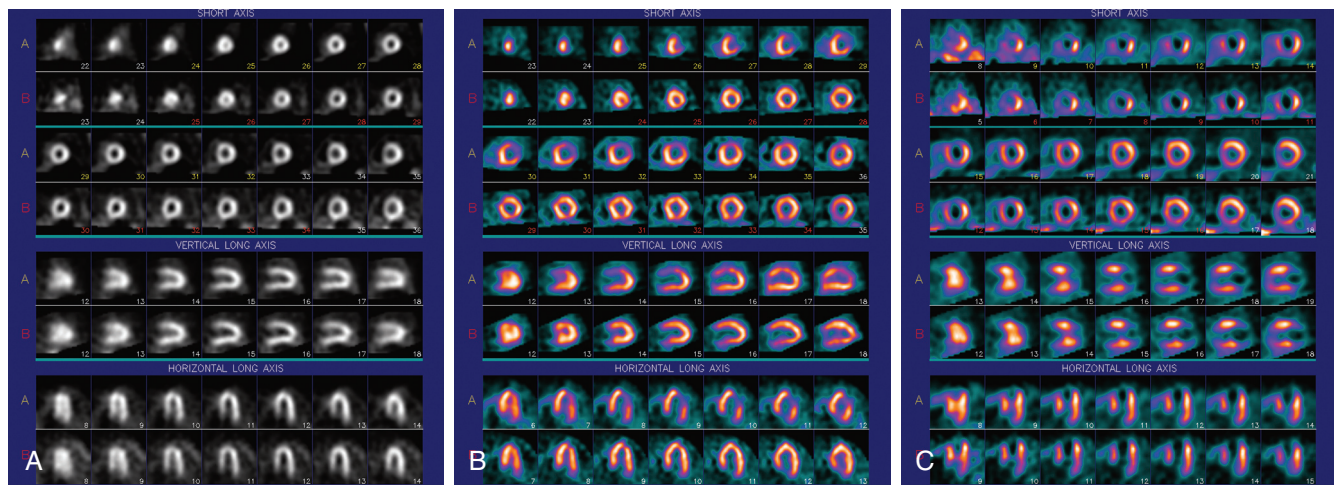


FIGURE 54-1 ■ Visual display of single photon emission computed tomography (SPECT) myocardial perfusion images. The stress study (rows labeled A) is shown immediately above the rest study (rows labeled B) for comparison. There are three representations of the same imaging procedure, each oriented differently: short-axis slices from apex to mid-ventricle and mid-ventricle to base (*top*), vertical long-axis slices from septum to lateral wall (*middle*), and horizontal long-axis slices from inferior to anterior wall (*bottom*). **A**, Normal study in grayscale, with uniform uptake of radiotracer on stress and rest. **B**, Color-enhanced study in which the stress images demonstrate a perfusion defect in the anterolateral wall, as evidenced by less radiotracer accumulation relative to other regions of the left ventricle. As the corresponding rest images show normal perfusion throughout the myocardium, the perfusion defect is considered “reversible,” consistent with ischemia. **C**, These SPECT images demonstrate large perfusion defects in the anteroapical, inferoseptal, and apical regions, which are present on both the stress and rest images. Because these defects do not show any change from stress to rest, they are termed *fixed defects*, consistent with scar (i.e., prior myocardial infarction).

STABLE CORONARY ARTERY DISEASE (DIAGNOSIS AND RISK STRATIFICATION)

Stress Testing in the Detection of Coronary Artery Disease

Nuclear cardiology is a central part of the evaluation of patients with suspected or proven coronary artery disease. The ability of SPECT myocardial perfusion imaging to detect CAD in patients with symptoms suggestive of ischemic heart disease has been validated extensively.

Exercise Stress Testing

Exercise stress testing without adjunct noninvasive imaging is frequently used as the initial screening test in patients without known coronary artery disease who have chest pain syndromes or symptoms suggestive of ischemia. The premise of exercise stress testing is that the increased myocardial oxygen demand during exercise will produce clinical signs of ischemia (e.g., angina, ECG changes) in the setting of a flow-limiting stenosis that impairs myocardial blood supply. The diagnostic performance of this test varies greatly depending on the pretest likelihood of the population being studied. In patients with an intermediate pretest probability of CAD on the basis of symptoms and risk factors, exercise treadmill testing is useful as an initial screening test. However, the overall sensitivity of treadmill exercise testing is approximately 70%. A meta-analysis of more than 24,000 patients undergoing exercise stress testing and coronary angiography observed a mean sensitivity on 68% and a mean specificity of 77%. Accuracy was greatest in patients with

multivessel coronary disease and those with left main or three vessel coronary artery disease.⁶

Exercise Stress Myocardial Perfusion Imaging

Exercise treadmill testing relies on changes in the 12-lead ECG as a surrogate of ischemia, rendering the accuracy of the test highly dependent on the baseline electrocardiogram. Abnormalities, such as previous myocardial infarction (Q waves or left bundle branch block) or ST-T wave changes owing to left ventricular hypertrophy or therapy with digoxin, hamper the ability to interpret ischemic changes accurately during exercise. In patients with an abnormal ECG, myocardial perfusion imaging adds significant diagnostic accuracy to the treadmill test for detecting coronary artery disease. Large studies have consistently shown that SPECT myocardial perfusion imaging with technetium-labeled agents, such as sestamibi, yields a greater than 90% sensitivity for the detection of coronary artery disease.⁷⁻⁹ False-negative scans tend to occur in the setting of single-vessel disease, particularly in the left circumflex artery distribution, with a mild degree of stenosis (<70%), or when the patient is unable to achieve the target heart rate or is taking anti-anginal therapy. These studies have also observed that the specificity of stress SPECT imaging is in the range of 68%. The less optimal specificity can be attributed to referral bias (performing angiography in only those patients with abnormal scans) and false-positive scans with defects resulting from artifacts produced by soft tissue attenuation (diaphragm, breast) or patient motion. Contemporary imaging techniques that use ECG-gating have facilitated the simultaneous assessment of myocardial perfusion and function. Examination of regional wall

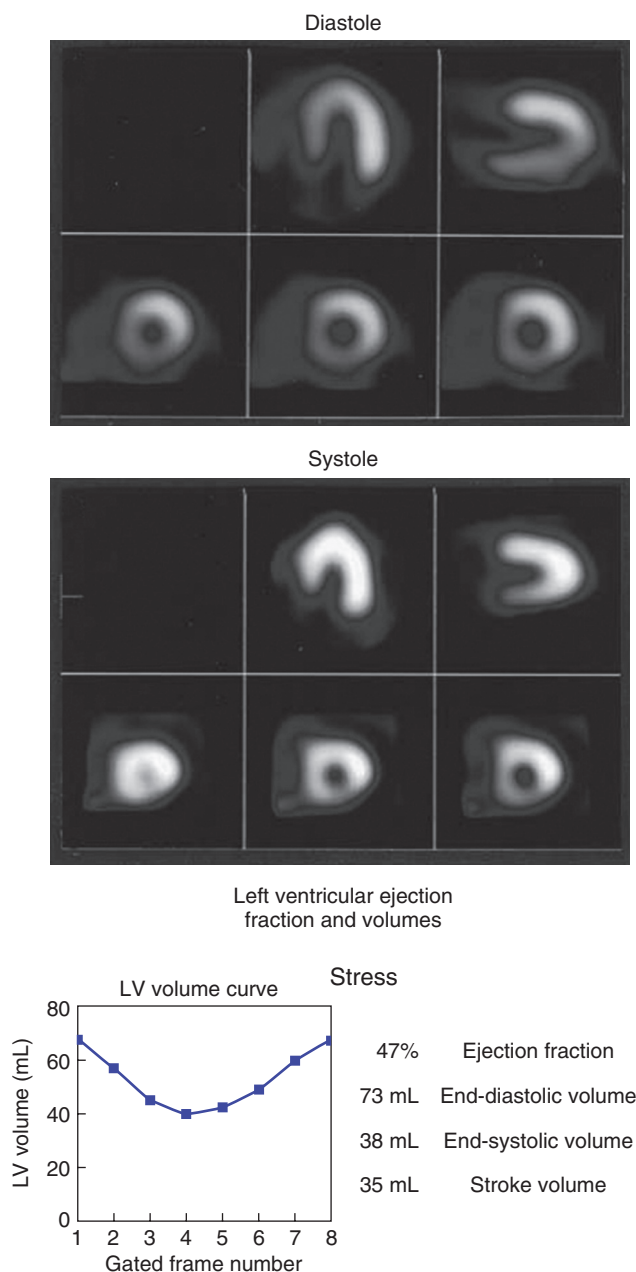


FIGURE 54-2 ■ Gated single photon emission computed tomography (SPECT) still-frame images of diastole and systole. During SPECT image acquisition, the acquired images can be stored in relationship to the cardiac cycle using the R-R interval of the electrocardiogram. The resulting images that are "gated" to the cardiac cycle can then be viewed as a cine-loop from diastole to systole. Moreover, these data can be used to calculate left ventricular (LV) volumes during diastole and systole, as well as the corresponding left ventricular ejection fraction (diastole-systole).

motion and thickening enhances the evaluation of a suspect area of hypoperfusion by providing the ability to distinguish true myocardial scarring from attenuation. Specificity can also be enhanced with the use of attenuation correction. These algorithms incorporate additional data obtained from an external radioactive source or computed tomography to create a soft tissue attenuation image of the chest and then to adjust the regional counts

on the emission scan to correct for the loss of counts because of attenuation from overlying breast, diaphragm, and chest wall structures.¹⁰

Stress-Only Imaging

For patients who have normal stress imaging, rest imaging can result in increased patient inconvenience, radiation exposure, laboratory inefficiency, and cost.¹¹ As a result, stress-only imaging protocols have been examined. A study of 460 stress-rest technetium myocardial perfusion studies noted that in 20% of studies, the stress images were completely normal and that the addition of rest images added no additional information.¹² In addition to reduced radiation exposure and patient cost, stress-only imaging has been verified from a prognostic standpoint as well, with follow-up studies of patients with normal stress-only studies demonstrating a less than 1% annualized cardiac event rate.¹³

Pharmacologic Stress Myocardial Perfusion Imaging

Many patients are unable to perform physical exercise to a workload adequate for a diagnostic exercise stress test; therefore, myocardial perfusion imaging performed after pharmacologic stress is used frequently as an alternative. This imaging is typically performed after the intravenous infusion of a vasodilator, such as dipyridamole, adenosine, or regadenoson, or after administration of the inotropic dobutamine. Dipyridamole stimulates the release of endogenous adenosine in the distal coronary vasculature, which then binds adenosine receptors in the vasculature, producing the desired effect of coronary artery vasodilation and undesirable effects such as flushing, bronchospasm, headache, and transient heart block. This vasodilation of the resistance vessels increases myocardial blood flow, mimicking the effects of physical exercise. Dipyridamole is typically administered intravenously as a bolus injection over 4 minutes with peak effect occurring at 8 minutes, at which time the radiotracer is injected.¹⁴ A 4- to 6-minute continuous infusion of intravenous adenosine is now used more commonly.^{15,16} Both agents are equally effective in increasing myocardial blood flow threefold to fivefold over rest, which is similar to that produced by exercise; however, adenosine tends to achieve maximal flow in more patients than dipyridamole does, and side effects are more common with adenosine. Regadenoson is an adenosine A2a receptor agonist that selectively increases coronary blood flow without producing side effects, such as hypotension, AV block, chest pain and flushing, which are common with adenosine and dipyridamole.¹⁷⁻¹⁹ Regadenoson can be used as an alternative stressor in patients with lung disease, because its receptor selectivity helps to avoid bronchospasm that can occur with the other vasodilators.^{20,21}

An intravenous infusion of dobutamine is also effective for pharmacologic stress. It is typically used as an alternative to vasodilator stress in patients with bronchospasm and pulmonary disease. The dobutamine infusion produces increased myocardial oxygen demand by increasing heart rate, blood pressure, and myocardial contractility.²²

All the currently used pharmacologic stress agents have similar ability to produce flow heterogeneity and corresponding perfusion defects in the presence of a significant (>50% to 70%) stenosis of a coronary artery. A meta-analysis of dipyridamole SPECT imaging demonstrated a sensitivity of 89% and specificity of 65% for the detection of coronary artery disease. Dipyridamole and adenosine tests had essentially similar sensitivities and specificities. The sensitivity of dobutamine SPECT imaging to detect CAD is approximately 80%, which is slightly lower than the vasodilator agents.²³

Pharmacologic Stress and Low-Level Exercise Combination

Failure to achieve target heart rates during exercise MPI tests decreases the sensitivity to diagnose coronary artery disease. Studies have shown that combined exercise and adenosine infusion approach was well tolerated and resulted in the detection of a greater amount of myocardial ischemia on MPI, while also allowing for the assessment of functional capacity.²⁴

A study of patients who underwent a combination of exercise and pharmacologic stress not only felt better than those who only underwent pharmacologic stress; they also had better image quality in terms of target-to-background ratio. This combination approach may be useful in patients undergoing MPI who are unlikely to achieve a goal heart rate.²⁴

Prognosis and Risk Stratification

Stable Angina

The goals of stress testing extend beyond the detection of coronary artery disease alone. For stress testing information to be useful, results must reliably identify patients of sufficiently low risk that further evaluation or intervention can be safely avoided, while also providing additional information to the clinical risk assessment when results are abnormal. The ability of exercise and pharmacologic MPI to add incremental prognostic information to the clinical risk assessment in patients with known CAD has been evaluated in thousands of patients.²⁵ Several large studies of patients with known or suspected CAD, including both men and women, have demonstrated the incremental prognostic value of a normal MPI.²⁶⁻³⁰ Perhaps of greatest clinical utility is that these studies have consistently shown that patients with normal MPI have a subsequent annual rate of cardiac death and nonfatal myocardial infarction (MI) of less than 1%, even in patients with known CAD.^{31,32} When the results are abnormal, the SPECT scan provides incremental prognostic information beyond that obtained by clinical, ECG, and stress testing combined. Moreover, the value of SPECT MPI in determining prognosis is such that the information obtained from subsequent coronary angiography does not provide any incremental prognostic information beyond that obtained by the SPECT results.^{33,34} The increase in the risk of hard events increases in proportion to the severity and extent of the perfusion defect when assessed by semiquantitative methods or automated

quantitative approaches. The degree of ischemia on SPECT is associated with an increase in the short-term incidence of nonfatal MI, whereas scar size is more predictive of cardiac death.³² Important stress MPI variables that are predictive of future cardiac events include defects in more than 1 vascular territory (multivessel disease), transient left ventricular cavity dilation during stress,³⁵ and increased pulmonary uptake of radiotracer^{36,37} (suggesting increased LV filling pressures), as well as other parameters outlined in [Box 54-1](#). The prognostic ability of stress MPI is also enhanced by inclusion of ECG-gated SPECT, which permits assessment of left ventricular global systolic performance, the most potent predictor of event-free survival, as well as analysis of regional wall motion and left ventricular volumes.³⁸⁻⁴⁰

Medical Therapy versus Revascularization

One of the most important contributions of stress MPI in the clinical evaluation of patients with known or suspected CAD is the ability to provide prognostic information that can be used to guide further testing and therapies. Because the extent and severity of ischemia on a stress MPI study is directly proportional to the risk of future cardiac events, this information can be incorporated into the decision-making process concerning medical or revascularization therapies for a given patient. Patients with mild ischemic defects that are not high risk generally can be safely treated medically, whereas high-risk findings (e.g., transient ischemic dilation, multivessel disease pattern, large territory at risk) should be strongly considered for more invasive evaluation with a lower threshold for revascularization. A 3-year follow-up study of patients with mild to moderate defects on stress SPECT myocardial perfusion imaging treated with medical therapy noted a 2% incidence of cardiac death or nonfatal infarction and a less than 5% rate of revascularization, suggesting that SPECT imaging is highly useful in selecting patients with CAD at a sufficiently low risk for events

BOX 54-1 Stress Testing Variables Associated with Worse Prognosis

PERFUSION PARAMETERS

- Multivessel disease pattern
- Large reversible (ischemic) defect
- Large scar, >14% of left ventricle
- Transient left ventricular dilation with stress
- Right ventricular uptake
- Resting left ventricular dysfunction
- Pulmonary uptake of ²⁰¹Tl

NONPERFUSION PARAMETERS

- Poor exercise capacity
- Angina at low workload
- Dynamic ST-segment depression ≥ 3 mm with exercise
- Exercise-induced ventricular arrhythmias
- Vasodilator stress-induced ST-segment depression ≥ 1 mm
- Hypotensive blood pressure response

such that revascularization is not necessary.⁴¹ In contrast, the benefit of revascularization over medical therapy has been characterized in patients with high-risk stress SPECT MPI findings. Hachamovitch and colleagues³² followed 5183 patients after stress MPI for a mean of 2 years; they found that the rates of MI and cardiac death did not differ substantially from patients treated with medical therapy or revascularization after a normal or mildly abnormal scan. However, patients with severely abnormal scans had significantly higher annualized cardiac death rate when treated medically (4.6% per year) compared to those referred for revascularization (1.3% per year; Fig. 54-3). Patients with a greater ischemic burden on imaging were also found to benefit more from revascularization than from medical therapy, with serial imaging studies showing a greater reduction in reversible defect size in those treated with revascularization. A subsequent observational study of 10,627 consecutive patients with no prior infarct or revascularization demonstrated a survival advantage in patients with no or mild ischemia treated with medical therapy versus medical therapy, with revascularization having prognostic benefit beyond medical therapy in patients with moderate to severe ischemia.⁴² The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial⁴³ showed no difference in the incidence of death or myocardial infarction in 2287 with stable angina randomized to optimal medical therapy or percutaneous revascularization. A substudy of this trial showed that the addition of percutaneous revascularization to optimal medical therapy resulted in more effective reduction of ischemia than medical therapy alone, with less angina.⁴⁴ Moreover, regardless of treatment assignment, the degree of residual ischemia on follow-up perfusion imaging was proportional to the risk of subsequent cardiac events. More recently, the Bypass Angioplasty Revascularization Investigation 2 Diabetes Trial (BARI 2D) was completed in search of the optimal treatment for diabetic patients with stable ischemic heart disease. The two groups compared were prompt revascularization therapy with intensive medical therapy versus intensive medical therapy alone. At 5 years, there was no significant difference in the rates of death and major cardiovascular events between the two groups.⁴⁵ In the COURAGE and BARI 2D trials, the decision of revascularization or intensive medical therapy was made after cardiac catheterization. Based on these studies, it appears that revascularization can be used selectively in patients with CAD based on the extent and severity of the ischemic burden. Patients with low-risk findings can be treated medically, whereas extensive ischemia is best treated with more aggressive interventions.

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial is an ongoing trial comparing revascularization and optimal medical therapy against optimal medical therapy alone before cardiac catheterization in a group of higher-risk patients with stable ischemic heart disease.

These principles have been shown to have favorable effects in terms of patient outcomes and cost when applied clinically. Several large studies have focused on

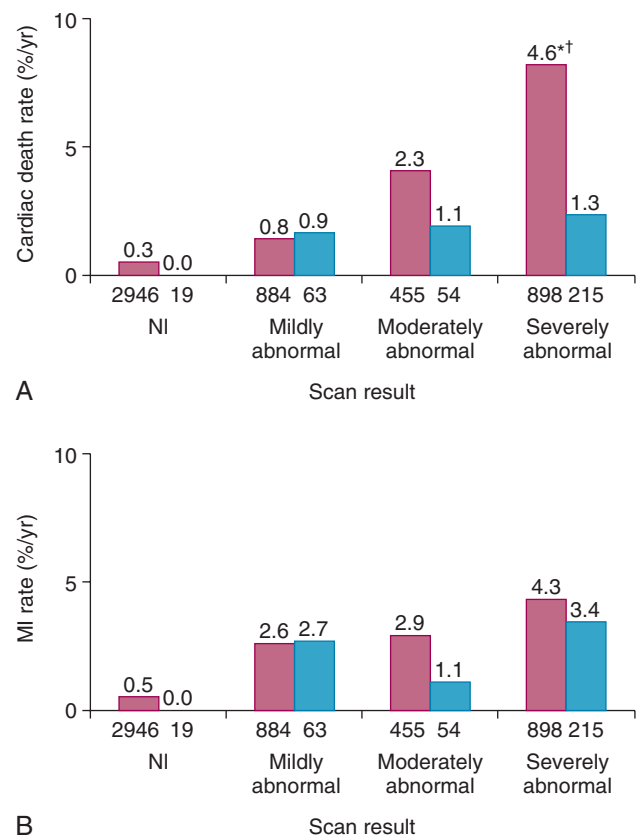


FIGURE 54-3 ■ Single photon emission computed tomography (SPECT) myocardial perfusion imaging and prognosis. This large retrospective analysis of patients undergoing stress SPECT myocardial perfusion imaging demonstrates the incremental prognostic information obtained with the imaging results. The annualized incidence of cardiac death (**A**) and myocardial infarction (MI) (**B**) is displayed for patients treated medically (solid columns) and for those undergoing revascularization (gray columns) with respect to the myocardial perfusion image result. Annualized cardiac events were low (<1%) in both groups with normal SPECT studies. However, event rates increased with respect to the degree of SPECT abnormality. Survival was significantly improved in those with severely abnormal scans who underwent revascularization. * $P < 0.01$ compared with patients undergoing revascularization early after nuclear testing; † $P < 0.001$ compared with patients treated with medical therapy after nuclear testing. *Abnl*, Abnormal; *NI*, normal. (Reprinted with permission from Hachamovitch R, Berman DS, Shaw LJ, et al: Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation* 97:535–543, 1998.)

the clinical use of stress MPI to guide patient management, and they have shown that referral for coronary angiography is accordingly low ($\approx 3.5\%$) after a normal stress MPI, but increases to 60% when the stress MPI is moderately to severely abnormal.^{32,46,47} This finding demonstrates that clinicians can incorporate MPI into their practice appropriately, particularly when deferring further invasive evaluation when the MPI is normal. The use of stress MPI to guide patient management has also been demonstrated to be cost-effective. An “ischemia-guided” approach to managing patients with CAD has been shown to optimize the use of angiography and

subsequent revascularization procedures.⁴⁸ The Economics of Noninvasive Diagnosis study^{49,50} compared differences in cost in 11,372 consecutive patients referred for either stress MPI or cardiac catheterization as the initial approach. The rates of subsequent myocardial infarction were the same in the two groups, and costs were significantly higher for the direct cardiac catheterization group as compared with the MPI ischemia-guided approach. Moreover, patients sent directly to cardiac catheterization were more likely to be treated with coronary revascularization in all subsets of risk when compared with those undergoing stress MPI initially. The ischemia-guided approach to stable angina was found to be less costly, with fewer interventions and similar cardiac event rates. These cost differences can be attributed directly to a decrease in apparent unnecessary procedures in patients with negative MPI results.

Preoperative Evaluation for Noncardiac Surgery

Perioperative cardiac events are an important cause of morbidity and mortality during and after noncardiac surgery, and they occur in more than 2% of patients undergoing these procedures. Much of this risk can be assessed preoperatively with clinical evaluation using the Revised Cardiac Risk Index (e.g., history of coronary artery or cerebrovascular disease, congestive heart failure, renal insufficiency, diabetes requiring insulin, high-risk surgical procedure) to identify patients at high risk for cardiac complications who might benefit from risk-reduction strategies (i.e., specific perioperative medical therapy or revascularization) and subjects of sufficiently low risk for whom further evaluation before surgery is not necessary.⁵¹ However, patients with an intermediate risk for cardiac complications may benefit from further noninvasive testing to identify ischemia and provide further risk stratification before surgery.⁵² Provocative testing for ischemia is typically performed for such patients; however, exercise testing is not always feasible in patients with pulmonary disease or low exercise capacity, and in particular those undergoing orthopedic or vascular surgery. Pharmacologic stress MPI has been shown to add significant information to preoperative risk stratification⁵³; it is recommended for patients with intermediate clinical risk predictors (e.g., prior MI, diabetes, renal insufficiency) who have poor functional capacity or those undergoing a high-risk surgical procedure (e.g., emergent surgery, aortic or peripheral vascular surgery, prolonged procedures with anticipated large blood loss or volume shifts). When results of stress MPI are normal, the incidence of perioperative cardiac events has been shown to be approximately 1% for all procedures, including major vascular surgery.⁵⁴ Although the severity and extent of ischemia remains an important predictor of adverse cardiac events during and after surgery, recent studies have shown that revascularization before noncardiac surgery does not appear to affect outcome in terms of death and nonfatal myocardial infarction.⁵⁵ As such, the 2014 ACC/AHA guidelines now recommend nuclear stress imaging selectively in patients with a high clinical risk of perioperative cardiac events.

ACUTE CORONARY SYNDROMES

Territory at Risk and Infarct Size

Resting MPI has been used to determine the territory at risk during an acute coronary syndrome, and it can be used to assess the extent of myocardial salvage achieved with reperfusion strategies.⁵⁶ Tc-99m-labeled radiopharmaceuticals can be injected at rest in the setting of an acute ST-segment elevation myocardial infarction upon presentation. After initial treatment and stabilization with either pharmacologic or mechanical reperfusion, perfusion images can be acquired that represent the initial myocardial area at risk during the coronary occlusion. These images are then compared to those acquired at rest after a subsequent injection after reperfusion. The difference in the size of the defect on these two scans is the *salvage index* (initial territory at risk-to-ultimate scar, which represents the degree of myocardium that was rescued by reperfusion).^{57,58} This methodology is not used widely in clinical practice, but it is a useful tool in the evaluation of therapies used in the treatment of acute myocardial infarction. The salvage index has been validated as a surrogate marker of patient outcome, and provides a quantitative means to compare the efficacy of therapeutic strategies.⁵⁹ The use of the infarct size, territory at risk, and the salvage index has played a central role in trials focusing on the efficacy of angioplasty^{57,60} and thrombolysis.⁶¹ This methodology can also assist in determining important clinical factors associated with reperfusion outcome such as time to reperfusion.⁶⁰

Myocardial infarct size can be measured quantitatively after MI and has been shown to be highly predictive of poor outcome.^{58,59,62,63} The ischemic burden on cardiac stress SPECT imaging is associated with future nonfatal myocardial infarction, whereas fixed perfusion defects and a depressed ejection fraction are predictive of future cardiac death.⁶⁴ Quantification of the infarct size as a percentage of the left ventricle is effective to risk stratify a patient's risk for cardiac death over the near term. Studies using Tc-99m SPECT after acute myocardial infarction have observed that mortality within the subsequent 24 months is approximately 8% if the infarct encompasses more than 12% to 14% of the left ventricle.^{63,65}

Rest Myocardial Perfusion Imaging for Acute Coronary Syndrome

The triage of patients presenting to the emergency department with acute chest pain is a substantial diagnostic challenge. Radionuclide myocardial perfusion imaging has been shown to have favorable diagnostic and prognostic value in this setting, with an excellent sensitivity to detect acute myocardial infarction that is not recognized by other testing modalities (i.e., serum markers, ECG).⁶⁶⁻⁷⁰ A major advantage of a triage protocol that uses rest SPECT MPI is that ischemia and infarction can be detected earlier than with serum markers. A patient with chest pain and an ECG that is normal or nondiagnostic for ischemia or infarction can receive an injection

in the emergency department and then be imaged within 30 to 60 minutes. Several observational and randomized studies have repeatedly shown that a normal resting perfusion imaging study has a negative predictive value greater than 99% to exclude myocardial infarction and that defects at rest are associated with a higher incidence of death and MI at 30 days.⁶⁹⁻⁷² A recent trial by Lim and colleagues⁷³ examined whether the addition of stress MPI to the standard emergency department evaluation of chest pain would improve decision making in terms of hospital admissions or subsequent cardiac events. In this trial, patients were observed in the emergency department for 6 hours with serial ECGs and cardiac marker evaluations. If results of their 6-hour stay was negative, they were randomized to either standard emergency department care or stress MPI. Findings of this study showed that patients in the stress MPI group had an 8% lower rate compared with those in the clinical assessment only group and no difference in the risk of cardiac events at 30 days.⁷³ As such, a normal resting MPI in a patient with chest pain essentially excludes acute MI (AMI) and is predictive of a sufficiently low risk of near-term adverse cardiac events that the patient can be discharged home. Alternatively, an abnormal study is associated with a worse near-term outcome, and hospitalization is warranted (Fig. 54-4). Once MI or unstable angina are excluded, provocative testing can be performed, with or without MPI, to identify stress-induced ischemia. Protocols that use immediate rest MPI to exclude an acute coronary syndrome and subsequent stress testing to evaluate for significant CAD have demonstrated both reductions in unnecessary hospitalizations and cost savings compared with routine care.⁷⁴

Postmyocardial Infarction Risk Stratification

Stress MPI has been shown to have excellent diagnostic value in patients after an AMI. Dipyridamole vasodilator stress MPI early after AMI is highly predictive of future cardiac events. In fact, recent studies have found that the most important predictors of future cardiac death and recurrent myocardial infarction are the extent and severity of degree of the reversible (ischemic) myocardial perfusion defect. Bateman and colleagues⁷⁵ reported the results of a multicenter trial that randomized 451 patients after a first AMI to either early (hospital days 2 to 4) dipyridamole stress MPI or routine predischarge (hospital days 6 to 12) submaximal exercise MPI. The extent and severity of the stress defect and the degree of defect reversibility were found to be the most important predictors of cardiac death and recurrent myocardial infarction. The early use of pharmacologic stress perfusion imaging after acute infarction was more predictive of early and late cardiac events, and provided greater incremental diagnostic and prognostic value than predischarge submaximal exercise perfusion imaging. One major advantage of this approach is that management decisions can be made much earlier in the hospital course after an uncomplicated acute myocardial infarction. More recently, the INSPIRE trial showed that MPI performed early after AMI in appropriate patients can safely and reliably identify patients with low-risk findings or lack of inducible ischemia who would be unlikely to benefit from an invasive approach as well as those with extensive ischemia in whom intensive anti-ischemic medical or interventional therapies are appropriate. As such, noninvasive

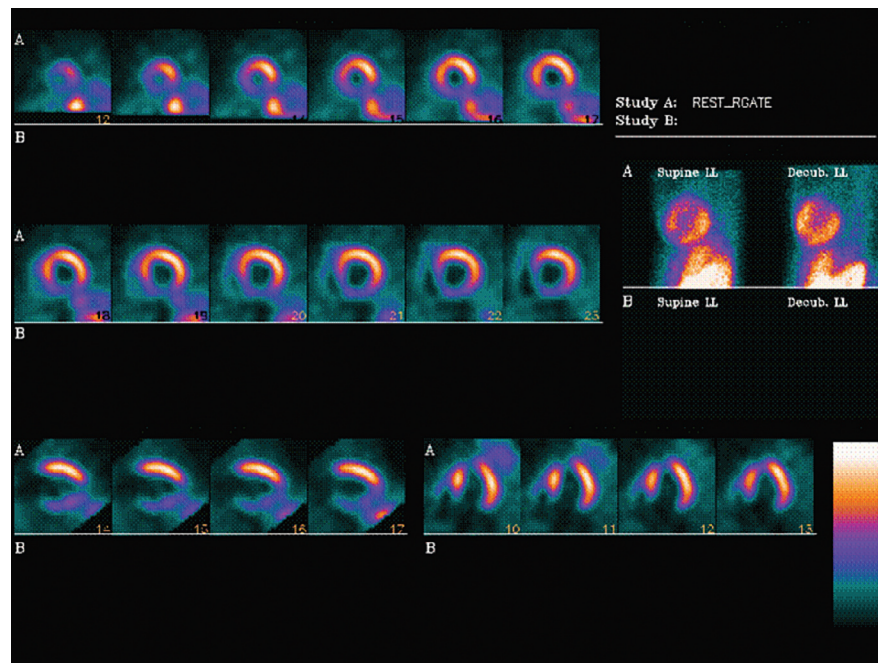


FIGURE 54-4 ■ Rest single photon emission computed tomography myocardial perfusion imaging during ongoing chest pain in a patient with a normal electrocardiogram. Injection of radiotracer during ongoing chest pain and subsequent imaging 45 minutes later demonstrates a moderate-sized area of decreased perfusion in the inferior wall. The patient was brought directly to cardiac catheterization, and coronary angiography demonstrated a 95% stenosis of the right coronary artery that was treated with angioplasty and intracoronary stenting.

imaging as an initial strategy for categorizing risk and triaging subsequent care in stable survivors of myocardial infarction who have not undergone acute coronary angiography seems reasonable.⁷⁶

ASSESSMENT OF MYOCARDIAL VIABILITY

Left Ventricular Ejection Fraction and Prognosis

Numerous studies have demonstrated that left ventricular systolic performance is a powerful and independent predictor of mortality in patients both with and without coronary artery disease. When the LVEF becomes depressed after MI or with chronic ischemic heart disease, the risk of sudden cardiac death increases substantially.^{38,77-79}

Data from the Thrombolysis in Myocardial Infarction trials indicated that the prognostic significance of LVEF assessment was also maintained after thrombolysis, although the overall mortality was lower than in the pre-thrombolytic era.⁸⁰ The powerful prognostic significance of resting LVEF assessed by radionuclide angiography is also important in patients treated with thrombolysis or primary angioplasty.^{77,81} Resting LVEF is not only the strongest predictor of 6-month mortality; it is also predictive of ventricular arrhythmias and sudden death in a similar group of patients. The prognostic significance of LVEF in patients with chronic coronary artery disease is also well established and is independent of the extent of anatomic disease.⁸²

All the available techniques used to assess left ventricular function, including nuclear techniques such as radionuclide angiography and gated-SPECT, as well as two and three-dimensional echocardiography, contrast ventriculography, and magnetic resonance imaging, can provide similar prognostic information in patients with myocardial infarction and chronic CAD. Radionuclide angiography is a highly accurate, widely validated, and reproducible technique, making it a useful tool when serial measurements of LVEF are required. However, the more widespread use of two-dimensional resting echocardiography, gated-SPECT MPI and MRI has led to these modalities replacing radionuclide angiography for the assessment of LVEF. Ejection fraction assessed during gated-SPECT stress MPI provides incremental prognostic information beyond the perfusion imaging results. In a study of 1680 patients undergoing stress MPI, patients with a gated SPECT LVEF $\geq 45\%$ had low mortality rates ($<1\%$ per year), even when associated with severe perfusion defects. However, patients with an LVEF $< 45\%$ on gated SPECT had a mortality rate of 9.2% per year, even if only mild to moderate perfusion abnormalities were present.⁸³ This finding underscores the importance of LVEF in determining prognosis, and the need to pursue aggressive medical and surgical strategies in patients with depressed LVEF. Gated SPECT indices of end-diastolic and end-systolic volumes consistent with left ventricular dilation have also been shown to add prognostic value in predicting cardiac death and nonfatal

myocardial infarction independent of the perfusion abnormalities on the scan.³⁸

PET and SPECT in Determining Myocardial Viability

Left ventricular ejection fraction is a major determinant of survival in patients with ischemic heart disease. As a result, therapeutic strategies that can improve systolic performance and thereby improve survival have been widely studied. Patients with chronic coronary artery disease and patients after acute myocardial infarction represent two important groups at risk for the development of left ventricular dysfunction. However, the left ventricular systolic dysfunction is not always due to scarring and fibrosis of the myocardium, and it may be the result of the repetitive or chronic myocardial ischemia. As such, left ventricular dysfunction at rest may not necessarily be irreversible. Thus, the evaluation of patients with ischemic cardiomyopathies because of chronic CAD or myocardial infarction becomes important to select which patients might have reversible dysfunction and potentially benefit from coronary revascularization.

Ischemic myocardial dysfunction can be produced by four pathophysiologic processes. After myocardial infarction, the myocardium within the vascular territory served by an acutely occluded culprit artery can undergo necrosis and scarring, leading to extensive fibrosis and subsequent regional dysfunction. With an acute coronary syndrome, if myocardial blood flow is restored either spontaneously or with a therapeutic reperfusion strategy such as angioplasty or thrombolysis, regional contractile dysfunction may occur even without myocardial necrosis, a state termed *stunning*. This postischemic dysfunction after a transient period of ischemia followed by reperfusion is characterized by normal flow but reduced function in the absence of myocardial scarring. Regional dysfunction can also be observed in chronic CAD, with reductions in blood flow presumably occurring more slowly. The contractile impairment is thought to be due to a compensatory downregulation of function during prolonged periods of myocardial hypoperfusion, a concept termed *hibernation*. Left ventricular dysfunction can also deteriorate because of remodeling, which is characterized by histologic and biochemical changes in the myocardium because of an ischemic insult.

Myocardial viability was initially defined as the ability to recover global or regional LV function after revascularization. In this paradigm, treatment of repetitive or chronic ischemia, defined pathologically as *stunning* and *hibernation*, respectively, was deemed responsible for the improvement in contractility. As such, the ability to identify dysfunctional but viable myocardium resulting from these pathologic states became important when considering a patient for potential revascularization.

Although recovery of function may be an important goal of revascularization, the central goal of assessing myocardial viability is to predict outcome with therapy—that is, to differentiate patients with potentially reversible left ventricular dysfunction whose prognosis might be improved with revascularization from those with large areas of infarct or scar who might not benefit (or even do

worse) with surgery. Thus, viability assessment provides better insight into the risk/benefit ratio in patients with ischemic left ventricular dysfunction by effectively stratifying those with a significant amount of viable myocardium who are at increased risk if treated medically from those who would be at high risk with either treatment.

Currently, there are a number of diagnostic approaches for assessing myocardial viability in patients with ischemic cardiomyopathy. The major nuclear cardiology modalities to determine viability include techniques that assess cell membrane integrity, regional perfusion, and myocardial metabolism.

Viability assessments are typically performed in a particular subset of patients, namely those with known coronary artery disease and left ventricular systolic dysfunction who are potential candidates for surgical revascularization. Most viability assessment is performed in patients with chronic ischemic cardiomyopathies or after acute myocardial infarction, because as many as 50% of patients with prior myocardial infarction will have residual viable myocardium.⁸⁴ The methods for viability assessment are similar to those used for prognostic assessment in patients with CAD. As such, protocols used for stress myocardial perfusion imaging can be easily modified to obtain information regarding viability. However, if the assessment of viability is the principal clinical question, a protocol designed to assess specifically viability should be used. In patients in whom the question of myocardial viability is primary, however, it is best to perform a specific viability imaging protocol. The nuclear cardiology techniques that have been validated extensively in the assessment of myocardial viability include the use of positron emission tomography (PET) imaging of myocardial metabolism, and resting SPECT perfusion imaging of ²⁰¹Tl and the ^{99m}Tc-labeled tracers sestamibi and tetrofosmin.

Positron Emission Tomography

Positron emission tomography (PET) has been evaluated extensively as a noninvasive imaging modality for viability assessment. PET viability studies involve the determination and comparison of both myocardial blood flow and the metabolic status of the myocardium.⁸⁵ Perfusion is usually assessed with ¹³N-labeled NH₃, and glucose utilization is typically assessed with ¹⁸F-fluorodeoxyglucose (FDG), which when taken up by the myocardium reflects glucose transport across the myocyte membrane. FDG accumulates in myocytes in proportion to glucose uptake, but undergoes phosphorylation by hexokinase to FDG-6-phosphate in the first step of glycolysis. FDG-6-phosphate is a form of deoxyglucose that becomes “trapped” in the myocyte and is not metabolized further. As such, FDG uptake reflects exogenous glucose utilization. Normal myocardium preferentially utilizes fatty acids for energy, but switches to increased glucose utilization during periods of ischemia. In myocardial regions with ischemic dysfunction, myocardial glucose uptake may be increased, and thus FDG uptake will be enhanced, reflecting viability. Conversely, FDG will not accumulate in areas of fibrosis or scar. FDG uptake is then compared with resting perfusion imaging. Perfusion-metabolism is considered “matched” if areas of preserved flow show

normal metabolic activity, and areas of reduced flow have diminished FDG uptake (scar); however, perfusion and metabolism may be discordant, or “mismatched.” In this scenario, FDG uptake will be present in areas of hypoperfusion, indicating that despite decreased blood flow, the myocardium is still metabolically active, hence viable. This mismatched defect is the most predictive of functional recovery after revascularization (Fig. 54-5).

Quantitative Methods. The clinical assessment of myocardial viability using FDG is based predominantly on comparison of its qualitative or semiquantitative uptake relative to a myocardial perfusion tracer. Quantification of myocardial glucose utilization is possible, but it requires kinetic modeling of transmembrane transport and phosphorylation to adjust for the behavior of injected FDG in relation to endogenous glucose.⁸⁶ A different quantitative approach is the assessment of myocardial glucose utilization, using dynamic PET acquisitions and sequential arterial blood sampling to measure fractional FDG uptake in relation to the delivered dose.

Perhaps of greater importance is the ability of cardiac PET to determine absolute myocardial blood flow using tracer kinetic models. Quantitative myocardial blood flow can be measured with dynamic imaging of ¹³N-ammonia, ⁸²Rb, or H₂¹⁵O. These agents can be used to determine regional myocardial blood flow. Flow can be measured at rest and after pharmacologic vasodilation to determine the myocardial blood flow reserve (ratio of maximal flow to resting flow). Reduction in coronary flow reserve has proved useful in the assessment of stenosis severity (flow limitation) in CAD,⁸⁷⁻⁹⁰ in patients with no known CAD but with risk factors,⁹¹ and to evaluate changes in flow after medical treatment of such CAD risk factors as hyperlipidemia,^{92,93} diabetes,⁹⁴ and smoking.⁹⁵

Flow reserve is also useful in differentiating viable from nonviable myocardium, because a certain degree of myocardial blood flow is necessary to maintain myocyte viability. In the setting of a functionally significant coronary artery stenosis, the vasculature distal to the lesion may retain the ability to vasodilate and thus increase regional myocardial blood flow. As such, regions of myocardium that can achieve this must therefore be viable. Flow reserve has been studied as a surrogate for myocardial viability in patients with previous infarction and chronic coronary artery disease.⁹⁶

Single Photon Emission Computed Tomography

Thallium. ²⁰¹Tl has been used as a tracer to assess both regional blood flow and myocardial viability.⁸⁴ ²⁰¹Tl is actively transported across the myocyte sarcolemmal membrane via the Na-K⁺ adenosine triphosphatase similar to potassium, and it is extracted from the blood in proportion to myocardial blood flow. Cellular extraction is only diminished when there is irreversible injury to the myocyte, making ²⁰¹Tl an attractive agent for imaging pathophysiologic conditions such as chronic hypoperfusion and posts ischemic dysfunction. Because retention of thallium in the myocardium corresponds to

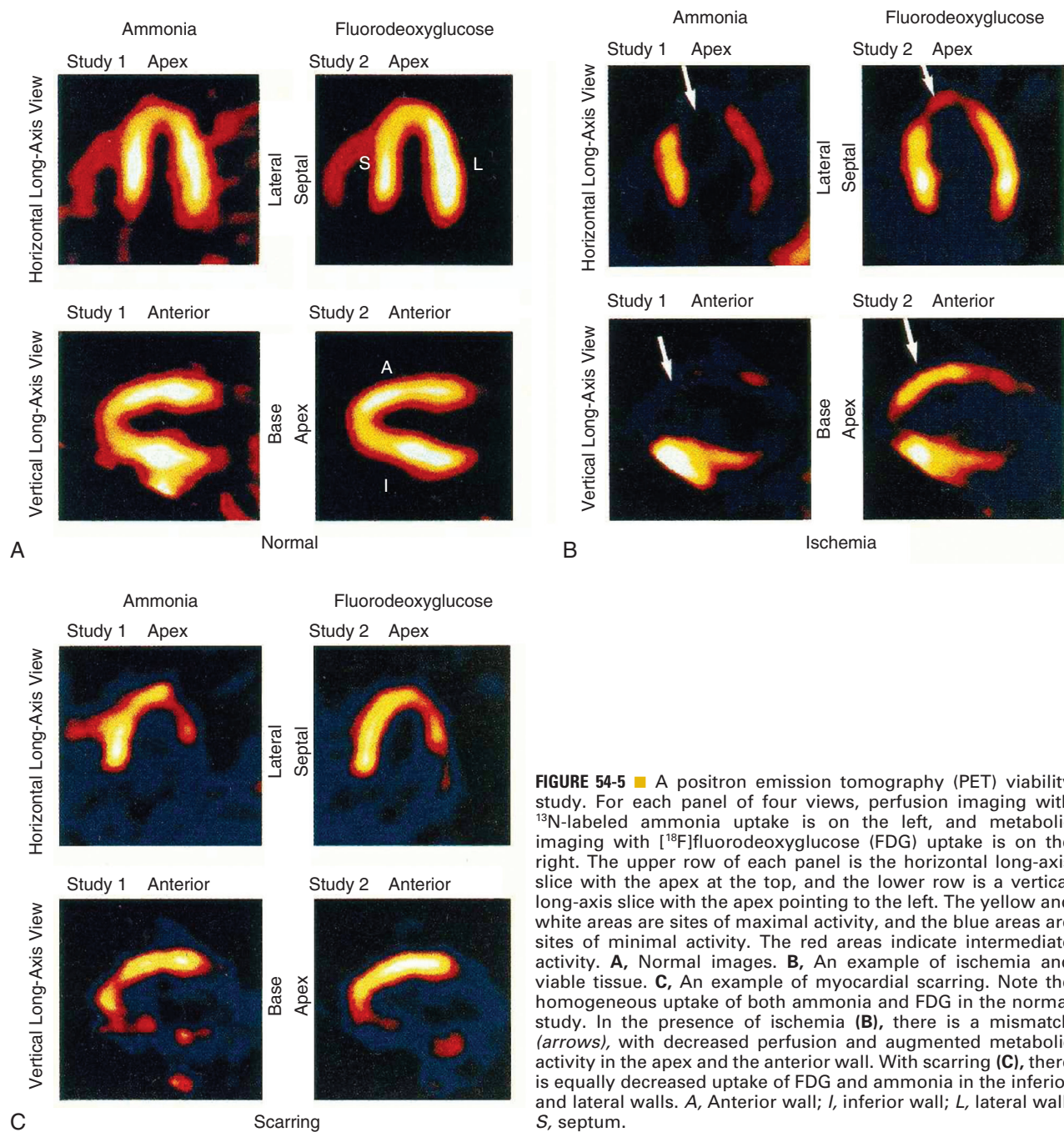


FIGURE 54-5 ■ A positron emission tomography (PET) viability study. For each panel of four views, perfusion imaging with ^{13}N -labeled ammonia uptake is on the left, and metabolic imaging with [^{18}F]fluorodeoxyglucose (FDG) uptake is on the right. The upper row of each panel is the horizontal long-axis slice with the apex at the top, and the lower row is a vertical long-axis slice with the apex pointing to the left. The yellow and white areas are sites of maximal activity, and the blue areas are sites of minimal activity. The red areas indicate intermediate activity. **A**, Normal images. **B**, An example of ischemia and viable tissue. **C**, An example of myocardial scarring. Note the homogeneous uptake of both ammonia and FDG in the normal study. In the presence of ischemia (**B**), there is a mismatch (arrows), with decreased perfusion and augmented metabolic activity in the apex and the anterior wall. With scarring (**C**), there is equally decreased uptake of FDG and ammonia in the inferior and lateral walls. A, Anterior wall; I, inferior wall; L, lateral wall; S, septum.

cell membrane integrity, regional uptake of thallium corresponds to viable myocardium. As such, decreased myocardial uptake early after ^{201}Tl injection can be due to reduced regional blood flow or infarction. After injection, ^{201}Tl redistributes in the myocardium via continuous exchange between the myocardium and the extracardiac compartments (interstitium, blood pool), driven by the concentration gradient of the tracer and intact myocyte viability. Imaging after redistribution will show less regional heterogeneity of initial ^{201}Tl distribution, thereby reducing the relative difference between the ischemic and normal regions. An increase in regional ^{201}Tl activity on the redistribution images is indicative of myocardium

that has reduced flow but more importantly intact cellular integrity, and thus viability. As such, ^{201}Tl redistribution has been used to distinguish viable from scarred myocardium. ^{201}Tl can be imaged at rest and again 4 hours later to assess redistribution, or by using another injection if part of a stress MPI protocol. Viability can also be assessed quantitatively with ^{201}Tl . The presence of ^{201}Tl uptake greater than 50% to 60% of maximum will be predictive of functional recovery in the majority of segments. Moreover, the final thallium uptake with redistribution appears to be more important than the degree of change from rest to redistribution in predicting recovery.^{97,98}

Technetium-Labeled Tracers. Technetium agents currently are used more commonly than thallium for stress MPI. These agents can still provide insight into the viability of the myocardium. The ability to determine viability from an initial stress-rest MPI study often obviates the need for further testing with PET or thallium protocols. Uptake and retention of the technetium perfusion tracers sestamibi and tetrofosmin require that the myocyte cell and mitochondrial membranes be intact. As such, tracer accumulation indicates cellular integrity, and thus reflects cellular viability.⁹⁹ Computer-assisted quantitative analysis of regional myocardial uptake of sestamibi has been shown to improve accuracy in predicting functional recovery after revascularization, and similar to ²⁰¹Tl, tracer uptake greater than 50% of peak is suggestive of myocardial viability.¹⁰⁰ The administration of nitrates to enhance resting blood and hence tracer uptake has also been studied with ^{99m}Tc-labeled agents because of issues regarding the underestimation of viability with sestamibi compared to PET imaging.^{101,102} Assessment of metabolism for viability with FDG can also be performed using SPECT systems with special equipment (high-energy collimators or coincidence detection).¹⁰³

Prognostic Implications of Viability Assessment

Despite recent advances in medical and antiarrhythmic device therapy for heart failure, patients with ischemic cardiomyopathy and congestive heart failure continue to have a poor prognosis.¹⁰⁴ As mentioned, most patients with chronic ischemic cardiomyopathies have a mixture of scar, hibernation, or stunning. An estimated 20% to 50% of patients with ischemic cardiomyopathies have a significant amount of viable myocardium, thus potentially benefitting from revascularization. Many of these patients would benefit from orthotopic heart transplant, but donor organ supply is limited; therefore, surgical revascularization is often considered to improve survival in these patients. Most observational studies have found that revascularization of hibernating myocardium improves survival and left ventricular function. The selection of appropriate patients for surgical revascularization is largely based on early surgical survival studies that provided insight as to which patients obtain the most benefit from surgical revascularization. The Veterans Administration Cooperative Trial¹⁰⁵ and the Coronary Artery Surgery Study¹⁰⁶ both demonstrated that patients with significant left main or multivessel CAD and depressed ejection fraction (35% to 50%) had better survival with revascularization than medical therapy. Not unexpectedly, these patients often have a high perioperative mortality with coronary artery bypass grafting (CABG).¹⁰⁷⁻¹⁰⁹ In many of these earlier studies, viability was based on the presence of angina. Objective assessment of viability can be useful in these patients to balance the potential benefits of revascularization with the risk of the procedure,¹¹⁰⁻¹¹² especially in those without angina. The potential to improve ventricular function (and moreover survival) with revascularization necessitates an evaluation for hibernating myocardium in most patients with left ventricular dysfunction. However, viability testing

might not be necessary if the patient has angina pectoris or if initial testing revealed stress-induced ischemia.

The clinical endpoints commonly used in viability assessment include recovery of regional or global ventricular function and improvement in symptoms, survival, or both. Most studies focusing on the assessment of myocardial viability have used improvement in ventricular function with revascularization as the clinical endpoint. While useful in comparing the accuracy of the various techniques to determine viability, functional improvement has been used largely as surrogate for outcome, because of the relationship of left ventricular function and outcome. The prognostic implications of PET perfusion-metabolism mismatch and the presence of viability on imaging with thallium or sestamibi has been demonstrated in several studies that have consistently shown similar findings.^{85,112,113} Patients with perfusion-metabolism mismatch have a high mortality when managed medically, and much lower mortality if revascularized. Conversely, those with matched defects, indicating scar, had no such difference in outcomes between medical and surgical management. Although the methods included a combination of techniques and outcomes used (death, nonfatal MI, unstable angina, need for transplant or revascularization) this distinction is not subtle. Patients with demonstrated viability had an annual event rate of 27% if treated medically compared with 6% in similar patients who underwent coronary revascularization.¹¹⁴ On the other hand, patients with matched defects suggesting no viability had similar event rates with medical or surgical treatment. This dichotomy in outcomes underscores the prognostic implication of determining viability. A meta-analysis of pooled data from 24 studies of viability using all currently used techniques encompassing more than 3000 patients further illustrates this point.¹¹² In patients with ischemic cardiomyopathy (mean LVEF, $32 \pm 8\%$), those with demonstrated viability had an annual mortality of 3.2% if treated with revascularization and 16% if treated medically. Those without viability had essentially similar outcomes (7.7% vs. 6.2% mortality, respectively). This analysis provides further evidence that the preoperative determination of viability provides information regarding not only functional recovery, but improvement in survival as well. Results from the recently completed Positron Emission Tomography and Recovery Following Revascularization-2 (PARR-2) showed a trend toward improved 1-year outcome when PET-FDG guided therapy was used compared with standard care.¹¹⁵

Most of the earlier studies performed were not randomized, resulting in an uncertain applicability of optimal medical therapy and inherent selection bias that can confound the results. In 2011, the STICH trial was the first randomized trial to compare surgical revascularization with medical therapy in LV dysfunction^{115a} with the primary outcome of all-cause mortality. At a median follow up of 56 months, medical therapy plus CABG surgery demonstrated no improvement in all-cause mortality; however, demonstrated significantly lower rates of cardiovascular death (28% vs. 33% with medical therapy alone). It is unclear whether the improvement in outcome with revascularization is entirely due to improvement in

LVEF after surgery. Samady and colleagues¹¹⁶ examined survival after CABG in 104 patients with an assessment of function before and after surgical revascularization. Outcome was similar in patients regardless of whether the LVEF improved after CABG, suggesting that revascularization of ischemic myocardium, even without improvement in ventricular function, can prevent future infarction and death. Of note, no formal viability assessment was performed in the majority of these patients. Based on studies such as these, some have advocated revascularization for all patients with ischemic cardiomyopathy asserting that hibernating myocardium should be considered in all patients with CAD and LV dysfunction.¹¹⁶ However, others maintain that preoperative viability assessment provides an opportunity to balance the potential benefit from surgical revascularization against the risks of the procedure.

Dobutamine echocardiography, and more recently cardiac MRI, are alternative modalities to assess myocardial viability. Interestingly, pooled data demonstrate that dobutamine echocardiography has a higher (84% vs. 75%) positive predictive value compared with nuclear and a lower negative predictive value (69% vs. 80%). Cardiac MRI with gadolinium enhancement is a newer modality that is gaining popularity for viability assessment. In cases with severe dysfunction of myocardium (dilated myocardium with thin walls), often conventional techniques (e.g., ²⁰¹Tl) will deem this nonviable territory; however, contrast enhanced CMR may be slightly more sensitive in this scenario.^{116a}

EVALUATION OF PATIENTS AFTER REVASCLARIZATION

Despite technical advances, the effectiveness of both percutaneous and surgical revascularization procedures is limited by restenosis and vein graft closure, respectively.

Progression of the underlying atherosclerosis or development of new stenoses can cause recurrent ischemia, manifesting as recurrence of symptoms, congestive heart failure owing to left ventricular dysfunction, MI, or cardiac death. Symptom status is not a reliable predictor of stenosis after coronary angioplasty, as evidenced by up to 25% of subjects having silent ischemia on treadmill testing.³⁶ However, routine exercise treadmill testing is not currently advocated after coronary angioplasty as it does not reliably detect restenosis.³⁴ SPECT imaging has been demonstrated to accurately detect restenosis, particularly in the 3- to 9-month window of greatest risk for restenosis, with positive and negative predictive values of approximately 90%.⁸⁰ A recent study demonstrated that ²⁰¹Tl stress defect size was predictive of cardiac death and MI, even up to 3 years after percutaneous transluminal coronary angioplasty.⁴⁹ Further study is necessary to evaluate whether routine stress MPI after angioplasty indeed alters prognosis, particularly in asymptomatic patients, and in high-risk subsets of patients (i.e., decreased LV function, multivessel or proximal left anterior descending artery disease, diabetes, renal failure) after angioplasty. The prognostic value of SPECT MPI after CABG

surgery has been studied in more than 2000 patients, consistently demonstrating that the finding of reversible defects on stress SPECT MPI is a strong predictor of worse cardiac outcome in symptomatic subjects early (1 to 5 years) after CABG, and in all subjects more than 5 years after surgical revascularization.

FUTURE DIRECTIONS

While the cornerstone of nuclear cardiology has been myocardial perfusion imaging with SPECT and PET techniques, the field is rapidly expanding in many arenas. Recent technologic advances in hardware and processing have led to the ability to acquire scans in a fraction of the time with conventional cameras. These advances will improve image quality and reduce both imaging time and radiation exposure. The field of cardiac computed tomography (CT) and CT angiography has also led to the development of hybrid cameras, such as PET/CT and SPECT/CT, which will ultimately permit fusion of the anatomic data from CT with the perfusion data from perfusion imaging, which will facilitate the simultaneous assessment of the ischemic burden produced by a given coronary artery stenosis. Novel radiotracers currently under investigation include the fatty acid analogue I-123 BMIPP, which appears to hold promise as a marker of recent myocardial ischemia with "ischemic memory" that can last up to 30 hours after an episode of cardiac chest pain.¹¹⁷ Another new tracer recently approved by the U.S. Food and Drug Administration is iodine-123 metaiodobenzylguanidine, a marker of cardiac adrenergic activity, which can be helpful in determining both response to medical therapy and prognosis in patients with left ventricular dysfunction and heart failure,¹¹⁸ as well as predicting which patients might benefit from an implantable cardiac defibrillator. Both myocardial perfusion imaging and gated blood pool imaging with phase analysis can be used to assess ventricular desynchronization that might be amenable to cardiac resynchronization therapies.¹¹⁹ Other areas currently under investigation include the concept of molecular imaging¹²⁰ of a variety of targets including angiotensin receptors,¹²¹ matrix metalloproteinases,^{122,123} integrins,^{124,125} and other processes involved in angiogenesis.¹²⁶ Advances in PET imaging^{127,128} include flurpiridaz F-18 labeled agents¹²⁹ and the Rb-82 perfusion¹³⁰ tracers. Phase 1 and 2 clinical studies have been completed for F-18, and they have demonstrated higher extraction and shorter positron range thus producing images of higher resolution. These improvements in SPECT technology hold promise to enhance the ability to image novel processes, as well as reducing both imaging time and radiation exposure.¹³¹ Such new approaches will undoubtedly contribute to the clinical utility of nuclear cardiology imaging techniques in the evaluation and management of patients with known or suspected heart disease.

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DIAGNOSTIC ECHOCARDIOGRAPHY (ULTRASOUND IMAGING IN CARDIOVASCULAR DIAGNOSIS)

Rosario V. Freeman

CHAPTER OUTLINE

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Echocardiography has broad utility in the diagnosis and management of cardiovascular disease. Echocardiography allows for real-time, precise anatomic definition and physiologic interrogation of cardiac and vascular structures at relatively low cost with minimal patient risk and discomfort. Common clinical applications for echocardiography include assessment of myocardial and valvular function, identification of structural abnormalities, and optimizing timing for surgical intervention.¹⁻⁴ Echocardiography has expanded beyond the diagnostic laboratory to include the intensive care unit, emergency department, operating room, and electrophysiology and cardiac catheterization laboratories.⁵ This chapter will briefly review the basic principles of ultrasound imaging, echocardiographic approaches, and clinical applications of echocardiography (Table 55-1).^{4,6}

BASIC PRINCIPLES

Echocardiographic images are generated from analyses of reflected ultrasound waves from piezoelectric crystals. Ultrasound waves are beyond audible sound wave range

(>20 kHz). Ultrasound waves reflect off internal structures, such as the heart and vasculature, and they are reflected back to the transducer. Analysis of the intensity and timing of these reflected sound waves allow for image generation. Propagation of ultrasound waves is optimal through liquid medium (blood). In contrast, air and bone cause significant acoustic impedance, resulting in poor ultrasound penetration. Therefore, suboptimal image generation occurs with intervening structures such as ribs or surface bandages, or if images are acquired through air-filled lungs or subcutaneous air. Factors that affect ultrasound propagation will affect image quality, such as ultrasound beam refraction, beam attenuation due to absorption of ultrasound energy by tissue, and disarrayed beam reflection or scatter.^{2,3}

ULTRASOUND IMAGING MODALITIES

Echocardiographic examinations include the use of several ultrasound modalities, including M-mode, two-dimensional imaging, color flow imaging, and spectral Doppler imaging, with continuous-wave and pulsed

TABLE 55-1 Indications for Echocardiography

Diagnosis	Key Echocardiographic Findings	Limitations of Echocardiography
Cardiomyopathy		
	LV size, wall thickness, and systolic function RV size and function PA pressure estimate Valvular anatomy and dysfunction	
Valvular Heart Disease		
Valve stenosis	Etiology and severity of stenosis LV and RV size and systolic function PA pressure estimate	May underestimate stenosis severity
Valve regurgitation	Mechanism and etiology of regurgitation Severity of regurgitation PA pressure estimate	TEE and 3D imaging may be needed to evaluate MR and valve anatomy
Prosthetic valves	Evidence for stenosis or regurgitation PA pressure estimate	Imaging prosthetic valves limited by artifact TEE needed for suspected prosthetic MR
Endocarditis	Detection of vegetations, abscess Presence, degree of valve dysfunction	TEE increases sensitivity for detecting vegetations and abscess
Coronary Artery Disease		
Acute MI	Segmental wall motion abnormality reflects “myocardium at risk” Global LV function (EF) Evaluate for MI complications	Coronary artery anatomy not directly visualized
Angina	Global and segmental LV function Exclude other causes of angina (e.g., AS, HOCM)	Resting wall motion may be normal despite significant CAD Stress echocardiography needed to induce ischemia
End-stage ischemic disease	Global and segmental LV function RV function, PA pressures	
Pericardial Disease		
	Pericardial thickening Detection, size, location of pericardial fluid Signs of tamponade physiology	Tamponade is a hemodynamic and clinical diagnosis (blood pressure, heart rate)
Aortic Disease		
Aortic root dilation	Etiology of aortic dilation Accurate aortic diameter measurements Associated aortic regurgitation	
Aortic dissection	Accurate aortic diameter measurements Imaging of dissection “flap” (dissection) Associated aortic regurgitation	TEE more sensitive and specific Cannot assess distal vascular beds
Cardiac Masses		
LV/LA thrombus	TTE has high sensitivity and specificity for LV thrombus	TEE is needed to detect LA thrombus reliably
Cardiac tumors	Size, location, and physiologic consequences of tumor mass	Extracardiac involvement not well seen Cannot distinguish benign from malignant, or tumor from thrombus
Pulmonary HTN		
	RV size and systolic function PA pressure estimate	
Congenital Heart Disease		
	Detection of anatomic abnormalities Quantitation of physiologic abnormalities LV and RV size and systolic function	No direct intracardiac pressure measurements Saline contrast may be needed to assess intracardiac shunts

3D, Three-dimensional; AS, aortic stenosis; CAD, coronary artery disease; EF, ejection fraction; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension; LA, left atrial; LV, left ventricular; MI, myocardial infarction; MR, mitral regurgitation; MV, mitral valve; PA, pulmonary artery; RV, right ventricular; TEE, transesophageal echocardiography; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

Adapted from Otto CM, Schwaegler RG, Freeman RV: *Echocardiography review guide*, ed 2, Philadelphia, 2011, WB Saunders, pp 89–91.

Doppler ultrasound. Because images are generated from reflected signals, they are not truly “real-time,” but image processing is rapid, making the time differential indiscernible. Two-dimensional (2D) echocardiography displays images using a simultaneous ultrasound array across a tomographic plane at a frame rate of 50 to 60 frames/

second. Transthoracic echocardiography uses transducer positions that provide acoustic access to the heart: parasternal, apical, subcostal, and suprasternal (Fig. 55-1). From these “windows,” tomographic image planes are aligned with respect to the cardiac anatomy in long-axis, short-axis, and apical four-chamber and two-chamber

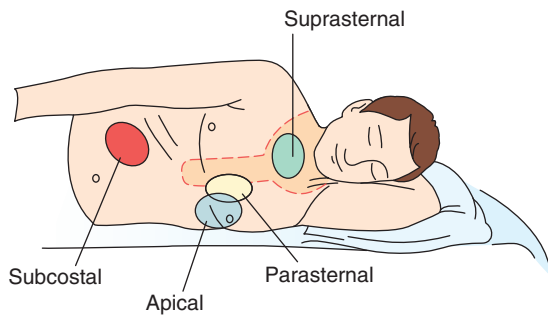


FIGURE 55-1 ■ Standard acoustic windows for transthoracic echocardiography. Parasternal and apical windows are obtained with the patient in a left lateral position. The subcostal window is obtained with the patient supine and legs flexed, to relax the abdominal wall. The suprasternal notch window is obtained with the patient's head tilted to the side to aid transducer placement. (From Otto CM, Schwaegler RG, Freeman RV: *Echocardiography review guide*, Philadelphia, 2011, WB Saunders, Figure 2-6.)

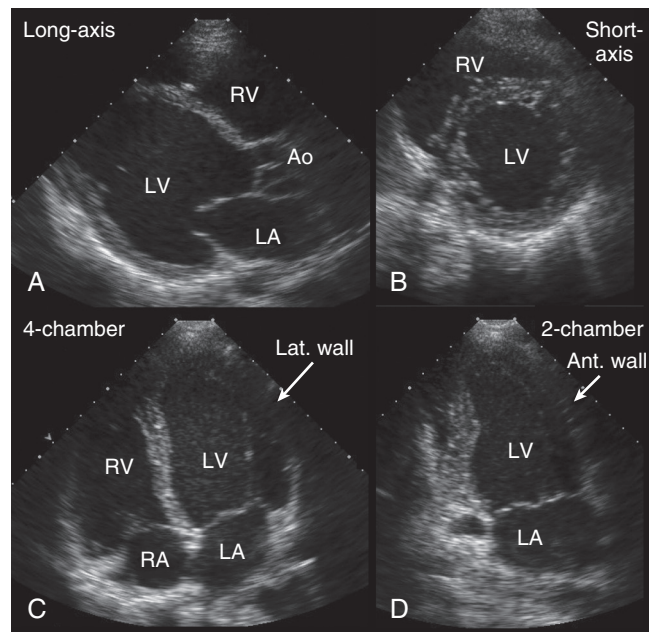


FIGURE 55-2 ■ **A**, Parasternal long axis view in a patient with dilated cardiomyopathy shows the anteroseptum and posterior wall of the left ventricle. **B**, Parasternal short axis view in a patient shows a cross-section through the mid-portion of ventricles. **C**, Apical four-chamber view shows the lateral (Lat. wall) and inferoseptal walls of the left ventricle (LV) and the free wall of the right ventricle. **D**, Apical two-chamber view shows anterior (Ant. wall) and inferior walls of the LV.

views (Fig. 55-2).⁷ Acoustic shadowing from structures that block ultrasound wave propagation, such as prosthetic valves or calcification, will block imaging distal to the structure. For example, a mechanical mitral prosthesis imaged from a transthoracic window creates acoustic shadowing of the left atrium and an inability to evaluate regurgitation severity (Fig. 55-3). Although most diagnostic echocardiography requires full ultrasound systems, smaller, handheld devices are increasingly available for portable, bedside diagnostic testing in intensive care units, emergency departments, and similar clinical settings. Recognition of ultrasound image artifacts is essential to identify abnormal findings correctly. Common

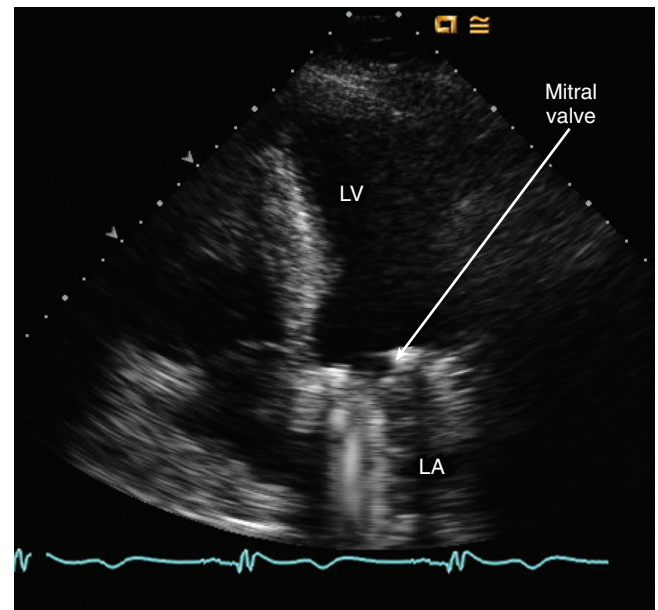


FIGURE 55-3 ■ Apical four-chamber view in a patient with a mechanical mitral valve. Acoustic shadowing distal to the valve obscures visualization of the left atrium (LA). LV, Left ventricle.

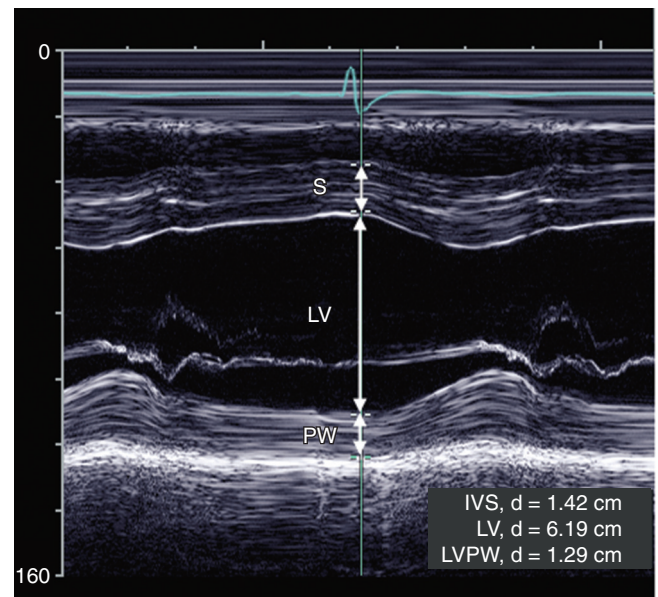


FIGURE 55-4 ■ M-mode tracing from a patient with aortic regurgitation and a dilated left ventricle (LV). LV wall thickness and chamber size are shown throughout the cardiac cycle. Diastolic measurements of the septum (S), LV chamber size, and posterior wall (PW) are shown.

artifacts include reverberations, beam width artifacts, and beam refraction, as well as external artifacts from electronic effects on the ultrasound machine, such as electrocautery during imaging.

M-mode (motion) echocardiography is produced by displaying reflected signals received from an ultrasound beam against the time dimension (Fig. 55-4). Because data from a single ultrasound beam are used, temporal (timing) resolution for M-mode is excellent, with an imaging frame rate greater than 1800 frames per second.

M-mode is useful for measurement of cardiac dimensions, for timing of events such as valve opening and closing, and for demonstrating rapid, fine motion such as fluttering of the anterior mitral valve leaflet with aortic regurgitation or independent mobility of valvular vegetations.

Transesophageal echocardiography (TEE) is a semi-invasive procedure in which the transducer is mounted on a flexible endoscope and positioned in the esophagus and stomach. Manipulation of the TEE probe is constrained by esophageal anatomy, and oblique image planes can hinder acquisition of standard images.⁸ However, image resolution for TEE is significantly improved over transthoracic echocardiography (TTE) because of the lack of intervening air or bone. Transesophageal imaging allows for better visualization of posterior cardiac structures, such as the mitral valve, left atrium, left atrial appendage, interatrial septum, and thoracic aorta. TEE is more accurate than TTE for identifying valvular vegetations and complications of endocarditis, aortic pathology, and mitral valve abnormalities. TEE is used to identify left atrial thrombus as a potential cardiac source of distal embolic disease and to exclude thrombus presence before direct current cardioversion for atrial fibrillation (Fig. 55-5).⁹ In the intensive care unit, TEE has been used in determining the etiology of unexplained hypotension,¹⁰ and it is helpful in evaluating patients after cardiac surgery at increased risk for ischemia, hypovolemia, and pericardial tamponade.¹¹ However, TEE usually requires conscious sedation to reduce patient discomfort, with additional monitoring and nursing support.

Three-dimensional (3D) echocardiographic images display cardiac anatomy using a simultaneous ultrasound array across a pyramidal volume.¹² Image processing from the large data set decreases the imaging frame rate even lower than 2D imaging, but spatial resolution is further

improved. Both transthoracic and transesophageal 3D imaging transducers are available. Image processing of 3D volume data sets can systematically “cut away” portions of the volume to provide two-dimensional image planes analogous to standard long-axis, short-axis, and four-chamber views. Intraprocedural 3D TEE imaging is increasingly being used to aid operators, such as in aortic annulus cross-sectional area sizing for transcatheter aortic valve placement, percutaneous closure device placement, and procedural success of mitral balloon valvuloplasty (Fig. 55-6).^{13,14}

Contrast echocardiography is performed in conjunction with echocardiography to opacify cardiac chambers. Contrast agents include intravenous agitated saline to opacify the right heart chambers for detection of intracardiac shunts (Fig. 55-7), and commercially made microbubble agents that traverse the pulmonary bed to provide left heart opacification. Opacification of the left-sided cardiac chambers enhances endocardial border definition to aid in wall motion analysis when image quality is suboptimal (Fig. 55-8).¹⁵ Although microbubble transpulmonary contrast can provide information on myocardial perfusion, this methodology is still in development.^{16,17}

Epicardial intraoperative echocardiography is performed by placing the transducer directly on the heart during cardiac surgery. This modality is used when anterior structures are suboptimally seen with a transesophageal approach. In intravascular ultrasound, imaging is performed via a percutaneously placed intravascular catheter. The most common use of this technique is intracoronary transducer placement to assist in plaque characterization and assessment of stenosis severity and intracardiac transducers used in the catheterization and electrophysiology laboratories for periprocedural aid in catheter placement.

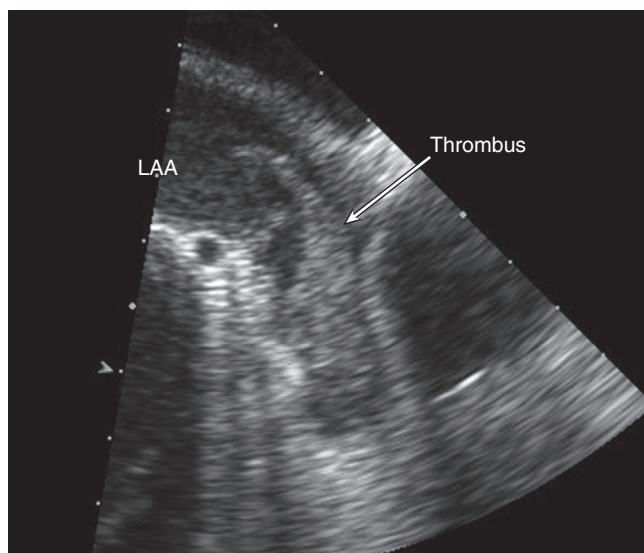


FIGURE 55-5 ■ Imaged using transesophageal echocardiography, an atrial thrombus is seen in the left atrial appendage (arrow) in a patient with atrial fibrillation undergoing evaluation for elective cardioversion. Low-velocity blood flow is evidenced by the spontaneous echo contrast seen at the ostia of the left atrial appendage.

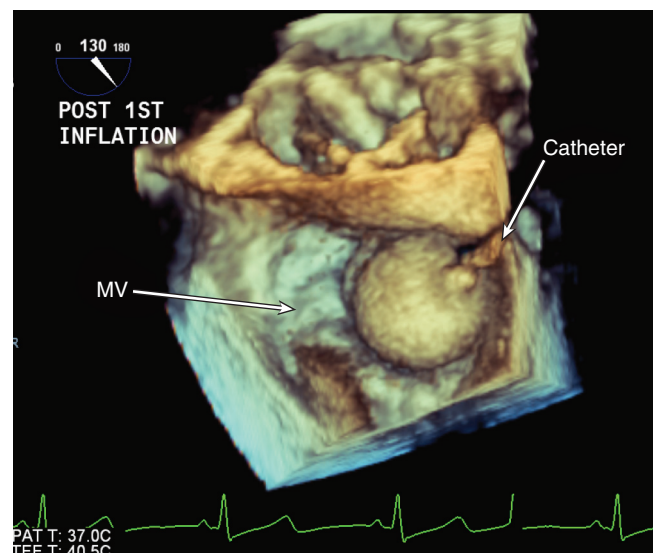


FIGURE 55-6 ■ Three-dimensional transesophageal echocardiography during a mitral valvuloplasty procedure imaged from the atrial side of the valve with a catheter crossing the valve and the valvuloplasty balloon inflated. MV, Mitral valve.

DOPPLER ECHOCARDIOGRAPHY

Doppler echocardiography provides information on the direction and velocity of blood flow.^{1,3} Reflected frequencies from an object moving toward a sound source are higher than the original signal, and are lower from an object moving away from the sound source. Doppler echocardiography measures Doppler shift in the reflected signals from moving red blood cells. By convention, frequency shifts toward the transducer are shown above the

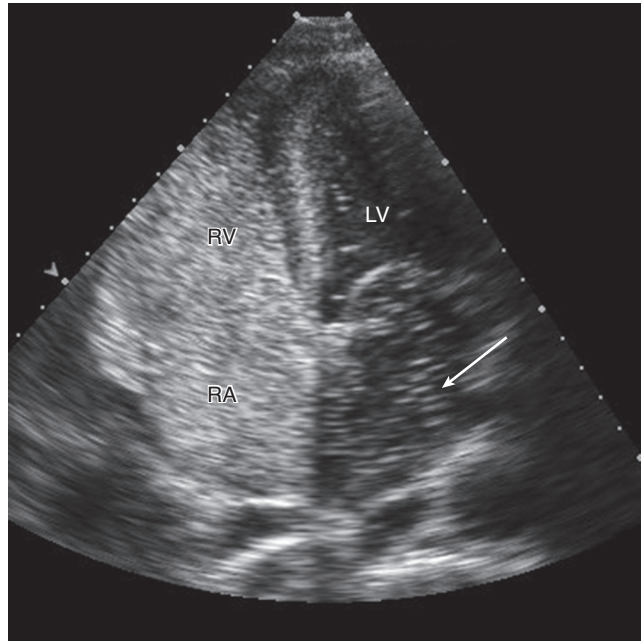


FIGURE 55-7 ■ Opacification of the right atrium (RA) and right ventricle (RV) with intravenous agitated saline contrast. The presence of an interatrial shunt is demonstrated by right-to-left shunting across the septum with bubbles (*arrow*) in the left atrium and left ventricle (LV) within three cardiac cycles.

zero baseline, and shifts away from the transducer are shown below the baseline. Importantly, detecting maximum velocity relies on parallel alignment of the ultrasound beam with the direction of blood flow, and a nonparallel intercept angle will result in erroneous data with underestimation of maximum velocity.

With pulsed wave Doppler (PWD), the transducer alternates between sending and receiving signals, sampling blood velocities at a specified depth along the ultrasound beam. There is a limited measurable maximal velocity with PWD (the “Nyquist limit”) beyond which the signal aliases and peak velocity cannot be accurately measured. With continuous wave Doppler (CWD), the transducer continuously transmits and receives signals along the entire length of the ultrasound beam. Although the specific depth origin of the CWD velocity cannot be localized, signal aliasing does not occur, and higher blood velocities, such as seen in stenotic valves, can be measured.

PWD and continuous wave Doppler (CWD) velocity data are displayed as a graph of velocity versus time, with signal strength displayed using a decibel grey scale. By convention, frequency shifts toward the transducer are shown above the baseline. The velocity time integral (VTI) is the integral of blood flow velocity over time, measured in distance. The shape, timing, and density of spectral Doppler images provide valuable qualitative evaluation of blood flow, and increased jet density suggests increased flow volume. Rapid equalization of pressure gradients between two cardiac chambers leads to steeper jet slopes (Fig. 55-9). Color Doppler echocardiography is an application of pulsed Doppler imaging in which data from multiple PWD samples across a 2D imaging sector are combined and velocities are mapped onto a color scale. These color maps are then superimposed onto a 2D image, providing directional blood flow information. By convention, flow toward the transducer is displayed in red and flow away is displayed in blue, with the color transition occurring at the Nyquist limit. Color Doppler echocardiography is used for qualitative

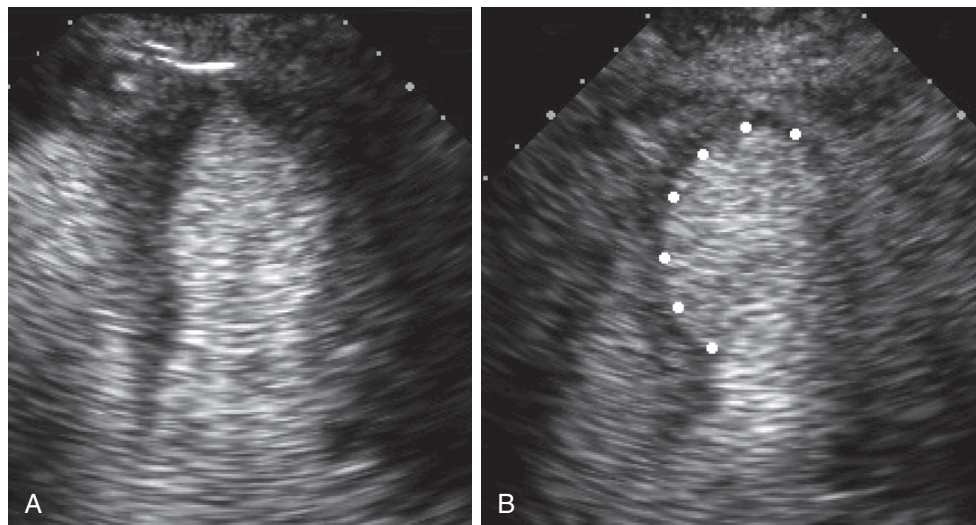


FIGURE 55-8 ■ Abnormal stress echocardiogram with images of the apical four-chamber view taken at rest (**A**) and following administration of dobutamine (**B**). Transpulmonary microbubble contrast is used to opacify the left ventricular chamber. After dobutamine administration, there is a wall motion abnormality, with hypokinesia and contour change in the apex and distal septum of the left ventricle (*dots*).

evaluation of valve regurgitation by examining the timing and extent of flow disturbance created by the regurgitant jet. Severity is usually rated on a scale of 1+ (mild) to 4+ (severe).

Doppler echocardiography is invaluable for evaluation of valve regurgitation.^{18,19} Color Doppler mapping aids in visualization of the jet origin and direction. Measurement of the narrowest jet width on color Doppler imaging (vena contracta) at or just distal to the regurgitant orifice is a simple measure that correlates with regurgitation severity (Fig. 55-10). Accuracy in measuring the vena contracta is crucial because small errors lead to inaccurate assessment of regurgitation severity. Other qualitative

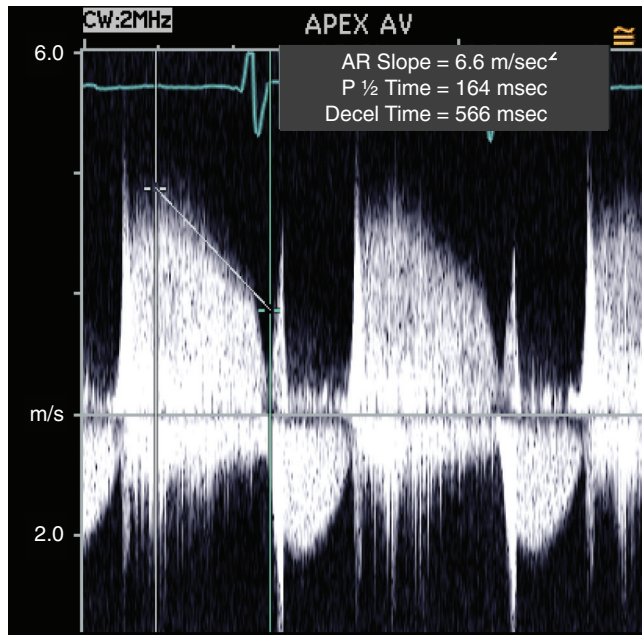


FIGURE 55-9 ■ Spectral Doppler tracing of a patient with severe aortic regurgitation. The Doppler density of regurgitant flow (above the baseline) is nearly equal to anterograde flow (below the baseline). There is a steep aortic regurgitant Doppler slope, suggesting rapid equalization of pressures between the aorta and left ventricle. AR, Aortic regurgitation; Decel, time duration for velocity deceleration; P ½, time duration for pressure gradient to decrease by half.

markers of regurgitation severity include flow reversal of the Doppler signal in adjacent upstream vascular structures, seen when regurgitation severity is moderate or greater.

When combined with qualitative measures, Doppler echocardiography allows for hemodynamic assessment, such as quantitation of valve stenosis and regurgitation severity, cardiac stroke volume, ventricular systolic and diastolic function, and intracardiac pressure calculation. There are three primary Doppler principles used in clinical practice: (1) flow quantitation (stroke volume calculation), (2) continuity of flow, and (3) pressure/velocity (Bernoulli's equation). The stroke volume (SV) traversing a cardiac orifice is the product of the cross-sectional area (CSA) at that point and the velocity time integral (VTI_{FLOW}).

$$SV = CSA \times VTI_{FLOW}$$

Cross-sectional area, assuming a circular orifice, is calculated by measuring the diameter at the point of interest ($Area = \pi r^2$). The velocity time integral is obtained from spectral Doppler interrogation. The principle of continuity of flow describes the concept that the stroke volume passing just proximal to an orifice (SV_{pre}) is the same as the stroke volume passing through the orifice ($SV_{orifice}$). The most common application of the continuity equation is in aortic valve area measurement for stenosis where the stroke volume (SV_{pre}) is measured at the left ventricular outflow tract, discussed in further detail in the valve stenosis portion of this chapter. The principle of continuity of flow is also used for the calculation of regurgitant orifice size and volumes using the flow convergence proximal to the regurgitant valve proximal isovelocity surface area [PISA]). The PISA method uses the principle that blood accelerates in a laminar fashion toward a regurgitant orifice, forming multiple “hemispheres” of isovelocity (Fig. 55-11). Effective regurgitant orifice size (EROA) can then be calculated from flow velocities.²⁰

When a blood flow stream narrows, (i.e., when traversing a valve orifice), flow velocity (v) increases in proportion to the degree of narrowing. Increases in velocity are correlated with increased pressure gradients across

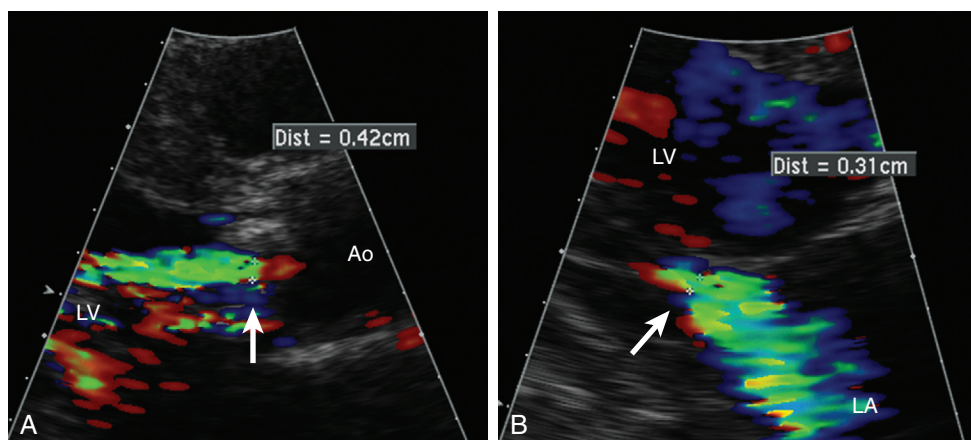


FIGURE 55-10 ■ Vena contracta, the narrowest portion of the jet just distal to the regurgitant orifice for aortic valve (A) and mitral valve (B) regurgitation. Ao, Aorta; LA, left atrium; LV, left ventricle.

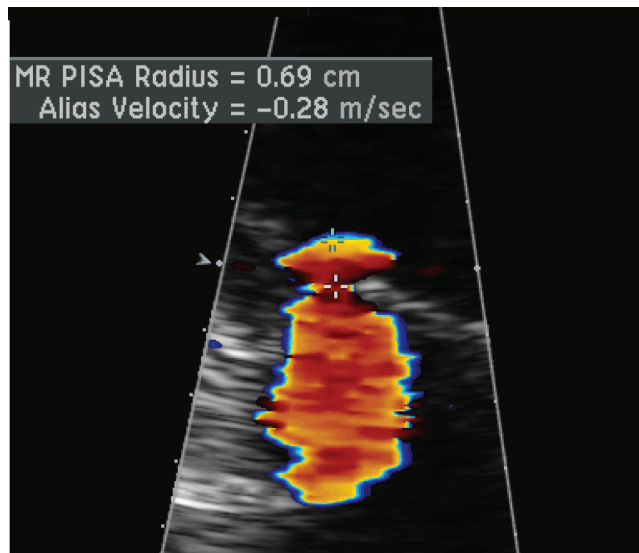


FIGURE 55-11 ■ Regurgitation severity quantification by proximal isovelocity surface area (PISA) method. As blood flow approaches a regurgitant orifice, velocity increases, forming concentric isovelocity hemispheres. Measurement of the aliasing blood velocity, measured at the hemisphere margin, and the radius provide data on the regurgitant instantaneous flow rate and the effective regurgitant orifice area.

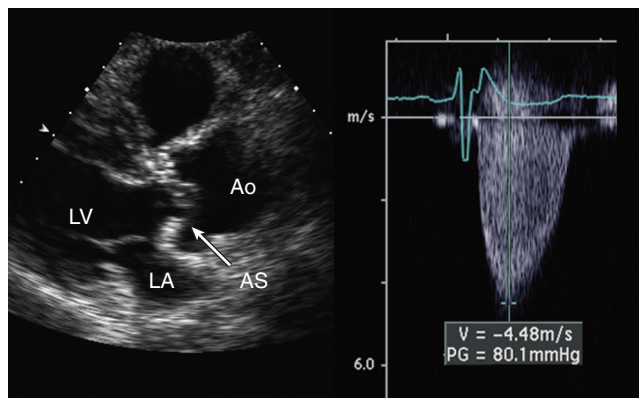


FIGURE 55-12 ■ Severe aortic stenosis (AS), with thickened, calcified aortic valve leaflets on the parasternal long axis view. On continuous Doppler imaging across the aortic valve, the peak velocity (V) is 4.5 m/s, corresponding to a peak gradient (PG) of 80 mm Hg, using the simplified Bernoulli equation. Ao, Aorta; LA, left atrium; LV, left ventricle.

the orifice, and this is described by the Bernoulli equation (pressure–velocity relationship). Ignoring the effects of viscous loss and local red blood cell acceleration, the relationship is simplified to:

$$\text{Pressure gradient} = 4v^2$$

Estimation of transvalvular pressure gradients is a common application of the Bernoulli equation (Fig. 55-12). Another common application is the estimation of pulmonary arterial pressures. The pressure gradient between the right ventricle and right atrium is calculated using the systolic velocity from the tricuspid regurgitant jet (Fig. 55-13). In the absence of pulmonary stenosis, pulmonary arterial systolic pressure is equal to the sum of

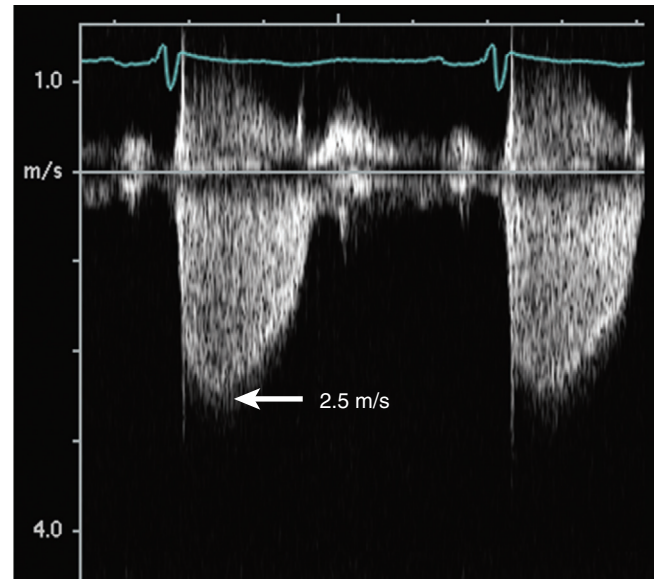


FIGURE 55-13 ■ Peak pressure gradient is calculated using peak velocity (V) from the continuous Doppler tracings of the tricuspid regurgitant jet using the simplified Bernoulli equation. Peak velocity of 2.5 m/s corresponds to a peak pressure gradient (right ventricular systolic pressure) of 25 mm Hg. Pulmonary arterial systolic pressure is obtained by adding estimated right atrial pressure to the peak gradient.

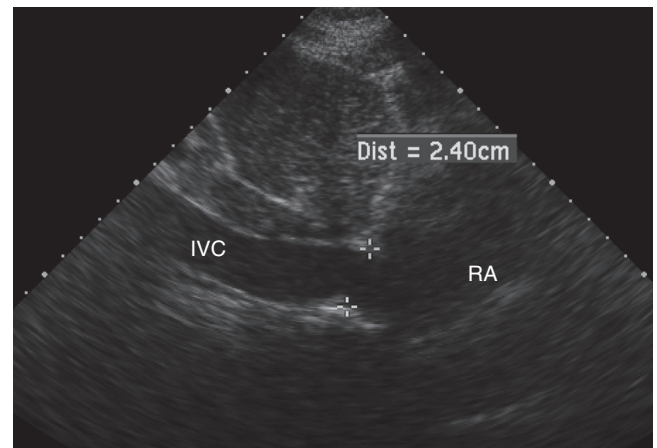


FIGURE 55-14 ■ Inferior vena cava (IVC) diameter at rest in a patient with mildly increased right atrial pressures. RA, Right atrium.

right ventricular (RV) systolic pressure and right atrial pressure. Right atrial pressure is obtained by examining inferior vena cava (IVC) diameter at rest and with inspiration, measured before the junction to the right atrium (Fig. 55-14 and Table 55-2).²¹ Measurement of pulmonary arterial systolic pressure is widely applicable as 90% of individuals have some degree of tricuspid regurgitation.

VENTRICULAR FUNCTION

Systolic Function

Echocardiographic imaging allows for rapid, accurate, and reproducible assessment of global and regional left

TABLE 55-2 **Right Atrial Pressure Estimation**

Inferior Vena Cava Diameter	Change in Diameter with Inspiration	Right Atrial Pressure Estimation
Normal ≤ 2.1 cm	Decrease in diameter > 50%	3 mm Hg
Normal ≤ 2.1 cm	Decrease in diameter ≤ 50%	8 mm Hg
Dilated ≥ 2.5 cm	Decrease in diameter ≤ 50%	15 mm Hg

From Rudski LG, Lai WW, Afalalo J, et al: Guidelines for the echocardiographic assessment of the right heart in adults. *J Am Soc Echocardiogr* 23:685–713, 2010.

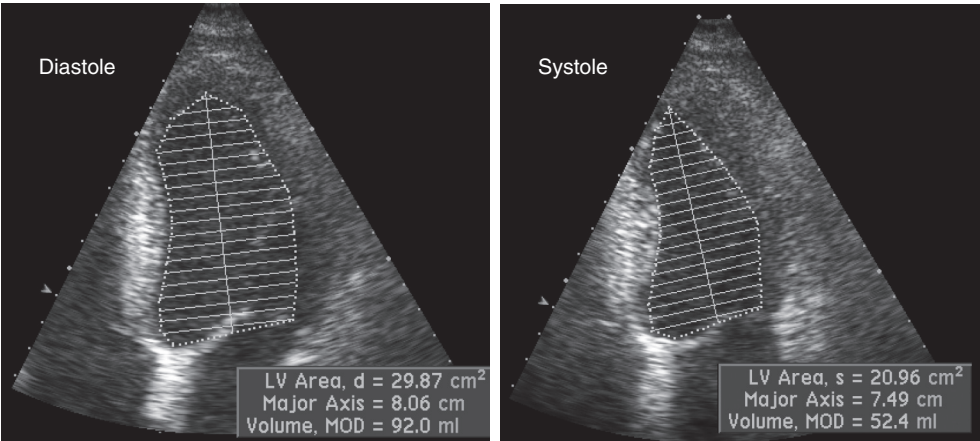


FIGURE 55-15 ■ Endocardial border tracings of the left ventricle (LV) from the apical four-chamber view during diastole and systole are used to calculate LV volumes. Using concordant LV volume calculations from the apical two-chamber view, ejection fraction is calculated using the apical biplane method of disks algorithm. *Volume, MOD, Calculated LV volume.*

ventricular (LV) systolic function. Left ventricular ejection fraction (EF), estimates global systolic function by using end-diastolic volume (EDV) and end-systolic volume (ESV).⁷ Volumes are typically calculated using geometric formulas based on endocardial border tracings from two orthogonal views of the LV (Fig. 55-15).

$$EF = 100\% \times (EDV - ESV) / EDV$$

The most commonly applied algorithm is the biplane apical summation of discs method. Because the LV is assumed to be symmetric and bullet shaped to make this calculation, standard, nonoblique imaging planes are needed for optimal measurement. Rather than using geometric assumptions to estimate LV volumes, direct measurement of LV volumes is now possible with 3D imaging. With visualization of variability in the LV endocardial contour, 3D-derived LV volumes tend to be larger than 2D volumes (Fig. 55-16). However, EF measurement accuracy relies on optimal endocardial definition, and image quality for 3D datasets remains relatively limited compared with 2D images. Therefore, 2D EF measurements remain the mainstay of LV systolic function assessment. A novel index of LV function, global longitudinal strain, uses computer algorithms which track natural acoustic markers in the myocardium (Fig. 55-17). Global strain imaging is primarily used in research applications and is not yet commonly applied in standard imaging.

Echocardiographic assessment of systolic function is more challenging with segmental wall motion abnormalities and with arrhythmia, in which variability in cardiac

cycle length affects beat-to-beat left ventricular volumes. Patients with conduction delay or who have previously undergone cardiac surgery may have dyssynchronous activation of the interventricular septum. When image quality precludes endocardial border tracing, qualitative assessment by an experienced echocardiographer is a reasonable alternative. Visual estimates of EF are usually reported in increment ranges of 5% or 10% (e.g., 50%-55% or 20%-30%).

A Doppler-derived measure of LV systolic function uses the early systolic rate of velocity increase in the mitral regurgitant jet, a relatively load-independent measure of contractility (Fig. 55-18). The slope of the mitral regurgitant jet between two points on the velocity curve represents the rate of change in LV pressure over time (dP/dt). A normal dP/dt is greater than 1000 mm Hg/sec; a lower dP/dt slope is concordant with a delay in LV systolic pressure generation and depressed LV function.

Right ventricular function is usually reported qualitatively on a scale of normal, mildly, moderately, or severely depressed. Multiple views of the right ventricle are often needed to provide a reasonable assessment of global systolic function. Semiquantitative measures of RV function are difficult because, as opposed to the LV, geometric assumptions of symmetry are not valid. The RV free wall “wraps” around the left ventricle, forming a crescent shaped chamber. The most commonly used measure is the tricuspid annular plane systolic excursion, a single-plane M-mode distance measurement for which greater than 1.8 cm suggests normal systolic function (Fig. 55-19).

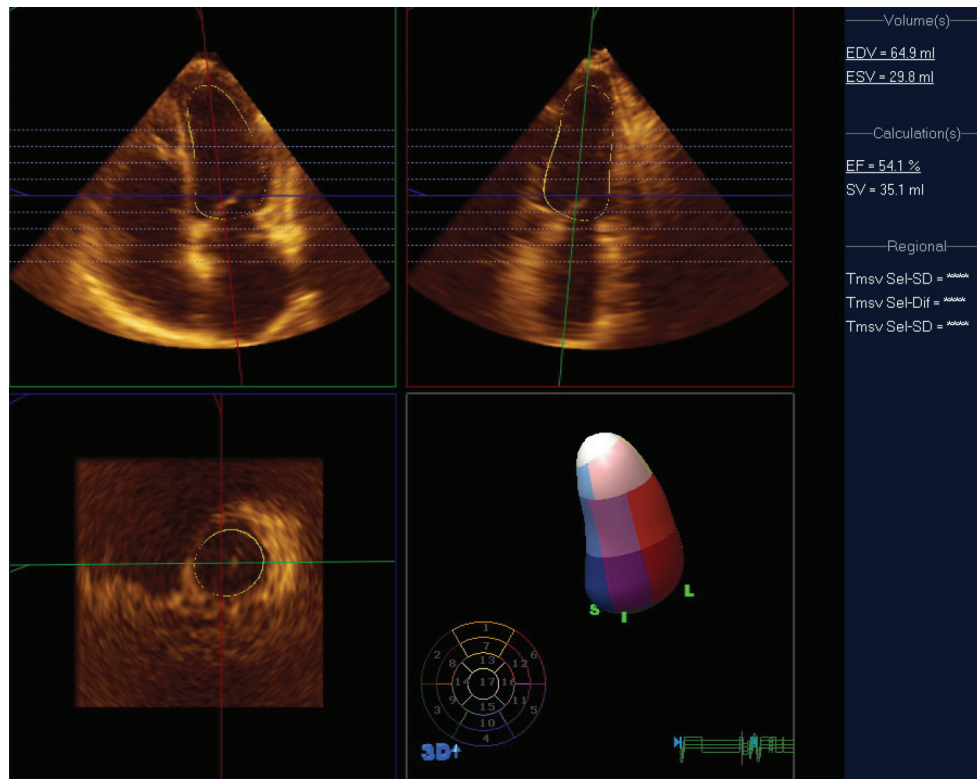


FIGURE 55-16 ■ Three-dimensional volume data set of the left ventricle (LV) with an end-diastolic volume (EDV) of 64.9 mL, an end-systolic volume (ESV) of 29.8 mL, a stroke volume (SV) of 35.1 mL, and an LV ejection fraction of 54.1%.

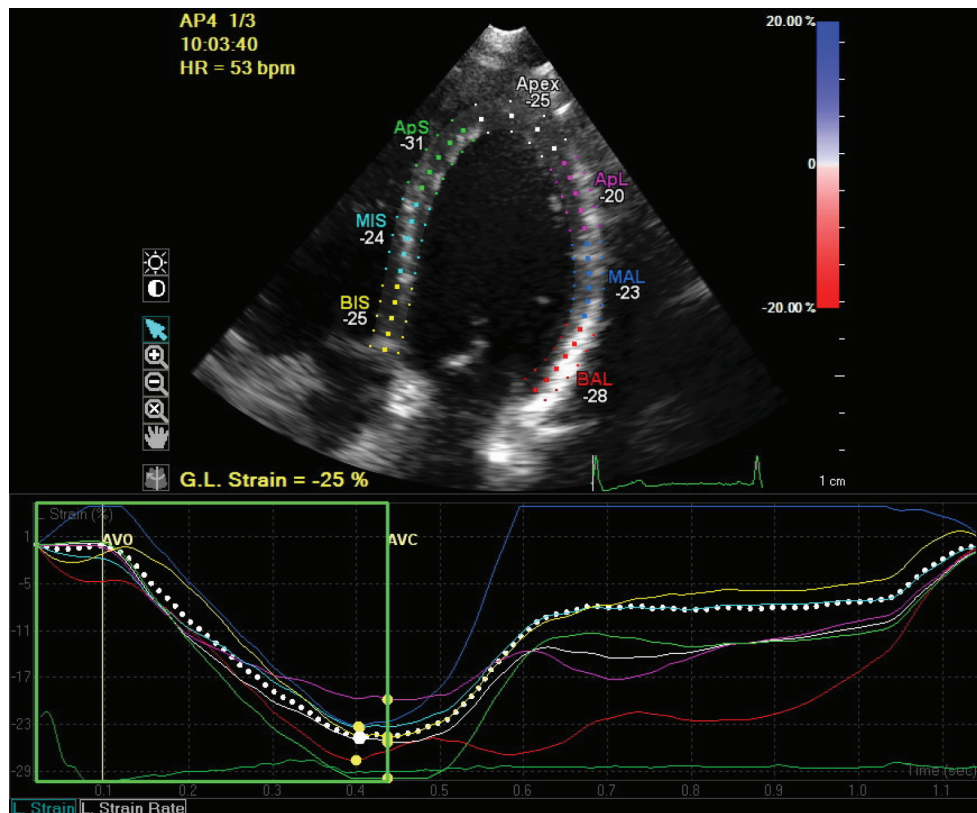


FIGURE 55-17 ■ Strain imaging from the apical four-chamber view. Strain measurement from each segment is color coded and displayed on the graph below the imaging against time. A composite “global” longitudinal strain measurement is provided in the lower left hand portion of the image (G.L. strain = -25%). Normal longitudinal strain measurement is less than -20. All segmental and global strain measurements are normal in this patient.

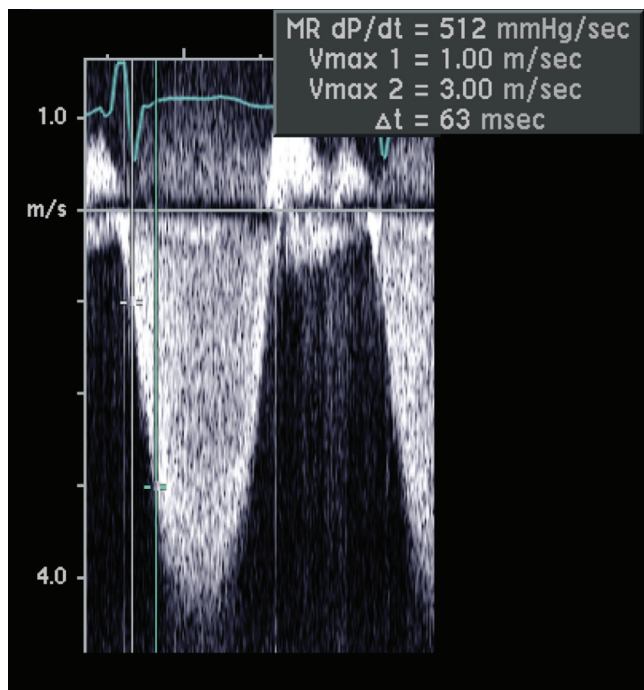


FIGURE 55-18 ■ Continuous wave Doppler tracings of the mitral regurgitant jet showing a decreased rate of rise to the peak LV cavity pressure during early systole in a patient with severely reduced LV systolic function and ejection fraction of 25% (dP/dt). With normal systolic function, the change in rate of rise in pressure over time should be greater than 1000 mm Hg/sec. Δt , Change in time; V_{max} 1, first velocity measured; V_{max} 2, second velocity measured.

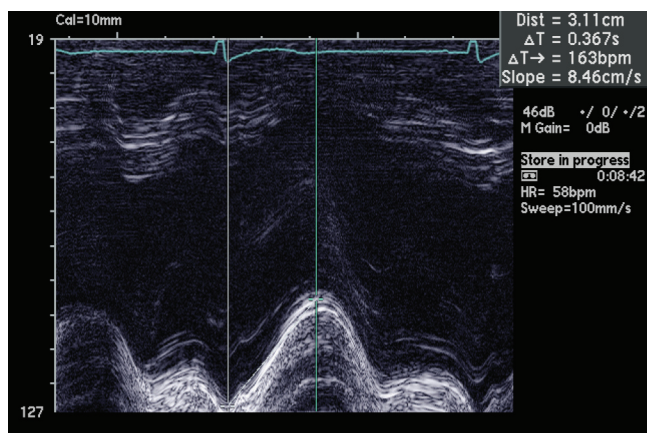


FIGURE 55-19 ■ M-mode tracing of the tricuspid annular motion against the time dimension. Vertical distance between the lowest point and greatest systolic motion is measured. This patient has a distance measurement of 3.1 cm (greater than 1.8 cm suggests normal systolic function). ΔT , Change in time.

Diastolic Function

Diastole comprises four phases: (1) isovolumic relaxation, (2) atrioventricular valve opening with passive early rapid ventricular filling, (3) diastasis, or deceleration of passive LV filling owing to equalization of atrial and ventricular pressures, and (4) late active ventricular filling owing to atrial contraction. Several echocardiographic parameters are used to evaluate diastolic function.^{22,23} Increased left atrial size is a surrogate measure of increased left atrial

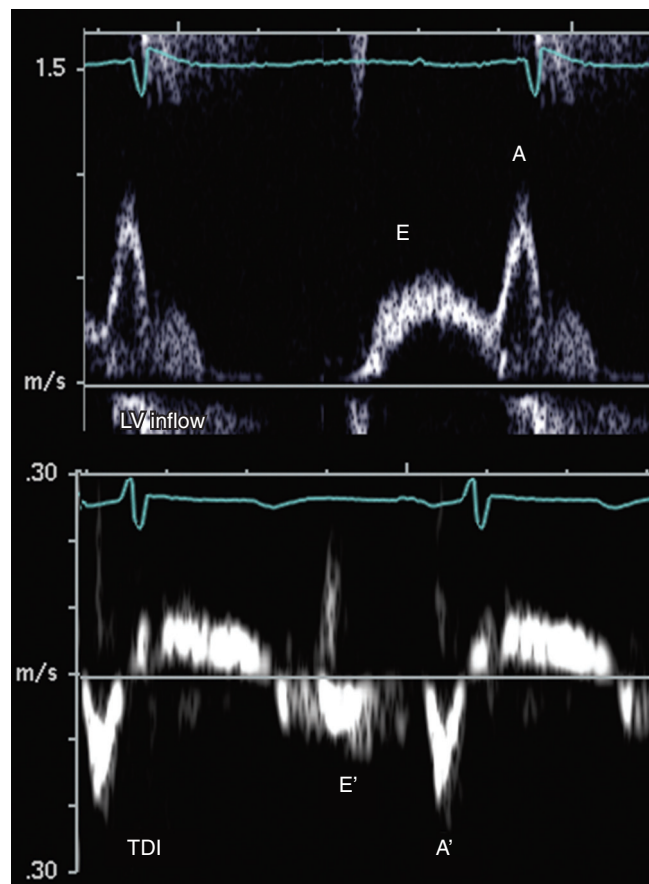


FIGURE 55-20 ■ Doppler indices for mild diastolic function. With impaired ventricular relaxation, peak early mitral inflow velocity is decreased. Increased reliance on atrial contribution to ventricular filling leads to reversal of the E:A ratio on the left ventricular (LV) inflow tracing. A ratio of LV inflow E wave to tissue Doppler velocity (TDI) E' wave (E:E' ratio) less than 8 implies normal left atrial pressure. In this case, E:E' = 0.6/0.1 = 6.

(and LV end-diastolic) pressures. Pulse wave Doppler indices include the evaluation of LV inflow velocities with early “E” wave filling and the atrial contribution to filling (“A” wave). The “E” wave deceleration time (DT) and isovolumic relaxation time (IVRT) are measures of LV relaxation.

In normal, young individuals, early filling is the dominant component of LV filling with atrial contraction contributing less than 20% to total filling volume. Therefore, the E wave is higher with an E:A ratio greater than 1. With aging, ventricular stiffness increases, there is delay or impaired myocardial relaxation, and the relative contribution of atrial contraction is increased, with reversal of the E and A velocities and E:A ratio less than 1 (Fig. 55-20). In advanced diastolic dysfunction, decreased LV compliance leads to rapid equalization of the transmitral diastolic pressure gradient. With increased LV end-diastolic pressure, atrial contribution to LV filling is small, manifesting as an E:A ratio greater than 2, a steep deceleration slope and shortened IVRT (Fig. 55-21). Although patients in transition from an impaired relaxation pattern to a restrictive pattern have decreased LV compliance, the E:A ratio may appear normal, making interpretation of diastolic indices difficult.

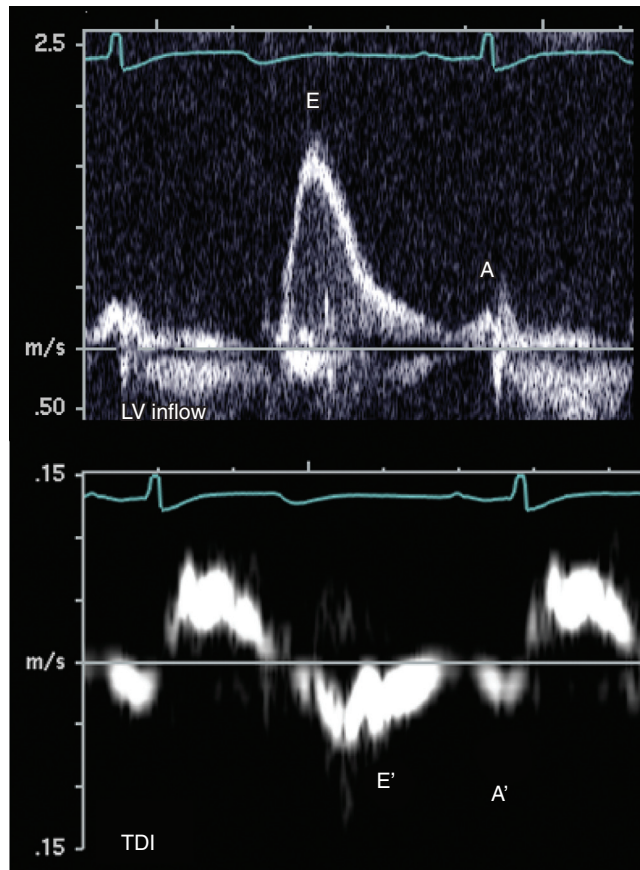


FIGURE 55-21 ■ With advanced diastolic dysfunction (restrictive filling), there is decreased left ventricle (LV) compliance. High left atrial pressures drive transmitral filling with a higher, early peaked E wave and E:A ratio greater than 2. A ratio of LV inflow E wave to tissue Doppler velocity (TDI) E' wave (E:E' ratio) greater than 15 implies elevated left atrial pressure. In this case, $E:E' = 1.7/0.07 = 24$.

Loading conditions (heart rate, volume overload, mitral regurgitation) affect left atrial pressure and transmitral gradients. Mitral inflow evaluation repeated during a Valsalva maneuver (transient preload decrease) can unmask diastolic dysfunction, aiding in diagnosis.

Tissue Doppler interrogation at the septum and lateral wall just below the mitral annulus allows evaluation of myocardial diastolic motion. Myocardial early (E') and atrial (A') waves correspond to mitral E and A waves and are less sensitive to atrial loading than mitral inflow (see Figs. 55-20 and 55-21). The transmitral E to myocardial E' (E:E') ratio is a strong surrogate measure of LV filling pressure, with a ratio less than 8 suggesting normal left atrial pressure and a ratio greater than 15 increased left atrial pressure. A ratio between 8 and 15 is indeterminate.

Abnormalities in diastolic indices can also be seen with extracardiac constraint of ventricular filling such as in constrictive pericarditis or tamponade. Normal RV filling demonstrates mild respiratory variation in transtricuspid velocities. On inspiration, there is an increase in systemic venous return and a transient increase in velocities, with normal magnitude increase less than 20%. Because left atrial filling is not respiratory dependent, transmitral velocities do not normally vary significantly with

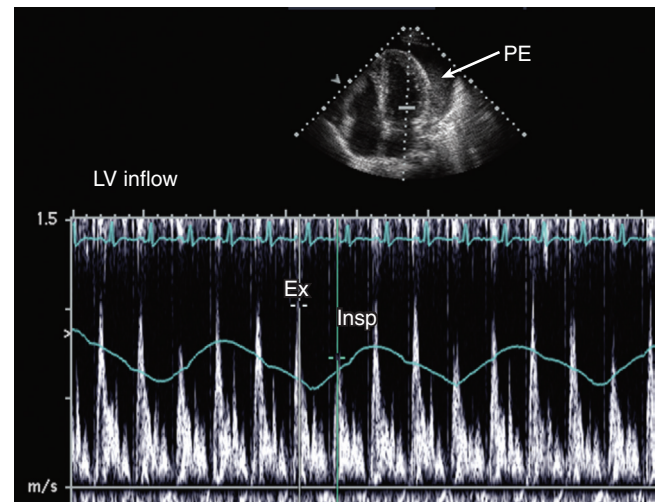


FIGURE 55-22 ■ Pericardial effusion (PE) in a patient with dyspnea. The transmitral pulsed Doppler tracing demonstrates respiratory variation in flow. Ex, Expiration; Insp, inspiration.

respiration. With pericardial tamponade and chronic pulmonary disease, exaggerated inspiratory-expiratory respiratory variation in the transtricuspid and transmitral velocities may be seen (Fig. 55-22).

ISCHEMIC HEART DISEASE

Direct visualization of coronary artery anatomy by echocardiography is rarely possible beyond visualization of coronary ostia. However, echocardiography is well suited to visualize effects of altered coronary perfusion on endocardial motion and wall thickening. With impaired coronary blood flow, segmental wall motion abnormalities are seen in affected myocardium. Myocardial responses to ischemia include hypokinesis (myocardial thickening with relatively less inward motion than the rest of the myocardium), akinesis (absence of thickening or inward motion), and dyskinesis (thinned and infarcted myocardium with paradoxical outward systolic motion).

Myocardial response to ischemia is to the severity of ischemia, hypokinesis progressing to akinesis in more severe cases. Although acutely infarcted myocardium appears hypokinetic, wall thickness may be normal as postinfarct remodeling has not yet occurred. In patients with an acute, ST elevation infarction, myocardial segments subject to prolonged ischemia are likely to remain hypocontractile in the long term, whereas segments subjected to only a short duration of coronary flow limitation may return to a normal contractile state. Postinfarction myocardial dysfunction that subsequently returns to normal is termed *stunned myocardium*. Irreversibly infarcted regions appear thinned and akinetic with persistent akinetic or dyskinetic wall motion on long-term evaluation.

Echocardiography is useful in the detection of coronary disease in patients with chest pain symptoms. In patients with active chest discomfort, the absence of regional wall motion abnormalities on a resting study is an effective means of ruling out acute ischemia (negative

predictive accuracy of $\approx 95\%$). In the operating room, intraoperative TEE allows for continuous monitoring of cardiac function and has been used during coronary revascularization and to monitor patients undergoing noncardiac surgery at high risk of cardiac events. TEE has also proven useful to evaluate cardiac function in the hemodynamically unstable patients in whom ischemia is suspected, but in whom transthoracic windows are suboptimal.

Takotsubo cardiomyopathy, or “stress cardiomyopathy,” is acute, cardiac syndrome characterized by chest pain or dyspnea following a significant emotional or physiologic stress. The echocardiographic manifestation is transient akinesis of the apical and mid-LV segments with regional wall motion abnormalities that extend beyond a single epicardial coronary arterial distribution. Angiography demonstrates the absence of obstructive coronary disease or acute plaque rupture. Outcome is generally good, and ventricular functional recovery is likely with supportive care.^{24,25}

Stress Testing for Coronary Disease

Stress echocardiography is useful for initial diagnosis of coronary disease, monitoring disease progression in patients with known coronary lesions, and evaluating the functional significance of residual lesions following revascularization. Stress echocardiography provides visualization of myocardial function during active stress, allowing for diagnosis of myocardial ischemia in a controlled setting.^{26,27} Accuracy for stress echocardiography to determine extent and location of myocardial ischemia is excellent, and it is particularly useful when baseline electrocardiograph (ECG) abnormalities render standard exercise ECG testing nondiagnostic. The addition of imaging increases sensitivity and specificity over standard exercise ECG stress testing. Various exercise (treadmill or bicycle ergometer) and nonexercise cardiac stressors (dobutamine) are used. Echocardiographic images are acquired at rest and at peak stress. For treadmill protocols, images are acquired immediately after cessation of exercise because of imaging difficulties while the patient is upright on the treadmill. Images are integrated with ECG data, exercise tolerance, and patient symptoms for final interpretation. Using standard views of the LV, side-by-side comparison of the rest and stress digital images allow identification of wall motion abnormalities (see Fig. 55-8). Ischemia diagnosis is dependent on accurate evaluation of segmental wall motion and interval change from rest images. As a consequence, diagnosis of ischemia is more difficult in patients with preexisting coronary artery disease and resting segmental abnormalities. When endocardial definition is suboptimal, intravenous contrast agents can be used to opacify the LV cavity and aid in endocardial border definition. Results of stress echocardiography testing offer long-term prognostic information.²⁸⁻³⁰

In the absence of significant coronary narrowing, the myocardial response to stress is augmentation of systolic function with hyperdynamic motion. Flow-limiting coronary lesions are associated with systolic dysfunction in the myocardial region distal to the lesion. In noninfarcted

myocardium, systolic function is preserved if coronary blood flow is adequate to meet oxygen demand at rest. The ischemic effect on ventricular wall motion and thickening is proportional to the severity of impaired coronary blood flow. For intermediate range lesions (50%-60% stenosed) or single-vessel disease in which only a few myocardial segments are affected, ischemic abnormalities may be subtle or transient. With cessation of the stressor and restoration of adequate coronary flow, wall motion returns to normal. A submaximal stress test lowers test sensitivity because provocation of ischemia is dependent on reaching an adequate workload. Prolonged delay in obtaining stress images also lowers sensitivity because ischemia detection requires the abnormality to persist long enough for image recording.

Exercise stress echocardiography is performed following a standard symptom limited protocol to achieve as high a workload as possible. When testing cannot be performed because of physical limitation or when exercise response may be limited, pharmacologic stressors such as dobutamine are alternatives to exercise. Dobutamine is typically initiated at 10 mg/kg/min and is increased at 3-minute intervals to a maximum of 40 mg/kg/min. If target heart rate (85% of the patient's maximum predicted heart rate) is not achieved, atropine can be additionally administered. Dobutamine stress testing is commonly used to monitor for transplant vasculopathy in post-cardiac transplant patients, in whom denervated hearts might not allow the achievement of target heart rate with exercise protocols.

Complications of Acute Myocardial Infarction

Echocardiography is the diagnostic tool of choice to evaluate for complications of myocardial infarction. Two-dimensional imaging allows assessment of myocardial function and regional wall motion abnormalities. Mitral regurgitation is a common complication of ischemic disease. In patients with regional wall motion abnormalities and LV chamber enlargement, significant mitral regurgitation can result from distortion of the mitral subvalvular apparatus. Mitral regurgitation can also occur as a direct result of papillary muscle ischemia, rupture of a necrotic papillary muscle head, and infarct scarring with tethering of the subvalvular apparatus.

Myocardial necrosis with ventricular rupture can be identified in the free wall and the interventricular septum. A ventricular septal defect is identified by characteristic color flow and continuous-wave Doppler flow across the defect. A ventricular pseudoaneurysm, a contained ventricular free wall rupture, often has an abrupt transition from normal myocardial tissue to the aneurysmal dilation and thrombus within the cavity (Fig. 55-23). Myocardial infarction with ventricular wall thinning can also lead to focal dilation and true aneurysm formation. As with pseudoaneurysms, thrombi can form within ventricular aneurysms and pose a risk of distal embolization.

Mural thrombi occur primarily in anterior and apical infarctions, and they are less frequent with early revascularization (Fig. 55-24). A cause of hypoxemia following inferior myocardial infarction is increased right-sided

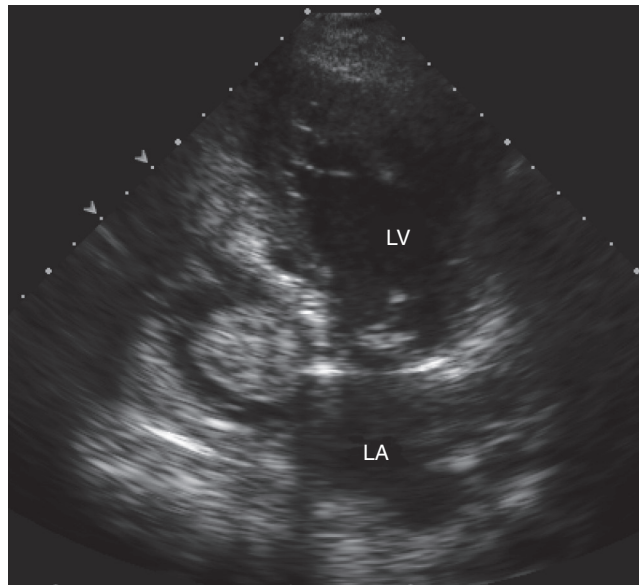


FIGURE 55-23 ■ Pseudoaneurysm in a patient with a prior ST elevation inferior myocardial infarction. The inferior wall of the left ventricle (LV) appears thinned and bright. There is a rupture of the base of the heart with a large pseudoaneurysm adjacent to the LV. Within the pseudoaneurysm, there is a large spherical thrombus. LA, Left atrium.

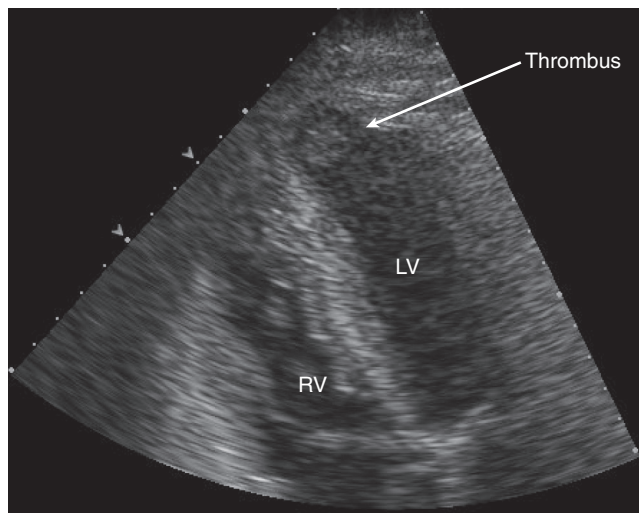


FIGURE 55-24 ■ Small apical thrombus (arrow) in the left ventricle (LV) in a patient with a recent anteroapical myocardial infarction. RV, Right ventricle.

pressures with resulting right-to-left shunting across a patent foramen ovale. This hypoxemia can be diagnosed by TEE evaluation of the intra-atrial septum with a contrast study using agitated saline contrast. A similar phenomenon has been described in postoperative hypoxemic patients with increased right atrial pressure.³¹

CARDIAC MASSES

Image resolution with echocardiography is excellent, with cardiac masses as small as 1 to 2 mm in diameter being visualized. It is important to correlate any findings of a potential cardiac mass with the clinical history to

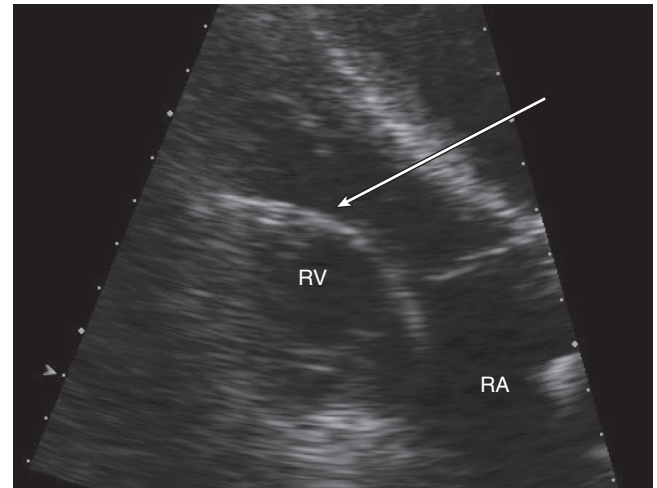


FIGURE 55-25 ■ Right ventricular pacer lead (arrow) seen crossing the tricuspid valve into the right ventricle (RV). RA, Right atrium.

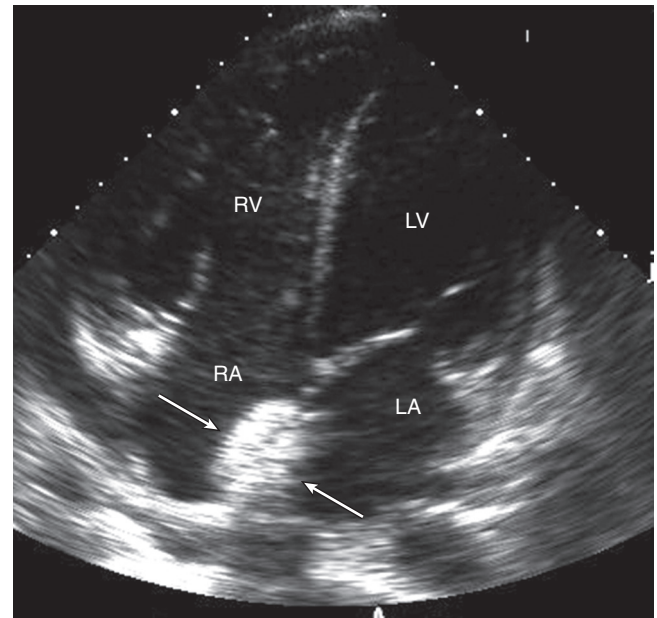


FIGURE 55-26 ■ Atrial septal defect closure device that was placed percutaneously. Prosthetic material appears bright and echogenic, spanning the interatrial septum (arrows). LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

identify expected structures such as pacing wires, central venous catheters, prosthetic valves, and intra-cardiac devices (Figs. 55-25, 55-26, and 55-27). In addition, potential masses seen on echocardiography should be scrutinized carefully to exclude ultrasound artifact and normal structural variants. Commonly encountered cardiac masses include normal structures, tumors, thrombi, and vegetations. These categories are not mutually exclusive (i.e., a vegetation often also includes adherent thrombi).

Findings suggesting low-velocity blood flow, such as myocardial hypofunction and spontaneous echo contrast, are associated with relative blood stasis and thrombus formation. In the LV, these findings are usually at the sites

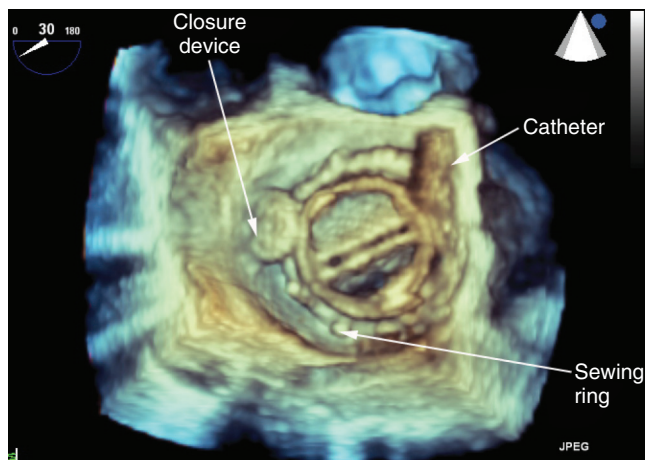


FIGURE 55-27 ■ Three-dimensional transesophageal echocardiographic image of a mechanical mitral valve prosthesis. Two valve occluders are seen in the midportion of the image. There is a sewing ring around the valve. This patient developed valve dehiscence with paravalvular regurgitation. A small closure device was placed at the site of the defect along the sewing ring (arrow). A second closure device was being placed at the time of the study (catheter; arrow).

of prior infarcts where myocardium is aneurysmal and hypokinetic, such as the LV apex. The sensitivity and specificity of TTE echocardiography for LV apical thrombi are approximately 95% and 88%, respectively. For TEE, transducer placement is constrained by esophageal anatomy, and the true apex is often not in view, decreasing diagnostic accuracy to visualize apical thrombi. In the left atrium, most thrombi occur in the atrial appendage, particularly in patients in atrial fibrillation or flutter, or with left atrial stasis such as with mitral stenosis. With the posterior anatomic position of the left atrial appendage, atrial thrombi are more optimally seen with TEE (see Fig. 55-5). The sensitivity and specificity of TEE to detect left atrial thrombus near 100%, but care is needed to visualize the appendage in at several planes. Overall, echocardiography is a poor diagnostic tool for pulmonary embolism.³² Rarely, large pulmonary emboli can be imaged in the main pulmonary artery. Often, the only evidence of a large pulmonary embolism is RV enlargement and dysfunction.

In patients with a systemic embolic event, echocardiography identifies a potential cardiac source in up to 30% of cases. Echocardiographic findings associated with increased embolic risk include left-sided thrombi, valve masses (endocarditis), and aortic atherosclerotic disease. Image quality for these abnormalities is improved with TEE, but the potential risks of TEE (conscious sedation, semi-invasive) also should be considered.³³ In addition, systemic embolism can occur if there is paradoxical embolism through an interatrial shunt, such as an atrial septal defect or patent foramen ovale (PFO; Fig. 55-28). Importantly, a PFO itself is not diagnostic for systemic embolism, because this is a common variant that is present in up to 20% of the general population. However, outcome studies in patients with cerebrovascular events suggest an association between stroke and PFO. Early data from PFO device closure trials suggest that for

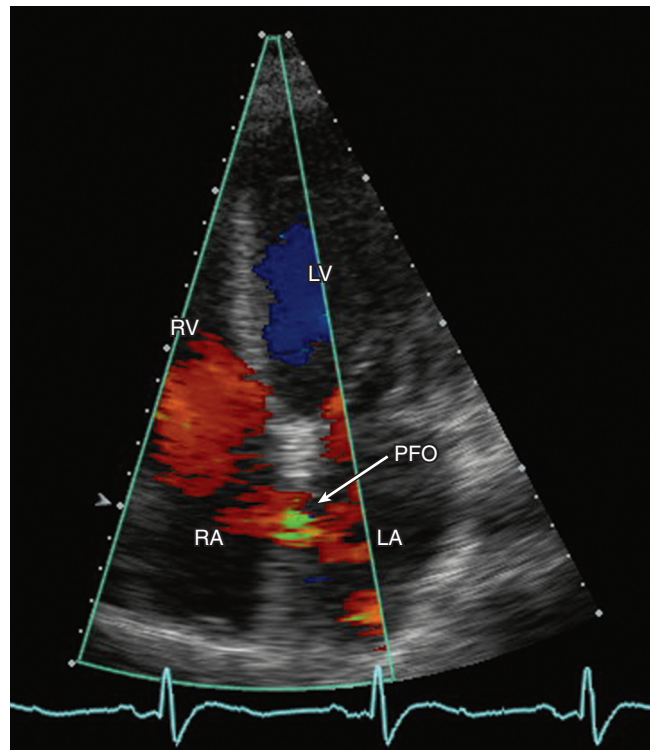


FIGURE 55-28 ■ Color Doppler imaging shows left to right flow across the interatrial septum, consistent with a patent foramen ovale (PFO). LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

carefully selected patients with history of cryptogenic stroke and PFO, there is evidence of stroke risk reduction from PFO closure over medical management alone. Although a PFO may be seen by color Doppler imaging, agitated saline contrast often provides a more definitive diagnosis (see Fig. 55-7). Valsalva maneuver during the contrast injection can transiently increase right atrial pressure, aiding in diagnosis. Shunting should be seen within three cardiac cycles after right atrial opacification; late contrast that appears after five cardiac cycles typically signifies an intrapulmonary shunt.

Valve vegetations appear echocardiographically as independently mobile masses attached to the upstream side of cardiac valves (e.g., ventricular side of the aortic valve or left atrial side of the mitral valve). Vegetations are most often due to infective endocarditis. Noninfectious etiologies include nonbacterial thrombotic endocarditis and benign masses such as papillary fibroelastomas. Other intracardiac attachment sites for vegetations include indwelling catheters or pacer leads and congenital abnormalities such as ventricular septal defects. With acoustic shadowing from nonbiological material, prosthetic valve endocarditis is often difficult to visualize, and TEE is typically needed to better visualize the valve.

Most tumors in the heart are noncardiac in origin. Primary cardiac tumors in the heart are rare, and the majority of these are benign. Atrial myxomas are the most common primary tumor, often seen as an incidental finding during transthoracic imaging. The most common metastatic tumors include lung, breast, lymphoma, leukemia, stomach, and melanoma, and they can involve the

pericardium, myocardium, and, in rare cases, endocardium. In the case of renal cell carcinoma, direct extension via the inferior vena cava into the right atrium can occur.

CARDIOMYOPATHIES

Congestive Heart Failure

Echocardiography is valuable for the assessment of ventricular systolic and diastolic function, measurement of chamber size and wall thickness, visualization of valve anatomy and function, and clinical evaluation of hemodynamic status in patients with heart failure. In addition, echocardiography can also identify a reversible cause of heart failure, such as valve stenosis or regurgitation. Congestive heart failure owing to ischemic heart disease can be recognized based on regional myocardial dysfunction. However, end stage ischemic disease can result in global biventricular dysfunction, indistinguishable from a primary cardiomyopathy.

Nonischemic, dilated cardiomyopathy is characterized by cardiac chamber enlargement and systolic dysfunction (see Fig. 55-2A). Systolic dysfunction is typically global in nature, but some heterogeneity in regional function may be observed. Ventricular dilation can tether the mitral subvalvular apparatus, resulting in significant mitral regurgitation. Systolic dysfunction and chronic volume overload can also lead to secondary pulmonary hypertension. Although systolic dysfunction is typically the dominant finding, diastolic dysfunction, with increased myocardial wall stress and intracardiac pressures, is also present. Diagnostic indices for dilated cardiomyopathy include systolic and diastolic function, valvular function, and pulmonary pressure estimates.³⁴

Hypertrophic and Restrictive Cardiomyopathy

Hypertrophic cardiomyopathy is characterized by abnormal myocardial thickening. The most common form of hypertrophic cardiomyopathy is asymmetric thickening of the basal interventricular septum (Fig. 55-29). In advanced cases, septal thickening can cause obstruction of LV outflow.³⁵ Severity of LV outflow obstruction can be altered by different loading conditions, with decreased intracardiac volume transiently increasing the severity of obstruction (Valsalva maneuver). Additional findings can include systolic motion of the anterior mitral valve leaflet and chordae into the LV outflow tract. Faulty systolic coaptation of the mitral valve results in posteriorly directed regurgitation. In patients with significant outflow obstruction, pressure gradients in the LV outflow tract can be measured (Fig. 55-30). Other variants of hypertrophy include diffuse, concentric, and apical.

Echocardiography is indispensable for management of hypertrophic cardiomyopathy, and it is used to monitor outflow tract gradients and assess mitral regurgitation severity.³⁶ This information aids timing of surgical or percutaneous myomectomy intervention, and it is used in the cardiac catheterization laboratory to guide percutaneous septal ablation procedures. Intraoperative TEE

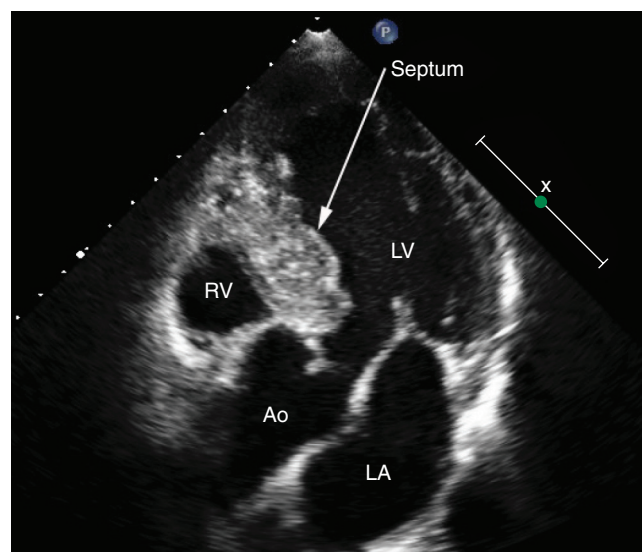


FIGURE 55-29 ■ Apical view with prominent hypertrophy of the interventricular septum (*arrow*) in a patient with hypertrophic cardiomyopathy. The aortic valve and ascending aorta (Ao) are seen as well. LA, Left atrium; LV, left ventricle; RV, right ventricle.

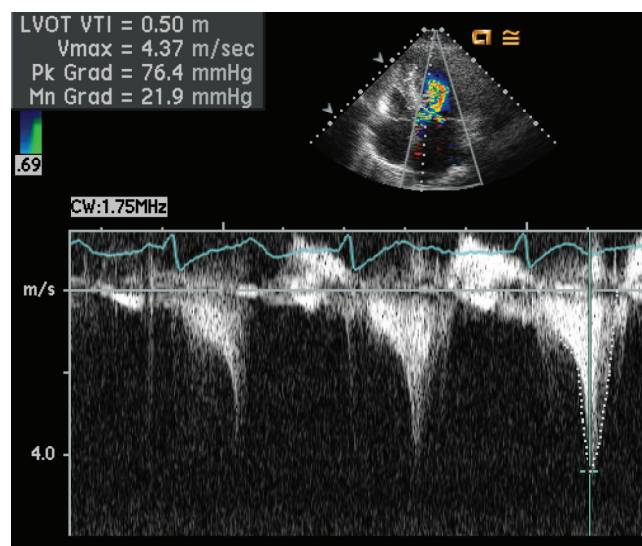


FIGURE 55-30 ■ Doppler sample in a patient with hypertrophic cardiomyopathy. The electrocardiogram tracing is shown above the Doppler tracing. During late systole, there is a late-peaking velocity curve with a peak velocity of 4.37 m/sec, which corresponds to a peak pressure gradient of 76.4 mm Hg per the simplified Bernoulli equation.

imaging is used to guide surgical myomectomy, and it can aid in monitoring for procedural complications, such as ventricular septal defect.³⁷ Because hypertrophic cardiomyopathy is associated with angina, arrhythmia, and sudden cardiac death, echocardiographic screening of family members of affected individuals is recommended.

Restrictive cardiomyopathy is uncommon. It is most commonly caused by an infiltrative disease process such as sarcoidosis and amyloidosis. Diastolic function is impaired, with decreased LV compliance and a restrictive

mitral inflow filling pattern.³⁵ Echocardiographic findings can include increased myocardial wall thickness, biatrial enlargement, and elevation in pulmonary arterial systolic pressures; however, these findings are not uniformly present, making restrictive cardiomyopathy difficult to diagnose definitively. Often, additional cardiac diagnostic imaging, such as cardiac magnetic resonance imaging or positron emission tomography, is needed to make the diagnosis.

Cardiac Transplantation

Echocardiography is beneficial to reassess LV function and to optimize intravascular volume status. In end-stage cardiac disease, echocardiography is used in decision-making and clinical management for an LV assist device (LVAD) or biventricular assist devices. For these devices, significant aortic regurgitation, severe mitral stenosis, or interatrial shunts can adversely affect optimal device performance. Functional issues, including assessment for peri-device hematoma, thrombus, and evaluation of RV function can be made, but acoustic shadowing from the device makes complete assessment difficult. Doppler interrogation of the device cannulae allows for an evaluation for partial occlusion or leakage. Serial echocardiography systematically evaluating LV chamber size and aortic regurgitation at a variety of LVAD settings ("ramp study") are used to optimize LVAD settings for individual patients.³⁸ Echocardiographic imaging is also used intraoperatively to aid surgeons in optimal placement of newer, mechanical circulatory support devices, such as percutaneous LVADs.

After cardiac transplantation, echocardiography is useful to monitor for biventricular function, pericardial effusion, and pulmonary hypertension and to assist in biptome placement during cardiac biopsies. Cardiac organ rejection is evidenced by myocardial thickening and diastolic dysfunction in the initial stages, progressing eventually to systolic dysfunction.³⁹ Normal findings after cardiac transplantation include biatrial enlargement from the suturing of the residual native atria to the transplanted heart, discerned as a linear echodensity along the mid-atrial wall. Doppler tracings along the aortic and pulmonic connections allow for assessment of anastomotic stenoses. For long-term follow-up after transplantation, dobutamine echocardiography has shown increased sensitivity over other stress testing modalities to screen for transplant vasculopathy.⁴⁰

PERICARDIAL AND CONSTRICTIVE HEART DISEASE

The pericardium is a thin, dense structure that forms an enclosed space around the heart. The pericardium is difficult to image because it is thin and is often directly in contact with other mediastinal structures, but it may be seen if adjacent fluid, which is echolucent, is present. A small amount of pericardial fluid is a normal finding. Abnormal pericardial findings visualized by echocardiography include fibrinous stranding, tumors, or hematoma.⁴¹

Large amounts of fluid in the pericardial space are abnormal and can cause external cardiac compression or tamponade. The size of a pericardial fluid collection alone does not determine hemodynamic significance. A slowly accumulating pericardial fluid collection can be accommodated, and more than 1 L can accumulate at a low pressure with few overt clinical signs. However, if fluid accumulates rapidly, intrapericardial pressures may exceed intracardiac pressure, leading to hemodynamic compromise or tamponade.

Echocardiographic findings in tamponade include systolic collapse of the right atrial free wall and diastolic collapse of the RV free wall owing to increased intrapericardial pressure (Fig. 55-31).⁴² However, if there is RV hypertrophy or pulmonary hypertension, higher intracardiac pressures can negate chamber collapse. Other echocardiographic findings include inferior vena cava dilation and exaggerated respiratory variation in inflow (>25%) across the atrioventricular valves. However, with clinical tamponade and a large pericardial effusion, the absence of echocardiographic markers for tamponade does not exclude the diagnosis. For example, after cardiothoracic surgery, focal hematomas that are loculated posterior and adjacent to the right atrium can impede atrial inflow. In these patients, suboptimal acoustic windows caused by limitations in patient positioning or surface bandages often limit image quality. If image quality is suboptimal, TEE imaging may be needed. Echocardiographic quantification and localization of pericardial fluid guide clinical decision making regarding approach and feasibility of surgical versus percutaneous pericardial drainage procedures.

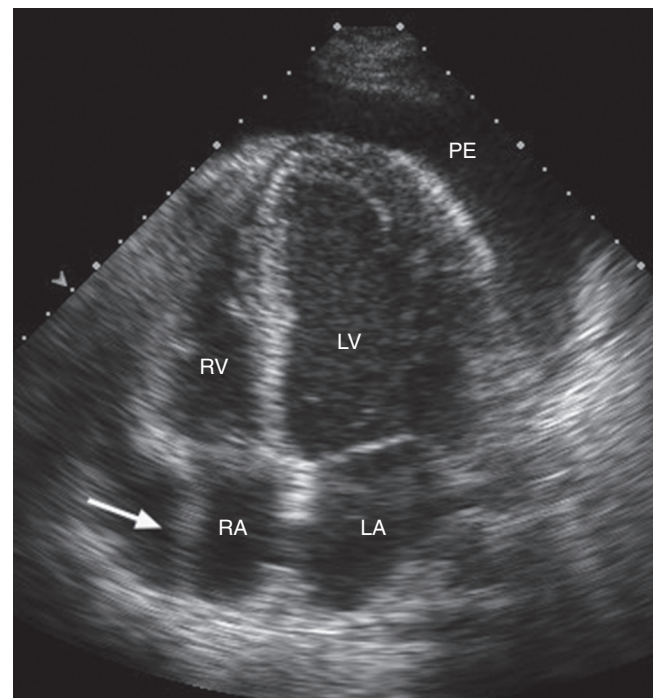


FIGURE 55-31 ■ Circumferential pericardial effusion (PEF) with right atrial systolic collapse on the apical four-chamber view (arrow).

Pericarditis is an inflammatory condition in which patients typically have chest pain, diffuse ST elevation on ECG, and an auscultated rub. Concurrent pericardial effusion may or may not be present. Pericardial thickening can occur, but can be difficult to image. With recurrent pericarditis, the pericardium can become thickened and adherent to the myocardium, causing impaired cardiac filling or “constriction.” Other causes of constriction include radiation therapy, prior trauma, or prior cardiac surgery. Exaggerated septal motion during the cardiac cycle signifies equalization of diastolic pressures in the cardiac chambers. Biventricular size and systolic function are usually preserved. Supporting echocardiographic findings for constrictive physiology include increased central venous pressure (inferior vena cava dilation), a prominent y descent on hepatic vein Doppler tracings, and a restrictive filling pattern on transmitral Doppler inflow with rapid early diastolic filling.⁴¹

Differentiation between pericardial constriction and restrictive cardiomyopathy can be challenging.⁴³ Both conditions have increased central venous pressures, usually with preserved systolic function. For restrictive cardiomyopathy, biatrial enlargement and pulmonary hypertension are more prominent findings. For pericardial constriction, marked respiratory variation in ventricular filling is more common, but not definitive. Often, supplementary diagnostic tests are needed to differentiate the diagnoses. These tests include computed chest tomography or magnetic resonance imaging, which allow measurement of pericardial wall thickness. Other diagnostic studies include simultaneous left- and right-sided pressure tracings, with volume loading in the cardiac catheterization laboratory, and myocardial biopsy for infiltrative myocardial disease.

VALVULAR HEART DISEASE

Echocardiography is invaluable for assessment of valve anatomy and function.⁴⁴⁻⁴⁶ Echocardiographic imaging has essentially supplanted the need for invasive valve diagnostics in the catheterization laboratory. Once valve disease is diagnosed, serial echocardiography is used to monitor for onset of adverse hemodynamic effects of valve dysfunction on cardiac function, pulmonary function, and intravascular volume.

Aortic Stenosis

Echocardiography allows for identification of the etiology of aortic stenosis and assessment of valve hemodynamics.⁴⁷ With severe stenosis, leaflet calcification and imaging artifacts often hinder definitive identification of valve morphology. Aortic stenosis severity is evaluated using peak instantaneous transaortic velocities acquired from continuous Doppler ultrasound tracings. Several acoustic windows should be used to ensure that maximal velocity is recorded (see Fig. 55-12). A velocity greater than 4 m/sec indicates severe stenosis, and a velocity of 2.5 to 3 m/sec indicates mild stenosis. Pressure gradients are calculated from the transaortic velocities using the simplified Bernoulli equation. Because transvalvular

pressure gradients vary with volume flow rate, higher pressure gradients and flow velocities will be recorded in the setting of increased stroke volume (i.e., aortic regurgitation), and lower pressure gradients and velocities will be recorded when flow rates are decreased (i.e., LV systolic dysfunction). Aortic valve area (CSA_{AV}) is calculated using the continuity equation where CSA of the LV outflow tract (LVOT) is calculated from LVOT diameter, VTIs in the LVOT are obtained with pulsed Doppler, and the highest aortic Doppler velocity signal is recorded.

$$CSA_{AV} \times VTI_{AV} = CSA_{LVOT} \times VTI_{LVOT}$$

$$\text{rearranged to: } CSA_{AV} = CSA_{LVOT} \times VTI_{LVOT} / VTI_{AV}$$

This equation can be simplified further by substituting peak velocities (V) in place of the VTI measurements:

$$CSA_{AV} = (CSA_{LVOT} \times V_{LVOT}) / V_{AV}$$

A valve area smaller than 1.0 cm² indicates severe stenosis, and a valve area of 1.0 to 1.5 cm² is consistent with moderate stenosis. Diagnostic limitations for echocardiography in evaluating aortic stenosis include measurement variability, optimal alignment of the ultrasound beam to maximize transaortic velocities, and accurate measurement of the LVOT diameter for LVOT area calculation.

Increased afterload in aortic stenosis leads to an increase in myocardial wall stress with LV hypertrophy and impaired diastolic filling. Systolic dysfunction is not common, but it can occur in the late stages of the disease. Transesophageal imaging is usually less optimal for diagnostic evaluation of aortic stenosis as TEE is limited by the inability to optimally align the Doppler ultrasound beam parallel with blood flow across the aortic valve. Direct planimetry of the aortic valve orifice is limited by nonplanar anatomy of the aortic valve, acoustic shadowing, and beam width artifact from leaflet calcification.

Aortic Regurgitation

Common causes of aortic regurgitation include bicuspid aortic valve, endocarditis, and aortic root dilation.¹⁹ The aortic valve and proximal ascending aorta are usually well visualized by TTE. Echocardiographic imaging can aid in surgical planning by determining whether regurgitation is due to aortic root disease or primary valve dysfunction.¹⁹ Doppler echocardiography has high sensitivity and specificity for visualizing regurgitation. Semiquantitative evaluation of regurgitant severity is possible by measuring the vena contracta jet diameter (see Fig. 55-10). Regurgitation can be evaluated qualitatively as mild, moderate, or severe based on the size of the color flow jet relative to the LVOT. With greater than moderate regurgitation, Doppler interrogation of the descending thoracic and proximal abdominal aorta shows holodiastolic flow reversal (Fig. 55-32). Eccentric regurgitant jets that are directed posteriorly may restrict diastolic opening of the anterior mitral valve leaflet. The density of the continuous-wave Doppler signal relative to antero-grade flow is another measure of regurgitant severity.

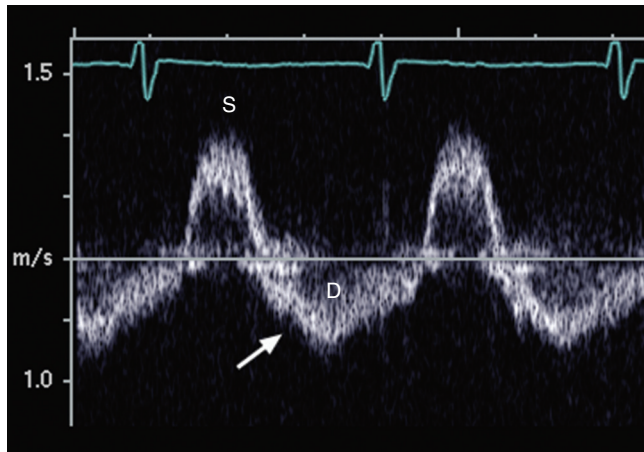


FIGURE 55-32 ■ Continuous Doppler ultrasound of the abdominal aorta with antegrade aortic flow during systole (S) and holodiastolic flow reversal during diastole (D), consistent with severe aortic regurgitation (arrow).

With acute or severe regurgitation, early diastolic equalization of aortic and LV pressures lead to a steep diastolic deceleration slope of the Doppler envelope and, in severe cases, late-diastolic velocity that approaches zero (see Fig. 55-9).

With significant, chronic aortic regurgitation, LV enlargement or dysfunction owing to increased hemodynamic load can occur. These patients usually develop cardiopulmonary symptoms such as dyspnea, decreased exercise tolerance, and congestive heart failure necessitating valve replacement. In asymptomatic patients, serial echocardiography is recommended to monitor regurgitation severity, ventricular size, and function. Surgery is recommended once adverse hemodynamic effect on LV size or function has occurred (fall in ejection fraction to less than 50% or an end-diastolic diameter that exceeds 70 mm).^{45,46}

Mitral Stenosis

Mitral stenosis is nearly uniformly due to rheumatic valve disease. Echocardiographic appearance of the valve includes commissural fusion, leaflet thickening, calcification, and restricted leaflet motion with diastolic doming of the leaflet in diastole owing to the inability of the valve to open fully (Fig. 55-33). In severe cases, the subvalvular apparatus is also affected with chordal thickening and fusion. Patients with moderate mitral stenosis (mean gradients 5-10 mm Hg) may be asymptomatic at rest, but develop dyspnea with increased cardiac demand, such as exercise or pregnancy. Progressive obstruction of mitral inflow leads to increased left atrial pressure and dilation and increased propensity to develop atrial fibrillation. Rare nonrheumatic causes of mitral stenosis include severe annular calcification and LV inflow obstruction from a vegetation or myxoma.

Peak and mean mitral pressure gradients are estimated from transmitral velocities using the Bernoulli equation. Mitral valve area (MVA) can be calculated from the empirically derived equation $MVA = 220/PHT$, where PHT (pressure half time) is the time duration for the peak

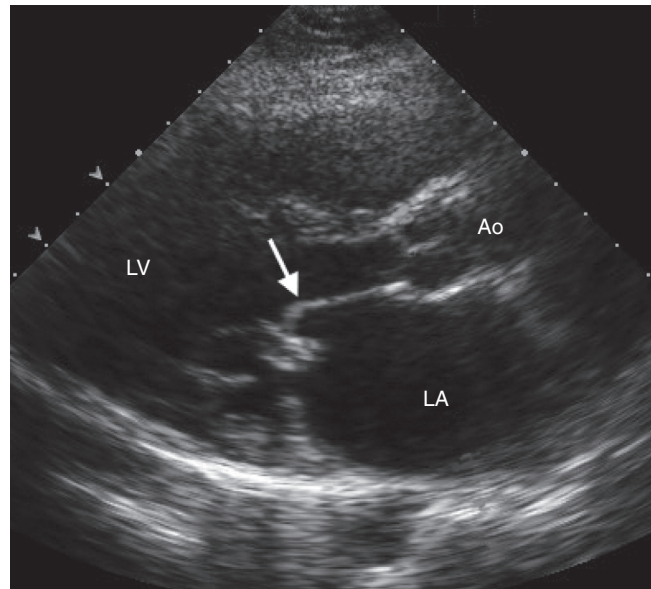


FIGURE 55-33 ■ Parasternal long axis view during diastole with mitral valve calcification and restricted leaflet opening in a patient with rheumatic mitral valve stenosis. There is also diastolic doming of the anterior leaflet (arrow). Ao, Aorta; LA, left atrium; LV, left ventricle.

early mitral inflow pressure gradient to drop by half. Another reproducible measurement for valve area is planimetry of the mitral valve orifice from a parasternal short-axis view (Fig. 55-34). Patients with significant mitral stenosis often have pulmonary hypertension, which can be estimated from the peak velocity of the tricuspid regurgitant jet. When clinical symptoms are discrepant with the hemodynamic severity of mitral stenosis, measuring the rise in pulmonary pressures during exercise echocardiography may be a helpful adjunct.

Echocardiographic valve characteristics that favor successful percutaneous balloon valvotomy include pliable mitral leaflets, minimal commissural fusion, and minimal valvular or subvalvular calcification. Percutaneous valvotomy is not performed if preprocedure TEE demonstrates a left atrial appendage thrombus or if there is greater than moderate mitral regurgitation. During the procedure, 3D echocardiography of the mitral valve during valvotomy aids in catheter placement and assessment of commissural fracture during balloon inflation, gauging the severity of postinflation mitral regurgitation (see Fig. 55-6).

Mitral Regurgitation

The first step in echocardiographic evaluation of mitral regurgitation is determining the cause and mechanism of regurgitation.¹⁹ Echocardiography is integral to visualize leaflet anatomy, assess ventricular geometry, and estimate pulmonary pressures. Common causes of primary mitral valve dysfunction include mitral valve prolapse, endocarditis, and rheumatic disease. In mitral valve prolapse, leaflets are thickened and redundant, and leaflet prolapse greater than 2 mm bowing into the left atrium is diagnostic (Fig. 55-35). Secondary or “functional”

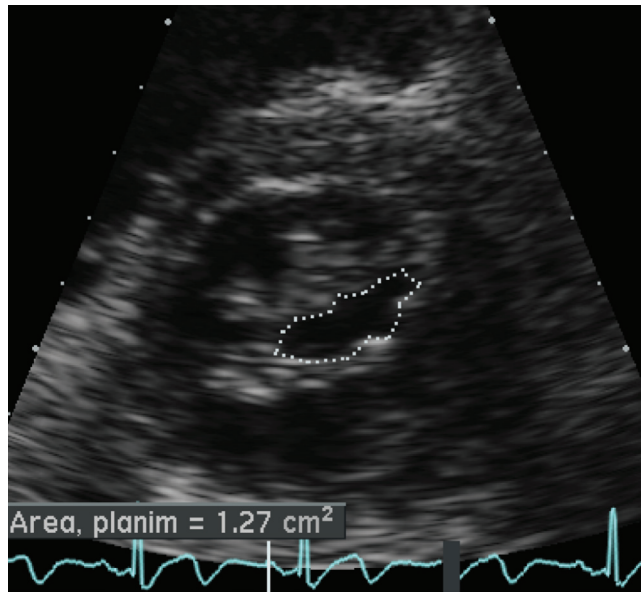


FIGURE 55-34 ■ Parasternal short-axis view allows for direct planimetry of the valve opening in a patient with rheumatic mitral stenosis (area = 1.3 cm²).

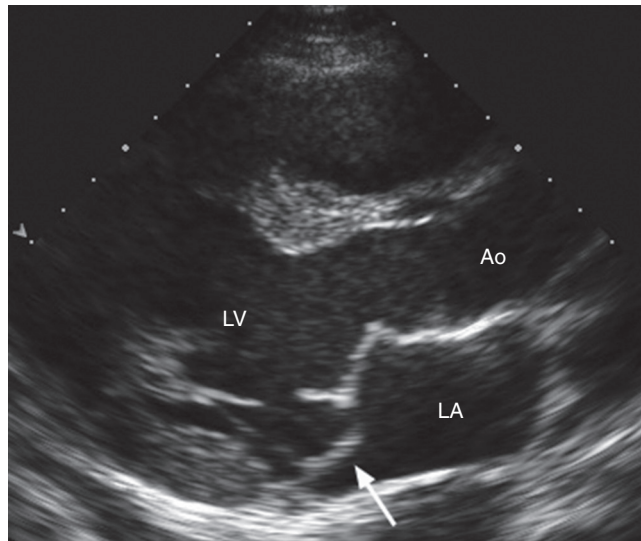


FIGURE 55-35 ■ Myxomatous mitral valve disease with redundant mitral valve leaflets and systolic prolapse of the mid-portion into the left atrium beyond the valve annulus. In this patient, prolapse of the posterior mitral leaflet is more prominent (arrow). Ao, Aorta; LA, left atrium; LV, left ventricle.

regurgitation of an otherwise anatomically normal mitral valve can occur with leaflet tethering or dilation of the mitral valve annulus.

Color Doppler mapping allows visualization and assessment of the regurgitant flow disturbance, jet size, direction, and jet eccentricity. Color Doppler has high sensitivity and specificity for detecting mitral regurgitation. A small degree of mitral regurgitation is common, present in up to 80% of normal individuals. By color Doppler, mitral regurgitant flow disturbances range from a small, localized area adjacent to the valve (mild) to a large flow disturbance that fills the entire left atrium (severe). Measurement of the vena contracta at the

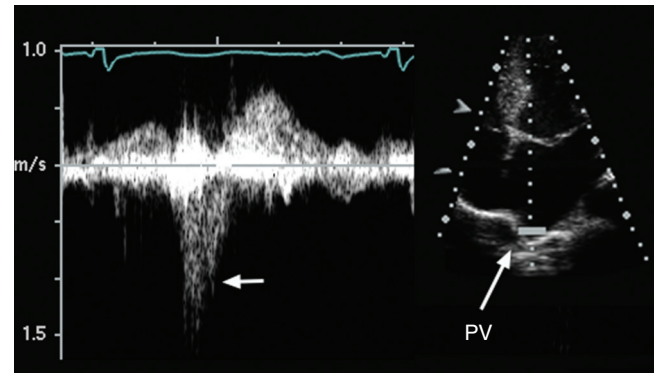


FIGURE 55-36 ■ Pulmonary vein tracing in a patient with significant mitral regurgitation. The Doppler signal is positioned in the right upper pulmonary vein (PV; right). Spectral Doppler tracing shows mid-late systolic flow reversal directed away from the transducer (arrow, left).

regurgitant orifice correlates with severity, even with eccentric jets. The shape and direction of the regurgitant jet aid in establishing the mechanism of valve dysfunction. For example, posterior mitral valve leaflet prolapse is usually associated with an anteriorly directed regurgitant jet. Eccentric jets that adhere to the atrial wall usually appear smaller than centrally directed jets; therefore, evaluation of the jet from at least two orthogonal views with careful adjustment of instrument settings is essential.

Greater regurgitation severity leads to increased left atrial pressures and regurgitant flow velocity. Doppler evaluation of the peak early inflow velocity (E wave) and the shape and intensity of the continuous-wave Doppler envelope provide added data on regurgitation severity, with worsened regurgitation leading to higher velocity, denser jets. Another qualitative measure of mitral regurgitant severity is the presence of systolic flow reversal of the pulmonary vein Doppler signal (Fig. 55-36).

Quantitative measures for regurgitation severity are preferred over qualitative assessment alone because color Doppler measures of jet size and flow disturbance are subject to transducer frequency and instrument settings. Quantitative evaluation includes measurement of regurgitant volume using the PISA, and calculation of the regurgitant orifice area. The PISA calculation assumes flow accelerates in a laminar fashion toward a regurgitant orifice, forming concentric hemispheres of isovelocity (see Fig. 55-11).²⁰ The EROA can be calculated once hemisphere surface area, blood velocity at that hemisphere (“aliasing velocity”), and orifice regurgitant velocity are measured. Calculation of EROA is more accurate when the regurgitant orifice is circular and the jet is not eccentric. Quantitative gradation of regurgitation by the American Society of Echocardiography is now incorporated in the AHA/ACC guidelines on valvular heart disease.^{19,45,46}

Progressive mitral regurgitant volume and increased hemodynamic cardiac load can lead to LV chamber enlargement and systolic dysfunction. Serial and echocardiographic measures of ventricular size and systolic function serve as the primary determinants for the timing of intervention in chronic mitral regurgitation. In

asymptomatic patients, surgery is recommended with an LV end-systolic diameter greater than 40 mm, ejection fraction less than 60%, onset of atrial fibrillation, or pulmonary hypertension.^{45,46}

With increased expertise in mitral valve repair and improved outcomes, many experienced surgical centers now advocate for earlier mitral valve repair, even in those with normal LV size and function, when likelihood of a successful repair exceeds 90%. Early intervention mandates a careful echocardiographic evaluation to ensure that regurgitation is severe by established quantitative guideline (EROA ≥ 0.4 cm², regurgitant volume ≥ 60 mL, regurgitant fraction $\geq 50\%$). Close collaboration between the echocardiographer and cardiac surgeon is needed to evaluate likelihood of a successful repair. During surgery, intraoperative TEE is used to evaluate adequacy of repair and identify residual mitral regurgitation.

Tricuspid Valve Disease

Most right-sided valvular disease in adults is secondary to left heart dysfunction. Trace to mild regurgitation of both the tricuspid and pulmonic valves is a normal finding, and it can be seen in more than 80% of normal adults. Significant functional tricuspid regurgitation may be due to pulmonary hypertension (>55 mm Hg), often with concurrent RV and annular dilation.⁴⁸ Other causes of tricuspid regurgitation include endocarditis, carcinoid disease, mediastinal radiation, and injury following pacer lead placement. Echocardiographic features of carcinoid include tricuspid leaflet calcification, thickening, and retraction. A congenital etiology of tricuspid regurgitation includes Ebstein anomaly, with apical displacement of the tricuspid septal leaflet and poor leaflet coaptation. Severe tricuspid regurgitation results in a wide vena contracta (>7 mm) and systolic flow reversal in the hepatic veins (imaged from the subcostal view). With progressive, right-sided volume overload, the right ventricle can become dilated, hypertrophied, and hypokinetic.

Prosthetic Valves

Prosthetic valves fall into two main classes: bioprosthetic and mechanical valves. Because of the sewing ring and struts in prosthetic valves, the functional valve area of prosthetic valves is smaller than with native valves, resulting in relatively higher antegrade velocities.⁴⁹ Knowledge of the individual flow dynamics of the different valve types is important to discriminate normal from abnormal transvalvular flow and function. Expected transvalvular velocities, areas, and gradients are dependent on valve size, patient size, valve type, and valve position. Optimal echocardiographic evaluation is often hindered by valve positioning, reverberations from artificial materials that hinder visualization of the valve occluders, and acoustic shadowing from artificial materials (see Fig. 55-3). This is particularly problematic when evaluating mitral prostheses for regurgitation because of shadowing of the left atrium. Transesophageal echocardiography (images posterior to the heart with improved image quality) is often needed for more definitive assessment (Fig. 55-37).⁵⁰

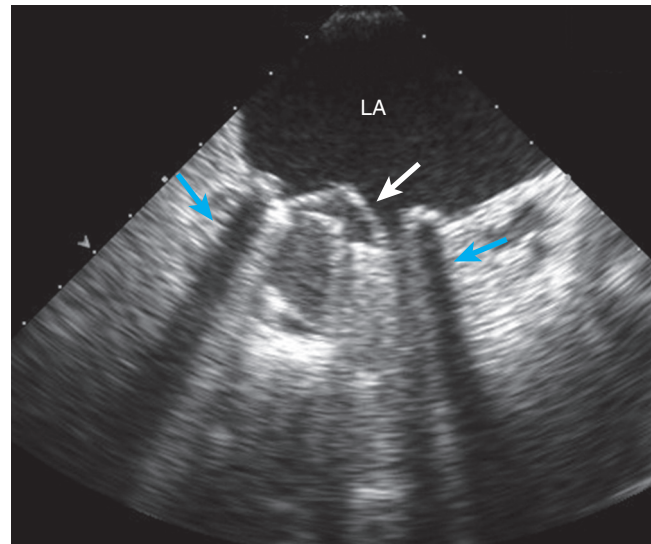


FIGURE 55-37 ■ St. Jude mechanical prosthesis (arrow) in the mitral position with acoustic shadowing of the left ventricle during TEE imaging. In patients with mitral prostheses, TEE is often needed to definitively evaluate for valve dysfunction, endocarditis, and regurgitation into the left atrium. LA, Left atrium.

For any prosthetic valve, it is not uncommon to see a small amount of regurgitant valvular flow. In the immediate postoperative period, tiny paravalvular regurgitant jets are common and usually resolve over time. With a single tilting disk valve, there is an asymmetrical flow profile with a major and minor antegrade flow identified and an eccentric, small regurgitant jet. Bileaflet mechanical valves have complex fluid dynamics with antegrade flow seen via two minor orifices corresponding to each leaflet, and one central major orifice. During valve closure, two small, central intersecting regurgitant jets are normally seen. Estimation of transvalvular gradients is relatively reliable for bioprosthetic valves. However, with mechanical valves, flow is heterogeneous across the entire orifice face, and high local velocities at the smaller leaflet orifices can lead to overestimation of the transvalvular gradient. Because of the absence of prosthetic material, the appearance of homograft and stentless tissue aortic valves may be echocardiographically indistinguishable from native valves.

Because prosthetic valve hemodynamics vary depending on patient habitus and valve type, a baseline echocardiogram (2-3 months) following surgery is recommended. Subsequently, serial examinations are typically not necessary unless the patient develops new cardiopulmonary symptoms or valve dysfunction is suspected. Complications, including endocarditis, pannus, or thrombus that impairs disk motion, can be diagnosed accurately with echocardiography. Because of improved image quality and more optimal transducer placement, TEE echocardiography is nearly always needed in the evaluation of prosthetic valve dysfunction.

Endocarditis

Used in combination with clinical and bacteriological data, echocardiography provides invaluable information

in the evaluation for endocarditis.⁵¹ The risk of endocarditis is highest in patients with valve prostheses, native valve disease, congenital heart disease, or a clinical risk factor, such as intravenous drug use. Major echocardiographic diagnostic criteria include echodense masses adherent to valve leaflets (vegetations) or endocardial surfaces, paravalvular abscesses, and prosthetic valve dehiscence (Fig. 55-38).

When endocarditis is suggested by predisposing factors, fever, sepsis, or embolic events, TTE is the initial procedure of choice. TTE allows for better manipulation of the transducer to evaluate possible fistulas and abnormal communications. However, although the specificity for TTE is adequate ($\approx 91\%$ - 98%), the sensitivity of TTE is relatively poor ($\approx 36\%$ - 90%) with more studies at the lower end of the spectrum. Therefore, patients with a negative transthoracic study, but in whom clinical suspicion for endocarditis is significant should also receive a TEE.⁵² Diagnostic accuracy for TEE is higher, and TEE more readily images complications of endocarditis. Regardless, if results of echocardiographic evaluation for endocarditis are negative, but clinical suspicion remains high, repeated echocardiography should be considered because a subsequent study result may be abnormal with disease progression.

Limitations for echocardiography and endocarditis include an inability to distinguish between acute and chronic lesions, vegetations and thrombus, reverberations from calcifications or prosthetic materials, and non-bacterial thrombotic lesions, as can be seen with systemic lupus erythematosus. False-positive findings include normal leaflet thickening, Lambl excrescences on the aortic valve, mitral leaflet redundancy resulting from myxomatous disease, partial flail leaflets, leaflet calcification, and degenerative changes.

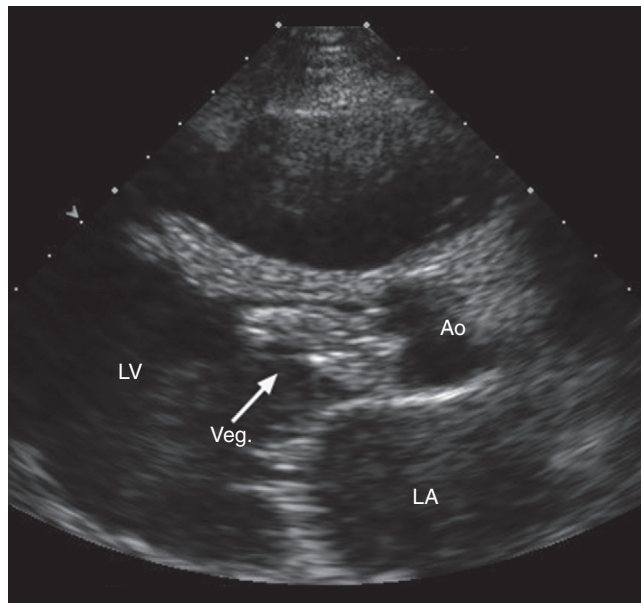


FIGURE 55-38 ■ Native aortic valve endocarditis in a patient with severe aortic regurgitation and cardiogenic shock. There is a large, mobile vegetation that is adherent to the aortic valve and that prolapses into the LV outflow tract (arrow). Ao, Aorta; LA, left atrium; LV, left ventricle; Veg., vegetation.

Common complications of endocarditis include involvement of other valves, leaflet perforation, paravalvular abscess, fistula development, and coronary embolization. Valve dysfunction associated with endocarditis usually leads to regurgitation. As with native valves, endocarditis of a bioprosthetic valve is often evidenced by vegetations. With mechanical valves, vegetations are less common. Instead, infection often causes valve instability, with dehiscence, paravalvular leak, or abscess. A paravalvular abscess in the aortic position may extend to the anterior mitral valve leaflet with involvement of the mitral-aortic intervalvular fibrosa (Fig. 55-39). Because of its communication with the LV cavity, flow into and out of the pseudoaneurysm can be demonstrated by color Doppler imaging. Infection that involves the aortic sinuses can lead to sinus of Valsalva aneurysm and rupture, with Doppler interrogation demonstrating flow into the cardiac chamber adjacent to the affected sinus.

AORTIC DISEASE

Transthoracic echocardiography is reliable in imaging aortic anatomy throughout most of the thoracic and proximal abdominal aorta. Standard aortic diameter measurements are taken from the aortic valve annulus, sinuses, sinotubular junction, ascending aorta, arch, and descending thoracic aorta.⁵³ Nonoblique imaging is essential for accurate measurement of internal aortic dimensions at end diastole. Image resolution with TTE is often limited by the aorta's posterior position and overlying air-filled structures such as the trachea and lungs. In addition, distance from the chest wall to the aorta

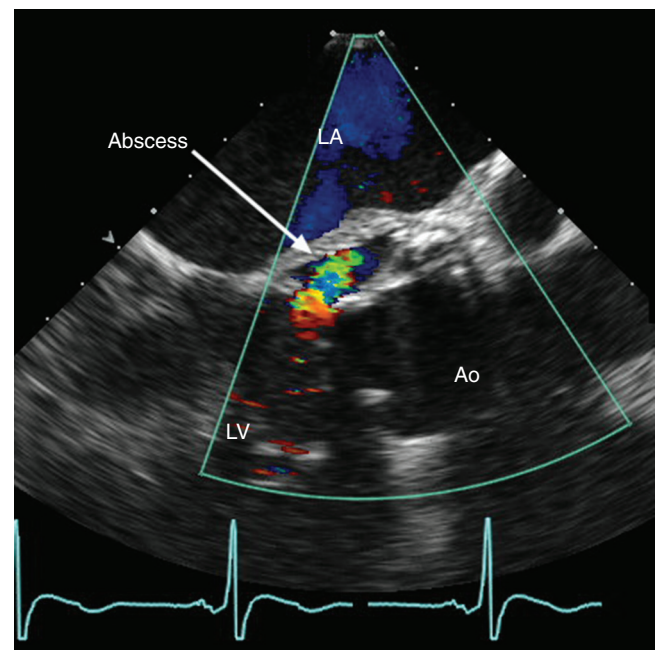


FIGURE 55-39 ■ Pseudoaneurysm of the mitral-aortic intervalvular fibrosa (arrow) in a patient with a mechanical aortic valve, imaged by transesophageal echocardiography. Systolic flow is seen by color Doppler into the left ventricle (LV) outflow tract. Ao, Aorta; LA, left atrium.

hinders optimal image resolution. Therefore, TEE, with the shorter distance between the transducer and the aorta and better ultrasound penetration, is often needed to complete a full echocardiographic aorta evaluation. Computed tomography and magnetic resonance imaging allow for better spatial imaging of the aorta; however, echocardiography allows for imaging in the absence of radiation or contrast exposure. Echocardiography also has the advantage of portability and allowing for identification of concurrent pericardial fluid and aortic regurgitation. Importantly, data are more readily available as limited imaging of the aorta is routinely performed on most transthoracic studies.

Asymptomatic dilation of the ascending aorta is associated with atherosclerosis, systemic hypertension, bicuspid aortic valves, and Marfan disease. Marfan disease is associated with dilation of the aortic sinuses with effacement of the sinotubular junction. Patients with aneurysmal dilation of the sinuses or ascending aorta are at increased risk of dissection and aortic rupture. Therefore, serial echocardiography is used to monitor for progressive enlargement, to time referral for prophylactic surgical repair.⁵³

Atherosclerotic disease is more easily imaged with TEE, in which the severity and extent of disease can be readily imaged along the length of the thoracic and proximal abdominal aorta (Fig. 55-40). Common findings include atherosclerotic plaques, ulceration, associated dilation, and adherent mobile thrombi, which are all considered potential sources of distal embolic disease. Intraoperative use of TEE and/or epiaortic scanning with a sterile transducer to localize atherosclerotic plaques directs optimal placement of the aortic cannula for the arterial bypass circuit and for aortic cross-clamping.

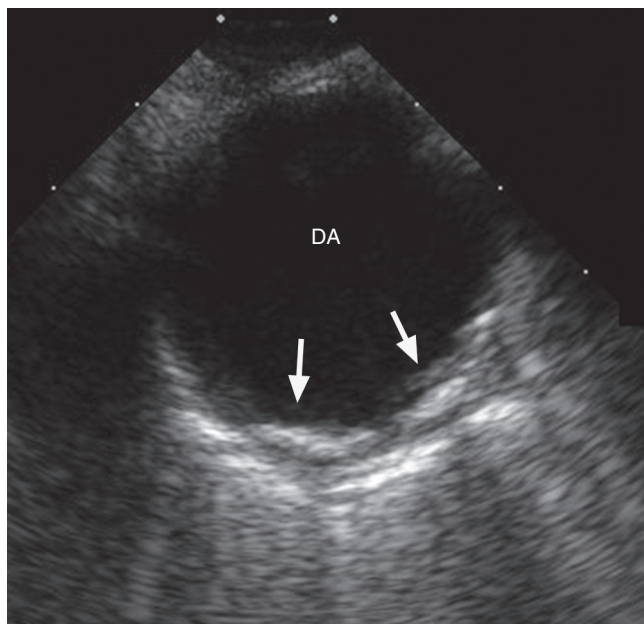


FIGURE 55-40 ■ Mild atherosclerosis (arrows) of the descending thoracic aorta (DA) imaged by transesophageal echocardiography. Calcification within the atherosclerotic plaque causes acoustic shadowing distally in the far field.

In aortic dissection, the flap appears as a thin, mobile echodensity within the aortic lumen (Fig. 55-41). The false lumen can contain thrombus, localize, or propagate distally. Color flow Doppler can be used to identify entrance and exit points to the false lumen. Associated findings with dissection can include intramural hematoma, extension of the dissection into the branch vessels or a coronary artery with resulting regional wall motion abnormalities, pericardial or pleural effusion, aortic root dilation, and flail aortic leaflet with aortic regurgitation. The sensitivity for TTE to detect aortic dissection ranges between 29% and 80%, limited by beam width artifacts and reverberations that increase false-positive results. The specificity of TTE is also low, because of difficulty imaging the posteriorly located aorta. In the hands of an experienced operator, TEE provides improved image quality and more complete evaluation of the length of the thoracic aorta, with sensitivity and specificity approaching 100%. Following surgical intervention, serial echocardiography is used to monitor for recurrent disease, evaluate the proximal and distal graft anastomotic sites, and assess prosthetic valve function. Computed tomography, TEE, and cardiac magnetic resonance imaging have equivalent diagnostic accuracy for aortic dissection.

CONGENITAL HEART DISEASE

Echocardiography is a key diagnostic modality in patients with congenital heart disease.⁵⁴ Indications for echocardiography include diagnosis, monitoring for hemodynamic progression of lesions on cardiac function, and anatomic definition or guidance for palliative or reparative interventions. Echocardiography accurately detects intracardiac shunts with Doppler interrogation and agitated saline contrast studies. By comparing the volume flow rates across the pulmonic and aortic valves, quantitation of the pulmonic-to-systemic shunt ratio can also be estimated.

For atrial septal defects, echocardiography allows distinction between secundum, primum, and sinus venosus defects with demonstration of left-to-right flow across the atrial septum on color Doppler flow imaging. Other

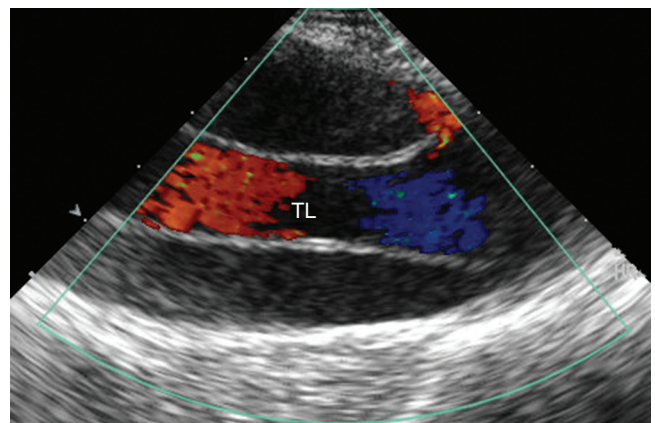


FIGURE 55-41 ■ A dissection flap is seen within an enlarged aorta, imaged by transesophageal echocardiography. The true lumen (TL) is visualized with color Doppler imaging.

findings associated with atrial septal defects include right heart enlargement, hypertrophy, and pulmonary hypertension. Three-dimensional echocardiography allows for improved spatial resolution of the inter-atrial septum and aids in decision making regarding size and placement of defect for percutaneous versus surgical closure. Ventricular septal defects can be identified by Doppler flow across the interventricular septum. In adults, most ventricular septal defects are small, with high-velocity left-to-right systolic flow and a relatively small shunt volume.

Bicuspid aortic valves are the most commonly occurring congenital abnormality (Fig. 55-42). Aortic root dilation is common in these patients, and serial echocardiography is indicated once diagnosed to monitor for progressive valve dysfunction and aortic dilation (Fig. 55-43). In patients with aortic coarctation, transthoracic

imaging can demonstrate the aortic narrowing. Doppler examination of the thoracic aorta shows increased antegrade flow velocity in the region of the coarctation, with antegrade aortic flow that persists into diastole. With a patent ductus arteriosus, color Doppler may show the communication between the pulmonary artery and aorta, and, if shunt flow into the pulmonary artery is large enough, may demonstrate aortic diastolic flow reversal.

The most common complex congenital heart disease seen in the adult population is tetralogy of Fallot. Most patients with tetralogy of Fallot have undergone surgical repair with ventricular septal defects closure and enlargement or patch repair of the RV outflow tract. Serial echocardiography is performed to monitor for pulmonic regurgitation related to the transannular pulmonic patch and RV size and function; this necessitates repeat surgical intervention. In patients with previous surgical repair of complex congenital heart disease, echocardiography is a key tool in monitoring for long-term complications of prior palliative or corrective surgeries. With knowledge of the previous surgical procedures and a careful and meticulous examination, anatomy and physiology are usually well demonstrated. However, in complex cases, other imaging procedures, including magnetic resonance imaging and cardiac catheterization, may be needed for complete patient evaluation. Prior operative reports often greatly assist the echocardiographer in interpreting the nature of congenital repair and in identifying complications.

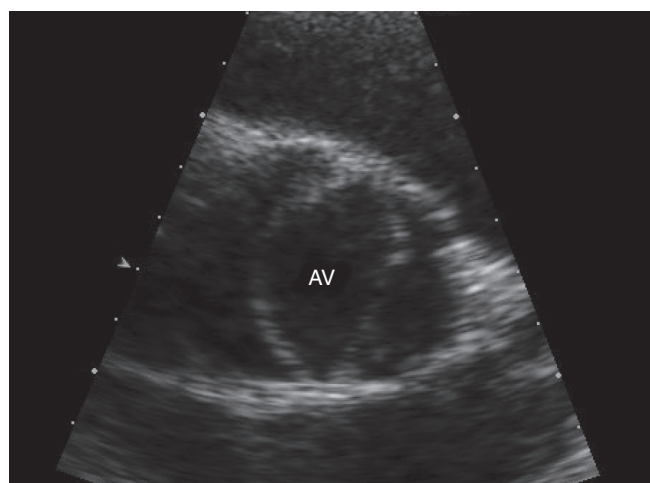


FIGURE 55-42 ■ Parasternal short-axis view of a bicuspid aortic valve, showing a linear anterior-posterior valve opening during systole. AV, Aortic valve.

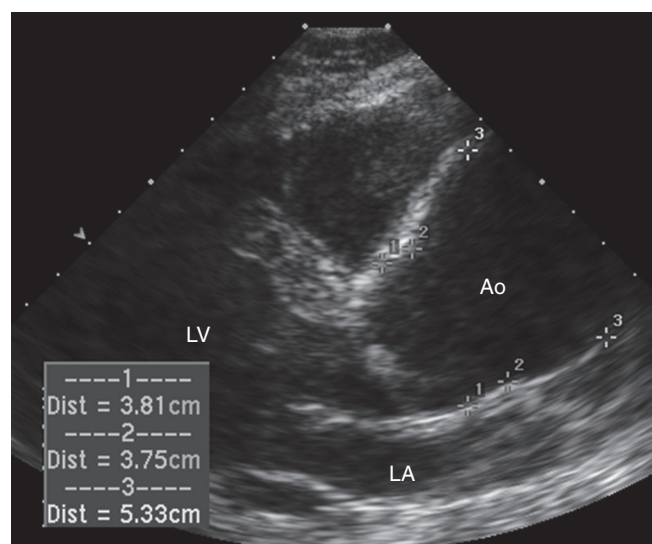


FIGURE 55-43 ■ Dilation of the aortic root and ascending aorta in a patient with a bicuspid aortic valve. Measurements are taken at the coronary sinuses (1), sinotubular junction (2), and proximal ascending aorta (3). Ao, Aorta; LA, left atrium; LV, left ventricle.

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MEDICAL- AND CATHETER- BASED TREATMENT OF CARDIOVASCULAR DISEASE

PART OUTLINE

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INTERVENTIONAL CARDIOLOGY

Stuart H. Chen • Duane S. Pinto

CHAPTER OUTLINE

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Interventional cardiology is a subspecialty of medicine that treats a variety of cardiovascular disorders using catheter-based therapeutics. Despite its humble beginnings in 1977, interventional cardiology now includes an array of procedures and techniques for the treatment of ischemic, valvular, and congenital heart disorders. The growth and maturation of the discipline have closely paralleled the rapid influx of new technologies and pharmacotherapeutics. This chapter will review the historical development in interventional cardiology, indications and techniques, and the evolution of the devices and medications used during these procedures.

HISTORICAL PERSPECTIVE

After the refinement of diagnostic coronary angiographic catheters by Sones, Judkins, and Abrams in the 1950s, the radiologist Charles Dotter performed the first endovascular dilation of a stenotic artery for therapeutic purposes in 1964.¹ Peripheral arterial lesions were treated with progressive coaxial catheter dilation to improve blood

flow. Complications including hematoma formation and distal embolization were common, and this technique, referred to as “dottering,” did not gain favor in the United States. However, European investigators continued to study and modify the technique. One such physician, Andreas Gruentzig, modified the Dotter multiple catheter system and developed a double-lumen catheter with a distensible balloon on the end that provided circumferential rather than coaxial pressure on the atherosclerotic plaque. Inflation of the angioplasty balloon within the atherosclerotic plaque led to fissuring and cracking of the intima with stretching of the media and adventitia (Fig. 56-1).

Gruentzig performed the first *peripheral* balloon angioplasty in 1974 and then the first human coronary angioplasty in the operating room during elective coronary artery bypass surgery. When Gruentzig performed the first *percutaneous* transluminal coronary angioplasty (PTCA) in September 1977, the discipline of interventional cardiology was born.²

Initially, balloon angioplasty was offered as an alternative to coronary artery bypass surgery in symptomatic

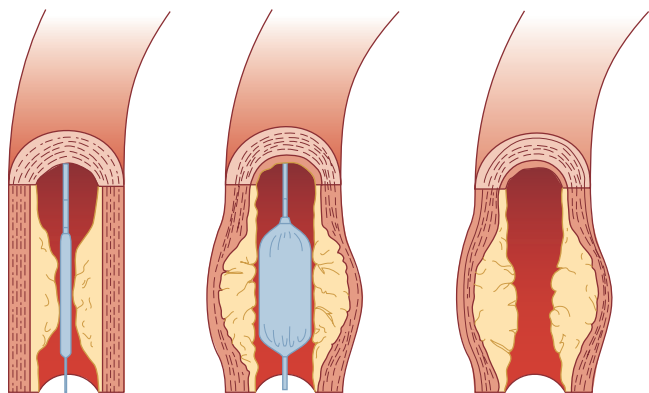


FIGURE 56-1 ■ Mechanism of lumen enlargement with angioplasty. (From Willerson JT: *Treatment of heart diseases*, New York, 1992, Hower Medical.)

patients with focal, proximal stenoses. Dilation of these arteries was usually associated with significant improvement in angina and in objective measures of ischemia.³ However, the application of PTCA was limited to a small fraction of coronary lesions, because first-generation fixed-wire balloons lacked the ability to be steered and the profile needed to traverse distal and tortuous vessels. Easier to use over-the-wire and rapid-exchange systems began to replace the initial fixed balloon-on-wire system developed by Gruentzig. The development of conformable, low-profile balloons facilitated dilation of distal lesions in tortuous and calcified vessels.

The major limitations of balloon angioplasty—abrupt vessel closure and restenosis—were addressed by the development of new devices in the late 1980s and early 1990s. With the introduction of atherectomy devices, laser balloon catheters, and endovascular stents, the more generic term *percutaneous coronary intervention* (PCI) replaced the term PTCA and referred to any catheter-based procedure intended to enlarge the lumen of a stenotic vessel. Atheroablative techniques such as directional and rotational atherectomy and excimer laser angioplasty were marketed initially as replacements for balloon angioplasty. Although these techniques improved technical success in certain high-risk subsets such as fibrocalcific and bifurcation stenoses, they were technically difficult to perform, did not have a major impact on restenosis, and have largely been abandoned as stand-alone therapies.

The widespread use of endovascular prostheses, or stents, unequivocally improved the acute safety and long-term efficacy of catheter-based treatment. As a result, more than 1 million PCIs are now performed each year in the United States to alleviate symptoms and reduce adverse cardiac events.⁴ Stents were originally approved to seal dissection flaps and reverse acute vessel closure after PTCA by inhibiting elastic recoil in the arterial wall. The Gianturco-Roubin coil stent was the first such device approved in the United States, and it was approved on the basis of its ability to stabilize dissections and thus reduce the incidence of abrupt vessel closure and early complications.⁵ In 1994, the balloon-expandable Palmaz-Schatz slotted tube stent was approved for elective use

after two randomized trials showed significant reductions in angiographic restenosis.^{6,7}

Thus, by the end of the millennium, stents became the default technology for catheter-based therapy, with 70% to 80% of all patients undergoing PCI receiving a stent. Despite the salutary effects of stents, restenosis still occurred in 10% to 30% of patients, who usually presented with recurrent ischemia. The use of adjunctive intravascular brachytherapy after balloon dilation of in-stent restenosis greatly reduced the need for subsequent revascularization procedures in patients who suffered restenosis despite stents, but it was associated with no significant impact on long-term outcome.⁸ As a result, this technology has been largely abandoned for use in coronary arteries.

In 2004, the U.S. Food and Drug Administration (FDA) approved the use of drug-eluting stents (DESs) that elute either sirolimus or paclitaxel into the vessel directly from a polymeric coating on the stent. The introduction of this technology dramatically reduced restenosis rates. Some of the initial enthusiasm for the DES was tempered by reports suggesting a higher incidence of very late stent thrombosis with DESs compared with bare metal stents (BMSs). This led to a more individualized approach to DES usage, with a BMS used in patients who had a high risk of hemorrhage or poor compliance with dual antiplatelet therapy. Presently, a DES is used in approximately 60% to 70% of all PCIs in the United States. Second-generation DESs featuring newer drugs, polymers, and stent delivery systems are now approved for use and are associated with lower rates of restenosis, stent thrombosis, and myocardial infarction compared with first-generation technology. Stents with bioabsorbable polymer coatings and others where the scaffolding is completely biodegradable are in use.^{9,10}

PERCUTANEOUS CORONARY INTERVENTION PROCEDURES

Coronary intervention, like diagnostic angiography, begins with placement of a vascular access sheath in the femoral, brachial, or radial artery. Although choice of access site is at the discretion of the operator, most interventional procedures are performed using the femoral artery.¹¹ Radial artery access has been the default strategy for many years in some countries and is gaining popularity in the United States. This approach has been associated with improved outcomes, particularly in ST-segment elevation myocardial infarction (STEMI), reduced vascular complications, and greater patient satisfaction.^{12,13} Procedural success rates are comparable across all access sites, but radiation exposure and procedure times are slightly longer with brachial or radial procedures.¹⁴ Use of the radial access site is limited by the small size of the artery, radial, subclavian, and aortic tortuosity, as well as operator familiarity and experience.

Arterial access is obtained via percutaneous puncture of the wall of the artery with a hollow needle.¹⁵ A guide-wire is advanced through the lumen of the needle or catheter, and the needle or catheter is removed. A vascular sheath is then inserted over this wire. Large-lumen

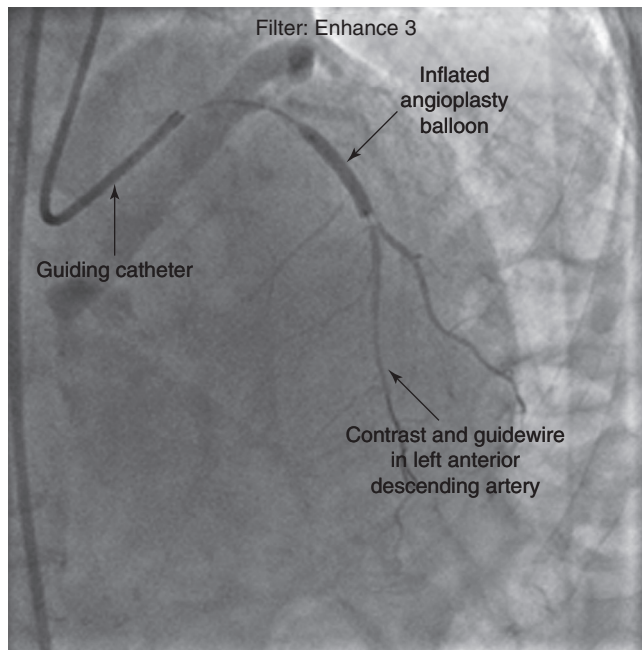


FIGURE 56-2 ■ Angiogram during percutaneous coronary intervention of the left anterior descending artery.

guiding catheters are then advanced through the arterial sheath and to the ascending aorta over a wire placed in the aorta. The guidewire is removed, and selective cannulation of the coronary arteries or bypass conduits is undertaken. If a stenosis is repaired, a 0.014-inch wire is used to traverse the stenosis, and the equipment used to treat the stenosis is advanced coaxially over this wire into the vessel (Fig. 56-2).

All PCI procedures require administration of antiplatelet and anticoagulant medications during the procedure. Unfractionated heparin, low-molecular-weight heparin, or the direct thrombin inhibitor bivalirudin are commonly used anticoagulants to support PCI. Aspirin is administered before the procedure, and an additional oral antiplatelet agent (clopidogrel, ticagrelor, or prasugrel) or an intravenous agent (eptifibatide, tirofiban, or abciximab) is also administered before, during, or after the procedure in most circumstances. The optimal timing and combinations of these agents in various clinical scenarios is an important consideration for PCI procedures but is beyond the scope of this discussion.

PCI for Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction

Current guidelines support the use of an early invasive management strategy with early coronary angiography for patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) who are at moderate or high risk for reinfarction or death. Those with positive cardiac biomarkers, ST-segment changes on 12-lead electrocardiogram, or clinical parameters such as congestive heart failure, refractory angina, or arrhythmia gain particular benefit.¹⁶ This strategy involves early

administration of antithrombotic and antiplatelet medications as well as early angiography for further risk stratification. When the coronary anatomy is suitable, revascularization with coronary artery bypass graft (CABG) or PCI is performed unless there is a strong contraindication. Typically, among moderate- and high-risk patients undergoing angiography for unstable angina or NSTEMI, approximately 30% are managed without revascularization, 55% to 60% with PCI, and 10% to 15% with CABG.¹⁷ Patients at low clinical risk can be treated with a selective invasive strategy. Revascularization can be reserved for patients with high-risk noninvasive test results or recurrent symptoms.

PCI for ST-Elevation Myocardial Infarction

The benefits of mechanical or pharmacologic reperfusion therapy in the setting of acute STEMI are well established. In comparison with PTCA alone, PCI with stent placement significantly reduces the incidence of death and ischemic target vessel revascularization, and the benefit is maintained for up to 5 years in patients with acute MI.¹⁸⁻²⁰ PCI in this setting is called primary PCI and has been shown to effectively reestablish normal epicardial coronary perfusion in more than 90% of patients. Assuming treatment times remain short and the artery can be opened expeditiously at an experienced center, PCI has been shown to be superior to fibrinolytic therapy even if transport is required.²¹ Treatment times are important operator and hospital quality benchmarks. The time from first medical contact to first device activation within the artery should be 90 minutes or less and less than 120 minutes for patients who require transfer to a PCI capable facility.^{22,23}

Long-term patency rates exceed 85%, and the risks of reinfarction and death are significantly reduced with PCI compared with fibrinolytic therapy.^{1,24-26} Initial reports suggested harm when combining fibrinolysis and PCI, but among the 30% to 50% of patients in whom fibrinolytic therapy does not restore arterial patency, so-called subsequent rescue PCI is associated with improved outcomes compared with fibrinolytic therapy alone.^{27,28} A pharmacoinvasive strategy has been advocated for patients with an anticipated delay to primary PCI. With this strategy, fibrinolytic therapy is administered and the patient is transported to a facility for rescue PCI if fibrinolytic therapy fails or for routine angiography and elective PCI 3 to 24 hours after fibrinolysis.^{29,30} Additional fibrinolytic therapy at the time of immediate PCI is called facilitated PCI and is associated with adverse consequences. Facilitated approaches, in which the intent is to improve outcomes of the PCI procedure with concurrent fibrinolytic therapy, should be distinguished from pharmacoinvasive strategies, in which the intent is to improve outcomes of fibrinolytic therapy by using adjunctive PCI.

Patients who develop cardiogenic shock in the setting of acute myocardial infarction (MI) also seem to benefit from immediate revascularization with PCI or CABG. Improved survival at 6 months has been shown in a randomized trial comparing immediate revascularization, using either PCI or CABG, with initial medical

stabilization using fibrinolytic therapy, delayed revascularization, or both. However, among the subset of patients older than 75 years, reduced survival was noted when immediate revascularization was used compared with medical stabilization followed by delayed revascularization.³¹

PCI for Chronic Stable Angina

Although medical therapy is preferred in patients with minimal symptoms and only a small area of ischemic myocardium, patients with large amounts of ischemic but viable myocardium in jeopardy have better anginal control if coronary revascularization is performed. Patients who are asymptomatic or whose symptoms can be controlled with medications, but who have high-risk noninvasive test findings, have been shown to have lower rates of death or MI when treated with revascularization compared with medical therapy alone.^{32,33}

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial found that in the initial management of stable coronary artery disease (CAD), PCI and medical management did not significantly differ in their reduction of death, MI, or adverse cardiovascular events.³⁴ By 5 years, there was no significant difference in angina symptoms, although PCI was associated with earlier palliation of angina. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for PCI, however, suggest that asymptomatic or minimally symptomatic patients with coronary lesions that are 50% stenosed or greater in one or two arteries undergo PCI if there is a high likelihood of success and a low risk of morbidity and mortality, and if the arteries supply a moderate or large area of viable myocardium.^{32,35} Thus, the decision to undergo elective PCI is largely based on the degree of myocardium at risk and failure of initial medical therapy.

Multivessel PCI

The comparative usefulness of multivessel PCI versus CABG has been the subject of significant debate. Whether to perform PCI or CABG is often based on the complexity, severity, and extent of disease, as well as on patient risk factors for ischemia and surgical complications. Perceived benefits of CABG compared with PCI are described in [Box 56-1](#). Various lesion subsets have been evaluated in registries that suggest a benefit for CABG compared with PTCA in patients with three-vessel disease or severe stenosis of the proximal left anterior descending artery.³⁶ Randomized comparisons have been performed of CABG and PTCA, BMS and DES ([Table 56-1](#)). The largest comparison of PTCA and CABG was the Bypass Angioplasty Revascularization Investigation (BARI) trial, which demonstrated that 5-year survival and survival free of Q-wave MI did not differ significantly between the PTCA and CABG groups (86.3% vs. 89.3% and 78.4% vs. 80.4%, respectively; $P = 0.19$). On the other hand, patients randomized to CABG were much less likely to require repeat revascularization. Nonetheless, 69% of patients initially assigned to PTCA avoided CABG over a 5-year period.³⁷ In this trial, CABG

BOX 56-1 Benefits of Coronary Artery Bypass Graft Surgery and Benefits of Percutaneous Coronary Intervention

CORONARY ARTERY BYPASS GRAFT

- Fewer subsequent procedures and hospitalizations
- More complete symptom relief at 1 and 3 years
- More complete initial revascularization
- Improved survival and fewer repeat procedures among diabetic patients and those with complex disease
- Established benefit in left main coronary disease

PERCUTANEOUS CORONARY INTERVENTION

- Can be performed among patients with increased peri-operative risk
- Quicker recovery from initial procedure
- Most patients asymptomatic at 1- and 3-year follow-ups
- With stents, 80% to 90% of patients do not require coronary artery bypass graft surgery

provided an important advantage over PTCA for diabetic patients ($n = 353$).³⁸ At 5-year follow-up, all-cause mortality was 19.4% in the 180 diabetic patients assigned to CABG, and 34.5% among the 173 patients assigned to PCI ($P = 0.003$). In a registry of patients screened but not randomized in the BARI trial, long-term follow-up demonstrated no significant difference in mortality between diabetic patients undergoing CABG and those assigned to PCI.^{39,40} In contrast to the randomized trial, patients in the BARI registry had their initial revascularization strategy chosen by their physicians, which may have been the reason for the difference in outcome.

Several studies have examined outcomes of multivessel BMS placement compared with CABG (see [Table 56-1](#)). Meta-analysis of the four major randomized trials comparing BMS and CABG revealed a 5-year safety profile for PCI that is similar to that for CABG. Lower repeat revascularization rates were found among the CABG patients (29.0% vs. 7.9%, respectively; hazard ratio [HR], 0.23; 95% confidence interval [CI], 0.18-0.29; $P < 0.001$) ([Fig. 56-3A](#)) with no difference in rates of death, stroke, or MI (see [Fig. 56-3B](#)). No subgroup, including diabetic patients and those presenting with three-vessel disease, was found to have a selective benefit with CABG.⁴¹

It was postulated that reductions in repeat revascularization rates associated with DES would lower adverse events after multivessel PCI sufficiently to favor this strategy over CABG. The Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial evaluated patients with three-vessel or left main coronary artery (LMCA) disease randomizing them to paclitaxel-eluting stents or CABG.⁴² Three- and five-year follow-up data from SYNTAX demonstrated higher rates of major adverse cardiovascular events with paclitaxel-eluting stents compared with CABG (28.0% vs. 20.2%; $P < 0.001$ at 3 years and 37.3% vs. 26.9%; $P < 0.0001$ at 5 years).^{43,44} Cardiac death was less with CABG (5.3% vs. 9.0%; $P = 0.003$) as was MI (3.8% vs. 9.7%; $P < 0.001$) and repeat revascularization (13.7% vs. 25.9%; $P < 0.001$).

TABLE 56-1 Randomized Clinical Trials Comparing Coronary Artery Bypass Graft (CABG) and Percutaneous Coronary Intervention (PCI)

Clinical Parameters						
	Trial	Mortality & MI	Angina Relief	Repeat Revascularization	Stroke	Cost Assessment
No stents used	GABI	PCI	PCI	CABG	n/a	n/a
	EAST	No difference	CABG		No difference	PCI
	RITA				n/a	n/a
	ERACI				n/a	PCI
	CABRI				n/a	n/a
	BARI				No difference	
BMS used	MASS-2	CABG (MI)	n/a		n/a	No difference
	AWESOME	No difference	No difference		No difference	n/a
	ERACI-2	PCI	n/a		n/a	No difference
	SoS	CABG (mortality)	CABG		n/a	n/a
	ARTSI	No difference	n/a		No difference	PCI
DES used	ARTSII				n/a	n/a
	MAIN-COMPARE				No difference	n/a
	LE MANS	No difference	n/a			
	SYNTAX	CABG	No difference			CABG
	FREEDOM		PCI		n/a	

BMS, Bare metal stent; CABG, coronary artery bypass graft; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Adapted from Levine GN, Bates ER, Blankenship JC, et al: 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 124:e574–e651, 2011.

The SYNTAX score, developed in this trial, is based on the angiographic complexity and extent of disease. Using this score, patients' coronary disease could be divided into three categories, low (0–22), intermediate (23–32) and high (≥ 33). When stratifying outcomes according to SYNTAX score, adverse outcomes at 5 years for CABG were not significantly different across these strata (28.6%, 25.8%, 26.8% for low, intermediate, and high SYNTAX scores, respectively). The comparative outcomes with PCI versus CABG, however, differed significantly. For patients with low SYNTAX scores, no significant differences in outcomes were noted for CABG versus PCI, but in patients with intermediate and high SYNTAX scores, the rates of MI and repeat revascularization were significantly higher with PCI.

The largest trial of patients with diabetes and multivessel disease was Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM), which randomized 1900 patients, 83% of which had three-vessel disease, to either PCI with DESs or CABG.⁴⁵ The 5-year rates of the primary outcome (a composite of death, nonfatal MI, and nonfatal stroke) were significantly reduced with CABG compared with PCI (18.7% vs. 26.6%; $P = 0.005$) because of increased rates of death and MI in the PCI group (16.3% vs. 10.9%; $P = 0.049$ and 13.9% vs. 6.0%; $P < 0.001$ in the PCI and CABG groups, respectively), whereas the rates of stroke were significantly higher with CABG at 5 years (2.4% vs. 5.2%; $P = 0.03$).⁴⁵ The benefit of CABG over PCI among diabetic patients with multivessel disease was present regardless of SYNTAX score, implying CABG is superior to PCI in diabetics with

multivessel coronary disease regardless of anatomic complexity.

Left Main-Stem Disease

Stent placement in the LMCA can be performed with high rates of procedural success. As is the case with multivessel PCI, PCI of the LMCA is associated with higher rates of repeat revascularization. The DES has rapidly and largely replaced the BMS for PCI of the unprotected LMCA. However, PCI is still chosen less frequently than CABG for unprotected left main revascularization. Registries describing outcomes after DES implantation or CABG for LMCA stenosis have demonstrated higher rates of repeat revascularization with PCI and lower mortality rates with CABG.^{46,47} It is unknown whether differences in patient risk and angiographic parameters affect these results. A subgroup analysis of the SYNTAX trial involving 705 patients with LMCA disease did not show a significant difference in 12-month rates of major adverse cardiovascular events with PCI (15.8%, vs. 13.7% with CABG; $P = 0.44$), but PCI had a significantly higher rate of repeat revascularization (13.5%, vs. 5.9% with CABG; $P < 0.001$).⁴² The increased rate of repeat revascularization with PCI was countered by a significantly lower rate of stroke (0.3%, vs. 2.7% with CABG; $P = 0.01$). These results remained consistent at 5-year follow-up.⁴⁴

The ACC/AHA guidelines for PCI strongly recommend (class I) CABG for patients with significant ($\geq 50\%$ diameter stenosis) left main stenosis. However, PCI for LMCA disease is recommended (class IIa) as a reasonable alternative to CABG in select patients with coronary

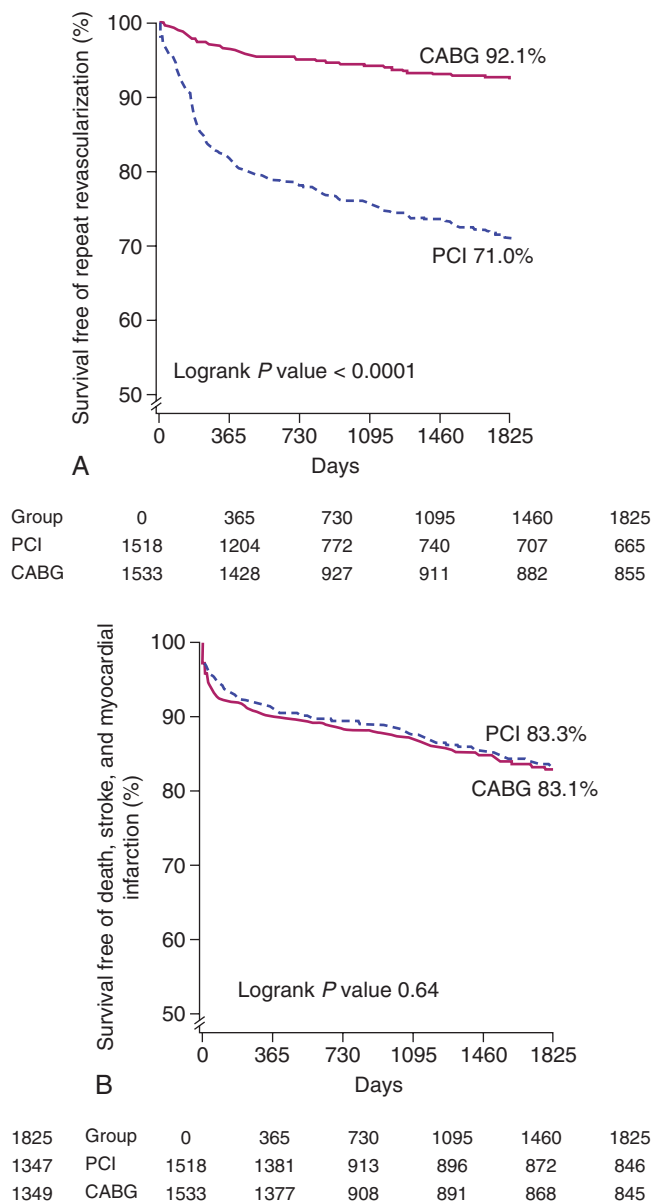


FIGURE 56-3 ■ Kaplan-Meier event-free survival analysis of repeat revascularization (**A**), and death, stroke, or myocardial infarction (**B**). CABG, Coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

anatomy predictive of a low PCI complication rate and good outcome (such as SYNTAX score ≤ 22 , ostial LMCA disease), as well as those patients with an increased risk of adverse surgical outcomes.⁴⁸ The updated Appropriate Use Criteria for Coronary Revascularization gave an “uncertain” rating to PCI for isolated left main stenosis or left main stenosis with low CAD burden (i.e., additional one- or two-vessel disease, low SYNTAX score); PCI for left main disease with additional, intermediate-to-high CAD burden (three-vessel disease, chronic total occlusion, high SYNTAX score) was rated “inappropriate.”⁴⁹ However, CABG for LMCA disease, with or without additional CAD burden, was rated “appropriate.” Therefore, the decision to treat left main CAD with PCI or CABG, similar to all patients with stable CAD, should depend on multiple factors, including coronary anatomy and relative surgical risk.

Elective PCI and Noncardiac Surgery

The incidence of perioperative cardiac events ranges from 2% to 6%, depending on the type of surgery performed and the patient’s clinical risk factors. Most studies have focused on patients requiring vascular surgery. It is recommended that patients with three or more clinical risk factors and poor functional capacity (class IIa) undergo further testing before vascular surgery. Those with one or two clinical risk factors and poor functional capacity undergoing intermediate-risk surgery or who have good functional capacity prior to vascular surgery (class IIb) may also undergo testing.⁵⁰ A study of patients with clinically significant CAD randomized to either revascularization or no revascularization prior to major elective vascular surgery found no difference in mortality rate at 2.7 years.⁵¹ The current ACC guidelines recommend PCI only for those who would receive a benefit of revascularization independent of surgery. Further cardiac testing is recommended prior to surgery only if it will change management.⁵² Moreover, surgery soon after PCI may be associated with adverse outcomes. Because uninterrupted dual antiplatelet therapy (DAPT) is necessary after stent implantation, bleeding complications may result in the perioperative period, or there may be catastrophic consequences caused by stent thrombosis resulting from discontinuation of antiplatelet medications or from a hypercoagulable state induced by surgery.

In a small cohort of 192 patients, the highest risk of cardiovascular events in the postoperative period occurred in those who discontinued DAPT prematurely after PCI (30.7% vs. 0%; $P = 0.026$).⁵³ Moreover, surgery at less than 6 weeks after stent placement has been associated with a higher incidence of adverse events such as death and MI⁵⁴ and should be avoided when possible.

COMPLICATIONS OF PERCUTANEOUS CORONARY INTERVENTION

Death

Mortality can occur during PCI from a variety of complications, including anaphylactoid reactions, acute MI, pericardial tamponade, stroke, or vascular trauma. Since stents have been used, mortality rates associated with elective coronary intervention have fallen to less than 0.3%.^{55,56} In fact, most elective PCI procedures are considered outpatient procedures and an increasing proportion of patients are discharged on the same day as the PCI procedure. Patients at higher risk include older adults, those undergoing emergency PCI or PCI on saphenous vein grafts, and those with decompensated heart failure or reduced cardiac ejection fraction, end-stage renal disease, cardiogenic shock, or acute MI.^{24,57}

Emergency Bypass Surgery

Although technical improvements allowed PTCA success rates of approximately 60%,²⁵ successful PTCA was limited by an inability to expand balloons in fibrocalcific lesions. In addition, the barotrauma associated with

dilation of stenotic lesions led to medial dissection and many of the complications of angioplasty. Abrupt vessel closure occurred in approximately 5% of cases and was caused by a combination of factors, including arterial dissection, vascular recoil, vasospasm, and thrombosis. Flow-limiting dissections and thrombosis were treated with prolonged balloon inflations and aggressive anticoagulation, but despite these treatments, emergency bypass surgery was required in almost 50% of cases of abrupt vessel closure. In the pre-stent era, emergency surgery was required in approximately 3% to 5% of procedures,^{25,58,59} with significantly greater morbidity and mortality rates than seen with elective bypass surgery.⁶⁰⁻⁶² The widespread use of stents has led to an evolution of the role of the cardiac surgeon in managing acute complications of PCI. The need for emergency surgery has fallen dramatically in recent years, paralleling improvements in stent technology and pharmacologic therapy, and it now occurs in less than 1% of cases.^{31,63} Cardiac tamponade may develop on occasion because of vessel perforation with the coronary guidewire or with balloon dilation.

The improvements in immediate PCI outcomes and the recognition of improved survival with PCI performed in the setting of acute MI have led to the development of programs performing primary PCI and, more recently, without cardiac surgical backup. Several studies have shown that nonemergency PCI in institutions without on-site surgical backup is safe and effective. Registry data support the safety of elective PCI in community hospitals without the presence of cardiac surgery backup for low-risk patients.^{64,65} The C-PORT study confirmed the safety of primary PCI without surgical backup.⁶⁶ A large, prospective trial conducted in Massachusetts, MASS COMM, randomly assigned 3691 patients presenting to a hospital without on-site cardiac surgery with an indication for nonemergency PCI to either undergo PCI at that hospital or another with surgical backup on-site. There was no significant difference between the rates of composite endpoint of MI, repeat revascularization, stroke, or death at 30 days (9.5% in hospitals without on-site cardiac surgery versus 9.4% in hospitals with on-site cardiac surgery, relative risk 1.00; $P < 0.001$ for noninferiority) or at 1 year (17.3% in hospitals without on-site cardiac surgery versus 17.8% in hospitals with on-site cardiac surgery, relative risk 0.98; $P < 0.001$ for noninferiority).⁶⁷ Current ACC/AHA guidelines for PCI, published prior to the results of CPORT and MASS COMM, recommend primary PCI in hospitals without cardiac surgery backup on-site (class IIa recommendation) provided that the facility can meet certain requirements, including having experienced operators and laboratory staff, rigorous quality assurance, and established protocols for rapid transfer of patients to a facility with cardiac surgery.⁴⁸

It is well known that operator experience and hospital volume play an important role in these cases. Various studies have correlated both limited operator experience (<75 cases/yr) and low hospital volume (<200 cases/yr) with less favorable outcomes for primary PCI.⁶⁸⁻⁷⁰ Particular lesion subsets that would ordinarily be attempted by operators with on-site surgical backup are proscribed when surgical backup is not available. Because of the risk

of catheter injury to the left main artery, culprit stenoses (i.e., occluded 60% or more) that are downstream from a lesion in the LMCA should be avoided. When there is normal flow in the infarct artery, and either the patient has three-vessel disease or the culprit lesion is long or angulated, PCI should be avoided as well. High-grade LMCA disease or hemodynamic instability should prompt rapid transfer to an institution equipped to perform bypass surgery.³²

Emergency CABG is performed mainly for persistent abrupt vessel closure, extensive vessel dissection, unstable LMCA stenosis or injury, uncontrolled vessel perforation, and cardiac tamponade that cannot be controlled. The Society of Thoracic Surgeons reported an operative mortality rate that exceeds 5% for patients requiring emergency bypass surgery within 6 hours of PTCA.^{63,71} Although the frequency of emergency surgery continues to fall, and surgical technique and postprocedure management continue to improve, patient outcomes continue to be significantly worse than for elective surgery. The poor outcomes in this population are not unexpected, because as PCI has improved, the patients who cannot be salvaged and require emergency surgery comprise a population with more unfavorable risk factors and comorbidities. Considerations such as conduit selection, myocardial protection, and the need for coronary artery repair make the surgical procedure technically demanding.

Myocardial Infarction

Although Q-wave MI occurs in less than 1% of patients, the incidence of postprocedure myonecrosis (as measured by elevation of cardiac markers such as creatine phosphokinase [CPK]-MB and troponins [cTn]) can be identified in almost one third of patients and is more common after atherectomy procedures, after PCI performed in thrombus-containing lesions, in the setting of acute coronary syndromes, or for treatment of saphenous vein graft disease.⁷²⁻⁷⁴ Periprocedural MI may result from acute vessel closure, perforation, or most commonly, embolization of thrombus or atheroma. A standard definition of post-PCI MI has been adopted. This definition includes stent thrombosis or elevations of cTn greater than 5 times the 99th percentile upper reference limit occurring within 48 hours of the procedure with normal baseline cTn concentrations and with clinical evidence of ischemia. If the baseline cTn values are elevated and are stable or falling, then a rise of more than 20% is required for the diagnosis of post-PCI MI.⁷⁵ There is controversy as to the importance of asymptomatic elevations in cardiac biomarkers, termed *myocardial injury*, after PCI. Myocardial injury after PCI is associated with increased risk of death in follow-up, but whether these elevations are causally related or simply a marker of an increased burden of comorbidity or generalized atherosclerosis remains a subject of debate.⁷⁶ Many laboratories do not routinely measure cardiac biomarkers after PCI, underestimating the rates of myocardial injury and periprocedural MI after PCI. Other complications of coronary intervention include arrhythmias, stroke caused by spontaneous intracerebral hemorrhage with anticoagulation,

and stroke caused by embolic debris or equipment from catheters, arteries, cardiac chambers, or valves.

Vascular Complications and Hemorrhagic Complications

The use of femoral access, antithrombotic, fibrinolytic, and antiplatelet agents, as well as aggressive anticoagulation and prolonged sheath placement is associated with an increase in vascular complications.⁷⁷ Impaired coagulation and the need for larger-lumen catheters for percutaneous intervention (typically size 5 to 24 Fr) lead to more frequent access-site complications compared with simple diagnostic angiography.

Complications include hematoma (1% to 5%), retroperitoneal hemorrhage, and pseudoaneurysm (1%) formation.⁷⁸ Patients with significant peripheral vascular disease are at higher risk for such complications. Infrequent (<1%) complications include arteriovenous fistula formation, infection of access site or closure device, cholesterol embolization, and vascular occlusion. Femoral access-site complications requiring surgical repair or transfusion occur in 2% to 5% of cases. Closure devices are used frequently to achieve rapid hemostasis and achieve earlier ambulation. These devices have not definitively reduced the rates of vascular complications. Various devices are in use, including those with collagen plugs and percutaneously deployed sutures.

Traditionally, surgery was performed to close pseudoaneurysms greater than 2 cm in diameter because of significant risk of spontaneous rupture. Ultrasound-guided injection of thrombin into the pseudoaneurysm has obviated the need for open surgical repair. Surgical exploration is undertaken for repair of fistulas and arterial lacerations and in cases of arterial occlusion and uncontrolled bleeding leading to hemodynamic compromise. Various studies have demonstrated significant reductions in the rates of vascular complications with radial access for PCI.^{12,13}

Contrast Nephropathy

Contrast-induced nephropathy (CIN) is an important clinical concern. The occurrence of CIN is associated with adverse clinical outcomes, including reductions in survival rates.^{79,80} Although most of these cases are self-limited, a fraction of patients require short-term dialysis and some require permanent dialysis. The risk of permanent dialysis is less than 1% overall. Various risk scores have been developed to predict the occurrence of CIN.⁸¹ Significant predictors include hypotension, intra-aortic balloon pump use, congestive heart failure, chronic kidney disease, diabetes, age older than 75 years, anemia, and volume of contrast. The patients at highest risk have a risk for CIN that exceeds 50%.^{79,80} Additional risk factors include dehydration, advanced age, multiple myeloma, exposure to nephrotoxic drugs, congestive heart failure, and liver disease.

The risk of contrast agent-induced nephropathy can be reduced by hydration with normal saline before and after the procedure. Forced diuresis, calcium antagonists, dopamine, and atrial natriuretic peptide have not been

shown to be beneficial.^{82,83} There is no evidence that *N*-acetylcysteine is of benefit, and thus routine use is not recommended.

Anaphylactoid Reactions

The term *anaphylaxis* is reserved for allergic, IgE-mediated immediate hypersensitivity reactions. *Anaphylactoid* reactions are clinically similar to anaphylaxis but are not IgE mediated. Both anaphylaxis and anaphylactoid reactions can produce immediate, potentially life-threatening systemic reactions because of the massive release of mediators such as histamine from mast cells and basophils.

The incidence of death from contrast media complications in the catheterization laboratory is estimated at 1 in 55,000. Mild cases may be associated with symptoms such as itching, urticaria, flushing, cough, sneezing, wheezing, abdominal cramps, diarrhea, headache, back and chest pain, nausea, vomiting, fever, and chills. More severe reactions lead to dyspnea, a sense of impending doom, and hypotension, infrequently resulting in cardiovascular collapse and death. Depending on the severity of the clinical findings, patients may require treatment with catecholamines, antihistamines, corticosteroids, or intravenous fluids. In patients with prior reactions, pretreatment with corticosteroids and diphenhydramine, and the use of nonionic contrast media have significantly reduced the potential of recurrent reaction.⁸⁴

Restenosis

Despite successful initial luminal enlargement, the Achilles heel of balloon angioplasty has always been restenosis. After the acute arterial injury that is a prerequisite for luminal enlargement, a complex interaction between the vessel and blood elements occurs. Although these processes are often viewed as pathologic, they recapitulate all the elements of wound healing. Immediately after balloon dilation, 20% to 30% of the initial gain may be lost because of vascular recoil. Platelets, neutrophils, and macrophages adhere to the site of injury, resulting in an inflammatory response and secretion of a variety of mitogens. Many of these growth factors, such as platelet-derived growth factor, stimulate a change in smooth muscle cells from a contractile to a proliferative phenotype. Matrix metalloproteinases promote smooth muscle cell migration from the media to the intima. The combination of smooth muscle cell proliferation, neointimal hyperplasia, and elastic recoil (i.e., negative remodeling) is a ubiquitous process that, in most vessels, results in mild to moderate renarrowing; however, in 20% to 50% of patients without stents, it may result in a clinically significant restenosis that may continue for 6 to 12 months.

Although angiographic restenosis may be silent clinically, many patients present with recurrent angina or inducible ischemia during functional testing. It is now recognized that restenosis may not be clinically benign. Approximately 10% of patients with restenosis present with acute MI.⁸⁵ Risk factors for restenosis after PTCA have been well documented (Table 56-2). In large

TABLE 56-2 Risk Factors for Restenosis

Patient Factors	Lesion Factors	Technical Factors
Diabetes	Small vessels	High residual posttreatment stenosis
End-stage renal disease	Left anterior descending location	
Unstable coronary syndrome	Long lesions	
	Prior restenosis	
	Ostial location	
	Bifurcation	

populations, late lumen loss follows a near-Gaussian distribution, with approximately 50% of the initial gain in lumen diameter lost by 6 to 8 months.⁸⁶ The slope of the gain-loss relationship is approximately 0.5, and it is similar across all devices used for PCI. The reduction in restenosis rates observed after BMS placement is entirely explained by the ability of these stents to safely maximize acute gain, thereby allowing greater tolerance for late loss. The DES also decreased neointimal and smooth muscle cell growth, reducing late loss as well, in addition to the greater acute gain seen with the BMS.

ADVANCED TECHNOLOGY IN PERCUTANEOUS CORONARY INTERVENTION

Drug-Eluting Stents

Despite improved outcomes compared with angioplasty alone, BMS restenosis remained a problem in interventional cardiology, with rates ranging from 12% to greater than 50% in certain subgroups with the BMS (see Table 56-2).^{21,87} The advent of the DES introduced local drug delivery from a polymer coating on the stent consisting of anti-inflammatory and antiproliferative medications with a slow controlled release that effectively reduced the incidence of restenosis from 30% to less than 10%.⁸⁸⁻⁹⁰ Restenosis after DES placement is generally treated with repeat PCI, with or without another DES, or with CABG.

DESs were approved for use in 2004 for the treatment of symptomatic ischemic disease in discrete de novo lesions of less than 30 mm long in native coronary arteries with a reference luminal diameter between 2.5 and 3.5 mm for the Cypher (sirolimus-coated stent) and less than 28 mm long in native arteries between 2.5 and 3.75 mm in diameter for the Taxus (paclitaxel-coated stent). As mentioned, with local delivery of polymer coatings eluting paclitaxel, sirolimus, zotarolimus, or everolimus, smooth muscle cell proliferation and neointimal hyperplasia are inhibited, and the incidence of restenosis is drastically reduced. These drugs inhibit neointimal and smooth muscle cell proliferation by either cytostatic or cytotoxic inhibition of the cell cycle. Drugs from the *limus* family also have anti-inflammatory and antimigratory properties. Currently, 60% to 70% of implanted

coronary stents are DESs. Many studies have shown a sustained, long-term benefit of the DESs over the BMSs in reducing target-lesion revascularization.⁹¹⁻⁹⁴

Off-label DES implantation is estimated by the FDA to account for 60% of its current use. Off-label uses include stenting in bifurcation stenoses, ostial or totally occluded lesions, bypass grafts, lesions longer than 30 mm, vessels smaller in diameter than 2.5 mm or larger than 3.5 to 3.75 mm, left main stenosis, or restenosis. The FDA currently concludes that off-label use of a DES may be associated with increased risks compared with a BMS, but studies suggest that these higher risk lesions may actually benefit to a greater degree than on-label uses.^{95,96}

A major concern with the use of a DES is the development of stent thrombosis. Stent thrombosis is classified as early (0 to 30 days), late (31 to 365 days), or very late (more than 365 days), with a level of certainty defined as either probable, possible, or definite. Definite stent thrombosis requires angiographic or autopsy-based evidence of thrombus or occlusion. Probable stent thrombosis is defined as unexplained death within 30 days of PCI, or acute MI in the territory of the stented lesion. Finally, possible stent thrombosis includes all unexplained deaths occurring after 30 days of the index procedure.⁹⁷

Initial pivotal studies showed the incidence of stent thrombosis to be low (0.6% for DES and 0.8% for BMS),^{88,89} with no significant difference in stent thrombosis between the BMS and DES. Studies have shown similar rates of stent thrombosis in the first year when comparing the BMS and DES but then a not statistically significant trend toward increased rates of stent thrombosis with the DES.⁹⁸⁻¹⁰⁰ Because of concern that the premature disruption of DAPT may increase the risk for late in-stent thrombosis, current guidelines recommend uninterrupted DAPT for at least 1 month in those receiving a BMS (minimum of 2 weeks if there is an increased risk of bleeding) and 12 months for DES.¹⁰¹ Various studies have reported similar outcomes with shorter duration DAPT and second-generation DESs, but these studies are not adequately powered to detect small differences in risk of stent thrombosis with premature discontinuation, interruption, or disruption of DAPT with second-generation DESs.¹⁰²

Atherectomy Devices

Atherectomy devices were designed to achieve luminal enlargement by plaque removal rather than dissection and vascular stretching. Directional coronary atherectomy involved a cup-shaped cutter housed in a rigid cylinder in which a window was etched. A balloon was attached to the opposite wall of the cylinder. During balloon inflation, the atheroma was directed into the housing, shaved by the rotating cutter, and compressed into the nose cone for removal. This device was used successfully for treatment of bifurcation, ostial, eccentric, and ulcerated lesions. However, because of technical difficulty and a high incidence of periprocedural MI, directional coronary atherectomy is no longer available.

Rotational atherectomy (RA or PTCRA) incorporates a nickel-plated, brass burr coated with diamond chips on



FIGURE 56-4 ■ Rotational atherectomy catheter. (Courtesy Boston Scientific, Natick, MA.)

its leading edge (Fig. 56-4). The burr is rotated at 140,000 to 200,000 revolutions/min and, using the principle of differential cutting, pulverizes plaque into 5- to 12-micron particles. These particles are cleared by the reticuloendothelial system. Orbital atherectomy includes a centrifugal component of force to the sanding procedure and is approved for use in peripheral and coronary arteries.¹⁰³ Rotational atherectomy and orbital atherectomy are currently used as “enabling devices” prior to PTCA or stenting, to improve vascular compliance in undilatable devices or to debulk heavily calcified plaque.

Thrombectomy and Distal Protection

Treatment of thrombus-containing lesions has been a challenge for the interventional cardiologist. Intraluminal thrombus is associated with a higher risk of periprocedural complications.¹⁰⁴ Current thrombectomy devices use various techniques, including transluminal extraction using a rotating helical auger at the tip of the catheter in conjunction with a luminal suction to remove clots or using an aspiration device, the AngioJet (Boston Scientific, Natick, MA), or simple suction thrombectomy using a variety of hollow-lumen catheters.

The Vein Graft AngioJet Study (VEGAS)-II trial compared intracoronary fibrinolysis with thrombectomy and demonstrated a reduction in 30-day major adverse cardiac events with thrombectomy compared with prolonged infusion of urokinase.¹⁰⁵ Despite effective thrombectomy, distal embolization remains common during treatment of saphenous vein graft disease and in acute coronary syndromes. This has led to the development of devices aimed at reducing distal embolization of plaque and thrombus during high-risk interventions. For example, the PercuSurge GuardWire is a balloon occlusion protection device that uses a coronary guidewire with a hollow hypotube allowing inflation of a distal occlusion balloon. Inflation creates a static column of blood in the vessel, trapping debris liberated during balloon inflation or stent deployment. A sump catheter is then advanced over the wire and used to aspirate the

static column of blood and debris. The Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial demonstrated a 50% reduction in periprocedural MI for patients randomized to the PercuSurge GuardWire compared with conventional systems during intervention on saphenous vein bypass grafts. These devices are approved for use during saphenous vein graft interventions only and have not been proved beneficial in native coronary arteries.¹⁰⁶⁻¹⁰⁸

Second-generation devices are balloon occlusion devices combined with a flush and extraction mechanism and filters mounted at the end of the wire to trap embolized material. The latter have the theoretical advantage over the distal protection balloons that antegrade blood flow can be preserved, limiting ischemic time resulting from occlusion.¹⁰⁹ Randomized comparisons of these devices demonstrated equivalent outcomes.^{110,111}

The routine use of thrombus aspiration in acute MI is controversial. The Thrombus Aspiration during Primary Percutaneous Coronary Intervention Study (TAPAS)¹¹² showed improved myocardial perfusion, ST-segment resolution, and 1-year survival with manual thrombectomy.¹¹³ Based on this study, the European Society of Cardiology (ESC) gave the IIA recommendation that routine thrombus aspiration in STEMI should be considered.¹¹⁴ Subsequently, the Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction (INFUSE-AMI) trial investigated the benefits of bolus intracoronary abciximab and manual aspiration thrombectomy in STEMI patients with proximal or mid LAD artery occlusions. Infarct size at 30 days, as measured by cardiac magnetic resonance imaging (MRI), was significantly reduced with intracoronary abciximab but not with aspiration thrombectomy.¹¹⁵ A meta-analysis (18 trials, $N = 3936$) evaluating thrombectomy compared with conventional PCI concluded that the rates of major adverse cardiac events and all-cause mortality were decreased with aspiration thrombectomy (RR = 0.71; 95% CI 0.51-0.99; $P = 0.049$).¹¹⁶ These results were mainly driven by TAPAS, the largest study at the time.

The Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction (TASTE) trial randomized the largest number ($N = 7244$) of patients with STEMI comparing routine thrombus aspiration before PCI to PCI alone. Despite being appropriately powered, this study showed no clinically relevant difference in 30-day mortality (2.8% vs. 3.0%; $P = 0.07$).¹¹⁷ Longer term data from the TASTE trial are pending.

The use of mechanical thrombectomy in STEMI appears to be harmful. In the AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction (AiMI) trial, a total of 480 patients were randomized to rheolytic thrombectomy with AngioJet or conventional primary angioplasty. The primary endpoint was infarct size estimated by technetium 99m sestamibi. This trial showed a larger infarct size and higher mortality in patients treated with mechanical thrombectomy compared with those treated with conventional primary angioplasty, an effect also observed in meta-analysis.¹¹⁶ Given the lack of benefit seen in randomized trials, the effectiveness of routine thrombus

aspiration in acute MI remains uncertain and should be reserved for selected cases with high thrombus burden and where a large amount of myocardium is at risk.

Intravascular Ultrasound

Intravascular ultrasound (IVUS) is an invasive tomographic imaging modality that provides visualization not only of the vessel lumen but also of the vessel itself, and therefore it can provide information regarding vessel cross-sectional area, plaque characteristics, and stent expansion, and it is helpful when angiography is inconclusive or inadequate. Newer IVUS devices allow in vivo histopathologic characterization. Techniques to identify vulnerable plaques using IVUS are currently in development.

Catheter-Based Therapy after Bypass

In the first year after bypass surgery, approximately 8% of patients require repeat revascularization because of a recurrence of ischemia.¹¹⁸ Over time, the number of patients who develop recurrences of symptoms increases substantially. The recurrences result from saphenous vein graft attrition in most cases, although progression of native vessel disease also contributes to recurrent ischemia. Approximately 7% of grafts fail in the first week, and another 15% to 20% in the first year. Thereafter, 1% to 2% each year fail during the first 5 to 6 years, and this increases to 3% to 5% each year in years 6 to 10 postoperatively.¹¹⁹ At 10 years postoperatively, approximately half of all saphenous vein graft conduits are occluded, and only half of the remaining patent grafts are free of significant disease.³² Arterial conduit grafts, especially the left internal mammary, are relatively resistant to atherosclerosis. Because of the increase in morbidity associated with repeat CABG,¹²⁰ PCI, if technically possible, is the preferred strategy. Graft failure in the first month of surgery is usually the result of thrombosis resulting from nonlaminar flow,¹²¹ whereas perianastomotic stenosis is usually the culprit 1 to 12 months after surgery and histologically resembles restenosis after PCI. The latter responds well to balloon dilation.

Ischemia occurring more than 1 year after surgery may result from progression of atherosclerotic disease in the native coronary vessels or accelerated atherosclerosis in bypass grafts.¹²² As the disease in these grafts progresses, the plaques become diffuse and are often degenerated, bulky, and thrombotic. Vein graft atherosclerotic lesions often lack thick fibrous caps. PCI on these vessels is associated with substantial risk of distal embolization and periprocedural MI.¹²³ This risk may be reduced by the use of thrombectomy devices and embolic protection devices.^{105,106} Even if PCI of a saphenous vein graft is performed successfully without adverse events, recurrent ischemic events are common as a result of restenosis and rapidly progressive disease in the saphenous vein graft and native vessels.¹²² Such patients, particularly those without a patent arterial conduit to the LAD artery, should receive serious consideration for repeat surgical revascularization. A DES in vein grafts has been shown to reduce restenosis compared with a BMS, although

the Reduction of Restenosis in Saphenous Vein Grafts with Cypher Sirolimus-Eluting Stent (RRISC) trial reported an excess of late mortality with DES.¹²⁴ Consensus guidelines have been published for PCI after CABG (Box 56-2).¹⁰¹

Hybrid Coronary Revascularization

Although bypass surgery has longer patency rates using left internal mammary artery grafts and decreased target lesion revascularization, the inherent limitations of vein graft conduits and improved outcomes with DES may require a multidisciplinary approach to revascularization. Therefore, these “hybrid revascularizations” use both stenting and internal mammary grafting through a mini-thoracotomy or minimally invasive direct coronary artery bypass (MIDCAB) grafting. In one study, the incidence of adverse cardiovascular events was decreased in the hybrid arm using DES compared with off-pump bypass surgery, both in the early postoperative period and at 1 year.¹²⁵ This approach requires further investigation.

BOX 56-2

Recommendations for Percutaneous Coronary Intervention (PCI) in Patients with Prior Coronary Artery Bypass Graft (CABG) Surgery

CLASS I: CONDITIONS FOR WHICH THERE IS EVIDENCE FOR AND/OR GENERAL AGREEMENT THAT THE PROCEDURE OR TREATMENT IS USEFUL AND EFFECTIVE

- Patients with early ischemia (usually within 30 days) after bypass surgery.
- It is recommended that distal embolic protection devices be used when technically feasible in patients undergoing PCI to saphenous vein grafts.

CLASS IIA: CONDITIONS WHERE THERE IS CONFLICTING EVIDENCE, BUT WEIGHT OF EVIDENCE/OPINION IS IN FAVOR OF USEFULNESS/EFFICACY

- Patients with ischemia occurring 1 to 3 years postoperatively and preserved left ventricular function with discrete lesions in graft conduits.
- Disabling angina secondary to new disease in a native coronary circulation. (If angina is not typical, the objective evidence of ischemia should be obtained.)
- Patients with diseased vein grafts more than 3 years after bypass surgery.
- PCI is reasonable and technically feasible in patients with a patent left internal mammary artery graft who have clinically significant obstructions in other vessels.

CLASS III: CONDITIONS FOR WHICH THERE IS EVIDENCE AND/OR GENERAL AGREEMENT THAT THE PROCEDURE/TREATMENT IS NOT USEFUL/EFFECTIVE AND, IN SOME CASES, MAY BE HARMFUL

- PCI to chronic total vein graft occlusions.
- Patients with multivessel disease, failure of or multiple saphenous vein grafts, and impaired left ventricular function unless repeat CABG poses excessive risk because of severe comorbid conditions.

PHARMACOLOGY

Surgical Considerations for Anticoagulation

An important consideration is the timing of surgery if antiplatelet medications have been administered. Low-dose aspirin should be continued. The incidence of increased bleeding is associated with the use of either thienopyridines or GP IIb/IIIa inhibitors when urgent CABG is performed. However, no increase in operative bleeding was seen when GP IIb/IIIa inhibitors were discontinued at least 2 hours before surgery.¹²⁶⁻¹²⁸ For clopidogrel and ticagrelor, it is advisable to delay cardiac surgery for 5 days and for 7 days with prasugrel.^{129,130} Platelet transfusion may reverse the effect of the GP IIb/IIIa receptor antagonist, abciximab, and reduce the incidence of bleeding but is of no usefulness with eptifibatide and tirofiban.^{131,132} Surgery within 12 hours of fibrinolytic therapy for patients with acute MI is associated with increased bleeding and transfusion and with a greater incidence of reoperation for perioperative bleeding.¹³³ Unfortunately, the clinical condition of the patient often supervenes and surgery must occur prior to the completion of a washout period. Although bleeding, chest tube output, and transfusion rates are increased in such circumstances, adverse outcomes in this population are likely related more to the underlying condition of the patient requiring urgent cardiac surgery than to the antiplatelet medication.^{132,134} A strategy of preoperative assessment of platelet function after withdrawal of clopidogrel shows promise in guiding the optimal timing of CABG.¹³⁵

Current guidelines suggest that DAPT should be administered for at least 1 month after BMS placement and for 1 year after DES placement (class I).^{32,35,101} Some data suggest that the duration of DAPT can be shortened with newer generation stents, but these data require further confirmation.¹⁰² Whether DAPT is necessary after 1 year remains controversial and is the subject of ongoing investigation.

NONCORONARY INTERVENTIONAL CARDIAC PROCEDURES

Improvements in catheters, guidewires, balloons, stents, and other technologies have facilitated the use of catheter-based therapies and have allowed interventional cardiologists to treat noncoronary cardiac problems such as valvular, congenital, and other structural heart diseases that previously were the purview of surgical therapy only. In addition, the development of percutaneous assist devices allows the interventional cardiologist to treat the highest risk patients with an added degree of safety.

Balloon Mitral Valvuloplasty

Inoue and coworkers in 1984 and Lock and colleagues in 1985 introduced percutaneous mitral balloon valvotomy (PMBV) for the treatment of selected patients with mitral

stenosis.^{136,137} A single deflated balloon or a double balloon is advanced from the venous access to the right atrium. Using a trans-septal approach, the balloon is advanced across the interatrial septum to the left atrium and then across the stenotic mitral valve. The balloon is inflated and rapidly deflated, fracturing calcifications of the leaflet tissue and separating fused commissures. Typically, the valve area increases from a critically stenotic value of less than 1.0 cm² to approximately 2.0 cm², a change associated in 80% to 95% of patients with a rapid reduction in left atrial pressure that is sufficient to produce substantial hemodynamic improvements, including a 50% to 60% decrease in the transmitral pressure gradient, a reduction in pulmonary artery pressure, and an increase in cardiac output.

Patients are selected for PMBV on the basis of echocardiographic and clinical criteria. PMBV is a reasonable option for patients who are candidates for surgical commissurotomy. The salutary long-term results, lower costs, and the avoidance of thoracotomy make this procedure the treatment of choice in young patients with pliable, noncalcified mitral valves and no left atrial thrombus.¹³⁸ In addition, percutaneous valvotomy can be considered a palliative procedure in patients who have severe valve deformities and are poor surgical candidates. Mitral valve repair or replacement is usually preferred in symptomatic patients with severe subvalvular or calcific disease or when left atrial thrombus or significant mitral regurgitation precludes safe balloon valvotomy. Closed commissurotomy is still performed in some developing nations where cost and lack of balloon catheters are continuing problems.

The ACC/AHA task force published recommendations for PMBV in 2006¹³⁹ and recommended consideration of PMBV for patients who have exercise intolerance, severe pulmonary hypertension, no left atrial thrombus, a calculated effective mitral valve area of 1.5 cm² or less with trace or mild mitral regurgitation, and appropriate mitral anatomy as determined by echocardiography.

Echocardiography is an essential screening procedure in patients being considered for PMBV.¹³⁸ The extent of valvular and subvalvular deformity can be evaluated, and the likelihood of a successful result can be assessed. This can be accomplished by applying the Wilkins score, which scores from 0 to 4 for each of four factors: (1) the degree of leaflet rigidity, (2) the severity of leaflet thickening, (3) the amount of leaflet calcification, and (4) the extent of subvalvular thickening and calcification. The maximum score is 16; higher scores indicate more severe anatomic disease and a lower likelihood of a successful PMBV.¹⁴⁰

The National Heart, Lung, and Blood Institute's Balloon Valvuloplasty Registry evaluated 736 patients older than 18 and treated with PMBV who were followed for 4 years. The actuarial survival rates at 1, 2, 3, and 4 years were 93%, 90%, 87%, and 84%, respectively. The event-free survival rates (freedom from death, mitral valve surgery, or repeat balloon valvotomy) at 1, 2, 3, and 4 years were 80%, 71%, 66%, and 60%, respectively.¹⁴¹ The clinical and hemodynamic results of PMBV have been compared with the different forms of surgical correction: closed surgical valvotomy and open and closed

surgical commissurotomy. The outcome after PMBV was as good as or better than after surgery for patients who are candidates for valvotomy.^{142,143} Long-term outcomes are actually improved in PMBV as compared with closed commissurotomy.^{26,142}

Complications of PMBV include severe mitral regurgitation in 2% to 10% of patients, mitral valve restenosis, or formation of an atrial septal defect. After PMBV, up to 21% of patients develop recurrent heart failure as a result of mitral valve restenosis. Although most of these patients undergo mitral valve replacement, repeat balloon valvuloplasty is an alternative approach, especially in patients who are not good surgical candidates.¹⁴⁴ In addition, mitral valve restenosis after previous commissurotomy can be treated with PMBV. The immediate hemodynamic results and the long-term hemodynamics appear to be identical to those seen with balloon valvotomy in unoperated mitral stenosis.¹⁴⁵

Percutaneous Mitral Valve Repair and Replacement

Percutaneous mitral valve replacement has been performed in both native¹⁴⁶ and bioprosthetic mitral valves.¹⁴⁷ Approximating an Alfieri stitch, the Evalve MitraClip system (Fig. 56-5) is approved for percutaneous mitral valve repair in those with moderate-severe or severe mitral regurgitation caused by valve degeneration. The Endovascular Valve Edge-to-Edge Repair Study (EVEREST) evaluated the trans-septal approach for applying a clip device (Evalve, Inc., Menlo Park, CA) to the mitral valve. The trial reported an 85% freedom from adverse events rate at 30 days and a freedom from valve surgery rate of 82% at 6 months.¹⁴⁸ The pivotal randomized controlled clinical trial, EVEREST II, compared the percutaneous MitraClip ($n = 184$) to mitral valve surgery ($n = 95$). At 4 years, the rate of the composite endpoint of freedom from death, surgery, or 3+ or 4+ MR in the intention-to-treat population was 39.8% versus 53.4% in

the percutaneous repair group and surgical groups, respectively ($P = 0.070$). Surgery for mitral valve dysfunction, however, occurred in 20.4% versus 2.2% ($P < 0.001$) at 1 year and 24.8% versus 5.5% ($P < 0.001$) at 4 years.¹⁴⁹ The EVEREST II trial also incorporated a nonrandomized high-risk arm evaluating subjects at elevated surgical risk. In this arm, the MitraClip procedure was attempted in 78 subjects. The observed mortality rate in this group was 7.7% at 30 days, comparing favorably to a mean predicted mortality by Society of Thoracic Surgeons (STS) score of 18.2%.¹⁵⁰ Numerous devices are in development for percutaneous treatment of mitral regurgitation. Given the complexity of the mitral valve apparatus, it is unlikely that one device will address the multitude of pathologies afflicting the mitral valve.

Balloon Aortic Valvuloplasty

Percutaneous balloon aortic valvuloplasty (BAV) can also be performed for aortic stenosis. Typically, one or more balloons are advanced across a stenotic valve in a retrograde manner and inflated to dilate the valve.¹⁵¹ This procedure has an important role in treating adolescents and young adults with congenital aortic stenosis. In patients with bicuspid or calcific valvular aortic stenosis, the mechanism of dilation is through fracture of calcific deposits in the valve leaflets as well as stretching of the annulus with separation of the calcified or fused commissures.¹⁵² Although there is often immediate and significant reduction in the transvalvular pressure gradient, the postvalvotomy valve area rarely exceeds 1.0 cm². Despite this modest change in valve area, symptomatic improvement is usually seen.¹⁵³

The role for BAV is limited by complications such as stroke ($\approx 2\%$), coronary occlusion ($\approx 0.5\%$), severe aortic regurgitation ($\approx 1\%$), and vascular complications ($>7\%$), as well as poor clinical durability.¹⁵³ Restenosis and clinical deterioration occur within 6 to 12 months in most patients, and, in contrast to the results after surgical aortic valve replacement, there is no impact on long-term survival. Thus, BAV should not be considered a substitute for aortic valve replacement.¹⁵⁴⁻¹⁵⁶ BAV can be performed in some cases as a bridge to surgical or transcatheter aortic valve replacement in patients who are at high risk for surgical aortic valve replacement or in asymptomatic patients who require urgent noncardiac surgery. BAV may also be performed for palliation of congestive heart failure in patients with serious comorbidities and limited life expectancy.¹⁵⁶ An additional role for BAV is in cases where, despite provocative testing, it remains unclear whether cardiac performance is limited by aortic stenosis or profound ventricular dysfunction. In such cases, valvuloplasty can be performed to determine whether there is clinical improvement so that a decision can be made whether surgical or transcatheter aortic valve replacement should subsequently be performed.¹⁵⁷

Ethanol Septal Ablation for Hypertrophic Obstructive Cardiomyopathy

Nonsurgical septal reduction therapy, also called alcohol septal ablation, is a procedure whereby percutaneous



FIGURE 56-5 ■ MitraClip percutaneous mitral valve repair catheter. (Courtesy Abbott Vascular, Inc., Abbott Park, IL.)

obliteration of the first or second septal perforating coronary arteries is performed using absolute alcohol, which causes an iatrogenic septal infarct to reduce left ventricular outflow tract obstruction and thereby improve symptoms. Alcohol is injected through the lumen of an inflated angioplasty balloon into the septal branch, causing the infarction. Transient heart block is common, necessitating placement of a prophylactic pacing wire.¹⁵⁸

Symptomatic patients with moderate to severe heart failure symptoms, an interventricular septal thickness of 18 mm or greater, a left ventricular outflow tract gradient at rest of at least 30 mm Hg, or an intraventricular gradient during provocation are potential candidates for this procedure.¹⁵⁹

Septal reduction therapy has been shown to produce impressive reductions in outflow tract gradient and in symptoms. Significant reductions in pulmonary pressures, outflow tract gradient, and left ventricular hypertrophy and mass have been demonstrated.^{160,161} Immediate hemodynamic results are comparable to those found with surgical myotomy or myectomy.¹⁶²⁻¹⁶⁴ The most common complication of the procedure is the development of complete heart block, requiring a permanent pacemaker in approximately 7% to 14% of patients¹⁶⁵⁻¹⁶⁷ up to 5 days after the procedure, right bundle branch block in greater than 40%, and primary atrioventricular conduction abnormality in greater than 50%.¹⁵⁸ The risk of complete heart block is increased with septal ablation in those with a baseline left bundle branch block, because ablation usually targets the basal septum, which lies closer to the right bundle. Right bundle branch block is a risk factor for heart block with septal myectomy.¹⁵⁸

Other complications include the development of coronary dissection, ventricular arrhythmia, or unwanted, extensive MI. Reported results at 1 year follow-up continue to show benefit, especially in those older than 65 years,^{168,169} and long-term efficacy data are currently being collected. The procedural complication rate for septal ablation is higher than for surgical myectomy, although the survival rates are similar.^{166,167}

Closure of Patent Foramen Ovale and Atrial Septal Defect

Patent foramen ovale (PFO), present in roughly 25% of adults, is a persistent flaplike opening between the remnants of the atrial septum primum and the secundum. It can be demonstrated in almost 50% of patients younger than 55 years with cryptogenic stroke.^{170,171} The presumed cause of stroke in these cases is paradoxical embolism, whereby venous thrombus is allowed to access the systemic circulation through the PFO during physiologic conditions when right atrial pressure exceeds left atrial pressure. Medical therapy with either warfarin or antiplatelet agents is the current standard of care for cryptogenic stroke in patients with PFO, but despite its use, the risk of recurrent stroke remains high. Patients with PFO and paradoxical embolism have an approximately 3.5% yearly risk of recurrent cerebrovascular events.¹⁷² Surgical closure has been effective in preventing recurrent stroke.¹⁷³

Because of the bleeding risks associated with chronic anticoagulant use, the costs of drugs and monitoring, and

the desire of physicians and patients to avoid prolonged recovery and open-heart surgery, percutaneous closure can be offered as a less invasive option for stroke prevention in these patients. Percutaneous PFO closure has been used in thousands of patients using a variety of occlusion devices. Procedural outcomes are excellent at selected high-volume centers, with an incidence rate of 0.79 events per 100 person-years and freedom from recurrent events of 91.6% at 10 years.¹⁷⁴⁻¹⁷⁷ Nevertheless, the effectiveness of percutaneous PFO closure compared with surgical closure or medical management for preventing recurrent embolic events is not established. Current evidence derived from a pooled analysis of intention-to-treat data from three randomized controlled trials (CLOSURE I, PC, and RESPECT) indicates that device closure of a PFO does not offer significant benefit over medical therapy alone for the prevention of recurrent stroke (risk ratio 0.66; 95% CI 0.37-1.19).¹⁷⁸⁻¹⁸⁰ These trials have some limitations including short duration of follow-up, enrollment bias, unequal dropout rates, and low event rates.

Data from 2303 patients were evaluated in a meta-analysis of the three randomized trials. The stroke HR for PFO closure versus medical therapy was 0.67 (95% CI 0.44-1.00, I² = 0%). Pooling trials using the Amplatzer PFO occluder (Fig. 56-6) device resulted in a significant reduction of stroke (HR 0.54; 95% CI 0.29-1.01, I² = 0%).¹⁷⁸⁻¹⁸¹ There is also a high prevalence of PFO in patients with classic migraine headaches, but to date no clear data support its use in this population.¹⁸²

Although PFO represents a potential communication between the left and right atria, atrial septal defects (ASDs) are congenital abnormalities characterized by a structural deficiency that leads to continuous, free communication between the atria. The defect is often asymptomatic until adulthood, but complications of an undetected lesion include irreversible pulmonary hypertension, right ventricular failure, atrial arrhythmias,

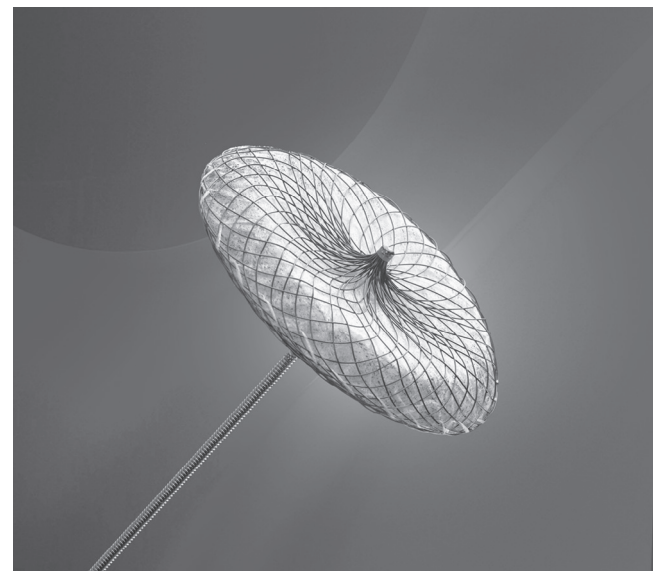


FIGURE 56-6 ■ Amplatzer septal occlusion devices used for percutaneous closure. (Courtesy AGA Medical Corporation, Plymouth, MN.)

paradoxical embolization, and cerebral abscess. These defects are generally repaired when the pulmonary-to-systemic flow ratio is 1.5 or greater, or in cases where the defect leads to symptoms, embolism, or right ventricular dysfunction. Scuba divers with neurologic compression sickness and ASD should be considered for closure.

Those with ostium primum defects, sinus venosus defects, or defects with less than 4 mm of surrounding tissue or a stretched diameter of greater than 38 mm are better served by surgical rather than percutaneous closure. Percutaneous closure is usually performed using septal occlusion devices similar to those used for PFO closure. Adjunctive transesophageal echocardiographic or intracardiac echocardiography is often used to assist in sizing and placement. One multicenter nonrandomized study compared 154 patients who underwent surgical closure and 442 who had closure with an Amplatzer septal occluder device. The methods had equal success rates, but percutaneous closure was associated with fewer complications (7.2% vs. 24.0%; $P < 0.0001$) and a shorter duration of hospitalization (1 vs. 3 days).¹⁸³

Endovascular ventricular septal defect (VSD) closure is associated with a postprocedural complete closure rate of 47%, which rose to 69.6% at 6 months and then 92.3% at 12 months using an Amplatzer VSD closure device in muscular VSDs.¹⁸⁴ Amplatzer VSD closure devices are also being studied for membranous VSDs, with complete closure demonstrated in phase I trials in 20 of 32 patients at 24 hours and 27 of 28 patients at 6-month follow-up.¹⁸⁵ Significant periprocedural complications (roughly 11.5%) have included device embolization and vascular and arrhythmogenic complications.¹⁸⁶ These investigational devices hold a promising future in the endovascular repair of congenital or post-MI ventricular defects.

Vascular plugs have been used for closure of paravalvular leaks (PVLs) in both surgical and transcatheter valves. Prosthetic valve replacement surgery is performed in approximately 210,000 patients annually worldwide. At least 3%, and possibly as many as 12.5%, of these valves will eventually demonstrate a clinically important PVL. Large series of percutaneous PVL closure have been published, with encouraging results with respect to both procedural success and clinical outcomes. Procedural success for percutaneous closure of paravalvular aortic leaks is approximately 90% in the different series, with low complication rates. Mitral leaks have been approached by transfemoral and transapical access; the reported success of this procedure ranges from 75% to more than 90% in different reports.¹⁸⁷

Percutaneous Circulatory Assist Devices

Circulatory assist devices are used in the catheterization laboratory to support high-risk PCI procedures and support patients in cardiogenic shock as a bridge to recovery or further therapy such as surgical ventricular assist devices or cardiac transplantation. These devices have been shown to improve cardiac hemodynamics, but identifying a relationship between use of these devices and improved survival has been challenging. The challenge stems, in part, from the inherent difficulty in identifying

and studying a population in whom the risk is high enough to warrant this therapy but in whom illness is not so severe that such therapy is futile regardless of hemodynamic improvement. As such, these devices are not used routinely and are reserved for selected cases such as patients who are in extremis but deemed salvageable.

The intra-aortic balloon pump (IABP) uses the principle of counterpulsation to increase diastolic blood flow to coronary arteries and to mechanically reduce the afterload on the heart during systole. This method was first described in 1952 in animals by Adrian and Arthur Kantrowitz.¹⁸⁸ The device consists of a double-lumen catheter from 7 to 9.5 Fr with a 25- to 50-mL balloon at its distal end. The inner lumen monitors arterial blood pressure, and the outer lumen allows the transfer of helium gas into the balloon. It is used in patients with cardiogenic shock or with mechanical complications of MI such as acute mitral regurgitation or VSD, or as a bridge for high-risk patients before bypass surgery.¹⁸⁹ The IABP is contraindicated in those with aortic regurgitation and significant peripheral vascular disease. A randomized trial of IABP versus standard care for anterior MI without cardiogenic shock demonstrated no survival advantage or reduction in infarct size and increased vascular complications.¹⁹⁰ In the IABP-SHOCK II study, patients with shock complicating MI who were to undergo PCI had no survival advantage (39.7% vs. 41.3%; $P = 0.69$; relative risk with IABP 0.96, 95% CI [0.79-1.17]) with the IABP.¹⁹¹ Despite these data arguing against routine use in these populations, it is clear that this technology can be lifesaving for selected patients.

Left ventricular assist devices maintain partial or total circulatory support in cases of profound myocardial dysfunction or temporarily during high-risk PCI. The Impella 2.5 device (Abiomed, Danvers, MA) is a catheter-mounted microaxial blood pump. It features a motorized pump that is inserted into the left ventricle through the aortic valve by means of the femoral artery. The pump produces a mean flow of 2.5 liter/min and mechanically “unloads” the left ventricle (Fig. 56-7) by aspirating

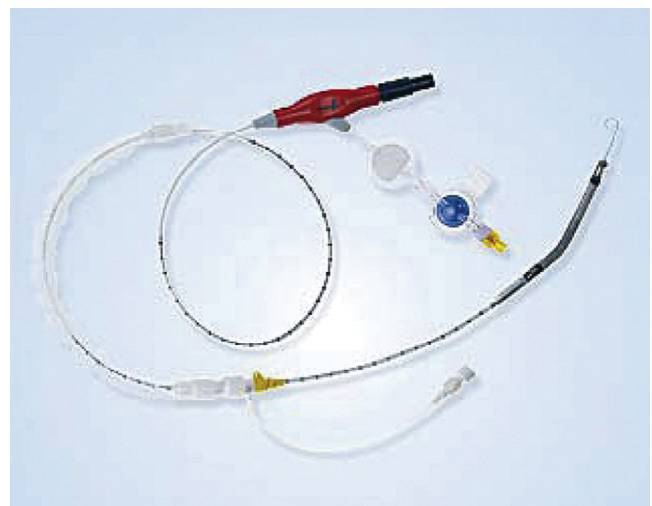


FIGURE 56-7 ■ The Impella 2.5 device used for percutaneous cardiac support. A flow of up to 2.5 liter/min can be provided by this device. (Courtesy Abiomed Corporation, Danvers, MA.)

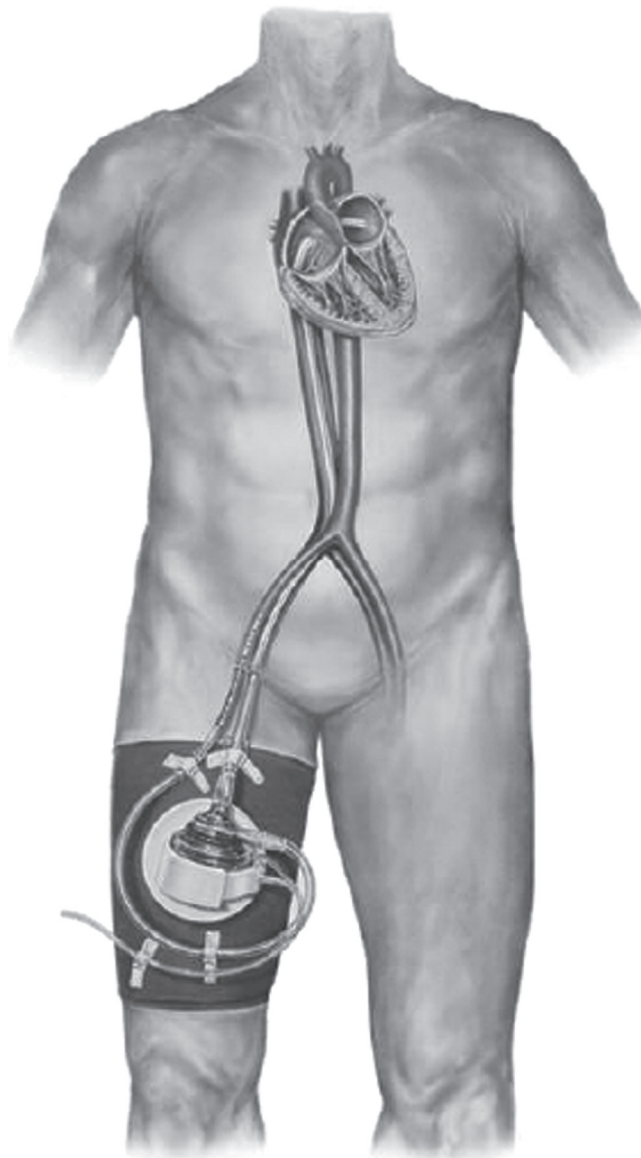


FIGURE 56-8 ■ The TandemHeart percutaneous ventricular assist device. The catheter is advanced through the femoral vein and across the interatrial septum into the left atrium. Blood is removed, and a pump returns blood to the patient's systemic circulation through an arterial cannula. A flow of up to 5 liter/min can be provided. (Courtesy Cardiac Assist, Inc., Pittsburgh, PA.)

blood from the left ventricle and then expelling it into the aorta by means of a rotor-driven pump. Current FDA approval allows the Impella device to be used for 6 hours, but studies have shown it to be safe for up to 7 days in humans. Randomized trials comparing Impella and IABP support for high-risk PCI^{192,193} have shown that at 90 days, the rates of composite endpoints were lower in the Impella group compared with the IABP group (rate of major adverse cardiac and cerebral events, 22% vs. 31%, $P = 0.034$, respectively). For primary PCI performed in patients with refractory cardiogenic shock,¹⁹⁴ significantly improved hemodynamics and a suggestion of improved outcomes with initiation of support prior to PCI has been noted in a registry. A larger Impella device that provides

up to 5 liter/min can be implanted via a surgical approach, and the Impella CP device provides greater than 2.5 liter/min support via a percutaneous approach.

The TandemHeart (Cardiac Assist, Pittsburgh, PA) is a left atrial-to-femoral artery bypass system comprising a trans-septal cannula, arterial cannulae, and a centrifugal blood pump (Fig. 56-8). The pump can deliver flow rates up to 5.0 liter/min at a maximum speed of 7500 rpm. In this case, blood is taken from the left atrium, significantly reducing left ventricular preload, alleviating pulmonary edema, and returned to the aorta retrogradely via the femoral artery and to augment cardiac output. In a randomized comparison between the TandemHeart and IABP in patients with cardiogenic shock, the improved cardiac index afforded by the TandemHeart device resulted in a more rapid decrease in serum lactate and improved renal function.¹⁹⁵ This pump has been used with a right atrial to femoral arterial cannulation and an in-line membrane oxygenator to provide both circulatory and oxygenation support. In this case, left ventricular preload is not reduced and afterload is increased, but an advantage is the circuit can be initiated within minutes. Additionally, a right atrial to pulmonary artery circuit has been used for right ventricular support.

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MEDICAL MANAGEMENT OF ACUTE CORONARY SYNDROMES

Robert N. Piana • Jayant Bagai

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ACUTE CORONARY SYNDROME

Definition

Acute coronary syndrome (ACS) refers to a constellation of clinical symptoms (usually including some type of chest discomfort) that is compatible with acute myocardial ischemia.¹ Patients with suspected ACS may eventually prove to have a diagnosis other than ischemia. However, true ACS can be classified into the following clinical subsets:

1. ST-segment elevation myocardial infarction (STEMI).
2. Non-ST-segment elevation ACS (NSTEMI). This can be subcategorized as either unstable angina (UA) or non-ST-segment elevation MI (NSTEMI).

Typically UA presents in one of three ways: prolonged angina at rest (usually >20 minutes); new-onset Canadian Cardiovascular Society (CCS) class III angina; or increasing frequency, severity, and class of angina (increased ≥ 1 class from baseline and reaching CCS class III or higher).² Frequently, UA is accompanied by ischemic electrocardiographic changes. NSTEMI is distinguished from UA by elevation of cardiac biomarkers suggestive of myocardial necrosis.

Epidemiology

Of 1,141,000 hospitalizations for ACS in 2010, approximately 70% were classified as myocardial infarction (MI) and 30% as UA.³ In the National Registry of Myocardial Infarction 4 (NRMI-4) and the Global Registry of Acute Coronary Events (GRACE), 29% of all MI patients and

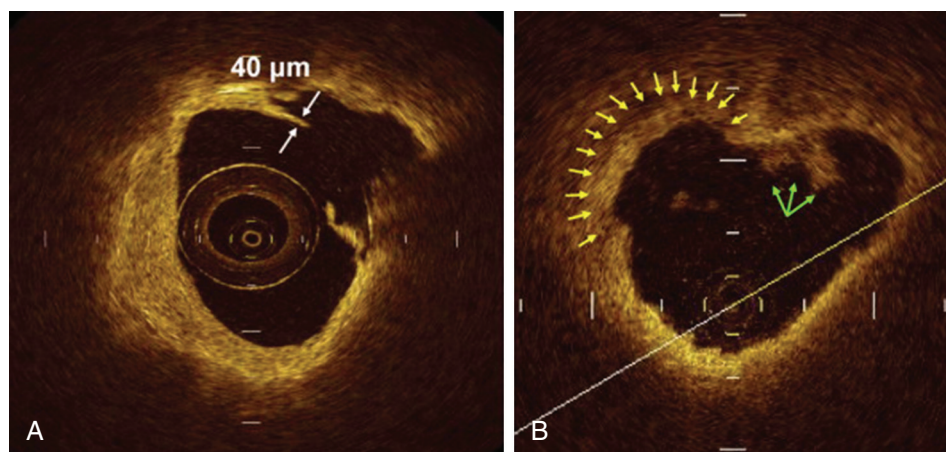


FIGURE 57-1 ■ Optical coherence tomographic images of disrupted plaque at culprit site in acute coronary syndrome. **A**, The thickness of ruptured fibrous cap is 40 μm , and crater formation is identified within lipid plaque in a ruptured plaque. **B**, Ulceration (yellow arrows) of thick fibrous cap is observed with white thrombus (green arrows) in plaque erosion. (From Akasaka T, Kubo T, Mizukoshi M, et al: Pathophysiology of acute coronary syndrome assessed by optical coherence tomography. *J Cardiol* 56:8–14, 2010.)

27% of ACS patients were diagnosed with STEMI, respectively.^{4,5} Aggressive treatment of patients with NSTEMI and STEMI has yielded significant reductions in recurrent MI, cardiogenic shock, and in-hospital mortality. Nevertheless, up to 25% of opportunities to provide American College of Cardiology/American Heart Association (ACC/AHA) guideline-recommended care are still missed, and these omissions correlate with increased in-hospital mortality.⁴ The recommendations for treatment of NSTEMI/ACS in this chapter are therefore based on the 2007 American College of Cardiology Foundation (ACCF)/AHA guidelines for the management of patients with UA/NSTEMI with incorporation of the 2012 focused update.¹ Recommended management of STEMI is based on the recently updated 2013 ACCF/AHA guidelines.⁶

Pathophysiology

Plaque Rupture/Erosion

Advanced atherosclerotic coronary lesions are characterized by a lipid-rich necrotic core encapsulated by a fibrous cap composed of smooth muscle cells, collagen, and elastin. Mechanisms such as digestion of the fibrous cap by matrix metalloproteinases, loss of smooth muscle cells through apoptosis, and plaque hemorrhage can create a thin-cap fibroatheroma (TCFA) or “vulnerable plaque.”⁷ Rupture of a TCFA is the most common precipitant of ACS (Fig. 57-1). Another mechanism of ACS involves superficial erosion of less advanced lesions, typically rich in proteoglycan matrix and smooth muscle cells. Both plaque rupture and erosion precipitate intracoronary thrombus formation via exposure of highly thrombogenic subendothelial collagen, necrotic material, and the lipid pool to von Willebrand factor (vWF) and platelets. In an autopsy study, plaque rupture or erosion with thrombus was noted in all patients who died of sudden cardiac death caused by ACS.⁸ Patients who had evidence of ruptured fibrous caps were older, were more often male, and had

greater luminal area stenosis, calcification, and macrophage and T cell infiltration than patients who had plaque erosion.

Central Role of Platelets

Platelets are central to the pathogenesis of ACS. Platelets adhere to collagen and soluble vWF immobilized by exposed subendothelial collagen. This is followed by the release of adenosine diphosphate (ADP), thromboxane A₂, and serotonin from platelet granules. Along with thrombin, collagen, and epinephrine, these factors promote platelet recruitment and “activation.” Activation involves platelet shape change, expression of pro-inflammatory ligands, and conversion of the glycoprotein (GP) IIb/IIIa receptor to its active form.⁸ Platelets then aggregate, by cross-linking with each other, via fibrinogen, which attaches to the active GP IIb/IIIa receptor. Thrombin, generated by tissue factor released from eroded plaque, results in formation of fibrin. Cross-linked platelets combine with fibrin to form an occlusive or subocclusive thrombus (Fig. 57-2). Platelet activators amplify the process by promoting each other’s release and induction of procoagulant activity.

Role of Inflammation

ACS is characterized by an acute inflammatory state. Platelets induce inflammation in endothelial cells, and inflamed intact or damaged endothelium is able to bind to platelets. Activated platelets secrete CD40 ligand, which binds to CD40 on endothelial cells. This process induces release of factors that stimulate expression of adhesion molecules, such as ICAM-1 on endothelial cells and P-selectin on platelets.⁹ The resultant platelet-monocyte-neutrophil interactions stimulate release of prothrombotic and proinflammatory factors, leukocyte attachment to the endothelium, and release of matrix metalloproteinase, leading to basement membrane degradation, thereby favoring plaque rupture.¹⁰

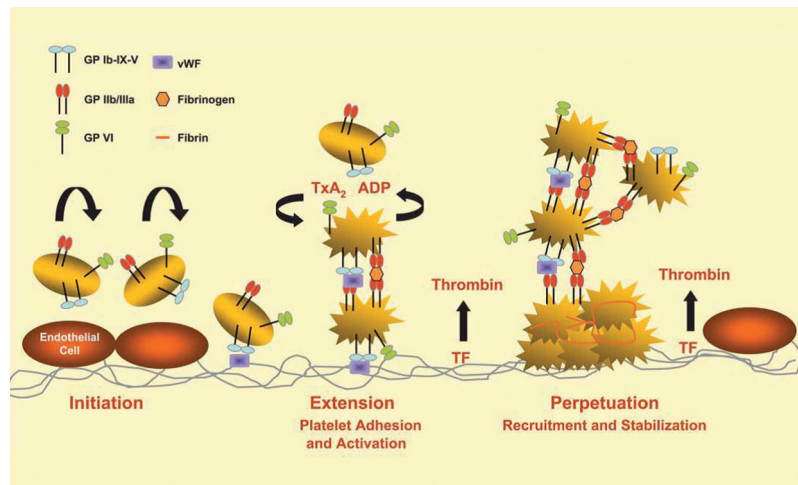


FIGURE 57-2 ■ Platelet plug formation. Vascular injury results in the exposure of collagen and von Willebrand factor (vWF) in the vessel wall. Circulating platelets adhere and form a monolayer of activated platelets on the collagen matrix, which drives the release of adenosine diphosphate (ADP) and thromboxane (Tx) A₂ from the adherent platelets. Secretion of ADP and TxA₂ promotes changes in platelet shape and amplification of platelet activation. Thrombin, generated by locally produced tissue factor (TF), is the most potent platelet activator. In the perpetuation phase, platelet contacts promote growth and stabilization of the platelet plug. GP, Glycoprotein. (From Jennings LK: Mechanisms of platelet activation: need for new strategies to protect against platelet-mediated atherothrombosis. *Thromb Haemost* 102:248–257, 2009.)

Diagnosis

Clinical Manifestations

The most common presentation of ACS is some type of prolonged chest discomfort. One third to one half of MIs may be clinically silent. Women, older patients, patients with diabetics, and those with a history of heart failure are more likely to present without chest discomfort. The lack of typical symptoms may lead to delays in presentation to the hospital, establishment of a diagnosis, and institution of medical therapy and revascularization. Symptoms other than chest pain that may reflect ACS include unexplained dyspnea, nausea or indigestion, arrhythmias, syncope, back or arm pain, and fatigue. Unexplained dyspnea, without angina, is associated with more than twice the risk of death compared with patients with typical angina.¹¹

Electrocardiography

The earliest manifestations of myocardial ischemia on an electrocardiogram (ECG) are typically ST-segment and T-wave changes. New horizontal or down-sloping ST depression greater than 0.5 mm or T-wave inversion greater than 1 mm in two contiguous leads is suggestive of ischemia in patients with symptoms compatible with NSTEMI/ACS.¹² ST-segment and T-wave changes can also be caused by left ventricular hypertrophy, pericarditis, early repolarization, or electrolyte imbalance. Therefore, comparison with available prior tracings and interpretation in the context of the clinical symptoms are recommended. The hallmark of STEMI is ST elevation in anatomically contiguous leads or a new left bundle branch block (LBBB). Of note, J point elevation of up to 2.5 mm can be noted in healthy men younger than 40 years.

Cardiac Biomarkers

The preferred biomarkers for diagnosis of MI are cardiac troponin (cTN) T or I. These proteins are part of the myocardial contractile apparatus and are highly sensitive and specific for the diagnosis of myocardial necrosis. However, it is now widely recognized that cTN elevation can occur in the setting of non-ischemic causes of myocardial necrosis or injury such as congestive heart failure (CHF), sepsis, renal failure, pulmonary embolism, or myocarditis. Another commonly used biomarker is CPK-MB, but this is much less specific because of its presence in skeletal muscle and other organs. It should therefore not be used as the sole test for diagnosis. The detection of a rise and/or fall of cardiac biomarkers, with at least one of the values exceeding the 99th percentile of a normal reference population (upper reference limit), in conjunction with symptoms of myocardial ischemia, ST-segment/T-wave changes, wall motion abnormalities on imaging, or presence of coronary thrombus are now required to meet the definition of MI.¹²

MANAGEMENT OF NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Initial Evaluation and Risk Stratification

A 12-lead ECG should be performed and evaluated by a physician within 10 minutes of patient's arrival to the emergency room. If the first tracing proves nondiagnostic in a patient with ongoing symptoms, serial ECGs should be done at 15- to 30-minute intervals for further assessment. Cardiac biomarkers, including cardiac-specific troponins T or I, CPK, and CPK-MB, should be obtained

and repeated to include the time frame of 8 to 12 hours from onset of chest pain. If the initial assessment suggests a diagnosis of ACS, the next step is risk stratification. The TIMI risk score is the most commonly used risk stratification tool, assigning 1 point for each of seven variables (age 65 years or older, three or more risk factors for coronary artery disease [CAD], known coronary stenosis at least 50%, ST-segment deviation at presentation, two or more anginal events in the previous 24 hours, use of aspirin in the previous 7 days, and elevated serum cardiac biomarkers).¹³ Patients with a score of 3 or higher have an exponential increase in short-term ischemic events and benefitted from an early invasive strategy compared with a conservative strategy in the TACTICS-TIMI 18 trial.¹⁴ The GRACE score can also be used to predict hospital and 6-month mortality rates in patients with UA, NSTEMI, and STEMI.¹⁵

Pharmacologic Management

Anti-ischemic Therapy

Table 57-1 shows selected recommendations for anti-ischemic therapy in patients with ACS.¹⁶

Antiplatelet Therapy

Aspirin. Aspirin irreversibly inhibits the COX-1 enzyme in platelets and thus prevents the formation of

thromboxane A₂, one of the mediators of platelet aggregation. Aspirin reduces the incidence of MI in patients with UA compared with placebo,¹⁷ and provides a mortality benefit in patients with STEMI.¹⁸ The minimal effective dose in the Antithrombotic Trialists' Collaboration meta-analysis was 75 mg, which was associated with a 22% reduction in vascular death, MI, and stroke.¹⁹ A dose-dependent increase in bleeding without reduction in thrombotic events was noted with aspirin doses higher than 200 mg.²⁰ Whereas earlier guidelines recommended variable doses of aspirin for maintenance therapy and after percutaneous coronary intervention (PCI), 81 mg per day is now recommended as a reasonable alternative to higher doses (class IIa).²¹

P2Y₁₂ Inhibitors (Clopidogrel, Prasugrel, Ticagrelor). These agents inhibit the binding of ADP to the platelet P2Y₁₂ receptor, thus limiting platelet activation. Adding clopidogrel to aspirin (dual antiplatelet therapy [DAPT]) reduces the incidence of cardiovascular death, MI, stroke, and urgent revascularization in ACS patients treated conservatively or with PCI.²⁰ The incidence of stent thrombosis is also reduced with DAPT compared with aspirin alone. Despite this robust efficacy data, clopidogrel has important shortcomings. It is a prodrug requiring a two-step bioactivation in the liver. The gene encoding the CYP2C19 enzyme responsible for most of this bioactivation demonstrates polymorphism in the general population. Carriers of loss-of-function *2 and *3

TABLE 57-1 Selected Recommendations for Anti-ischemic Therapy

Drug	Class I Recommendation	Class III Recommendation (Contraindicated)
Intravenous nitroglycerin	Administer for 48 hours for persistent ischemia, heart failure, or hypertension.	Systolic BP < 90 mm Hg HR < 50; HR > 100 in the absence of CHF Right ventricular infarction <24 hours of sildenafil <48 hours of tadalafil ANY sign of CHF Low output state
Oral beta blockers	Initiate within 24 hours if no contraindications.	Risk of cardiogenic shock* Advanced conduction disease† Active asthma/reactive airways
IV beta blockers (at any time)	Class IIa recommendation: May administer at any time for HTN if no contraindications.	Systolic BP < 100 mm Hg Do not administer IV ACEIs in the first 24 hours (risk of hypotension).
Oral ACEIs	Administer within 24 hours for pulmonary congestion or LVEF < 40%. ARBs may be given in case of ACEI intolerance (provided no angioedema with ACEI).	Do not administer immediate-release dihydropyridine CCB.
Non-dihydropyridine CCBs	Administer for ongoing/recurrent ischemia when beta blockers are contraindicated.	Do not use because of increased risk of myocardial rupture, CHF, and reinfarction.
NSAIDs		

*Age > 70, sinus tachycardia > 100, systolic BP < 120 mm Hg.

†PR interval > 0.24 sec, second- or third-degree atrioventricular block.

ACEIs, Angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BP, blood pressure; CCBs, calcium channel blockers; CHF, congestive heart failure; HR, heart rate; HTN, hypertension; IV, intravenous; LVEF, left ventricular ejection fraction; NSAIDs, nonsteroidal anti-inflammatory drugs.

From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 50:e1–e157, 2007.

alleles produce a truncated enzyme that results in lack of metabolic activation of clopidogrel and reduced efficacy. These carriers, especially homozygotes, have so-called high on-treatment platelet reactivity (HTPR) and have increased risk of MI and stent thrombosis despite clopidogrel therapy,²² which cannot be overcome by higher doses of clopidogrel.²³ On the other hand, carriers of the *17 allele are “hyper-responders” with an increased risk of bleeding. In addition, clopidogrel also demonstrates variable and overall modest inhibition of platelet aggregation coupled with a slow onset of action.

Newer P2Y₁₂ inhibitors have been developed to overcome these shortcomings. Prasugrel is also a prodrug but requires a one-step bioactivation and does not depend significantly on CYP2C19 for activation. It results in rapid onset of predictable and high-level platelet inhibition. Ticagrelor is a reversible, noncompetitive P2Y₁₂ receptor antagonist, which does not need hepatic activation and results in 85% to 95% platelet inhibition within 2 hours of administration. Both prasugrel and ticagrelor are effective in carriers of reduced-activity CYP2C19 alleles. In the pivotal TRITON-TIMI 38 trial, prasugrel resulted in lower rates of MI and stent thrombosis in patients with moderate- to high-risk ACS, including STEMI, compared with patients treated with clopidogrel.²⁴ Whereas prasugrel was associated with a higher incidence of major bleeding, net benefit still favored prasugrel use, except in three subgroups. Prasugrel had no net benefit in patients older than 75 and/or weighing less than 60 kilograms, and it showed net harm in the subset with prior stroke or transient ischemic attack (TIA). Of note, TRITON-TIMI 38 included only patients whose coronary anatomy had been defined by angiography and who were then selected for PCI. Prasugrel is therefore not currently indicated in conservatively managed patients.

In the PLATO trial, ticagrelor was associated with reduced overall mortality, MI, and stent thrombosis compared with clopidogrel, in patients managed both conservatively and with early PCI.²⁵ Unlike prasugrel, no increase in overall major bleeding was noted compared with clopidogrel. Non-CABG-related major bleeding and fatal intracranial hemorrhage, however, were higher in the ticagrelor cohort. The benefit of ticagrelor was not seen with higher aspirin doses, and concurrent administration of aspirin in doses higher than 100 mg is therefore not recommended.

To minimize bleeding complications, elective coronary bypass surgery (CABG) should be delayed 5 to 7 days after discontinuation of P2Y₁₂ antagonists. In the case of clopidogrel, platelet function testing has also been used to stratify patients to different waiting periods prior to elective CABG. This strategy has resulted in similar postoperative bleeding rates as compared to clopidogrel-naïve patients and reduced waiting periods prior to CABG.²⁶

Class I and III recommendations for oral antiplatelet drugs include the following:

1. An initial dose of 162 to 325 mg aspirin should be chewed (non-enteric-coated, with more rapid absorption) or swallowed (enteric-coated) when the diagnosis of ACS is suspected and should be

continued indefinitely. In the event of aspirin allergy or major gastrointestinal intolerance, an alternative antiplatelet drug should be given.

2. A loading dose, followed by maintenance doses, of either clopidogrel or ticagrelor, is recommended for all patients with medium- to high-risk definite ACS, regardless of initial invasive or conservative management strategy. Prasugrel is an alternative in patients in whom PCI is planned. These drugs should be given as early as possible before PCI or at the time of PCI, and no later than 1 hour after PCI.
3. Clopidogrel or ticagrelor should be given for 12 months in patients managed either conservatively or with PCI, whereas prasugrel should be given, for 12 months, only in post-PCI patients.
4. If the risk of bleeding outweighs expected benefits, P2Y₁₂ inhibitor therapy should be interrupted earlier than 12 months.
5. Prasugrel is contraindicated in patients with prior stroke, TIA, and active bleeding. It can be given to selected patients older than 75 years, provided benefits are expected to outweigh the risks (history of diabetes or prior MI). A lower maintenance dose of 5 mg/day is recommended for patients weighing less than 60 kilograms, although this has not been prospectively studied.

Novel Antiplatelet Agents (Cangrelor, Protease-Activated Receptor-1 Inhibitors). Cangrelor is an intravenous adenosine triphosphate (ATP) analogue that functions as a reversible competitor P2Y₁₂ inhibitor. Onset of action is immediate, and because of a short half-life of 3 to 6 minutes, there is full recovery of platelet function within 60 minutes. Compared to clopidogrel, cangrelor infusion started pre-PCI and continued for at least 2 hours or the duration of PCI, whichever was longer, was associated with lower rates of a composite ischemic endpoint (OR 0.78, 0.66-0.93, $P = 0.005$), without an increase in severe bleeding.²⁷ In this study 43% of patients had ACS. In another study, infusion of cangrelor maintained low levels of platelet reactivity in patients in whom clopidogrel had been interrupted prior to CABG surgery.²⁸ Cangrelor was discontinued 1 to 6 hours prior to CABG surgery and did not result in increased bleeding rates. Cangrelor is not currently commercially available in the United States but may have a future role in patients requiring PCI or awaiting surgery because of reliable absorption and platelet inhibition and its “on-off” effect.

Unfortunately, the incidence of major adverse cardiovascular events and major bleeding remains in the range of 10% to 11%, despite use of newer P2Y₁₂ receptor antagonists. Therefore, novel targets for platelet inhibition are being developed. Thrombin is a potent platelet activator and acts mostly via the protease-activated receptor 1 (PAR-1). PAR-1 inhibitors block thrombin-mediated platelet activation without disrupting thrombin-mediated cleavage of fibrinogen to fibrin. This property allows preservation of physiologic hemostasis. Clinical trials investigating the combination of a PAR-1 antagonist with aspirin and clopidogrel have shown mixed results. The

TRA-PCI study, a phase II trial in patients undergoing elective PCI, did not show an increased risk of bleeding compared with placebo.²⁹ However, the TRACER trial, a phase III study, showed a higher incidence of major bleeding and intracranial hemorrhage when a PAR-1 antagonist was given along with aspirin and a thienopyridine in patients with ACS.³⁰ The role of PAR-1 antagonists in the contemporary management of ACS and PCI is therefore not defined and further studies are required.

Glycoprotein IIb/IIIa Inhibitors

The GP IIb/IIIa receptor is abundant on the platelet surface ($\approx 50,000$ copies per cell) and undergoes a conformational change following platelet activation, allowing it to bind to fibrinogen.³¹ Fibrinogen cross-links multiple activated platelets by this mechanism. These receptors therefore represent the final common pathway of platelet aggregation, regardless of mode of platelet activation. By inhibiting these receptors, GPIs produce rapid and high levels of inhibition of platelet aggregation. Table 57-2 summarizes the three most commonly used GPIs.

Multiple randomized controlled trials have shown that GPIs clearly reduce ischemic complications in ACS patients managed with an invasive strategy, driven primarily by reduction in peri-PCI elevation of CPK.^{32,33} Whereas 48- to 72-hour infusions of tirofiban and eptifibatide reduced the incidence of death and nonfatal MI during the period of medical stabilization before PCI, prolonged administration of abciximab for 48 hours prior to PCI resulted in worse outcomes in the GUSTO IV ACS trial.³⁴⁻³⁶ Abciximab is therefore not indicated for prolonged (>24 hours) administration before PCI or in a planned medical management strategy for patients with ACS.

Although GPIs decrease ischemic events in PCI for ACS, routine use of these agents has waned in recent years for several reasons. Use of GPI incurs an increased risk of major bleeding,³¹ and bleeding after PCI has now been associated with increased 1-year mortality.³⁷ In addition, the pivotal ACUTY trial has now demonstrated that bivalirudin, a direct thrombin inhibitor, administered without GPI at the time of PCI improves the net clinical outcome of bleeding plus ischemic complications compared to heparin plus GPI.³⁸ Current pervasive use of P2Y12 inhibitors in early ACS management

may also dilute the historically observed benefit of up-front platelet inhibition with GPI. In the EARLY-ACS trial of high-risk ACS patients, upstream GPI administered for a median duration of 21 hours in conjunction with DAPT before PCI, was not superior to selective downstream GPI use.³⁹ A 42% increase in major hemorrhage was noted with upstream GPI. In the ACUTY-Timing trial, compared to upstream GPI, deferred selective GPI at the time of PCI lowered major bleeding by 20% with a nonsignificant increase in the endpoint of composite ischemia.⁴⁰ The 2012 update of the 2007 ACS guidelines focuses on rapid loading with potent oral antiplatelet agents rather than routine upstream GPI use. GP IIB/IIIA antagonists are recommended as a possible alternative to P2Y12 inhibitors before PCI in patients managed with an initial invasive strategy, and GPI may be added to oral antiplatelet therapy in patients who develop refractory ischemia while being managed conservatively. Otherwise, selective GPI use is recommended only during PCI.

Selected recommendations for GPI include:

1. At the time of PCI (class I).
2. As an alternative to a P2Y12 inhibitor in patients initially managed conservatively who develop signs and symptoms of ischemia, CHF, or ventricular tachycardia (VT). (Class IIa)
3. The use of upstream GPI may be considered in high-risk patients already receiving aspirin and a P2Y12 receptor inhibitor who are selected for an invasive strategy, such as those with elevated troponin levels, diabetes, or significant ST-segment depression, and who are not otherwise at high risk for bleeding. (Class IIb)
4. Abciximab should not be administered to patients in whom PCI is not planned. (Class III, no benefit)
5. In UA/NSTEMI patients who are at low risk for ischemic events (TIMI risk score ≤ 2) or at high risk of bleeding and who are already receiving aspirin and a P2Y12 receptor inhibitor, upstream GPIs are not recommended. (Class III, no benefit)

Antithrombotic Therapy

Unfractionated Heparin. Unfractionated heparin (UFH) is a naturally occurring glycosaminoglycan, which in its clinically used form consists of a heterogeneous mix

TABLE 57-2 Features of GPIs in Clinical Use

Name	Structure	Half-Life	Reversibility	Data in ACS
Abciximab	Chimeric human-murine monoclonal antibody Irreversible, noncompetitive inhibition of GP IIb/IIIa receptor	Initial: 10 min, second phase: 30 min	Platelet function recovers over 48 hr. BT returns to <12 min within 12-24 hr of discontinuation. Effect can be overcome with platelet infusion.	EPIC ³² GUSTO-ACS ³⁶
Eptifibatide and tirofiban	Synthetic "small molecules"	2-3 hr	Platelet function returns to normal within 4-8 hr of discontinuation. Effect cannot be reversed with platelet transfusion.	PRISM-PLUS ³⁴ PURSUIT ³⁵

BT, Bleeding time; GPIs, glycoprotein inhibitors.

of polysaccharide chains (mean weight 15,000 daltons). Approximately one third of chains contain a unique pentasaccharide sequence, which binds to and causes a conformational change in antithrombin (AT). This accelerates by 1000 fold the interaction of AT with factor Xa and accounts for its anti-Xa activity. To inactivate thrombin (IIa), heparin binds to both AT and IIa to form a ternary complex. Most of the chains in UFH have the more than 18 saccharide units required to form this ternary complex. Consequently, UFH has equal activity against factors IIa and Xa. Heparin is cleared by the reticuloendothelial system and by the kidneys. Its half-life is approximately 1.5 hours, dose dependent and prolonged in renal disease. The first randomized evaluation of heparin in UA compared outcomes in patients who were randomized to placebo, aspirin alone, heparin alone, or aspirin and heparin in combination.¹⁷ UFH alone (5000-U bolus, followed by 1000 U/hr) reduced the incidence of refractory angina, MI, and death compared with placebo. Similar reductions were noted with aspirin alone and the combination of aspirin and heparin. Heparin was noted to be particularly effective in reducing the incidence of MI to 0.8%, compared with 11.9% with placebo.

Low-Molecular-Weight Heparin. LMWH consists of fragments of UFH with a mean molecular weight of 5000 daltons (hence the name *low-molecular-weight heparin*). Less than half of the chains in LMWH have the 18 saccharide units required to form a ternary complex with AT and IIa. Consequently, LMWH has greater anti-Xa activity compared with anti-IIa activity. The anti Xa:IIa activity ratio of enoxaparin is 3.8:1. Its half-life is 2 to 4 hours after intravenous injection and 3 to 6 hours after subcutaneous injection, and anti-Xa activity persists longer than anti-IIa activity. In the SYNERGY trial, high-risk ACS patients were randomized to enoxaparin or UFH.⁴¹ Enoxaparin was associated with a reduced incidence of death and MI compared with UFH in patients who either did not receive pre-randomization anticoagulant therapy or who received the same pre-randomization anticoagulant therapy as that assigned in the study. Changing anticoagulant therapy between UFH and enoxaparin during the course of treatment was associated with increased risk of bleeding and lack of clinical benefit. In a meta-analysis of six trials comparing LMWH to UFH in ACS, the composite endpoint of death and nonfatal MI was significantly lower with LMWH at 30 days (10.1% vs. 11%, OR 0.91 [0.83-0.99]) with a more robust benefit in patients not receiving pre-randomization antithrombotic therapy.⁴² Although enoxaparin can be used safely during PCI, point-of-care anti-Xa level assays are generally not available to monitor the level of anticoagulation. Therefore, most interventionalists prefer a direct thrombin inhibitor or UFH. Vascular sheath removal should be delayed for 4 to 6 hours after an intravenous dose of enoxaparin, and for 6 to 8 hours after a subcutaneous dose.

Fondaparinux. Fondaparinux is a synthetic factor Xa inhibitor that inhibits the multiplier effects of downstream coagulation reactions and reduces the amount of thrombin generated. It is a relatively new addition to the

class I recommended anticoagulants for UA/NSTEMI. The OASIS trial randomized 20,078 patients with UA/NSTEMI to fondaparinux 2.5 mg subcutaneously (SQ) once daily versus enoxaparin 1 mg/kg SQ twice a day.⁴³ Fondaparinux was not inferior to enoxaparin for the primary efficacy outcome of death, MI, or refractory ischemia at 9 days, with a 1.9% absolute reduction in major bleeding compared with enoxaparin. Importantly, a threefold higher incidence of guide catheter thrombus was noted during PCI (performed in 37% of patients) with fondaparinux monotherapy. It is therefore recommended that additional UFH be administered during PCI in patients on fondaparinux.

Bivalirudin. As a direct thrombin inhibitor, bivalirudin directly inhibits (without requiring antithrombin III) both circulating and clot-bound thrombin. Unlike UFH, it does not activate platelets, and it has a short half-life (25 minutes). In the ACUTY trial, bivalirudin reduced major bleeding by almost half, compared with heparin plus GPI in ACS patients undergoing PCI.³⁸ Bivalirudin was also not associated with increased ischemic complications, provided patients were pretreated with clopidogrel prior to PCI. On the other hand, patients with ACS who underwent PCI and without pretreatment with a thienopyridine, tended to have a higher incidence of ischemic events with bivalirudin monotherapy compared with heparin plus GPI. ACUTY excluded ACS patients, who received angiography after 72 hours or were managed conservatively. Therefore, bivalirudin is not approved for use in either of these situations. Major clinical trials of bivalirudin are summarized in Table 57-3.^{38,44,45}

Class I recommendations for antithrombotic therapy include:

1. In patients managed with an early invasive approach, anticoagulant therapy with UFH, LMWH (enoxaparin), bivalirudin, or fondaparinux should be added to antiplatelet therapy as soon as possible.
2. In patients managed with a conservative approach, bivalirudin is not recommended. Fondaparinux, UFH, or LMWH can be used, although fondaparinux is specifically recommended for patients who are at increased risk of bleeding.
3. It is reasonable to proceed with PCI with bivalirudin as sole therapy in patients who were pretreated with at least 300 mg of clopidogrel administered at least 6 hours prior to PCI.
4. Discontinue anticoagulant therapy after PCI for uncomplicated cases.
5. For UA/NSTEMI patients in whom medical therapy is selected as a management strategy and in whom coronary artery disease was found on angiography, continue intravenous UFH for at least 48 hours or until discharge if given before diagnostic angiography, and enoxaparin for duration of hospitalization, up to 8 days, if given before diagnostic angiography.
6. For UA/NSTEMI patients, in whom CABG is selected as a postangiography management strategy, continue UFH. Discontinue enoxaparin 12 to 24 hours before CABG and dose with UFH per institutional practice.

TABLE 57-3 Selected Major Trials of Bivalirudin

Name of Trial	Study Design	Efficacy Outcome	Safety Outcome	Comments
REPLACE-2 ⁴⁴	Urgent or elective PCI: 14% UA N = 6010 1. Bivalirudin + provisional GPI 2. UFH + planned GPI	30-day death/MI/ urgent TVR/ major bleed 9.2% 10% P = 0.32	Major bleeding 2.4% 4.1% P < 0.001	Nonsignificant trend toward lower 1-year mortality with bivalirudin in all patient subgroups with greatest magnitude of benefit among high-risk patients.
ACUITY ³⁸	ACS Mandated angiography ≤ 72 hr N = 13,819 1. UFH/LMWH +/- upstream GPI 2. Bivalirudin +/- upstream GPI 3. Bivalirudin alone	11.7% 11.8% 10.1% P = 0.02 for 3 vs. 1	5.3% 5.7% 3.0% P < 0.001 for 3 vs. 1	In 3304 patients, not pretreated with clopidogrel before angiography or PCI, composite ischemic event rate was 9.1% in the bivalirudin-alone group vs. 7.1% in the heparin plus GPI group (P for interaction = 0.054)
ACUITY-PCI ⁴⁵ 4545	PCI patients in ACUITY N = 7789 1. UFH/LMWH +/- upstream GPI 2. Bivalirudin +/- upstream GPI 3. Bivalirudin alone (provisional GPI 9%)	13% 15% 12% P = 0.057 for 3 vs. 1	7% 8% 4% P < 0.0001 for 3 vs. 1	77% had elevated cTNI or ST deviation. Median time to PCI was 19.6 hours. Similar composite ischemia, but trend for better net clinical outcome with bivalirudin alone. 30-day ischemic endpoint higher with bivalirudin alone in those receiving no pre-/post-PCI clopidogrel.

cTNI, Cardiac troponin I; GPI, glycoprotein inhibitor; LMWH, low-molecular-weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization; UFH, unfractionated heparin.

Oral Anticoagulants. Despite potential benefits, oral anticoagulants are generally not used for ACS treatment because of increased bleeding with warfarin and hepatotoxicity with the factor IIa inhibitor ximelagatran. Rivaroxaban, an oral factor Xa inhibitor, was recently studied as adjunctive treatment for ACS (including STEMI) after initial stabilization with revascularization or medical therapy. Rivaroxaban added to background DAPT with aspirin and clopidogrel for a mean duration of 11 months reduced the composite endpoint of cardiac death, MI, and stroke by 16% and stent thrombosis by 31% compared to placebo.⁴⁶ Patients with prior stroke, TIA, and intracranial hemorrhage were excluded. At a dose of 2.5 mg twice daily, the drug reduced cardiac and all-cause mortality by 32% to 34% compared with placebo but was associated with an increase in non-CABG-related major hemorrhage. Very low-dose oral anticoagulation may therefore be useful in post-ACS patients who are not at high risk of bleeding.

The need for DAPT in patients requiring long-term oral anticoagulation therapy (OAT) is noted frequently in patients with ACS. The combination of DAPT and OAT, known as “triple therapy,” significantly increases risk of overall bleeding compared with DAPT alone (15.5% vs. 3.7%, $P = 0.02$).⁴⁷ In patients who would typically be treated with triple therapy, the WOEST trial demonstrated a marked reduction in bleeding using a combination of clopidogrel and warfarin, compared with the combination of aspirin, clopidogrel, and warfarin (19.5% vs. 44.9%, hazard ratio [HR] 0.36, [0.26-0.50], $P < 0.001$).⁴⁸ All-cause mortality was lower without increased risk of ischemic complications.

Invasive Management

In parallel with institution of anti-ischemic, antiplatelet, and anticoagulant therapies, patients hospitalized with NSTEMI/ACS are triaged to one of two management pathways.

1. Early invasive strategy: patients (a) are taken urgently from the emergency room to the cardiac catheterization laboratory because of ongoing chest pain or hemodynamic instability, despite absence of ST elevation on the ECG, or (b) undergo early but nonurgent coronary angiography within 72 hours of admission.
2. Initial conservative/selective invasive strategy: patients are managed medically, with angiography reserved for those who fail pharmacologic therapy or have a concerning stress test.

Symptoms and signs of ischemia, risk scores (TIMI and GRACE), and patient preferences drive the strategy selection. In high-risk patients, the early invasive pathway generally yields a lower incidence of death/MI and refractory ischemia compared to a conservative strategy. High-risk criteria are outlined in [Table 57-4](#).

Recommendations for an early invasive strategy:

Refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures)

In initially stabilized patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events (see [Table 57-4](#))

TABLE 57-4 Criteria for Selection of Management Strategy

Preferred Strategy	Patient Characteristics
Invasive	High-risk criteria, which include one or more of the following: • Recurrent angina or ischemia at rest/with low-level activity despite intensive medical therapy • Elevated cTNI/cTNT • New ST-segment depression • Signs or symptoms of CHF or new or worsening MR • High-risk noninvasive test findings • Hemodynamic instability • Sustained VT • PCI within 6 months • Prior CABG • High risk score (e.g., TIMI, GRACE) • LVEF < 40%
Conservative	• Low risk score (e.g., TIMI, GRACE) • Patient or physician preference in absence of high-risk features

CABG, Coronary artery bypass grafting; CHF, congestive heart failure; cTNI/cTNT, cardiac troponin I/cardiac troponin T; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; VT, ventricular tachycardia.

From Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 50:e1–e157, 2007.

Recommendations *against* an early invasive strategy:

An early invasive strategy is *not* recommended in patients with extensive comorbidities (e.g., liver or pulmonary failure, cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization, or in patients who will not consent to revascularization regardless of the findings.

These two approaches have been compared in individual trials and meta-analyses. Whereas individual trials have shown discrepant results, meta-analyses have shown the early invasive approach resulted in reductions in death, MI, angina, and hospitalization among patients with UA.⁴⁹ Practical advantages of an early invasive approach include identification of patients with left main or three-vessel CAD with left ventricular ejection fraction (LVEF) of less than 40%, who will benefit from CABG, and the 10% to 20% of patients who have no significant angiographic CAD.

In addition, early PCI of unstable coronary lesions may prevent ischemic events on medical therapy. This hypothesis was tested in a trial of 410 patients who were randomized to early (median 2.4 hours) versus delayed (median 86 hours) angiography and revascularization.⁵⁰

Despite intensive treatment with antiplatelet and anticoagulant therapy, the delayed group had a higher incidence of death and large MI during the “cooling off” period. A larger trial of 3031 patients with high-risk ACS showed that early (median 14 hours from presentation) angiography and intervention reduced the secondary endpoint of refractory ischemia by 30% compared to a delayed approach (median 50 hours).⁵¹ The largest benefit was noted among patients in the highest tertile of the GRACE risk score (>140). These patients had a 35% reduction in the combined primary endpoint of death, MI, and stroke (number needed to treat 14). Patients with a GRACE score of 140 or lower did not experience a reduction in this primary outcome. The TACTICS-TIMI 18 trial also showed that the benefit of early intervention was confined to higher risk patients (cTNT > 0.01 ng/mL, ST-segment deviation, and TIMI risk score ≥ 3).¹⁴ When an invasive strategy is selected in NSTEMI/ACS, angiography should be performed early, but immediate catheterization does not appear to be necessary. In the ABOARD trial, angiography and PCI at a median of 70 minutes from randomization did not improve outcomes compared with a delay of approximately 24 hours.⁵²

The following general observations can be made from analysis of contemporary trials comparing early versus delayed angiography.

1. Early angiography reduces refractory ischemia, which if left untreated is associated with more than a fourfold risk of MI.
2. Patients at the highest risk, for example, with a GRACE score higher than 140 and TIMI risk score of higher than 3, have the most to gain from an early invasive approach.
3. In high-risk patients, prolonged (>72 hours) “cooling off” with medical therapy is not effective and may be associated with harm, as seen in the ISAR-COOL trial.⁵⁰
4. Therefore, angiography and intervention within 24 hours of presentation represents a reasonable balance between too early and too late.

ST-ELEMENT ELEVATION MYOCARDIAL INFARCTION

Definition

STEMI is universally defined as new ST-segment elevation at the J point in two contiguous leads with the following cutpoints: 1 mm or greater in leads other than V2–V3; in leads V2–V3, ST elevation of 2 mm or greater in men older than 40 years or 1.5 mm or greater in women is required for diagnosis.¹² Other findings indicative of evolving STEMI include a new LBBB in the presence of symptoms of ischemia or horizontal ST depression in leads V1–V3 (transmural posterior injury current).

Risk Assessment

The TIMI risk index, a modification of the TIMI risk score is calculated by the following equation: heart rate × [age/10]²/systolic blood pressure.⁵³ This risk index

Risk Index	Risk Group	Risk of Death		
		24 hr	In-hospital	30 days
≤12.5	1	0.2	0.6	0.8
>12.5-17.5	2	0.4	1.5	1.9
>17.5-22.5	3	1.0	3.1	3.3
>22.5-30	4	2.4	6.5	7.3
>30	5	6.9	15.8	17.4

1) Calculate risk index* 2) Assign risk group 3) Mortality estimate (data from InTIME II)

*Heart rate $\times$ (Age/10)² / Systolic blood pressure. Heart rate in beats per min; systolic blood pressure in mm Hg.

FIGURE 57-3 ■ Correlation between TIMI risk index and short-term mortality in patients with ST-segment elevation myocardial infarction. (From Morrow DA, Antman EM, Giugliano RP, et al: A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. *Lancet* 358:1571–1575, 2001.)

appears to be an independent predictor of 24-hour and 30-day mortality ($P < 0.0001$) with an average 43% relative increase for each 5-point rise in the risk index after adjusting for other major predictors of mortality (Fig. 57-3). The Killip classification has also been used for risk assessment in both STEMI and NSTEMI. The four Killip classes are class I (no evidence of pulmonary congestion or shock), class II (mild pulmonary congestion or S3), class III (pulmonary edema), and class IV (hypotension/shock).⁵⁴

Reperfusion Therapy

Reperfusion therapy consists of fibrinolytic therapy, primary PCI, or some combination of the two, referred to as “facilitated PCI.” Although early reperfusion is critical to management of patients with STEMI, data from the CRUSADE registry suggest that 7% of eligible patients do not receive this therapy.⁵⁵ Very old patients, women, and patients on dialysis are particularly likely to receive delayed reperfusion therapy or none at all.

Fibrinolytic Therapy

Fibrinolytic therapy is most effective if it is administered within the first 1 to 2 hours from symptom onset (the “golden hour”). In this situation, it can be more effective than delayed primary PCI. In fact, prehospital fibrinolysis is associated with a 17% reduction in all-cause mortality compared with hospital-based therapy.⁵⁶ Contemporary fibrinolytic agents include tenecteplase (TNK-tpa), administered as a single weight-based bolus, and reteplase, given as two 10-unit intravenous boluses 30 minutes apart. Both result in establishment of TIMI 2 or 3 flow in approximately 85% of patients.^{57,58} Absolute contraindications include prior intracranial hemorrhage, known cerebral vascular lesion/neoplasm, ischemic stroke within 3 months, intracranial/spinal surgery within 2 months, closed head/facial trauma within 3 months, suspected aortic dissection, severe uncontrolled hypertension (HTN), and active bleeding/diathesis.

The following are recommendations for fibrinolytic therapy, based on the most recent 2013 STEMI guidelines.

1. Onset of symptoms less than 12 hours from presentation with no contraindications to fibrinolysis and delay to primary PCI greater than 120 minutes from first medical contact. (Class I recommendation)
2. Onset of symptoms 12 to 24 hours from presentation, with ongoing ischemia (as evidenced by symptoms or ECG) and either large area of myocardium in jeopardy or hemodynamic instability, without capability for primary PCI. (Class IIa recommendation)
3. Fibrinolytic therapy should NOT be administered in the presence of contraindications or in the presence of ST depression alone (unless a true posterior MI is suspected). (Class III recommendation)

Antiplatelet agents and anticoagulants are administered with fibrinolytics on first medical contact with the intention of improving patency of the coronary artery and preventing reocclusion after successful fibrinolysis. Current recommendations include:

1. Aspirin: 162- to 325-mg loading dose, preferably chewed as a non-enteric-coated formulation. This is followed by 81 to 325 mg indefinitely.
2. Clopidogrel: 300-mg loading dose for patients younger than 75 years and no loading dose for patients older than 75 years. A 75-mg daily maintenance dose is continued for a minimum of 2 weeks and ideally 1 year in the absence of bleeding.
3. UFH: initial bolus of 60 U/kg (maximum 4000 U) and infusion of 12 U/kg/hr (maximum 1000 U/hr), adjusted to keep partial thromboplastin time (PTT) between 1.5 and 2 times control for 48 hours or until revascularization. UFH is most commonly used in the United States. Alternatives include enoxaparin or fondaparinux, both given for a total of 8 days or until revascularization. Enoxaparin dosing is 30 mg IV followed by 1 mg/kg SQ every 12 hours in patients younger than 75 years, or 0.75 mg/kg SQ every 12 hours without an IV bolus in those older than 75 years. Fondaparinux is administered 2.5 mg IV on day 1, followed by 2.5 mg SQ starting on day 2. In the setting of renal impairment, these agents should be avoided or dosing should be reduced.

Rescue Percutaneous Coronary Intervention

Ongoing chest pain and the absence of a reduction in the height of ST elevation by at least 50% in the worst lead by 60 to 90 minutes after fibrinolytic therapy should prompt immediate transfer to a PCI-capable hospital for “rescue” PCI, especially when a large area of myocardium is in jeopardy (such as anterior MI, or extensive inferior MI with right ventricular involvement) and definitely in the presence of hemodynamic or electrical instability (cardiogenic shock, heart failure, ventricular arrhythmias). The REACT trial showed a reduction in reinfarction with rescue PCI compared with conservative management or repeat fibrinolysis.⁵⁹ Rescue PCI has

been given a class IIa recommendation (reasonable to perform).

Routine Percutaneous Coronary Intervention after Successful Fibrinolysis

A strategy of early (<24 hours after fibrinolytic therapy) coronary angiography with or without PCI has been compared with the approach of reserving early PCI for failure of fibrinolytic therapy (rescue PCI) in multiple randomized controlled trials. A meta-analysis of seven randomized trials showed a reduction in the combined endpoint of death and reinfarction at 30 days and 6 to 12 months with early PCI compared to delayed PCI, without an increase in major bleeding.⁶⁰ Therefore, routine coronary angiography and PCI can be performed without increased risk and with potential benefit within 3 to 24 hours of successful fibrinolytic therapy, but should not be performed routinely immediately after fibrinolysis (which is referred to as facilitated PCI, discussed later). This approach has been given a class IIa recommendation (reasonable to perform). High-risk STEMI patients initially treated with fibrinolytic therapy at hospitals without PCI capabilities should be transferred immediately to a PCI-capable hospital for early angiography. In one randomized study, this approach lowered the combined endpoint of death, reinfarction, recurrent ischemia, CHF, and shock, compared to the more conservative approach of delayed angiography or selective transfer for rescue PCI.⁶¹

Delayed Percutaneous Coronary Intervention

In patients who underwent initial successful fibrinolysis or those who never received fibrinolysis, coronary angiography and PCI are strongly recommended (class I recommendation) for patients with any one of the following:

1. Cardiogenic shock or acute severe heart failure that develops after initial presentation
2. Spontaneous or easily provoked myocardial ischemia
3. Intermediate or high-risk findings on predischarge stress testing

Delayed PCI of a totally occluded infarct artery more than 24 hours after onset of STEMI in stable patients is not indicated (class III, no benefit).⁶²

Facilitated Percutaneous Coronary Intervention

This term refers to planned immediate coronary angiography and PCI following administration of a full or half dose of fibrinolytic agent combined with GP. Contemporary trials of this strategy have shown no benefit or net harm.^{63,64} Therefore, this strategy is discouraged in the recent guidelines.

Primary Percutaneous Coronary Intervention

Primary PCI refers to the strategy of catheter-based reperfusion as an initial or primary strategy. Primary PCI

is given a class I recommendation in the following scenarios:

1. In all patients with STEMI presenting within 12 hours of onset of symptoms, as an alternative to fibrinolytic therapy. The goal is a “door-to-balloon” time (time from first medical contact to balloon inflation in the occluded coronary artery) of 90 minutes.
2. In patients with onset of symptoms less than 12 hours from presentation and who have contraindications to fibrinolytic therapy, regardless of the time delay to PCI.
3. Cardiogenic shock or acute severe heart failure irrespective of time delay from the onset of symptoms.

Primary PCI should be restricted to the infarct-related artery, except in the situation of hemodynamic compromise related to ischemia from significant stenosis in the non-infarct-related artery/arteries.

ADDITIONAL CONSIDERATIONS IN ACUTE CORONARY SYNDROME MANAGEMENT

Radial Access for Percutaneous Coronary Intervention

Radial access reduced the composite of death/MI/stroke and non-CABG-related major bleeding by 40% and all-cause mortality by 61% compared with femoral access in patients with STEMI but not in patients with NSTEMI/ACS.⁶⁵ Mortality at 30 days in patients undergoing primary PCI via radial access was only 1.3%, compared with 3.2% with femoral access. There was a 5-minute delay in door-to-balloon time in the radial group. Radial access cut major bleeding and vascular complications by half, in patients with both STEMI and NSTEMI/ACS. Similar findings were noted in the RIFLE-STEMI study, in which radial access resulted in an absolute risk reduction in cardiac mortality by 4% (number needed to treat [NNT] = 25) and bleeding by 4.6% (NNT = 22).⁶⁶ Access site bleeding was 60% lower in the radial group, with no difference in non-access site bleeding.

Implications for Pharmacologic Therapy when Coronary Artery Bypass Grafting Is Required

Clopidogrel and ticagrelor should be discontinued at least 5 days before planned CABG, whereas a longer period of discontinuation of 7 days is recommended for prasugrel. When urgent CABG is required, some studies have shown an increased risk of major bleeding in patients exposed to clopidogrel, whereas others have not.^{67,68} In addition, clopidogrel use before CABG reduced composite ischemia compared with no use before CABG.⁶⁹ In a subgroup analysis of the PLATO trial, rates of major CABG-related bleeding, after stopping clopidogrel or ticagrelor within 1 to 7 days before surgery, were high

but not significantly different from one another.⁷⁰ Prasugrel resulted in greater bleeding post CABG as assessed by chest tube output, compared to clopidogrel but nevertheless was associated with lower mortality.⁷¹ Eptifibatide and tirofiban should be discontinued 2 to 4 hours before urgent CABG and abciximab at least 12 hours before CABG (or reversed with platelet infusion if urgent CABG is needed).

Cardiogenic Shock

Cardiogenic shock is defined as a systolic blood pressure of lower than 90 mm Hg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of 90 mm Hg or higher and end-organ hypoperfusion. Shock occurred in 8.6% of STEMI patients in the large NRM database.⁷² In the pivotal SHOCK trial, mechanical revascularization with either PCI or CABG was associated with improved 6- and 12-month survival compared with fibrinolytic therapy.⁷³ Whereas the SHOCK trial randomized only patients with onset of shock within 36 hours of the MI, the latest guidelines for the management of STEMI recommend emergency revascularization of shock patients with either PCI or CABG, irrespective of the time delay from onset of MI. Fibrinolytic therapy remains a class I recommendation in patients with cardiogenic shock who are unsuitable for PCI or CABG. In addition, whereas the original SHOCK trial demonstrated no benefit of mechanical revascularization in patients older than 75 years, data from the SHOCK registry showed improved survival even in clinically selected older patients.⁷⁴ Therefore, the 2013 guidelines recommend mechanical revascularization in all suitable shock patients without distinction of age.

Postrevascularization Therapy

Cardiac Rehabilitation

A systematic meta-analysis of randomized controlled trials showed a significant reduction in all-cause and cardiac mortality with cardiac rehabilitation.⁷⁵ When only post-MI trials were considered, a 19% reduction in all-cause mortality was noted (OR = 0.81; 95% CI: 0.70–0.93). In this study, benefits were also noted in patients who had undergone surgical or percutaneous revascularization, which supports the value of cardiac rehabilitation even in contemporary patient populations with high rates of mechanical revascularization.

Secondary Prevention

Antiplatelet agents, beta blockers, and statins form the cornerstone of secondary preventive therapy following ACS, whereas angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, and aldosterone receptor antagonists are typically reserved for patients with heart failure, LVEF less than 0.40, or diabetes. Statins should be given to all patients after admission for UA/NSTEMI and STEMI and continued indefinitely in the absence of contraindications. Aggressive LDL reduction with high-dose atorvastatin reduced the composite

endpoint of all-cause death, stroke, MI, UA, and revascularization starting as early as 30 days of therapy, with benefits maintained at 2-year follow-up.⁷⁶ Traditionally the goal low-density lipoprotein (LDL) level has been less than 100 mg/dL, although several trials have shown added benefits of lowering LDL to less than 70 mg/dL.^{76,77}

CONCLUSION

The past few years have seen several important advances in our understanding of the pathophysiology of ACS, platelet biology, pharmacogenomics, and the adverse impact of bleeding, which have resulted in the development of powerful and novel antiplatelet drugs and a focus on reducing bleeding with bivalirudin largely supplanting the use of GPI. This has translated into improved outcomes for patients. The focus in NSTEMI/ACS remains on rapid initiation of anti-ischemic, antiplatelet, and antithrombotic therapy with triage to an early invasive approach for high-risk patients. For STEMI patients, the focus remains on immediate revascularization with concurrent administration of medical therapy.

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THE PHARMACOLOGIC MANAGEMENT OF HEART FAILURE

Eric H. Awtry • Wilson S. Colucci

CHAPTER OUTLINE

PATHOPHYSIOLOGY OF HEART FAILURE

Acute Heart Failure
Chronic Heart Failure

PHARMACOLOGIC AGENTS USED IN THE TREATMENT OF HEART FAILURE

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Diuretics
Vasodilators
Neurohormonal Inhibiting Agents
Inotropic Agents
Other Agents
Natriuretic Peptides

APPROACH TO THE MANAGEMENT OF HEART FAILURE

Initial Approach and Clinical Assessment
Pharmacologic Treatment of Chronic Compensated Systolic Heart Failure
Treatment of Decompensated Systolic Heart Failure
Treatment of Diastolic Heart Failure
Flash Pulmonary Edema
Perioperative Heart Failure

Heart failure has become an increasingly important cause of morbidity and mortality in the United States and in other industrialized nations. Despite improvement in heart failure treatment, its prevalence continues to rise, in large part as a result of the aging of the population and the improved survival of heart failure patients. In 2010, the most recent year for which statistics are available, the estimated prevalence of heart failure in the U.S. population over the age of 20 years was 5.7 million. In the same year, heart failure was listed as the primary diagnosis in over 1 million hospital discharges, a number that has remained stable since 2000. The economic impact is staggering, with a yearly cost of caring for these patients estimated at more than \$32 billion, more than half of which is accounted for by direct hospital costs. Despite improvements in therapies, one in five patients will die within 1 year of the initial diagnosis with heart failure, and in the United States alone, heart failure is listed as the principal cause for almost 56,000 deaths annually and as a contributing cause in more than 274,000 deaths.

From a surgical standpoint, heart failure has a significant impact on perioperative morbidity and mortality. Preoperative heart failure is a strong predictor of adverse outcome in patients undergoing noncardiac surgery, and a history of heart failure or depressed left ventricular systolic function is an independent predictor of mortality after coronary artery bypass surgery. A thorough understanding of the pathophysiology and treatment of heart failure is therefore essential for those physicians who manage patients in the perioperative period. Effective

preoperative management of heart failure may prevent perioperative decompensation, and rapid recognition and treatment of postoperative heart failure are essential to prevent progressive pulmonary congestion and organ hypoperfusion. For the well-compensated patient, an understanding of the medical management of chronic heart failure ensures continuation of appropriate therapy both perioperatively and at the time of hospital discharge.

This chapter focuses primarily on the various pharmacologic modalities available for the treatment of heart failure, including their mechanisms of action, benefits as shown in clinical trials, and suggested usefulness in the management of patients with acute and chronic heart failure. The use of many of these pharmacotherapies is based on our current understanding of the pathophysiologic mechanisms underlying heart failure. Therefore, a brief mechanistic overview is provided in an effort to place these therapies in a pathophysiologic context.

PATHOPHYSIOLOGY OF HEART FAILURE

Our understanding of the pathophysiology of heart failure has evolved dramatically during the past 2 decades. The traditional hemodynamic model, although still applicable in the setting of acutely decompensated heart failure, is less relevant in the setting of chronic heart failure, for which the concepts of progressive ventricular remodeling and neurohormonal activation have come to

the forefront. These processes are briefly discussed here as they relate to the pharmacologic treatment of heart failure.

The term *heart failure* does not refer to a single entity; rather, it denotes a syndrome that is characterized by signs or symptoms of intravascular volume overload or manifestations of inadequate tissue perfusion. It is the end result of a variety of cardiac injuries and the ensuing pathologic remodeling that impair the heart's ability to fill with or to eject blood; it may originate from a wide range of disorders of the myocardium, pericardium, endocardium, or intracardiac valves (Table 58-1). Heart failure can be categorized pathophysiologically in several ways.

- *Left-sided heart failure* is characterized by signs and symptoms of pulmonary congestion (dyspnea, orthopnea, pulmonary rales, pleural effusions). *Right-sided heart failure* is characterized by peripheral congestion (elevated jugular venous pressure, peripheral edema, hepatic congestion).
- *Systolic heart failure* refers to that occurring in the setting of left ventricular systolic dysfunction (i.e., reduced ejection fraction). *Diastolic heart failure* refers to that resulting from impaired left ventricular diastolic filling despite normal left ventricular systolic function. These two abnormalities often coexist, although one usually predominates.
- *Acute heart failure* denotes the sudden development of heart failure in the absence of preexisting cardiac dysfunction or the sudden decompensation in a patient with previously stable cardiac disease. This results from an abrupt alteration in cardiac structure or function (e.g., after an acute myocardial infarction or after valvular rupture) and is generally associated with clinical instability. *Chronic heart failure* results from a more indolent process of myocardial dysfunction and may be associated with less clinical severity because of the development of compensatory mechanisms (see later).
- *Low-output heart failure* is that resulting from a reduction in cardiac output (caused by either systolic or diastolic dysfunction) and is usually characterized by venous congestion and increased arterial resistance (i.e., vasoconstriction). *High-output heart failure* occurs in the setting of increased cardiac output (e.g., thyrotoxicosis, anemia, beriberi, Paget disease, arteriovenous fistulas) and is characterized by venous congestion and normal or reduced arterial resistance.
- *Backward heart failure* refers to the hypothesis that the manifestations of heart failure are primarily the result of an accumulation of fluid (and pressure) behind the failing ventricle. *Forward heart failure* proposes that heart failure results from a primary reduction in cardiac output with resultant organ hypoperfusion, sodium and water retention, and subsequent venous congestion. This is not as useful a distinction, because both mechanisms probably operate in most patients with heart failure.

Heart failure may be classified symptomatically on the basis of its clinical severity (Table 58-2). Despite the varied causes and classifications of heart failure, the

TABLE 58-1 Common Causes of Heart Failure

Myocardial

Ischemia or infarction
 Viral myocarditis
 Idiopathic cardiomyopathy
 Hypertrophic cardiomyopathy
 Hypertension
 Toxins (alcohol, cocaine, chemotherapeutic agents)
 Infiltrative diseases (amyloidosis, hemochromatosis)
 Infectious (Lyme disease, Chagas disease)
 Peripartum cardiomyopathy
 Thyroid dysfunction
 Metabolic abnormalities (thiamine or selenium deficiency)

Valvular

Aortic stenosis
 Aortic regurgitation
 Mitral stenosis
 Mitral regurgitation

Arrhythmic

Tachycardia-mediated cardiomyopathy

Pericardial

Constrictive pericarditis

TABLE 58-2 Clinical Classifications of Heart Failure

New York Heart Association Classification

Class I	Symptoms only with greater than usual activity
Class II	Asymptomatic at rest but with symptoms during normal activities
Class III	Asymptomatic at rest but with symptoms during minimal exertion
Class IV	Symptoms at rest

American College of Cardiology/American Heart Association Classification

Stage A	Patients with structurally normal hearts, asymptomatic, but at risk for the development of heart failure resulting from the presence of risk factors (e.g., hypertension, coronary artery disease, diabetes)
Stage B	Patients with structurally abnormal hearts (e.g., left ventricular systolic dysfunction, left ventricular hypertrophy, valvular dysfunction, prior myocardial infarction) but without symptoms of heart failure
Stage C	Patients with structurally abnormal hearts and current or prior symptoms of heart failure
Stage D	Patients with end-stage heart failure symptoms not responsive to standard therapy

manifestations all reflect intravascular volume overload, inadequate tissue perfusion, or their combination. A thorough explanation of all these forms of heart failure is beyond the scope of this chapter. The following discussion, therefore, focuses primarily on left ventricular systolic failure in both the acute and chronic setting.

Acute Heart Failure

The response of the cardiovascular system to the onset of myocardial dysfunction and the pathophysiologic mechanisms underlying the subsequent progression to

heart failure depends in large part on the acuity of the dysfunction. An acute cardiac insult results in a series of hemodynamic alterations that account for the clinical manifestations of left ventricular failure. This occurs irrespective of whether the initial insult depresses myocardial contractility (systolic dysfunction) or impairs ventricular filling (diastolic dysfunction). The cascade begins with a rise in left ventricular end-diastolic pressure. This elevated pressure is transmitted to the left atrium and subsequently to the pulmonary venous and capillary system. The increased intravascular pressure results in transudation of fluid into the pulmonary interstitium where it interferes with gas exchange, resulting in hypoxemia and dyspnea. In addition, there is often an associated reduction in cardiac output resulting in inadequate delivery of blood to the arterial system with resultant organ hypoperfusion.

The heart's response to these hemodynamic alterations is the activation of several compensatory mechanisms (Table 58-3). A rapid, generalized activation of the adrenergic system occurs and is associated with a withdrawal of parasympathetic tone. Direct sympathetic stimulation of the heart and β -adrenergically induced release of epinephrine and norepinephrine from the adrenal glands result in tachycardia and an increase in myocardial contractility, both of which serve to augment cardiac output. Catecholamine-induced peripheral arterial vasoconstriction redirects the available cardiac output away from relatively nonessential organs (i.e., skin, skeletal muscle, gut, kidney) and helps maintain sufficient blood pressure to ensure adequate perfusion of more vital organs (i.e., heart and brain). Furthermore, β -adrenergic stimulation of the juxtaglomerular apparatus in the

kidneys results in the release of renin and activation of the renin-angiotensin system. The angiotensin II thus produced is a potent vasoconstrictor and acts in concert with the direct α -adrenergic stimulation of the vasculature to maintain blood pressure. The reduced renal blood flow from depressed cardiac output and redistribution of blood volume results in activation of renal baroreceptors. This further stimulates renin release and augments sympathetic activation, thereby contributing to vasoconstriction.

In addition to producing these hemodynamic alterations, acute heart failure is characterized by marked sodium and water retention. This occurs through a variety of mechanisms. Angiotensin II directly promotes the reabsorption of sodium in the proximal nephron and indirectly promotes the reabsorption of sodium from the distal nephron, this latter effect being mediated through angiotensin II-induced release of aldosterone from the adrenal cortex. Furthermore, angiotensin II and norepinephrine stimulate hypothalamic release of arginine vasopressin, resulting in further vasoconstriction and free water reabsorption. These changes produce an expansion of intravascular volume and augmentation of venous return, thereby increasing ventricular end-diastolic volume (*preload*). The increased preload results in an increase in stroke volume by the Frank-Starling mechanism (Fig. 58-1) and thereby helps support the cardiac output.

Chronic Heart Failure

In combination, the aforementioned mechanisms serve a compensatory role in acute heart failure, helping to

TABLE 58-3 Compensatory Mechanisms in Heart Failure

Compensatory Response	Stimuli	Beneficial Effects	Adverse Effects	Potential Pharmacologic Interventions
Renin-angiotensin system activation	↓CO/BP ↓Renal blood flow ↑ β -Adrenergic activity	Maintain vital organ perfusion through vasoconstriction and sodium retention	↑Afterload → worsened LV function Adverse LV remodeling (apoptosis, myocyte hypertrophy)	ACE inhibitors ARBs
Adrenergic activation	↓CO/BP	↑CO through ↑ in heart rate and contractility ↑BP	↑Ischemia ↑Afterload → worsened LV function ↑LVEDP → pulmonary congestion Adverse LV remodeling (apoptosis, myocyte hypertrophy)	β -Adrenergic blocking agents
Renal salt and water retention	↑Antidiuretic hormone ↑Norepinephrine ↑Angiotensin II ↑Aldosterone ↓Renal blood flow	↑Preload → ↑stroke volume and CO	Pulmonary and systemic congestion Adverse LV remodeling	Diuretics Aldosterone inhibitors ACE inhibitors, ARBs β -Adrenergic blocking agents
↑Natriuretic peptide secretion	Volume expansion (atrial stretch)	Diuresis Natriuresis Partial inhibition of renin-angiotensin system and norepinephrine	None known	Natriuretic peptides

ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CO, cardiac output; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure.

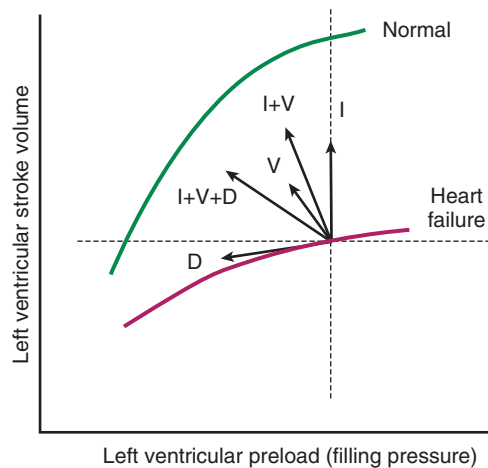


FIGURE 58-1 ■ Frank-Starling curve with normal systolic function and with heart failure and the hemodynamic effect of pharmacologic therapy. In the normal setting, an increase in preload results in an increase in stroke volume. In heart failure, this relationship is blunted, and at any given stroke volume, the preload must be higher (*horizontal dotted line*). Similarly, for any given preload, the stroke volume is lower (*vertical dotted line*). Diuretic therapy (D) reduces preload without a significant effect on stroke volume, whereas inotropic therapy (I) augments stroke volume without an appreciable effect on preload. Vasodilator therapy (V) has moderate beneficial effects on both preload and stroke volume; however, the greatest effects are seen with combination therapy (I + V, I + V + D).

maintain cardiac output and blood pressure to allow adequate perfusion of vital organs. These compensatory mechanisms may initially be adequate to allow clinical stability, and the patient may subsequently go through a stage of asymptomatic ventricular dysfunction, maintained in part by chronic stimulation of the adrenergic and renin-angiotensin systems. As heart failure progresses, the hemodynamic overload induces changes in the shape and size of the ventricle, a process known as *ventricular remodeling*. The specific changes that occur depend in part on the hemodynamic stressors facing the ventricle. In predominantly pressure-overloaded conditions (e.g., hypertension, aortic stenosis), there is a rise in systolic wall stress that results in left ventricular hypertrophy. If this hypertrophy is insufficient to normalize the wall stress, dilation occurs. Under conditions of volume overload (e.g., aortic or mitral insufficiency), there is a rise in diastolic wall stress that induces ventricular dilation. This dilation in turn results in increased systolic wall stress (by the Laplace relationship) and subsequent hypertrophy. These hypertrophic changes help maintain systolic wall stress within a normal range and help preserve ventricular contractile function. However, with continued hemodynamic overload, there is progressive ventricular dilation, eventuating in the development of a dilated, spherical heart. This altered ventricular morphology produces less efficient ventricular contraction, may induce mitral regurgitation caused by annular dilation and malcoaptation of the valve leaflets, and is associated with an adverse prognosis.

The stimuli that induce ventricular remodeling are varied and the mechanisms underlying the remodeling process are complex (Table 58-4). It appears that increased

TABLE 58-4 Factors Involved in Ventricular Remodeling

Stimulants of Ventricular Remodeling	Molecular and Cellular Events That Mediate Ventricular Remodeling
Altered hemodynamic load (increased preload, afterload, wall stress)	Myocyte hypertrophy Myocyte loss (necrosis and apoptosis)
β -Adrenergic stimulation	Myocyte "slippage"
Activation of the renin-angiotensin system	Transition to fetal myocyte phenotype
Inflammatory cytokines (e.g., tumor necrosis factor α , interleukins 1 and 6)	Neurohormonal activation Fibroblast proliferation
Vasoactive peptides (e.g., endothelin)	Alterations in the interstitial matrix
Oxidative stress	Alterations in excitation-contraction coupling

wall stress (resulting from ventricular dilation and increased afterload) and neurohormones (i.e., β -adrenergic and renin-angiotensin systems), vasoactive peptides (e.g., endothelin), and cytokines (e.g., tumor necrosis factor α) mediate remodeling. These factors may have direct effects on the cardiac myocytes or may act indirectly through stimulation of second-messenger systems and thereby induce a variety of changes in myocyte structure and function. On a cellular level, myocyte hypertrophy results from the replication of sarcomeres either in parallel (producing ventricular hypertrophy) or in series (producing ventricular dilation). Alterations in the expression of various contractile proteins occur with reexpression of fetal genes and reduced expression of adult contractile genes, resulting in abnormalities of calcium handling and excitation-contraction coupling. Chronic stimulation of the sympathetic system is accompanied by a reduction in the density of β -adrenergic receptors in the myocardium and an uncoupling of the receptors from their intracellular mediators. This results in a blunted response of the failing myocardium to either endogenous (e.g., exercise) or exogenous (e.g., dopamine or dobutamine) adrenergic stimulation.

In addition to these alterations of the contractile apparatus within the myocytes, there is a progressive reduction in the number of myocytes, in part the result of apoptosis induced by the various stimuli of remodeling. Furthermore, changes occur in the extracellular matrix related to fibroblast proliferation, interstitial fibrosis, and increased expression of degradative enzymes such as matrix metalloproteinases. The last factor results in the loss of mechanical coupling of myocytes and may contribute to the remodeling process by facilitating "myocyte slippage" and, thereby, ventricular dilation.

As the remodeling process develops, the neurohormonal effects of the β -adrenergic and renin-angiotensin systems on the peripheral vasculature and renal salt and water handling continue. The intense vasoconstriction, while maintaining flow to vital organs, contributes to hypoperfusion of the kidneys and progressive renal dysfunction. The augmented preload and cardiac output

resulting from sodium and water retention help maintain circulating blood volume and tissue perfusion. However, the associated increase in end-diastolic pressure and increased ventricular wall stress contribute to progressive ventricular remodeling and result in pulmonary and systemic venous hypertension and precipitation of congestive symptoms. Thus, these initially compensatory changes become deleterious in the chronic setting. The inhibition of these processes offers not only a mechanism for the treatment of heart failure but also the potential to reverse the adverse remodeling seen in the chronic state (see [Table 58-3](#)).

PHARMACOLOGIC AGENTS USED IN THE TREATMENT OF HEART FAILURE

Most pharmacologic agents used for the treatment of heart failure effect benefit either by interfering with the hemodynamic alterations described earlier or through inhibition of the neurohormonal activation underlying these alterations (see [Fig. 58-1](#)). These medications fall into several categories: diuretics, vasodilators, inotropic agents, and neurohormonal inhibitors. Diuretics act to reduce preload (leftward shift on the Frank-Starling curve), resulting in decreased filling pressures and improved congestive symptoms. Although this fall in preload may be associated with a reduction in stroke volume, this effect is minimal in patients with elevated filling pressures. Pure venodilators similarly reduce filling pressures and congestive symptoms and have minimal effect on stroke volume. Arterial vasodilators and inotropic agents predominantly augment cardiac output and thereby improve organ perfusion; arterial vasodilators act indirectly through a reduction in vascular resistance,

whereas inotropic agents directly increase contractility and stroke volume. Although the increased cardiac output seen with these agents may result in a fall in filling pressures, the effect may be relatively modest. As a result of the differential effects of these agents, many patients with heart failure attain the greatest benefit from combination therapy. Neurohormonal inhibitors may have mixed hemodynamic effects. The blockade of adrenergic tone (beta blockers) and inhibition of the renin-angiotensin system (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]) results in vasodilation and augmented cardiac output. These agents may also decrease preload and reduce filling pressures through a reduction in neurohormonally mediated renal sodium and water retention.

Specific Agents

Diuretics

Diuretics have long played an important role in the symptomatic treatment of heart failure ([Table 58-5](#)). The induced diuresis and natriuresis reduce extracellular volume and ventricular filling pressures, thereby ameliorating congestive symptoms. This effect occurs without a significant decrease in cardiac output or systemic blood pressure unless excessive diuresis and intravascular volume depletion occur. Whereas diuretics are beneficial in controlling symptoms and improving exercise capacity in patients with heart failure, with the exception of aldosterone inhibitors (spironolactone and eplerenone) diuretic use has not resulted in a decrease in mortality.

Loop diuretics act in the thick ascending limb of the loop of Henle, where they inhibit the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ transporter, resulting in increased delivery of sodium and

TABLE 58-5 Diuretics Commonly Used in the Treatment of Heart Failure

Class and Examples	Daily Dose Range	Duration of Action	Adverse Effects (by Class)
Loop Diuretics			
Furosemide (Lasix)	20-480 mg PO 20-300 mg IV	4-6 hours	Hypokalemia, hyperuricemia, metabolic alkalosis, ototoxicity at high doses
Torsemide (Demadex)	5-200 mg PO	12 hours	
Bumetanide (Bumex)	0.5-5 mg PO	4-6 hours	
Ethacrynic acid (Edecrin)	25-100 mg PO	12 hours	
Thiazide Diuretics			
Chlorothiazide (Diuril)	125-500 mg PO	6-12 hours	Hypokalemia, hyponatremia, hyperuricemia, hyperglycemia, hyperlipidemia
Hydrochlorothiazide (HydroDIURIL)	12.5-50 mg PO	12-18 hours	
Chlorthalidone (Hygroton)	25-100 mg PO	24 hours	
Thiazide-like Diuretics			
Metolazone (Zaroxolyn)	0.5-10 mg PO	24 hours	Hypokalemia, hypomagnesemia
Aldosterone Inhibitors			
Spironolactone (Aldactone)	25 mg PO	8-12 hours	Hyperkalemia, nausea, gynecomastia (spironolactone)
Eplerenone (Inspra)	25-50 mg PO	4-6 hours	
Potassium-Sparing Diuretics			
Amiloride (Midamor)	5-10 mg PO	24 hours	Hyperkalemia when combined with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
Triamterene (Dyrenium)	50-100 mg PO	12 hours	

water to the distal nephron. They also decrease the tonicity of the medullary interstitium and thereby limit the osmotic reabsorption of free water from the collecting tubules. Currently available loop diuretics include furosemide, bumetanide, torsemide, and ethacrynic acid. Ethacrynic acid carries an increased risk of ototoxicity; therefore, this agent should be reserved for patients who are allergic to or intolerant of other agents.

Furosemide is the loop diuretic most commonly used for the treatment of heart failure. For patients with mild to moderate congestive symptoms, it can be given orally at initial doses of 20 to 40 mg daily. Its bioavailability ranges from 40% to 70%, and gradual dose titration is frequently required. Furosemide has a relatively short half-life. Once renal tubular levels of the drug decline, avid sodium reabsorption occurs throughout the nephron, potentially limiting or preventing effective natriuresis. A twice-daily dosing regimen may therefore be required to produce adequate salt and water loss. In patients with more severe volume retention or decompensated heart failure, intravenous administration of furosemide (20 to 100 mg) may produce a more rapid and effective diuresis. The maximum intravenous dose is 300 mg; however, the risk of ototoxicity increases at such high doses. For patients who require frequent high doses of intravenous furosemide, a continuous infusion may be used and may be associated with less hypotension; however, it does not appear to be any more effective at reducing symptoms or stimulating diuresis than are intermittent intravenous boluses. The infusion is usually started at 5 to 10 mg/hr and titrated as needed to obtain the desired effect. Bumetanide and torsemide have greater bioavailability than does furosemide ($\approx 80\%$) but have not demonstrated better efficacy and are significantly more expensive.

Thiazide diuretics act in the distal convoluted tubule, where they inhibit the $\text{Na}^+\text{-Cl}^-$ cotransporter. Their efficacy is dependent on the delivery of sodium to the distal nephron; therefore, their diuretic effect is limited by sodium reabsorption from more proximal regions, as occurs during intravascular volume depletion or in low-flow states. In addition, they are ineffective when glomerular filtration rates fall below 30 mL/min. Thiazides may be useful as the sole diuretic in treatment of mild congestive symptoms; however, their predominant role in the management of more advanced heart failure is as an adjunct to other diuretic therapy in patients who exhibit diuretic resistance. Although several thiazides are available, the most frequently used are hydrochlorothiazide (12.5 to 50 mg daily) and metolazone (2.5 to 10 mg daily). These agents exhibit synergism with loop diuretics and should be given approximately 30 minutes before administration of furosemide, bumetanide, or torsemide.

Spironolactone is a competitive inhibitor of aldosterone in the distal convoluted tubule, whereas eplerenone is a selective aldosterone blocker. These agents stimulate a mild natriuresis and potassium reabsorption and may be most effective in patients with advanced heart failure, in whom marked activation of the renin-angiotensin-aldosterone system results in aldosterone levels as high as 20 times normal. In the Randomized Aldactone Evaluation Study (RALES), patients with moderate to severe congestive heart failure (NYHA class III-IV) were treated

with spironolactone (25 to 50 mg daily) and had improved symptoms, reduced rates of hospitalization for heart failure, and 30% reduction in mortality. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), patients with acute myocardial infarction, left ventricular ejection fraction of 40% or less, and evidence of heart failure were treated with eplerenone (25 to 50 mg daily) and had a 15% reduction in mortality and significantly fewer episodes of heart failure. The mechanism of benefit of these agents is unlikely to be related to a diuretic effect because they are relatively weak diuretics. Rather, it probably reflects inhibition of aldosterone-induced myocardial fibrosis and ventricular remodeling. The major side effect of spironolactone is gynecomastia, which is not seen with eplerenone because of its selective mineralocorticoid blockade. The dose of these agents should not exceed 50 mg daily because of the risk of hyperkalemia, especially in patients with a serum creatinine concentration of 2.5 mg/dL or higher or when they are used in conjunction with an ACE inhibitor or ARB for the treatment of heart failure.

Amiloride and triamterene inhibit the reabsorption of sodium in the distal convoluted tubule and proximal collecting duct, resulting in a mild natriuresis and reduction of the ionic gradient required for potassium secretion into the urine. These agents produce a mild diuresis without the potassium wasting seen with loop diuretics and thiazides and may be effective for the control of mild congestive symptoms. However, when they are given alone, they are not effective in maintaining a negative fluid balance in patients with advanced heart failure. In such patients, these agents may provide benefit as part of a combination diuretic regimen, especially given their potassium-sparing properties.

Patients treated with diuretics require close monitoring of their renal function and serum electrolytes. Loop diuretics and thiazides can lead to profound hypokalemia and hypomagnesemia, especially when they are used in combination; spironolactone may result in hyperkalemia. In contrast to loop diuretics, thiazides do not alter the tonicity of the renal medullary interstitium and may produce significant hyponatremia as a result of the reabsorption of free water from the distal convoluted tubule in the face of a preserved interstitial gradient. In addition to these metabolic effects, thiazides may adversely affect serum lipid levels, and spironolactone may induce gynecomastia.

Vasodilators

Nitrovasodilators. Nitric oxide is formed by normal endothelial and smooth muscle cells throughout the vasculature and functions in both a paracrine and an autocrine fashion. Its primary mechanism of action involves an induced increase in intracellular cyclic guanosine monophosphate, which results in vascular smooth muscle relaxation. Nitrovasodilators such as sodium nitroprusside and organic nitrates (i.e., nitroglycerin) are metabolized to nitric oxide within the vasculature. They are potent vasodilators and, as such, are useful in the management of heart failure.

Nitroprusside is the sodium salt of nitric oxide and ferricyanide. It is a balanced vasodilator and produces both vasodilation and venodilation in both systemic and pulmonary systems. These effects result in favorable hemodynamic changes, including a decrease in right atrial and pulmonary capillary wedge pressures (i.e., decreased preload), a reduction in pulmonary and systemic vascular resistance (i.e., decreased afterload), and an increase in stroke volume and cardiac output/index (Fig. 58-2). In contrast to other arterial vasodilators, nitroprusside does not cause a significant increase in heart rate, and its use is usually associated with a decrease in myocardial oxygen demand. Nitroprusside is useful for the management of heart failure associated with elevated filling pressures, low cardiac output, and high vascular resistance, as occurs in patients with decompensated systolic failure. It is also ideally suited for the management of heart failure associated with profound hypertension, acute mitral regurgitation, acute aortic insufficiency, or acute ventricular septal defect.

Nitroprusside is administered as a continuous infusion. Its onset of action is rapid (within 30 seconds), and it reaches peak effect within 2 minutes. Similarly, its effects completely resolve within 3 minutes of discontinuation of its infusion. Because of these rapid changes in hemodynamics, it is best administered under the guidance of pulmonary (i.e., Swan-Ganz catheter) and systemic arterial monitoring. The usual starting dose is 0.1 to 0.25 $\mu\text{g}/\text{kg}/\text{min}$. The dose may be titrated up by 0.25 $\mu\text{g}/\text{kg}/\text{min}$ every 5 to 10 minutes until the desired effect is achieved or the maximum dose is reached (10 $\mu\text{g}/\text{kg}/\text{min}$). The use of nitroprusside may be limited by the development of hypotension, especially in patients with normal left ventricular systolic function or low filling pressures. Rapid cessation of nitroprusside may result in

rebound hypertension, probably reflecting neurohormonal activation. Nitroprusside is metabolized in the vasculature to nitric oxide and cyanide; cyanide is further metabolized in the liver to thiocyanate, which is excreted by the kidneys. Accumulation of these toxic metabolites is more likely to occur when nitroprusside is infused at higher doses or for prolonged periods, especially in the setting of hepatic and renal dysfunction. Cyanide toxicity may be manifested as abdominal pain, confusion, or seizure and is usually preceded by lactic acidosis. Thiocyanate toxicity usually manifests as nausea, confusion, fatigue, psychosis, and, in rare cases, coma. If toxicity is suspected, the infusion should be discontinued and serum levels of the metabolites should be measured. Cyanide toxicity can be treated with sodium nitrite (300 mg) or sodium thiosulfate (12.5 g), but thiocyanate toxicity may require hemodialysis.

Nitroglycerin, like nitroprusside, is a potent vasodilator; however, it has dose-dependent effects in the arterial and venous systems. At low doses, it is a relatively selective venodilator, resulting in increased venous capacitance and decreased left and right ventricular filling pressures. At higher doses, it is also an arterial dilator and results in a fall in pulmonary and systemic vascular resistance, although less predictably and to a lesser extent than nitroprusside. Intravenous nitroglycerin is an effective agent in the management of acute decompensated heart failure characterized by increased filling pressures and elevated vascular resistance. In addition, nitroglycerin has a significant vasodilative effect on epicardial coronary arteries and may indirectly improve left ventricular function by improving blood flow to ischemic myocardium. It is thus an agent of choice in managing heart failure associated with acute myocardial ischemia or infarction.

Intravenous nitroglycerin is usually initiated at 20 $\mu\text{g}/\text{min}$ and titrated up by 10 to 20 $\mu\text{g}/\text{min}$ every 5 to 10 minutes until the desired hemodynamic effect is achieved or the maximum dose is reached (400 $\mu\text{g}/\text{min}$). Its effects are immediate and resolve rapidly after discontinuation of the infusion. Nitroglycerin may result in hypotension, especially at high doses and in patients with low filling pressures. Its use is commonly associated with a headache, occasionally requiring down-titration or discontinuance of the infusion. Nitrate tolerance frequently develops but can usually be overcome by increasing the infusion rate.

Hydralazine. Hydralazine is a direct vasodilator that causes relaxation of arteriolar smooth muscle by an unknown mechanism. It does not cause venodilation or dilation of epicardial coronary arteries; thus, its hemodynamic effects are primarily limited to a reduction in vascular resistance. Hydralazine is an effective antihypertensive agent, especially when it is used in combination with other agents. When it is administered to patients with congestive heart failure, it is most effective in combination with venodilating agents (e.g., organic nitrates). The combination of hydralazine and oral nitrates, when it is added to a regimen of digoxin and diuretics, has been shown in randomized trials to reduce mortality, to improve left ventricular systolic function, and to reduce symptoms in patients with heart failure. However, the

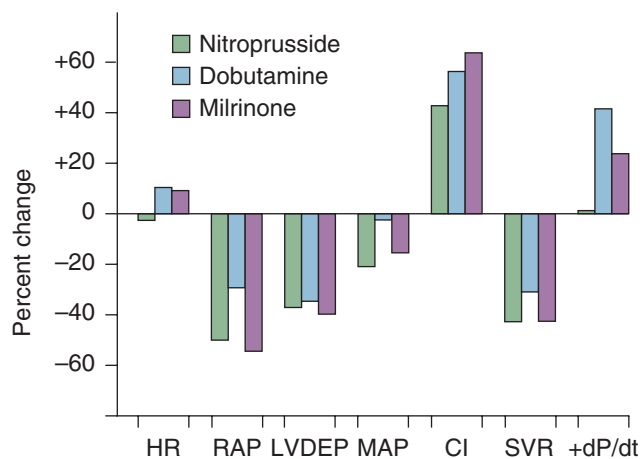


FIGURE 58-2 ■ Comparative hemodynamic effects of maximally tolerated doses of nitroprusside, dobutamine, and milrinone in patients with severe heart failure. CI, Cardiac index; dP/dt, change in pressure per change in time; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; MAP, mean arterial pressure; RAP, right atrial pressure; SVR, systemic vascular resistance. (Modified from Colucci WS, Wright RF, Jaski BE, et al: Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. *Circulation* 73:11175-183, 1986.)

benefit of this regimen on mortality and left ventricular function is less than that of ACE inhibitors. In general, hydralazine is not a first-line agent for the treatment of heart failure. Nonetheless, it should be considered in patients who are intolerant of ACE inhibitors because of allergy or renal insufficiency, and it is the agent of choice for afterload reduction in pregnant patients. In addition, it may offer further relief in patients with heart failure who remain symptomatic despite treatment with ACE inhibitors.

Hydralazine therapy is initiated at a dose of 10 mg four times daily and titrated upward as blood pressure tolerates to a maximum dose of 100 mg four times daily. Organic nitrates are given concurrently (i.e., isosorbide dinitrate, 30 to 120 mg daily). Hydralazine-induced vasodilation is associated with a baroreceptor-mediated increase in sympathetic activity, resulting in a reflex tachycardia, increased ventricular contractility, increased renin activity, and fluid retention. In patients with underlying coronary artery disease, the arteriolar dilation may result in a coronary steal phenomenon and, combined with the tachycardia, may precipitate myocardial ischemia. Coadministration with β -adrenergic blocking agents may prevent this complication; nonetheless, hydralazine should be used with caution in patients with an ischemia cardiomyopathy. Other side effects occur more frequently and include headaches, flushing, palpitations, nausea, and dizziness. A lupus-like syndrome occurs in 5% to 10% of patients and may require discontinuation of the drug.

Calcium Channel Blocking Agents. In general, the use of calcium channel blocking agents for the treatment of heart failure has been disappointing, despite the fact that they are relatively potent vasodilators. Verapamil and diltiazem have negative inotropic effects and may worsen symptoms in patients with systolic heart failure. However, these agents may improve diastolic function because of their rate-slowing effects and induced alterations in calcium homeostasis and thus may be beneficial in the treatment of diastolic heart failure. The first-generation dihydropyridine nifedipine has been associated with an increase in adverse effects, including a trend toward increased mortality in patients with systolic heart failure. This may relate to neurohormonal activation resulting from fluctuations in its hemodynamic effects, especially with short-acting formulations. Newer second-generation dihydropyridines, such as amlodipine and felodipine, appear to be safe in patients with heart failure but have not demonstrated significant benefit with regard to morbidity or mortality. Therefore, although these agents could be considered for the treatment of hypertension or angina in patients with left ventricular systolic dysfunction, calcium channel blocking agents in general should not be used for primary treatment of heart failure.

Neurohormonal Inhibiting Agents

Angiotensin-Converting Enzyme Inhibitors. ACE inhibitors have a variety of beneficial effects on the pathophysiologic mechanism of heart failure. Hemodynamically, ACE inhibitors are potent vasodilators and

reduce both preload and afterload. The subsequent fall in intracardiac pressures and reduction in wall stress result in a decrease in myocardial oxygen demand, potentially reducing ischemia, and a decrease in the activity of the sympathetic nervous system, thereby reducing electrical instability. In addition, the ACE inhibitor-induced reduction in angiotensin as well as the subsequent reduction in adrenal aldosterone release may have direct effects on the extent of fibrosis and collagen deposition that characterize myocardial remodeling in heart failure. The effects of ACE inhibitors are primarily mediated by inhibition of the enzyme responsible for the conversion of angiotensin I to angiotensin II, thereby decreasing production of angiotensin II. However, some of the benefit of ACE inhibitors may result from their effects on the kinin system; ACE inhibitors decrease the degradation of kinins (e.g., bradykinin) and thereby enhance their vasodilative effects and potentiate kinin-mediated synthesis of vasodilative prostaglandins.

ACE inhibitors have been extensively studied in a wide variety of patients with heart failure and have almost universally demonstrated benefit in hemodynamics, symptoms, exercise capacity, hospitalization, and mortality. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), patients with severe (NYHA class IV) systolic heart failure who were already treated with digoxin and diuretics had a 40% reduction in mortality at 6 months when treated with enalapril. Patients with less-severe heart failure (NYHA class II-III and an ejection fraction $\leq 35\%$) were studied in the treatment arm of the SOLVD (Studies Of Left Ventricular Dysfunction) trial. In this trial, patients who were treated with enalapril had a 16% reduction in mortality and a 26% reduction in the risk of death or hospitalization for worsening heart failure. In the Acute Infarction Ramipril Efficacy study, patients with symptomatic heart failure, a recent myocardial infarction, and ejection fractions below 40% demonstrated a 27% decrease in mortality after 30 days of treatment with ramipril. Furthermore, several studies have demonstrated that asymptomatic patients with depressed ejection fractions ($<35\%$ to 40%) have reduced morbidity and mortality when treated with ACE inhibitors, although the magnitude of this benefit is less than that seen in patients with overt heart failure. Thus, the results of clinical trials with ACE inhibitors reveal a consistent benefit in patients with symptomatic heart failure or asymptomatic left ventricular dysfunction (Fig. 58-3).

The various ACE inhibitors that are currently available (Table 58-6) differ in plasma half-life, dosing regimen, and ability to inhibit ACE at the tissue level. However, available data suggest that the beneficial effects of these agents are a class effect and not dependent on individual pharmacologic characteristics. Nonetheless, in selecting an ACE inhibitor for the treatment of heart failure, preference should be given to those agents that have demonstrated efficacy in large-scale trials (enalapril, captopril, lisinopril, and ramipril). ACE inhibitors should be initiated at low doses, especially in patients with hypotension before treatment. If initial doses are tolerated hemodynamically, the dose should be gradually titrated upward over several days to several weeks. In general,

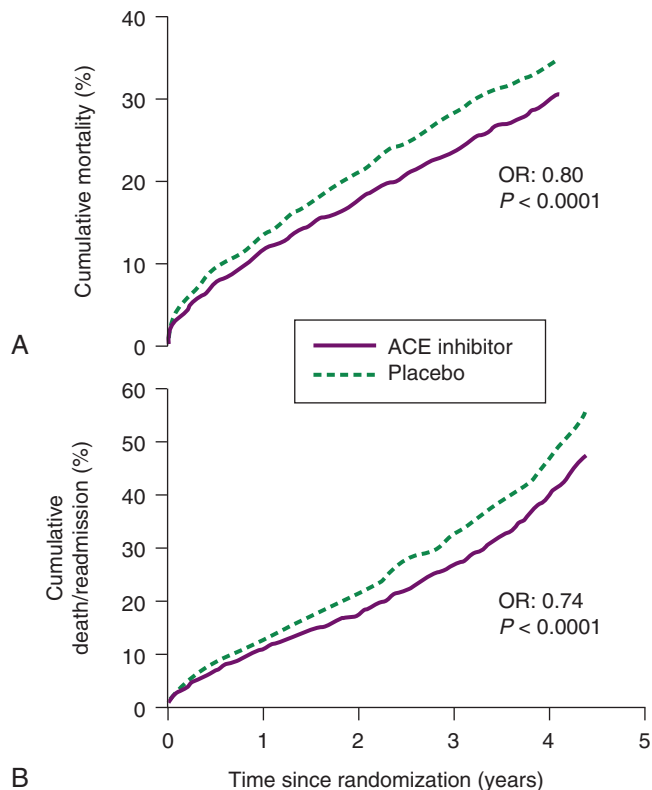


FIGURE 58-3 ■ The effect of angiotensin-converting enzyme (ACE) inhibitors on the total mortality (**A**) and total mortality plus readmission for heart failure (**B**) in patients with heart failure or left ventricular systolic dysfunction. OR, Odds ratio. (Modified from Flather MD, Yusuf S, Kober L, et al: Long-term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 355:1575–1581, 2000.)

these agents should be titrated upward to goal doses as determined by clinical trials or to the highest dose that can be tolerated. Although lower doses may offer mortality benefit similar to that of higher doses, higher doses are associated with augmented symptom control. In patients with decompensated heart failure who cannot receive oral agents, intravenous enalaprilat can be used. Enalaprilat is the active form of the oral ACE inhibitor enalapril. When it is given intravenously, it is a balanced vasodilator resulting in a reduction in left and right ventricular filling pressures and vascular resistance.

Use of ACE inhibitors may be limited by the development of side effects. Hypotension is the most common adverse effect, occurs most frequently during the initiation of therapy, and is more common in patients who are volume depleted. It can usually be managed by reducing diuretic dosing and titrating the ACE inhibitor slowly. Moderate hypotension (systolic blood pressure >85 mm Hg) can frequently be tolerated as long as organ hypoperfusion is not present. ACE inhibitors produce vasodilation of renal efferent arterioles and thereby reduce glomerular filtration rate. Worsening renal function can be seen in 5% to 30% of patients treated with these agents; the risks are significantly higher in patients with more severe heart failure and in those with bilateral renal artery stenosis. Hyperkalemia may also occur, even in the

absence of declining renal function. At least 5% to 10% of patients treated with ACE inhibitors develop a dry, nonproductive cough. This probably results from the inhibition of bradykinin metabolism and resolves with cessation of the drug. Less than 1% of patients develop angioedema when they are treated with ACE inhibitors. This can be life-threatening and precludes further use of the drug. Both the efficacy and side effect profile of ACE inhibitors are affected by volume status, and careful monitoring of volume and appropriate diuretic dosing are important. Volume overload will blunt the therapeutic effects of ACE inhibitors, and whereas dietary sodium restriction may enhance the response to ACE inhibitors, volume depletion will exaggerate their hypotensive effects.

Angiotensin Receptor Blocking Agents. ARBs differ from ACE inhibitors in that they inhibit the binding of angiotensin to its receptor rather than block its production. Theoretically, ARBs should be more effective at inhibiting the renin-angiotensin-aldosterone system because they block angiotensin produced by both ACE and non-ACE pathways; however, clinical trials of ARB therapy in heart failure have not demonstrated consistent superiority over ACE inhibitors. A meta-analysis of 17 trials comprising more than 12,000 patients demonstrated that ARBs were not superior to ACE inhibitors in reducing morbidity or mortality of patients with heart failure, although they appeared to be beneficial in patients who are not already taking ACE inhibitors. The results of the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trials have shed more light on this subject. These studies revealed that in patients with class II–IV heart failure and left ventricular ejection fraction of 40% or lower, treatment with the ARB candesartan resulted in clinically important reductions in mortality and hospitalization for heart failure. Importantly, the benefit was seen in patients who were intolerant of ACE inhibitors. Furthermore, in patients who were already receiving an optimal dose of an ACE inhibitor, the addition of candesartan produced additive clinical benefit.

ARBs have a risk of hypotension, renal dysfunction, and hyperkalemia similar to that of ACE inhibitors, and combination ARB and ACE inhibitor therapy is associated with an increased incidence of these adverse effects. The risk of angioedema appears to be decreased with ARBs compared with ACE inhibitors. In addition, because ARBs do not affect the kinin system, the incidence of cough is significantly less than that with ACE inhibitors. In general, ARBs are not yet considered first-line therapy for heart failure; however, they are a reasonable alternative in patients who are intolerant of ACE inhibitors because of the development of a persistent cough or angioedema and should be considered additive therapy in patients with persistent heart failure symptoms despite ACE inhibitor use.

β -Adrenergic Blocking Agents. The recent understanding of heart failure not only as a hemodynamic syndrome related to left ventricular systolic dysfunction but as a state of adverse neurohormone-mediated remodeling

TABLE 58-6 Oral Agents Commonly Used in the Treatment of Heart Failure

Class and Examples	Starting Dose	Target or Maximum Dose	Adverse Effects (by Class)
Nitrovasodilators			
Isosorbide mononitrate (Imdur)	30 mg qd	120 mg qd	Headache; nitrate tolerance with continuous use
Isosorbide dinitrate	10 mg tid	30 mg tid	
Direct-Acting Vasodilators			
Hydralazine (Apresoline)	10 mg qid	100 mg qid	Reflex tachycardia, lupus-like syndrome
Angiotensin-Converting Enzyme Inhibitors			
Captopril (Capoten)	6.25 mg tid	50 mg tid	Hypotension, cough, rash, angioedema, hyperkalemia
Enalapril (Vasotec)	2.5 mg bid	20 mg bid	
Lisinopril (Zestril, Prinivil)	2.5 mg qd	40 mg qd	Renal dysfunction (especially in patients with bilateral renal artery stenosis)
Ramipril (Altace)	2.5 mg qd	10 mg qd	
Quinapril (Accupril)	10 mg bid	40 mg qd	
Fosinopril (Monopril)	10 mg qd	40 mg qd	
Trandolapril (Mavik)	0.5 mg qd	8 mg qd	
Angiotensin Receptor Blockers			
Losartan (Cozaar)	50 mg qd	100 mg qd	Hyperkalemia
Candesartan (Atacand)	4 mg qd	32 mg qd	Renal dysfunction (especially in patients with bilateral renal artery stenosis)
Valsartan (Diovan)	80 mg qd	320 mg qd	
β-Adrenergic Blocking Agents			
Carvedilol (Coreg)	3.125 mg bid	25 mg bid	Bradycardia, hypotension, bronchospasm May worsen heart failure during initiation and titration
Metoprolol (Toprol XL)	25 mg qd	200 mg qd	
Bisoprolol (Zebeta)	1.25 mg qd	10 mg qd	
Inotropic Agents			
Digoxin (Lanoxin)	0.125 mg qd	Serum digoxin level: 0.5-0.8 ng/mL	Nausea, bradycardia, heart block, ventricular tachyarrhythmias
Calcium Channel Blockers*			
Amlodipine (Norvasc)	2.5 mg qd	10 mg qd	Amlodipine: pedal edema Verapamil and diltiazem: bradycardia, worsened systolic heart failure
Verapamil (Calan, Verelan)	120 mg qd	480 mg qd	
Diltiazem (Cardizem, Dilacor)	120 mg qd	540 mg qd	

*Calcium channel blockers should not be routinely used for the treatment of systolic heart failure. Although amlodipine is safe in this setting, verapamil and diltiazem may worsen systolic heart failure, and their use is limited to the treatment of diastolic heart failure.

has prompted extensive investigation into the use of beta-blocking agents in the treatment of heart failure. Basic studies have shown that these agents can inhibit the adverse effects of norepinephrine on the myocardium and result in upregulation of cardiac β -adrenergic receptors. The long-term administration of these agents is associated with a reversal of left ventricular remodeling, resulting in a decrease in left ventricular volume and an increase in ejection fraction with concomitant improvement in hemodynamics.

Large clinical trials encompassing more than 10,000 patients have demonstrated that these effects translate into significant clinical benefit. Although the enrollment criteria and the specific beta-blocking agent used varied among the trials, they all included patients with systolic heart failure (left ventricular ejection fraction of <35% to 45%) who were already being treated with a regimen of an ACE inhibitor and a diuretic, with or without digoxin. In sum, these trials demonstrated an approximately 35% reduction in mortality and 40% reduction in hospitalization due to heart failure in patients treated with beta-blocking agents. In addition, treatment with beta blockers reduces symptoms of heart failure and improves exercise capacity, although these effects may not be evident for several weeks or months after initiation of treatment (Fig. 58-4).

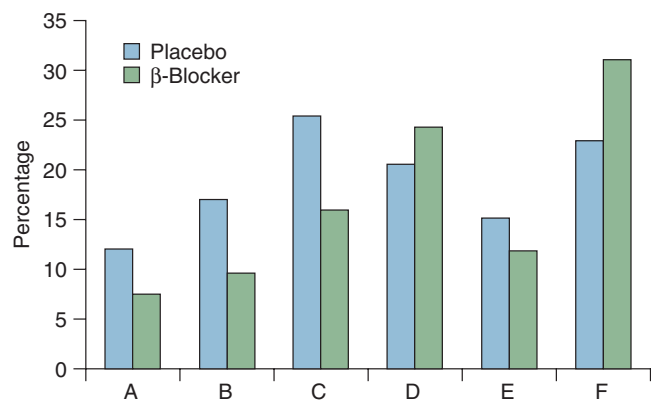


FIGURE 58-4 The effect of beta blocker therapy on clinical endpoints in patients with heart failure. Data from trials using metoprolol, carvedilol, bucindolol, and nebivolol. **A**, All-cause mortality; **B**, hospitalization for heart failure; **C**, combination of A and B; **D**, improved NYHA class; **E**, deteriorated NYHA class; **F**, left ventricular ejection fraction (LVEF). LVEF was measured after at least 5 months of therapy and reflects an unweighted mean increase of 29% with beta blocker therapy. (Modified from Lechat P, Packer M, Chalon S, et al: Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 98: 1184-1191, 1998.)

Three beta-blocking agents are currently approved by the Food and Drug Administration for the treatment of systolic heart failure: metoprolol, carvedilol, and bisoprolol. Metoprolol and bisoprolol are β_1 receptor specific; carvedilol inhibits the β_1 , β_2 , and α_1 receptors and has both vasodilative and antioxidant properties. The absolute magnitude of benefit is similar with these agents, and current trial data are inadequate to support use of one agent over another. Beta blocker therapy for heart failure should be initiated at lower doses than is routinely used for the treatment of hypertension or angina and gradually titrated upward to doses that have demonstrated benefit in clinical trials (see [Table 58-6](#)).

Use of beta-blocking agents can be associated with significant adverse effects in patients with heart failure. The renal hemodynamic effect of these agents may result in volume retention, which in combination with their negative inotropic effect may cause an initial worsening of heart failure symptoms. This adverse effect is more common in patients who are volume overloaded before beta blocker therapy and usually responds to an increase in diuretic dose. Hypotension is frequently seen after the initiation of beta blockers and may limit use of these agents. This effect is more pronounced with carvedilol because of its peripheral vasodilating effects and can usually be managed with a reduction in dose or changing to a β_1 receptor-specific agent. Other frequent side effects include fatigue and bradycardia, both of which can usually be managed with reduction of the dose of beta blocker or discontinuation of other atrioventricular nodal blocking agents (e.g., digoxin). Given the strength of the data supporting their use, beta blockers should be administered to all patients with systolic heart failure who do not have a contraindication to their use. Nonetheless, beta blockers should be avoided in patients with decompensated heart failure, symptomatic hypotension, or significant resting bradycardia or heart block in the absence of a permanent pacemaker.

Inotropic Agents

Digoxin. Digoxin is a cardiac glycoside and, as such, is a selective inhibitor of the membrane-bound Na^+/K^+ -ATPase. The binding of digoxin to this enzyme results in increased intracellular calcium with a resultant augmentation of myocardial contractility. In general, the overall effect on global left ventricular systolic function is relatively small, with an average absolute increase in ejection fraction of 1% to 2%. Digoxin also affects the cardiac conduction system through increases in vagal tone and decreases in sympathetic tone. This results in decreased automaticity of the atria and atrioventricular nodal tissues and prolongation of the refractory period and reduction in conduction velocity of the atrioventricular node. The net result is a slowing of the atrial rate and blockade of the atrioventricular node.

Several clinical trials have evaluated the role of digoxin in the treatment of patients with heart failure. The Prospective Randomized Study Of Ventricular Failure and Efficacy of Digoxin (PROVED) and the Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) trials studied the

effects of withdrawal of digoxin from clinically stable patients with class II or class III heart failure and systolic dysfunction. They found that withdrawal of digoxin was associated with a significant worsening of heart failure symptoms and deterioration of functional capacity. The Digitalis Investigation Group (DIG) trial evaluated the effect of starting digoxin in patients with systolic heart failure who were already receiving therapy with diuretics and ACE inhibitors. In this trial, digoxin use was associated with a decrease in the risk of hospitalization for heart failure but no change in overall mortality. Thus, digoxin can no longer be considered a first-line therapy for patients with heart failure; however, it appears useful in patients who remain symptomatic despite therapy with other agents. In this setting, the serum digoxin level should be maintained at 0.5 to 0.8 ng/mL; higher doses may be associated with adverse outcomes.

Digoxin may also be useful in the control of supraventricular arrhythmias in patients with depressed left ventricular systolic function. When it is used in this setting, digoxin may be given as an initial load (0.25 mg orally or intravenously every 8 hours for 24 hours) followed by a single daily dose of 0.125 mg or 0.25 mg. When it is used for the treatment of heart failure, there is little value in a loading dose, and once-daily dosing is appropriate. Digoxin is excreted unchanged by the kidney, and its dose must be adjusted in the setting of renal failure. It has a relatively narrow therapeutic window, and intermittent monitoring of its serum level is required. Higher serum digoxin levels (>2.0 ng/mL) are associated with an increased risk of toxic side effects ([Table 58-7](#)), especially in the presence of hypokalemia or hypomagnesemia. Mild digoxin toxicity (ectopic beats, first-degree atrioventricular block, gastrointestinal symptoms) may only require withholding of the drug. More severe toxicity (profound bradycardia, high-degree atrioventricular block, ventricular tachyarrhythmias) requires administration of digoxin-specific antibodies. Hemodialysis is ineffective for the treatment of digoxin toxicity.

Dopamine. Dopamine is the immediate metabolic precursor of epinephrine and norepinephrine. It is an endogenous catecholamine that functions as an essential neurotransmitter and is involved in the central regulation of movement and in the regulation of the cardiovascular system. Exogenously administered dopamine does not

TABLE 58-7 Signs and Symptoms of Digoxin Toxicity

Nausea, vomiting, abdominal pain
Anorexia
Fatigue, malaise
Confusion, delirium
Visual changes (yellow vision, halo around visual field)
First-, second-, or third-degree heart block
Excessively low ventricular rate in atrial fibrillation
Paroxysmal atrial tachycardia (classically with associated heart block)
Premature ventricular depolarizations
Ventricular tachycardia

cross the blood-brain barrier, and thus its effects are predominantly cardiovascular. The cardiovascular response to dopamine infusion is mediated by dopaminergic, β -adrenergic, and α -adrenergic receptors. At low doses (1 to 2 $\mu\text{g/kg/min}$), dopamine binds to dopaminergic receptors in the renal, mesenteric, and peripheral vasculature, stimulating a rise in intracellular cyclic adenosine monophosphate (cAMP) and inducing vasodilation in these beds. Although it produces a mild fall in systemic vascular resistance, its main effect is to increase glomerular filtration rate, renal blood flow, and renal sodium excretion, thereby augmenting urine output. At intermediate doses (2 to 5 $\mu\text{g/kg/min}$), dopamine induces the release of norepinephrine from sympathetic nerve terminals in the heart and directly stimulates cardiac β_1 -adrenergic receptors. This results in positive inotropic and chronotropic effects, augmenting cardiac output and causing tachycardia. Although intermediate-dose dopamine may be associated with increased systolic blood pressure, the systemic vascular resistance is usually unchanged because of renal and splanchnic vasodilation. At high doses of dopamine (5 to 15 $\mu\text{g/kg/min}$), α -adrenergic stimulation occurs, resulting in generalized vasoconstriction. A further rise in systolic blood pressure results; however, this occurs in association with an increase in systemic vascular resistance, which may suppress left ventricular systolic function because of the increase in afterload. In addition, at high doses, the α -adrenergic effects overcome the vasodilative effects in the renal and splanchnic vessels, and renal blood flow and urine output may decline.

The varied hemodynamic effects of dopamine make it a potentially useful agent for the treatment of heart failure in a variety of clinical settings. In the patient with congestion and oliguria but with adequate blood pressure, low-dose dopamine increases renal blood flow, thereby improving renal function, and augments urine output, thereby decreasing ventricular filling pressures. In the patient with cardiogenic shock, higher-dose dopamine is useful to maintain an adequate blood pressure. When the higher doses are used, patients must be monitored closely for signs of worsening heart failure; placement of a pulmonary arterial catheter is helpful in this regard. Although the increased systemic vascular resistance may be partially offset by the increase in cardiac contractility, in many patients, the ventricular filling pressures rise as a result of increased afterload. In addition, the venoconstricting effects augment venous return, thereby increasing ventricular preload. For these reasons, dopamine is not routinely used alone for inotropic support of the failing heart. Rather, for the treatment of patients with congestive heart failure, dopamine is often combined with another inotrope (e.g., dobutamine) or vasodilator (e.g., nitroprusside).

Although dopamine may have beneficial effects in some patients with congestive heart failure, there are few data to suggest an improvement in long-term outcomes. The use of dopamine is often limited by the development of tachycardia, which may precipitate ischemia in patients with coronary artery disease. Both supraventricular and ventricular arrhythmias may occur. In addition, dopamine may cause nausea, vomiting, and headaches

and may precipitate myocardial ischemia. Marked vasoconstriction may result in digital gangrene, especially in patients with peripheral vascular disease, and ischemic skin necrosis may occur at sites of cutaneous infiltration.

Dobutamine. Dobutamine is a synthetic catecholamine that acts by direct stimulation of α - and β -adrenergic receptors and is available as a racemic mixture of its (+) and (–) stereoisomers. The (–) isomer is a potent α_1 receptor agonist and a relatively weak β_1 receptor agonist. The (+) isomer is a potent β_1 and β_2 receptor agonist and an α_1 receptor antagonist. The net effect is relatively selective β_1 receptor stimulation, resulting in augmentation of contractility and increased cardiac output (see Fig. 58-2). In contrast to the hemodynamic effects of dopamine, the inotropic effect of dobutamine is associated with relatively little increase in heart rate and with a modest reduction in left ventricular filling pressure and peripheral resistance. The latter effect results from β_2 receptor-mediated vasodilation. Dobutamine does not bind to dopamine receptors; thus, it does not result in renal or splanchnic vasodilation. Nonetheless, renal blood flow may increase as a reflection of increased cardiac output.

The hemodynamic effects of dobutamine make it an ideal agent for the treatment of decompensated heart failure, either alone or in combination with other inotropic or vasodilating agents. Dobutamine is usually started at a dose of 2.5 $\mu\text{g/kg/min}$ and up-titrated in increments of 2.5 $\mu\text{g/kg/min}$ as needed until an adequate therapeutic effect is obtained, adverse effects occur, or the maximum therapeutic dose is reached (15 to 20 $\mu\text{g/kg/min}$). Patients with more advanced heart failure may have a greater degree of β -receptor downregulation and require higher initial doses of dobutamine. Patients receiving chronic beta blocker therapy may initially have relatively little inotropic response to dobutamine but a moderate vasopressor response resulting from the unmasking of α_1 -adrenergic vasoconstriction in the presence of β -receptor blockade.

If an adequate therapeutic response is not achieved despite maximal doses of dobutamine, a second agent should be added. For patients with increased ventricular filling pressures and adequate systolic blood pressure, the addition of a diuretic and a vasodilator (such as nitroprusside) should be considered. Alternatively, a phosphodiesterase inhibitor such as milrinone (see later) may be of value in this setting by further augmenting cardiac output and vasodilation. Patients with congestive heart failure associated with hypotension may require the addition of a vasopressor (i.e., high-dose dopamine) to augment blood pressure and to allow effective diuresis.

Dobutamine has proved an effective agent in the management of hospitalized patients with congestive heart failure. Intermittent administration of dobutamine to outpatients with severe heart failure has been associated with increased risk of death and should be avoided. Continuous infusions of dobutamine are usually well tolerated for up to several days, although tolerance may develop and limit the efficacy of longer term infusion. Dobutamine administration is occasionally limited by the

development of excess tachycardia; however, it is not uncommon to see a slight fall in the heart rate after dobutamine infusion as a result of withdrawal of sympathetic tone as the patient's hemodynamic status improves. Patients with a prior history of hypertension may have a marked hypertensive response to dobutamine; those with volume depletion may become hypotensive as a result of mild vasodilation. Like dopamine, dobutamine may precipitate atrial and ventricular arrhythmias and may aggravate myocardial ischemia.

Phosphodiesterase Inhibitors. Phosphodiesterase (PDE) is a membrane-bound enzyme that breaks down cAMP. It exists in several forms; PDE type 3 is the predominant isoform in cardiovascular tissue. Milrinone and amrinone inhibit this enzyme and thereby result in increased cytosolic cAMP. This in turn results in increased myocardial contractility and augmentation of cardiac output. In the vasculature, these agents are potent vasodilators and venodilators, resulting in reductions in systemic and pulmonary vascular resistance (afterload) and in right- and left-sided filling pressures (preload).

The mixed hemodynamic effects of PDE inhibitors distinguish them from other inotropes or vasodilators. Compared with dobutamine, milrinone produces a greater reduction in systemic vascular resistance for a given increase in cardiac output. Similarly, compared with nitroprusside, milrinone produces a greater increase in cardiac output for a given reduction in systemic vascular resistance (Fig. 58-5). Thus, PDE inhibitors may be useful for the management of patients with decompensated heart failure that is characterized by reduced cardiac output, elevated systemic vascular resistance, and elevated filling pressures. PDE inhibitors also have antiplatelet effects and cause dilation of epicardial coronary arteries and bypass grafts. These properties, combined with the previously noted reductions in pulmonary arterial pressure and pulmonary vascular resistance, have

given these agents an important role in the hemodynamic support of patients after cardiac surgery.

Amrinone (now renamed inamrinone) is less selective for the PDE3 isoenzyme, has a longer elimination half-life (2 to 3 hours vs. 30 to 60 minutes), and is approximately 10-fold less potent than milrinone. In addition, it has been associated with significant thrombocytopenia in 10% of patients in whom it is administered. For these reasons, amrinone has fallen out of favor and milrinone has become the PDE inhibitor of choice for the management of decompensated heart failure. Milrinone is given as an initial loading dose (50 $\mu\text{g/kg}$ over 10 minutes) followed by a continuous infusion (0.25 to 1.0 $\mu\text{g/kg/min}$). It is excreted predominantly by the kidney; in patients with renal failure, a 50% reduction in the infusion rate is required. Titration may be limited by the development of tachycardia and arrhythmias, both of which are mediated by the increase in cAMP. Because of the potent vasodilative properties of PDE inhibitors, they should be used with care in patients who have normal or low vascular resistance or filling pressures. These patients may be intolerant of the vasodilation, and marked hypotension may result.

Clinical trials have demonstrated the efficacy of intravenous milrinone in improving hemodynamics and reducing symptoms in hospitalized patients with decompensated heart failure. However, a mortality benefit has not been demonstrated, and when milrinone is administered routinely to patients with less-severe congestive heart failure (i.e., no evidence of end-organ hypoperfusion), it does not appear to offer benefit over usual treatment with ACE inhibitors and diuretics.

Other Agents

Natriuretic Peptides

Natriuretic peptides are naturally occurring peptides that are produced in low levels in the normal heart. Atrial natriuretic peptide (ANP) is produced in the atria, whereas brain natriuretic peptide (BNP; originally isolated from porcine brain tissue) is produced in the ventricles. In patients with heart failure, both ANP and BNP are secreted at high levels in response to increased intracardiac pressure and volume. These peptides act through a receptor-mediated guanosine monophosphate pathway in vascular smooth muscle cells and are degraded by neutral endopeptidase. They have potent balanced vasodilating actions resulting in decreased ventricular preload and afterload. In the kidney, these peptides cause vasodilation of the afferent arteriole, thereby increasing glomerular filtration rate, and inhibit sodium reabsorption in the renal collecting ducts and aldosterone secretion by the adrenal glands, thereby resulting in natriuresis and diuresis.

Nesiritide is a recombinant peptide that is identical to endogenous BNP and has both vasodilatory and natriuretic properties. In addition, it antagonizes the renin-angiotensin-aldosterone system. When it is administered to patients with heart failure, nesiritide reduces right atrial and pulmonary capillary wedge pressures, decreases systemic vascular resistance, increases cardiac output, and

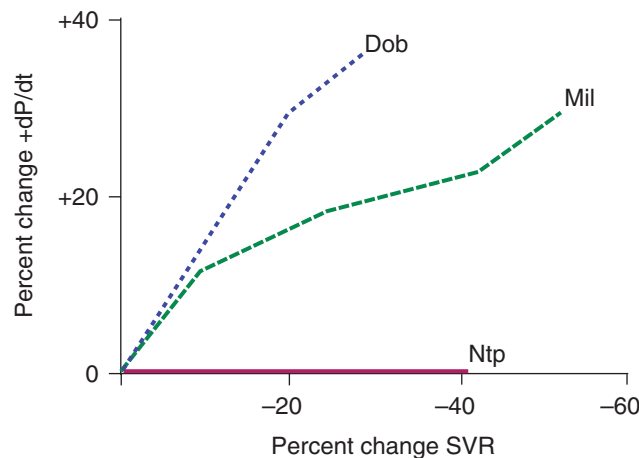


FIGURE 58-5 ■ The relative effects of varying doses of nitroprusside (Ntp), dobutamine (Dob), and milrinone (Mil) on the peak positive change in pressure per change in time (dP/dt) and systemic vascular resistance (SVR). (Modified from Colucci WS, Wright RF, Jaski BE, et al: Milrinone and dobutamine in severe heart failure: differing hemodynamic effects and individual patient responsiveness. *Circulation* 73:11175–183, 1986.)

produces diuresis and natriuresis. Clinical studies have demonstrated persistent hemodynamic effects of prolonged (24- to 48-hour) infusions and improvements in clinical status that may be greater than those seen with intravenous nitroglycerin. Nesiritide is usually given as an initial bolus of 2 µg/kg followed by an infusion of 0.01 µg/kg/min. Its hemodynamic effects are apparent within 15 minutes and persist for up to 4 hours after discontinuation of the infusion. Nesiritide does not aggravate arrhythmias and has no toxic metabolites; however, significant and prolonged hypotension can occur with this agent and is the most common limiting factor. Furthermore, several recent meta-analyses have suggested an increased risk of death and worsened renal function after administration of nesiritide to patients with acutely decompensated heart failure. Thus, the use of nesiritide should be limited to the treatment of decompensated congestive heart failure characterized by volume overload and increased filling pressures in patients who are intolerant of inotropic agents and resistant to usual diuretics.

APPROACH TO THE MANAGEMENT OF HEART FAILURE

Initial Approach and Clinical Assessment

The treatment of heart failure is dependent on its recognition. Because heart failure may manifest in a variety of ways, the clinician must maintain a high index of suspicion, especially in the patient with a prior history of heart failure or with risk factors for the development of heart failure. Acute heart failure usually manifests dramatically with signs and symptoms of pulmonary and systemic congestion, at times associated with evidence of hypoperfusion (Table 58-8). In this setting, the clinical examination is usually striking and the diagnosis is rarely overlooked. Conversely, chronic heart failure may have a more indolent course, and the associated dyspnea, fatigue, and edema may be mistaken for other noncardiac conditions.

TABLE 58-8 Signs and Symptoms of Heart Failure

Evidence of Congestion	Evidence of Hypoperfusion
Symptoms	
Orthopnea	Fatigue, weakness
Dyspnea on exertion	Confusion
Paroxysmal nocturnal dyspnea	Symptomatic hypotension
Anorexia, nausea	
Signs	
Pulmonary rales	Cool extremities
Elevated jugular venous pressure	Mottled extremities
Hepatojugular reflux	Narrowed pulse pressure
Edema	Worsening renal insufficiency
Ascites	Progressive hyponatremia
Loud S ₃	Cheyne-Stokes respirations

In addition, the physical examination of patients with chronic heart failure may be somewhat misleading in that they often have clear lung fields despite having significantly elevated filling pressures.

The initial evaluation of the patient with heart failure should include an assessment of the disease severity. The most common classification in this regard is that devised by the New York Heart Association (see Table 58-2), which categorizes patients with symptomatic heart failure on the basis of their functional level. A broader classification scheme has recently been proposed by the American College of Cardiology/American Heart Association and includes patients with structurally normal hearts but at risk for development of heart failure (stage A), those with asymptomatic structural heart disease (stage B), those with overt heart failure (stage C), and those with severe heart failure that requires specialized care such as mechanical assistance or transplantation (stage D). Although the functional class may vary over time, these classifications remain useful because they provide an objective measure by which to follow disease progression and response to therapy. The choice of specific therapies is, in part, additionally dependent on disease severity. Patients with severe decompensated heart failure require the rapid administration of intravenous pharmacologic therapy to reduce pulmonary congestion, to augment perfusion of vital organs, and to attain hemodynamic stability. Conversely, patients with chronic compensated heart failure can frequently be treated with oral medications with the goal of controlling symptoms, improving functional capacity, and reducing long-term mortality.

In addition to the initiation of pharmacologic therapy, the initial approach to the care of the patient with heart failure should always include a thorough evaluation of the cause of heart failure and a careful search for aggravating or precipitating factors (Table 58-9). Although the history and physical examination may provide clues to the underlying cardiac abnormality, a formal assessment of cardiac function by echocardiography should be performed in all patients with new or significantly worsened heart failure. This test permits identification and characterization of pericardial, myocardial, and valvular disease and allows the quantification of left ventricular systolic and diastolic function. Initial laboratory evaluation should also include a chest radiograph (to assess cardiac size, pulmonary

TABLE 58-9 Potential Aggravating Factors Contributing to Decompensation in Chronic Heart Failure

Myocardial ischemia or infarction
Systemic hypertension
Tachyarrhythmias (ventricular or supraventricular)
Superimposed valvular heart disease
Exacerbation of underlying lung disease
Pulmonary embolism
Infection
Thyroid disease
Anemia
Medication noncompliance
Dietary indiscretions (excessive salt and water intake)
Excessive alcohol use

congestion, and structural intrathoracic abnormalities), electrocardiogram (to evaluate for evidence of ischemic heart disease or ventricular hypertrophy), complete blood count, electrolyte values, thyroid function tests, and assessment of renal function.

All patients with heart failure should be counseled about lifestyle modifications that may help alleviate their symptoms. This includes moderate sodium restriction (≤ 2 g sodium daily); compliance with treatment regimens; and avoidance of alcohol, cigarettes, and nonsteroidal anti-inflammatory agents. Most heart failure patients do not require fluid restriction, but close monitoring of weight is essential for the early recognition of volume retention.

Pharmacologic Treatment of Chronic Compensated Systolic Heart Failure

Patients with chronic compensated heart failure represent a spectrum of patients ranging from those with asymptomatic left ventricular dysfunction to those with previously decompensated heart failure who have responded to medical therapy. The goals of treatment in this population include maintenance of a symptom-free state, improvement in functional capacity, prevention of decompensation, and reduction of mortality. Several individual classes of medications have proven efficacy in this regard (Table 58-10), although in general, most patients with systolic heart failure require multidrug therapy.

All patients with left ventricular systolic dysfunction should receive treatment with an ACE inhibitor because these agents improve mortality of patients with all classes of heart failure and delay the onset of symptoms in patients with asymptomatic left ventricular dysfunction. Therapy should be initiated at low doses and slowly titrated upward if it is tolerated (i.e., systolic blood pressure >90 mm Hg, no symptoms of hypotension) to doses that have been proved efficacious in randomized trials (see Table 58-6). Renal function should be monitored closely, especially in patients with concomitant vascular disease. Other vasodilators should be considered in patients with symptomatic heart failure who are unable to tolerate ACE inhibitors because of side effects. Whereas ARBs should not be used as first-line therapy for heart failure, they are the preferred agents for patients who develop cough with ACE inhibitors. Patients who develop progressive renal insufficiency or hyperkalemia

with ACE inhibitors are equally likely to develop these complications with ARBs; these agents should not be used in this setting. The combination of hydralazine and nitrates is a less effective regimen than ACE inhibitors but is a reasonable alternative in patients who are intolerant of these agents or ARBs.

All patients with class II-IV heart failure should also receive a beta blocker because these agents provide a marked mortality benefit. Care must be taken to ensure that patients are hemodynamically stable and near euvolemic before beta blocker therapy is started because initiation of beta blockade may be associated with orthostatic hypotension and worsening of heart failure symptoms. These agents should always be started at low doses (see Table 58-6), titrated very slowly (increasing dose every 2 weeks), and avoided in patients who recently required intravenous diuretics or inotropic agents. They should also be avoided in patients with a heart rate below 60 beats per minute, systolic blood pressure of less than 100 mm Hg, or evidence of atrioventricular block, and they should be used with care in patients with bronchospastic lung disease. Most patients with heart failure who receive beta blocker therapy should be concomitantly treated with diuretics, especially those patients with current or recent volume retention. If heart failure symptoms worsen after beta blockers are started, diuretic therapy should be initiated or increased; this often allows for continued beta blocker use. Clinical trials suggest that beta blocker therapy can be safely initiated in patients who are hospitalized for heart failure, providing they do not require intravenous inotropic support, the drug is started at a low dose, and there is careful assessment before further up-titration. It is generally preferable to initiate ACE inhibitor therapy before beta blocker therapy because ACE inhibitors result in rapid relief of symptoms and may facilitate the initiation of beta blockade.

Patients with symptoms or signs of congestion may respond to afterload-reducing therapy alone; however, most require the addition of a diuretic. Loop diuretics such as furosemide are preferred because they are more effective than thiazide diuretics, especially in patients with renal insufficiency (serum creatinine concentration >2.5 mg/dL). If volume overload persists despite upward titration of the loop diuretic, addition of a thiazide (e.g., metolazone 2.5 mg orally given 30 minutes before the loop diuretic) should be considered and provides effective combination therapy. This combination can lead to profound potassium and magnesium wasting and requires

TABLE 58-10 Beneficial Effects of Oral Pharmacotherapy for Chronic Heart Failure

Medication	Improves Mortality	Improves Symptoms	Reduces Recurrent Heart Failure	Heart Failure Class for Which Treatment Is Indicated
Angiotensin-converting enzyme inhibitors	Yes	Yes	Yes	Class I-IV*
Beta blockers	Yes	Yes	Yes	Class II-IV
Hydralazine	Yes	Yes	No	Class II-IV†
Spironolactone	Yes	Yes	No	Class III-IV
Diuretics	No	Yes	No	Class II-IV
Digoxin	No	Yes	Yes	Class II-IV

*Also indicated in patients with asymptomatic left ventricular systolic dysfunction.

†Not a first-line drug but should be considered in patients who are intolerant of angiotensin-converting enzyme inhibitors.

close monitoring of serum electrolytes. Spironolactone (25 to 50 mg daily) should be added to the regimen of patients with class III-IV heart failure because it provides a mortality benefit in this setting.

Digoxin should be considered in any patient who continues to have symptomatic heart failure despite treatment with an ACE inhibitor and beta blocker. Although this agent has not demonstrated a mortality benefit in any class of heart failure, when it is used as part of a multidrug regimen, it is useful for controlling symptoms and reducing hospital admissions. It may be particularly beneficial in patients with atrial fibrillation, in whom improved heart rate control may lead to symptomatic improvement.

Treatment of Decompensated Systolic Heart Failure

Patients with chronic systolic heart failure may have periods of relative stability interrupted by periods of decompensation. These periods of decompensation may be precipitated by medication noncompliance, dietary indiscretion (i.e., excessive sodium or water intake), or progression of the underlying myopathic process. The patient often reports a gradual worsening of symptoms or progressive weight gain during the course of several days, although the clinical presentation may appear relatively acute.

Patients with decompensated heart failure may present with hemodynamic instability and usually have evidence of systemic and pulmonary congestion with or without evidence of decreased organ perfusion. Although pulmonary arterial catheterization is sometimes necessary to precisely define the hemodynamic derangement, many patients with decompensated heart failure can be adequately evaluated on the basis of their clinical history and physical examination findings, specifically whether they have evidence of pulmonary or systemic congestion or organ hypoperfusion. Congestion may be evidenced by an elevation in the jugular venous pressure, the presence of pulmonary rales, or peripheral edema. These patients are usually dyspneic with minimal exertion or even at rest and often report increased orthopnea and paroxysmal nocturnal dyspnea. Hypoperfusion may be manifested as cold extremities, mottled skin, cyanosis, mental obtundation, or declining renal function. Measurement of the pulse pressure (the difference between the systolic and diastolic blood pressures) may be helpful; in patients with heart failure, the pulse pressure narrows. A pulse pressure of less than 25% of the systolic blood pressure generally correlates with a cardiac index of less than 2.2 liters/min/m².

For patients in whom the hemodynamic profile needs to be more accurately defined or in whom initial therapy yields suboptimal results, direct measurement of hemodynamic parameters should be performed through the insertion of a Swan-Ganz catheter (Table 58-11). The information thus obtained may be used to guide the selection and titration of specific pharmacologic therapy. Such tailored therapy should be undertaken with the goal of manipulating medications to achieve optimal hemodynamics, including a right atrial pressure of less than 8 mm

TABLE 58-11 Potential Indications for Invasive Hemodynamic Assessment in Patients with Heart Failure

Assessment of volume status when clinical assessment is uncertain
Distinguishing heart failure from other causes of dyspnea (e.g., pulmonary disease)
Assessment of hemodynamic response to vasoactive medications
Guidance in achieving ideal hemodynamic goals (tailored therapy)
Assessment of filling pressure in patients with persistent symptoms of heart failure despite aggressive medical therapy
Determination of appropriate therapy in patients with persistent congestion and progressive renal insufficiency after diuretic therapy
Assessment of pulmonary vascular resistance during evaluation for cardiac transplantation
Perioperative monitoring of volume status in patients with severe left ventricular dysfunction undergoing prolonged procedures associated with significant volume shifts or in patients with decompensated heart failure on preoperative assessment

Hg, a pulmonary capillary wedge pressure of less than 18 mm Hg, a cardiac index above 2.2 liters/min/m², and a systemic vascular resistance of 800 to 1200 dynes/sec/cm⁻⁵.

Taken together, these findings can be used to classify the severity of hemodynamic impairment of a patient presenting with decompensated heart failure and to help make decisions about appropriate initial therapy (Fig. 58-6). Patients with left ventricular dysfunction who are well compensated generally have acceptable filling pressures and adequate cardiac outputs, do not have congestion, and appear well perfused. These patients require chronic heart failure therapy as outlined earlier for symptom control and mortality reduction. Patients with decompensated heart failure who have evidence of congestion without hypoperfusion have elevated filling pressures with adequate cardiac output. These patients may simply be volume overloaded and require aggressive diuresis. If the blood pressure is adequate, addition of a vasodilator (e.g., ACE inhibitor) may further augment cardiac output and facilitate diuresis. Patients with signs of hypoperfusion but without congestion have acceptable filling pressures but decreased cardiac output. Therapy in this setting should be guided by the patient's blood pressure; patients with hypotension require inotropic therapy, whereas patients with adequate systolic blood pressure (>100 mm Hg) should receive vasodilators with or without inotropic agents to augment cardiac output. These patients do not generally require aggressive diuresis and, in fact, may be volume depleted and require gentle hydration. Patients with evidence of both congestion and hypoperfusion have both elevated filling pressures and decreased cardiac output and are the most difficult to manage. These patients frequently require combination therapy with inotropic agents, intravenous vasodilator therapy, and use of diuretics. Invasive hemodynamic monitoring may be most helpful in guiding

therapy in this group of patients, especially in patients with associated hypotension.

Various intravenous agents are available for use in the treatment of patients with decompensated heart failure (Table 58-12). Initial management should be guided by

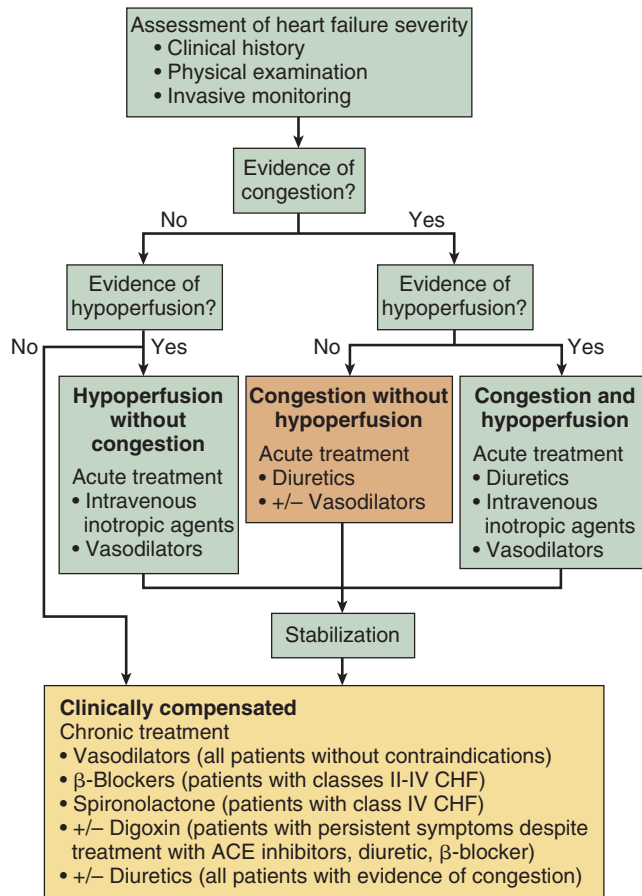


FIGURE 58-6 ■ An approach to treatment of acute or decompensated heart failure. ACE, Angiotensin-converting enzyme; CHF, congestive heart failure.

the patient's specific hemodynamic alterations. In patients with severe hypotension leading to organ dysfunction, stabilization of the blood pressure is the primary goal. Dopamine at moderate to high doses has traditionally been used as the initial drug of choice in this setting; however, recent data suggest that in the management of cardiogenic shock, treatment with norepinephrine is associated with fewer arrhythmias and lower mortality than is treatment with dopamine. In general, vasoconstrictors should be avoided in patients with left ventricular dysfunction because they may lead to further depression of cardiac output. In patients with adequate blood pressure whose predominant manifestation of heart failure is congestion, initial treatment with nitroprusside (or nitroglycerin or nesiritide) is usually effective. In patients whose predominant manifestation is hypoperfusion, dobutamine, milrinone, nitroprusside, or nesiritide may be effective. Most patients with decompensated heart failure also require administration of intravenous diuretics and careful management of fluid balance.

Treatment of Diastolic Heart Failure

In contrast to the treatment of systolic heart failure, the treatment of diastolic heart failure has not been extensively studied, and there are no large-scale randomized trials by which to guide therapeutic recommendations. The general approach is aimed at treatment of the underlying cause and the relief of symptoms with medications that intuitively should reduce diastolic pressures. The impairment in diastolic filling results in an increase in atrial pressure early in the course of this disease, with resultant pulmonary and venous congestion. Diuretics therefore play an important role in the management of this syndrome and help control congestive symptoms. Care must be taken to avoid overdiuresis because these patients depend on an elevated filling pressure to maintain stroke volume. Calcium channel blockers (verapamil or diltiazem) and beta blockers slow the heart rate,

TABLE 58-12 Intravenous Agents Used in the Treatment of Decompensated Heart Failure

Medication	Hemodynamic Effects	Potential Adverse Clinical Effects
Dopamine		
Low dose	Splanchnic vasodilation, ↑GFR, ↑urine output	Myocardial ischemia, arrhythmias
Intermediate dose	↑HR, ↑contractility, ↑CO, ↑BP, ↑/–SVR	Myocardial ischemia, arrhythmias, ↑CHF, worsened renal function
High dose	↑HR, ↑↑contractility, ↑↑BP, ↑↑SVR, ↓CO, ↑PCW, ↓/–GFR	Myocardial ischemia, arrhythmias
Dobutamine	↑HR, ↑↑contractility, ↑CO, ↑/–BP, ↓SVR, ↓PCW	Myocardial ischemia, arrhythmias
Isoproterenol	↑↑HR, ↑contractility, ↑CO, ↓SVR	Myocardial ischemia
Epinephrine	↑HR, ↑contractility, ↑SVR, ↑BP	Myocardial ischemia, arrhythmias, ↑CHF, worsened renal function
Norepinephrine	↑HR, ↑contractility, ↑↑SVR, ↑↑BP	Myocardial ischemia, arrhythmias, ↑CHF, worsened renal function
Milrinone	↑Contractility, ↑↑CO, ↓↓SVR, ↓PVR, ↓↓PCW	Myocardial ischemia, arrhythmias, hypotension
Nitroprusside	↑↑CO, ↓↓SVR, ↓PVR, ↓↓PCW	Hypotension, cyanide and thiocyanate toxicity
Nitroglycerin	No effect on contractility ↑CO, ↓SVR, ↓PVR, ↓↓PCW, coronary vasodilation	Hypotension, headache, nitrate tolerance
Nesiritide	No effect on contractility ↑CO, ↓SVR, ↓↓PCW, ↑GFR Natriuresis, diuresis	Hypotension

BP, Blood pressure; CHF, congestive heart failure; CO, cardiac output; GFR, glomerular filtration rate; HR, heart rate; PCW, pulmonary capillary wedge (pressure); PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

prolong diastole, and allow increased time for left ventricular filling. In addition, these agents may improve diastolic ventricular function (i.e., decrease left ventricular stiffness and improve left ventricular relaxation) by improvement in calcium homeostasis. In patients who are intolerant of these medications or who have continued symptoms despite their use, ACE inhibitors may offer further benefit. Data suggest that ventricular hypertrophy is associated with stimulation of the renin-angiotensin system and that chronic activation of this system results in fluid retention as well as myocardial fibrosis and increased ventricular stiffness. Inhibition of this system with ACE inhibitors or ARBs may therefore offer further treatment of the underlying pathophysiologic changes characteristic of diastolic heart failure. Inotropic therapy, including digoxin, should be avoided in diastolic heart failure; these agents are unlikely to be beneficial in the face of preserved systolic function and may worsen diastolic function, leading to further elevation of filling pressures and progressive heart failure.

Other therapies for diastolic heart failure are aimed at treating the underlying cause of the dysfunction and correcting associated abnormalities that may worsen this dysfunction. Hypertension is the most common condition that predisposes to diastolic heart failure. Small studies suggest that it is the extent of hypertension control, not the specific antihypertensive agent used, that results in improved diastolic function. Patients with secondary causes of hypertension (e.g., renal artery stenosis, hyperadrenalism) should undergo definitive therapy when possible. Patients with coronary artery disease should be aggressively treated with antianginal therapy, and coronary revascularization should be performed when appropriate. Aortic stenosis should be surgically corrected when it is associated with diastolic heart failure, even in the absence of systolic dysfunction. Patients with diastolic heart failure are highly preload dependent and may experience acute decompensation if they develop atrial fibrillation. This occurs in part because of the loss of the active atrial contribution to left ventricular filling and in part because the increased heart rate associated with the development of atrial fibrillation shortens diastole and allows less time for left ventricular filling. All efforts should be made to restore and maintain sinus rhythm in these individuals.

Flash Pulmonary Edema

Decompensated heart failure that develops acutely in a previously asymptomatic or well-compensated patient is often the result of an abrupt change in cardiac structure or function (Table 58-13). The precipitous nature of the presentation of these patients accounts for the commonly used descriptive term *flash pulmonary edema*. In this setting, patients are often hemodynamically unstable and develop severe pulmonary congestion, although they frequently are not fluid overloaded. These patients are pharmacologically treated similarly to the decompensated patients described earlier; however, specific therapy should be guided by the underlying precipitating factor. Patients with ischemia precipitating acute heart failure frequently have severe coronary artery disease (i.e.,

TABLE 58-13 Precipitants of Flash Pulmonary Edema and Their Therapeutic Implications

Acute	Specific Therapeutic Considerations
Ischemia or infarction	Cardiac catheterization and revascularization
Hypertension	Intravenous vasodilators (nitroprusside, enalaprilat) with 25% reduction in mean arterial pressure as initial goal
Renal artery stenosis	Percutaneous renal artery revascularization
Aortic stenosis	Aortic valve replacement after initial stabilization with diuretics, $\pm$ vasopressors, $\pm$ inotropic agents
Acute aortic insufficiency (endocarditis, aortic dissection)	Aortic valve replacement after initial stabilization with vasodilators $\pm$ inotropic agents
Acute mitral regurgitation (ischemia, endocarditis, ruptured chordae)	Consider intra-aortic balloon pump for hemodynamic stabilization before coronary revascularization for ischemic mitral regurgitation or mitral valve replacement for structural mitral regurgitation
Supraventricular tachyarrhythmias	Rate control or electrical cardioversion

three-vessel or left main coronary artery disease) or have papillary muscle dysfunction resulting in acute mitral regurgitation (most common with disease of the right coronary artery). In addition to heart failure therapy as dictated by their clinical presentation, these patients should receive aggressive antianginal therapy with intravenous nitrates and antiplatelet agents (i.e., aspirin, heparin, $\pm$ IIb/IIIa inhibitors), and urgent cardiac catheterization and coronary revascularization should be considered. For patients with refractory heart failure and ischemia, intra-aortic balloon pump counterpulsation may be a beneficial adjuvant therapy while awaiting definitive revascularization.

Severe hypertension may precipitate acute heart failure. Classically, this occurs with hypertension associated with pheochromocytomas, renal artery stenosis, and alcohol or cocaine use, but it can be seen also in patients with preexisting heart failure who are noncompliant with medications or dietary sodium restriction. Appropriate therapy in this setting is dependent on blood pressure control. Intravenous antihypertensive agents (e.g., nitroprusside, enalaprilat) should be started with the goal of lowering the mean arterial pressure by 25% in the first several hours and reducing the systolic blood pressure below 160 mm Hg within the first 24 hours. Acute severe aortic insufficiency as occurs with endocarditis or aortic dissection should be managed with intravenous inotropic agents or vasodilators (depending on systemic blood pressure) while preparing for emergent surgical therapy. Acute mitral regurgitation often responds to vasodilator therapy but may require intra-aortic balloon pump counterpulsation for stabilization before valve replacement.

Perioperative Heart Failure

For various reasons, the incidence of heart failure is increased in the perioperative period. Many anesthetic agents have negative inotropic effects and can precipitate heart failure in patients with left ventricular systolic dysfunction, and the vasodilative effects of these agents may result in hypotension. Aggressive fluid resuscitation in this setting may lead to volume overload, elevated filling pressures, and pulmonary congestion. Similarly, appropriate replacement of blood products in the face of intraoperative blood loss may be poorly tolerated and may require the concomitant administration of diuretics. Mechanical ventilation produces beneficial hemodynamic effects in heart failure because of a reduction in venous return induced by the increased intrathoracic pressure. Conversely, the decrease in intrathoracic pressure associated with extubation may be followed by a sudden rise in preload and result in heart failure. Fluid that entered the extravascular space during the perioperative period reenters the vascular space several days postoperatively as patients begin to mobilize. This rise in circulating blood volume may similarly precipitate heart failure. These adverse effects are more likely to occur in patients with preexisting left ventricular dysfunction and in patients with overt heart failure preoperatively.

In the preoperative setting, the identification of decompensated heart failure is essential. The presence of pulmonary or systemic congestion or signs of hypoperfusion should prompt a thorough assessment of the patient's cardiac status, reevaluation of the patient's current therapy, and delay or cancellation of all but emergent procedures until the patient's status is stabilized. If the patient's ventricular function is not known, echocardiography should be performed to aid in determining the mechanism of heart failure and to guide appropriate therapy. In the postoperative period, heart failure may be mistaken for pneumonia, atelectasis, exacerbation of chronic obstructive pulmonary disease, or pulmonary embolism. Patients are often unable to communicate their symptoms to the treating physicians because of sedation and mechanical ventilation; thus, the physician's vigilance is essential. Identification of pulmonary rales, jugular venous distention, hepatojugular reflux, gallop rhythm, or peripheral edema should raise the concern of worsening heart failure, and close monitoring of the patient's weight and fluid balance should alert the physician to the possibility of volume overload.

In patients with more advanced heart failure (class III or IV) or with severely depressed left ventricular systolic function (<25%), placement of a pulmonary arterial catheter preoperatively should be strongly considered, especially for such patients who are undergoing prolonged procedures that are associated with significant fluid shifts. In patients with decompensated heart failure, placement of this catheter the day before surgery allows time for optimization of their hemodynamic status, thereby potentially decreasing their overall perioperative risk. Continued invasive hemodynamic monitoring for 24 to 48 hours after surgery may be appropriate in some patients.

Patients with chronic heart failure are often dependent on medications to maintain their hemodynamic stability,

and every effort should be made to continue these medications in the perioperative period. Although it may be appropriate to hold diuretics on the day of surgery, careful attention to volume status is obligatory postoperatively, and intravenous diuretics should be administered at the first signs of congestion. Beta blockers and ACE inhibitors should likewise be continued because the sudden withdrawal of these agents may result in neurohormonal activation and worsening of heart failure. Intravenous formulations may be substituted for many oral medications in patients who are unable to take oral agents postoperatively because of the nature of their surgery. However, well-compensated patients often tolerate withholding of their usual medications and can be managed for several days with intravenous diuretics and topical nitrates for preload reduction. If refractory congestion or signs of organ hypoperfusion develop, use of intravenous vasodilators or inotropes may become necessary. These agents may be transitioned to oral formulations as gut absorption improves. For patients who remain hemodynamically labile postoperatively, use of short-acting agents may be appropriate for several days; long-acting agents may be reinstituted when the volume shifts and hemodynamic derangements improve. Given the tenuous nature of these patients, it is often helpful to involve a cardiology consultant to help manage the complex hemodynamic changes that occur in the perioperative period.

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PART D

PERIOPERATIVE AND INTRAOPERATIVE CARE OF THE CARDIAC SURGICAL PATIENT

PART OUTLINE

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ANESTHESIA AND INTRAOPERATIVE CARE OF THE ADULT CARDIAC PATIENT

Mario Montealegre-Gallegos • Khurram Owais • Feroze Mahmood • Robina Matyal

CHAPTER OUTLINE

PREOPERATIVE EVALUATION

Indications for Cardiac Surgery
Identification and Optimization of Risk Factors
Information Relevant for Selecting Appropriate Monitoring Modalities and Management Techniques

INTRAOPERATIVE MANAGEMENT

Monitoring
Choice of Anesthetic Agents
Regional Anesthesia and Analgesia

Intraoperative Blood Glucose Control
Acid-Base Management during Hypothermia
Anticoagulation for Cardiopulmonary Bypass
Use of Antifibrinolytics
Cerebral Protection
Hemodynamic Support on Separation from Cardiopulmonary Bypass

SPECIAL CONSIDERATIONS

Off-Pump Coronary Artery Bypass
Minimally Invasive Cardiac Surgery
Robotic-Assisted Cardiac Surgery

Anesthesia was successfully demonstrated for the first time in 1846. Prior to that time, it was deemed impossible to perform major surgical procedures because of the associated pain and discomfort.¹ Anesthesia has been one the greatest catalysts in the evolution of surgery since the 1840s. The first successful cardiac surgical procedure occurred in 1902, when Hill closed a stab wound to the heart of a 13-year-old boy. Over the years, the anesthesiologist's role has evolved from mere drug administrator to being an integral partner in the perioperative management and support of the cardiac surgical patient. Today, transesophageal echocardiography (TEE) plays an essential role in the patient's intraoperative diagnosis, monitoring, and prognostication, with the anesthesiologist taking part in the surgical planning and decision making.² The discipline of cardiac anesthesia encompasses an ever-expanding body of knowledge. This chapter provides a brief overview of preoperative anesthetic evaluation and intraoperative anesthetic management for adult cardiac surgery.

PREOPERATIVE EVALUATION

The preoperative anesthetic evaluation of the cardiac surgical patient includes the following: (1) review of the events that led to the indication for cardiac surgery, (2) identification and optimization of risk factors that could lead to increased mortality and morbidity resulting from cardiac surgery, and (3) gathering of information relevant to selecting appropriate monitoring modalities and management techniques during surgery.

Indications for Cardiac Surgery

A detailed history should be obtained on the evolution of disease in question, with emphasis on current and past symptoms, previous need for hospitalization, and current functional capacity.

An important part of functional capacity assessment is the evaluation of limitation in the activities of daily living. Patients who can normally walk up a flight of stairs or a hill and do heavy work around the house (scrubbing floors, etc.) have a lower risk of cardiopulmonary complications associated with surgery.³

Identification and Optimization of Risk Factors

Higgins and colleagues⁴ performed a retrospective logistic regression on data from more than 5000 patients who underwent coronary artery bypass grafts and then prospectively applied the retrospectively identified risk factors to a group of more than 4000 patients. They found that 30-day mortality was predicted by the emergency of the procedure, preoperative serum creatinine of more than 168 mmol/L, left ventricular ejection fraction of less than 35%, preoperative hematocrit level of less than 35, age older than 70 years, chronic pulmonary disease, prior vascular surgery, reoperation, and mitral regurgitation. Emergency cases included transfers from the coronary care unit with unstable angina (48%), complications of percutaneous intervention (40%), and complications of routine cardiac catheterizations (12%). In addition to these risk factors, nonfatal morbidity was

predicted by diabetes mellitus, body weight of 65 kg or less, aortic stenosis, and cerebrovascular disease. Presence of these risk factors needs to be ascertained when obtaining preoperative history prior to cardiac surgery.

Several standardized scores can be used for assessing risk in the cardiac surgical population. In the 1980s, Parsonnet et al described a score useful for assessing risk of mortality related to cardiac surgery.⁵ This original model has been substituted in recent years by other models, including the European System for Cardiac Operative Risk Evaluation (euroSCORE) or the Society of Thoracic Surgeons risk calculator.⁶⁻¹⁰ Some of the factors associated with mortality during cardiac surgery are shown in Table 59-1. A recent study analyzed more than 29,000 patients undergoing elective cardiac surgery. In this study, an index that included patient age, creatinine levels, and ejection factors showed definitive association with mortality and the score was comparable to euroSCORE risk estimation.¹¹

Patients' current use of medications should be sought, and their dose and frequency noted. In general, all cardiovascular medications should be continued even on the day of surgery, except diuretics and angiotensin-converting enzyme inhibitors. Preoperative β -adrenergic blocker use has been associated with increased survival after coronary artery surgery.¹²

Of particular interest are anticoagulant and thrombolytic drugs, because they can cause increased bleeding in the perioperative period. Relevant information about anticoagulant use includes current as well as prior treatment with heparin or warfarin, along with dosage and time of the last dose, and history of heparin resistance or heparin-induced thrombocytopenia, use of warfarin with dosage, and time of the last dose.

Emergency patients may have received thrombolytics and/or inhibitors of platelet aggregation. Clopidogrel (Plavix) and ticlopidine (Ticlid) inhibit adenosine diphosphate (ADP)-induced platelet aggregation by irreversibly modifying platelet P2 receptors. Abciximab (ReoPro) is a monoclonal antibody fragment against glycoprotein (GP) IIb/IIIa receptor, which allows platelet binding to von Willebrand factor and fibrinogen. Abciximab is administered intravenously with an initial bolus of 0.25 mg/kg, followed by an infusion of 0.125 mcg/kg/min (up to 10 mcg/min) for 12 hours. After discontinuance of Abciximab, platelet function recovers gradually over the next 48 hours.^{13,14} Eptifibatide (Integrilin) is a

peptide inhibitor of GP IIb/IIIa receptor with an elimination half-life of 1 to 2 hours. After discontinuance, platelet function (as measured by bleeding time) recovers in 2 to 4 hours.¹⁵ Tirofiban (Aggrastat) is a peptidomimetic antagonist of GP IIb/IIIa receptor with an elimination half-life of about 2 hours; platelet function returns to normal within 4 to 8 hours after discontinuing the medication.^{16,17} Abciximab could prolong the activated clotting time (used for heparin effect monitoring) by 30 to 50 seconds, and a reduction in the dosage of heparin is necessary. Eptifibatide does not have a similar effect on activated clotting time.¹⁸

Information Relevant for Selecting Appropriate Monitoring Modalities and Management Techniques

In every cardiac surgical patient, contraindications to TEE have to be evaluated (e.g., esophageal disease or previous esophageal surgery). Furthermore, a history of cold agglutinin antibody may contraindicate hypothermic cardiopulmonary bypass (CPB), whereas a history of antiphospholipid syndrome will adversely affect measurement of activated clotting time while the patient is on CPB. The possibility of previous thoracic surgery or radiation, and the presence of a pacemaker or an implantable cardioverter/defibrillator, should also be evaluated.

Physical examination should be focused on assessing the airway, cardiovascular, and respiratory systems. The airway examination should include evaluation of dentition: any evidence of infection or abscess must be ruled out. Blood pressure should be measured on both arms, and any significant difference should raise suspicion of subclavian artery stenosis. The Allen test may be performed in case a radial artery harvest is being considered to provide a conduit, or invasive blood pressure monitoring on the radial artery is planned. Femoral pulsation should be palpated, and the presence of any peripheral vascular disease should be noted (this may make the placement of an intra-aortic balloon pump challenging). Carotid bruits should be listened for, and cardiac sounds should be auscultated. Hepatomegaly, jugular venous distention, and peripheral edema should also be noted.

Preoperative laboratory tests should include hematocrit, platelet count, coagulation parameters, electrolytes, serum creatinine, glucose, 12-lead electrocardiogram,

TABLE 59-1 Conditions Commonly Associated with Increased Mortality after Cardiac Surgery

Patient Related	Comorbidities	Disease Related	Surgery Related
Age (>60) Gender (female) Obesity	Extracardiac arteriopathy Diabetes mellitus Renal impairment	Recent myocardial infarction Left ventricular dysfunction Pulmonary hypertension	Previous cardiac surgery Urgent surgery Surgical procedure other than or associated with coronary artery bypass graft
Poor mobility	Dialysis	Cardiogenic shock	Surgery on the descending thoracic aorta
Critical preoperative state Poor functional capacity	Chronic lung disease Atrial fibrillation	Intra-aortic balloon pump Left main coronary artery disease	

and a chest radiograph. An echocardiogram, if obtained, provides not only information about preoperative ventricular and valve function and anatomy but also a baseline to which intraoperative TEE findings can be compared. The catheterization report should be reviewed for the distribution of coronary artery disease, ventricular systolic and diastolic dysfunction, valvular abnormalities, pulmonary hypertension, and intracardiac shunt.

INTRAOPERATIVE MANAGEMENT

Monitoring

The American Society of Anesthesiologists standards for basic anesthetic monitoring include electrocardiography, pulse oximetry, capnography, noninvasive blood pressure determination, and temperature monitoring.¹⁹

On surface electrocardiogram (ECG), ST-segment analysis should be continuously performed. In a classic study by London et al, patients were evaluated with a 12-lead ECG during noncardiac surgery, and ischemia was defined as either ST depression of at least 1 mm or elevation of at least 1.5 mm in a non-Q wave lead. In this study the sensitivity of the V5 lead alone for detection of ischemia was 75%; that of V5 and V4 combined was 90%; V5 and II 80%; and V5, V4, and II combined was 96%.²⁰ Use of the standard five-lead ECG system does not allow simultaneous monitoring of V5 and V4, and the most practical alternative is to monitor leads V5 and II, the latter of which is also the most useful for arrhythmia monitoring. When right-sided ischemia is of concern, the right shoulder electrode may be placed in the right precordial area, and then lead I becomes the right precordial lead (V₄R). Simultaneous monitoring of V5, II, and V₄R allows for the detection of virtually 100% of all

ischemic episodes that are detectable with a full 12-lead ECG.²¹

In addition to the noninvasive monitors, invasive monitors are routinely used in cardiac surgery (Fig. 59-1). An arterial line should be placed before or immediately after induction for continuous blood pressure monitoring and intermittent blood sampling. The radial artery is most commonly used, but the brachial, ulnar, axillary, femoral, and dorsalis pedis arteries are alternative sites of cannulation. If the internal mammary artery is to be used as a graft, the contralateral radial artery should be selected because of the theoretical concern of subclavian artery compression by the retractor during conduit harvest. If the surgery involves the takeoff of the innominate artery or the left subclavian artery, or if the radial artery is to be harvested as a conduit, the corresponding radial artery should not be used for an arterial line, and an alternative site should be sought. For an operation of the descending thoracic aorta, two arterial lines with one proximal to the proximal clamp and one distal to the distal clamp are recommended. The proximal arterial line (usually in the right radial artery) provides information about the perfusion pressure of the myocardium and the brain. The distal arterial line (usually a femoral artery line or, in the absence of a peripheral vascular disease, a dorsalis pedis line), in conjunction with an intrathecal catheter, allows the calculation of the perfusion pressure of the spinal cord.

A central venous line (CVL) is routinely used in cardiac surgery to allow for reliable administration of cardiovascular medications and heparin and to monitor central venous pressures. Whether the use of a pulmonary artery catheter (PAC) should be routine or selected on an individual basis in cardiac surgery is a matter of debate. In a prospective comparison of a CVL with a PAC in 1094 patients undergoing coronary artery surgery

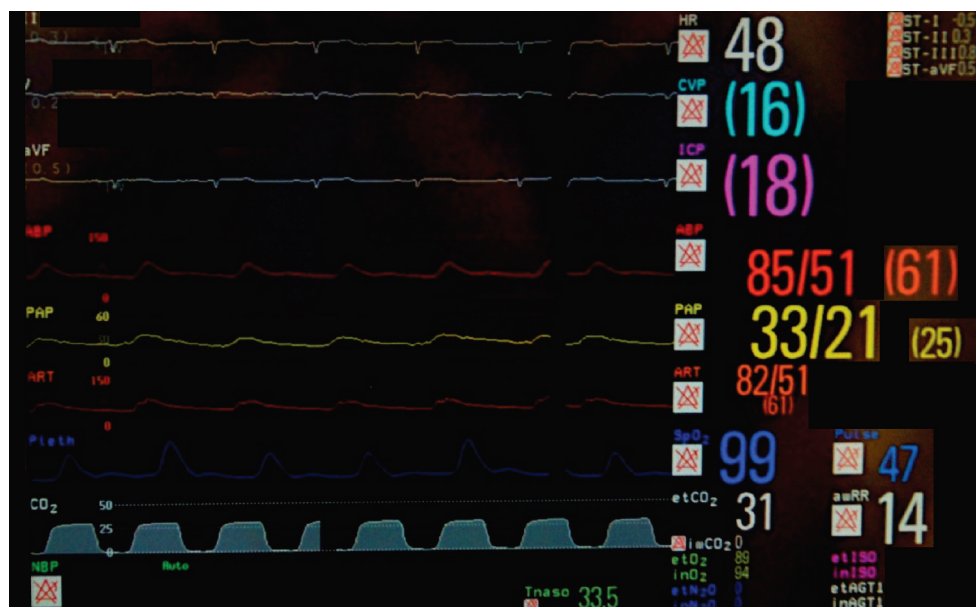


FIGURE 59-1 ■ Monitoring. Parameters monitored during complex cardiac surgery include a multiple-lead electrocardiogram, intracranial pressure, pulmonary artery pressure, one or multiple arterial lines, pulse oxymetry, capnogram, and nasopharyngeal temperature.

(including the highest risk patients), Tuman and colleagues²² found that there was no difference in outcome. Similarly, Schwann and coworkers²³ reported that, in their experience with 2685 consecutive patients undergoing coronary artery bypass surgery, the use of a PAC was limited to 9% (2.4% unplanned—i.e., converted from a CVL) of the patients and predicted by ejection fraction, Society of Thoracic Surgeons risk score, intra-aortic balloon pump, congestive heart failure, re-do surgery, and New York Heart Association class IV. With such a selective use, their observed-to-expected ratio of mortality as compared with the Society of Thoracic Surgeons database was 0.73. Furthermore, the presence of a PAC has not been shown to influence anesthetic management during induction,²⁴ which is generally considered one of the higher risk periods during anesthesia. These studies suggest that the anesthesiologist should be highly selective when choosing cardiac surgery patients in whom to use a PAC. However, a PAC, unlike a CVL, can provide information about cardiac output, systemic and pulmonary vascular resistance, and mixed venous saturation, and some models allow for venous pacing of the heart. On the other hand, TEE may negate some of the potential advantages of a PAC over a CVL: cardiac output measured by TEE can be reliable and comparable with that measured by a PAC,²⁵ TEE-guided right and left ventricular oximetry may be feasible,²⁶ and pulmonary artery pressures can be estimated by TEE.²⁷

TEE has emerged as one of the most important tools in the planning and execution of cardiac surgical procedures. The American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists have published guidelines for the comprehensive intraoperative TEE examination, a full discussion of which is beyond the scope of this chapter.²⁸ The impact of TEE on surgical decision making and clinical outcomes is well established.²⁹⁻³¹ Given this evidence and its safety profile,³² TEE is now routinely indicated as frequently useful in several clinical scenarios (Box 59-1). In addition to serving as a monitor of myocardial and valvular function, TEE is an invaluable guide for the placement of coronary sinus and intra-aortic catheters, for the delineation of the anatomy and pathology of valve lesions, and for before-and-after comparison of myocardial perfusion and function and valvular anatomy and function.³³ In addition, TEE may be used to assess the delivery of cardioplegia^{34,35} and to predict changes in regional myocardial function after coronary artery bypass.³⁶ In valve repair procedures, TEE is indispensable in assessing the presurgical severity as well as the immediate quality and result of repair.

Three-dimensional TEE imaging has gained significant clinical importance in terms of ability to reveal more accurate information than traditional methods to base clinical decisions on. Studies have shown TEE's superiority in determining aortic valve area in the context of assessing severity of aortic stenosis as well as mechanism, thereby impacting intraoperative clinical decisions regarding valve replacement. For aortic valve replacement, for example, multiple methods for valve area assessment are currently in practice. However, studies show that images obtained using three-dimensional

BOX 59-1 Indications for Transesophageal Echocardiography

Indications—Category I: Supported by strongest evidence or expert opinion; transesophageal echocardiography (TEE) is frequently useful in improving clinical outcomes in these settings and is often indicated, depending on individual circumstances (e.g., patient risk and practice setting).

- Intraoperative evaluation of acute, persistent, and life-threatening hemodynamic disturbances in which ventricular function and its determinants are uncertain and have not responded to treatment
- Intraoperative use in valve repair
- Intraoperative use in congenital heart surgery for most lesions requiring cardiopulmonary bypass
- Intraoperative use in repair of hypertrophic obstructive cardiomyopathy
- Intraoperative use for endocarditis when preoperative testing was inadequate or extension of infection to perivalvular tissue is suspected
- Preoperative use in unstable patients with suspected thoracic aortic aneurysms, dissection, or disruption who need to be evaluated quickly
- Intraoperative assessment of aortic valve function in repair of aortic dissections with possible aortic valve involvement
- Intraoperative evaluation of pericardial window procedures
- Use in intensive care unit for unstable patients with unexplained hemodynamic disturbances, suspected valve disease, or thromboembolic problems (if other tests or monitoring techniques have not confirmed the diagnosis or patients are too unstable to undergo other tests)

echocardiography are able to capture the elliptical shape of the left ventricular outflow tract (LVOT), complete with information regarding major and minor axes.³⁷ This allows more accurate planimetric assessment of the LVOT and, therefore, calculation of aortic valve area by continuity equation. In addition, short axis TEE views are helpful in interrogating cusp symmetry and origin of the aortic regurgitation jet. In planning the repair, it is important to know whether the jet is central, commissural, cuspal, or all along the coaptation line (Fig. 59-2).

The advent of three-dimensional echocardiographic data has also allowed precise assessment of complex structures such as heart valves without geometric assumptions (Figs. 59-3 and 59-4). Using multi-planar reformatting, orthogonal views can be extracted from volumetric echocardiographic data to make accurate linear measurements (Fig. 59-5). Quantitative analyses of valvular apparatus are particularly valuable in identifying indices of remodeling to establish the chronicity and severity of valvular pathology (e.g., mitral regurgitation). This helps in identifying patients who may be unsuitable candidates for repair procedure because of irreversible remodeling of valvular apparatus. Increasingly, echocardiographic assessment during cardiac surgery is evolving from a qualitative interrogation to a quantitative analysis including, but not limited to, quantification of regurgitation, linear dimensions, and stress patterns before and after repair.

In surgeries of the descending thoracic aorta, cerebrospinal fluid pressure (CSFP) may be measured with an intrathecal catheter. If such a catheter is placed, CSFP should be maintained at less than or equal to 10 cm H₂O, and cerebral spinal fluid (CSF) should be allowed to drain when CSFP is greater than 10 cm H₂O.³⁸ However, spinal cord perfusion depends not only on CSFP but also on the arterial pressure distal to the distal clamp, and maintenance of the distal arterial pressure may be just as important when using, for example, a partial bypass or a shunt. Whether monitoring of CSFP and drainage of CSF to maintain CSFP at less than 10 cm H₂O prevents paraplegia after descending thoracic aortic surgery is still under debate.³⁹

Choice of Anesthetic Agents

High-dose opioid anesthesia was developed in the late 1960s by Lowenstein and colleagues.⁴⁰ This technique

was based on the observation that patients on mechanical ventilation after cardiac surgery tolerated large dosages of morphine (0.5 to 3 mg/kg) for sedation and analgesia with minimal hemodynamic effects. Such large dosages were then tried as a component of anesthesia for cardiac surgery, with significant success.⁴¹ Opioids by themselves do not ensure amnesia, and they require supplementation with an amnesic such as a benzodiazepine or scopolamine. Synthetic opioids such as fentanyl (50 to 100 mg/kg) or sufentanil (5 to 10 mg/kg) provided similar hemodynamic effects, with the advantage that fluid retention often seen with high-dose morphine anesthesia did not occur with these agents. Although highly successful and popular in the 1980s and early 1990s, high-dose opioid anesthesia has gradually given way to a balanced anesthetic technique that involves a lower dosage of opioids, in conjunction with inhalational anesthetics and other intravenous adjuncts, that results in a faster onset and offset to facilitate early extubation and discharge from the intensive care unit (ICU).

There has been increasing evidence that inhalational agents precondition the heart, thus protecting it from subsequent ischemic episodes in a fashion analogous to that of ischemic preconditioning, whereby a brief period of ischemia protects the heart from subsequent prolonged ischemic episodes.⁴²⁻⁴⁴ Anesthetic preconditioning was initially described in an animal model, in which 0.75 minimum alveolar concentration of halothane attenuated ST-segment elevation after coronary artery occlusion.⁴⁵ The mechanism for this increased tolerance to ischemia is thought to occur in part via activation of adenosine triphosphate (ATP)-sensitive potassium channels on the cardiac myocyte.⁴⁶ This effect is independent of changes in systemic and coronary hemodynamics and persists despite discontinuation of the volatile anesthetic.⁴⁶ Some clinical trials have postulated that anesthetic preconditioning could occur in patients during coronary as well as valvular surgery,⁴⁷⁻⁴⁹ whereas others have failed to confirm it.⁵⁰⁻⁵² Currently, inhalational agents are the mainstay of anesthesia for cardiac surgery, and these are supplemented with muscle relaxants and a modest amount of opioids for analgesia.

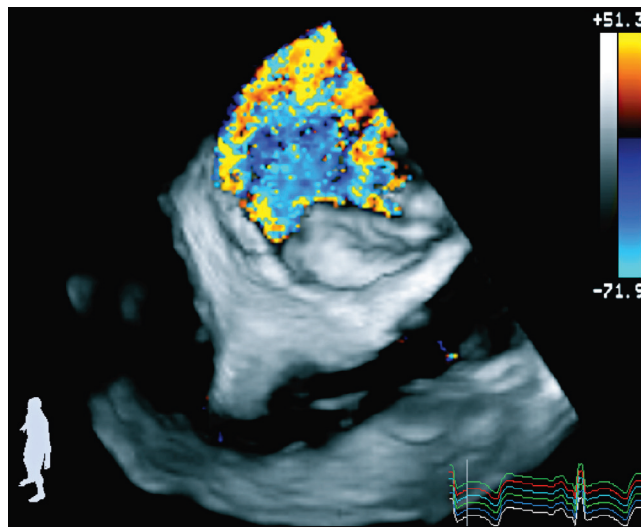


FIGURE 59-2 ■ Three-dimensional color flow Doppler. Three-dimensional transesophageal echocardiographic image of a mitral regurgitation jet that extends throughout the coaptation line.

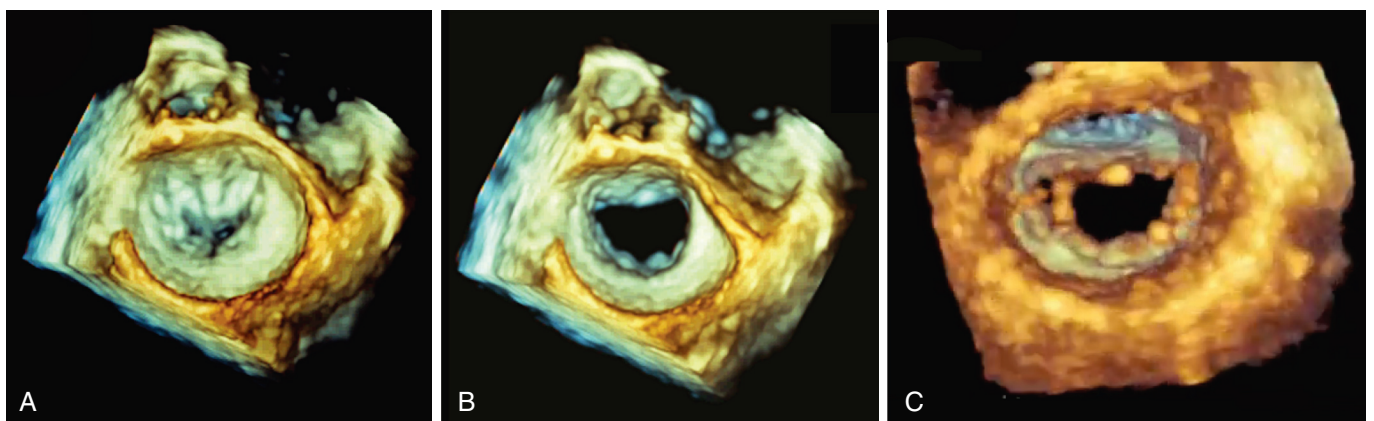


FIGURE 59-3 ■ Mitral valve open/closed. En face view of the mitral valve obtained with three-dimensional transesophageal echocardiography demonstrates the valve in a closed (A) and open position (B). The image can then be rotated to reveal valve anatomy as seen from the left ventricle (C).

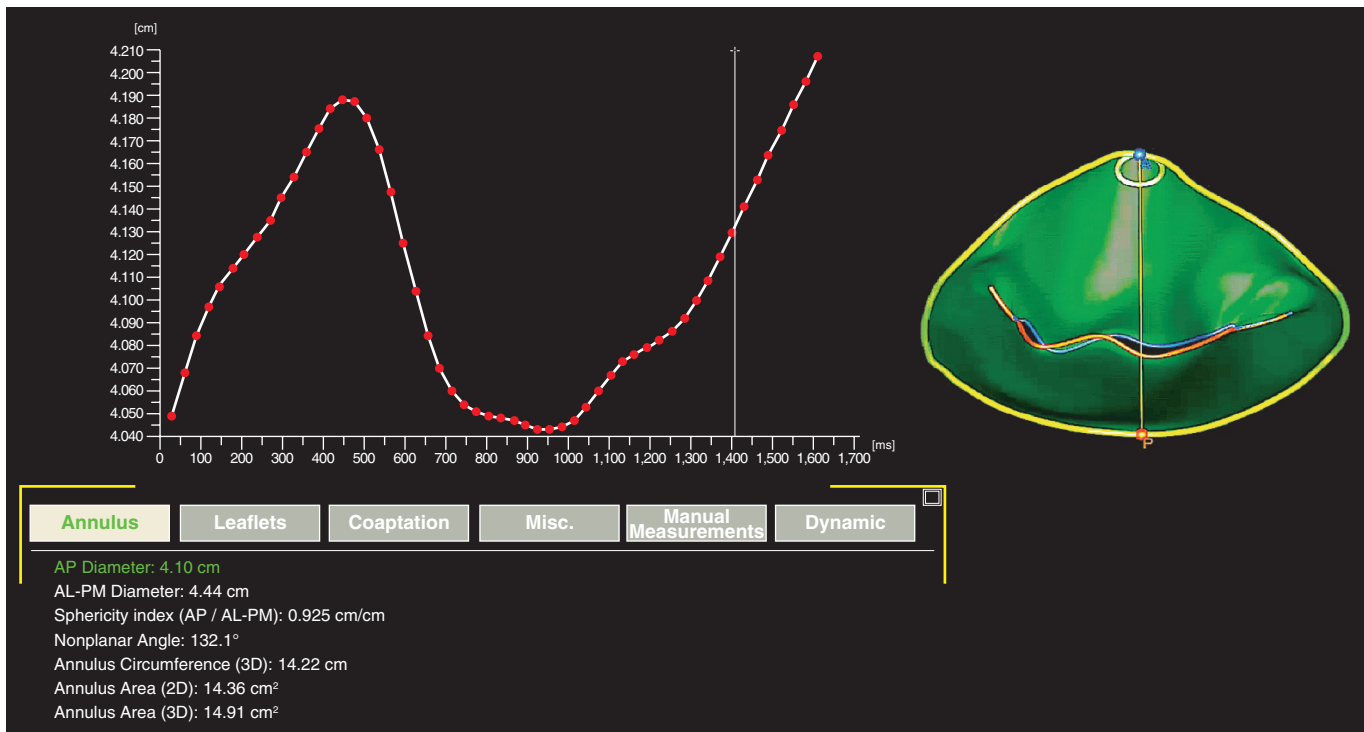


FIGURE 59-4 ■ AP diameter. Three-dimensional echocardiographic imaging may allow for better visualization of heart anatomy and the changes it undergoes throughout the cardiac cycle. A three-dimensional reconstruction of the mitral valve and the changes it undergoes in its AP annular diameter is demonstrated here. AL, Anterolateral; AP, anteroposterior; PM, posteromedial.

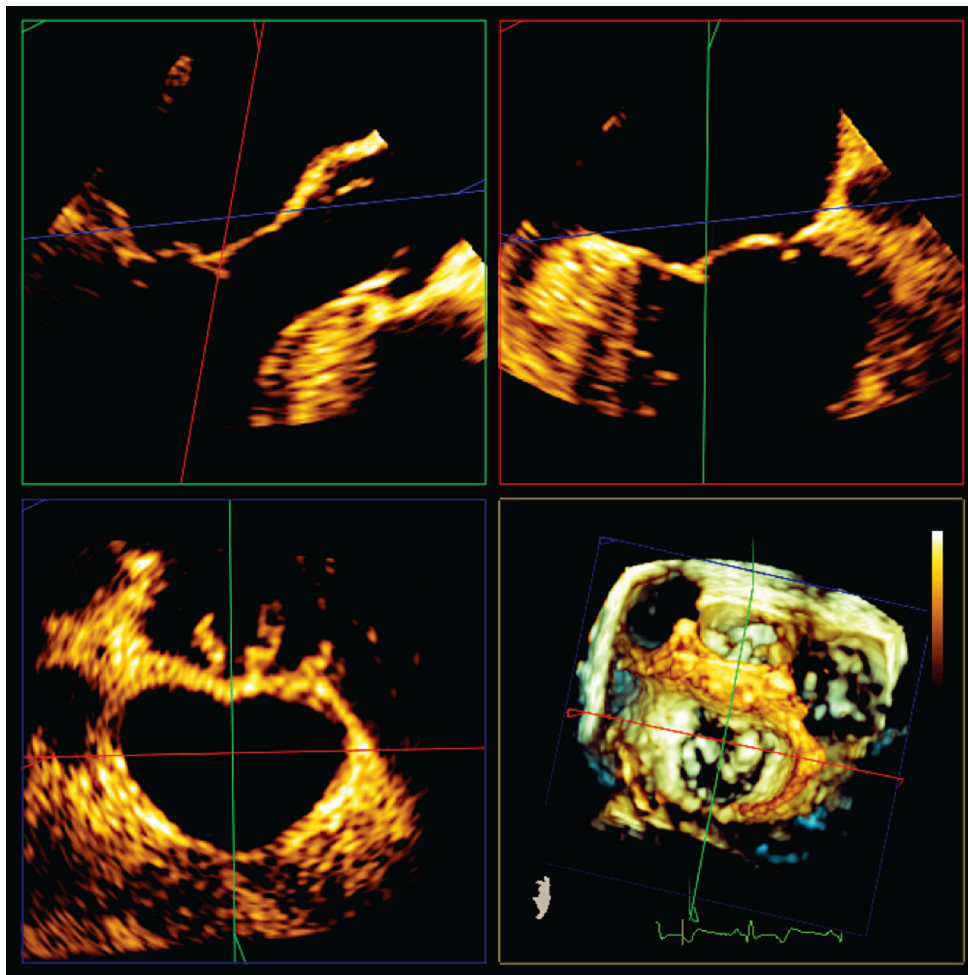


FIGURE 59-5 ■ Multiplanar reformatting (MPR) of three-dimensional echocardiographic images can allow for more precise measurements by aligning orthogonal planes across structures of interest. In this case the planes are aligned so that the area and diameters of the mitral annulus (*bottom left*) can be measured.

Although the observation by Reiz and colleagues⁵³ in 1983 that isoflurane may cause coronary steal (a phenomenon in which coronary blood flow is diverted away from the collateral-dependent region of the myocardium) tended to discourage the use of the inhalational agent, subsequent investigators failed to duplicate the findings.⁵⁴⁻⁵⁶ The newer agents sevoflurane and desflurane do not cause coronary steal either.^{57,58} In addition, animal studies suggested that isoflurane may preferentially dilate large coronary arteries rather than arterioles (thus mimicking the effect of nitroglycerin⁵⁹) and normal coronary arterioles rather than arterioles from a collateral-dependent region of the myocardium.^{60,61}

Fast-track cardiac surgery (FTCS) refers to a multidisciplinary approach to providing care to cardiac surgical patients, with emphasis placed on early tracheal extubation (within 6 to 10 hours postoperatively) and expedited mobilization of the patient (with consequent reductions in ICU and hospital lengths of stay and cost).⁶² Factors that predict the success or failure of this approach (other than age) are intraoperative and postoperative clinical process variables, such as intraoperative inotrope use, intraoperative placement of an intra-aortic balloon pump, and postoperative atrial arrhythmias; thus, there is no need to preselect patients for FTCS, and everyone may be considered a potential candidate for early extubation.⁶² An important component of FTCS is an anesthetic technique that allows early extubation and mobilization of the patient.⁶³ Instead of a long-acting muscle relaxant (e.g., pancuronium), a shorter-acting agent (e.g., rocuronium, cisatracurium) may be used.⁶⁴⁻⁶⁶ Any residual blockade at the end of surgery or during the initiation of weaning may be reversed with an acetylcholinesterase inhibitor (e.g., neostigmine) in combination with an antimuscarinic agent. Instead of a high-dose opioid technique, a low- or moderate-dose opioid technique in combination with inhalational anesthetics may facilitate early tracheal extubation.⁶⁷ Hypothermia at the end of surgery should be prevented.⁶⁸ Although early extubation is favored, there is no benefit to pushing for tracheal extubation in the operating room.⁶⁹ The cost of extended operating room time and the risk of cardiorespiratory instability during the early postoperative period should also be considered. In both a retrospective review⁷⁰ and a prospective randomized controlled trial,⁷¹ it has been demonstrated that FTCS is not associated with any increase in hospital mortality or morbidity. Rather, the rate of nosocomial pneumonia may be decreased with FTCS.⁷⁰ The reintubation rate is not significantly different between FTCS and the conventional approach, and both ICU and hospital length of stay are decreased with FTCS. In response to concerns that FTCS may result in cost shifting rather than cost savings, Cheng and colleagues⁷² examined the resource use of both FTCS and conventional patients for a year after hospital discharge. Although insurance claims for outpatient visits were not significantly different at 3 months and 12 months, insurance claims and costs for inpatient care were significantly lower for the FTCS group. The savings in inpatient care were 68% at 3 months and about 50% at 1 year. Thus, FTCS may lead to savings during both the initial hospitalization for the surgery and the subsequent follow-up period.

Regional Anesthesia and Analgesia

The use of thoracic epidural anesthesia (TEA) as a supplement to general anesthesia carries several potential advantages. TEA attenuates the sympathetic stress response to surgical stimulation, reduces heart rate and myocardial oxygen consumption, and decreases the release of troponin T.^{73,74} Postoperatively, TEA provides superior analgesia, thus enabling early extubation and vigorous pulmonary toilet and reducing the incidence of lower respiratory tract infections as compared with conventional intravenous analgesia.^{75,76} Despite these advantages, TEA has not been widely accepted for cardiac surgery because of concern for a potential epidural hematoma in patients that are heparinized for CPB. The true incidence of an epidural hematoma in cardiac surgery is not known, and this complication is infrequent in cardiac surgical settings.⁷⁷ A mathematical model suggests that the risk ranges from 1:150,000 to 1:1500.⁷⁸

Recently, with the advent of off-pump, minimally invasive cardiac surgery, several European groups have reported using TEA as the sole anesthetic modality without endotracheal intubation in patients undergoing coronary artery bypass surgery^{79,80} and aortic valve replacement.⁸¹ The authors state that potential advantages of avoiding general anesthesia might include the use of the patient's mental status as a monitor of cerebral ischemia and achievement of truly FTCS. In a study of this modality by Karagoz and colleagues,⁷⁹ 8 out of 137 patients went home the day of surgery, and 58 of these 137 did not require any ICU stay, for an overall mean hospitalization of 1 day. However, 39 out of the 137 patients had a pneumothorax, and 4 of them had to be converted to general anesthesia because of pneumothorax-related respiratory difficulties. Potential disadvantages of an awake technique in cardiac surgery include the stress response of an awake patient to surgical maneuvers such as sternotomy, and a delay in surgical progress.⁸²

TEA for cardiac surgery has not yet found acceptance in the United States mainly because of the risk of epidural hematomas, its medicolegal implications, and limited evidence of an outcome benefit.

Intraoperative Blood Glucose Control

Acute and chronic hyperglycemia increase the risk of myocardial ischemic injury through several mechanisms.⁸³ Hyperglycemia decreases coronary collateral blood flow, causes endothelial dysfunction, and compromises the salutary effect of ischemic preconditioning or anesthetic-induced pharmacologic preconditioning.^{84,85} Among oral hypoglycemic agents, sulfonylureas and other insulin secretagogues impair K_{ATP} channel activation and may therefore hinder ischemic or pharmacologic preconditioning. Such agents should be discontinued for 24 to 48 hours before surgery.⁸³

Hyperglycemia occurs frequently in patients with and without diabetes during cardiac surgery.⁸⁶ Intraoperative hyperglycemia is associated with a higher morbidity and mortality in patients undergoing cardiac surgery,⁸⁷⁻⁸⁹ which might suggest that tight intraoperative glycemic control would reduce postoperative complications.

Although postoperative strict blood glucose control with insulin has been shown to definitely decrease mortality and morbidity in patients after cardiac surgery,^{90,91} similar results have not been obtained when the control was initiated during the surgery.⁹² Furnary et al⁹³ performed a prospective study of almost 2500 consecutive diabetic patients undergoing cardiac surgery who were randomized to receive either intensive insulin therapy with continuous infusion to maintain blood glucose at less than 200 mg/dL or intermittent subcutaneous insulin injections on a sliding scale. Blood glucose was better controlled with intravenous infusion (85% of patients with blood glucose <200 mg/dL on postoperative day 1, with a mean level of 199 ± 1.4 mg/dL) than with subcutaneous injections (47% of patients with <200 mg/dL, with a mean level of 241 ± 1.9 mg/dL). The incidence of deep sternal wound infection was significantly reduced in the infusion group (0.8% vs. 2.0%, $P = 0.01$) and approached that of the nondiabetic patients. Mortality was likewise reduced with intensive insulin therapy (3.0% vs. 6.1%, $P = 0.03$). In a retrospective review of 3554 diabetic patients from the same group,⁹⁴ mortality was directly related to postoperative mean glucose; it was demonstrated to be 0.9% for those with a level of less than 150 mg/dL, 1.3% for those with 150 to 175 mg/dL, 2.3% for those with 175 to 200 mg/dL, 4.1% for those with 200 to 225 mg/dL, 6.0% for those with 225 to 250 mg/dL, and 14.5% for those with greater than 250 mg/dL.

Intensive insulin therapy to tightly control blood glucose should not be employed intraoperatively only but should be extended into the postoperative period in the ICU. In a prospective study of 1548 patients in the surgical ICU (about two thirds of whom had been through cardiac surgery), intensive insulin therapy to maintain a glucose level between 80 and 110 mg/dL was associated with a lower mortality as compared with conventional therapy to maintain a glucose level between 180 and 200 mg/dL (4.6% vs. 8.0%, $P < 0.04$).⁹⁰ However, in a more recent randomized controlled study,⁹⁵ tight glucose control (81 to 108 mg/dL) was associated with a higher mortality in comparison to liberal control (<180 mg/dL). This increased mortality was not entirely explained by hypoglycemia; it is thought to be because of increased variability in glucose concentrations in the tight control group.

For perioperative glycemic control in diabetic patients, Martinez and colleagues⁹⁶ have suggested that all patients, even those not on an oral diet, require a basal insulin infusion and that exogenous insulin must be given for insulin-deficient patients. Their recommendation was to maintain the blood glucose level at less than 180 mg/mL at all times (between 80 and 110 mg/mL in the ICU), to avoid oral hypoglycemic agents until the patients are on an oral diet, to provide basal insulin to patients who are insulin deficient,⁹⁷ and to implement a hypoglycemia-prevention protocol.⁹⁶

Acid-Base Management during Hypothermia

As the temperature decreases, the solubility of a gas increases and the neutral pH of water (at which $[H^+] =$

$[OH^-]$) also increases. As a result of this, even though the total content of CO_2 does not vary, its partial pressure decreases during hypothermia. The two approaches for acid-base management during hypothermic CPB are pH-stat and alpha-stat management. With pH-stat management, the clinical objective is to maintain a pH of 7.4 at the patient's true core temperature. Blood gases and pH are measured with a correction for temperature. To maintain a pH of 7.4 at hypothermic temperatures usually requires the addition of exogenous CO_2 to maintain a temperature-corrected $PaCO_2$ of 35 to 40 mm Hg. The objective of alpha-stat management is to maintain electroneutrality. With this approach, blood gases and pH are measured without temperature correction (i.e., as if the patient's temperature were always 37°C) and maintained at a $PaCO_2$ of 40 mm Hg and a pH of 7.4. The actual pH is allowed to vary with body temperature.

With pH-stat measurement, the addition of CO_2 corrects the hypothermia-induced leftward shift of the oxyhemoglobin dissociation curve and may improve oxygen delivery to the tissues. On the other hand, because the cerebral blood flow response to CO_2 is preserved during hypothermia, pH-stat management may lead to excessive cerebral blood flow and interference with cerebral autoregulation and flow-metabolism coupling.^{98,99} However, clinical neuropsychologic outcome has not been shown to differ between pH-stat and alpha-stat management.¹⁰⁰

Anticoagulation for Cardiopulmonary Bypass

Heparin was first isolated in 1918 from liver tissue, and its name is derived from the Greek word *hepar*, meaning "liver."¹⁰¹ Heparin sulfate, which is currently produced from either porcine gut or bovine lung, is used to mimic the natural role of heparan sulfate on the vascular endothelial surface. Heparin, although it has no anticoagulant effect by itself, complexes with and enhances the activity of antithrombin (AT) in irreversibly neutralizing thrombin and activated factor X. Heparin also increases the activity of heparin cofactor II to inhibit the action of thrombin.¹⁰² What constitutes a safe and effective level of heparinization for CPB has not been established, in part because of the inconsistent relationship between heparin dosage, plasma heparin concentration, and clinical effect (as measured by the activated clotting time [ACT]), and in part because the ACT is a nonspecific test affected not only by heparin but also by platelets and temperature.¹⁰³ Most currently accepted heparin regimens use an initial dosage of 250 to 400 IU/kg to maintain an ACT of greater than 400 to 480 seconds.¹⁰⁴ However, animal studies suggest that reduced heparin administration to maintain an ACT between 250 and 300 seconds may be just as adequate.¹⁰⁵

Administration of heparin may be associated with hyperkalemia¹⁰⁶ or hypotension; the latter may be as a result of heparin-induced production of nitric oxide.¹⁰⁷ Heparin resistance may be defined as the failure of 500 IU/kg of heparin to prolong the ACT to 480 seconds or greater.¹⁰⁸ Factors that predict heparin resistance include AT levels of 60% or less, preoperative

subcutaneous or intravenous heparin therapy, platelet count of 300,000 or more per milliliter, and age of 65 years or older.¹⁰⁹ AT levels may be low because of reduced synthesis caused by genetic defects or from acquired causes such as liver disease, oral contraceptive use, and disseminated intravascular coagulation. Furthermore, increased consumption of AT may be related to disseminated intravascular coagulation, extensive deep vein thrombosis, sepsis, or preeclampsia; or from concomitant use of heparin, nitroglycerin, or the chemotherapeutic agent L-asparaginase. Treatment of heparin resistance with increasingly higher dosages of heparin is intended to maximally bind all available AT and sometimes may be effective. Alternatively, the patient may receive fresh frozen plasma¹¹⁰ or AT concentrate. In vivo recovery of AT activity is about 1.4% per unit of administered AT concentrate,¹¹¹ and the therapeutic goal should be to maintain AT activity at more than 80%.

Heparin-induced thrombocytopenia (HIT) is a potential complication of heparin treatment. This condition is also known as heparin-associated immune thrombocytopenia, heparin-associated thrombocytopenia and thrombosis (HITT), and white clot syndrome.^{112,113} HIT is divided into two types. Type I HIT is characterized by platelet activation and mild thrombocytopenia occurring within the first 2 days of treatment. Type II HIT is a serious immune-mediated disorder that can progress to arterial or venous thrombosis. It presents usually within 4 to 10 days after heparin treatment,¹¹² but it may also occur after heparin has been withdrawn¹¹⁴ or rapidly after the start of heparin administration (median time, 10.5 hours for early-onset HIT).¹¹⁵

Unfractionated heparin (UFH), which is used for anticoagulation during CPB, is associated with a higher risk for HIT than low-molecular-weight heparin (LMWH).¹¹⁶ The incidence of clinically significant HIT was low in cardiac surgery with CPB,¹¹⁷ although the incidence of heparin-dependent immunoglobulin G (IgG) antibodies was 15% to 20% in patients undergoing cardiac surgery.¹¹⁸ Patients who have a history of HIT but are negative for HIT antibodies at the time of surgery, and who require CPB, have been successfully anticoagulated with a brief course of treatment with UFH, without complications.¹¹⁹ If perioperative HIT is diagnosed, all exposure to heparin should be immediately ceased, and argatroban, lepirudin, or bivalirudin should be considered for prophylactic therapy of thrombosis until the platelet count has recovered.

After separation from CPB, heparin activity is neutralized by the administration of protamine, a compound isolated from fish sperm. To reverse the effects of heparin, protamine is given in a ratio of 1 mg of protamine per 100 UI of heparin. The use of additional doses during CPB and the variable half-life of heparin (30 to 150 min) may make dose calculations more difficult.¹²⁰ Automated heparin-protamine titration assays can also be used to calculate the protamine dose needed for reversal. Just as incomplete reversal of heparinization may lead to excessive post-bypass bleeding, excessive protamine can decrease both platelet number and function,¹²¹ can prolong ACT,¹²² and can reduce the effect of thrombin.¹²³ Determining whether a prolonged ACT after an adequate dosage of protamine indicates incomplete

heparin reversal or excessive protamine may require measurement of the thrombin time and the heparinase-ACT.

An important differential diagnosis of bleeding after CPB despite a seemingly adequate dose of protamine is heparin rebound. Besides binding to AT, heparin also binds nonspecifically to other plasma and PLT-derived proteins, as well as to endothelial cells. The affinity of heparin through this nonspecific binding process is much less than its affinity to AT. After its administration, heparin binds to AT and to other plasma proteins. When protamine is administered, it binds and displaces a large proportion of heparin from its plasma protein binding sites. The resulting heparin/protamine complexes are then cleared from the circulation by the reticuloendothelial system. Heparin rebound occurs because not all of the heparin is bound to and cleared by protamine. Instead, a proportion remains nonspecifically bound to plasma proteins and provides a reservoir of heparin that dissociates over time and produces an anticoagulant effect when it binds to AT.¹²⁴ Postoperative protamine infusion eliminates heparin rebound.¹²⁵

Five types of protamine-related adverse reactions have been recognized. First, rapid administration of protamine (>5 mg/min) may at times induce the release of histamine from mast cells and thus cause systemic hypotension.¹²⁶ Second, protamine may act like an antigen and initiate an IgG- or IgE-mediated anaphylactic reaction, especially in diabetic patients who take daily subcutaneous protamine-containing insulin preparations,¹²⁷⁻¹²⁹ and possibly in those with a fish allergy or those who have just had a vasectomy.¹³⁰ Third, protamine-heparin complexes may activate the complement system, thereby leading to an anaphylactoid reaction.^{131,132} Fourth, protamine-heparin-mediated complement activation may lead to thromboxane A₂ generation, precipitating catastrophic pulmonary hypertension¹³³; this is in contrast to the low systemic and pulmonary pressures seen in classic anaphylactoid reactions. In a pig model, this reaction was preventable by prior administration of indomethacin or a thromboxane A₂ receptor antagonist.¹³⁴ Last, fulminant noncardiogenic pulmonary edema and systemic anasarca have been reported 15 minutes to more than 1 hour after the administration of protamine.¹³⁰ Treatment of a protamine reaction is mainly supportive, and various agents (e.g., diphenhydramine, steroids) and hemodynamic support have been suggested. In a patient with a history of prior adverse reaction to protamine, it should be determined whether the reaction was immunologically mediated. Levels of IgG, IgE, thromboxane, and C5a at the time of the reaction, if available, may be useful, but a skin test or enzyme-linked immunosorbent assay has not been found to be useful.¹²⁶ When the cause of the reaction is uncertain, some people advocate pretreatment of the patient with steroids and histamine receptor blockers and slowing the administration of protamine. If a true immunologically mediated protamine reaction were to occur, it would be best to avoid it. Protamine alternatives that are being tested include recombinant platelet factor 4,¹³⁵ hexadimethrine,¹³⁶ heparinase,¹³⁷ and a heparin removal device that uses a venovenous circuit with a poly-L-lysine-agarose surface.¹³⁸

Use of Antifibrinolytics

Despite adequate heparinization, CPB is usually accompanied by a low-level activation of coagulation and fibrinolysis,¹³⁹ which leads to the consumption of coagulation factors and increased postoperative bleeding. Three antifibrinolytics in common use are ε-aminocaproic acid (EACA), tranexamic acid (TA), and aprotinin. EACA and TA are synthetic analogs of the amino acid lysine and competitively block the lysine binding sites between plasmin and fibrin or fibrinogen. They reduce fibrinolysis and, by reducing fibrin split products, indirectly prevent platelet dysfunction. No uniform dosage regimen has been established for either EACA or TA. For EACA, a plasma level of 130 mg/mL is needed for the complete inhibition of fibrinolysis,¹⁴⁰ and dosage regimens include three doses of 10 g (before the incision, on pump, and after bypass) or a weight-based initial loading of 150 mg/kg followed by an infusion of at least 15 mg/kg/hr. For TA, Horrow and colleagues¹⁴¹ recommend a 10-mg/kg load followed by an infusion of 1 mg/kg/hr, but other regimens have also been published. Both EACA and TA are renally eliminated. TA has been found to be as effective as, or more effective than, EACA for reducing blood loss, but both were better than placebo.^{142,143} In patients requiring deep hypothermic circulatory arrest (DHCA), there have been reports of fatal thrombosis in association with EACA use.¹⁴⁴

Aprotinin is a serine protease inhibitor that inhibits plasmin, trypsin, kallikrein, and bradykinin-kinin. The activity of aprotinin is measured in kallikrein-inhibiting units (KIU), and 1 mg of aprotinin is equal to 7140 KIU. In addition to inhibiting fibrinolysis, aprotinin may reduce the consumption of coagulation factors and the activation of mediators of inflammation. Aprotinin is at least as effective as TA or EACA for reducing perioperative blood loss, but it is much more costly.¹⁴² High-dose (also referred to as full-dose) aprotinin involves a loading dose of 2,000,000 KIU (280 mg) followed by an infusion dose of 500,000 KIU/hr, with an additional 2,000,000 KIU in the pump. Because of concern about the cost and side effects of the medication, a low-dose (half-dose) regimen, which consisted of a loading dose of 1,000,000 KIU (280 mg) followed by an infusion dose of 250,000 KIU/hr, with an additional 2,000,000 KIU in the pump, has been tried and appears to be equally effective.¹⁴⁵⁻¹⁴⁷ Aprotinin is cleared renally and may cause thrombotic sludging in the renal tubules, thus leading to a risk-adjusted increase in serum creatinine level and renal dysfunction but not renal failure.^{148,149} A nonrandomized retrospective study by Mangano and coworkers demonstrated that aprotinin was associated with a doubled risk of renal failure requiring dialysis.¹⁵⁰ However, other studies showed that aprotinin was not associated with clinically significant renal dysfunction.^{151,152} Aprotinin has been used safely even in patients with chronic renal failure or preexisting renal dysfunction.^{153,154} In one report, renal dysfunction and thrombotic complications were noted with aprotinin use in patients requiring DHCA,¹⁵⁵ but other authors found aprotinin to be safe even with DHCA.¹⁵⁶⁻¹⁵⁸ Although nonrandomized retrospective studies have shown that aprotinin was

associated with higher mortality, myocardial infarction, and stroke,^{148,150,159} another meta-analysis of 138 randomized controlled trials did not demonstrate any significant risks for mortality, stroke, or myocardial infarction with aprotinin use.¹⁴⁹ A multicenter randomized blinded trial with a head-to-head comparison of aprotinin, ε-aminocaproic acid, and tranexamic acid concluded that although aprotinin was a more effective hemostatic agent, it was associated with increased 30-day hospital mortality.¹⁶⁰ As a result of these findings, aprotinin has been withdrawn from the market in several countries, including the United States. Because aprotinin is isolated from bovine-lung mast cells, there is a risk of allergic reactions, with the incidence of anaphylaxis reported to be less than 0.6% on initial exposure but up to 5% with reexposure within 6 months,¹⁶¹ although the incidence falls rapidly to 1.9% in the 6- to 12-month period, and to 0.4% in the > 12-month period.¹⁶¹

Cerebral Protection

Central nervous system injury is a frequent complication of cardiac surgery. A large multicenter study found an overall incidence of 6.1% of adverse cerebral outcomes.¹⁶² Perioperative stroke worsens prognosis in patients who have undergone cardiac surgery, increasing mortality at 1 year up to 30% when compared to patients without stroke.¹⁶³

Brain injury associated with cardiac surgery is multifactorial, and the main role of the anesthesiologist is to provide supportive measures to prevent it. Brain oxygen supply and demand balance must be maintained. This involves prevention and aggressive management of hypotension with vasoactive medications or volume expansion. Adequate gas exchange and oxygenation must be ensured. Depth of anesthesia should be controlled, to diminish brain metabolism, hence augmenting tolerance to ischemia. Hyperglycemia and high body temperature should be avoided because both can increase neurologic damage.

Deep hypothermic circulatory arrest (DHCA) is an important management strategy for acquiring a bloodless surgical field in certain types of surgery, particularly in aortic arch reconstruction. Techniques that have been used to ameliorate ischemic injury of the brain during DHCA include selective cannulation and perfusion of cerebral vessels, retrograde cerebral perfusion, pharmacologic brain protection, and the achievement of deep hypothermia. At normothermia, roughly half of the oxygen consumed is used to maintain cellular integrity ("basal" cerebral metabolic rate [CMRO_2]), and the other half is used to maintain electrical activity ("functional" CMRO_2).¹⁶⁴ Hypothermia has a greater effect on the basal CMRO_2 than on the functional CMRO_2 .¹⁶⁵ The electroencephalogram (EEG) becomes isoelectric at 18° C, and below this temperature, any further reduction in CMRO_2 is from a decrease in basal CMRO_2 . Barbiturates, which reduce functional CMRO_2 without having much effect on basal CMRO_2 , do not produce any additional metabolic suppression under conditions of deep hypothermia (15° C), and they are not likely to be of benefit.¹⁶⁶ On the other hand, barbiturates may be of benefit for ameliorating the effects of temporary focal

ischemia (e.g., from an air embolus on normothermic bypass) by the suppression of functional CMRO₂.

Ischemic injury from DHCA may be temporally divided into four phases.^{167,168} The first phase is marked by failure in energy production and membrane depolarization. After ischemic depolarization occurs, detrimental neuroexcitatory transmitters such as glutamate are released. With the restoration of blood flow, the third phase ensues, marked by an increased release of oxygen free radicals and subsequent tissue damage. In the fourth phase, ischemia may also trigger apoptosis or programmed cell death over the ensuing weeks. Inhalational anesthetics lower the critical cerebral blood flow to a level below which the majority of patients develop ischemic EEG changes.^{169,170} At normothermia, the critical cerebral blood flow is 10 mL/100 g/min for isoflurane, 11.5 mL/100 g/min for sevoflurane, 15 mL/100 g/min for enflurane, and 20 mL/100 g/min for halothane. This metabolic suppression effect of inhalational agents amounts to delaying the first phase of ischemic injury. In addition, isoflurane may inhibit excitotoxicity from the accumulation of glutamate during the second phase of ischemic injury. Isoflurane has been shown to reduce the release of glutamate during ischemia¹⁷¹ and may also be an antagonist of glutamate receptors, thereby diminishing deleterious calcium influx.¹⁷² Because of its effect on the first two phases of ischemic injury, isoflurane may buy time before irreversible neuronal damage sets in. However, in aortic surgery settings where DHCA is used, anesthetics have not been demonstrated to be of benefit. Similarly, although various other pharmacologic modalities (e.g., diuretics, steroids, calcium channel blockers) have been used, none has been demonstrated to be of benefit in DHCA.

Hemodynamic Support on Separation from Cardiopulmonary Bypass

Separating a patient from CPB may be considered a form of cardiopulmonary resuscitation, and thus it should start with the confirmation of a patent airway (usually with an endotracheal tube) and the reestablishment of ventilation. For support of the circulation, the anesthesiologist needs to continually assess and treat alterations in preload, afterload, contractility, rate, and rhythm. Furthermore, the metabolic parameters that affect myocardial function, such as pH, electrolytes (especially potassium, calcium, and magnesium), oxygen-carrying capacity (hemoglobin), and temperature, have to be controlled. In addition, the anesthesiologist needs to maintain constant communication with the surgical team, because certain maneuvers may mechanically affect myocardial function. TEE assessment of the adequacy of the surgery (e.g., valvular anatomy and function) and the patient's tolerance of separation from CPB also needs to be communicated to the surgeon.

Usually, epicardial pacing wires are placed, and the pacing function is tested before separation. A rhythm that preserves the atrial augmentation of ventricular preload is preferred (e.g., sinus rhythm, atrioventricular sequential pacing). If the pump flow is set at an adequate cardiac output, the vascular tone of the patient may be adjusted

to the desired mean arterial pressure while the patient is still on CPB; this way, the mean pressure will be in the desired range if the patient generates the desired cardiac output after separation. Then, the heart is filled, a process that is guided by its appearance in the surgical field and on TEE, as well as by the filling pressures (see Fig. 59-3). Wall motion on TEE and cardiac output measurement serve as practical surrogate measures of contractility. Further adjustment of preload may be made by additional filling or draining of the heart by the perfusionist, by adjustment of the operating table position, or by intravenous fluid administration. Adjustment of the afterload to maintain the systemic and pulmonary vascular resistance in the desired range may be made with vasopressors (e.g., phenylephrine, norepinephrine, dopamine) or vasodilators (e.g., nitroglycerin, nitroprusside). In cases of catecholamine-resistant refractory hypotension, vasopressin in dosages of 0.02-0.06 U/min may be attempted.¹⁷³ Inotropic assistance to augment myocardial contractility may be provided by inotropic agents (e.g., epinephrine, dopamine, dobutamine) or phosphodiesterase inhibitors (e.g., milrinone).¹⁷⁴ When pharmacologic and metabolic support prove insufficient, consideration should be given to mechanical support devices (e.g., an intra-aortic balloon pump, ventricular assist devices) or to returning the patient to CPB for further surgical management. Only when the patient is hemodynamically stable after separation from CPB should reversal of heparinization be started.

SPECIAL CONSIDERATIONS

Off-Pump Coronary Artery Bypass

Off-pump coronary artery bypass (OPCAB) involves bypass grafting on a beating heart without using CPB. Although OPCAB was first performed in 1967,¹⁷⁵ the number of OPCABs being performed only peaked in the past decade, when 25% of coronary artery bypass surgeries performed in North America in 2004 were OPCAB.¹⁷⁶

Early retrospective studies suggested OPCAB was associated with a lower incidence of perioperative stroke, decreased postoperative major bleeding, and decreased length of stay and risk-adjusted mortality.^{177,178} However, more recent prospective studies have failed to demonstrate a clear advantage of OPCAB to on-pump bypass,^{179,180} and growing concerns about a higher incidence of incomplete revascularization, decreased long-term graft patency, and increased late mortality in OPCAB have significantly decreased its popularity during the past decade.¹⁸¹⁻¹⁸⁴ Although still controversial, the main role of OPCAB in the future may be in patients with porcelain or severely sclerotic aortas, or patients in whom prolonged heparinization should be avoided.¹⁷⁶

For an anesthesiologist, OPCAB involves more challenging and intensive hemodynamic management, with the potential for instability because of retraction and compression of the heart and consequent potential myocardial ischemia.¹⁸⁵ After sternotomy and exposure of the heart, each target vessel is identified, and a specialized retractor is applied to provide exposure of the target site.

Test occlusion of the target vessel to assess its effect on myocardial function or to provide ischemic preconditioning (or both) is performed in some centers. To perform certain grafts, particularly in the circumflex and posterior descending arteries, the exposure of the target artery will be possible only with the use of stabilization systems.¹⁸⁶ In these cases the heart may be lifted and tilted to improve surgical exposure, and this maneuver may compromise the filling of the cardiac chambers, lowering stroke volume and arterial blood pressure and raising the CVP and right ventricular end-diastolic pressure.¹⁸⁷ The distortion of the mitral and tricuspid annulus may also lead to valve regurgitation,¹⁸⁸ and the compression of the thin-walled right ventricle against the interventricular septum may decrease diastolic filling.¹⁸⁹ A decrease in coronary blood flow of up to 50% has been documented also during exposure of target sites in OPCAB.¹⁹⁰ To maintain coronary perfusion pressure, the patient may be placed in a 20-degree head-down position, given fluids, and supported with a vasopressor (e.g., phenylephrine). Constant communication between the anesthesiologist and the surgeon is the key to preventing unexpected hemodynamic compromise. The diagnosis of ischemia during OPCAB is particularly difficult, because retraction of the heart is associated with a significant decrease in the amplitude of the ECG signal.¹⁸⁵ Furthermore, stabilization devices may produce nonischemic regional wall motion abnormalities on TEE. With lifting of the heart, visualization by TEE is also compromised, and the team must rely on direct visualization of the surgical field and traditional hemodynamic monitors such as an arterial line and a PAC. Proximal anastomoses are performed with a side-biter clamp on the aorta. Systemic blood pressure and aortic wall tension need to be controlled for the application and removal of the side biter.

The level of heparinization required for OPCAB has not been standardized.^{191,192} At some centers, “full” heparinization to maintain the ACT at more than 480 seconds is used, whereas others use limited heparinization to maintain the ACT in the 200- to 300-second range, as is done for vascular procedures. Neither approach has been demonstrated to be clearly superior.

Minimally Invasive Cardiac Surgery

The port-access system is used for minimally invasive cardiac surgery (MICS) that requires the institution of CPB. Preoperative preparation of the patient requires discussion between the surgeon and the anesthesiologist about the exact nature of the surgery planned.^{193,194} The usual intravenous access and monitoring modalities (i.e., those used for conventional cardiac surgery) need to be placed. TEE is an essential modality, and contraindications to the use of TEE would almost preclude port-access MICS. A modified lateral decubitus position is frequently used, and this may have important implications for line placement. To provide lung isolation, a double-lumen tube or a bronchial blocker may be used. Position of the lung-isolating device should be confirmed with a fiberoptic bronchoscope upon placement and again after final positioning of the patient. The bronchoscope should be readily available throughout the

procedure, because any malposition of the tube can result in lung inflation and thus make the surgery almost impossible through the limited incision. Before positioning the patient, external cardioversion pads should be applied for urgent pacing or cardioversion, because the limited access means that internal paddles cannot be employed.

The mainstays of the port-access system are the coronary sinus catheter (CSC) for administration of retrograde cardioplegia, the pulmonary artery vent (PAV), and the endovascular aortic cannula, which also acts as an endovascular clamp (Fig. 59-6). Unlike the regular PAC, the CSCs are not heparin bonded by the manufacturers, so 5000 units of heparin are administered before placement of these types of catheters. Before CSC placement, a persisting left-sided superior vena cava needs to be excluded by TEE. This anatomic variant is asymptomatic and relatively frequent among the general population,¹⁹⁵ occurring in up to 0.3% to 2% of the population.¹⁹⁶ A persistent left-sided superior vena cava drains into the coronary sinus, so it should be suspected if the coronary sinus appears dilated during TEE examination. Injection of contrast into a left-side intravenous line would cause contrast to appear inside the coronary sinus if this abnormality is present.

Under TEE guidance, the success rate of CSC placement has been reported to be 95% and to be superior to fluoroscopy.^{33,197} After successful placement of the CSC, its position is further confirmed by balloon inflation and visualization of the arterialization of the pressure tracing. Although it is not essential, keeping the balloon inflated and the wire loaded into the catheter until immediately before administration of retrograde cardioplegia may help prevent catheter dislodgement. The PAV is also inserted through the right internal jugular vein and guided into the pulmonary artery in the same manner as

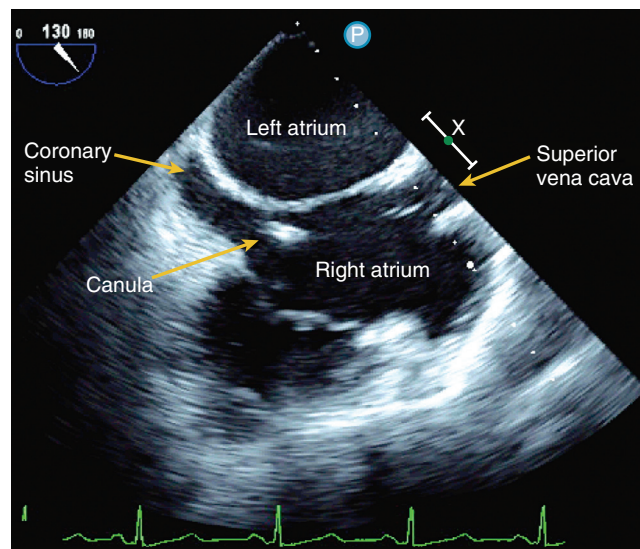


FIGURE 59-6 ■ Coronary sinus catheter. Percutaneous cannulation of the coronary sinus for cardioplegia administration in minimally invasive cardiac surgery. The introducer for this catheter was placed in the right internal jugular vein, and the catheter was advanced inside the right atrium and then directed toward the coronary sinus.

a regular PAC. However, central venous pressure cannot be measured with the PAV. Venous access or a drainage line is placed through the femoral vein, and TEE is used to accurately position the cannula. Similarly, the endovascular aortic cannula can be accurately placed under TEE guidance. The positions of the catheters should be confirmed after a change of position from supine to lateral and before commencement of CPB, because poor visibility makes it difficult to reposition the catheters after commencement of CPB.

Regardless of the type of surgery, recognizing intracardiac air and monitoring the success of de-airing maneuvers are always important aspects of TEE examination. The left ventricular apex, which may not be accessible to the surgeon for needle aspiration, needs to be carefully examined by TEE. TEE is the only monitor used to assess the completeness of de-airing.¹⁹⁷

Other factors to consider during MICS include the possible need for urgent cardiac pacing and external cardioversion; suture placement in sites that are difficult to access (which can lead to bleeding); unsatisfactory valve repair resulting in residual regurgitation; and air embolism. Even a small amount of bleeding in a minimally exposed place can result in tamponade after chest closure. The duration of anesthesia and surgery tends to be prolonged, and there is always a risk of a technically unsatisfactory result and need for conversion to an open surgery. At the end of the surgery, the CSC is removed, and, depending on the condition of the patient, the PAV may be replaced with a PAC for postoperative monitoring of the patient.

Robotic-Assisted Cardiac Surgery

Robotic-assisted cardiac surgery (RACS), the next step in the evolution of MICS, is available in only a few places in the world. Its goal is to perform the procedure with as small an incision as possible, with an outcome that would be equivalent or superior to that of the conventional procedure.^{198,199} Anesthetic management for RACS requires all of the techniques outlined earlier for port-access MICS, and the possibility of significantly prolonged surgery and the potential for positional neurovascular injuries (e.g., to the brachial plexus) must also be considered.¹⁹⁹ Preliminary reports indicate faster recovery and a reduction in complications,^{200,201} but long-term results are still pending.

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CRITICAL CARE FOR THE ADULT CARDIAC PATIENT

Judson B. Williams • Carmelo A. Milano • Peter K. Smith

CHAPTER OUTLINE

IMMEDIATE POSTOPERATIVE CARE

Initial Evaluation

- Airway and Ventilation
- Neurologic Examination
- Initial Cardiac Auscultation and Electrocardiogram
- Abdominal and Genitourinary Examination
- Peripheral Perfusion
- Body Temperature
- Hemodynamics
- Lines, Tubes, Devices, and Dressings
- Chest Radiograph

Cardiac Surgery with Cardiopulmonary Bypass

Cardiac Surgery without Cardiopulmonary Bypass

Pericardiotomy Syndrome

CARDIAC DYSFUNCTION AFTER CARDIAC SURGERY

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INFECTION

This chapter will familiarize providers with the expected management of patients following adult cardiac surgery using a systematic approach. The common and important side effects or complications of cardiac surgery are described, and their managements are reviewed. The provided references support evidence-based approaches to common postoperative conditions and represent important sources for more detailed analysis of individual topics. The chapter is not meant to be comprehensive but instead focuses on common conditions encountered by those caring for patients in the intensive care unit (ICU) following adult cardiac surgery.

IMMEDIATE POSTOPERATIVE CARE

Initial Evaluation

A systematic evaluation of the patient should be performed immediately on arrival in the ICU. The first step is a structured hand-off or debriefing, which occurs jointly between the surgical, anesthesia, and critical care teams and is critical for patient safety.¹ This structured hand-off may be tailored to individual institutions but should provide a review of the relevant patient history, including comorbid conditions and allergies; pertinent

details of the procedures performed; intraoperative hemodynamic management; discussion of lines, tubes, devices, and dressings; active/ongoing medications; and any expected deviations from routine postoperative care. Although attention may be focused initially on one aspect of the patient's condition (e.g., hypotension), a systematic approach to initial hand-off and evaluation is essential. Following the structured hand-off or briefing, a more detailed evaluation is undertaken by the critical care provider as follows.

Airway and Ventilation

The trachea should be palpated and confirmed to be in the midline, and breath sounds should be auscultated bilaterally. Adequacy of ventilation and absence of tension pneumothorax should be confirmed. The ventilator should be functioning normally and without alarms—if it is not, the patient should be immediately converted to hand-controlled ventilation. The peak inspiratory pressure should be noted. High inspiratory pressures may indicate a tension pneumothorax, inappropriate ventilator settings, or severe pulmonary or chest wall restriction. Pulse oximetry, mixed venous oximetry, and direct measurement of arterial gas tensions are used to confirm adequate oxygen delivery and CO₂ elimination.

Neurologic Examination

Evaluation of the patient's neurologic status should be performed frequently. Uncontrollable hypertension or extreme variability of peripheral vascular resistance may result from severe neurologic injury initially ascribed to residual anesthetic agent.

Initial Cardiac Auscultation and Electrocardiogram

The cardiac examination should document normal heart sounds and the character of any murmurs. The initial electrocardiogram (ECG) may be difficult to interpret because of lead placement changes related to surgical dressings, cardiac pacing, and the presence of conduction abnormalities. Right bundle branch block and first-degree atrioventricular (AV) block occur frequently but usually resolve within the first few postoperative hours. Maintaining a normal sinus rhythm with an adequate rate is important in the early postoperative period when cardiac output may be transiently impaired because of intraoperative ischemia or because of temporary diastolic dysfunction resulting from myocardial edema. First-degree AV block can result in substantial reduction in the instantaneous end-diastolic left ventricular (LV) volume, which determines stroke volume. The use of atrial or AV sequential pacing can overcome these transient derangements, and, in the latter case, it is common to see improved cardiac function with normalization of the AV interval despite abnormal ventricular activation with the ventricular pacing component.

Atrial fibrillation is poorly tolerated in the first postoperative day, and every effort should be made to maintain sinus rhythm, even in patients with preexisting

chronic atrial fibrillation. Immediate cardioversion is often required in the ICU, although atrial fibrillation occurring on the third postoperative day or later is usually well tolerated.

Ventricular arrhythmias may result from early graft failure or coronary spasm, which should be ruled out. A malpositioned pulmonary artery catheter irritating the right ventricular (RV) outflow tract is more easily correctable. Arrhythmias may have many contributing factors (e.g., hypothermia, electrolyte derangement, acid-base imbalances, drug effects), which must be considered and addressed.

Abdominal and Genitourinary Examination

Abdominal examination will reveal the presence of a well-positioned nasogastric or orogastric tube. Exclusion of unexpected masses, organomegaly, pain, or abdominal distention should be documented. Correct placement and securing of the indwelling urinary catheter should be confirmed. Urine should be clear, not concentrated, and free of hemoglobin or frank blood. This is also the time for evaluation of groin or inguinal surgical sites, which are of particular importance when recovering patients following transcatheter and minimally invasive procedures.

Peripheral Perfusion

The adequacy of global and regional perfusion should be assessed by physical examination of the vascular system, including examination of accessible pulse character and the quality of skin and soft tissue perfusion. Intraoperative embolization, vascular injury, or low cardiac output in the setting of peripheral vascular disease may compromise limb perfusion. Special attention should be paid to perfusion distal to any intra-arterial cannulas or lines. This is also the time for evaluation of upper or lower extremity surgical sites as from vessel harvest or vascular cannulation.

Body Temperature

Initial hypothermia is best avoided by expeditious operation and adequate rewarming while the patient is on cardiopulmonary bypass. Hypothermia compromises cardiac function, impairs surgical site healing, causes shivering and increased metabolic demand, interferes with coagulation, and may aggravate or cause rhythm disturbances.² Blankets, other auxiliary warming devices, and fluid warmers for intravenous infusions should be used, particularly in the bleeding patient. Fever is poorly tolerated in the early postoperative period and should be treated aggressively with antipyretics and possibly with intravenous steroids if there is associated hemodynamic compromise.

Hemodynamics

With appropriate cardiac rhythm, the patient should have a cardiac index of greater than 2 liter/min/m² with blood pressure adequate for systemic perfusion. This requires consideration of the patient's age, preoperative blood

pressure, and renal function. The importance of generating adequate cardiac output has been established by several studies with mortality as the outcome variable.³ Acceptance of lower cardiac output occasionally results in good outcome when associated with reasonable mixed venous oxygen saturation (MVO₂) (>55%), adequate urine output (>20 mL/hr without stimulation), and evidence of good peripheral and central perfusion (physical examination, maintenance of acid-base balance). There is no evidence that supranormal cardiac output is beneficial.

Elevated central venous pressure (CVP), especially when associated with facial edema or facial discoloration, must be aggressively evaluated. Possible causes include cardiac tamponade, volume overload, right heart dysfunction, or technical errors that have compromised superior vena caval flow. Elevated pulmonary artery pressures may indicate LV dysfunction or cardiac tamponade, or may be related to preoperative changes in pulmonary vascular resistance. All central pressures should be related to initial values obtained during preoperative studies. Central pressure measurements are also quite sensitive to afterload, which can vary widely and rapidly in the early postoperative course in patients who are often hypovolemic. Elevation of intrathoracic pressure can frequently mimic cardiac failure in the patient with chest wall rigidity because of emergence from anesthetic effect and shivering. The latter process can also increase metabolic demand and reduce MVO₂ to very low levels.

Lines, Tubes, Devices, and Dressings

The type, size, and location at the incisors of the patient's endotracheal tube should be noted. A discussion of the ease of intubation is typically part of the initial debriefing/hand-off with the anesthesia team upon ICU arrival.

All indwelling lines must be confirmed to be functional, particularly those delivering vasoactive drugs. Transport of the patient can partially or completely dislodge intravenous lines. Hemodynamic instability resulting from failure of drug delivery and tissue injury resulting from drug infiltration must be avoided. Mediastinal and pleural space tubes (chest tubes) are placed to underwater seal and are usually set to have -20 cm H₂O suction applied. Mediastinal tubes should be examined for the quantity and quality of drainage. The initial amount of drained blood should be less than 100 mL, and larger amounts should be explained by the surgical team. The initial rate of drainage may reflect drainage of blood or irrigation fluid that has accumulated, particularly in the left thoracic gutter. Nonetheless, an initial assessment of the bleeding rate, tube patency and clotting in the tubes, and correlation of drainage with intravascular volume replacement are critically important. When multiple chest tubes are present, good practice is the labeling of these tubes (e.g., mediastinal vs. pleural, right vs. left) by the operating room nurse to avoid errors and improve communication throughout the patient's recovery.

Pacemaker, intra-aortic balloon pump, or ventricular assist device settings should be recorded. Sutures and dressings securing these various devices at the skin should be confirmed to be intact.

Surgical site dressings are commonly kept intact during the first 48 hours for infection control. If dressings must be disturbed for diagnostic purposes or if they become saturated during this time, strict aseptic technique should be followed. If negative pressure dressings are used or special antimicrobial dressings for lines or devices, then the planned strategy for maintenance of these should be discussed at the initial hand-off upon ICU arrival.

Chest Radiograph

A portable chest radiograph should be obtained and interpreted immediately on arrival. Critical aspects include (1) position of the endotracheal tube, (2) pneumothorax or mediastinal shift, (3) lobar atelectasis, (4) pleural and extrapleural fluid collections, (5) size of the mediastinal silhouette, (6) correct intravascular location of lines, and (7) satisfactory position of radiopaque markers for any devices, sternal wires, or drainage tubes.

Cardiac Surgery with Cardiopulmonary Bypass

Cardiopulmonary bypass (CPB) induces many of the physiologic changes encountered in the postoperative patient, and its duration is a primary determinant of the rapidity of recovery. CPB nonspecifically activates the inflammatory system,⁴ a phenomenon that begins with the interaction of heparinized blood and the bypass circuit.^{5,6} Generalized complement activation is seen, with elevations in C3a and C5a anaphylatoxins after discontinuation of CPB.^{5,7-9} This activation can lead to pulmonary sequestration of leukocytes and the production of superoxides and other products of lipooxygenation.^{5,7} This causes further leukocyte activation and the generation of leukotactic circulating factors that increase the local inflammatory response, including elevations in tumor necrosis factor- α (TNF- α), interleukin (IL)-1, and prostaglandin E₁.¹⁰⁻¹² The generalized inflammatory reaction seen after CPB may change vascular permeability and cause pulmonary hypertension as well as bronchial hyperreactivity.¹³ Together with transient elevations in left atrial pressure, reduced oncotic pressure from hemodilution and increased vascular permeability also contribute to increased pulmonary shunt from the resultant extravascular water.¹⁴

Cellular components that play a significant role in inflammatory response to CPB include circulating cells (platelets, neutrophils, monocytes) and regulatory cells (endothelial cells). Platelets are activated by shear forces, heparin, foreign surfaces, and activated thrombin, a potent platelet agonist. Despite full anticoagulation with heparin, thrombin continues to be generated.¹⁵ The clinical consequences of platelet activation include generation of microemboli, thrombosis, and bleeding from diminution of platelet number and function.¹⁶ Additionally, vasoactive substances may be liberated from platelets in response to CPB or protamine infusion, which can cause pulmonary hypertension and systemic hypotension.¹⁷

Neutrophil activation occurs consequent to the complex interaction of blood with the CPB circuit.

Proinflammatory mediators (e.g., IL-1, -2, -6, and -8, TNF α), complement anaphylatoxins (C3a and C5a), platelet activating factor (PAF), and leukotriene-B4 (LTB4) increase the number of cell surface adhesion molecules and promote neutrophil adhesion to the pulmonary endothelium. Neutrophil adherence and transmigration into the lung occurs under the influence of IL-8. Proteolytic enzyme and oxygen free radical release from activated neutrophils promote further tissue injury and inflammatory activation of endothelial cells.¹⁸

Endothelial cells are a central player in inflammation and coagulation. Specific agonists responsible for endothelial activation have been characterized and include IL-1 β , TNF α , C5a, and thrombin.⁹ Endothelial cell activation results in a procoagulant, vasoconstrictive, and proinflammatory response. Once activated, the anticoagulant properties of the endothelial cell are dramatically reduced, with loss of heparan sulfate proteoglycan, conformational changes in the endothelial cell resulting in increased exposure to tissue factor and von Willebrand factor in the cellular submatrix, increased expression of tissue factor and plasminogen activator inhibitor type 1, and loss of thrombomodulin. The vasoconstrictive effects occur through the production of endothelin-1 and thromboxane A2. Proinflammatory changes are seen with increased expression of P and E selectins and consequent recruitment and sequestration of inflammatory cells.⁶

Cardiac Surgery without Cardiopulmonary Bypass

On-pump coronary artery bypass surgery has been demonstrated by randomized controlled trials to both reduce symptoms and prolong life in every decade since the first coronary artery bypass graft (CABG) procedures were performed in the 1960s. Despite the proven benefits and ever-increasing safety of this procedure, room for improvement remains with regard to neurocognitive complications, atrial fibrillation, transfusions, stroke, and death.¹⁹ Because CPB is perhaps the most invasive aspect of conventional coronary revascularization, and because much of the morbidity of coronary revascularization can be attributed to hypothermic cardiac arrest, aortic cannulation, cross-clamping, and the bypass circuit itself, surgeons may consider performing coronary anastomoses on the beating heart without CPB. Some individual surgeons or institutions perform most coronary revascularization procedures without CPB. The term *off-pump coronary artery bypass (OPCAB)* generally refers to multi-vessel coronary artery bypass performed off the CPB machine, through a standard sternotomy.

Here we will focus on those differences between OPCAB and conventional on-pump revascularization procedures that may substantially impact the patient's recovery. During OPCAB procedures, coronary arteries are individually snared proximally and occluded during the performance of the coronary anastomosis. Depending on whether intracoronary shunts are used, there may be periods of local ischemia without cardioplegic arrest. However, unlike in the conventional on-pump procedures, there are no periods of aortic cross-clamping

and global cardiac arrest. For these reasons, the degree of myocardial stunting during OPCAB may be reduced relative to on-pump procedures. Furthermore, during OPCAB, normothermic pulsatile flow is maintained throughout the procedure, whereas conventional on-pump procedures include a period of nonpulsatile perfusion and generally some degree of systemic cooling and rewarming. Finally, although both techniques require anticoagulation with heparin, many centers practice reduced-heparin dosing for OPCAB. Despite multiple randomized controlled trials, the issue of off-pump versus on-pump myocardial revascularization remains an area of debate.^{20,21} The inflammatory response to CPB appears to be a nonspecific response that includes complement and leukocyte activation.^{4,5,7,10} Although the exact mechanism of activation is unclear, the strongest stimulant for the response is the blood-artificial surface contact that occurs with CPB. This response can be modified by coating the tubing and oxygenator surfaces with biological materials and by improving the hemodynamic performance of the system. Theoretically, by eliminating the heart-lung machine entirely, this response could be significantly reduced.

Several quality studies have investigated the inflammatory response during heart surgery, comparing groups in which coronary revascularization is performed with and without CPB.^{22,23} Angelini and colleagues looked at four important inflammatory markers: neutrophil elastase, an endopeptidase released with neutrophil activation; IL-8, a potent neutrophil chemotactic and activating factor; and C3a and C5a, fragments generated with activation of the common complement pathway.²⁴ These markers were measured at four time-points within the first 24 hours postoperatively. Patients were randomized to two groups: standard coronary revascularization with CPB and OPCAB. The OPCAB group demonstrated significantly lower levels of all four markers and had reduced leukocyte, neutrophil, and monocyte counts. These findings support a reduced inflammatory response with OPCAB; however, the clinical significance of this difference remains unclear. It is interesting that by 4 hours into the recovery period, the activated complement components had decreased in the on-pump group to OPCAB levels.²⁵

OPCAB requires less intraoperative anticoagulation and avoids blood-artificial surface contact, which should reduce platelet activation and destruction. Furthermore, systemic cooling, which may further negatively impact coagulation function, can be avoided with OPCAB. Several studies have compared on-pump procedures to OPCAB and report significant reduction in postoperative bleeding, reduced need for perioperative transfusion, and reduced rate of take-back for bleeding.²⁶ Indeed, when coagulation and fibrinolysis variables have been studied, marked changes in fibrinolytic and coagulation variables occur within the first 24 hours. Conventional on-pump revascularization causes a transient decrease in the platelet count, fibrinogen level, and activation of plasminogen with increased D-dimer formation, which only after 24 hours approximate the levels seen in OPCAB.²⁷ Two contemporary multicenter randomized controlled trials have supported reduced need for blood transfusion and

reoperation for bleeding following off-pump compared to on-pump CABG; however, rates of rate of death, myocardial infarction, stroke, or renal failure requiring dialysis were no different.^{20,21}

Pericardiotomy Syndrome

A specific manifestation of the inflammatory response in cardiothoracic surgery is the post-pericardiotomy syndrome.²⁸ This syndrome, occurring in 10% to 30% of patients, is a self-limited condition beginning in the second or third week after surgery. It is associated with fever and pleuritic, precordial, or substernal chest pain.²⁹ Chest radiographs in patients with post-pericardiotomy syndrome commonly show pleural and pericardial effusions (Fig. 60-1). This syndrome has been associated with specific reactive antibodies and may be seen after any operation that violates the pericardium.²⁹ It is treated with nonsteroidal anti-inflammatory agents, although corticosteroids may be necessary in severe cases.³⁰

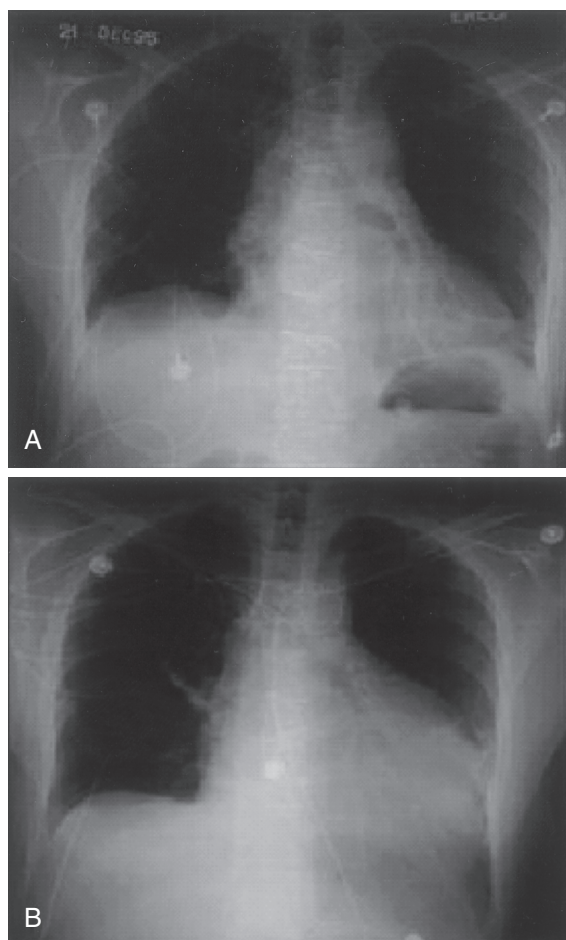


FIGURE 60-1 ■ Post-pericardiotomy syndrome is commonly associated with pericardial and pleural effusions. **A**, Chest radiograph on a patient soon after aortic valve replacement shows expected postoperative findings. **B**, Chest radiograph 2 weeks later shows pericardial effusion compatible with the clinical symptoms of post-pericardiotomy syndrome.

CARDIAC DYSFUNCTION AFTER CARDIAC SURGERY

Low Cardiac Output Syndrome

Output and Filling Pressure

Low cardiac output after CPB has historically been recognized as a cause of sudden death.³¹ Low cardiac output resulting from ventricular dysfunction causes a series of adaptive neurohumoral responses as well as geometric changes—dilation and hypertrophy—in the heart. Acute loss of 20% to 25% of functioning myocardium³² causes significant reduction in cardiac output and carries extremely poor short-term³³ and long-term prognoses.³⁴

Measurement and therapeutic manipulation of both cardiac output and central filling pressures are critical to the postoperative care of cardiac surgical patients and are predictive of survival (Fig. 60-2). Central pressures, cardiac output, and venous saturation are routinely measured by means of a flow-directed pulmonary artery catheter. The cardiac index, or cardiac output expressed as liters per minute per meter squared, has a normal range of 2.1 to 4.9 liter/min/m².³⁵ In adults, a cardiac index of at least 2.0 liter/min/m² during the immediate postoperative period is generally required for normal convalescence.

Oxygen Delivery

Shock may be conceptualized as a clinical syndrome resulting from an imbalance between tissue oxygen demand and tissue oxygen supply. The general goals of postoperative care are to prevent shock and provide adequate oxygen delivery. Oxygen delivery of less than 335 mL/min/m² has been associated with a decrease in

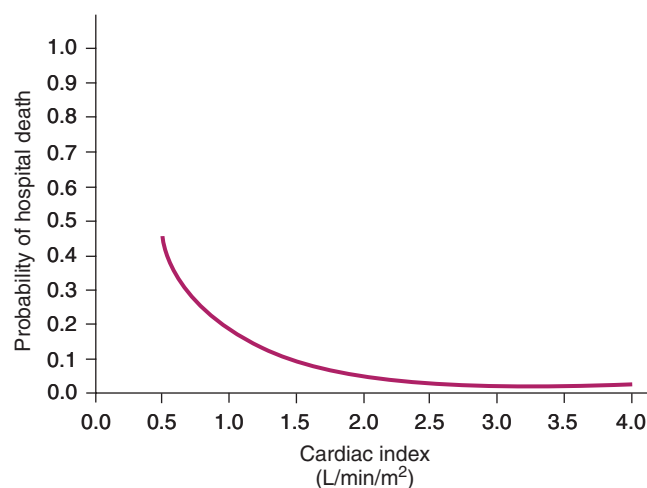


FIGURE 60-2 ■ The graph shows the relationship between postoperative cardiac index and probability of death for adults after mitral valve replacement. (Reproduced with permission from Kouchoukos NT: Detection and treatment of impaired cardiac performance following cardiac surgery. In Davila JC, editor: *Henry Ford Hospital International Symposium on Cardiac Surgery*, ed 2, New York, 1977, Appleton-Century-Crofts.)

oxygen consumption and with the development of progressive lactic acidosis.³⁶ Lactic acidosis has been suggested as a metabolic monitor to correlate with total oxygen debt, the magnitude of hypoperfusion, and the severity of shock.^{37,38} However, a direct relationship to total oxygen delivery has been disputed.³⁹ MVO_2 provides a useful index of the adequacy of circulation and reflects, to some extent, mean tissue oxygen level.⁴⁰ MVO_2 is measured with specialized pulmonary artery catheters, and patients with a saturation of less than 60% or those who demonstrate a decrease of more than 5% suffer more frequent postoperative complications.⁴¹ However, others have shown poor correlation between saturation, or trends in saturation, and outcome.⁴² Rapid changes in whole-body oxygen consumption may reduce its overall predictive value.

Adequate regional oxygen delivery is even more difficult to determine. Organ requirements and hormonally activated reflex changes in regional blood supply may occur in the postoperative state. For example, the kidneys, skin, and resting muscles are blood-supply independent and maintain viability by increased oxygen extraction. The heart and brain, on the other hand, are blood-supply dependent, with near maximal oxygen extraction at rest. Sympathetically controlled reflexes compensate for these differences by a shift of blood flow from the skin and splanchnic region at low circulating volumes.⁴³ Splanchnic hypoperfusion is known to be a cause of persistent acidosis.⁴⁴

Acute changes in regional blood supply may be mediated by differing degrees of sympathetic innervation to

precapillary sphincters and arterioles.⁴⁵ Alterations in metabolic activity are common after heart surgery and may be monitored through capnography, which determines the partial pressure of CO_2 in expired gases.⁴⁶ Peripheral vasodilation and shivering during rewarming have been shown to increase metabolic and circulatory demands and can be eliminated with paralysis and sedation, which promotes hemodynamic stability and decreases the need for inotropic support.⁴⁷ A diagnosis of low cardiac output syndrome must include evidence of inadequate oxygen delivery relative to consumption. Objective measurements of cardiac output and MVO_2 must be coupled with clinical evidence of diminished peripheral perfusion and end-organ ischemia to establish the diagnosis of low cardiac output syndrome.

Preload

Maintenance of adequate preload is fundamental in the postoperative management of cardiac surgical patients (Fig. 60-3). The optimal pulmonary capillary wedge pressure in postoperative cardiac surgical patients is unknown, but a range of 14 to 18 mm Hg has been suggested, with increases in extravascular lung water occurring above this level.⁴⁸ Preload correlates directly with the force of ventricular contraction, and the result is a ventricular volume change from end diastole to end systole determined by transmural pressure and compliance of the ventricular wall. Pericardial pressure is normally reflected by the right atrial pressure (Fig. 60-4). However, tight closure of the pericardium may adversely affect transmural

Illustrations for Pulmonary Artery Pressure

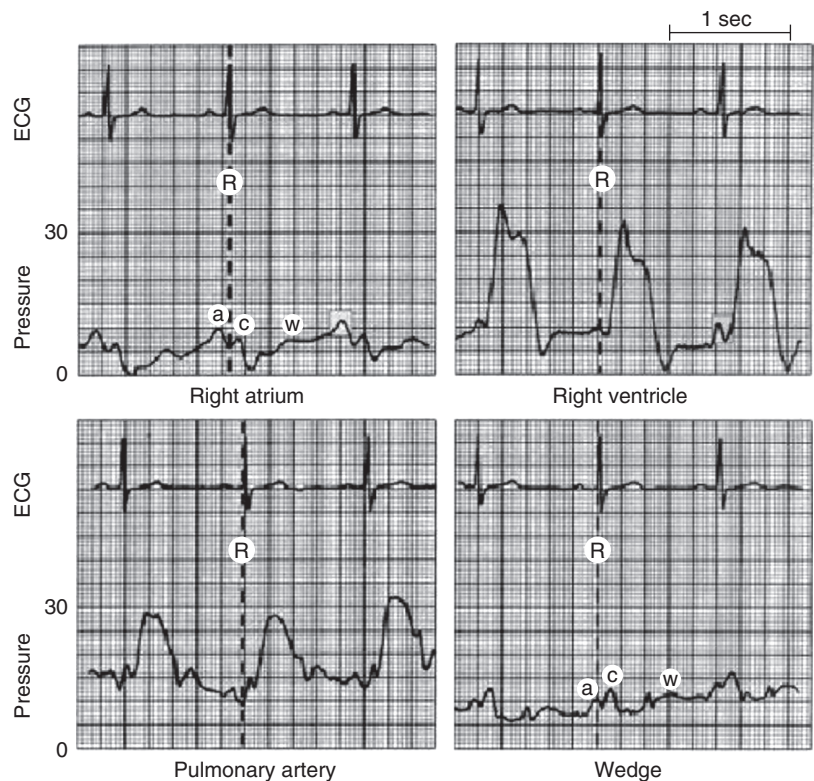


FIGURE 60-3 ■ Pulmonary artery pressure waveforms recorded from a pulmonary artery catheter as it passes through the right atrium and right ventricle to the pulmonary artery and wedge positions. Right ventricular end-diastolic pressure is measured at the time of the electrocardiographic (ECG) R wave and is estimated best by the right atrial a wave pressure peak. The a, c, and w waves are recorded from both the right atrium and pulmonary artery wedge positions. (Reproduced with permission from Mark JB: *Atlas of cardiovascular monitoring*, New York, 1998, Churchill Livingstone.)

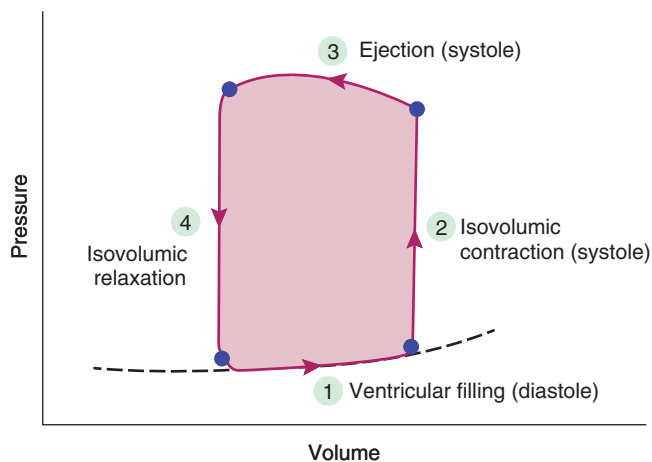


FIGURE 60-4 ■ Idealized pressure-volume loop for the left ventricle represents a single cardiac cycle. (Reproduced with permission from Chatterjee K, Parmley WW: The role of vasodilator therapy in heart failure. *Prog Cardiovasc Dis* 19:301–325, 1977.)

pressure and decrease stroke volume.^{24,49} Pulmonary artery wedge pressures and the CVP, surrogates for LV and RV volumes respectively, more accurately reflect reduced filling pressures, whereas high filling pressures may be determined by changes in transmural pressure or myocardial compliance rather than accurately reflecting preload.

CVP, the downstream pressure of the systemic venous system, is frequently measured in patients recovering from cardiac surgery. Existing literature focuses on the degree to which CVP gives information on RV end-diastolic pressure and the limitations of CVP as a surrogate variable for left ventricular preload, although the clinical prognostic value of CVP measurement remains unknown.⁵⁰ Many post-cardiac surgery patients are being managed without a pulmonary artery catheter or under “fast-track” protocols for early removal of pulmonary artery catheters.⁵¹ However, CVP usually can be measured in these patients by way of a central venous catheter with its tip in the superior vena cava. Emerging data suggest that CVP may be a useful predictor of patient outcome and the postsurgical patient with elevated CVP may warrant further workup to investigate the cause (renal failure, pericardial tamponade, right heart failure, etc.).⁵²

Most postoperative cardiac surgical patients are relatively hypovolemic and have a labile reactive vasculature.⁵³ In the immediate postoperative period, causes of hypovolemia include large urine volumes, ongoing blood loss, and a significant cross-sectional increase in vascular beds with rewarming. The summation of these physiologic changes is a reduced preload, particularly in the left ventricle. This trend should be anticipated and managed with appropriate volume therapy to prevent precipitous hypotension and low cardiac output. Immediate preload augmentation may be achieved with passive straight leg raising, with a transient 8% to 10% increase in cardiac output,⁵⁴ although this should be viewed as only a temporizing measure and should be quickly supplanted by appropriate volume resuscitation.

Afterload

Postoperative Effects

After a cardiac operation, elevation in afterload is a well-recognized phenomenon. The incidence varies with cardiac pathology, operative procedure, and definition of the resulting hypertension. After valve replacement, the reported incidence ranges between 8% and 12%.⁵⁵ After myocardial revascularization, afterload is elevated in 8% to 61% of patients.^{56,57} Increased systemic vascular resistance at the arteriolar level appears to be the major determinant of arterial pressure after coronary artery surgery.⁵⁸ The cause of postoperative hypertension remains unclear, but contributing factors include decreased baroreceptor sensitivity⁵³ and elevated renin-angiotensin activity.⁵⁹

Sympathetic stimulation and elevated levels of catecholamines also have been identified in the early postoperative period.^{57,60,61} Furthermore, postoperative pain may increase afterload and can be managed with the administration of an analgesic.⁶²

Although pulmonary artery pressures are measured directly (RV afterload), the ascending aortic pressure is inferred by measurements made at a peripheral artery, typically the radial artery. Systolic amplification may occur, elevating the measured systolic radial artery pressure relative to central arterial pressure; however, mean pressures are generally similar between these regions.

In the control of afterload, autoregulation at various sites should be considered. The central nervous system autoregulates mean blood pressures of 50 to 150 mm Hg.⁶³ A reset lower limit for autoregulation may be higher in hypertensive patients.⁶⁴ Renal autoregulation requires a mean blood pressure of 70 mm Hg.⁴³ The heart with residual coronary disease also requires adequate mean arterial pressure (65 mm Hg), as do patients with pathologic concentric myocardial hypertrophy.⁶⁵

Acute afterload reduction in the postoperative period is frequently beneficial (Fig. 60-5). However, afterload reduction with low filling pressures often produces a compensatory tachycardia, which may be deleterious. In addition, adequate preload must be achieved before the institution of vasodilating agents. When applying afterload reduction to patients with high filling pressures, there is usually no change or a slight reduction in heart rate. Experimental evidence suggests that afterload reduction, when applied to low or normally filled ventricles, may increase infarct size⁶⁶; when applied in a setting of high preload, infarct size may be reduced.^{67,68} This may have implications in patients after incomplete myocardial revascularization.

Therapeutic Approaches

Afterload reduction generally improves cardiovascular function and diminishes preload. The degree to which hemodynamic improvement can be obtained with afterload reduction is difficult to predict. Therapeutic results depend on the end-systolic pressure–volume relationship of each patient. Preload augmentation coupled with afterload reduction has additional positive effects on

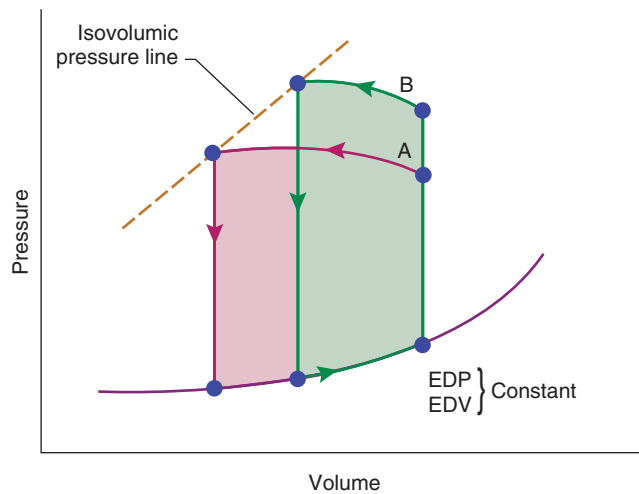


FIGURE 60-5 ■ Acute postoperative afterload reduction. Two idealized pressure-volume loops are at the same level of contractility and end-diastolic volume (EDV), but with a reduction in arterial pressure from loop B to loop A, which results in an increase in stroke volume. EDP, End-diastolic pressure. (Reproduced with permission from Chatterjee K, Parmley WW: The role of vasodilator therapy in heart failure. *Prog Cardiovasc Dis* 19:301–325, 1977.)

overall cardiac function.⁶⁹ Afterload reduction also improves forward ejection in patients with residual mitral and aortic insufficiency.^{70,71}

Although various afterload-reducing agents are available, nitroglycerin, nitroprusside, and nicardipine are among the frequently used agents in the immediate postoperative period. Nitroglycerin improves coronary collateral flow and may prevent coronary spasm, and it is frequently used for the first 12 to 24 hours after coronary revascularization.^{72,73} Nicardipine is short-acting, does not have direct myocardial contractility effects, and is growing in popularity with regard to aortic surgery. Nitroprusside is similarly short-acting but may increase ST-segment elevation in perioperative ischemia and cause significant intracoronary shunt.⁷² Nonetheless, nitroprusside continues to be used for the acute management of postoperative hypertension, mandating a knowledge of this agent's adverse effects.⁷⁴

When nitroprusside is used at high doses (greater than 7 µg/kg/min) for prolonged therapy, cyanogen, cyanide, and thiocyanate are potential toxic breakdown products. Signs of toxicity are subtle and include a narrowing of the arteriovenous oxygen difference and the development of metabolic acidosis.⁷⁵ Thiocyanate levels may be measured under these circumstances, with levels of 50 to 100 mg/liter associated with cyanate toxicity, and 200 mg/liter may be lethal. Discontinuance and dialysis are the mainstays of treatment, although prophylactic infusion of hydroxocobalamin (25 mg/hr) has been shown to decrease cyanate concentration. In surgery for aortic disease, nitroprusside has been shown to be associated with an increased incidence of neurologic complications believed to be referable to reduced spinal cord blood flow.⁷⁶

Alternative parenteral agents should be considered when high-dose nitroprusside therapy is necessary. Intravenous nitroglycerin may achieve afterload reduction as

well as coronary dilation. Hydralazine, although longer acting, may also be effective.⁷⁷ Nicardipine is a calcium channel blocking agent with effects more selective to vascular smooth muscle as opposed to cardiac muscle and does not impede myocardial function. Beta blockers are effective in the management of postoperative hypertension and are being used more commonly in patients with LV failure. Esmolol, a short-acting selective beta blocker, may be particularly useful in this setting, although these agents may have a significant negative inotropic effect.

Many patients require afterload reduction throughout their postoperative course. Patients with persistent hypertension and with reduced LV function will benefit from long-term afterload reduction and should be converted to oral medications. Chronic afterload reduction, in patients with significant congestive heart failure, has been shown to have a positive impact on survival. In patients with symptomatic congestive heart failure (New York Heart Association [NYHA] class II and class III), a significant reduction in long-term morbidity and mortality has been seen in those treated with enalapril, an angiotensin-converting enzyme (ACE) inhibitor.⁷⁸ Additional studies have confirmed that ACE inhibitors are particularly useful for afterload reduction in patients with heart failure.^{79,80} Patients with asymptomatic LV dysfunction (NYHA class I and class II) may also benefit from long-term therapy with ACE inhibitors or aldosterone antagonist therapy. Echocardiographic studies in post-myocardial infarction patients have shown that ACE inhibitors attenuate LV enlargement.⁸¹ Nitrates and hydralazine have also been used but are less effective than ACE inhibitors.⁸² Recently, in a large community-based study, decreased hospital readmission for symptoms of congestive heart failure has been associated with the prescription of aldosterone antagonist therapy among older patients hospitalized with heart failure and reduced ejection fraction.⁸³

Heart Rate

The postoperative control of heart rate is important and encourages standard application of temporary, epicardial, bipolar atrial, and ventricular pacing wires in most patients. Normal sinus rhythm, through synchronized end-diastolic preload augmentation, is responsible for approximately 25% of cardiac output in the postoperative setting (Fig. 60-6).⁸⁴ Changes in heart rate are common after cardiac surgery and include sinus bradycardia, junctional rhythm, and first-, second-, or third-degree heart block. These phenomena are usually transient and may be related to perioperative beta blockade, intraoperative antiarrhythmics, or metabolic damage during cardioplegic arrest including potassium or magnesium abnormalities.⁸⁵ Inadequate myocardial protection may cause ischemia of the conduction system.⁸⁶ Permanent injury to the conduction system is most often the result of direct surgical injury during intracardiac procedures. Management of disturbances in heart rate must be individualized. Simple atrial pacing (in the range of 90 to 110 beats/min) is optimal for sinus bradycardia. With AV nodal blocks, AV pacing with an interval in the range of 150 to 175 msec is usually optimal.^{87,88} The AV interval also depends

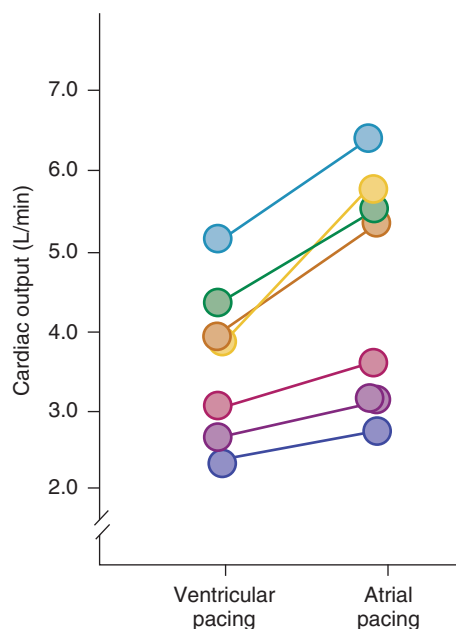


FIGURE 60-6 ■ Synchronized end-diastolic preload augmentation. A comparison of cardiac output with ventricular pacing (without synchronous atrial systole) and with atrial pacing shows an overall increase in cardiac output with atrial pacing of approximately 26% in patients after cardiac surgery. (Reproduced with permission from Hartzler GO, Maloney JD, Curtis JJ, et al: Hemodynamic effects of atrioventricular sequential pacing after cardiac surgery. *Am J Cardiol* 40:232–236, 1977.)

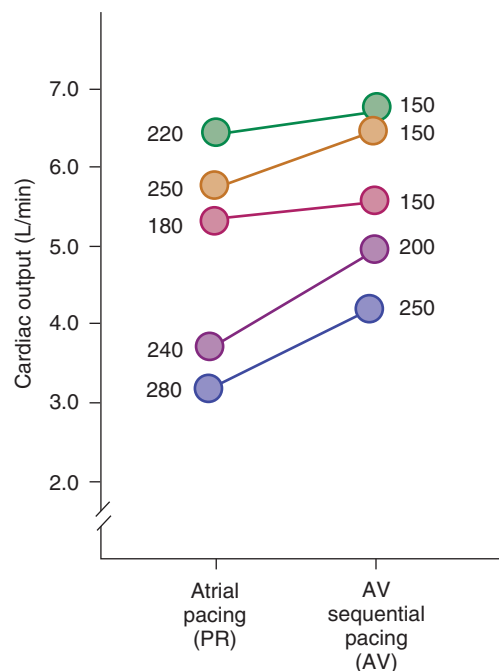


FIGURE 60-7 ■ Cardiac output with atrioventricular (AV) sequential versus atrial pacing. A comparison of AV sequential pacing and atrial pacing in patients with a prolonged postoperative PR interval (intrinsic and paced PR intervals are shown in milliseconds to the left for atrial pacing and to the right for AV sequential pacing). Note the uniform increase in cardiac output that is induced by pacing, despite absolute differences in the shortening of the PR interval, and the overlap between paced PR intervals and intrinsic PR intervals between patients. (Reproduced with permission from Hartzler GO, Maloney JD, Curtis JJ, et al: Hemodynamic effects of atrioventricular sequential pacing after cardiac surgery. *Am J Cardiol* 40:232–236, 1977.)

on selected heart rate (Fig. 60-7). The normalization of AV synchrony by these means is associated with a loss of the normal ventricular activation sequence, depressing ventricular function at constant preload and afterload by approximately 10% to 15%. Optimal heart rate determination must be individualized for each patient with reference to measurements of cardiac output.

When in place, temporary pacing wires constitute a direct current pathway to the heart and must be insulated when not in use. Caution is needed when connecting a rapid-pacing device to the wires to ensure atrial connection. Temporary pacing wires are usually removed in the early postoperative period but may be left in place indefinitely. High pacing thresholds usually develop within 2 weeks, unlike permanent endocardial electrodes. When temporary pacing is not possible, bradyarrhythmias may be treated pharmacologically with atropine or isoproterenol. Alternatively, a pulmonary artery catheter with an additional pacing port or a transthoracic pacemaker may be used.⁸⁹

Inotropic Support

Inotropic agents may be necessary to achieve adequate cardiac function (Fig. 60-8) and to maintain peripheral oxygen delivery. Improvement in cardiac function by pharmacologic intervention is generally achieved at the expense of increased myocardial oxygen consumption. Wide variability among cardiac surgery centers exists with regard to the routine use of inotropic and vasoactive medications, with some centers using positive vasoactive medications for almost all patients.⁹⁰ In general, inotropic agents should be considered only after manipulations of heart rate, preload, and afterload have been maximized. Myocardial function typically improves throughout the postoperative course, allowing weaning from inotropic support.⁹¹

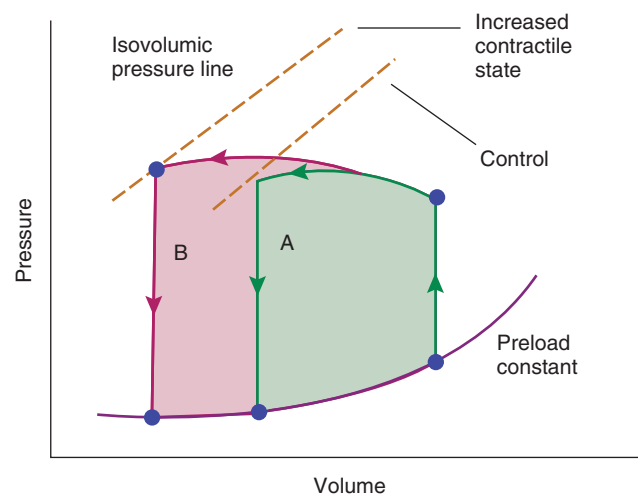


FIGURE 60-8 ■ Pressure-volume loops inscribed under conditions of constant preload and afterload. An induced increase in inotropic state from loop A to loop B shifts the end-systolic pressure-volume relationship (dashed lines) and results in increased stroke volume in loop B. (Reproduced with permission from Chatterjee K, Parmley WW: The role of vasodilator therapy in heart failure. *Prog Cardiovasc Dis* 19:301–325, 1977.)

Various inotropic agents are available, and all are administered by either intravenous bolus or continuous infusion. These agents should be administered through a central venous or pulmonary artery catheter whose intravascular position has been ascertained to prevent perivascular infiltration. Most inotropic agents act through stimulation of adrenergic receptors (Table 60-1). β -Adrenergic agonists mediate an increase in intracellular calcium concentration.⁹² Clinical experience with multiple inotropic agents has demonstrated synergism despite in vitro evidence that the maximal positive inotropic effect of one drug precludes augmentation by another.⁹³ This may be because of alterations in the adenylate cyclase system in patients with heart failure, or because of alterations in beta-adrenoreceptor density.^{92,94-96}

Nonadrenergic inotropes include digoxin, calcium chloride, phosphodiesterase inhibitors (amrinone, milrinone, and enoximone), and triiodothyronine. The presence of metabolic acidosis may interfere with the effectiveness of inotropic agents.⁹⁷ Most inotropic agents, most importantly β -adrenergic agonists, have proarrhythmic effects. Improved cardiac output must be balanced against risks of inducing either atrial or ventricular arrhythmias. Patients who require high doses of dopamine, epinephrine, or norepinephrine experience dangerous vasoconstrictive effects because of the α -adrenergic agonist effect of these agents at higher doses. This effect can result in limb, mesenteric, or renal ischemic injury.

Intra-aortic Balloon Pump

Mechanical ventricular support should be considered before the patient suffers significant end-organ hypoperfusion, which may impede ultimate recovery. Insertion of an intra-aortic balloon pump (IABP) via a percutaneous femoral arterial approach is the initial step in mechanical ventricular support. A properly functioning IABP provides increased diastolic coronary perfusion and augmented cardiac output by reducing LV afterload (Fig. 60-9). Greater deterioration of ventricular function may warrant assist devices that provide complete support; these devices are used as bridges to either myocardial recovery or possible cardiac transplantation.

Cardiac Tamponade

Cardiac tamponade results from occupation of the mediastinal space by fluid or clotted blood, which restricts the end-diastolic volume of both ventricles. It has been reported to occur acutely in 3% to 5% of open heart surgery cases.⁹⁸⁻¹⁰⁰ The constellation of findings associated with acute postoperative cardiac tamponade includes (1) increased variation in blood pressure with respiration (pulsus paradoxus); (2) equalization and elevation of the CVP, pulmonary artery diastolic pressure, and left atrial pressure or pulmonary artery wedge pressure¹⁰¹; (3) a fall in urine output (often an early finding); (4) excessive chest tube drainage or, paradoxically, minimal or no chest tube drainage, especially with heavy clots noted within the chest tubes; (5) mediastinal widening on chest film; (6) low cardiac output (late); and (7) hypotension (late). No single finding or combination of findings is sufficient to establish the diagnosis, and a high index of clinical suspicion should be maintained. Early postoperative tamponade is treated by reoperation. Patients in extremis may require reopening of their sternotomy in the ICU. Temporizing management consists of (1) volume loading, (2) reduction of airway pressure (removal of positive end-expiratory pressure [PEEP], anesthetizing agents, diminishing tidal volume with increasing ventilatory rate), and (3) inotropic support.

Cardiac tamponade may be present with any amount of retained blood or fluid, which commonly is circumferential but which may be loculated and still adversely affect cardiac function.^{102,103} In patients with decreased ventricular function, smaller amounts of space occupation will result in tamponade physiology.¹⁰⁴ For patients with severe ventricular dysfunction, simple reapproximation of the sternum after cardiac surgery may not be possible. Delayed sternal closure may be necessary in 1% to 2% of high-risk patients, and subsequent closure is usually possible between 1 and 4 days after initial operation.¹⁰⁵

To a certain extent, the pleural and mediastinal spaces are continuous, and resulting intrathoracic pressure is distributed to affect the lungs and cardiac chambers simultaneously. An open pericardium and pleural space

TABLE 60-1 Inotropes

Vasoactive Drug	Dose ($\mu\text{g/kg/min}$)	AR Activation			Physiologic Response				
		α_1	β_1	β_2	SVR	MAP	CO	HR	PAWP
Dopamine	<5	—	++	—	$\leftrightarrow$	$\uparrow$	$\uparrow$	$\uparrow$	$\leftrightarrow$
	>5	++	++	—	$\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow$	$\uparrow$	$\uparrow$
Dobutamine	2-20	—	++	+	$\downarrow$	$\uparrow$	$\uparrow$	$\uparrow$	$\downarrow$
Epinephrine	<0.05	—	++	+	$\downarrow$	$\uparrow$	$\uparrow$	$\uparrow$	$\downarrow$
	>0.05	++	++	+	$\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow$	$\uparrow$	$\uparrow$
Norepinephrine	0.03-1.0	++	+	—	$\uparrow\uparrow$	$\uparrow\uparrow$	$\leftrightarrow$	$\uparrow$	$\uparrow$
Phenylephrine	0.6-2.0	++	—	—	$\uparrow\uparrow$	$\uparrow\uparrow$	$\downarrow$	$\leftrightarrow$	$\uparrow$
Isoproterenol	0.03-0.15	—	++	++	$\downarrow$	$\leftrightarrow$	$\uparrow$	$\uparrow\uparrow$	$\downarrow$
Milrinone	0.3-1.5	—	PDEI*	—	$\downarrow$	$\leftrightarrow$	$\uparrow$	$\leftrightarrow$	$\downarrow$
Amrinone	5-20	—	PDEI*	—	$\downarrow$	$\leftrightarrow$	$\uparrow$	$\leftrightarrow$	$\downarrow$

*Amrinone and milrinone are common phosphodiesterase inhibitors (PDEIs).

α_1 , Peripheral vasculature; AR, adrenergic receptor (activation); β_1 , myocardium; β_2 , peripheral vasculature and myocardium; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PAWP, pulmonary arterial wedge pressure; SVR, systemic vascular resistance.

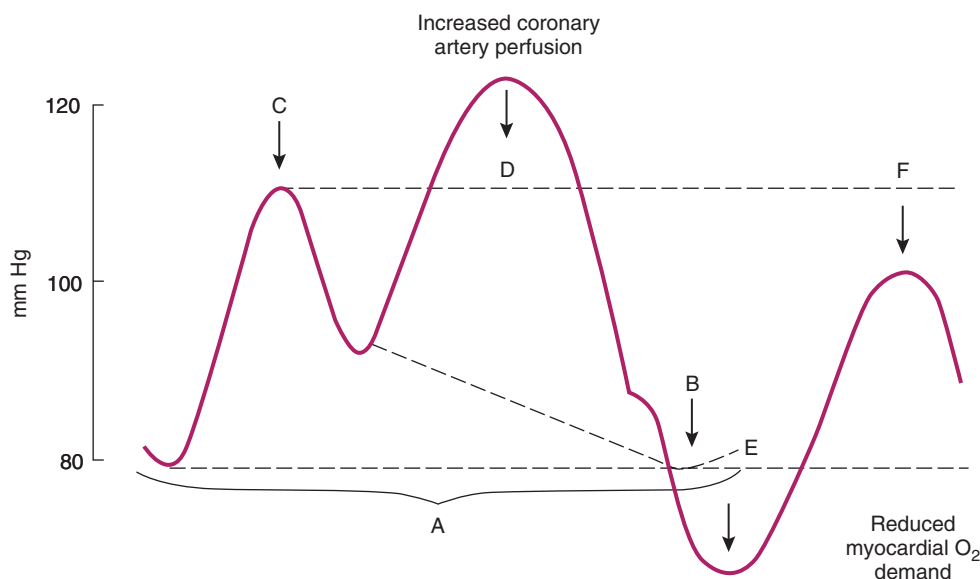


FIGURE 60-9 ■ Intra-aortic balloon pump (IABP) timing: synchronization with the cardiac cycle. Arterial pressure waveform with correct IABP timing: A, one complete cardiac cycle; B, unassisted aortic end-diastolic pressure; C, unassisted systolic pressure; D, diastolic augmentation; E, reduced aortic end-diastolic pressure; F, reduced systolic pressure. (Reproduced with permission from Helman DN: Intracorporeal support: the intra-aortic balloon pump. In Goldstein DJ, Oz MC, editors: *Cardiac assist devices*, New York, 2000, Futura, p 298.)

can neither prevent nor minimize cardiac tamponade. Increases in airway pressure, which may result from changing lung compliance or the application of PEEP, or a change in chest wall compliance may be directly transmitted to the heart. Such increases in airway pressure cause additive space occupation and may result in tamponade physiology at lower volumes of retained fluid.

Although cardiac tamponade usually presents within the first 24 hours after surgery, there is a definite incidence of late presentation.^{103,106} Most cases occur in patients with large amounts of postoperative bleeding, those who require anticoagulation, or those with active inflammation (post-pericardiotomy syndrome). Delayed diagnosis is attributed to the associated nonspecific symptoms of malaise, dyspnea, chest pain, and anorexia. Echocardiography remains the mainstay in diagnosis of delayed cardiac tamponade.¹⁰⁷⁻¹⁰⁹

Vasoplegic Syndrome

CPB induces a systemic inflammatory response that in some patients may manifest as vasodilatory shock. The clinical state of profound hypotension, low systemic vascular resistance, massive volume requirement, and increased use of vasopressors is called vasoplegic syndrome (VS). This syndrome has generally been defined as an arterial pressure of less than 50 mm Hg, a cardiac index of greater than 2.5 liter/min/m², a right atrial pressure of less than 5 mm Hg, a left atrial pressure of less than 10 mm Hg, and low systemic vascular resistance (<800 dyne • sec/cm⁵).¹¹⁰ The incidence of VS has been reported to range between 8% and 10% after cardiac surgery and up to 42% after left ventricular assist device (LVAD) placement.^{111,112}

Several factors are associated with VS, including preoperative intravenous heparin, ACE inhibitors, and

calcium channel blockers, with reported incidences as high as 56%, 44%, and 47%, respectively. Other reported risk factors include the use of alcuronium, the presence of diabetes, the use of protamine, and preoperative heart failure.¹¹² The mortality associated with this condition is considerable.¹¹³ Standard vasopressors such as norepinephrine, phenylephrine, or vasopressin have been used both intraoperatively and postoperatively to provide hemodynamic support. However, a small percentage of patients remain in vasodilatory shock despite aggressive treatment. In these patients, methylene blue has been demonstrated to be well tolerated, to significantly increase systemic vascular resistance, and to reduce mortality when given as an intravenous infusion (1.5 to 2 mg/kg over 20 to 60 min).¹¹² Side effects of methylene blue include arrhythmias; vasoconstriction of coronary, renal, mesenteric, and pulmonary vascular beds; reduced cardiac output; and angina. Most side effects, however, are dose dependent and do not occur with dosages of less than 2 mg/kg.¹¹⁰ It should not be used in patients with severe renal insufficiency, with hypersensitivity to previous administration, or with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Also, it should be used with caution in patients receiving dapsone because of its potential to cause hemolytic anemia. Although use as a rescue agent is occasionally warranted, the data are not sufficient to support use as a first-line agent.¹¹²

Right Heart Dysfunction

Although right heart dysfunction is most commonly secondary to left heart failure, it may occur as an isolated condition. In this setting, the left ventricle (LV) may display relatively preserved intrinsic function, but cardiac output remains low because of poor LV filling. Other important manifestations of isolated right heart failure

include elevated CVP, poor RV contractility, and elevated pulmonary vascular resistance. With severely impaired RV function, pulmonary artery pressures may not be elevated. Treatment strategies for isolated right heart dysfunction are similar to those used to manage a low cardiac output state caused by more conventional LV dysfunction. RV preload, as measured by the CVP, may need to be increased to greater than 20 mm Hg. Heart rate and rhythm should be optimized (sinus rhythm, rate 90 to 100). β -Adrenergic receptor agonists may be helpful, but higher doses of epinephrine, norepinephrine, or dopamine may further increase pulmonary vascular resistance and exacerbate right heart failure. Milrinone is an important agent in these circumstances, because it provides a positive inotropic effect for the right ventricle but also reduces pulmonary artery pressures as well as pulmonary vascular resistance. Finally, inhaled nitric oxide represents the most specific pulmonary vasodilator; nitric oxide, unlike milrinone, does not induce systemic hypotension. The starting dose for inhaled nitric oxide is typically 20 parts per million. A final strategy for isolated right heart failure is a RV assist device. In general, this invasive strategy should be used only after less invasive approaches have failed.

Arrhythmias

Atrial Flutter

Atrial flutter is generated by a macro-reentrant phenomenon and can be treated rapidly and effectively with electrical stimulation.¹¹⁴ Although this arrhythmia may be interrupted by a single, appropriately timed atrial extrasystole, it is most commonly interrupted by one of the following methods: (1) Entrainment, which is accomplished by determining the atrial rate and instituting atrial pacing at a slightly higher rate to capture the atria. Regularization of the ventricular response and an altered P-wave morphology are usually produced. Termination of pacing is then ordinarily followed by normal sinus rhythm (Fig. 60-10). (2) Nonspecific rapid atrial pacing or stimulation.¹¹⁵ Rapid atrial pacing is performed by introducing trains of atrial pacing at rates in the range of 450 to 600 beats/min. Short trains (less than 1 second) effectively introduce single extra stimuli within the effective refractory period of the pacing site and thus can interrupt atrial flutter and reinstate the normal sinus rhythm. If the train of rapid atrial pacing is too long, it may induce atrial fibrillation, which cannot be treated with these pacing techniques. However, in the atrial fibrillation that may ensue, the ventricular response is usually slower and thus better tolerated than that of atrial flutter.¹¹⁶ Moreover, it is not uncommon for atrial fibrillation induced in this manner to revert spontaneously to normal sinus rhythm.

Atrial Fibrillation

Incidence and Risk. Atrial fibrillation is the most common supraventricular arrhythmia after cardiac surgery. The incidence has varied from 28% to 54% of patients undergoing cardiac operations.^{99,100,117,118} The

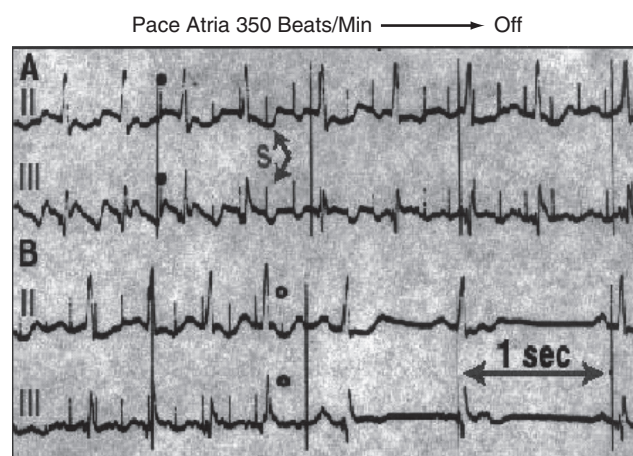


FIGURE 60-10 ■ Atrial flutter in postoperative cardiac patients. Electrocardiograph leads II and III show atrial flutter with 2:1 atrioventricular block. A and B are not continuous. At the *black dot* in A, the P-wave morphology has changed from negative to positive, which indicates entrainment. In B, after 30 seconds of pacing at 350 beats/min, atrial pacing is terminated (*open circle*). Sinus rhythm appears spontaneously. S, Stimulus artifact. (Reproduced with permission from Waldo AL, MacLean WAH: *Diagnosis and treatment of cardiac arrhythmias following open-heart surgery*, Mt. Kisco, NY, 1980, Futura.)

cause is unknown, but atrial fibrillation may result from (1) unprotected ischemia,¹¹⁹ (2) multidose cardioplegic solution administration with high potassium concentration,⁸⁵ (3) atrial dilation or inadequate atrial protection,¹²⁰ or (4) postoperative pericarditis.¹²¹

The incidence of postoperative atrial fibrillation is higher in patients with echocardiographic evidence of pericardial effusion. Certain patients may also have an inherent propensity to develop supraventricular arrhythmias related to the preoperative accumulation of catecholamines in intramyocardial axons.¹²² Additional risk factors predictive of an increased incidence of atrial fibrillation include advanced age, chronic obstructive pulmonary disease, prolonged cross-clamp periods,¹²³ and discontinuation of preoperative beta blockers. Although this arrhythmia has not been shown to increase the 30-day mortality rate, it does prolong length of hospital stay in patients undergoing CABG. Furthermore, there is an increased incidence of malignant ventricular rhythms (both ventricular tachycardia and ventricular fibrillation) and a significant increase in the postoperative stroke rate.¹²³

Diagnosis and Treatment. Diagnosis is by direct examination of atrial and ventricular bipolar ECGs.¹¹⁵ The presence of chaotic and rapid atrial depolarization indicates atrial fibrillation, whereas a regular rapid atrial depolarization with an organized ventricular response (usually 2:1 or 3:1) indicates atrial flutter (Fig. 60-11). Therapeutic objectives in patients with atrial fibrillation, in order of importance, are (1) heart rate control, (2) conversion to sinus rhythm, and (3) prevention of embolic complications. Rapid supraventricular arrhythmias causing significant hemodynamic compromise should be treated by cardioversion or defibrillation. In hemodynamically stable patients, one therapeutic option

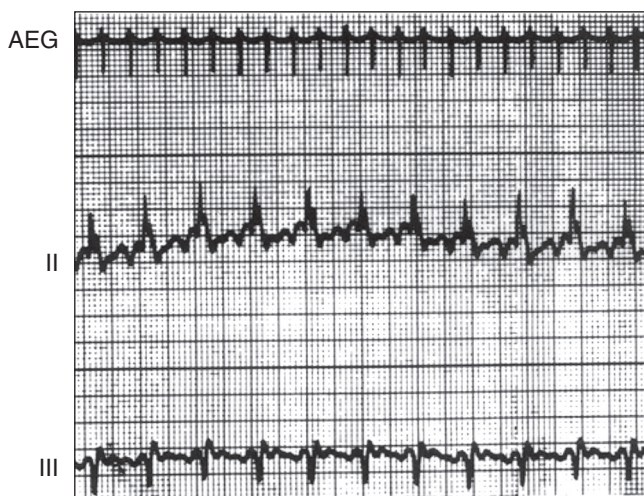


FIGURE 60-11 ■ Bipolar atrial electrogram (AEG) showing atrial flutter is seen in the upper trace, with simultaneous electrocardiograph leads II and III that show atrial flutter with 2:1 atrioventricular block. Recording speed is 25 mm/sec. (Reproduced with permission from Waldo AL, Cooper TB, MacLean WAH: *Cardiac pacing in the treatment of cardiac arrhythmias following open heart surgery: use of temporarily placed atrial and ventricular wire electrodes*. In Samet P, El-Sherif N, editors: *Cardiac pacing*, ed 2, New York, 1980, Grune & Stratton.)

for controlling ventricular response is a calcium channel antagonist: either verapamil, administered in 2.5- to 5-mg boluses to a total of 20 mg, or diltiazem given as an intravenous load followed by a continuous infusion. Diltiazem is given as a 0.25 mg/kg bolus over 2 minutes followed by an infusion of 10-15 mg/hr. These agents rapidly reduce the ventricular response by increasing AV block.¹²⁴ Verapamil is more negatively inotropic than diltiazem and must be used with caution in patients with heart failure and low cardiac output syndrome; however, the salutary effect of reduction in ventricular rate is usually more important than the negative inotropic effect of these drugs.¹²⁵ Adverse effects of calcium channel antagonists may be treated with calcium infusion, glucagon, or inotropic agents.¹²⁶⁻¹²⁸

Alternatively, beta blockers, especially those with short action (esmolol), have been studied for the acute management of atrial fibrillation. The response to beta blockade varies considerably when it is used to treat atrial fibrillation in the post-CABG patient. In addition, hypotension may be a significant side effect in as many as 20% to 40% of patients treated. Digoxin has been similarly used, although immediate heart rate control is rarely achieved.¹²⁹ Multidrug combinations can be hazardous in patients without temporary pacing wires. The combination of digoxin, verapamil, and a β -adrenergic antagonist can lead to complete heart block, and verapamil and a β -adrenergic antagonist may lead to sinus arrest.¹³⁰ Once heart rate control has been achieved, conversion to and maintenance of sinus rhythm with an antiarrhythmic agent may be necessary.

Two agents that have been used extensively for postoperative atrial fibrillation are amiodarone and sotalol. Relative to class IA agents, these drugs are believed to have equivalent efficacy and improved side effect profiles. These agents are very effective at converting atrial fibrillation, and both retard AV nodal conduction, thereby

reducing the ventricular response to atrial fibrillation. Amiodarone is typically administered as a 1-g intravenous infusion, which is given over a 24-hour period, with the initial 150 mg given over 20 minutes. Subsequent doses are given orally (400 mg, three times a day). Sotalol is available only as an oral preparation, 40 to 160 mg, given twice a day. A common approach is to first attempt chemical cardioversion with these agents, and if this fails, to perform electrical cardioversion. Sotalol can induce significant bradycardia and generally should not be combined with other beta blockers. In addition, harmful proarrhythmic effects, including ventricular tachycardia, have been described with sotalol. The incidence of these harmful rhythms has correlated with QT prolongation, and this should be monitored. Chronic amiodarone therapy can induce pulmonary fibrosis and hypothyroidism. In general, the risk of postoperative atrial fibrillation is considerably reduced after the first month, and antiarrhythmics initiated for isolated postoperative atrial fibrillation should be discontinued after this point.

There has been much interest in the prophylactic use of antiarrhythmic agents to diminish the incidence of supraventricular arrhythmias (atrial fibrillation, in particular) after cardiac surgery. However, prophylactic use of antiarrhythmics in all patients may lead to unwanted side effects in patients who would otherwise convalesce normally. As attempts to identify perioperative risk factors continue, many prefer to treat arrhythmias only when they are present.¹³¹

Ventricular Arrhythmias

Sustained ventricular arrhythmias are an uncommon postoperative issue but are life threatening and require a prompt and organized treatment strategy. Immediate electrical cardioversion should be followed by a thorough investigation for treatable causes, which may include electrolyte imbalance, hypoxia, malpositioned Swan-Ganz catheter, and proarrhythmic effects of inotropes or other agents. Myocardial ischemia should always be ruled out as the cause of the ventricular arrhythmias. A 12-lead ECG should be performed, and if ischemic changes are present, catheter-based coronary angiography should be promptly considered. Persistent ventricular arrhythmias in the postoperative patient lead quickly to hypoperfusion and a dangerous spiral. For this reason, early placement of IABP for ventricular assistance is often helpful. Persistent arrhythmias also warrant initiation of either lidocaine or amiodarone intravenously. Formal electrophysiologic testing and an implantable defibrillator may be indicated. Ventricular arrhythmias occur frequently after left ventricular assist device implantation in end-stage heart failure, often with implantable cardioverter-defibrillator required.¹³² Among patients undergoing transcatheter aortic valve replacement, heart block requiring permanent pacemaker implantation is emerging as one of the predominant complications of these procedures.¹³³

Graft Occlusion

Early graft failure usually results from technical factors, although it may be produced by scarring and is seen more

frequently in patients with inflammatory pericardial syndromes. Early graft failure may manifest as ventricular arrhythmias or as hemodynamic compromise with evidence of ischemia; alternatively, the occurrence may be clinically silent. Factors that affect the presentation include the nature of the collateral blood supply from other grafts or from the native coronary circulation. Also important is the amount of viable myocardium at risk. Patients with ventricular arrhythmias, hemodynamic change, and evidence of ischemia warrant urgent coronary angiography. Graft failure can be addressed with percutaneous interventions, or the patient can be returned to the operating room for graft revision. Perioperative myocardial infarction is defined by ECG changes, serum biomarker measurements, and the development of new regional LV dysfunction. Perioperative myocardial infarction does not result solely from graft or coronary occlusion; it may also result from compromised myocardial protection or atheroembolic events. Treatment is mainly supportive, with intravenous nitroglycerin and afterload reduction. Inotropic agents or IABP may be required during a period of myocardial recovery.

Graft patency is enhanced by the perioperative administration of antiplatelet agents. Early graft occlusion after CABG is known to result from platelet thrombus due to endothelial damage and altered blood flow in the graft. Clopidogrel is thought to potentially act in a synergistic fashion with aspirin in preventing the early platelet thrombus in bypass grafts. Initially, aspirin and dipyridamole have been used, but subsequent work suggests that low-dose aspirin alone is as effective as a combination of agents.^{134,135} Aspirin should typically be administered the morning after surgery. Clopidogrel bisulfate has also been considered for postoperative antiplatelet therapy. Clopidogrel is an inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation. It acts as a direct inhibitor of ADP by binding ADP receptors on platelets and preventing the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex. The clinical evidence for the efficacy of clopidogrel in patients with coronary artery disease is derived from the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.¹³⁶ Among surgical patients, Clopidogrel After Surgery for Coronary Artery Disease (CASCADE), a small randomized placebo-controlled trial, evaluated the impact of clopidogrel and aspirin versus aspirin alone on graft patency and clinical outcomes after CABG throughout 1 year. Patients first received the study drug, without bolus, when postoperative chest tube drainage had decreased to less than 50 mL/hr for 2 consecutive hours. Investigators found a nonsignificant 14.8% reduction in the primary outcome of intravascular ultrasound-measured vein graft intimal hyperplasia in the clopidogrel group. Additionally, in this small trial that was underpowered for clinical events, there were no differences in secondary endpoints of vein graft patency, postoperative cardiovascular events, or major bleeding.¹³⁷

Postoperative clopidogrel is currently recommended in addition to aspirin for patients who undergo CABG following non-ST-segment elevation acute coronary syndromes and for aspirin-allergic patients. It remains to be evaluated whether newer, more potent antiplatelet agents, including the thienopyridine prasugrel and reversible

ADP antagonist ticagrelor, as well as novel anticoagulants, including factor X and II inhibitors, might improve post-CABG angiographic and clinical outcomes.¹³⁸

Echocardiography and Advanced Monitoring

Multiplane transesophageal echocardiography (TEE) has become commonplace for intraoperative monitoring during cardiac surgery. TEE is used to measure myocardial and valvular function, identify aortic dissection, assess de-airing of the heart, confirm placement of cannulae, and more. In the postoperative patient, TEE is also used for single-episode assessment of function, to assess for thrombus or pericardial tamponade, and to guide therapies such as cardioversion or IABP placement. However, the ideal method of advanced cardiovascular monitoring for guiding hemodynamic treatment in the postoperative patient is one that is reliable, continuous, noninvasive, operator-independent, and cost-effective.

Transthoracic echocardiography (TTE) is commonly used and often quite valuable in the management of post-cardiac surgery patients. Although less invasive than TEE, TTE use is also limited in the immediate postoperative period by the presence of an open chest, dressings, tubes, and lines; by difficulty in allocating technicians, machines, and probes; and by the single snapshot of data provided. More continuous hemodynamic monitoring is generally not possible with TTE.

Recently, a flexible, miniaturized, and disposable TEE probe has been approved by the U.S. Food and Drug Administration (FDA) and may remain in situ for 72 hours. These probes provide the benefit of performing frequent direct qualitative and quantitative assessments of myocardial function in the dynamic post-cardiac surgery patient. Conventional TEE probes are 10 to 15 mm in diameter, whereas the miniaturized probe is 5.5 mm in diameter and may be placed by intensivists. Recent studies have indicated that the miniaturized indwelling TEE probes are useful for better defining clinical scenarios in unstable patients and in patients being weaned from venoarterial extracorporeal membrane oxygenation.¹³⁹

A number of technologies have been developed to provide clinicians with continuous indexes of cardiovascular function to guide decision making and responses to therapy. Minor invasive arterial thermodilution remains the standard for the estimation of cardiac output. Less invasive and continuous techniques such as pulse contour cardiac output and arterial waveform analysis are also available although concerns persist regarding the accuracy and reliability of these techniques. Noninvasive continuous techniques such as bio-impedance and bio-reactance require further investigation.

Esophageal Doppler monitoring (EDM) measures blood flow velocity in the descending thoracic aorta using a flexible transesophageal Doppler ultrasound probe similar in size to a nasogastric tube. Cardiac output and stroke volume are estimated using an estimate of aortic cross-sectional area derived from the patient's age, height, and weight. EDM allows optimization of a patient's volume status or LV preload, and experience with use of

this probe is growing among anesthesia and critical care providers. The EDM probe is significantly smaller than a traditional TEE probe and provides continuous data as opposed to a single snapshot.¹⁴⁰

POSTOPERATIVE BLEEDING

Postoperative bleeding is always present to some degree after cardiac surgery. Bleeding is related to a combination of mechanical factors as well as coagulopathy. A surgically correctable cause predominates in less than 3% of cases and is indicated by brisk hemorrhage (>200 mL/hr), normal or near-normal coagulation studies, and the appearance of blood clots in the mediastinal drainage tubes. The amount of bleeding that occurs after surgery, the number of transfusions required, and the filtering of transfused components are related to outcome.¹⁴¹

Coagulopathy

Coagulopathy is a common feature of patients recovering from cardiac surgery. There exist multiple opportunities for intervention in the pathway to adequate sustained clot formation (Fig. 60-12). Following CPB, the predominant cause of abnormal bleeding is a fall in platelet number and impaired platelet function. Its effects are exacerbated by the preoperative use of antiplatelet agents,

thrombolytic agents, and heparin.^{142,143} Hypothermia associated with CPB also contributes to decreased platelet function and postoperative coagulopathy and hemorrhage.^{98,144,145} Platelet dysfunction is related to passage through the extracorporeal circuit, with resulting decrease in platelet membrane receptors for fibrinogen as well as for glycoprotein Ib and glycoprotein IIb/IIIa complex. A second important mechanism for coagulopathy is progressive fibrinolytic state of variable intensity related to the length of time of the CPB. Fibrinogen is critical for effective clot formation, and its monitoring and guided supplementation in the treatment of major bleeding is increasingly recognized.¹⁴⁶

Coagulopathy may be associated with variable or no bleeding and is recognized by the presence of abnormal clotting parameters (prothrombin time [PT], partial thromboplastin time [PTT], fibrinogen level, platelet count) and the absence of solid clot formation in the mediastinal drainage tubes. Algorithms involving point of care testing, including thromboelastography and thromboelastometry, have the potential to reduce transfusion requirements.¹⁴² Any or all of the following abnormalities may be present and should be considered.

Heparin Effect

The heparin effect is demonstrated by a prolonged PTT or a prolonged activated clotting time (ACT), or both.

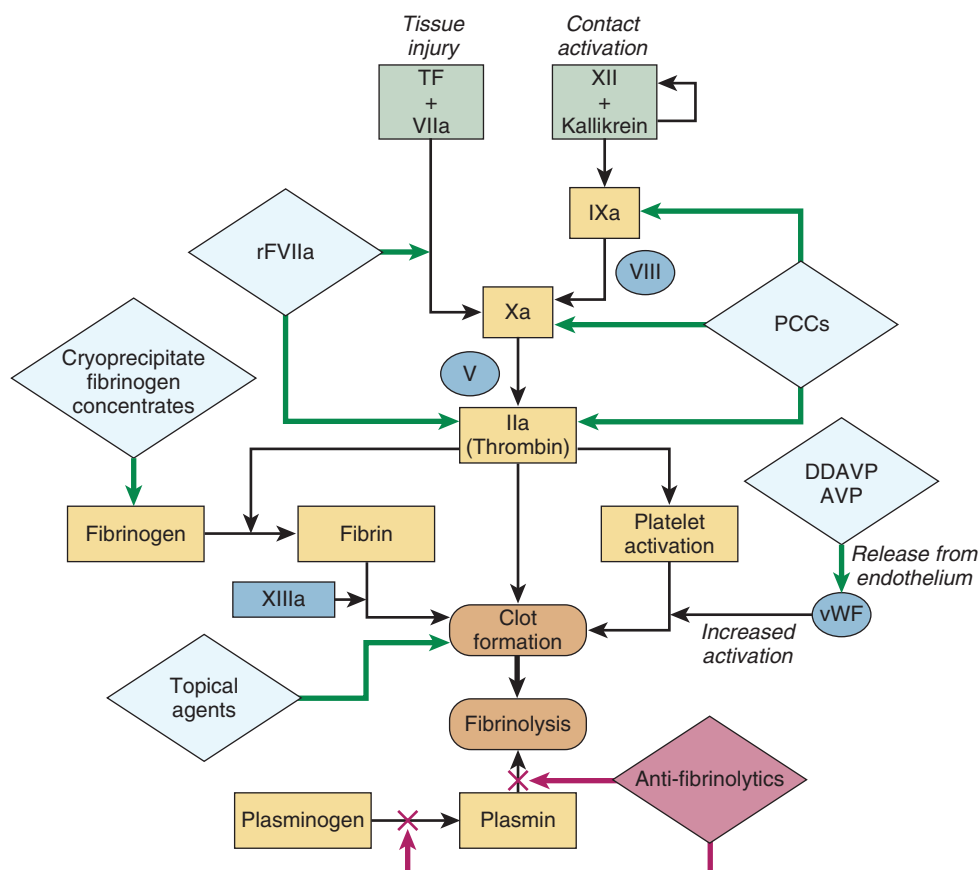


FIGURE 60-12 ■ An overview of clot formation, demonstrating points of intervention. AVP, Arginine vasopressin; DDAVP, desmopressin; PCCs, prothrombin complex concentrates; rFVIIa, recombinant factor VII; TF, tissue factor; vWF, von Willebrand factor. (Reproduced with permission from Sniecinski RM, Levy JH: Bleeding and management of coagulopathy. *J Thorac Cardiovasc Surg* 142:662–667, 2011.)

Residual heparin effect should be assessed on admission to the ICU because the heparin effect is usually seen early in the postoperative course (the half-life of heparin is approximately 1 hour).¹⁴⁷ The specific treatment is administration of protamine sulfate (25 mg doses are given, and the ACT is repeated).¹⁴⁸ Consideration of CPB time and dosages of heparin and protamine must guide decision making.

Randomized data have shown that higher heparin dosages using point-of-care, patient-specific monitoring during CPB reduce transfusion compared with empiric dosages. Higher stable heparin concentrations result in decreased thrombin generation, inhibition of clot-bound thrombin, and preserved platelet function after prolonged (>2 hr) CPB.^{149,150} In addition, heparin reversal with empiric half-dose or protamine titration methods (protamine-to-heparin ratio < 1) may also decrease chest tube drainage and transfusion requirements.¹⁵⁰

Thrombocytopenia

Thrombocytopenia results from destruction of platelets during CPB or from consumption.^{151,152} In the absence of other abnormalities, treatment is platelet transfusion. Notably, if a patient is not actively bleeding, thrombocytopenia is generally not corrected with transfusion, because the platelet level usually normalizes spontaneously over the next few days. Among the many patients maintained preoperatively on heparin, persistent postoperative thrombocytopenia may be induced by the presence of heparin-dependent antibodies. In this setting, resulting thromboembolic events and significant bleeding have been observed.¹⁵³ Diagnosis of heparin-induced thrombocytopenia can be made with heparin-platelet aggregation testing and a platelet factor intravenous assay to confirm the presence of antibodies in vitro. All heparin should be discontinued promptly in these patients.

Thrombasthenia

In patients with thrombasthenia, the platelet count is normal but clot formation is inadequate. This remains a significant problem in the postcardiac surgical patient.¹⁴³ It can be documented by measuring the thromboelastogram (TEG).¹⁵⁴ Qualitative defects in platelet function result from CPB^{143,155} or from antiplatelet therapy.¹⁵⁶ Aspirin and clopidogrel irreversibly affect platelet function, the life span of which is 6 to 7 days. Therefore, a single dose administered within the 7 days before the operation diminishes platelet function, which can result in a significant increase in bleeding complication and transfusion requirements.^{157,158} Current guidelines from the American College of Cardiology and American Heart Association (ACC/AHA) and Society of Thoracic Surgeons (STS) recommend discontinuing ADP inhibitors 5 to 7 days before cardiac surgery, if possible.^{150,159}

Specific Factor Deficiencies

Specific factor deficiencies are usually manifested by elevation of the PT or the PTT. Abnormalities may result from a specific genetic disorder, liver disease, prior

Coumadin therapy, hemodilution, or disseminated intravascular coagulation (DIC). These disorders are generally treated by specific factor therapy, fresh-frozen plasma, or cryoprecipitate.

Management of Bleeding

Specific treatment consists of blood component therapy based on an accurate diagnosis and an understanding of the changes that occur during CPB. Guidelines for transfusion support as well as management of postoperative patients with significant hemorrhage have been suggested.¹⁵⁰ The observed rate of bleeding must be correlated with its character (the initial bleeding rate may reflect drainage of sequestered blood or irrigation fluid) and hemodynamic effect (ineffective drainage may lead to an underestimate of ongoing intravascular depletion). The quality of blood clotting may be effectively estimated by close observation of the drainage tube contents and manual manipulation of the tubes. Large amounts of clot that repeatedly obstruct the tubes indicate a surgical source of bleeding. Nonclotting, freely draining blood or the presence of loosely organized clot indicates that a state of coagulopathy exists.

Bleeding at a rate of more than 200 mL/hr requires immediate action to search for and correct the underlying cause. Delays in laboratory testing frequently preclude accurate and timely diagnosis. The single most practical treatment is to administer platelet concentrate, which is often effective despite an apparently adequate platelet count when the platelets are dysfunctional. Fresh-frozen plasma fraction is used to replenish coagulation factors manifested as a prolongation of the PT for PTT. Available sources of fibrinogen for supplementation include fresh-frozen plasma, cryoprecipitate, and fibrinogen concentrates. With appropriate treatment of coagulation deficiencies, coagulopathy usually resolves within a few hours. Bleeding usually diminishes to modest levels (50 to 100 mL/hr) within 4 hours, and rarely is the total amount drained more than 1 liter.

Reoccurrence of high drainage rates should be addressed immediately, despite the fact that sudden drainage of sequestered blood is common when the patient is repositioned. It is not uncommon for a new bleeding site to develop with clot lysis or after a brief episode of severe hypertension. A common scenario is initial bleeding at rates of 150 to 250 mL/hr, followed by alternating periods of inconsequential drainage and substantial drainage. This often indicates surgically correctable bleeding, with a large burden of intramediastinal clot and ineffective tube drainage resulting from clot obstruction. When the bleeding issue is not resolved within a few hours, a second chest radiograph should be obtained to ensure that mediastinal and pleural drainage has been effective.

Massive transfusion coagulopathy that occurs in cardiothoracic trauma, complex aortic surgery, and other massive bleeding patients should prompt consideration of a transfusion protocol involving fixed ratios of fresh-frozen plasma, platelets, and red blood cells. Algorithms outlining empiric treatment are usually developed with input from surgeons and blood bank directors. While

there is certainly no substitute for meticulous surgical technique, the cause of unusually high transfusion requirement is often multifactorial after complex aortic surgery, referable to a multitude of interrelated factors including interference with the vascular integrity, surgical dissection, deep hypothermia for circulatory arrest, ischemia and reperfusion, dilution of coagulation factors from large-volume fluid resuscitation, transient need for heparinization, and the use of CPB. Deep hypothermia for neuroprotection in thoracic aortic surgery slows coagulation cascade activity, reduces coagulation factor synthesis, increases fibrinolysis, decreases platelet count, and impairs platelet function. The prosthetic grafts used for aortic repair consume platelets and other factors, and aortic disease itself may also predispose to coagulopathy via the exposure of tissue factor and other mechanisms.

The major side effects of postoperative bleeding are volume loss and retention of clotted blood in the mediastinum. Nonspecific therapy consists of continuous, adequate volume replacement, maintenance of free drainage, and prevention of hypothermia. Hypothermia has a generalized anticoagulant effect that increases PT and PTT measurements in direct accordance with the degree of temperature change.¹⁶⁰ Mechanical means should be used to maintain mediastinal chest tube patency, including (1) application of suction, (2) stripping and milking of chest tubes (note that mechanical stripping of chest tubes can create negative pressures as high as 1500 mm Hg and can be potentially damaging to entrapped tissues), and (3) if necessary, Fogarty catheter thrombectomy of the mediastinal tubes. Sterile endotracheal tube suction catheters may also be used for thrombectomy of mediastinal tubes with great care to avoid passing any catheter beyond the length of the mediastinal chest tube. Catheter thrombectomy usually precedes reoperation and may relieve significant tamponade.

Other nonspecific measures include strict control of blood pressure and induction of mild controlled hypotension, which can markedly diminish bleeding rate. However, afterload reduction can be particularly dangerous in the hypovolemic patient with ongoing blood loss and early cardiac tamponade. Levels of PEEP in the range of 10 to 12 cm H₂O have been suggested as a means to reduce postoperative bleeding.¹⁶¹ The efficacy of PEEP in slowing postoperative bleeding remains controversial,¹⁵⁰ and acute reduction in preload with this level of PEEP is potentially dangerous.¹⁶²

Crystalloid and Colloid Volume Resuscitation

Crystalloid solutions may be provided as normal saline or lactated Ringer solution. Colloid solutions include the following:

1. Serum albumin as a 25% solution. Serum albumin in its 25% solution must recruit extravascular fluid to result in effective volume replacement.
2. Plasma protein fraction (Plasmanate) as a 5% protein solution containing both albumin and alpha and beta globulins. Plasmanate may cause a paradoxical hypotension attributed to the use of acetate,

present as a buffer, or may cause the presence of Hageman-factor fragments.^{163,164}

3. Hydroxyethyl starch (Hetastarch). Hetastarch provides plasma volume expansion for more than 24 hours and may be safely used to a total volume of 1.5 liters. Because Hetastarch has a chemical composition similar to that of dextran, associated urticarial and anaphylactoid reactions may occur. There are continuing concerns regarding the effect of Hetastarch solutions on blood coagulation.¹⁶⁵

The choice of colloid versus crystalloid must be made on an individual basis. The largest randomized prospective clinical trial available comparing saline to albumin in a diverse group of intensive care patients was unable to demonstrate any difference in numbers of days spent in the ICU, days spent in the hospital, days of mechanical therapy, or days of renal-replacement therapy.¹⁶⁶

Blood Conservation

Blood conservation requires a programmatic approach but is essential to improving patient outcomes. There is level I evidence that blood and blood products negatively influence outcome, expose patients to viral and bacterial infection, and may reduce host resistance to infection.¹⁴¹ In addition to these risks, blood transfusions are expensive and blood supply is scarce. As a result, blood use and transfusion outcomes are under renewed scrutiny by health care institutions, regulatory agencies, and accreditation organizations. The tolerance of a reduced hematocrit in the postoperative cardiac patient is an important component in the avoidance of blood transfusion. In the past, a hematocrit greater than 0.30 was believed to be important⁴³; however, this teaching has changed with the findings of recent clinical trials showing that restrictive transfusion practices are equivalent or better than liberal transfusion practices. Guidelines have been published by the National Institutes of Health, and more recently by the STS, stating that it is reasonable to transfuse blood in postoperative patients with a hemoglobin of less than 7 g/dL.¹⁶⁷ It is reasonable to not transfuse a postoperative patient who has a hemoglobin of 7 g/dL or greater based on the patient's clinical situation and if end-organ ischemia is not demonstrated. In addition, supplements with oral iron therapy, and occasionally folic acid, may restore normal hematocrit within 6 weeks of surgery.

Pharmacologic Considerations

A variety of pharmacologic agents represent important tools in the recovery of patients following cardiac surgery. Clinical evidence of an association between the incorporation of non-transfusion-based strategies for treating coagulopathy and decreased use of blood products is increasing.

Desmopressin

Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP), a synthetic analog of L-arginine vasopressin, has been shown to improve platelet function and reduce hemorrhage in a variety of clinical disorders. DDAVP

appears to act by increasing the concentration of von Willebrand factor, an important mediator of platelet adhesion. No consensus exists regarding the prophylactic use of DDAVP.¹⁶⁸ However, patients who have ongoing hemorrhage may be considered for administration of 3 µg/kg given over 15 minutes. Among patients with severe aortic stenosis, DDAVP may help reduce perioperative blood loss given the common finding of acquired von Willebrand syndrome in this population.¹⁶⁹ A similar condition of acquired von Willebrand syndrome is also known to exist among patients with ventricular assist devices.

Aprotinin

Aprotinin is a nonspecific protease inhibitor extracted from bovine lung and has been used as a method of reducing postoperative mediastinal bleeding. Administration of aprotinin before CPB can preserve platelet function otherwise lost during CPB.¹⁷⁰ Aprotinin is a serine protease inhibitor of multiple enzymes including plasmin, trypsin, kallikrein, chymotrypsin, activated protein C, and thrombin. The beneficial effects of aprotinin are mediated by its antifibrinolytic, antithrombotic, and anti-inflammatory effects. More than 70 randomized controlled trials including from 20 to 796 patients showed the efficacy of aprotinin in limiting the need for allogeneic transfusions in patients undergoing cardiac surgery. However, three contemporary trials called into question the safety of aprotinin,¹⁷¹⁻¹⁷³ and these findings, combined with the early termination of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) because of an increase in all-cause 30-day mortality in patients receiving aprotinin, led to suspension of the marketing and distribution of aprotinin in the United States.¹⁷⁴

ε-Aminocaproic Acid and Tranexamic Acid

ε-Aminocaproic acid (EACA) and tranexamic acid (TXA) are two synthetic antifibrinolytic agents in common use in modern cardiac surgery. These agents are lysine analogs and competitively inhibit the activation of plasminogen to plasmin. Prophylactic antifibrinolytic therapy with intraoperative and postoperative administration of these agents is now commonplace. Most of the clinical efficacy data are of TXA, with several trials reporting a decrease in bleeding complications with TXA use. However, several reports have noted seizures associated with TXA, believed to be a result of the ability of TXA to block gamma-aminobutyric acid (GABA) receptors in the frontal cortex.¹⁷⁵

Recombinant Activated Factor VII

Activated coagulation factor VII is a vitamin K–dependent glycoprotein that promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. As a new hemostatic agent, recombinant factor VIIa (rFVIIa) is increasingly being used off-label in cardiac surgery for the treatment of severe coagulopathy-related bleeding that is not responsive to typical factor replacement.

rFVIIa in the treatment of bleeding following cardiac surgery is commonly administered at doses up to 1000 times the physiologic level and has a half-life of approximately 2.5 hours.¹⁷⁶ Although rFVIIa acts by generation of thrombin on thrombin-activated platelets and therefore is theoretically localized to sites of vessel-wall injury, systemic activation of coagulation may occur. As such, the primary concern surrounding the use of rFVIIa is its potential as a hemostatic agent to induce thromboembolic events.¹⁷⁷ Nonetheless, clinical studies continue to emerge indicating rFVIIa administration in appropriately selected patients may correct coagulopathy early in the course of refractory blood loss associated with cardiac surgery, although appropriately powered randomized studies are necessary to confirm the safety and efficacy of this approach.¹⁷⁸

NEUROLOGIC COMPLICATIONS

Neurologic dysfunction is a major cause of death and disability after cardiac surgery. Neurologic injury encompasses a spectrum of disorders such as stroke, encephalopathy, and cognitive dysfunction. Recent analysis of annual data from the Society of Thoracic Surgeons National Cardiac Database reveals a peak stroke rate for CABG of 1.7% in the year 2000. The stroke rate falls to approximately 1.2% in 2008 and has remained constant since then. Clinical variables found to increase risk include neurologic disease, age, hypertension, female sex, atherosclerosis of the ascending aorta, and diabetes.¹⁷⁹

The cause of neurologic dysfunction after cardiac surgery is multifactorial and is the focus of active research and quality improvement initiatives.¹⁸⁰ Causal factors for neurologic dysfunction include (1) particulate and gaseous emboli from the CPB apparatus, (2) macroemboli from aortic manipulation, (3) macroemboli from the extracranial cerebral vasculature, (4) regional malperfusion resulting from extracranial vascular obstruction, (5) regional malperfusion resulting from generalized hypoperfusion during CPB (watershed cerebral infarction), (6) regional malperfusion resulting from impaired cerebral autoregulation (more prevalent in diabetics), and (7) generalized central nervous system edema after CPB.

Major stroke is often caused by atherosclerotic emboli originating in the aorta; more subtle neuropsychologic deficits may be caused by microemboli.¹⁸¹ Autopsy studies in patients who have undergone CPB have detected microscopic emboli, composed primarily of lipid, dispersed in the cerebral microvasculature.¹⁸² The arterial line filters that have become standard equipment on most CPB circuits do not eliminate the microscopic lipid deposit that enters shed blood in the mediastinum (Fig. 60-13).¹⁸³ Moreover, the use of cardiotomy suction to recover shed blood in combination with CPB results in significantly more microembolic events relative to CPB alone. Other studies have introduced the possibility that processing shed blood by washing and centrifugation with a cell-saver device before return to the CPB circuit may reduce these events.¹⁸⁴

Given the mechanism of neurocognitive injury with cardiac surgery involving CPB (i.e., emboli from

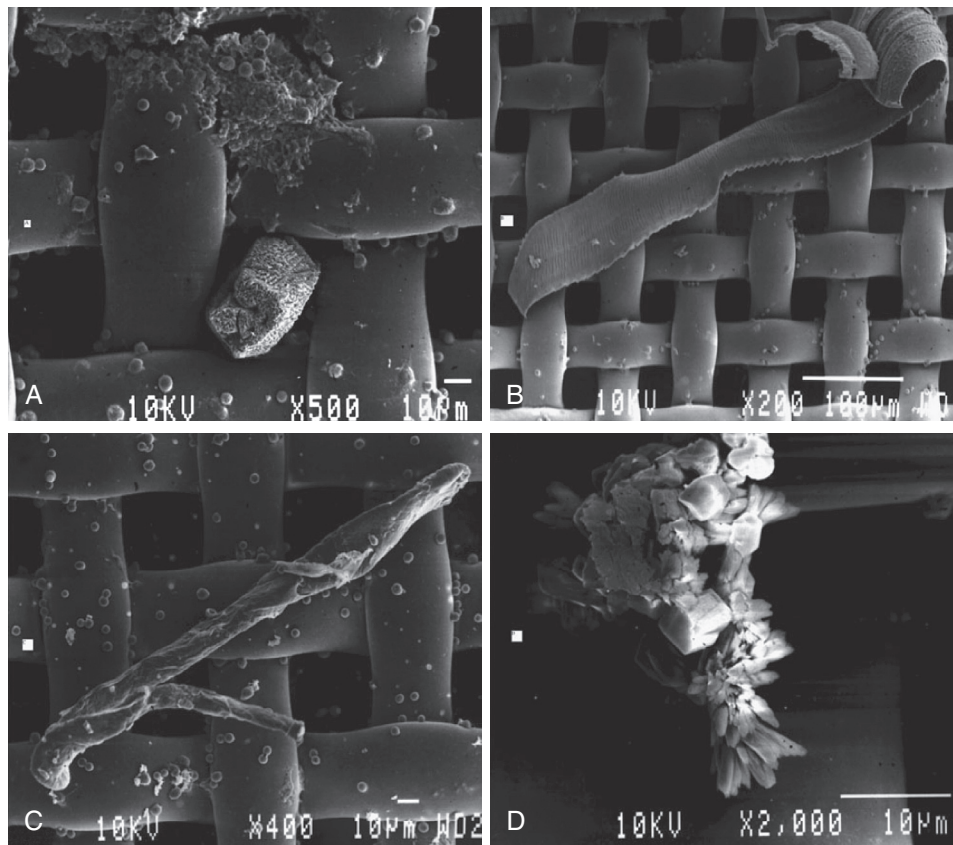


FIGURE 60-13 ■ Debris commonly found on in-line arterial filters. Scanning electron micrographs of 40-micron arterial line filters after clinically uneventful cardiopulmonary bypass. **A**, Crystalline material can be seen embedded in the filter mesh with an adherent mass of fibrinous material incorporating erythrocytes. **B**, Particle measuring approximately $80 \times 600 \mu\text{m}$, thought to be spalled silicone rubber. **C**, Exogenous, organic fiber. **D**, Complex crystalline deposit. (Reproduced with permission from Hogue CW Jr, Palin CA, Arrowsmith JE: Cardiopulmonary bypass management and neurologic outcomes: an evidence-based appraisal of current practices. *Anesth Analg* 103:21–37, 2006.)

cannulation and fatty or gaseous microemboli that are not filtered with standard CPB techniques), OPCAB has been suggested as a potential avenue to improve neurocognitive outcomes. There is clear evidence that there are fewer microemboli to the brain in patients having OPCAB than in those having conventional on-pump revascularization.¹⁸⁵ The significance of fewer microembolization events, however, is not entirely clear. A large prospective randomized clinical trial failed to show any difference in cognitive decline between off- and on-pump revascularization after 5 years of follow-up.¹⁸⁶ Furthermore, a four-arm prospective cohort study compared (1) patients who had on-pump coronary surgery, (2) patients who had off-pump coronary surgery, (3) patients with medically managed coronary disease, and (4) patients without coronary disease. There was no difference in cognitive outcome between all groups with coronary disease at 3 years, whether they had conventional CPB, OPCAB, or medical management. The patients without coronary disease had significantly higher cognitive performance than any of the other three groups at all time points through 6 years.¹⁸⁷ These results suggest that coronary artery disease may be a surrogate marker for occult cerebrovascular disease and these patients are at increased risk for future neurologic dysfunction independent of CABG.

Other factors that contribute to neurologic dysfunction, particularly in older adults, include (1) “ICU psychosis” related to stress, environmental impact, and loss of ability to compensate to surroundings; (2) sleep deprivation; (3) adverse drug reactions; and (4) revelation of previously well-compensated mild dementia.

Often, focal deficits are completely reversible if the patient is appropriately managed. The maintenance of adequate perfusion and oxygen delivery is critical to recovery. Cerebral blood flow is improved by head elevation to reduce edema and hyperventilation to provide moderate hypocapnia. General support includes protection of the patient’s airway, management of pulmonary secretions, avoidance of pulmonary aspiration, and provision of nutrition. Because dramatic recovery is frequent, patient and family support should be aggressive in the first few days after surgery unless a definitive mortal injury can be defined.

Delirium is known to be a common condition (3% to 72% depending on method of assessment) in the ICU following adult cardiac surgery. Postoperative delirium is associated with increased length of stay, complications, and higher mortality. Prevention focuses on frequent orientation and noise reduction, early mobilization out of bed, and having a familiar face at the bedside. Delirium may be classified as hyperactive, hypoactive, or mixed.

For each type, management includes a thoughtful search for and treatment of underlying causes of the delirium, nonpharmacologic measures, and symptomatic drug therapy. The patient's medication list should be critically reviewed, and any drugs with anticholinergic side effects should be tapered. Benzodiazepines are GABA agonists and may therefore decrease consciousness and REM sleep—tapering these agents may alleviate delirium. Haloperidol remains the recommended agent for severe agitation, given in doses of 0.5 to 5 mg. The α_2 -adrenergic agonists clonidine and dexmedetomidine may also be useful in those patients with sympathetic overactivity. Suspected signs of delirium should not be ignored and instead promptly investigated and treated.¹⁸⁸

INFECTION

The incidence of fever decreases exponentially throughout the postoperative course. Fevers not related to infectious causes are most commonly low grade ($<38.9^\circ\text{C}$, rectal), and most resolve before the 15th postoperative day. A temperature higher than 38.9°C at any time in the postoperative course is more likely to be related to a specific infection. The presence or absence of leukocytosis has not been helpful in this differentiation.¹⁸⁹ Historically, from days 4 to 9 postoperatively, approximately 25% of fevers are related to serious infection.¹⁹⁰

When infection is suspected, aggressive evaluation is indicated. Aerobic and anaerobic cultures of blood, urine, sputum, and abnormal fluid collections are mandatory and should precede broad-spectrum antibiotic coverage. Indwelling catheters should be considered potential infectious sites. Evidence-based infection control practices help to prevent serious infections stemming from catheter use.¹⁹¹

Soft tissue infection is most commonly caused by *Staphylococcus aureus*, although *Staphylococcus epidermidis* has emerged as an important pathogen. *Pseudomonas* and other gram-negative infections become more common when the intensive-care stay exceeds 7 days and in patients receiving broad-spectrum antibiotic therapy.¹⁹² Prolonged intensive care and antibiotic use can also cause systemic fungal infections and loss of the gastric mucosal barrier.¹⁶² These infections are particularly difficult to diagnose because of their protean manifestations. Mediastinitis is of particular concern in all cardiac surgical patients and can be cryptic in presentation. The incidence has been reported to range from 0.8% to 1.86%.¹⁹³ The risk factors associated with mediastinitis have been determined (Table 60-2), as has a negative impact on long-term survival independent of other preoperative risk factors (Fig. 60-14). Sternal and mediastinal infections must be differentiated from simple subcutaneous fat necrosis, sterile sternal dehiscence, and the post-pericardiotomy syndrome.

Deep sternal infections and mediastinitis are commonly associated with systemic symptoms (fever, leukocytosis), localized tenderness, severe persistent chest pain, and sternal instability.¹⁹³ Chest film, computed tomography, and indium-111 leucocyte scanning can be used to confirm the clinical diagnosis. Initial treatment

TABLE 60-2 Univariate Logistic Regression Analysis*

Variable	Coefficient	χ^2	P
Obesity [†]	1.3	10.94	0.009
NYHA congestive heart failure class [†]	0.32	9.34	0.002
Diabetes mellitus (DM)	0.62	6.87	0.009
Previous heart surgery [†]	0.85	6.83	0.009
Duration of bypass [†]	0.005	5.48	0.02
Comorbid condition	0.64	4.56	0.03
Hemostasis at closure	1.2	2.94	0.09
Peripheral vascular disease	0.37	1.55	0.21
IMA graft (0, 1, or 2)	NA	0.95	0.62
IMA graft (yes/no)	0.21	0.79	0.37
Chronic obstructive pulmonary disease	0.39	0.61	0.43
Sex	0.18	0.56	0.45
Renal insufficiency	0.35	0.4	0.53
Preoperative intra-aortic balloon pump	-0.3	0.38	0.54
Coronary artery disease index	0.003	0.22	0.64
Length of stay (before surgery)	-0.008	0.15	0.71
Age	-0.003	0.1	0.75
Ejection fraction	-0.002	0.05	0.82
DM with bilateral IMA graft	NA	0.03	Diabetes, 0.01 Bilateral IMA, 0.30 Interaction, 0.28
Cardiac shock	0.07	0.01	0.92
Operation type	-0.02	<0.0001	0.96

*Univariate logistic regression analysis predicting mediastinitis; variables listed in order of significance. Variables with univariate $P < 0.1$ were included in the multivariate analysis.

[†]Significant predictions by multivariate analysis.

IMA, Internal mammary artery; NA, not applicable; NYHA, New York Heart Association.

From Milano CA, Kesler K, Archibald N, et al: Mediastinitis after coronary artery bypass graft surgery: risk factors and long-term survival. *Circulation* 22:45–51, 1995.

consists of operative wound exploration, débridement, and drainage.¹⁹⁴ Diminished morbidity has been reported with pectoral flap or omental flap closure.^{195,196} Flap closure may be performed as a primary procedure with accompanying sternal débridement¹⁹⁷ or as a staged procedure with sternal débridement followed by closure in 3 or 4 days.^{195,198} A recent cohort study demonstrated similar survival rates of patients with mediastinitis treated with vacuum-assisted closure and patients without mediastinitis who underwent coronary revascularization alone, suggesting that vacuum-assisted closure may be as effective as flap closure.¹⁹⁹

Soft tissue infections involving saphenous vein harvest, although usually minor, represent a significant source of morbidity after coronary revascularization. This complication has been reported to occur in 3% of patients and is more common in the thigh harvest site. They are best prevented by careful selection of harvest sites and the use of meticulous surgical technique. Endoscopic vein harvest

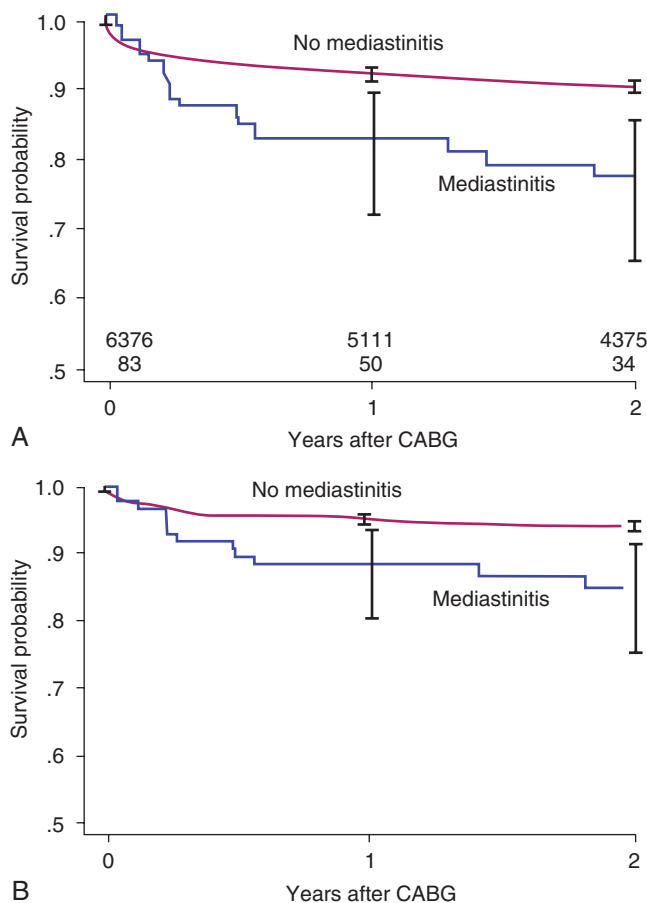


FIGURE 60-14 ■ **A**, Unadjusted Kaplan-Meier survival plot is shown for patients with and without mediastinitis after coronary artery bypass graft (CABG) surgery. The numbers of surviving patients in each group at 0, 1, and 2 years after surgery are shown at the bottom of the graph. **B**, Variable-adjusted survival plot after CABG surgery. Kaplan-Meier survival plot is adjusted for age, ejection fraction, extent of coronary artery disease, peripheral vascular disease, cerebrovascular disease, recent myocardial infarction, angina status, and mitral insufficiency. (Reproduced with permission from Milano CA, Kesler K, Archibald N, et al: Mediastinitis after coronary artery bypass graft surgery: risk factors and long-term survival. *Circulation* 92:2245–2251, 1995.)

appears to have made a favorable impact on the rate of this complication.²⁰⁰ Most saphenous vein harvest site infections may be treated effectively by simple drainage, dressing changes, and prescription of antibiotics. However, in severe cases, wide débridement and skin grafting may be necessary.

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CRITICAL CARE FOR WAR-RELATED THORACIC INJURIES

Jeremy W. Cannon • Jeffrey D. McNeil

CHAPTER OUTLINE

A BRIEF HISTORY OF WAR-RELATED CHEST WOUNDS

MODERN PRINCIPLES OF COMBAT CASUALTY CARE

DAMAGE CONTROL RESUSCITATION AND SURGERY

ICU MANAGEMENT AND EVACUATION

SPECIFIC THORACIC INJURIES

LONG-TERM OUTCOMES

SUMMARY

In contrast to set-piece wars of the past, modern warfare is characterized by a “nonlinear” battlefield with intermittent engagements of an elusive enemy.¹ Soldiers wear advanced protective gear including helmets, ballistic eyewear, ceramic torso plates, and Kevlar neck, arm, and groin pieces. Even transport vehicles are surrounded in ballistic armor. In addition to typical weapons such as high-velocity automatic rifles, mortars, and grenades, high-energy improvised explosive devices (IEDs) are used. The protective gear of modern warfare has significantly reduced injury rates among deployed soldiers; however, direct strikes that find gaps in the body armor or indirect fire attacks on bases, where soldiers without protective gear are targeted, can result in highly destructive injuries.

Combat medical care has also evolved significantly in recent times.^{2,3} There is a renewed emphasis on combat medic training to provide lifesaving care under fire; in-theater transport care is now more commonly provided by highly trained medics and even midlevel practitioners and physicians; and advanced surgical care has been pushed closer to combat activities as part of the in-theater trauma system. Although hemorrhage remains the most common cause of prehospital death,⁴ soldiers with historically nonsurvivable injuries are now arriving alive at forward facilities. As a result of these many advances, and despite the injury severity of our combat wounded reaching historically high levels, the case fatality rate is at an all-time low of less than 10%.⁵

Thoracic injuries still represent a significant proportion of combat wounds, including both blunt and penetrating injuries. Ballistic vests afford significant protection to our soldiers, converting potentially lethal injuries into minor contusions in many cases (Fig. 61-1). However, significant chest injuries still occur in 5% to 10% of casualties (Fig. 61-2). These patients require advanced

management by multiple teams of providers in several medical facilities over many thousands of miles. This chapter describes the historical context of this management strategy and the current approach to complex thoracic injuries in multiply injured combat casualties.

A BRIEF HISTORY OF WAR-RELATED CHEST WOUNDS

Prior to World War I, surgical intervention on a combat chest wound was rare, and mortality from these injuries was over 60% (Fig. 61-3). The concept of negative intrathoracic pressure was first demonstrated by Ludwig in 1847 and then by Aron in 1900.⁶ However, in the early 1900s, the nuances of thoracic physiology and its clinical implications remained poorly understood. Indeed, the significance of negative intrathoracic pressure was not fully appreciated until 1923.⁶

It was in this era that Dr. Evarts Graham was appointed to the Surgeon General’s Empyema Commission.⁶ This famous commission was tasked with determining the optimal treatment for complex parapneumonic effusion and empyema resulting from streptococcal pneumonia, which had spread among enlisted troops afflicted by the influenza pandemics of 1917 and 1918 and was associated with a mortality of up to 90% in some of the camps. The commission determined that, in contrast to pneumococcal empyema, which responded well to open drainage, the preferred treatment in patients with streptococcal infections was repeated thoracentesis followed by delayed open drainage. This new approach reduced the mortality from streptococcal empyema to less than 5%. Graham was inspired to further explore respiratory mechanics and to confirm his clinical observations in the laboratory by developing an animal model of streptococcal empyema.



FIGURE 61-1 ■ Two different soldiers who suffered a direct hit to the anterior plate of their body armor. The strike plate absorbed the energy of the blast and prevented a devastating penetrating injury to the chest. These patients suffered minor chest wall contusions. (A, Courtesy Col David L. Smith, MD, USAF, Retired; B, From McNeil JD, Pratt JW: Combat casualty care in an Air Force theater hospital: perspectives of recently deployed cardiothoracic surgeons. *Semin Thorac Cardiovasc Surg* 20(1):78–84, 2008, Figure 5, with permission.)



FIGURE 61-2 ■ A, Destructive injury of the chest characteristic of combat injuries involving high-velocity projectiles. B, The avulsed latissimus was reattached to the posterior chest wall.

Through this work, he determined conclusively that the mediastinum was, in fact, not a fixed structure as it had been viewed previous to his work and that patients with streptococcal empyema subjected to early thoracotomy very likely died of the open pneumothorax in the setting of minimal respiratory reserve.

Dr. Graham continued to exert his influence in World War II by ensuring that thoracic-trained surgeons were appointed to the Second Auxiliary Surgical Group, which then formed the first Thoracic Surgery Center in Tunisia in 1943. Among these surgeons was Dr. Lyman Brewer who, along with Dr. Edward Churchill, shaped the approach to managing combat thoracic injuries and postinjury empyema.⁷ World War II saw a significant increase in the use of formal thoracotomy for the management of combat wounds; in fact, in many cases, thoracotomy was being overused. Brewer, with Churchill's support, called for a more measured approach and outlined the indications for thoracotomy⁷:

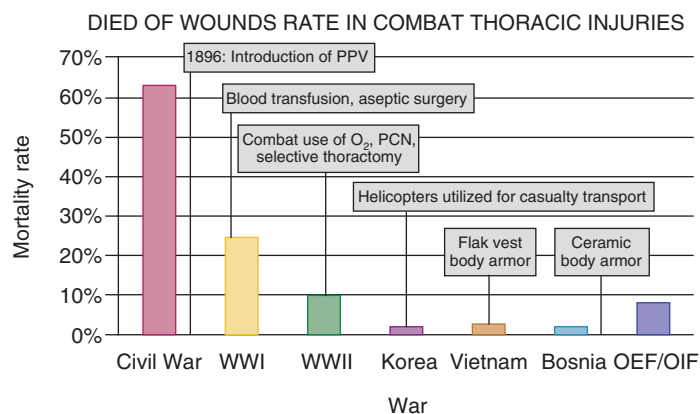
1. Continued bleeding (severe)
2. "Traumatic" thoracotomy (large sucking wound)
3. Thoracoabdominal wound
4. Miscellaneous
 - a. Heart or esophagus repair
 - b. Trachea or bronchus repair
 - c. Foreign body larger than 2 cm

Interestingly, these indications for thoracotomy largely apply even in modern combat casualty care.

Routine use of tube thoracostomy was not widely accepted during World War II.⁸ Although the thoracic drainage system developed by Lilienthal in 1926 was available in WWII, intermittent thoracentesis was favored for the management of pleural effusions and hemothorax.

The modern three-chamber drainage system was described in 1952 by Howe, and the technique of tube

FIGURE 61-3 ■ Mortality from combat thoracic injuries over time. OEF/OIF, Operation Enduring Freedom/Operation Iraqi Freedom; PCN, penicillin; PPV, positive pressure ventilation. (From Ivey KM, White CE, Wallum TE, et al: Thoracic injuries in US combat casualties: a 10-year review of Operation Enduring Freedom and Iraqi Freedom. *J Trauma Acute Care Surg* 73:S514–S519, 2012, Figure 1, with permission.)



thoracostomy was being widely used in civilian trauma.⁹ However, repeated thoracentesis remained the primary management strategy for traumatic pneumothorax and hemothorax along with instillation of antibiotics into the thoracic cavity even through the Korean War.⁸ It was not until multiple civilian centers reported the usefulness of tube thoracostomy in thoracic trauma in the 1960s that this approach became the mainstay for both primary management of simple intrathoracic problems like pneumothorax and postoperative management following major thoracotomy for trauma.

Although positive pressure ventilation with a facemask was first used by Brewer as early as 1944 for the management of posttraumatic pulmonary edema (i.e., modern-day acute respiratory distress syndrome),^{7,10,11} it was not until the development of plastic endotracheal tubes, rapid blood gas analysis, and the polio epidemic of 1952 (negative pressure ventilation) that mechanical ventilation became a routine part of critical care management of patients with severe thoracic trauma. All of these capabilities are now readily available, even in the most austere combat casualty care environments. In addition to these routine management tools, modern combat casualty care has also advanced the concepts of damage control surgery, damage control resuscitation, and critical care air transport to maximize survival of combat casualties as summarized in the remainder of this chapter.

MODERN PRINCIPLES OF COMBAT CASUALTY CARE

One of the greatest advances in modern combat casualty care has been the establishment of a formal trauma system for the care of our wounded soldiers.¹² In November 2004, the Joint Theater Trauma System (JTTS) was created to apply lessons learned from civilian trauma systems across the United States to the combat theaters in Iraq and Afghanistan. The fundamental aspects of this system included the continual presence of a senior trauma surgeon—the theater trauma director—and a cadre of nurse specialists trained in performance improvement and data collection.

Now in its 10th year of operation, this team is responsible for educating deployed medical units on the most current clinical practice guidelines (CPGs) (available at

http://www.usaisr.amedd.army.mil/clinical_practice_guidelines.html). This team also conducts a weekly performance-improvement case-based teleconference that spans the globe. Finally, this team and its parent organization, the Joint Trauma System (JTS), track outcomes over time and advocate for policy and practice changes in order to continually improve the care that is delivered. This systematic approach stands in stark contrast to the first Gulf War, during which the lack of an organized trauma system resulted in numerous mistakes in combat casualty care.¹³ As the result of almost a decade of work, the value of this is evidenced by the lowest case fatality rate among combat casualties in all of recorded history.⁵

It is interesting to note the current deployment patterns for surgeons by specialty and military branch. Currently, all three branches have cardiothoracic surgeons on active duty and in the reserves. These surgeons function primarily as general surgeons when deployed. In one report, 79% of cases performed by cardiothoracic surgeons were general surgical cases, whereas 21% were index thoracic or major vascular procedures (Table 61-1).¹⁴ The U.S. Army does not differentiate surgical subspecialists for deployment purposes. Cardiothoracic surgeons, trauma surgeons, vascular surgeons, colorectal surgeons, surgical oncologists, pediatric surgeons, and laparoscopic surgeons all deploy as general surgeons. This is true of both active duty and reserve surgeons in the army. During the height of the operational tempo, the U.S. Air Force deployed both cardiothoracic and vascular surgeons specifically to the aeromedical evacuation hubs in Iraq and Afghanistan to ensure definitive vascular reconstruction was performed prior to long-range transport in patients with major vascular injuries in the torso or extremities.¹⁴ In at least one case, the deployed cardiothoracic surgeon also functioned as the “trauma czar,” who was responsible for ensuring the stability and readiness of each casualty prior to evacuation. Similarly, the U.S. Navy has deployed at least one cardiothoracic surgeon as the theater trauma director, who is tasked with supervising the research team while also ensuring uniformity across the various treatment facilities in theater and adherence to the CPGs as much as possible. Consequently, maintaining a broad skill set is vitally important for all military surgeons regardless of their specialty.¹⁵ Cardiothoracic surgeons, as a result of comprehensive

TABLE 61-1 Surgical Caseload of Four Cardiothoracic Surgeons Deployed to a Level III Combat Facility in Balad, Iraq

	Total Cases	Thoracotomy	Sternotomy	Major Vascular	Cardiac/Thoracic Aorta	Total General Surgery <i>N</i> (%)	Total Cardiothoracic or Vascular <i>N</i> (%)
Surgeon 1	104	8	2	19	0	75 (72)	29 (28)
Surgeon 2	151	10	5	15	3	121 (80)	30 (20)
Surgeon 3	204	12	2	21	2	169 (83)	35 (17)
Surgeon 4	186	14	4	17	0	151 (81)	35 (19)
Mean <i>N</i> (%)	161 (100)	11 (7)	3 (2)	18 (11)	1 (0.6)	127 (79)	34 (21)

Modified from McNeil JD, Pratt JW: *Combat casualty care in an Air Force theater hospital: perspectives of recently deployed cardiothoracic surgeons*. *Semin Thorac Cardiovasc Surg* 20(1):78–84, 2008.

training in general surgery, thoracic surgery, vascular surgery, and critical care, are uniquely prepared to provide care to the multiply injured combat casualty.

By far, most potentially preventable combat deaths result from hemorrhage. This finding is true of deaths prehospital (killed in action [KIA]) and those patients who arrive at a medical facility with detectable vital signs but then go on to expire (died of wounds [DOW]).^{4,16} Consequently, great emphasis has been placed on identifying new means of controlling both compressible (i.e., extremity) and noncompressible hemorrhage using hemostatic dressings,¹⁷ inflatable polymers,¹⁸ and endo-aortic balloon placement.^{19–21}

Other potentially preventable causes of death include airway obstruction, tension pneumothorax, and multiorgan failure. Airway management has been addressed by teaching combat medics placement of a cricothyroidotomy in tactical situations.²² For tension pneumothorax, the traditional anterior needle decompression approach has received scrutiny because postmortem studies have shown that often the needle does not enter the pleural space.²³ This finding has generated interest in identifying alternative approaches such as the lateral placement technique and modification of existing devices such as a Veress needle, which can be used if tension pneumothorax is suspected.^{24–26} Finally, multisystem organ failure deaths are being addressed by introducing advanced organ support modalities like renal replacement therapy (RRT) and extracorporeal membrane oxygenation (ECMO) further forward in the combat theater (Fig. 61-4).²⁷

Increased attention has also been paid to the care delivered en route from point of injury to a military treatment facility (MTF). For the most critically injured soldiers, dispatching transport teams with flight paramedics who have a higher level of training has been shown to improve survival.²⁸ The United Kingdom has taken this one step further and has created a team with flight nurses and physicians, who recover casualties from point of injury. This so-called medical emergency response team (MERT) has also proven beneficial for the most severely injured casualties.²⁹

In a mature combat theater, combat casualties typically pass through multiple levels of care prior to evacuation.³⁰ Within the combat theater, there are three levels of MTFs, ranging from an aid station with no surgical capability (level I) to a site with far forward general and orthopedic surgeons (level II) and finally an austere



FIGURE 61-4 ■ A combat casualty with severe respiratory failure managed with venovenous extracorporeal membrane oxygenation (VV ECMO). (Courtesy MAJ Matthew Bacchetta, MD.)

hospital-type facility that has more advanced imaging capabilities and more surgical subspecialties (level III).³¹ However, movement through this system is not always a strictly linear process. The JTS has been instrumental in advocating that a balance be struck between expedient transport and transport to a location where the patient's problem can be managed. For example, a patient with an open skull fracture would typically be moved to a level III facility with a neurosurgeon, if at all possible, and a patient with an open chest wound and shock would be taken to either a level II or level III facility—whichever is closer—rather than a level I facility.

All combat casualties within the theater who cannot return to duty eventually filter into the level III facility designated as the aeromedical hub for long-range evacuation to a level IV facility (Landstuhl Regional Medical Center in Germany in this case) and then on to a level V facility in the United States where they receive definitive care. Modern ICU-level care can be provided in transport by a Critical Care Air Transport Team (CCATT); however, the patient should be stabilized or at least “stabilizing” prior to transport.^{32,33} For patients with thoracic trauma, this typically means that any intrathoracic (i.e., noncompressible) hemorrhage has been controlled, any air leaks are managed with tube thoracostomy that is well secured to the patient, any coagulopathy has been



FIGURE 61-5 ■ A combat casualty managed with independent lung ventilation. (Courtesy Lt. Col. Phillip Mason, MD.)

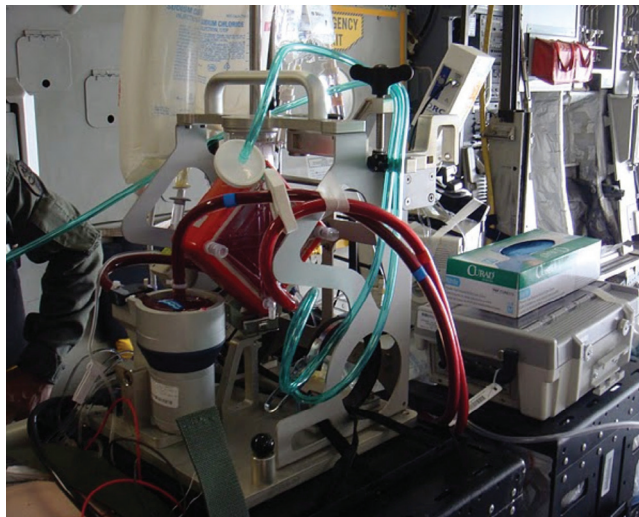


FIGURE 61-6 ■ Extracorporeal membrane oxygenation used to transport a combat casualty with severe early respiratory failure. (Courtesy LTC Sandra Wanek, MD.)

reversed, and the patient is on stable and moderate to low ventilator settings or even extubated. In the vast majority of cases, these requirements can be met during a short stay in the level III facility. However, in some cases, advanced maneuvers such as independent lung ventilation (Fig. 61-5), inhaled pulmonary vasodilators, rescue ventilator modalities, or even ECMO are required to ensure safe transport.²⁷ The need for such interventions, which are beyond the standard CCATT capabilities, was first recognized in 2005 and resulted in the establishment of the Acute Lung Rescue Team (ALRT) based at the level IV facility.^{34,35} As of 2010, this team had performed 24 complex patient transports, and as of 2011, 10 U.S. patients had been transported with either pumpless lung support or full ECMO with a 90% survival (Fig. 61-6).^{36,37}

DAMAGE CONTROL RESUSCITATION AND SURGERY

Modern combat casualty trauma care has fully embraced the principles of damage control resuscitation (DCR) and damage control surgery. This approach requires rapid

TABLE 61-2 Predictors of MT Using Physiologic Parameters and Lab Values from the Trauma Bay

Predictor	OR (95% CI) for MT	Sensitivity	Specificity
INR > 1.5	2.5 (1.7-3.7)	37	87
SBP < 90 mm Hg	1.7 (1.2-2.5)	44	76
Hb < 11 g/dL	1.8 (1.3-2.6)	54	70
BD ≥ 6	2.0 (1.4-2.9)	75	51
HR ≥ 120 bpm	1.2 (0.8-1.7)	42	77
Penetrating	0.9 (0.6-1.3)	39	72
FAST (+)	1.8 (1.2-2.5)	36	65
Any two of the above	3.9 (2.6-5.8)	85	41

Bold signifies statistical significance.

BD, Base deficit; bpm, beats per minute; CI, confidence interval;

FAST, focused assessment with sonography for trauma;

Hb, hemoglobin; HR, heart rate; INR, international normalized ratio; MT, massive transfusion; OR, odds ratio; SBP, systolic blood pressure.

From Callcut RA, Cotton BA, Muskat P, et al: Defining when to initiate massive transfusion: a validation study of individual massive transfusion triggers in PROMMTT patients. *J Trauma Acute Care Surg* 74(1):59-65, 67-68; discussion 66-67, 2013.

recognition of the patient in shock who has already developed, or who is at risk for developing, the deadly triad of hypothermia, coagulopathy, and acidosis. In such patients, reversible causes of shock are rapidly excluded (e.g., tension pneumothorax) and so-called DCR is rapidly initiated en route to the operating room. This includes initiation of a massive transfusion (MT) protocol with balanced transfusion of hemostatic products (plasma, platelets, fresh whole blood, and/or cryoprecipitate) and red blood cells, avoidance of crystalloid, avoidance of hypertension, avoidance of hypothermia, and consideration of hemostatic adjuncts (e.g., tranexamic acid).^{38,39}

One significant challenge in this area is prospectively identifying patients who may need DCR. In both standard trauma resuscitations and multiple casualty events, finding those patients with occult life-threatening injuries who have bled significantly or who have the potential to bleed has been greatly simplified with the development of simple decision tools such as the Assessment of Blood Consumption (ABC)⁴⁰ or the Individual Transfusion Trigger (ITT). The predictors for MT most commonly used are listed in Table 61-2. A recent study using prospective data collected in 297 MT patients as part of the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study identified an INR greater than 1.5 as the strongest individual predictor for MT (adjusted OR, 2.5; 95% confidence interval, 1.7-3.7), and any two predictors present identified patients managed with MT with an 85% sensitivity (OR, 3.9; 95% confidence interval, 2.6-5.8).⁴¹

In the patient with multiple penetrating injuries, a high index of suspicion for simple or tension pneumothorax and cardiac injury with tamponade must be maintained, particularly in patients presenting with tachycardia and hypotension. Focused assessment with sonography for trauma (FAST) examination can be rapidly performed to determine if there is pericardial fluid, and it can be

repeated if a patient's clinical condition deteriorates following an initially negative FAST exam. Patients with multiple penetrating injuries who are hemodynamically normal can undergo computed tomography (CT) scan imaging of chest/abdomen/pelvis to more fully evaluate the location and trajectory of the fragments. CT scanning can be valuable in better characterizing the location of any projectiles and any associated injuries. In contrast, when a patient presents in shock with multiple penetrating injuries of the abdomen and thorax, a rapid sequence of diagnostic procedures, including chest x-ray (CXR) and FAST exam, is used to localize the sites of hemorrhage and determine which body cavity is addressed first. If profound shock is present and there is evidence of penetrating thoracic trauma, rapid placement of bilateral tube thoracostomies will allow assessment for pneumothorax and hemothorax.

Positive findings during these diagnostic procedures will guide decisions about initial operative therapy. Any evidence of penetrating cardiac injury with hemopericardium must be addressed first. If there is no associated massive hemothorax, median sternotomy provides optimal exposure to the heart and great vessels. If associated massive hemothorax is present, anterior thoracotomy with the patient "bumped" up on the side of injury is the preferred initial approach.

Indications for resuscitative thoracotomy are generally the same in combat as in civilian centers: patients in extremis with penetrating thoracic injury should rapidly undergo emergent left anterior thoracotomy for relief of tamponade by incising the pericardium anterior to the phrenic nerve. If there is no evidence of tamponade, other causes of exsanguinating hemorrhage should be evaluated. If the left pleural space is unrevealing, then extending the incision across the sternum to evaluate the right pleural space should be rapidly performed.

The recent Western Trauma Association algorithm has generated some controversy because it recommends very liberal thoracotomy indications compared with what has been historically advocated.⁴² However, in combat, because the patients are young and otherwise vital, such a liberal resuscitative thoracotomy approach is warranted and is espoused in the current version of the combat CPG on this topic.⁴³ To date, there are two reports on resuscitative thoracotomy in theater. Edens et al retrospectively found a 12% survival in a mixed population of U.S. and host nation casualties after resuscitative thoracotomy.⁴⁴ There were no survivors after blunt injuries (0/7). Of the survivors, 6 had primarily thoracic injuries and 6 had extrathoracic injuries (2 abdominal, 3 extremity, and 1 head/neck). Morrison et al reported 14 survivors of 65 patients (21.5%) who underwent resuscitative thoracotomy in a level III facility in Helmand Province, Afghanistan.⁴⁵ In this report, the time of loss of vitals correlated strongly with survivability. Of those who arrested prior to transport, 0 of 10 survived; of those who arrested in transport, 3 of 29 survived (10%); and of those who arrested in-hospital, 11 of 26 survived (42%).

An alternative resuscitative approach in patients with profound shock after trauma is balloon aortic occlusion, which is less invasive than resuscitative thoracotomy and in preclinical studies demonstrated improved outcomes.¹⁹

Early reports from two centers suggest that balloon aortic occlusion has merit in select patients although this would typically not include patients with penetrating thoracic injuries.²⁰ Another approach for patients in profound shock with extrathoracic injuries is to either apply a junctional tourniquet during resuscitation or to explore the injury directly to achieve proximal vascular control.^{46,47}

In the operating room, as the DCR continues, the surgeon must address the site of hemorrhage. Isolated injuries to the chest or abdomen are the exception rather than the rule in combat surgery, however. Just as in civilian trauma, thoracoabdominal wounds represent a significant challenge in the operating room because entering the wrong cavity at the outset greatly increases the patient's mortality.⁴⁸ Diagnostic adjuncts in the trauma bay or the operating room in such patients include tube thoracostomy and bedside ultrasound. In a patient in profound shock with multiple penetrating injuries, the focus should be placed on the cavity with obvious bleeding. If the FAST is positive for pericardial blood, a median sternotomy or bilateral anterior "clamshell" thoracotomy should be performed. The "clamshell" approach is often preferable in patients with multiple thoracic fragmentation wounds because it affords maximal exposure to both pleural spaces as well as the mediastinal structures (Fig. 61-7). In patients who respond initially to resuscitation, or in semi-stable patients with other potential causes for shock who require operative intervention, subxiphoid pericardial window remains a useful diagnostic adjunct. In patients with an indication for laparotomy and penetrating thoracic injuries, we advocate insertion of unilateral or bilateral tube thoracostomies (depending on whether the thoracic injuries are unilateral or bilateral) as the laparotomy is being performed. If there is suspicion of cardiac injury in a patient undergoing laparotomy, a transabdominal pericardial window through the central tendon of diaphragm can be performed to assess for hemopericardium. The presence of pericardial blood

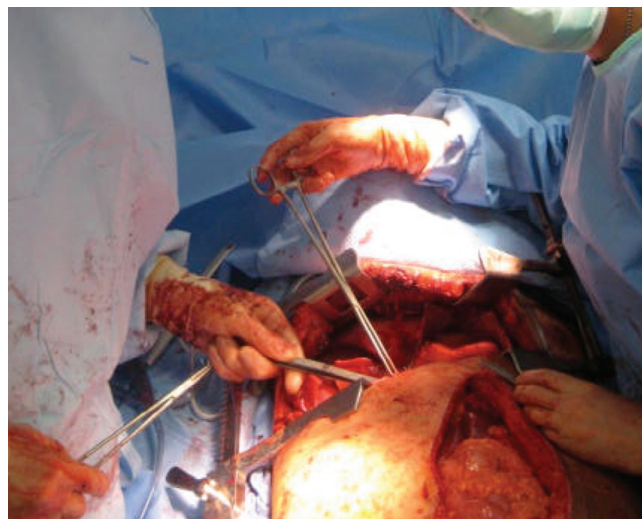


FIGURE 61-7 ■ Clamshell thoracotomy and laparotomy in a patient with penetrating thoracoabdominal injuries. This patient required repair of a ventricular laceration and colonic resection for a destructive transverse colon injury.

then warrants a sterno-laparotomy or a separate clam-shell thoracotomy if there is also significant hemorrhage from the chest tubes.

In damage control thoracic surgery, the principles of gaining hemostasis and controlling soilage apply just as they do in abdominal damage control.⁴⁹ (Management of specific thoracic injuries is addressed later in this chapter.) In patients with multiple injuries who have undergone DCR, a temporary closure should be performed for ready reexploration if hemorrhage occurs and for easy access to the body cavity of interest by others within the chain of evacuation. Prior to temporary closure, ongoing diffuse hemorrhage from raw surfaces should be treated with topical hemostatic agents such as spray thrombin either with or without Gelfoam, if available. Laparotomy pads or hemostatic dressings such as Combat Gauze (Z-Medica Corporation, Wallingford, CT) can also be applied to diffuse bleeding surfaces.⁵⁰

There are a number of approaches to temporary chest closure in such situations. One retrospective review demonstrated no deleterious outcomes from temporary chest closure with or without packing, although the closure techniques used were not well described in this report.⁵¹ In our opinion, tight packing must be avoided, because this will theoretically diminish venous return and hinder resuscitation efforts. Typically, if the lung is allowed to reexpand, the measures previously described will result in hemorrhage control when combined with aggressive repletion of coagulation factors. Our preferred approach is to fashion a “vac-pack” for the chest.⁴⁹ Thoracostomy tubes are inserted and positioned as if the chest will be closed definitively. A clear plastic sheet with fenestrations cut into it is then placed over the lung and the tubes and acts like the parietal pleura for the open chest cavity. Laparotomy pads, blue towels, or a vacuum sponge is then placed over the plastic sheet. If a negative pressure vacuum sponge is used, this is connected to the commercial vacuum canister and set at 75 mm Hg suction and the chest tubes placed to 20 cm H₂O suction. For the custom vac pack, another large chest tube or large-size channel drains are placed over the blue towel followed by more blue towels followed by a large Ioban (3M, Minneapolis, MN) adhesive dressing. The vac-pack drain is then connected to a Heimlich valve to prevent loss of negative pressure if suction is temporarily interrupted and then to wall suction at 75 mm Hg. This approach prevents lung herniation and tends to tamponade any chest wall bleeding, both of which can occur if skin-only (stapled) temporary closure is used.

ICU MANAGEMENT AND EVACUATION

In the ICU, patients with operative or nonoperative thoracic injuries should be closely monitored with continuous pulse oximetry, frequent vital signs, periodic laboratory tests (i.e., CBC, chemistries, ABG, lactate, PT/PTT), and either thromboelastography (TEG) or rotational elastometry (ROTEM). Lung-protective ventilator settings should be used for intubated patients (6–8 mL/kg predicted body weight). Crystalloid and colloid resuscitation should be minimized in favor of

blood product resuscitation until all coagulation parameters and TEG values are normalized and the base excess and lactate are either trending toward or within normal limits (>-6 and <2 mmol/L, respectively). Tube thoracostomies are generally kept on suction for at least the first 24 hours after placement, with CXR obtained after insertion and every morning thereafter. Swan-Ganz catheters are occasionally used for monitoring and guiding resuscitation in theater. However, with more recent evidence suggesting little benefit to this approach,^{52,53} Swan-Ganz catheters are generally reserved for older host-nation casualties with combined cardiac dysfunction and renal insufficiency.^{54,55}

Respiratory failure including mild, moderate, or severe acute respiratory distress syndrome (ARDS) can occur early in combat casualties who undergo massive resuscitation.^{56–58} In a retrospective analysis of the JTTR data, 6.4% of intubated casualties developed ARDS, which was independently associated with increased mortality.⁵⁸ Factors that increased the development of ARDS included large volumes of crystalloid and plasma. Thus, it is imperative that crystalloid use be minimized during hemostatic resuscitation and that plasma administration be curtailed once hemostasis has been achieved. A CPG for optimal management of patients who develop ARDS is currently under review. The principles of lung-protective ventilation and use of select adjunctive therapies still apply. However, in some cases, to safely evacuate these patients and make room for more casualties in the theater hospitals, ECMO-facilitated transport is both safe and prudent.^{27,37}

In level II facilities, plain films and ultrasound are used extensively, and follow-up CT imaging is used once the patient arrives at the level III facility. All level III facilities now have CT scan capabilities, which are used extensively to guide further interventions after the initial management. Images are available via network connection to minimize repeat imaging as much as possible. Such cross-sectional imaging is helpful in developing a management plan for patients who are hemodynamically stable but have multiple penetrating torso injuries.⁵⁹ Examples of diagnoses made with CT imaging (either alone or as a confirmatory study) during the authors' deployments and the indicated management are listed in [Table 61-3](#).

In recent years, the historic approach to hemostasis evaluation with TEG has been applied to trauma resuscitation.^{60,61} TEG measures the various phases of clot formation and remodeling with a wire filament immersed in a rotating cuvette, which contains a whole blood sample (with or without various reagents). Another similar series of assays, termed ROTEM, differs from TEG only in that rather than the cuvette spinning, the pin is immersed in the sample spins. The ROTEM system has a more rugged construction and seems to be more resistant to vibrational artifact, which makes it more appealing for use in an austere environment. Nonetheless, both TEG and ROTEM have been used to good effect in theater.^{62,63} The most attractive feature of using these assays is that the specific coagulopathic deficiency can be identified with more precision and thereby managed with targeted therapy. This includes not only factor deficiencies responsive to plasma infusion but

also defects in clot strength and even fibrinolysis managed with platelet infusion or antifibrinolytic therapy, respectively.

SPECIFIC THORACIC INJURIES

With regard to thoracic trauma, the establishment of the JTS and the research database, now called the Department of Defense Trauma Registry (DoDTR), has allowed a careful evaluation of both thoracic injuries and thoracic complications from trauma such as ARDS. Three reports on thoracic injuries have been published from the wars in Iraq and Afghanistan (Table 61-4). These include one

report exclusively on U.S. combat casualties⁶⁴ and two reports on all combat casualties with thoracic injuries.^{65,66} All of these retrospective reviews used the DoDTR and extracted injury information based on ICD-9 codes. Because the registry is continuously updated, the number of injuries identified and the overall incidence of thoracic trauma changed with time. However, it does appear that the thoracic trauma mortality rate has been overall higher in this conflict than in prior wars. The most likely explanation for this observation is that more critically injured patients are arriving at medical facilities with detectable vitals regardless of their salvageability. Thus, all of these patients, including those with nonsurvivable injuries, are listed in this mortality rate. A more useful number, which captures the entire system of care and also reflects the quality of preventive measures such as ballistic armor, is the case fatality rate, which is simply all deaths divided by all injuries regardless of where the death occurs—such an analysis for patients with thoracic trauma has yet to be done for the most recent conflicts.

The prevalence of IEDs in recent conflicts has led to patients frequently presenting with multiple fragmentation injuries. These IEDs often contain ball bearings, bolts, or other scrap metal pieces intended to be projectiles. In addition, by obscuring the device as a roadside bomb buried under soil and rocks, the dirt and rocks become projectiles, leading to massively contaminated wounds involving multiple body cavities. Another common design for IEDs is large caliber munitions strung together. These munitions often produce large fragments of the shell casing, which can cause large wounds (see Fig. 61-2).

When assessing patients with multiple penetrating injuries, standard advanced trauma life support (ATLS) algorithms are followed to guide initial resuscitation. Patients with injuries involving both the thorax and abdomen add an additional layer of complexity to the initial evaluation. Similarly, multiple traumatic extremity amputations from a blast event can add even more confusion because there may or may not be additional occult sites of hemorrhage. All of these different types of patients challenge the most experienced surgeon, and mistakes in management can have dire consequences.

Almost all of these patients with large, complex open wounds will require surgical intervention for wound débridement at a minimum. If the patient is stable at presentation, CT imaging is useful in identifying smaller fragment injuries that have violated the thoracic cavity. If the patient is unstable at presentation, CT imaging after initial stabilization can also be helpful given the number

TABLE 61-3 Diagnoses Made with CT either as a Stand-alone Study or as a Confirmatory Test

Injury	Management
Occult pneumothorax	Follow-up CXR prior to aeromedical evacuation
Enlarging pneumothorax	Tube thoracostomy
Retained hemothorax	Tube thoracostomy, VATS, or thoracotomy
Pulmonary laceration	ICU monitoring
Cervical tracheal transection	Primary repair, tracheostomy below injury
Empyema, bronchopleural fistula	Thoracotomy, decortication, intercostal muscle flap
Pericardial effusion	Cardiac repair
Intracardiac fragment	Cardiac repair, removal of projectile
Blunt traumatic descending thoracic aortic injury	Thoracotomy, primary aortic repair
Left subclavian artery/vein transection	Sternotomy, trap door extension, direct suture repair
Superior vena cava/right atrial junction injury	Sternotomy, primary repair
Evolving tension bilothorax	Thoracotomy, bile/blood evacuation and laparotomy with diaphragm repair, posterior hepatorrhaphy, and anterior closed suction drainage
Ascending aortic dissection (nontraumatic)	Blood pressure control, CCATT transport, definitive repair in Germany

CCATT, Critical Care Air Transport Team; CT, computed tomography; CXR, chest x-ray; ICU, intensive care unit; VATS, video-assisted thoracic surgery.

TABLE 61-4 Retrospective Reviews on Combat Thoracic Injuries from Iraq and Afghanistan

Study	Population	Years	N	Incidence	Mortality	Notes
Propper et al ⁶⁵	All casualties	2002-2008	1660	4.9%	12%	U.S. troops = 565; coalition troops = 261; civilians = 819
Ivey et al ⁶⁴	U.S. only	2003-2011	2049	8.6%	8.3%	Battle injuries = 1713; nonbattle injuries = 336
Keneally and Szpisjak ⁶⁶	All casualties	2002-2012	7570	10%	10.5%	Pulmonary laceration and thoracic vascular injury increase mortality

of small fragments and possible occult injury. Simple pneumothorax or hemothorax is managed with tube thoracostomy with typical indications for proceeding to thoracotomy. All open wounds require aggressive soft tissue débridement to prevent sepsis, as described in one of the most important combat CPGs.⁶⁷ These wounds are often heavily soiled and require multiple repeat débridements. The combination of single-lung ventilation and video thoracoscopy is available at level III MTFs in-theater and is used selectively for foreign body removal based on size, degree of contamination, and location (Fig. 61-8). Fragments located in mediastinum or pericardial space should be surgically evaluated in most cases because of the risk of occult injury to nearby structures (Fig. 61-9). The surgical approach can be full or partial sternotomy, thoracotomy, or video thoracoscopy based on location and suspicion for visceral injury.

Large chest wall defects lead to open pneumothorax and respiratory failure (see Fig. 61-2 and Video 61-1). Endotracheal intubation with positive pressure

ventilation followed by operative repair can be lifesaving. Our review of patients with thoracic injury⁵⁷ identified 264 patients with open chest wound and another 26 with flail chest. These patients should be considered to have underlying pulmonary contusion and lung-protective ventilation, and judicious administration of crystalloid and plasma volume can minimize progression of acute lung injury and development of ARDS. Exposure of intrathoracic organs may be adequate using the original soft tissue defect, but the addition of a standard posterolateral thoracotomy can improve exposure. Sparing of the latissimus dorsi muscle for potential rotational flap closure is an important consideration during the initial surgery; however, control of hemorrhage and repair of bronchial tree injuries must take priority over future reconstruction. At the initial surgery, once hemostasis is obtained, ongoing significant air leak should be addressed and gross contamination and devitalized tissues débrided. For definitive closure, several large-bore thoracostomy tubes should be placed, ribs should be approximated with either heavy monofilament sutures or wire, and chest wall musculature closed if possible. Superficial layers of the chest wall should remain open and negative pressure wound therapy should be used. If there is a soft tissue defect that does not allow adequate closure of the chest wall, a temporary closure using either negative pressure wound therapy dressing or modified “vac-pack” (as previously described) can be used. Pain control and adequate pulmonary toilet after such injuries can be difficult and may require that the patient remain intubated and sedated.

Among patients presenting with thoracic injuries in the conflicts in Iraq and Afghanistan,⁵⁷⁻⁵⁹ injuries to the heart (3.8%), esophagus (1.5%), bronchus (0.6%), aorta (0.6%), or vena cava (0.6%) are rare, and even lung laceration (9.3%) and other major vessel injury (9.6%) are uncommon. The reasons behind this are twofold: (1) relative protection due to location and use of body armor and (2) lethality of injuries to these structures. Despite their rarity, rapid diagnosis and appropriate intervention can produce good outcomes.

For thoracic aortic or arch vessel injuries, direct suture repair (Fig. 61-10) or interposition grafting is often required. For extremity vascular injuries, use of a temporary shunt has been shown to successfully restore distal flow while then permitting a thorough reassessment of other injuries in the setting.^{68,69} A similar approach can be applied to injuries of the aortic arch branches but should be used only in extreme circumstances.

Hemorrhage from peripheral pulmonary parenchymal injuries can be managed with tractotomy and suture repair of bleeding pulmonary lacerations or with nonanatomic pulmonary resection. Massive bleeding from the pulmonary hilum can be temporarily controlled by dividing the inferior pulmonary ligament and 180-degree rotation of the lung. This maneuver will occlude the pulmonary vasculature and stop the hemorrhage. If necessary, placement of a hilar clamp can be used to gain hemostasis (Fig. 61-11), although this will likely commit the patient to a pneumonectomy. Pneumonectomy for traumatic injuries carries a high mortality (>50%), frequently is associated with acute pulmonary

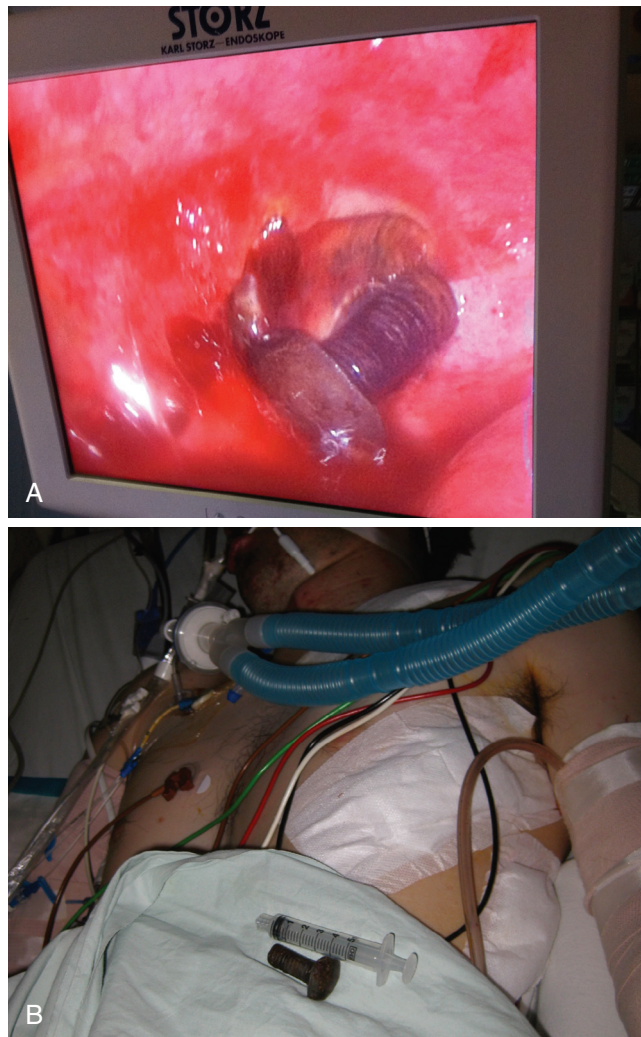


FIGURE 61-8 ■ **A**, Thoracoscopic view of an intrathoracic bolt from a blast event. **B**, The bolt was successfully retrieved, and the patient recovered uneventfully. (Courtesy Lt. Col. Rachel Hight, MD.)

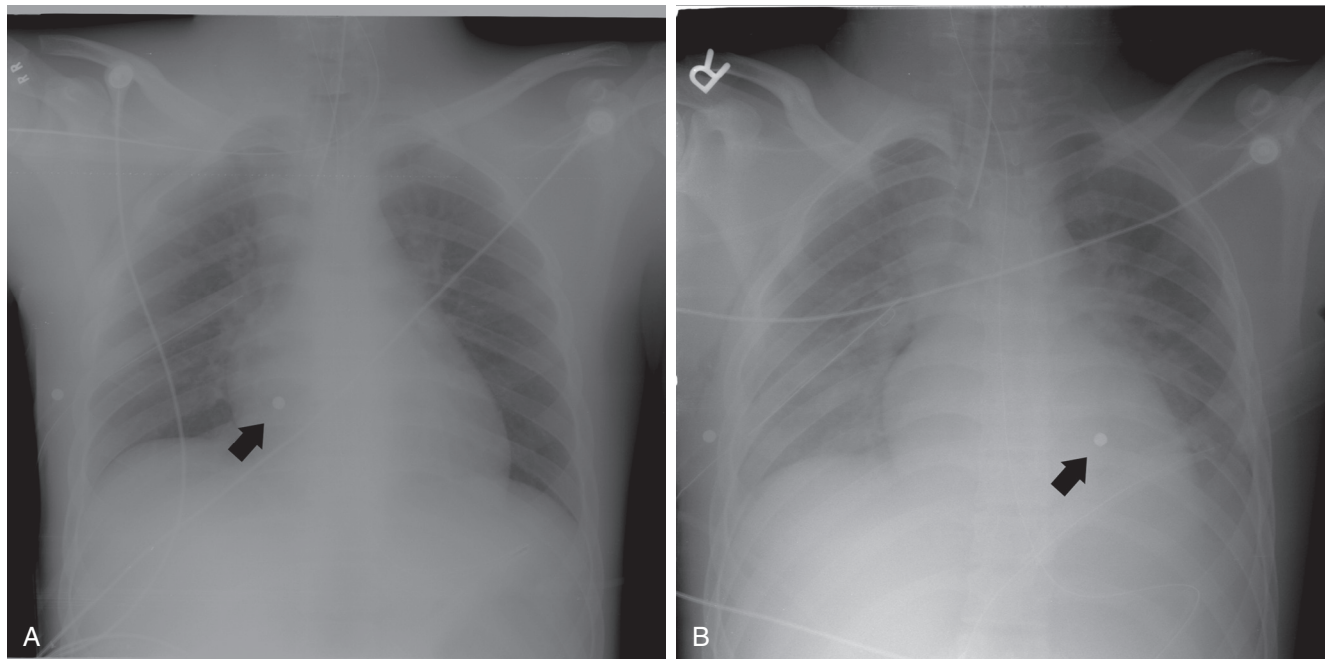


FIGURE 61-9 ■ **A**, A patient with multiple fragmentation injuries underwent a complete trauma evaluation and was found to have a ball bearing in the region of the right heart (*arrow*). Pericardial FAST was negative for fluid and he had indications for a trauma laparotomy. **B**, Postoperatively, the patient underwent a follow-up chest x-ray, which demonstrated that the ball bearing had migrated (*arrow*). A follow-up computed tomography scan demonstrated that the fragment was likely in the pericardium. Consequently, the patient underwent exploration through a median sternotomy and was found to have a small laceration of the right ventricle, which was repaired primarily. FAST, Focused assessment with sonography for trauma.

hypertension and right ventricular failure, and may necessitate institution of ECMO to achieve survival.

Cardiac lacerations must typically be repaired directly during damage control surgery to eliminate ongoing bleeding and cardiac tamponade. Most cardiac injuries that arrive at level II or III MTFs can frequently be repaired with polypropylene sutures placed in a horizontal mattress fashion using polytetrafluoroethylene (PTFE) felt or autologous pericardial pledgets. In the deployed setting, cardiopulmonary bypass capability does not exist; so intracardiac repair for septal defects or valvular dysfunction is not feasible. Some techniques, mostly of historical interest only, used in civilian trauma centers are worth mentioning as an adjunct for repair of more extensive myocardial injuries.

Induction of ventricular fibrillation using epicardial electrodes with alternating current (AC) device was commonly used in the early years of cardiac surgery and is still occasionally used by some surgeons. This technique will reliably stop a vigorously beating tachycardic heart and allow the rapid placement of several repair sutures in the ascending aorta, aortic arch vessels, or ventricular myocardium. When followed by defibrillation with standard internal paddles within 2 or 3 minutes, cardiac function can typically be readily resumed. If necessary, internal cardiac massage can be performed to assist with defibrillation because the distended fibrillating heart can be resistant to defibrillation. Typically 20 Joules is used for defibrillation with internal paddles, but increasing energy levels up to 40 Joules is acceptable. Alternatively, if a large laceration of one of the atria is present and not easily controlled by application of partial occlusion clamp or

simple suture ligation, in-flow occlusion will rapidly empty out the heart and allow improved visualization. This is performed by snaring or clamping both the superior and the inferior vena cava at their junction to the right atrium and thereby preventing filling of the right-sided cardiac chambers. The surgeon must be prepared to deal with ventricular fibrillation with this approach as well; prolonged inflow occlusion will lead to decreased coronary perfusion and fibrillation.

Exposure and repair of descending thoracic aorta or the major arch vessels within the mediastinum or left pleural space can be challenging. The surrounding hematoma can make obtaining proximal and distal control difficult, and once the injury is decompressed, the patient will rapidly exsanguinate without vascular control. Precise identification of site of bleeding from vena cava or other large veins is often difficult. In select situations in combat hospitals, endovascular therapy has been used. Several techniques may be used with open surgical repair of these injuries. Simple digital compression at the site of vascular injury should be used as initial control, if possible. This will usually control most bleeding and maintains distal perfusion while a more carefully planned approach is developed. Once digital control of the bleeding is obtained, the anesthesiologist can “catch up” on resuscitation without excessive administration of crystalloid. For small injuries, digital compression can be converted to compression by an assistant with a sponge stick or Kittner while suture repair with 3-0 or 4-0 polypropylene on an appropriately large needle is performed. If a more extensive injury is present, placement of vascular clamps around the injury may be required. Primary suture repair,

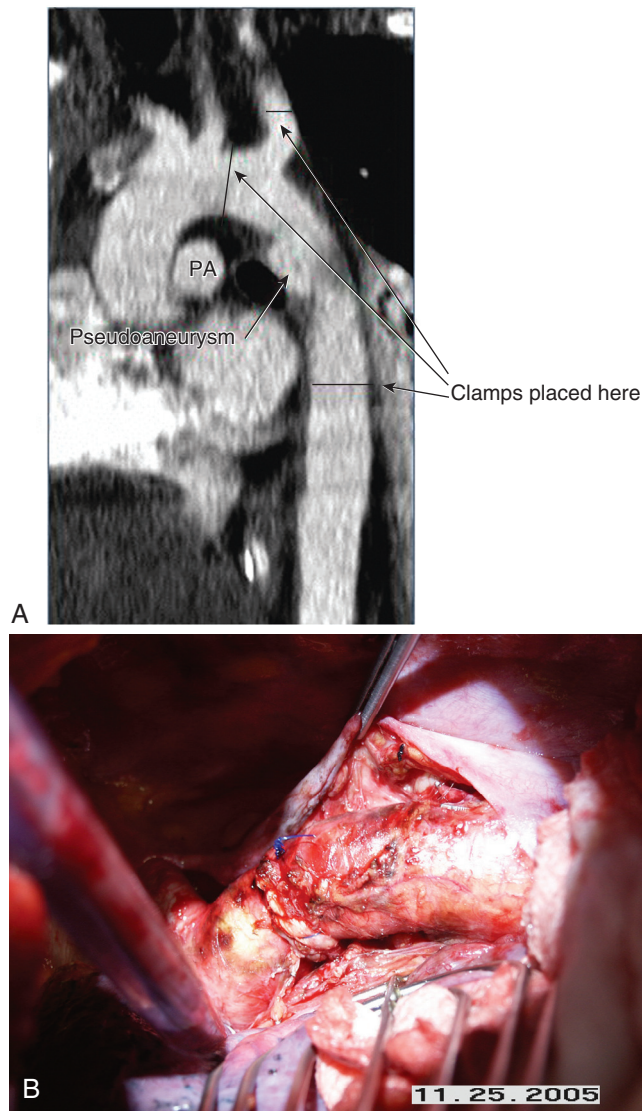


FIGURE 61-10 ■ **A**, Blunt aortic injury with a pseudoaneurysm seen on computed tomography scan. **B**, The injury was repaired primarily using a clamp and sew technique through a left thoracotomy. *PA*, Pulmonary artery.

patch angioplasty, or interposition grafting with appropriate size Dacron or ePTFE conduit is then performed. Saphenous vein is not large enough to use as conduit for such large caliber vessels, and use of prosthetic graft material is justified if primary repair cannot be performed. Large veins can undergo venorrhaphy for hemorrhage control even if the lumen is somewhat compromised. Ligation for control of hemorrhage is occasionally required. Interposition grafting of large veins with prosthetic material is typically not recommended because of poor patency and risk of thrombosis and pulmonary embolism.

Esophageal injuries are unusual in penetrating trauma, and their management in the combat environment is similar to that in civilian practice. Management is determined by the site of primary injury, associated injuries, condition of the patient, degree of local suppuration, condition of the esophageal tissues, and delay since injury.

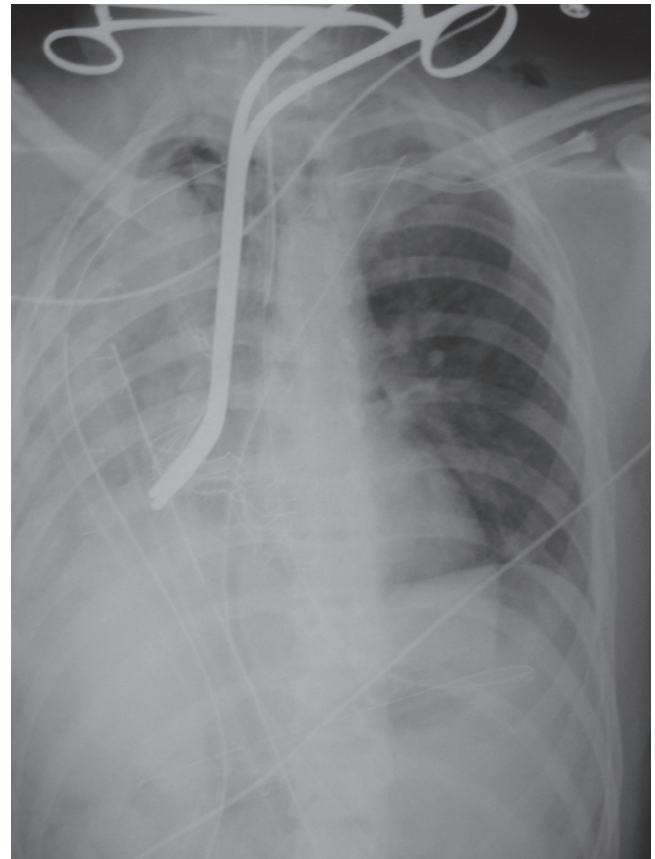


FIGURE 61-11 ■ A hilar clamp was applied emergently in this combat casualty to achieve hemostasis following a transmediastinal gunshot wound. The patient was returned to the ICU for resuscitation. A pneumonectomy was required upon return to the operating room. (Courtesy American College of Surgeons.)

Primary repair using a two-layer closure with tissue buttressing (such as intercostal muscle flap) and adequate drainage is the preferred method. Establishment of reliable enteral feeding access in the setting of an esophageal injury is an important adjunct that makes dealing with any esophageal leak much easier to manage. In the markedly unstable patient or when faced with a delayed diagnosis with extensive contamination, placement of T tube, adequate drainage tubes, and proximal/distal decompression can be a temporizing option. Esophageal replacement is rarely required and should not be considered a good option in the multiply injured patient.

LONG-TERM OUTCOMES

In previous wars, destructive thoracic injuries and limited experience with soft tissue coverage techniques resulted in significant chest wall deformities (Fig. 61-12). In our most recent experience, however, patients with combat thoracic injuries generally have an excellent functional recovery. This has included patients with bronchial stump leaks and those initially managed with ECMO following trauma pneumonectomy. Formal testing of pulmonary function in these patients is sometimes limited by long-term rehabilitation from extremity trauma,

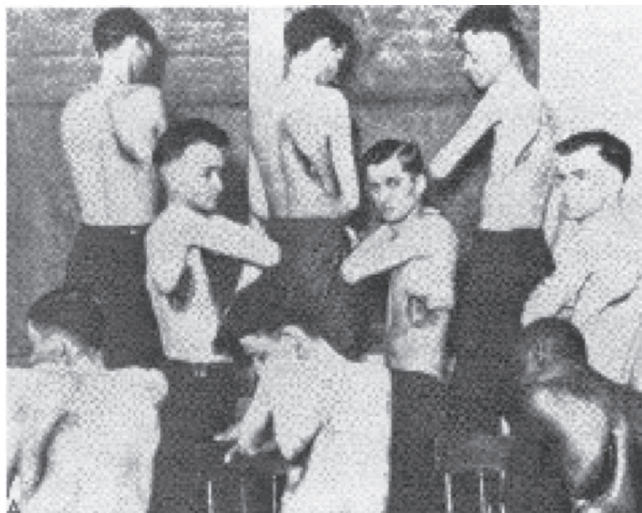


FIGURE 61-12 ■ Posttraumatic empyema was managed with open drainage and thoracoplasty during World War I. This resulted in significant chest wall deformities that were quite disabling. Modern thoracic surgical techniques result in much more functional outcomes. (From Brewer LA: The contributions of the Second Auxiliary Surgical Group to military surgery during World War II with special reference to thoracic surgery. *Ann Surg* 197[3]:318–326, 1983, Figure 7, with permission.)

but this has prompted new interest in defining alternative testing standards comparable to established functional studies such as the 6-minute walk test. To date, there has not been a formal longitudinal study of survivors with thoracic injuries from the recent conflicts; however, plans to undertake this important study are currently in development.

SUMMARY

Significant advances in our system of care for multiply injured patients have improved outcomes for severely injured patients. In those with thoracic injuries, the mortality remains relatively high; this should prompt us to continue to push for improved identification and management of these challenging injuries. Going forward, we need to continue to glean lessons from both our combat experience and from our experiences in high-volume civilian trauma centers so that in future conflicts, our outcomes will be even better than they are today. In the combat theater, cardiothoracic surgeons, trauma surgeons, and many other subspecialists have a part in the care of these patients—a paradigm that will likely continue into the future with our all-volunteer military medical corps. Thus, we need to continue to prepare all of these medical professionals to manage patients with challenging combat wounds, including complex thoracic injuries, to ensure we provide the best possible support for those individuals who are risking their lives in defense of our freedom.

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States Army, the Department of Defense, or the United States Government.

The authors have nothing to disclose.

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NEUROPSYCHOLOGIC DEFICITS AND STROKE

John W. Hammon • David A. Stump

CHAPTER OUTLINE

ASSESSMENT

POPULATIONS AT RISK

MECHANISMS OF INJURY

STRATEGIES FOR REDUCING INJURY

NEUROPROTECTIVE STRATEGIES

PROGNOSIS

The brain is the effector organ for all behavior, innate and learned. It is the monarch of blood flow and will shut down all other vascular systems to preserve its own supply. Conversely, dysfunction in other organs can adversely affect brain function. It monitors other organ systems and is acutely sensitive and responsive to both the external and internal environment. Thus, even small injuries to the brain may produce symptomatic, functional losses that would not be detectable or important in other organs. Regional hypoperfusion, edema, microemboli, circulating cytotoxins, or subtle changes in blood glucose, insulin, or calcium may result in changes in cognitive function, ranging from subtle to profound. A small 2-mm infarct may cause a disruption of behavioral patterns. Physiologic and physical function changes can pass unnoticed, be accepted and dismissed, or profoundly compromise the patient's quality of life. Move the lesion half a centimeter, and the same volume lesion may result in a catastrophic stroke. Thus the brain is the most sensitive organ exposed to damage by cardiopulmonary bypass (CPB) and cardiac surgery and also the organ that, with the heart, is most important to protect.

ASSESSMENT

Routine assessment of neurologic injury, which occurs in the setting of cardiac surgery, is not done for most patients because of the priority of the cardiac lesion and because of costs in time and money. General neurologic examinations by members of the surgical team or individuals lacking specialized training are not adequate to rule out subtle neurologic injuries, and this is the principal reason that the incidence of stroke, neurologic, or neuropsychologic injury varies widely in the surgical literature.¹⁻³

For studies designed to assess or reduce neurologic injury in the setting of cardiac surgery, nonroutine preoperative and postoperative tests are required. These special tests include a complete neurologic examination

by a neurologist or a well-trained surrogate. To improve accuracy, a single neurologist should conduct all serial examinations. A standardized protocol of examination should be followed, with uniform reporting of results. The basic, structured examination includes a mental state examination; cranial nerve, motor, sensory, and cerebellar examinations; and examination of gait, station, deep tendon, and primitive reflexes.

The most obvious neurologic abnormalities are paresis; loss of vital brain functions such as speech, vision, and comprehension; and coma. These are commonly lumped under the general heading of stroke. Disorders of awareness or consciousness can include coma, delirium, and confusion, but transitory episodes of delirium and confusion are often dismissed as being caused by anesthesia or medications. More subtle losses are determined by comparison of preoperative and postoperative performances using a standard battery of neuropsychologic tests prepared by a group of neuropsychologists.⁴ A neuropsychologic examination is basically an extension of the neurologic examination with a much greater emphasis on higher cortical function. Dysfunction is objectively defined as a deviation from the expected, relative to a large population. For example, although performing at a 95 IQ level is in the normal range, it is low for a physician, and a search for a neurologic impairment would be triggered by such a poor performance. A 20% decline in two or more of these tests, compared to the patient's own baseline, suggests a neuropsychologic deficit that should be followed until resolved or not resolved.⁵ In studies involving long-term follow-up, the inclusion of a control group of unoperated patients with the same disease and of similar demographics helps define the causes of neuropsychologic decline that occurs later than 3 to 6 months after surgery.⁶

Computed axial tomograms or magnetic resonance imaging (MRI) scans are essential for the definitive diagnosis of stroke, delirium, or coma. Preoperative imaging is usually not necessary when new techniques such as

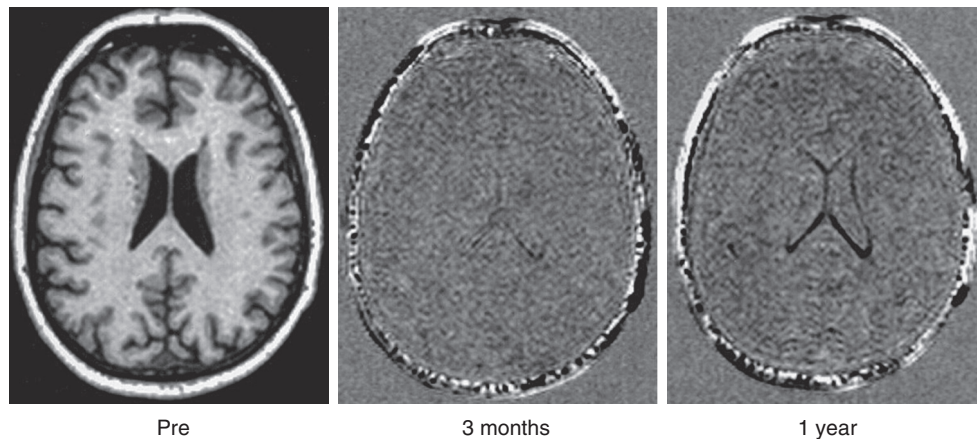


FIGURE 62-1 ■ Preoperative brain MRI from patient undergoing extensive cardiac surgery superimposed on identical images taken at 3 months and 1 year after surgery. The appearance of the ventricles at 1 year indicates brain shrinkage, presumably from apoptosis of neurons.

diffusion-weighted MRI imaging, MRI spectroscopy, or MRI angiography are used to assess possible new lesions after surgery.⁷⁻⁹ However, recent studies demonstrate patients with dementia have a loss in cell volume as a result of micro-infarctions that are not detectable with current radiologic techniques.¹⁰ Histologic studies performed on patients who did not survive cardiac surgery have demonstrated millions of small lipid microemboli, which may result in massive cell loss and increased volume of ventricles (Fig. 62-1).

Biochemical markers of neurologic injury after cardiac surgery are relatively nonspecific and inconclusive. Neuron-specific enolase (NSE) is an intracellular enzyme found in neurons, normal neuroendocrine cells, platelets, and erythrocytes.¹¹ S-100 is an acidic calcium-binding protein found in the brain.^{12,13} The beta dimer resides in glial and Schwann cells. Both S-100 and NSE increase in spinal fluid with neuronal death^{12,13} and may correlate with stroke or spinal cord injury after CPB.¹⁴ However, plasma levels are contaminated by aspiration of wound blood into the pump and hemolysis and are often elevated following prolonged CPB in patients without otherwise detectable neurologic injury.¹⁵ Newer bloodborne biochemical markers are being identified but, as of yet, have not been shown to be diagnostic for subtle neurologic injury.

POPULATIONS AT RISK

Advancing age increases the risk of stroke or cognitive impairment in the general population, and surgery, regardless of type, increases the risk still higher.¹⁶ In 1999 Hogue and colleagues reported the risk of stroke during coronary artery bypass graft (CABG) surgery to be directly related to age and other factors.¹⁷ A European study compared 321 older adult patients without surgery to 1218 patients who had noncardiac surgery and found a 26% incidence of cognitive dysfunction 1 week after operation and a 10% incidence at 3 months.¹⁸ Between 1974 and 1990 the number of patients undergoing cardiac surgery who were older than 60 years and older than 70 years increased twofold and sevenfold, respectively.¹⁹

Today patients 75 years of age and older commonly receive cardiac surgery.²⁰ Genetic factors also influence the incidence of cognitive dysfunction following cardiac surgery.²¹ The incidence of cognitive dysfunction at 1 week following cardiac surgery is approximately double that of noncardiac surgery.

As the age of patients undergoing cardiac surgery increases, the number of patients with multiple risk factors for neurologic injury also increases. Risk factors for adverse cerebral outcomes are listed in Table 62-1.²² These factors are divided into stroke with a permanent fixed neurologic deficit (type 1) and coma or delirium (type 2). Hypertension and diabetes occur in approximately 55% and 25% of cardiac surgical patients, respectively.²³ Fifteen percent have carotid stenosis of 50% or greater, and up to 13% have had a transient ischemic attack or prior stroke. The total number of MRI atherosclerotic lesions in the brachiocephalic vessels adds to the risk of stroke or cognitive dysfunction,²⁴ as does the severity of atherosclerosis in the ascending aorta as detected by epiaortic ultrasound scanning.²⁵ Palpable ascending aortic atherosclerotic plaques markedly increase the risk of right carotid arterial emboli as detected by Doppler ultrasound.²⁶ The incidence of severe aortic atherosclerosis is 1% in cardiac surgical patients younger than 50 years and is 10% in those aged 75 to 80 years.²⁷

MECHANISMS OF INJURY

The three major causes of neurologic dysfunction and injury during cardiac surgery are microemboli, hypoperfusion, and a generalized inflammatory reaction, all three of which can occur in the same patient at the same time for different reasons. Most intraoperative strokes are caused by the embolization of atherosclerotic material from the aorta and brachiocephalic vessels. This occurs as a result of manipulation of the heart and major thoracic vasculature as well as dislodgement of atheromata from shearing forces directed at the walls of vessels from inflow CPB cannulae.²⁸ Microemboli are distributed in proportion to blood flow²⁹; thus, reduced cerebral blood flow reduces microembolic injury but increases the risk of

TABLE 62-1 **Adjusted Odds Ratios for Type I and Type II Cerebral Outcomes Associated with Selected Risk Factors**

Factor	Model for Type I Cerebral Outcome	Model for Type II Cerebral Outcome
Significant Factors, <i>P</i> < 0.05		
Proximal aortic atherosclerosis	4.52	
History of neurologic disease	3.19	
Use of intra-aortic balloon pump	2.60	
Diabetes mellitus	2.59	
History of hypertension	2.31	
History of pulmonary disease	2.09	2.37
History of unstable angina	1.83	
Age (per additional decade)	1.75	2.20
Systolic blood pressure > 180 mm Hg at admission		3.47
History of excessive alcohol consumption		2.64
History of CABG		2.18
Dysrhythmia on day of surgery		1.97
Antihypertensive therapy		1.78
Other Factors (<i>P</i> not significant)		
Perioperative hypotension	1.92	1.88
Ventricular venting	1.83	
Congestive heart failure on day of surgery		2.46
History of peripheral vascular disease		1.64

CABG, Coronary artery bypass graft.
Modified from Roach GW, Kanchuger M, Mangano CM, et al: Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. *N Engl J Med* 335:1857–1863, 1996.

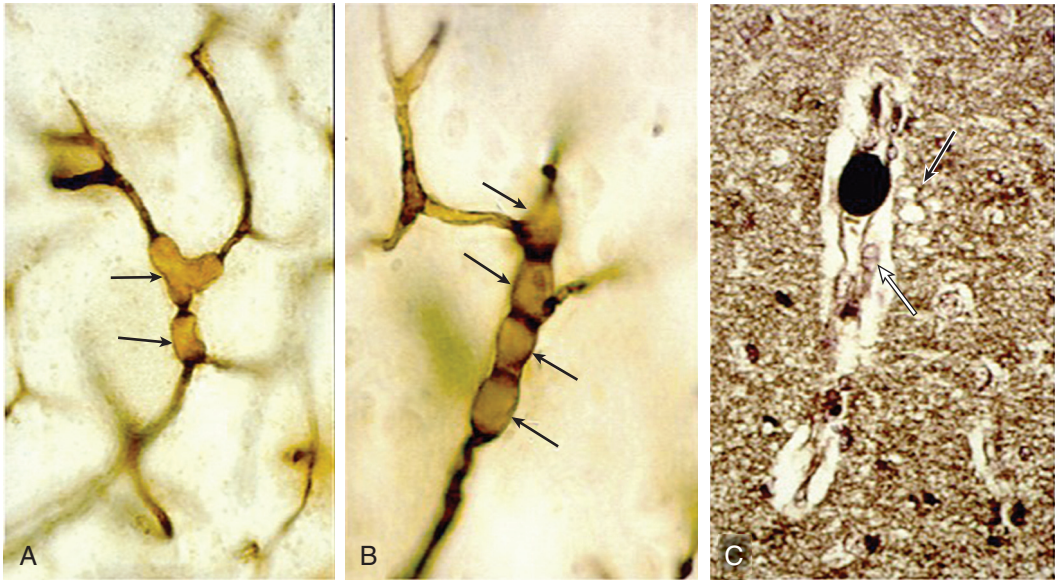


FIGURE 62-2 ■ High-magnification photomicrograph showing small capillary arteriolar dilations (SCADs) from the brain of a patient dying soon after cardiac surgery. **A** and **B**, SCADs in arterioles (dark arrows), vasospasm. (Alkaline phosphatase–stained, celloidin-embedded, $\times 50$.) **C**, SCADs stained black with osmium, indicating fat. Arrows indicate tissue edema and vacuoles from injury. (Osmium-stained, paraffin-embedded, 5- μ m-thick section.)

hypoperfusion.³⁰ During CPB both alpha-stat acid-base management and phenylephrine reduce cerebral injury in adults, probably by causing cerebral vessel vasoconstriction and reducing the number of microemboli.^{31,32} Air,³³ atherosclerotic debris,³⁴ and fat are the major types of microemboli causing brain injury in clinical practice, and all cause neuronal necrosis by blocking cerebral vessels.³³ Massive air embolism causes a large ischemic injury, but gaseous cerebral microemboli may directly damage

endothelium in addition to blocking blood flow.³⁴ The recent identification of unique small capillary arteriolar dilations (SCADs) in the brain associated with fat emboli (Fig. 62-2)³⁵ raises the possibility that these emboli not only block small vessels but also release cytotoxic free radicals, which may significantly increase the damage to lipid-rich neurons.

Anemia and elevated cerebral temperature increase cerebral blood flow but may cause inadequate oxygen

delivery to the brain³⁶; however, these conditions are easily avoided during clinical cardiac surgery. Although some investigators speculate that normothermic and/or hyperthermic CPB surgery cause cerebral hypoperfusion,³⁷ experimental studies indicate that cerebral blood flow increases with temperature.³⁸ Brain injuries associated with this practice are more likely the result of increased cerebral microemboli, which produce larger lesions at higher cerebral temperatures.³⁹ Reduced brain temperature is protective against neural cell injury and remains an important neuroprotective strategy (Fig. 62-3).

All surgery, like accidental trauma, triggers an acute inflammatory response that can result in neurologic injury, but the continuous exposure of heparinized blood to nonendothelial cell surfaces followed by reinfusion of wound blood and recirculation within the body greatly magnifies this response in operations in which CPB is used. Although far from fully described and understood, this primary “blood injury” produces a unique response, which is different in detail from that caused by other threats to homeostasis.

The principal blood elements involved in this acute defense reaction are contact and complement plasma protein systems, neutrophils, monocytes, endothelial cells, and, to a lesser extent, platelets. When activated during CPB, the principal blood elements release vasoactive and cytotoxic substances, produce cell-signaling inflammatory and inhibitory cytokines, express complementary cellular receptors that interact with specific cell-signaling substances and other cells, and generate a host of vasoactive and cytotoxic substances that circulate.⁴⁰ Normally these reactive blood elements mediate and regulate the defense reaction,⁴¹⁻⁴³ but during CPB an orderly, targeted response is overwhelmed by the massive activation and circulation of these reactive blood elements. This massive attack damages the endothelium, increases the size of ischemic lesions, and causes organ dysfunction. The parenchyma of the brain is shielded from this attack by the blood-brain barrier. However, embolization and cytotoxic substances damage the barrier and cause neuronal injury and necrosis. This liberates

S-100, NSE, and other neuronal proteins into the spinal fluid and produces cerebral edema.⁴⁴

STRATEGIES FOR REDUCING INJURY

Important methods for reducing emboli deserve emphasis. Principles include adequate anticoagulation, the washing of blood aspirated from the surgical wound, the filtering of arterial inflow and venous outflow, strict control of all air entry sites within the perfusion circuit, removal of residual air from the heart and great vessels, and avoidance of atherosclerotic emboli.^{45,46}

Many intraoperative strategies are available to reduce cerebral atherosclerotic embolization. These include routine direct contact epiaortic echocardiography of the ascending aorta to detect both anterior and posterior atherosclerotic plaques and to find sites free of atherosclerosis for placing the aortic cannula and grafts.⁴⁷ Special catheters with or without baffles or screens have been developed to reduce the number of atherosclerotic emboli that reach the cerebral circulation.⁴⁸ In patients with moderate or severe ascending aortic atherosclerosis, a single application of the aortic clamp as opposed to partial or multiple applications is strongly recommended and has been shown to reduce postoperative neurocognitive deficits in a large clinical series.⁴⁹ Retrograde cardioplegia is preferred over antegrade cardioplegia in these patients to avoid repeated aortic injections of cardioplegic solution.⁵⁰ No aortic clamp may be safe or even possible in some patients with severe atherosclerosis or porcelain aorta. If intracardiac surgery is required in these patients, deep hypothermia may be used with or without graft replacement of the ascending aorta. If only revascularization is needed, pedicled single or sequential arterial grafts,⁵¹ T- or Y-grafts from a pedicled mammary artery,⁵² or vein grafts anastomosed to arch vessels can be used. Patients with intracardiac thrombus or vegetations require aortic cross clamping before cardiac manipulation to avoid dislodging embolic material. In open cardiac surgery, the removal of air from cardiac chambers is important to avoid embolization. Flooding the field with

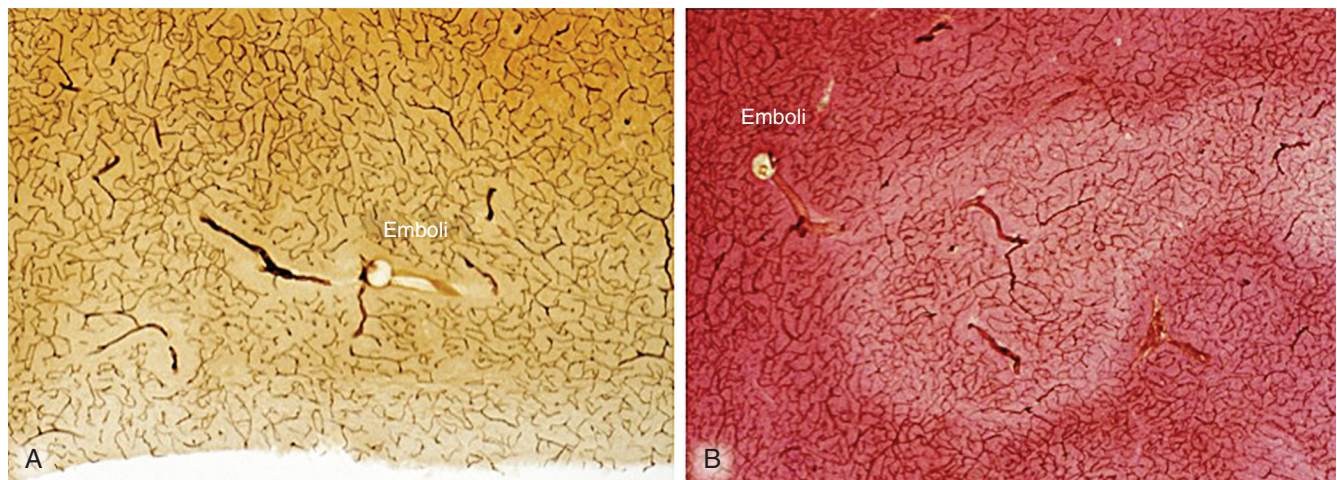


FIGURE 62-3 ■ Experimental brain ischemia from glass bead embolization. **A**, Large area of ischemia in an animal at normothermia. **B**, From an animal embolized at 32°C with no evident ischemia. Paraffin-embedded, stained for heat shock protein.

carbon dioxide is one answer to the problem but is cumbersome and potentially dangerous to the surgical team.⁵³ The advent of routine transesophageal echocardiography to detect and aid in air removal has made this adjunct less important.⁵⁴

In-depth or screen filters are essential for cardiectomy reservoirs, although washing cardiectomy blood is important because fat emboli are not effectively filtered. The efficacy of arterial line filters is controversial; screen filters with a pore size less than 20 μm cannot be used because of flow resistance across the filter.⁵⁵ However, air and fat emboli can pass through filters, although 20- μm screen filters more effectively trap microemboli than do larger sizes.⁵⁶ The Northern New England Cardiovascular Disease Study Group has published innovative techniques using small-pore venous reservoir and arterial line filters to eliminate microemboli generated in CPB circuits.⁵⁷

NEUROPROTECTIVE STRATEGIES

Recommended conditions for protecting the brain during CPB include mild hypothermia (32°C to 34°C) (see Fig. 62-3) and hematocrit above 25%.³⁸ Temporary increases in cerebral venous pressure caused by superior vena cava obstruction and excessive rewarming above blood temperatures of 37°C should be avoided.^{39,58} A randomized study in which patients were mildly rewarmed to 35°C core temperature demonstrated improved neurocognitive outcomes over patients rewarmed to 37°C.⁵⁹ Either jugular venous bulb oxygen saturation or near-infrared cerebral oximetry is recommended for monitoring cerebral perfusion in patients who may be at high risk for cerebral injury.⁶⁰ A randomized study demonstrated improved overall outcomes using near-infrared spectroscopy but no significant improvement in stroke incidence.⁶¹ This may indicate that maintenance of adequate cerebral oxygenation is a surrogate for overall adequate perfusion during bypass but has little effect on microembolic brain damage.

Barbiturates reduce cerebral metabolism by decreasing spontaneous synaptic activity⁶² and provide a definite neuroprotective effect during clinical cardiac surgery using CPB.⁶³ Unfortunately these agents delay emergence from anesthesia and prolong intensive care unit stays. One study of high-risk patients randomized to aprotinin or placebo found a powerful protective effect against stroke for full-dose aprotinin in CABG patients.⁶⁴ However, renal and cardiac toxic side effects limit effectiveness. NMDA (*N*-methyl-D-aspartate) antagonists, which are effective in animals, provide mild protection compared to control patients, but have a high incidence of neurologic side effects.⁶⁵ A small study demonstrated a neuroprotective effect of lidocaine, but this beneficial effect has not been reproduced.⁶⁶ Currently no pharmacologic agent is recommended for protection of the central nervous system during CPB.

Off-pump myocardial revascularization theoretically avoids many of the causes of cerebral injury resulting from CPB, but, as noted earlier, many causes of neuronal injury are independent of CPB and related to

atherosclerosis and air entry sites into the circulation. Many surgeons believe that off-pump coronary artery bypass (OPCAB) surgery is safer than on-pump operations, but studies testing this hypothesis have yielded inconsistent results in measured neurologic outcomes. Nonrandomized measurements of carotid emboli by Doppler ultrasound indicate fewer emboli and slightly improved neurocognitive outcomes in high-risk patients who have off-pump surgery.⁶⁷ Two smaller studies suggest that high-risk patients benefit disproportionately from off-pump coronary surgery.^{68,69} The only large trial that demonstrated superior results from OPCAB was a meta-analysis of 120,000 propensity-matched patients that demonstrated highly statistically significant benefits in mortality and stroke.⁷⁰ One year later, a large database review found no advantage in any outcome measures for off-pump surgery.⁷¹ Until the results of a large prospective randomized trial are published, no firm conclusions can be made regarding neuroprotection.

PROGNOSIS

Patients with intraoperative stroke or who develop stroke symptoms in the first week after surgery often improve in direct relation to the lesion size and location on imaging studies. Neuropsychologic deficits that are present after 3 months are almost always permanent.⁷² Assessments after that time are confounded by development of new deficits, particularly in older adult patients.^{10,73}

The difficulty of separating intraoperative brain injury from that which occurs in the early or late postoperative period has been addressed by a reanalysis of data published earlier. The authors tracked specific neuropsychologic deficits that persisted unchanged for 6 months (persistent deficits) and separated them from new deficits that appeared after surgery⁷⁴ (Fig. 62-4). Using this

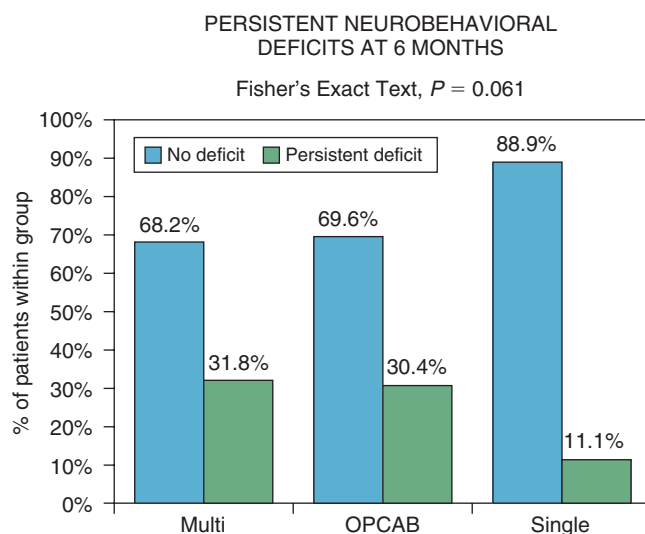


FIGURE 62-4 ■ Bar graph with results of neuropsychologic testing at 6 months after coronary artery bypass graft (CABG) surgery performed using three different techniques. Note patients with single aortic clamping have many fewer persistent neuropsychologic deficits than patients operated with multiple aortic clamping or off-pump coronary artery bypass (OPCAB).

technique it is possible to accurately measure surgical brain injury and design techniques to eliminate this important cause of morbidity. Late follow-up studies should include a control group with similar risk factors but not having cardiac operations.⁷⁵ This technique demonstrated similar outcomes in surgical and nonsurgical controls at 3 years, putting to rest the previous fear that surgical patients had recurrent neurocognitive deficits and were thus at greater risk for poor long-term outcomes. In a recent study, a group of surgical patients who were evaluated with preoperative and postoperative neuropsychologic studies had rigid control of postoperative cardiovascular risk factors.⁷⁶ They demonstrated no delayed or late cognitive decline. This result offers hope that aggressive medical therapy can complement skillful surgery in preventing neurologic injury.

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CARDIOPULMONARY BYPASS: TECHNIQUE AND PATHOPHYSIOLOGY

Hadi D. Toeg • Fraser D. Rubens

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THE FUTURE OF CARDIOPULMONARY BYPASS

INTRODUCTION AND HISTORY

Cardiopulmonary bypass (CPB) is one of the most important biomedical inventions in the history of health care, rivaling the development of roentgenography and hemodialysis in its clinical impact. The scope of its application is far reaching. Its birth paralleled the evolution of an entire surgical subspecialty, and without its use, surgeons would be intimidated by the prospect of intracardiac repair.

Despite the belief that the need for CPB would be significantly diminished because of the surge in interest in off-pump coronary artery bypass grafting (CABG), the predictions have not materialized. Off-pump trends peaked at 24% in 2003, steadily declining thereafter to a stabilized percentage of 19% in 2011.¹ In many practices,

complex multiple arterial reconstruction and minimal-access surgery such as mini-thoracotomy mitral valve surgery are more comfortably and accurately approached using longer periods of CPB and optimized myocardial protection. Therefore, every surgeon must have a comprehensive understanding of all aspects of CPB, from the physiology of gas exchange to the molecular mechanisms characteristic of biocompatibility.

The evolution of CPB reflects ingenuity bred of necessity. A parallel discovery that contributed to the feasibility of extracorporeal circulation was the isolation of the natural anticoagulant heparin. Dr. John H. Gibbon, Jr. (Fig. 63-1), a “receptive and talented surgeon with foresight ... who could envision an intact surviving patient beyond the isolated organ studies,”² was the inventor of the Gibbons-IBM oxygenator. In 1953, this device was successfully used to correct an atrial septal defect. Although

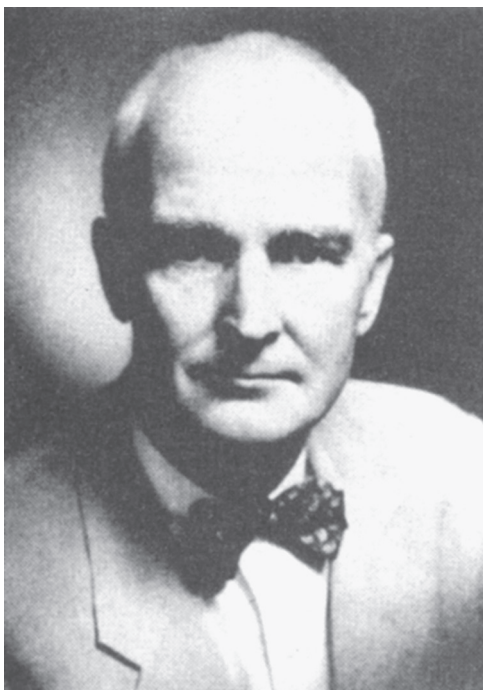


FIGURE 63-1 ■ Dr. John H. Gibbon, Jr. (1903-1973).

it was initially successful, three subsequent attempts at intracardiac repair were fatal, resulting in a self-imposed moratorium on its clinical use. Nevertheless, the feasibility of this approach had been demonstrated.

The first clinically successful film and bubble oxygenators brought blood in direct contact with respiratory gases to equilibrate with them. Complications related to blood trauma eventually led to a decline in their popularity, and they are rarely used today. Membrane oxygenators were introduced in the 1950s after the observation by Kolff and Berk³ that venous blood was oxygenated while flowing through a cellophane dialysis tube in contact with O₂-containing dialysate. The first membranes were relatively impermeable to gases, requiring huge surface areas and massive priming volumes. Formed of silicone rubber, they were designed in either an extraluminal format (blood flowing on the outside of the tube with gas on the inside) or, less often, in an intraluminal format (the reverse). The next generation of oxygenators were prepared with silicone-coated polypropylene, whereas currently many commercial oxygenators use polymethylpentene fibers. Other refinements have been subtle but significant, and we now have oxygenators with surface areas of over 2.0 m² configured with minimal blood volume. The resulting minimization of prime volume has contributed more than any other factor to blood conservation practice in modern-day cardiac surgery.

TECHNICAL ASPECTS

Device Overview

Inflow and outflow cannulas from the patient are attached to the oxygenator device with tubing composed of poly-

vinylchloride, polyurethane, or silicon rubber. Blood enters the venous reservoir from the venous circulation. Through separate inflows on the reservoir, blood can also be returned from the pericardial well (cardiotomy blood) and from cardiac and aortic vents. A pump is used to divert the venous reservoir blood to the oxygenator. After the blood passes through the integrated heat exchanger and oxygenator, it is circulated through an arterial filter and bubble trap and returned to the patient through the arterial cannula (Fig. 63-2). Cardioplegia setups are often intimately incorporated into the CPB circuit.

Principles of Current Oxygenator Design and Function

Diffusion of gases at the blood-membrane interface can be predicted by Fick's law, which states that the rate of diffusion is proportional to the partial pressure gradient of the gas in the direction of diffusion. The rate of gas transfer is also inversely proportional to the distance through which it must pass (the thickness of the membrane). The rate also depends on the property of *diffusivity* of the membrane biomaterial. Currently used membranes are permeable to O₂, but they are often less permeable to CO₂. The problem of poor diffusion of CO₂ was solved by the introduction of microporous membranes. These surfaces allow transient blood-gas interfacing at pore structures smaller than blood cells; however, the hydrophobic nature of the membrane results in changes in blood surface tension, blocking actual contact between the two phases. As a result, the interface in microporous membranes behaves like a very thin stagnant film of plasma water that offers little resistance to gas exchange. Progressive protein accretion at the pores occurs over time, resulting in a finite functional capacity, detected by worsening efficiency in gas transfer, which is why oxygenators must be replaced with long CPB runs (Fig. 63-3).

As opposed to the relatively facile transfer of O₂ gas through a membrane, when the O₂ is dissolved in plasma or blood, its diffusivity is 25 times less than that of CO₂. This difference is due to the more facile dissolution of CO₂ in plasma and due to the linear shape of the CO₂ dissociation curve as compared to the sigmoid shape of the O₂ dissociation curve. The patient's PaCO₂ can be decreased by increasing the rate of fresh gas flow, whereas alteration of the PaO₂ can be achieved only by enhancing the rate of blood flow exposure to the surface. This latter can be accomplished either by increasing the overall flow or by enhancing the efficiency of exposure. To achieve this, the path length (the distance the blood travels as it passes the gas-exchange surface) must be maximized. This modification is limited by the parallel need to increase the priming volume. Second, disturbed flow patterns can be used to promote mixing and to bring deoxygenated blood closer to the exchange surface. Mechanisms that interfere with the development of fully developed flow patterns enhance diffusion by keeping the boundary layer narrow. In an oxygenator, this can be accomplished by making the surface irregular or by positioning elements in the flow stream to disrupt smooth flow and to enhance mixing. This is the rationale for the extraluminal hollow fiber design.

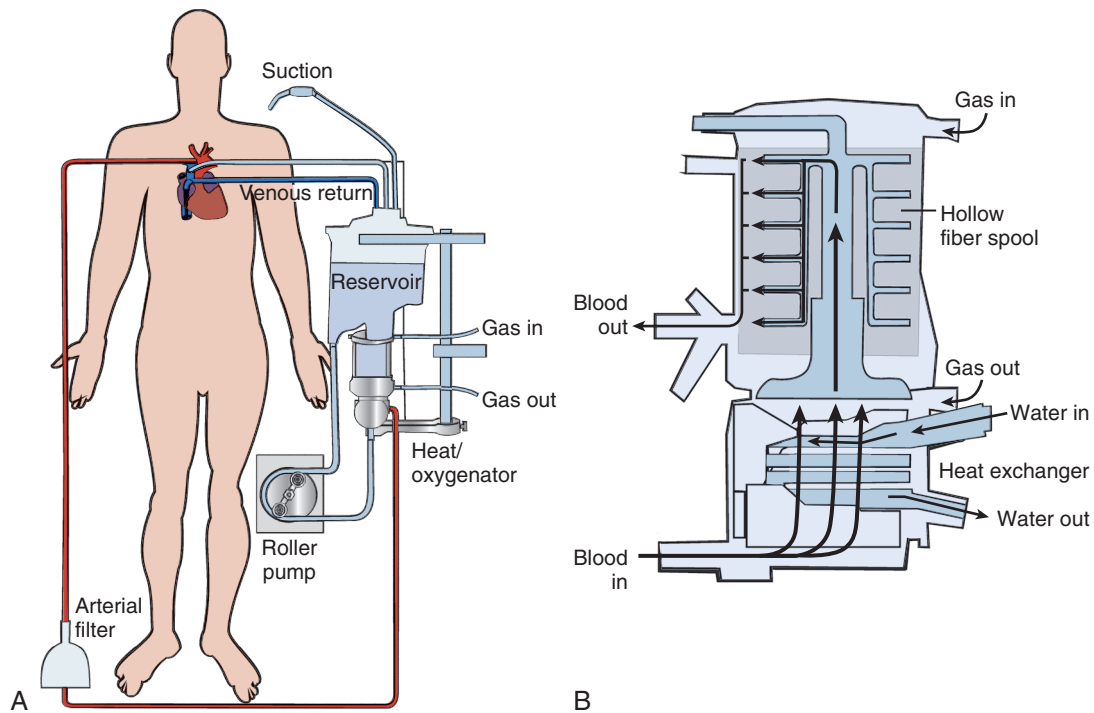


FIGURE 63-2 ■ **A**, Overview of the cardiopulmonary bypass circuit. **B**, Typical integrated heat exchanger-membrane oxygenator.

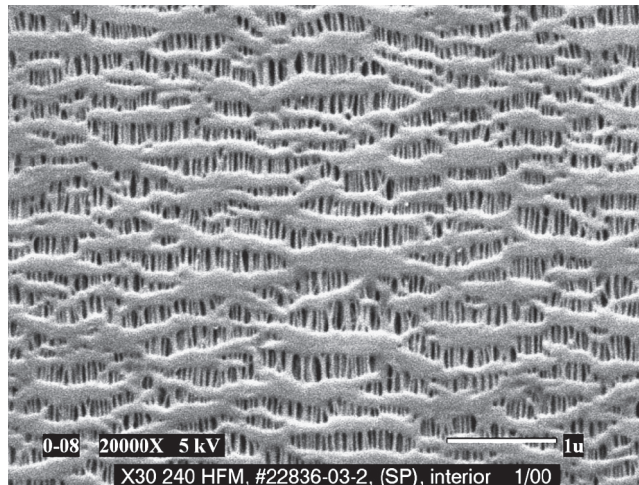


FIGURE 63-3 ■ Scanning electron micrograph of a microporous membrane (Celgard) used in a membrane oxygenator ($\times 20,000$). (Courtesy Membrana GmbH, Germany.)

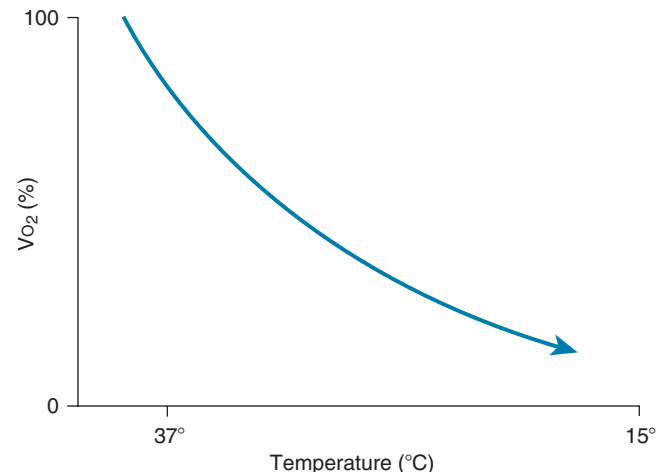


FIGURE 63-4 ■ The effect of hypothermia on oxygen consumption (VO_2).

Hypothermia and Acid-Base Balance

The feasibility and applicability of hypothermia for heart surgery was first suggested by Bigelow and colleagues in 1950.⁴ They demonstrated the safety benefit of hypothermia as a means to decrease O_2 consumption during inflow occlusion in an animal model. O_2 consumption decreases by 50% for every $10^{\circ}C$ drop in temperature (Fig. 63-4). Lower flows decrease collateral flow and rewarming of the heart from contact with adjacent tissues, and they provide a margin of safety if equipment fails.

Hypothermia is associated with marked changes in blood pH and PCO_2 levels. With a rise in temperature,

CO_2 becomes less soluble in blood, and there is a greater tendency for the dissolved CO_2 to come out of solution (increased gaseous phase). Similarly, CO_2 solubility increases with decreasing temperature. When blood from a hypothermic patient (e.g., $24^{\circ}C$) is introduced into a CO_2 electrode for measurement, it is first warmed to $37^{\circ}C$ (increasing the amount of CO_2 in the gaseous phase), and therefore the measured partial pressure of CO_2 is higher than it was in reality at the cooler temperature. The correction for PCO_2 is based on a calculated decrease of 4.5% per degree Celsius. On the other hand, the pH increases 0.015 units per degree Celsius drop in temperature. This shift in pH is partially related to the

influence of buffers such as the imidazole moiety of histidine, but it is also related to the dynamics of the Henderson-Hasselbalch equation, $\text{pH} = \text{pK} + [\text{HCO}_3^-]/(0.03 \times \text{PCO}_2)$.

Because alkalosis and hypocarbia trigger a decrease in cerebral blood flow (CBF), some investigators have suggested the addition of CO_2 during hypothermia to compensate and to keep the pH unchanged (pH-stat strategy). In 1987, Murkin and coworkers⁵ confirmed that pH-stat management results in a greater ratio of CBF to cerebral metabolic rate (CMRO_2) than alpha-stat management (i.e., no active correction of pH with hypothermia). Most agree that a pH-stat strategy is probably preferable in children, where increased CBF increases the rate of cooling and thus increases the chance of achieving uniform cerebral hypothermia.⁶ The rate of brain oxygen depletion during deep hypothermic circulatory arrest is also considerably slower with pH-stat strategy. As a result, pH-stat substantially prolongs the interval between the onset of arrest and the exhaustion of brain oxygen stores and may be associated with better clinical outcomes in this group.

In contrast, in adults, an alpha-stat strategy may provide greater cerebral protection during hypothermia on CPB.⁷ Alpha-stat management is certainly easier to accomplish, and a justification is that most cellular mechanisms are capable of maintaining intracellular pH despite fluctuations in extracellular conditions. Because excess CO_2 is added in a pH-stat strategy, brain acidosis may occur during rewarming, and, combined with decreased O_2 delivery after CPB, this may augment CNS injury in adults. Most importantly, as mentioned, a pH-stat strategy results in excessive CBF, which may increase embolic load. Finally, pH-stat strategy is associated with a decreased ability to maintain autoregulation at low pressures. Three randomized controlled trials have demonstrated a small but present benefit of alpha-stat strategy in terms of neurologic and neurocognitive outcome in adults, especially when CPB time exceeded 90 minutes and therefore evidence-based guidelines now support that patients undergoing moderate hypothermic CPB should be handled with an alpha-stat pH management (Class I, Level A).⁸

Hematocrit and Priming

In the 1960s, crystalloid (dextrose 5% in water, or D5W) in prime was introduced as an alternative to routine whole blood prime. An increase in efficiency of oxygenation and a decrease in end-organ complications were seen with this approach.⁹ Now hemodilution is commonly practiced in virtually all adult and pediatric cardiac surgeries, with the hematocrit (Hct) maintained between 20% and 25% during CPB. Hemodilution has a major effect on blood viscosity, primarily at the capillary level where the radius is small and the shear rate is low. Low flow at the capillary level increases viscosity of the blood, further increasing the resistance, but this effect is counterbalanced by the effect of hemodilution.

The drop in O_2 content at most levels of moderate hemodilution may be compensated by augmented cardiac output (CO), so total O_2 delivery ($\text{CO} \times \text{O}_2$ content of

blood) is increased. Hypothermia complicates the effects of hemodilution, as the decreased temperature causes increased viscosity and induces vasoconstriction.

The optimal Hct for CPB remains a topic of significant controversy. A post hoc assessment of the impact of low Hct on admission of cardiac patients to the intensive care unit (ICU) by Spiess and colleagues¹⁰ showed an inverse correlation between admission Hct and the risk of Q-wave myocardial infarction (MI). On the other hand, studies have demonstrated that an Hct of less than 20% may be associated with abnormal distribution of blood flow to organs, and that an Hct of less than 15% may lead to maldistribution of coronary flow away from the subendocardium in the presence of residual coronary stenosis.¹¹ Retrospective observational studies of consecutive patients undergoing isolated CABG have demonstrated that a lower minimum Hct is associated with a significantly increased risk of renal injury¹² and mortality.^{13,14} These relationships have also been demonstrated in patients with low Hct during CPB who did not receive any transfusion so as to differentiate that this was not an effect of blood products that these patients might otherwise receive.^{15,16} As excessive hemodilution also increases CBF, it may cause a parallel increase in microembolization and thus may theoretically be a contributor to neurologic damage after CPB and the increased risk of stroke observed with lower Hct on CPB.¹⁷

Most centers prime the CPB circuit with a solution of balanced salt with or without the addition of a colloid solution such as pentastarch. Infants and children often need blood added directly to the prime, depending on the anticipated Hct after initiation of bypass (calculated from standard nomograms). Other additives to the prime may include calcium, mannitol, and pharmacologic agents such as heparin and aprotinin. The patient's circulating volume and the pump prime volume mandate the minimum priming volume. Although the prime volume averages 1 liter, experienced practitioners can achieve as low as 200 mL in pediatric circuits.

Flow Rates, Perfusion Pressure, and Autoregulation

Flow is generally kept in the range of 2.2 to 2.5 liter/min/ m^2 to provide a margin of safety during CPB, because systemic blood flow distribution and O_2 consumption remain normal at this level. At normothermia, a target mean blood pressure of 50 to 70 mm Hg is used. (As a rule of thumb in adults, the mean pressure chosen should be equal to the patient's age.) The perfusionist can control the pressure by increasing or decreasing flow or by the addition of vasoconstrictors or vasodilators (inhalational anesthetics). At lower temperatures, a mean pressure of 35 mm Hg is still generally accepted as safe, but these findings are controversial.^{18,19}

Although the brain comprises only 2% of body weight, its metabolic needs demand 15% of the cardiac output, extracting as much as 25% of the delivered O_2 . Temperature is the most important element influencing CBF during CPB. As the temperature is dropped, the CMRO_2 decreases exponentially and the CBF decreases linearly (Fig. 63-5). As a consequence, the ratio of CBF to CMRO_2

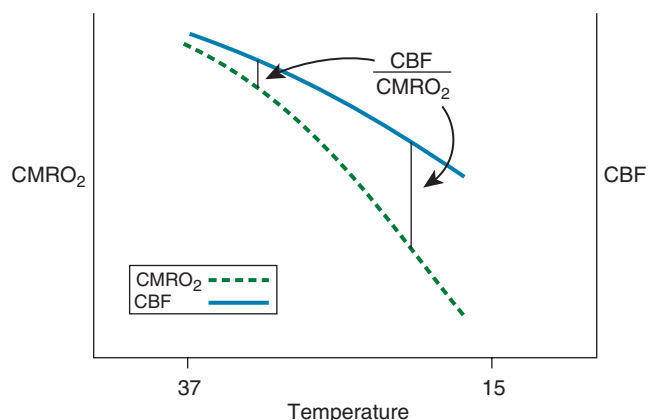


FIGURE 63-5 ■ The effect of hypothermia on cerebral metabolic rate (CMRO₂) and cerebral blood flow (CBF).

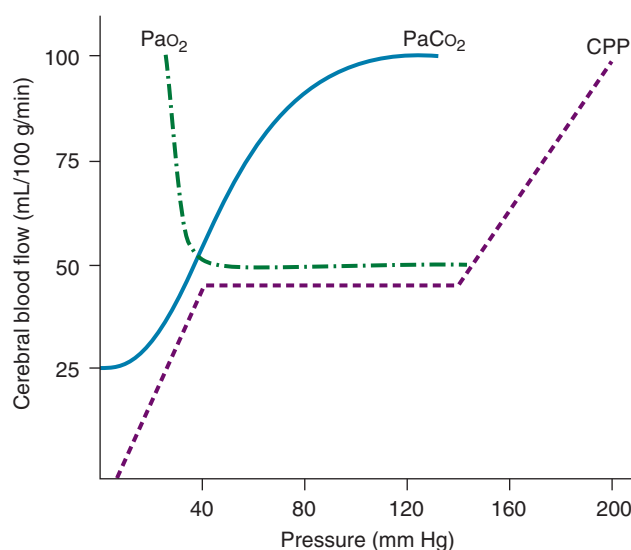
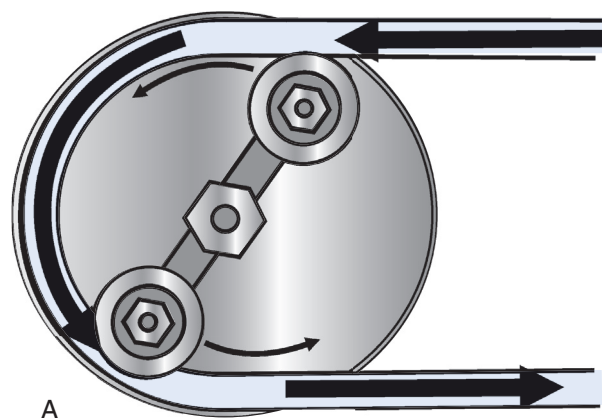


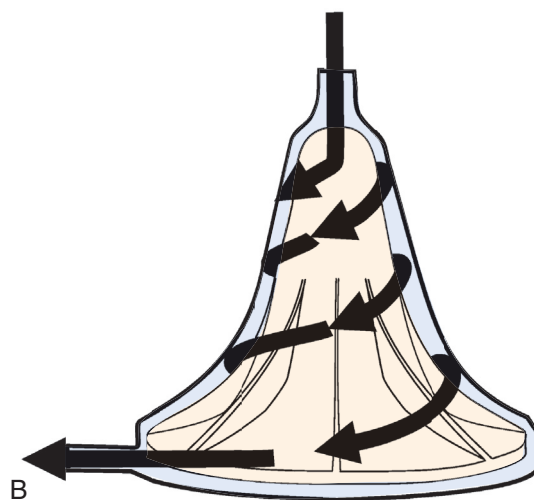
FIGURE 63-6 ■ Through autoregulation, cerebral blood flow (CBF) is constant from cerebral perfusion pressure (CPP) 40 to 140 mm Hg. Other factors that independently affect CBF include PaCO₂ and PaO₂. (Modified with permission from Kelly BJ, Luce JM: Current concepts in cerebral protection. *Chest* 103:1246–1254, 1993. Copyright 1993, American College of Chest Physicians.)

increases, resulting in “luxuriant” flow, further facilitated by hemodilution.

Autoregulation of CBF is also related to changes in perfusion pressure. At normothermia, a mean pressure of 50 mm Hg is the threshold at which the brain autoregulates flow, but with hypothermia (26°C), the threshold drops to 30 mm Hg (Fig. 63-6). At deep hypothermia (<20°C), there is a loss of pressure-flow autoregulation, as severe temperature reductions impair cerebral vascular relaxation and changes in cerebral perfusion pressure alone result in corresponding proportional changes in CBF. Other factors that influence CBF and CMRO₂ include blood viscosity, intracranial pressure and central venous pressure (CVP), and the blood gas status (pH, PaCO₂, PaO₂). CBF varies linearly with the PaCO₂, in the range of 20 to 80 mm Hg, whereas a PaO₂ of less than 50 causes cerebral vasodilation, which overrides pressure-flow autoregulation.



A



B

FIGURE 63-7 ■ **A**, A double roller pump has rotating arms oriented at 180 degrees like spokes on a wheel. Spool-shaped rollers are located at the ends of the arms. A length of tubing is locked inside a curved track at the outer circumference of a partial circle of 210 degrees. **B**, A typical centrifugal pump has a cone-shaped outer housing with an upper inlet and a single lower outlet. The inner chamber contains spinning concentric smooth cones or fins, mounted on a central impeller. Arrows indicate direction of blood flow.

Pumps

The two commonly used types of pumps for CPB involve either roller or centrifugal fluid propulsion. With the former, noninterrupted contact of the rollers with the tubing in the track results in the nonpulsatile nature of the flow (Fig. 63-7A). Flow is calculated from the RPM of the roller pump knowing the diameter of the tubing and thus precisely the volume displaced. A low compression will result in inadequate flow, whereas excessive compression may aggravate hemolysis and tubing wear. Other complications associated with the use of the roller pump include (1) cavitation caused by excess pressure and (2) spallation (the release of particles from the inner surface).

Centrifugal pumps (see Fig. 63-7B) are a popular alternative to the roller pump, particularly in pediatric cardiac surgery. A rotating impeller spins at 2000 to 5000 revolutions per minute on a small bearing, or the blades are magnetically suspended. This creates a vortex that draws blood into the pumphead and thrusts it to the oxygenator.

The advantages of this device include its relatively small priming volume and its reliability (with fewer technical failures as compared to a roller pump device). Whereas with a roller pump, venous drainage to the reservoir from the patient is dependent on gravity drainage, centrifugal pumps are not constrained by this action. The flow in a centrifugal pump is preload and afterload dependent, and it is not predictable solely based on the calculated revolutions per minute, so an in-line flowmeter is essential. Aside from their expense (\$150 per case), these devices are susceptible to air locks, thus requiring vigilance by the perfusionist. On the other hand, this may be protective, because there is less chance of pumping large volumes of air into the patient via an inadvertent leak, and the lines cannot be overpressurized with distal obstruction, as occurs with roller pumps. These devices are also not valved, and if rotation stops without clamping the outflow, rapid retrograde flow from the arterial line occurs in milliseconds, potentially exsanguinating the patient. Finally, roller pumps can be operated manually, but a power outage with a centrifugal pump can be a disaster.

A recent meta-analysis comparing roller versus centrifugal pumps for CPB, which included 18 randomized controlled trials with 1868 patients (predominantly isolated CABG), identified no significant difference for hematologic variables, blood loss and transfusions, neurologic outcomes (albeit not amenable to pooled analysis), or mortality rate.²⁰

Cardiotomy

Cardiotomy blood is the extravascular blood collected in the thoracic wound during CPB. In general, blood from the wound cavity is aspirated through a sucker device and transferred to a cardiotomy reservoir. Because of the close proximity of tissues in the wound and the potential for particulate matter to be collected, a filter and a defoaming chamber are incorporated into the cardiotomy reservoir. Mechanical injury, such as hemolysis, may result from the air-blood interface at the sucker, as well as from the compressive effects of the roller pump. Other mechanical complications from cardiotomy suction include the formation of particulate emboli, including fibrin, macroaggregates of denatured proteins and lipoproteins, fat globules, platelet and leukocyte aggregates, calcium, cellular debris, talc, and suture material.

Cardiac Venting

Cardiac venting involves the active aspiration of blood from the heart, thus creating a bloodless field to facilitate visualization. Venting in some form is necessary in virtually all cardiac operations involving CPB, primarily to aid visualization but also to avoid chamber distention. When the aorta is cross-clamped and the native coronary collateralization remains, particularly related to bronchial artery flow and return from the thebesian veins. Blood flow can also occur through the heart as a result of continued transit of blood through the right heart, through the lungs, and into the left heart. Potential sites for

cardiac venting include the pulmonary artery, the superior pulmonary vein, the left atrium, the left ventricle, and the ascending aorta.

Cannulation

Venous Cannulation

Siphonage generates the negative pressure necessary to draw blood from the venous circulation. The determinants of drainage include the height of the patient above the venous reservoir, the patient's blood volume, the resistance of the tubing, and the cannula dimensions (as this is the narrowest part of the venous return). Augmented venous return refers to the use of either a pump (e.g., centrifugal) inserted in series between the venous line and the reservoir (kinetic-assisted venous drainage) or the application of a vacuum to a closed hard-shell venous reservoir (vacuum-assisted venous drainage).

In most cases of cardiac surgery, venous cannulation is directly through the right atrium. Bicaval cannulation refers to the use of two single-stage cannulas introduced into the superior vena cava (SCV) and the inferior vena cava (IVC), usually through the right atrial wall. Cavoatrial cannulation involves the use of a two-stage venous cannula, inserted through the right atrium in the region of the atrial appendage, with the tip of the cannula directed into the IVC. The cannula is constructed with a fenestrated basket at the level of the right atrium to allow collection of blood from the coronary sinus and from the SVC. Bicaval cannulation is used when an "airless" right atrium is required, such as in tricuspid valve surgery. It is also preferred in mitral valve surgery, when distortion of the right atrium with retraction may lead to a compromise in SVC blood return and a rise in the CVP. Placing tourniquets around the SVC and IVC during bicaval cannulation allows the institution of *total* as opposed to *partial* bypass. With partial bypass, some return of venous blood still takes place through the tricuspid valve and subsequently through the pulmonary circulation. Occasionally in some pediatric cases or in complex adult or reoperative surgery, it is necessary to directly cannulate into the innominate vein, the jugular vein, or the SVC. Alternative sites for venous access include the femoral, iliac, and axillary veins.

Cannula size should be chosen so that the anticipated pressure drop across the cannula is equal to, or less than, the siphonage pressure that is applied based on the height of the patient above the pump and on the patient's blood volume. If this principle is not followed, the CVP might increase, which could compromise cerebral perfusion pressure. Like aortic cannulas, venous cannulas are often wire reinforced, and the tips may be constructed of thin metal to optimize the inner-to-outer-diameter ratio.

Arterial Cannulation

Oxygenated blood is returned to the arterial circulation through specially designed arterial cannulas, which come in a variety of configurations. Cannula characteristics include their length, diameter, orientation of the tip (straight or right angle), presence of a flange, and distal

tapering. The arterial cannula is the narrowest portion of the CPB circuit after the oxygenator, and thus it is the site of the highest potential gradient; gradients in excess of 100 mm Hg can be associated with hemolysis. Finally, although the size and shape of the cannula have not been shown to influence the rate of transcranial Doppler-detected microemboli,²¹ design concepts such as tips to diffuse the sand-blasting effect of flow, differential flow to the arch vessels, and distal baskets to capture debris have been introduced to minimize, at least theoretically, the potential that the cannula may contribute to atheroemboli.

Complications of ascending aortic cannulation include aortic intramural hematoma and dissection (0.01% to 0.09%), atheroemboli either directly from the cannula or from a jet effect, carotid hypoperfusion, air embolism, injury of the back wall of the aorta, and misdirection of the tip of the cannula either posteriorly across the aortic valve (causing severe aortic insufficiency) or anteriorly into the arch vessels or against the wall of the aorta. Femoral cannulation is most commonly used in situations of reoperative surgery and anticipated substernal adhesions. The dissection rate with femoral cannulation is between 0.2% and 3%. Retroperitoneal access to the iliac vessels by suprainguinal retroperitoneal dissection may also be necessary. Another attractive approach, particularly in cases of aortic dissection, involves the use of axillary cannulation. This artery is less likely to be involved with atherosclerosis than are the lower extremities. There is exceptional collateral flow compared with the leg vessels, so the procedure is well tolerated and only infrequently results in limb ischemia. The direction of flow during axillary cannulation also favors noncerebral embolization should there be atherosclerotic disease in the arch of the aorta, and there is less chance of inappropriate extension and malperfusion of a false lumen in cases of aortic dissection.²² Complication rates of this procedure are minimized by cannulation through a short tube graft, anastomosed in an end-to-side manner to the axillary artery, as opposed to direct cannulation.

One of the most perplexing problems related to arterial cannulation is the management of patients with extensive aortic calcification. With bypass grafting, the use of off-pump surgery with a "no-touch" technique may be considered. Alternatively, femoral or axillary cannulation can be used with fibrillatory arrest, left heart venting, and arterial grafting. A third potential strategy involves the threading of a long cannula beyond the atheroma, into the descending thoracic aorta. Borger and Feindel²³ demonstrated that cannulation beyond the cerebral vessels with a long cannula decreased the count of cerebral emboli as detected by transcranial Doppler. Finally, in extreme cases, surgeons may cannulate the apex of the left ventricle with an armored venous cannula passed through the apex into the ascending aorta across the aortic valve. Epi-aortic scanning has been advocated as a means to detect problems with the aorta and, when used consistently, may alter surgical management in terms of cannulation and clamp site as well as offering the option to proceed with off-pump surgery.²⁴ This modality is effective in trained hands and more sensitive than transesophageal echocardiography (TEE) and

digital palpation. Guidelines strongly support intraoperative TEE or epi-aortic ultrasound scanning of the aorta to detect nonpalpable plaque (class I, level B), and reduce the cerebral embolic load (class IIa, level B) in patients at high risk of adverse neurologic events.²

PATHOPHYSIOLOGY

Noncellular Response

The pathophysiology of CPB relates to the unique responses that occur when blood contacts a biomaterial surface (biomaterial-dependent processes), non-contact-related processes such as cardiotomy blood collection and the effect of nonpulsatile flow. Within milliseconds of the blood's contacting the synthetic surfaces of the CPB circuit, plasma proteins become adsorbed to the biomaterial. Although the amount, composition, and conformation of protein adsorption may differ between surfaces, there is no surface on which this process is completely inhibited, and each surface has a characteristic blood-adsorption pattern. Further exposure of the surface to blood results in activation of proteins of the contact activation system (Fig. 63-8). This system comprises four primary plasma proteins: factors XII and XI, prekallikrein, and high-molecular-weight kininogen (HMWK). In the presence of the negatively charged biomaterial, a conformational change occurs in factor XII that permits its activation in the presence of prekallikrein and HMWK. Factor XIIa activates factor XI and initiates the intrinsic coagulation pathway, with the subsequent generation of thrombin and the cleavage of fibrinogen to produce fibrin, which is cross-linked by activated factor XIII. Factor XIIa also activates prekallikrein to form kallikrein within seconds of the start of bypass. Kallikrein catalyzes the conversion of HMWK to bradykinin and plays a role in the activation of the fibrinolytic system. Bradykinin has a very short half-life in the plasma because of its rapid metabolism by angiotensin-converting enzyme in the pulmonary circulation²⁵ and by the vascular endothelium.²⁶ It is believed to be a key mediator of increased

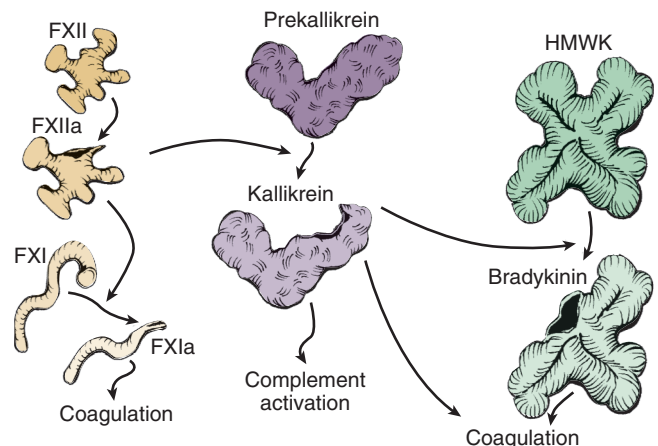


FIGURE 63-8 ■ Proteins of the contact activation system. *FXI*, Factor XI; *FXIa*, activated factor XI; *FXII*, factor XII; *FXIIa*, activated factor XII; *HMWK*, high-molecular-weight kininogen.

capillary permeability and the development of tissue edema. Bradykinin mediates vasodilation by stimulating the release of endothelial nitric oxide,²⁶ and it may also be an important mediator of cerebral ischemia.²⁷

Activation of the fibrinolytic system during CPB is evidenced by increased levels of tissue plasminogen activator (tPA) and plasmin-antiplasmin complexes. Thrombin and bradykinin contribute to fibrinolysis through the direct activation of endothelial cells and the release of tPA, which further increases plasmin generation.²⁸ Kallikrein activates the fibrinolytic system through its role in catalyzing the conversion of plasminogen to plasmin and the activation of pro-urokinase.²⁹ Another mechanism by which plasmin generation may contribute to bleeding is through its direct effect on platelet receptors during CPB.³⁰

The complement system is activated through several mechanisms during CPB (Fig. 63-9). First, the third component of complement (C3), adsorbed to the CPB surface after releasing the potent chemoattractant C3a, is joined by the inactive factor B and properdin to produce the active proteolytic enzyme C3 convertase. C3 convertase cleaves the fifth component C5 to generate the active fragment C5a and the terminal complement complex C5b-9. Other mechanisms for complement generation through alternative pathways include the direct cleavage of C5 by kallikrein to produce C5a and the direct cleavage of C3 by plasmin. Complement generation has also been reported to be induced directly by endotoxin or directly by the cytokines tumor necrosis factor (TNF) and interleukin (IL)-6.³¹ Heparin-protamine complexes formed at the end of CPB activate the classical complement pathway, as does immunoglobulin bound on the biomaterial surface, which complexes with C1q.³²

The generation of complement plays a key role in the recruitment of leukocytes, the upregulation of neutrophil activation markers, and the production of cytokines. Studies by Kirklin's group³³ confirmed that the incidence and degree of deranged function of the heart, lung, and kidney after CPB could be related to the raised plasma concentration of the complement fragment C3a. Furthermore, inhibition of production of terminal complement complex by a protease inhibitor was associated with

a significant reduction in the deleterious effects of ischemia-reperfusion to the myocardium after CPB.³⁴

Nitric oxide (NO) is a potent inflammatory mediator whose production is increased after CPB. Endogenously produced NO may cause tissue injury through formation of toxic peroxynitrites, activation of cyclooxygenase, and DNA deamination. Studies have reported a significant increase in inducible nitric oxide synthase (iNOS) expression in human lung after CPB, which may be related to cytokine release (e.g., TNF, IL-1, IL-6).³⁵ This induction has also been shown to be associated with myocardial depression secondary to reperfusion injury.³⁶

Finally, CPB initiates a cascade of events that results in cytokine release. This response may be triggered by changes in bowel mucosal blood flow and by bacterial translocation, as lipopolysaccharide (LPS) concentration increases by 100% immediately on CPB institution, with another significant increase seen after aortic cross-clamp release. LPS induces a broad range of immunologic effects and is considered the most potent stimulator of TNF- α production from macrophages. TNF induces monocyte IL-1 production, and TNF and IL-1 in concert induce IL-6 production and release.³⁷ Peak concentration of IL-6 occurs a few hours after the end of CPB, with a gradual decrease toward preoperative levels in the following 24 hours.³⁸

Investigators have demonstrated a correlation between the release of IL-6 and myocardial dysfunction after CABG surgery.³⁹ TNF may be released locally in the myocardium, and this may be related to postischemic myocardial stunning.⁴⁰ Jansen and coworkers⁴¹ demonstrated that a rise in TNF can be detected after release of the aortic cross-clamp. TNF, IL-6,⁴² and IL-8 levels also correlated with the duration of the cross-clamping and the degree of myocardial injury as reflected by increased levels of serum troponin.⁴²

Cellular Activation: Platelets, Endothelial Cells, Leukocytes

Although the cellular events during CPB are influenced by the dynamic nature of the activation by the unique soluble products produced at the biomaterial, they are

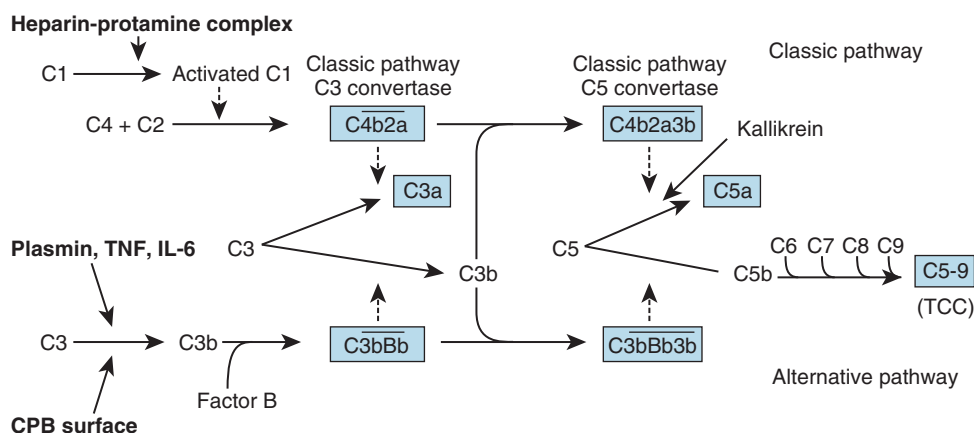


FIGURE 63-9 ■ Mechanisms of complement activation during cardiopulmonary bypass (CPB). *IL-6*, Interleukin 6; *TCC*, terminal complement complex; *TNF*, tumor necrosis factor.

more significantly affected by the composition of proteins adsorbed on the nonendothelial surface. Surface-adsorbed fibrinogen is the key mediator of platelet accumulation on foreign materials. Platelet adhesion to artificial surfaces increases with increasing surface concentration of adsorbed fibrinogen if the bound fibrinogen maintains a conformation such that the functional domains of the molecule are recognizable by the activated platelet glycoprotein (GP) IIb/IIIa receptor. This latter interaction is probably the most important factor mediating platelet consumption during CPB. The three-dimensional conformation of adsorbed fibrinogen also influences the degree of platelet accumulation.

CPB is associated with a consistent increase in the proportion of activated circulating platelets. Agonists of platelet activation during CPB include thrombin, adenosine diphosphate (ADP), heparin, protamine, activated complement, and plasmin. Physical activators of platelets include hypothermia and the process of cardiotomy blood collection. The latter effect may be related to the air-blood interface, the blood-tissue interface, or the exposure to thrombin generation in cardiotomy blood.

The most consistently documented measure of CPB-related activation is an increase in the expression of guanosine monophosphate (GMP)-140 (P-selectin).⁴³ Platelet GP IIb/IIIa is also likely activated.⁴⁴ Platelet microparticles, which may be highly procoagulant, can be consistently detected by flow cytometry after CPB.⁴⁵ Other platelet products increased after CPB include β -thromboglobulin and platelet factor 4 (PF4).⁴⁶

In clinical CPB, thrombocytopenia is seen commonly, with platelet counts dropping more than 50%, resulting not only from platelet adhesion to surfaces but also from hemodilution, platelet aggregate formation, and the formation of platelet-leukocyte complexes. With these changes, it is not surprising that the most predictable alteration in hemostatic function observed after CPB is platelet dysfunction. Clinical reflectors of this process include a universal prolongation of the bleeding time that is directly related to postoperative blood loss.⁴⁷ Platelet aggregation to ADP and epinephrine is consistently abnormal,⁴⁸ and there is decreased response to thrombin agonist receptor peptide (TRAP), consistent with a decrease in receptor sensitivity.⁴⁹

The endothelial layer is the front line of many of the cellular responses related to CPB. It is now evident that it is the activation of these cells that mediates many of the injurious processes such as reperfusion injury. The generation of cytokines is a major contributor to endothelial cell activation, primarily because they upregulate receptors necessary for neutrophil-endothelial cell binding.⁵⁰ Endothelial cells undergo upregulation of intercellular adhesion molecule (ICAM) and E-selectin. The latter binds to the integrin CD11a/CD18 present on resting polymorphonuclear leukocytes (PMNs). PMNs and monocytes may be activated with upregulation of the integrin CD11b/CD18 complex,⁵¹ which also binds ICAM on endothelial cells.⁵² Further cellular activation is evidenced by the acute rise in soluble P-selectin, with a concomitant fall in soluble E-selectin, and by increased elastase release.⁵³ Leukocytes interact with platelets during CPB as another means of systemic inflammation.

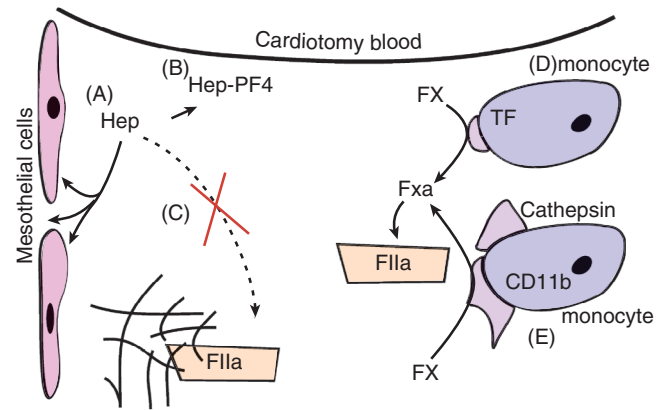


FIGURE 63-10 Mechanisms contributing to thrombin generation in cardiotomy blood. Heparin (Hep) levels are decreased as a result of (A) binding to wound surfaces and (B) binding to platelet factor 4 (PF4). Heparin is also ineffective because of (C) its inability to inhibit clot-bound thrombin. Thrombin generation occurs through other monocyte-dependent processes such as (D) tissue factor (TF) and (E) cathepsin/CD11b complex-mediated factor X (FX) activation.

Increased GMP140 on the platelet surface is essential to mediate complex formation of platelets and monocytes or PMNs.⁵² Monocyte-platelet conjugates increased from 18% to 44%, whereas PMN-platelet conjugates increased only slightly.⁵²

Nonbiomaterial-Related Activation

Exposure of cardiotomy blood to wound surfaces is probably the most important source of thrombin generation during CPB (Fig. 63-10). Two factors contribute to persistent thrombin generation in cardiotomy blood. First, heparin levels in the cardiotomy blood are well below those found in the systemic blood⁵⁴ because heparin may be bound to nonplasma components such as platelets or debris and it may be consumed by PF4. Furthermore, any heparin that is present is not capable of inhibiting thrombin completely, especially thrombin that is bound to fibrin.⁵⁵ Second, thrombin is generated via coagulation pathways other than the intrinsic pathway, and these are less effectively inhibited by heparin. Tissue factor on the wound surface and on the surface of activated monocytes contributes to coagulation,⁵⁶ as does the monocyte CD11b activation of factor X.⁵⁷ Cardiotomy blood also contributes to fibrinolysis induction⁵⁸; this may enhance systemic fibrinolysis after cardiotomy blood readministration and also has been proposed to be a factor in postoperative bleeding.

HEPARIN-PROTAMINE AXIS

Heparin: Pharmacology, Dosage, and Complications

Heparin, derived from bovine or porcine intestinal mucosa, is a glycosaminoglycan composed of chains of alternating residues of D-glucosamine and uronic acid. Heparin is commonly used in its unfractionated form

(UFH) consisting of a spectrum of molecular weights between 1000 and 30,000 Da with a mean of 15,000. ATIII is a natural inhibitor of thrombin, but heparin, acting as a cofactor, accelerates this action more than 4000-fold. Heparin's effect is accounted for by a unique pentasaccharide sequence with a high-affinity binding sequence to ATIII. There is also an 18 pentasaccharide unit fraction that allows for simultaneous binding of ATIII and thrombin. Heparin is then able to dissociate from this ternary complex to be reused in the circulation. UFH-ATIII complexes can catalyze the inhibition of factors IIa (thrombin), IXa, Xa, and Xia,⁵⁹ but they have little effect on factor XIIa.⁶⁰ Heparin's other actions as an anticoagulant include the facilitation of thrombin inhibition by heparin cofactor II, which inhibits the extrinsic pathway by heparin-mediated release of tissue factor pathway inhibitor. Finally, there is evidence that heparin's principal inhibitory effect on coagulation is through the inhibition of thrombin-induced activation of factors V and VIII.⁶¹

The clearance of heparin is influenced by its molecular size, with higher-molecular-weight species being removed from the circulation more rapidly than the lower-molecular-weight species. UFH is cleared through two phases: a rapid saturable phase and a slower phase of first-order mechanism; thus, anticoagulant response is not linear but increases in intensity and duration with increasing dosage.⁶² After injection, UFH is bound by a number of plasma proteins, including histidine-rich glycoprotein, PF4, vitronectin, fibronectin, and von Willebrand factor (vWF). This contributes to the variability of anticoagulant response to fixed-dosage heparin and the laboratory phenomenon of heparin resistance. The binding of UFH to endothelial cells and macrophages also contributes to its complicated pharmacokinetics.

During CPB, heparin is generally used in generous dosages of up to 300 U/kg, with an aim to achieve and maintain a target activated clotting time (ACT) of 400 to 480 seconds. This rather primitive test, although automated, involves the addition of an aliquot of whole blood to a test tube containing a blood activator (Celite or kaolin). In the Hemochron ACT device (International Technidyne Corp., Edison, NJ), when a clot forms, resistance to movement of a small magnet in the tube is detected and the timer stops. The HemoTec ACT device (Medtronic HemoTec, Englewood, CO), which uses kaolin as an activator, uses a plastic plunger for continuous mixing. The absence of plunger fall after a clot forms is detected photo-optically and the counter ceases.

Heparin may contribute to the bleeding diathesis after surgery, independent of its action as an antithrombotic. UFH may cause platelet dysfunction directly⁶³ or through its ability to bind to vWF. Heparin has an independent role as a profibrinolytic agent⁶⁴ before the initiation of CPB, which may be related to its activation of the kallikrein system.

Two forms of thrombocytopenia are related to heparin administration independent of CPB. The first is a benign reversible nonimmune thrombocytopenia, which immediately responds to the discontinuation of heparin and may be related to direct weak activation of platelets by heparin. The second, more serious reaction is an

IgG-mediated immune thrombocytopenia referred to as heparin-induced thrombocytopenia and thrombosis (HITT). The syndrome is secondary to platelet activation from an IgG that binds the FcγII receptor.⁶⁵ The heparin-PF4 complex on the platelet surface is the responsible target antigen. A secondary thrombogenic diathesis may result from platelet activation related to microparticle release.⁶⁶

HITT usually begins 5 to 10 days after the commencement of heparin therapy, but recent data have suggested that it can be detected within a mean of 10 hours of commencement of heparin in patients with previous exposure. This rapid response is not the result of an anamnestic immune response but rather that these patients continue to have circulating antibodies for up to a maximum of 100 days.⁶⁶ In general, 1% of heparinized patients will develop HITT at 7 days and 3% at 14 days.⁶⁷ Although thrombocytopenia may be evident, the surgeon must be wary of a normal platelet count in the postoperative period in the presence of unexplained thrombosis, when reactive thrombocytosis should be evident.

The diagnosis of HITT should be considered with a positive ELISA test for HITT along with an intermediate to high pretest probability score. This pretest probability score, known as the "4 T's" places weighted values on various aggregated factors, including the level of thrombocytopenia, timing of platelet count fall, thrombotic events, and ruling out other possible causes of thrombocytopenia.⁶⁸ The ELISA is highly sensitive but not specific for HITT and, if strongly suspected, the disease should be confirmed by the measurement of the release of radiolabelled serotonin from donor platelets after patient serum exposure.⁶⁹ It is of note that compared to other patients exposed to heparin, for some reason cardiac surgery patients more frequently have positive ELISA testing whereas a fewer percentage have actual HITT.⁶⁸

Surgical approaches to patients with HITT depend on the degree of urgency of the anticipated procedure. In elective situations, when surgery for patients with a history of HITT can be postponed (>100 days), heparin administration should be the primary strategy (Fig. 63-11).⁷⁰ If the surgery cannot be postponed, avoidance of CPB with off-pump techniques may be considered, but some form of anticoagulation is still necessary during anastomosis. Each institution should develop a strategy for the emergency management of CPB in the presence of HITT. A platelet-"paralyzing" agent such as prostacyclin may be used with careful titration of the drug to optimal platelet aggregation inhibition to minimize the attendant hypotension.⁷¹ Of the alternatives to UFH, low-molecular-weight heparin (LMWH) is not suitable as there is greater than 90% immune cross-reactivity with UFH, and CPB with LMWH is associated with significant bleeding.⁷² The heparinoid danaparoid (Orgaran, NV Organon, The Netherlands) has less than 10% antibody cross-reactivity and less than 5% clinical cross-reactivity⁷³ and thus may be useful, but no neutralizing agent is available and because of danaparoid's long half-life, significant bleeding must be anticipated after its use.⁷⁴ Ancrod (Viprinex, Abbott Laboratories, Canada) is a defibrinogenating agent derived from snake venom. The clinical experience with this agent is limited, and its

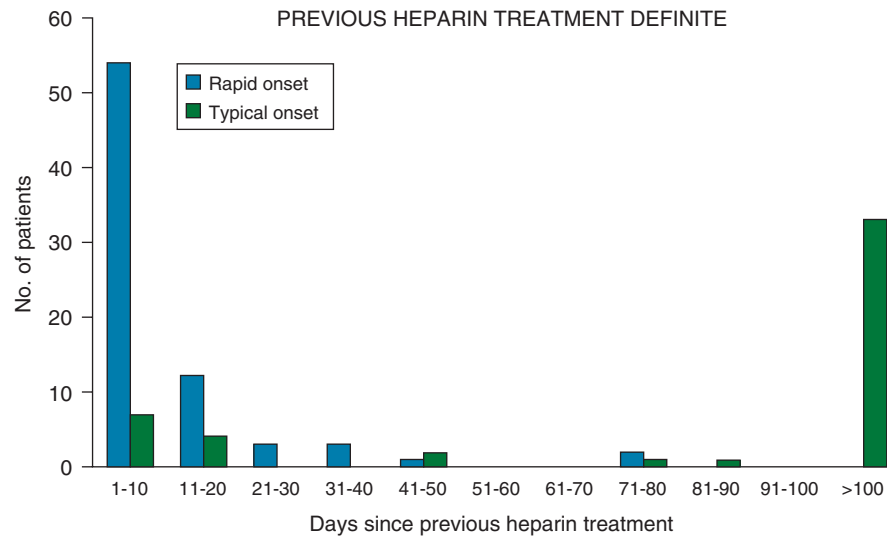


FIGURE 63-11 ■ Temporal pattern of heparin-induced thrombocytopenia in relation to previous treatment with heparin. None of the patients whose prior heparin treatment had occurred more than 100 days earlier had rapid-onset thrombocytopenia. (Reproduced with permission from Warkentin TE, Kelton JG: Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 344:1286-1292, 2001. Copyright 2001, Massachusetts Medical Society.)

drawbacks include that it blocks neither thrombin generation nor platelet activation, it is antigenic, and a delay of 12 hours for the full effect is required.

ATIII-independent thrombin inhibitors such as hirudin, bivalirudin, and argatroban hold promise as the best alternatives for CPB management in these difficult situations. Recombinant hirudin (Refludan, Hoechst, Kansas City, MO) binds the catalytic and fibrinogen binding sites of thrombin. It has been successfully used in clinical CPB⁷⁵ and in deep hypothermic circulatory arrest.⁷⁶ This drug can be monitored using the ecarin clotting time.⁷⁷ Argatroban also specifically binds the catalytic site of thrombin. Its potential benefit over hirudin relates to its shorter half-life (15 to 30 minutes, compared with 30 to 60 minutes for hirudin), which compensates for its lack of a reversing agent. This drug has been used in CPB,⁷⁸ but greater experience is needed before giving it a universal recommendation. Bivalirudin has been demonstrated as safe as heparin for on-pump surgery,⁷⁹ and it may be easier to use than hirudin because of its shorter half-life.⁸⁰ Updated guidelines recommend the use of bivalirudin over other nonheparin anticoagulants or heparin plus antiplatelet agents (Grade 2C) for patients with acute or subacute HIT requiring emergent cardiac surgery⁸¹; however, this drug is not safe if circulatory arrest or low flow is anticipated, because clotting will occur in the oxygenator.⁸²

Protamine: Pharmacology, Complications

Protamine is a polycationic protein derived from salmon sperm. The positive charges on protamine combine ionically with the negative moieties of the heparin molecule, separating it from ATIII and producing a stable precipitate that is rapidly cleared from the circulation. The drug is given intravenously at a fixed ratio of 1 to 1.3 mg/100 U administered heparin. The most common problem

related to protamine is heparin rebound, which is a frequent cause of postoperative bleeding. This phenomenon is related to the delayed desorption of heparin from plasma proteins and endothelium after the first dose of protamine has been cleared. It usually becomes evident 2 to 3 hours after arrival in the ICU, and its presence is reflected by increasing chest tube losses accompanied by a new prolongation of the ACT or thrombin time. The problem can be obviated by the routine addition of a protamine drip after surgery.

Protamine has a direct antithrombin effect; however, this effect is seen only at extremely high dosages. Preformed platelet-activating anti-protamine-heparin antibodies have been demonstrated to be causative in cases of unexplained early and prolonged postoperative thrombocytopenia.⁸³ Hypotension is another common consequence of protamine administration, particularly with rapid intravenous administration. The mechanism of this rate-related effect is not known, but its magnitude is greater in situations of low preload and afterload. Protamine may also be responsible for several idiosyncratic hypotensive reactions. Anaphylactoid reactions are mediated primarily by complement and histamine. Anaphylactic reactions involve the IgE-mediated release of histamine and other vasoactive mediators. Both reactions are characterized by edema, hives, and bronchospasm in the presence of low filling pressures. The most serious form of protamine-related hypotension is catastrophic pulmonary vasoconstriction. In contrast to the other two forms of idiosyncratic protamine reactions, this syndrome may be associated with bronchospasm, and with pulmonary hypertension with an elevated CVP. The mechanism is probably related to IgG release with activation of complement, activation of PMN, and release of platelet thromboxane A₂.⁸⁴ Theoretically, patients at risk for protamine reactions include those with previous vasectomy, previous exposure to protamine, or previous exposure to protamine-containing insulin.

When problems with protamine have been detected in advance, the cardiac surgeon must consider alternative strategies. In minor cases with low risk, premedication with steroids (at least 12 to 24 hours in advance) and histamine blockers may suffice. A small test dose (5 mg) should be given to ensure safety. Avoidance of neutralization after the massive dosages required for CPB may be difficult because of the prolonged half-life of heparin. Recombinant PF4 has shown promise as an alternative to protamine.⁸⁵

The rationale for heparinizing to an ACT of between 400 and 480 seconds during CPB is based on early work that demonstrated that at this level of ACT, no gross evidence of thrombosis occurred in the circuit. However, many researchers have expressed doubt about the validity of using ACT as gold standard for anticoagulation during CPB. In particular, there is clear evidence that the ACT does not reflect the heparin level accurately, particularly after a long duration of CPB, and that other factors, such as hypothermia, hemodilution, and drugs, may contribute (Fig. 63-12).⁸⁶ The Hepcon device (Medtronic HemoTec, Englewood, CO) is composed of a series of ACT cuvettes containing incrementally increased protamine dosages that can be used to precisely calculate the circulating heparin level. Patient-specific preoperative standard curves with target heparin concentrations can be precisely calculated. It is interesting that with this technique, overall heparin requirements are higher (25%). However, factor consumption during CPB is decreased, most likely related to an inhibition of low-grade coagulation. In clinical trials, this technique also resulted in a shorter bleeding time on arrival in the ICU that was associated with decreased blood product use.⁸⁷ A fixed-effects meta-analysis model analyzing standard versus titrated dosing of protamine has confirmed significantly less postoperative bleeding with the latter strategy.⁸⁸

PHARMACOLOGIC AND HEMATOLOGIC ADJUNCTS TO MINIMIZE CONSEQUENCES

Randomized controlled trials have confirmed that leukocyte depletion successfully decreases IL-2 and C3a⁸⁹ and IL-6 and TNF.⁹⁰ This strategy also appears to minimize myocardial damage and to decrease the incidence of perioperative atrial fibrillation.⁸⁹

Steroids are widely used for the suppression of inflammation in chronic inflammatory diseases. During CPB, steroids blunt complement activation, upregulation of glycoprotein CD11b,⁹¹ and the release of histamine,⁹² TNF, IL-8,⁹³ IL-6,⁹⁴ and neutrophil elastase.⁹⁵ Finally, steroids reduce airway NO concentrations during CPB⁹⁶ compatible with inhibition of bronchial epithelial iNOS expression. Steroids have also been demonstrated to be associated with decreased CK MB.⁹⁷ The inhibition of these aspects of inflammation may explain the stabilizing effect of these drugs on hemodynamics after CPB. Contrary to expectations, steroid use has not been demonstrated to be associated with postoperative wound infection in cardiac surgery.⁹⁸ Three meta-analyses have failed to demonstrate any other major benefits in terms of mortality and morbidity other than a decrease in the incidence of postoperative atrial fibrillation.⁹⁸⁻¹⁰⁰ Whereas routine administration of steroids for adult cardiac surgery patients remains controversial, this is not the case for pediatric surgical patients; at least 40% of centers routinely administer steroids, particularly in neonates and cases involving deep hypothermic circulatory arrest.¹⁰¹

Although aprotinin has anti-inflammatory effects, its use has come under significant scrutiny as a result of ongoing debate regarding its possible prothrombotic effects.¹⁰²

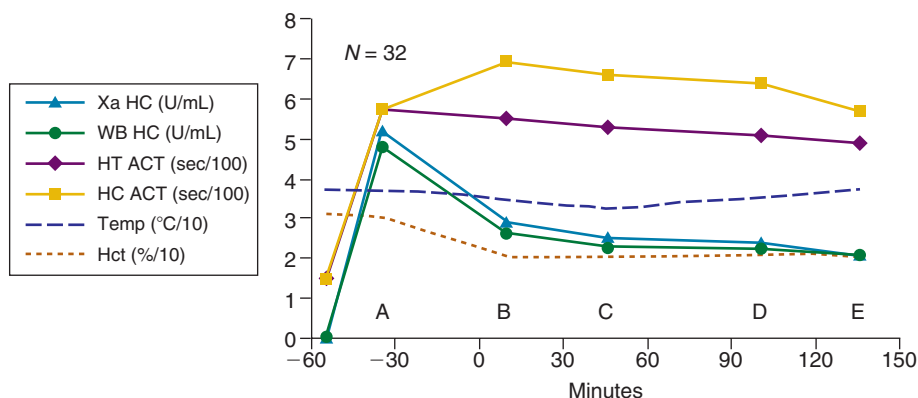


FIGURE 63-12 ■ Time course of physiologic and hematologic mean values for patient with cardiopulmonary bypass (CPB). Mean values for activated clotting time (ACT) expressed in seconds per 100 for both Hemochron (HC ACT) and Hepcon (HT ACT) assays. Plasma-equivalent heparin concentration (WB HC) and anti-Xa plasma heparin concentration (Xa HC) expressed in units per milliliter. Hematocrit (Hct) values expressed as percent divided by 10 (%/10), and core body temperature (Temp) expressed in degrees centigrade divided by 10 (°C/10). Mean values for derived physiologic and hematologic variables are plotted as a function of time in minutes. Phase II time points begin before heparin administration and then 10 minutes after each of the following: heparin administration (A), initiation of CPB (B), achievement of hypothermia (C), rewarming (D), and immediately before discontinuation of CPB (E). (Reproduced with permission from Despotis GJ, Summerfield AL, Joist JH, et al: Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. *J Thorac Cardiovasc Surg* 108:1076-1082, 1994. Copyright 1994, Mosby-Year Book Inc.).

BIOMATERIAL-DEPENDENT STRATEGIES TO MINIMIZE BLOOD ACTIVATION

A biomaterial-dependent strategy involves the choice of a CPB circuit composed of a biomaterial with enhanced biocompatibility. The quest for an ideal biomaterial substrate for the construction of CPB circuits has culminated in three types of surface modifications that either have been tested in human trials or are on the verge of clinical evaluation.

Biomembrane Mimicry

A biomaterial has been developed that mimics the anti-thrombotic behavior of natural cell membranes. It is coated with a derivative of phosphorylcholine, which is the major lipid head group component found on the outer surface of biologic cell membranes.¹⁰³ In vitro data have demonstrated the efficacy of this modified surface (Memsys, Sorin Biomedica) in inhibiting fibrinogen adsorption and platelet deposition. Other biocompatible-coated CPB circuits include hyaluronan (Vision HFO-GBS-HF, Gish Biomedical, Rancho Santa Margarita, CA) based heparin free coating and Bioline coating (Quadrox, Maquet-Dynamed, Hirrlingen, Germany). Differences at the molecular level may exist between phosphorylcholine-coated, albumin-heparin-coated, or synthetic polymer-coated circuits, but no significant clinical benefits between these systems have been observed other than a reduction in atrial fibrillation and a shortened ICU length of stay.¹⁰⁴

Heparin-Coated Circuits

There are two types of commercially relevant heparin-coated circuits. In the first group, heparin is bound so that it may be slowly released into the circulation from the surface. The original binding, pioneered by Gott and colleagues,¹⁰⁵ existed as a surface in which the heparin was ionically bound to benzalkonium attached to the substrate polymer. In the second group, heparin is immobilized permanently on the biomaterial surface by covalent bonding. Polyethylene oxide is used as a spacer group, as its hydrophilic character and its dynamic motion further inhibit platelet interactions. The Carmeda product (Carmeda, Medtronic, Minneapolis, MN) is a commercial example of this technology for CPB, in which heparin is covalently bound via an endpoint immobilization technique. The Trillium Biopassive Surface (Medtronic, Minneapolis, MN) is a similar covalent coating process involving two polymers on the substrate surface. The first polymer functions as a primer, strongly bonding to the surface of the substrate. The second polymer, which is bound to the primer coat, is composed of sulfate and sulfonate groups, the latter providing a negative surface charge, as well as polyethylene oxide chains covalently bound to heparin. BioLine (Jostra, Germany) is a hybrid surface (i.e., a combination of heparin-releasing and heparin-immobilized) in which heparin is adsorbed onto a layer

of immobilized polypeptides through a combination of ionic interactions and covalent bonds.

Convincing *in vitro* evidence of the thromboresistant behavior of heparin-coated surfaces led to the hypothesis that less intense anticoagulation would be required for CPB when heparin-coated circuits were used. Many of the early clinical trials compared outcomes after CPB in which heparin-coated circuits were combined with lower dosages of heparin (one third to one half) versus control (uncoated) circuits and standard heparin dosages (300 U/kg). Advantages included decreased perioperative bleeding and transfusion. In a large clinical trial reported by Aldea and colleagues,¹⁰⁶ an integrated blood conservation strategy that included heparin-coated circuits and decreased heparin dosing was applied. This approach resulted in decreased blood transfusion requirements and significantly improved clinical outcomes as measured by ICU and hospital lengths of stay and by duration of ventilatory support. This translated into cost savings of approximately \$1700 per patient.¹⁰⁷

Compelling as these clinical results are, neither thrombin generation nor fibrinolysis has been consistently demonstrated to be decreased during CPB with heparin-coated circuits in human trials, with either standard or decreased heparin dosages compared with standard (non-heparin-coated) circuits.¹⁰⁸ Therefore, it is difficult to justify decreasing the heparin dosage, given the potential risk of low-grade thrombosis. Also, any measured differences in a patient's clinical and biochemical outcomes may be related to differences in the amounts of administered heparin and not to the surface, as heparin itself can induce myriad cellular and biochemical changes such as fibrinolysis and platelet dysfunction.⁶⁴ As the dosage of the protamine must also be increased, it is anticipated that changes such as complement activation must be proportionally increased. In most clinical trials in which the same dosages of heparin are used with both heparin-coated circuits and standard circuits, little clinical benefit has been consistently demonstrated, except perhaps in high-risk patients.¹⁰⁹

Beneficial clinical impacts of heparin-coated circuits are almost entirely related to their intrinsic anti-inflammatory effect. What has been consistently demonstrated is the capacity of heparin-coated surfaces to decrease complement activation¹¹⁰ independent of the heparin dosage. Other demonstrated anti-inflammatory effects of heparin-coated surfaces include decreased leukocyte surface activation markers or receptors,¹¹¹ decreased cytokine production,¹¹² and decreased monocyte tissue factor.¹¹³ The anti-inflammatory action of heparin-coated circuits in the absence of coagulation inhibition may be related to its action as a selective "protein sink" for such proteins as HMWK.¹¹⁴ Surface-adsorbed HMWK may interact with antithrombin III in the presence of surface heparin to potentiate heparin-mediated inhibition of kallikrein.¹¹⁵

In summary, heparin-coated surfaces have been demonstrated to exhibit potent antithrombotic behavior in *in vitro* testing. Although there is no evidence of decreased thrombogenicity when used clinically, there is consistent evidence that inflammation related to complement activation is decreased, and this may be responsible

for the improvement seen in some clinical outcomes after CPB.

Surfaces with Modified Protein Adsorption

Another biomaterial-dependent strategy involves surfaces designed to modify protein adsorption characteristics. An example of this approach includes a new generation of biomaterials into which a surface-modifying additive (SMA) has been incorporated.¹¹⁶ The additive is a triblock-copolymer with polar and nonpolar polymer chains. During the manufacturing process, the SMA migrates to the surface of the base polymer, yielding a stable microdomain-like configuration. Although the mechanism of action by which SMA decreases blood protein and cellular activation is not precisely known, it is hypothesized that the alternating hydrophobic and hydrophilic regions of the microdomain surface lead to uniform adhesion of fibrinogen, so that all of the sites for potential platelet interaction with surface-bound fibrinogen are competitively blocked. A randomized controlled trial in which patients underwent CPB using a standard control circuit or a circuit prepared “tip-to-tip” with the SMA copolymer (SMA-CPB)¹¹⁷ showed striking changes in the effect of this surface on markers of coagulation, fibrinolysis, and platelet number and function. Thrombin generation was significantly decreased with SMA-CPB compared with controls, despite carefully matched heparin dosages in the two groups. Defraigne and coworkers¹¹⁸ in a larger clinical trial confirmed the same degree of platelet preservation with SMA-CPB and a similar decreased release of β -thromboglobulin. In addition, there was evidence of a decreased need for the transfusion of platelets and fresh-frozen plasma in the group with SMA-CPB circuits.

Terumo Corporation (Tokyo, Japan) developed a surface for CPB circuits with a biocompatibility profile similar to that of SMA, in that it was engineered to positively influence protein adsorption. Surfaces are coated with poly(2-methoxyethylacrylate) (PMEA), which has a hydrophobic polyethylene backbone, and its residue has mild hydrophilicity with no chemical functional groups such as -OH or -NH₂. It was predicted that as the outer side of the PMEA molecule is inactive chemically, the surface would have little tendency to react with blood components. Although clinical studies in humans are not available, promising data from in vitro and in vivo models support the potential improved biocompatibility of PMEA-coated surfaces.¹¹⁹ Analysis of the composition of the adsorbed protein layer on PMEA-coated surfaces demonstrated a striking decrease in the amount of adsorbed IgG. This finding correlated with platelet count preservation as compared with uncoated surfaces, as surface-bound IgG is a well-known platelet activator. The use of the PMEA circuit was also associated with a significant decrease in CD35-positive monocytes during CPB.¹²⁰ Decreased adsorption of immunoglobulin is again probably the causative mechanism for decreased complement activation. Plasma bradykinin levels are decreased with PMEA, as are thrombin-antithrombin III levels.¹¹⁹

RELATED ORGAN DERANGEMENTS

Neuroendocrine Response

The changes in neuroendocrine response related to CPB are different from those observed in noncardiac surgery. Hormones under hypothalamic-pituitary control include growth hormone, vasopressin, the adrenal cortical axis, and the thyroid hormone system. Growth hormone increases significantly during and after CPB.¹²¹ Vasopressin is a key regulator of renal water excretion and peripheral vascular resistance, and it may contribute to endothelial activation through release of vWF.¹²² Marked increases in vasopressin are seen after cardiac surgery with CPB, with the elevated levels persisting for hours.¹²³ This may be a protective effect, as depressed levels postoperatively are associated with vasodilatory shock.¹²⁴

There is a definite increase in adrenocorticotrophic hormone with CPB.¹²⁵ Total plasma cortisol concentrations typically decrease immediately on initiation of CPB as a consequence of hemodilution, but later values return to normal or higher than baseline accompanied by parallel increases in unbound cortisol, suggesting that this increase is related to increased total secretion.¹²⁶ Thyroid hormone dysfunction may play a role in the unique clinical response seen after CPB. Investigators have demonstrated that although thyroid-stimulating hormone remains normal, total and free T₃ drop and remains depressed for 24 hours after surgery, and reverse T₃ shows a fourfold rise at 8 and 24 hours postoperatively, thus producing a picture of sick euthyroid syndrome.¹²⁷

The catecholamines epinephrine and norepinephrine are both increased after CPB, which may be a contributing cause of severe postoperative hypertension.¹²⁸ The sympathetic system regulates glucose control at the level of the pancreas by controlling the release of insulin and glucagon. After the onset of CPB, blood glucose concentrations rise steadily in parallel with a drop in insulin levels, and insulin resistance is seen with higher than average dosages.¹²⁹ During and after CPB, renin levels increase, and this is associated with a rise in measured angiotensin II and aldosterone.¹³⁰

Among the locally released hormones, atrial natriuretic factor levels are probably reduced during CPB, especially in patients with preoperative elevations, but elevated levels may be seen in the presence of complications.¹³¹ Other locally released factors include histamine and serotonin, related to leukocyte and platelet activation.¹³² Histamine produces vasodilation and hypotension and may contribute to tPA release.¹³³ Its increase may be abolished by high-dose steroids and prostacyclin infusions.¹³⁴ Finally, CPB provides a consistent stimulus for prostacyclin and inflammatory eicosanoid formation, as evidenced by a marked increase in 6-keto-prostaglandin F_{1a} (a stable metabolite of prostacyclin),¹³⁵ thromboxane B₂,¹³⁶ and prostaglandin E₂ concentrations.¹³⁷

Central Nervous System Injury

Cerebral damage during heart surgery may be the complication most feared and respected by cardiac surgeons. Three major types of neurologic injury can occur after

CPB, but the distinction between them is blurred and they probably reflect a continuum of pathologic changes based on location, extent, and permanence of the injury.¹³⁸ Stroke is the easiest injury to recognize after CPB. Its incidence is difficult to pinpoint, but the best estimate is around 3% of patients undergoing CABG.¹³⁹ Based on the information from the Society of Thoracic Surgeons database, this complication is increased in women and in older adults. The incidence rises to 8% after isolated valve surgery and 11% after CABG combined with other surgery.¹⁴⁰ The cause is probably related to macroemboli from great vessels. Stroke is associated with a marked increase in 30-day mortality, and its occurrence doubles hospital stay and cost.¹³⁹

Delirium, seen in up to 3% of patients, is a state characterized by confusion and disorientation in the presence of an altered state of consciousness. This complication may increase hospital stay fivefold.¹⁴¹ Risk factors include increased age, hypertension, reoperative surgery, and a history of previous CABG, pulmonary disease, postoperative anemia, preoperative cognitive dysfunction, major depression, alcohol abuse, atrial fibrillation, prolonged intubation, and postoperative hypoxia.¹⁴²

Cognitive decline (postoperative cognitive deficit [POCD]) is defined as a change in memory, concentration, psychomotor speed, or dexterity. Although it may go unnoticed, sometimes the patient recognizes inability to complete previously facile tasks, or this inability may be recognized by the family. Quantitation depends on sensitive neuropsychological findings involving a reproducible battery of tests. A pooled analysis of six highly comparable studies by Van Dijk and colleagues¹⁴³ yielded a proportion of POCD after CPB of 22.5% (95% confidence interval, 18.7%-26.4%). Newman and colleagues,¹⁴⁴ Robinson and colleagues,¹⁴⁵ and Borowicz and colleagues¹⁴⁶ provide comprehensive reviews of studies of POCD after CABG; the reported incidences in larger studies range from 35% to 75% early postoperatively and 11% to 40% after more than 6 months. Sotaniemi and coworkers^{146a} found that even if the early postoperative changes disappeared, affected individuals were more likely to show early dementia 5 years later, as the underlying neuronal loss may make an individual more vulnerable to age-dependent cell loss in the future. Furthermore, Newman and coworkers¹⁴⁷ showed that patients demonstrating significant impairment early had reduced quality of life and were more likely to be impaired at 5 years, compared with patients not having early deficits.

One characteristic pathologic finding in canine and human cerebral tissue after CPB is referred to as small capillary and arteriolar dilations (SCADs) (Fig. 63-13). These are believed to be the sites of fat, particulate, or gas emboli.¹⁴⁸ Transcranial Doppler studies of patients during CPB have confirmed the frequent occurrence of embolic material in the cerebral circulation. Furthermore, the cerebral embolic load was found to be directly proportional to the length of CPB in an autopsy study by Brown and colleagues.¹⁴⁹ There is a direct correlation between POCD and retinal microemboli on fluorescein angiography.¹⁵⁰ Magnetic resonance imaging immediately after CABG has identified global cerebral swelling even in low-risk patients.¹⁵¹ Finally, there is strong

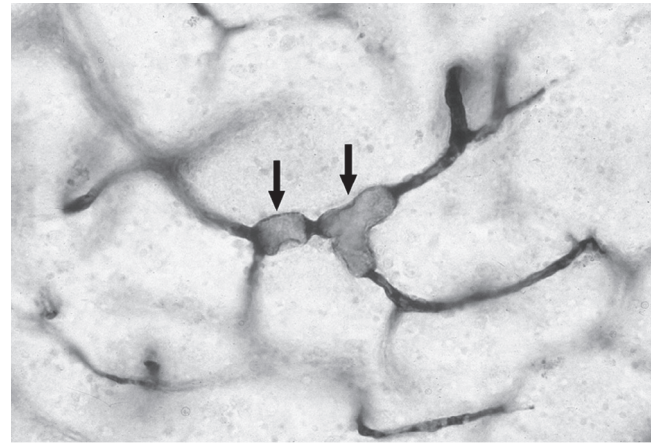


FIGURE 63-13 ■ Postmortem specimen of brain section illustrating small capillary and arteriolar dilation (arrows) after cardiopulmonary bypass. (Courtesy Dr. Dixon Moody, Wake Forest University.)

experimental evidence that cardiotomy suction blood may be the most important source of lipid emboli.^{152,153} Two recent clinical trials had different results as to whether processing cardiotomy blood has an impact on neurocognitive outcome, but this intervention did result in a significant increase in postoperative bleeding and transfusion, and thus it is debatable whether cardiotomy blood processing is safe.^{154,155}

Recently, however, the relationship of CPB to neurocognitive dysfunction after cardiac surgery has been called into question. First, several prospective randomized controlled trials have failed to show a clear benefit of off-pump compared with on-pump surgery in terms of the incidence of neurocognitive dysfunction.¹⁵⁶ Second, it was shown that nonsurgical control populations with coronary disease undergoing medical therapy or percutaneous intervention have the same rate of neurocognitive decline as those patients undergoing on-pump CABG.¹⁵⁷ Finally, the use of neurocognitive testing as a measure is debatable, as these evaluations were never designed as a pre-post test.

Pulmonary Dysfunction

Whereas 12% of patients develop mild lung injury after CPB, 1.3% develop frank acute respiratory distress syndrome (ARDS).¹⁵⁸ This problem is more common in older, obese adults and patients with low cardiac output or pulmonary hypertension, and after long CPB.¹⁵⁸ In most cases of CPB-related lung injury, full recovery occurs, but severe lung injury has a mortality of greater than 50%.¹⁵⁹ Clinical findings of lung injury include an increase in the alveolar-arterial oxygen pressure difference and the pulmonary shunt fraction, together with a decrease in the functional residual capacity. There may be increased pulmonary vascular resistance as well as evidence of increased lung permeability.¹⁶⁰ The cause of CPB-related lung injury does not appear to be related to hypoxia induced by partial CPB, because the bronchial circulation is adequate to prevent necrosis.¹⁶¹ There is, however, definite evidence of increased pulmonary inflammation with increased bronchoalveolar lavage

fluid-activated neutrophils,¹⁶² increased matrix metalloproteinases and myeloperoxidase levels,¹⁶³ and increased IL-8 and elastase,¹⁶⁴ all of which may contribute to breakdown of the pulmonary ultrastructure.¹⁶⁵ This ultimately can lead to endothelial cell swelling, extravasation of plasma protein and debris, release of proteolytic enzymes, congestion of alveoli with inflammatory cells, and massive interstitial pulmonary edema and altered gas exchange.

Factors that have not consistently proven beneficial in protecting the lungs during cardiac surgery include off-pump surgery,¹⁶⁶ steroids,¹⁶⁷ maintenance of mechanical ventilation during CPB,¹⁶⁰ and modifications of temperature management.¹⁶⁰ Heparin-coated circuits have been shown to improve lung compliance and pulmonary vascular resistance, with particular improvement seen when low heparin protocols are used.¹⁰⁶ Maintaining lung perfusion during CPB (Drew-Anderson technique) refers to using the patient's own lungs as an oxygenator and supplying only biventricular pump function; this may have some clinical benefits,¹⁶⁸ but its practicality is not universally accepted.

Renal Dysfunction

Data from the Multicenter Study of Perioperative Ischemia Research Group¹⁶⁹ demonstrated a 7.7% incidence of postoperative renal dysfunction after on-pump CABG, with 1.4% of all patients needing dialysis. Renal insufficiency is associated with increased hospital and ICU stay and mortality, emphasizing its clinical relevance. Although factors such as nonpulsatile flow and obstructive atheromatous microemboli may contribute, the diffuse inflammatory change related to CPB may have an independent toxic effect on the kidneys.

Numerous strategies have been advocated as potentially renal-protective during CPB. Leukodepletion has been shown in a prospective randomized controlled trial to decrease the need for continuous furosemide infusion and renal replacement therapy.¹⁷⁰ Mannitol is a popular diuretic agent that can increase diuresis if added in dosages of 10 to 30 g. This drug has also been shown to preserve creatinine levels and lower urinary albumin excretion rates after pediatric cardiac surgery.¹⁷¹ Renal-dosage dopamine (2 to 3 µg/kg/min) has been assessed in several randomized controlled trials of patients at high risk for renal failure, and the results have been controversial.¹⁷² Fenoldopam, a selective dopamine-1 receptor agonist, was shown in a randomized controlled trial to preserve renal function as demonstrated by a lower rate of acute kidney injury, particularly in those patients requiring inotropic support.¹⁷³ Other options that have shown promise in renal protection during heart surgery include avoidance of transfusions¹⁷⁴ and early initiation of statin therapy.¹⁷⁵ The use of off-pump techniques has not been definitively proven to decrease the incidence of renal insufficiency after heart surgery.¹⁶⁶

EXTRACORPOREAL TEMPORARY CARDIOPULMONARY SUPPORT

The ability to offer prolonged periods of external cardiopulmonary support became possible with the advent of

modified oxygenators that minimized blood trauma. This strategy is commonly referred to as extracorporeal membrane oxygenation (ECMO), and its first reported successful use involved posttraumatic ARDS.¹⁷⁶ The application was subsequently tested in a randomized controlled trial in 1979 in a larger ARDS cohort, but the survival results were equal or worse than in controls, possibly because of technical issues and bleeding complications.¹⁷⁷

On the other hand, in neonates it was proposed that the goals of ECMO in respiratory failure were different in that temporary support was only deemed necessary until persistent fetal circulation resolved. This hypothesis was born out by the first neonatal survival reported in 1975.¹⁷⁸ The strategy was subsequently strongly confirmed in trials in this population such that it became standard therapy. Currently the most common application worldwide of ECMO is in neonates with congenital diaphragmatic hernia.¹⁷⁹

Subsequent improvements in technology, experience, and cannulas provided the grounds for resurgence in interest in its use in adults, with more judicious early application. The CESAR trial provided the first strong support in terms of long-term survival to discharge from the ICU in adults with severe lung failure.¹⁸⁰ Cases worldwide are reported by participating organizations in a registry and the volume has been increasing steadily each year.¹⁷⁹ There was a particular upsurge in cases at the time of the H1N1 crisis, with reports of up to 70% survival in this desperately ill cohort, further solidifying the credibility of this strategy.¹⁷⁹

Indications and Options for Temporary Support

Mechanical means of lung support (exclusive of traditional endobronchial ventilation) can be applied for CO₂ removal and/or O₂ delivery. It can be used in short-term situations with reversible lung injury with the primary goal to remove CO₂ (respiratory dialysis), such as with exacerbations of COPD. Isolated lung support is also indicated in patients with severe potentially reversible respiratory failure when the predicted mortality with optimal medical therapy is expected to exceed 80%.¹⁸¹ Techniques do not treat the underlying lung condition; rather they improve gas exchange while enabling the institution of protective lung strategies to prevent further ventilator-mediated damage. Lung support can be used as a bridge to lung transplant in patients with irreversible lung injury and as a bridge to recovery post lung transplant. In many situations, respiratory failure is associated intimately with secondary cardiac failure and support is required for both systems, but treatment can be modified to lung-specific support as the hemodynamics stabilize.

Temporary mechanical cardiac support refers to mechanical strategies exclusive of ventricular assist devices (Table 63-1). It has been applied in situations of bridge to recovery (e.g., postcardiotomy shock, cardiogenic shock post resuscitation)¹⁸² as well as in transport of critically ill patients with portable devices.¹⁸³ It may also be the procedure of choice in "bridge to decision" in which there is severe shock with organ failure or an unknown neurologic status, whereby recovery must be

TABLE 63-1 Indications for Temporary Cardiopulmonary Mechanical Support

Pulmonary	Extracorporeal CO ₂ removal (reversible lung injury) Bridge to recovery (acute reversible lung injury) Bridge to transplant (irreversible lung injury)
Cardiac	Post lung transplant Bridge to recovery (e.g., post cardiectomy, cardiogenic shock) Bridge to decision Bridge to transplant
Both	Bridge to recovery Bridge to transplant

demonstrated before more definitive commitment with a long-term device is made.

Finally, in cases with severe pulmonary hypertension, combined organ support may be the targeted strategy. This may involve support until recovery if it is deemed the pulmonary pressures may improve or as a bridge to transplant such as with end-stage decompensated primary pulmonary hypertension.

Technical Factors

In the most common form of temporary support (venoarterial [VA]), a combination of venous outflow and arterial inflow is used. There are multiple options for venous inflow depending on the goals of therapy and the minimum required flow, including peripheral (e.g., femoral vein) and central (e.g., right atrial). Arterial outflow can also include peripheral or central (aortic). Peripheral femoral inflow in the absence of some degree of native ventilation to ensure oxygenation of aortic root blood may result in cardiac dysfunction. Femoral cannulation is also associated with a high risk of limb ischemia, but the leg can be perfused with a distally oriented cannula in the superficial femoral artery or in the dorsalis pedis artery.¹⁸⁴ Axillary return may allow for improved options for patient ambulation,¹⁸⁵ but it may be associated with hyperperfusion of the arm. Finally, in pediatric ECMO, the internal jugular vein and the internal carotid artery are used preferentially.

Venovenous (VV) ECMO is a novel strategy primarily used for isolated pulmonary support. In this scenario, blood is withdrawn from a distal venous site to undergo gas exchange, and the oxygenated blood is then returned in the region of the tricuspid valve continuing to the left circulation via the pulmonary bed. Originally this was accomplished with two carefully positioned catheters, but it may now be achieved with a double-lumen single-cannula (Fig. 63-14) Avalon catheter.

Centrifugal pumps are preferentially used for ECMO; however, in children, the use of the centrifugal pump during prolonged ECMO has been associated with increased hemolysis, hyperbilirubinemia, need for inotropic support, and renal failure as compared to roller pumps.¹⁸⁶

As a result of the use of biocompatible circuits and the absence of a cardiectomy, a lower ACT ($1.5 \times$ baseline)

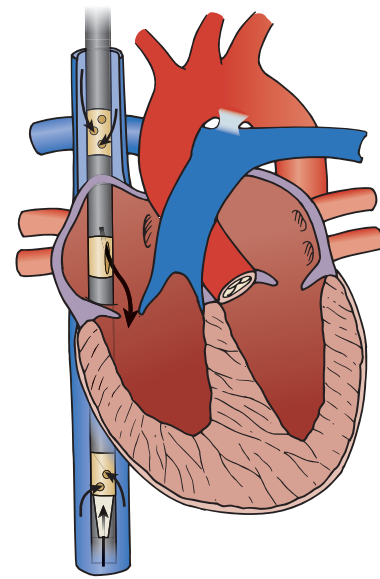


FIGURE 63-14 Integrated dual-lumen catheter for venovenous extracorporeal membrane oxygenation.

may be employed with temporary support. Native ventilation is commonly used to varying degrees to prevent atelectasis, during partial support and during weaning. Management is reproducible in experienced teams, and nurses with advanced training can supervise patients independently in high-volume units. Support can be continued for weeks to months if necessary. Principles of care include daily monitoring for hemolysis, maintenance of normal hemoglobin, treatment of coagulopathy, permissive mild thrombocytopenia ($50,000\text{--}100,000 \times 10^9/\text{liter}$), and optimal flows ($50\text{--}100 \text{ mL/kg/min}$, titrated to $\text{SaO}_2 > 80\%$). Drugs must be carefully titrated because of impaired bioavailability of as much as 65% related to tubing circuit adsorption.¹⁸⁷

Currently with all forms of support, ventilator weaning should be considered, and long-term support of extubated patients may significantly decrease the risk of critical illness deconditioning.¹⁸⁸

Contraindications to the use of temporary cardiopulmonary support include irreversible neurologic injury, nonmanageable coagulopathy, and limited anticipated survival related to other issues (advanced malignancy, end-stage liver failure). Lung assist is contraindicated in the setting of high-pressure positive pressure ventilation more than 1 week. Relative contraindications include trauma, sepsis, pulmonary hemorrhage, and malignancy.

Complications of ECMO include systemic thromboembolism, limb ischemia, maldistribution of O_2 , increased left ventricular wall tension, and cannulation site bleeding. The latter must be addressed with compulsive cannula site exploration and correction of any coagulopathy.

Lung Assist

Whereas ECMO provides complete lung replacement, newer, less invasive technologies offer lung assist.¹⁸⁹ CO_2 removal and O_2 delivery can be considered separately and can use a combination of the ventilator and extracorporeal support to achieve these goals.

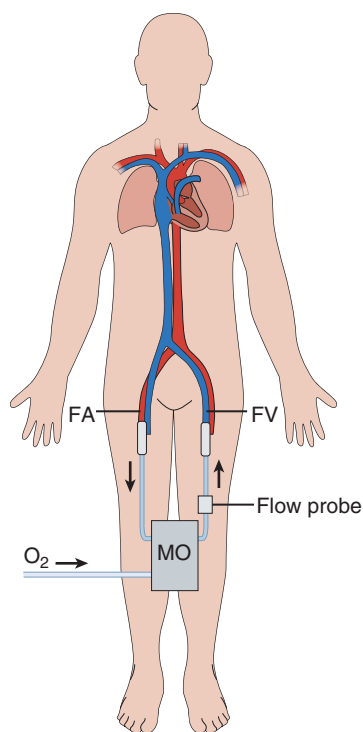


FIGURE 63-15 ■ Interventional lung assist (iLA Novalung, Hechingen, Germany) for extracorporeal CO₂ removal in severe respiratory failure. FA, Femoral artery; FV, femoral vein; MO, membrane oxygenator.

Lung assist devices are primarily effective for CO₂ removal (extracorporeal CO₂ removal [ECCOR]) using the native lung for oxygenation.¹⁹⁰ The interventional lung assist (iLA Novalung, Hechingen, Germany) consists of a low-resistance gas exchange device with a diffusion membrane of polymethylpentene fibers (Fig. 63-15). The design incorporates a complex flow pattern created with fiber weaving to maximize O₂ and CO₂ diffusion but primarily affecting CO₂ removal. With an inflow cannula from the femoral artery of one leg and outflow to the femoral vein of the other, flow is driven by the patient's pressure up to 2.5 liter/min. An external pump can be incorporated to increase flows up to 5.5 liter/min.

This device has been used as a bridge to recovery or lung transplantation in neonates and young children,¹⁹¹ in trauma,¹⁹² and influenza (H1N1).¹⁹³ The iLA has been used as a bridge with central cannulation between the pulmonary artery and the left atrium in decompensated patients with primary pulmonary hypertension awaiting transplant.¹⁹⁴ Limb ischemia remains the most common complication with this device.

Low-flow CO₂ removal devices have also been introduced for clinical use. The HemoLung device (Alung, Pittsburgh, PA) consists of heparin-coated siloxane dual-lumen venous catheters in femoral and jugular format, which can be used for respiratory dialysis. Flow through the integrated centrifugal pump is only 350 to 550 mL/min and the patients can be completely ambulatory. Other low-flow devices include the Hemodec (Salerno, Italy), the iLA active (Novalung, Hechingen, Germany), and the Decap system (Hemodec, Salerno, Italy).

THE FUTURE OF CARDIOPULMONARY BYPASS

There is great potential for continuing evolution of CPB circuit design and techniques that may enhance clinical outcomes with cardiac surgery. For example, newer devices have incorporated novel technology to integrate all CPB components to markedly minimize the pump prime and the surface area (mini-circuits). In a prospective randomized controlled trial with a preestablished transfusion protocol, these devices have been demonstrated to minimize the effect of hemodilution and platelet consumption, resulting in decreased blood loss and a significant decrease in the transfusion of red cells.¹⁹⁵ However, the universal application of mini-circuits will necessitate marked acceptance of modified surgical techniques (e.g., retrograde autologous priming, absence of venous reservoir or cardiectomy), which may limit their generalized acceptance and facility.

An illustrative paper by Bartels and coworkers¹⁹⁶ demonstrated our previous naiveté with regard to the means by which we conduct CPB. "On the basis of our scientific evaluation of the current literature on 48 principles of CPB, not a single condition was of sufficient scientific merit to conclude that we were dealing with a principle for which there is clear evidence, scientific agreement, or both, that a given procedure or treatment is useful and effective."¹⁹⁶ On the other hand, positive steps have now been taken to apply evidence-based guidelines to perfusion practice.⁸ It is only through this contemplation of our everyday actions in the operating room that we can hope to continue to minimize the effect of CPB on our patients.

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DEEP STERNAL WOUND INFECTION

Pierre Voisine • Richard Baillot • François Dagenais

CHAPTER OUTLINE

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Most cardiac surgery procedures are performed through a median sternotomy, an approach pioneered by Milton in 1897.¹ Although fairly uncommon, infective complications for this type of incision remain a difficult challenge for cardiac surgeons.

DEFINITION

Sternal wound complications have been classified by El Oakley and Wright² as follows:

1. *Mediastinal dehiscence*: median sternotomy wound breakdown in the absence of clinical or microbiologic evidence of infection.
2. *Mediastinal wound infection*: clinical or microbiologic evidence of infected presternal tissue and sternal osteomyelitis, with or without mediastinal sepsis and with or without unstable sternum. Subtypes include *superficial wound infection*, wound infection confined to the subcutaneous tissue; and *deep wound infection (mediastinitis)*, wound infection associated with sternal osteomyelitis with or without infected retrosternal space.

It is the latter subtype that will be the focus of this chapter. According to the guidelines from the Centers for Disease Control and Prevention in the United States,³ deep sternal wound infection (DSWI) can be defined by one of the following: (1) the presence of an organism isolated from culture of mediastinal tissue or fluid; (2) evidence of mediastinitis seen during operation; (3) one of the following conditions: chest pain, sternal instability or fever ($>38^{\circ}\text{C}$) *in combination* with either purulent discharge from the mediastinum or an organism isolated from blood culture or culture of mediastinal drainage.

INCIDENCE AND CAUSES

The incidence of DSWI in most recent series ranges from 0.75% to 2.4%.⁴⁻⁷ In our institution, prospectively collected results for 23,499 sternotomies performed between 1992 and 2007 were retrospectively reviewed. A total of 267 patients presented with DSWI, accounting for 1.1% of the surgical population.⁸ *Staphylococcus aureus* and coagulase-negative staphylococci are the most commonly found microorganisms.⁹ In their review of 30,102 consecutive patients undergoing sternotomy for cardiac surgery between 1990 and 2003, Tang and collaborators found them to be respectively responsible for 42% and 24% of DSWI.¹⁰ Gram-negative bacteria and fungi are less commonly encountered. These offending organisms have been associated with different predisposing factors and modes of presentation.^{11,12} Coagulase-negative staphylococci colonize the wound from the normal skin flora and proliferate within a self-contained pocket protected by an extracellular polysaccharide biofilm. The infection is mostly seen in obese patients and those affected by chronic obstructive pulmonary disease (COPD), associated with a slow and late onset with resulting sternal instability but fewer systemic signs.

S. aureus infections are more aggressive in nature and more often associated with classic systemic signs and bacteremia. Perioperative contamination and nasopharyngeal colonization are important sources for this type of infection. Gram-negative bacteria are more commonly associated with a more complicated postoperative course, prolonged intensive care unit (ICU) stay, and concomitant nosocomial infections such as pneumonia, urinary tract infections, and abdominal sepsis, which were found in almost 25% of patients in our series.⁸

RISK FACTORS

Host predispositions and numerous perioperative environmental and technical aspects can play a significant role in the development of DSWI. There is a vast body of literature concerning the most important of these factors, commonly divided as preoperative, perioperative, and postoperative, which have been associated with a higher incidence of DSWI.^{4,5,13-25}

Obesity, diabetes mellitus, COPD, heart failure, renal failure, smoking, poor dental hygiene, older age, and male gender have consistently been identified in patients more prone to DSWI. Preoperative considerations also include prolonged hospital stay or the use of an intra-aortic balloon pump.

Untimely administration of antibioprophyllaxis,²⁶ poor management of hyperglycemia, use of both internal thoracic arteries (ITAs), redo surgeries, excessive use of bone wax, and prolonged procedural times have all been described as perioperative contributing factors, whereas postoperative reexploration for bleeding, transfusions, prolonged ICU stay, and prolonged intubation time are commonly associated with the postoperative period. Specific mechanisms have been proposed to account for the increased risk seen in patients affected by these conditions.

Poor distribution of antibiotics in adipose tissue and inadequate skin preparation in obese patients, impaired wound healing by elevated blood glucose in diabetes mellitus, improper sternal vascularization associated with the use of both ITAs, and heart failure-induced low cardiac output are common examples. In our series,⁸ prolonged intubation was the strongest predictor of DSWI with an odds ratio of 5.9, probably reflecting composite indices of risk and patient fragility. Bilateral internal mammary artery grafting was the second strongest predictor, with an odds ratio of 2.7 in the latest period.

DIAGNOSIS

DSWI diagnosis should be suspected whenever sternal tenderness or instability, erythema, fluid collection, wound dehiscence, or purulent discharge is found, especially in the presence of fever or leukocytosis. The diagnosis is essentially clinical and is based on the criteria listed in the previous "Definition" section. Blood cultures should be done when patients present with pyrexia, and identification of a staphylococcal bacteremia is almost pathognomonic. Any fluid discharge from the wound should also be cultured. Chest radiography has limited interest for diagnostic purposes but may reveal ruptured or malpositioned wires as well as sternal fractures or dehiscence as indirect signs of DSWI.²⁷ Computed tomography (CT) can help determine the extent, depth, and localization of the infectious process. It has been associated with 95.3% sensitivity and 81.7% specificity.²⁸ CT is also useful for guided needle aspiration and culture.

Nuclear imaging has not been used extensively, but leukocytes labeling with ^{99m}Tc-HMPAO has shown

promise as a reliable method for the early diagnosis of sternal infections in a small cohort of 41 patients.²⁹

We suggest that a transthoracic and/or transesophageal echocardiogram be performed in patients presenting with DSWI following a valvular replacement, to rule out the presence of a concomitant prosthetic endocarditis.

PREVENTION

Modifiable preoperative risk factors are intuitive targets for DSWI prevention. Smoking cessation and weight loss should be sought whenever possible. Perioperative strategies to reduce DSWI are numerous and individually described in this section; overall attention to these multiple details is of utmost importance. The incidence of nasal colonization with *S. aureus* ranges from 10% to 15% in the normal population and increases the risk of sternal wound infection.¹² Perioperative intranasal mupirocin application is a safe and inexpensive method to significantly reduce DSWI.³⁰⁻³² Skin preparation should be performed immediately before surgery, and hair should be removed preferably by clipping rather than by shaving.³

Prophylactic antibiotics prior to surgery are recommended and should be administered so that therapeutic concentrations can be reached before the initial incision and maintained throughout the procedure and for several hours following closure. The use of cefazolin 1 g or cefuroxime 1.5 g intravenously is recommended within 30 to 60 minutes preprocedure; vancomycin should be used, in a dose adjusted to renal function, for patients with a history of penicillin allergy or at risk for methicillin-resistant *S. aureus*.³ Unless there is evidence of ongoing sepsis, prophylactic use of antibiotics should not be extended beyond 36 to 48 hours.³³

Blood glucose levels should be controlled, because maintenance at or below 110 mg/dL has been shown to decrease morbidity and mortality among critically ill patients, regardless of a presurgical history of diabetes.³⁴ The efficacy of local antibiotic-eluting products remains controversial. Gentamicin-collagen sponges placed retrosternally before suture closure have been associated with reduction of DSWI in a controlled randomized study,³⁵ results that have been disputed in other trials.³⁶⁻³⁸ As stated in a meta-analysis by Mavros et al,³⁹ the statistical heterogeneity among existing studies underlines the need for additional large, high-quality randomized controlled trials.

Furnary and coworkers have demonstrated that maintenance of blood glucose between 150 and 200 mg/dL through continuous insulin infusion, compared with intermittent subcutaneous insulin, led to a significant reduction in the incidence of DSWI (0.8% vs. 2%).⁴⁰ During surgery, caution while performing a precise midline sternotomy and discriminate use of electrocautery and bone wax are simple ways to help prevent DSWI. The use of both ITAs should also be weighed against potential risks of infection and tailored for each patient. Diabetic patients are particularly at risk, especially when other factors such as obesity and COPD are present.⁴¹ There is growing evidence that skeletonized bilateral ITA

grafting can contribute to lowering the risk of DSWI in these patients.⁴²⁻⁴⁷

A closure technique that affords sternal stability should be adopted.⁴⁸ A sufficient number of sternal wires should be used, especially in high-risk patients.^{49,50} Newer sternal closure systems using titanium, nitinol, and cable-tie devices or based on sternal bone adhesive offer promising alternatives for optimal sternal fixation and have been associated with lower rates of sternal wound complications.⁵¹⁻⁵⁴ External systems used to reduce sternal instability, such as vests or corsets, can be useful adjuncts.^{55,56} A review of a variety of primary closure techniques designed to further stabilize the sternum and lower the risks of dehiscence and infection is proposed by Losanoff and coworkers.⁵⁷

SURGICAL MANAGEMENT

As for any surgical wound infection, DSWI management requires appropriate assessment of the underlying causes, including identification of the causing pathogens, and usually involves surgical revision, thorough débridement and wound preparation for reconstruction, with or without soft tissue flaps and/or plate fixation. Poststernotomy mediastinitis was initially approached by surgical revision with frequent dressing changes to promote granulation leading to sternal rewiring or secondary wound closure. The method was flawed by long hospital stays, secondary superinfection with fungi, hemorrhage, and mortality rates as high as 45%.⁵⁸

Primary Closure and Irrigation

An important contribution to the treatment of DSWI came in 1963 from Shumaker and Mandelbaum,⁵⁹ who first described the technique of débridement, sternal reclosure, and mediastinal antibiotic irrigation. The technique offers the advantages of a closed wound and a stable sternum but is associated with limitations in patient mobility and slower rehabilitation; high rates of failure are still being reported.⁶⁰ Nonetheless, this approach is still used and is a viable option.

Poncelet and coworkers⁷ proposed an algorithm including primary closure for most patients with DSWI. Multiple procedures, eventually including the use of muscle flaps, were necessary in more than a third of the patients, and the 90-day mortality rate for patients with DSWI remained high at 14.5%. Using multiperforated (Redon) catheters that are used for irrigation and progressively removed over the course of several days, another group reported an overall in-hospital mortality of 23.6%.⁶¹ These results contrast with those reported by Molina and coworkers,⁶² who have used a single approach for 24 years that consists of débridement, lateral reinforcement of the sternum, and the placement of a combination of irrigation catheters and suction tubes both anterior and posterior to the closed sternum. The skin is closed, the irrigation catheters are kept in place for 1 week, and then suction tubes progressively are taken out over 5 to 7 additional days. The authors report a 98% cure rate and no mortality in 114 patients. A more recent

retrospective analysis comparing the use of Redon drains and vacuum-assisted closure therapy (see [Vacuum-Assisted Closure Therapy](#), later) showed a reduction in hospital stay with no significant impact on mortality, which remained high in both groups (14.0% and 12.5%, respectively).⁶³

Soft Tissue Flaps

Omental Flaps

Based on the greater omentum's rich blood supply, immunologic properties and potential capacity to nourish infected tissue and improve wound healing, Lee and colleagues introduced the idea of omental flaps to treat DSWI in 1976.⁶⁴

Despite good flap viability and interesting protection afforded by the technique, with a reported 16% mortality in a cohort of 47 patients of whom more than 50% had methicillin-resistant *S. aureus* infection,⁶⁵ donor-site complications resulting from omental flap transposition remain high⁶⁶ and include abdominal wall herniation (20%), hematoma (8%), and seroma (4%). Omental flaps are now mostly used as an adjunct to other therapeutic modalities or as a second resort when previous techniques have failed, and it is thus difficult to fully appreciate the intrinsic benefits of the approach. A study⁶⁷ reviewing their use in 52 patients over a 15-year period demonstrated a 60-day mortality of 11% when used for primary reconstruction compared to 29% when used as a salvage procedure. Flap-related complications occurred in 23% of cases, with complete flap loss in 3.8%. Donor-site complications were seen in 27% of cases.

More recently, minimally invasive laparoscopic harvesting of the omentum has been proposed as an alternative to formal laparotomy.⁶⁸ This less invasive approach, associated with fewer abdominal complications, is increasingly used in our institution.

Pectoralis Major Muscular Flaps

Flaps derived from the pectoralis major are dependent on its primary and secondary blood supplies, respectively the thoracoacromial neurovascular bundle and the perforators from the ITAs.⁶⁹ Complete transposition by folding the muscle over on itself requires transection of the thoracoacromial artery and can obviously not be done on the side where an internal mammary artery has been harvested; however, partial flaps can be created by preserving the primary blood supply and advancing part of the muscles to cover the sternum. In most cases both muscles are prepared using this latter approach, detached from their insertions on the humeri and advanced into the wound, perfused by the thoracoacromial arteries. One of the muscles can also be folded using the secondary blood supply for the pedicle if the ipsilateral ITA is intact. This can allow for the splitting of the muscle along its midline, extending the surface that can be covered. In a review of 67 patients receiving 91 tissue flaps, Zahiri and coworkers found that overall complication rates were significantly higher after pectoralis major advancement (32.5%) versus turnover (3.7%) reconstruction.⁷⁰

When the entire sternum cannot be covered, concomitant use of the rectus abdominis is sometimes required. However, by skeletonizing the vascular pedicle back to near the origin of the thoracoacromial axis to create an extended island flap of the pectoralis major,^{71,72} the need for additional muscle flap preparation can be virtually eliminated.

In a review of their 20-year experience with mediastinitis management using pectoralis major flaps in 76.6% of their last 186 patients, Jones and coworkers reported a 9.1% mortality with 18.8% flap closure complications.⁷³

Rectus Abdominis Muscular Flaps

The rectus abdominis can be used as a muscular or myocutaneous vertical flap, using the superior epigastric artery and vein for blood supply, assuming integrity of the arteriovenous arcade connecting the inferior and superior epigastric vessels.⁶⁹ This approach is used mostly when pectoralis major flap transposition does not provide adequate coverage of the wound or has failed. Oh and coworkers⁷⁴ report 12% mortality with 29% flap complications in 34 patients operated over a 10-year period. Another report, from Jacobs and coworkers,⁷⁵ using at least one intercostal artery as additional blood supply to the superior gastric artery in 72 patients over 15 years, demonstrates 7% mortality and 7% morbidity. Retrospectively comparing the results of 41 patients and 56 patients, respectively undergoing pectoralis and rectus abdominis reconstruction, Davison and coworkers⁷⁶ showed similar success rates (defined as a healed wound and discharged patient at 30 days) of 85% and 86%, 34% morbidity for both approaches as well as 5% and 7% respective mortality rates. Rectus abdominis transposition proved more efficient at preventing dehiscence of the inferior third of the sternum, whereas an advantage was found for pectoralis transposition in preventing superior third complications.

Use of muscle flap for chest wall reconstruction is the subject of a comprehensive and recent review by Bakri and coworkers.⁷⁷

Fixation

Rigid titanium plates can be used for sternal edges apposition to promote bony union in complicated sternal closures. These plates are used mostly when there is sternal instability, which is usually seen in early presentations of DSWI. Plates are transversally placed across the sternal halves at separate levels (manubrium, second, third, and fourth ribs) (Fig. 64-1). Plate fixation was used in 50 such cases in conjunction with simple bilateral pectoralis advancement flaps for repair of sternal wound dehiscence, osteomyelitis, and nonunion after median sternotomy. Complete bony union was achieved in 98% of cases, with only 2% recurrences.⁷⁸ The technique has also been used in prophylaxis in 326 patients between 2000 and 2005, and results were compared to those of 215 patients with similar risk profiles treated with a standard approach.⁷⁹ Fixation plates were associated with a reduction in mediastinitis complications from 13% to none,

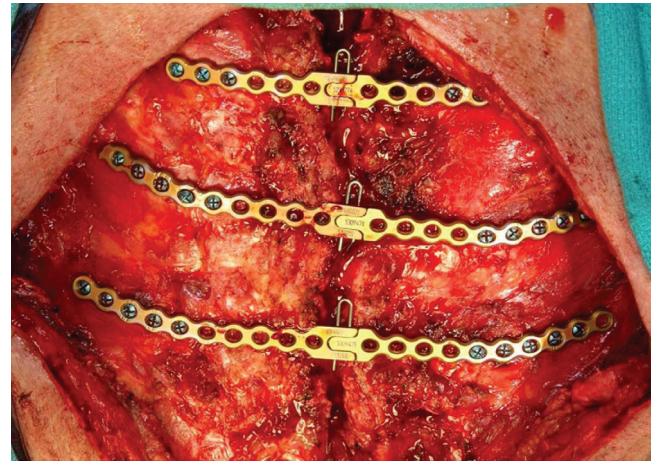


FIGURE 64-1 ■ Titanium fixation plates fixed with locking screws on the cartilaginous portions of the ribs.

and mortality from 8.6% to 3.8%. The benefits of plating appear to be maximal during the early postoperative period, but late sternal wound complications remain an issue. Both our group and Snyder and coworkers found a 10% recurrence rate after primary plating.^{80,81} Although the management of these patients requires rehospitalization and removal of osteosynthesis material, infections tend to be superficial and secondary treatment with vacuum-assisted closure is usually successful.

Vacuum-Assisted Closure Therapy

The use of vacuum-assisted closer (VAC) therapy for wound healing, a concept introduced by Morykwas in 1997,⁸² is based on the application of local negative pressure through an open-pore polyurethane foam covered with an adhesive drape and connected to a vacuum source (Fig. 64-2). Continuous drainage in an otherwise moist environment increases blood flow in the wound and favors cellular organization and granulation tissue formation while providing sternal stabilization to allow for physiotherapeutic mobilization of the patient.¹³ This technique can be used as a single-line treatment modality followed by reclosure, or as a temporary means of providing optimal conditions for second-line procedures such as flap transposition or plate fixation. It has been successfully applied by several groups^{13,19,83-89} and shown to shorten the length of hospital stays to improve survival in DSWI patients. Bleeding remains the most frequent complication associated with the use of VAC therapy, but this can be avoided by covering the right ventricle with paraffin gauze and performing débridements in the safe environment of a proper operating room.^{90,91}

Based on the demonstration that C-reactive protein levels can be used to guide the optimal timing for VAC cessation,⁹² an algorithm for treatment has been proposed by Sjögren and coworkers.¹³

Treatment Algorithm

A similar algorithm has been concomitantly developed in our institution starting in January 2002.⁸ Of 10,319

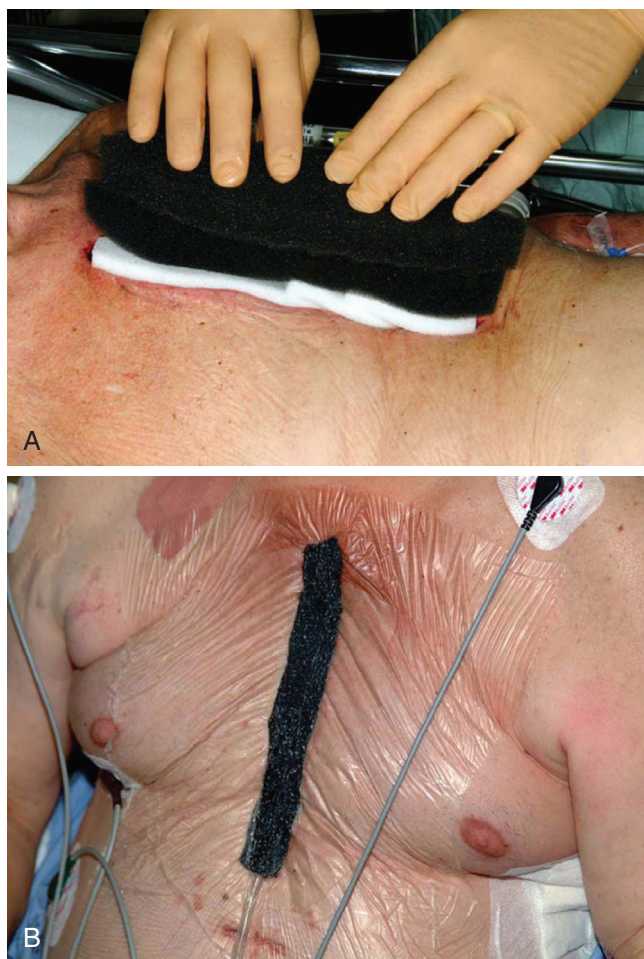


FIGURE 64-2 ■ Installation of the vacuum-assisted closure (VAC) system. **A**, Open-pore foam sponges used to fill the space between sternal halves. **B**, Complete system with adhesive drape and suction tubing connected to vacuum source.

patients undergoing cardiac surgery, 149 presented with DSWI (1.4%) during that period. Patients were systematically brought to the operating room for débridement, removal of all foreign material (including sternal wires), and wound culture at different levels. Appropriate antibiotherapy was instituted and a VAC system installed with negative pressure ranging from -75 mm Hg to -125 mm Hg. Wound care with additional débridement was performed as needed every 2 to 3 days, with return to the operating room when necessary, until the wound was clean, repeated cultures were negative, and C-reactive protein levels were below 60 mg/L. Thick paraffin gauzes were used under the foam sponges to protect the right ventricle. Most patients were then treated with bilateral pectoralis major muscle flap advancement without humeral detachment and titanium plate fixation (62%), while 22% had VAC therapy followed by pectoralis major transposition only, and 16% were closed by rewiring only. In comparison to the remaining 13,180 who were treated without VAC therapy as a first-line approach, in-hospital mortality was lowered from 14.1% to 4.8% ($P = 0.009$). After adjustment for risk factors, early survival at 1, 2, and 3 years was also better after VAC therapy (respectively 93% vs. 83%, 90% vs. 76%, and 88% vs. 61% at

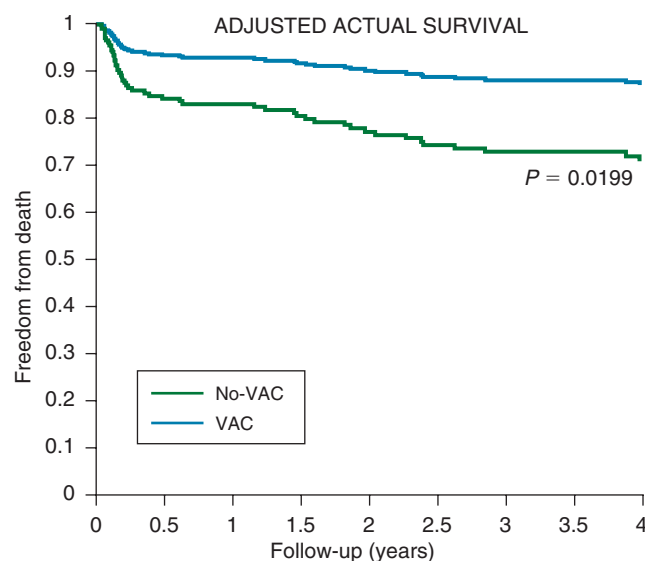


FIGURE 64-3 ■ Adjusted survival for patients treated with multimodal therapy, including rewiring with or without pectoralis major flap advancement with or without plate fixation, either with (VAC) or without (No-VAC) preparation with vacuum-assisted closure therapy.

1, 2, and 3 years for the VAC vs. non-VAC groups, $P = 0.02$) (Fig. 64-3).

In our experience, more complex muscle flap transpositions, including laparoscopic omentopexy combined with pectoralis muscle flap wound coverage, have been limited to those cases in which bony union could not be achieved (e.g., following total sternectomy in cases of severe sternal osteomyelitis) and have been performed mostly for mediastinal protection purposes.

Deep sternal wound infection remains an important problem after median sternotomy, associated with significant morbidity and mortality rates. Good clinical practice based on appropriate preventive measures, early recognition, and treatment are mandatory because they have been shown to provide significant improvement in outcome.

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MYOCARDIAL PROTECTION

Sidney Levitsky • James D. McCully

The heart ... moves of itself and does not stop unless forever.
LEONARDO DA VINCI (DELL'ANATOMIA, FOGLIA B)

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Despite meticulous adherence to presently known principles of myocardial protection, perioperative myocardial damage related to ischemia-reperfusion injury continues to occur after cardiac operations that have been performed in a technically adequate manner. Ischemia-reperfusion injury associated with surgically induced myocardial ischemia secondary to aortic cross-clamping results from the attenuation or cessation of coronary blood flow such that oxygen delivery to the myocardium is insufficient to meet basal myocardial requirements to preserve cellular membrane stability and viability. Recovery after surgically induced ischemic arrest involves (1) resumption of normal oxidative metabolism and the restoration of myocardial energy reserves; (2) reversal of ischemia-induced cell swelling, loss of ion gradients, and adenine nucleotide losses; and (3) repair of damaged cell organelles such as mitochondria and the sarcoplasmic reticulum.

HISTORICAL DEVELOPMENT

After the initiation of open heart surgery with use of extracorporeal circulation by Gibbon,¹ it soon became obvious that aortic cross-clamping was necessary to provide a bloodless field to facilitate the precise repair of intracardiac defects, to prevent air embolism when the left side of the heart was opened, and to avoid a turgid myocardium resistant to retraction. To overcome the difficulties of operating on a rheumatic mitral valve in a patient with aortic regurgitation, Melrose and colleagues² introduced the concept of “elective cardiac arrest” by rapidly injecting into the aortic root, after aortic cross-clamping, a 2.5% potassium citrate solution in warm blood to arrest the heart. Soon thereafter, experimental and clinical evidence³ demonstrated the development of severe myocardial necrosis associated with the Melrose technique.

During the 1960s, two distinct technical pathways for management of ischemic arrest evolved. The “rapid operators” performing uncomplicated cases with short ischemic times adopted the use of normothermic ischemic arrest, until operative mortalities from the “stone heart” syndrome related to ischemic contracture of the myocardium⁴ associated with low levels of high-energy phosphate moieties became apparent.⁵ Intermittent aortic cross-clamping, involving reperfusion of the coronary circulation for 5 minutes after 15 minutes of ischemic arrest, is an empirical technique, still in use, and was based on the concept that after 15 minutes of ischemia, a sufficient concentration of high-energy phosphate moieties remained in the myocardium to allow replenishment of myocardial stores during the reperfusion period.⁶ Later studies demonstrated that there was no functional or metabolic advantage to intermittent reperfusion for normothermic ischemic periods up to 60 minutes.^{7,8} Nevertheless, intermittent cross-clamping accompanied by ventricular fibrillation continues to be used for coronary artery bypass surgery with results comparable to those of cardioplegic techniques.⁹

Fibrillatory Arrest

Electrically induced ventricular fibrillation with coronary perfusion was introduced by Glenn and Sewell¹⁰ and Senning¹¹ as a means of avoiding air embolism. However, Buckberg and Hottenrott¹² and Hottenrott and coworkers¹³ demonstrated subendocardial ischemia and necrosis with this technique, particularly in the hypertrophied ventricle. Later studies showed that if ventricular distention is avoided and coronary perfusion is maintained, postischemic fibrillation is not deleterious in the nonhypertrophied heart.¹⁴ Further validation of this technique, modified by mild hypothermia and the avoidance of aortic cross-clamping, has produced comparable clinical results for coronary revascularization.^{15,16}

Continuous Coronary Perfusion

In an attempt to mimic the physiologic state, continuous coronary perfusion with a beating heart at normothermia or mild hypothermia at 32°C to prevent the onset of ventricular fibrillation became the preferred technique of myocardial preservation in the late 1960s and early 1970s, particularly after the report by McGoon and colleagues¹⁷ of 100 consecutive aortic valve replacements with no deaths. When aortic valve regurgitation was present or aortic root surgery was performed, the heart was kept beating by perfusing the individual coronary arteries with cannulas inserted into the ostia. However, continuous perfusion became intermittent as coronary perfusion was often discontinued to achieve better visualization of the operative field during critical portions of the procedure.¹⁸ In addition, problems with the coronary cannula, such as poor fixation, leaking associated with calcified ostia, early division of the left main coronary artery resulting in high perfusion pressure necrosis, and damage to the coronary artery such as dissection and late stenosis, continued to occur.^{19,20} Nevertheless, the technique of continuous coronary artery perfusion, either during the performance

of complex aortic root surgery or for special situations, such as re-do mitral valve surgery through a right thoracotomy incision after previous coronary artery revascularization with arterial conduits, continues to be used.²¹

Hypothermia

The earliest attempts to perform open heart surgery before the advent of the heart-lung machine used systemic hypothermia produced by surface cooling not only to protect the heart but to protect the brain and other organs during circulatory arrest.^{22,23} Hypothermia protects the ischemic myocardium by decreasing heart rate, slows the rate of high-energy phosphate degradation,²⁴ and decreases myocardial oxygen consumption (Fig. 65-1).^{25,26} However, uniform cardiac hypothermia is difficult to achieve solely by the introduction of cold intracoronary perfusates, and systemic hypothermia is necessary, particularly in the presence of coronary obstruction, ventricular hypertrophy, rewarming of the right ventricle by the liver's acting as a “heat sink,” and environmental rewarming.²⁷ In an attempt to overcome this problem, Shumway and associates²⁸ introduced the concept of profound local (topical) hypothermia by filling the pericardial sac with ice-cold saline.²⁹ Although this technique is still used as an adjunct to other methods of myocardial protection, it is rarely used as the sole protective method because of the problem of warm bronchial collateral flow reaching the heart cavity, resulting in transmural temperature gradients and resultant ischemia.^{30,31}

Reintroduction of Cardioplegia

Whereas cardioplegia had been abandoned for alternative techniques in the United States after the adverse experience with the Melrose potassium solution, in Germany, Bretschneider³² continued studying induced cardiac arrest with use of a histidine protein buffer, sodium-poor, calcium-free, procaine-containing solution (Bretschneider solution). Clinical application soon followed,

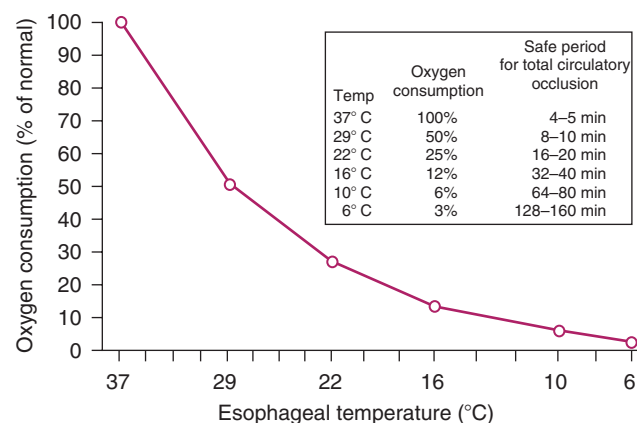


FIGURE 65-1 ■ Relationship between body temperature and oxygen consumption in dogs cooled by means of an extracorporeal pump (mean value for 10 dogs). (From Gordon AS, Meyer BW, Jones JC: Open heart surgery during deep hypothermia without an oxygenator. *J Thorac Cardiovasc Surg* 40:787–812, 1960.)

with Kirsch and associates³³ using a magnesium aspartate–procaine solution. Hearse and coworkers³⁴ introduced the concept of using an extracellular rather than an intracellular solution (St. Thomas' solution), which was first applied clinically by Braimbridge and coworkers.¹⁸ On the basis of improved clinical outcomes, North American investigators^{35–38} initiated experimental studies using potassium cardioplegia followed by clinical reports^{39,40} demonstrating the efficacy of cardioplegia. During the next 3 decades, numerous investigators have continued their “quest for ideal myocardial protection.”^{41–44}

BIOLOGY OF SURGICALLY INDUCED MYOCARDIAL ISCHEMIA

Global ischemia is not an all-or-nothing phenomenon; rather, it is heterogeneous in that at any moment of time, myocardial cells will have varying extents of damage.^{45,46} These changes affect cellular metabolism, ion transport, electrical activity, contractile function, vascular responsiveness, tissue ultrastructure, changes in nuclear and mitochondrial DNA, release of free radical oxygen species, and activation of inflammatory components.⁴⁷

Myocardial Oxygen Consumption

Because the heart is an obligate aerobic organ, it depends on a continuous supply of oxygen to maintain normal function. Myocardial oxygen reserve is exhausted within 8 seconds after the onset of normothermic global ischemia.⁴⁸ Myocardial oxygen consumption (MVO_2) is compartmentalized into the oxygen needed for external work of contraction (80% to 90%) and the unloaded contraction, such as basal metabolism, excitation-contraction coupling, and heat production.^{49,50}

A unique aspect of myocardial energetics is that 75% of the coronary arterial oxygen presented to the myocardium is extracted during a single passage through the heart; thus, depressed coronary venous oxygen content persists despite a wide range of cardiac workloads. Therefore, the heart is susceptible to the limitations of oxygen delivery, whereby an increase in MVO_2 can be met only by augmentation of coronary blood flow. This is diametrically opposite to skeletal muscle, in which increased oxygen demand can initially be met by an increase in oxygen extraction. Clinically, a marked increase in coronary blood flow is observed at the beginning of the reperfusion period, after the aortic clamp is removed.

Biochemical Alterations

Under aerobic conditions, the heart derives its energy primarily from mitochondrial oxidative processes, using substrates such as glucose, free fatty acids, lactate, pyruvate, acetate, ketone bodies, and amino acids.^{51,52} However, oxidation of fatty acids provides the major source of energy production and is used in preference to carbohydrates.⁵³

As tissue PO_2 falls, oxidative phosphorylation, electron transport, and mitochondrial adenosine triphosphate

(ATP) production cease. Early in ischemia, the heart depends on the energy production of glycogenolysis and aerobic glycolysis (Pasteur effect). However, unlike other organs, the heart requires a minimum threshold of ATP to prevent irreversible ischemic contracture.⁵⁴ Reduced mitochondrial activity leads to the accumulation of glycolytic intermediaries, reduced NADH, and the reduction of pyruvate to lactate. The resultant severe intracellular acidosis impairs contractile function, enzyme transport, and cell membrane integrity. This results in a cellular loss of potassium and pathologic accumulation of sodium, calcium, and water (Fig. 65-2).⁵⁵

Ischemia-Reperfusion Injury

Ischemia-reperfusion injury occurs as the result of attenuation or cessation of coronary blood flow such that oxygen delivery to the myocardium is insufficient to meet basal myocardial oxygen requirements to preserve cellular membrane stability and viability. The initiation of myocardial injury requires an ischemic episode that, by itself, may induce reversible or irreversible cellular injury.^{56,57}

Reversible ischemia-reperfusion injury may be manifested as either stunning or hibernation. Stunning “describes the mechanical dysfunction that persists after reperfusion despite the absence of myocellular damage and despite the return of normal or near-normal perfusion.”^{58,59} A second form of reversible ischemia-reperfusion injury is hibernation, which is a syndrome of reversible, chronically reduced contractile function as a result of one or more recurrent episodes of acute or persistent ischemia, referred to as chronic stunning.

As in stunning, hibernating myocardium is viable but not functional and is reversible with coronary revascularization.^{60,61} There is good clinical evidence that despite seemingly adequate application of modern methods of myocardial protection, all patients undergoing cardiac surgery have varying degrees of myocardial stunning.^{62,63} Evidence to support this concept is based on the requirement of inotropic support for separation from bypass for hours or days after surgery in some patients who are eventually weaned from these drugs as the stunning abates, without objective evidence of a myocardial infarction.⁶⁴

Two major theories have been proposed as possible mechanisms leading to ischemia-reperfusion injury (Fig. 65-3). The calcium hypothesis suggests that the inability of the myocyte to modulate intracellular and intraorganellar calcium homeostasis induces a cascade of events culminating in cell injury and death (Fig. 65-4). Ischemia leads to the induction of metabolic acidosis and the activation of the sodium-proton exchanger, resulting in the transport of hydrogen ions to the extracellular space and the movement of sodium into the cytosol. As the sodium-calcium exchanger is activated, sodium is transported to the extracellular space and calcium is taken up into the cytosol, increasing cytosolic calcium concentration ($[Ca^{2+}]_i$). Increased $[Ca^{2+}]_i$ accumulation is also augmented by ischemia-induced depolarization of the membrane potential, which allows the opening of the L-type calcium channels and further calcium entry into the myocyte.

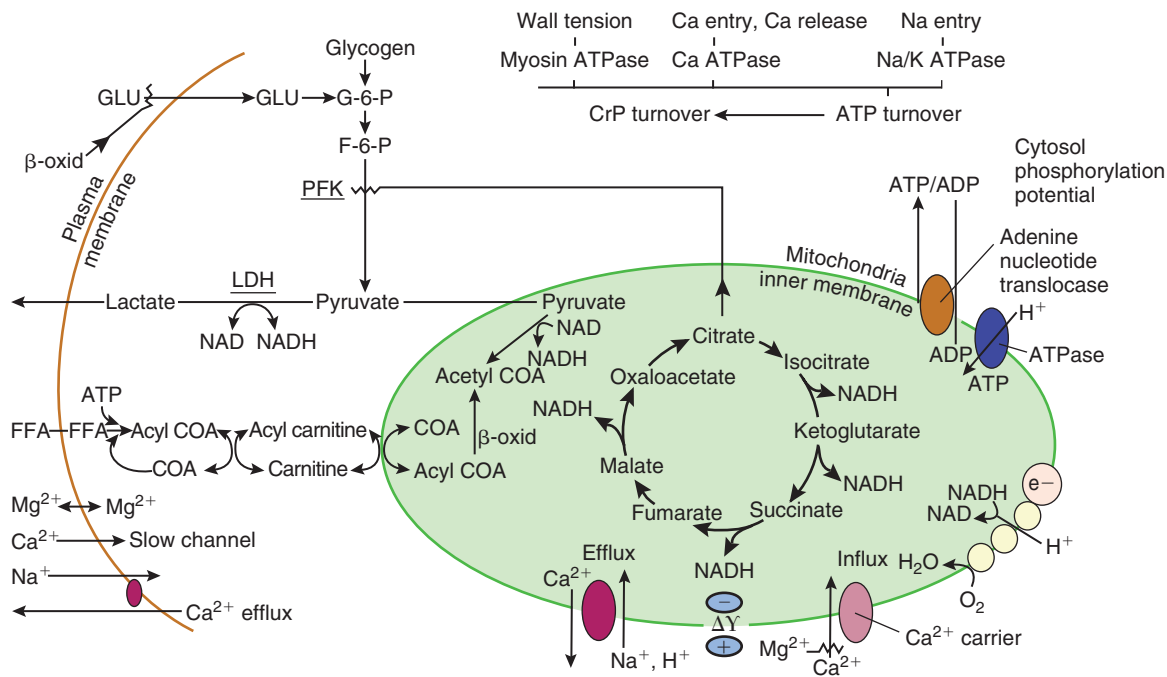


FIGURE 65-2 ■ The biochemical anatomy of the normal functioning myocardial cell. The three main reactions using ATP are (1) myosin ATPase involved in the development of wall tension, (2) Ca^{2+} , Mg^{2+} -ATPase involved in sequestration of Ca^{2+} that enters the cell with each beat and the Ca^{2+} that is liberated from sarcoplasmic reticulum in the activation of contractile protein, and (3) Na^{+} , K^{+} -ATPase involved in Na^{+} efflux. The action of this vectorial ATPase establishes the monovalent cation gradient across the membrane that is used to maintain cell excitability and the efflux of Ca^{2+} . (From Feinberg H, Levitsky S: *Biochemical rationale of cardioplegia*. In Engelman RM, Levitsky S, editors: *A textbook of clinical cardioplegia*, New York, 1982, Futura, pp 131–139.)

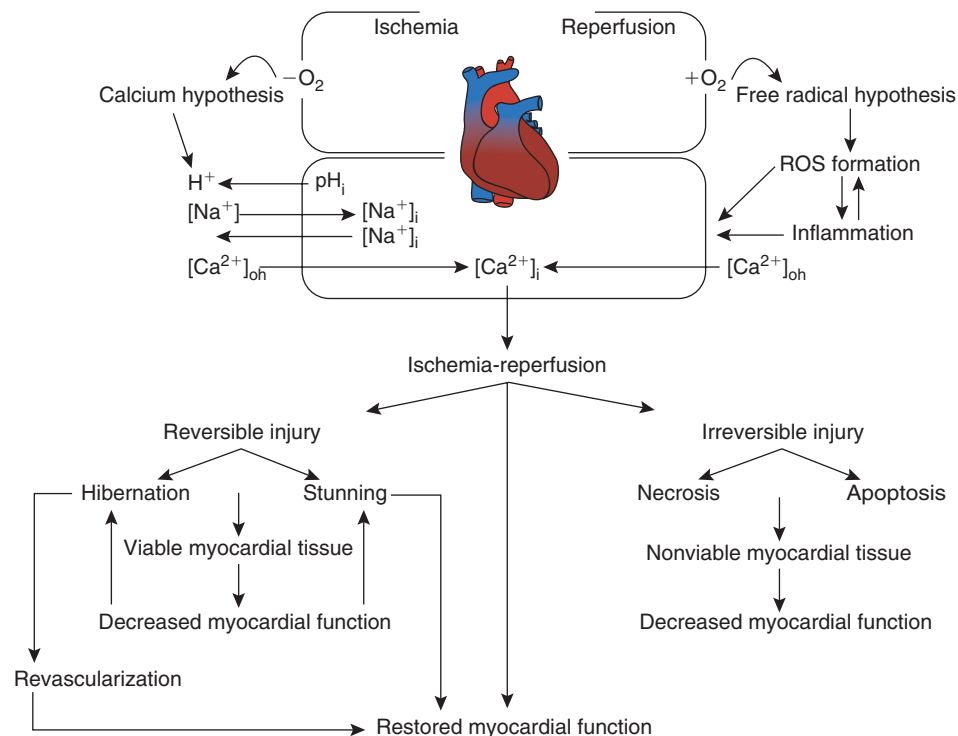


FIGURE 65-3 ■ Mechanisms of ischemia-reperfusion injury. Putative mechanisms of the calcium and free radical hypotheses and inflammation in the generation of ischemia-reperfusion injury. ROS, Reactive oxygen species.

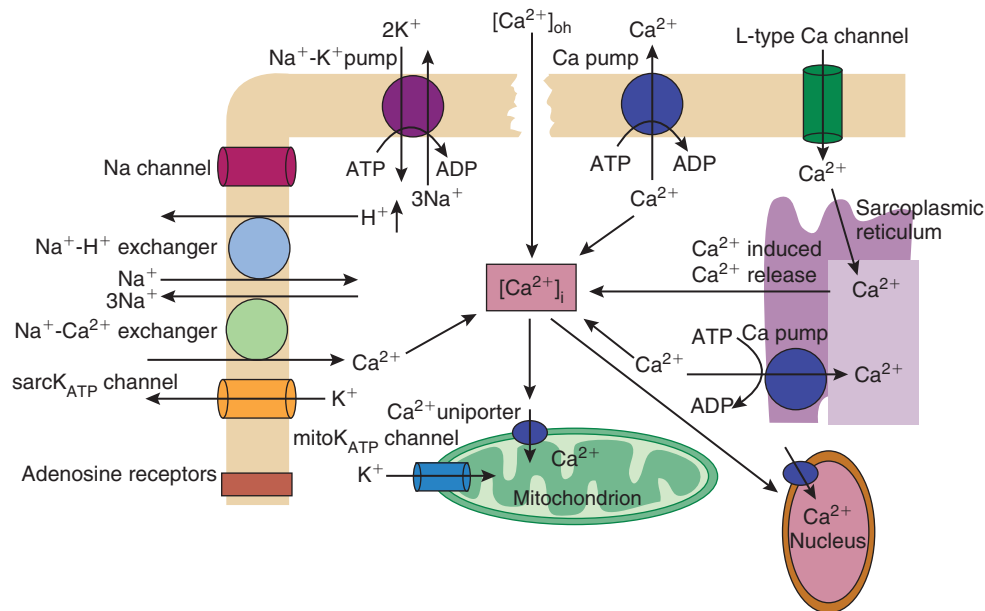


FIGURE 65-4 ■ Sources of calcium regulation. The inability of the myocyte to modulate intracellular and intraorganellar calcium homeostasis during ischemia and during early reperfusion is the basis of the calcium hypothesis for ischemia-reperfusion injury. Increased intracellular calcium ($[Ca^{2+}]_i$) induces a cascade of events culminating in increased mitochondrial and nuclear calcium accumulation and cell injury and death.

Cellular and cytosolic calcium-dependent phospholipases and proteases are in turn activated, inducing membrane injury and the further entry of calcium into the cell. These processes alter myocardial cellular homeostasis, leading to cellular dysfunction or, if they are of sufficient duration or intensity, cell injury or death. Alternative explanations include the concept of reperfusion-induced myocardial contracture resulting from rapid re-energization of contractile cells with persistent calcium overload affecting myofibrillar calcium sensitivity.⁶⁵

The free radical hypothesis suggests that the accumulation of partially reduced molecular oxygen, collectively known as reactive oxygen species, during the early stages of reperfusion causes myocardial cellular damage and cell death through microsomal peroxidation of the cellular phospholipid layer, leading to loss of cellular integrity and function (Fig. 65-5).⁶⁶ The generation of reactive oxygen species is believed to be mediated by xanthine oxidase, activation of neutrophils, or dysfunction of the mitochondrial electron transport chain. It has been suggested that the generation of reactive oxygen species may induce cellular membrane damage, thus facilitating calcium entry and the induction of cellular death. This hypothesis unifies both prevailing theories and is currently considered to be valid. However, therapeutic attempts to control calcium and reactive oxygen species overload have not yielded meaningful advantage.⁶⁷

Alternative explanations include the concept of lethal reperfusion injury, defined as death of myocardial cells that were viable immediately before reperfusion.⁶⁸ In an excellent review by Yellon and Hausenloy,⁶⁹ alternative cardioprotective strategies are suggested to manage this injury by reperfusion injury salvage kinase pathways and targeting mitochondrial permeability transition pores to avoid mitochondrial calcium overload. Cyclosporine, a

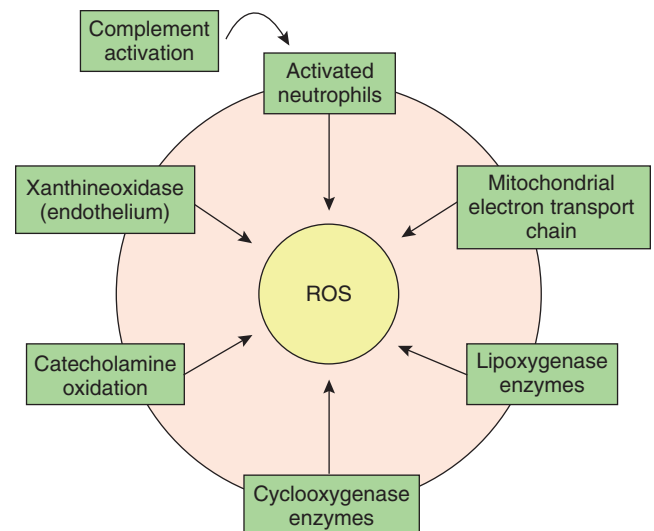


FIGURE 65-5 ■ Sources of reactive oxygen species generation. The free radical hypothesis suggests that accumulation of partially reduced molecular oxygen, collectively known as reactive oxygen species (ROS), during the early stages of reperfusion causes myocardial cellular damage and cell death. Reactive oxygen species are formed by the acquisition of a single electron, making them highly reactive and cytotoxic. The major reactive oxygen species in order of production are superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxy radical ($\cdot OH$), and lipid peroxides. ROS formation has been shown to cause myocellular injury through microsomal peroxidation of the cellular phospholipid layer, leading to loss of cellular integrity and function.

potent inhibitor of mitochondrial permeability transition pores, has recently been shown to limit infarct size after percutaneous coronary intervention during acute myocardial infarction.⁷⁰

Irreversible Cell Injury

Irreversible cell injury, described ultrastructurally by Schaper and coworkers,⁴⁶ occurs by two morphologically distinct pathways, necrosis and apoptosis. Necrosis is initiated by noncellular mechanisms with cell swelling, depletion of ATP stores, and disruption of the cellular membrane involving fluid and electrolyte alterations.⁷¹ In contrast, apoptosis (programmed cell death)⁷² is an evolution-based mode of cell death characterized by a discrete set of biochemical and morphologic events involving the regulated action of catabolic enzymes (proteases and nucleases) that results in the ordered disassembly of the cell, distinct from cell death provoked by external injury.^{73,74}

Inflammation

Inflammation has been implicated as a secondary mechanism contributing to injury after reperfusion. It is initiated through complement activation leading to the sequential formation of a membrane attack complex, which creates a cellular lesion and eventual cell lysis.⁷⁵ In addition, cytokines, vasoactive and chemotactic agents, adhesive molecule expression, and leukocyte and platelet activation participate in the inflammatory process, producing cytotoxic molecules that facilitate cell death.^{76,77} Oxygen-derived free radical scavengers have also been used to limit reperfusion injury.⁷⁸ Tissue factor, an inflammatory and procoagulant mediator, initiates the extrinsic coagulation cascade, resulting in thrombin generation and fibrin deposition, and may be related to the no-reflow phenomenon.⁷⁹ Clinical applicability of anti-inflammatory agents awaits well-designed clinical trials because studies up until now have not shown any “meaningful cardioprotective effect.”^{69,80,81}

In addition, endothelium-dependent microvascular responses and coronary artery spasm may be related to reduced myocardial perfusion after reperfusion.⁸²

Effects of Age

The vulnerability of the heart to ischemia-reperfusion injury is altered with temporal development. The newborn heart is more resistant to the effects of ischemia-reperfusion, which may be related to developmental differences in calcium transport and sequestration, and it is better able to restore myocardial function and myocardial high-energy phosphate stores after an ischemic event.⁸³⁻⁸⁵ Others have postulated that, in the neonate, during ischemia, anaerobic glycolysis is the only metabolic pathway that can produce high-energy phosphates.⁸⁶

In the adult heart, functional recovery is significantly delayed, and the recovery of high-energy phosphate stores is slower in returning to preischemic levels.⁸⁷ As the heart ages, there are anatomic, mechanical, ultrastructural, and biochemical alterations that compromise

the adaptive response of the heart.⁸⁸ As a result, the senescent myocardium is less tolerant than the mature myocardium to surgically induced ischemia.⁸⁹ The susceptibility of the aged myocardium to ischemia-induced injury is evident at many levels. Morphologically, with age, left ventricular mass is increased and the size of the left ventricular cavity is reduced, accompanied by increased calcification of the valve annulus and coronary arteries.⁹⁰ Ultrastructurally, there is decreased mitochondria-to-myofibril ratio, cardiac myocyte enlargement, and loss of mitochondrial organization as well as alteration in myocardial contractile properties.⁹¹ As a consequence of these changes, cardiac surgical operative mortality increases with age.⁹²

Cyanosis

Cyanosis significantly increases the vulnerability of the myocardium to ischemia-reperfusion injury.^{93,94} However, cyanotic myocardial cells exhibit normal metabolism when they are provided with adequate oxygen and substrate.⁹⁵ Mortality rates in patients undergoing elective repair for tetralogy of Fallot are related to the method of myocardial protection as well as to the patient's age, duration and extent of cyanosis, and extent of hypertrophy.⁹⁶

Ventricular Hypertrophy

Increased myocardial mass is an adaptive response to prolonged increases in myocardial workload as a result of pressure or volume overload. If it is untreated, progressive ventricular hypertrophy results in ventricular dilation and contractile dysfunction.⁹⁷ Hypertrophied hearts have an increased vulnerability to ischemic injury, which has been attributed to accelerated loss of high-energy phosphate moieties,⁹⁸ increased accumulation of lactate and hydrogen ions, earlier onset of ischemic contracture, and accelerated calcium overload after reperfusion.^{87,99,100} With ventricular hypertrophy, epicardial coronary arteries dilate in response to increased oxygen demands, and decreased capillary density and vascular dilation reserve in the subendocardial regions result in increased ischemic vulnerability.¹⁰¹ Subendocardial ischemia leading to necrosis can occur during periods of hypotension, inadequate cardiopulmonary bypass, and ventricular fibrillation.¹⁰² The hypertrophied heart is particularly susceptible to ischemic injury in the early postoperative period, when hypotension associated with surgically induced myocardial stunning, hypothermia, and vasoconstrictor agents are present.¹⁰³

CARDIOPLEGIA: BASIC PRINCIPLES

A rational approach for protecting the heart during surgically induced ischemia not only must focus on the requirements for sustaining the ischemic cell but also must be compatible with the technical aspects of the operative procedure. Operative procedures require a flaccid arrested heart, a bloodless operative field, and sufficient time for the satisfactory repair of complex cardiac defects. Moreover, the ability of the heart to

assume normal electromechanical function adequate to support the systemic circulation must rapidly follow the ischemic interval. The need for inotropic support or mechanical support devices (e.g., intra-aortic balloon assist device, ventricular assist device) to wean the patient from cardiopulmonary bypass when support was not required preoperatively represents a failure of myocardial protection. Studies demonstrate that dopamine treatment of postischemic myocardial stunning induces apoptosis.¹⁰⁴ Nevertheless, despite meticulous adherence to known principles of myocardial protection, these events not infrequently and randomly occur and represent the limitations of present knowledge. Most investigators agree that the basic principles for adequate myocardial protection include (1) rapid induction of arrest, (2) mild or moderate hypothermia, (3) appropriate buffering of the cardioplegic solution, (4) avoidance of myocardial edema, and (5) avoidance of substrate depletion.¹⁰⁵⁻¹⁰⁷

Rapid Cardiac Arrest

Rapid cardiac arrest remains the mainstay of adequate myocardial protection and is “achieved by targeting various points in the excitation-contraction coupling pathway” (Fig. 65-6).¹⁰⁸ The induction of immediate cardiac arrest after the aorta has been clamped minimizes the depletion of high-energy phosphate moieties by useless mechanical work (Table 65-1). Potassium is the most common agent used for chemical cardioplegia and produces rapid diastolic arrest (Fig. 65-7). As the extracellular potassium concentration increases, the resting myocardial cell membrane becomes depolarized; the voltage-dependent fast sodium channel is inactivated, arresting the heart in diastole; and the slow calcium channel is activated, resulting in cytosolic calcium overload.^{109,110} The optimum concentration of potassium is thought to vary between 15 and 40 mmol/liter,¹¹¹ although

it has been suggested that concentrations exceeding 20 mmol/liter promote calcium overload and subsequent injury.¹¹² Because the heart will remain arrested until the concentration of extracellular potassium or other cardioplegic ingredient is decreased by noncoronary collateral mediastinal blood flow, reinfusions of cardioplegia are necessary every 15 to 30 minutes.¹¹³ Clinical studies indicate that despite the infusion of large volumes of hyperkalemic cardioplegic solution for complex procedures requiring prolonged ischemic times, serum potassium levels in patients with normal renal function rarely exceed 5.5 mEq/liter, because increased urinary excretion of potassium rapidly compensates for the endogenous administration of potassium.¹¹⁴

Agents inducing polarized arrest, in which the cell membrane potential remains close to resting potential, have significant advantages by limiting ionic movement and thereby reducing myocardial energy use.¹⁰⁸ Sodium channel blockade, which arrests the heart by preventing the rapid sodium-induced depolarization of the action potential, includes procaine¹¹⁵ and tetrodotoxin.¹¹⁶ This class of drugs has been used successfully experimentally but is rarely used clinically at present. Potassium channel openers induce arrest by membrane hyperpolarization, couple the membrane potential to the cellular metabolic status, and afford cardioprotection by a similar mechanism associated with ischemic preconditioning.¹¹⁷ Two potassium-adenosine triphosphate (K_{ATP}) channel subtypes have been shown to coexist in the myocardium; one subtype is located in the sarcolemma (sarc K_{ATP}) membrane and the other in the inner membrane of the mitochondria (mito K_{ATP}), and they can be pharmacologically manipulated by openers and blockers.^{106,118,119}

Potassium channel openers have been used in conjunction with hyperkalemic and magnesium-containing cardioplegic solutions, although their clinical use remains controversial.^{120,121} However, mitochondria-specific

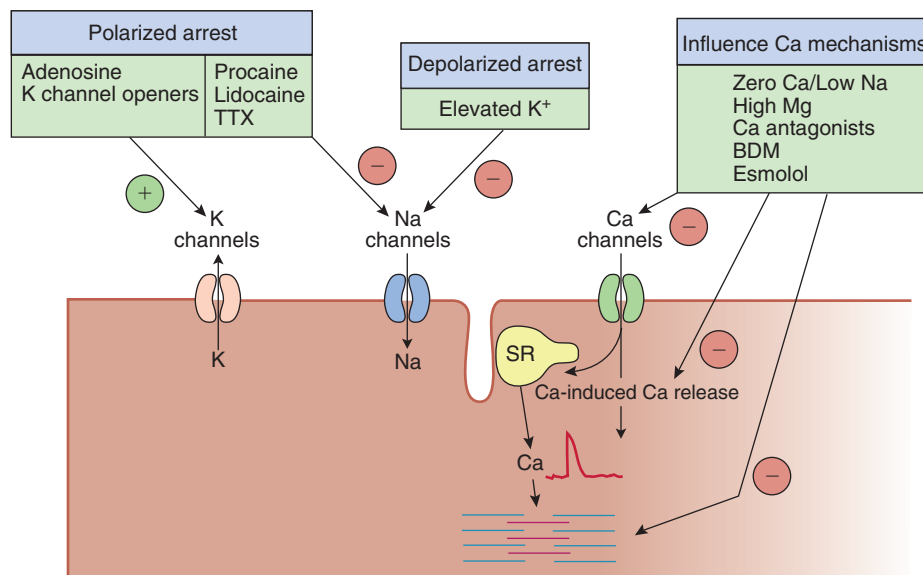


FIGURE 65-6 ■ Excitation-contraction coupling in depolarized and polarized arrest. Excitation-contraction coupling and the targets within this pathway are inhibited or activated by agents that induce depolarized arrest, polarized arrest, or arrest by influencing calcium mechanisms. BDM, 2,3-Butanedione monoxime; SR, sarcoplasmic reticulum; TTX, tetrodotoxin. (From Chambers DJ: Mechanisms and alternative methods of achieving cardiac arrest. *Ann Thorac Surg* 75:S661-S666, 2003.)

TABLE 65-1 Cardioplegia Solutions in Common Use

Depolarizing Cardioplegia Formulas

	Buckberg					HTK	del Nido	DSA	GIK	St. Thomas' I	St. Thomas' I	St. Thomas' II
	Adenosine	Induction	Maintenance	Reperfusion	Bretschneider							
K ⁺ (mmol/L)	16	16-20	8-10			9	13	12	80-100	20	20	16
KCl (2 mEq/mL) (mL)												
NaCl (mmol/L)						15						
Mg ⁺⁺ (mmol/L)	16			10		4	4	0.8		16	16	16
Mg ⁺⁺ (20%) (mL)												
Na ²⁺ (mmol/L)	117									144	142	117
Ca ²⁺ (mmol/L)	1.2									2.2	1.7	1.2
HCO ₃ ⁻ (mmol/L)	25						13			30-40		25
HCO ₃ ⁻ (8.4%) (mL)												
Citrate-phosphate-dextrose (mL)		225	50	50								
THAM (mmol/L)								2				
Tromethamine (300 mmol/L) (mL)		225	200	50								
Adenosine (mmol/L)	0.5											
Dextrose (50% in water) (mL)		40						2.7				
Dextrose (5% in water) (mL)		200	550									
Glucose (mmol/L)				1000					30-50			
Mannitol (20%) (mL)							16.3					
Mannitol (25%) (mL)				50					25-70			
Insulin (IU/L)										1	1	1
Procaine (mmol/L)	1											
Lidocaine (1%) (mL)												
Histidine (mmol/L)						180	13					
Histidine-HCl (mmol/L)						18						
Tryptophan (mmol/L)						2						
α-Ketoglutarate (mmol)						1						
L-Aspartate (mmol/L)		13										
L-Glutamate (mmol/L)		13										
Hematocrit (%)	10-12	20	20	20		10-12		10-12		10-12		10-12
pH	5.5-7.0	7.5-7.7	7.6-7.8	7.5-7.6		7.4	7.4	7.4		7.4		5.5-7.0
mOsmol	294	380-400	340-360	340-360		310	310	310		310-330		294
Blood: crystalloid	4:1	4:1	4:1	4:1		4:1	1:4	4:1		4:1		4:1
Infusion interval												
Infusion rate (mL/kg/hr)			15 min						0.75-1.5			
Volume (mL)												

DSA, Deaconess Surgical Association; GIK, glucose-insulin-potassium; HTK, histidine-tryptophan-ketoglutarate; THAM, Tris (hydroxymethyl) aminomethane hydrochloride. del Nido solution is in Plasma-Lyte A (Baxter Healthcare Corporation, Deerfield, IL) 140 mEq/L sodium, 5 mEq/L potassium, 3 mEq/L magnesium, 98 mEq/L chloride, 27 mEq/L acetate, and 23 mEq/L gluconate; pH 7.4.

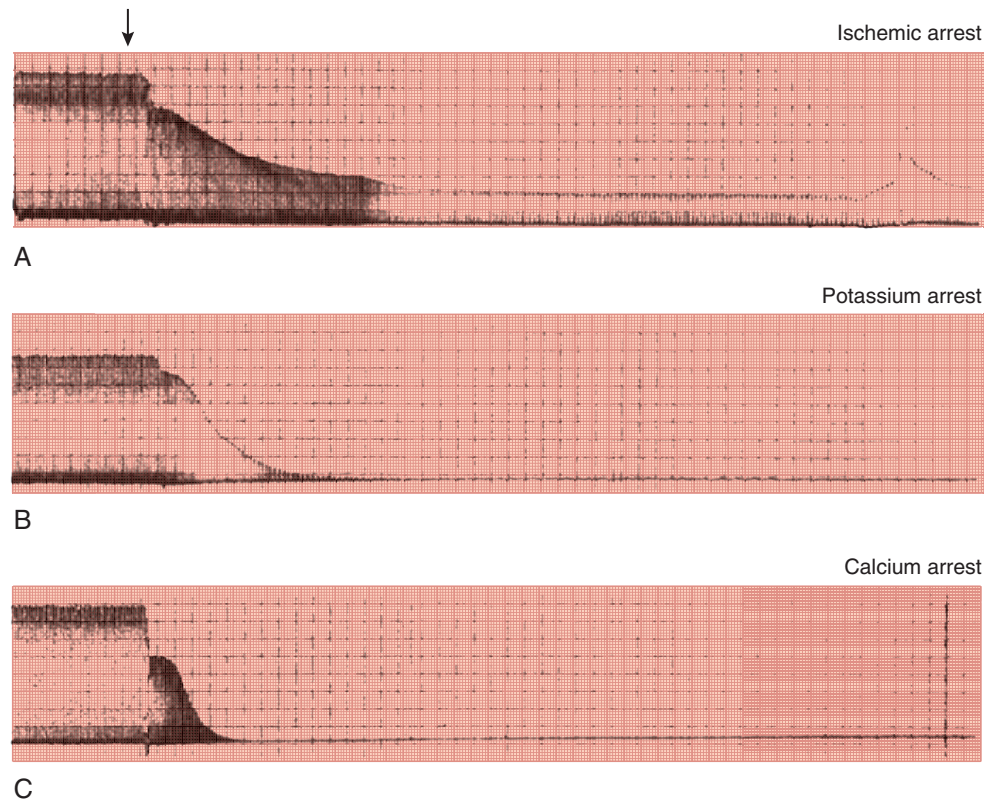


FIGURE 65-7 ■ The induction of cardiac arrest: **A**, by unmodified ischemia; **B**, by potassium cardioplegia; **C**, by calcium depletion. (From Hearse DJ, O'Brien K, Braimbridge MV: Protection of the myocardium during ischemic arrest. Dose-response curves for procaine and lignocaine in cardioplegic solutions. *J Thorac Cardiovasc Surg* 81:873–879, 1981.)

potassium channel openers, such as diazoxide, have been demonstrated to have potential benefits when they are used with magnesium-supplemented potassium cardioplegia.^{122,123}

Adenosine is an endogenous nucleoside formed as a consequence of the breakdown of high-energy phosphate and is rapidly phosphorylated by adenosine kinase to adenosine monophosphate and incorporated into the high-energy phosphorus pool or deaminated by adenosine deaminase, present in erythrocytes, to inosine, which is transported from the cell.¹²⁴ Extracellular adenosine is cleared through cellular uptake, primarily by erythrocytes and vascular endothelial cells, and has a reported half-life of less than 10 seconds in whole blood, which limits its use during a prolonged period of surgically induced ischemia.¹²⁵ Adenosine induces hyperpolarized cardiac arrest by antagonizing calcium channels and has been shown to inhibit both the sinoatrial and the atrioventricular nodes and atrial myocardial contraction.¹²⁶ Adenosine, by its ability to antagonize the direct depressant effects on both the sinoatrial and atrioventricular nodes and atrial tissue, results in sinus slowing and arrest. Clinically, adenosine has been used as a pretreatment before the initiation of cardiopulmonary bypass, when it has been shown to increase postoperative cardiac index and to reduce creatine kinase release¹²⁷; as an arresting agent by bolus infusion¹²⁸; and as an additive to potassium cardioplegia, when it reduces the time to arrest¹²⁹ and reduces potassium-induced cytosolic calcium overload.¹³⁰ It may also improve functional recovery when it is infused

during the reperfusion period.¹³¹ Compared with the acellular St. Thomas cardioplegic solution, the addition of adenosine appeared to enhance postoperative cardiac function in a series of patients undergoing coronary revascularization.¹³² Phase II studies suggest that adenosine may reduce postoperative complications,¹³³ although the results are open to question.¹³⁴ Nevertheless, additional clinical trials are suggested.¹³⁵

Hypothermia

Hypothermia, whether it is mild (tepid at the room temperature range of 28°C to 32°C) or moderate (22°C to 25°C), continues to remain an indispensable adjunct for adequate myocardial protection. As noted earlier (see [Historical Development](#)), hypothermia decreases the rate of the metabolic degradation of energy stores during surgically induced ischemia. In addition, experimental evidence shows a significant decrease of left ventricular MVO_2 of the heart in the beating nonworking, fibrillating, and arrested states at 22°C compared with a myocardial temperature of 37°C (Fig. 65-8).¹³⁶ However, there is minimal advantage in reducing the myocardial temperature below 22°C, because the MVO_2 is decreased by only a minimal amount, from 0.31 mL at 22°C to 0.27 mL at 15°C per 100 g of left ventricular tissue per minute.¹³⁷ Moreover, in the clinical setting, it is virtually impossible to maintain a uniform myocardial temperature below 22°C solely by the use of cold (4°C) intracoronary cardioplegia infusates accompanied by

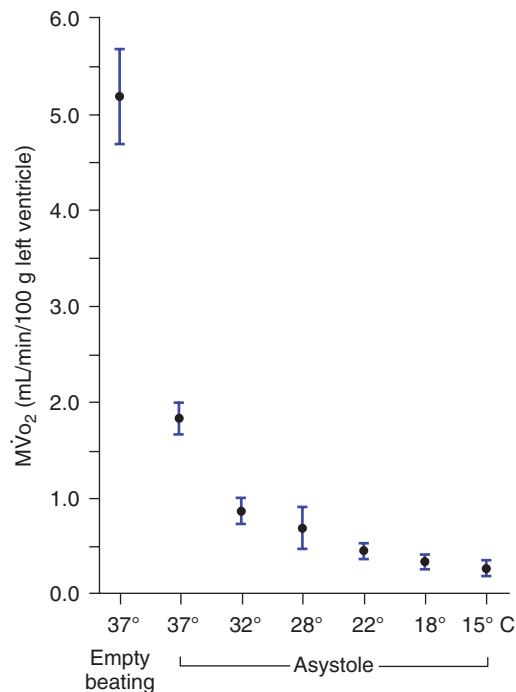


FIGURE 65-8 ■ Effects of hypothermia on myocardial oxygen consumption in the potassium-arrested dog heart. (From Chitwood WR, Sink JD, Hill RC, et al: The effects of hypothermia on myocardial oxygen consumption and transmural coronary blood flow in the potassium-arrested heart. *Ann Surg* 190:106–116, 1979.)

regional hypothermia, particularly in the presence of coronary obstructions, ventricular hypertrophy, and variations in mediastinal noncoronary collateral blood flow. In addition, the atrial and ventricular septa are warmed by systemic and pulmonary venous return, heat sinks such as the liver warm the base of the heart, and the anterior-situated right ventricle is warmed by the operative environment. Because of the lack of uniformity of myocardial temperatures in various myocardial segments, there is no correlation between myocardial tissue acidosis and temperature, leading to the recent abandonment by many surgeons of routine myocardial temperature monitoring during operative procedures.^{138,139}

Buffering of the Cardioplegic Solution

Buffering of the cardioplegic solution is necessary to combat the unremitting intracellular acidosis associated with surgically induced myocardial ischemia. Because the myocardium has the highest oxygen use of any organ in the body related to its concentration of mitochondria, ischemia results in the rapid accumulation of hydrogen ions and the reduction of intracellular pH, which has been quantified by the measurement of tissue PCO₂ and hydrogen ion with phosphorus P 31 nuclear magnetic resonance spectroscopy in the laboratory and a pH probe in the operating room.^{87,140} With the recent development of a myocardial tissue pH probe, there is clinical evidence that maintenance of the tissue pH of 6.8 or greater is associated with adequate myocardial protection (Fig. 65-9).¹⁴¹ Thus, frequent infusions of cardioplegia, every 15 to 20 minutes, are necessary to prevent intracellular

acidosis from reaching irreversible metabolic levels. In addition, hypothermia assists in the neutralization of acidosis because pH rises 0.0134 unit for each decrease in degree centigrade.¹⁴² However, the infusion of hypothermic cardioplegia does not restore pH_i to prearrest levels but rather prevents further deterioration of the pH. When intermittent warm blood cardioplegia is used, lengthening of the ischemic period progressively increases intracellular metabolic acidosis and is probably associated with increased injury during repeated episodes of normothermic arrest.^{143,144} Bicarbonate, phosphate, aminosulfonic acid, tris(hydroxymethyl)aminomethane (THAM), and histidine buffers have all been used as cardioplegia additives to modulate pH.

Avoidance of Myocardial Edema

Avoidance of myocardial edema by controlling osmolarity is important to control volume regulation of the fluid compartments of the heart because myocardial edema is a known consequence of ischemia.¹⁴⁵ The extent of myocardial edema has been shown to be directly modulated by osmolarity and onconicity of cardioplegia, with decreases being directly associated with increased myocardial edema and impaired diastolic filling.¹⁴⁶ Hypotonic cardioplegic solutions cause myocardial edema¹⁴⁷; hyperosmotic cardioplegia with an osmolarity in excess of 400 mOsm/liter has been shown to cause myocardial dehydration.¹⁴⁸ Isotonic solutions in the range of 290 to 330 mOsm/liter or slightly hyperosmolar solutions appear to have the greatest clinical use, which is of particular importance in dealing with acellular cardioplegic solutions.⁴⁰ Inert sugars including mannitol and sorbitol as well as metabolizable sugars such as glucose and dextrose have been used to increase osmolarity. However, when large volumes of continuous cardioplegia are administered, there is concern about producing hyperglycemia. Oncotic agents such as albumin and macromolecules, including dextrans and hydroxyethyl starches, have been used to prevent myocardial edema.¹⁴⁹ In addition to cardioplegic infusions, the hemodilution from crystalloid priming of the extracorporeal circuit, the activation of humoral and cellular mediators that increase microvascular permeability, and the impairment of myocardial lymphatic function may play major roles in the development of myocardial edema. Myocardial lymphatic function is dependent on the beating heart to transport fluid and is significantly reduced or completely stopped during cardiac arrest. Experimental evidence has indicated that during normothermic continuous antegrade blood cardioplegia, myocardial lymph flow is reduced to less than 20% of that in the normal beating heart.¹⁵⁰

ALTERNATIVE ARRESTING AGENTS AND ADDITIVES

Beta Blockers

As the ascending aorta is clamped, the non-exocytotic release of norepinephrine from the cardiac sympathetic nerves acts on β-adrenergic receptors on the outer surface

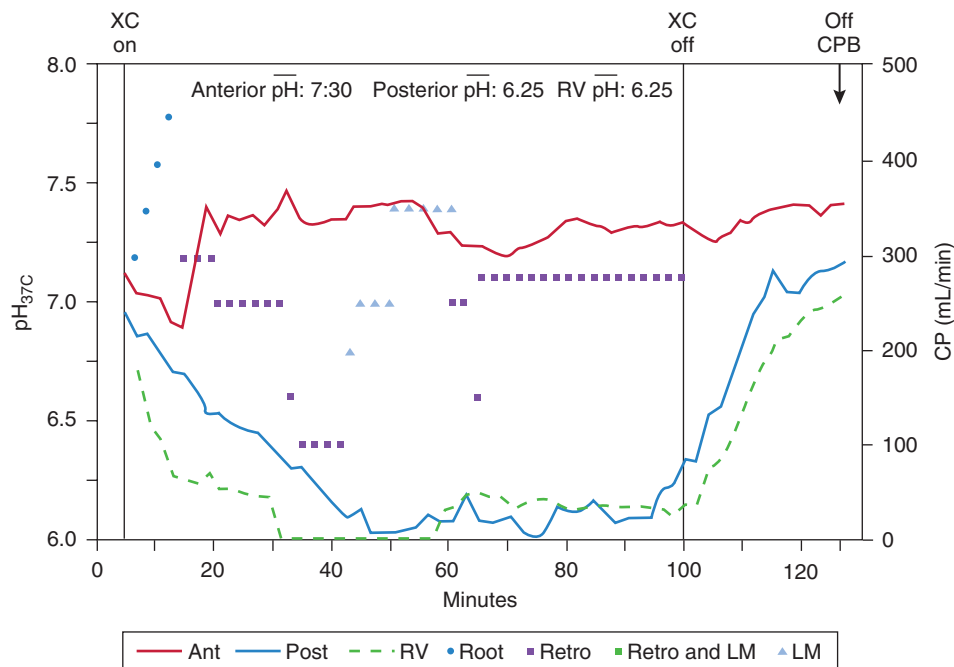


FIGURE 65-9 ■ pH and myocardial protection. pH (37°C) tracing in the left ventricular wall in a 67-year-old man undergoing complex aortic valve replacement. Measurements were obtained from three sites: anterior left ventricular (LV) wall, posterior LV wall, and anterior right ventricular (RV) wall. pH_{37C} reached a low of 6.0 in the posterior LV wall and 5.8 in the RV wall. This marked discrepancy between anterior and posterior wall pH_{37C} occurred in the face of continuous delivery of blood cardioplegia at high rates, mostly through the coronary sinus. Delivery of cardioplegic solutions through the ostium of the left main (LM) alone, through the coronary sinus alone, or simultaneously through the LM and coronary sinus failed to reverse the fall in pH_{37C} in the posterior LV and anterior RV walls. Integrated mean pH_{37C} during the period of aortic clamping was 7.30 in the anterior LV wall, 6.2 in the posterior LV wall, and 6.05 in the anterior RV wall, indicating poor protection of the posterior LV wall and anterior RV wall. The patient had to be defibrillated three times and required significant inotropic support to be weaned from cardiopulmonary bypass (CPB). He continued to require inotropic support for 24 hours postoperatively. CP, Cardioplegia; XC, cross-clamping. (From Khuri SF, Josa M, Marston W, et al: First report of intramyocardial pH in man: II. Assessment of adequacy of myocardial preservation. *J Thorac Cardiovasc Surg* 86:667–678, 1983.)

of the sarcolemma, causing an increase in cAMP-dependent protein kinase activity, phosphorylation of the calcium release channels, and increased Ca²⁺ influx, resulting in increased Ca²⁺-dependent contractility and rapid depletion of glycogen stores.¹⁵¹ Early studies suggested that long-acting beta blockers improved myocardial protection during ischemia but unfortunately have a prolonged negative inotropic effect, which limits their clinical use.¹⁵² For the most part, beta blockers such as propranolol have been used as an adjunct to anesthesia to block β-adrenergic-stimulating episodes associated with coronary ischemia during the course of the operative procedure. Ultra-short-acting cardioselective beta blockers such as landiolol and esmolol provide polarized cardiac arrest by maintaining the membrane potential at or near the resting membrane potential.¹⁵³ The cardioselectivity of these agents is 50 to 250 times that of propranolol, and the half-life of esmolol is only 9 minutes because it is rapidly hydrolyzed by red blood cell esterase.¹⁵⁴ Esmolol has been used to enhance myocardial protection during intermittent arrest¹⁵⁵ and has been shown to provide myocardial preservation equivalent to or better than cold crystalloid or blood cardioplegia.^{156–158} With esmolol cardioplegia, there is a slow undulating ventricular contraction that may decrease myocardial edema but does not provide a quiescent operating field.

Adenosine-lidocaine (adenocaine) cardioplegia provides an exciting alternative to depolarizing cardioplegia.¹⁵⁹ Adenosine-lidocaine cardioplegia has been shown to provide a shorter time to electromechanical arrest, greater postischemic recoveries of aortic flow, a lower coronary vascular resistance during infusion, and greater MVO₂ as compared to St. Thomas' Hospital solution, while maintaining the myocardial cell membrane potential at its resting state.¹⁶⁰

Agents Affecting Calcium Transport

The infusion of calcium-free cardioplegic solutions induces rapid diastolic cardiac arrest by inhibiting excitation-coupling and increases permeability of the sarcolemma.¹⁶¹ When a calcium-containing perfusate is then reinfused, during reperfusion, there is a rapid influx of calcium into the cell, resulting in myocardial contracture and extensive ultrastructural damage, the "calcium paradox."^{162,163} Nevertheless, hypocalcemic cardioplegic solutions have been used during hypothermic arrest to prevent ischemic contracture and necrosis.¹⁶⁴ Calcium antagonist agents administered before ischemia have been proposed as a possible mechanism to reduce ischemic cellular injury. Calcium channel blocking agents, including verapamil, diltiazem, and nifedipine, prevent

calcium-induced calcium release in myocardial cells and, as an adjunct to normothermic cardioplegia, have been shown to improve postischemic systolic function.¹⁶⁵ Calcium blockers have no effect if they are administered before reperfusion, are temperature dependent, and have limited effect during hypothermia. Because high concentrations are required for cardioprotection, their prolonged membrane binding prevents rapid recovery, thus limiting their clinical usefulness.

Magnesium inhibits calcium entry into the cell by displacing calcium from its binding sites in the sarcolemmal membrane.^{166,167} It has limited use as an arresting agent because high concentrations are required, cardiac arrest is delayed, and postischemic functional recovery is decreased in comparison to potassium cardioplegia.² The advantages of magnesium have been shown to be optimal when it is included with high-potassium cardioplegia, in which it has been demonstrated to ameliorate cytosolic, nuclear, and mitochondrial calcium accumulation; preserve high-energy phosphate moieties; and enhance postischemic functional recovery.^{168,169}

Avoidance of Substrate Depletion

Metabolic substrates have been added to cardioplegic solutions to enhance anaerobic metabolism during ischemia or to provide citric acid cycle intermediaries to facilitate homeostasis during reperfusion. Agents used include glucose and insulin^{170,171}; nucleosides,¹⁷² such as adenosine,¹⁷³ aspartate, and glutamate¹⁷⁴; and L-arginine to stimulate nitric oxide production.¹⁷⁵ Although metabolic substrate enhancement has been used in various clinical situations, none has achieved universal adoption.

CRYSTALLOID (ACELLULAR) AND BLOOD CARDIOPLEGIA

Crystalloid Cardioplegia

With the advent of myocardial protection, asanguineous solutions composed of varying electrolyte compositions, but always featuring hyperkalemic diastolic arrest, were clinically used in Europe^{17,30,32} in the early 1970s and in the United States^{38,39} in the late 1970s. However, these solutions contained minimal amounts (0.6 mL/100 mL at a PO₂ of 100 mm Hg at a temperature of 10°C) of dissolved oxygen, whereas the myocardium consumes 0.33 mL of oxygen per 100 g at 15°C. Because even a short period of ischemia results in the gradual accumulation of oxygen debt, moderate to severe myocardial hypothermia is necessary to prevent the rapid degradation of energy stores (Fig. 65-10).^{38,176} To overcome the oxygen deficit issue, oxygenation of crystalloid cardioplegia has been clinically used and has demonstrated a decrease in creatine kinase MB levels in patients when the cross-clamping time exceeded 29 minutes compared with a group of patients who received unoxygenated cardioplegia.¹⁷⁷ Nevertheless, subsequent clinical studies with unoxygenated crystalloid documented significant decreases in rates of operative mortality and perioperative myocardial infarction

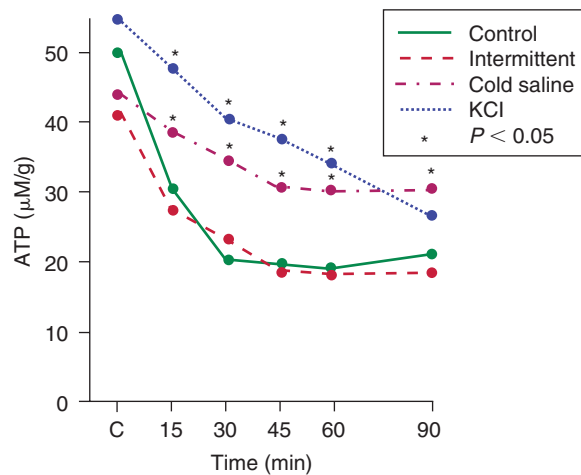


FIGURE 65-10 ■ High-energy phosphates. Adenosine triphosphate (ATP) values during aortic cross-clamping (60 min) and reperfusion (30 min) for control (no treatment), intermittent reperfusion (15-min cross-clamping and 5-min reperfusion), regional hypothermia, and potassium (KCl) cardioplegia. (From Wright RN, Levitsky S, Rao KS, et al: Potassium cardioplegia: an alternate method of myocardial protection. *Arch Surg* 113:976-980, 1978.)

for coronary artery surgery, as demonstrated by the large Collaborative Study in Coronary Artery Surgery.¹⁷⁸ For the most part, most groups at that time, including our own, used Ringer solution (sodium chloride, 147.3 mmol/liter; potassium, 4.02 mmol/liter; and calcium chloride, 2.25 mmol/liter) to which was added 24 mmol/liter of potassium chloride to effect a total dose of 28 mmol/liter, 7 g/liter of glucose, and 0.8 mL of THAM.¹⁷⁹ The resultant solution had an osmolarity of 375 mOsmol/liter and a pH of 7.42 at 37°C. The classic St. Thomas' solution differed by having a lower concentration of potassium chloride, 19.59 mmol/liter, and added 15.90 mmol/liter of magnesium chloride and 1 mmol/liter of procaine hydrochloride.¹⁸

Clinical steps for myocardial protection with use of crystalloid cardioplegia include the following.

1. Before the onset of surgery, the operating room temperature is cooled to 63°F to 65°F (17°C to 19°C) to avoid warming of the anterior surface of the heart by convection and radiation from high-intensity lighting.
2. Cardiopulmonary bypass is initiated at a temperature of 28°C. A cannula is placed in the ascending aorta proximal to the aortic root for the antegrade infusion of cardioplegic solution and for the removal of air after the clamp is removed from the ascending aorta and as the patient is weaned from bypass.
3. A myocardial electrocardiographic lead and temperature probe are placed on the anterior wall of the right ventricle because it constitutes two thirds of the anterior surface of the heart, and its rewarming during surgically induced ischemia may partially explain the occasional observation of selective right ventricular failure after the termination of bypass.¹⁸⁰ In addition, an insulation pad is placed in the posterior pericardial sac and along the left ventricular lateral wall to protect the left phrenic nerve

from thermal injury associated with regional hypothermia and to prevent rewarming of the heart from heat sinks (i.e., liver).

4. The systemic perfusate temperature is temporarily decreased to 10°C to 15°C to “precool” the heart (infusion hypothermia), and iced saline slush is placed into the pericardial sac to achieve rapid myocardial cooling. Transient periods of ventricular fibrillation during this period of initial cooling appear to have no adverse effects.
5. When a myocardial temperature of 28°C is reached, the ascending aorta is cross-clamped and cold crystalloid cardioplegia solution at a temperature of 5°C is infused into the aortic root at a pressure not exceeding 90 mm Hg. The initial volume has been empirically determined to be 10 mL/kg body weight. The myocardial temperature rapidly decreases to 10°C to 15°C, and asystole usually occurs within 10 to 15 seconds.
6. At the termination of the initial cardioplegic infusion, the systemic temperature is elevated to 20°C, and the systemic perfusion flow rate is decreased from 2.2 to 1.5 liter/min/m². In this manner, the collateral aortocoronary and bronchopulmonary blood flow is kept cold, and the lowered systemic perfusion pressure prevents rapid dilution and washout of the cardioplegic solution. Every 15 to 20 minutes, or earlier if there is an increase in myocardial temperature above 20°C or if there is any electrocardiographic activity or observed ventricular motion, the solution is reinfused at a volume of 5 mL/kg.
7. Five minutes before removal of the aortic clamp, the systemic perfusate temperature is raised to 30°C, and flow is increased to 2.2 liter/min/m². After the aortic cross-clamp is removed, the perfusate temperature is raised to 38°C and the room temperature is raised to 25°C to 30°C. Cardiopulmonary bypass is continued until the esophageal temperature is 37°C and the rectal temperature is in the range of 35°C to 37°C. Rewarming is usually necessary in the early postoperative period.

The major disadvantage of this technique is the extensive rewarming period, which may exceed 30 to 45 minutes. Nevertheless, this prolonged period on bypass allows the restabilization of metabolic inequities and the subsequent smooth weaning from bypass. Evidence includes clinical reports of the safe use of crystalloid cardioplegia for periods exceeding 150 minutes.¹⁸¹ However, clinical studies evaluating myocardial metabolism and ventricular function indicate that cold crystalloid cardioplegia results in slow recovery of myocardial metabolism and a poor response to postoperative hemodynamic stress.¹⁸² Although most surgeons in the United States have switched to blood cardioplegia techniques, many groups throughout the world continue to use crystalloid cardioplegia and to obtain excellent outcomes.

Blood Cardioplegia

In an attempt to avoid the oxygen deficits associated with crystalloid cardioplegia, blood was introduced as a

suitable vehicle to obtain optimum oxygenation.^{183,184} Alternative methods of increasing oxygenation, including oxygenated crystalloid,¹⁷⁷ fluorocarbons,⁷⁶ and stroma-free hemoglobin,¹⁸⁵ have never achieved significant clinical use. Moreover, experimentally, blood cardioplegia has been demonstrated to be superior to oxygenated crystalloid cardioplegia (Fig. 65-11).⁴⁸ In addition to the enhanced ability to exchange oxygen and carbon dioxide, the physiologic advantages of blood include the buffering and reducing capacity, the presence of colloid to avoid adverse oncotic pressure gradients, and the presence of oxygen free radical scavengers.¹⁸⁶ In addition, blood and albumin-containing crystalloid cardioplegia solutions have been shown to preserve microvascular responses compared with crystalloid cardioplegia.¹⁸⁷ However, concerns associated with cold blood cardioplegia include (1) the hypothermic shift to the left of the oxyhemoglobin dissociation curve, thereby reducing the release of oxygen at the tissue level; (2) the experimental evidence that blood cardioplegia may not protect the myocardium at low temperatures¹⁸⁸; and (3) the potential of hypothermia-induced sludging and red cell rouleau formation. Other studies have demonstrated that hypothermia at 5°C to 10°C does not affect capillary flow¹⁸⁹ and that the viscosity of blood is not significantly affected by hypothermia unless the hematocrit is greater than 50%,¹⁹⁰ which would be unlikely because during bypass, hemodilution maintains the hematocrit in the 20% to 25% range. Numerous experimental and clinical studies have advocated the superiority of either crystalloid or blood cardioplegia, without arriving at a definitive conclusion.¹⁹¹⁻¹⁹⁵

The ratio of blood to crystalloid in formulating the blood cardioplegic solution has undergone progressive change since the initial clinical introduction of this technique. The early blood cardioplegia solutions used a ratio of four parts blood to one part crystalloid (4:1) as hemodiluted blood was withdrawn from the perfusion circuit and mixed with a crystalloid solution containing citrate-phosphate-dextrose to lower ionic calcium, THAM for buffering, and potassium adjusted to produce a concentration of 20 to 30 mmol/liter to induce diastolic arrest. Experimental studies demonstrated that a hematocrit as low as 9% provided sufficient oxygen transport at hypothermic levels of 5°C to 10°C (Fig. 65-12).¹⁹⁶⁻¹⁹⁸ To avoid excessive hemodilution associated with administration of large volumes of cardioplegia solution, leading to dilutional coagulopathy, the blood-to-crystalloid ratio has been gradually increased from 4:1 to 8:1. This change has also been accompanied by increased use of tepid and warm cardioplegic techniques; the associated higher temperatures require a higher hematocrit to achieve oxygen transport to support myocardial metabolism. Miniplegia, or whole blood cardioplegia using minimal amounts of potassium and magnesium to achieve arrest, avoids the problem of hemodilution, eliminates concerns about buffering, and avoids pharmaceutical costs.¹⁹⁹ Although experimental studies have not shown any significant advantage in reperfusion myocardial edema in comparing miniplegia with 4:1 blood cardioplegia, the comparative hematocrits of 12% ± 2% and 7% ± 1%, respectively, used in this study are not in the clinical range of 22% to 25% for miniplegia, which may have adversely affected

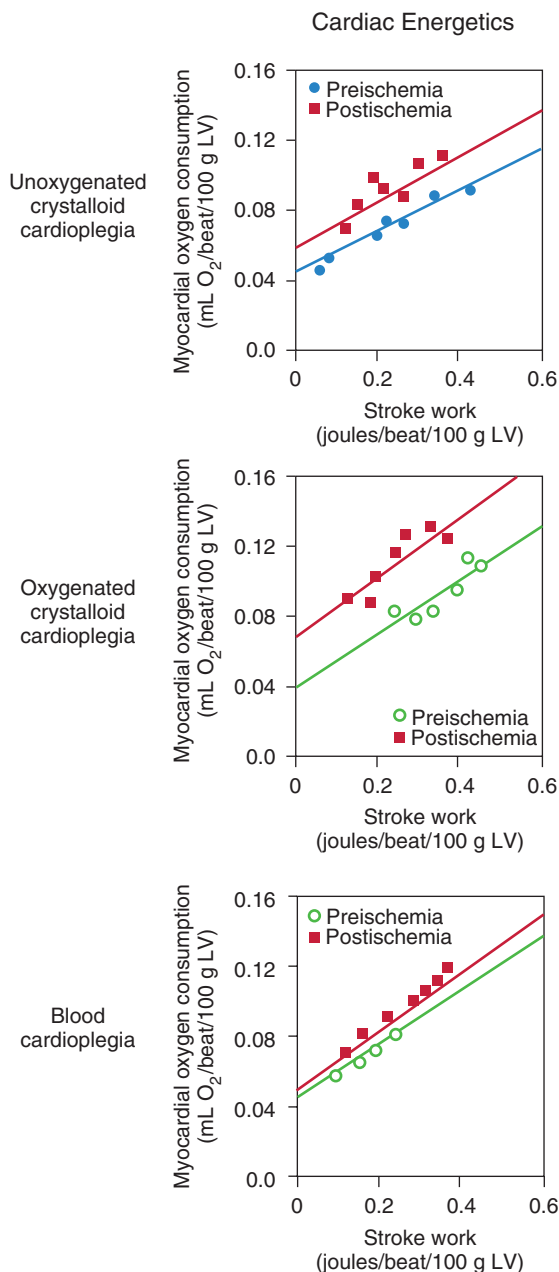


FIGURE 65-11 ■ Myocardial oxygen consumption and stroke work. Energetic plots of myocardial oxygen consumption versus stroke work before (preischemia) and after (postischemia) unoxxygenated crystalloid cardioplegia, oxygenated crystalloid cardioplegia, and blood cardioplegia. Postischemic myocardial oxygen consumption versus stroke work relationships were significantly increased with both unoxxygenated crystalloid cardioplegia and oxygenated crystalloid cardioplegia arrest; in blood cardioplegia, the preischemia and postischemia myocardial oxygen consumption versus stroke work relationships were superimposable. LV, Left ventricle. (From Krukenkamp IB, Silverman NA, Levitsky S: The effect of cardioplegic oxygenation on the correlation between linearized Frank-Starling relationship and myocardial energetics in the ejecting postischemic heart. *Circulation* 76[5 Pt 2]:V122-V128, 1987.)

the results.²⁰⁰ However, in a clinical study comparing miniplegia with standard 4:1 blood cardioplegia, there was significantly greater $\dot{M}V\text{O}_2$, lower lactate release, and better postoperative left ventricular function in the miniplegia group.²⁰¹ Others have demonstrated decreased

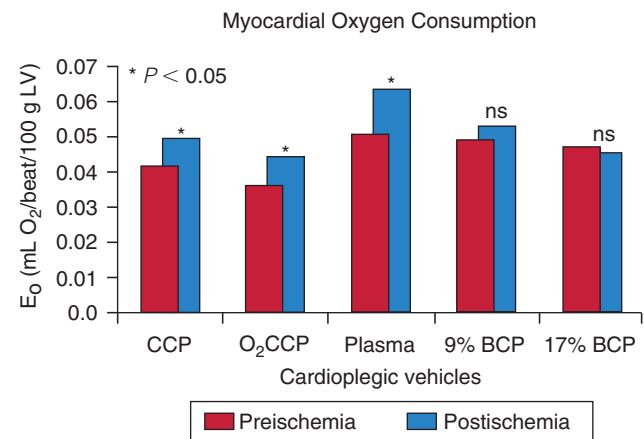


FIGURE 65-12 ■ Oxygen use and hematocrit concentration. The increased postischemic oxygen use for maximally unloaded contraction (E_0) can be prevented by having a critical red cell mass in cardioplegic solution. This salutary effect of red blood cells cannot be accounted for solely by their oxygen-carrying capacity, as oxxygenated crystalloid and plasma solutions did not have similar efficacy. BCP, Blood cardioplegia with hematocrit of 9% and 17% volume; CCP, crystalloid cardioplegia; LV, left ventricle; ns, not significantly different; O_2CCP , oxxygenated crystalloid cardioplegia. (From Silverman NA, Del Nido P, Krukenkamp I, et al: Biologic rationale for formulation of antegrade cardioplegic solutions. In Chitwood WR, editor: *Cardiac surgery: state of the art reviews*, Philadelphia, 1988, Hanley & Belfus, pp 181-195.)

postoperative inotropic use with miniplegia compared with 4:1 blood cardioplegia, suggesting a decrease in postoperative stunning.²⁰²

Del Nido cardioplegia techniques used with neonates relies on the concept that anaerobic glycolysis produces high-energy phosphates during ischemia. The cardioplegia solution is administered as a single dose, using dilute blood in a 1:4 ratio, and uses histidine as a proton buffer, glucose as a substrate, low sodium and calcium concentrations and lidocaine for depolarization to limit sodium influx by blocking the window current.^{203,204} Recent studies suggest that del Nido solution may also be useful in the senescent heart.²⁰⁵

Methodologies

Cardioplegia Temperature. The debate regarding the appropriate cardioplegia temperature has shifted from the classic cold (5°C to 10°C) to warm (37°C) in the recent past and to tepid (28°C to 32°C) at present. Warm heart surgery assumes that aerobic arrest, whereby the heart is electromechanically arrested and continuously perfused with warm blood cardioplegia, is the ideal state for the performance of safe cardiac surgery.^{206,207} The apparent advantages of this technique include the presumed elimination of anaerobic ischemic injury with cross-clamp times safely extended up to 6.5 hours²⁰⁸; the early resumption of a normal sinus rhythm after removal of the aortic clamp; the avoidance of a prolonged rewarming and reperfusion time, thus decreasing total bypass time; and the elimination of systemic hypothermia and associated vasoconstriction in the early postoperative period. However, difficulties in visualization of the operative field, particularly in performing distal coronary anastomoses, mandated temporary discontinuation of the

warm cardioplegic infusion, resulting in ischemic injury if the ischemia time exceeded 15 minutes.¹⁴⁴ Additional problems include (1) ischemic injury when antegrade warm blood cardioplegia cannot be delivered homogeneously in the presence of aortic insufficiency and left main coronary ostial stenosis,²⁰⁹ (2) difficulties in maintaining complete electromechanical arrest, (3) the need for vasoconstrictive alpha agonists during bypass to maintain adequate perfusion pressure because of severe systemic vasodilation,²¹⁰ and (4) the risk of neurologic events related to cardiopulmonary bypass and associated microemboli, which is exacerbated if the brain is not cooled.²¹¹ Nevertheless, warm heart surgery offered the promise to resuscitate ischemically jeopardized myocardium during the course of the operative procedure.²¹² In addition, late results of the Warm Heart Trial demonstrated that late survival at 6 years was not significantly greater in the warm cardioplegia patients compared with the cold cardioplegia group and was significantly reduced in the group with nonfatal perioperative events.²¹³

Tepid (29°C) cardioplegia was introduced as a means of overcoming the deficits of warm cardioplegia, without the adverse effects of cold cardioplegia. In a series of clinical studies, Hayashida and coworkers²¹⁴ demonstrated that reducing the cardioplegia temperature from 37°C to 29°C did not alter MVO_2 , reduced anaerobic lactate and acid release during arrest, and preserved myocardial function. Further postoperative cardiac function enhancement was obtained with a combination of intermittent antegrade and continuous retrograde tepid cardioplegia.²¹⁵ In a series of low-risk patients undergoing coronary artery bypass, no difference in cardiac troponin release was found when comparing warm and tepid cardioplegia.²¹⁶

Delivery Systems. Numerous clinical studies have documented the efficacy of various cardioplegia delivery systems and perfusion intervals. All of these reports suffer from the variability in disease (e.g., extent of ischemic or fibrotic myocardium and the variation in segmental coronary disease) as well as the lack of prospective head-to-head comparisons of large numbers of patients. All of these issues contribute to the wide variety of empirical clinical choices. Antegrade administration of cardioplegia, by use of a catheter or needle, in the ascending aorta has been the initial, traditional approach. Difficulties include (1) rupture of an atherosclerotic plaque at the insertion site, resulting in either microemboli or aortic dissection; (2) aortic insufficiency, resulting in ventricular dilation and inadequate flow into the coronary arteries; (3) left main ostial, occlusive, and variable coronary artery obstructions, leading to cardioplegic maldistribution; and (4) enlargement of the catheter-induced aortic opening at the insertion site, particularly in association with a thin-walled aorta related to poststenotic aortic dilation.

Retrograde perfusion of the coronary sinus, initially described by Pratt,²¹⁷ was first used clinically by Lillehei and colleagues²¹⁸ during the early days of open heart surgery to protect the heart during aortic valve replacement. Interest was renewed with this technique after Menasché and associates²¹⁹ reported improved outcomes for aortic valve replacement, prompting numerous studies

on the anatomy and physiology of the coronary sinus.²²⁰ Although most clinicians use direct cannulation of the coronary sinus with a balloon-tipped catheter, Fabiani and coworkers,²²¹ in a series of clinical studies, suggested infusion into the pressurized right atrium (obtained by occluding the vena cava and main pulmonary artery) to impede shunting of the cardioplegic solution into the right atrium through the thebesian veins.

Major advantages of retrograde perfusion include (1) distribution of the cardioplegic solution to myocardial segments perfused by obstructed or occluded coronary arteries or the internal mammary artery during re-do coronary surgery; (2) avoidance of the need for direct coronary ostial cannulation, with its attendant traumatic injury and subsequent stenotic potential, in performing aortic root procedures; (3) ability to administer cardioplegia during mitral valve surgery without removal of the retractor; (4) ability to provide continuous cardioplegia; and (5) avoidance of debris and subsequent embolization from atheromatous vein graft material during re-do coronary surgery.

Problems associated with retrograde cardioplegia include (1) slowness in achieving diastolic arrest if it is used for the initial introduction of cardioplegia, (2) occasional difficulty in blind insertion of the catheter into the coronary sinus, (3) easy dislocation of the catheter into the right atrium despite the use of ribbed balloon-tipped catheters, (4) traumatic injury and perforation during insertion of the catheter and occasionally spontaneous rupture of the great cardiac vein in fragile older patients even with autoinflatable balloon-tipped catheters, and (5) inadequate perfusion of the right ventricle and posterior ventricular septum (Fig. 65-13).^{222,223} Major technical issues include the requirement to measure coronary sinus pressure constantly to avoid infusion pressures exceeding 30 mm Hg and never to exceed an infusion rate greater than 200 mL/min because venovenous anastomoses and shunts at higher flows will direct more than 60% of the potential "nutrient flow" into the ventricular cavities through the thebesian channels.^{224,225}

Descriptions of the simultaneous delivery of cardioplegia have been confused by variations in the definition

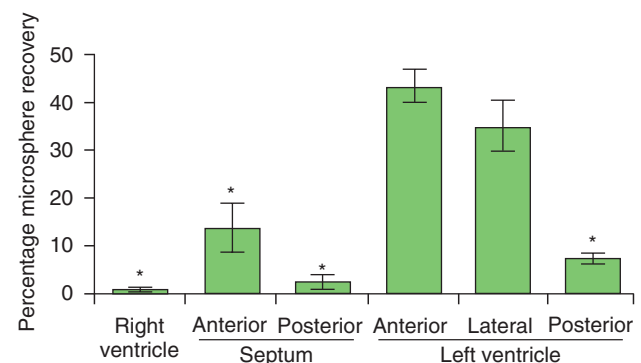


FIGURE 65-13 ■ Warm retrograde cardioplegia distribution. Percentage microsphere recovery according to anatomic site. Data are presented as the mean $\pm$ the standard error of the mean. The asterisk (*) denotes $P < 0.01$ versus the anterior left ventricle (post hoc Tukey test). (From Calderone CA, Krukenkamp IB, Misare BD, et al: Perfusion deficits with retrograde warm cardioplegia. *Ann Thorac Surg* 57:403–406, 1994.)

of the methodology. Most authors have avoided delivery of cardioplegia solution simultaneously into the coronary sinus and the aortic root to avoid excessive pressurization with subsequent injury to the coronary microvasculature and to allow rapid egress of the solution.²²⁶ Delivery of cardioplegia through the coronary sinus (retrograde) and concurrently antegrade through each completed vein graft by use of a manifold with multiple side arms and a single pump head, in association with venting of the aortic root, has been designated *combination delivery*.²²⁷ This technique has been especially useful after completion of all the distal anastomoses during coronary revascularization as the proximal anastomoses are being performed or during closure of the left atrium or aortotomy during valve surgery, and if it is performed at 37°C for approximately 20 minutes, it is essentially the first stage of reperfusion and allows the restoration of postischemic oxygen uptake to return to baseline levels.²²⁸ For the most part, most surgeons use all of these techniques, termed *integrated cardioplegia*, which involves antegrade, retrograde, and combination delivery systems in either a continuous or alternate manner, depending on the clinical circumstances.

Warm induction with warm oxygenated cardioplegia has been suggested as a means of achieving “active resuscitation” in energy-depleted hearts, before proceeding with maintenance cardioplegia by any means or temperature level.²²⁹ Whether 5 minutes is sufficient time to reverse the adverse biochemical effects of depleted high-energy phosphate stores remains open to question, although functional experimental studies demonstrate improvement.²³⁰

Terminal warm blood cardioplegia (“hot shot”) for 3 to 5 minutes before aortic unclamping has been experimentally and clinically demonstrated to improve post-bypass ventricular performance after cold maintenance blood cardioplegia.^{231,232} However, a controlled trial of terminal warm cardioplegia for 5 minutes versus simple reperfusion did not demonstrate any advantage.²³³ As with warm induction, the question of whether 3 to 5 minutes of warm blood reperfusion is sufficient to restore energy stores is open to question. To overcome this deficit, combination blood cardioplegia delivery may be the preferred approach with a better chance of restoring energy stores. On occasion, prolonged terminal warm cardioplegia may lead to intracellular potassium accumulation with resultant reperfusion asystole during the early reperfusion period and requires temporary ventricular pacing to wean the patient from bypass.²³⁴ Secondary cardioplegia, which involves rearresting the heart for a prolonged period (more than 20 minutes) of warm cardioplegia, is an extension of the concept of terminal warm cardioplegia and may be useful in patients difficult to wean from bypass or with uncontrolled arrhythmias.^{235,236}

Clinical steps for myocardial protection with use of blood cardioplegia include the following.

1. Hypothermia at the initiation of cardiopulmonary bypass is avoided, and both the perfusate and the cardioplegia temperature are allowed to equilibrate with room temperature (tepid, at approximately 29°C).
2. As the ascending aorta is cross-clamped, whole blood (miniplegia) antegrade cardioplegia is infused into the aortic root at a rate of 100 to 200 mL/min at an aortic root pressure of 90 mm Hg. A potassium concentration of 28 to 30 mmol/liter is initially used until diastolic arrest occurs, and then the potassium concentration is gradually dialed down until the lowest concentration (usually 3 to 5 mmol/liter) that will maintain arrest is achieved. After 5 mL/kg is administered antegrade, an additional 5 mL/kg is administered retrograde.
3. The occluded or most severely stenosed coronary vessel is bypassed first.
4. After each vessel is bypassed, cardioplegia, 5 mL/kg, is infused simultaneously down the conduits in an antegrade direction and the retrograde cannula by use of a single pump head with a multiport manifold.
5. After completion of the last bypass graft, systemic perfusate and cardioplegia rewarming is initiated. The proximal bypass grafts are inserted on the ascending aorta as blood is aspirated from the aorta to maintain a level of blood just below the opening in the aorta to avoid obscuring the operative field.
6. As the last proximal anastomosis is completed, potassium is discontinued in the retrograde infusion, and whole blood is infused to wash out potassium. Air is evacuated from the aorta and ventricles as the heart starts to contract, and the clamp is removed from the aorta.
7. After hemostasis is confirmed, cardiopulmonary bypass is discontinued. If the heart remains in asystole, temporary atrial and ventricular pacing is instituted.

PRE-, POST-, AND REMOTE CONDITIONING

Ischemic Preconditioning

Ischemic preconditioning (IPC), first described by Murry and coworkers,²³⁷ is an adaptive response of endogenous myocardial protection, in which the imposition of one or more brief periods of sublethal ischemia (3 to 5 minutes) followed by reperfusion protects the heart such that injury manifested by infarct size, apoptosis, and reperfusion-associated arrhythmias is significantly reduced during a subsequent period of sustained ischemia.²³⁸ Numerous studies have indicated that IPC, in a species-dependent manner, is associated with the preservation of creatine phosphate, ATP, and intracellular pH; decreased ultrastructural abnormalities; induction of heat-shock proteins; increased release of adenosine and activation of the adenosine receptors; activation of G proteins; and activation of protein kinase C.²³⁹ The effects of ischemic IPC are bimodal, occurring in two phases: an early phase and a delayed late phase or “second window” of cardioprotection. In the early phase, the protective effects of IPC are transitory, with infarct limitation being lost if the subsequent sustained ischemic insult is delayed beyond 30 to 120 minutes.²⁴⁰ Approximately 24 to 96

hours after the induction of IPC, a second window of less potent cardioprotection occurs in which the infarct protection is reestablished.^{241,242}

Collateral evidence exists to suggest that IPC may occur in patients undergoing balloon angioplasty²⁴³ or may be elicited by the trauma associated with the onset of cardiopulmonary bypass.²⁴⁴ Yellon and coworkers²⁴⁵ have shown that in patients on cardiopulmonary bypass, the use of IPC (two 3-minute periods of ischemia and 2 minutes of reperfusion) before 10 minutes of ischemia significantly preserved ATP measured during the initial reperfusion period. Additional studies also reported that the use of IPC in coronary artery bypass graft surgery significantly decreased troponin T levels at 72 hours compared with cold crystalloid St. Thomas' cardioplegia solution; no comparison with conventional blood cardioplegia was performed.²⁴⁶ Others have reported that either IPC provided no benefit compared with cold blood cardioplegia, because cardiopulmonary bypass per se induces preconditioning,^{244,247} or its use was deleterious in human cardiac surgery.^{248,249}

The use of IPC in off-pump coronary artery bypass grafting also is controversial. Laurikka and colleagues,²⁵⁰ in a randomized, controlled study, induced IPC by occluding the left anterior descending coronary artery with a silicon tape placed proximal to and distal to the site of the anastomosis for two cycles of 2 minutes of occlusion and 3 minutes of reperfusion; the IPC group had a significantly increased recovery of the mean stroke volume index with a significant decrease in mean heart rate on the first postoperative day and a significantly lower cardiac troponin I level compared with controls. Others²⁵¹ using similar protocols found no statistically significant differences between the IPC and control groups.

Remote ischemic preconditioning (RIPC), defined as transient ischemia and reperfusion in a tissue or organ remote from the heart (e.g., the extremities), has been demonstrated to protect the heart after surgically induced myocardial ischemia in both children and adults by decreasing postoperative serum troponin T release^{252,253} by protecting mitochondrial integrity.²⁵⁴ The mechanisms through which RIPC provides cardioprotection are believed to involve possible neural and humoral pathways or systemic responses that interact with known IPC effectors.²⁵⁵ In a large ($N = 332$) clinical study using peak 24-hour troponin I level as the primary outcome measure, Carrasco-Chinchilla et al²⁵⁶ reported no differences between remote preconditioning and control groups and reported that it was harmful in diabetic patients. However, in a well-controlled randomized clinical trial, others²⁵⁷ demonstrated RIPC reduced perioperative myocardial injury as measured by cardiac troponin I, increased survival, and lowered cardiac and cerebrovascular events. Additionally, a meta-analysis of 19 randomized trials involving 1235 patients undergoing cardiac surgery, demonstrated decreased cardiac troponin I levels in patients subjected to RIPC.²⁵⁸

Postconditioning

The induction of postconditioning occurs during the initiation of reperfusion rather than before index sublethal

ischemia, thus improving clinical usefulness.^{259,260} Various algorithms involving different reperfusion-ischemia and reperfusion times and sublethal index ischemia and reperfusion times have been formulated. The postconditioning algorithm consists of repeated ischemia and reperfusion episodes, resulting in an interrupted or stuttering reperfusion that ameliorates the effects of reperfusion injury.²⁶¹ The efficacy of postconditioning in a clinical setting has not met with as much success as in animal models and more study has been suggested to allow for clinical efficacy.²⁶² In human studies using percutaneous coronary intervention for acute ST-segment elevation myocardial infarction, postconditioning has been shown to be efficacious in reducing myocardial cell injury.^{263,264}

There is also controversy about the use of IPC in female patients and older adults. Previous studies have shown that young women have a greater resistance to myocardial ischemic injury and that this resistance is lost after menopause.^{265,266} Others have shown in the rodent model that IPC is less effective in the female than in the male.²⁶⁷ These differences are the result of differences in hormonal mediation of threshold stimulation, and the stimulus for IPC may need to be prolonged (i.e., prolonged initiating ischemic event) to achieve cardioprotection similar to that in males.²⁶⁸ In older adult hearts, IPC is less effective in ameliorating myocardial injury than in the mature heart.^{266,269}

SODIUM-HYDROGEN EXCHANGERS

Sodium-hydrogen exchangers (NHEs) play a central role in the regulation of intracellular sodium and calcium concentrations, pH homeostasis, and volume regulation by facilitating the electroneutral exchange of intracellular hydrogen ions for extracellular sodium ions across the cell membrane.²⁷⁰ Under basal conditions, the sodium-calcium exchanger extrudes calcium to maintain normal intracellular calcium concentration. However, during ischemia, intracellular sodium accumulates because of inactivation of the ATP-dependent sodium extrusion system. NHE-mediated sodium influx during ischemia reduces activity of the sodium-calcium exchanger, resulting in a net increase in intracellular calcium, which is exacerbated during reperfusion. Consequently, inhibition of the isoform NHE-1, located on the plasma membrane of the cardiac myocyte, is thought to inhibit calcium overload and to serve as a myoprotective agent.²⁷¹ The NHE isoforms can be nonspecifically inhibited by various antagonists, including amiloride and its 5-amino-substituted analogs as well as the benzoylguanidine derivative cariporide (HOE-642). The use of cariporide has been shown to reduce myocardial infarct size and to improve postischemic functional recovery after ischemia and reperfusion.²⁷² The administration of NHE-1 antagonists before ischemia or both before ischemia and during reperfusion has been shown to provide significantly greater cardioprotection compared with administration during reperfusion alone.^{273,274} Clinical trials in patients treated for an acute myocardial infarction by coronary angioplasty with cardiac enzyme release as a biological endpoint have resulted in conflicting results.^{275,276} In an

additional randomized clinical trial (GUARDIAN) of 11,590 patients with unstable angina and non-ST-segment elevation myocardial infarction undergoing either angioplasty or surgical revascularization, NHE inhibition with cariporide failed to reduce the incidence of myocardial infarction and death.²⁷⁷ However, in a subgroup analysis of patients undergoing coronary artery bypass, there was a decrease in rates of myocardial infarction or death 6 months postoperatively, provoking another trial (EXPEDITION) limited only to patients undergoing surgical revascularization, which demonstrated a decrease in myocardial infarction rate accompanied by an increase in the incidence of stroke.²⁷⁸

MOLECULAR MANIPULATION

During the normal temporal development of the myocardium, there is the phenotypic induction, expression, and synthesis of a defined number of genes. Under pathophysiologic conditions including stress, disease, and induction resulting from intrinsic or extrinsic insult, there is an adaptive remodulation of gene synthesis that is often not initially apparent at the gross anatomic or histologic level. Recent advances in molecular, cellular, and genetically based technologies have allowed these events and altered genes and gene products to be identified, which may aid in the development of new therapeutic interventions.²⁷⁹

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CLINICAL QUALITY AND SAFETY IN ADULT CARDIAC SURGERY

Nassrene Y. Elmadhun • Justine M. Carr • Frank W. Sellke

CHAPTER OUTLINE

NATIONAL LANDSCAPE FOR QUALITY AND SAFETY

EVOLVING LANDSCAPE OF QUALITY AND SAFETY IN CARDIAC SURGERY

CARDIAC SURGERY TEAMWORK AND COMMUNICATION

PERIOPERATIVE CARE

Preprocedure Verification, Marking, Time-Out, and Briefing

Antibiotic Administration

Preoperative Beta Blockade

Postoperative Glucose Control

POSTOPERATIVE MORBIDITY

Ventilator-Associated Pneumonia

Central Line Infections

Deep Sternal Wound Infections

Response to Changes in a Patient's Condition

Medication Safety and Reconciliation

Active Involvement of Patients in Their Own Care

Communication among Caregivers

MEASUREMENT OF CARE

CONCLUSION

At the turn of the 20th century, Dr. Ernest A. Codman (1869-1940) was rejected by the Boston medical community for his maverick ideas supporting the evaluation and publication of surgical outcomes. Codman eventually founded his own hospital dedicated to the study of “end results” and published his outcomes.¹ His work was seminal in the establishment of the American College of Surgeons and the Joint Commission. A half-century later, the Boston medical community redeemed itself with the landmark report by Beecher and Todd, “A Study of the Deaths Associated with Anesthesia and Surgery.”² Death was the designated outcome under study, as it was the one that could be agreed on by all investigators.³ Two decades later, the focus shifted to the application of the critical incident technique and identification of remediable factors that contribute to anesthesia-related morbidity and mortality, and the eventual creation of the Anesthesia Patient Safety Foundation.⁴⁻⁶

In the spirit of Codman’s focus on end results and the Anesthesia Patient Safety Foundation’s focus on remediation, cardiac surgeons have played a major role in the study of outcomes and the implementation of quality improvement techniques. The relative uniformity and limited types of cardiac operations, together with their case volume, aggregate cost, and high public profile, impelled interested stakeholders to quantify outcomes. In 1972, the Department of Veterans Affairs (VA) created a Cardiac Surgery Consultants Committee Advisory Group, which resulted in the first multi-institutional

cardiac surgery outcomes database. Until 1988, the main outcomes were volume and unadjusted mortality.⁷ In 1987, the Health Care Financing Administration (HCFA) published raw institution-specific mortality rates for Medicare patients.⁸ Mortality rates were generated for entire hospitals in aggregate, as well as for specific diagnosis-related groups (DRGs), including coronary artery bypass graft (CABG). With growing concern over the confusion developing from raw mortality rates, the VA introduced a risk-adjustment model and created what is now known as the VA Continuous Improvement in Cardiac Surgery Program.⁹ Motivated by both clinical and statistical imperatives, in 1989 the Society of Thoracic Surgeons (STS) developed its own voluntary, risk-adjusted database for cardiac surgery. Also in 1989, Parsonnet and colleagues pioneered a predictive model that classified patients into five groups of increasing operative risk according to 14 preoperative risk factors.¹⁰ The model proved to be highly predictive when applied to a large number of patients in three hospitals. In the 1990s various statistical methods were developed to adjust for preoperative risk hazard as well as social and geographic differences.^{11,12} In 1987 in New England, a consortium of hospitals, the Northern New England Cardiovascular Disease Study Group, began to collect data uniformly in a common registry.¹³ The Alabama Coronary Artery Bypass Grafting Cooperative project gathered data beginning in 1995.¹⁴ However, among these and other registries established in the early and mid-1990s, the

universal finding was that operative mortality varied widely among institutions, even after risk adjustment.¹⁴⁻¹⁶ This observation presaged complementary movements: (1) public reporting of statewide outcomes and (2) strategic interventions to improve outcomes. Hannan and coworkers' studies of CABG mortality in New York State led to the first statewide reporting of operative mortality.^{17,18} Statutory requirement for public reporting was subsequently adopted in Pennsylvania, New Jersey, and Massachusetts.¹⁹⁻²¹

An equally important result has been the cooperative analysis of outcomes with a focus on performance improvement. The Northern New England Cardiovascular Disease Study Group became a leader in this movement, in which surgeons, cardiologists, anesthesiologists, nurses, and perfusionists collaborated to review data and current practice, target key variables that drive outcomes, and organize improvement projects, such as inter-institutional site visits and study protocols, with resultant decline in CABG mortality rates.¹⁵ A number of regional, national, and even international groups have followed this registry and quality improvement model, establishing benchmarks for the cardiac surgical "industry."²²⁻²⁴

Around the turn of the 21st century, national specialty societies began establishing guidelines for the application of interventional and surgical technologies. The American College of Cardiology (ACC) and American Heart Association (AHA) published their first *Guidelines for Coronary Bypass Surgery* in 1999, with updates in 2004 and 2011.^{25,26,26a} These include class I, useful and effective; class IIa, evidence favors usefulness; class IIb, evidence less well established; class III, not useful or effective and, in some cases, harmful. Similar guidelines have been established for valvular surgery.^{27,28}

The net impact of all these activities is dramatically apparent when viewing the decline in the ratio of observed (O) to expected (E) CABG mortality of patients, as measured by the STS database (Fig. 66-1).²⁹

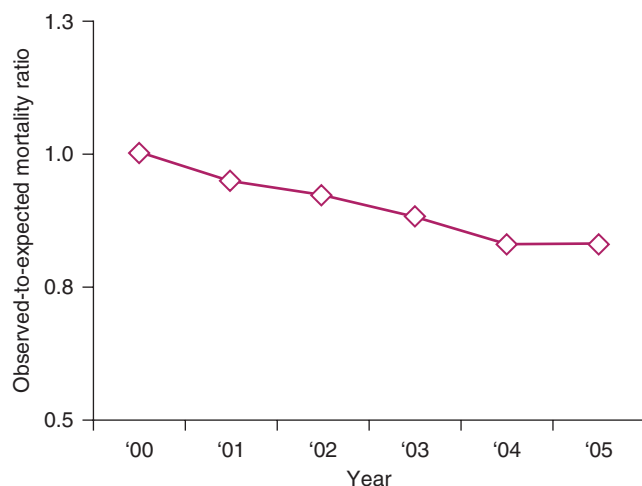


FIGURE 66-1 ■ Observed-to-expected mortality ratio for all isolated coronary artery bypass graft patients from 2000 to 2005. Graph shows the results of logistic modeling for patient risk. The decline over the 5 years is statistically significant ($P < 0.0001$) for the trend (2000-2005). (From Grover FL: The bright future of cardiothoracic surgery. *Ann Thorac Surg* 85:8-24, 2008.)

NATIONAL LANDSCAPE FOR QUALITY AND SAFETY

In addition to quality and safety initiatives specific to cardiac surgery, a major cultural change has occurred in the United States during the early 21st century. Leadership in the prioritization of quality and safety has come from the Institute of Medicine (IOM). In a groundbreaking publication in 1999, "To Err Is Human," the IOM made several important contributions.³⁰ First, the report estimated that up to 98,000 patients each year die as a result of medical error. They identified that errors are often caused by faulty systems, processes, and conditions. They cited the work of Lucian Leape and colleagues, who codified four types of errors: diagnostic, treatment, preventive, and other (Box 66-1).³¹

To achieve a better safety record, the IOM report recommended a four-tiered approach:

1. Establishing a national focus to create leadership, research, tools, and protocols to enhance the knowledge base about safety
2. Identifying and learning from errors by developing a nationwide public mandatory reporting system and by encouraging health care organizations and practitioners to develop and participate in voluntary reporting systems
3. Raising performance standards and expectations of improvements in safety through the actions of oversight organizations, professional groups, and group purchasers of health care
4. Implementing safety systems in health care organizations to ensure safe practices at the delivery level (i.e., a culture of safety)

BOX 66-1 Types of Medical Errors

DIAGNOSTIC

- Error or delay in diagnosis
- Failure to use indicated tests
- Use of outmoded tests or therapy
- Failure to act on results of monitoring or testing

TREATMENT

- Error in the performance of an operation, procedure, or test
- Error in administering the treatment
- Error in the dosage or method of using a drug
- Avoidable delay in treatment or in responding to an abnormal test
- Inappropriate (not indicated) care

PREVENTIVE

- Failure to provide prophylactic treatment
- Inadequate monitoring or follow-up of treatment

OTHER

- Failure of communication
- Equipment failure
- Other system failure

Adapted from Leape L, Larwthers AG, Brennan TA, et al: Preventing medical injury. Qual Rev Bull 19:144-149, 1993.

Two years later, the IOM published another landmark report, “Crossing the Quality Chasm,”³² which set a national agenda aimed at narrowing differences in quality among providers of medical care. Instead of focusing attention on a single outcome, the IOM focused on the quality of the entire patient experience, defining it in six key dimensions as being “safe, effective, efficient, timely, patient-centered, and equitable.” The model promulgated a balanced approach to assessment of quality, incorporating clinical outcomes with patient experience and the appropriate allocation of resources. Furthermore, the report identified key redesign imperatives for care delivery:

- Reengineered care processes
- Effective use of information technologies
- Knowledge and skills management
- Development of effective teams
- Coordination of care across patients—conditions, services, sites of care—over time

One other key focus of this IOM report addresses patient engagement:

- Care is based on continuous healing relationships.
- Care is customized according to patient needs and values.
- Patient is the source of control.
- Knowledge is shared and information flows freely.
- Transparency is necessary.
- Needs are anticipated.

These two IOM reports raised the bar to a new level of excellence that transcended the expertise of a single care provider. In 2006, a third IOM report, “Performance Measurement: Accelerating Improvement,” laid the groundwork for performance measurement.³³ Achieving excellence now required a careful orchestration of care delivery, incorporating evidence-based care processes, as well as coordinated care infrastructure across the care delivery continuum—both inpatient and outpatient. Hardwiring for excellence became a priority, leading the Joint Commission (formerly known as JCAHO) to begin requiring demonstration of evidence-based and safe practices in the delivery of care. Payers and purchasers followed suit. The Centers for Medicare and Medicaid Services (CMS) instituted the requirement for submission of “core measures,” evidence-based practices in the care of patients with acute myocardial infarction, heart failure, pneumonia, and selected surgeries (including cardiac surgery).

Another key player has been the National Quality Forum (NQF), a public-private partnership created to develop and implement a national strategy for health care quality measurement and reporting. NQF member organizations have worked together to promote a common approach to measuring health care quality and fostering system-wide capacity for quality improvement. Yet another influence has come from the Leapfrog Group, an association of private and public sector group purchasers, who have created a market-based strategy to improve safety and quality. Their public ranking includes recognition for the use of computerized provider order entry, evidence-based hospital referrals, and the staffing of intensive care units with physicians credentialed in critical care medicine. In addition, they generate an aggregate

Safety Score (A through F) for each hospital based on these data.

An outcome of these various national initiatives is the standardization of surgical care. Postoperative complications have a significant impact on mortality, length of stay (3 to 11 days), and cost.³⁴ In a study of Medicare beneficiaries in 2009, surgical patients had a 30-day readmission rate of 12.7%.³⁵ To decrease readmissions, CMS began reporting 30-day readmission rates for certain diagnoses in 2009. In October 2012, CMS began a pay-for-performance program in which hospitals with excessive readmissions for particular reportable medical diagnoses are penalized. The goal of the pay-for-performance program set forth by CMS and the secretary of Health and Human Services was to reduce readmissions by 20% by the end of 2013, and 18.5% reduction was achieved in 2012.

In 2002, CMS, in collaboration with the Centers for Disease Control and Prevention, implemented the National Surgical Infection Prevention Project with the goal of decreasing the morbidity and mortality rates associated with postoperative surgical site infections by promoting appropriate selection and timing of prophylactic antimicrobials.³⁶ In April 2003, this group joined with representatives of the VA, American College of Surgeons, American Society of Anesthesiologists, Agency for Healthcare Research and Quality, American Hospital Association, and Institute for Healthcare Improvement to align efforts to reduce surgical complications and mortality. This collaboration resulted in the development of the Surgical Care Improvement Project (SCIP), a national quality partnership of organizations committed to improving the safety of surgical care through the reduction of postoperative complications.³⁶ The rapid rate of adoption of the SCIP measures can be tracked on the CMS website Hospital Compare (www.hospitalcompare.hhs.gov), showing rates of compliance with these measures in hospitals across the country.

EVOLVING LANDSCAPE OF QUALITY AND SAFETY IN CARDIAC SURGERY

From 1989 to 2007, the STS database grew to become the largest and most comprehensive single-specialty clinical database in health care in the world.³⁷ In view of the increasing interest of payers and regulators to compare cardiac surgery quality, the STS established a Quality Measurement Task Force (QMTF). The task force’s goal was to develop a methodology for comprehensive assessment of adult cardiac surgery quality of care. The assessment was to include both individual measures and a composite quality score. Guiding principles included the following³⁸:

- Quality assessment should be at the level of the program or hospital, rather than the individual surgeon.
- Initial quality reports should focus on CABG surgery.
- Quality measures should be chosen from among those endorsed by the National Quality Forum.
- Quality measure selection should be consistent with the principles and criteria recommended in

BOX 66-2 Society of Thoracic Surgeons Quality Measures**PERIOPERATIVE MEDICAL CARE**

- Preoperative beta blockade
- Discharge antiplatelet therapy
- Discharge beta blockade
- Discharge antilipid therapy
- Antibiotic prophylaxis duration and selection

OPERATIVE CARE

- Use of at least one internal mammary artery

OPERATIVE MORTALITY RISK-ADJUSTED**POSTOPERATIVE MORBIDITY: ABSENCE OF ANY SERIOUS COMPLICATION**

- Renal failure
- Deep sternal wound infection
- Reexploration for any cause
- Stroke
- Prolonged ventilation/intubation

Adapted from Shabian DM, Edwards FH, Ferraris VA, et al: Quality measurement in adult cardiac surgery. Part 1: Conceptual framework and measure selection. Ann Thorac Surg 83(Suppl):S3–12, 2007.

the 2006 IOM report “Performance Measurement: Accelerating Improvement.”

- Quality measures should be available as data elements in the STS National Adult Cardiac Surgery Database.
- Quality scores should take into account structure, process, and outcomes.
- Quality scores should assess three temporal domains—preoperative, operative, and postoperative.
- Quality scores should satisfy multiple criteria for validity.
- Quality scores should be interpretable and actionable by providers.

In 2007, the STS QMTF created 11 measures within four domains: perioperative medical care, intraoperative care, risk-adjusted operative mortality, and postoperative morbidity.³⁹ Statistical analysis was based on actual 2004 STS data, representing 133,149 coronary artery bypass procedures.³⁸ The STS QMTF measures are listed in [Box 66-2](#).

CARDIAC SURGERY TEAMWORK AND COMMUNICATION

Defining best practice through quality and safety measures has been a major accomplishment. Implementing these measures has proved to be a challenge because it has required a reengineering of workflow and, in some cases, a redesigning of care delivery. Successful implementation of best practices depends on teamwork across medical specialties and across disciplines, as well as with the patients and their families. The interventions that can contribute to the quality and safety of care delivered to cardiac surgery patients follow. Central to the effective care of cardiac surgical patients is effective teamwork.

The critical elements of teamwork include the 6 “Cs”: communication, cooperation, coordination, cognition (shared understanding of patient care goals), conflict resolution, and coaching (team training).⁴⁰ In a review of malpractice litigation, 87% of system failures were a result of communication breakdown, primarily between caregivers.⁴¹ The Joint Commission reported that communication failures were the leading root cause of 65% of sentinel events between 2004 and 2012.⁴²

Breakdown in communication and surgery workflow is exceedingly common. In one study of intraoperative communication failures during complex operations, communication failures occurred in every case at a rate of one every 8 minutes.⁴³ In another study of disruptions in a cardiac surgical operating room, breakdown in teamwork and communication occurred at a rate of 11 per case.⁴⁴ Although some of these disruptions can seem innocuous and do not seem to affect patient outcome, minor events during cardiac surgery can accumulate and impair the team’s ability to recover from major events and are significantly associated with death and near misses.⁴⁵ Catchpole and colleagues reported that for every 3 minor problems above the mean of 9.9 per case, intraoperative performance was hindered, and operative time increased.⁴⁶ Thus nontechnical skills in the operating room such as teamwork and communication have been shown to negatively impact patient outcomes.

Measurement tools have emerged to assess nontechnical skills such as communication and teamwork dynamics. The Oxford Non-Technical Skills (NOTECHS) is a teamwork assessment tool that was adapted from the aviation industry and measures skills in four categories: problem solving/decision making, situational awareness, leadership/management, and cooperation/teamwork. The Observational Teamwork Assessment for Surgery (OTAS) is another teamwork assessment tool that uses a procedural task checklist centered on patient, equipment, and communication task ratings. Both the NOTECHS and the OTAS have been validated and found to be reliable in measuring nontechnical skills in the operating room.^{47,48} The purpose of using these measurement tools is to test the efficacy of proposed interventions to improve nontechnical skills before implementation.

Teamwork dynamics has been extensively studied in the aviation industry after several aviation accidents were attributed to teamwork failure. In an effort to improve communication and effective teamwork, the aviation industry developed crew resource management (CRM), which is a training protocol designed for high-stress, high-stakes situations where human error can result in devastating consequences. CRM training aims to foster team empowerment and a safety culture in which any team member can raise concerns and respectfully question authority if he or she believes that an error is occurring. Training in CRM focuses on communications, situational awareness, problem solving, leadership, decision making, and adaptability in order to promote safety and optimize team efficiency. Given the proven efficacy of CRM, medicine has followed suit in implementing an adapted version of CRM in critical areas of medicine and surgery. In a study using CRM-style teamwork training in general and vascular surgery, Oxford researchers

reported that NOTECHS teamwork scores significantly improved and procedural error rates were reduced.^{48,49} In a national prospective teamwork training study, the VA's medical team training program demonstrated that CRM-based team training significantly reduced annual mortality by 18%, reduced the incidence of wrong-site surgery, and improved compliance with best practices.⁵⁰⁻⁵³ This study also demonstrated that there is a dose-response relationship between team training duration and mortality: for every 3 months of team training, there was a reduction of 0.5 deaths per 1000 operations.⁵⁰

One other key area in communication and teamwork, as articulated by the IOM, is the active engagement of the patient. Providing the patient with the information he or she needs, engaging the patient in the plan, and sharing decision making while respecting the patient as the ultimate decision maker yields benefits for caregivers as well as patients and ensures alignment of goals and supports patient participation in the recovery process.

PERIOPERATIVE CARE

Preprocedure Verification, Marking, Time-Out, and Briefing

Much has been written about the importance of the Universal Protocol for Preventing Wrong Site, Wrong Procedure, and Wrong Person Surgery, and few would dispute the value of this preprocedure checking.⁵⁴⁻⁵⁷ Time-outs, checklists, and briefings have been shown to reduce errors in communication and improve teamwork. Although a major focus was initially on operating room (OR) procedures, the Universal Protocol applies to most other procedures that involve puncture or incision of the skin, or insertion of an instrument or foreign material into the body—for example, peripherally inserted central catheter lines, percutaneous aspirations, biopsies, cardiac and vascular catheterizations, and endoscopies. Growing experience has demonstrated the value of hardwiring the Universal Protocol with specific rules and clear accountability. Workflow must be reengineered to ensure the availability of critical parties. Introduction of stopgap measures are helpful (e.g., the blade is not put on the scalpel until the time-out is completed). Whereas checklists are structured and closed-ended and involve reading aloud and verifying specific information, briefings are open-ended and involve a dialogue to confirm procedure details, identify problems, exchange information, and ask questions. In a study of 35,000 cases, briefings have been shown to shorten the duration of surgical procedures by reducing interruptions and distractions and only take 2.9 minutes on average (range 1 to 5 minutes).⁵⁸⁻⁶⁰ Although studies have demonstrated that briefings can reduce intraoperative distractions and improve workflow, to date, it is not universally implemented because of individual and institutional resistance to routine briefings.

Antibiotic Administration

The goal of antibiotic prophylaxis is to use an agent that is safe and cost-effective and that has a spectrum of action

that covers most of the probable intraoperative organisms.^{61,62} Antibiotic administration must be completed before incision and should not be given more than 1 hour before incision (except for vancomycin, which can be given 2 hours before incision). Antibiotic selection should align with evidence-based recommendations. There should be coordination between anesthesiologist and surgeon. Communication from surgeon to anesthesiologist about antibiotic selection is most effective when it occurs in a standardized fashion. Reasons for exceptions to standard antibiotic protocol need to be documented and communicated. Pharmacy staff also need to be in the communication loop to ensure that drug preparations are available for timely infusion and completion before surgery. Postoperative orders need to be clear about the number of postoperative antibiotic doses due and by what time the last dose should be completed to stay within the 48-hour postoperative window. Although there is some evidence that single-dose prophylaxis or 24-hour prophylaxis may be as effective as 48-hour prophylaxis, the STS published a practice guideline recommending 48 hours of prophylaxis, because few studies have directly compared 24 hours of prophylaxis with 48 hours of prophylaxis.⁶³ In a meta-analysis comparing short-term perioperative antibiotic prophylaxis (<24 h) compared to longer term antibiotic prophylaxis (>24 h), patients receiving antibiotics for more than 24 hours had a 38% decreased risk in developing sternal surgical site infection.⁶⁴ However, prophylaxis should be concluded at 48 hours, because administration for longer periods has been associated with an increased risk of infection with drug-resistant organisms.⁶⁵

Preoperative Beta Blockade

An observational analysis of 629,877 patients undergoing CABG between 1996 and 1999 demonstrated that preoperative beta blocker therapy was associated with a small but consistent survival benefit, except among patients with a left ventricular ejection fraction of less than 30%.⁶⁶ Furthermore, many studies have demonstrated the benefit of preoperative beta blockers in reducing the incidence of postoperative atrial fibrillation.⁶⁷ Atrial fibrillation occurs in up to one third of patients after open heart surgery. In an analysis of 52 published studies representing almost 10,000 patients undergoing open heart surgery, supraventricular tachycardias, including atrial fibrillation, occurred in 29% of patients who did not receive prophylactic drugs and in 19% of patients given beta blockers.⁶⁷

Postoperative Glucose Control

Glucose control through continuous infusion of insulin has been shown to reduce mortality and surgical site infections in both diabetic and nondiabetic patients.⁶⁸⁻⁷¹ Intraoperatively, several factors contribute to hyperglycemia, including cardiopulmonary bypass (CPB) pump prime fluid composition, temperature while on CPB, and medications such as catecholamines and glucocorticoids.⁷² The current measure of glucose control is based on the value identified at 6 AM postoperatively, with a

goal of less than or equal to 200 mg/dL. During the first 24 postoperative hours, glucose control is best achieved through intravenous insulin titrated on a sliding scale, based on fingerstick glucose levels measured every 1 to 2 hours, and this requires effective nursing leadership. Although previous studies advocated aggressive glycemic control (blood glucose 90 to 120 mg/dL) in patients undergoing cardiac surgery, this has been associated with increased incidence of hypoglycemic events. As a result, it is now recommended that diabetic cardiac surgical patients have a blood glucose maintained between 120 and 180 mg/dL.^{73,74} Protocols should incorporate mechanisms to recognize when the patient's endogenous glucose regulation begins to normalize, so as to avoid hypoglycemia. Full implementation of these interventions requires careful orchestration of critical care staff members, including nursing, respiratory therapy, midlevel practitioners, and physicians, with clear designation of accountability for tracking and reporting.

POSTOPERATIVE MORBIDITY

Ventilator-Associated Pneumonia

Most cardiac surgery patients are extubated within a day of surgery. However, for those who remain intubated for longer, meticulous attention to prevention of ventilator-associated pneumonia (VAP) is critical. VAP is an airway infection that develops more than 48 hours after intubation. Ventilated patients with VAP have a mortality rate of 46% as compared with 32% for ventilated patients without VAP.⁷⁵ On the basis of a growing body of literature, the Institute for Health Care Improvement identified four best practices that can decrease the incidence of VAP: (1) elevation of the head of the bed, (2) daily "sedation vacations" and assessment of readiness to extubate, (3) peptic ulcer disease prophylaxis, and (4) deep venous thrombosis prophylaxis.^{76,77}

Central Line Infections

Central line infections are another source of morbidity and mortality, with mortality estimates ranging from 4% to 20%.⁷⁸ The Institute for Health Care Improvement recommends five key interventions to decrease central line infections: (1) hand hygiene; (2) maximal barrier precautions on insertion; (3) chlorhexidine skin antisepsis; (4) optimal catheter site selection, with subclavian vein as the preferred site for nontunneled catheters; and (5) daily review of line necessity, with prompt removal of unnecessary lines. As with VAP, reduction in the incidence of central line infection is a shared responsibility among critical care staff.^{79,80}

Deep Sternal Wound Infections

Deep sternal wound infections are estimated to occur in 1% to 3% of cardiac surgery patients; they result in an in-hospital mortality rate of up to 20% and, in some studies, an increase in the long-term mortality rate as well.^{81,82} Risk factors include obesity, malnutrition,

diabetes mellitus, smoking, preoperative hemodynamic instability, preoperative renal failure on dialysis, use of bilateral internal thoracic arteries, and sepsis or endocarditis after CABG.⁸¹⁻⁸⁴ *Staphylococcus aureus* is a common pathogen.⁸⁵ Infection-reduction strategies include glucose control for diabetic as well as nondiabetic patients, reduction of colonization through a chlorhexidine scrub the night before surgery, mupirocin to the nares preoperatively and postoperatively, appropriate antibiotic selection, optimal administration time and duration, and the minimizing of traffic in and out of the OR during surgery.^{69,82-84} Surgical interventions include standardized preparation and draping, hair clipping instead of shaving, and meticulous wound closure.^{82-84,86}

Postoperatively, there is evidence for the benefit of sports-bra support for large-breasted patients.⁸⁴ Deep sternal wound infection (mediastinitis) is viewed as a preventable condition by CMS. Therefore, patients who develop a deep sternal wound infection during the admission for cardiac surgery no longer receive the incremental payment for this condition.

Response to Changes in a Patient's Condition

Most patients who experience a cardiac arrest in the hospital demonstrate identifiable signs of deterioration before the arrest. The most common signs are abnormal vital signs and hypoxia.⁸⁷⁻⁸⁹ A rapid response team (RRT) is a group of clinicians who deliver emergency care to a patient at the bedside. The RRT does not replace the patient's care team but ensures that immediate assistance is available when there is a sudden deterioration. The RRT may include the critical care nurse or physician as well as a respiratory therapist. The RRT may be called at any time by anyone in the hospital to assist in the care of a patient who appears acutely ill, so as to avoid cardiac arrest or other adverse event. Facilities that have implemented RRTs have reported a reduction in the number of cardiac arrests and deaths, as well as a reduction in intensive care unit and hospital length of stay among survivors of cardiac arrest.⁸⁹ On surgical services, implementation of RRTs has been associated with a reduction in the incidence of respiratory failure, stroke, severe sepsis, acute renal failure, and postoperative mortality.⁹⁰

Medication Safety and Reconciliation

The IOM estimated that medication errors have accounted for 7000 deaths each year.³⁰ Injuries attributable to the use of medications are designated as adverse drug events (ADEs). Hospitalized patients who experience an ADE have a mortality rate that is almost twice that of patients without an ADE.⁹¹ Prevention of ADEs has been designated a national priority.⁹² The Joint Commission has identified four categories of high-risk medications: anticoagulants, insulin, sedatives, and opioids. Most cardiac surgery patients receive most or all of these types of medications. Attention to administration is critical during the hospital stay, during transfers in and out of critical care or recovery units, and at discharge.

Anticoagulation errors can be reduced with the implementation of standardized protocols for initiation and dosage adjustment of coumadin and heparin. Anticoagulation protocols should specify target laboratory values and frequency of monitoring, as well as designated accountability for dose adjustments. Insulin administration protocols should also specify target glucose values and frequency of monitoring. Protocols for administration of intravenous insulin infusion outside a critical care setting should address nursing staff ratios to ensure timely and frequent glucose monitoring. Sedation and opioid protocols should address the management of sleep apnea, identifying high-risk patients in advance of surgery.⁹³ Timely pain assessment and control is critical for the patient's experience and recovery. Use of an objective pain scale can assist in monitoring, ensuring that the targets afford patient comfort without jeopardizing respiratory status. For example, a pain level of 0 may be a sign of overmedication and thus a risk for respiratory depression.

Of all medication errors, 46% occur at transition points (e.g., admission to hospital, transfer between units, discharge from hospital).⁹⁴ Medication reconciliation across the continuum of care ensures that patients receive all intended medications and no unintended medications after transitions in care locations. The Joint Commission has defined medication reconciliation as the process of comparing a patient's medication orders to all of the medications that the patient has been taking. The purpose is to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions. Medication reconciliation should be performed at every transition of care in which new medications are ordered or existing orders are rewritten. The process has five steps: (1) develop a list of current medications, (2) develop a list of medications to be prescribed, (3) compare the medications on the two lists, (4) make clinical decisions based on the comparison, and (5) communicate the new list to appropriate caregivers and to the patient. Medication reconciliation has been shown to significantly decrease medication errors.⁹⁴

Active Involvement of Patients in Their Own Care

Patient activation has been shown to be a critical factor in improving outcomes and influencing costs.⁹⁵ Patients and their families play an active role in the medication reconciliation process. They should review all medications and understand both generic and proprietary names. For cardiac surgery patients being discharged on coumadin, the patient and family should receive instructions on how to take the medication, the foods and medications that can affect coumadin effectiveness, and how to recognize and what to do for signs and symptoms of bleeding. The clinician responsible for monitoring and dose adjustments should be clearly designated and an appointment for the post-discharge blood level monitoring made.

Communication among Caregivers

Transitions across units and in and out of the hospital are periods of risk. Standardized handoffs by clinical

staff are a way of ensuring that each caregiver has complete information. There must be timely and complete communication with the primary care physician who will be caring for the patient after discharge.

MEASUREMENT OF CARE

The IOM has provided clinicians with a clear roadmap for improvement, focusing on safety and quality and the assessment of outcomes and patient experience. Regular and frequent measurement is essential to achieving and maintaining excellence. The NQF is a nonprofit organization that operates under a three-part mission to improve the quality of American health care by:

- Building consensus on national priorities and goals for performance improvement and working in partnership to achieve them;
- Endorsing national consensus standards for measuring and publicly reporting on performance; and
- Promoting the attainment of national goals through education and outreach programs.

NQF measures ensure standardization and validation and are used by STS and by CMS for the Hospital Inpatient Quality Reporting Program (IQR), including SCIP (Table 66-1). Participation in national and state databases affords the opportunity to compare performance with that achieved in benchmark institutions. However, as these reports may lag by many months, performance must also be tracked in real time for early detection of variances. In addition to manual data abstraction, some vendors and payers may calculate and publicize morbidity and mortality rates based on proprietary risk-adjustment models derived from International Statistical Classification of Diseases and Related Health Problems (ICD)-9 codes. ICD-9 codes are assigned by coders at the time of discharge and are based on documentation in the chart from physicians, nurse practitioners, and physician assistants. The precision of the documentation has an impact on the level of detail of the ICD-9 codes assigned. Complete capture of all relevant ICD-9 codes ensures that risk-adjustment models accurately depict a patient's risk. Notable is the fact that coders cannot code from laboratory results, only from the notes of a physician or mid-level practitioner. For example, a patient who has a creatinine of 2.5 is not assigned a diagnosis of renal failure or renal insufficiency unless those words appear in the documentation. Furthermore, clinicians should review terminology definitions. *Renal failure* is major comorbidity or complication reflecting an acute rise in creatinine from baseline. *Renal insufficiency*, in contrast, is a chronic steady-state condition and does not contribute to the coded risk profile. In October 2014, ICD-9 codes ($N = 14,000$) will be retired and replaced with ICD-10 ($N = 69,000$), which requires greater specificity in documentation in some areas.

Finally, a great advance in the measurement of care is the availability of the patient's own assessment of the care delivered. In 2006, CMS introduced the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey. The survey is administered, usually by mail, to a statistically significant subset of discharged

TABLE 66-1 National Quality Forum (NQF) Measures

Measure	NQF Status	Description
STS CABG Composite Score	NQF #0696 endorsed	This multidimensional performance measure assesses surgical performance based on a combination of 11 NQF-endorsed CABG process and outcomes measures, grouped into four domains: 1. Perioperative medication domain, scored all-or-none and consisting of: 0127—Preoperative beta blockade 0117—Beta blockade at discharge 0116—Antiplatelet medication at discharge 0118—Antilipid treatment at discharge 2. Operative care process domain 0134—Use of an internal mammary artery in CABG 3. Risk-adjusted operative mortality 0119—Risk-adjusted operative mortality for CABG 4. Risk-adjusted morbidity, scored any-or-none and consisting of: 0131—Stroke/cerebrovascular accident 0115—Surgical reexploration 0130—Deep sternal wound infection rate 0114—Postoperative renal failure 0129—Prolonged intubation (ventilation) Participants receive a score for each of the four domains, plus an overall composite score. The overall composite score was created by “rolling up” the four domain scores into a single number. In addition to receiving a numeric score, participants were assigned to rating categories designated as one (below average performance), two (average performance), or three (above average performance) stars.
Outcome Measures		
Risk-Adjusted Deep Sternal Wound Infection Rate	NQF #0130	Percentage of patients aged 18 years and older undergoing isolated CABG who, within 30 days postoperatively, develop deep sternal wound infection involving muscle, bone, and/or mediastinum requiring operative intervention
Risk-Adjusted Operative Mortality for Aortic Valve Replacement (AVR)	NQF #0120	Percentage of patients undergoing AVR who die, including both (1) all deaths occurring during the hospitalization in which the procedure was performed, even if after 30 days, and (2) those deaths occurring after discharge from the hospital, but within 30 days of the procedure
Risk-Adjusted Operative Mortality for AVR + CABG Surgery	NQF #0123	Percentage of patients undergoing combined AVR and CABG who die, including both (1) all deaths occurring during the hospitalization in which the procedure was performed, even if after 30 days, and (2) those deaths occurring after discharge from the hospital, but within 30 days of the procedure
Risk-Adjusted Operative Mortality for CABG	NQF #0119	Percentage of patients aged 18 years and older undergoing isolated CABG who die, including both (1) all deaths occurring during the hospitalization in which the CABG was performed, even if after 30 days, and (2) those deaths occurring after discharge from the hospital, but within 30 days of the procedure
Risk-Adjusted Operative Mortality for Mitral Valve (MV) Repair	NQF #1501	Percentage of patients undergoing MV repair who die, including both (1) all deaths occurring during the hospitalization in which the procedure was performed, even if after 30 days, and (2) those deaths occurring after discharge from the hospital, but within 30 days of the procedure
Risk-Adjusted Operative Mortality for MV Repair + CABG Surgery	NQF #1502	Percentage of patients undergoing combined MV repair and CABG who die, including both (1) all deaths occurring during the hospitalization in which the procedure was performed, even if after 30 days, and (2) those deaths occurring after discharge from the hospital, but within 30 days of the procedure
Risk-Adjusted Operative Mortality for Mitral Valve (MV) Replacement	NQF #0121	Percentage of patients undergoing MV replacement who die, including both (1) all deaths occurring during the hospitalization in which the procedure was performed, even if after 30 days, and (2) those deaths occurring after discharge from the hospital, but within 30 days of the procedure
Risk-Adjusted Operative Mortality for MV Replacement + CABG Surgery	NQF #0122	Percentage of patients undergoing combined MV replacement and CABG who die, including both (1) all deaths occurring during the hospitalization in which the procedure was performed, even if after 30 days, and (2) those deaths occurring after discharge from the hospital, but within 30 days of the procedure
Risk-Adjusted Postoperative Renal Failure	NQF #0114	Percentage of patients aged 18 years and older undergoing isolated CABG (without preexisting renal failure) who develop postoperative renal failure or require dialysis

TABLE 66-1 National Quality Forum (NQF) Measures—cont'd

Measure	NQF Status	Description
Risk-Adjusted Prolonged Intubation (Ventilation)	NQF #0129	Percentage of patients aged 18 years and older undergoing isolated CABG who require intubation for more than 24 hours
Risk-Adjusted Stroke/Cerebrovascular Accident	NQF #0131	Percentage of patients aged 18 years and older undergoing isolated CABG who have a postoperative stroke (i.e., any confirmed neurologic deficit of abrupt onset caused by a disturbance in blood supply to the brain) that did not resolve within 24 hours
Risk-Adjusted Surgical Reexploration	NQF #0115	Percentage of patients aged 18 years and older undergoing isolated CABG who require a return to the operating room for bleeding with or without tamponade, graft occlusion, valve dysfunction, or other cardiac reason
Process Measures		
Antilipid Treatment at Discharge	NQF #0118	Percentage of patients aged 18 years and older undergoing isolated CABG who were discharged on a statin or other lipid-lowering regimen
Antiplatelet Medication at Discharge	NQF #0116	Percentage of patients aged 18 years and older undergoing isolated CABG who were discharged on antiplatelet medication
Use of IMA in CABG	NQF #0134	Percentage of patients aged 18 years and older undergoing isolated CABG who received an IMA graft
Preoperative Beta Blockade (CMS SCIP Card-2)	NQF #0127	Percentage of patients aged 18 years and older undergoing isolated CABG who received beta blockers within 24 hours preceding surgery
Beta Blockade at Discharge	NQF #0117	Percentage of patients aged 18 years and older undergoing isolated CABG who were discharged on beta blockers
Prophylactic Antibiotic Received within One Hour Prior to Surgical Incision (SCIP Inf-1)	NQF #527	Percentage of patients who received prophylactic antibiotics within 1 hour prior to surgical incision
Selection of Antibiotic Prophylaxis for Cardiac Surgery Patients (CMS SCIP Inf-2)	NQF #0126	Percentage of patients aged 18 years and older undergoing cardiac surgery who received preoperative prophylactic antibiotics recommended for the operation
Duration of Antibiotic Prophylaxis for Cardiac Surgery Patients (CMS SCIP Inf-3)	NQF #0128	Percentage of patients aged 18 years and older undergoing cardiac surgery whose prophylactic antibiotics were discontinued within 48 hours after surgery end time
Cardiac Surgery Patients with Controlled Postoperative Blood Glucose (SCIP Inf-4)	NQF #300	Percentage of cardiac surgery patients with controlled 6 AM postoperative blood glucose
Urinary Catheter Removed on Postoperative Day 1 or Postoperative Day 2 (SCIP Inf-9)	NQF #453	Percentage of surgical patients with urinary catheter removed on postoperative day 1 or postoperative day 2 with the day of surgery being day zero
Venous Thromboembolism Prophylaxis (SCIP VTE-2)	NQF #218	Percentage of surgery patients who received appropriate VTE prophylaxis within 24 hours prior to anesthesia start time to 24 hours after anesthesia end time
Structure Measures		
Participation in a Systematic Database for Cardiac Surgery (CMS IQR)	NQF #0113	Participation in a clinical database with broad state, regional, or national representation that provides regular performance reports based on benchmarked data
Congenital Heart Surgery Measures		
Outcome Measures		
Operative Mortality Stratified by the Five STS-EACTS Mortality Categories	NQF # 0733	Operative mortality stratified by the five STS-EACTS mortality levels, a multi-institutional validated complexity stratification tool
Surgical Volume for Pediatric and Congenital Heart Surgery	NQF # 0732	Surgical volume for pediatric and congenital heart surgery: total programmatic volume and programmatic volume stratified by the five STS-EACTS mortality levels, a multi-institutional validated complexity stratification tool
Surgical Volume for Pediatric and Congenital Heart Surgery: Total Programmatic Volume and Programmatic Volume Stratified by the Five STS-EACTS Mortality Categories		
Participation in a National Database for Pediatric and Congenital Heart Surgery	NQF # 0734	Participation in at least one multicenter, standardized data collection and feedback program that provides benchmarking of the physician's data relative to national and regional programs and uses process and outcome measures

AVR, Aortic valve replacement; CABG, coronary artery bypass graft; CMS, Centers for Medicare and Medicaid Services; IMA, internal mammary artery; IQR, inpatient quality reporting; MVR, mitral valve replacement; NQF, National Quality Forum; SCIP, Surgical Care Improvement Project; STS-EACTS, Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery; VTE, venous thromboembolism.

patients. It includes questions about the treatment of pain, the communication by physicians and nurses, and the clarity of discharge instructions. Although these are publicly reported in aggregate (with a delay of months), it is possible and important to review them close to real time and stratify by surgeon. High performance in this survey is considered vital in support of patient engagement, and sub-par performance is penalized in the CMS value-based purchasing program as well as many other pay-for-performance models.

CONCLUSION

Cardiac surgery outcomes have continued to improve over the past decade. Quality of care has increased as performance improvement initiatives have expanded. Initial focus was on the technical expertise and experience of the surgeon; this focus has expanded to include the entire care team—inside and outside the operating room—and its role in evidence-based care and harm prevention. The most recent advance is the recognition of the active involvement of patients and families in care processes and desired outcomes. The importance of the patient is underscored by the national measures of quality that include HCAHPS patient satisfaction, addressing the patient's assessment of communication and care, and ensuring that interventions by caregivers were effective for the patient, the most important person in the care delivery.

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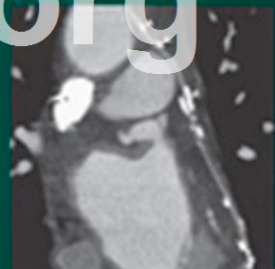
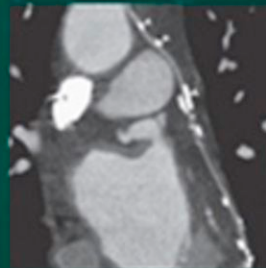
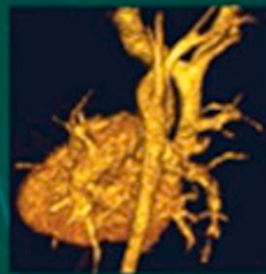
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SURGERY *of the* CHEST

Frank W. Sellke, MD

Karl Karlson & Gloria Karlson Professor and Chief of Cardiothoracic Surgery
Warren Alpert Medical School of Brown University and Rhode Island Hospital
Director, Lifespan Cardiovascular Institute
Providence, Rhode Island

Pedro J. del Nido, MD

William E. Ladd Professor of Surgery
Harvard Medical School
Chairman, Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Scott J. Swanson, MD

Director, Minimally Invasive Thoracic Surgery
Brigham and Women's Hospital
Vice Chair, Cancer Affairs
Department of Surgery, Brigham and Women's Hospital
Chief Surgical Officer
Dana-Farber Cancer Institute
Professor of Surgery
Harvard Medical School
Boston, Massachusetts

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*To my wife, Amy, who gives me love, inspiration,
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They provide us with unlimited pleasure.*

FWS

*To Martha, my loving wife, and to my children,
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To my patients: the inspiration to work hard and do
better every day.*

SJS

CONTRIBUTORS

Brian G. Abbott, MD

Associate Professor of Medicine
Cardiovascular Institute
Warren Alpert Medical School of Brown University
Providence, Rhode Island

J. Dawn Abbott, MD

Associate Professor of Medicine
Director, Interventional Cardiology
Fellowship Training Program
Warren Alpert Medical School of Brown University
Interventional Cardiologist
Rhode Island Hospital
Providence, Rhode Island

David H. Adams, MD

Professor and Chairman
Department of Cardiovascular Surgery
The Mount Sinai Medical Center
New York, New York

Talal Al-Atassi, MD, CM, MPH

Chief Resident
Division of Cardiac Surgery
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Ali Al-Dameh, MD

Clinical Fellow in Thoracic Surgery
Brigham and Women's Hospital
Boston, Massachusetts

Mark S. Allen, MD

Professor of Surgery
Thoracic Surgery
Mayo Clinic
Rochester, Minnesota

Nasser K. Altorki, MB, BCh

Professor of Cardiothoracic Surgery
Weill Cornell Medical College
Chief, Division of Thoracic Surgery
Cardiothoracic Surgery
New York Presbyterian Hospital/Weill Cornell
Medical College
New York, New York

Jatin Anand, MD

Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Cardiovascular Research
Center for Cardiac Support
Texas Heart Institute
Houston, Texas

Robert H. Anderson, BSc, MD, FRC Path

Emeritus Professor
Institute of Child Health
University College
London, United Kingdom;
Visiting Professor
Division of Pediatric Cardiology
Medical University of South Carolina
Charleston, South Carolina;
Visiting Professor
Institute of Human Genetics
Newcastle University
Newcastle Upon Tyne, United Kingdom

Masaki Anraku, MD, MSc

Assistant Professor
Department of Thoracic Surgery
Graduate School of Medicine
The University of Tokyo
Tokyo, Japan

Anelechi C. Anyanwu, MD

Professor and Vice Chairman
Department of Cardiovascular Surgery
The Mount Sinai Medical Center
New York, New York

Amit Arora, MD

Department of Cardiovascular Surgery
The Mount Sinai Medical Center
New York, New York

Erle H. Austin, III, MD

Professor and Vice Chairman
Department of Cardiovascular and Thoracic Surgery
University of Louisville
Chief, Cardiothoracic Surgery
Kosair Children's Hospital
Louisville, Kentucky

Eric H. Awtry, MD

Associate Professor of Medicine
 Boston University School of Medicine
 Vice Chair for Clinical Affairs
 Division of Cardiology
 Boston Medical Center
 Boston, Massachusetts

Emile A. Bacha, MD, FACS

Chief, Division of Cardiothoracic and Vascular Surgery
 Department of Surgery
 Columbia University Medical Center
 New York Presbyterian Hospital
 New York, New York

Leah M. Backhus, MD

Assistant Professor
 Division of Cardiothoracic Surgery
 University of Washington
 Seattle, Washington

Jayant Bagai, MD

Assistant Professor of Medicine
 Division of Cardiovascular Medicine
 Vanderbilt University Medical Center
 Nashville, Tennessee

Richard Baillot, MD, FRCSC

Institut Universitaire de Cardiologie et de
 Pneumologie de Québec
 Québec City, Québec, Canada

Christopher W. Baird, MD

Assistant Professor of Surgery
 Harvard Medical School
 Associate in Cardiac Surgery
 Boston Children's Hospital
 Boston, Massachusetts

David J. Barron, MD, FRCP, FRCS(CT)

Consultant Cardiac Surgeon
 Birmingham Children's Hospital
 NHS Foundation Trust
 Birmingham, United Kingdom

Joseph E. Bavaria, MD

Brooke Roberts/William Maul Measey Professor of
 Surgery
 Vice Chair, Division of Cardiovascular Surgery
 Director, Thoracic Aortic Surgery
 Department of Surgery
 Division of Cardiovascular Surgery
 University of Pennsylvania
 Hospital of University of Pennsylvania
 Philadelphia, Pennsylvania

Jose M. Bernal, MD, PhD

Consultant and Professor of Surgery
 Department of Cardiovascular Surgery
 Hospital Valdecilla
 University of Cantabria
 Santander, Spain

Valentino J. Bianco, DO, MPH

Research Fellow, Thoracic Surgery
 Department of Cardiothoracic Surgery
 University of Pittsburgh School of Medicine
 University of Pittsburgh Medical Center
 Pittsburgh, Pennsylvania

David P. Bichell, MD

Cornelius Vanderbilt Chair in Surgery
 Professor of Surgery
 Cardiac Surgery
 Vanderbilt University School of Medicine
 Nashville, Tennessee

Sigurbjorn Birgisson, MD

Department of Gastroenterology
 Digestive Disease Institute
 Cleveland Clinic
 Cleveland, Ohio

Nick J.R. Blackburn, BSc

Division of Cardiac Surgery
 University of Ottawa Heart Institute
 Department of Cellular and Molecular Medicine
 University of Ottawa
 Ottawa, Ontario, Canada

Johannes Bonatti, MD

Chairman, Department of Cardiothoracic Surgery
 Cleveland Clinic Abu Dhabi
 Abu Dhabi, United Arab Emirates

Munir Boodhwani, MD, MMSc

Associate Professor
 Division of Cardiac Surgery
 University of Ottawa Heart Institute
 Ottawa, Ontario, Canada

Edward L. Bove, MD

Helen F. and Marvin M. Kirsh Professor of Cardiac
 Surgery
 Chair, Department of Cardiac Surgery
 Professor of Cardiac Surgery
 Professor of Pediatrics and Communicable Disease
 University of Michigan
 Ann Arbor, Michigan

William J. Brawn, CBE, FRCS, FRACS

Consultant Cardiac Surgeon
 Birmingham Children's Hospital
 NHS Foundation Trust
 Birmingham, United Kingdom

Christian P. Brizard, MD

Associate Professor
 University of Melbourne Faculty of Medicine,
 Dentistry
 Health Sciences School of Medicine
 Cardiac Surgery Unit
 Royal Children's Hospital
 Melbourne, Victoria, Australia

Julie A. Brothers, MD

Assistant Professor of Pediatrics
Perelman School of Medicine
University of Pennsylvania
Attending Physician, Cardiology
Medical Director, Coronary Anomaly Management
Program
Medical Director, Lipid Heart Clinic
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Lisa M. Brown, MD, MAS

Cardiothoracic Surgery Fellow
Division of Cardiothoracic Surgery
Washington University
St. Louis, Missouri

Ayesha S. Bryant, MD

Assistant Professor of Surgery
Division of Cardiothoracic Surgery
University of Alabama at Birmingham
Birmingham, Alabama

Harold M. Burkhart, MD

Professor of Surgery
Section of Cardiothoracic Surgery
The University of Oklahoma Health Sciences School of
Medicine
Director of Pediatric Cardiovascular Surgery
Medical Director of Pediatric Cardiovascular Surgical
Services
The Children's Hospital
Oklahoma City, Oklahoma

Christopher A. Caldarone, MD, FRCSC

Cardiovascular Surgery
The Hospital for Sick Children
Toronto, Ontario, Canada

Jeremy W. Cannon, MD, SM, FACS

Lieutenant Colonel, U.S. Air Force
Chief, Trauma and Critical Care
San Antonio Military Medical Center
San Antonio, Texas
Associate Professor of Surgery
Uniformed Services University of the Health Sciences
Bethesda, Maryland

Justine M. Carr, MD

Chief Medical Officer
Steward Health Care System
Senior Director, Department of Clinical Resource
Management
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Serenella Castelvechio, MD

Department of Cardiac Surgery
IRCCS Policlinico San Donato
Milan, Italy

Javier G. Castillo, MD

Department of Cardiovascular Surgery
The Mount Sinai Medical Center
New York, New York

Frank Cecchin, MD

Professor of Pediatrics
Pediatric Cardiology
New York University
New York, New York

Robert J. Cerfolio, MD

Chief of Thoracic Surgery
Professor of Cardiothoracic Surgery
University of Alabama at Birmingham
Birmingham, Alabama

A. Alfred Chahine, MD

Associate Professor of Surgery and Pediatrics
George Washington University School of Medicine
Attending Surgeon
Children's National Medical Center
Chief of Pediatric Surgery
MedStar Georgetown University Hospital
Washington, DC

Elliot L. Chaikof, MD, PhD

Johnson and Johnson Professor of Surgery
Chairman, Roberta and Stephen R. Weiner
Department of Surgery
Harvard Medical School
Surgeon-in-Chief
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Vincent Chan, MD, MPH

Assistant Professor
Division of Cardiac Surgery
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Sunit-Preet Chaudhry, MD

Cardiovascular Institute
Warren Alpert Medical School of Brown University
Providence, Rhode Island

Frederick Y. Chen, MD, PhD

Associate Professor of Cardiac Surgery
Harvard Medical School
Department of Surgery
Division of Cardiac Surgery
Brigham and Women's Hospital
Boston, Massachusetts

Stuart H. Chen, MD

Clinical Fellow in Medicine
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Aaron M. Cheng, MD

Assistant Professor
Division of Cardiothoracic Surgery
University of Washington
Seattle, Washington

Victor Chien, MD

Research Fellow in Surgery
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Alvin J. Chin, MD

Professor of Pediatrics, Emeritus
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Cynthia S. Chin, MD

Director of the Women's Cancer Program Services
Thoracic Surgery
White Plains Hospital
White Plains, New York

Peter Chiu, MD

Resident, Department of Cardiothoracic Surgery
Stanford University School of Medicine
Stanford, California

Joseph C. Cleveland, Jr., MD

Professor of Cardiothoracic Surgery
Surgical Director, Cardiac Transplantation and MCS
University of Colorado Anschutz Medical Center
Aurora, Colorado

Lawrence H. Cohn, MD

Hubbard Professor of Cardiac Surgery
Harvard Medical School
Department of Surgery
Division of Cardiac Surgery
Brigham and Women's Hospital
Boston, Massachusetts

William E. Cohn, MD

Professor of Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Director, Center for Technology and Innovation
Director, Cullen Cardiovascular Research Laboratory
Texas Heart Institute
Houston, Texas

Yolonda L. Colson, MD, PhD

Professor
Department of Surgery
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

Wilson S. Colucci, MD

Thomas J. Ryan Professor of Medicine
Professor of Physiology
Boston University School of Medicine
Chief, Section of Cardiovascular Medicine
Co-Director, Cardiovascular Center
Boston Medical Center
Boston, Massachusetts

Andrew C. Cook, PhD

Senior Lecturer
Cardiac Unit
UCL Institute of Cardiovascular Science
Great Ormond Street Hospital
NHS Foundation Trust
London, United Kingdom

Joseph S. Coselli, MD

Professor and Chief
Division of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Chief, Section of Adult Cardiac Surgery
The Texas Heart Institute
Houston, Texas

Todd C. Crawford, MD

Division of Thoracic Surgery
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Melissa Culligan, BSN, RN

Department of Thoracic Surgery
University of Pennsylvania Health System—Presbyterian
Philadelphia, Pennsylvania

François Dagenais, MD, FRCSC

Institut Universitaire de Cardiologie et de Pneumologie
de Québec
Québec City, Québec, Canada

Ralph J. Damiano, Jr., MD

Evarts A. Graham Professor of Surgery
Chief, Division of Cardiothoracic Surgery
Washington University School of Medicine
Barnes-Jewish Hospital
St. Louis, Missouri

Thomas A. D'Amico, MD

Gary Hock Endowed Professor and Vice Chair of
Surgery
Duke University School of Medicine
Chief, Section of General Thoracic Surgery
Program Director, Thoracic Surgery
Duke University Medical Center
Durham, North Carolina

Philippe G. Dartevelle, MD

Head, Service de Chirurgie Thoracique, Vasculaire et
Transplantation Cardiopulmonaire
Hôpital Marie Lannelongue
Le Plessis Robinson, France

Tirone E. David, MD

Professor of Surgery
University of Toronto
Attending Surgeon
Peter Munk Cardiac Centre
Toronto General Hospital
Toronto, Ontario, Canada

Jonathan D'Cunha, MD, PhD

Associate Professor of Surgery
Vice Chairman, Academic Affairs and Education
Surgical Director, Lung Transplantation
Associate Program Director, Thoracic Surgery
Department of Cardiothoracic Surgery
University of Pittsburgh
Pittsburgh, Pennsylvania

Kim I. de la Cruz, MD

Assistant Professor of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Clinical Staff
The Texas Heart Institute
Houston, Texas

Joseph A. Dearani, MD

Professor of Surgery
Chair, Cardiac Surgery
Division of Cardiovascular Surgery
Mayo Clinic
Rochester, Minnesota

Daniel T. DeArmond, MD

Cardiothoracic Surgery
University of Texas Health Science Center
San Antonio, Texas

Pedro J. del Nido, MD

William E. Ladd Professor of Surgery
Harvard Medical School
Chairman, Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Tom R. DeMeester, MD

Professor and Chairman, Emeritus
Department of Surgery
University of Southern California
Los Angeles, California

Philippe Demers, MD, MSC, FRCSC

Associate Professor of Surgery
Cardiac Surgery
University of Montreal
Cardiovascular Surgeon
Montreal Heart Institute
Montreal, Quebec, Canada

Todd L. Demmy, MD

Chairman, Department of Thoracic Surgery
Roswell Park Cancer Institute
Buffalo, New York

Elisabeth U. Dexter, MD

Assistant Professor of Oncology
Department of Thoracic Surgery
Roswell Park Cancer Institute
Assistant Professor of Surgery
SUNY University at Buffalo
Buffalo, New York

Rajeev Dhupar, MD

Assistant Professor of Surgery
Department of Cardiothoracic Surgery
Division of Thoracic and Foregut Surgery
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

James A. DiNardo, MD

Professor of Anesthesia
Boston Children's Hospital
Harvard Medical School
Boston, Massachusetts

Thomas P. Doyle, MD

Associate Professor of Pediatrics
Division of Cardiology
Vanderbilt University School of Medicine
Nashville, Tennessee

Afshin Ehsan, MD

Assistant Professor of Surgery
Brown Alpert Medical School
Rhode Island Hospital
Providence, Rhode Island

Gebrine El Khoury, MD, PhD

Professor
Department of Cardiovascular and Thoracic Surgery
Cliniques Universitaires Saint-Luc
Brussels, Belgium

Ethan R. Ellis, MD

Harvard-Thorndike Electrophysiology Institute
Cardiovascular Division
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Nassrene Y. Elmadhun, MD

Research Fellow
Cardiovascular Research Center
Warren Alpert Medical School
Brown University
Providence, Rhode Island
Surgical Resident
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Sitaram M. Emani, MD

Assistant Professor in Surgery
 Harvard Medical School
 Assistant in Cardiac Surgery
 Surgical Director, Adult Congenital Heart Program
 Director, Complex Biventricular Repair Program
 Surgical Director, Division of Cardiovascular Critical Care
 Boston Children's Hospital
 Boston, Massachusetts

Jeremy J. Erasmus, MD

Professor
 Department of Diagnostic Imaging
 The University of Texas MD Anderson Cancer Center
 Houston, Texas

Dario O. Fauza, MD

Associate Professor of Surgery
 Harvard Medical School
 Associate in Surgery
 Boston Children's Hospital
 Boston, Massachusetts

Adam S. Fein, MD

Cardiac Services
 Beth Israel Deaconess Medical Center
 Boston, Massachusetts

Amy G. Fiedler, MD

Clinical Fellow in Surgery
 Department of Surgery
 Division of Cardiac Surgery
 Brigham and Women's Hospital
 Boston, Massachusetts

Murilo Foppa, MD, DSc

Department of Medicine
 Cardiovascular Division
 Harvard-Thorndike Laboratory
 Harvard Medical School
 Beth Israel Deaconess Medical Center
 Boston, Massachusetts;
 Division of Cardiology
 Hospital de Clinicas de Porto Alegre
 Federal University of Rio Grande do Sul
 Brazil

Rosario V. Freeman, MD, MS

Medical Director, Echocardiography
 Program Director, Cardiology Fellowship Programs
 University of Washington
 Seattle, Washington

Joseph Friedberg, MD, FACS

Chief of Thoracic Surgery
 University of Pennsylvania Health System–Presbyterian
 Philadelphia, Pennsylvania

Michael Friscia, MD

Associate, Thoracic and Cardiac Surgery
 Geisinger Health System
 Danville, Pennsylvania

Francis Fynn-Thompson, MD

Assistant Professor of Surgery
 Surgical Director, Heart and Lung Transplantation
 Surgical Director, Mechanical Circulatory Support Program
 Program Director, Congenital Cardiac Surgery
 Residency/Fellowship
 Department of Cardiac Surgery
 Boston Children's Hospital
 Harvard Medical School
 Boston, Massachusetts

J. William Gaynor, MD

Professor of Surgery
 Perelman School of Medicine
 University of Pennsylvania
 Attending Surgeon
 Director, Fetal Neuroprotection and Neuroplasticity Program
 Daniel M. Tabas Endowed Chair, Pediatric Cardiothoracic Surgery
 The Children's Hospital of Philadelphia
 Philadelphia, Pennsylvania

Liang Ge, PhD

Assistant Professor of Surgery
 Department of Surgery
 University of California, San Francisco School of Medicine
 Department of Surgery
 San Francisco VA Medical Center
 San Francisco, California

Tal Geva, MD

Professor of Pediatrics
 Harvard Medical School
 Chief, Division of Noninvasive Cardiac Imaging
 Senior Associate, Department of Cardiology
 Boston Children's Hospital
 Boston, Massachusetts

Neil M. Gheewala, MD

Cardiovascular Institute
 Warren Alpert Medical School of Brown University
 Providence, Rhode Island

A. Marc Gillinov, MD

The Judith Dion Pyle Chair in Heart Valve Research
 Department of Thoracic and Cardiovascular Surgery
 Cleveland Clinic
 Cleveland, Ohio

Donald D. Glower, MD

Professor of Surgery
Department of Surgery
Division of Cardiovascular and Thoracic Surgery
Duke University School of Medicine
Durham, North Carolina

Andrew B. Goldstone, MD

Postdoctoral Research Fellow
Department of Cardiothoracic Surgery
Stanford University School of Medicine
Stanford, California

Shawn S. Groth, MD, MS

Assistant Professor of Surgery
Division of General Thoracic Surgery
Baylor College of Medicine
Houston, Texas

Frederick L. Grover, MD

Professor of Cardiothoracic Surgery
University of Colorado Anschutz Medical Center
Aurora, Colorado

Julius Guccione, PhD

Professor of Surgery
Department of Surgery
University of California, San Francisco School of
Medicine
Associate Professor of Surgery
San Francisco VA Medical Center
San Francisco, California

Richard Ha, MD

Clinical Assistant Professor
Surgical Director, Mechanical Circulatory Support
Program
Department of Cardiothoracic Surgery
Stanford University School of Medicine
Stanford, California

John W. Hammon, MD

Wake Forest University Baptist Medical Center
Winston-Salem, North Carolina

Jennifer M. Hanna, MD

Resident, General Surgery
Duke University School of Medicine
Durham, North Carolina

David G. Harrison, MD

Betty and Jack Bailey Professor of Medicine and
Pharmacology
Director, Division of Clinical Pharmacology
Director, Center for Vascular Biology
Vanderbilt University Medical Center
Nashville, Tennessee

Thomas H. Hauser, MD, MMSc, MPH

Department of Medicine
Cardiovascular Division
Harvard-Thorndike Laboratory
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Matthew C. Henn, MD

Resident, Division of Cardiothoracic Surgery
Washington University School of Medicine
Barnes-Jewish Hospital
St. Louis, Missouri

Jennifer C. Hirsch-Romano, MD

Assistant Professor of Cardiac Surgery
University of Michigan
Ann Arbor, Michigan

Chuong D. Hoang, MD

Assistant Professor
Department of Cardiothoracic Surgery
Division of Thoracic Surgery
Stanford University School of Medicine
Stanford, California

Wayne L. Hofstetter, MD

Professor of Surgery
Director of Esophageal Surgery
Department of Thoracic and Cardiovascular Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Osami Honjo, MD, PhD

Cardiovascular Surgery
The Hospital for Sick Children
Toronto, Ontario, Canada

Tam T. Huynh, MD

Professor
Department of Thoracic and Cardiovascular Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Carlos E. Bravo Iñiguez, MD

Postdoctoral Fellow
Division of Thoracic Surgery
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Sebastian Iturra, MD

Structural Heart and Valve Center
Division of Cardiothoracic Surgery
Joseph B. Whitehead Department of Surgery
Emory University School of Medicine
Atlanta, Georgia

Jeffrey P. Jacobs, MD, FACS, FACC, FCCP

Professor of Surgery
 Division of Cardiac Surgery
 Department of Surgery
 Johns Hopkins University
 Baltimore, Maryland;
 Chief, Division of Cardiovascular Surgery
 Director, Andrews/Daicoff Cardiovascular Program
 Surgical Director of Heart Transplantation and
 Extracorporeal Life Support Programs
 Johns Hopkins All Children's Heart Institute
 All Children's Hospital and Florida Hospital for
 Children
 Saint Petersburg, Tampa, and Orlando, Florida

Marshall L. Jacobs, MD

Division of Cardiac Surgery
 Department of Surgery
 Johns Hopkins University
 Baltimore, Maryland

Michael T. Jaklitsch, MD

Associate Professor
 Surgeon, Division of Thoracic Surgery
 Brigham & Women's Hospital
 Harvard Medical School
 Boston, Massachusetts

Stuart W. Jamieson, MB, FRCS

Distinguished Professor of Surgery
 Endowed Chair, Division of Cardiothoracic Surgery
 University of California, San Diego
 San Diego, California

Doraid Jarrar, MD

Thoracic Surgeon
 Einstein Healthcare
 East Norriton, Pennsylvania

Craig M. Jarrett, MD

Department of Thoracic and Cardiovascular Surgery
 Cleveland Clinic
 Cleveland, Ohio

David R. Jones, MD

Professor and Chief of Thoracic Surgery
 Memorial Sloan-Kettering Cancer Center
 New York, New York

Mark E. Josephson, MD

Harvard-Thorndike Electrophysiology Institute,
 Cardiovascular Division
 Harvard Medical School
 Beth Israel Deaconess Medical Center
 Boston, Massachusetts

Lilian P. Joventino, MD

Wentworth Health Partners Cardiovascular Group
 Dover, New Hampshire

Amy L. Juraszek, MD

Associate Professor
 Departments of Pediatrics and Pathology
 University of Texas Southwestern Medical Center
 Dallas, Texas

Stefan S. Kachala, MD

Department of Thoracic and Cardiovascular Surgery
 Cleveland Clinic
 Cleveland, Ohio

Larry R. Kaiser, MD

Dean and Professor of Surgery
 Temple University School of Medicine
 President and CEO
 Temple University Health System
 Sr. Executive Vice President for the Health Sciences
 Temple University
 Philadelphia, Pennsylvania

Kirk R. Kanter, MD

Professor of Surgery
 Pediatric Cardiac Surgery
 Emory University School of Medicine
 Atlanta, Georgia

John M. Karamichalis, MD

Clinical Instructor in Surgery
 Department of Surgery
 Division of Pediatric Cardiothoracic Surgery
 University of California, San Francisco
 San Francisco, California

Aditya K. Kaza, MD

Assistant Professor of Surgery
 Harvard Medical School
 Associate in Cardiac Surgery
 Department of Cardiac Surgery
 Boston Children's Hospital
 Boston, Massachusetts

Clinton D. Kemp, MD

Division of Thoracic Surgery
 The Johns Hopkins Medical Institutions
 Baltimore, Maryland

Kemp H. Kernstine, Sr., MD, PhD

Professor and Chief, Division of Thoracic Surgery
 Department of Cardiovascular & Thoracic Surgery
 University of Texas Southwestern Medical Center
 Dallas, Texas

Suresh Keshavamurthy, MD

Cleveland Clinic
 Cleveland, Ohio

Shaf Keshavjee, MD, MSc, FRCS, FACS

Surgeon-in-Chief, University Health Network
 James Wallace McCutcheon Chair in Surgery
 Professor, Division of Thoracic Surgery
 University of Toronto
 Toronto, Ontario, Canada

Deborah J. Kozik, DO

Assistant Professor of Surgery
Department of Cardiovascular and Thoracic Surgery
University of Louisville
Cardiothoracic Surgery
Kosair Children's Hospital
Louisville, Kentucky

Roger J. Laham, MD

Associate Professor of Medicine
Harvard Medical School
Research Investigator
CardioVascular Institute
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Michael J. Landzberg, MD

Director, Boston Adult Congenital Heart (BACH) and
Pulmonary Hypertension Program
Department of Cardiology
Brigham and Women's Hospital and Boston Children's
Hospital
Boston, Massachusetts

Christopher P. Lawrance, MD

Resident, Division of Cardiothoracic Surgery
Washington University School of Medicine
Barnes-Jewish Hospital
St. Louis, Missouri

Lawrence S. Lee, MD

Clinical Fellow in Surgery
Harvard Medical School
Department of Surgery
Division of Cardiac Surgery
Brigham and Women's Hospital
Boston, Massachusetts

Scott A. LeMaire, MD

Professor and Vice Chair for Research
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Professional Staff, Department of Cardiovascular
Surgery
The Texas Heart Institute
Houston, Texas

Sidney Levitsky, MD

David W. and David Cheever Professor of Surgery
Harvard Medical School
Director, Cardiothoracic Surgery Care Group
Senior Vice Chairman, Department of Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Jerrold H. Levy, MD, FAHA, FCCM

Professor of Anesthesiology
Associate Professor of Surgery
Departments of Anesthesiology, Surgery, and Critical
Care
Co-Director, Cardiothoracic ICU
Duke University School of Medicine
Duke University Medical Center
Durham, North Carolina

Philip A. Linden, MD

Associate Professor of Surgery
Case Western Reserve School of Medicine
Chief, Division of Thoracic and Esophageal Surgery
University Hospitals Case Medical Center
Cleveland, Ohio

Michael J. Liptay, MD

The Mary and John Bent Professor and Chairperson
Department of Cardiovascular and Thoracic Surgery
Rush University Medical Center
Chicago, Illinois

Virginia R. Litle, MD, FACS

Associate Professor of Surgery
Department of Surgery
Division of Thoracic Surgery
Boston University School of Medicine
Boston, Massachusetts

Mauro Lo Rito, MD

Cardiovascular Surgery
The Hospital for Sick Children
Toronto, Ontario, Canada

James D. Luketich, MD

Henry T. Bahnson Professor and Chairman
Department of Cardiothoracic Surgery
Chief, Division of Thoracic and Foregut Surgery
University of Pittsburgh School of Medicine
Director, Thoracic Surgical Oncology
Co-Director, Lung Cancer Center
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Bruce W. Lytle, MD

Chairman, Strategic Development and Planning
for Cardiovascular Medicine and Surgery
The Heart Hospital Baylor Plano
Plano, Texas

Michael Madani, MD

Professor of Surgery
Chief, Division of Cardiothoracic Surgery
University of California, San Diego
San Diego, California

Feroze Mahmood, MD

Associate Professor of Anaesthesiology
Harvard Medical School
Director, Vascular Anesthesia/Perioperative
Echocardiography
Beth Israel Deaconess Medical Center
Harvard Medical Faculty Physicians at Beth Israel
Deaconess Medical Center
Boston, Massachusetts

Hari R. Mallidi, MD

Associate Professor of Surgery
Chief, Division of Transplant & Assist Devices
Lester and Sue Smith Endowed Chair in Surgery
Baylor College of Medicine
Houston, Texas

Abeel A. Mangi, MD

Associate Professor of Surgery, Section of Cardiac
Surgery
Surgical Director, Center for Advanced Heart Failure,
Mechanical Circulatory Support and Heart
Transplantation
Surgical Director, Trans-Catheter Therapies
Yale University
New Haven, Connecticut

Warren J. Manning, MD

Departments of Medicine and Radiology
Cardiovascular Division
Harvard-Thorndike Laboratory
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Edith M. Marom, MD

Professor
Department of Diagnostic Imaging
The University of Texas MD Anderson Cancer Center
Houston, Texas

Audrey C. Marshall, MD

Chief, Invasive Cardiology
Boston Children's Hospital
Boston, Massachusetts

Mauricio Perez Martinez, MD

Division of Thoracic Surgery
Brigham and Women's Hospital
Harvard Medical School
Boston, Massachusetts

Christopher E. Mascio, MD

Assistant Professor of Clinical Medicine
Perelman School of Medicine
University of Pennsylvania
Pediatric Cardiothoracic Surgeon
Division of Cardiothoracic Surgery
The Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

David P. Mason, MD

Chief, Thoracic Surgery and Lung Transplantation
Department of Thoracic Surgery
Baylor University Medical Center
Dallas, Texas

Douglas J. Mathisen, MD

Chief of Thoracic Surgery
Massachusetts General Hospital
Boston, Massachusetts

Kenneth L. Mattox, MD, FACS

Professor of Surgery
Division of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Houston, Texas

Robina Matyal, MD

Associate Professor of Anaesthesiology
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

James D. McCully, PhD

Associate Professor of Surgery
Harvard Medical School
Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Robert J. McKenna, Jr., MD

Director, Thoracic Surgery
Surgery
Cedars-Sinai Medical Center
Los Angeles, California

Ciaran McNamee, MD

Instructor in Surgery
Harvard Medical School
Associate Surgeon
Brigham and Women's Hospital
Boston, Massachusetts

Jeffrey D. McNeil, MD

Colonel, U.S. Air Force
Chief, Cardiothoracic Surgery Service
San Antonio Military Medical Center
San Antonio, Texas
Clinical Assistant Professor, Cardiothoracic Surgery
University of Texas Health Science Center, San
Antonio
San Antonio, Texas

Lorenzo Menicanti, MD

Chief of Cardiac Surgery
IRCCS Policlinico San Donato
Milan, Italy

Carlos A. Mestres, MD, PhD, FETCS

Senior Consultant
Department of Cardiovascular Surgery
Hospital Clinico
University of Barcelona
Barcelona, Spain;
Cardiothoracic and Vascular Surgery
Heart and Vascular Institute
Cleveland Clinic Abu Dhabi
Abu Dhabi, United Arab Emirates

Bret A. Mettler, MD

Assistant Professor
Division of Pediatric Cardiac Surgery
Vanderbilt University School of Medicine
Department of Cardiac Surgery
Vanderbilt University Medical Center
Nashville, Tennessee

Bryan Fitch Meyers, MD, MPH

Patrick and Joy Williamson Professor of Surgery
Chief, Thoracic Surgery
Washington University School of Medicine
St. Louis, Missouri

Stephanie Mick, MD

Cardiovascular Surgeon
Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Tomislav Mihaljevic, MD

Chief of Staff and Chairman of the Heart and Vascular
Institute
Cleveland Clinic Abu Dhabi
Abu Dhabi, United Arab Emirates;
Attending Surgeon
Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Professor of Surgery
Cleveland Clinic Lerner College of Medicine at Case
Western University
Cleveland, Ohio

Carmelo A. Milano, MD

Professor of Surgery
Cardiovascular and Thoracic Surgery
Duke University
Durham, North Carolina

D. Craig Miller, MD

Thelma and Henry Doelger Professor of
Cardiovascular Surgery
Department of Cardiovascular Surgery
Stanford University School of Medicine
Department of Cardiothoracic Surgery
Stanford University Medical Center
Stanford, California

Daniel L. Miller, MD, FACS

Clinical Professor of Surgery
Georgia Regents University
Chief, General Thoracic Surgery
WellStar Health System
Mayo Clinic Care Network
Marietta, Georgia

Meagan M. Miller, RN, BSN

Vanderbilt University Medical Center
Nashville, Tennessee

John D. Mitchell, MD

Courtenay C. and Lucy Patten Davis Endowed Chair
in Thoracic Surgery
Professor and Chief, Section of General Thoracic
Surgery
Division of Cardiothoracic Surgery
University of Colorado School of Medicine
Aurora, Colorado

Mario Montealegre-Gallegos, MD

Department of Anaesthesia
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Neal G. Moores, MD

Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Charles E. Murphy, MD

Assistant Professor of Surgery
Division of Cardiovascular and Thoracic Surgery
Duke University School of Medicine
Duke University Medical Center
Durham, North Carolina

Raghav A. Murthy, MD

Department of Cardiovascular & Thoracic Surgery
University of Texas Southwestern Medical Center
Dallas, Texas

Sudish C. Murthy, MD, PhD

Section Head, General Thoracic Surgery
Surgical Director, Center for Major Airway Disease
Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Sacha Mussot, MD

Hôpital Marie Lannelongue
Service de Chirurgie Thoracique, Vasculaire et
Transplantation Cardiopulmonaire
Le Plessis Robinson, France

Yoshifumi Naka, MD, PhD

Professor of Surgery
Columbia University College of Physicians and Surgeons
Attending Surgeon
New York–Presbyterian Hospital
New York, New York

Meena Nathan, MD, FRCS

Instructor in Surgery
Harvard Medical School
Staff Cardiac Surgeon
Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Kurt D. Newman, MD

President and Chief Executive Officer
Children's National Medical Center
Washington, DC

Chukwumere Nwogu, MD

Associate Professor
Department of Thoracic Surgery
Roswell Park Cancer Institute
Buffalo, New York

Kirsten C. Odegard, MD

Associate Professor
Department of Anesthesiology, Perioperative and Pain Medicine
Boston Children's Hospital
Boston, Massachusetts

Daniel S. Oh, MD

Assistant Professor of Surgery
Division of Thoracic Surgery
University of Southern California
Los Angeles, California

Richard G. Ohye, MD

Professor of Cardiac Surgery
University of Michigan
Ann Arbor, Michigan

Mark W. Onaitis, MD

Associate Professor of Surgery
Department of Surgery
Division of Cardiovascular and Thoracic Surgery
Duke University School of Medicine
Duke University Medical Center
Durham, North Carolina

Aleksandra Ostojic, MSc

Division of Cardiac Surgery
University of Ottawa Heart Institute
Department of Cellular and Molecular Medicine
University of Ottawa
Ottawa, Ontario, Canada

Harald C. Ott, MD

Division of Thoracic Surgery
Massachusetts General Hospital
Boston, Massachusetts

Maral Ouzounian, MD, PhD

Assistant Professor of Surgery
University of Toronto
Cardiovascular Surgeon
Division of Cardiovascular Surgery
University Health Network
Toronto General Hospital
Toronto, Ontario, Canada

Khurram Owais, MD

Department of Anaesthesia
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Massimo Padalino, MD, PhD

Department of Cardio Thoracic and Vascular Sciences
University Hospital
Padova, Italy

Konstantinos Papadakis, MD

Instructor in Surgery
Harvard Medical School
Department of Surgery
Boston Children's Hospital
Boston, Massachusetts

G. A. Patterson, MD

Evarts A. Graham Professor of Surgery
Chief, Division of Cardiothoracic Surgery
Washington University
St. Louis, Missouri

Edward F. Patz, Jr., MD

Professor
Department of Radiology
Duke University
Durham, North Carolina

Subroto Paul, MD

Associate Professor
Department of Cardiothoracic Surgery
Weill Cornell Medical College
New York, New York

Arjun Pennathur, MD

Sampson Family Endowed Chair in Thoracic Surgical Oncology
Associate Professor of Cardiothoracic Surgery
Department of Cardiothoracic Surgery
University of Pittsburgh School of Medicine
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Yaron Perry, MD

Clinical Associate Professor of Surgery
Case Western Reserve University School of Medicine
Director, Minimally Invasive Esophageal Surgery
University Hospitals Case Medical Center
Cleveland, Ohio

Robert N. Piana, MD

Professor of Medicine
Division of Cardiovascular Medicine
Director, Adult Congenital Interventional Program
Vanderbilt University Medical Center
Nashville, Tennessee

Frank A. Pigula, MD

Associate Professor of Surgery
Harvard Medical School
Senior Associate in Cardiac Surgery
Clinical Director, Cardiac Surgery Program
Director, Neonatal Cardiac Surgery Program
Boston Children's Hospital
Boston, Massachusetts

Duane S. Pinto, MD, MPH

Associate Professor of Medicine
Harvard Medical School
Associate Director, Cardiac Catheterization Laboratory
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Jose L. Pomar, MD, PhD, FETCS

Senior Consultant and Professor of Surgery
Department of Cardiovascular Surgery
Hospital Clinico
University of Barcelona
Barcelona, Spain

Ourania Preventza, MD

Assistant Professor of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Clinical Staff
The Texas Heart Institute
Houston, Texas

Bradley Pua, MD

Assistant Professor of Radiology
Weill Cornell Medical College
Program Director, Interventional Radiology Fellowship
Director, Lung Cancer Screening Program
New York Presbyterian Hospital/Weill Cornell Medical Center
New York, New York

Varun Puri, MD

Assistant Professor of Surgery
Division of Cardiothoracic Surgery
Washington University
St. Louis, Missouri

Luis Quinonez, MD

Instructor in Surgery
Harvard Medical School
Assistant in Cardiac Surgery
Department of Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Siva Raja, MD, PhD

Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Mark Ratcliffe, MD

Professor of Surgery
Department of Surgery
University of California, San Francisco
Chief Surgical Consultant
Sierra Pacific VA Network
San Francisco, California

Michael J. Reardon, MD

Professor of Cardiothoracic Surgery
Allison Family Distinguished Chair of Cardiovascular Research
Houston Methodist DeBakey Heart & Vascular Center
Houston, Texas

John J. Reilly, Jr., MD

Dean
University of Colorado School of Medicine
Vice Chancellor for Health Affairs
University of Colorado
Aurora, Colorado

Karl G. Reyes, MD

Department of Thoracic and Cardiovascular Surgery
Cleveland Clinic
Cleveland, Ohio

Thomas W. Rice, MD

Head, Section of General Thoracic Surgery
Department of Thoracic and Cardiovascular Surgery
Heart and Vascular Institute
Cleveland Clinic
Cleveland, Ohio

Robert C. Robbins, MD

President and Chief Executive Officer
Texas Medical Center
Houston, Texas;
Consulting Professor
Stanford Cardiovascular Institute
Stanford, California

Gaetano Rocco, MD, FRCS(Ed), FECTS

Director, Department of Thoracic Surgery and Oncology
National Cancer Institute, Pascale Foundation
Naples, Italy

Fraser D. Rubens, MD, MSc, FACS, FRCSC

Professor of Surgery
Division of Cardiac Surgery
Residency Program Director
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Marc Ruel, MD, MPH

Professor and Chair
Division of Cardiac Surgery
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Valerie W. Rusch, MD

Attending Surgeon, Thoracic Service
Vice Chair for Clinical Research
Miner Family Chair in Intrathoracic Cancers
Department of Surgery
Memorial Sloan-Kettering Cancer Center
New York, New York

Ashraf A. Sabe, MD

Clinical Teaching Fellow, General Surgery
Harvard Medical School
Resident, General Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts;
Research Fellow, Cardiothoracic Surgery
Warren Alpert Medical School of Brown University
Providence, Rhode Island

Sameh M. Said, MD

Senior Associate Consultant
Division of Cardiovascular Surgery
Mayo Clinic
Rochester, Minnesota

Pamela P. Samson, MD, MPH

Resident, Department of Surgery
Washington University and Barnes-Jewish Hospital
St. Louis, Missouri

Stephen P. Sanders, MD

Professor of Pediatrics
Harvard Medical School
Director, Cardiac Registry
Departments of Cardiology, Pathology, Cardiac Surgery
Boston Children's Hospital
Boston, Massachusetts

Eric L. Sarin, MD

Assistant Professor of Surgery
Structural Heart and Valve Center
Division of Cardiothoracic Surgery
Joseph B. Whitehead Department of Surgery
Emory University School of Medicine
Atlanta, Georgia

Hartzell V. Schaff, MD

Professor of Surgery
Mayo Clinic
Rochester, Minnesota

Lara W. Schaheen, MD

Resident, Department of Cardiothoracic Surgery
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Christopher W. Seder, MD

Assistant Professor of Thoracic and Cardiac Surgery
Rush University Medical Center
Chicago, Illinois

Frank W. Sellke, MD

Karl Karlson & Gloria Karlson Professor and Chief of
Cardiothoracic Surgery
Warren Alpert Medical School of Brown University
and Rhode Island Hospital
Director, Lifespan Cardiovascular Institute
Providence, Rhode Island

Boris Sepesi, MD

Assistant Professor
Department of Thoracic and Cardiovascular Surgery
Division of Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Rohit Shahani, MD

Cardiothoracic Surgery
Hudson Cardiothoracic Surgeons
Poughkeepsie, New York

Robert C. Shamberger, MD

Robert E. Gross Professor of Surgery
Harvard Medical School
Chief of Surgery
Boston Children's Hospital
Boston, Massachusetts

Oz M. Shapira, MD

Professor and Chairman
Department of Cardiothoracic Surgery
Hebrew University
Hadassah Medical Center
Jerusalem, Israel

Steven S. Shay, MD

Department of Gastroenterology
Digestive Disease Institute
Cleveland Clinic
Cleveland, Ohio

Joseph B. Shrager, MD

Professor, Department of Cardiothoracic Surgery
Chief, Division of Thoracic Surgery
Stanford University School of Medicine
Stanford, California

Ming-Sing Si, MD

Assistant Professor of Cardiac Surgery
University of Michigan
Ann Arbor, Michigan

Steve K. Singh, MD, MSc, FRCSC

Assistant Professor of Surgery
Division of Transplant & Assist Devices
Baylor College of Medicine
Houston, Texas

Peter K. Smith, MD

Professor and Chief, Thoracic Surgery
Duke University
Durham, North Carolina

Neel R. Sodha, MD

Assistant Professor of Surgery
Cardiothoracic Surgery
Warren Alpert Medical School of Brown University
Providence, Rhode Island

R. John Solaro, PhD

Distinguished University Professor and Head
Department of Physiology and Biophysics
University of Illinois at Chicago College of Medicine
Chicago, Illinois

Harmik J. Soukiasian, MD

Associate Director, Thoracic Surgery
Cedars-Sinai Medical Center
Los Angeles, California

David Spurlock, MD

Junior Fellow, Cardiac Surgery
University of Michigan
Ann Arbor, Michigan

Giovanni Stellin, MD

Director of Pediatric and Congenital Cardiac Surgery
Department of Cardio Thoracic and Vascular Sciences
University Hospital
Padova, Italy

Brendon M. Stiles, MD

Associate Professor of Cardiothoracic Surgery
Weill Cornell Medical College
Cardiothoracic Surgery
New York Presbyterian Hospital/Weill Cornell Medical
College
New York, New York

Michaela Straznicka, MD

Thoracic Surgeon
Sutter Health Medical Center
Walnut Creek, California

David A. Stump, PhD

Wake Forest University Baptist Medical Center
Winston-Salem, North Carolina

David J. Sugarbaker, MD

Director, The Lung Institute
Chief, Division of Thoracic Surgery
The Olga Keith Wiess Chair of Surgery
Baylor College of Medicine
Houston, Texas

Erik J. Suuronen, PhD

Division of Cardiac Surgery
University of Ottawa Heart Institute
Department of Cellular and Molecular Medicine
University of Ottawa
Ottawa, Ontario, Canada

Lars G. Svensson, MD, PhD

Professor of Surgery, Thoracic and Cardiovascular
Surgery
Chairman, Heart and Vascular Institute
Cleveland Clinic
Cleveland, Ohio

Scott J. Swanson, MD

Director, Minimally Invasive Thoracic Surgery
Brigham and Women's Hospital
Vice Chair, Cancer Affairs
Department of Surgery, Brigham and Women's
Hospital
Chief Surgical Officer
Dana-Farber Cancer Institute
Professor of Surgery
Harvard Medical School
Boston, Massachusetts

Wilson Y. Szeto, MD

Associate Professor of Surgery
Division of Cardiovascular Surgery
Department of Surgery
University of Pennsylvania
Philadelphia, Pennsylvania

Sharven Taghavi, MD

Resident, Department of Surgery
Temple University
Philadelphia, Pennsylvania

Hiroo Takayama, MD, PhD

Assistant Professor of Surgery
Columbia University College of Physicians and
Surgeons
Attending Surgeon
New York-Presbyterian Hospital
New York, New York

Koji Takeda, MD, PhD

Assistant Professor of Surgery
Columbia University College of Physicians and
Surgeons
Attending Surgeon
New York-Presbyterian Hospital
New York, New York

Ravi R. Thiagarajan, MBBS, MPH

Senior Associate in Cardiology
Associate Professor of Pediatrics
Boston Children's Hospital
Boston, Massachusetts

Patricia A. Thistlethwaite, MD, PhD

Professor of Surgery
Program Director, Division of Cardiothoracic Surgery
University of California, San Diego
San Diego, California

Vinod H. Thourani, MD

Professor of Surgery
Structural Heart and Valve Center
Division of Cardiothoracic Surgery
Joseph B. Whitehead Department of Surgery
Emory University School of Medicine
Atlanta, Georgia

Hadi D. Toeg, MD, MSc

Surgical Resident
Division of Cardiac Surgery
University of Ottawa Heart Institute
Ottawa, Ontario, Canada

Michael Z. Tong, MD, MBA

Associate Staff, Thoracic and Cardiovascular Surgery
Heart and Vascular Institute
Cleveland Clinic
Cleveland, Ohio

Alexander G. Truesdell, MD

Cardiac and Vascular Interventionalist
PinnacleHealth CardioVascular Institute
Harrisburg, Pennsylvania

Peter I. Tsai, MD, FACS

Assistant Professor of Surgery
Division of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Houston, Texas

Harold C. Urschel, Jr., MD[†]

Professor of Cardiovascular and Thoracic Surgery
University of Texas Southwestern Medical School
Chair, Cardiovascular and Thoracic Surgical Research,
Education, and Clinical Excellence
Department of Cardiovascular and Thoracic Surgery
Baylor University Medical Center
Dallas, Texas

[†]Deceased.

Anne Marie Valente, MD

Associate Professor of Pediatrics and Internal Medicine
Harvard Medical School
Outpatient Director, Boston Adult Congenital Heart
Disease and Pulmonary Hypertension Program
Department of Cardiology
Boston Children's Hospital
Department of Medicine
Division of Cardiology
Brigham and Women's Hospital
Boston, Massachusetts

Prashanth Vallabhajosyula, MD, MS

Assistant Professor of Surgery
Division of Cardiovascular Surgery
Department of Surgery
University of Pennsylvania
Philadelphia, Pennsylvania

Jeffrey B. Velotta, MD

Thoracic Surgery
Oakland Medical Center
Oakland, California

Vladimiro Vida, MD, PhD

Department of Cardio Thoracic and Vascular Sciences
University Hospital
Padova, Italy

Gus J. Vlahakes, MD

Professor of Surgery
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Pierre Voisine, MD, FRCSC

Department of Cardiac Surgery
Institut Universitaire de Cardiologie et de Pneumologie
de Québec
Québec City, Québec, Canada

Matthew J. Wall, Jr., MD, FACS

Professor of Surgery
Division of Cardiothoracic Surgery
Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Houston, Texas

Garrett L. Walsh, MD

Professor of Surgery
Department of Thoracic and Cardiovascular Surgery
Division of Surgery
The University of Texas MD Anderson Cancer Center
Houston, Texas

Dustin M. Walters, MD

Division of Cardiothoracic Surgery
University of Washington Medical Center
Seattle, Washington

Benjamin Wei, MD

Assistant Professor of Surgery
Division of Cardiothoracic Surgery
University of Alabama at Birmingham
Birmingham, Alabama

Ian J. Welsby, MB BS

Associate Professor of Anesthesiology
Departments of Anesthesiology, Surgery, and Critical
Care
Duke University School of Medicine
Durham, North Carolina

Margaret V. Westfall, PhD

Associate Professor
Department of Cardiac Surgery
University of Michigan School of Medicine
Ann Arbor, Michigan

Daniel C. Wiener, MD

Assistant Professor of Surgery
Harvard Medical School
Thoracic Surgeon
Brigham and Women's Hospital
Boston, Massachusetts

Benson R. Wilcox, MD[†]

Professor of Surgery
Department of Cardiothoracic Surgery
University of North Carolina at Chapel Hill
University of North Carolina Hospital
Chapel Hill, North Carolina

Judson B. Williams, MD, MHS

Resident, Cardiothoracic Surgery
Duke University
Durham, North Carolina

Jay M. Wilson, MD

Associate Professor of Surgery
Harvard Medical School
Senior Associate in Surgery
Boston Children's Hospital
Boston, Massachusetts

Y. Joseph Woo, MD

Norman E. Shumway Professor and Chair
Department of Cardiothoracic Surgery
Stanford University School of Medicine
Professor, by courtesy, Department of Bioengineering
Stanford University
Stanford, California

Douglas E. Wood, MD

Professor and Chief, Endowed Chair in Lung Cancer
Research
Division of Cardiothoracic Surgery
University of Washington
Seattle, Washington

John V. Wylie, Jr., MD

Tufts University School of Medicine
St. Elizabeth's Medical Center
Boston, Massachusetts

Stephen C. Yang, MD

Professor of Surgery
The Johns Hopkins Medical Institutions
Baltimore, Maryland

Sai Yendamuri, MD

Associate Professor
Department of Thoracic Surgery
Roswell Park Cancer Institute
Buffalo, New York

Susan B. Yeon, MD, JD

Department of Medicine
Cardiovascular Division
Harvard-Thorndike Laboratory
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts;
Deputy Editor
UpToDate
Wolters Kluwer Health
Waltham, Massachusetts

Peter J. Zimetbaum, MD

Associate Professor of Medicine
Harvard Medical School
Cardiac Services
Beth Israel Deaconess Medical Center
Boston, Massachusetts

[†]Deceased.

PREFACE

Since its beginning as a specialty to treat tuberculosis and empyema, thoracic surgery has undergone constant change. Indeed, much has evolved in the fields of adult and pediatric cardiovascular and thoracic surgery even since our last edition. Our new ninth edition contains the latest information on the diagnosis and treatment of disease of the thorax. Especially in such areas as repair of aortic and mitral valvular disease, intervention for congenital heart disease, minimally invasive thoracic and cardiac surgery, surgical treatment of arrhythmias, and endovascular treatment of aortic disease, the field has markedly transformed. As with the previous editions, many of the same authors were asked to update their chapters, but some chapters have been added or eliminated and many others have been completely rewritten. Often new authors were chosen not based on poorly written previous chapters but to provide a novel perspective. We hope that the ninth edition will be received with the same enthusiasm as the last.

Several years ago, we lost one of the former editors of this textbook and a giant in the field of surgery, Dr. David Sabiston. We are fortunate to still have with us another editor, Dr. Frank Spencer. Dr. Spencer is not only one of the true pioneers in our specialty but a great mentor to many in our field. We are all indebted to both Dr. Sabiston and Dr. Spencer for their innumerable contributions to the field of surgery.

Finally, we would like to thank our families for providing immeasurable support not only for this textbook but for our entire careers.

Frank W. Sellke
Pedro J. del Nido
Scott J. Swanson

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¹From Coselli JS, LeMaire SA: Extent II repair of thoracoabdominal aortic aneurysm secondary to chronic dissection. *Ann Cardiothorac Surg* 1(3):394–397, 2012.

²Courtesy Ralph Chitwood, MD, Karen A. Gersch, MD, Michael W. Chu, MD, L. W. Nifong, MD, and Jerome Fuller, MD.

³From *Sabiston & Spencer Surgery of the Chest*, ed 8.

⁴From Vassiliades TA: Endoscopic and traditional minimally invasive direct coronary artery bypass. In Sellke FW, editor: *Atlas of cardiac surgical techniques*, Philadelphia, 2009, Elsevier.

⁵Courtesy Keith Horvath, MD.

⁶From Frazier OH: Implantation of the Heart Mate II. In Sellke FW, editor: *Atlas of cardiac surgical techniques*, Philadelphia, 2009, Elsevier.

⁷From Reitz BA, Baumgartner WA, Borkon AM, the American College of Surgeons Video-Based Education Collection.

⁸Courtesy Lorenzo Menicanti, MD, and Marisa Di Donato, MD.

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SABISTON & SPENCER

SURGERY *of the* CHEST

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SURGICAL MANAGEMENT OF AORTIC DISEASE

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SURGERY OF THE AORTIC ROOT AND ASCENDING AORTA

Tirone E. David

CHAPTER OUTLINE

FUNCTIONAL ANATOMY OF THE AORTIC ROOT

PATHOLOGY OF THE AORTIC ROOT AND ASCENDING AORTA

Degenerative Aneurysms of the Proximal Aorta

Inherited Aneurysms of the Proximal Aorta

Marfan Syndrome

Loeys-Dietz Syndrome

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Infectious Aneurysms

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FUNCTIONAL ANATOMY OF THE AORTIC ROOT

The aortic root is the anatomic segment between the left ventricle and the ascending aorta. It contains the aortic valve and other anatomic elements, which function as a unit. The aortic root has several anatomic components: the subcommissural triangles, the aortic annulus, the aortic cusps, the aortic sinuses or sinuses of Valsalva, and the sinotubular junction.

The subcommissural triangles are part of the left ventricular outflow tract, but they play an important role in the function of the aortic valve. The subcommissural triangles of the noncoronary aortic cusp are fibrous extension of the intervalvular fibrous body and membranous septum, whereas the subcommissural triangle beneath the left and the right aortic cusps is an extension of the muscular interventricular septum (Fig. 67-1). The aortic annulus, a fibrous structure with a scalloped shape, attaches the aortic valve to the left ventricle. It is attached directly to the myocardium in approximately 45% of its circumference, and to fibrous structures in the remaining

55%. Histologic examination of the aortic annulus reveals that the aortic root has a fibrous continuity with the anterior leaflet of the mitral valve and membranous septum, and it is attached to the muscular interventricular septum by fibrous strands (Fig. 67-2). An important structure immediately below the membranous septum is the bundle of His. The atrioventricular node lies in the floor of the right atrium between the tricuspid annulus and the coronary sinus orifice. This node gives origin to the bundle of His, which travels through the right fibrous trigone along the posterior edge of the membranous septum to the muscular interventricular septum. At this point, the bundle of His divides into left and right bundle branches, which run subendocardially along both sides of the interventricular septum.

The normal aortic valve has three cusps. Each cusp has a semilunar shape and has a base and a free margin. The base is attached to the aortic annulus in a crescent fashion. The point at which the free margin of a cusp joins its base is the commissure, and the ridge in the aortic wall that lies immediately above the commissures is the sinotubular junction. The spaces contained between the aortic annulus and the sinotubular junction are the



FIGURE 67-1 ■ The inside of the aortic root.

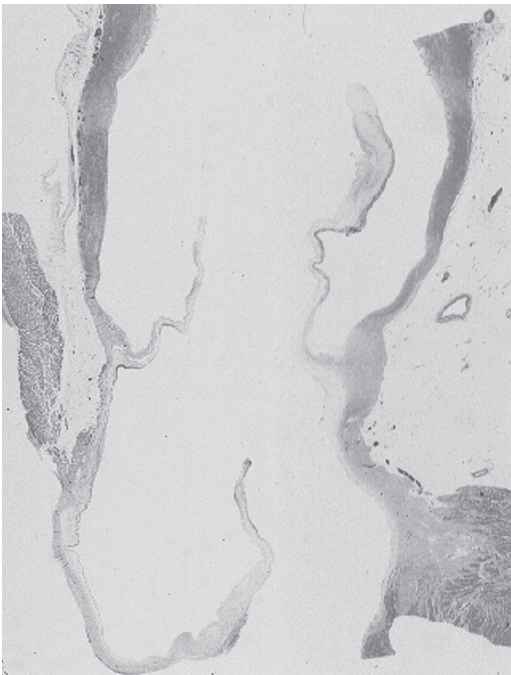


FIGURE 67-2 ■ Microphotograph of the aortic annulus, cusps, and sinuses.

aortic sinuses, or sinuses of Valsalva. There are three cusps and three sinuses: left cusp and sinus, right cusp and sinus, and noncoronary cusp and sinus. The left main coronary artery arises from the left aortic sinus, and the right coronary artery arises from the right aortic sinus.

The normal aortic root has a fairly consistent shape, and the sizes of the cusps, the aortic annulus, the aortic sinuses, and the sinotubular junction are somewhat interdependent.¹⁻⁴ Thus, large cusps have a proportionally large annulus, sinus, and sinotubular junction. The three aortic cusps often have different sizes in a person, and the right and noncoronary cusps are usually larger than the left cusp.³ The same cusp may have different sizes in individuals with the same body surface area.^{3,4} There are, however, certain geometric parameters that are fairly constant among the various components of the aortic root, and this knowledge is indispensable to understanding the principles of aortic valve repair or replacement with stentless biological valves.

The free margin of an aortic cusp extends from one of its commissures to the other. The length of the free margin of an aortic cusp is approximately 1.5 times the length of its base (Fig. 67-3). During diastole, the free margins and part of the body of the three cusps touch each other approximately in the center of the aortic root to seal the aortic orifice. Thus, the average length of the free margins of three aortic cusps must exceed the diameter of the sinotubular junction to allow the cusps to coapt centrally and render the aortic valve competent. If a pathologic process causes shortening of the length of the free margin of a cusp, or if the sinotubular junction dilates, the cusps cannot coapt centrally, resulting in aortic insufficiency (Fig. 67-4). If the length of a free margin is elongated, the cusp prolapses, and depending on the degree of prolapse, aortic insufficiency ensues (Fig. 67-5).

The diameter of the aortic annulus is 10% to 20% larger than the diameter of the sinotubular junction of the aortic root in young patients (see Fig. 67-3). As the number of elastic fibers in the arterial wall decreases with age, the sinotubular junction dilates, and its diameter tends to become equal to that of the aortic annulus in older patients.

Dilation of the aortic annulus pulls the belly of the aortic cusps apart, decreasing the coaptation area, and it

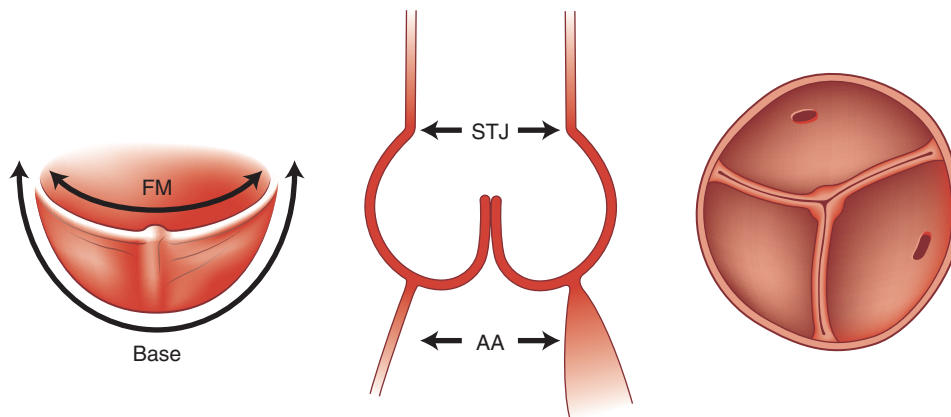


FIGURE 67-3 ■ Geometric relationship between the free margin (FM) and base of the aortic cusps, sinotubular junction (STJ), and aortic annulus (AA).

eventually causes aortic insufficiency (Fig. 67-6). With dilation of the aortic annulus, the subcommissural triangles of the noncoronary cusp tend to become more obtuse as the crescent shape of the aortic annulus along its fibrous insertion flattens (see Fig. 67-6). The subcommissural triangle beneath the right and left cusps does not change much in patients with annuloaortic ectasia, because it is part of the muscular interventricular septum and is not affected by the connective tissue disorder that causes dilation of the fibrous skeleton of the heart.

The aortic sinuses facilitate closure of the aortic valve by creating eddies and currents between the cusps and arterial wall (Fig. 67-7). They also prevent the cusps from

occluding the coronary artery orifices during systole, thus guaranteeing myocardial perfusion during the entire cardiac cycle. Isolated dilation of the aortic sinuses does not cause aortic insufficiency.⁵

The aortic root of young individuals is elastic and very compliant. It expands and contracts during the cardiac cycle. Expansion and contraction of the aortic annulus are heterogeneous, probably because of its attachments to contractile myocardium and to fibrous structures such as the membranous septum and intervalvular fibrous body. On the other hand, the expansion and contraction of the sinotubular junction are more uniform. The aortic root also displays some degree of torsion during isovolumic contraction and ejection of the left ventricle.⁶ Compliance decreases with aging because of loss of elastic fibers, and the movements of the aortic annulus, cusps, sinuses, and sinotubular junction also change.

PATHOLOGY OF THE AORTIC ROOT AND ASCENDING AORTA

The wall of the aorta is composed of three layers: intima, media, and adventitia. The intima is a thin layer of ground substance lined by endothelium, and it is easily traumatized. The media is the thickest of the three layers, and it is made of elastic fibers arranged in spiral fashion to increase the tensile strength. The adventitia is a thin, fibrous layer and contains the vasa vasorum, which carries the nutrients to the media. The aorta is highly compliant, and it expands and contracts during the cardiac cycle because of the elastic fibers in the media. Compliance decreases with aging because of fragmentation of the elastic fibers and an increase in the amount of fibrous tissue in the media. Hypertension, hypercholesterolemia, and coronary artery disease cause premature aging of the aorta.⁷⁻⁹ Exercise seems to protect the elasticity of the aorta.⁸

Degenerative diseases of the media with aneurysm formation are the most common disorders of the aortic root

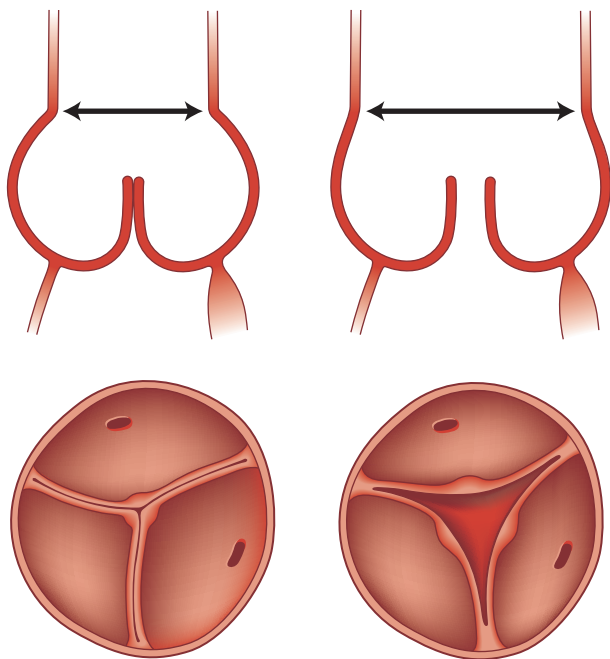


FIGURE 67-4 ■ Dilation of the sinotubular junction causes aortic insufficiency.

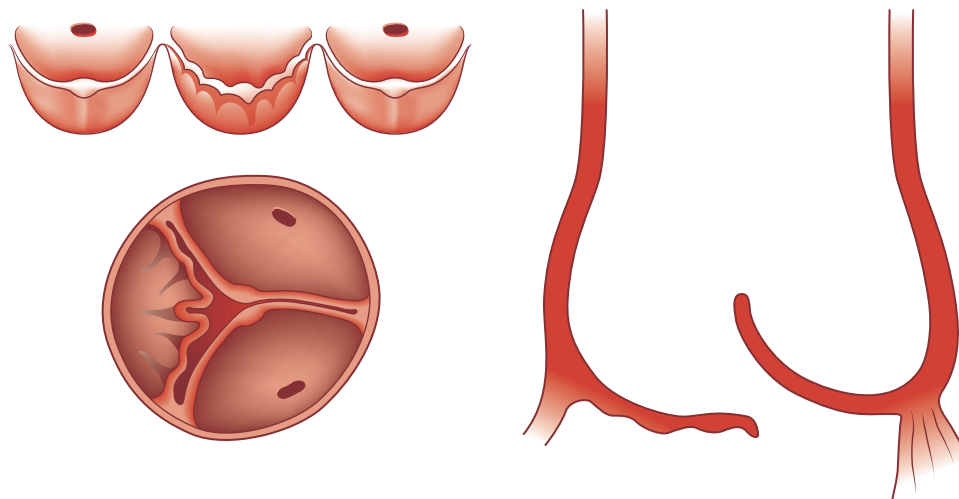


FIGURE 67-5 ■ Elongation of the free margin of an aortic cusp causes prolapse with resulting aortic insufficiency.

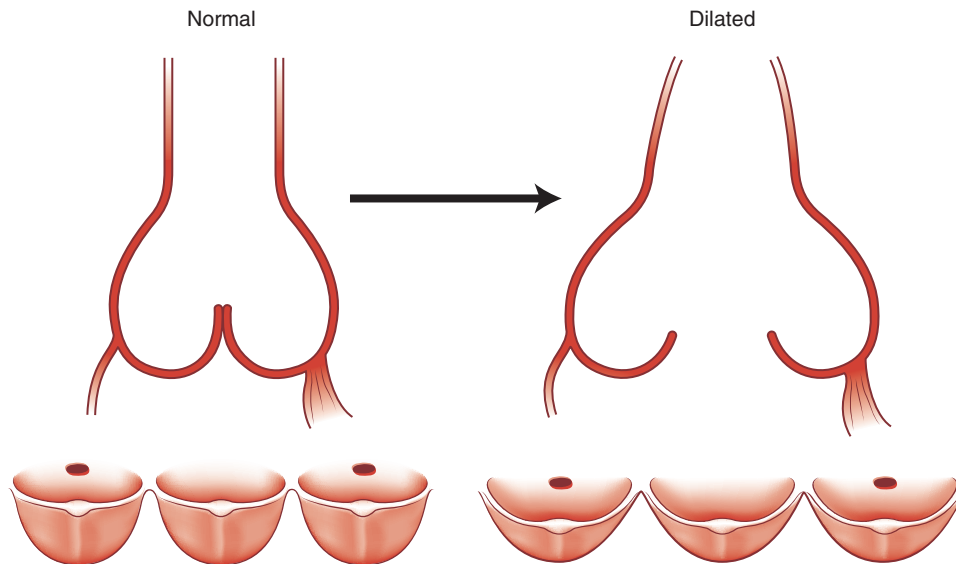


FIGURE 67-6 ■ Dilation of the aortic annulus. The subcommissural triangles of the noncoronary cusp become more obtuse.

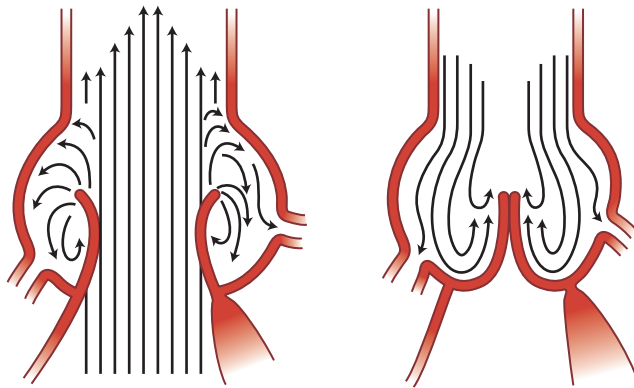


FIGURE 67-7 ■ The aortic sinuses create eddies and currents and facilitate aortic valve closure.

and ascending aorta. A broad spectrum of pathologic and clinical entities is grouped under degenerative disorders, ranging from severe degeneration of the media, which can become clinically important early in life in cases such as Marfan syndrome in children, to cases of the not so important mild dilation of the ascending aorta in older adults. Bicuspid and unicuspid aortic valve diseases are often associated with dilation of the aorta. Atherosclerosis, infectious and noninfectious aortitis, and trauma are other pathologic entities with which the cardiac surgeon must be familiar. Primary tumors of the aortic root and ascending aorta are rare. False aneurysms and aortic root abscess are problems commonly encountered in clinical practice.

Degenerative Aneurysms of the Proximal Aorta

Degenerative aneurysms of the thoracic aorta in older patients are often related to risk factors such as smoking, hypertension, and hyperlipidemia. In young patients without risk factors, the explanation for aneurysm

formation is on a genetic basis. Genetic aneurysms of the aorta can be classified into three main groups:

1. Inherited syndromes predisposing to early onset of aortic aneurysms, such as Marfan syndrome, Loeys-Dietz syndrome, and aneurysm-osteoarthritis syndrome
2. Familial aneurysms
3. Sporadic aneurysms including young patients without family history of aneurysm

Aneurysms of the proximal aorta are often caused by cystic medial degeneration (cystic medial necrosis). Histologically, necrosis and disappearance of muscle cells in the elastic lamina, and cystic spaces filled with mucoid material are often observed. Although these changes occur more often in the proximal aorta, they can affect any portion or the entire aorta. These changes weaken the arterial wall, which dilates and forms a fusiform aneurysm. The aortic root may be involved in this pathologic process, and in patients with Marfan syndrome, the aneurysm usually begins in the aortic sinuses. Patients with aortic root aneurysms are usually in their second or third decade of life when the diagnosis is made. Other patients have relatively normal aortic roots but develop ascending aortic aneurysms. These patients are usually in their fifth or sixth decade of life. Finally, certain patients have extensive degenerative disease of the entire aorta and develop the so-called mega-aorta syndrome with dilation of the thoracic and abdominal aorta.

Ascending aortic aneurysms tend to increase in size and eventually rupture or cause aortic dissection. The transverse diameter of the aneurysm is the most important predictor of rupture or dissection. In a study by Coady and associates¹⁰ of 370 patients with thoracic aneurysms (201 ascending aortic aneurysms), during a mean follow-up of 29.4 months, the incidence of acute dissection or rupture was 8.8% for aneurysms smaller than 4 cm, 9.5% for aneurysms of 4 to 4.9 cm, 17.8% for 5 to 5.9 cm, and 27.9% for those larger than 6 cm. The median size of the ascending aortic aneurysm at the time of rupture or dissection was 5.9 cm.

The growth rates of thoracic aneurysms are exponential.¹⁰ In the study by Coady and associates,¹⁰ the growth rate ranged from 0.08 cm/yr for small (<4 cm) aneurysms to 0.16 cm/yr for large (8 cm) aneurysms. The growth rates for chronic dissecting aneurysms were much higher than for chronic nondissecting aneurysms. Other studies found greater annual growth rates than did the Coady group.^{11,12} In addition, the growth rates for aortic root aneurysms may be different from those of ascending aortic aneurysms.

Most patients with aortic root or ascending aortic aneurysms are asymptomatic, and the aneurysm is usually found during routine chest radiographs, which show a widened mediastinum.¹³ Tracheal and esophageal displacement may be observed in the posterolateral view of the chest radiographs. Approximately one third of the patients complain of vague chest pain.¹³ In patients with a massive ascending aortic aneurysm, signs of superior vena cava obstruction may be present. If aortic insufficiency is present, there may be cardiac enlargement and the physical findings associated with it. The diagnoses of aortic root and ascending aortic aneurysm can be confirmed with echocardiography.

Transesophageal echocardiography is the best diagnostic tool to study aortic root aneurysm and the mechanism of aortic insufficiency. The echocardiographer should obtain information on each component of the aortic root, and particularly the aortic cusps. The number of cusps, their thickness, the appearance of free margins, and the excursion of each cusp during the cardiac cycle must be observed carefully. The coaptation areas of the cusps should also be investigated in multiple views, and Doppler imaging should be recorded. Information regarding the morphologic features of the aortic sinuses, sinotubular junction, and ascending aorta is also important. The diameters of the aortic annulus, aortic sinuses, sinotubular junction, and ascending aorta should be obtained in multiple views. The lengths of the free margins of the cusps should be estimated if possible. The mechanism of aortic insufficiency can often be determined with transesophageal echocardiography. Dilation of the sinotubular junction is a common cause of aortic insufficiency in patients with ascending aortic aneurysm and normal aortic cusps. Dilation of the aortic annulus and of the sinotubular junction is usually the cause of aortic insufficiency in patients with aortic root aneurysm. Although fenestrations in the cusps are not easily seen with echocardiography, a regurgitant jet in a commissural area is suggestive of fenestration.

Computed tomography (CT) with intravenous contrast enhancement permits accurate evaluation of the extent and size of the aneurysm. Three-dimensional imaging techniques can provide additional information on the extensiveness and type of aneurysm (e.g., fusiform or saccular).

Magnetic resonance imaging (MRI) provides even more information than CT scanning because it visualizes the arterial wall and surrounding structures with greater contrast. In addition, it has been increasingly used in the diagnosis and management of patients with heart diseases.¹⁴ Magnetic resonance angiography is replacing contrast angiography.¹⁵

Inherited Aneurysms of the Proximal Aorta

Marfan Syndrome

Marfan syndrome is an autosomal dominant, variably penetrant, inherited disorder of the connective tissue in which cardiovascular, skeletal, ocular, and other abnormalities may be present to variable degrees. The prevalence is estimated to be approximately 1 in 5000 individuals. It is caused by mutations in the gene that encodes fibrillin-1 (*FBNI*) on chromosome 15. This is a large gene (approximately 10,000 nucleotides in the messenger RNA), and identification of the mutation is a complex task. More than 1000 mutations in *FBNI* have been identified. The phenotype is highly variable because of varying genotype expression.

The clinical features of Marfan syndrome were thought to be caused by weaker connective tissues resulting from defects in *FBNI*, a glycoprotein and principal component of the extracellular matrix microfibril. This concept was inadequate to explain the overgrowth of long bones, osteopenia, reduced muscular mass and adiposity, and craniofacial abnormalities often seen in Marfan syndrome.¹⁶ Dietz and colleagues^{16,17} showed in experimental mice with Marfan syndrome that many findings are the result of abnormal levels of activation of transforming growth factor β (TGF- β), a potent stimulator of inflammation, fibrosis, and activation of certain matrix metalloproteinases, especially matrix metalloproteinases 2 and 9. Excess TGF- β activation in tissues correlates with failure of lung septation, development of a myxomatous mitral valve, and aortic root dilation in mice.¹⁸ This combination of structural microfibril matrix abnormality, dysregulation of matrix homeostasis mediated by excess TGF- β , and abnormal cell-matrix interactions is responsible for the phenotypic features of Marfan syndrome.¹⁶⁻¹⁸ Ongoing destruction of the elastic and collagen lamellae and medial degeneration result in progressive dilation of the aortic root, as well as in a predisposition to aortic dissection from the loss of appropriate medial layer support. Loss of elasticity in the media causes increased aortic stiffness and decreased distensibility.¹⁹

The main features of Marfan syndrome include disproportionate long bone overgrowth, ectopia lentis and aortic root aneurysm. Diagnosis is not always simple, and a multidisciplinary approach is needed to diagnose and manage patients with this autosomal dominant disorder. In 1996, a panel of experts developed the "Ghent criteria" for the diagnosis of Marfan syndrome.²⁰ Table 67-1 shows the original Ghent criteria, which contain a set of "major" and "minor" manifestations in various organs including cardiovascular, ocular, skeletal, pulmonary, dura mater, and skin.²⁰ The presence of major criteria in two separate systems and involvement of a third (minor or major) was needed to establish the diagnosis of Marfan syndrome.²⁰ Using these criteria, a high proportion of patients diagnosed as Marfan are found to have *FBNI* mutations. However, some manifestations contained in the Ghent criteria are age dependent, and there are patients with skeletal abnormalities and ectopia lentis without aortic root aneurysm, even in the presence of

TABLE 67-1 Diagnostic Criteria for Marfan Syndrome*

System	Major Criteria	Minor Criteria
Family history	Independent diagnosis in parent, child, sibling	None
Genetics	Mutation in <i>FBN1</i>	None
Cardiovascular	Aortic root dilation Dissection of ascending aorta	Mitral valve prolapse Calcification of the mitral valve (age < 40 yr) Dilation of the pulmonary artery Dilation or dissection of the descending aorta
Ocular	Ectopia lentis	Two needed: Flat cornea Myopia Elongated globe
Skeletal	Pectus excavatum needing surgery Pectus carinatum Pes planus Wrist and thumb sign Scoliosis > 20 degrees or spondylolisthesis Arm span–height ratio > 1.05 Protrusio acetabula (radiograph, MRI) Diminished extension elbows (<170 degrees)	Two major or one major and two minor signs: Moderate pectus excavatum High, narrowly arched palate Typical facies Joint hypermobility
Pulmonary	—	Spontaneous pneumothorax Apical bullae
Skin	—	Unexplained stretch marks (striae) Recurrent or incisional hernia
Central nervous	Lumbosacral dural ectasia (CT or MRI)	—

*The presence of major criteria in two separate systems and involvement of a third (minor or major) are needed to establish the diagnosis of Marfan syndrome.

CT, Computed tomography; MRI, magnetic resonance imaging.

BOX 67-1 Revised Ghent Criteria for the Diagnosis of Marfan Syndrome

IN THE ABSENCE OF FAMILY HISTORY

1. Aortic root dilation ($Z > 2$) or dissection and ectopia lentis = Marfan
2. Aortic root dilation ($Z > 2$) or dissection and *FBN1* mutation = Marfan
3. Aortic root dilation ($Z > 2$) or dissection and systemic score ≥ 7 points = Marfan
4. Ectopia lentis and *FBN1* known to associated aortic root dilation/dissection

IN THE PRESENCE OF FAMILY HISTORY

5. Ectopia lentis and family history of Marfan
6. Systemic score (≥ 7 points) and family history of Marfan
7. Aortic root dilation ($Z \geq 2$ in >20 years of age; $Z \geq 3$ in <20 years of age) and family history of Marfan

From Loeys BL, Dietz HC, Braverman AC, et al: The revised nosology for the Marfan syndrome. *J Med Genet* 47:476–485, 2010.

FBN1 mutations. Experts in this area got together again and developed a “Revised Ghent Nosology for the Marfan Syndrome” (Box 67-1) which emphasizes aortic root aneurysm, ascending aortic dissection and ectopia lentis.²¹

The most common cardiovascular features of Marfan syndrome are aortic root aneurysm and mitral valve prolapse. These anatomic abnormalities may cause aortic rupture, aortic dissection, aortic insufficiency, and mitral insufficiency.

Mitral valve prolapse is age dependent and is more common in women. It is caused by myxomatous

degeneration of the mitral valve apparatus, which is present in up to 80% of patients with Marfan syndrome, but only 25% of them develop mitral insufficiency. The posterior mitral annulus is grossly dilated in patients with mitral insufficiency, and it is often displaced posteriorly.²² The mitral annulus can also become heavily calcified and display a horseshoe appearance on radiographs.

The dilation of the aortic root is often progressive, and the rate of expansion, which varies somewhat, is usually less than 1 or 2 mm/yr. Shores and colleagues¹² randomized 70 patients with Marfan syndrome into propranolol-treated and placebo groups. The growth rates of the aortic root aneurysms in untreated patients were slightly more than three times those of patients who received β -adrenergic blockage. This study has been the scientific basis to treat these patients with a β -blocker agent. Calcium antagonists and angiotension-converting enzymes have also been reported as effective in delaying aortic dilation, but at present, β -blocker remains the drug of choice.²³ A prospective randomized clinical trial showed that losartan is effective in reducing the rate of aortic root dilation in patients with Marfan syndrome, and it reduces the rate of dilation of the arch after aortic root replacement.²⁴ The combination of losartan with a β -blocker was more effective in preventing dilation of the aortic root than β -blocker alone in a small, randomized trial in children.²⁵

Aortic dissection is rare in patients with aortic root aneurysm of less than 50 mm, unless they have a family history of aortic dissection.²⁶ The dissection in most patients starts at the level of the sinotubular junction (Stanford type A aortic dissection). Surgery of the aortic root is recommended when the transverse diameter of the aortic sinuses reaches 50 mm. In patients with family

history of dissection, surgery should be considered when the diameter reaches 45 mm. Without surgery, most patients with Marfan syndrome die in their third decade, from complications of aortic root aneurysm such as rupture, aortic dissection, or aortic insufficiency.^{27,28} In approximately 10% of patients, the dissection starts just beyond the left subclavian artery (Stanford type B aortic dissection).

Patients with Marfan syndrome should be followed at regular time intervals. Doppler echocardiography is the best diagnostic tool for monitoring changes in the mitral valve and aortic root. Patients with an aortic root greater than 40 mm should be followed with echocardiographic measurements twice yearly. MRI of the remaining thoracic and abdominal aorta should also be used when indicated.

Pregnancy in women with Marfan syndrome has two potential problems: the risk of having a child who will inherit the disorder and the risk of acute aortic dissection during the third trimester, parturition, or the first postpartum month. Offspring have a 50% risk of inheriting the syndrome. The risk of aortic dissection is less known, but it appears to be low in patients with normal aortic root and cardiac function.²⁹

Loeys-Dietz Syndrome

Mutations in the genes encoding TGF- β receptors 1 and 2 have been found in association with a continuum of clinical features. On the mild end is a presentation similar to that of the Marfan syndrome, or familial thoracic aneurysm and dissection,^{30,31} and on the severe end, there is a complex phenotype in which aortic dissection or rupture commonly occurs in childhood.³² This complex phenotype is characterized by the triad of hypertelorism, bifid uvula (or cleft palate), and generalized arterial tortuosity with widespread vascular aneurysm and dissection. This phenotype has been classified as Loeys-Dietz syndrome.³² Affected patients have a high risk of aortic dissection or rupture at an early age and at relatively small aortic diameters. CT angiograms should be obtained from the head to the pelvis. Surgery is recommended for adults when the aortic root exceeds 4 cm or the descending thoracic aorta exceeds 5 cm. If the craniofacial features are severe in children, surgery is recommended when the aortic root z-score is greater than 3, or when the expansion is greater than 0.5 cm in 1 year.³³

Ehlers-Danlos Syndrome

The Ehlers-Danlos syndrome encompasses a group of heterogeneous connective tissue disorders that involve the skin and joints and cause hyperelasticity and fragility of the former and hypermobility of the latter. It can also involve the cardiovascular system. Vascular Ehlers-Danlos syndrome is a rare autosomal dominant inherited disorder of the connective tissue resulting from mutation of the *COL3A1* gene encoding type III collagen.³⁴ Afflicted individuals are prone to serious vascular, intestinal, and obstetric complications. These problems are rare during infancy but occur in up to 25% of affected persons before the age of 20 years and in 80% before the

age of 40. Median survival is 48 years. Spontaneous rupture without dissection of large- and medium-caliber arteries, such as the abdominal aorta and its branches, the branches of the aortic arch, and the large arteries of the limbs accounts for most deaths. Intestinal perforation, usually involving the colon, is less often fatal. Pregnancy is a high risk for women with this syndrome. Aortic root dilation was present in 28% in a series of 71 patients with Ehlers-Danlos syndrome.³⁵ Aortic dissection is uncommon.

As with many rare diseases, delayed or incorrect diagnosis can lead to inadequate or inappropriate management. Diagnosis is based on clinical findings, including specific facial features, thin translucent skin, propensity to bleeding, and rupture of vessels or viscera. Diagnosis can be confirmed by biochemical assays showing qualitative or quantitative abnormalities in type III collagen secretion, or by molecular biology studies demonstrating mutation of the *COL3A1* gene. Varied molecular mechanisms have been observed with different mutations in each family. No correlation has been established between genotype and phenotype. Diagnosis should be suggested in any young person with arterial or visceral rupture or colonic perforation. There is currently no specific treatment for this syndrome.

Bicuspid Aortic Valve Disease

Congenital aortic valve malformations include a phenotypic continuum of unicuspid valves (severe form), the various types of bicuspid aortic valves (moderate form), tricuspid valves (normal), and the rare quadricuspid valves.³⁶

Bicuspid aortic valve, the most common of these malformations, occurs in 1% to 2% of the population. Movahed and colleagues³⁷ recently reviewed 24,265 patients who had echocardiograms performed for various clinical reasons, and 1742 echocardiograms obtained by screening teenage athletes in Southern California, and found a prevalence of bicuspid aortic valves of 0.6% in the large cohort and 0.5% in the smaller one. Males are affected more than females at a ratio of 4:1. There is a relatively high incidence of familial clustering, which suggests an autosomal dominant inheritance with reduced penetrance^{38,39}; however, it remains unproved that bicuspid aortic valve is an inherited disorder. Patients with bicuspid aortic valve usually have three aortic sinuses and two cusps of different sizes. The larger cusp, usually the one attached to the interventricular septum, contains a raphe, which probably represents an incomplete commissure. The raphe extends from the mid portion of the cusp to the aortic annulus, and its insertion in the aortic root is at a lower level than the other two commissures. Bicuspid aortic valves with two cusps and two sinuses are uncommon and called "type 0"; the most common type is with one raphe and is called "type 1," and finally with two raphes is "type 2."⁴⁰ Types 1 and 2 can be subclassified according to the fused cusps: left-right is the most common form (a raphe in between the left and right cusps). Abnormal origin of the coronary arteries and circumflex artery dominance are common in patients with bicuspid aortic valve.⁴¹

Normally functioning bicuspid aortic valves may last the patient's lifetime. Others become stenotic by the fourth or fifth decade of life. Aortic insufficiency can also occur, and it is often associated with dilated aortic annulus.⁴² It is more common in younger patients, and it results from the prolapse of one cusp, usually the one that contains the raphe.

Both bicuspid and unicuspid aortic valves are often associated with premature degenerative changes in the media of the wall of the aortic root and ascending aorta.^{43,44} These patients are at risk of developing chronic degenerative aneurysms of the ascending aorta and type A aortic dissection.⁴⁵

Atherosclerosis

Atherosclerosis of the ascending aorta and transverse arch is a common cause of stroke.^{46,47} Sometimes, atherosclerosis can cause extensive calcification of the aortic root, ascending aorta, and transverse arch, which is often associated with coronary artery disease, stenosis of one or both coronary arteries orifices, and aortic valve stenosis. Extensive calcification of the ascending aorta is clinically described as "porcelain" aorta.^{48,49} Atherosclerotic aneurysms of the ascending aorta are uncommon; they are more common in the abdominal aorta and to a lesser degree in the descending thoracic aorta. Atherosclerosis often causes irregular and saccular aneurysms of the ascending aorta rather than the more fusiform shape of those caused by degenerative disease of the media.

Infectious Aneurysms

Syphilis was a common cause of aneurysm of the ascending aorta, but it is now rare. The spirochetal infection destroys the muscular and elastic fibers of the media, which are replaced by fibrous and other inflammatory tissues. The ascending aorta is the most common site of involvement, and the aneurysm is usually saccular.⁵⁰ The wall of the ascending aorta is frequently calcified. Syphilitic aortitis also causes coronary ostial stenosis and aortic valve insufficiency.⁵⁰ Although rare, other bacteria can also cause aneurysm of the ascending aorta.

Aortitis

Various types of aortitis can involve the ascending aorta.⁵¹⁻⁵⁶ Giant cell arteritis is among the more common, and it involves medium-sized arteries, but the aorta and its branches are involved in approximately 15% of cases.⁵⁵ The etiology of aortitis, also called *temporal arteritis*, is unknown. The characteristic lesion is a granulomatous inflammation of the media of large- and medium-caliber arteries, such as the temporal artery. Narrowing of the aorta is rare. Occasionally, the inflammatory process weakens the aorta, leading to aneurysm formation, aortoannular ectasia, and aortic insufficiency.⁵⁴ Patients are usually older than 50 years, with a mean age of 67 years, and most are women. Diagnosis is established by biopsy of the involved artery, usually the temporal artery.

Takayasu arteritis is a chronic inflammatory disease that often involves the aortic arch and its major branches.

The pulmonary artery may also be involved. The lesions are purely stenotic in 85% of patients, aneurysmal in 2%, and mixed in 13%.^{52,53} Aortic insufficiency occurs in approximately 25% of the cases. It has been classified as type I when the aortic arch is involved, type II when the arch is free of disease but the thoracoabdominal aorta and its branches are affected, type III when both areas are affected, and type IV when the pulmonary artery is involved.^{53,56} The etiology is unknown, but it is probably an autoimmune disorder. It occurs worldwide, but most cases are seen in Asia and Africa. The disease affects women more than men at a ratio of 8:1.^{51,53} The mean age at the time of the diagnosis is 29 years.

Ankylosing spondylitis, Reiter syndrome, psoriatic arthritis, and polyarteritis nodosa can cause aortic insufficiency because of annuloaortic ectasia. Behçet disease can cause aneurysm of the ascending aorta.

Aortic Dissection

Aortic dissections are discussed in [Chapters 70](#) and [71](#).

Ascending Aorta Tumors

Primary tumors of the ascending aorta are extremely rare. Most aortic tumors are located in the descending thoracic or abdominal aorta, and they are usually sarcomas.^{57,58}

Ascending Aorta Trauma

Nonpenetrating traumatic injuries of the ascending aorta are often fatal and diagnosed at autopsy.⁵⁹ The penetrating trauma is usually a bullet or stab wound, and it causes cardiac tamponade when the intrapericardial portion of the aorta is involved. These injuries are frequently fatal.

SURGICAL TREATMENT OF ASCENDING AORTIC ANEURYSM

Although ascending aortic aneurysms may be isolated lesions, more often they are associated with aortic valve disease. Both bicuspid and tricuspid aortic valve diseases may be associated with degenerative aneurysms of the ascending aorta, but bicuspid aortic valve disease appears to be associated with premature degeneration of the media of the aorta.

Ascending aortic aneurysm can cause aortic insufficiency in patients with anatomically normal aortic valve cusps if the sinotubular junction becomes dilated (see [Fig. 67-4](#)). These patients can develop symptoms related to the aortic insufficiency, but more often the aneurysm is asymptomatic and is discovered during a routine chest radiograph or echocardiogram as part of the workup for an unrelated problem. Surgery should be considered when the transverse diameter of the ascending aorta exceeds 55 mm.⁶⁰ If there is moderate or severe aortic insufficiency, the aortic valve cusps are normal by echocardiography, and the valve is judged to be repairable, then operation is justifiable when the ascending aorta reaches 50 mm in diameter.⁶¹ If the aneurysm is

associated with a genetic syndrome, surgery should be considered when the diameter reaches 50 mm.⁶⁰ If associated with a normally functioning bicuspid aortic valve, surgery is recommended when the diameter reaches 55 mm.^{60a}

Operative Techniques

Surgery for ascending aortic aneurysm is performed using cardiopulmonary bypass, which is established by cannulating the transverse aortic arch, right axillary artery or femoral artery, and the right atrium. In patients with bicuspid aortic valve the aneurysm frequently extends up to the innominate artery and a brief period of circulatory arrest is necessary to resect the proximal arch and perform the distal anastomosis. The proximal anastomosis should be performed at the level of the sinotubular junction. The Dacron graft used to replace the ascending aorta should not be too long or too large. When the ascending aorta expands to develop an aneurysm, it also becomes elongated. Thus, during its

replacement, the graft should be much shorter than the aneurysm. In fact, a graft of 4 to 6 cm in length is all that is needed to replace the entire ascending aorta from sinotubular junction to the level of the innominate artery. Longer grafts can kink and cause partial obstruction and even hemolysis. A single graft can be used, but it should be beveled at the distal anastomosis, and its shorter side should be aligned with the medial part of the arch (Fig. 67-8). The diameter of the graft should be between 24 and 32 mm, depending on the patient's body surface area. When the diameter of the graft used is larger than the diameter of the sinotubular junction by more than a couple of millimeters, its caliber should be reduced to that of the sinotubular junction at the level of the anastomosis. This is easily done by plication of that end of the graft. Matching the diameter of the graft to that of the sinotubular junction is important to prevent late development of aortic insufficiency.

If the aortic valve is incompetent but the aortic cusps are normal and the sinotubular junction is dilated, all that is needed to reestablish valve competence is to reduce the

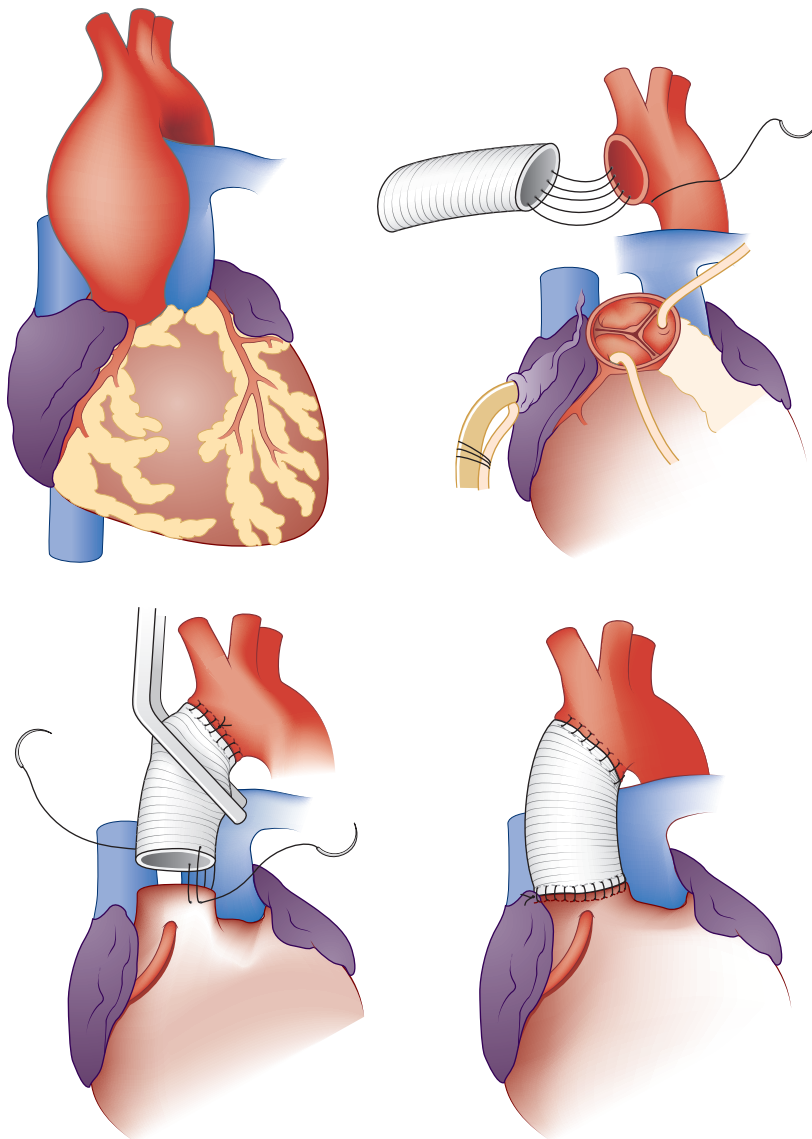


FIGURE 67-8 ■ Replacement of the ascending aorta for aneurysm.

diameter of the sinotubular junction to allow the cusps to coapt again. The ascending aorta is transected 5 mm above the sinotubular junction. All three commissures are pulled upward and approximate to each other until the cusps coapt centrally. The diameter of an imaginary circle that contains all three commissures is the correct diameter of the sinotubular junction. A graft of that diameter is then sutured to the remnants of ascending aorta wall at the level of the sinotubular junction. Because the aortic cusps are frequently of different sizes, the spaces between the commissures should reflect that during performance of the proximal anastomosis. Aortic valve competence can be assessed by injecting cardioplegia solution under pressure in the graft and observing the left ventricle for distention. In our group, we prefer to use two separate segments of grafts when aortic valve repair is necessary and the entire ascending aorta or transverse arch, or both, need replacement. We usually do the distal anastomosis first (under hypothermic circulatory arrest) and work on the aortic valve during rewarming of the patient. The distal and proximal grafts are trimmed and sutured to one another (Fig. 67-9).

If the noncoronary aortic sinus is aneurysmal, it should be replaced along with the ascending aorta. This is accomplished by selecting a graft of an appropriate diameter, as previously described, and then creating a neo-aortic sinus in one of its ends. The width of the neo-aortic sinus is equal to the distance between the commissures of the cusp, and the height is approximately equal to the diameter of the graft. This neo-aortic sinus is sutured directly to the remnant of arterial wall and aortic annulus (Fig. 67-10).

Sometimes one aortic cusp is slightly elongated, and its free margin coapts at a level lower than the other two cusps. The free margin can be shortened by plication of the central portion along the nodule of Arantius (Fig. 67-11). If the free margin is elongated and thinned or has a fenestration near a commissure, it can be reinforced

with a double layer of a 6-0 expanded polytetrafluoroethylene suture (Fig. 67-12).

Patients with a normally functioning bicuspid aortic valve, normal aortic root, and ascending aortic aneurysm can be treated with simple replacement of the ascending aorta.

Patients with aortic valve disease that is not amenable to repair and an ascending aortic aneurysm are treated with aortic valve replacement and supracoronary replacement of the ascending aorta. If only the noncoronary aortic sinus is dilated, aortic valve replacement of the ascending aorta with a graft extension into the noncoronary sinus (see Fig. 67-10) is preferable to composite

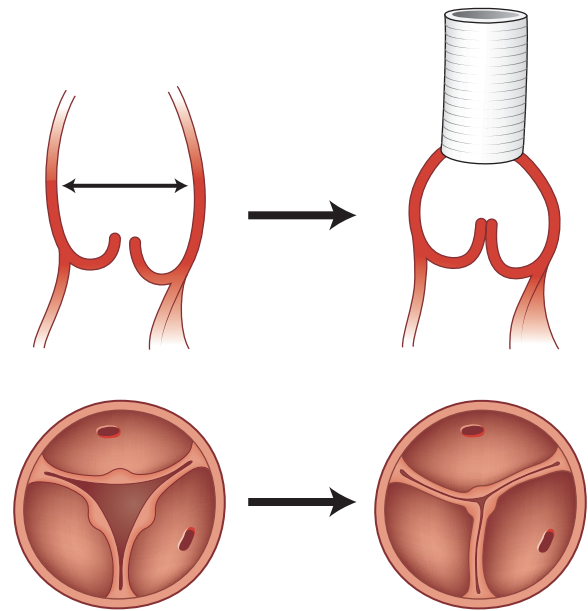


FIGURE 67-9 ■ Replacement of the ascending aorta with adjustment of the diameter of the sinotubular junction.

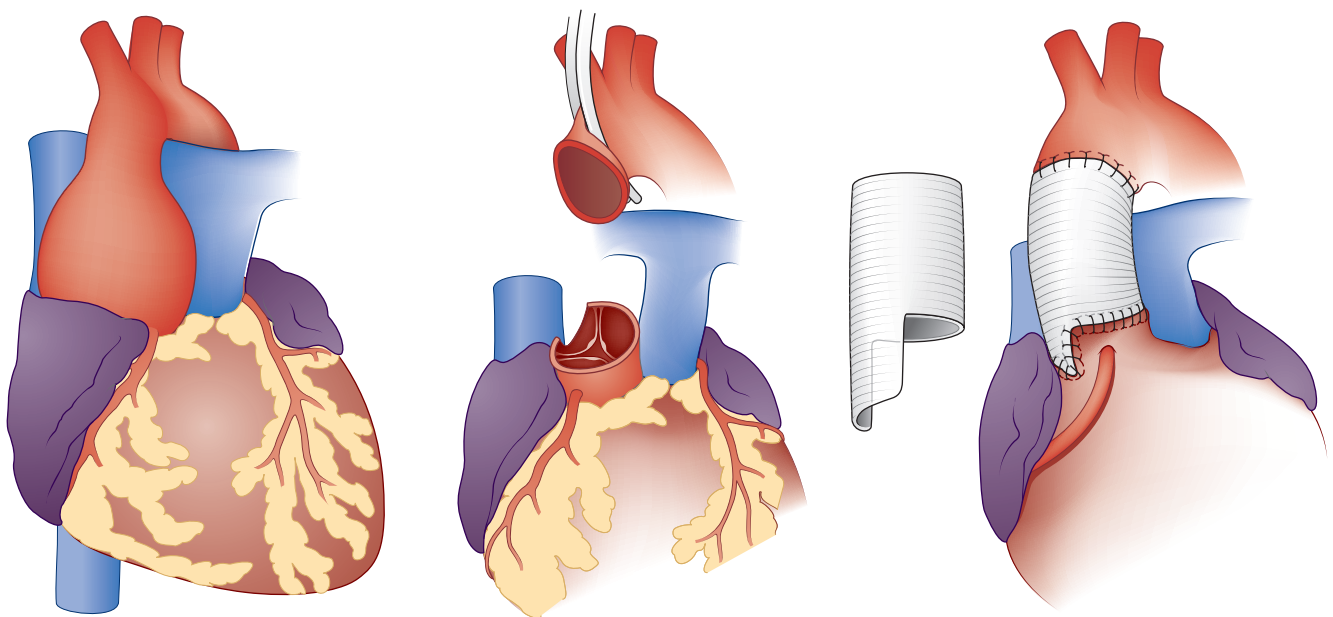


FIGURE 67-10 ■ Replacement of the ascending aorta and noncoronary aortic sinus.

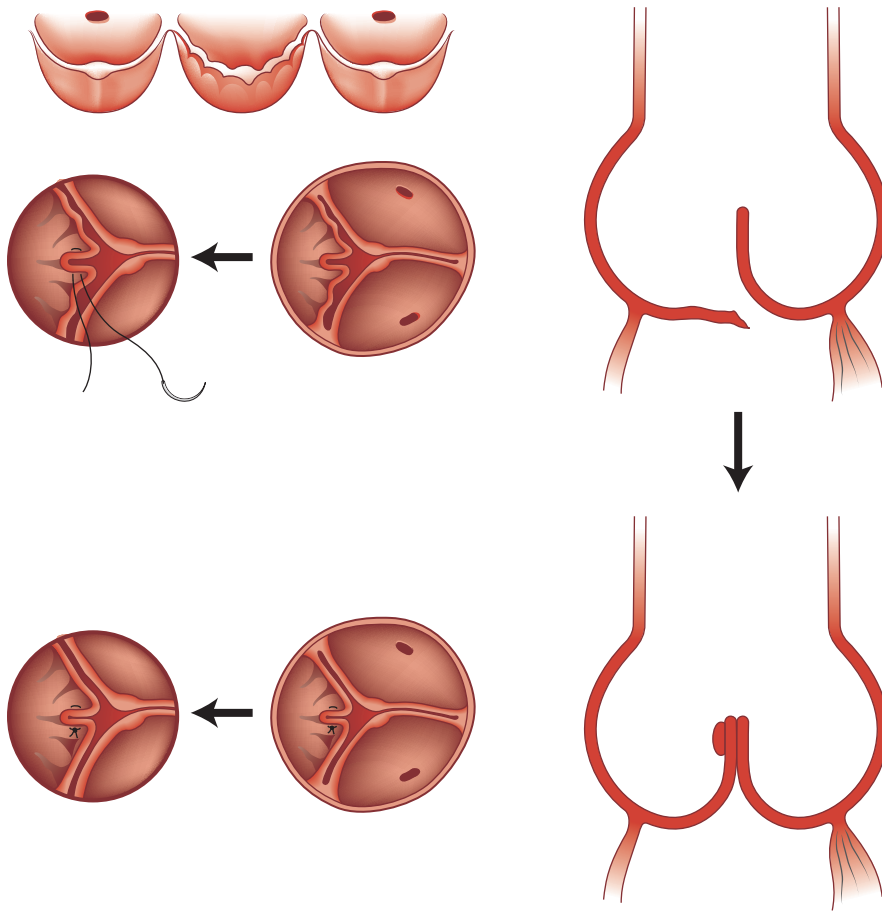


FIGURE 67-11 ■ Repair of aortic cusp prolapse by shortening its free margin.

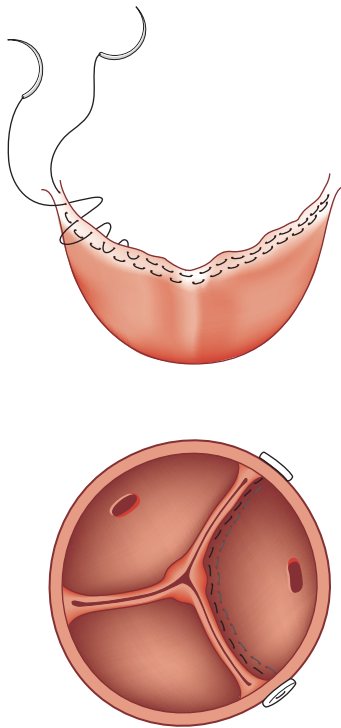


FIGURE 67-12 ■ Reinforcement of the free margin of the aortic cusp with a double layer of a 6-0 expanded polytetrafluoroethylene suture.

replacement of the aortic valve and ascending aorta with reimplantation of the coronary arteries. If two aortic sinuses are dilated, composite replacement of the aortic valve and ascending aorta with reimplantation of the coronary arteries should be performed as described for aortic root aneurysm.

Clinical Outcomes

Isolated replacement of the ascending aorta for chronic aneurysm is uncommon.^{61,62} Patients with ascending aortic aneurysm often have aortic insufficiency or aortic valve disease that may also need surgical attention. Whether the operation is performed in isolation or combined with other procedures, the operative mortality for elective surgery is low.⁶¹⁻⁶⁴ In our experience with 103 patients who had aortic valve-sparing operations for ascending aortic aneurysm and aortic insufficiency, only one patient died perioperatively.⁶¹ We reviewed our experience with aortic valve replacement and supracoronary replacement of the ascending aorta at Toronto General Hospital during a 12-year interval and identified 132 patients.⁶⁴ There were six operative deaths, and the series included acute aortic dissections, acute infective endocarditis, and reoperations.⁶⁴ Cohn and colleagues⁶² also reported a low operative mortality for replacement of the ascending aorta. The operative mortality for ascending aortic surgery has decreased over the past four decades.⁶⁵

Age, functional class, and associated diseases play an important role in the operative risk.

The long-term survival of our 103 patients who had aortic valve-sparing operations for ascending aortic aneurysm and aortic insufficiency was only 54% at 10 years, but most of them had extensive vascular disease including transverse aortic arch disease or mega-aorta syndrome.⁶¹ Our patients who had aortic valve replacement and supracoronary replacement of the ascending aorta had a 10-year survival of 70%, but they were younger than those who had aortic valve repair and had less extensive vascular disease.⁶⁴

Patients who had replacement of the ascending aorta with or without aortic valve surgery must be evaluated annually with echocardiography to assess the size of the retained aortic root and the function of the aortic valve; they should also have CT scans or MRI of the remaining thoracic and abdominal aorta. Aneurysms of the aortic root, false aneurysms, valve dysfunction, and infections in the graft or aortic valve are problems that can develop and need surgical treatment.⁶⁶

Patients who had aortic valve repair or replacement with bioprosthetic valves do not need anticoagulation if they are in sinus rhythm. Two recent retrospective observational studies in older patients with bioprosthetic aortic valves suggested that anticoagulation during the first 6 months was associated with a survival benefit, but there was a higher risk of bleeding.^{67,68} Our clinical experience does not support that, and we continue to recommend aspirin only for these patients.⁶⁹ Replacement of the ascending aorta with a tubular Dacron graft appears to have no effect on the durability of bioprosthetic heart valves.⁷⁰ Patients with mechanical valves should be anticoagulated with warfarin sodium.

SURGICAL TREATMENT OF AORTIC ROOT ANEURYSMS

Patients with Marfan syndrome and other genetically linked aortic root aneurysm should be considered for surgery when the transverse diameter of the aortic sinuses reaches 50 mm.⁶⁶ In Loeys-Dietz syndrome, the threshold is 42 mm.⁶⁶ In older patients without a known aortic genetic link, it may be appropriate to wait until the root reaches 55 mm,⁶⁶ unless the cusps are normal and an aortic valve sparing is feasible, in which case 50 mm is reasonable. As mentioned before, if there is family history of dissection, surgery should be considered at an earlier stage of dilation of the aortic root.

The aortic cusps are often normal or minimally stretched when the indication for surgery is the diameter of the aortic sinuses and an aortic valve sparing operation should be performed.^{66,71} If the cusps are abnormal, composite replacement of the aortic valve and ascending aorta with reimplantation of the coronary arteries should be performed.⁷²

Operative Techniques

The two basic types of aortic valve-sparing operations for patients with aortic root aneurysms are remodeling

of the aortic root and reimplantation of the aortic valve.^{66,71}

Remodeling of the Aortic Root

The aortic root is dissected circumferentially down to the level of the aortic annulus, and the three aortic sinuses are excised, leaving approximately 5 mm of tissue attached to the aortic annulus and around the coronary artery orifices. The three commissures are gently suspended upward and are approximated until the three cusps coapt. The diameter of an imaginary circle that includes all three commissures is approximately the diameter of the tubular Dacron graft to be used for reconstruction of the aortic sinuses (Fig. 67-13). One of the ends of this graft is tailored to create neo-aortic sinuses. The widths of the neo-aortic sinuses are based on the distance between commissures of each cusp when they are pulled upward to determine the diameter of the graft. The heights of the neo-aortic sinuses should be approximately equal to their width. The three commissures are secured on the outside of the graft immediately above the neo-aortic sinuses, and the remnants of aortic wall and aortic annulus are sutured to the neo-aortic sinuses with a continuous 4-0 polypropylene (see Fig. 67-13). The coronary arteries are reimplanted into their respective sinuses. If an aortic cusp coapts at a level lower than the other two, shortening of the free margin corrects the problem (see Figs. 67-11 and 67-12).

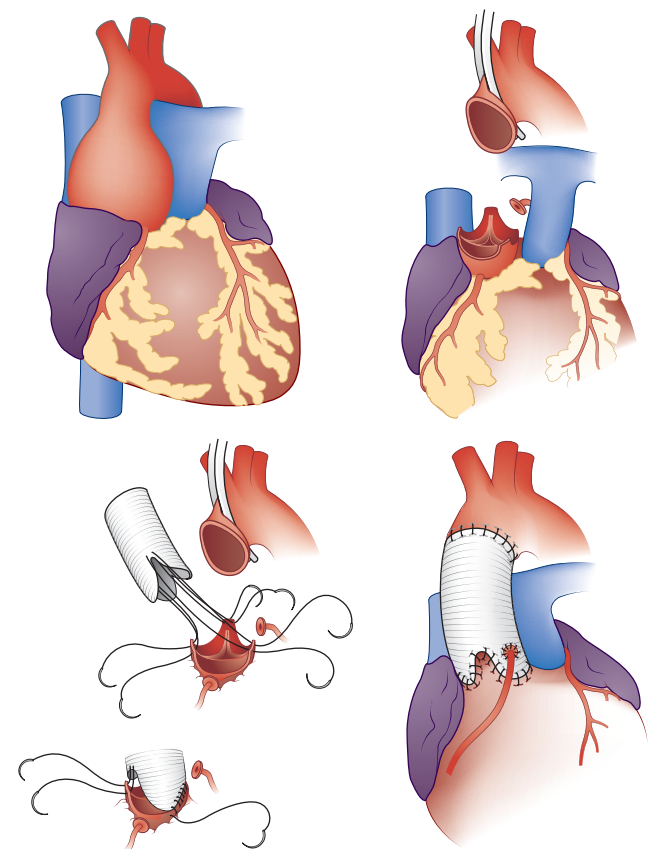


FIGURE 67-13 ■ Aortic valve-sparing operation: remodeling of the aortic root.

Reimplantation of the Aortic Valve

The aortic root is dissected circumferentially to a level immediately below the aortic annulus. This is not possible beneath the commissure between right and non-coronary aortic cusps, and it should be stopped where the right ventricle and atrium are attached to the root. Next, multiple 2-0 or 3-0 polyester sutures with Teflon felt pledgets are passed from the inside to the outside of the left ventricular outflow tract through a single horizontal plane corresponding to the lowest portion of the aortic annulus along its fibrous components and following the scalloped shape of the annulus along its muscular component and slightly less so along the membranous septum to avoid the bundle of His (Fig. 67-14). The diameter of the sinotubular junction is estimated by pulling the three commissures upward until the cusps coapt. A tubular Dacron graft 4 to 6 mm larger than the diameter of the sinotubular junction is selected, and a small triangular excision is made in one of its ends and the remaining portion is plicated in two or three places to reduce its

diameter by 2 to 4 mm depending on the diameter of the aortic annulus. Most grafts that we currently use are 28 to 34 mm in diameter, depending on the size of the patient and the aortic cusps. The sutures passed through the left ventricular outflow tract are then passed from the inside to the outside of the tailored end of the graft. If reduction in diameter of the aortic annulus is desirable, it is done beneath the commissures of the noncoronary cusp. This is accomplished by placing the sutures closer in the graft than they are beneath the commissures of the noncoronary cusp. The aortic valve is placed inside the graft and all sutures are tied on the outside. The spatial distribution of these sutures is important to prevent tears or distortion of the aortic annulus. The three commissures are suspended inside the graft and secured to it with 4-0 polypropylene sutures with Teflon felt pledgets. These sutures are then used to secure the aortic annulus and remnants of the aortic sinuses to the graft. The coronary arteries are reimplanted into their respective sinuses. The spaces between commissures are plicated to create a slight bulge in the neoaortic sinuses and to reduce the diameter of the graft to that of the desirable sinotubular junction. Cusp prolapse or reinforcement of the free margin with fine Gore-Tex sutures can be done if needed (see Figs. 67-11 and 67-12).

Patients with a normally functioning bicuspid aortic valve and aortic root aneurysm are also candidates for aortic valve-sparing operations.

There is a commercially available Dacron graft with neo-sinuses of Valsalva.⁷³ Some surgeons who have wide experience with aortic valve sparing procedures have used the "Valsalva graft" for aortic valve reimplantation.⁷⁴ We have not used it because we believe that it deforms the aortic annulus, which normally evolves along a single horizontal plane. If the aortic annulus is correctly resuspended into the Valsalva graft, the annulus plane changes from a horizontal to a curved shape. This may compromise the durability of the repair.

Aortic Root Replacement

Replacement of the aortic root is performed when the aortic cusps are abnormal and cannot be safely repaired.^{63,64} The aortic cusps are excised and the coronary arteries detached from their sinuses with 5 or 6 mm of aortic sinus wall around them. A valved conduit is then used to replace the aortic root. This conduit can be a commercially available Dacron tube with a mechanical valve already attached to one of its ends. The valved conduit is sutured to the aortic annulus, and the coronary arteries are reimplanted into the graft (Fig. 67-15).

An aortic homograft or a xenograft can also be used for aortic root replacement. It is not wise to use a pulmonary autograft for replacement of the aortic root in patients with aortic root aneurysms, because the pulmonary autograft may become aneurysmal when subjected to systemic pressures. Finally, aortic root replacement also can be performed with a conduit prepared in the operating room. When a stented bioprosthetic valve is desirable, the bioprosthesis and the Dacron tube can be secured to the aortic annulus using the same sutures. Another method is to secure the bioprosthetic valve

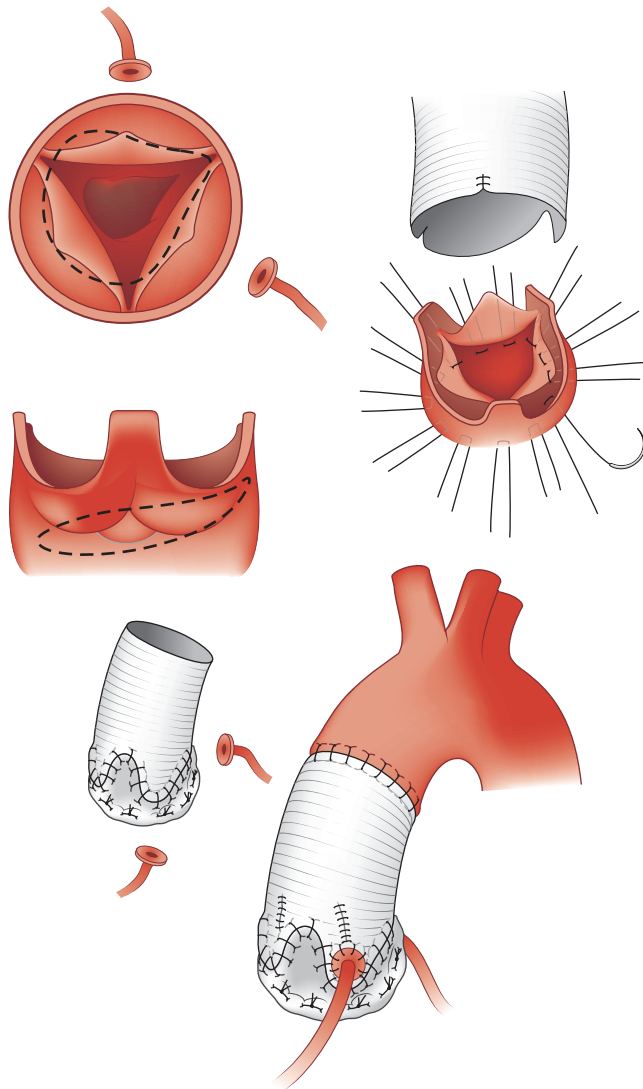


FIGURE 67-14 ■ Aortic valve sparing operation: reimplantation of the aortic valve.

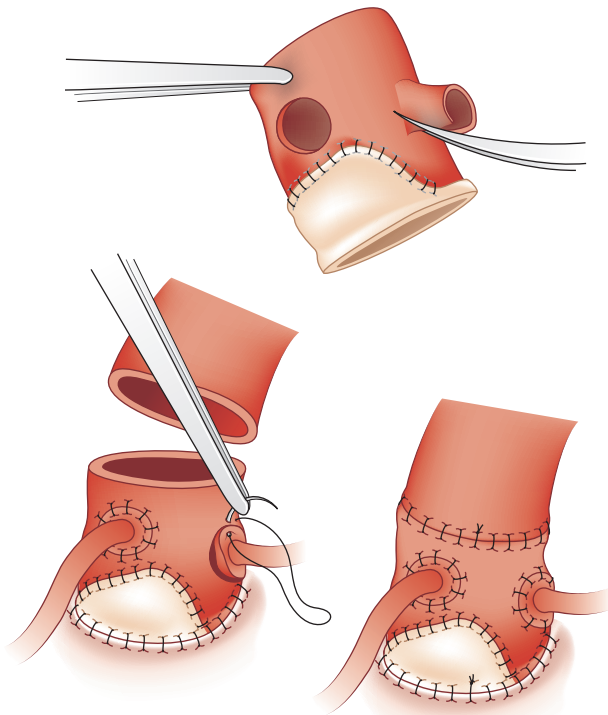


FIGURE 67-15 ■ Composite replacement of the ascending aorta and aortic valve with a stentless porcine aortic root.

inside a tubular Dacron graft 1 cm from one of its ends and secure the Dacron graft alone to the annulus (Fig. 67-16). This approach allows aortic valve re-replacement without taking down the original graft or the coronary arteries when the bioprosthetic valve fails. The technique of securing a tubular Dacron graft in the left ventricular outflow tract before implanting a prosthetic valve into it is very useful when there is, for example, a narrow or destroyed aortic annulus resulting from multiple previous operations, calcification, or endocarditis. The Dacron graft can be tailored to conform to the anatomy of the left ventricular outflow tract before it is sutured to it.⁷⁵

In the original description of aortic root replacement by Bentall and DeBono in 1968,⁷² the aneurysm was opened and a tubular Teflon graft containing a mechanical valve was sutured to the aortic annulus, to the coronary arteries (by suturing the graft to the aortic sinus wall around their orifices), and to the distal aorta. The aneurysm wall was wrapped around the graft and closed tightly for hemostasis. Pseudoaneurysm formation at the coronary artery and the aortic anastomoses was a complication of this technique.⁷⁶ To decompress the space between the graft and aneurysm wall, Cabrol and colleagues⁷⁷ described the creation of a shunt between that space and the right atrium. Kouchoukos and coworkers⁷⁶ stressed the importance of not wrapping the graft with the aneurysm wall to avoid tension on the anastomoses when accumulation of blood occurs between the aneurysmal wall and the graft. They recommended an open technique in which the coronary arteries are detached from the aortic sinuses and sutured to the tubular Dacron

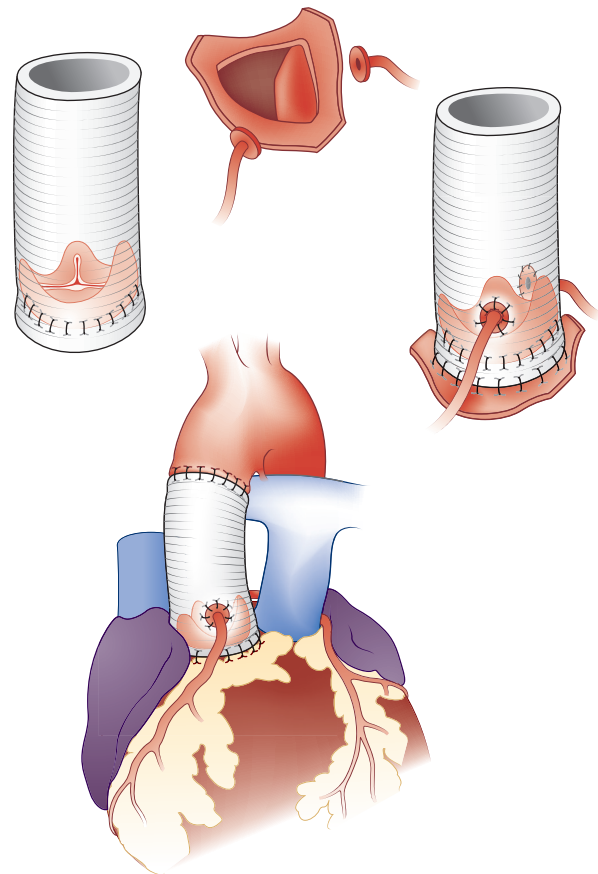


FIGURE 67-16 ■ Composite replacement of the ascending aorta and aortic valve with a bioprosthetic valve.

graft.⁷⁶ Cabrol and colleagues⁷⁸ described another technique whereby the two coronary arteries were connected to each other with a smaller graft and anastomosed side to side with the valved conduit. This technique, however, has not provided long-term results that were as good as direct coronary artery reimplantation.⁷⁹

Clinical Outcomes

Surgery for aortic root aneurysm is associated with low operative mortality and morbidity, particularly when performed electively. In a report of our experience with aortic valve sparing operations, there were only three operative deaths among 220 patients operated for aortic root aneurysms, including 24 with acute type A aortic dissection.⁸⁰ Other series showed similarly low operative mortality rates.^{74,81-83} Long-term outcomes of aortic valve sparing operations have been excellent.⁸¹⁻⁸⁴ We recently reported our experience with aortic valve sparing operations for aortic root aneurysm in 371 patients.⁸⁵ Their mean age was 47 ± 15 years, 78% were men, 35.5% had Marfan syndrome, 12% had type A aortic dissection, and 9% had bicuspid aortic valves. Approximately one half of the patients had moderate or severe aortic insufficiency before surgery. The technique of remodeling of the aortic root was used in 75 patients and the reimplantation of the aortic valve in 226. There were 4 operative and 35 late deaths. Patients' survival at 18 years was 76.8% and

approximately 10% lower than that of the general population matched for age and gender. Ten patients required reoperation on the aortic valve (5 reimplantation and 5 remodeling) for aortic insufficiency in 8 and infective endocarditis in 2. One valve was re-repaired and 9 replaced; all patients survived reoperation. The freedom from reoperation on the aortic valve at 18 years was 94.8%. Eighteen patients developed moderate or severe aortic insufficiency (12 reimplantation and 6 remodeling). Overall freedom from moderate or severe aortic insufficiency at 18 years was 78% and similar for both types of aortic valve sparing operations. These findings suggest that aortic valve sparing operations provide excellent long-term outcomes, but there is evidence of gradual deterioration in aortic valve function during the first two decades of follow-up. Patients with Marfan syndrome and other inherited aortic root aneurysms seem to have a more stable aortic valve function after reimplantation of the aortic root than after remodeling of the aortic root.^{86,87} Kerchov and colleagues⁸⁸ have shown that this is also true with incompetent bicuspid aortic valves which frequently have dilated aortic annulus.

The principal cause of early failure after aortic valve sparing operations is technical errors,⁸⁹ probably because of unrecognized cusp prolapse after reconstruction of the aortic root.

It remains unknown whether aortic valve sparing operations offer a survival benefit over aortic valve replacement with either biological or mechanical valves. Comparative studies suggest similar outcomes, but most studies contain series with relatively short-term follow-up because aortic valve sparing operations are relatively new in comparison with aortic root replacement.

Aortic root replacement with valved conduit is probably more frequently performed than aortic valve sparing operations during surgical treatment of aortic root aneurysm. In a report by Gott and coworkers⁹⁰ on the outcomes of aortic root surgery in patients with Marfan syndrome operated on at 10 experienced surgical centers, the operative mortality was 1.5% among 455 patients who had elective surgery, 2.6% among 117 who had urgent surgery, and 11.7% among 103 who had emergency surgery, mostly for acute aortic dissection. However, in the experience of Gott and colleagues at the Johns Hopkins Hospital,⁹¹ there was no operative death among 235 patients who had elective surgery and only two deaths among 36 who had urgent or emergent surgery. In our personal experience with 105 patients with Marfan syndrome in whom 44 had root replacement and 61 had aortic valve sparing, there was only one operative death, which occurred in a patient who was in preoperative cardiogenic shock because of end-stage aortic insufficiency.⁹² Patients with Marfan syndrome are usually young when they require aortic root surgery, which is one reason the operative mortality is low. Surgery in older patients is associated with higher risk.^{79,93} Age and clinical presentation are important determinants of outcome.^{63,79,93,94} Surgery in patients with acute type A aortic dissection is associated with higher operative and late mortality (see Chapter 70). Overall, the operative mortality for aortic root replacement is around 5% to 10%.^{63,64,79,93,94}

The long-term survival after aortic root replacement in patients with Marfan syndrome is very good. Gott and associates⁹⁰ reported from multiple institutions that the 10-year survival after aortic root surgery ranged from 60% to 80%, depending on the clinical presentation, but the 10-year survival was 81% in their experience at Johns Hopkins.⁹¹

An unresolved problem with patients with inherited aortic root aneurysms is the risk of aortic dissection late after repair of the aortic root, regardless of the technique used to repair the aortic root.^{74,81,84,90,91,95}

Thromboembolism, hemorrhage, and endocarditis remain problems for patients who have aortic root replacement with mechanical valves,^{79,90,92,93} and tissue degeneration and reoperation are problems for those who have a biological aortic valve.⁹²

Patients who have aortic root replacement require periodic checkups including a transthoracic echocardiogram and CT scans or MRI of the residual aorta. Patients with Marfan syndrome should receive a β -blocker after repair of the aortic root aneurysm.

Reoperations in the aortic root after replacement with valved conduits can be difficult, but in the hands of experts it can be done with relatively low operative mortality.^{75,96,97} When the problem is graft infection, the use of an aortic homograft is believed to offer the patient the best chance of cure.^{98,99} We and others have obtained similar results by using an approach of radical resection of infected tissues and reconstruction with synthetic grafts.¹⁰⁰⁻¹⁰²

ROSS PROCEDURE

The Ross procedure is a complex operation whereby the diseased aortic valve is replaced with the patient's own normal pulmonary valve, and a biological valve, usually a pulmonary homograft, is used to replace the pulmonary valve. This operation was first described in the experimental laboratory by Lower and colleagues¹⁰³ in 1960 and clinically performed by Ross in 1967.¹⁰⁴ The original technique consisted of implanting the pulmonary autograft inside the aortic root in a subcoronary position. For the next two decades, Donald Ross was practically the only surgeon performing this procedure.¹⁰⁵ Interest in this operation increased after the initial report by Stelzer and colleagues¹⁰⁶ in the late 1980s, who performed it using the technique of aortic root replacement, a more reproducible method.

The Ross procedure is ideal for children because the pulmonary autograft grows with the child.¹⁰⁷ Although the Ross procedure can be used in patients of any age,¹⁰⁸ most surgeons prefer to use it in children and young adults.^{109,110} Some surgeons consider it ideal for treating patients with active infective endocarditis.¹¹¹ The Ross procedure also has been performed in patients with dilated ascending aorta or even aneurysms.¹¹² It should not be used in patients with known genetic disorders of the proximal aorta or in patients with connective tissue disorders.

Although the Ross procedure was developed almost five decades ago, it gained popularity only in the 1990s.

According to the Society of Thoracic Surgeons Database, its peak usage in adults was in 1998 with 1.2% of all isolated aortic valve replacements; its use declined steadily to 0.09% in 2010.¹¹³

Operative Techniques

The three basic methods to transfer the pulmonary autograft into the aortic position are subcoronary implantation, aortic root replacement, and aortic root inclusion.

Subcoronary Implantation

The aortic valve should be exposed through a transverse aortotomy 1 cm above the sinotubular junction. The diseased aortic valve is excised, and all calcified tissues are completely débrided from the aortic annulus, membranous septum, and anterior leaflet of the mitral valve. The diameters of the aortic annulus and sinotubular junction are measured with a metric sizer. The pulmonary artery is opened just before its bifurcation, and the valve cusps are inspected. If the cusps are normal, the pulmonary root is excised. The incision in the right ventricular outflow tract is made along a single horizontal plane approximately 3 mm below the lowest level of the pulmonary annulus. Care must be exercised to prevent damage to the left anterior descending artery and the first septal perforator branch. It is difficult to measure the diameter of the pulmonary annulus because it is entirely attached to distensible muscle, but it can be estimated by measuring the diameter of the sinotubular junction of the pulmonary root. The diameter of the pulmonary annulus is 15% to 20% larger than the diameter of the sinotubular junction. If the diameters of the aortic annulus and sinotubular junction of the two roots are similar, the technique of subcoronary implantation will work well. If there is mismatch in size, an alternative technique should be used, and the difference in diameters should be corrected.¹¹⁴ When the pulmonary annulus is slightly larger than the aortic annulus, it can be reduced by placing the sutures beneath the subcommissural triangles close together in the left ventricular outflow tract rather than in the pulmonary autograft. The smallest pulmonary sinus (usually the posterior sinus) should be oriented toward the left aortic sinus. The pulmonary autograft is secured to the left ventricular outflow tract and aortic annulus with multiple interrupted 4-0 polyester sutures. All sutures must be distributed precisely along a single horizontal plane at the level where the pulmonary annulus coincides with the level of the aortic annulus. We agree with Yacoub and colleagues,¹¹⁵ who believe that it is important to excise the muscle beneath the commissures of the pulmonary autograft before implanting it into the left ventricular outflow tract. This makes it easier to place the pulmonary annulus to the same level of slightly below the level of the aortic annulus. One has to be meticulous about the spatial distribution of the three subcommissural spaces and maintenance of the normal scallop-shaped pulmonary annulus. Once the inflow suture line is completed, the three commissures are precisely suspended in the aortic root, and stay sutures through both arterial walls are placed immediately above the commissures. The sinuses of the

pulmonary autograft that face the left and right coronary arteries are partially excised and sutured to the aortic sinuses around the coronary artery orifices with a continuous 6-0 or 5-0 polypropylene suture. The sinus of the pulmonary autograft that faces the noncoronary aortic sinus need not be excised, and it is sutured to the aortic root at the level of the sinotubular junction. It is important not to alter the diameter of the sinotubular junction of the pulmonary autograft when it is being sutured to the aortic root or when the aortotomy is closed. The right side of the heart is reconstructed with a pulmonary homograft. This homograft should be larger than the pulmonary autograft. [Figure 67-17](#) illustrates the technique of subcoronary implantation.

Aortic Root Replacement

Aortic root replacement with a pulmonary autograft is performed as described previously for aortic root aneurysm. The aortic valve is excised and so are the sinuses, leaving 5 mm of arterial wall around the coronary artery orifices. The same steps described previously are used to harvest the pulmonary autograft and measure it. If the aortic annulus is larger than the pulmonary annulus, a reduction annuloplasty is necessary. This can be accomplished by closing the subcommissural triangles of the noncoronary sinus of the aortic root ([Fig. 67-18](#)). The pulmonary autograft is secured to the left ventricular outflow tract with simple multiple interrupted 4-0 polyester sutures along a single horizontal plane. A strip of Teflon felt in this suture line improves hemostasis and may prevent annular dilation. The coronary arteries are reimplanted into the respective sinuses. The pulmonary autograft is sutured to the ascending aorta. If the ascending aorta is dilated, it may need replacement or plication ([Fig. 67-19](#)). A strip of Dacron fabric or Teflon felt along this anastomosis prevents late dilation of the sinotubular junction.¹¹⁶

Aortic Root Inclusion

Another method of implanting the pulmonary autograft is the aortic root inclusion technique. The noncoronary aortic sinus should be incised vertically toward the aortic annulus to enhance exposure of the aortic root. The pulmonary autograft is secured to the aortic annulus using the technique described previously. After suturing the pulmonary autograft in the left ventricular outflow tract, the three commissures are pulled gently upward to determine the positions of the right and left coronary artery orifices in the pulmonary autograft. Small openings (5 or 6 mm in diameter) are made in the pulmonary autograft sinuses that correspond to the coronary artery orifices. The arterial wall of the pulmonary sinus is then sutured to the aortic sinus around the coronary artery orifices with a continuous 6-0 polypropylene suture. The three commissures of the pulmonary autograft are also sutured to the aortic wall, and the aortotomy is closed, including the aortic and pulmonary arterial walls. The incision made in the noncoronary sinus of the aortic root should be closed only if there is no bleeding between the two roots and if closure causes no distortion of the pulmonary

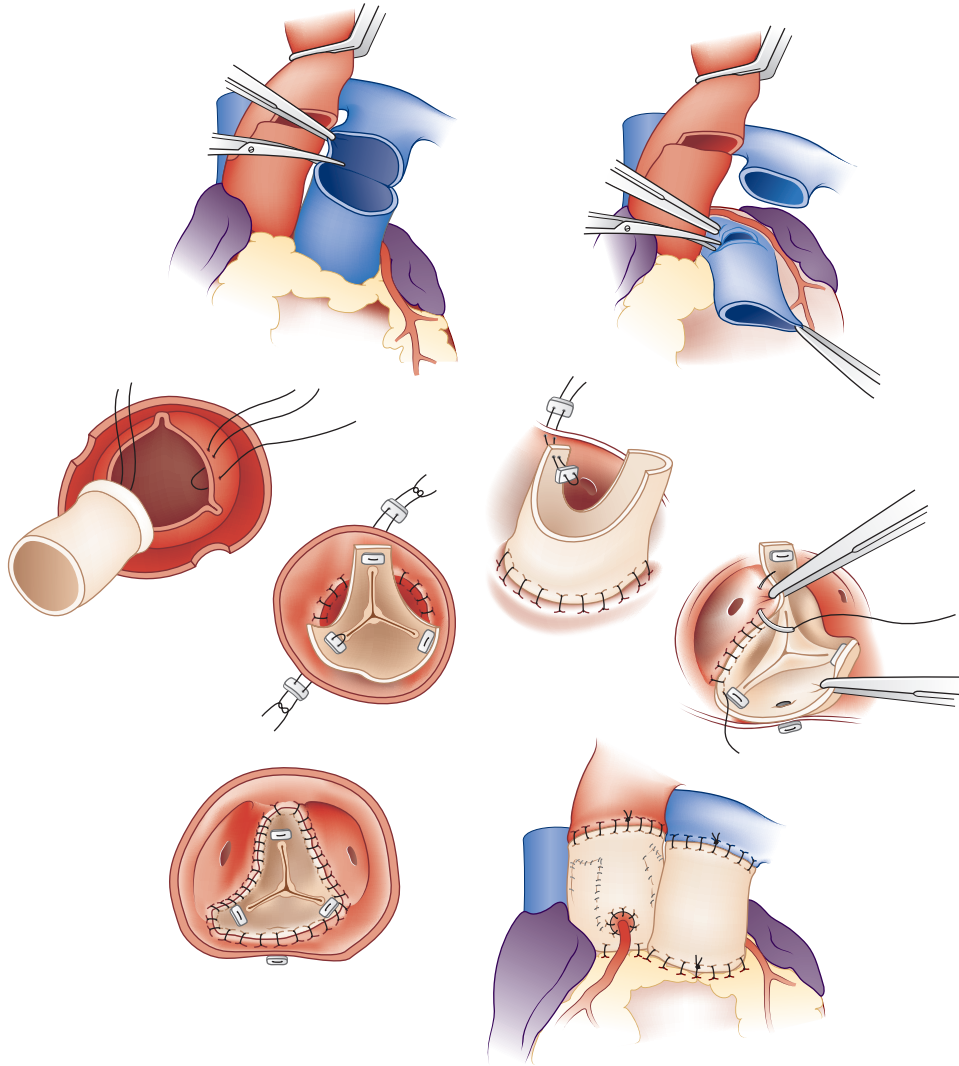


FIGURE 67-17 ■ The Ross procedure: subcoronary implantation.

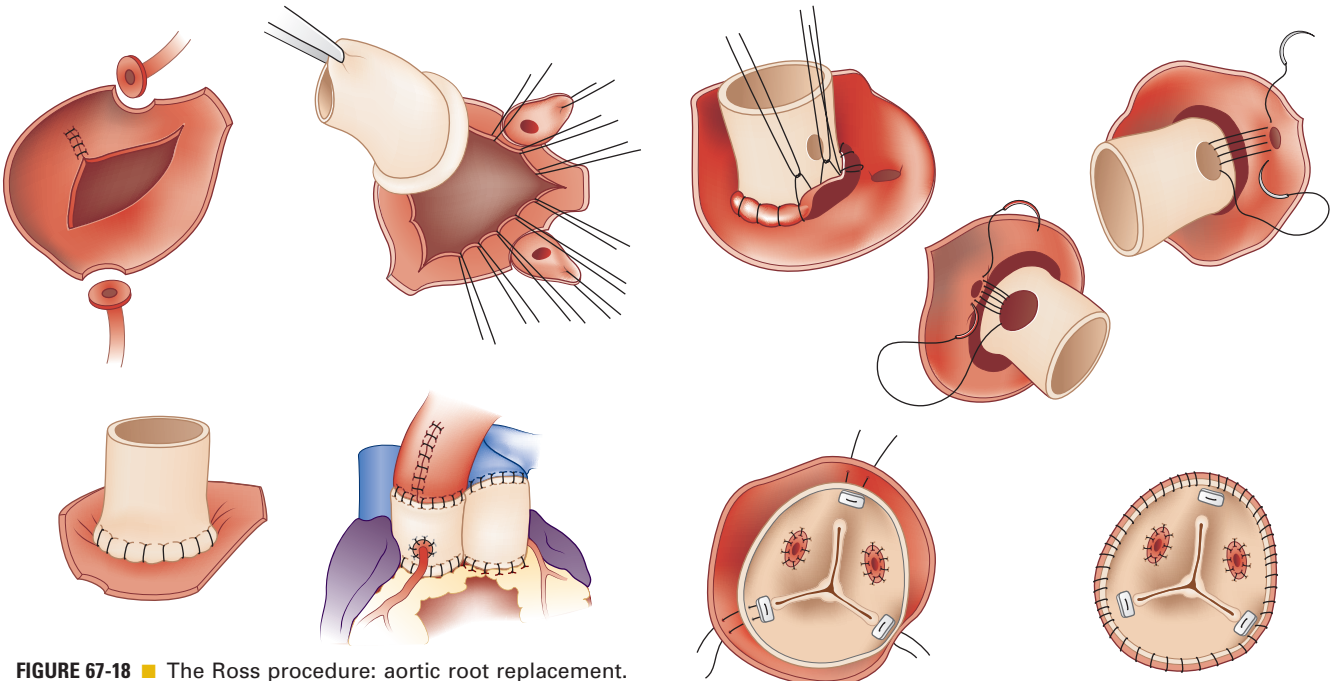


FIGURE 67-18 ■ The Ross procedure: aortic root replacement.

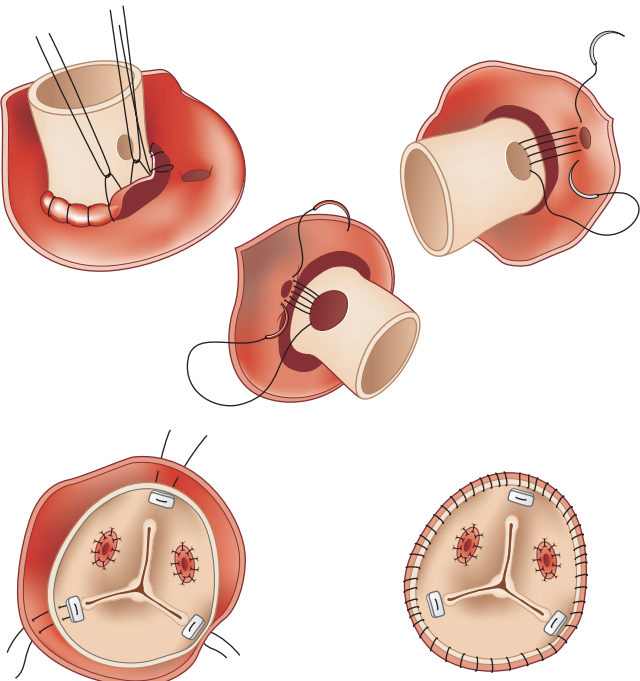


FIGURE 67-19 ■ The Ross procedure: aortic root inclusion.

autograft after unclamping the aorta. Figure 67-19 illustrates the technique of aortic root inclusion.

Clinical Outcomes

Despite its technical complexity, the operative mortality associated with the Ross procedure is reportedly low in centers with large experience.^{108-110,117-119} However, in the STS Database the risk adjusted operative mortality for the Ross procedure was higher than for isolated aortic valve replacement in adults.¹¹³ The main problem with the Ross procedure is that it can potentially transform a patient with isolated aortic valve disease to one with both aortic and pulmonary valve disease and even coronary artery disease, because they may undergo reimplantation if the technique of aortic root replacement is used. Early aortic insufficiency is usually due to technical errors.¹¹⁴ Thromboembolic complications are rare because of the nature of the valves used and the patients' ages. Once the pulmonary autograft is healed in the aortic root, it should not be the source of thrombus. We have documented a few episodes of transient ischemic attacks during the first few weeks after surgery, but seldom after 2 or 3 months. The risk of infective endocarditis is also very low, and when it happens it is usually in the pulmonary homograft.¹¹⁹ Subaortic false aneurysm is rare, but it may occur during the first postoperative year.¹¹⁹ Long-term survival after the Ross procedure is excellent and in some series appears to be similar to that of the general population.¹¹⁷⁻¹¹⁹

Patients who had the Ross procedure should have annual Doppler echocardiography to assess the function of the neo-aortic valve and pulmonary homograft, and to measure the size of the aortic root. The early development of aortic insufficiency is usually the result of technical problems,¹¹⁴ and late aortic insufficiency is caused by dilation or degeneration of the pulmonary autograft.^{109,110,117-119} Dilation of the aortic root is less common after the subcoronary and aortic root inclusion techniques than after aortic root replacement.¹¹⁸⁻¹¹⁹ Preoperative aortic insufficiency and dilated aortic annulus (≥ 15 mm/m²) are predictors of aortic insufficiency.^{110,118-121} Aneurysms of the sinuses of the pulmonary autograft have been described; if the pulmonary cusps remain normal, an aortic valve sparing operation is feasible.^{120,121}

We recently published our experience in a cohort of 212 patients followed prospectively with periodic assessment of valve function, and the freedom from reoperation for any reason in the pulmonary autograft was 93% at 15 years and 81.8% at 20 years.¹¹⁹ Other investigators have reported similar results^{117,118,122} and some reported worse outcomes.^{109,110} In series by Mokhles and colleagues,¹⁰⁹ the freedom from reoperation on the pulmonary autograft was 51% at 18 years. The reasons for these differences in failure rates are unclear. Pathology of the aortic valve, patient age, operative technique, and surgeon experience can all play a role.¹¹⁹

Many surgeons believe that patients who have aortic root replacement with pulmonary autograft should be treated with a β -blocker or angiotensin-converting enzyme inhibitor, or both, during the first postoperative year to prevent dilation during the adaptation of the graft

to systemic pressures, but there are no scientific data to support this treatment.

Another problem with the Ross procedure is dysfunction of the biological valve used to reconstruct the right ventricular outflow tract. A pulmonary homograft is probably the best conduit to use, but it is not free from complications, and a number of patients develop stenosis, insufficiency or both.^{109,118-119} In our series, eight patients have required reintervention for a freedom from reoperation of 92.7% at 20 years.¹¹⁹ When the homograft fails, percutaneous deployment of a stented tissue valve is often feasible, and the results are good.¹⁰⁸

The usefulness of the Ross procedure remains controversial, but we believe that it is an excellent valve for women during child-bearing years and for young adults who are physically active.

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SURGERY OF THE AORTIC ARCH

Michael Z. Tong • Lars G. Svensson

CHAPTER OUTLINE

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SUMMARY

The history of cardioaortic surgery has been replete with new techniques for ascending and aortic arch repairs since 1956, when Denton Cooley and Michael DeBakey replaced the ascending aorta with a homograft using cardiac bypass.^{1,2} In 1957, DeBakey and colleagues first described aortic arch replacement using antegrade brain perfusion.³ Before this, one of the few successful ascending aortic repairs was reported in 1932 by Blalock, who repaired a stab wound of the ascending aorta caused by an ice pick.⁴ By removing the occluding clot, Blalock noted the “bright red blood that shot over the screen at the head of the table on the anesthetist’s clothes.” Using only nitrous oxide and oxygen for anesthesia in a patient with cardiac tamponade most likely contributed to the hypertension and description of the procedure.

With the advent of cardiopulmonary bypass, many technical problems of aortic arch surgery were largely overcome. In 1950, Bigelow first published the results of his experiments in dogs using deep hypothermia for cardiovascular operations without cardiopulmonary bypass.⁴ Nonetheless, it was not until 1963 that Barnard combined deep hypothermia with circulatory arrest and cardiopulmonary bypass for aortic arch operations and dissection.⁵ In 1964, Borst reported using deep hypothermia and circulatory arrest to repair an arteriovenous fistula between the innominate vein and the aorta caused by shrapnel.⁴ The routine use of deep hypothermia and circulatory arrest did not, however, become popular until 1975, when Griep reported a series of aortic arch replacements using deep hypothermia and circulatory arrest.⁴ In 1983, Borst

and colleagues^{6,7} and others⁸ reported replacing the aortic arch and leaving a tube graft lying free in the descending aorta, which they called the elephant trunk technique. In 1990, Crawford and Svensson^{4,9} reported replacement of the entire aorta as a staged procedure using a modified elephant trunk technique. The modification of inverting the graft into the descending aorta while sewing the distal anastomosis resulted in a more secure anastomosis with less risk of bleeding or rupture. Subsequently, in 1993, Svensson and colleagues⁴ successfully replaced the entire aorta from the aortic valve to the aortic bifurcation during a single operation using a combined mediastinal and thoracoabdominal incision with deep hypothermia and circulatory arrest.³

Aortic arch surgery has become relatively common and safe, with a mortality risk of 2% and a stroke risk of 2%.¹⁰ In 2012, we performed 1282 aorta operations: 1065 on the thoracic aorta and 724 on the ascending aorta and aortic arch. Our approach is discussed later. In this chapter, we discuss the potential causes of aortic arch aneurysms, the association with some pathologic entities, diagnostic workup, brain protection, perfusion methods, different operative approaches, and outcomes after aortic arch surgery.

DEFINITIONS AND CLASSIFICATION

Anatomically, the aortic arch is defined as the segment of aorta between a line at a right angle proximal to the

innominate artery origin and extending to a line drawn at a right angle distal to the origin of the left subclavian artery. Aneurysms are irreversible dilations of the aorta exceeding the normal diameter for the age and height of the patient.⁴ The exact size at which the aorta is labeled “aneurysmal” varies. Definitions vary from 1.5 times to twice the normal diameter of the aorta. For patients with Marfan syndrome, we suggest that when the cross-sectional area (in square centimeters) divided by the patient’s height (in meters) exceeds a ratio of 10, it should be considered significant and an indication that the patient requires surgical repair.¹¹ Thus, in some respect, the definition of an aneurysm is not absolute but rather refers to the significant dilation of the aorta.

Aneurysms can be divided further into aortic aneurysms without penetration through the aortic adventitia (true aneurysms) and those that penetrate through the adventitia and are contained by the surrounding tissue, which prevents exsanguination of the patient (false aneurysms).⁴ In addition, aneurysms are classified according to their likely causes: medial degenerative aneurysms (typically showing loss of elastic tissue); those related to aortic dissection; other disorders of connective tissue, particularly loss of collagen as in Ehlers-Danlos syndrome or loss of elastic tissue as in Marfan syndrome; those associated with blunt trauma; aortitis; primary aortic infections or after previous cardiovascular surgery, especially graft infection in the ascending aorta; and congenital abnormalities.⁴

We prefer the term *medial degenerative aneurysms* to *atherosclerotic aneurysms* simply because not all medial degenerative aneurysms have atherosclerosis.⁴ Furthermore, atherosclerosis does not necessarily appear to be the sole causative factor in the development of medial degenerative aneurysms. It appears that atheroma formation, fibrosis, and calcification are results of degeneration that follow the primary injurious event that caused the aneurysm.

Aneurysms can be either fusiform, showing uniform dilation, or saccular in appearance.⁴ The three most common sites for saccular aneurysms are on the lesser curve of the aortic arch, on the descending aorta, and opposite the visceral vessels.⁴ The saccular aneurysms in the aortic arch are usually related to penetrating ulcers, often with localized dissection or mycotic aneurysm formation.⁴ Fusiform aneurysms of the aortic arch are typically associated with dilation of the ascending aorta, particularly when associated with inflammatory aortitis. Medial degenerative aneurysms of the root are known as *annuloaortic ectasia*, a term coined by Cooley.⁴ This results in a flasklike or hourglass appearance of the aortic root (Erdheim deformity), which is also associated, in particular, with Marfan syndrome. For example, in patients with Marfan syndrome, initiation of aortic root dilation results early in the annuloaortic ectasia stage, and, if it is not treated, there is subsequent development of aortic root, ascending aorta, and aortic arch aneurysm formation. In fact, at this late stage, aortic dissection often precedes aortic arch aneurysm formation.

The human artery consists of five distinct layers. The first or innermost layer (the endothelial layer, which lies on a basement membrane) is known as the tunica intima.

Between the tunica intima and the tunica media is a fenestrated sheath of elastic fibers known as the internal elastic lamina. The tunica media has several layers of elastic-tissue lamellae arranged concentrically along the length of the aorta, and it forms the bulk of the aortic wall. The amount of elastic tissue decreases in amount from the sinotubular ridge as the aorta progresses down to the aortic bifurcation. In the tunica media lie smooth muscle cells and the ground substance of the aorta. The latter consists of proteoglycans. The outer third of the tunica media receives its nutrition from the vasa vasorum, lymphatics, and nerves. On the outside of the tunica media is the external elastic lamina, which separates the media from the adventitia. The tunica adventitia consists of strong, tough layers of collagen and elastic fibers. Because of its strength, this is the critical layer wherein the surgeon must suture the graft placement.⁴

No clear, systematic classification of aortic pathology appears in the literature, and different pathologists have coined various terms. We favor a definition of aortic pathology based on hematoxylin and eosin (H&E) findings and elastic tissue stains. Thus, medial degenerative disease is defined as a loss of elastic fibers, and medial necrosis as a loss of smooth muscle cells. The presence of atherosclerosis superimposed on degenerative disease is described as atherosclerotic with or without calcification. Atheroma is also frequently superimposed. Inflammatory disease is diagnosed when there is evidence of chronic inflammatory cell infiltrates. The intima and adventitia may also show various degrees of hyperplasia.⁴

CAUSATIVE AND PREDISPOSING FACTORS

Congenital Aneurysms

Congenital aneurysms of the aortic arch are extremely rare, although they may be associated with aberrant right subclavian arteries from a Kommerell diverticulum situated in either the distal aortic arch or the proximal descending aorta (Figs. 68-1 and 68-2).⁴ Similarly, aneurysms can be associated with one of two types of right-sided congenital arches. For the Felson and Palayew type I right-sided arches, a vascular ring encircles and compresses the esophagus and trachea (Fig. 68-3).¹² The distal arch and descending aorta may be aneurysmal. In patients with type II right-sided arches (Fig. 68-4), the anatomy is basically a mirror image of an aberrant right subclavian artery with a Kommerell diverticulum. Thus, an aberrant left subclavian artery comes off the right-sided descending aorta.¹² More frequently, however, the aortic arch, in association with these two varieties, is hypoplastic unless the hypoplasia is severe enough to cause aortic stenosis, and prestenosis or poststenosis aneurysm formation occurs. Coarctation of the aorta is often associated with a bicuspid valve and an ascending aortic aneurysm, but, if left untreated, it may be associated with aortic arch aneurysm formation. A history of patent ductus arteriosus or ventricular septal defect may also be noted. More rarely, adult patients who have been

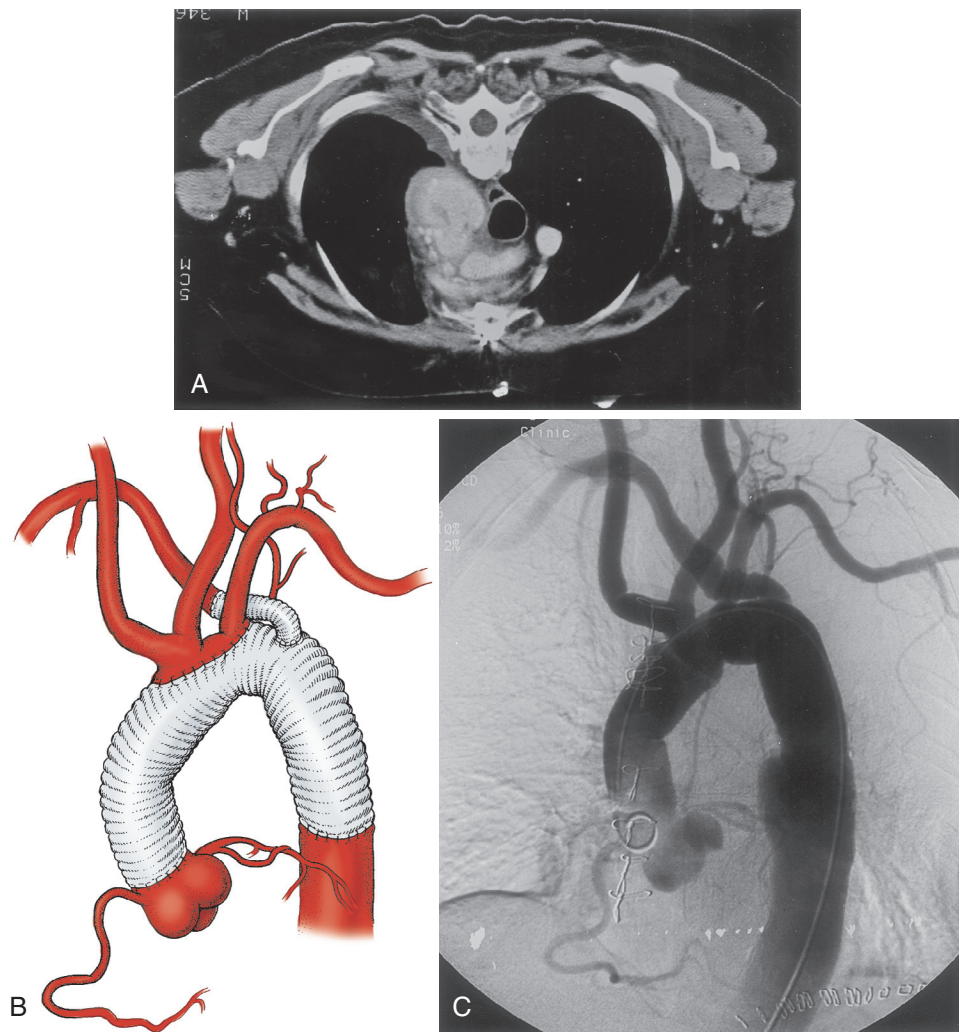


FIGURE 68-1 ■ **A**, Computed tomography scan of an aortic arch aneurysm associated with an aberrant right subclavian artery that was treated by a modified elephant trunk technique. **B**, The first stage of the elephant trunk procedure was done with an anastomosis between the left subclavian artery and the aberrant right subclavian artery, and the second stage was performed with an interposition graft to the right subclavian artery. **C**, Angiogram of the completed repair. Note the tube graft to the right subclavian artery arising from the more distal part of the aortic arch.

previously operated on for an interrupted aortic arch can develop ascending and aortic arch aneurysms.⁴

Medial Degenerative Aneurysms

Medial degenerative aneurysms typically occur in older adult patients who were long-term smokers or have a long history of hypertension. If the smoking history is severe and there is presence of chronic obstructive pulmonary disease (COPD), extensive atheroma formation may also be found in the aneurysms. These types of aneurysms, with extensive atheroma and atherosclerosis formation, typically involve not only the ascending aorta and the aortic arch but also the descending and thoracoabdominal aorta. Coronary artery disease and carotid artery disease are also common associations. When the aorta is inspected, small ulcers are often observed, and these can later form penetrating ulcers that result in dissection in the medial adventitial plane or false aneurysm formation if the adventitia is penetrated.⁴ Less typically, medial degenerative aneurysms are associated with

systemic inflammatory disease and various types of arthritis or vasculitis (see Vasculitis and Aortitis, later).

Aortic Dissection

The DeBakey and Stanford classifications of aortic dissection differ, and there are also different classes of dissection (Fig. 68-5)¹³ regarding replacement of the aortic arch. The class of intimal tear also influences the aortic arch repair technique.¹³

Mycotic Aneurysms

For reasons not entirely clear, true primary mycotic aneurysms of the aorta, as described by Svensson and Crawford,⁴ have a tendency to occur either on the lesser curve of the aortic arch, with a variable extent of involvement, or opposite the visceral vessels in the abdomen. It is unclear whether this is related to the structure of the aorta or to the flow patterns that result in turbulence in these areas opposite the branches of the aorta. The typical

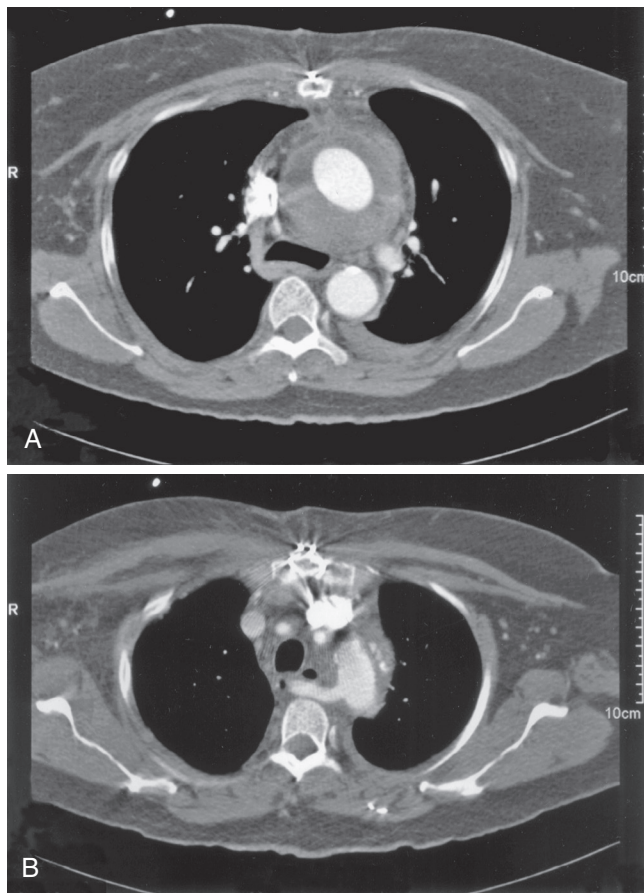


FIGURE 68-2 ■ **A**, Computed tomography (CT) scan from a patient with an ascending and arch aneurysm, with extensive clot formation in the aneurysm, associated with an aberrant right subclavian artery. **B**, CT scan after the repair. The repair was done from the aberrant right subclavian artery ostium, through the aortic arch, using a long “tongue” extension into the descending aorta. The ascending aorta was replaced with a composite valve graft. Note the aberrant right subclavian artery coming off the distal aorta and running posterior to the esophagus and trachea.

infective organisms are *Escherichia coli*, staphylococci, *Salmonella*, and streptococci, including *Streptococcus pneumoniae*. Other strains, however, may sometimes be detected. Some of these may be related to atherosclerotic ulcers, which initially act as a nidus for subsequent infection. Mycotic aneurysms frequently penetrate through the aortic arch wall, resulting in false aneurysms or free rupture. Osler called these aneurysms mycotic because the gray, slimy lining reminded him of fungal growth. Fungal infections in the vessel walls are, on the whole, very rare, except in patients who have had graft-related infections.⁴

Vasculitis and Aortitis

Inflammatory infiltrates of the aorta are not infrequent. In a prospective examination of histologic specimens by both H&E and elastic-tissue stains, inflammatory infiltrates were found in many of the specimens. Although these inflammatory infiltrates consist of various types of leukocytes, often associated with the diseases listed later, an associated systemic illness may be absent. This suggests that the original cause of the aortic injury was unrecognized, subsequently appearing as a medial degenerative aneurysm, with formation of atherosclerosis and calcification. Previous chest radiation for Hodgkin disease or breast malignancies may also be noted in the history. Radiation-induced vasculitis is associated with severe calcification and a porcelain aorta. A stiff left ventricle, scarred right ventricle, and fixed cardiac output increase the risk of surgery.

Inflammatory systemic diseases may result in aneurysms. For example, the development of aortitis is commonly associated with Takayasu disease (nonspecific aortoarteritis) (Fig. 68-6); giant cell arteritis (Horton disease); temporal arteritis; polymyalgia rheumatica; Behçet, Buerger, Logan, Sjögren, Reiter, or Kawasaki disease; relapsing polychondritis; systemic lupus erythematosus (often mycotic); rheumatoid arthritis; sarcoid

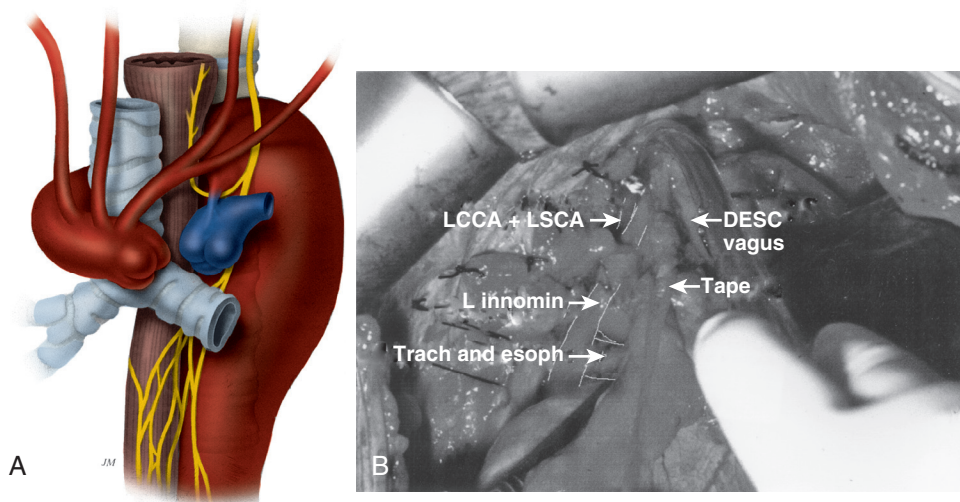


FIGURE 68-3 ■ **A**, Illustration of right-sided aortic arch with vascular ring. **B**, Intraoperative findings. DESC, Descending aorta; esoph, esophagus; L innomin, left innominate artery; LCCA, left common carotid artery; LSCA, left subclavian artery; trach, trachea.

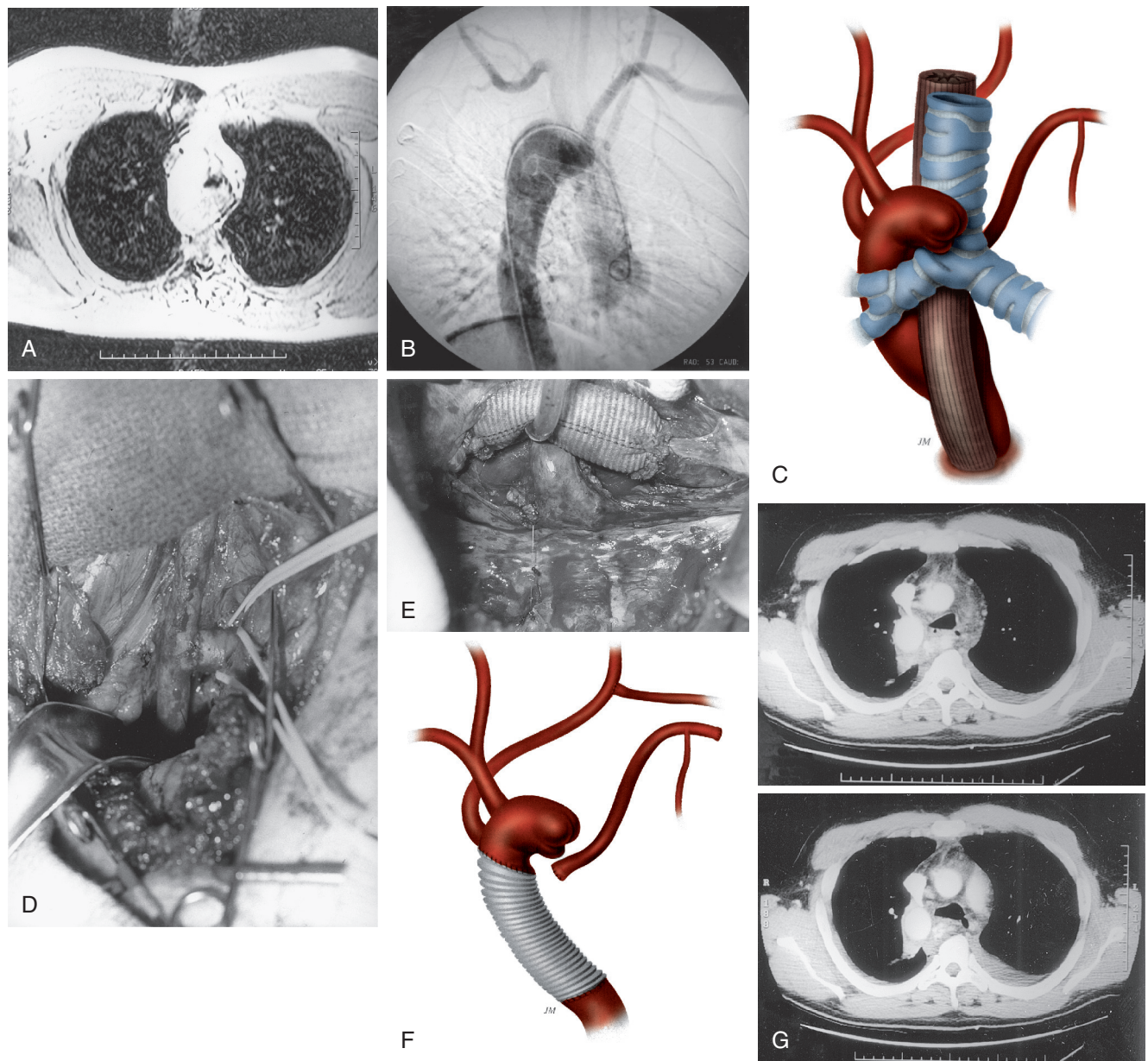


FIGURE 68-4 ■ **A**, Magnetic resonance imaging of a right-sided arch compressing the trachea, bronchus, and esophagus. **B**, Angiogram. **C**, Anatomy illustration. **D**, Left subclavian-to-carotid anastomosis. **E**, Distal arch and descending aorta replacement with Kommerell diverticulum oversewn (a stay suture is attached to the stump). **F**, Illustration of repair. **G**, Postoperative computed tomography scans with tracheal compression relieved.

and ankylosing spondylitis; osteoarthritis of unknown origin; ulcerative colitis; and potentially autoimmune diseases of the thyroid, such as Hashimoto.

Histologically, Takayasu disease has panaortitis, severe intimal hyperplasia, and severe adventitial fibrosis with perivascular inflammation. In contradistinction, giant cell aortitis has inflammatory margins around areas of medial necrosis and inflammation of the media. Fibrosis and intimal hyperplasia are minimal.

Trauma

Ten percent of traumatic lesions of the aorta occur in the aortic arch. The remaining 90% occur in other segments

that are discussed in [Chapters 69](#) and [75](#). The aneurysms are most often related to tears at the hinge point of the aorta during acceleration or deceleration injuries. Thus, the usual sites of primary tears are the origin of either the innominate artery or the subclavian artery (70% to 80%), although the origin of the common carotid artery may also be involved.⁴ Although blunt trauma is the most common cause in the United States, traumatic arch injuries are more frequently caused by penetrating injuries from shrapnel or bullets or knife injuries in developing countries. With penetrating lesions, involvement of the trachea, esophagus, venous system, nerves, and vertebral column significantly complicates management.

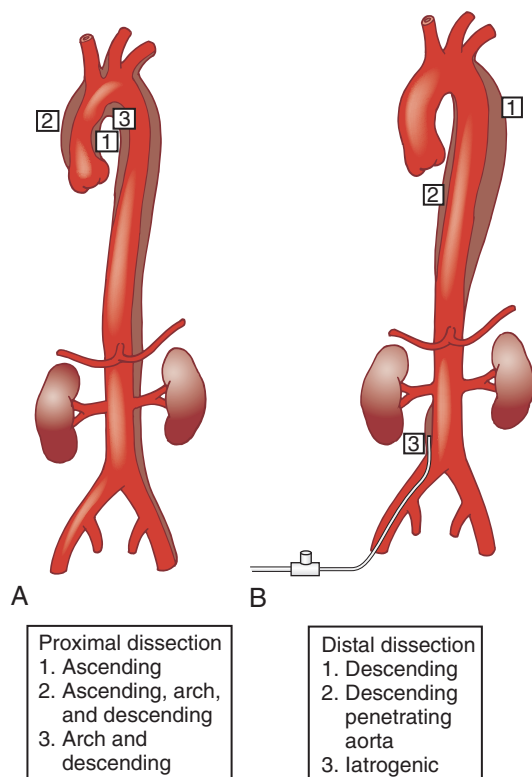


FIGURE 68-5 ■ Aortic dissection classification. **A**, Proximal dissection: (1) involvement of the ascending aorta only; (2) ascending, aortic arch, and descending aorta involvement; and (3) arch and descending involvement. **B**, Distal dissection: (1) involvement of the descending aorta with or without the abdominal aorta; (2) penetrating aortic ulcer with descending dissection; and (3) abdominal dissection (usually iatrogenic).

Tumors of the Arch

Tumors of the aortic arch are extremely rare, but when they occur they are usually found distal to the subclavian artery. Very rarely have tumors been related to prosthetic grafts.⁴

Reoperations

Patients who have undergone previous cardiovascular surgery may require reoperation either for new aneurysm formation or for false aneurysm formation. Approximately half of all patients undergoing arch operations have had previous cardiovascular surgery. There are two typical scenarios.

The first scenario involves a patient who earlier underwent acute dissection repair and subsequently developed an aortic arch aneurysm because the aorta, weakened from the dissection, had dilated over the course of time. This situation occurs commonly in patients with Marfan syndrome. It is preferable to repair only the ascending aorta at the time of the acute dissection repair,^{4,14} first because the first priority is to save the patient's life, and second because trying to repair the aortic arch simultaneously carries a much higher mortality risk.^{4,14} Furthermore, the risk of a patient's requiring another operation after acute dissection repair is, in most cases, small.^{4,14} It is, however, important that the initial acute dissection

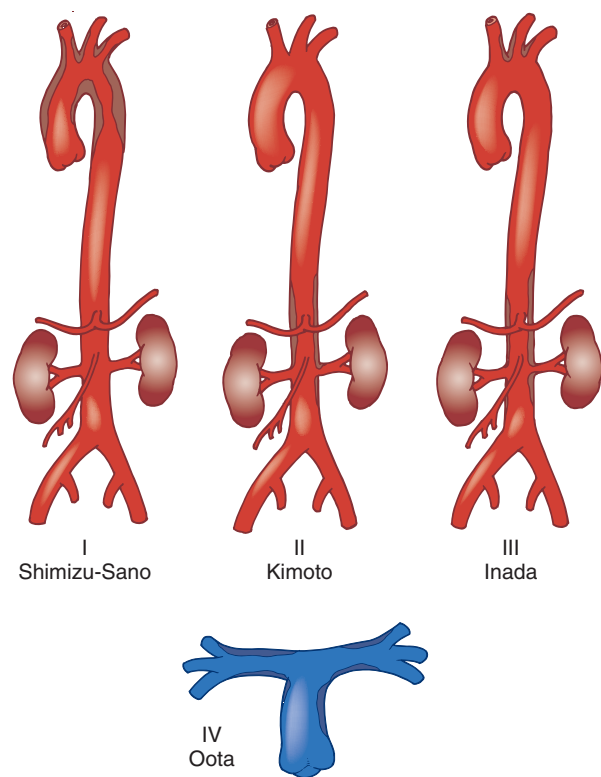


FIGURE 68-6 ■ Classification of Takayasu aortitis. Subtypes and their extents are depicted. (From Svensson LG, Crawford ES: *Cardiovascular and vascular diseases of the aorta*, Philadelphia, 1997, Saunders, pp 42–83.)

repair should be performed with circulatory arrest unless the dissection is a DeBakey type II. This is so that the inside of the aortic arch can be inspected and a more complete hemiarch repair can be performed at the initial operation. A tear in the aortic arch can often be repaired with pledgeted 4-0 Prolene running sutures.^{4,14} The use of biological glues may also increase the risk of recurrent aneurysms.

The second scenario for reoperation involves a patient in whom there was progression of the aneurysm formation in the aortic arch after initial ascending aorta repairs, or, at the time of the ascending aorta repair, not enough of a hemiarch was repaired, particularly when circulatory arrest was not performed.

An uncommon group of patients who require reoperations are those who form aneurysms at either the origin of the greater vessels, most typically the innominate artery, or at the site where a Carrel patch of the aorta was used for reattachment of the greater vessels. The site becomes aneurysmal and enlarges. This latter scenario should be watched for particularly in patients with Marfan, Loeys-Dietz, or Ehlers-Danlos syndrome, especially if they have suffered aortic dissection and the aorta is fragile.^{4,14,15}

Although aortic graft infections are rare in our experience, such cases are often referred to us. They require extensive débridement and repair, usually with homografts (allografts). Alternatively, if homografts are not available, rifampin-soaked Gelweave grafts can be used. We also like to put in an irrigation system with a Blake

drain infusing appropriate antibiotic depending on sensitivity or 5% Betadine in saline at 50 mL/hr over a few days. If there is a cavity, omental or muscle flaps are used to fill the space (Fig. 68-7). Patients are kept on lifelong antibiotics or, for fungal infections, fungal antimicrobials, particularly the newer, less toxic form of amphotericin B. In sick, high-risk patients, conservative approaches with either percutaneous or surgical drainage have also been reported with some success as long as the infection does not involve any suture-line, graft-enteric fistulas or involve invasive gram-negative organisms such as *Pseudomonas* or *Salmonella*.^{16,17}

Syndromes Associated with Aortic Arch Pathology

Aneurysms may form in association with genetic diseases such as Marfan syndrome, Ehlers-Danlos syndrome, Erdheim syndrome (annuloaortic ectasia), Noonan syndrome, hereditary polycystic kidney disease, osteogenesis imperfecta, and Turner syndrome.⁴

HISTORY AND PHYSICAL EXAMINATION

When patients have a potential aortic arch aneurysm, neither questioning about symptoms nor physical examination is particularly informative. During the questioning, however, any history of aortic valvular disease associated with aortic root aneurysms needs to be sought, along with any history of neurologic or neurocognitive events. Computed tomography (CT) scans or magnetic resonance imaging (MRI) studies before aortic arch surgery have shown that between 40% and 60% of patients have evidence of brain injury. In a prospective randomized study, 38% of our patients, excluding those who had strokes with residual deficits and those older than 75 years, had a neurocognitive deficit before undergoing aortic arch surgery.^{18,19}

If the aortic arch aneurysms are particularly large, hoarseness may develop, particularly if the distal aortic arch is enlarged. The reason is that the left recurrent nerve wraps around the distal aortic arch at the

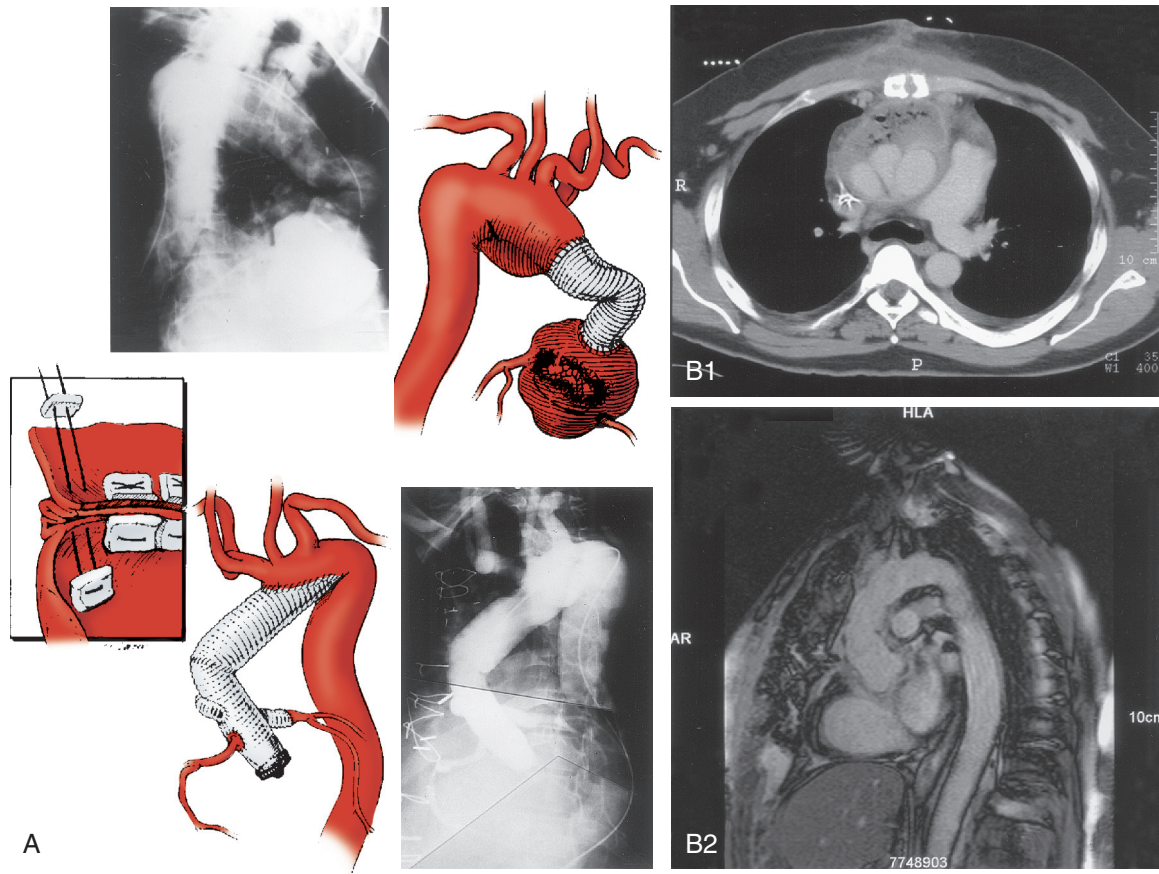


FIGURE 68-7 ■ **A**, An infected ascending aorta graft after initial replacement followed by reoperation with graft insertion (done elsewhere). During the third procedure, a new composite valve graft was inserted. The left main and the right coronary arteries were reattached as buttons, and the hemiarch was replaced with a separate graft. The annulus had to be reconstructed because of extensive annular abscess. Although the organism was *Staphylococcus aureus*, the patient, on suppressive antibiotics, has continued to be free of further infection. An omental flap was swung into the chest to fill dead space. **B1**, Computed tomography scan from a patient who had undergone two previous heart operations, including a composite valve graft insertion that became infected. The patient also underwent a limited sternal débridement elsewhere but later developed an abscess under the skin and associated air in the mediastinum. **B2**, The postoperative magnetic resonance angiogram after the repair. The patient had two allografts (homografts) inserted to replace the aortic root and the aortic arch. In addition, an omental flap was swung into the chest to fill the dead space.

ligamentum arteriosum and can become stretched by the aneurysm. Dysphagia may also occur, but this is more frequent with congenital lesions (see Fig. 68-4). In 1794, Bayford called this “lusoria,” referring to the Latin term *lusus naturae* meaning “a freak of nature.” This is often described as dysphagia lusoria or arteria lusoria. Dyspnea can also be a symptom when the pulmonary artery or left bronchus is constricted.⁴

Patients may complain of occasional mid-scapular pain if the aneurysms are large, although this is associated more with enlarged descending or thoracoabdominal aorta aneurysms. With aortic dissection or a false aneurysm related to a penetrating ulcer or mycotic aneurysm, severe chest pain may be present. This may be anterior or posterior chest pain with extension into the neck (see Chapters 70 and 71).

On examination, most patients do not have any physical findings specifically related to the aortic arch aneurysm, although, when the aneurysm is large, the anterior chest wall may be pulsatile and, in the worst of circumstances, may have eroded through the sternum or manubrium, particularly if infected. An associated pulsatile mass or a fullness of the neck with a pulsatile mass in the lower neck may be present. Displacement of the arch cranially may result in tortuosity of the carotid arteries. Palpation above the clavicle on the left side, at the thoracic outlet, may reveal a pulsatile mass.

During examination, the patient's arm, neck, and head pulses should be checked, because there may be discrepancies or absent pulses related to aortic dissection or aortitis, particularly giant cell arteritis or Takayasu disease.

Preoperative Studies

In addition to routine laboratory work, preoperative investigations include pulmonary function tests, because many patients may have predisposing factors such as a smoking history, Marfan syndrome with bullae formation, obstructive lesions related to the arch aneurysms (particularly with a congenital aberrant right subclavian artery lesion) (see Fig. 68-2), and right-sided aortic arches (see Fig. 68-3). Some patients are treated for a number of years for asthma because of expiratory wheezes caused by compression of the trachea or bronchi by aneurysms.⁴

Brain MRI or CT should be performed before surgery to detect any asymptomatic infarcts or brain lesions.²⁰ Most patients undergo carotid ultrasound studies if a history of coronary artery disease, peripheral vascular disease, or left main coronary artery stenosis is present. All patients undergo echocardiography before surgery,^{21,22} and, if possible, good views of the ascending aorta and descending aorta are obtained by transesophageal echocardiography to check for atheromatous disease, as this will affect the method of cannulation for arterial inflow. All patients should also undergo cardiac catheterization to identify the presence of any coronary artery disease or valvular heart disease. If time allows, we obtain preoperative neurocognitive test results. Routine 24-hour Holter monitor examinations are included in the preoperative workup because many of these patients have cardiac

arrhythmias, most likely related to valvular heart disease, chronic hypertension, coronary artery disease, or displacement of the left ventricle and the heart downward and to the left by the aneurysm. Patients with some syndromes, such as Marfan syndrome, exhibit more frequent prolonged QT intervals. Indeed, some aneurysms enlarge not only in diameter but also in length. Arrhythmias may also be related to abnormal vagal and sympathetic innervation stimulation.

At the time of cardiac catheterization, cardiologists are requested to obtain left anterior-oblique views of the aortic arch with injection of contrast material immediately proximal to the innominate artery. This is one of the best methods for obtaining good views of the aortic arch and determining the extent of the aortic arch repair that is required, including the need for an elephant trunk procedure. In the preoperative workup, before referral, patients have usually undergone contrast CT of the chest or MRI studies. CT three-dimensional reconstruction is also useful for planning.

Aortography is no longer done in all patients because of the time needed for scheduling and because it is invasive and because the dye load, often administered the day before the surgery, could compromise renal function. The operative procedure planned is discussed with the patient. On the basis of preoperative studies, it can usually be accurately predetermined whether a hemiarch, a total arch, or a total arch plus elephant trunk procedure is necessary. Additionally, it can be ascertained whether the greater vessels require bypasses because of stenotic lesions or aneurysmal disease, particularly in association with aortic dissection.

Next, again determined from preoperative studies, a decision is made as to the site of the arterial inflow for the operation. For most patients undergoing aortic arch surgery, the right subclavian artery is preferentially used for arterial inflow. In young patients, however, who need only a hemiarch procedure, particularly for Marfan syndrome, the right femoral artery is most often used. Usually, the left femoral artery is not used in patients with aortic dissection because the dissection typically extends into the left iliac artery and, thus, the femoral artery perfusion cannula may perfuse the false lumen, resulting in a flutter-valve effect and inadequate perfusion. Similarly, the aortic arch is not used because (1) it limits the extent of the repair, (2) the cannula gets in the way of the operation, (3) aortic dissection may be precipitated, and (4) if a graft is inserted, the cannula must be repositioned, either through a side graft or directly into the new aortic graft. Occasionally, the right subclavian artery is dissected and the femoral artery or aorta is used.

CARDIOPULMONARY PERFUSION ASPECTS

When the right subclavian artery is used, the technique is similar to that previously reported and shown in Figure 68-8. In a prospective randomized study, it was thought this would be a useful means for antegrade brain perfusion.^{18,19} To do this, the innominate artery, in addition to the common carotid artery, was occluded with a balloon

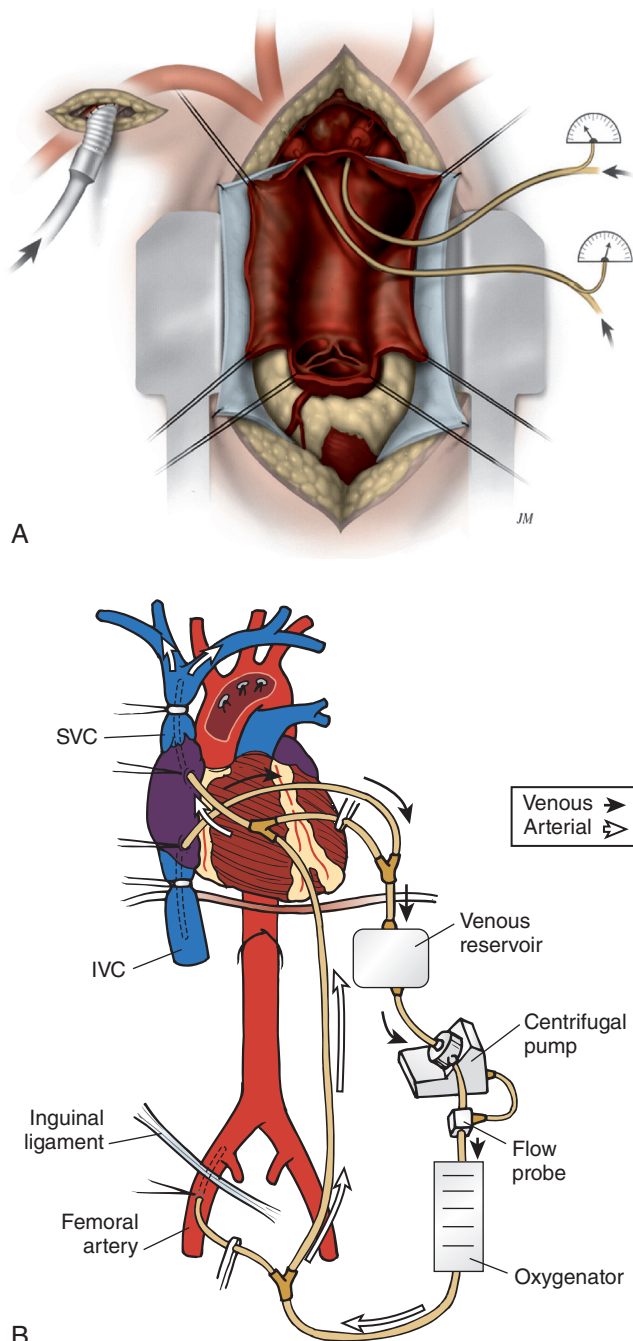


FIGURE 68-8 ■ **A**, Cannulation methods for antegrade brain perfusion with a side graft attached to the right subclavian artery and balloon occlusion catheters in the innominate and common carotid arteries. If a right brachial or radial artery pressure-monitoring cannula has not been inserted, pressures can be monitored in the innominate balloon catheter and, similarly, if perfusion is carried out through the left common carotid cannula, the pressure can also be monitored. **B**, Diagram of the usual setup for retrograde brain perfusion with a cannula in the superior vena cava (SVC) that has been looped with a Y arterial line that can be run through the SVC. IVC, Inferior vena cava.

catheter. The balloon catheter in the common carotid artery allowed perfusion of the left side of the brain (see Fig. 68-8). This has proved to be a safe and effective technique.

Our preference is to attach a side graft to the subclavian artery, defined as the part of the artery proximal to the lateral edge of the first rib. The reason for this is that there are fewer branches in this area and the nerve that swings across the artery to the pectoral muscles more distally does not obstruct the view. It does, however, require that the subclavius muscle be divided with electrocautery under the clavicle. Caution should be taken that the vein is not injured during this procedure. To dissect the axillary artery more laterally, care should be taken to retract the nerves out of the way and also to not injure the arterial branches. We have found the safest and best method for obtaining perfusion of the subclavian artery is to attach an 8-mm side graft, end to side. This is sewn into position with a 5-0 Prolene suture, and any leaks are oversewn with 6-0 Prolene. This allows perfusion of the vessel, both proximally and distally, and greater flow rates. Thus, by avoiding direct cannulation of the subclavian artery, there are fewer tears and there is less difficulty in repairing the artery at the end. Also, it circumvents the problem of the cannula's being inserted too far into the subclavian artery, which could result in occlusion of the common carotid artery or inadequate flow if the cannula presses up against the innominate artery wall. In our report on 1336 circulatory arrest patients, use of a side graft in the subclavian artery reduced the risk of stroke by 40%.²³

An exception to the use of the subclavian artery, however, is that it should be avoided in patients who have had aortic dissection and when the extension of the aortic dissection is noted in the vessel (see Fig. 68-5A). In three patients in whom we used the subclavian artery, when dissection was present in the artery, two suffered postoperative strokes, probably from malperfusion related to the dissection. In patients exceeding 250 pounds, a larger 10-mm side-graft is usually used.

The graft is attached after the patient is heparinized, and a basket or coil sucker is placed in the wound to collect any leaking blood or blood that accumulates within the subclavian incision pocket. The graft is carefully de-aired and connected to a three-eighths-inch to quarter-inch perfusion connector that is then connected to the arterial line of the cardiopulmonary bypass machine.

As mentioned, when the femoral artery is used, the right femoral artery is preferable. When the femoral artery is used, care must be taken, as much as possible, to ascertain that there is no atheroma present in the arterial system that may potentially embolize with retrograde pumping through the femoral artery up to the brain. Thus, the femoral artery is avoided in older adult patients and patients with atherosclerotic disease, aneurysms of the descending thoracoabdominal and abdominal aorta, reoperations, DeBakey type I and type III aortic dissections, or extensive aortitis. Similarly, when we plan to use antegrade brain perfusion or the elephant trunk procedure (see Operative Techniques, later) or acute dissection repair, the subclavian artery is the vessel of choice.^{10,18,19}

BRAIN PROTECTION

Multiple viewpoints are held about how to best protect the brain during aortic arch surgery. The areas of consideration are the degree of hypothermia at onset of circulatory arrest, either moderate (24° to 28° C) or deep (18° to 20° C); and brain perfusion, either none, retrograde, selective antegrade through right axillary, or bilateral through right axillary and left carotid. The reasoning and some of the research that we have performed resulting in the techniques we recommend are discussed here. In summary, our findings include the following: the subclavian artery is the preferred cannulation site (see earlier discussion) and the femoral artery is less so, deep hypothermia to 20° C is preferable although moderate hypothermia at 28° C with antegrade brain perfusion may be as safe if circulatory arrest times are less than 45 minutes,²⁴⁻²⁶ electroencephalogram (EEG) silence is desirable,²⁴ antegrade or retrograde brain protection should be used although antegrade is preferable for longer circulatory arrest times (exceeding 40 minutes), long cardiopulmonary bypass times are harmful (particularly with inadequate filtration), and excessive rewarming may be harmful.²⁷⁻²⁹

Brain protection will be discussed from three aspects: (1) avoidance of doing harm during aortic arch surgery, (2) prevention of stroke, and (3) prevention of neurocognitive deficits.

Primum non nocere: First Do No Harm

Before the safe use of cardiopulmonary bypass, aortic arch operations were designed to use bypass shunts from the ascending aorta to the greater vessels to avoid using a heart-lung machine. These operations were generally limited to patients who had a normal aortic root and not extensive aneurysms, but the techniques were associated with a high incidence of stroke and death. With the advent of cardiopulmonary bypass, the operations became considerably safer. Nevertheless, attempts by Crawford and coworkers³⁰ to directly cannulate aortic arch greater vessels for perfusion of the brain during aortic arch operations were associated with a high incidence of stroke—occurring in up to one third of the patients. Their view was that this was related to injury of the greater vessels by balloon catheters and occluding clamps, or by atheroma resulting in stroke. Barnard⁵ and Borst and colleagues^{6,7} independently pioneered deep hypothermia for arch surgery; however, the technique was popularized by Griep. Deep hypothermia and circulatory arrest, without perfusion of the greater vessels, thus became popular.^{4,10,31,32} Cooley³³ and Livesay emphasized the usefulness of doing an “open” distal anastomosis.

In 1993, we reported a 10% mortality and a 7% stroke rate in a series of 656 patients with deep hypothermia and circulatory arrest alone for aortic arch operations (Fig. 68-9).³⁴ In this paper, however, we described retrograde brain perfusion (see Fig. 68-8B) in 50 patients with initial encouraging results. Our subsequent study in animals also showed promising findings.^{4,35} At that time, the consensus was that strokes were related to embolic events or

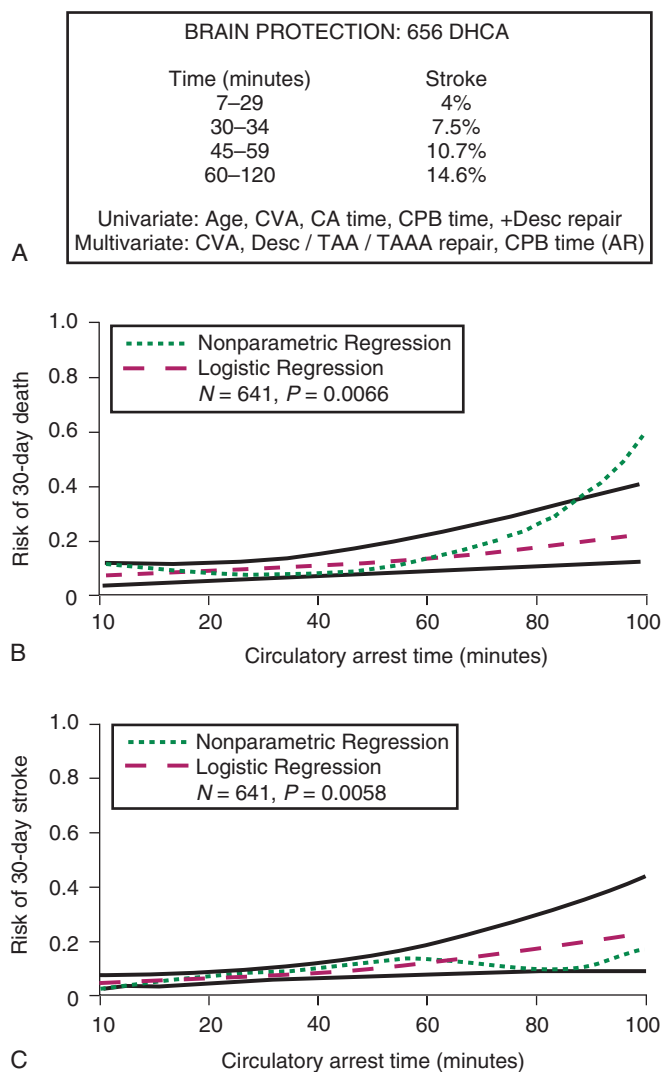


FIGURE 68-9 ■ **A**, Incidence of stroke in 656 patients undergoing deep hypothermia with circulatory arrest according to the length of time of circulatory arrest (*left column*). **B**, Relationship between circulatory arrest time and the risk of 30-day death. Note that after 65 minutes, there is an exponential increase in the risk of death. **C**, Relationship between circulatory arrest time and the risk of 30-day stroke. Note that after 40 minutes, there is an increase in the risk of stroke; however, at 60 minutes, the risk appears to decline. This is a statistical aberration because, after 60 minutes of circulatory arrest, there is a rapid increase in the risk of death and, therefore, patients could not necessarily be assessed for neurologic function. AAA, Abdominal aneurysm repair; AR, aortic valve regurgitation (in parentheses because aortic valve regurgitation was significantly associated with lower risk); CA, circulatory arrest; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident (history); +Desc, with descending aorta repair at the same time; DHCA, deep hypothermia and circulatory arrest; TAA, thoracoabdominal aneurysm repair.

ongoing brain metabolism during deep hypothermia with circulatory arrest. As reports showed increasing success with retrograde perfusion of the heart during cardiac arrest, it was hoped that retrograde brain perfusion might have a protective role. Mills and Ochsner³⁶ reported using retrograde brain perfusion in a patient in whom air embolization occurred to the brain from the arterial

inflow cannula.^{10,29,37} They placed the patient on cardiopulmonary bypass with arterial blood flow into the superior vena cava to try to “retrograde flush-out” air from the arterial system. Subsequently, Lemole reported using retrograde brain perfusion for aortic arch operations.⁴ This was later popularized by Ueda.^{2,4,20} More recent studies by Griep’s group,³⁸ Okita and colleagues, and others, however, have indicated that retrograde brain perfusion may also be associated with harmful side effects, including a higher incidence of stroke or neurocognitive deficits and depression.^{10,39} It has been speculated that brain edema may be a factor. In our initial use of retrograde brain perfusion, we were careful not to exceed a perfusion pressure of between 25 and 30 cm H₂O, because we knew patients with congestive heart failure could tolerate a central venous pressure at this level. Subsequently, studies suggest that a higher perfusion pressure is needed to obtain any retrograde perfusion of the brain. Furthermore, this group demonstrated that perfusion pressures that exceed 60 cm H₂O resulted in brain edema. Retrospective studies, however, show that in comparison with historical controls, results are improved.⁴⁰ There is no doubt that this method is effective in removing embolic material from the aortic arch, including atheromatous emboli. Nevertheless, the technique may be associated with harmful side effects. In our prospective, randomized study from 2000, depression appeared more common in this group of patients, and there appeared to be no neurocognitive benefit over deep hypothermia and circulatory arrest alone. In our more recent prospective, randomized study of 121 patients undergoing total aortic arch replacement in 2012, comparing retrograde and antegrade brain perfusion for total aortic arch replacements, both in conjunction to deep hypothermic circulatory arrest, there was no difference in clinical stroke rates, radiologic evidence of stroke or neuropsychologic decline. The mortality rate of the cohort was 0.8%, and clinically detected stroke occurred at a rate of 0.8%.

Milewski also showed no difference between retrograde brain perfusion/deep hypothermic circulatory arrest and antegrade brain perfusion/moderate hypothermic circulatory arrest in terms of permanent neurologic deficit, temporary neurologic dysfunction, renal failure, or death when the circulatory arrest time is less than 45 min.⁴¹ Likewise, many recent large series and randomized clinical trials have shown the safety of moderate hypothermic circulatory arrest when used with antegrade brain perfusion for circulatory arrest times less than 45 minutes. There are advantages to moderate hypothermia: it avoids the long cooling and rewarming periods, decreases cardiopulmonary bypass times, and avoids the side effects of deep cooling, mainly coagulopathy.^{26,42-45} However, should the circulatory arrest times exceed 45 minutes because of technical difficulties or the need to perform individual head vessel anastomosis, at moderate hypothermia there is a risk of systemic ischemic injury, multiple organ failure, and injury to the spinal cord. For this reason and because the procedure is not entirely predictable, we prefer always performing circulatory arrest under deep hypothermia. Finally, for circulatory arrest durations of longer than 45 minutes, bilateral antegrade brain perfusion is advisable.

Prevention of Stroke

As our knowledge of cardiopulmonary pathophysiology improved, it became clear that most strokes after cardiac surgery were related to microemboli. Most of these emboli seem to be the result of atheromatous or calcific debris from the aorta. For most patients undergoing aortic arch surgery, other sources, such as from the left atrium in patients with chronic atrial fibrillation or transiting through an atrial septal defect, are less of a problem. Another potential source of emboli is from the descending aorta or abdominal aorta or iliac and femoral arteries during femoral artery perfusion; hence, we advocate the routine use of cannulating the right axillary artery with an 8 mm graft as our aortic inflow. We prefer the use of an 8 mm graft as opposed to direct cannulation of the axillary because we have previously shown that it decreases the incidence of stroke by 40%.⁴⁶ With modern cardiopulmonary bypass techniques, the risk of massive air embolism or pump failure that can result in strokes has been greatly lessened.^{4,47} Various techniques have been used to reduce the risk of embolic-related strokes. We have not tested every method, but early on, we established a protocol based on the level of knowledge at the time that we considered of value (Table 68-1). With reference to cardiopulmonary bypass, it appears that the following are beneficial: a centrifugal pump, arterial line filtration (at least 25 μ m), leukocyte filtration, closed-bag venous reservoir, cell saver, avoiding pump suction, and reducing cardiopulmonary bypass time. If a leukocyte filter is used, it is important to use immediate preoperative plasmapheresis to remove platelets and clotting factors from the patient, because leukocyte filters tend to remove platelets from the circulation. The platelet-rich plasma is reinfused at the end of the operation. For pH management during cardiopulmonary bypass and circulatory arrest, we favor using the alpha-stat method. In the pediatric age group, there is more convincing evidence that the pH-stat method works better. In adults, however, the alpha-stat method is generally preferred, although no prospective or randomized studies have definitively answered the question of which is best in adults. An advantage with the alpha-stat method is that the lactic acid that accumulates in the brain during circulatory arrest can, to some extent, be buffered by histamine molecules on hemoglobin.^{4,10,29,47}

We advise flooding the field with carbon dioxide so any air accumulating in the heart or the field will be displaced.⁴⁸ This includes the aortic arch so that when circulation to the brain is restarted, any potentially gaseous material is carbon dioxide rather than air. Carbon dioxide is reabsorbed approximately 25 times faster than air, reducing the risk of microcirculation obstruction related to gaseous material.

In addition to perfusion aspects and the site of cannulation, we recommend packing the patient’s head in ice because it reduces the risk that the ambient operating room temperature might raise the temperature of the patient’s head during circulatory arrest.

The usage of neuroprotective agents during circulatory arrest remains controversial. Thiopental may be useful by lowering oxygen consumption, although the

TABLE 68-1 Brain Protection Protocol

Population	Protective Measures
All patients	Electroencephalogram silence Temperatures less than 20°C Head packed in ice Mannitol prime and after arrest Alpha-stat pH control LeukoGuard filter CO ₂ flooding of field Thiopental 5 mg/kg 5 min before arrest Lidocaine 200 mg before arrest Magnesium sulfate 2 g Centrifugal pump Membrane oxygenator Closed-circuit bag venous reservoir Pre-bypass plasmapheresis Routine use of cell saver device
Patients receiving antegrade brain perfusion	Right subclavian and side graft Innominate and carotid balloon occlusion (retrograde cardioplegia balloon occlusion catheter) Pressure maintained at 40-60 mm Hg Sequential removal of catheters as arch anastomosis completed
Patients receiving retrograde brain perfusion	Superior vena cava cannula Snared below azygous vein Flow rate: 300-500 mL/min Pressure: <25-35 mm Hg

evidence on clinical benefit is inconclusive. However, there is suggestion that if thiopental is administered before circulatory arrest, it may replete the cerebral energy state before arrest and prove detrimental.⁴⁹ The usage of barbiturates has declined over the years partly because of its unavailability. In a German registry for type A dissection of over 2000 patients, only 48% of patients received a neuroprotective agent such as steroids, mannitol, or barbiturates. The stroke rates were slightly lower in patients receiving steroids versus no agents (7.1% vs. 10.6%), and usage of mannitol led to lower 30-day mortality. These results are observational and have not been shown in prospective studies.⁵⁰

In our randomized clinical trial in 2012 comparing retrograde brain perfusion to antegrade brain perfusion, only 0.8% of patients had clinically evident stroke, but 9% had showed evidence of new MRI or CT infarcts or brain tissue changes, suggesting that many infarcts are clinically silent.⁵¹ In this study, we also gave patients neurocognitive tests preoperatively and 4 to 6 months after the index procedure. For each neurocognitive test, the baseline and follow-up data were used to calculate a test-retest reliability coefficient, a reliable change index (RCI), and associated 90% confidence interval for the RCI. A patient was considered to have declined neurocognitively if he or she had two or more RCIs that fell below the lower 90% confidence limit for the respective, corrected reliable change interval. Surprisingly, there was little correlation between patients who had neurocognitive dysfunction and patients who had new radiologic evidence of stroke. In total, 14% of patients had neurocognitive deficits. Of these patients, only 18% had evidence of infarct on CT or MRI, and 56% of patients with

radiologic evidence of stroke had neurocognitive decline. From the remaining 5 patients who had radiologic evidence of stroke without neurocognitive decline, 4 had strokes located in the occipital or cerebellar areas. On multivariate analysis, neither retrograde brain perfusion nor antegrade brain perfusion was an independent predictor of neurocognitive decline, clinical stroke, or radiologic stroke. To summarize, our study showed that clinical exam for neurologic events was insensitive, MRI detects more events, and the most sensitive is neurocognitive examination, which may not detect occipital or cerebellar events.

Prevention of Neurocognitive Deficits

With improved results for aortic arch surgery and fewer complications such as strokes, interest has focused on prevention of postoperative neurocognitive deficits. As mentioned, 38% of patients in our prospective randomized study were found to have, before surgery, neurocognitive deficits.^{18,19} The reason is not entirely clear, but it may be related to silent brain injury before surgery. There is also a correlation between neurocognitive deficits and other preoperative factors such as heart failure and New York Heart Association degree of dyspnea.²⁹ This would be in keeping with the finding that patients who exhibit a greater degree of systemic cardiovascular disease experience more neurocognitive deficits. The possible reasons include inadequate brain perfusion, brain edema, other factors affecting the brain vasculature, general overall poor health, and silent ischemia and white matter injury, as we have documented. Indeed, it is our impression that patients with preoperative neurocognitive deficits do not tolerate deep hypothermia and circulatory arrest well. In a previous study of 656 patients undergoing deep hypothermia and circulatory arrest,³⁴ older patients did not tolerate circulatory arrest as well as younger patients, putting them more at risk for stroke. The same probably holds true for the risk of neurocognitive deficits, but this has not been formally studied.

The incidence of neurocognitive deficits after cardiac surgery remains controversial.^{18,19,28} So much depends on the method of defining when neurocognitive deficits occur. There are many reasons why deficits can occur (e.g., preoperative neurocognitive dysfunction or atherosclerosis of the microvasculature of the brain, similar to that affecting coronary arteries). Some large studies that have examined neurocognitive dysfunction after coronary bypass surgery have used cardiopulmonary bypass pump setups that were out of date. It is also instructive that some studies have shown no differences between off-pump and on-pump incidences of neurocognitive deficits, suggesting that other factors, such as anesthesia management, are important. Studies have also shown no differences between coronary artery bypass surgery and major abdominal aortic surgery. Indeed, there is no difference between percutaneous coronary intervention and coronary bypass operations. Patients who undergo anesthesia often have neurocognitive dysfunction after surgery despite having no obvious risk factors that cause neurologic dysfunction. In our prospective, randomized study, although over 90% of patients had neurocognitive

dysfunction 3 to 6 days after surgery, by 2 to 3 weeks only 9% had a new neurocognitive deficit, and by 6 months all had recovered.^{18,19} The entire field of neurocognitive dysfunction requires further study to determine when a deficit occurs in an individual patient and what the change in global scores for an entire group of patients means. In our prospective randomized study from 2000 (Fig. 68-10), we found that patients' IQs improved after circulatory arrest over time, which clearly is not likely! The explanation was that the patients underwent repeated IQ testing (four) and learned to do the tests over time. Nevertheless, it was gratifying to note that the patients' IQs did not deteriorate after deep hypothermia and circulatory arrest. Indeed, the practice effect on reported neurocognitive scores is difficult to compensate for. Figure 68-11 shows the serum S-100 protein value changes of each group studied.

There are many reasons for potential neurocognitive dysfunction after surgery. Anesthetic gases and pharmacologic agents, including barbiturates, are factors. Other potential reasons are brain edema and swelling from third-space fluid accumulation. Undoubtedly, chemical and metabolite accumulation also play a role. Microemboli, in the form of small fat globules, or air or carbon dioxide gaseous emboli, may also be a factor.

It was once thought that emboli to the frontal lobes were largely silent and that there was selective streaming of emboli, including platelet aggregates, to the middle cerebral artery, resulting in middle cerebral artery territory infarcts. A study was done using radioactive platelet aggregates in a baboon model to test this theory.⁵² We found injection of the platelet aggregates into the left atrium resulted in equal distribution across the brain, including occipital lobes and distribution to the eye, as expected from an anatomic point of view. Injection into the common carotid arteries had a similar effect, although

the occipital lobes were spared. Injection into the internal carotid artery did not reveal any preferential streaming into the middle cerebral artery. From this we infer that the emboli to the frontal lobes do cause infarcts of equal frequency, although these may be more silent in the sense that critical motor and sensory functions are not affected. We do, however, believe that these so-called silent infarcts affect neurocognitive function, as expected from a more recent understanding of brain pathophysiology. Some neurocognitive decline after cardiopulmonary bypass may thus be related to microemboli to the frontal lobes and infarction. This is an evolving field, and the correlation between microembolic phenomena and postoperative neurocognitive function needs to be further defined. For example, it is unclear how high-intensity transient Doppler signals, produced by aortic valve prostheses, affect neurocognitive function both early and in the long term. Studies in patients with various types of aortic valve prostheses suggest that many of these are gaseous microemboli, but that they are usually transient and rapidly return into solution without causing permanent brain dysfunction.^{10,53}

In our 2000 prospective randomized study, we failed to show any benefit from antegrade or retrograde brain perfusion regarding neurocognitive function when compared with deep hypothermia with circulatory arrest alone. However, the circulatory arrest was relatively short, and for hemiarch repairs, antegrade brain perfusion resulted in significantly longer circulatory arrest time because of the time required to insert the common carotid artery catheter and the innominate artery catheter and then to work around them. For total arch replacement, there were no differences in circulatory arrest times. Retrograde brain perfusion was associated with slightly longer circulatory arrest times compared with circulatory arrest alone, probably because retrograde brain perfusion results in blood

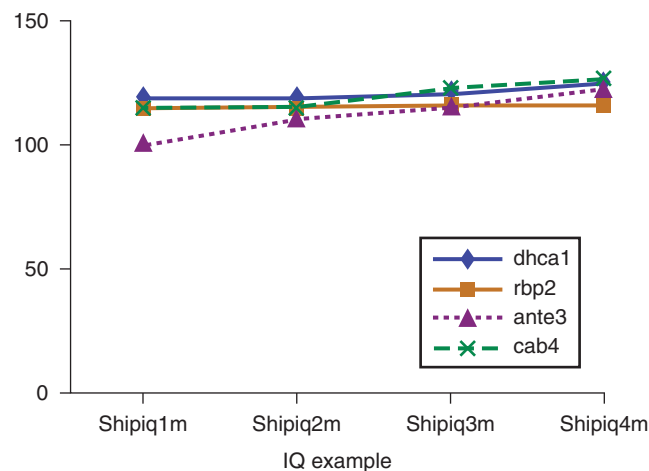


FIGURE 68-10 ■ A, Illustration of Shipley IQ (Shiqiq) scores over time in patients who underwent deep hypothermia with circulatory arrest (dhca), retrograde brain perfusion (rbp), antegrade brain perfusion (ante), and coronary artery bypass (cab). The first tests were done preoperatively (1m), then 3 to 6 days after surgery (2m), 2 to 3 weeks after surgery (3m), and 6 months after surgery (4m).

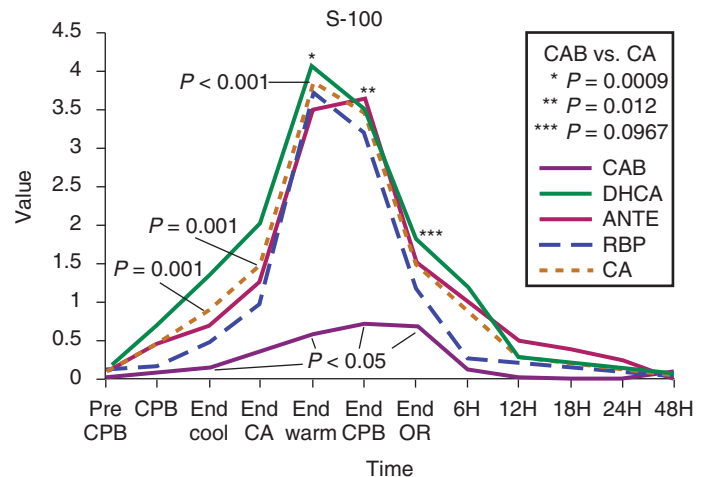


FIGURE 68-11 ■ Relationship of time point during operation to the serum S-100 protein value. Graphed curves: ANTE, Antegrade brain perfusion; CA, all circulatory arrest patients; CAB, coronary artery bypass; DHCA, deep hypothermia and circulatory arrest alone; RBP, retrograde brain perfusion. On x-axis: CA, Circulatory arrest; CPB, cardiopulmonary bypass; H, time after surgery in the intensive care unit; OR, operating room.

accumulating in the operative field, which obscures the field when suturing. If we expect atheroma in the aorta at the time of surgery, and if the patient may require endarterectomy, we use antegrade perfusion via the right subclavian artery (as discussed) or retrograde brain perfusion to flush out embolic material.^{18,19}

When patients are undergoing total arch replacement and the circulatory arrest time may exceed 30 to 40 minutes, antegrade or retrograde brain perfusion is used for the repair. Data in the pediatric cardiac surgical literature show that, as with pulmonary embolectomy in adults for thrombotic material, circulatory arrest with intermittent periods of brain perfusion followed by circulatory arrest is better than one long period of circulatory arrest. For one patient undergoing a fourth complex cardiac reoperation at deep hypothermia, we were able to successfully protect the brain for more than 90 minutes by running antegrade brain perfusion for 5-minute periods every 30 minutes. He was extubated the day after surgery without a neurologic deficit. We therefore usually run antegrade brain perfusion, if not throughout the period of circulatory arrest for total arches, at least at intermittent intervals when convenient from the point of view of visualizing the field and suturing. The balloon occlusion catheter can easily be led out of the field so that it does not obstruct the view. Because the right subclavian artery is perfused in these patients, once the balloon catheter is withdrawn from the arch, the arch is flushed of any embolic material before anastomosis is completed. If an elephant trunk procedure is being used, a side graft to the elephant trunk is not required for antegrade perfusion, because the right subclavian artery is being perfused. Similarly, in patients undergoing acute dissection repairs, a side graft to the aortic arch is not required because the subclavian artery is being perfused.^{1,10,4,18,19}

Fourteen percent of patients have an incomplete circle of Willis; however, extracranial collaterals will still allow the perfusion of the left brain in most of these patients. Although unilateral perfusion is adequate for shorter circulatory arrest times, (<45 min), bilateral perfusion through an additional left carotid cannula would be advisable.^{1,4,10,18-20,42,54}

Future research is needed to determine the best perfusion method for brain protection during total arch replacements, including the best temperature.

OPERATIVE TECHNIQUES

The operative procedures for aortic arch replacement are most commonly hemiarch repairs or entire arch repairs, with or without a distal descending elephant trunk procedure.⁴ Other unusual types of operations are options in specific situations. To a large extent, the choice of aortic arch procedure is influenced by the proximal aortic root or by the ascending aorta operative technique, whether it is a composite graft, root remodeling, separate valve and graft, valve reimplantation, Ross procedure, or no valve procedure. Also, in choosing a valve type, it is important to consider durability, particularly for biological valves, as a third or fourth operation will be complicated.⁵³

Hemiarch Replacement

Hemiarch replacement of the aortic arch is the simplest and quickest operative technique. The anastomosis can be achieved in 5 to 15 minutes depending on the aortic arch pathology. Once the patient has been cooled down and the method of brain protection and perfusion has been decided, the patient's circulation is stopped with the patient in the head-down position. In patients undergoing reoperations, we use one of two approaches: either full median sternotomy or a minimally invasive approach. The ascending aorta is then opened between stay sutures. A decision is made as to whether the aortic arch should be transected for the anastomosis. Briefly, transection of the aorta is indicated for acute aortic dissections in those patients who have had an aortic root procedure in which the aorta has already been transected proximally, and for most patients who need hemiarch replacements. The reason is that it is easier to obtain hemostasis at the distal anastomosis if the aorta was transected, and thus the risk of false aneurysm formation is also less. The transection line usually runs from the proximal base of the innominate artery to the midpoint of the lesser curve of the aortic arch. In patients with acute dissections, it is important to be certain that all layers are transected, and that the adventitia is freed of the posterior-lying pulmonary artery and a bit further cranial to the pulmonary artery to ensure adequate tissue is present for effective suturing. The anastomosis is performed with a running 4-0 or 3-0 Prolene suture, dependent on the pathology. For patients with acute dissections, it is best to use a 4-0 or even 5-0 Prolene. When the anastomosis is near completion, the graft and arch are filled with blood by restarting the arterial flow from the pump. Any potential embolic material is sucked away, and gaseous pockets are evacuated. To further reduce risk of gaseous embolism, carbon dioxide is run into the operative field during the procedure. The anastomosis is completed and the suture is tied down. The patient is rewarmed, and the proximal ascending aorta anastomosis or aortic root procedure is completed.

In patients who have either had aortic root remodeling using techniques described by David and Feindel, Sarsam and Yacoub, or us, or who have a modified valve reimplantation procedure, an interposition graft is usually required between the aortic root graft and the aortic arch.^{37,55-57} If, however, the valve remodeling was done while cooling, an interposition graft may not be necessary. However, when the patient has undergone aortic valve replacement only, the hemiarch graft is used to suture the proximal anastomosis immediately above the aortic valve and coronary arteries. When a composite valve graft will be inserted, the proximal anastomosis of the composite valve graft to the aortic valve annulus and the left main coronary artery anastomosis can first be performed while cooling the patient, and the hemiarch anastomosis can be done directly to the composite graft without using an interposition graft, but always being careful to de-air the graft. Alternatively, if the patient cools quickly, a separate hemiarch graft is placed and later anastomosed to the proximal composite valve graft with a graft-to-graft anastomosis while the patient is rewarmed.

In patients who have had a homograft inserted with an aortic root repair, a decision needs to be made as to whether prosthetic polyester graft material should be used for the hemiarch, or whether a homograft (without an aortic valve) (see Fig. 68-7) should be used to bridge the gap between the aortic valve and the homograft. In patients with extensive infection of a previously inserted graft (e.g., a composite graft), we replace the aortic root with a new homograft and use another homograft to bridge the gap between the root homograft and the aortic arch so that there is no prosthetic material other than Prolene suture material (see Fig. 68-7B). In most cases, these grafts are wrapped with omentum to further obliterate any dead space. For those patients undergoing reoperations who have extensive scar tissue formation that restricts the ability to transect the proximal and distal aorta, the hemiarch anastomosis may be done inside the aortic arch without transecting the aorta. Rarely, if bleeding cannot be controlled, a Cabrol fistula can be formed from the aneurysm sac to the right atrium or the superior vena cava.

A variation on the hemiarch replacement is a long tongue of the graft used to replace the entire aortic arch, potentially down onto the descending aorta to approximately the middle third of the descending aorta, depending on the size of the aortic arch aneurysm (see Fig. 68-2). When using a long tongue for the total aortic arch replacement and down the descending aorta, there are some points worth noting. First, if the anastomosis is quite far down the descending aorta, parachuting the distal anastomosis makes it easier. Second, the patient should be warned before surgery that hoarseness may occur because the recurrent laryngeal nerve often cannot be preserved where it wraps around the distal aortic arch. Third, hemostasis at the distal anastomosis must be secure before continuing the operation, after doing the arch repair, because obtaining hemostasis is much more difficult once the graft is pressurized and connected proximally. Fourth, the extent distally to which the anastomosis can be performed may be judged, to some extent, by examining the CT scan or the left anterior oblique view of the arch on magnetic resonance angiography or cardiac catheterization. As a rule, an anastomosis can be easily performed no more than a few centimeters beyond the lowest level of the lesser curve of the aortic arch: the larger the aortic arch aneurysm is, the farther down the descending aorta within the descending aorta the anastomosis can be performed. If the anastomosis cannot be performed through the aortic arch, an alternative method should be considered (see Replacement of the Entire Aortic Arch, later). When doing a hemiarch with these long "tongues," care must be taken that the aortic graft not become stenosed or badly kinked. This may obstruct blood flow through the repaired aortic arch, resulting in excessive cardiac afterload. This may progress to either early acute heart failure or later ventricular hypertrophy and congestive heart failure if the gradients are too large.

Replacement of the Entire Aortic Arch

Replacement of the entire aortic arch can be done with or without a distal elephant trunk procedure. The

procedures involving an elephant trunk will be discussed first (Fig. 68-12).

Multiple variations of elephant trunk procedures have been used, including hybrid procedures. We have classified them as follows (Fig. 68-13).⁵⁸

Type I: Classic elephant trunk: ascending tube graft with total arch replacement and elephant trunk anastomosis in classic position distal to left subclavian artery (LSCA)

Type Ia: Type I repair with stent graft

Type II: Ascending aorta tube graft with arch replacement and elephant trunk anastomosis proximal to LSCA

Type IIa: Subsequent thoracic stent graft with proximal landing zone covering LSCA and a descending-to-LSCA bypass

Type III: Elephant trunk placed into large descending aortic aneurysm used as a landing zone for distal thoracic stent graft

Type IV: Ascending aorta tube graft with classic elephant trunk anastomosis into distal thoracic aneurysm with branched graft for total arch replacement

Type IVa: Ascending branched graft for replacement of ascending aorta and arch, with end-to-side elephant trunk in classic position

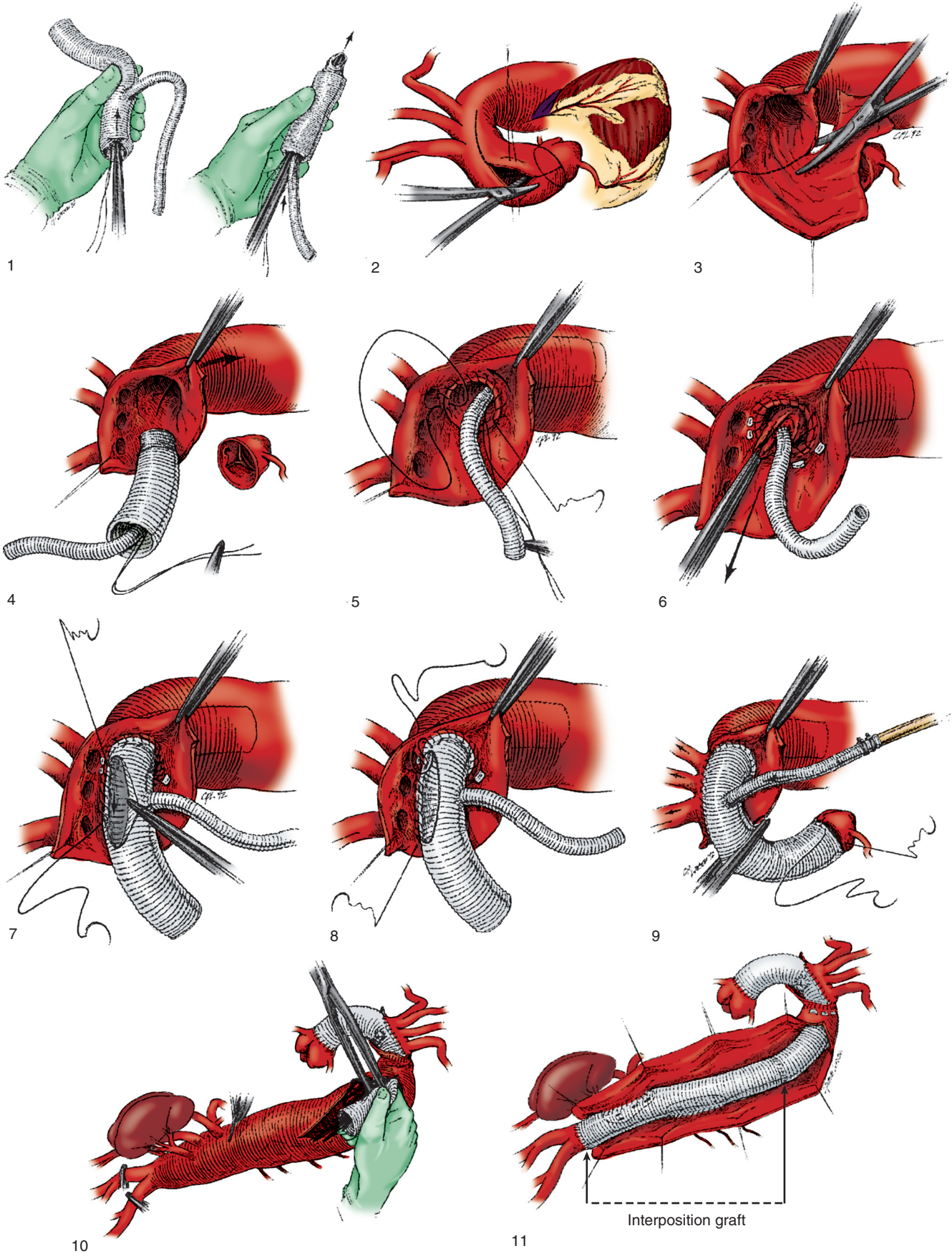
Type IVb: Subsequent thoracic stent graft in type IV repair

Type V: Ascending aorta tube graft with elephant trunk anastomosis proximal to brachiocephalic artery and a branched graft for total arch replacement

Type Va: Type V repair configuration with thoracic stent graft in distal aneurysm

In type I repairs, to shorten the period of circulatory arrest, the elephant trunk and inverted graft should be prepared while the patient is cooled. This is done by first suturing and tying a silk stitch to the end of the graft that will be used for the proximal repair of the ascending aorta. The distal elephant trunk should be approximately 10 to 15 cm in length. If the second stage will be done with stent grafts (type Ia) because of comorbid disease (e.g., chronic pulmonary disease), then metal clips and a loop of wire (pacing) are attached to the distal end. The proximal part with the stitch attached to it is then inverted into the distal elephant trunk. It is important to ensure that the edge of the inversion is at the same level and smooth. If retrograde brain perfusion or circulatory arrest alone is used and the subclavian artery has not been used for arterial inflow, a side graft needs to be attached to the aortic arch and inverted into the distal elephant trunk. This side graft should be attached approximately 2 to 4 cm proximal to the edge of the inverted graft. If the right subclavian artery is used for arterial inflow, there is no need to attach a side graft to the elephant trunk graft.

Once circulatory arrest is established and the patient is in a head-down position, the graft is fed into the descending aorta, ensuring it is neither kinked nor twisted into a spiral. In patients with chronic dissection, the septum or flap should be excised as much as possible so that the graft perfuses both true and false lumens.



Perfusion of either the true or false lumen alone may result in paraplegia or renal failure. It is also important that the elephant trunk not be excessively long. In a previous review of 84 elephant trunk procedures,⁹ three patients developed paralysis postoperatively, one with dense paraplegia and the other two with paraparesis from excessively long elephant trunks. Subsequent to shortening the length of the elephant trunk, this has not been a problem. The reason for this appears to be either that the elephant trunk is too long and perfusion of the intercostal arteries is inadequate, or that, as noted at the second-stage procedure, extensive clot formation occurs around the elephant trunk, which can occlude critical intercostals. Because of this clot formation, when using the elephant trunk, patients often require multiple platelet transfusions as the clot builds up around the elephant trunk in the descending aorta.

The elephant trunk graft material should be one of the collagen-coated woven grafts and not a gel-coated graft. The gel of gel-coated grafts is absorbed quickly. At the time of the second-stage operation, bleeding from a proximal elephant trunk can be excessive and potentially uncontrollable because the graft is porous after the gel has been absorbed.

The anastomosis between the inverted edge of the elephant trunk graft and the distal aortic arch beyond the left subclavian artery is then performed. The patient should be warned that hoarseness may occur postoperatively, as this procedure is in the region of the recurrent laryngeal nerve.

Reasons for inverting the graft on itself and placing it in the descending aorta are several.⁹ First, the anastomosis is easier to perform, even though it can be difficult to drive the needle through a double layer of graft material. However, with collagen-coated grafts, this is not much of a problem. Second, when the inverted graft is withdrawn from inside the elephant trunk, it has the effect of tightening the anastomosis, improving hemostasis at the distal anastomosis. Third, the larger contact surface area between the graft and aortic wall is increased so that there is less bleeding past the anastomosis. Fourth, if the graft is not inverted, suturing in a tight space between a graft and the aorta in a deep V results more often in the aorta's tearing, with the potential for a disastrous rupture in the postoperative period. This problem of rupture was experienced in the early period of using the elephant trunk technique without inverting it.⁹

One of the problems with elephant trunk procedures is the risk of rupture during the interval between the first

operation and the second-stage operation. Rupture of the descending aorta continues to be a potential risk of the elephant trunk procedure during the postoperative period, because the systemic inflammatory response results in release of collagenase and elastinase, which can result in rupture of the aneurysm. Furthermore, the aneurysm may grow in the interim, while the patient is recovering from the first operation. In Safi and colleagues' series from 2001, the interim mortality rate was 3.6%, and 75% of deaths were caused by aneurysm rupture.⁵⁹ Because of the interval aneurysm growth and risk of rupture, patients need to be closely followed. If a hybrid second-stage procedure is planned, this can be done at the time of the first stage or before hospital discharge. We reviewed our series of elephant trunk and endovascular completion and demonstrated good early and mid-term results. In the mid to late term, there is a risk of stent migration and endoleak; therefore, lifelong imaging follow-up is required. Alternatively, a stent graft can be inserted antegrade into the elephant trunk to anchor it, or the separate stent graft can be sewn into position in the distal arch; the latter approach, however, has a tendency toward higher complication risk^{58,60} (see [Frozen Elephant Trunk](#), below).

A second-stage operation is usually planned after the patient's recovery from respiratory problems related to the first operation, usually 6 weeks to 4 months after the first stage. Alternatively, if the patient is in poor condition after the first operation, including experiencing respiratory problems, we electively proceed to stent grafting the elephant trunk as part of the second-stage procedure, provided that the descending aorta down to the celiac artery can be stented. On occasion, a limited thoracoabdominal incision has been used to place bypasses from the iliac artery to the visceral vessels and, thereafter, a stent graft has been inserted to replace the remaining aorta from the elephant trunk down to the aortic bifurcation or iliac arteries. With the increasing use of thoracoabdominal stents, second-stage stenting with inclusion of the thoracoabdominal aorta is also an option. In patients with acute dissection, total arch replacement is avoided if possible. If total arch replacement must be done, an elephant trunk can be placed in the true lumen in the descending aorta after transecting the aorta beyond the left subclavian artery. Transecting the aorta ensures that all layers are cut and a completely hemostatic suture line is achieved with a rim of Teflon felt around the aorta. The recurrent nerve usually ends up being transected.

FIGURE 68-12 ■ Steps for the elephant trunk procedure technique modified by inverting the graft and placing it in the descending aorta. (1) A side graft is sewn to the graft that will be used for the aortic replacement and then the graft is inverted on itself, including the side graft. The distal extent of the elephant trunk should be 10 to 15 cm in length, and a rim of approximately 1 to 2 cm is left between the side graft and the inverted edge turned down for sewing. If the right subclavian artery is used for arterial inflow, the side graft is not necessary. (2) When the patient is cold enough, circulation is arrested and the aorta is opened. (3) The aorta can be transected to improve exposure, if needed. (4) The previously prepared graft is then placed in the descending aorta. (5) The distal anastomosis is performed starting at the three-o'clock position as the surgeon looks at the anastomosis. (6) The inner inverted tube is then pulled back into the operative field. (7) The posterior suture line is performed for the aortic arch. (8) The anterior suture line is performed. Once the anastomosis has been completed, arterial inflow is started through the side graft again to perfuse the brain if the right subclavian artery has not been used. (9) At the second stage of the operation, the graft is exposed in the aneurysm and clamped. It is not necessary to encircle the aorta to perform this, because the graft is surrounded by clot and can be exposed without much bleeding and then digitally clamped before applying a mechanical clamp. (10) The remainder of the aorta is then repaired. (11) For thoracoabdominal aneurysms, an interposition graft is necessary to complete the repair.

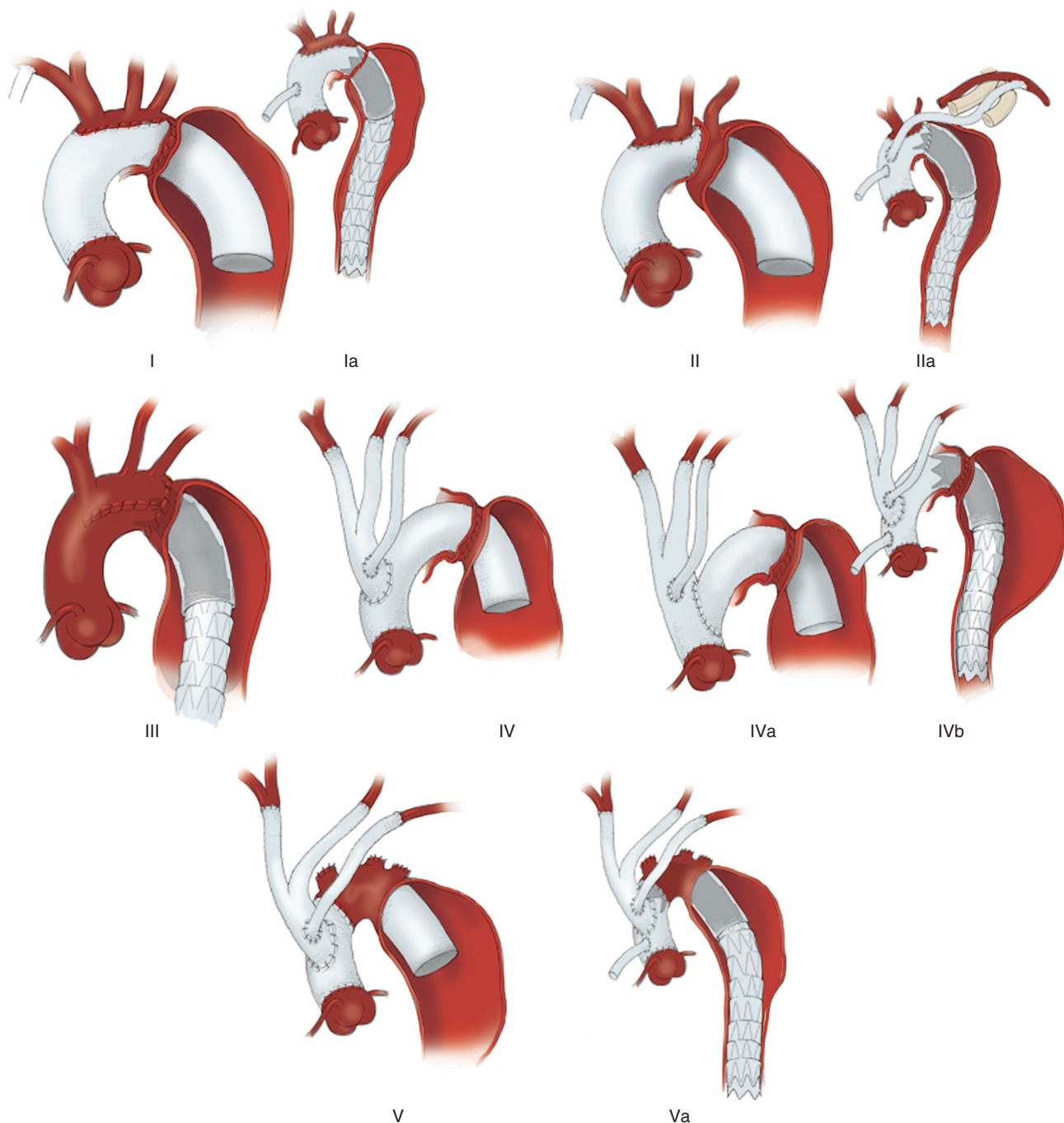


FIGURE 68-13 ■ Classification of anastomotic sites of elephant trunk for repair of thoracic aorta disease. Classic elephant trunk: (I) ascending tube graft with total arch replacement and elephant trunk anastomosis in classic position, distal to left subclavian artery (LSCA); (Ia) this repair with subsequent stent graft. (II) Ascending aorta tube graft with arch replacement and elephant trunk anastomosis proximal to LSCA; (IIa) subsequent thoracic stent graft with proximal landing zone covering LSCA, and a descending-to-LSCA bypass. (III) Elephant trunk placed into large descending aortic aneurysm to be used as a landing zone for distal thoracic stent graft. (IV) Ascending aorta tube graft with classic elephant trunk anastomosis into distal thoracic aneurysm, with branched graft for total arch replacement; (IVa) ascending branched graft for replacement of ascending aorta and arch, with end-to-side elephant trunk in classic position; (IVb) subsequent thoracic stent graft in type IV repair. (V) Ascending aorta tube graft with elephant trunk anastomosis proximal to brachiocephalic artery and a branched graft for total arch replacement; (Va) this repair configuration with thoracic stent graft in distal aneurysm.

Type II is the most common alternative elephant anastomosis; using this type, the anastomosis is performed between the common carotid and the left subclavian artery (Fig. 68-14).⁶¹ If the distal aortic arch beyond the left subclavian artery is enlarged and there is no “landing

site” for doing the distal anastomosis, then the aortic arch is often more narrow between the left common carotid and left subclavian artery. Thus, doing the anastomosis at this site results in a shorter circulatory arrest period, because the suture line is shorter and exposure is better.

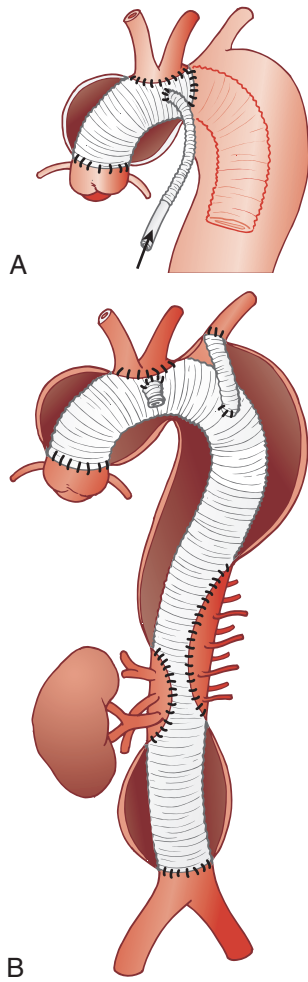


FIGURE 68-14 ■ **A**, Diagram of a modified elephant trunk technique with an anastomosis performed between the left common carotid and left subclavian arteries. **B**, Completion of the second stage of the elephant trunk procedure, with a tube graft to the left subclavian artery.

The downside of doing the anastomosis between the left common carotid and left subclavian arteries is that the left subclavian artery needs to be anastomosed to the elephant trunk during the second-stage operation. This is typically done with an interposition graft. An alternative method is to attach the left subclavian artery to the left carotid artery at the first-stage operation. Another strategy would be to oversew the left subclavian artery and use a sidearm graft through the first or second intercostal space to revascularize the left axillary artery, as described by Baeza and Svensson.⁶²

Once the distal anastomosis has been performed, the inner inverted graft is withdrawn and an opening is made opposite the greater vessels. The posterior suture line is performed, followed by the anterior suture line. The graft is flushed, any potential embolic material is removed, and then the graft is clamped. The graft is checked for hemostasis at both the distal anastomosis and the aortic arch. The proximal anastomosis is performed to the ascending aorta, depending on the root technique used.

Increasingly, patients who are referred for descending thoracic or thoracoabdominal operations have severe

cardiac disease, either valvular or coronary.⁶³ If the proximal descending aorta or distal arch is also enlarged, we place a descending thoracic elephant graft with the proximal anastomosis sewn just beyond the left subclavian artery in preparation for the second-stage operation or stent grafting (type III). One reason for this is that the left subclavian artery can also be used. If not, the distal arch could not be clamped at the second operation with a patent left internal mammary artery.

Japanese surgeons, when doing aortic arch replacements, like to use branch grafts to the greater vessels. Branch grafts have a neo-aortic larger graft with four-sided grafts attached end to side, typically 8 or 10 mm in size, or larger. The distal anastomosis is first performed between the neo-aortic graft and the descending aorta, followed by the greater vessel anastomoses. The left subclavian artery and the left common carotid and innominate artery are anastomosed to the branch grafts sequentially. Cannulas in the transected greater vessels are used to maintain antegrade perfusion while these anastomoses are performed. The fourth side graft is used for perfusing the aortic arch and reestablishing blood flow to the greater vessels as they become attached to the branch graft. This approach is not generally favored by most surgeons in Europe and the United States, although there is some virtue to this technique in patients with extensive calcification and atheroma of the aortic arch, when suturing beyond the atheroma and calcification in the greater vessels is required. Disadvantages of this technique are a very long pump time, potential kinking of the graft or side branches, prolonged total body systemic circulatory arrest, and the longer period of nonpulsatile flow to the brain. Indeed, for aortic arch surgery, the pump time is the best predictor of mortality and risk of stroke.^{4,34} A method we have used in conjunction with subclavian arterial perfusion is to sew a bifurcated graft to the innominate artery and carotid artery first, and then to do an elephant trunk procedure and left carotid bypass (type IV). These are then connected to the neo-aortic graft. The advantage is that the brain arrest time is 5 to 15 minutes.

A technique that can be used occasionally is to place a bifurcated graft on the anterolateral aspect of the ascending aorta, suturing the other ends of the bifurcated graft to the greater vessels so that the native greater vessel stumps in the aortic arch can be oversewn. A separate graft is used to bypass the left subclavian artery, or a left carotid subclavian bypass can be done. The aortic arch and descending aorta are then addressed with an elephant trunk (type V) or are stented (type Va) as needed, either immediately through a side graft or later. If a stent graft is to be used, a large clip can be placed at the heel of the anastomosis between the graft and the aorta to guide stent placement. The stent graft is oversized by 10% to 20% and placed with a stiff guidewire placed in the left ventricle as a rail. The major advantage of this procedure is that it can often be done without circulatory arrest and sometimes off pump. Lee and coworkers compared the series of arch debranching procedures to standard elephant trunk procedures and found equivalent results with the aortic debranching group needing cardiopulmonary bypass in 68% of patients and circulatory arrest in only

27%.⁶⁴ The rates of spinal cord ischemia, stroke, and 30-day mortality were 0%, 11%, and 16%, respectively, for arch debranching and 0%, 10%, and 20%, respectively, for standard elephant trunk.

If the entire thoracic aorta or the entire aorta is going to be replaced through both a mediastinal and a left thoracoabdominal incision, the distal anastomosis in the aortic arch does not need to be done; only the anastomosis to the greater vessels is needed. This operative technique is discussed in [Chapter 69](#). Also, if the descending aorta, arch, and ascending aorta are replaced through a “clam-shell” incision, a distal arch anastomosis is not needed.

If the elephant trunk procedure is not used for the distal anastomosis, the distal anastomosis is performed in the descending aorta with a simple running suture ([Fig. 68-15](#)). Usually, the aorta is not transected because of the risk of cutting the recurrent laryngeal nerve. The transition between the aneurysm to the normal aorta usually has fairly tough tissue to suture. As mentioned, if this is

within the proximal third of the descending aorta, the anastomosis can be performed without a problem, particularly if the parachuting technique is used. If there is an aberrant right subclavian artery without a Kommerell diverticulum aneurysm, it can be included in the repair (see [Fig. 68-2](#)). An alternative is a technique in which the graft is placed in the descending aorta while the anastomosis is performed, and then the inverted graft in the descending aorta is withdrawn for the aortic arch repair.⁴

Other Techniques

In patients with saccular aneurysms with a fairly narrow neck, a patch of graft material can be sewn to the neck in the aortic arch, usually on the lesser curve. One needs to ensure that the edge of the aorta is strong and will hold sutures. This technique is also useful for saccular aneurysms of the proximal descending aorta. However, a decision has to be made as to whether a mediastinal approach or a left thoracotomy is better. When a patch technique

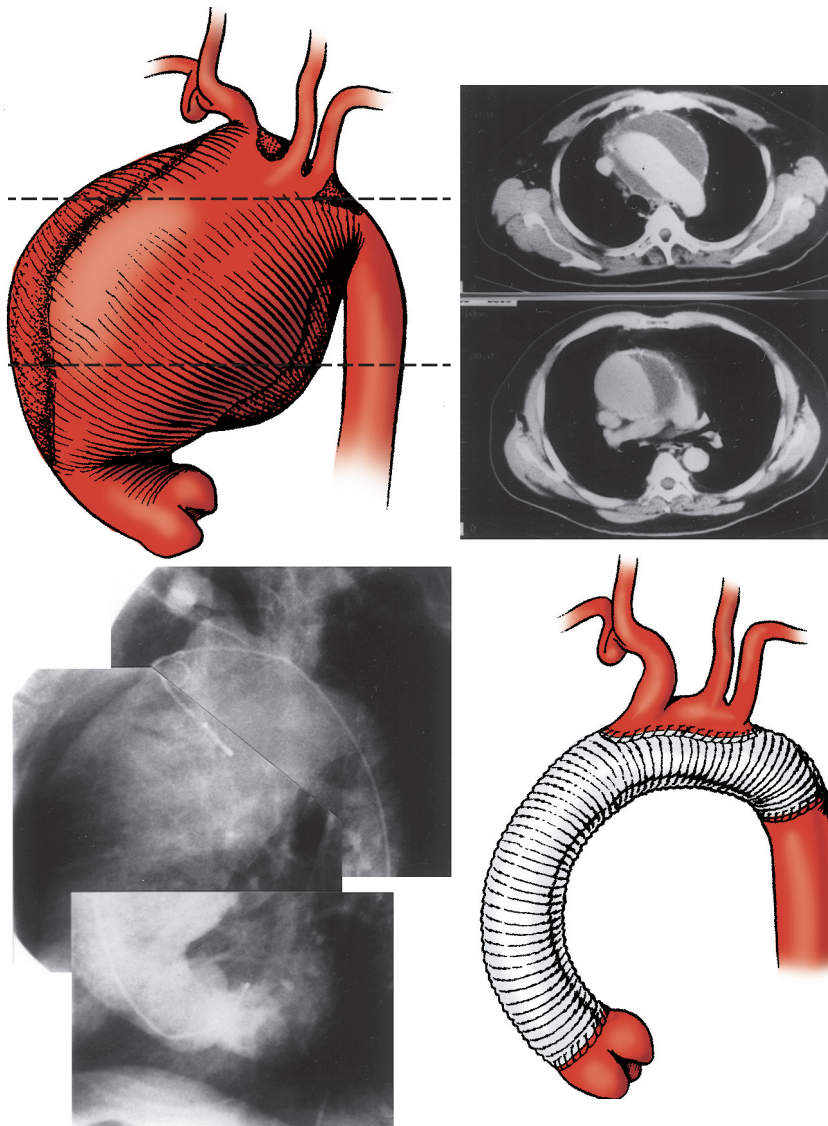


FIGURE 68-15 ■ For this aneurysm involving only the ascending and aortic arch and proximal descending aorta, an elephant trunk procedure was not necessary. Note the extensive clot formation in the aneurysm shown on the computed tomography scan. The arch was repaired by sewing the graft into the proximal descending aorta and then reattaching the greater vessels as a Carrel patch.

is used, because there is usually extensive atheroma, it is advisable to use the right subclavian artery for arterial inflow to ensure that any potential embolic material is not flushed back up into the brain but rather washed into the descending aorta.

Griep and the Mt. Sinai group have described a technique of suturing a large graft to the greater vessels island and then perfusing this graft from the pump while another graft is used for doing both distal and proximal anastomoses in the aorta.^{31,38,65} Finally, an anastomosis between the graft to the greater vessels and the separate aortic arch graft is performed. This technique allows a shorter circulatory arrest to the brain but requires that additional anastomoses be performed.

In patients with extensive atheroma and calcification, endarterectomy of the aortic arch also may be required. In our experience with 45 patients, the results have been surprisingly good when doing endarterectomies at the same time as aneurysm repairs of the aortic arch.²⁹ When performing endarterectomies of the aortic arch and greater vessels, a meticulous technique must be used to ensure that no embolic material gets into the ostia of the greater vessels. For this reason, we use antegrade brain perfusion and often combine this with retrograde brain perfusion to ensure maximal flushing of the greater vessels while doing these types of repairs.²⁹

Another option is using a minimal invasive approach for re-do aortic arch surgery. The advantage of using this method at reoperations is that the rest of the heart and the right atrium do not need to be dissected out. Because the patient has typically undergone a previous aortic root procedure, an elephant trunk procedure can be done distally and the proximal anastomosis performed to the ascending aorta. We have used this method now in 125 patients with a 95% survival rate and a 2.6% stroke incidence.^{47,66,67}

We do not use the new biological glues extensively for aortic arch repairs. In our experience, patients who return for reoperations who have had repairs with these glues often have tissue that is extremely thick, hard, and often calcified, making it difficult to work with. In addition, there is the risk in aortic arch surgery that some of the glue may embolize distally; this is particularly the case with the gelatin-resorcinol-formaldehyde (GRF) glues. Infection and false aneurysms also can be problems.

For patients with aneurysms or stenosis of the greater vessels, various operative techniques can be used at the time of aortic arch surgery. Most of these involve placing bypasses from the neo-aortic graft to a more distal normal segment of the greater vessel. Sometimes, if only the origin of the greater vessels of the aortic arch is involved, these procedures can be performed without placing the patient on cardiopulmonary bypass. For example, a side-biting clamp can be placed on the ascending aorta and a bifurcated graft sewn to the ascending aorta. Alternatively, the ascending aorta can be replaced by a tube graft and the bypass graft attached to it. The distal grafts can then be used to bypass the innominate, the common carotid, or the subclavian arteries. [Figure 68-16](#) shows magnetic resonance angiograms of a patient in whom this technique was used to attach the bifurcated graft to the ascending aorta using a side-biting clamp; the two distal

grafts were routed through the chest pleural spaces and through the first intercostal space to the bilateral axillary arteries, where anastomoses were performed.⁶²

Frozen Elephant Trunk

The frozen elephant trunk technique is a single-stage approach for the repair of arch and thoracic aortic disease where a stent graft is first delivered in the descending aorta either antegrade or retrograde. The distal anastomosis of the aortic arch graft is then sewn on to the distal aortic arch with the suture line incorporating the stent.^{68,69} According to European E-vita Open Registry data, the use of the frozen elephant trunk technique for chronic dissection leads to an 80% rate of complete thrombosis in the false lumen.^{70,71} In patients with acute type A dissection, the residual dissected descending aorta present in 50% of cases is prone to aneurysmal enlargement, and up to 40% of these patients require reintervention. Roselli and colleagues described a simplified frozen elephant trunk technique to potentially address this issue.⁷² A single commercially available thoracic stent graft is delivered antegrade down the descending aorta into the true lumen. The proximal end is then trimmed and sutured into the aortic arch. In this series of 17 patients, no perioperative deaths occurred and 88% of patients had a fully thrombosed false lumen at follow-up. In a large Japanese series of 156 patients, of which 100 had dissection and 56 had aneurysmal disease, the rates for mortality, stroke, and paraplegia were 3.2%, 2.6%, and 2.0%, respectively. At 12 months, the false lumen shrank in 46% of cases and was obliterated in 37% of patients. Whether this improved remodeling of the aorta leads to long-term survival advantage is yet to be demonstrated.

Occasionally, the aortic arch cannot be replaced or operated on. A valved conduit from the left ventricular apex to the descending aorta is one option of treatment in this event ([Fig. 68-17](#)).

Finally, as hybrid operating rooms are becoming increasingly common, and with increasing familiarity and comfort with percutaneous and endovascular techniques, an expanding array of complex cases can be addressed with minimally invasive approaches. We recently performed a case where the left common carotid artery and descending aorta were concomitantly stented with a transapical transcatheter aortic valve replacement.

OUTCOMES

In a historical study from 1993 and an analysis of 656 patients who underwent deep hypothermia and circulatory arrest, mostly for aortic arch replacements, the mortality rate was 10% and the stroke rate was 7%.³⁴ This large study noted that the longer the circulatory arrest was, the greater was the risk of stroke. It is of interest that some patients tolerated circulatory arrest periods of up to 120 minutes without developing frank strokes. In this series of patients, the predictors of stroke by multivariate analysis were history of cerebrovascular disease, previous aortic surgery beyond the left subclavian artery, and cardiopulmonary bypass time ($P < 0.05$).³⁴

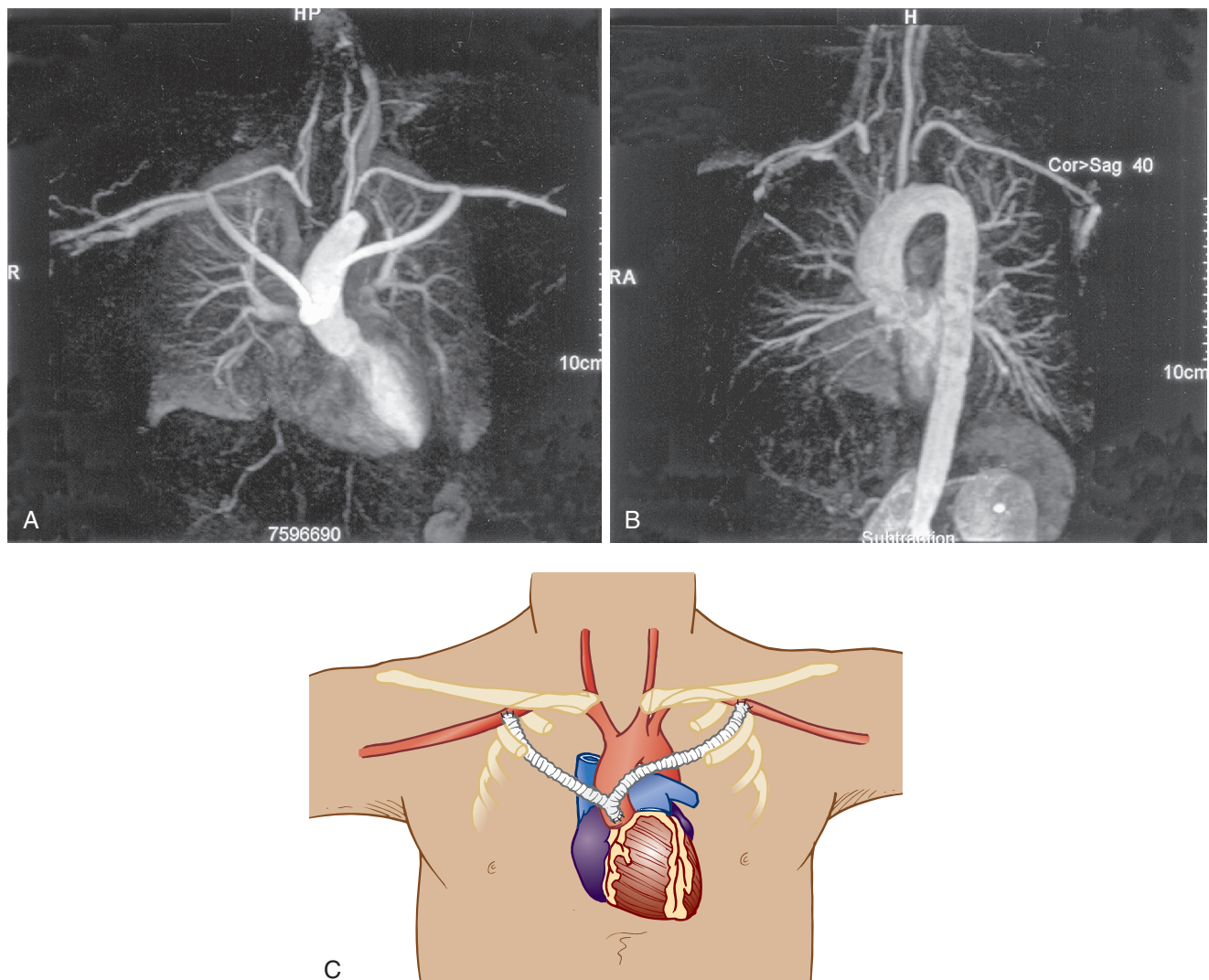


FIGURE 68-16 ■ **A**, Magnetic resonance angiogram (MRA) shows occluded innominate and left subclavian arteries and 50% narrowing of the left common carotid artery. **B**, Postoperative MRA after off-pump insertion of a bifurcated graft from the ascending aorta to both axillary arteries with a transpleural approach. **C**, Diagram of the completed procedure.

Results with aortic arch surgery continue to improve. Safi and colleagues' series from 2001 had a 5.1% 30-day mortality for the first stage, 3.6% interval mortality, and 6.2% 30-day mortality for the second stage. In our series of 526 unselected elephant trunk procedures, the survival rate for the first operation was 92%, with no statistical significant difference between the LCCA-LSCA (left common carotid artery–left subclavian artery) group and the classic group. The overall stroke rate was 8%. The 1-, 4-, and 8-year risk of death before second-stage elephant trunk was 16%, 22%, and 27%, respectively; the larger the descending aorta is, the greater the likelihood is of a second-stage completion.

In a prospective randomized study, we reported a survival rate of 100%, and no patient suffered stroke after aortic arch repairs.²⁹ Although 91% of patients had a neurocognitive deficit when tested between 3 and 6 days after undergoing aortic arch repairs, by 2 to 3 weeks after surgery, with repeat testing using 51 neurocognitive tests, 9% had a deficit, and by 6 months, all the patients with

new neurocognitive deficits had recovered. As mentioned, 38% of patients had had a preoperative deficit. In another analysis, of 403 patients undergoing ascending and aortic arch operations using a protocol to protect the brain as much as possible from strokes and neurocognitive deficits, the survival rate was 98%, stroke rate 2%, and incidence of neurocognitive gross clinical deficits 2.5%.⁵⁴ The predictor of death by multivariate analysis was pump time; for stroke it was aorta symptom grade, peripheral vascular disease, and pump time; and for neurocognitive dysfunction, it was New York Heart Association dyspnea class, pump time, arrest time, day extubated, and antegrade perfusion. In our recent randomized clinical trial of 121 patients with aortic arch repairs, only 0.8% had clinically evident stroke, although 9% had radiologic evidence of new stroke and 14% had new onset of neurocognitive dysfunction.⁵¹ These studies emphasize the importance of awareness that patients may have suffered silent strokes and developed neurocognitive deficits before undergoing aortic arch surgery.

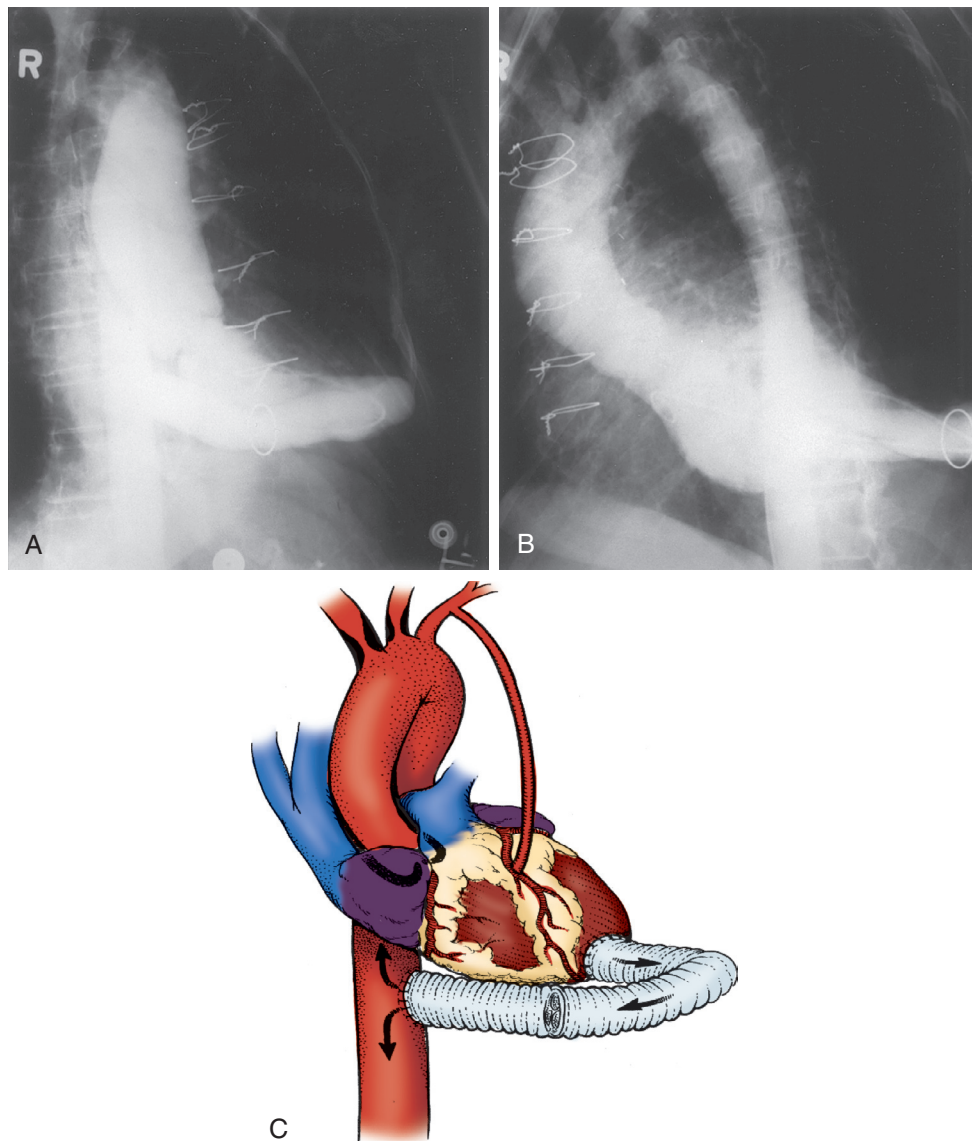


FIGURE 68-17 ■ This patient had undergone previous coronary artery bypass surgery, had systemic lupus and renal disease, was on high-dose steroids, and had heart failure from aortic valve stenosis. There was extensive calcification of the ascending aorta and aortic arch, including modest stenosis of the greater vessels. **A** and **B**, A valved tube graft was placed from the left ventricle apex to the descending aorta. The operation was done without cardiopulmonary bypass. **C**, Diagram of the operative procedure.

SUMMARY

In the past, aortic arch surgery was among the most formidable of cardiovascular operations. With modern techniques, surgery for the aortic arch is considerably safer, and satisfactory results can be achieved in most patients.

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DESCENDING THORACIC AND THORACOABDOMINAL AORTIC SURGERY

Joseph S. Coselli • Kim I. de la Cruz • Ourania Preventza • Scott A. LeMaire

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INTRODUCTION

Aortic aneurysm is defined as a localized dilation of the aorta that is at least 50% greater than that of nondiseased adjacent aorta. In the distal aorta, namely the descending thoracic and thoracoabdominal aorta, most aneurysms form as a result of nonspecific medial degeneration, expansion related to chronic aortic dissection, or the disease processes of connective tissue disorders. Whereas aortic

aneurysms may be either fusiform (a symmetrical dilation of the aorta) or saccular (a localized outpouching of the aorta), saccular aneurysms are uncommon in the distal aorta and tend to be associated with infection. False aneurysms (also called pseudoaneurysms) may occur and are caused by a disruption of the aortic layers that then permits leaking blood to be contained by the outermost layer of the aorta and may additionally involve the periaortic tissue. Under such conditions, the aortic wall may become dilated beyond its capacity to expand and subsequently rupture.

Contemporary surgery involves a balanced approach toward maximizing the patient's long-term benefit by replacing as much diseased aorta as possible with the need to limit aortic resection to reduce ischemic and other operative risk. Our contemporary approach to open surgical repair of the descending thoracic and thoracoabdominal aorta is presented in this chapter.

Developing a Surgical Approach to Repair

The replacement of aneurysmal sections of the distal aorta built on the successful homograft-replacement repairs of aortic coarctation by Gross and others in the mid-1940s.^{1,2} In 1950, Swan used a homograft to replace an 8-cm section of the descending thoracic aorta in a teenage patient with a coarctation-related aneurysm.³ However, it remained unclear how patients with degenerative aneurysm, who were typically far older, would respond to aortic clamping, because they tended to lack the extensive collateral circulation present in patients with congenital coarctation. Soon after Swan's initial repair, Lam and Aram⁴ attempted to replace a fusiform aneurysm of the descending thoracic aorta with a homograft. Despite the use of a shunt to maintain distal perfusion and of other adjuncts in use in this era, this repair failed because the patient became septic; the authors speculated that a successful repair may necessitate full aneurysm extirpation. In 1953, DeBakey and Cooley⁵ were able to successfully "clamp and sew" a homograft replacement of a very large aneurysm of the descending thoracic aorta that impinged on the celiac axis (this would arguably be considered an extent I thoracoabdominal aortic aneurysm [TAAA] repair today). And in 1955, Etheredge and colleagues⁶ reported a successful homograft replacement of a TAAA, and they perfused the distal aorta by using a small temporary shunt. Also in 1955, Rob⁷ reported several TAAA repairs performed by using a clamp-and-sew approach.

Over the next decade, the emerging availability of Dacron grafts facilitated the use of an extra-anatomic approach in which the graft would be placed around the aneurysm—before completely resecting it—such that it could be used as a bypass shunt during repair. For TAAAs, these repairs would be done in a bottom-to-top fashion to quickly restore blood flow to the visceral organs. Notably, all early grafts had significant limitations. Early Dacron grafts were extremely porous and readily permitted blood to seep through. Early aortic repairs were associated with high rates of death, paraplegia, and kidney failure.⁸

In 1974, Crawford⁹ detailed his experience with 28 TAAA patients. His technique for TAAA repair was vastly different from the established extra-anatomic approach embraced by DeBakey and his contemporaries. By drawing on a variety of techniques devised by others,^{10,11} as well as developing new techniques to expedite repair, he achieved an impressive survival rate of 92%. Crawford used an anatomic endoaortic-graft-inclusion technique and chose to avoid full resection of the aneurysm, carefully securing the remaining aortic wall around the replacement graft to reduce bleeding; he used island

reattachment strategies to reimplant the visceral vessels and select intercostal arteries to restore perfusion to the viscera and spinal cord. Although Crawford's approach was not immediately adopted, it became the foundation for contemporary surgical approaches to TAAA repair, and his classification¹² of TAAA repairs (Fig. 69-1) remains in use.

Natural History

Whereas the aorta expands very slowly in normal circumstances, the distal aorta tends to grow at a faster rate than the proximal aorta. Documented growth rates for the distal aorta range from 0.1 to 0.3 cm per year; growth rates are further increased in larger diameter aortas (8 cm and larger) and in patients with chronic dissection.¹³⁻¹⁵ Elefteriades and his colleagues at Yale¹⁶ identified aortic diameter as a strong predictor of rupture, dissection, and mortality. A critical diameter of 7.0 cm was identified for descending thoracic aortic aneurysms (DTAAs), with a corresponding risk of rupture or dissection of 43%. Saccular aneurysms tend to grow faster and less predictably than do fusiform aneurysms. Although it typically takes years for an aneurysm to reach a diameter-based threshold for repair, many distal aortic aneurysms increase in size and eventually progress to cause serious complications. In addition, as distal aortic aneurysms form, they are commonly lined with substantial amounts of friable, atheromatous plaque and mural thrombus.

CLASSIFICATION BY EXTENT OF REPAIR

Repair of the distal aorta poses substantially different risks than proximal aortic repair. Subsequently, operative strategy and expected outcomes vary with the extent of aortic replacement; generally speaking, risk increases as longer sections of the aorta are replaced. Thus, repair of TAAAs is typically more complicated than repair of DTAAs. Understanding of the extent of aortic involvement is the key to planning an appropriate strategy for operative repair.

Distal aortic disease may be limited to short sections of the descending thoracic aorta, or it may involve long sections of the aorta and necessitate substantial exposure. Aneurysms may begin near the left subclavian artery (LSCA) and extend beyond the level of the diaphragmatic hiatus to include varying segments of the abdominal aorta. DTAAs usually begin just distal to the LSCA and extend toward (but not past) the crura of the diaphragm. Conversely, repair of TAAAs necessitates exposing the aorta above and below the diaphragm and involves incorporating the segment from which the visceral arteries arise into the repair.

The Crawford classification schema¹² conveys useful information about TAAA repair and divides these repairs into four "extents" according to the amount of aorta replaced (see Fig. 69-1). Crawford extent I repairs involve the aorta from just distal to the LSCA to the origins of the celiac axis and superior mesenteric arteries and may also involve the renal arteries; however, these repairs do not extend into the infrarenal aorta. Extent II is the most

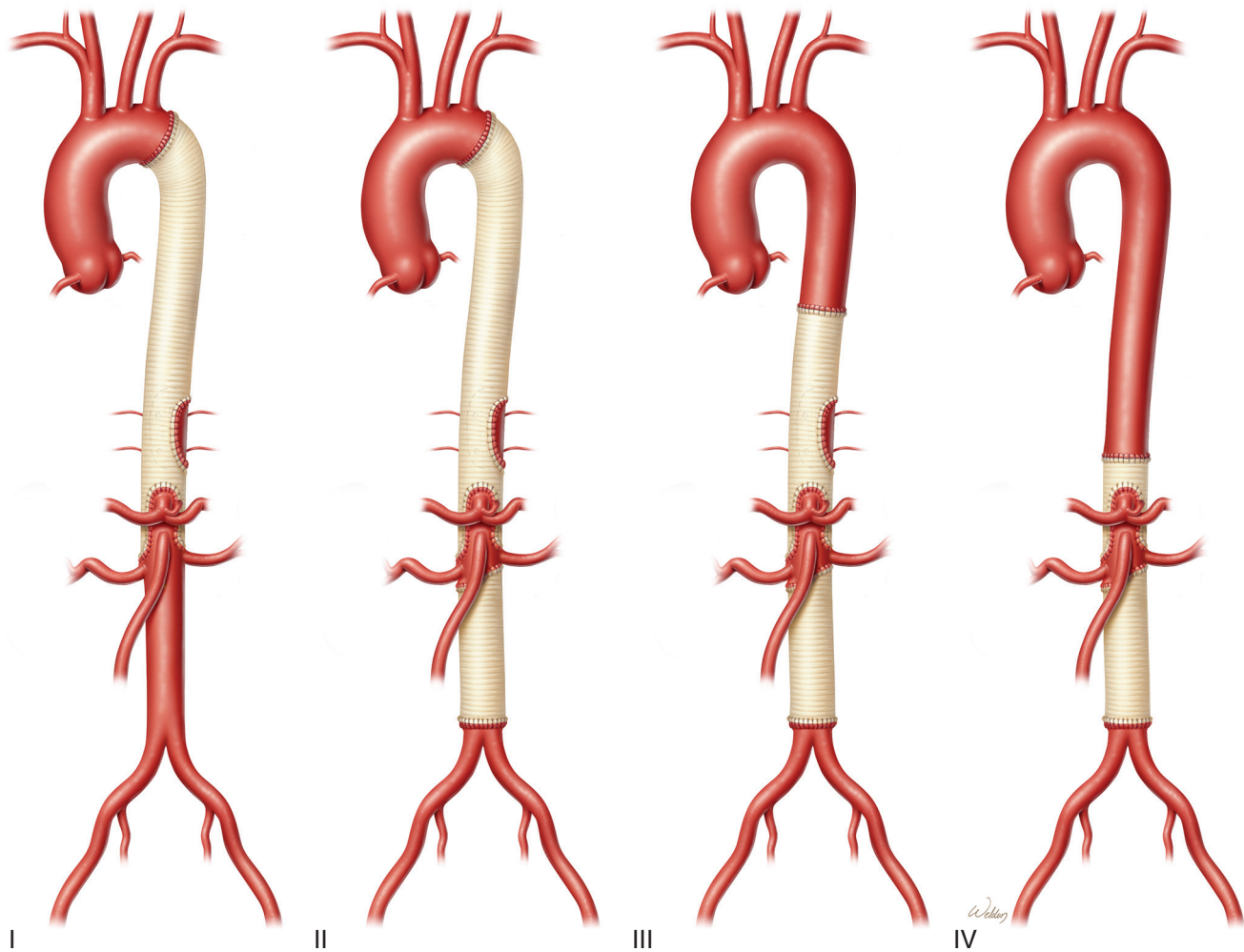


FIGURE 69-1 ■ The Crawford classification system for describing the extent of thoracoabdominal aortic aneurysm repair. (Used with permission of Baylor College of Medicine.)

extensive repair and involves almost the entire distal aorta, from near the LSCA to the infrarenal abdominal aorta, and it often extends to the aortoiliac bifurcation; extent II repairs generally incur the greatest operative risk. Extent III repairs involve the mid-descending thoracic aorta (below the sixth rib) and a variable amount of the abdominal aorta. Extent IV repairs begin within the diaphragmatic hiatus and extend through the abdominal aorta. Although some centers use a modified Crawford classification schema that includes an extent V repair,¹⁷ we do not; extent V repairs tend to fall under the extent III category of repair, and these two types of repair typically have similar outcomes.

CAUSES AND PREDISPOSING FACTORS

Nonspecific Medial Degeneration

Although the underlying mechanisms of aortic disease remain unknown, nonspecific medial degeneration is the most common cause of thoracic aortic aneurysms and dissections. Although the fragmentation of elastic fibers and loss of smooth muscle cells are to be expected in the

aging aorta, these processes are accelerated in medial degenerative aortic disease and lead to continual weakening of the aortic wall, aneurysm or dissection formation, and eventual rupture. Although atherosclerosis is often construed as a cause of thoracic aortic aneurysms, it may be merely a concomitant condition rather than a distinct cause of aortic aneurysm.

Chronic Aortic Dissection

Chronic dissection is a common cause of TAAA; consequently, reported rates range from 15% to almost 40% of TAAA repairs.^{18,19} Aortic dissection (which is more fully covered in [Chapters 70 and 71](#)) usually begins as a tear in the innermost layer of the aortic wall. This tear allows pulsatile blood flow to cause a progressive separation of the medial layers, thereby creating two channels of blood flow within the aorta ([Fig. 69-2A](#)). This process substantially weakens the outer aortic wall, leading to aortic dilation and eventual aneurysm formation. Chronic dissection in the distal aorta occurs in survivors of acute DeBakey type I and III dissection events. Although it is generally assumed that chronically dissected aortas of either type dilate at similar rates, emerging evidence

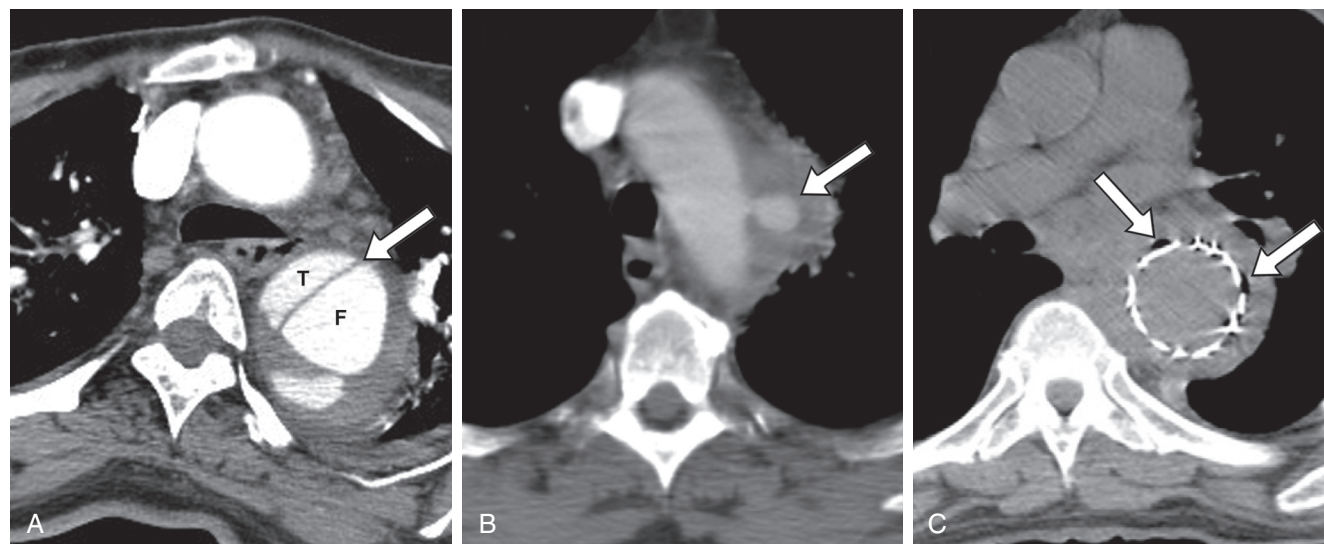


FIGURE 69-2 ■ Computed tomography scans showing key diagnostic findings. **A**, Chronic distal aortic dissection; the dividing septum is relatively straight (arrow), and the true (T) and false (F) lumens are indicated. **B**, Mycotic aneurysm, which is sacular in shape (arrow). **C**, Infection of an endograft; gas bubbles, indicated by arrows, may be seen near the endograft. (Used with permission of Baylor College of Medicine.)

suggests there may be differing rates of expansion between types.²⁰ Moreover, for incompletely understood reasons, patients with chronic dissection may also develop a superimposed acute dissection; this is a dangerous development, and urgent treatment is warranted.

Connective Tissue and Genetic Disorders

Connective tissue and related genetic disorders occur in 4% to 14% of patients who undergo DTAA or TAAA repair.^{19,21-24} These disorders range from the relatively well-established Marfan syndrome (MFS) to lesser known, emerging disorders such as Loeys-Dietz and aneurysms-osteoarthritis syndromes. Of these conditions, MFS is the most common in DTAA and TAAA patients; however, surgeons should be aware of the other, more aggressive disorders so as to best formulate individualized strategies for treatment. Most of these syndromes are suspected on the basis of clinical features or a positive family history; as needed, confirmatory genetic tests should be conducted.

Marfan syndrome is an autosomal dominant genetic disorder that predisposes patients to aortic aneurysm and dissection. Although most patients with MFS have a family history of the disease, a substantial number of patients develop the mutation *de novo*; numerous mutations in the fibrillin-1 gene have been discovered.^{25,26} It was long thought that the presence of abnormal fibrillin in the extracellular matrix reduced the strength of the aortic wall (and thus predisposed the aorta to dilation), but emerging evidence indicates that the abnormal fibrillin alters biomolecular pathways, leading to aberrant signaling of transforming growth factor beta (TGF- β) and a related cascade of events and, ultimately, to degeneration of the aortic wall matrix.²⁵ The clinical features of MFS usually include a tall and lanky stature with long limbs, eye lens disorders, mitral valve prolapse, joint

hypermobility, high palate, and aortic aneurysms in young adults.

Most commonly, MFS affects the proximal aorta, namely the ascending aorta and aortic root. Most patients with MFS who undergo distal aortic aneurysm repair have chronic aortic dissection. Whereas most of these patients are operative survivors of acute DeBakey type I dissection, a substantial number of repairs are done in patients with initially medically managed DeBakey type III aortic dissection.²⁷

Loeys-Dietz syndrome is an aggressive aortic disease that tends to affect patients at a much younger age than does MFS.²⁸ Characterized by widespread systemic arterial tortuosity and aneurysm formation, clinical features include the presence of a bifid uvula or cleft palate and widely spaced eyes (hypertelorism). In the past, many of these patients were identified as having MFS,²⁹ and like that disorder, this condition is autosomal dominant. However, Loeys-Dietz syndrome is caused by heterozygous mutations in the genes encoding TGF- β receptors I and II.³⁰ Patients with Loeys-Dietz syndrome require exceedingly careful monitoring because they are predisposed to dissection and rupture at far smaller aortic diameters than are patients with MFS.³¹

Other disorders,³² such as Ehlers-Danlos syndrome, aneurysms-osteoarthritis syndrome, and nonsyndromic familial aortic aneurysm and dissection, are currently thought to be infrequently encountered in patients who need distal aortic repair. Ehlers-Danlos syndrome comprises a spectrum of disorders of collagen synthesis; the vascular subtype (previously referred to as “type IV”) of Ehlers-Danlos syndrome involves a defect in type III collagen synthesis that lends itself to cardiovascular manifestations, chief among which is spontaneous arterial rupture.³³ Poor aortic tissue integrity tends to complicate surgical repair.³⁴ Recently identified, aneurysms-osteoarthritis syndrome is an autosomal dominant disorder caused by a mutation in the gene

responsible for transcribing TGF- β , *SMAD3*.³⁵ Clinically, this syndrome is reminiscent of Loeys-Dietz syndrome, but, in contrast, these patients also have early-onset osteoarthritis. Of note, these patients have a high incidence of aortic dissection at moderately dilated aortic diameters (4 to 4.5 cm), well below standard thresholds of repair.³⁶ Several other heritable mutations, affecting families with variable expression, have been documented in the genes for TGF- β receptors, TGF- β 2, β -myosin, *SMAD3*, and α -smooth muscle cell actin.³⁷⁻⁴¹ Although familial aortic thoracic aneurysms most commonly affect the proximal aorta, such heritable nonsyndromic disease may present as dissection or aneurysm in the distal aorta.

Aortitis

In rare cases, systemic autoimmune disorders, such as giant cell arteritis, Takayasu arteritis, and Behçet disease, may also lead to aneurysm formation in the distal aorta. A granulomatous inflammation may occur in patients with giant cell arteritis (temporal arteritis) that involves the entire thickness of the aortic wall and thus cause intimal thickening and medial destruction. Although Takayasu arteritis generally produces severe intimal thickening that causes obstructive lesions, it can also lead to aneurysm formation. A more common presentation of aortitis occurs when patients with preexisting degenerative aortic aneurysms then develop localized transmural inflammation. Although the reasons for this inflammation remain unclear, its onset can lead to expansion and further weaken the aortic wall. In addition, fibrosis and an infiltrate of plasma cells, giant cells, and lymphocytes can develop in the affected tissue. In Behçet disease, both arteries and veins are affected, and the disease process involves lymphocytic infiltration of the medial layer, which may progress to aneurysm or pseudoaneurysm formation.

Mycotic Aneurysm

In rare cases, infection of the native aorta precipitates distal aortic aneurysm formation. Such lesions are commonly called *mycotic aneurysms*, even though the responsible pathogens are usually bacteria rather than fungi. Mycotic aneurysms may form as bacteria inoculate healthy aortic tissue, which then contributes to subsequent aneurysm formation, or they may result from the secondary infection of an existing aneurysm. In addition, mycotic aneurysms may be pseudoaneurysms, rather than true aneurysms, and can develop as a late complication of previous iatrogenic aortic injury created during invasive imaging procedures or cardiac or aortic operations (e.g., aortic cannulation sites). Establishing a diagnosis for patients with a mycotic aneurysm can be exceedingly difficult because symptoms can be vague, such as a persistent low-grade fever or unexpected weight loss, and such infection is rare.⁴² Further complicating matters, there are a variety of mechanisms by which the source bacteria may infect the aorta; these include vertebral or other abscess, general sepsis or septic emboli, empyema, infected lymph nodes,⁴³ and other factors that can be difficult to elucidate. Unlike most other distal aortic

aneurysms, which tend to be fusiform in shape, mycotic aneurysms are often saccular in shape (see Fig. 69-2B) and correspond to localized areas of tissue destruction. Common causative organisms include *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella*, and *Streptococcus*.⁴⁴ and more than one pathogen may be present. Outside the United States, tuberculosis aortitis may present as saccular aneurysm of the thoracoabdominal aorta, and sometimes even as multiple saccular aneurysms.⁴⁵ Of note, saccular aneurysms can be unpredictable, are prone to rapid growth rates, and tend to rupture more readily than fusiform aneurysms caused by medial degeneration; when mycotic saccular aneurysm is suspected, urgent evaluation is warranted.⁴⁶

Repair after Previous Open Aortic Repair (Noncongenital)

Over time, late complications of previous distal aortic repair may develop (Fig. 69-3); such complications include pseudoaneurysms and aneurysms that develop around sites of aortic reattachment (e.g., buttons of tissue surrounding reattached visceral or intercostal arteries may later become aneurysmal). In addition, aortic disease may progress such that previously normal sections of the aorta adjacent to the site of a previous repair may later become aneurysmal. Late complications tend to occur more frequently in patients with MFS and other connective tissue disorders and in patients with aortic infection. Overall, distal redo operation (previous open repair of the descending thoracic, thoracoabdominal, or abdominal aorta) rates tend to range from 16% to 27% in reported series of TAAA repairs.^{18,19,47,48}

Pseudoaneurysms often represent chronic leaks that are contained by surrounding tissues. The outer wall of a pseudoaneurysm develops from organized thrombus and associated fibrosis. Pseudoaneurysms can arise from primary defects in the aortic wall (such as a leak from a fistula or contained rupture) or from degraded suture lines or graft material (anastomotic leaks were common in the era of silk suture, which readily degraded, and graft infection may also degrade the suture line), from sites of previous cannulation (leaks that occur after cardiovascular surgery), or from a wire penetrating or otherwise damaging the aorta during invasive aortic imaging and testing. Anastomotic pseudoaneurysms can also be caused by tension between the graft and native aortic tissue. With modern suture, graft material, and technique, the incidences of pseudoaneurysm and other late complications have decreased; however, should they occur, urgent evaluation is warranted because they have a tendency toward rupture.

Repair after Previous Endovascular Aortic Repair

In the contemporary era, the use of aortic stent-grafts in the distal aorta is common in patients with aneurysm and dissection (this topic is fully covered in Chapters 70 and 71). Occasionally, patients who have undergone endovascular aortic repair develop problems that necessitate open repair.⁴⁹⁻⁵⁵ Open aortic repair after endovascular aortic

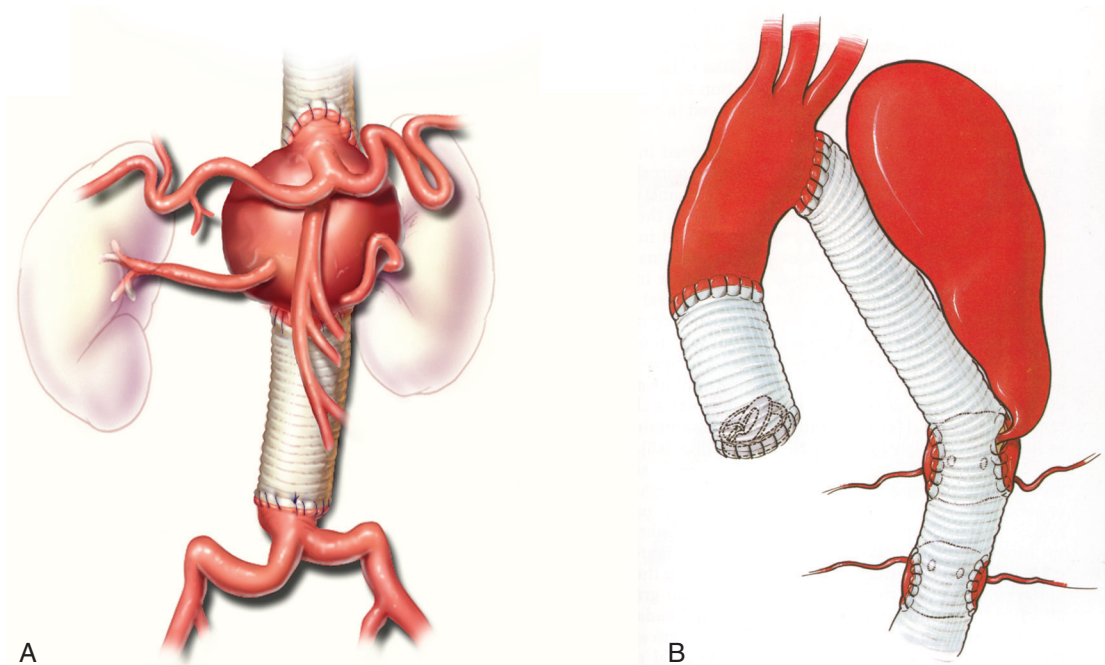


FIGURE 69-3 ■ Illustration showing late complications of open aortic repair. **A**, A visceral patch aneurysm has developed in the residual native aortic tissue. **B**, A pseudoaneurysm has developed near the suture line of an intercostal artery reattachment site.

procedures may be necessary to treat continued dilation of the aorta at or near the stent-graft landing zones, infection of the endograft (see Fig. 69-2C), the development of a fistula (Fig. 69-4), stent-graft collapse or migration, or ongoing aneurysm expansion, which may result in rupture. Progressive expansion of the aneurysm may occur because of an inadequate seal between the stent-graft and aorta (type I endoleak), bleeding into the aneurysmal sac from any covered branching artery (type II endoleak), a gap between overlapping stent-grafts (type III endoleak), retrograde perfusion through the false lumen into the aneurysmal sac in patients with extensive aortic dissection, or other causes.

Coarctation in the Adult (Congenital)

Aortic coarctation may occur in patients with bicuspid aortic valve or other congenital heart disease or in patients with Turner syndrome.⁵⁶ The typical presentation of aortic coarctation involves a narrowing of a short section of the descending thoracic aorta, located just beyond the LSCA; the quality of aortic tissue in this section is generally poor because it is delicate and friable. Over the past several decades, several open approaches have been used to treat aortic coarctation in early childhood, including subclavian flap repair, patch aortoplasty, and interposition aortic grafting. In adults, open or endovascular repair may be needed to treat previously undiscovered native coarctation or late complications (aneurysm, pseudoaneurysm, or restenosis) of previously repaired coarctation,^{57,58} which tend to develop in the first or second decade after initial repair.⁵⁹ The ideal repair for discrete and previously unrepaired coarctation in adults is somewhat controversial; current guidelines indicate that either an endovascular or an open repair may be performed.⁵⁶

In rare cases, adults need primary repair for extreme forms of previously untreated coarctation, such as an interrupted or a hypoplastic aortic arch (Fig. 69-5), or a long-segment aortic coarctation (also known as middle aortic syndrome and sometimes seen with rib notching); for these patients, current guidelines recommend open repair (Class I recommendation, level of evidence B). For patients with discrete restenosis after open repair, endovascular repair is recommended unless significant aortopathy is also present (Class I recommendation, level of evidence B).⁵⁶ Today, many experienced centers achieve good results by using a variety of approaches to coarctation repair, including open, endovascular, and hybrid techniques.^{57,58,60-64}

Patients with aortic coarctation commonly have hypertension, and even with treatment, hypertension remains difficult to control. It is thought that uncontrolled hypertension plays a role in the late development of aneurysms, both in patients with previous aortic repair and in those without. In previously untreated adults, extensive collateral circulation may develop; during open repair, these branching vessels may enhance the risk of operative bleeding, and these vessels are commonly ligated when possible. Patients with long-segment coarctation may be treated with extra-anatomic bypass grafts rather than in situ graft replacement.

INDICATIONS FOR REPAIR

Descending thoracic and thoracoabdominal aortic aneurysms most commonly present in asymptomatic, older patients (60 years of age and older) and are often incidentally discovered through imaging studies ordered to evaluate other, unrelated health problems. In patients

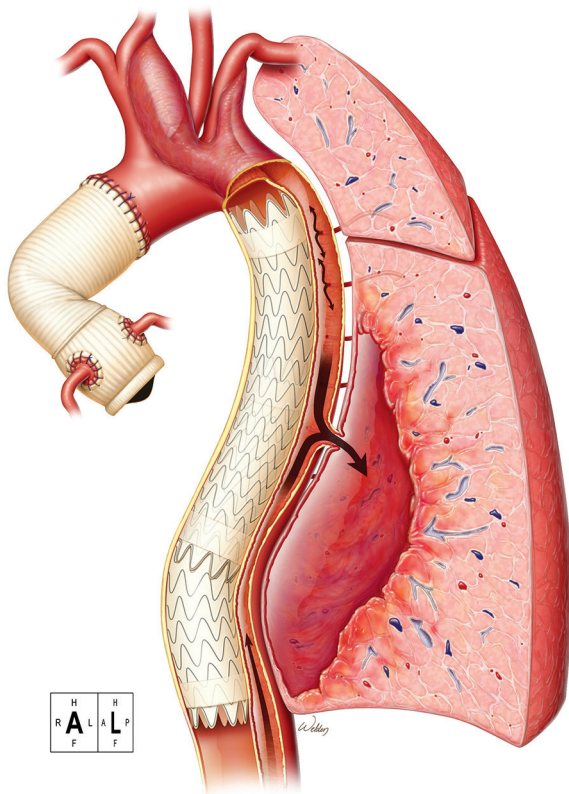


FIGURE 69-4 ■ Illustration showing the development of an aortopulmonary fistula, a rare late complication of thoracic endovascular aortic repair. Here, the stent-graft is shown to be within the true lumen. The distal descending thoracic aorta has ruptured into the lower lobe of the left lung (arrow); the false lumen continued to be perfused from re-entry sites below the distal landing zone of this stent-graft. Blood flow from collateral vessels additionally perfused the false lumen. (From Matos JM, de la Cruz KI, Ouzounian M, et al: Endovascular repair as a bridge to surgical repair of an aortobronchial fistula complicating chronic residual aortic dissection. *Tex Heart Inst J* 41:198–202, 2014, Fig. 5. Reproduced with permission. Copyright the Texas Heart Institute.)

with known risk factors for distal aortic aneurysms (as described in the previous section), imaging studies are used to carefully monitor the aorta until diameter-based thresholds of repair are met or until symptoms develop. Therefore, the management of distal aortic disease is typically dependent on regularly repeated imaging studies and enhanced awareness of emerging symptoms through patient education and optimization efforts (at a minimum, optimization efforts include strict blood pressure control and cessation of smoking).

Diagnostic Imaging Evaluation

Although developing an appropriate distal aortic imaging strategy is somewhat dependent on local expertise and equipment availability, recently efforts have been made to standardize image acquisition and reporting by suggesting specific aortic landmarks to measure (Fig. 69-6); for the distal aorta, these include the isthmus or proximal descending thoracic aorta (2 cm distal to the LSCA), the middle of the descending aorta (between the isthmus and the diaphragm), the aorta at the diaphragm (roughly 2 cm above the celiac axis), and the aorta at the origin of the celiac axis.⁴³ Aortic imaging reports should clearly state the location of aortic abnormalities (using the previously mentioned locations whenever possible) and report the maximum external aortic diameter (reporting the internal lumen diameter may fail to account for aortic wall inflammation, intraluminal clot, or mural thrombus, or identify both channels in cases of aortic dissection). Any extension of disease into branching vessels, such as is possible with chronic distal aortic dissection and other conditions, should be documented. Evidence of rupture should be reported, as well as any identified calcification or internal filling defects that are consistent with thrombus or atheroma. Ideally, results should be compared with the most recent prior imaging study available; precise measurement is needed because the yearly rate of aortic



FIGURE 69-5 ■ Computed tomographic angiograms in a patient with bicuspid aortic valve, related proximal and distal aortopathy, and coarctation. **A**, Three-dimensional reconstruction showing coarctation of the descending thoracic aorta. **B**, Axial image showing hypoplasia and tortuosity of the aortic arch. **C**, Post-repair three-dimensional reconstruction showing surgical correction of the aortic arch, descending thoracic aorta, and the left subclavian artery. (From Preventza O, Livesay JJ, Cooley DA, et al: Coarctation-associated aneurysms: a localized disease or diffuse aortopathy. *Ann Thorac Surg* 95:1961–1967, 2013, Fig. 1. Used with permission. Copyright Society of Thoracic Surgeons.)

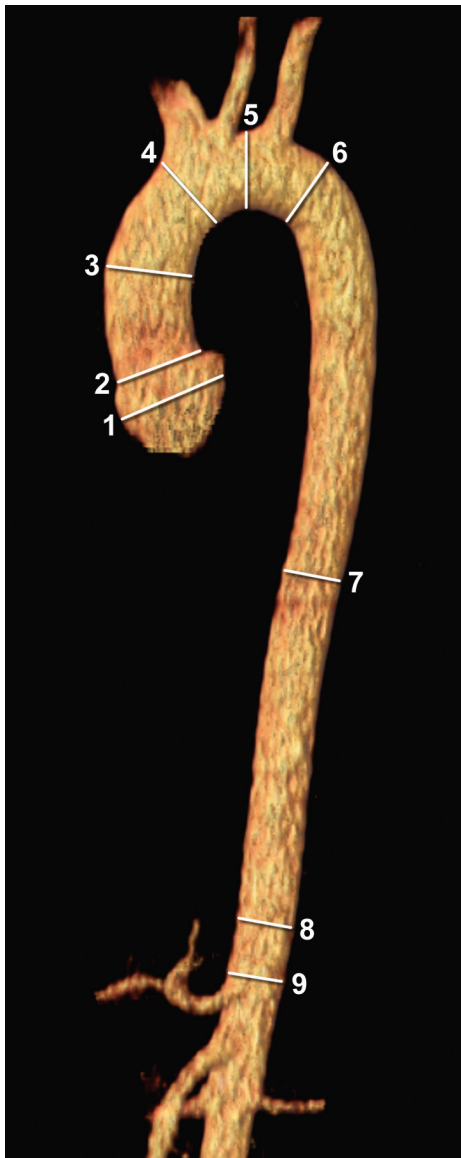


FIGURE 69-6 ■ Current practice guidelines⁴³ seek to standardize the reporting of aortic diameters by indicating key anatomic locations to be measured. These include (1) the sinuses of Valsalva, (2) the sinotubular junction, (3) the mid-ascending aorta, (4) the proximal aortic arch at the origins of the innominate artery, (5) the mid-aortic arch, which is between the left common carotid and left subclavian arteries, (6) the proximal descending thoracic aorta, which begins at the isthmus (approximately 2 cm distal to the origins of the left subclavian artery), (7) the mid-descending thoracic artery, (8) the aorta at the diaphragm, and (9) the abdominal aorta at the origins of the celiac axis. (Used with permission of Baylor College of Medicine.)

expansion is generally quite small, and thus, detecting a small but abnormal growth rate can be challenging.

Although a routine chest radiograph may suggest an aortic abnormality, the most useful diagnostic imaging modalities include computed tomographic (CT) and magnetic resonance imaging or angiography scans of the chest and abdomen to delineate the extent of aortic and branch-vessel involvement. Since the CT was first reported to identify aortic disease in 1976,⁶⁵ it has become widely available and is the most commonly used imaging

modality for identifying aortic aneurysms. Information about the aneurysm's location and extent, external diameter, the presence of aortic dissection, the relationship to branching vessels, and anatomic abnormalities are all readily provided by iodinated intravenous contrast-enhanced CT imaging (Fig. 69-7). Such imaging may also aid in determining the presence of aortic infection, because nearby gas bubbles can be readily identified.⁴² Benefits of CT imaging include the short time needed to acquire the imaging data, the ability to render three-dimensional imaging, and the ability to provide multiplanar evaluation, as well as locating the presence of any aortic calcification or thrombus. Disadvantages of contrast-enhanced CT scanning include repeated exposure to ionizing radiation and the possibility of contrast-induced allergy or contrast-induced acute renal dysfunction in patients. Whenever possible, surgery is performed at least 1 day after contrast administration to allow time to observe renal function and, if needed, to permit renal function to return to normal.

Although magnetic resonance angiography (MRA) is not used as commonly as CT imaging to detect aortic aneurysm, it produces comparable or better aortic images and does not expose patients to ionizing radiation. It offers excellent visualization of all facets of branching vessels and facilitates the identification of left ventricular dysfunction. Disadvantages of MRA include the generally higher expense, the extended time needed to acquire imaging data (which poses a challenge in the critically ill patient), the suboptimal identification of aortic calcification, and the generation of artifacts created by ferromagnetic materials (such as pacemakers and other implants). In addition, the contrast agent for MRA, gadolinium, is associated with nephrogenic systemic fibrosis in patients with comorbid renal dysfunction.^{66,67} In young and otherwise healthy patients, such as those with MFS, MRA may be a valuable supplement to lifelong surveillance imaging because it avoids exposure to radiation. Echocardiography and ultrasonography are not used to evaluate DTAAAs because these techniques cannot adequately visualize disease involving this segment.

Diameter-Based Thresholds for Repair

All aneurysms are repaired to prevent fatal rupture. Although replacing the aorta can be life-saving in patients with aortic disease, surgical intervention carries substantial risks for both morbidity and mortality. Because of the inherent risks associated with surgical intervention, surgery is generally indicated only when the risk of rupture or other catastrophic aortic complications exceeds it. Studies of the natural history of distal aortic aneurysms (as described in a previous section) helped to formulate diameter-based thresholds of repair in asymptomatic patients. Current practice guidelines⁴³ recommend elective open aortic repair in asymptomatic patients when the diameter of a TAAA exceeds 6.0 cm; a lower threshold is recommended if the patient has a connective tissue disorder (Class I recommendation; level of evidence C). In patients with chronic aortic dissection, elective open repair is indicated when the descending thoracic aorta exceeds 5.5 cm (Class I recommendation; level of

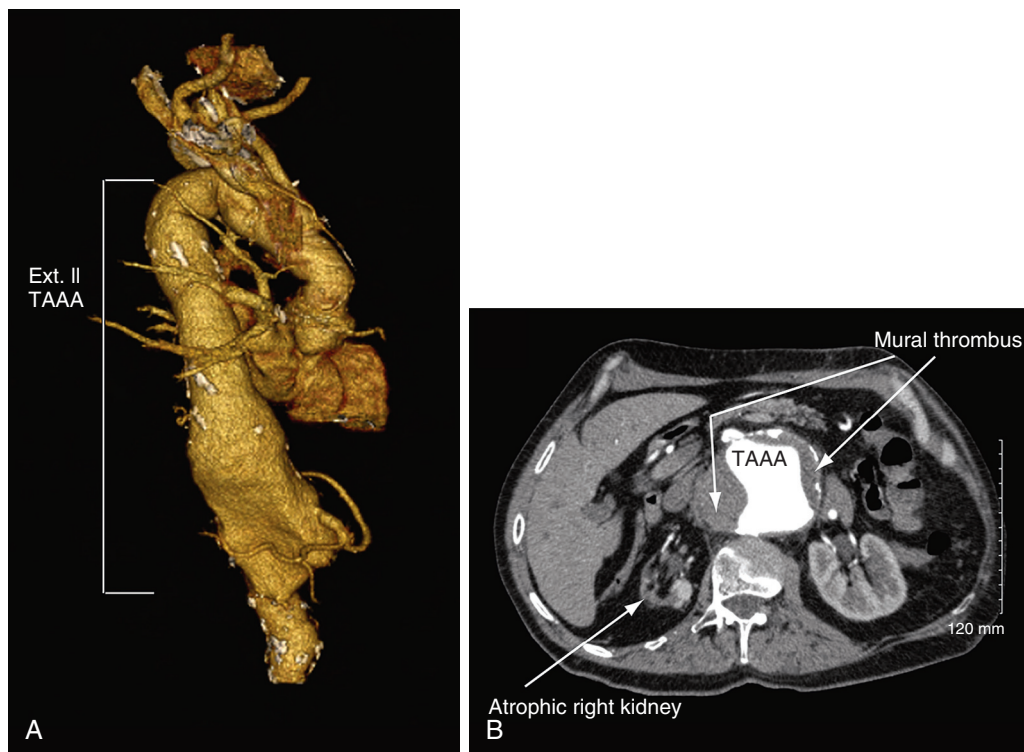


FIGURE 69-7 ■ Three-dimensional reconstruction (A) and axial contrast-enhanced computed tomographic image (B) of a thoracoabdominal aortic aneurysm (TAAA). Note that the aneurysm is lined with thrombus and that the right kidney is severely atrophic (arrows). (From Vaughn SB, LeMaire SA, Collard CD: Case scenario: anesthetic considerations for thoracoabdominal aortic aneurysm repair. *Anesthesiology* 115:1093–1102, 2011, Fig. 1. Used with permission.)

evidence B). Although not expressly recommended for the distal aorta, elective repair of the proximal aorta is recommended when the rate of dilation exceeds 0.5 cm per year; it is reasonable to follow this recommendation in distal aortic repairs also, because such rapid growth indicates an unstable aneurysm.

Symptoms

When specific symptoms are present, they are usually related to aneurysmal expansion and compression of surrounding structures or to malperfusion related to aortic dissection. The onset of symptoms is usually considered an indication of impending rupture or significant malperfusion and should prompt urgent evaluation. Pain, the most common symptom, may be located in the chest, back, abdomen, or left flank; it may be described as a sharp or stabbing acute pain or as refractory pain. However, pain may be chronic and the cause poorly understood in these typically older patients.

Myriad other symptoms can arise, and whenever possible, a careful medical history should be obtained from each patient. In rare cases, fistulas can develop in patients with distal aortic aneurysm, and unexplained bleeding may be present. Dysphagia can result from compression of the esophagus, whereas coughing, wheezing, or pneumonitis can result from impingement on the trachea or proximal bronchi; hemoptysis may result from erosion into these structures. Hoarseness may result from partial vocal cord paralysis if the recurrent laryngeal nerve is

compromised. Pressure from expanding aneurysms can erode spinal bodies (often resulting in pain) or the bowel wall (causing gastrointestinal bleeding). Duodenal obstruction may occur through related compression. In rare cases, jaundice can result from compression of the biliary tract. Compression of the inferior vena cava or iliac vein can result in distal venous stasis and can present as an abdominal bruit, with widened pulse pressure and edema, and may result in heart failure.

Additional symptoms related to embolization, frank rupture, or either acute-onset dissection or expanding chronic dissection can result. Plaque and thrombus may embolize distally, causing occlusion and thrombosis of the visceral, renal, or lower extremity branches and subsequent malperfusion. Shock, refractory hypertension, or rapid aortic expansion may indicate existing or pending rupture; DTAAAs tend to rupture into the pleural cavity, often resulting in severe hemorrhagic shock. Spontaneous paraplegia; abdominal pain; cold, blue, or painful extremities; nausea; vomiting; and incontinence or abnormal urination can be signs of malperfusion caused by aortic dissection.

The assessment of possibly aneurysm-related symptoms is essential to developing an appropriate management plan. Patients who develop symptoms undergo surgical repair regardless of aneurysm diameter. The most common indication for emergent repair of a TAAA is aortic rupture or an acute dissection superimposed on an existing chronic dissection; often such dissection rapidly progresses to aortic rupture. Although emergent

repair is well understood to carry greater operative risk than does elective repair, any inappropriate delay of repair risks death; appropriate delay includes transfer to an experienced center.

Contraindications to Repair

Contraindications to open repair of the distal aorta are patient-specific and individualized to the experience of each surgeon. In general, patients with limited life expectancy are not candidates for open surgical repair, although aortic repair in survivable forms of cancer may be warranted before its treatment. Although patients at prohibitive risk of open surgical repair are sometimes offered hybrid endovascular repair, such repair in patients with TAAA involves invasive debranching of the visceral arteries and is generally poorly tolerated by patients, except in a handful of centers.⁶⁸ Operative risk models for TAAA repair commonly identify advanced age as a predictor of early death⁶⁹; operative results in patients 80 years and older tend to be somewhat poor.⁷⁰ In addition, patients should be presented with information regarding the risk of developing life-altering complications such as stroke, renal failure resulting in dialysis dependence, and paraplegia. Other patient-specific comorbid risks include chronic renal insufficiency, chronic obstructive pulmonary disease, heart failure, and coronary artery disease.^{71,72}

STRATEGY FOR REPAIR

Preoperative Evaluation

Comorbidities that are typically considered predictive of operative risk should be carefully evaluated and modified whenever possible to mitigate risk; similarly, preoperative evaluation of patients' physiologic reserve is critical to obtaining a beneficial outcome. Except in those patients who require emergent repair, all patients should undergo a thorough preoperative evaluation emphasizing cardiac, pulmonary, and renal function, as well as a careful review of imaging studies. As needed, additional studies may be warranted; in patients identified as high risk for carotid artery disease, carotid Doppler ultrasonography is warranted, and potential clotting problems or cirrhosis may be evaluated with coagulation and liver function tests.

Cardiac Function

Patients need significant cardiac reserve to tolerate thoracic aortic clamping. Transthoracic echocardiography and electrocardiography are routinely used to assess cardiac function. Patients with an ejection fraction less than 30% or with symptoms of coronary artery disease should additionally undergo cardiac catheterization or, when necessary, a noninvasive assessment of myocardial perfusion (such as dobutamine echocardiography or a dipyridamole thallium scan). When significant coronary artery disease is identified in an elective surgical candidate, myocardial revascularization is recommended before aortic replacement. Patients who have already undergone coronary artery revascularization should be

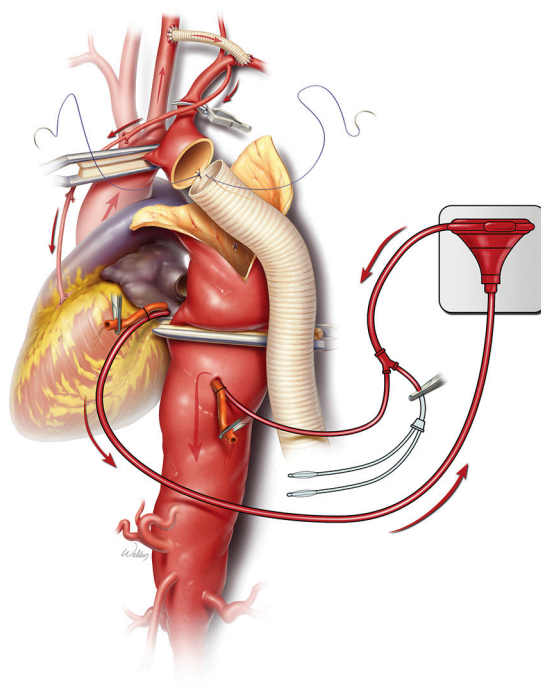


FIGURE 69-8 ■ Drawing of a thoracoabdominal aortic aneurysm repair in a patient with a patent left internal thoracic artery-to-left anterior descending coronary artery graft. The proximal anastomosis is being performed while the aorta is clamped between the left common carotid and subclavian arteries. Myocardial perfusion is maintained through the carotid-subclavian bypass graft. Thus, the potential for causing cardiac ischemia during repair is mitigated. (From Jones MM, Akay M, Murariu D, et al: Safe aortic arch clamping in patients with patent internal thoracic artery grafts. *Ann Thorac Surg* 89:e31–32, 2010, Fig. 2. Used with permission. Copyright Society of Thoracic Surgeons.)

carefully assessed; if the left internal thoracic artery has been used to revascularize the heart, and if the aortic clamp may need to be placed proximal to the origin of the LSCA (a common placement site for DTAA and extent I and II TAAA repairs), a left carotid-to-subclavian artery bypass (Fig. 69-8) can be performed before aortic replacement to avoid myocardial ischemia.⁷³

Pulmonary Function

Sufficient pulmonary function is needed to tolerate the single-lung ventilation that is commonly used in distal aortic repair; pulmonary complications are the most common form of postoperative complication and typically affect 30% or more of patients with distal aortic repair. In most patients, lung function is assessed with pulmonary function studies, including forced expiratory volume in 1 second (FEV₁) and arterial blood gas analysis. All patients with an FEV₁ greater than 1.0 liters and a blood carbon dioxide partial pressure (PCO₂) less than 45 mm Hg are considered satisfactory surgical candidates. Whenever possible, in patients with an FEV₁ less than 1.0 liter or a PCO₂ of greater than 45 mm Hg, pulmonary function is optimized over a period of 1 to 3 months by means of smoking cessation, bronchodilator therapy, weight loss, an appropriate exercise regimen, and

pulmonary rehabilitation. Optimizing lung function preoperatively is thought to lessen postoperative pulmonary complications. In addition, diaphragm-sparing techniques may be selectively used in patients with particularly poor pulmonary function.

Renal Function

Preoperative renal dysfunction is an important predictor of early postoperative mortality and morbidity after aortic replacement.^{48,71} Unfortunately, CT imaging (which is often used in planning aortic repair) may adversely affect renal function through the necessary use of nephrotoxic contrast agents. In patients with borderline renal function, preventive measures are taken before imaging studies are conducted. A solution of 5% dextrose and Ringer lactate solution with 25 g/liter mannitol and 1 amp/liter sodium bicarbonate may be administered intravenously before image acquisition. In addition, acetylcysteine may be administered before and after such studies to further reduce the risk of contrast-induced nephropathy. When possible, after CT scanning or aortography, surgery is delayed for 24 hours or longer until renal function has returned to baseline.

Evaluation of Imaging Studies

Essential to forming an operative strategy, available imaging studies should be carefully reviewed and, if necessary, additional imaging studies should be obtained to clarify findings. The diameter of the aorta throughout the diseased and nonaneurysmal portions is established. Potential sites for aortic clamping and cannulation are reviewed for calcification, dissection, and mural thrombus. Close attention is paid to anatomic variants, such as a retroaortic left renal vein, as well as any previous use of the left internal thoracic artery to provide coronary revascularization. The locations of particularly large intercostal arteries are noted. Branching vessels, such as the visceral and renal arteries, are carefully assessed for stenotic origins, their spatial orientation relative to each other, and, in cases of chronic aortic dissection, whether blood is supplied by the true lumen, false lumen, or both.

Anesthesia

It is crucial to establish communication among the surgeon, anesthesiologist, and perfusionist during distal aortic repair. Adequate intraoperative monitoring and venous access must be ensured because patient hemodynamics can fluctuate greatly during aortic clamping and unclamping. Patients generally undergo placement of a right radial or brachial arterial line, a pulmonary artery catheter, and a large-bore central venous catheter that permits rapid fluid administration. Whenever blood flow through the LSCA will be compromised by the site of aortic clamping, the arterial catheter is placed in the right radial artery. To monitor temperature, a probe is placed in the patient's nasopharynx.

A method for anesthesia induction is specifically chosen according to each patient's hemodynamics, cardiac contractile function, and whether or not motor-evoked

potential monitoring of the spinal cord will be used. Muscle relaxation is typically achieved by using pancuronium bromide. Because the presence of many muscle relaxants will not allow a proper motor-evoked potential response to be generated, shorter acting muscle relaxants are used during intubation and then reversed. A double-lumen endobronchial tube or left mainstem bronchial blockade is used to orotracheally intubate all patients and permit selective deflation of the left lung; this ensures adequate exposure of the descending thoracic aorta and reduces the chance of damage to the lung from handling while the patient is heparinized. If the tracheobronchial anatomy becomes distorted from pressure exerted by a large aneurysm, a standard left-sided double-lumen tube will be difficult to use; in this case, a right-sided tube, placed with fiberoptic guidance, will usually work. In extent IV TAAA repairs, left lung isolation is not as critical to obtaining sufficient exposure.

Attention to volume status by the operative team during aortic replacement is important for avoiding wide fluctuation in blood pressure and, perhaps, distal organ ischemia. Frequent arterial blood gas analysis and close monitoring of serum electrolytes and hematocrit are necessary. To maintain filling pressures, hydration with crystalloid solutions begins at the start of the operation. Mannitol may also be administered at the induction of anesthesia to help maintain diuresis and enhance renal perfusion. Aortic cross-clamp placement causes a large increase in afterload. During aortic cross-clamping, all attempts should be made to keep systemic blood pressure within a normal range and thus avoid hypertension related to clamping. As needed, vasodilating agents such as nitroglycerin, nicardipine, and nitroprusside may be used. When left heart bypass is used as an adjunct, an effective means of blood pressure control in the vessels above the proximal clamp site is to increase flow through the left heart bypass circuit. Blood loss is carefully monitored, and lost blood is replaced. Reinfusion of shed blood recycled from a cell-saving device is useful in decreasing the amount of transfused blood and blood products. During periods when blood loss is extensive (such as when the aorta is being opened), rapid reinfusion permits the use of unwashed, filtered whole blood. Although the meticulous reinfusion of shed blood may at times avoid the need for transfusion, in many cases, fresh-frozen plasma and platelet transfusion are used to restore adequate clotting function and thus facilitate hemostasis.

As repair nears completion, the hypotension that usually occurs when the aortic clamp is removed is avoided or mitigated by discontinuing the use of vasodilating agents shortly before unclamping and also by infusing fluids to account for any volume lost during the repair. Typically, one can achieve hypervolemia with rapid fluid administration just before aortic clamp release. A sodium bicarbonate infusion may be used to treat any acidosis encountered during aortic cross-clamping. Whenever possible, at the conclusion of repair, the double-lumen tube may be exchanged with a single-lumen one; however, this is not always possible at this time because upper airway edema is common, so this exchange is often delayed for several hours.

Positioning

To facilitate adequate exposure, the patient is positioned on a beanbag in a modified right lateral decubitus position with the shoulders at 60 to 80 degrees and the hips flexed to 30 to 40 degrees from horizontal. To maintain the patient's position, the beanbag is suction-deflated and secured as the left arm is elevated and extended at an angle above the shoulders, similar to a freestyle swimming stroke position. Sterile draping should allow access to the entire left chest, abdomen, and both groins. Although removing a rib was common in past eras, we now avoid doing so whenever possible and instead use a table-mounted retractor to provide sufficient exposure during the repair. To reduce the risk of graft and surgical wound infection, we often soak the graft in an antibiotic solution before use; whenever possible, prophylactic broad-spectrum intravenous antibiotics are administered 1 hour before skin incision.

Multimodal Strategy Based on Extent of Repair

Despite the significant innovation that has taken place in the field of aortic surgery over the past 6 decades, successful repair remains challenging; this is largely because aortic clamping causes downstream ischemia, which may adversely affect multiple organs. Although the strategy of repair (Box 69-1) remains largely dictated by the extent of repair, we routinely use moderate heparinization (1 mg/kg), mild passive hypothermia (32–34°C), the aggressive reattachment of segmental arteries (especially

those between T8 and L1), sequential aortic clamping when possible, and cold crystalloid renal perfusion whenever the renal ostia are accessible.

Aortic repair has grown to encompass novel adjuncts designed to mitigate specific surgical morbidities, such as the major causes of morbidity and mortality in distal aortic repair—renal ischemia and spinal cord ischemia. The development and use of surgical adjuncts like left heart bypass, visceral perfusion, and cerebrospinal fluid drainage have significantly reduced the mortality and morbidity rates traditionally associated with extensive aortic repair.⁷⁴

Left Heart Bypass

Left heart bypass (LHB) is a well-supported strategy to provide distal aortic perfusion and reduce ischemic conditions.⁴³ We typically reserve LHB for patients undergoing extensive TAAA repairs (extent I and II TAAA repairs), as well as for select patients with poor cardiac function, in whom LHB effectively unloads the left ventricle and improves their ability to tolerate aortic clamping. As the proximal anastomosis is performed, we use a closed-circuit in-line centrifugal pump (without a warming device, oxygenator, or cardiotomy reservoir) to deliver isothermic oxygenated blood distal to the aortic segment being repaired. After heparin is administered (1 mg/kg), cannulas (24 Fr angled-tip cannulas) are placed first in the left inferior pulmonary vein to enter the left atrium and second in the distal descending thoracic aorta or the left femoral artery. Our preferred approach is cannulating the distal descending thoracic aorta a few centimeters proximal to the origin of the celiac axis, because this approach eliminates the need for, and potential risks associated with, femoral artery cannulation. After LHB is initiated (at a modest flow of 500 mL/min), a straight, padded aortic cross-clamp is applied to the aorta at the previously identified proximal site. A second clamp, generally a large Crawford clamp, is then placed across the mid-descending thoracic aorta to isolate the proximal descending segment. With a goal mean arterial pressure of 80 mm Hg, flows of LHB are generally increased to 1.5 to 2.5 liter/min. As mentioned earlier, using LHB allows rapid adjustment of the proximal arterial pressure and minimizes the need for pharmacologic intervention.

BOX 69-1 Current Multimodal Strategy for Surgical Repair of Distal Thoracic Aortic Aneurysms

ALL EXTENTS OF DISTAL AORTIC REPAIR

- Mild passive hypothermia (32–34°C, nasopharyngeal)
- Moderate heparinization (1 mg/kg)
- Aggressive reattachment of intercostal and lumbar arteries (especially between T8 and L1)
- Sequential aortic clamping (when possible)

ALL THORACOABDOMINAL AORTIC REPAIRS

- Cold renal perfusion (4°C) when renal ostia are accessible

CRAWFORD EXTENT I AND II THORACOABDOMINAL AORTIC REPAIRS AND SELECT OTHER REPAIRS

- Cerebrospinal fluid drainage
- Left heart bypass (during proximal anastomosis)
- Selective perfusion of celiac axis and superior mesenteric artery (following completion of left heart bypass)

CERTAIN EXTENSIVE OR HIGHLY COMPLEX AORTIC REPAIRS

- Hypothermic circulatory arrest
- Elephant trunk completion or reversed elephant trunk repair
- Extraction, full salvage, or partial salvage of prior endovascular repair

Visceral Protection

On completion of the proximal anastomosis, the LHB circuit is generally discontinued; however, typically, the LHB circuit is then converted such that it can be used to provide selective visceral perfusion with minimal added risk. As is the case with LHB, the direct perfusion of visceral arteries is often limited to those patients with extent I or II TAAA repairs. Within the origins of the celiac and superior mesenteric arteries, 9 Fr balloon perfusion catheters are used to perfuse these respective arteries with isothermic oxygenated blood, using a Y-branch off of the arterial return tubing of the LHB circuit. This greatly minimizes the total mesenteric and hepatic ischemic time during these complex aortic repairs. Although

evidence supporting this technique is lacking,⁴³ we believe its potential benefits, such as the reduced risk of postoperative coagulopathy and bacterial translocation from the bowels, outweigh any added risk. Additional techniques to enhance visceral perfusion include endarterectomy of the exposed origins, stenting with balloon-expandable stents, and replacing unsalvageable or widely displaced arteries with branch grafts.

Spinal Cord Protection

During distal aortic replacement, a large number of intercostal and lumbar arteries are sacrificed; this sacrifice is greatest during the most extensive repair (i.e., extent II TAAA repair). This loss of spinal-perfusing arteries (Fig. 69-9) is coupled with substantial fluctuations in blood pressure that are related to aortic clamping and

enhances the risk of spinal cord ischemic deficits, namely paraplegia or paraparesis. Thus, in patients who undergo the most extensive distal aortic replacement procedures (extent I and II TAAA repairs), we routinely use cerebrospinal fluid (CSF) drainage. We also use this adjunct in select patients undergoing less extensive repairs if they have previously had portions of their descending thoracic or abdominal aorta replaced. Current guidelines recommend the use of CSF drainage during both open and endovascular repairs in patients at high risk of developing paraplegia (Class I recommendation, level of evidence B).⁴³ Known risk factors for paraplegia include advanced age, comorbid renal dysfunction, emergency surgery, aortic rupture, acute dissection, extensive repair, and extended duration of surgery, as well as the position of the aortic cross-clamp, prior abdominal aortic surgery, and exclusion of the hypogastric artery.⁴³

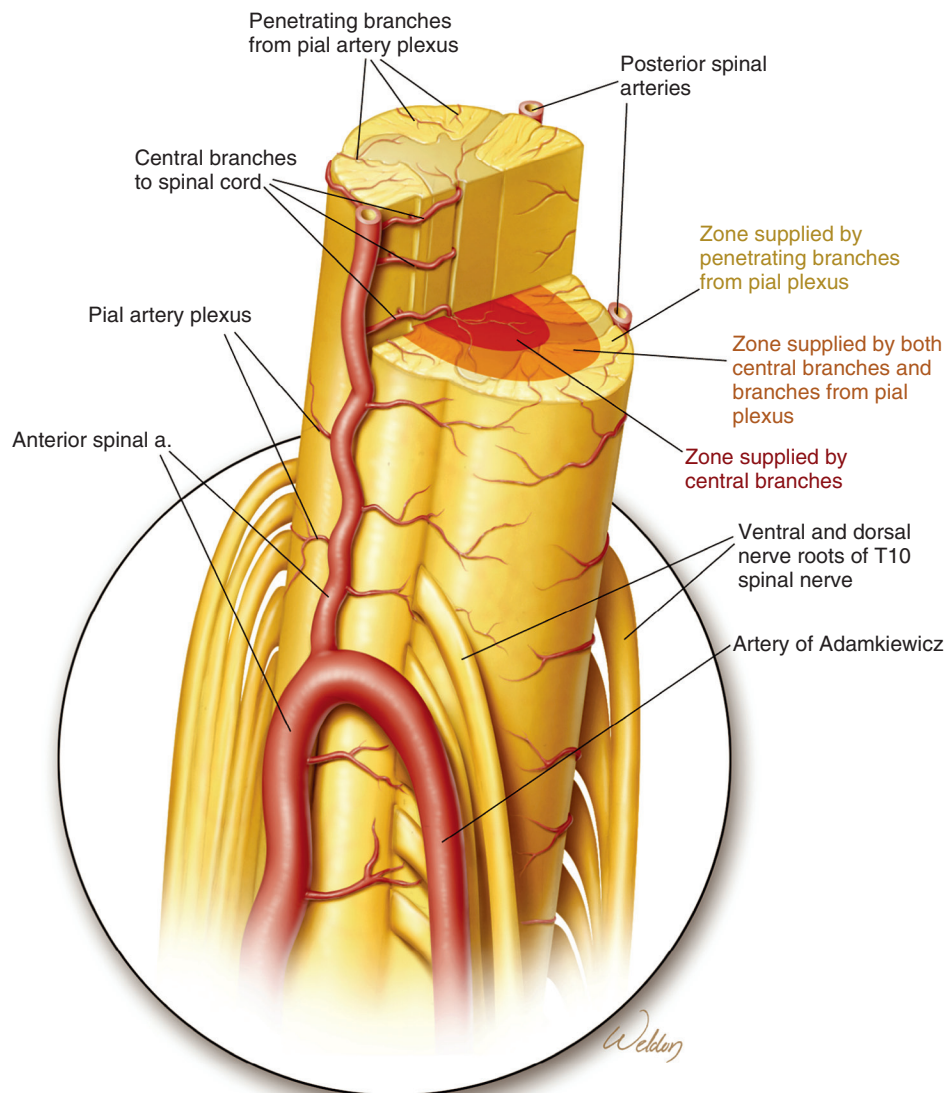


FIGURE 69-9 ■ Illustration showing spinal cord blood supply. A single anterior spinal artery supplies the anterior two thirds of the spinal cord, and two posterior spinal arteries supply the posterior third of the spinal cord. The artery of Adamkiewicz is the largest radicular artery supplying the spinal cord and is considered to play an integral role in preserving spinal cord function. (From Vaughn SB, LeMaire SA, Collard CD: Case scenario: anesthetic considerations for thoracoabdominal aortic aneurysm repair. *Anesthesiology* 115:1093–1102, 2011, Fig. 5. Used with permission.)

CSF drainage enhances spinal perfusion by reducing competing CSF pressure. After induction of anesthesia, an 18-gauge intrathecal catheter is placed through the second or third lumbar space. The catheter permits passive drainage of CSF while allowing the CSF pressure to be carefully monitored during the operation and afterward. During repair, we aim to achieve a target pressure between 8 and 10 mm Hg. The CSF drain is left in place for approximately 48 hours after the aortic repair because spinal cord ischemia may occur immediately or in a delayed fashion postoperatively. Careful postoperative monitoring is necessitated and even brief periods of hypotension should be avoided. The benefits of this CSF drainage in extensive aortic repair have been confirmed in a prospective, randomized trial performed by our group.⁷⁵ Significant drawbacks associated with CSF drainage include intracranial bleeding, paraspinal hematoma, and meningitis, all of which can result in death. Less serious complications include a related headache, which is the most common complaint.⁷⁶

In addition, we routinely reattach pairs of large intercostal arteries, particularly if they exhibit minimal back-bleeding, to restore spinal cord perfusion. Although some groups routinely use motor-evoked or somatosensory-evoked potentials to monitor the spinal cord throughout the operation, we have not adopted this practice.^{77,78} Such approaches monitor spinal cord motor neuron function during aortic replacement to guide the selection of specific intercostal arteries for reattachment. These monitoring techniques also provide general indications to either increase spinal perfusion pressure or increase the rate of CSF drainage. Monitoring motor-evoked potentials requires preserving basal motor function, and thus, as mentioned previously, commonly used anesthetic agents to relax muscle function interfere with testing, so alternate strategies must be used. Additional strategies to preserve spinal cord function include direct epidural infusion of cold perfusate to induce regional spinal hypothermia or reducing spinal metabolism with the use of naloxone and other barbiturate-based agents. However, none of these strategies is as widely used or as highly recommended by current guidelines as is CSF drainage.

Renal Protection

Current guidelines for thoracic aortic repair⁴³ support both the administration of intraoperative mannitol (Class IIb recommendation, level of evidence C) and direct perfusion of the renal arteries with cold crystalloid or blood (Class IIb recommendation, level of evidence B). We liberally use both of these strategies. Our first randomized clinical trial compared cold crystalloid with isothermic blood and showed that cold renal perfusion mitigates acute renal dysfunction.⁷⁹ More recently, our second randomized clinical trial compared cold blood perfusion with cold crystalloid perfusion and found no benefit to using cold blood⁸⁰; therefore, to avoid potential disadvantages associated with using cold blood, we generally use cold crystalloid perfusion. Whenever the renal ostia are accessible, we insert 9 Fr balloon perfusion catheters and use these to deliver 200- to 400-mL boluses of cold (4°C)

lactated Ringer solution (prepared with 12.5 g/liter mannitol and 125 mg/liter methylprednisolone) every 15 to 20 minutes. Careful monitoring is needed to ensure that the patient is not overloaded with fluid or overcooled. In patients with a small arterial orifice, branch-vessel dissection, or atherosclerotic occlusive disease, it may be challenging to insert perfusion catheters into the renal arteries. A 6 Fr catheter, rather than the standard 9 Fr catheter, may be used in patients with small renal ostia. Catheters should be used with great care so as to avoid perforating or dissecting the renal arteries; similarly, overexpansion of catheter balloons can rupture these arteries. Similar to its use in visceral arteries, endarterectomy or stenting (or both) may be needed to improve renal perfusion; however, the risk of perforation or rupture is particularly high after endarterectomy. Bleeding related to right renal artery perforation is difficult to identify; the blood flows into the right retroperitoneum. Any unexplained hypovolemia after blood flow is restored to the visceral arteries should prompt a careful evaluation of the mesentery and retroperitoneal anatomy to rule out branch-vessel rupture. If small and readily accessible, the perforation may be sutured; if extensive or multiple perforations are present, a replacement branch graft may be needed.

Hypothermia

Although Kouchoukos and others^{81,82} routinely use deep hypothermic circulatory arrest (HCA) during DTA and TAAA repair, we prefer to use mild permissive hypothermia (32°C to 34°C) as our standard approach. Deep HCA (typically conducted between 15°C and 18°C) may introduce risks, namely coagulopathy, cold injury to the lung, retraction injury to a heparinized lung, adult respiratory distress syndrome, and an enhanced risk of stroke. We limit the use of deep HCA to scenarios where aortic clamping would be extremely challenging or generate added risk, such as rupture, aneurysms that are prohibitively large or extend into the distal transverse aortic arch (such as a “mega-aorta”), or prior endovascular repair that hinders clamping. Additional factors that may limit aortic clamping in select patients include severe atherosclerosis or calcification (i.e., porcelain aorta) and large thrombus.

When HCA is necessary, cardiopulmonary bypass is initiated by establishing venous drainage, using a 28 Fr to 32 Fr, long, multiholed cannula inserted into the left femoral vein and positioned in the right atrium. Correct positioning is crucial, and this is verified by transesophageal echocardiography. Vacuum-assisted venous drainage is initiated at flows of 1.8 to 2.4 liter/min/m² or 50 mL/min/kg. Although a cannula may be placed in the left atrial appendage or the pulmonary artery to prevent left ventricular distention, we prefer to use an angled cannula (20 Fr or 22 F) that is connected to a Y-branch of the venous line and placed through the inferior pulmonary vein into the left atrium.

The location of the return cannula depends on patient-specific factors. In older patients with severe atherosclerosis or thrombus, a 22 Fr angled cannula is placed in the lower descending thoracic aorta, whereas in younger

patients with minimal atherosclerosis, the arterial return cannula is a 20 Fr or 22 Fr straight cannula placed in the left femoral artery. Other return cannulation sites include the left common carotid artery or the left axillary artery. As systemic cooling is initiated, we administer methylprednisolone (5 to 10 mg/kg), sodium thiopental (10 to 15 mg/kg), lidocaine (100 mg), and a short-acting beta blocker for added protection. Circulatory arrest is initiated once the patient has been cooled to electrocerebral silence (usually at a nasopharyngeal temperature of 15°C to 18°C). The aneurysm is then opened, and the proximal anastomosis is constructed. Additional protective adjuncts are not used during repair because the profound systemic hypothermia achieved confers sufficient protection to downstream organs. On completion of the proximal anastomosis, the arterial line is connected to a side

branch of the graft; the main graft is then de-aired and clamped distal to the side branch, permitting pump flow to be restored to the upper body, and the remainder of the aortic repair is performed.

OPERATIVE TECHNIQUE

Exposure

DTAAs are repaired through a left thoracotomy made after single right-lung ventilation is initiated (Fig. 69-10). Commonly, this is done by entering through the sixth intercostal space; as needed, the fifth intercostal space may be used to enhance exposure of the distal aortic arch in case of rupture or large aneurysm involving the

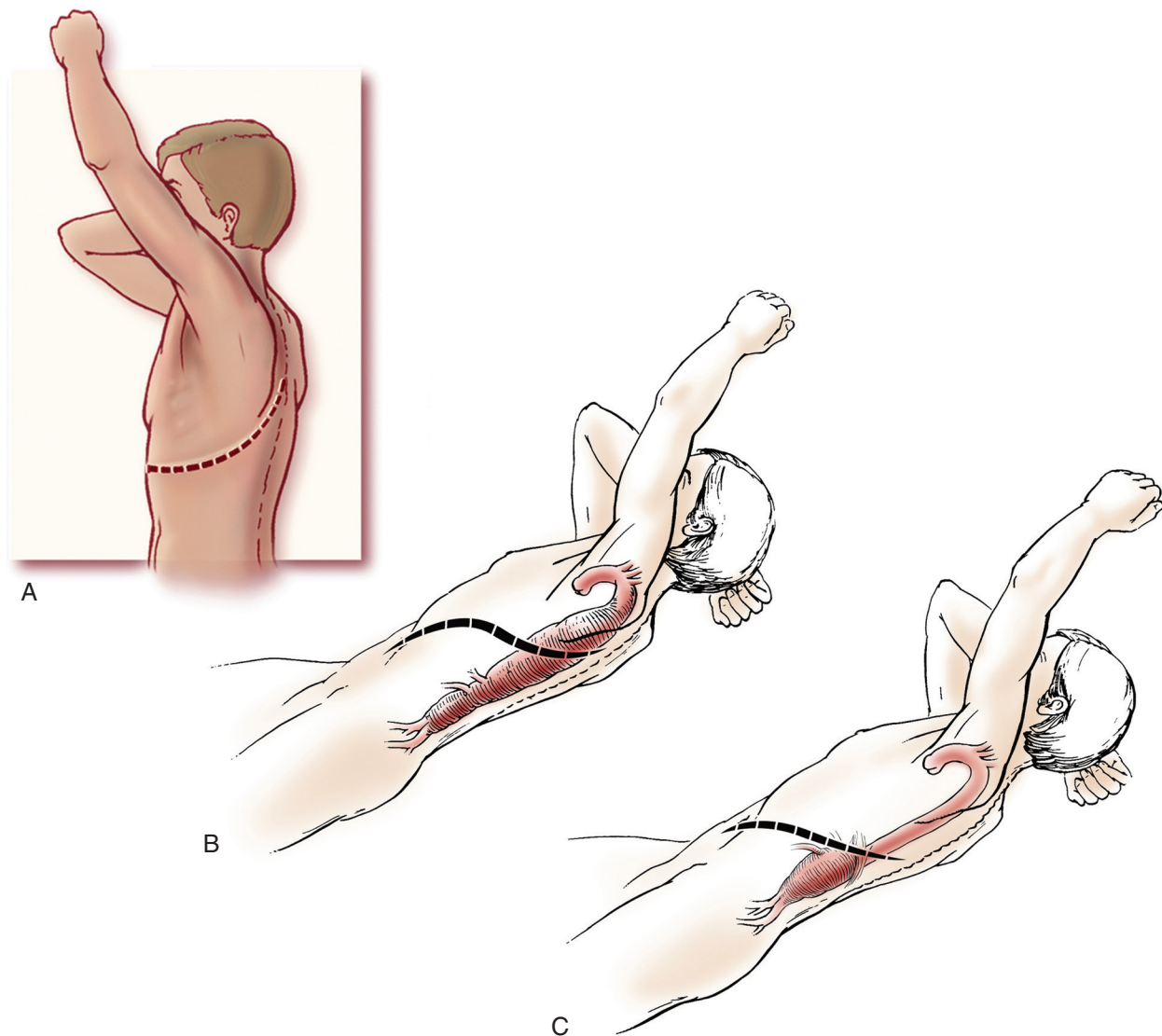


FIGURE 69-10 ■ Approaches to exposure in descending thoracic and thoracoabdominal aortic repairs of different extents. The patient is positioned in a modified right lateral decubitus position that optimizes exposure of the descending thoracic and thoracoabdominal aorta while also facilitating exposure of the femoral arteries, if needed. **A**, A lateral thoracotomy is used for descending thoracic aortic repairs. **B**, For Crawford extent I, II, and III thoracoabdominal aortic repairs, a curvilinear incision is made. **C**, For Crawford extent IV thoracoabdominal aortic repairs, a more linear oblique incision suffices. (Reproduced with permission from Baylor College of Medicine.)

proximal descending thoracic aorta. For extensive repairs, such as extent I and II TAAA repairs, the incision is extended across the costal margin and into the abdomen and commonly terminates at the level of the umbilicus; if further exposure is necessary, this incision may be extended to address iliac artery disease. For the less extensive extent III repair, the seventh or eighth intercostal space is entered, and the incision is then curved into the abdomen. To prevent tissue necrosis, acute angulations near the costal margin should be avoided. For the predominantly abdominal extent IV repair, a straight oblique incision is made through the ninth or tenth interspace to better control the thoracic aorta. As noted previously, we generally do not remove a rib to increase exposure.

For TAAA repairs, we use a transperitoneal approach to perform medial visceral rotation. Equally acceptable, a retroperitoneal approach may be used, but our preference is for a transperitoneal approach because it enables direct evaluation of the bowel and spleen before and after aortic repair. Electrocautery is used to dissect along the line of Toldt, and the diaphragm is divided circumferentially so as to leave a 3- to 4-cm rim of diaphragm along the lateral and posterior chest wall. One or two retraction sutures are placed along the edge of the divided diaphragm on the cardiac side. Exposure generally continues distally into the intra-abdominal aorta and, when necessary, to the aortic bifurcation. The origin of the left renal artery is identified, and all attempts are made to keep the planned aortotomy incision posterior to the left ureter and gonadal vein.

Proximal Anastomosis

For patients undergoing DTAA (Fig. 69-11) or extent I or II TAAA repair (Fig. 69-12; see Video 69-1), the proximal clamp site is typically prepared in the most proximal aspect of the descending thoracic aorta, just distal to the origin of the LSCA. During preparation of the proximal clamp site, the ligamentum arteriosum is often divided, and the vagus and recurrent laryngeal nerves are identified and protected; not infrequently, the vagus and left recurrent laryngeal nerves are adherent to the aortic wall and are at risk of injury. Preserving the left recurrent laryngeal nerve is particularly important in patients with compromised pulmonary function. In cases of postoperative hoarseness, vocal cord paralysis should be suspected; if it is confirmed by endoscopic examination, patients should be offered restorative treatment via direct cord medialization.

If possible, the proximal clamp is placed distal to the LSCA to preserve its contribution to spinal cord flow. As needed, however, the proximal aortic clamp may be positioned between the left common carotid artery and the LSCA (a separate bulldog clamp is applied here; this alternate approach is helpful when there is a large distal arch aneurysm). In extent III TAAAs, the proximal clamp site is prepared more distally, corresponding to a lower incision made through the seventh or eighth intercostal space. For extent IV TAAA repairs, the proximal clamp is placed just superior to the diaphragm, and the proximal anastomosis is typically done end to end at the level of

the diaphragm or as a bevel that lies behind the origins of the visceral arteries.

The distal aortic clamp site is often located at the junction of the upper and middle thirds of the descending thoracic aorta and is prepared anterior to the hemiazygos and intercostal veins; a few of these veins may be clipped for safe positioning of the distal clamp. A distal clamp is rarely used during DTAA repair, permitting an open distal anastomosis to suitable aortic tissue; consequently, only the proximal clamp site is prepared.

In extensive distal aortic repair (extents I and II TAAA repairs), LHB is initiated, and the isolated aortic segment is confirmed to be unpressurized. This segment is then opened longitudinally with electrocautery, and the aneurysmal wall edges are retracted with size 0 silk sutures.

As the aorta is opened, it is cleared of any thrombus or debris. Typically, in DTAA and extent I and II TAAA repairs, all upper intercostal arteries are oversewn to prevent back-bleeding, thereby reducing blood loss and “steal” from the spinal cord.

The proximal descending thoracic aorta is then transected 2 to 3 cm from the proximal clamp to prepare a cuff of tissue. This cuff is carefully separated from the underlying esophagus so as not to injure or inadvertently incorporate the esophagus into the proximal anastomosis. Injury to the esophagus during the proximal anastomosis can have catastrophic consequences, including the development of a secondary aortoesophageal fistula.

For all extents of repair, an appropriately sized Dacron graft (commonly 20, 22, or 24 mm in diameter) is selected and is sewn end to end to the proximal aortic cuff with continuous 3-0 polypropylene sutures (finer suture, such as 4-0 polypropylene suture, may be needed in patients with connective tissue disorders or other conditions that make the aortic tissue fragile). Because meticulous suturing is needed to achieve hemostasis, the primary suture line is often reinforced circumferentially with either a second layer of continuous suture or with a series of interrupted pledgeted horizontal mattress sutures. If the proximal aortic clamp has been placed between the LSCA and the left common carotid artery, whenever possible, it is now repositioned onto the graft to allow perfusion of the LSCA, which provides collateral circulation to the spinal cord.

In extensive TAAA repair, after the proximal anastomosis is complete, LHB is slowly discontinued; typically, this circuit is now converted to provide isothermic visceral perfusion to the celiac axis and superior mesenteric artery. The distal aortic clamp is removed, and electrocautery is used to open the thoracoabdominal aorta down to the aortic bifurcation. As the distal aortic segment is prepared, any large pieces of thrombus are removed. In patients with chronic aortic dissection, the septum is excised (this is discussed in greater detail later). As the renal ostia become accessible, cold crystalloid is used to perfuse the left and right renal arteries.

Reattachment Strategies and Other Considerations

As mentioned earlier, we aggressively reattach one or more pairs of intercostal or lumbar arteries (segmental

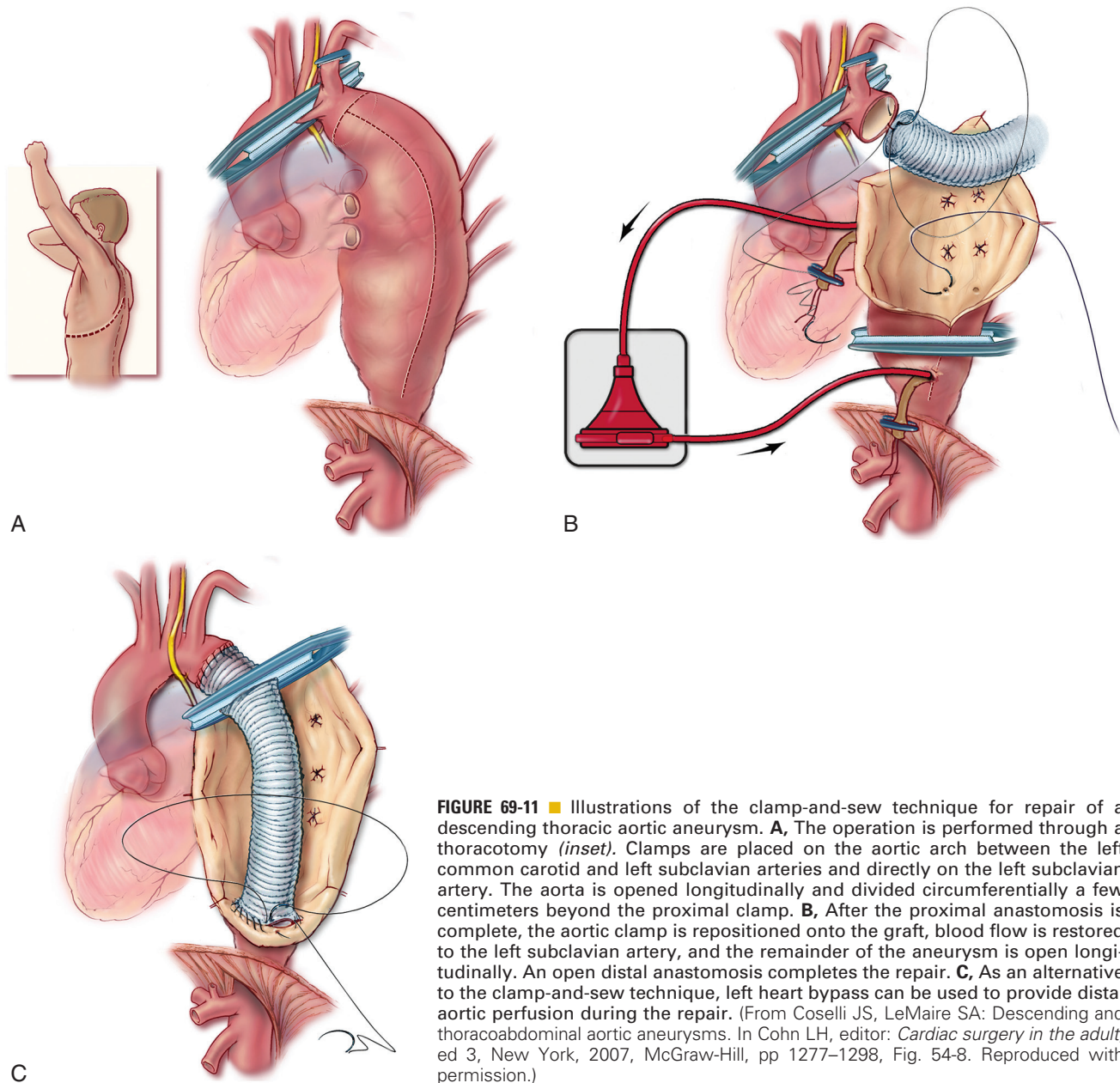


FIGURE 69-11 ■ Illustrations of the clamp-and-sew technique for repair of a descending thoracic aortic aneurysm. **A**, The operation is performed through a thoracotomy (*inset*). Clamps are placed on the aortic arch between the left common carotid and left subclavian arteries and directly on the left subclavian artery. The aorta is opened longitudinally and divided circumferentially a few centimeters beyond the proximal clamp. **B**, After the proximal anastomosis is complete, the aortic clamp is repositioned onto the graft, blood flow is restored to the left subclavian artery, and the remainder of the aneurysm is open longitudinally. An open distal anastomosis completes the repair. **C**, As an alternative to the clamp-and-sew technique, left heart bypass can be used to provide distal aortic perfusion during the repair. (From Coselli JS, LeMaire SA: Descending and thoracoabdominal aortic aneurysms. In Cohn LH, editor: *Cardiac surgery in the adult*, ed 3, New York, 2007, McGraw-Hill, pp 1277–1298, Fig. 54-8. Reproduced with permission.)

arteries) as aortic repair progresses distally; such arteries that are not incorporated into the repair are carefully oversewn to prevent ongoing back-bleeding, which may contribute to spinal cord ischemia. Patent segmental arteries, particularly those between T8 and L1, are carefully inspected. We tend to select segmental arteries that are large and do not exhibit significant back-bleeding, provided that nearby aortic tissue is of suitable quality for anastomosis. Commonly, segmental arteries are reimplanted as a patch by making a small opening in the graft and constructing a side-to-side anastomosis with continuous 3-0 or 4-0 polypropylene suture. Alternatively, a small-diameter interposition graft may be used to incorporate segmental arteries into the repair by end-to-side reattachment. Whenever possible, the proximal aortic clamp is then moved immediately distal to the intercostal

patch (see Fig. 69-12F) to reperfuse that portion of the spinal cord.

The visceral arteries are incorporated into thoracoabdominal aortic repair in accordance with the extent of repair and taking into account factors such as the age of the patient, the presence or likelihood of connective tissue disease, and whether the origins of the arteries are widely displaced from one another. In addition, any stenosis or other disease involving the visceral arteries may necessitate endarterectomy or stenting to improve circulation before incorporation into the overall aortic repair. In extent I TAAA repairs, the visceral arteries are usually incorporated by surrounding them with a beveled distal anastomosis. Similarly, a beveled approach may be used in the proximal anastomosis of select extent IV TAAA repairs. In older patients with degenerative aortic disease

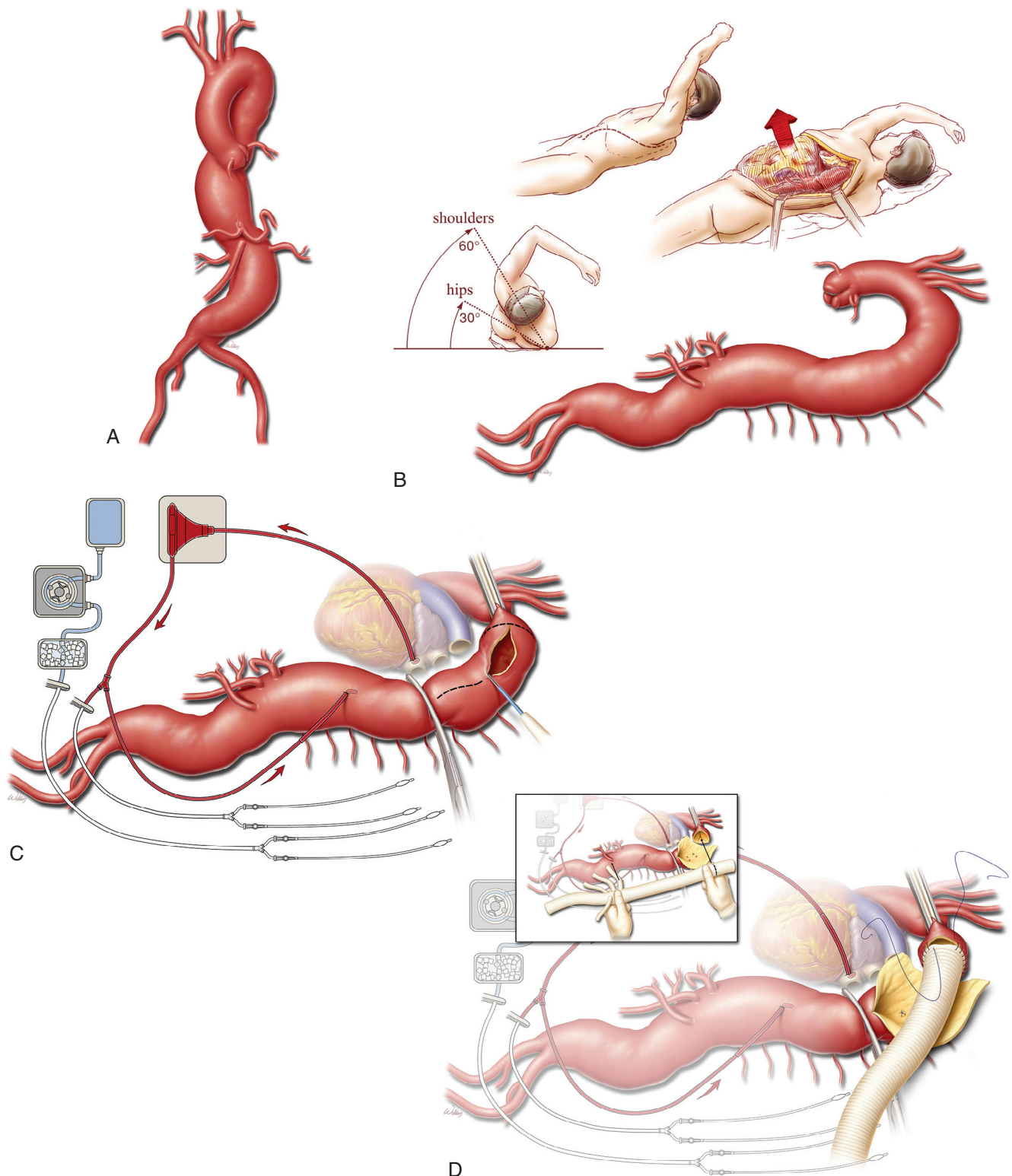


FIGURE 69-12 ■ Illustration of an extent II thoracoabdominal aortic aneurysm repair using a multibranched graft. **A**, A typical patient undergoing such a repair will have an aneurysm extending from the left subclavian artery down to the aortic bifurcation. In this patient, the visceral arteries are widely displaced from each other, making the traditional reattachment approach using a visceral patch difficult. **B**, The chest is entered through the sixth intercostal space. Left medial visceral rotation and circumferential division of the diaphragm enable exposure of the entire thoracoabdominal aorta. The use of table-mounted self-retaining retractors maintains stable exposure throughout the procedure. **C**, Left heart bypass (LHB) is initiated by placing a cannula in the left atrium via a left inferior pulmonary venotomy and then connecting it to the drainage line of the LHB circuit. After LHB flow is initiated, the proximal aortic clamp is placed just distal to the left subclavian artery, and the distal aortic clamp is applied across the mid-descending thoracic aorta. The aortic segment between the two clamps is opened longitudinally by using electrocautery. **D**, After back-bleeding intercostal arteries are ligated, the aorta is transected 2 to 3 cm distal to the aortic clamp and separated from the underlying esophagus. A four-branched aortic graft is tailored by stretching the graft so that it is taut, lining up the origin of the celiac graft with the origin of the left renal artery, and cutting the proximal end of the aortic graft at the point where it reaches the proximal anastomosis site (inset).

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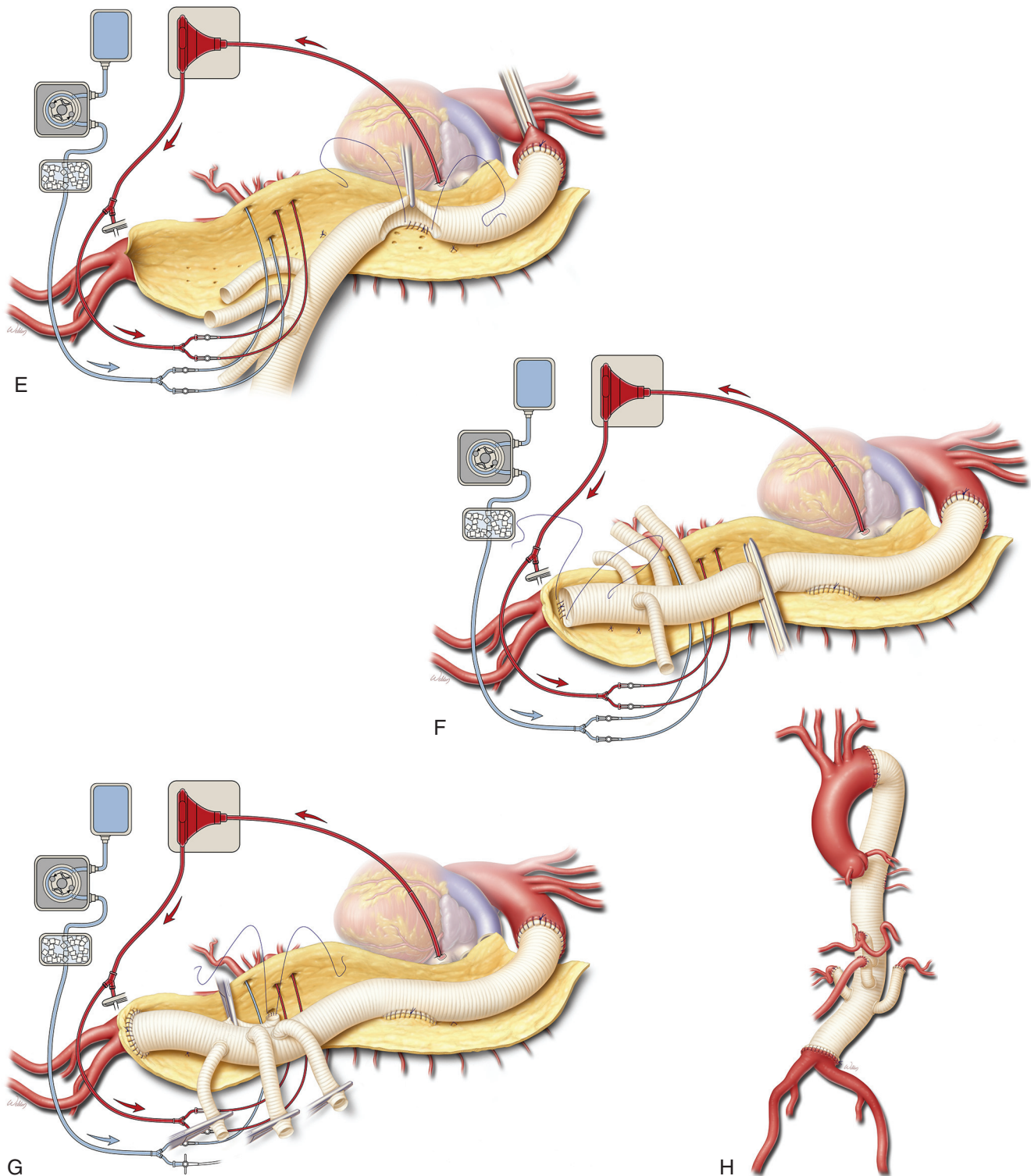


FIGURE 69-12, cont'd ■ E, After the proximal anastomosis is completed, LHB is stopped. The aorta is opened longitudinally down to the aortic bifurcation. The celiac and superior mesenteric arteries are cannulated with the balloon perfusion catheters, and selective perfusion is initiated. The renal arteries are similarly cannulated with balloon perfusion catheters to enable intermittent perfusion with cold crystalloid solution. **F,** The aortic cross-clamp is moved down to the aortic graft distal to the intercostal patch. After the graft is trimmed, the distal anastomosis is performed. **G,** The right renal artery is anastomosed. **H,** The completed repair is shown. (Reproduced with permission from Baylor College of Medicine.)

who are free of connective tissue disorders and whose four vessels are in close proximity to one another, the origins of all four arteries may be reattached in one patch to an oval opening in the graft; in such patients, this is the simplest and most expeditious method of reattachment, and there is only a small chance a patch aneurysm will develop in the near future. Typically, in this approach, the anastomosis is made immediately adjacent to the edges of the ostia of the vessels to reduce the amount of native aortic tissue that is incorporated into the repair.

However, for various reasons, some patients need an alternate strategy for reattachment. For example, patients with connective tissue disorders are at high risk for the late development of patch aneurysms if the inherently compromised residual aortic tissue is not minimized through use of an alternate reattachment strategy. In these patients, as well as in those in whom the visceral vessels are otherwise diseased or anatomically displaced, one or more of the visceral arteries can be individually attached with either separate buttons or small-diameter Dacron grafts sewn to the aortic graft, or with a prefabricated, multi-branched aortic graft (with four pre-sewn branches). Commonly, when the left renal artery is widely displaced from the other visceral branches because of chronic dissection or extensive aneurysm expansion, it is separately reattached on a button of tissue or with a separate branch graft. In addition, in a younger patient with connective tissue disease, we generally use a multibranched graft to reimplant each vessel separately to effectively minimize native aortic tissue. An advantage of using a multibranched graft is that it permits the distal aortic anastomosis to be performed before the visceral branches are reattached; this restores blood flow to the iliac arteries and provides a needed source of collateral perfusion to the at-risk spinal cord. Although the order of reattachment depends on patient-specific anatomy and baseline renal function, the general order is right renal artery, superior mesenteric artery, celiac axis, and left renal artery.

Chronic aortic dissection is relatively common in patients undergoing TAAA repair. Although the operative approach used in these patients is similar to the one used in patients without chronic dissection, there are some key differences to consider. The dissecting membrane within the aorta is excised to locate all important branch vessels and to clearly identify the true and false lumens. If the dissection extends beyond the ostia of the visceral arteries, there are a couple of options. The false lumen can be obliterated with suture or small-diameter intraluminal stents, or the membrane can be fenestrated. Also, because of asymmetrical expansion, the left renal artery commonly becomes widely displaced; a separate opening in the graft can be used to reattach it as a small button, or it can be replaced with a separate branch graft. Care should be taken when constructing the proximal and distal anastomoses to remove a wedge of the dissecting membrane to facilitate perfusion of both true and false lumens.

Distal Anastomosis

Selecting the location of the distal anastomosis depends on the extent of repair and the degree of dilation of the distal aorta, iliac, and femoral vessels. In patients with

chronic dissection, repair is typically limited to those sections with substantial dilation, leaving the residually dissected aortic tissue in place, in the hope of increasing early survival. In DTAA repairs, the graft is typically anastomosed with continuous suture to the distal descending thoracic aorta in an open fashion. In extent I TAAA repairs, the visceral arteries are incorporated into a beveled distal anastomosis. In preparation for the distal anastomosis in extent II-IV repairs, the aortic clamp is moved distal to the site of visceral artery reattachment; this permits visceral-organ reperfusion. The distal anastomosis is then carried out in an open fashion without a clamp (an open-distal technique). If the aorta is of sufficient quality (and without substantial dilation) proximal to the iliac bifurcation, an end-to-end anastomosis is made at this level with continuous suture.

If disease continues beyond the bifurcation, we secure an additional, prefabricated bifurcated abdominal graft to the replacement graft in an end-to-end fashion by using continuous 2-0 or 3-0 polypropylene suture. The limbs of this graft are then anastomosed to the common iliac, external iliac, or common femoral arteries; flow into the internal iliac arteries is preserved whenever possible. As a general guideline, we limit replacement and target a proximal location on each bifurcation that has distal arteries of sufficient quality and caliber. If acute dissection extends beyond the location of the distal anastomosis, the false lumen is obliterated by inclusion within the suture line, effectively directing the blood flow entirely to the true lumen; as mentioned previously, chronic dissections are fenestrated to avoid malperfusion. In addition, as discussed earlier, the use of a four-branched TAAA graft permits the distal aortic anastomosis to be performed before the visceral arteries are reattached, thus facilitating perfusion of the spinal cord.

Elephant Trunk Approaches

Open repairs of extensive aortic aneurysm (i.e., repairs that involve replacing the aorta almost entirely, which are often called “mega-aorta” repairs) require a specialized approach to enable sufficient exposure. Although such repair is performed in a single stage in some centers,⁸³ in our practice these repairs are usually done in two stages and generally with an elephant trunk approach. Traditional elephant trunk repair, as introduced by Borst⁸⁴ and modified by Svensson⁸⁵ and others,⁸⁶ involves a staged approach in which the proximal aorta is replaced during the first operation and the distal aorta is replaced during the second operation (Fig. 69-13). However, if the distal aorta is at risk of rupture, or if the patient has related symptoms, the distal aorta is replaced in the first operation and the proximal aorta is replaced at a later time. This approach is called the reversed elephant trunk (Fig. 69-14), and we first used this approach almost 2 decades ago.⁸⁷

Traditional elephant trunk repairs involve first replacing the ascending aorta and aortic arch (using a standard island or contemporary Y-graft approach) and incorporating a segment of Dacron graft into the distal anastomosis such that it hangs into the proximal descending thoracic aorta. In the recent past, this was commonly done by using an island patch approach to arch replacement and

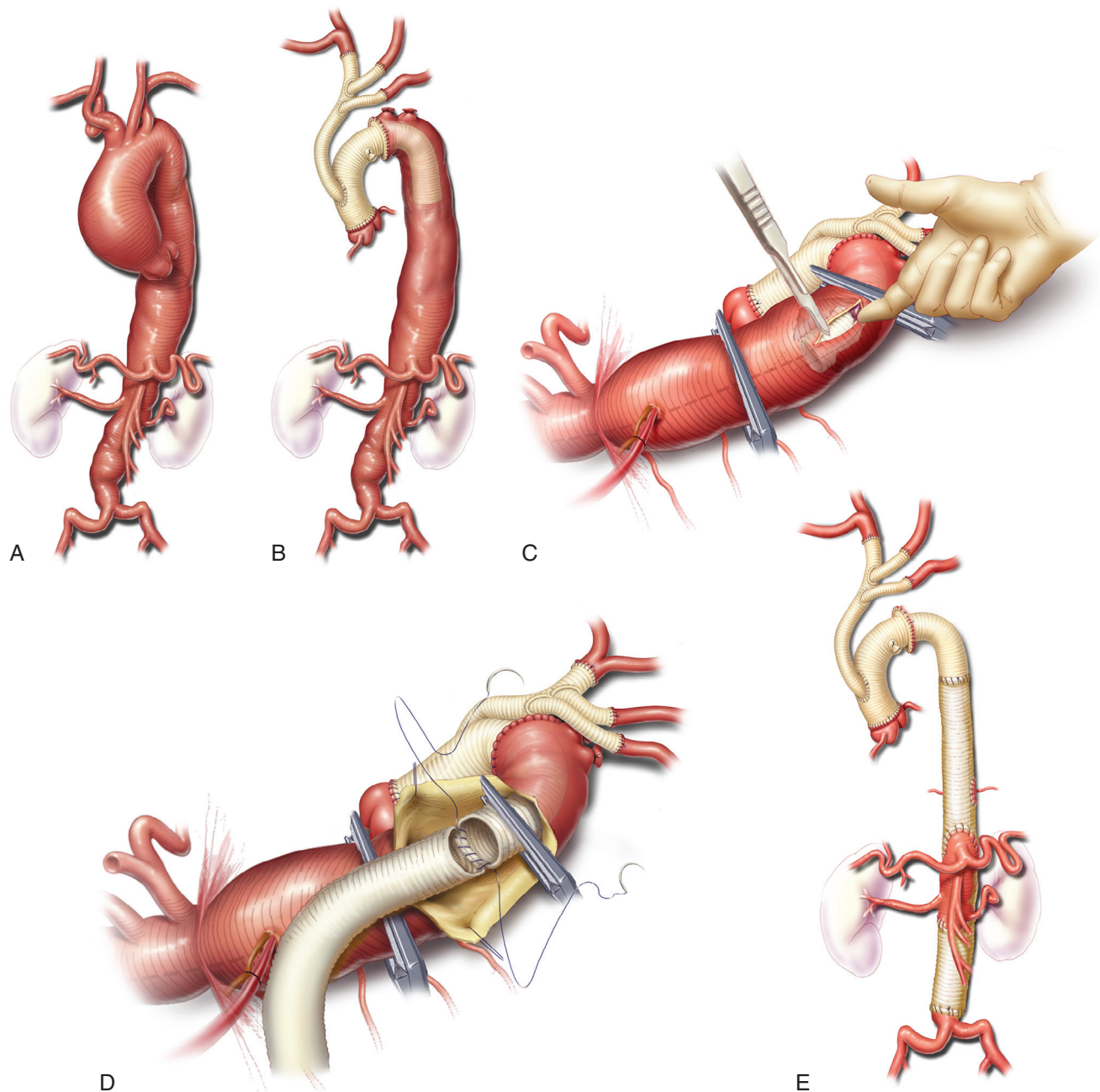


FIGURE 69-13 ■ Illustration of the elephant trunk approach to repair for (A) extensive aortic aneurysms that involve the ascending aorta, the aortic arch, and the thoracoabdominal aorta. B, During the first-stage procedure, the large aneurysm of the ascending aorta and aortic arch is replaced with a graft, a segment of which (the elephant trunk) is left suspended inside the aneurysmal descending thoracic aortic segment. C, This trunk is retrieved during the second-stage procedure and (D) used to create the proximal anastomosis. E, The completed repair is shown. (Reproduced with permission from Baylor College of Medicine.)

incorporating the trunk (usually ≈ 10 cm of extra graft material) into the distal anastomosis, which was typically located just beyond the anatomic origins of the LSCA. Contemporary approaches include the use of Y-graft arch debranching techniques⁸⁸ with a prefabricated, collared elephant trunk graft; this approach permits the distal anastomosis to be brought proximally—generally in line with the anatomic origins of the innominate artery—and the collar reduces anastomotic tension because the diameter of residual aorta can be matched by trimming the collar. Both of these approaches may be encountered in

second-stage repair, and the use of relatively short “trunks” is generally supported in the United States. In Japan, longer elephant trunks have been used, but this appears to increase the risk of paraplegia.⁸⁹

Elephant trunk repairs may be done on a prophylactic basis (such as in the case of patients with distal aortic dilation that does not yet meet a diameter-based threshold for repair) or as part of a planned extensive repair in which the second stage is usually performed within several weeks. During the second-stage completion repair, the elephant trunk greatly facilitates the proximal

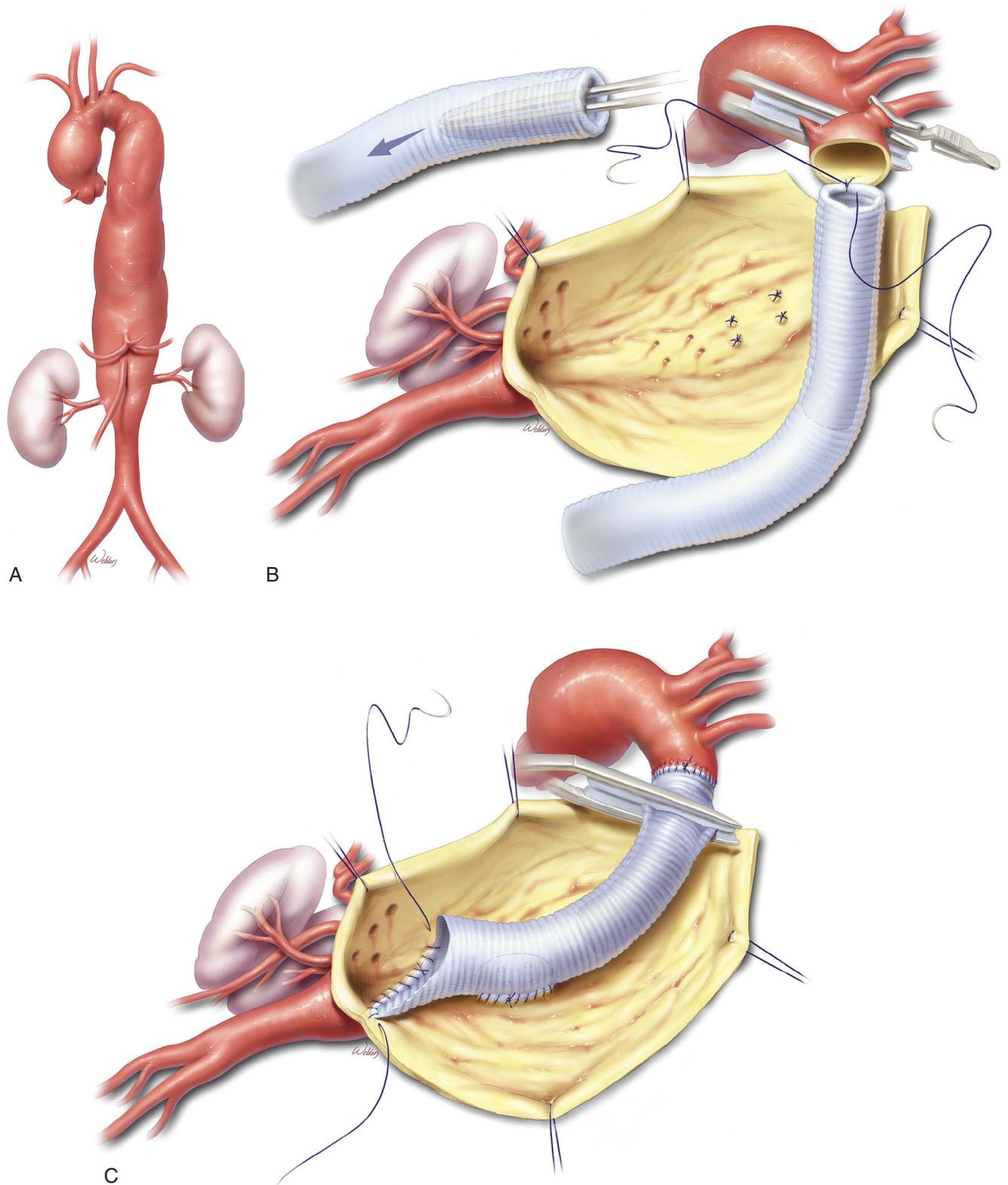


FIGURE 69-14 ■ Illustration of the reversed elephant trunk approach to repair for (A) extensive aortic aneurysms that involve the ascending aorta, the aortic arch, and the thoracoabdominal aorta. In this repair, the distal aorta is of greatest concern, so it is repaired first. B, During the first-stage procedure, the thoracoabdominal aorta is replaced with a graft whose proximal portion is invaginated. The folded edge is used to create the proximal anastomosis. C, After intercostal arteries are reattached, a beveled distal anastomosis is created behind the visceral ostia.

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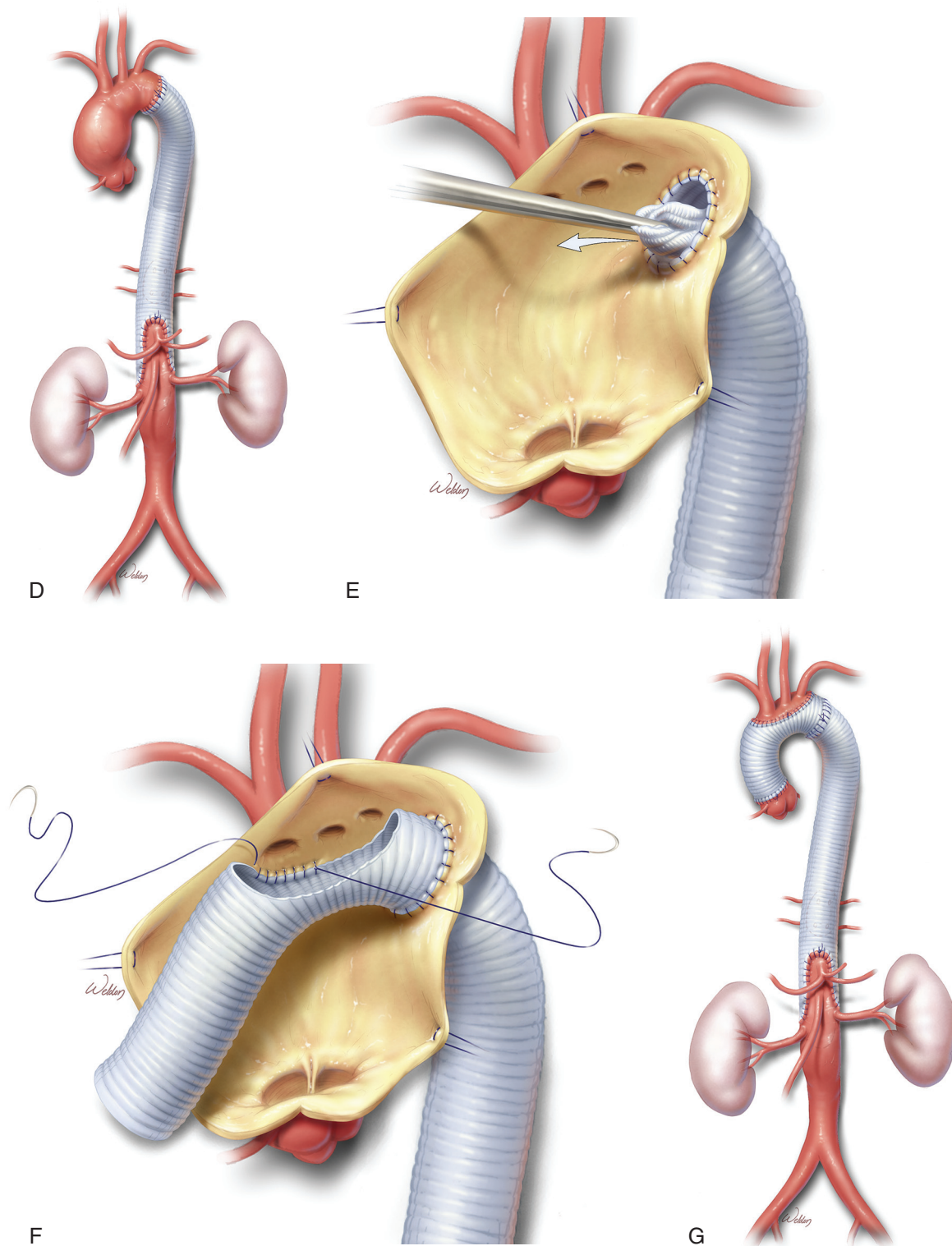


FIGURE 69-14, cont'd ■ **D**, At the end of the first-stage procedure, the graft trunk remains suspended inside the descending thoracic aortic graft. **E**, The graft trunk is retrieved through the open aortic arch during the second stage and **(F)** is used to replace the ascending aorta and aortic arch. **G**, The repair is complete. (From Coselli JS, LeMaire SA, Carter SA, et al: The reversed elephant trunk technique used for treatment of complex aneurysms of the entire thoracic aorta. *Ann Thorac Surg* 80:2166–2172, 2005, Figs. 1-6 and 8. Reproduced with permission. Copyright Society of Thoracic Surgeons.)

anastomosis because it allows direct and secure clamping of the elephant trunk, rather than clamping the replaced arch or proximal descending thoracic aorta, which are often surrounded by dense scar tissue after the initial operation. This is especially helpful when there is a very large aneurysm involving the proximal descending thoracic segment. In patients with DTAA, elephant trunk completion repairs may be done endovascularly rather than by an open approach through a thoracotomy^{90,91}; however, this approach necessitates the availability of at least 2 cm of aortic tissue above the celiac axis to use as the distal landing zone for the endograft. Radiographic clips are usually placed on the end of the elephant trunk graft, and these can be used to guide deployment.

In a reversed elephant trunk procedure, the distal aorta is generally determined to be at greater risk of rupture than is the proximal aorta. At the initiation of repair, the graft is invaginated into itself and the proximal anastomosis is constructed between the aorta and the folded edge of the graft. During the second-stage repair of the proximal aorta, the invaginated segment of graft is retrieved and used to replace the aortic arch and ascending aorta. This approach obviates the need to perform a distal anastomosis at the aortic arch.^{87,92}

Open Repair after Endovascular Aortic Repair

In several ways, open distal aortic repair after endovascular aortic repair (Fig. 69-15) is similar to the methods

described previously, with the extent of repair dictating our standard use of surgical adjuncts. The presence of a stent-graft may limit the surgeon's ability to safely clamp the proximal aorta; when the stent-graft covers a substantial portion of the aortic arch, HCA may be necessary. In patients who present with repair failure after a previous endovascular procedure, a high degree of suspicion regarding endograft infection should be maintained, even in asymptomatic patients; the presence of infection may warrant the use of additional techniques, such as omental wrapping, placing antibiotic-irrigation catheters, and soaking the graft in antibiotics. Occasionally, an extra-anatomic approach may be justified in an infected field. When open repair is performed after previous abdominal aortic endovascular repair, an oblique incision, such as that used for extent IV TAAA repairs, is often used to ensure sufficient exposure of the visceral vessels.

Depending on circumstances, stent-grafts may be fully or partly salvaged (Fig. 69-16) in patients without infection and should be completely removed in patients with infection. The entire stent-graft can be left in place when the new aneurysm results from a progression of adjacent aortic disease rather than a late endovascular failure. Partial salvage may involve leaving a very small portion of the stent-graft proximally if it has been previously sutured directly to the aortic wall (rather than risking further damage by removing it), as is commonly done in the frozen elephant trunk approach, or more commonly, leaving relatively large portions of bifurcated abdominal stent-grafts in place after the main body of the stent-graft

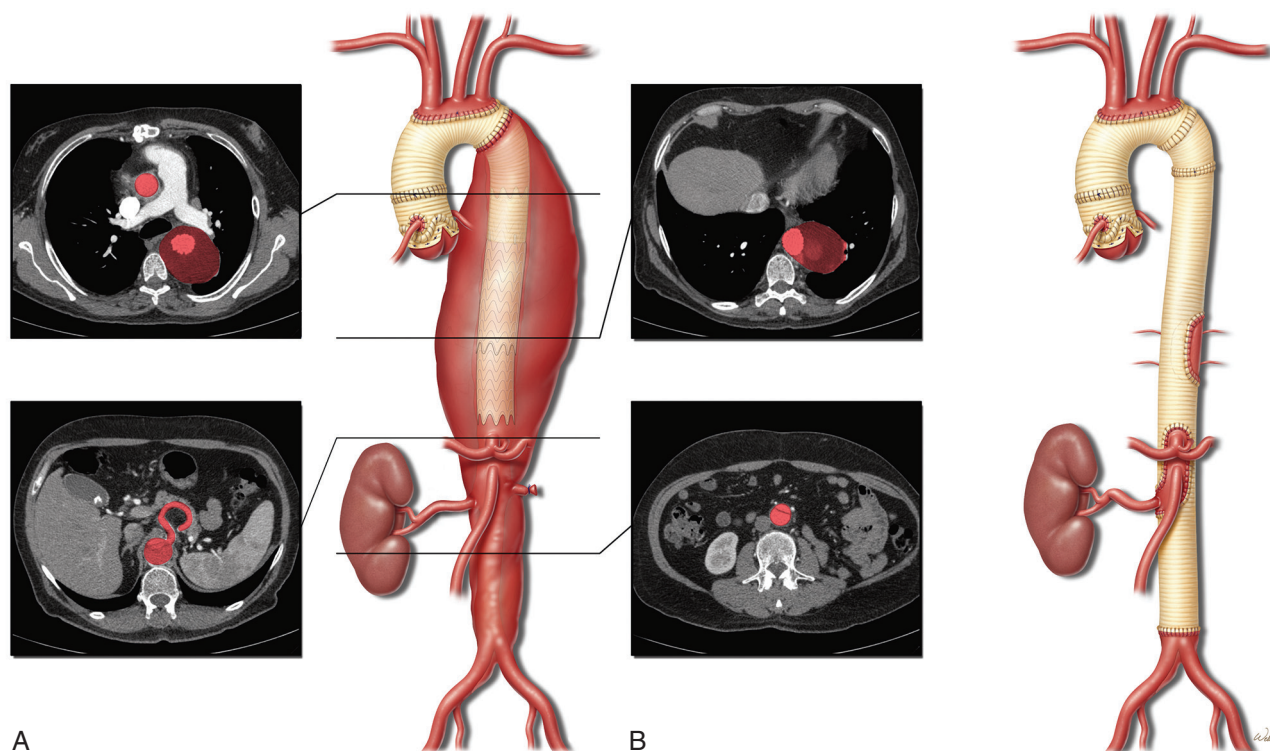


FIGURE 69-15 ■ Preoperative drawing and computed tomography images illustrating (A) a thoracoabdominal aortic aneurysm caused by chronic dissection in a patient who previously underwent replacement of the aortic root, ascending aorta, and aortic arch, followed by endovascular repair of the descending thoracic aorta using the elephant trunk graft as the proximal landing zone. B, Repair involved complete removal of the stent-graft and extent II graft replacement of the thoracoabdominal aorta. (Used with permission of Baylor College of Medicine.)

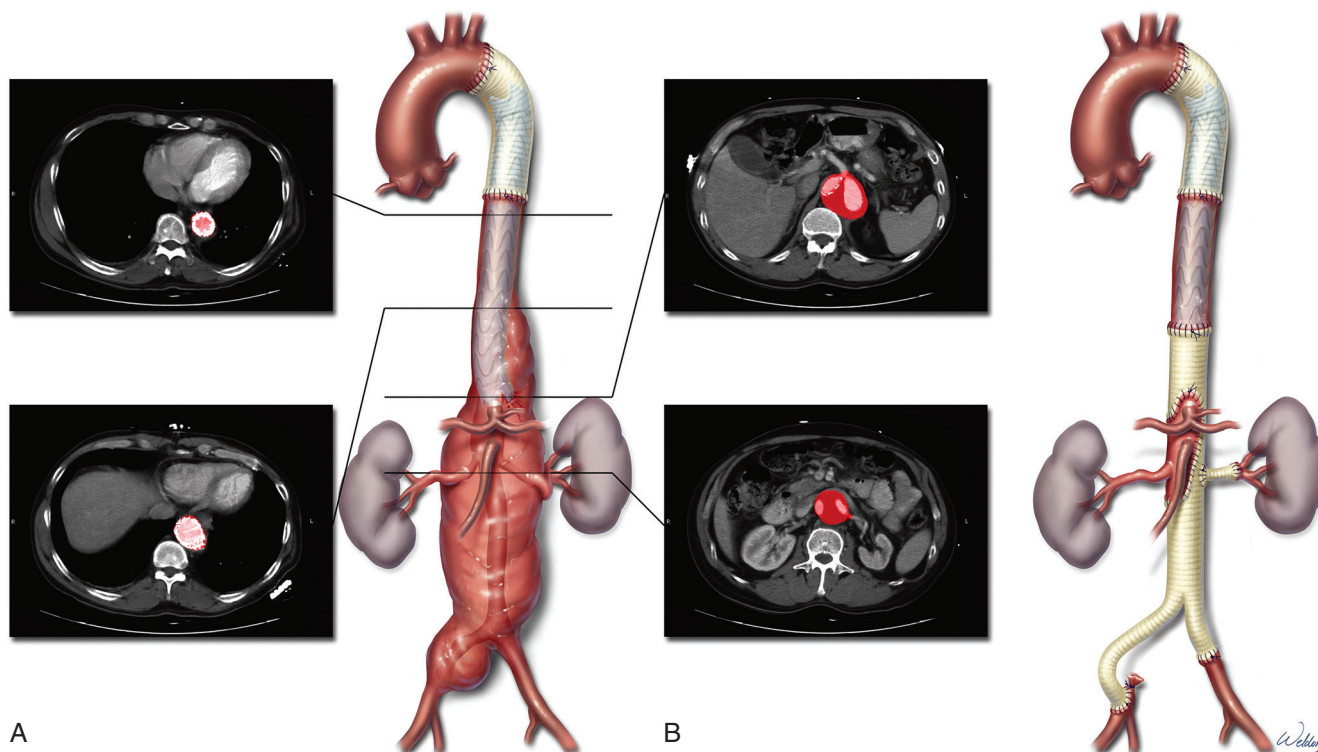


FIGURE 69-16 ■ Preoperative drawing and computed tomography images illustrating (A) a thoracoabdominal aortic aneurysm caused by chronic dissection in a patient who previously underwent open graft replacement of the proximal descending thoracic aorta and endovascular repair of the distal descending thoracic aorta. Over time, the aortic disease progressed to include additional segments of the distal aorta. **B**, Repair involved partial removal of the stent-graft and extent III graft replacement of the thoracoabdominal aorta. A portion of the stent-graft was well-adhered to the aortic tissue, which permitted partial salvage of the device. (Used with permission of Baylor College of Medicine.)

is trimmed, particularly if the extension limbs are well adhered. These anastomoses are typically performed end to end and incorporate the endovascular device, the residual aortic wall, and the replacement polyester graft. Ideally, a full thickness of the aortic wall, surrounding and adherent to the stent-graft, is incorporated in the anastomosis to prevent excessive bleeding from needle holes in the endograft material. In cases of infection, a careful inspection of adjacent tissues is warranted, because there is a possibility of concomitant fistulae. An in situ swab or other measures should be used to identify the infecting agent so that an appropriate antibiotic regimen can be implemented.

Closure

On aortic unclamping and repair completion, systemic heparinization is reversed with intravenous protamine sulfate, and the adequacy of renal perfusion is assessed by administering indigo carmine dye. It is crucial to obtain secure hemostasis, so each anastomosis and cannulation site is carefully inspected for bleeding. As needed, anastomoses may be additionally secured by using reinforcing sutures with felt strips or pledgets and by prudent use of surgical adhesives.⁹³

To gently rewarm the patient and to further assess hemostasis, the field is irrigated with warm water; if necessary, additional blood products are administered.

Sufficient perfusion to the visceral organs, as well as the iliac and femoral arteries, is confirmed. The appearance of the bowel is noted, and the spleen is assessed to ensure that there are no subcapsular hematomas or capsular tears. The residual aneurysmal wall is then wrapped around the aortic graft and secured with continuous suture.

Thoracic drainage tubes are placed within the pleural cavity (anteroapical and posterobasal), and a closed-suction abdominal drain is placed in the retroperitoneum. The diaphragm is reapproximated with a continuous #1 polypropylene suture, and the intercostal space is closed with heavy braided suture and stainless steel wire. Pericostal catheters are placed to allow delivery of local anesthetic postoperatively, and the abdominal fascia, serratus anterior, and latissimus dorsi are then closed with continuous suture.

POSTOPERATIVE MANAGEMENT

Immediate Postoperative Management

A systematic approach to postoperative care is extremely important because operative complications are not uncommon and early correction is the key to minimizing the impact of emerging complications. Laboratory results are carefully reviewed, drains and fluid outputs are carefully assessed, and peripheral pulses are monitored closely.

Ideally, the patient is weaned from the ventilator and extubated within the first 24 to 36 hours after the operation; physical therapy and ambulation are emphasized early in the recovery process.

In the early postoperative period, aortic anastomoses are extremely fragile. Thus, for the first 24 to 48 hours, blood pressure is meticulously kept within a narrow range—mean pressures are maintained between 80 and 90 mm Hg. Typically, this is achieved with nicardipine and intravenous beta antagonists. For patients with particularly fragile aortic tissue, such as patients with connective tissue disorders or acute dissection, the target range for mean pressure may be reduced to 70 to 80 mm Hg. Hypotension is avoided because it can lead to ischemic complications such as delayed paraplegia or paraparesis. Even brief hypertension can disrupt suture lines, leading to severe bleeding and hypotension, or to pseudoaneurysm formation.⁹⁴

When a CSF drain is in place, intrathecal pressure is kept between 10 and 12 mm Hg during the early postoperative period. As necessary, CSF is passively drained. As soon as the patient awakens from anesthesia and before further sedatives are administered, lower extremity movement is assessed; once satisfactory motor function of the legs is confirmed, the CSF pressure target may be increased to 12 to 15 mm Hg. Patients are carefully monitored because delayed paraplegia or paraparesis accounts for roughly half of all spinal cord complications. Often, the CSF drain is stopped for several hours, and if the patient remains neurologically intact, the CSF drain is then removed; this usually takes place within 48 hours. If paraplegia or paraparesis does arise, it is treated aggressively because it can often be fully or partially reversed. If a CSF drain is not in place, one is inserted immediately; the intrathecal pressure is then reduced to less than 10 mm Hg. Additional rescue measures that may be used in conjunction with CSF drainage include optimizing hemodynamics, raising the mean arterial blood pressure to a higher range (85 to 95 mm Hg), administering steroids and osmotic diuretics, correcting anemia, and reducing fever, if present.

As emerging complications arise, corrective measures are immediately taken. Pulmonary complications are relatively common, and affected patients may need to resume ventilator support. Creatinine levels are carefully monitored, and if a significant increase occurs, we increase the patient's blood pressure by adjusting medications to better perfuse the kidneys.

It is crucial to prevent graft infection after aortic replacement, given the associated increased risk of mortality. During surgery, close attention is paid to technique and sterility, and topical antibiotics may be used prophylactically to prepare the graft. Broad-spectrum antibiotics are administered during the early postoperative course until all drains and central venous catheters are removed. After 24 hours, the retroperitoneal closed suction drain may be removed; typically within 72 hours, thoracic drainage tubes are removed provided that drainage is less than 300 mL/day.

In cases of postoperative hoarseness, vocal cord paralysis should be suspected. If it is confirmed by endoscopic

examination, patients should be offered restorative treatment with direct cord medialization.

Long-Term Management

Long-term patient education and surveillance protocols are initiated when patients prepare for discharge. Patients should be made aware that they should seek urgent treatment if concerning symptoms develop (such as the sudden onset of pain or any ischemic complications). In addition, patients should be counseled that they remain at risk for subsequent aneurysm formation in any remaining native aortic segments, including reattachment sites, even if they have no connective tissue disorders or other major risk factors for aneurysm development. Furthermore, many of our patients tend to have poorly controlled hypertension, which can contribute to the gradual weakening of suture lines and lead to the development of pseudoaneurysms. In rare cases, aortic replacement grafts become infected, which can also lead to suture-line disruption and pseudoaneurysm formation. We recommend that all patients undergo at least yearly CT imaging of the chest and abdomen. In younger patients, it is reasonable to use magnetic resonance imaging to reduce lifetime radiation exposure. Adequate surveillance imaging is especially important in patients with connective tissue disorders, especially the aggressive forms such as Loeys-Dietz syndrome.

Additional education regarding lifestyle modifications may be warranted. Maintaining a healthy blood pressure, heart rate, and weight is ideal. Patients should be educated regarding the association between smoking and aneurysmal disease. Patients in whom cocaine or methamphetamine use has precipitated dissection are counseled about the importance of cessation of drug abuse. Whereas light aerobic exercise is generally beneficial to overall health, extreme isometric exercise such as weightlifting should be limited. Similarly, although many patients can expect a full return to employment, strenuous manual labor should be avoided.

OUTCOMES

Although it is difficult to predict with certainty the consequences of distal aortic repair for individual patients, distal aortic repair poses the risk of operative death and of life-altering complications such as paraplegia, renal failure necessitating lifelong dialysis, and stroke. In general, advanced age (65 years and older), urgent or emergent repair, rupture, and extensive repair are the most valuable predictors of early death and adverse outcomes.^{69,71} Other patient-specific factors that increase operative risk include a history of stroke and poor cardiac, renal, or pulmonary function.^{48,71} Whenever possible, elective repair is planned to follow any interventions needed to improve health; in patients with known aortic disease (even those with prior repair), adherence to an imaging-surveillance protocol is crucial to avoiding emergent repair, which more than quadruples the risk of early death and substantially increases the risk of other major complications.^{48,71,95}

Without doubt, pulmonary complications are the most common type of complication to arise after distal aortic repair, affecting approximately 30% to 40% of patients.^{19,96} Pulmonary complications are highly varied and are, in many ways, largely unavoidable, because single-lung ventilation is typically necessary to provide sufficient surgical exposure. Although the lack of standardization in defining complications makes it difficult to compare complication rates over time, it is generally understood that the outcomes of distal aortic repair are better now than they were in decades past. For example, the risk of developing permanent postoperative paraplegia is now almost half of what it was in the Crawford era,^{19,48} and there is much greater awareness of the risk factors related to its development, including delayed-onset paraplegia.⁹⁴ In contrast, the risk of developing renal failure necessitating dialysis is only slightly lower now than it was in the Crawford era.^{19,48}

Descending Thoracic Aortic Aneurysm Repair

Today, the widespread use of endovascular approaches to aortic repair has reduced the use of open surgical approaches to DTAA repair. In fact, this shift has resulted in a tendency to reserve open surgery for the more complex DTAA repairs (such as those performed in patients with a failed prior endovascular repair or a connective tissue disorder). Contemporary results of open repairs of DTAA indicate that early mortality rates range from 3% to 6%, renal failure rates range from 1% to 8%, and paraplegia rates range from 1% to 5%.^{21,24,97-99} Stroke is relatively uncommon after open DTAA repair but may be more likely when HCA is used (2% vs. 3% to 7%, respectively).^{21,24,97} Regarding open coarctation-related DTAA repair, experienced centers report excellent outcomes, and results show up to 1% for early mortality and 1% to 3% for renal failure; no paraplegia has been reported.^{58,60,61}

Thoracoabdominal Aortic Aneurysm Repair

Volume-based analysis suggests that open TAAA repair is most successful when performed in high-volume centers, whereas operative mortality tends to be excessive when this procedure is performed in low-volume centers.¹⁰⁰ In experienced centers, contemporary outcomes for open TAAA repairs range from 4% to 10% for early mortality, from 4% to 6% for renal failure, and from 2% to 8% for paraplegia.^{19,81,101,102} As with open DTAA repair, stroke rates associated with TAAA tend to be relatively low. A recent analysis of National Surgical Quality Improvement Program data found a stroke rate of 2.2%.⁹⁶ Not unexpectedly, results vary greatly by the extent of TAAA repair; early mortality ranges from 5% to 8% for extent I repair, from 8% to 9% for extent II, from 7% to 13% for extent III, and from 3% to 6% for extent IV.^{18,19,22,103} Extent II TAAA repairs have been traditionally associated with the highest rates of mortality and morbidity.⁹⁵ For patients who undergo complex thoracoabdominal aortic repairs, such as reversed elephant trunk procedures or elephant trunk completion procedures, early mortality rates range

TABLE 69-1 Results of 840 Contemporary (2006-2013) Open Distal Aortic Repairs

Extent of Repair	N	30-Day Deaths	Permanent Paraplegia	Permanent Renal Failure
DTAA	84	3 (4%)	1 (1%)	3 (4%)
Extent I TAAA	192	6 (3%)	2 (1%)	7 (4%)
Extent II TAAA	239	16 (7%)	14 (6%)	23 (10%)
Extent III TAAA	148	7 (5%)	12 (8%)	14 (9%)
Extent IV TAAA	177	7 (4%)	4 (2%)	8 (5%)
Total	840	39 (4.6%)	33 (3.9%)	55 (6.5%)

DTAA, Descending thoracic aortic aneurysm;
TAAA, thoracoabdominal aortic aneurysm.

from 9% to 16%.^{92,104-106} Several centers have reported their experience with open thoracoabdominal aortic repair after endovascular repair. In many reports, these patients' outcomes are not substantially different from those of patients without prior endovascular repair unless infection is present, in which case patients with prior endovascular repair do poorly.^{52,54,55} Notably, patients with connective tissue disorders, as well as those with chronic aortic dissection, tend to have better outcomes after distal aortic repair than do other patients, probably because of their younger age, better health, and lower atherosclerotic burden.^{107,108}

Previously, we published the results of large series of DTAA and TAAA repairs that were performed over a span of 2 decades.^{24,109} In Table 69-1, we present our experience with 840 patients who underwent various extents of DTAA ($n = 84$) and TAAA repair ($n = 756$) over a recent 7-year interval. Overall, the 30-day mortality rate was 4.6%, and operative mortality (as defined by Overman et al¹¹⁰) was 7.3%. By extent of repair, 30-day mortality varied from 3% in extent I TAAA repair patients to 7% in extent II TAAA repair patients. Our overall rate of permanent paraplegia was 3.9% and ranged by extent of repair from 1% in DTAA and extent I TAAA repairs to 8% in extent III TAAA repairs. Renal failure necessitating hemodialysis at discharge remains a significant complication, with an overall rate of 6.5%. Similar to other outcomes, the rates of renal failure varied by extent, ranging from 4% in DTAA and extent I TAAA repairs to 10% in extent II TAAA repairs.

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Disclosure

Dr. Coselli serves as a consultant for Vascutek Ltd., a subsidiary of Terumo Corporation, and Medtronic, Inc.;

in addition, he is the principal investigator for ongoing clinical trials for GlaxoSmithKline, WL Gore & Associates, and Medtronic, Inc. Dr. Preventza serves as a consultant for Medtronic, Inc., and has had conference-related travel expenses paid by WL Gore & Associates, and Cook, Inc. Dr. LeMaire serves as a consultant for Medtronic, Inc.

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TYPE A AORTIC DISSECTION

Philippe Demers • D. Craig Miller

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Acute aortic dissection is one of the most common catastrophes involving the aorta. Dissection of the aorta is characterized by the separation of the aortic media by pulsatile blood, with variable extents of proximal and distal extension along the aorta and its branches. The process of dissection creates a false lumen in the aortic wall that parallels the aortic true lumen. In the majority of cases, a primary intimal tear initiates the dissection and allows blood flow communication between the true and false lumens, which are separated by a dissection flap or septum. Because this acute event is rarely associated with a preexisting aneurysm and the aortic intima (true lumen)

is actually smaller than normal, the older term *dissecting aneurysm* is misleading and inappropriate; to be semantically correct, an aortic dissection should be called a *false aneurysm*. A thorough understanding of the pathophysiology of aortic dissection is critical for prompt diagnosis and effective management in the acute setting. On the other hand, aortic dissection in its chronic phase is responsible for a substantial proportion of thoracic aortic disease and aortic rupture due to false aneurysmal degeneration of the false lumen. Numerous advances in diagnostic modalities, medical and surgical treatment, and long-term management have changed the prognosis for

patients with this lethal condition. This chapter summarizes current knowledge regarding the diagnosis and treatment of Stanford type A aortic dissection.

HISTORICAL NOTE

The observations by Morgagni in 1761 were followed by multiple early anatomic and postmortem reports describing aortic dissection, including the famous autopsy report on King George II of England in 1776.¹ In 1802, Maunoir, describing this disease, used the term *dissection*.² Almost 20 years later, René Laennec coined the term *aneurysme dissequant*, or dissecting aneurysm, believing that this entity represented the early stage of a saccular aneurysm.³ Later, in 1863, Peacock published a comprehensive review of 80 cases of aortic dissection.⁴ Until the last half of the twentieth century, the diagnosis of aortic dissection was almost exclusively an autopsy finding. Antemortem diagnosis was made in only 6 of 300 cases reviewed by Shennan in 1934.⁵ The use of contrast angiography for the diagnosis of aortic dissection was reported by Paullin and James.⁶ The first attempt to treat this condition was described in 1935 by Gurin and colleagues,⁷ who used surgical iliac artery fenestration to relieve lower extremity ischemia. Although quickly abandoned, cellophane wrapping of the dissected aorta was also attempted to prevent rupture.⁸ In 1955, DeBakey and associates⁹ launched the modern era of surgical management with graft replacement of the dissected aorta. Subsequently, the same group introduced the use of cardiopulmonary bypass during clamping of the descending thoracic aorta.¹⁰ The first large clinical series of patients with an aortic dissection was published in 1958 by Hirst and colleagues¹¹; analyzing 505 cases allowed these authors to emphasize the high mortality rate and the glaring rarity of antemortem diagnosis at that time. The modern medical approach to aortic dissection with use of pharmacologic agents to diminish aortic dP/dt (anti-impulse therapy) was introduced by Wheat and associates in 1965.¹² The venerable DeBakey type I, II, III classification of aortic dissection was introduced the same year. The simplified Stanford classification system (type A or type B) based on pathophysiologic characteristics was proposed in 1970 by Daily and colleagues.^{13,14} Since then, other important advances have followed, such as less invasive and more accurate diagnostic modalities, improved anesthetic methods, safer extracorporeal perfusion techniques, profound hypothermic circulatory arrest for thoracic aortic arch surgery (introduced by Griep and coworkers¹⁵ from Stanford in 1975), improved and safer prosthetic vascular grafts, and refinement of cardiovascular surgical techniques.

CLASSIFICATION

It is important to understand and to apply accurately the classification of aortic dissection in order to treat patients most appropriately and to compare rigorously the results of various medical and surgical therapeutic interventions reported from different institutions. Considerable

confusion about classifying aortic dissections has arisen in the past. Numerous systems have been proposed, beginning in 1955 with nine categories initially suggested by DeBakey and associates.⁹ The more widely used DeBakey type I, type II, and type III three-category classification scheme was introduced in 1965¹⁴; importantly, DeBakey modified this scheme in 1982¹⁶ to conform with the Stanford A/B functional criteria based on whether the ascending aorta is involved, regardless of the location of the tear and distal extent of dissection. Despite the use of different labels, a consensus has emerged concerning the essential elements of a common functional classification system of aortic dissection. The key point of all classification systems used today is the presence or absence of involvement of the ascending aorta, regardless of the location of the primary intimal tear and irrespective of the antegrade extension of the dissection process.¹⁷ The simplified Stanford classification approach as proposed by Daily and associates¹³ in 1970 has gained broad acceptance during the past 44 years. If the dissection involves the ascending aorta, it is a Stanford type A, which corresponds to a DeBakey type I,¹⁶ University of Alabama “ascending,”¹⁸ Massachusetts General Hospital “proximal,”¹⁹ and Najafi “anterior” dissection.²⁰ Both DeBakey type I and type II dissections involve the ascending aorta; type I extends beyond the innominate artery, whereas type II is confined just to the ascending aorta. If the ascending aorta proximal to the innominate artery is not involved in the process, the dissection is called a Stanford type B, DeBakey type III, descending, distal, or posterior dissection (Fig. 70-1), even though many of these patients have some limited extent of retrograde dissection involvement in the arch, a point that is not broadly appreciated. A subtype of dissection in which the primary intimal tear is in the descending aorta or even farther distal, yet the dissection process propagates in a retrograde fashion to involve the arch and ascending aorta, was originally termed a *DeBakey type III-D* by Reul and colleagues²¹ in 1975, but now is simply termed a *retro-A dissection*. Retro-A dissections constitute approximately 6% of all type A dissections,²² and recently they have been seen more frequently as a complication of stent-graft descending thoracic endovascular aortic repair (TEVAR).

This functional classification approach reflects the pathophysiology of aortic dissection, considering that involvement of the ascending aorta is the principal predictor of the biological behavior of the disease process and the most common fatal complications; moreover, it simplifies diagnosis because it is easier to identify involvement of the ascending aorta accurately than to determine the exact site of the primary intimal tear (or tears) or the extent of propagation of the dissection process. Furthermore, the Stanford classification system facilitates clinical decision making and expedites definitive management. Patients with acute Stanford type A dissections should be treated surgically in essentially all cases; individuals with Stanford type B dissections can be treated with open surgical intervention, with an endovascular TEVAR, or with medical management, depending on the presence or absence of major complications. More specifically, patients with type A dissections require a median sternotomy, total cardiopulmonary bypass (CPB), and

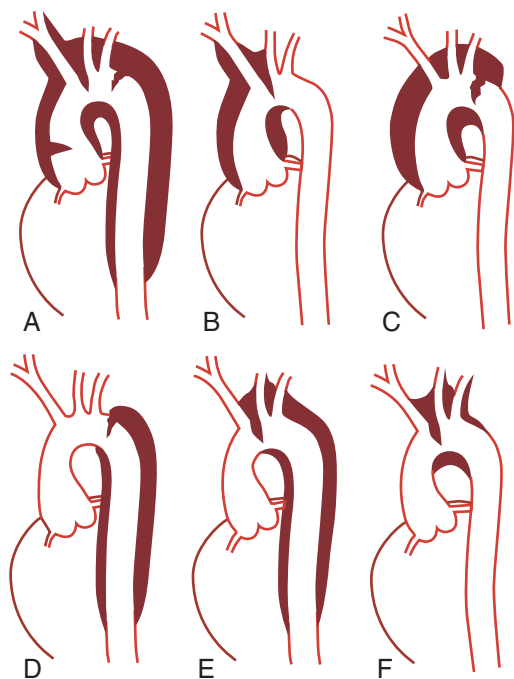


FIGURE 70-1 ■ Schematic illustration of the Stanford classification system of aortic dissections. The three examples in the top row are all type A aortic dissections because the ascending aorta is involved. The primary intimal tear can be located in the ascending aorta (A), in the transverse arch (B), or in the descending thoracic aorta (C). This last example is now called a *retro-A dissection* and is equivalent to a type III-D dissection. The dissections in (D) and (E) are type B dissections; whether the tear is in the descending thoracic aorta or the arch, the ascending aorta is not involved. The last example (F) is an isolated arch dissection without retrograde or antegrade propagation; these are rare. (From Miller DC: Surgical management of aortic dissections: indications, perioperative management, and long-term results. In Doroghazi RM, Slater EE, editors: *Aortic dissection*, New York, 1983, McGraw-Hill, p 196.)

profound hypothermic circulatory arrest (PHCA); those with type B dissections are approached surgically using a left posterolateral thoracotomy, total CPB with PHCA, partial CPB, or isolated left heart bypass.

Aortic dissections diagnosed within 14 days of the onset of presenting symptoms are defined as acute; those diagnosed more than 14 days after onset are classified as chronic dissections.²³⁻²⁵ According to the International Registry of Acute Aortic Dissection (IRAD) investigators,²⁴ the cumulative mortality after acute type A and type B dissection treated medically reached a plateau after the fourteenth day after presentation, demonstrating the prognostic importance of this venerable but arbitrary 14-day time distinction (Fig. 70-2). DeBakey and colleagues¹⁶ introduced the term *subacute* to describe dissections between 2 weeks and 2 months old, but this distinction has been rarely used; however, the term *subacute* has recently gained popularity because of the use of TEVAR and can mean anything between 2 weeks and 6 or more months. Its use should be rejected because it is ambiguous.

During the past two decades, advances in vascular imaging technology have led to increasing recognition of intramural hematoma (IMH) and penetrating atherosclerotic ulcers (PAUs) as distinct pathologic variants in the

spectrum of acute aortic diseases, which can evolve into classic aortic dissection.^{26,27} Both are characterized by the absence of the classic intimal flap dividing the aorta into true and false channels. IMH can be caused by an ulcer penetrating into the internal elastic lamina or can occur spontaneously without any intimal disruption. IMH can involve the ascending aorta (type A IMH) as well as the descending aorta (type B IMH). On occasion, IMH can suddenly evolve into classic aortic dissection with blood flow in both lumens,²⁸ as different phases of a dynamic aortic pathologic process. PAUs occur most commonly in the descending thoracic aorta in older patients. Distinguishing IMH (with or without a PAU) or PAU from classic aortic dissection is critical because the pathophysiologic process, clinical behavior, prognosis, and management of these lesions can differ,^{29,30} depending on which segment of the aorta is involved and the patient's symptomatic status.

EPIDEMIOLOGY

Aortic dissection is seen in all age groups, although the majority of the cases occur between the ages of 50 and 69 years. In a series of 464 patients reviewed in the IRAD registry, mean age was 63 years.²⁴ Two thirds of aortic dissections involve the ascending aorta (Stanford type A) and a third involve the descending aorta (Stanford type B).²⁴ Typically, patients with type B dissection are older than those with type A dissection.^{10,24} Dissection in patients younger than 40 years typically is a type A dissection. According to the IRAD investigators, younger patients with acute aortic dissections are less likely to be hypertensive and are more likely to have Marfan syndrome, bicuspid aortic valve, some other connective tissue disorder, or prior aortic surgery.³¹ In all studies, there is a clear male predominance with an estimated male-to-female ratio ranging from 2:1 to 3:1. Although less frequently affected by acute aortic syndromes, women are older at the time of diagnosis with a mean age of 67 years and have worse outcomes, perhaps due to atypical symptoms and delay in diagnosis.^{24,32} Hirst and colleagues¹¹ found a higher incidence of aortic dissection in African Americans, which might be related more to hypertension than to any intrinsic racial pathologic weakness of the aorta. Similarly, a high prevalence of hypertension may also explain why the incidence of aortic dissection and its variants is higher in Japan and other Asian countries.

The true incidence of aortic dissection is difficult to determine because many patients die without the correct diagnosis being made antemortem.³³ It is not widely appreciated that acute aortic dissection is the most common clinical catastrophe involving the aorta. Moreover, its incidence has been increasing in the industrialized world, in part because of increasing life expectancy and more years exposed to elevated blood pressure. In a 1964 Danish study of 6480 autopsies covering 90% of a regional population, the incidence of acute aortic dissection was 5.2 per million population per year, higher than the incidence of ruptured abdominal aortic aneurysm (3.6 per million population per year) and more than four

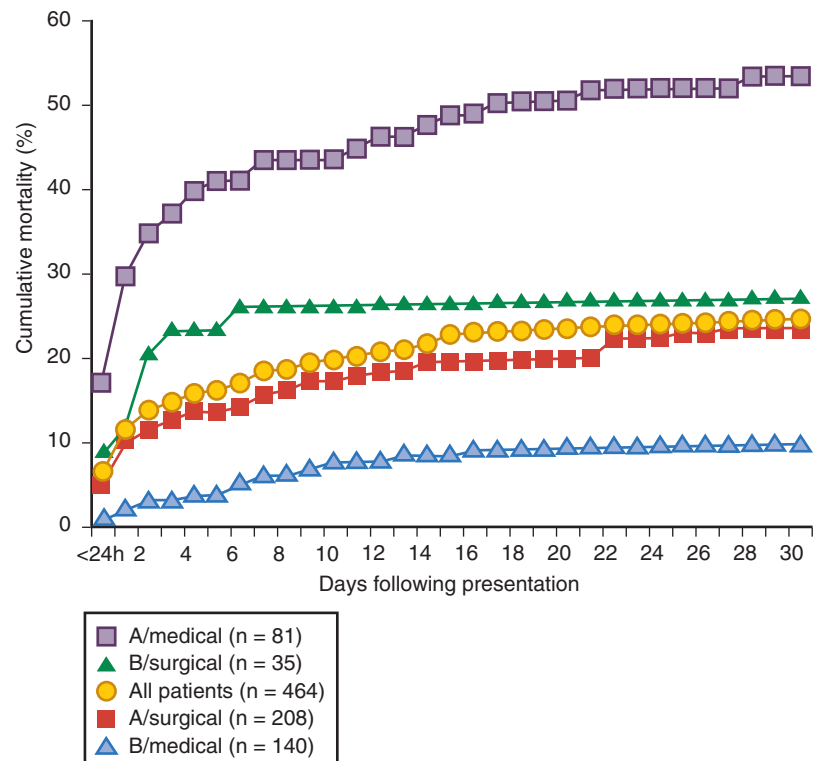


FIGURE 70-2 ■ Thirty-day mortality according to dissection type and management in the International Registry of Acute Aortic Dissection. (From Hagan PG, Nienaber CA, Isselbacher EM, et al: The International Registry of Acute Aortic Dissection [IRAD]: new insights into an old disease. *JAMA* 283:897–903, 2000.)

times the prevalence of ruptured thoracic aortic aneurysm (1.2 per million population per year).³⁴ In the seminal 1958 pathologic series by Hirst and associates,¹¹ acute aortic dissection was found in 1% to 2% of autopsies. In the 1970s, it was estimated that the incidence of acute aortic dissection in an urban population containing many African Americans in the southeastern United States might be as high as 10 to 20 cases per million population per year,³⁵ or approximately 2000 to 4500 new cases each year.³⁶ According to a review of all thoracic aortic diseases among the residents of Olmsted County, Minnesota, between 1980 and 1994, the annual incidence of acute aortic dissection was estimated at 3.5 per 100,000 person-years.³³ More recently, in a comprehensive review of the entire Swedish national health-care registry during a 15-year period, it was observed that the incidence of thoracic aortic aneurysm and dissection had increased substantially between 1987 and 2002; specifically, the incidence of thoracic aortic disease rose by 52% in men and by 28% in women during this period to reach 16.3 cases per 100,000 per year and 9.1 cases per 100,000 per year, respectively.³⁷ In general, these prevalence estimates undoubtedly underestimate the real incidence because they do not capture patients who die suddenly of a complication of aortic dissection and who are presumed to have succumbed to coronary disease or an arrhythmic event in the absence of a postmortem examination; importantly, this was not the case in the report from Sweden, where many dissections were identified only at the time of forensic autopsy, which is still performed almost universally in that country. Most physicians tend to think that ruptured abdominal aortic aneurysms are more common; this misconception comes from the fact that ruptured abdominal aortic aneurysm is

diagnosed correctly more often than is acute aortic dissection.

NATURAL HISTORY

According to the historical autopsy analyses, untreated acute aortic dissection is a highly lethal event. In the study by Shennan published in 1934,⁵ 40% of patients with dissection involving the ascending aorta died immediately, 70% within the first 24 hours, 94% within the first week, and 100% within 5 weeks. In 1967, Lindsay and Hurst³⁸ reported that one third of patients sustaining an acute aortic dissection died within 24 hours, 50% within 48 hours, 80% within 7 days, and 95% within the first month. In patients with chronic dissection, only 15% were still alive after 5 years. In patients with dissection involving the descending thoracic aorta (Stanford type B), 25% had died 1 month after onset. Later, Anagnostopoulos and coworkers,³⁹ in a large collected series of 963 cases of patients not surgically treated with aortic dissection of all types, reported a cumulative mortality of 70% at 1 week and 90% at 3 months, but as in other retrospective investigations the true patient denominator was unknown.

Most patients with untreated acute type A dissection die of intrapericardial rupture culminating in cardiac tamponade; other causes of death include acute aortic valvular regurgitation resulting in left ventricular failure, coronary ostial compromise causing acute myocardial ischemia, occlusion of aortic branches supplying the cerebral or visceral circulation, and free aortic rupture. Patients with untreated acute type B dissection usually die of aortic rupture or of distal end-organ malperfusion (occlusion

of major aortic branches resulting in ischemic injury to vital abdominal organs, termed thoracoabdominal malperfusion).²³ In the Stanford experience, lower extremity ischemia at presentation did not significantly increase surgical mortality risk, whereas occlusion of major abdominal tributaries resulting in renal or splanchnic ischemia was associated with very high mortality rates.^{40,41}

Only 10% of acute dissections are estimated to “heal” spontaneously, eventually becoming chronic dissections. Distal reentry sites are found in nearly all cases, allowing decompression of the false lumen.^{42,43} After acute aortic dissection, the false lumen usually remains patent but may thrombose rarely, depending mainly on the presence, size, and site of distal false lumen reentry sites. When the false lumen remains patent, it is prone to progressive expansion over time, resulting in the formation of a false aneurysm. It is noteworthy that a large fraction of acute serious or fatal dissection complications are caused by a *non-reentering* false lumen, which compromises distal blood flow by extrinsically narrowing or occluding the true lumen.

PREDISPOSING FACTORS

Hypertension

In patients with aortic dissection, the prevalence of hypertension varies between 45% and 80%,^{10,23,24,43,44} being highest in patients with acute type B dissection. Untreated hypertension promotes medial smooth muscle cell degeneration and other changes in the aortic wall, which may increase the susceptibility for aortic dissection.⁴⁵ Although there is no evidence to suggest that hypertension initiates the actual process, it is a major risk factor.

Connective Tissue Disorders

Heritable connective tissue disorders such as Marfan, Ehlers-Danlos, and Loeys-Dietz syndromes are associated with an increased risk of aortic dissection. The Marfan syndrome is inherited as an autosomal dominant trait and is characterized by mutations of the *FBN1* gene encoding the glycoprotein fibrillin 1, which is a major component of elastic fibers of the extracellular matrix in various organs.^{46,47} In addition to cardiovascular manifestations, including mitral valve prolapse, progressive aortic root dilation, aortic valve regurgitation, and aortic dissection, these patients can have several other ocular and musculoskeletal abnormalities. The diagnosis of Marfan syndrome is made according to the revised 2010 Ghent criteria (major and minor), which characterize the involvement of different organ systems, as well as genetic testing identifying a *FBN1* mutation.^{48,49} When a patient demonstrates the classic Marfan syndrome phenotype, the diagnosis is rarely in doubt; however, many patients have only some of the characteristic phenotypic features (variable penetrance), including aortic root dilation with or without aortic valve regurgitation, which has been called the *forme fruste* of Marfan syndrome.⁴⁶ Aortic-related complications, including acute dissection and

rupture, are the leading causes of death in patients with Marfan syndrome. If a patient with Marfan syndrome has a family history of aortic dissection or other aortic catastrophe at an early age, the risk of dissection or rupture is considerably higher.^{47,49} The prevalence of Marfan syndrome in patients presenting with acute aortic dissection ranges between 5% and 12%.^{10,24,44,50}

Patients with Ehlers-Danlos syndrome, particularly those with type IV (vascular type) Ehlers-Danlos syndrome, which is transmitted in most cases as an autosomal dominant trait, have arterial weakness of all large and muscular arteries; type IV Ehlers-Danlos syndrome is characterized by a procollagen type 3 (COL3A1) abnormality and an increased risk of aortic dissection or spontaneous rupture of peripheral arteries or a hollow abdominal viscus.⁵¹ Aortic rupture has also been reported in patients with Ehlers-Danlos syndrome type I and type VI. Extremely fragile arteries are found in patients with Ehlers-Danlos syndrome, and vascular procedures, including simple arterial puncture and suture repair, can be fraught with devastating complications.⁵² The diagnosis of (vascular type) Ehlers-Danlos syndrome is based on genetic testing identifying a mutation in the gene *COL3A1* coding for type III procollagen.^{49,53,54}

Loeys-Dietz syndrome is a more recently recognized autosomal dominant connective tissue disorder characterized by premature arterial aneurysms (typically aortic root aneurysm) and aortic dissection along with diffuse peripheral arterial tortuosity. It is caused by heterogeneous mutations in the genes encoding transforming growth factor β receptors 1 and 2 (TGFB1 and TGFB2), and the diagnosis is confirmed through identification of these mutations.^{49,55} Phenotypic features of Loeys-Dietz syndrome include hypertelorism, bifid uvula or cleft palate or both, hyperlucent skin, and generalized arterial hypertortuosity, especially of the extracranial carotid or iliac arteries. In these patients, the risk of aortic rupture and aortic dissection exceeds that of any other known connective tissue disorders. In addition, aortic rupture and dissection occur at a younger age (even in infants) and at small (almost normal) aortic diameters.

More recently, a genetic basis of nonsyndromic familial thoracic aortic aneurysms and dissection has been defined involving multiple defective genes. Specifically, several gene mutations have been identified causing various defects in cell signaling pathways (TGFB2 mutations different than in Loeys-Dietz syndrome) and protein synthesis of components in the contractile apparatus of vascular smooth muscle cells (MYH11 and ACTA2 mutations), resulting in thoracic aortic aneurysms and aortic dissection occurring at aortic diameter less than 5 cm.^{43,49,56}

Congenital Abnormalities

Congenital heart problems, such as bicuspid aortic valve and coarctation of the aorta, are associated with an increased risk of aortic dissection compared with that in the general population. In an analysis of 186 autopsies of patients who died of type A aortic dissection, it was found that the prevalence of unicuspid or bicuspid aortic valves was 9%.⁵⁷ The risk of perioperative and late postoperative

dissection is also increased in patients with a bicuspid aortic valve after any type of cardiac surgery, especially in patients with dilation of the ascending aorta.^{49,58,59} Aortic dissection predominantly involves the ascending aorta in patients with coarctation and the transverse arch is relatively hypoplastic,⁶⁰ and the dissection may not propagate beyond the aortic isthmus. Simultaneous management of an acute type A aortic dissection in patients with uncorrected severe coarctation is challenging and may require modification of the CPB arterial cannulation strategy and occasionally the use of an extra-anatomic thoracic aortic graft to bypass the coarctation.^{61,62}

Iatrogenic Injury

Aortic dissection is a rare complication of cardiac catheterization and other percutaneous diagnostic and therapeutic interventional techniques involving manipulation of catheters inside the thoracic aorta.⁶³ Catheter and guidewire injuries are usually self-limited, localized subintimal dissections that only rarely require surgical intervention. On the other hand, life-threatening iatrogenic dissections can occur during endovascular device deployment (TEVAR or transfemoral percutaneous aortic valve replacement) or open surgical procedures; among 7000 cardiac operations, iatrogenic aortic dissection complicated 0.3% of cases.⁶⁴ These can be due to ascending aortic cannulation, retrograde dissection after femoral artery cannulation, aortic cross-clamp or partial occluding clamp injury, and intimal injury at the site of a proximal bypass graft anastomosis.^{63,65} The incidence of iatrogenic perioperative type A aortic dissection is higher in patients undergoing off-pump coronary artery bypass grafting, which was attributed to multiple ascending aortic manipulations for construction of the proximal anastomoses.⁶⁶

Pregnancy

In women younger than 40 years, approximately 50% of dissections occur during the third trimester or during labor and delivery; a substantial proportion of these women have connective tissue disorders, such as Marfan syndrome, or a bicuspid aortic valve associated with a dilated tubular segment of the ascending aorta.^{67,68} The hemodynamic and hormonal alterations of pregnancy, culminating in the third trimester, are thought to be the causes of dissection in susceptible individuals.

Illicit Drug Related

One of the cardiovascular complications of cocaine use, particularly crack cocaine inhalation, is acute aortic dissection.^{69,70} Aortic dissection in this setting occurs presumably as a consequence of abrupt, severe hypertension and catecholamine release, and this diagnosis should be considered in cocaine or methamphetamine abusers presenting with chest pain.

Other Associations

Aortic dissections also occur more frequently than in the general population in patients with autosomal dominant

polycystic kidney disease, Turner syndrome, Noonan syndrome, and Alagille syndrome.^{49,71} Inflammatory diseases such as Takayasu arteritis, giant cell arteritis, Behçet disease, autoimmune disorders such as systemic lupus erythematosus, and infection of the aorta, such as syphilis, have been rarely associated with acute aortic dissection.^{42,43,49}

PATHOPHYSIOLOGY AND PATHOLOGIC FINDINGS

Medial Degeneration

In 1929, Erdheim⁷² was the first to describe what he called “cystic medial necrosis,” a nonspecific pathologic process involving medial smooth muscle cell loss, elastic lamellar disruption, and acid mucopolysaccharide accumulation within the aortic media. This abnormal architecture is believed to lead to changes in the distribution of both circumferential wall stress and shear stress in the aortic media, potentially leading to an intimal tear.⁷³ The word *cystic* is actually a misnomer, because these medial lesions do not form true cysts (they are not lined by epithelial cells). The term *necrosis* is also incorrect because it is singularly absent. In young patients (particularly those with a heritable connective tissue disorder), the elastic elements of the aortic media are disrupted and disorganized; in older individuals, it is the smooth muscle elements of the aortic media that are abnormal because of aging and hypertension,^{74,75} and probably represent changes associated with repeated aortic wall injury and repair. Thus, the well-known moniker “cystic medial necrosis” should be abandoned and replaced by more specific terms relating to alterations of the elastic fibers (“elastic type”) and smooth muscle cells (“smooth muscle type”) in the media in younger and older patients, respectively. In patients with inherited connective tissue disorders, such as Marfan syndrome, pathologic examination of the aortic wall frequently revealed pronounced medial degeneration, with severe loss of elastic lamellae and accumulation of mucoid substance within the media. These young patients typically have an acute type A dissection. On the other hand, in older individuals, type B dissections are more common and are associated with medial degeneration characterized by loss of smooth muscle cells. It was proposed that the coexistence of activated T lymphocytes and macrophages and markers of apoptotic vascular cell death in the aortic media of patients with aortic dissection may contribute to the two pathways leading to medial degeneration, namely, loss of vascular smooth muscle cells and degradation of the extracellular matrix.⁷⁶ Increased contents of collagen types I and III as well as increased activity of connective tissue growth factor have been observed in the media and adventitia of patients with aortic dissection⁷⁷; these phenomena are likely to be responsible for the reduced aortic distensibility and compliance. Another contributing factor to progressive degradation of the extracellular matrix is excessive activation of matrix metalloproteinases, particularly matrix metalloproteinase 9, which are zinc-dependent proteolytic enzymes that can disrupt the

balance composition of vascular smooth muscle cells and extracellular matrix proteins.⁷⁸ Specific nucleotide polymorphism of the gene encoding matrix metalloproteinase 9, more specifically, the presence of the -8202A/G allele, seems to be associated with an increased risk of aortic dissection.⁷⁹

Primary Intimal Tear

Most authorities believe that the initiating event in aortic dissection is a tear in the intima allowing blood to enter the aortic wall that culminates in progressive separation of the medial layers of the aorta (elastic and circumferential smooth muscle fibers) with propagation of the dissecting hematoma. The primary intimal tear allows communication between the true aortic lumen and the false lumen. Only 2% to 4% of aortic dissections do not have an identifiable primary intimal tear and are usually confined to the descending thoracic aorta.¹¹ Rarely in patients with connective tissue disorders, a localized intimal disruption can be present without extensive undermining of the intima, pseudoaneurysm development, or any false lumen,⁸⁰ what we colloquially call “intimal stretch marks.” If they are associated with a localized hematoma within the wall, they have a “mushroom cap” appearance. Whether an intimal tear is the precipitating event in all aortic dissections is still debated.⁷³ IMH owing to rupture of the vasa vasorum is another potential but infrequent initiating event leading to frank dissection. Rupture of the intima usually happens at points of maximal wall stress along the thoracic aorta. Intimal tears are usually transverse in orientation and typically involve one half to two thirds of the aortic circumference. Infrequently, total disruption of intimal continuity with a complete circumferential tear can lead to intimo-intimal intussusception and mechanical obstruction of blood flow⁸¹ because of gross prolapse of the circumferential intima. In type A dissections, the majority of intimal tears (60% to 70%) are located in the ascending aorta, usually just distal to the sinotubular junction (Fig. 70-3).^{11,82,83} In 10% to 20%, the intimal tear is located in the aortic arch, most commonly on the lesser curvature.^{84,85} The intimal tear can also originate in the proximal one third of the descending aorta, near the aortic isthmus (“retro-A dissection”). In less than 5% of cases, the intimal tear can be located in the abdominal aorta, and the dissection will either be confined to the abdominal aorta or propagate in a retrograde fashion to involve the ascending thoracic aorta.^{86,87}

Propagation and Reentry

Within the aortic wall, the false lumen is situated between the inner two thirds and the outer one third of the aortic media. On pathoanatomic examination, the dissected aorta is a false aneurysm, because the aortic intima containing the true lumen is not dilated and actually is smaller than normal. Once initiated, aortic dissections usually propagate antegrade or “downstream” but may also extend in a retrograde direction. The dissection often proceeds in a spiral fashion down along the aorta. Propagation of the dissection depends on several factors,

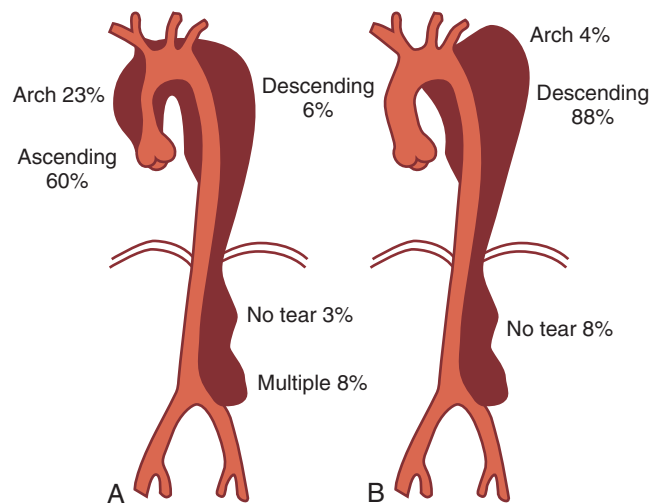


FIGURE 70-3 ■ Location of the primary intimal tear in a series of 168 patients who underwent operative repair of (A) acute type A aortic dissection ($n = 169$) and (B) acute type B aortic dissection ($n = 29$). (From Lansman SL, McCullough JN, Nguyen KH, et al: Subtypes of acute aortic dissection. *Ann Thorac Surg* 67:1975–1978, 1999.)

including rate of increase of aortic systolic pressure (or aortic dP/dt), magnitude of aortic diastolic elastic recoil and stiffness, mean and peak arterial pressure, and aortic wall integrity and strength.^{42,43,88,89} The mainstay of medical treatment of aortic dissection, as described by Wheat and Palmer in 1965, is directed at reducing aortic dP/dt , called *anti-impulse therapy*.¹² In the ascending aorta, the false lumen usually occupies the right anterior portion; in the arch, the false lumen usually is located along the greater curvature and may extend into the innominate, left carotid, or left subclavian arteries. In the descending and abdominal aorta, the false lumen often runs along the anterior and lateral aortic walls, frequently incorporating the take-off of the left renal artery.¹¹ Distal progression of the dissection may be limited by extensive atherosclerosis or anatomic constraints such as aortic coarctation, infrarenal abdominal aortic aneurysm, or abdominal aortic graft anastomosis.⁶⁰ Otherwise, in young individuals the dissection almost always involves the entire thoracic and abdominal aorta and extends into the iliac arteries. Limited Stanford type A, DeBakey type II dissections are rare in our experience. In patients surviving the acute episode, the false lumen usually remains patent but rarely may thrombose spontaneously. The presence of distal reentry sites or fenestrations contributes to persistent patency of the false lumen. Partial or complete thrombosis of the false lumen may allow “healing” of the aorta; conversely, if the false lumen reenters distally and stays patent, it is prone to progressive false aneurysmal enlargement. A patent distal false lumen is observed in up to 90% of patients after surgical repair of acute type A dissections and may portend an adverse prognosis associated with a higher incidence of late “downstream” false aneurysmal degeneration.^{90,91} Reentry sites are usually multiple and frequently occur at the ostia of sheared off branches, such as the intercostal, visceral, renal, or iliac arteries. Reentry into the true lumen,

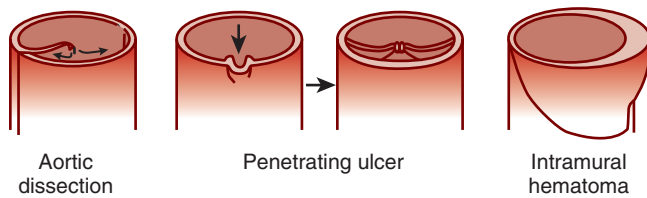


FIGURE 70-4 ■ Schematic illustration of classic aortic dissection with a distinct intimal flap separating the true and false lumens (*left*), penetrating atherosclerotic ulcer with a localized intimal lesion burrowing into the media and leading in some cases to localized dissection (*middle*), and intramural hematoma without intimal lesion (*right*). (From Coady MA, Rizzo JA, Elefteriades JA: Pathologic variants of thoracic aortic dissections. Penetrating atherosclerotic ulcers and intramural hematomas. *Cardiol Clin* 17:637–657, 1999.)

described by Peacock in 1843 as “an imperfect natural cure of the disease,”¹ allows decompression of the false lumen and is the rationale behind surgical and percutaneous flap fenestration techniques.^{92,93}

Intramural Hematoma

In 1920, Krukenberg⁹⁴ first described aortic IMH as a “dissection without intimal tear.” IMH is believed to originate from rupture of the vasa vasorum within the outer third of the media, resulting in the circumferential accumulation of blood (Fig. 70-4), with no apparent intimal defect visualized on imaging studies.²⁹ IMH can occur spontaneously in predisposed individuals (e.g., older and hypertensive patients) or be a secondary phenomenon after the rupture of an atheromatous plaque through the internal elastic lamina and the formation of a penetrating atherosclerotic ulcer allowing extravasation of blood into the aortic wall (see Fig. 70-4).²⁷ The natural history of these lesions was not well characterized until the last two decades. The evolution of IMH may either be benign, with a stable clinical course and eventual healing, or a progressive, often fatal disease, with extension, evolution into classic aortic dissection, aneurysmal degeneration, or aortic rupture.^{28–30,95} In recent years, it was recognized that IMH involving the ascending (type A IMH) or descending (type B IMH) aorta can occasionally portend a different clinical course from that of classic aortic dissection, especially if it is detected incidentally in asymptomatic patients undergoing cross-sectional imaging. Conversely, patients with acute severe chest pain are more prone to disease progression and aortic rupture, similar to those with full-blown acute dissections, especially in the presence of an associated deep penetrating ulcer.^{26,30,95,96} We believe that IMH of the ascending aorta usually has a malignant prognosis almost identical to that of acute type A aortic dissection, and these patients should be treated accordingly.

Aortic Branch Compromise

Peripheral branch vessel ischemia or malperfusion arises when the dissection process compromises blood flow to various aortic tributaries through several mechanisms, including extrinsic compression of the true lumen by the

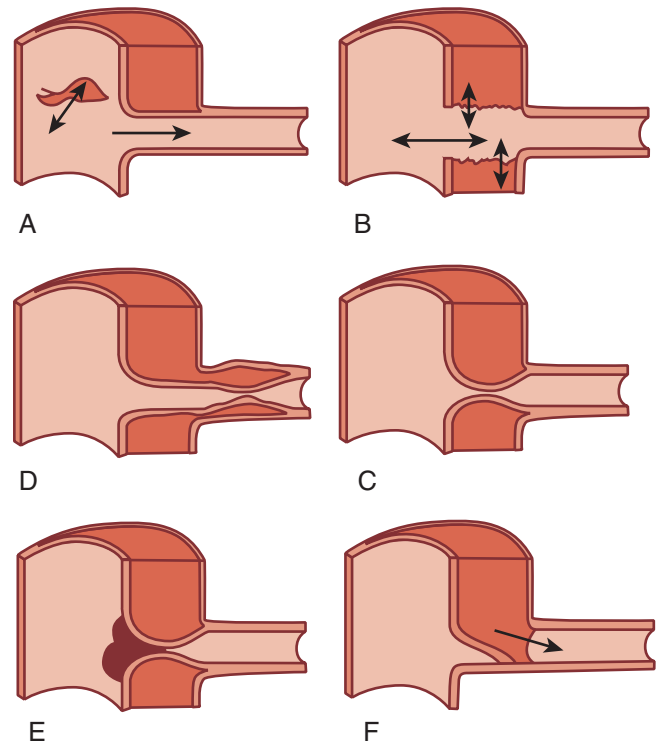


FIGURE 70-5 ■ Examples of branch artery involvement in aortic dissection. Continued adequate perfusion of an aortic tributary is illustrated in (A), (B), and (F); however, perfusion is from the true lumen in (A) and (B) and through the false lumen in (F). Obstruction of an aortic tributary owing to extrinsic compression is shown in (C) and (D), whereas compromise of the ostium of the true lumen with secondary thrombosis is shown in (E). In (F), reentry of the dissection into the branch vessel has created an intimal flap. This can become a permanent situation if the flap heals to the opposite wall of the artery in the chronic phase, thus rendering this branch solely dependent on false lumen perfusion. (From Miller DC: Surgical management of aortic dissections: indications, perioperative management, and long-term results. In Doroghazi RA, Slater EE, editors: *Aortic dissection*, New York, 1983, McGraw-Hill.)

pressurized false lumen (particularly a false lumen that does not reenter), an intimal flap compromising the orifice of the branch artery (Fig. 70-5), and occlusion of the tributary if the dissection continues into the branch because of false lumen extrinsic compression of the true lumen distally. A useful pathophysiologic classification of aortic branch compromise was proposed by Williams and associates⁹⁷: *static obstruction* occurs when the dissection flap extends into a branch vessel, resulting in mechanical compromise of flow; *dynamic obstruction* occurs when the dissection flap narrows the aortic true lumen above the branch because of a large false lumen or when the flap prolapses into the vessel origin. As the dissection progresses in a spiral fashion along the aorta, some aortic branches may be spared and continue to be perfused by the true lumen, whereas other arteries may be perfused exclusively from the false lumen after being sheared off; in this latter scenario, the affected branch subsequently becomes permanently dependent on the false lumen for perfusion. In some cases, compression by the false lumen may almost eliminate the entire aortic true channel (true lumen collapse or true lumen obliteration) with resultant

severe distal thoracoabdominal malperfusion.^{97,98} The pattern of branch artery involvement and the degree of perfusion compromise determine the clinical presentation, which is enormously variable and often leads to delay before the correct diagnosis is established. Indeed, acute aortic dissection has been called “The Great Masquerader” because the symptoms can mimic those of many other acute illnesses. In the large autopsy series by Hirst and colleagues,¹¹ the most commonly affected aortic branches were the iliac arteries, followed (in descending order) by the innominate, left common carotid, left subclavian, coronary, renal, superior mesenteric, and celiac axis.

CLINICAL MANIFESTATIONS

Patient Characteristics

Patients with type A dissections are usually younger, including those with Marfan syndrome and other heritable connective tissue disorders or congenital aortic valve disease, whereas type B dissection is usually seen in middle-aged and older men. Either type of dissection can occur in women, usually at an older age, but is exceptionally rare in children and teenagers.^{10,24,32,43} Older patients usually have coexisting medical conditions, including hypertension and generalized arteriosclerosis, as well as associated medical comorbidities, such as cerebrovascular, cardiac, pulmonary, and renal disease.

Acute Type A Dissection

Pain

The most common presenting symptom of aortic dissection is severe chest pain, usually originating in the anterior chest or in the interscapular region, which correlates with the location of the dissection. The onset of pain is typically abrupt and most severe at onset, described as sharp or tearing, and it is thought to be due to stretching of the aortic adventitial nerve fibers by the dissection; the pain typically then migrates down the chest and into the abdomen. Persistence of pain suggests continuing expansion within the chest or distal propagation. Differentiation of the chest pain associated with acute aortic dissection from other causes, such as acute myocardial ischemia, pulmonary embolism, or pericarditis, is critical in the initial evaluation of these patients to allow prompt management. The presence of additional clinical findings, such as a diastolic murmur, blood pressure difference between arms or legs, and new neurologic deficit, increase the likelihood of an acute type A aortic dissection in the presence of chest pain.⁹⁹ In some patients, the initial pain will disappear either spontaneously or with institution of medical treatment; recurrent pain thereafter is an ominous sign suggesting impending aortic rupture or continuing downstream extension of the dissection.¹⁰⁰ On occasion, acute dissection can be painless. A high clinical index of suspicion is required for patients with aortic dissection as its manifestations can mimic any other acute medical or surgical illness. In an IRAD report,

pain of abrupt onset was the presenting symptom in 85% of patients, and the most common site was the chest. It was located anteriorly in 71% of patients with type A dissection, but 47% and 22%, respectively, of these patients reported back pain and abdominal pain.^{24,43}

Systemic Manifestations

One third to half of all patients with acute aortic dissection demonstrate signs and symptoms secondary to cardiac and other organ system involvement.* Aortic branch compromise, aortic rupture or leak, and compression of adjacent organs by an expanding false lumen are the most common mechanisms responsible for complications of aortic dissection.

Cardiovascular Manifestations

Patients with acute aortic dissection appear pale and poorly perfused peripherally but generally have elevated blood pressure because of preexisting arterial hypertension, high circulating levels of catecholamines, pain, or renal artery compromise by the dissection. Blood pressure must be recorded in both arms, and a thorough evaluation of peripheral pulses in all four extremities is essential. Hypotension in patients with acute dissection suggests cardiac tamponade¹⁰³ or impending rupture; shock is usually due to intrapericardial rupture with tamponade, intrathoracic rupture, or acute left ventricular failure secondary to myocardial ischemia or acute, severe aortic valve regurgitation. Aortic rupture is the most frequent cause of death in the acute setting¹¹; the most common site of rupture is near the site of the primary intimal tear.⁸⁹ Ascending aortic and arch involvement can rupture into the pericardial cavity or the mediastinum; however, rupture of a more distal thoracic aortic segment is also possible with exsanguination into the left pleural space or rarely the retroperitoneum. Aortic valve regurgitation is present in 20% to 50% of patients with acute type A dissection.^{10,23-25,104} Extension of the dissection retrograde into the aortic root with shearing off of one or more aortic valve commissures causes diastolic prolapse of the cusps. A murmur of aortic regurgitation is heard in 25% to 45% of patients and may be associated with an S₃ gallop and pulmonary rales.^{24,42} Acute, severe aortic regurgitation leading to left ventricular failure is the second most common cause of death in patients with type A dissection, after aortic rupture. Less commonly, proximal extension of the dissection into the coronary ostia can impair coronary perfusion and cause myocardial ischemia or infarction.¹⁰⁵ In this situation, involvement of the right coronary artery is more common than involvement of the left coronary artery, and the electrocardiographic findings may include changes consistent with acute inferior myocardial infarction. Contained or frank aortic rupture or, more commonly, transudation of fluid from the false lumen through the intact aortic epicardial layer (there is no adventitia because the ascending aorta is an intrapericardial structure) into the pericardial cavity can

*References 10, 24, 42, 43, 99, 101, 102.

lead to pericardial effusion and cardiac tamponade associated with jugular venous distention, Kussmaul sign, paradoxical pulse, or pericardial friction rub. Cardiac tamponade is reported in 10% to 20% of patients with acute type A dissection and mandates emergency surgical intervention.¹⁰³ Rarely, the expanding false lumen may compress surrounding structures, such as the pulmonary artery or the superior vena cava, or rupture into one of the cardiac chambers, resulting in an aorto-atrial or aortoventricular fistula.^{106,107} Heart block can be seen in cases with involvement of the membranous and interatrial septum by a pressurized dissection-related hematoma.¹⁰⁸

Peripheral Vascular Complications

Systemic arterial manifestations of aortic dissection are the result of the propagation of the dissection process leading to aortic branch compromise and ischemia or infarction of various end organs. Approximately 30% of patients initially exhibit symptoms related to acute peripheral arterial compromise or will develop such complications.^{16,101,102,109,110} Clinical manifestations include coma, stroke, paraplegia, upper or lower extremity ischemia, and anuria or abdominal pain due to renal or mesenteric ischemia.

In a historical review of the Stanford University experience with management of aortic dissection associated with acute peripheral vascular complications by Fann and associates,¹⁰² 85 (31%) of 272 patients (128 acute type A, 40 acute type B dissection) had one or more peripheral arterial manifestations. Among these 168 patients, 4% presented with acute carotid occlusion and stroke, 5% had acute paraplegia secondary to spinal cord ischemia, 33% sustained loss of one or more peripheral pulses, 11% had impaired renal perfusion demonstrated angiographically, and 6% had compromised visceral perfusion by angiography. The prevalence of these complications according to type of dissection and the operative mortality after definitive intrathoracic surgical management are summarized in Table 70-1. Those with advanced intra-abdominal ischemia or infarction had a dismal prognosis, but simple loss of a peripheral pulse did not predict higher mortality or morbidity. In the literature, it is essential to differentiate between visceral (or renal) ischemia defined on a clinical or symptomatic basis (the

most important issue) or on an imaging basis, which overestimates the incidence of clinically meaningful complications.

Acute stroke or transient ischemic attack with hemiplegia is the most common neurologic manifestation. These result from cerebral hypoperfusion secondary to aortic arch involvement or obstruction of the true lumen in a carotid or vertebral artery. Stroke or transient ischemic attack usually occurs in patients with an acute type A dissection, and the reported incidence ranges from 3% to 7% in large series.^{16,101,110,111} Beside stroke, altered cerebral perfusion can lead to altered or fluctuating mental status, coma, or syncope in as much as 12% of patients.²⁴ Extensive dissection can compromise perfusion of the spinal cord by shearing off critical intercostal arteries, thereby interrupting flow to the radicularis magna artery and causing paraplegia or paraparesis in 2% to 6% of cases.^{16,101,102} Symptoms related to involvement of peripheral nerves, such as paresthesia and Horner syndrome, are due to peripheral ischemic neuropathy or to direct compression of a nerve by the expanding false lumen. In rare circumstances, stroke, paraplegia, or syncope without chest pain may be the only clinical manifestation of aortic dissection.²⁴

The incidence of renal ischemia owing to acute dissection varies from 5% to 25%.^{43,101,102,110} This wide variability is probably related to methods of detection (ultrasonography, computed tomography, angiography versus autopsy) more than to true population differences. Whether and how it is defined on a clinical or imaging basis is also of paramount importance. Dissection resulting in renal artery compromise may be asymptomatic and remain undetected unless diagnostic imaging studies are performed, but can be associated with oliguria or anuria and worsening renal function. Other clinical manifestations of impaired renal perfusion include refractory hypertension, flank pain, and hematuria. In contrast to previous reports observing that the left renal artery is more frequently involved,¹¹ the right renal artery was more often compromised in our experience¹⁰²; nonetheless, the left renal artery is more frequently fed by the aortic false lumen than by the true lumen.

Aortic dissection involving the visceral arteries leads to mesenteric ischemia or infarction, which is a highly lethal complication. Compromised splanchnic perfusion causing clinical events is relatively uncommon, occurring in less than 5% of cases, although autopsy studies suggest that dissection involvement of the celiac or superior mesenteric arteries is present in more than 10% of patients.^{11,102} At Stanford, the incidence of angiographically defined visceral ischemia was 6% in patients with acute type A dissection. Visceral ischemia portends a grave prognosis,^{101,102} but it can have various clinical presentations ranging from asymptomatic angiographic evidence of visceral hypoperfusion to frank bowel infarction. The cardinal association of abdominal pain out of proportion to the findings on physical examination should lead to prompt consideration of gut ischemia.

Peripheral pulse loss occurs in 30% to 50% of patients with acute type A dissection and 25% of all patients irrespective of dissection type.¹⁰² The clinical course of patients with peripheral limb ischemia is highly variable

TABLE 70-1 Peripheral Vascular Complications and Associated Operative Mortality Rates Among 128 Patients with Acute Type A Aortic Dissection

Peripheral Vascular Complication	Prevalence (n)	Mortality (n)
Stroke	6% ± 3% (7)	14% ± 14% (1)
Paraplegia	6% ± 3% (7)	43% ± 19% (3)
Pulse deficit	38% ± 5% (48)	25% ± 6% (12)
Renal ischemia	12% ± 4% (15)	53% ± 13% (8)
Visceral ischemia	6% ± 3% (8)	50% ± 18% (4)

Data from Fann JI, Sarris GE, Mitchell RS, et al: Treatment of patients with aortic dissection presenting with peripheral vascular complications. *Ann Surg* 212:705–713, 1990.

and dynamic; therefore, frequent comprehensive pulse examinations are important. In the Massachusetts General Hospital experience, one third of these patients experienced either spontaneous resolution of the pulse deficit or a fluctuating clinical picture.¹⁰¹ This phenomenon is thought to be related to spontaneous reentry of flow into the true lumen from the false lumen when the false lumen earlier was non-reentering and compromising the true lumen by means of extrinsic compression. Alternatively, loss of a peripheral pulse can be asymptomatic, especially in the upper extremities. Rarely, proximal descending thoracic aortic obstruction owing to “true lumen collapse” or dynamic “true lumen obliteration” can cause severe ischemia of the entire lower body.⁹⁸

Chronic Type A Dissection

Patients surviving the initial acute phase of acute dissection, surgically treated or not, will be at risk for development of aortic complications in the chronic phase of the disease. Most patients with chronic type A dissection are asymptomatic until they develop problems related to progressive expansion of the downstream aortic false lumen with aneurysmal degeneration, worsening aortic valve regurgitation, aneurysmal degeneration of preserved sinuses of Valsalva, or false aneurysms from previous surgical graft anastomoses. It has been estimated that up to one fourth of patients will develop downstream false lumen aneurysmal degeneration and require reoperation or interventional reintervention within 10 to 15 years after an acute dissection, emphasizing the importance of indefinite, comprehensive follow-up care and serial imaging studies.^{16,90,112-114} Uncommonly, patients who had an asymptomatic acute dissection may present many months to years later with a thoracic aortic false aneurysm discovered incidentally on a chest radiograph or a computed tomographic (CT) scan done for an unrelated problem. Progressive expansion of the false lumen may produce compression, obstruction, or erosion into adjacent mediastinal structures. Therefore, symptoms related to aortic aneurysmal enlargement can include chest pain, dyspnea, wheezing or stridor, hoarseness, dysphagia, superior vena cava syndrome, hemoptysis (aortobronchial or aortopulmonary fistula), and hematemesis (aortoesophageal fistula). Signs and symptoms of heart failure can result if the degree of aortic regurgitation becomes severe. Rarely, late thrombosis of the false lumen can compromise flow in a critical branch perfused solely by the false lumen, resulting in complications such as paraplegia, lower extremity ischemia, new-onset renal failure, refractory arterial hypertension, or abdominal angina (visceral ischemia). Late aortic rupture can occur into the pericardium, bronchi, esophagus, or pleural cavity, causing tamponade or exsanguination. Nonetheless, a large majority of patients with chronic aortic dissection problems remain asymptomatic and are diagnosed incidentally.

DIAGNOSTIC MODALITIES

Prompt and accurate diagnosis of acute aortic dissection is crucial to determine the optimal treatment strategy.

The initial diagnostic step is exercising a high degree of clinical suspicion, which is especially important considering that aortic dissection has been referred to as the great clinical masquerader. Historically, aortography was considered the gold standard for the diagnosis of aortic dissections, but major developments in cardiovascular cross-sectional imaging during the past 35 years have greatly expanded the spectrum of less invasive modalities available for evaluation of thoracic aortic disease. Specifically, CT scanning, transesophageal echocardiography (TEE), and magnetic resonance imaging (MRI) can quickly and accurately confirm the diagnosis of aortic dissection. It is rare that one must resort to angiography today, unless a catheter interventional procedure is being performed for malperfusion. In selecting which imaging study is best, the clinician should keep in mind what information is needed most in patients with suspected acute aortic dissection. As a general rule, the best initial diagnostic imaging study is the one that can be performed most rapidly in any particular hospital.^{43,44,49,99,115-117} In most medical centers, the procedure of choice is either CT or TEE, which can reliably confirm or rule out the suspected diagnosis quickly. The imaging modality determines conclusively whether the dissection involves the ascending aorta (Stanford type A) or is restricted to the descending thoracic aorta and/or arch (Stanford type B). Determining the severity of aortic valve regurgitation and identification of a large pericardial effusion are also important, which reinforces the clinical utility of TEE.¹¹⁸ Last, localization of the primary intimal tear, determination of the extent of the dissection process, status of the false lumen (patent, partially thrombosed, or completely thrombosed), and the presence or absence of aortic branch compromise are additional key features that should be identified. Interestingly, in an IRAD report, two thirds of patients with acute aortic dissection required two or more imaging studies before a definitive diagnosis could be made before definitive management was begun.¹¹⁹

Although chest radiography is neither sensitive nor specific for the diagnosis of aortic dissection, some findings may be suggestive. Widening of the mediastinal silhouette can be present in up to 50% of cases.^{24,99} Other findings can include the displacement of intimal calcification, a localized hump on the ascending aorta or arch, a widening of the aortic knob, a double aortic shadow, and a pleural effusion.¹²⁰ Similarly, electrocardiographic findings, such as ST-segment or T-wave changes, are non-specific, and an abnormal electrocardiogram can be observed in up to two thirds of patients.²⁴

Aortography

Historically, after the introduction of retrograde catheter aortography through the femoral artery in 1953 by Seldinger this technique became the diagnostic method of choice for acute dissection of the aorta.^{121,122} Diagnosis of aortic dissection relies on the detection of direct or indirect angiographic signs. Direct signs include evidence of a double lumen or an intimal flap; indirect signs are suggestive of acute dissection and include compression of the true lumen by the false lumen, thickening of the aortic

wall, aortic regurgitation, ulcer-like projections in the aortic wall, and abnormal position of the guide wire or catheter in the aorta.^{115,123} Biplane angiographic imaging of the thoracic aorta is mandatory because single-plane aortography can easily miss the diagnosis. The reported sensitivity and specificity of aortography in the evaluation of aortic dissection range between 80% and 90% and 85% and 95%, respectively.^{43,115} An aortic root injection can also detect coexistent coronary artery disease. In emergency situations, selective coronary angiography is not recommended unless the patient has undergone previous coronary bypass grafting or has a compelling clinical history suggesting severe coronary artery disease, because it delays institution of definitive treatment and can be hazardous. Aortography is an invasive technique and requires the use of iodinated contrast agents, which is another reason that catheter aortography is only of historical interest today. Aortography can be time consuming and is not an innocuous technique; moreover, concerns have been raised about the risk of iatrogenic proximal propagation or perforation of the dissection during manipulation of a guide wire or catheter within the aorta.¹²⁴

Computed Tomography

Harris and associates¹²⁵ were the first to report on the use of CT scanning in the diagnosis of aortic dissection in 1979. CT scanning is noninvasive, easy, and rapid to perform and can usually be performed without delay in emergency situations because a CT scanner is available near the emergency department in almost all hospitals, large or small. Because of major technological advances, acquisition of a large number of thin-slice images within seconds during one breath hold is now possible to create a CT angiogram (CTA). The newer dual-energy multi-detector CT machines substantially also reduce the amount of radiation required. Currently we use a second-generation dual-source scanner with two 128-slice detector systems, 270-ms gantry rotation time, and 75-ms temporal resolution (Siemens FLASH). A third-generation dual-source technology scanner is being installed soon. Furthermore, computer technology allows for complex reconstruction of high-quality CTA two-dimensional data, creating three-dimensional images or four-dimensional "cine" reconstructed video clips. The definitive diagnosis of aortic dissection requires the identification of blood flow in two distinct lumens separated by an intimal flap¹¹⁵; ancillary findings include compression of the true lumen by the false lumen, displaced intimal calcification, thrombosed false lumen or IMH, and ulcer-like projection of contrast material within the aortic wall consistent with a penetrating aortic ulcer.¹²⁶ A CTA is useful for accurate measurement of the aortic lumen diameters, and it can detect pericardial and pleural effusions; it also provides information about extent of dissection, arch involvement, and perfusion status of all major aortic branches. ECG-gated CTA can also image the coronary arteries adequately if the heart rate is not too high. The CT scan can also rule out other causes of acute chest pain. In the evaluation of patients with suspected aortic dissection, contrast-enhanced CTA has a

sensitivity of 82% to 100% and a specificity of 90% to 100%.[†] Disadvantages (beside the requirement for intravenous administration of contrast and use of ionizing radiation) of CT include the occasional inability to localize the primary intimal tear accurately, not being able to determine the severity of aortic regurgitation, and occasional poor visualization of rapidly moving flaps in an acutely dissected aorta because of relatively slow temporal resolution or motion artifacts, which has been minimized with the advent of ECG-gated thin-slice three-dimensional CTA.

Magnetic Resonance Imaging

The initial description of the use of MRI in the diagnosis of acute aortic dissection was made in 1983. MRI also is noninvasive; unlike aortography and CT scanning, MRI does not require the mandatory use of iodinated contrast even though magnetic resonance angiography (MRA) uses intravenous administration of gadolinium. MRI relies on the hydrogen ion concentration of blood and tissues to generate images.¹¹⁹ MRI can produce high-quality images of the aorta in the transverse, coronal, sagittal, and oblique projections, allowing excellent delineation of the entire aorta, reasonably accurate diameter measurement, and excellent assessment of associated pathoanatomic features (e.g., extent, localization of the primary intimal tear, branch artery involvement, and the presence of a pericardial effusion). Dynamic imaging with ECG-gated sequences and cine MRI modes can provide information about severity of aortic valve regurgitation and flow timing and direction in the aortic false and true lumens.^{115,117} In nonemergency situations, phase-contrast MRI has the unique capability to depict time-resolved three-dimensional blood aortic flow patterns as four-dimensional cine video clips. As with CT scanning, the criterion for the diagnosis of acute aortic dissection with MRI is the identification of two lumens with blood flow separated by an intimal flap. Similarly, identification of ancillary findings, as described before for CT imaging, is suggestive but not diagnostic of dissection.¹¹⁵ Several studies have shown that MRI is associated with sensitivity and specificity rates in the range of 95% to 100%.[‡] Immediate availability of MRA in urgent circumstances is not always present; another shortcoming of MRI is that it cannot be performed safely in patients with implanted pacemakers, defibrillators, or other ferrous metallic devices.¹³⁰ In the context of acute aortic dissection, MRI has many other limitations because of the relatively long time necessary for image acquisition and the inability to monitor and to treat severely ill, hemodynamically unstable patients while they are in the magnet. These practical factors make MRI not the first choice in patients with acute aortic dissection.

Echocardiography

Echocardiography is an attractive technique for the evaluation of patients with suspected aortic dissection because

[†]References 43, 44, 49, 115-117, 119, 126-129.

[‡]References 43, 44, 49, 115, 117, 119, 127-129.

it is ubiquitous, noninvasive, and easily performed at the bedside, and it does not necessitate the use of contrast material.^{115,117} Initially, only M-mode transthoracic echocardiography was available, but the introduction of two-dimensional echocardiography, color flow Doppler mapping, and now real-time three-dimensional echocardiography greatly improved visualization of the heart and the ascending aorta and permitted accurate assessment of valvular abnormalities and ascending aortic flow patterns.^{42,114,131,132} Transthoracic echocardiography only has a limited role because of suboptimal accuracy compared to other modern imaging modalities.^{117,127,133} The development of TEE overcame most of the technical limitations of transthoracic echocardiography in the evaluation of aortic dissection. High-resolution imaging of the heart and the thoracic aorta is possible with TEE because of the proximity of the esophagus to the aorta and heart. In addition, TEE provides information about aortic valve function, flow characteristics within the true and false lumens, left ventricular size and systolic function, and other associated cardiac valvular problems. Furthermore, TEE can also image the main left and right coronary arteries to rule out proximal coronary disease or involvement by the dissection. A limitation of TEE with the use of first-generation monoplane probes was limited visualization of the distal portion of the ascending aorta and the proximal arch because of the interposition of the trachea and left bronchus¹¹⁶; this limitation is now minimal with the use of multiplane or phased-array TEE probes. TEE can be performed in the emergency department, cardiac care unit, intensive care unit, or operating room with light sedation and topical anesthesia. Ideally, TEE should be performed after a fasting period of 1 hour or more to minimize the risk of aspiration, but in emergency situations this is not usually possible in the emergency diagnosis of acute aortic dissection. Close monitoring of vital signs is important during TEE. Contraindications to TEE include known esophageal disease (e.g., stricture, varices) and possibly severe coagulopathy.¹¹⁷ In the evaluation of patients with suspected aortic dissection, the most important diagnostic finding is the identification and location of an intimal flap, ideally seen in more than one view, undulating independently from the motion of the aortic wall or other cardiac structures.^{115,116,127,132,134} Visualization of different flow patterns in the true and false lumens and extrinsic compression in cases of false lumen thrombosis are other findings that suggest dissection or one of its variants, such as IMH or penetrating atherosclerotic ulcer with or without IMH.^{135,136} TEE for assessment of suspected aortic dissection has a sensitivity rate of 97% to 100% and a specificity rate of 68% to 98%.[§] False-positive test results, accounting for the lower specificity, were usually due to reverberation artifacts from surrounding cardiac structures or the aortic wall itself, producing echo images that were misinterpreted as an intimal flap in the ascending aorta.^{115,127} M-mode echocardiography can distinguish between a genuine intimal flap in the ascending aorta and reverberation artifact.¹³⁴ The main limitations of TEE

involve operator experience to interpret the findings accurately and the inability to assess branch vessel involvement (other than the coronary arteries) and extent of the dissection below the celiac axis level.

DIAGNOSTIC STRATEGY AT STANFORD UNIVERSITY AND SPECIAL DIAGNOSTIC CONSIDERATIONS

Stanford Diagnostic Strategy

Transesophageal echocardiography is currently the initial diagnostic procedure of choice for patients with suspected acute type A dissection because of its accuracy, safety, rapidity, and convenience. Patients with clear-cut TEE diagnostic findings are taken directly to the operating room for repair, whereas patients with inconclusive TEE findings require additional diagnostic studies (CTA or possibly MRA). Most patients transferred from outlying hospitals with suspected dissection have usually already undergone a contrast-enhanced CT scan and are taken directly from the helipad to the operating room, where the diagnosis is confirmed with TEE. In patients with symptoms of malperfusion or branch artery compromise, thin-slice gated CT angiography is the preferred diagnostic modality to evaluate both ascending aortic involvement and perfusion of major aortic branches in the chest and the abdomen. If malperfusion persists after proximal aortic repair, another emergency CT scan is performed immediately postoperatively to delineate the mechanism of persistent branch vessel compromise, which will guide appropriate endovascular catheter interventions to restore satisfactory distal perfusion.^{41,93,110} On the other hand, CTA or MRA is the best modality today to plan surgical intervention in patients with chronic type A dissection as well as to follow the aorta postoperatively. We prefer CTA preoperatively because it provides more detailed anatomic information for operative planning, but we use MRA liberally for serial surveillance follow-up scanning to minimize cumulative radiation exposure.^{49,99}

Intramural Hematoma

Criteria for the diagnosis of IMH involving the ascending aorta are displaced intimal calcification, a crescent-shaped nonopacified area along the aortic wall of more than 5 mm thickness, increased aortic wall diameter, and no evidence of aortic intimal disruption or flap.^{135,139} TEE, CTA, and MRA can detect IMH accurately and are capable of assessing progression or regression of the process during follow-up.¹⁴⁰ In this setting, MRI methods can estimate the age of the hematoma on the basis of the degradation of hemoglobin into methemoglobin after the acute event, resulting in high-intensity signals within the aortic wall on both T1- and T2-weighted images.²⁸

Coronary Angiography

The need for a selective coronary angiogram before surgical repair of patients with acute aortic dissection is

[§]References 43, 44, 49, 99, 115-117, 119, 127-129, 134, 137, 138.

vanishingly rare today and confined solely to special circumstances. The incidence of clinically important coronary artery disease (at least one stenosis $\geq 50\%$ or left main stenosis $\geq 75\%$ diameter reduction) in patients with acute type A dissection is between 10% and 35%.^{141,142} Ideally, patients in stable condition with an acute type A aortic dissection and a history of chronic angina, myocardial infarction, ischemic heart disease, or coronary artery bypass grafting should undergo coronary angiography preoperatively.¹⁴²⁻¹⁴⁴ On the other hand, coronary angiography should not be performed in patients who are unstable, which is frequently the case.⁴⁴ The drawbacks of coronary angiography include the obligate delay, technical difficulties, risk, and potential for false-positive findings. The Cleveland Clinic group reported that preoperative coronary angiography before emergency aortic surgery did not reduce perioperative mortality and did not affect the proportion of patients requiring coronary artery bypass grafting at the time of ascending aortic repair because 74% of coronary bypass grafts were performed for coronary dissection and not intrinsic coronary artery disease.¹⁴⁴ An earlier study from the Brigham and Women's Hospital by Rizzo and colleagues¹⁴⁵ indicated that coronary angiography was a surrogate for preoperative delay, which actually increased operative risk.

Biomarkers

The development of a reliable biomarker for the diagnosis of acute aortic dissection, in addition to imaging modalities, would help in the early identification of acute aortic syndromes in patients presenting with acute chest pain. Several such biomarkers have been investigated, such as D-dimer, circulating smooth muscle myosin heavy chain protein, soluble elastin fragments, calponin, and C-reactive protein.^{44,146-149} However, there currently is no rapid and reliable biomarker available that has been validated to confirm or to rule out the diagnosis of acute aortic dissection and its variants. More research in this arena is ongoing.

MANAGEMENT

Acute Type A Dissection

The aim of therapy in patients with acute aortic dissection is to prevent death and irreversible end-organ damage. A high clinical index of suspicion is mandatory in patients with suggestive signs and symptoms, followed by prompt confirmation of the diagnosis to determine the optimal management strategy. All patients with acute type A aortic dissections should be considered for emergency surgical repair of the ascending aorta to prevent life-threatening complications such as aortic rupture or tamponade.[¶] Exceptions to early operative intervention in patients with acute type A dissection are few, including those with an irreversible major stroke or deep coma,^{10,17,99,111} those with advanced, debilitating systemic

diseases that limit life expectancy or preclude meaningful rehabilitation, and perhaps those older than 80 years who have multiple major complications.¹⁵¹ These relative contraindications, however, have been challenged by some authors.¹⁵²⁻¹⁵⁵ For example, according to recent IRAD reports, patients with major brain injury or mesenteric malperfusion should not be denied early surgical intervention because their early and long-term prognosis is significantly improved compared with medical therapy only,^{111,155} because a majority of patients with stroke may experience partial or complete neurologic recovery after graft replacement of the ascending aorta. Individuals with paraplegia should also not necessarily be denied emergency operation; however, the chance of recovery of spinal cord function is almost zero. In our opinion, surgical repair of the ascending aorta should precede percutaneous vascular interventions addressing peripheral arterial complications of the dissection because "proximal" or "central" aortic repair will usually obviate the need for such distal revascularization procedures.^{102,156} In the Stanford experience focusing on aortic dissection associated with peripheral vascular complications, additional procedures after thoracic aortic repair were necessary in less than 10% of patients.¹⁰² Over the last 15 years, an alternative strategy has been advocated by the University of Michigan group that relies on initial percutaneous catheter interventions (flap fenestration, true lumen bare metal stenting) to restore end-organ perfusion with delayed repair of the ascending aorta after resolution of the malperfusion syndrome.^{157,158} This approach is attractive in that it allows immediate reperfusion and stabilizes the patient, and planned operative repair of the ascending aorta can be performed under better circumstances. In addition, if the end-organ ischemia or infarction has already become irreversible at the time of the catheter intervention, these complications are usually fatal, precluding attempting ascending aortic repair. Conversely, according to the limited data available so far, up to 15% of patients treated according to this alternative approach may die of aortic rupture during the stabilization period.

In most centers in North America and Europe, including Stanford, patients with acute type A IMH are managed identically to those with an acute type A aortic dissection because of the high complication risk that patients with acute type A IMH face.[¶] The rationale behind this approach is to prevent aortic rupture and cardiac tamponade as well as to avoid the rapid evolution of IMH into a classic full-blown dissection.^{**} This approach has been challenged by some, particularly in Korea, where intensive medical therapy is advocated for certain patients with uncomplicated acute type A IMH.¹⁵⁹⁻¹⁶¹ If a patient with acute type A IMH is treated medically, frequent serial imaging studies are mandatory because these patients can progress to overt dissection or aortic rupture within a short time; indeed, most ultimately require surgical intervention within 1 to 2 months.

As soon as the diagnosis of acute type A aortic dissection is suspected, comprehensive monitoring of neurologic status, arterial blood pressure, electrocardiogram,

[¶]References 14, 16, 17, 20, 23, 24, 35, 38, 40, 42-44, 49, 83, 99, 146, 150.

[¶]References 26, 28, 43, 44, 49, 95, 99.

^{**}References 26, 28, 30, 95, 135, 140.

urine output, and peripheral pulses is initiated. An arterial line, a central venous catheter, and a urinary catheter should be inserted. Intensive anti-impulse or negative inotropic therapy (lowering mean and diastolic arterial pressure and, more important, aortic dP/dt) is an integral part of the surgical management of patients with acute type A dissection before and after surgical repair to minimize propagation of the dissection, to decrease the risk of aortic rupture, and to control pain.¹² Intravenous anti-hypertensive and negative inotropic therapy should be started emergently, as soon as acute aortic dissection is suggested, using a beta blocker (e.g., intravenous esmolol, labetalol) initially or, if required, adding a short-acting arteriolar vasodilator, such as sodium nitropruside.^{17,43,44,49,162} Calcium channel antagonists can be used if contraindications to beta blockade exist. Hemodynamic instability suggests free aortic rupture, intrapericardial rupture with tamponade, or acute left ventricular failure secondary to severe aortic valve regurgitation or coronary compromise. In patients with severe hypotension and evidence of tamponade, pericardiocentesis should be attempted to resuscitate the patient only if immediate surgical intervention is not practical, with the goal of aspirating only enough fluid to allow the patient's blood pressure to rise to the lowest acceptable level to minimize the risk of frank aortic rupture (which can occur if the tamponade is completely relieved, causing arterial blood pressure to increase dramatically to high levels).¹⁰³

Surgical Principles

The primary goal of surgical treatment of patients with acute type A dissection is to replace the ascending aorta and proximal arch to prevent aortic rupture or proximal extension of the process with resultant tamponade. The primary intimal tear should be completely resected if it is located in the ascending aorta or the arch. The dissected aortic layers are reconstituted proximally and distally with fine continuous sutures (5-0 Prolene on C1 needle) with or without reinforcement to obliterate the false lumen. Aortic blood flow is redirected into the true aortic lumen distally, increasing the likelihood of reperfusion of aortic branches previously compromised by static or dynamic obstruction. When aortic valve regurgitation is present, aortic valve competence is achieved by reconstruction of the sinuses of Valsalva and aortic root with resuspension of the commissures, which is possible in many cases.^{99,104,163} If one or more of the sinuses of Valsalva is severely damaged by the dissection process, the patient has Marfan syndrome or other connective tissue disorder, a large root aneurysm is present, the patient has severe annuloaortic ectasia, or the valve needs to be replaced for other reasons (e.g., severe aortic stenosis), then complete aortic root replacement with reimplantation of the coronary ostia is indicated by use of either a composite valve graft (CVG) or a valve-sparing aortic root replacement technique, as advocated by Yacoub and David.¹⁶⁴⁻¹⁶⁶ In most cases, the noncoronary sinus of Valsalva is the most severely traumatized and can be treacherous to reconstruct satisfactorily; replacement of just the noncoronary sinus and the tubular ascending aorta (a "uni-Yacoub" procedure) is a simple approach that works

well in these circumstances. Valve-sparing aortic root replacement using David's reimplantation method might be the ideal technique in the setting of acute aortic dissection in young patients with normal valve leaflets, resulting in complete removal of all diseased tissue, less bleeding, and low incidence of need for late reintervention for aortic root or aortic valve problems.¹⁶⁷ The older technique of separate aortic valve replacement and supra-coronary aortic graft replacement is not used frequently any longer in patients with acute type A aortic dissections, but it is appropriate in older patients in whom the sinuses can be salvaged but aortic valve competence is not achievable otherwise.

Technical Considerations

Satisfactory hemostasis remains one of the chief technical challenges surrounding surgical repair of acute type A aortic dissection because of the friable dissected aortic tissue and the coagulopathy that may be present preoperatively. In the past, inclusion-wrap CVG methods (Bentall procedure) and ringed intraluminal grafts were used in an attempt to minimize bleeding; however, these techniques were associated with high failure rates and late problems, including perigraft leakage and false aneurysm formation with the former technique and migration, erosion, and stenosis with the latter.^{168,169} Most surgical authorities now believe that replacement of the dissected aorta includes complete transection of the aorta both proximally and distally and use of full-thickness aorta-to-graft anastomoses to minimize the risks of late complications.¹⁷⁰⁻¹⁷² A precise anastomotic technique is critical; deep suture bites should be used, with a continuous 5-0 C1 or 4-0 BB ($\frac{3}{8}$ circle needles) polypropylene (Prolene, Ethicon, Somerville, NJ). The needle must be advanced carefully on its full curve through the aortic tissue paying particular attention to the needle follow-through to avoid needle hole tears, which can cause troublesome bleeding or anastomotic disruption. If the aortic tissue is highly friable, reinforcement of the dissected aortic layers can be facilitated by reapproximation of the dissection flap to the aortic wall with strips of autologous or bovine pericardium or Teflon felt. European surgeons in the 1980s pioneered the use of gelatin-resorcin-formalin (GRF; "French glue") biological glue to reapproximate the dissected aortic layers which strengthened the aortic tissue to facilitate anastomotic suturing.¹⁷³ Despite wide use and good early results in many centers around the world,¹⁷⁴ concerns soon arose about the potential toxicity of the formalin component of GRF glue; late aortic wall necrosis leading to false aneurysm formation or anastomotic dehiscence occurred.^{175,176} As an alternative to GRF glue, a tissue adhesive composed of purified bovine serum albumin and 10% glutaraldehyde is currently approved (BioGlue, CryoLife, Inc., Kennesaw, GA) in the United States and can be used if necessary. This surgical adhesive is easy to use, facilitates the aortic repair, and decreases blood loss,^{177,178} but it is important to apply BioGlue cautiously. Minimal amounts should be used (just a 2-mm-thick layer extending only 2 cm into the false lumen is recommended), the regions of the coronary ostia must be

avoided, and the adhesive should not be applied far downstream where it may inadvertently enter the true lumen through a flap fenestration. Long-term results after the use of BioGlue are not available, but it also can cause necrosis of the delicate aortic wall. We have seen many cases in which the use of a large amount of BioGlue during the acute type A dissection repair later resulted in false aneurysms of the thoracic aorta, graft dehiscence, and full-thickness aortic necrosis 1 to 3 years later. Technical problems seen in earlier years with stiff woven vascular grafts have been eliminated by the advent of soft-woven, double-velour Dacron grafts that are presealed with bovine collagen impregnation (WDV Hemashield, Maquet Corp., Sunnyvale, CA), which are now routinely used for thoracic aortic surgery.¹⁷⁹ Satisfactory woven vascular grafts presealed with other types of biological sealants (e.g., gelatin in the Terumo Vascutek GelWeave grafts; Vascutek Ltd., Renfrewshire, Scotland) are also now available. Prophylactic administration of coagulation components including small, graduated doses of NovaSeven is also practiced today.

During the past two decades, PHCA, now coupled with selective antegrade cerebral perfusion (SACP) using axillary or innominate artery CPB cannulation, has become routine and safe in patients with acute type A dissection.^{85,99,180,181} This allows careful inspection of the aortic arch and performance of an open distal aortic anastomosis replacing the bulk of the transverse arch. Careful inspection of the arch minimizes the possibility of leaving unrecognized intimal tears in the arch, which are present in up to 20% to 30% of patients^{22,182} and increase the risk of late distal aortic reoperation. Radical “hemiarach” replacement is preferred, sewing obliquely from the ligamentum arteriosum on the lesser curve of the arch to the innominate artery take-off on the greater curve, which eliminates as much dissected aorta as possible. Simply performing an oblique “open” anastomosis in the distal ascending aorta is not recommended. Careful construction of a sound, completely hemostatic distal anastomosis is technically easier in the absence of an aortic cross-clamp, which itself can also traumatize the fragile dissected aortic tissue and tear the intima. An earlier analysis of all acute type A dissection repairs performed with or without PHCA at Stanford using propensity score analysis methodology demonstrated that aortic repair with circulatory arrest was associated with comparable early complication and survival rates.¹⁸³ This lack of superiority favoring PHCA was explained by the fact that in cases in the early years of this experience, PHCA was usually resorted to in desperate circumstances (e.g., aortic disruption or uncontrollable bleeding after the initial repair without PHCA). Although the long-term survival and late distal aortic complications were not improved after the use of PHCA in this risk-adjusted analysis, all surgeons at Stanford use PHCA with SACP routinely today in these patients on the basis of the technical advantages and theoretical potential merit of PHCA associated with an open distal aortic anastomosis. Adjunctive and more aggressive treatment of the distal dissected descending thoracic aorta using a “frozen elephant trunk” (FET) graft has recently gained favor in some experienced centers, as described later.

Operative Technique

General anesthesia is induced intravenously. After intubation, anesthesia is maintained with a combination of inhalation agents and short-acting narcotics. An antifibrinolytic agent such as ϵ aminocaproic acid (Amicar) or tranexamic acid is used routinely to minimize fibrinolytic activity typically observed with CPB and PHCA.¹⁸⁴ Electrocardiography, arterial pulse oximetry, radial and femoral arterial pressure, central venous pressure, bladder (or nasopharyngeal) and tympanic membrane temperatures, and noninvasive near-infrared cerebral oximetry are monitored throughout the operation. TEE is used in all patients to assess the dissected aorta, flow patterns in both the true and false lumens (before, during, and after CPB), aortic valve competency, and left ventricular size and systolic function.

A midline sternotomy incision is used for repair of acute type A dissection. Simultaneous exposure of the right axillary artery is made for arterial CPB cannulation, which is used preferentially in patients with acute type A dissections to provide antegrade blood flow during CPB perfusion and cooling,^{49,99,185-187} and then SACP when PHCA is instituted; this technique is safe, is simple to perform, and avoids retrograde femoral arterial perfusion, which can lead to inadvertent false lumen pressurization and thoracoabdominal or cerebral malperfusion as well as cerebral embolization from debris in the abdominal or descending aorta. Subclavian arterial cannulation is performed with a short, 6- or 8-mm knitted double velour (Microvel Hemashield, Maquet Corp., Wayne, NJ) Dacron graft anastomosed end-to-side to the right axillary artery. If the artery is dissected, it is essential to sew the perfusion graft to the true lumen for safe CPB perfusion. A two-stage venous cannula is inserted into the right atrium through the appendage. The typical CPB circuit used for the surgical management of acute type A aortic dissection is illustrated in [Figure 70-6](#). CPB is established slowly with continuous TEE monitoring of the flow pattern within the ascending and descending aorta and arch to detect any evidence of distal malperfusion, which is suspected if the true lumen becomes small or obliterated. If this occurs, direct cannulation of the aortic true lumen in the arch using the Seldinger technique either with TEE guidance^{99,188-190} or by passing a longer arterial cannula through the left ventricular apex and across the aortic valve into the true lumen (as originally described by Wada and Kazui in the 1970s for mitral valve surgery through a left thoracotomy).^{99,191} One drawback of direct aortic or transapical LV arterial CPB cannulation is that additional steps are necessary to institute SACP when the pump is turned off to do the arch anastomosis; this might explain the high neurologic complication rates seen in Hannover and Essen, Germany, where the direct aortic cannulation technique was popularized. In emergency situations, starting with femoral CPB cannulation is acceptable followed by CPB perfusion from the ascending aortic graft or a side-branch. Alternatively, carotid artery cannulation has been described.¹⁹² A vent is inserted into the left ventricle through the right superior pulmonary vein or directly across the ventricular apex to prevent

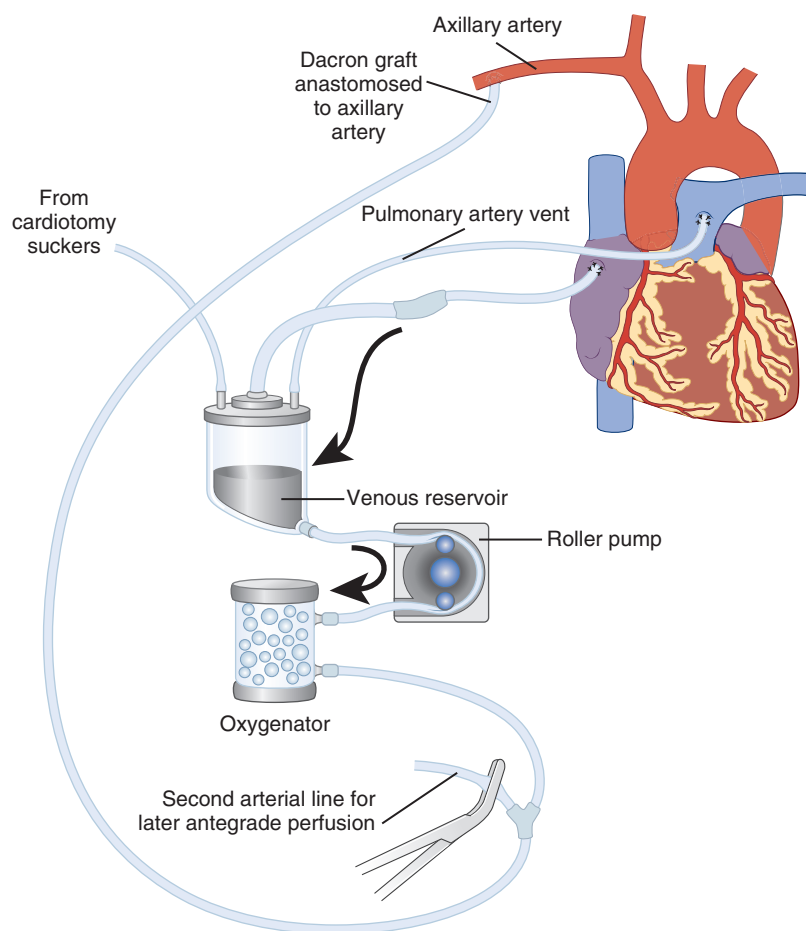


FIGURE 70-6 ■ Schematic of the cardiopulmonary bypass circuit for repair of an acute type A aortic dissection with an open distal anastomosis during a period of hypothermic circulatory arrest and selective antegrade cerebral perfusion. Arterial cannulation is performed with a short 6-mm Dacron graft anastomosed end to side to the right axillary artery.

distention. Systemic cooling is initiated, avoiding gradients of more than 10°C between the patient and the arterial perfusate temperature, and continued for at least 30 minutes or until tympanic temperatures approaches 20°C ; bladder temperature is usually in the range of 25° to 28°C . It is important to monitor the tympanic membrane temperatures and cerebral oximetry during cooling and rewarming to detect inadequate or asymmetric cerebral CPB perfusion. If such perfusion occurs, the aorta is examined using TEE to determine why one of the arch branches is not being perfused adequately, and recannulation needs to be considered. In addition, preparations are made in advance to perfuse the left common carotid artery and/or left subclavian artery with balloon-tipped perfusion cannulae when SACP is instituted. During cooling, the aortic root and ascending aorta are carefully dissected away from the right and left atria, right ventricular outflow tract myocardium, pulmonary valve annulus, and main and right pulmonary arteries. The pericardial reflection (or "veil") covering the left main coronary artery, which extends anteriorly and leftward to the pulmonary annulus, must be divided following the right and main pulmonary arteries. The ascending aorta is not clamped during cooling except when unmanageable severe aortic valve insufficiency mandates aortic clamping to prevent left ventricular distention. Dexamethasone (8 to 12 mg) is administered before commencement of CPB to enhance cerebral and spinal cord

protection. Mannitol (0.3 to 0.4 g/kg) and furosemide (40 to 80 mg) are given when commencing CPB to minimize ischemic reperfusion injury (hydroxyl and superoxide free radical scavengers). The head is packed in ice. The field is flooded with CO_2 gas. After CPB flow is reduced to 10 mL/kg/min , the cross-clamp is removed, the aorta is opened, and SACP is begun slowly. After confirmation that CPB pump flow is entering the arch from the true lumen of the innominate artery, the innominate artery is clamped, and the back-bleeding down the left common carotid artery and then the left subclavian artery is inspected, indicating patency of the circle of Willis. If the back-bleeding is red and relatively brisk, these two arch branches are sequentially clamped. If the left common carotid artery or subclavian artery back-bleeding is visually judged to be inadequate (trickle back flow or dark blood returning) or asymmetric tympanic membrane temperatures or cerebral oximetry is detected, additional perfusion cannulas can be inserted directly into the left common carotid and/or subclavian arteries. Unilateral SACP is usually adequate in our experience, but it should be noted that Dr. Kazui's original SACP method involved perfusion of all three arch branches at a total flow rate of 10 mL/kg/min .¹¹¹ Intermittent retrograde cold blood cardioplegia and topical cooling (Daily Cooling Jacket, Daily Medical Products, Luke Medical, Inc., Plymouth, MN) are used for myocardial protection.

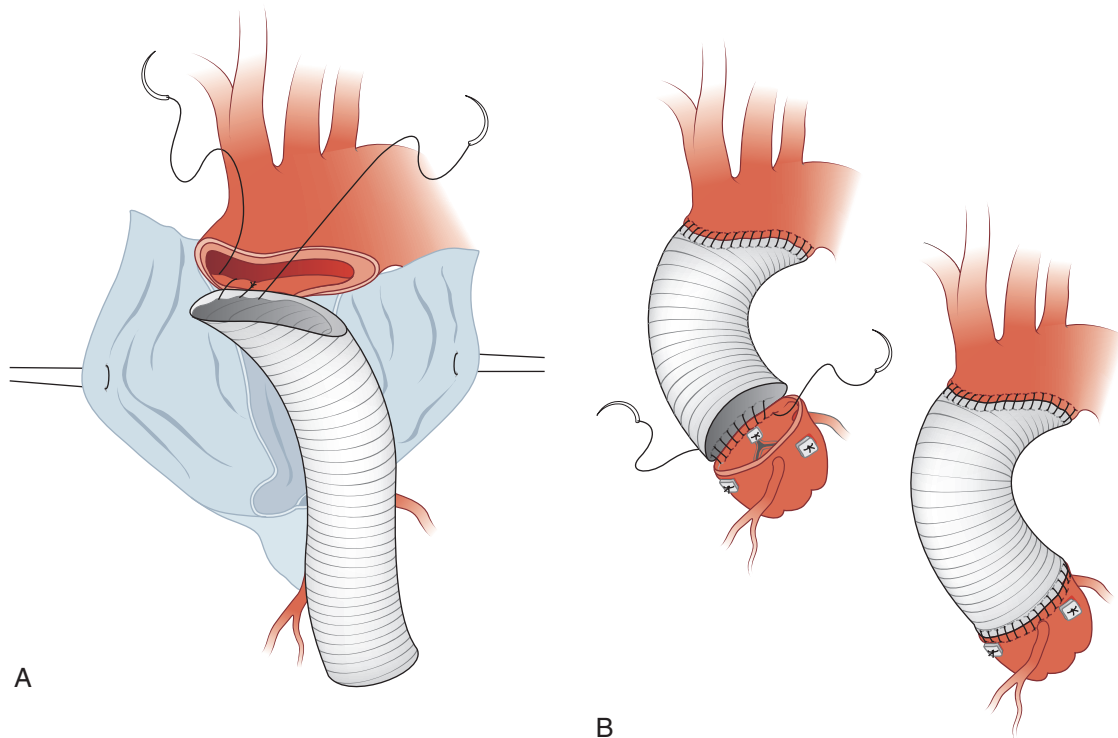


FIGURE 70-7 ■ **A**, An open distal anastomosis is always used to avoid intimal damage with a clamp and to allow inspection of the aortic arch. The aorta is transected immediately proximal to the innominate artery and distally toward the lesser curvature to the level of the left subclavian artery. An appropriately sized graft is beveled and anastomosed with 4-0 polypropylene suture. The Gripp method of rotating the beveled end of the graft 180 degrees such that the “toe” of the graft actually apposes the greater curve of the arch near the innominate artery is used, which tucks the completed graft into the natural curve of the arch and prevents excessive angulation of the graft. Most commonly, the false lumen is obliterated with the anastomotic suture line without reinforcing material. **B**, After aortic root reconstruction and resuspension of the valve commissures, the graft is anastomosed to the reconstructed proximal aortic cuff in an end-to-end fashion with a running 4-0 polypropylene suture.

The ascending aorta is opened to locate the primary intimal tear and to evaluate the aortic valve and sinuses, and then the arch and proximal descending thoracic aorta are inspected. The aortic segment containing the intimal tear is resected, and the aortic arch is trimmed circumferentially in an oblique fashion in preparation for extended hemiarch replacement. Reapproximation of the distal aortic layers is preferentially accomplished as part of the distal anastomotic suture line in the arch; if absolutely necessary, a small amount of tissue adhesive or BioGlue the dissected layers can be helpful. An end-to-end aortic anastomosis is then carried out with an appropriately sized and beveled woven, double velour Hemashield Dacron graft with a continuous 5-0 C1 or 4-0 BB polypropylene suture (Fig. 70-7A). We do not prefer to do so, but suturing two strips of pericardium or Teflon felt (one inside the false lumen and one externally) with a separate 4-0 BB polypropylene suture line to form a solid full-thickness distal aortic cuff can be done to reconstitute very friable aortic layers before the distal arch anastomosis. The counter-intuitive technique pioneered by Dr. Randall Gripp of rotating the beveled distal end of the graft 180 degrees such that the “toe” of the graft actually apposes the greater curve of the arch near the innominate artery is important and always is used, which tucks the completed graft tightly into the natural curve of the arch and prevents the lesser curve of the graft from being too long, which causes excessive

angulation of the graft rightward and anteriorly and kinking. When the arch anastomosis is completed, the left subclavian artery, left common carotid artery, and innominate artery clamps are sequentially removed with the patient placed in steep Trendelenburg position, and the arch and great vessels are de-aired using manual massage. CPB flow is resumed in an antegrade fashion using the original axillary artery cannula, and the arch graft is clamped. Flow in the descending aorta is quickly assessed with TEE to ensure that the true lumen has not become obliterated by a pressurized false lumen. After 10 minutes of cold systemic reperfusion, gradual rewarming of the patient to 35° C (bladder) is initiated.

The aortic root and valve are then evaluated and additional intimal tears are excised. If aortic root replacement is not necessary, the ascending aorta is transected immediately above the sinotubular junction. Valvular regurgitation secondary to commissural detachment can be corrected by resuspension of the tops of the commissures at the level of the sinotubular junction using pledgeted 5-0 polypropylene sutures at each commissure to approximate the dissected layers of the sinuses of Valsalva; this technique will result in aortic valve competence in 70% to 80% of patients.^{104,163,193} A second woven double velour graft of appropriate diameter is then anastomosed to the reconstructed proximal aortic cuff in an end-to-end fashion with a running 5-0 C1 or 4-0 BB polypropylene suture (see Fig. 70-7B). Finally, the two grafts are

shortened on reverse bevels such that the lesser curve side is much shorter, and a graft-to-graft anastomosis is constructed using 3-0 RB1 polypropylene. We use two separate grafts to avoid geometric distortion and torquing the friable aortic anastomoses. A needle vent is inserted in the graft for de-airing, and the cross-clamp is released. TEE rapidly confirms whether the aortic valve is competent, and the anastomoses are inspected. Short-axis TEE views of the aortic root confirm satisfactory main coronary artery perfusion. When the patient is adequately rewarmed, CPB is discontinued, and protamine sulfate is administered after all anastomoses are judged to be technically satisfactory with minimal bleeding. Platelets, fresh-frozen plasma, cryoprecipitate, or small fractionated doses of NovaSeven are administered if diffuse hemorrhage from needle holes, suture lines, and raw surfaces is evident after a normal activated clotting time is achieved. Coagulation abnormalities identified by rotational thromboelastography guides administration of specific coagulation components.¹⁹⁴

More Radical Management of the Aortic Root

Patients with dissection-related destruction of the aortic root, individuals with Marfan syndrome or other connective tissue disorder (including bicuspid aortic valve), and those with markedly dilated sinuses of Valsalva or annuloaortic ectasia should undergo CVG root replacement or valve-sparing aortic root replacement using the David reimplantation method with complete excision of the sinuses of Valsalva (see [Chapter 67](#)), rather than resuspension of the aortic valve and preservation of the sinuses. A conservative approach limited to replacement of just the tubular segment of the ascending aorta in these cases is associated with suboptimal long-term results and a high likelihood of subsequent aortic or aortic valve problems requiring reoperation.^{104,171,195} Complete aortic root replacement with a CVG has become more popular over the past decade since it is reliable and no residual dissected or weak sinus tissue remains, but does expose the patient to the consequent cumulative morbidity associated with valve replacement.

Since the noncoronary sinus of Valsalva usually is the one most severely involved by the dissection process, an alternative technique is a “uni-Yacoub” procedure where the entire noncoronary sinus is replaced using a single proximal “U-shaped” tongue fashioned from the aortic graft suturing close to the hinge of the aortic cusp with a fine (5-0 C1) polypropylene suture. Occasionally, even a “bi-Yacoub” procedure—replacing the noncoronary and the right sinuses of Valsalva with right coronary artery reimplantation—can be useful if both sinuses are destroyed. If the aortic valve is markedly abnormal or cannot be repaired in a durable fashion, separate valve and supracoronary aortic graft replacement is a reasonable alternative in certain patients if it is performed according to the tenets of the original Wheat-Shumway-Groves procedure, in which minimal sinus tissue remains above the annulus except for tongues surrounding the left and right coronary ostia.¹⁹⁵ Direct extension of the dissection into the coronary ostia is not common (more

often in the right coronary artery), and can be challenging to correct.¹⁰⁵ The flap in the sinus running close to the proximal main coronary ostium can usually be glued together in the proximal aortic reconstruction. On occasion, the safest solution is complete CVG root replacement with reimplantation of reconstituted coronary artery ostia as full-thickness Carrel patches (or buttons) into the graft, either directly or using a short interposition saphenous vein graft as introduced by Zubiarte and Kay.¹⁹⁶ Alternative techniques include the Cabrol-II moustache coronary reconstruction with a small synthetic graft¹⁹⁷ and, in exceptional circumstances, suture ligation of the coronary and bypass grafting.^{105,198}

Management of the Aortic Arch

In up to approximately 30% of patients, the primary intimal tear is found in the aortic arch, which has historically been associated with a poorer prognosis.^{22,84,85,182} Most tears are located on the lesser curve of the arch under the innominate artery, permitting complete resection of the tear using the extended arch technique with a single sigmoid-shaped suture line running from the ligamentum on the lesser curve to the innominate artery on the greater curve. In cases in which the primary intimal tear is located more distally in the arch, on the greater curve in proximity to branch vessels, or when arch rupture or a preexistent arch aneurysm is encountered, total arch replacement is required, but is associated with higher perioperative mortality and morbidity, especially in older and critically ill patients.^{84,85,199,200} With a primary tear located in the arch, failure to include the arch in the repair increases the probability of requiring subsequent distal aortic reoperation and reduces long-term survival.⁸⁵ Improvements in surgical techniques and brain protection during PHCA and SACP²⁰¹ have made concomitant total arch replacement a reasonable and safe option in selected patients when necessary.^{99,202} A recent report from the German Registry for Acute Aortic Dissection Type A (GERAADA) evaluating cerebral protection methods in 1558 patients operated between 2006 and 2009 found that the operative mortality and the incidence of permanent neurologic dysfunction were lower using SACP compared with PHCA only, especially for longer circulatory arrest periods that are required for complex arch reconstructions.²⁰¹ In these circumstances, total arch replacement is performed using a distal elephant trunk graft technique, which can be a simple downstream FET stent-graft in the aortic true lumen tacked around the left subclavian artery takeoff, as popularized by Pochettino and colleagues^{203,204} and Roselli and colleagues²⁰⁵ (discussed later), or complete arch replacement. Instead of using the original 1982 Borst arch replacement with elephant trunk graft technique, in which the three arch branches were reimplanted en bloc as a single island (see [Chapter 68](#)),²⁰⁶ a multibranched arch graft is used when complete arch replacement is necessary.^{207,208}

Distal Frozen Elephant Trunk Graft

The open arch replacement approach enables one to add a downstream surgical elephant trunk graft or a FET

stent-graft in the true lumen of the descending aorta, which theoretically will reduce the rate of late false lumen aneurysmal degeneration. Pochettino and Roselli in the United States, Karck, Jakob, Haverich, Mestres, and Di Bartolomeo in Europe, Kazui and others in Japan, and Sun in China have championed this approach,^{203,205,209-211} which can be performed by modifying a commercial thoracic aortic stent-graft or using a specially designed commercial device. This downstream adjunctive procedure, however, does increase the chance of spinal cord injury, and may incrementally increase operative mortality risk. In Europe, this is being accomplished using commercial hybrid integrated stent-graft devices such as the Terumo Vascutek Thoraflex multi-branch graft (Vascutek Ltd.) and the Jotec "E-vita open" system (Jotec, Hechingen, Germany), which are specially designed integrated commercial devices that incorporate the arch graft segment and the distal stent-graft.²¹² In China, the Cronus FET (MicroPort Medical, Shanghai, China) along with a standard four-branch arch graft have been used extensively by Sun and his group in Beijing.²¹³ While this approach is gaining popularity, what is not known is which patients are at highest risk for subsequent downstream aortic complications who theoretically would benefit most from this more aggressive adjunctive procedure during the initial operation.²¹⁴ Results of future investigations using these devices will help to define who will benefit from this aggressive downstream surgical approach. Ideally, a multicenter, prospective randomized controlled trial will be launched to investigate this question, but securing adequate funding for such a trial has been unsuccessful.

Special Situations

Primary Intimal Tear in the Descending Thoracic Aorta (Retro-A Dissection). In 5% to 10% of cases, acute type A aortic dissection is due to retrograde extension of the dissecting process from a primary intimal tear located in the descending thoracic aorta, a situation that Reul and Cooley in 1975 termed a *DeBakey type III-D dissection*.^{17,21} We prefer the simpler term *retro-A dissection*, as introduced by Lansman, Griepp, and the Mount Sinai group.²² Furthermore, the incidence of retro-A dissections has increased considerably as a devastating complication of endovascular descending aortic stent-grafting (TEVAR). Patients with this subtype of acute type A dissection were thought to have a poor prognosis because of intraoperative complications,^{17,22} including hemorrhage from the distal aortic anastomosis, or rupture of the descending aortic false lumen during or after ascending aortic replacement.^{22,215} To prevent these complications, single-stage resection of the primary intimal tear in the descending aorta with replacement of the ascending aorta and entire arch through a median sternotomy or left thoracosternotomy incision has been proposed in carefully selected patients with a patent false lumen in the ascending aorta, aortic regurgitation, cardiac tamponade, or marked dilation of the ascending aorta.²¹⁵

In patients in whom the false lumen of the ascending aorta has thrombosed and no dilation of the ascending aorta or aortic regurgitation is present, continuing medical therapy may be reasonable^{216,217}; however, our

philosophy usually calls for more aggressive surgical treatment, meaning at least graft replacement of the ascending aorta and partial or total arch replacement in younger individuals if they are suitable operative candidates. More recently, TEVAR has been applied in patients with a natural retro-A dissection with favorable midterm results^{218,219} as an isolated procedure designed to cover the primary intimal tear in the descending aorta hoping this will accelerate thrombosis of the false lumen in the arch and ascending aorta, or in conjunction with extended surgical replacement of the ascending aorta and arch.²¹¹ Arch replacement plus a distal frozen elephant trunk approach, described above, can also be an option in these circumstances.^{203-205,209-215}

Type A Aortic Dissection and Coarctation. Acute aortic dissection in the presence of an untreated aortic coarctation is a rare problem, with few reported cases in adults.^{60,62} Simultaneous repair through a median sternotomy incision is advocated by most authors if the patient is young. Retrograde femoral arterial CPB perfusion of the brain through the coarctation is problematic in this situation, with resultant cerebral hypoperfusion; this potential problem is avoided with right axillary artery CPB cannulation coupled with simultaneous femoral CPB perfusion if the obstruction at the coarctation is severe. In addition to standard ascending aortic and arch dissection repair, the coarctation can be treated with a bare metal stent, TEVAR, or an extra-anatomic bypass from the ascending aortic graft to the distal descending aorta, through the posterior pericardium.^{61,62}

Postoperative Malperfusion. Diligent surveillance postoperatively is needed to detect persistent or new malperfusion before irreversible infarction of important end organs occurs. Today, most if not all of the persistent or new malperfusion syndromes after surgical repair of aortic dissection can be managed with endovascular techniques, including stent-graft implantation, balloon flap fenestration, and direct stenting of the true lumen of compromised branches.^{41,99} Specific management of branch vessel malperfusion is discussed in more detail in [Chapters 71](#) and [72](#).

Chronic Type A Dissections

Indications for Operative Intervention

Operation for patients with chronic type A dissection is indicated if symptoms occur or if progressive aortic enlargement is present, including symptoms of congestive heart failure or evidence of left ventricular dysfunction or dilation because of severe aortic valvular regurgitation. In asymptomatic patients, surgical intervention is generally recommended when the diameter of the ascending aorta is greater than 55 to 60 mm (50 mm in patients with Marfan syndrome) or if the documented rate of expansion is greater than 5 to 10 mm during 1 year.^{49,112,220,221} Dissected thoracic aortas rupture at a smaller size than do degenerative or atherosclerotic thoracic aortic aneurysms.²²² Seasoned surgical judgment is important on an individualized basis. The expected

benefits of graft replacement of the aorta in asymptomatic patients must be weighed against the operative risk, taking into account the frequent medical comorbidities these patients have that increase surgical risk or otherwise limit life expectancy; these risk factors, paradoxically, are also the same variables that portend a higher risk of aortic rupture (e.g., Marfan syndrome, other connective tissue disorders, uncontrolled hypertension, increasing age, and chronic obstructive pulmonary disease).^{220,221} Expansion of the size of the false lumen in the distal aorta (usually the proximal descending thoracic aorta) after successful proximal aortic repair or local complications of a previous operation (e.g., aortic root aneurysm, anastomotic false aneurysm, worsening aortic regurgitation) are also indications for operation in patients with a chronic type A aortic dissection.^{112,223}

Surgical Technique

More extensive resection and more complex aortic reconstruction are generally necessary in patients with chronic type A dissections compared to their acute type A counterparts. Preservation of the aortic valve and sinuses of Valsalva is usually not achievable in these circumstances; if it is possible, the repair may not be durable. Aortic root replacement using a CVG is required in most circumstances. In highly select young patients, the Tirone David reimplantation technique valve-sparing aortic root replacement may be feasible to avoid long-term anticoagulation, but only if minimal scarring is present or if there is not too much deformity and scar around the synthetic material used at a previous operation (see [Chapter 67](#)).^{164,166} Since large false lumen aneurysmal degeneration frequently exists in the aortic arch and descending thoracic aorta in the setting of chronic type A dissection, total arch replacement with an elephant trunk graft after flap septectomy in the descending thoracic aorta is often necessary to facilitate staged subsequent replacement of the descending thoracic aorta; alternatively, if there are no or few large fenestrations in the dissection flap in the descending aorta, then a stent-graft (TEVAR or FET) deployed antegrade carefully in the true lumen of the descending aorta can result in subsequent false lumen thrombosis proximally, which hopefully progresses caudad over time (see [Chapters 68 and 72](#)).^{112,206,223-225} Alternatively, a single-stage “arch first” approach using PHCA (with antegrade SACP via the right axillary artery) for patients with chronic type A dissections as pioneered by Kouchoukos using a bilateral anterior thoracotomy or clamshell incision provides excellent long-term durability with reasonable operative mortality and morbidity risks.²²⁶ The most common complication is respiratory insufficiency requiring temporary tracheostomy. This simultaneous approach involves replacement of the transverse arch first under deep hypothermic circulatory arrest to minimize cerebral ischemic time, followed by descending thoracic or thoracoabdominal aortic replacement.²²⁶

In contrast to patients with acute dissection, perfusion of downstream vital organs may depend solely on a patent false lumen in the chronic phase of dissection; hence, maintaining antegrade flow in both the true and the false

lumens can be vital to avoid iatrogenic malperfusion after aortic repair. To achieve this goal, flap septectomy with or without distal flap fenestration is performed to allow blood flow to perfuse both the distal aortic true and false lumens downstream with a short dangling elephant trunk graft in the distal “common chamber” of the descending thoracic aorta or supraceliac abdominal aorta.

RESULTS

Early Survival

Contemporary reports have documented improved surgical outcome in patients with aortic dissection, with perioperative mortality rates decreasing from 30% to 60% in the 1960s to 5% to 25% in the last 2 decades.^{††} These lower early mortality rates were attributed to progressive advances in diagnosis and imaging; improved surgical methods, better myocardial protection, more sophisticated CPB techniques; improved perioperative management; and increased surgical experience. Other factors, such as patient referral patterns and patient selection bias, however, must also be considered when comparing retrospective results between various eras and between different institutions. It is sobering to note that the most recent IRAD 2014 report showed that the early mortality rate in surgically treated patients with acute type A dissection was greater than 20% between 1996 and 2013 in 1995 patients collected from 24 centers worldwide.²⁴⁰ At Stanford University between 1963 and 1992, the overall operative mortality rate was 26% in 174 consecutive patients undergoing surgical repair for acute type A aortic dissection, decreasing from 38% in the 1963-1976 period to 27% in the 1988-1992 period.¹⁰ In this 30-year experience, the independent determinants of early mortality were earlier operative year, older age, hypertension, preoperative cardiac tamponade, and renal dysfunction. More recently, the early mortality rate decreased to 17% in a series of 151 patients presenting with an acute type A aortic dissection operated on between 1993 and 1999 (see [Fig. 70-7](#)),¹⁸³ consonant with other large contemporary series of surgical treatment of patients with acute type A dissections.^{††} In the entire cohort of Stanford patients, the independent risk factors for early death were again earlier operative year, older age, preoperative tamponade, and renal dysfunction. Overall, it appears that patient-specific factors and not treatment strategies (e.g., the use of PHCA) were the main determinants of adverse outcome. The only potentially modifiable factors, moreover, were cardiac tamponade and renal dysfunction, which might theoretically be lower if the diagnosis is made earlier. Interestingly, site of intimal tear, pulmonary disease, and arterial hypertension, which were significant in earlier analyses,¹⁵⁰ did not increase the likelihood of death in the later years of this 37-year series.

These observations parallel findings reported in other contemporary reports from centers with special expertise

^{††}References 10, 16, 24, 37, 38, 43, 44, 49, 82-84, 99, 150, 170, 180, 183, 227-239.

^{††}References 37, 82, 180, 227-229, 232, 233, 235, 237.

in thoracic aortic surgery. According to older analyses by Crawford and colleagues, earlier operative date, severe symptoms, presence of coronary artery disease, diabetes mellitus, reoperation for bleeding, postoperative stroke, and cardiac complications were independent risk factors for early death after surgical treatment of type A dissection.^{84,234} In the Cleveland Clinic experience with 135 acute and 73 chronic type A dissections, independent predictors of early mortality were earlier operative year, hemodynamic instability, not using PHCA, longer PHCA time, need for composite valve graft for aortic root replacement, and concomitant coronary artery bypass grafting.²³³ Increasing age, hemodynamic compromise, and absence of hypertension were identified as risk factors for hospital death in the Mount Sinai experience⁸²; renal or mesenteric ischemia and preoperative shock predicted early deaths in Kazui's experience in Japan.²²⁹ In a retrospective analysis of a U.S. national administrative database (nationwide inpatient sample [NIS]) including 3013 patients undergoing surgical repair of acute type A aortic dissection between 1995 and 2003 in the United States, the mortality rate was 26% and the only independent determinants of early death were increasing age and operation in a nonacademic hospital.²³⁷ Another analysis of outcomes in 5184 patients operated for acute aortic dissection from 2003 to 2008 in the U.S. NIS database observed an overall mortality rate of 21.6% (19.1% between 2005 and 2008) and found a strong inverse relationship between operative mortality and both surgeon and institutional volume, suggesting that repair of acute aortic dissection may display a volume-outcome relationship similar to what is seen in other cardiovascular surgical diseases.²³⁹ Among 526 patients in IRDA with acute type A dissection enrolled prospectively between 1996 and 2001, predictors of early death were previous aortic valve replacement, migrating chest pain, shock or tamponade at presentation, and preoperative peripheral malperfusion,²³⁶ again emphasizing the importance of patient-specific factors and dissection-related complications in terms of surgical risk.

Finally, perhaps all is not stagnant in this field. In 2014, a report from Duke University demonstrated that these sobering surgical results for acute type A aortic dissection can be improved if a dedicated multidisciplinary thoracic aortic team is implemented.²⁴¹ They compared their results over 5-year intervals before (1999-2005) and after (2005-2011) this team was established. In the earlier era, an average of nine acute type A repairs were performed each year by 11 different surgeons. After 2005, an average of 12 cases was done annually, but 97% of them were performed by two specially trained thoracic aortic surgeons. Operative mortality rate fell from 34% to 2.8%, and this translated directly into improved 4- to 5-year survival results. Using the IRAD predicted risk algorithm, the observed-to-expected 30-day mortality ratio fell from 1.26 to 0.15; although the more recent patient substrate was at somewhat lower risk, this is a tremendous achievement. Although an annual acute type A dissection volume of 9 to 12 cannot be considered to be a high-volume institution, one of the NIS studies revealed that only 15 NIS-participating institutions in the United States performed over 10 cases per year,

which is an astoundingly low number.²³⁷ Nonetheless, the accompanying editorial declared that ample opportunity clearly exists in the United States and presumably other countries around the world to improve outcomes if health policy regulators and payers enforce strict regionalization of thoracic aortic surgical services such that the vast majority of patients with all types of thoracic aortic disorders—including acute type A dissections—would be cared for in a small number of institutions with greater experience and special expertise.²⁴² The editorialist opined that in the United States only one thoracic surgical center would be necessary for every 5 to 10 million inhabitants, meaning only 32 or possibly 64 specialized institutions in the United States (out of approximately 1325 hospitals performing more than one thoracic aortic case per year between 1999 and 2010) would be reimbursed for thoracic aortic surgery cases to cover our population of 316 million.²⁴² This health policy process improvement step is long overdue.

On the other hand, early mortality risk after surgical treatment of patients with chronic type A dissection is generally lower than that for patients with acute dissections. In the 1995 summary of the Stanford 30-year experience, early mortality rate was 17% in 106 patients with chronic type A dissections and only 6% in the subgroup of patients with Marfan syndrome.¹⁰ In an analysis of 690 patients with aortic dissections during a 33-year period, Crawford and colleagues²³⁴ observed a 30-day mortality rate of 12% in patients with chronic type A dissections operated on before 1986 and only 8% in those operated on after 1986. Independent determinants of death were severity of symptoms, previous aortic surgery, concomitant coronary artery disease, use of intra-aortic balloon pump, cardiac complications, and postoperative stroke. Similarly, Sabik and associates²³³ from the Cleveland Clinic reported an early mortality rate of 11% in 73 patients with chronic type A dissections treated surgically. More recently, refinements in surgical techniques, including the use of the FET technique or the arch-first technique, have led to improvements in surgical outcomes with reported early mortality rates as low as 4%.^{112,223,226}

Late Survival

In DeBakey's seminal 1982 report on long-term results in 527 surgically treated patients with aortic dissection (type A or B, acute or chronic), the overall survival estimates were 57%, 32%, and 5%, after 5, 10, and 20 years, respectively.¹⁶ In patients with type A dissections, 29% of late deaths were attributed to complications related to rupture of the dissected aorta in a remote downstream location, emphasizing the long-term life-threatening nature of aortic dissection and the need for improved long-term imaging surveillance, prophylactic reoperation when indicated, and intensive medical follow-up care.

In the 30-year Stanford experience, the overall survival rates (including hospital deaths) for patients with acute type A dissections at 1, 5, 10, and 15 years were 67%, 55%, 37%, and 24%, respectively.¹⁰ For patients with chronic type A dissections, long-term survival estimates at these same times were, respectively, 76%, 65%, 45%,

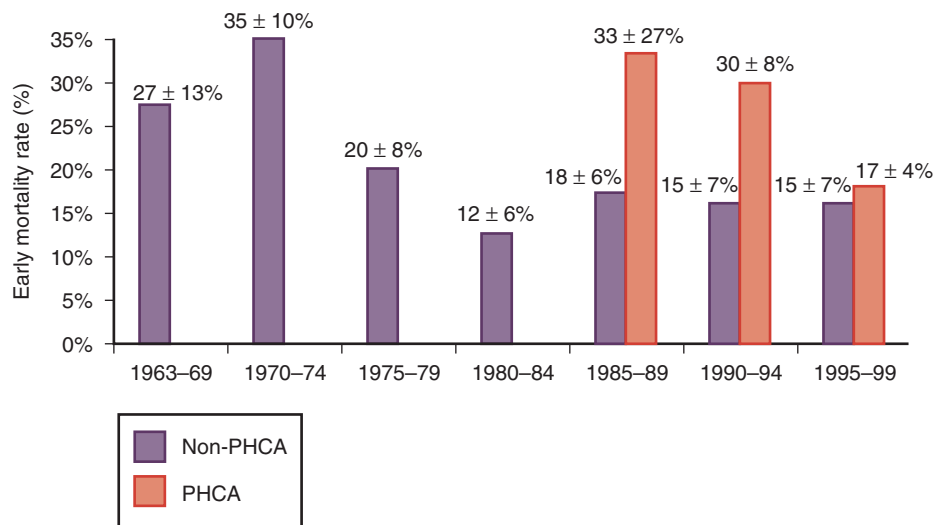


FIGURE 70-8 ■ Operative mortality rates as a function of time for patients with acute type A dissection operated on between 1963 and 1999 at Stanford University and broken down according to treatment method. *Non-PHCA*, No circulatory arrest; *PHCA*, profound hypothermic circulatory arrest. (From Lai DT, Robbins RC, Mitchell RS, et al: Does profound hypothermic circulatory arrest improve survival in patients with acute type A aortic dissection? *Circulation* 106:1218-1228, 2002. Copyright 2002, American Heart Association.)

and 27%. For patients with acute type A dissections, the late survival estimate for discharged patients was 91%, 75%, 51%, and 32% at 1 year, 5 years, 10 years, and 15 years, respectively, compared with 93%, 79%, 54%, and 33% for those with chronic type A dissections. One third of the late deaths were cardiac related, but at least 15% of deaths were due to complications related to the downstream chronic aortic dissection. Multivariable analysis identified older age and previous cardiovascular operation to be significant risk factors for late death; interestingly, previous stroke, remote myocardial infarction, chronic renal dysfunction, and earlier operative date, which were independent predictors of adverse late outcome in the 1985 Stanford analysis,⁴⁰ no longer emerged as risk factors in the larger, more recent analysis. In the more recent report from Stanford of patients with surgically treated acute type A dissections, independent determinants of late death were increasing age, previous sternotomy, prior stroke, hypertension, liver disease, tamponade, arch involvement, and earlier year of operation; use of PHCA and resection of the intimal tear were not identified as significant predictors of late death.¹⁸³ Actuarial survival after surgical repair of acute and chronic type A aortic dissections in the patients operated on at Stanford University between 1963 and 2000 is shown in Figures 70-8 and 70-9.

In Crawford's 1990 report, survival at 1, 5, and 10 years in patients with proximal dissections (acute or chronic) was 78%, 63%, and 55%, respectively²³⁴; life expectancy was significantly worse in patients with acute dissections (67% for acute versus 81% for chronic at 1 year, and 51% versus 68% at 5 years). Independent predictors of late death in all patients included severity of symptoms, New York Heart Association (NYHA) functional class, distal extent of resection, unresected residual aneurysm, postoperative complications, and earlier year of operation. In his 1992 updated series focusing only on acute type A aortic dissections,⁸⁴ Crawford reported

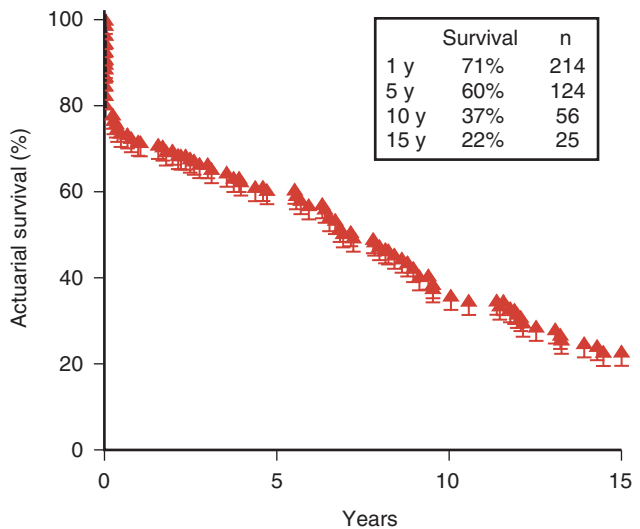


FIGURE 70-9 ■ Actuarial survival after operative repair of acute type A aortic dissection in 323 consecutive patients operated on between 1963 and 2000 at Stanford University Medical Center.

survival estimates at 5, 10, and 20 years after surgical repair of 56%, 46%, and 30%, respectively. Determinants of mortality in this series were earlier year of operation, inclusion of the arch in the repair, NYHA functional class, diabetes, and concomitant coronary artery bypass grafting. In the Cleveland Clinic experience, long-term survival was comparable between those with acute and those with chronic type A dissections; older age, higher blood urea nitrogen concentration, aortic arch replacement, and earlier date of operation were incremental risk factors for late death.²³³

Recent, large single-center and multicenter clinical reports corroborate these results and show only modest improvement in the long-term prognosis after surgical repair of acute type A aortic dissections during the last

two decades. In their extensive experience with 315 patients operated on during a period of 27 years, Tan and colleagues from the Netherlands reported survival (of discharged patients only) at 1 year, 10 years, and 20 years of 96%, 68%, and 39%, respectively. In their series, advancing age and renal failure were the only predictors of late death.^{242a} In the Mt. Sinai analysis of their contemporary cohort of patients operated on with a standardized surgical approach, Griep and colleagues reported survival estimates at 1, 5, and 10 years of 91%, 78%, and 66%, respectively, for hospital survivors.¹¹³ Independent risk factors for late mortality were advancing age, neurologic deficit at presentation, and patent false lumen postoperatively. Finally, in the IRAD analysis of long-term survival after acute type A aortic dissection, patients who survived initial surgical repair had 1- and 3-year survival rates of 96% and 89%, respectively.²³⁸ The only significant predictors of late death identified were history of atherosclerosis and previous cardiac surgery. These figures need to be interpreted with caution, however, as the IRAD consortium did not mandate long-term follow-up after initial hospital discharge; late vital status and clinical data were available in approximately half of their patients.

Reoperation

After repair of acute type A aortic dissection, growth rates of the arch and thoracoabdominal aorta have been estimated to be 1 to 5 mm per year by several investigators.^{113,114} As such, despite successful intervention in the acute or chronic phase of the disease, aneurysmal degeneration of the false lumen in other downstream segments of the aorta can occur in a substantial proportion of patients, which can lead to late aortic rupture and death or require reintervention. As discussed previously, aortic root aneurysm, new or recurrent severe aortic regurgitation, and anastomotic false aneurysm are other indications that require repeat surgical intervention. Late reoperations for aortic dissection can be technically challenging, usually require extensive aortic reconstruction, and frequently involve thoracoabdominal aortic repair which have been considered high-risk procedures, especially in the emergency setting.^{10,112,171} More recently, however, reoperative early mortality rates between 4% and 11% have been reported from centers with large experience in thoracic aortic surgery.^{113,114,223,226}

In the Stanford 30-year experience, freedom from late reoperation for patients with acute type A dissections at 1, 5, 10, and 15 years was 94%, 83%, 65%, and 65%, respectively.¹⁰ For chronic type A dissections, these freedom estimates were 96%, 88%, 65%, and 52%, respectively. Younger age was the only significant, independent risk factor portending a higher likelihood of reoperation. In the more recent Stanford report focusing on patients with acute type A dissections, male gender, Marfan syndrome, coronary artery disease, peripheral pulse deficit, and arch involvement were associated with a higher likelihood of late distal aortic reintervention.¹⁸³ Freedom from proximal or distal aortic reoperations after surgical repair of acute or chronic type A aortic dissections in the patients operated on at Stanford University

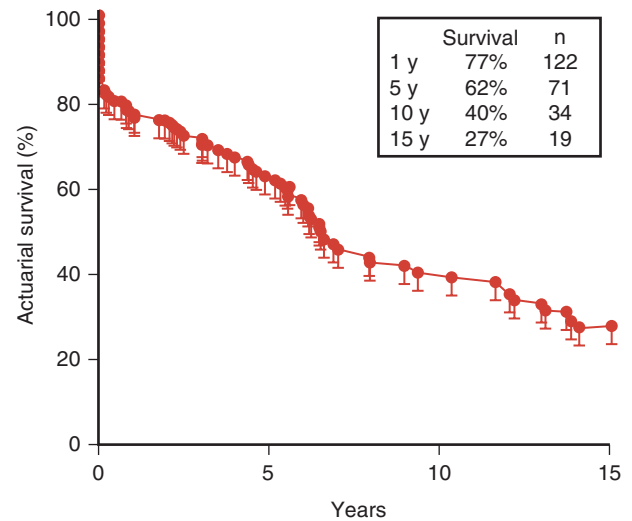


FIGURE 70-10 ■ Actuarial survival after operative repair of chronic type A aortic dissection in 165 consecutive patients operated on between 1964 and 2000 at Stanford University Medical Center.

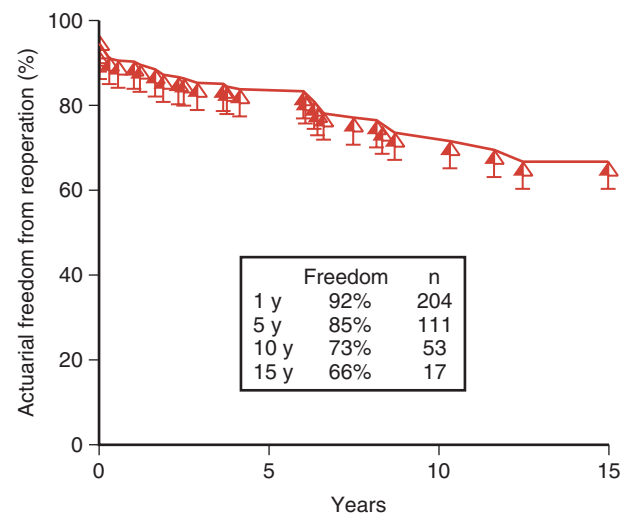


FIGURE 70-11 ■ Actuarial freedom from proximal or distal aortic reoperation after operative repair of acute type A aortic dissection in 323 patients operated on between 1963 and 2000 at Stanford University Medical Center.

between 1963 and 2000 is shown in [Figures 70-10 through 70-12](#).

In the Baylor experience, overall freedom from reoperation for patients with all types of dissections was 96%, 91%, and 78% at 1 year, 5 years, and 10 years, respectively.²³⁴ In the Cleveland Clinic series, these respective freedom from reoperation estimates were 98%, 91%, and 85% for patients with type A dissections.²³³ On the other hand, freedom from reoperation after repair of acute type A dissection was 66%, 58%, 52%, and 43% at 1 year, 5 years, 10 years, and 15 years, respectively, in the experience of Loisan and colleagues.²⁴³ In the recent report from the Washington University in St. Louis, freedom from reoperation was 74% at 10 years¹¹⁴; in the University of Pennsylvania experience from 1993 to 2004,

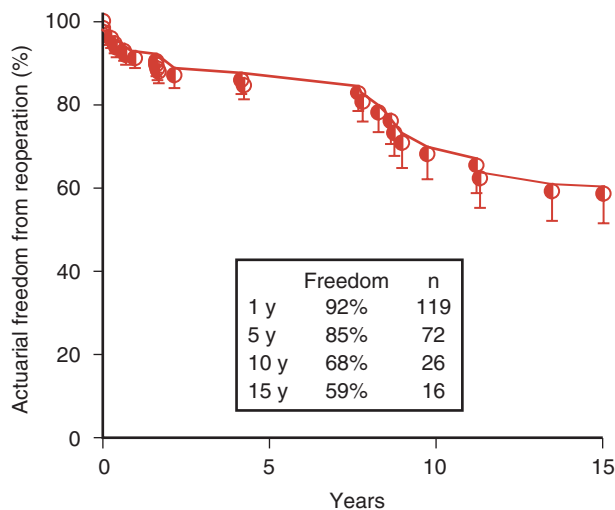


FIGURE 70-12 ■ Actuarial freedom from proximal or distal aortic reoperation after operative repair of chronic type A aortic dissection in 165 patients operated on between 1964 and 2000 at Stanford University Medical Center.

actuarial freedom from any reoperation was 87% at 5 years and 70% at 10 years.²⁴³ Interestingly, using the systematic Mt. Sinai long-term clinical and radiologic follow-up database, the estimated risk of reoperation on the distal aorta was only 16% 10 years after initial surgical repair of acute type A dissection using open arch repair and aggressive resection of the primary intimal tear.¹¹³

Younger age at the initial operation has been a strong risk factor for late aortic reinterventions.^{114,233,243-245} Marfan syndrome has also been associated with a higher risk of recurrent problems in the aortic root as well as the distal thoracic aorta, suggesting that a more radical approach is justified in patients with connective tissue disorders to reduce the incidence of late reoperations.^{113,114,228,243-245} More severe aortic valve regurgitation at the time of the initial operation has been identified by different authors to be a risk factor portending a higher probability of proximal reoperation on the aortic root and valve.^{243,246} The wisdom of using GRF or fibrin glue to reconstruct the dissected aortic root and distal aorta has also been questioned because of its late complications, including false aneurysms.^{175,176,228} Failure to excise the primary intimal tear, leaving behind unresected residual aneurysm at the index operation, and persistent patency of the false lumen have also been linked to a higher incidence of late distal aortic reoperations.^{91,114,229,233,243,245}

Concerning both late survival and need for late reoperation, it remains to be determined whether contemporary surgical techniques of total or partial arch replacement using a distal surgical elephant trunk graft in the descending thoracic aorta or a FET in the distal aortic true lumen will be associated with fewer late deaths and reoperations.^{203-205,209-215} We must learn which patients with acute type A dissections are at highest risk for untoward late complications such that these more aggressive techniques can then be selectively applied to optimize the risk-to-benefit ratio.

FOLLOW-UP

Close medical follow-up and careful periodic imaging surveillance on a rigorous basis are mandatory for all patients with aortic dissections forever. After operative repair, early postoperative serial CTA or MRI of the thoracic and abdominal aorta is essential to define the baseline pathoanatomy and thereafter to detect dissection complications; these scans should be performed at 3- to 6-month intervals during the first year and then every 12 months indefinitely. A transthoracic echocardiogram should also be performed annually to evaluate the aortic root and aortic valve function. Strict long-term blood pressure control is critical for all these patients, as uncontrolled hypertension in the chronic phase of aortic dissection has been associated with an increase in late aortic complications.¹¹⁴ A combination of conventional antihypertensive agents and negative inotropic medications, such as oral beta blockers which have been shown to improve late survival in type A aortic dissection, is required and must be continued indefinitely.²⁴⁷ Antihypertensive drugs such as the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which paradoxically increase aortic dP/dt, should be avoided, if at all possible; if severe hypertension requires more aggressive therapy and one of these drugs, it is essential that adequate beta blockade be maintained concomitantly.

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TYPE B AORTIC DISSECTION

Philippe Demers • D. Craig Miller

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FOLLOW-UP

Occurring more frequently than ruptured abdominal aortic aneurysm, aortic dissection is the most common catastrophe involving the aorta. Because major aortic branch occlusion can complicate the clinical presentation of patients with acute dissection and thus mimic many other acute medical and surgical problems, a high index of clinical suspicion is necessary to diagnose this life-threatening condition early. The lethal nature of acute aortic dissection mandates prompt medical, interventional, or surgical treatment. In the chronic phase, aortic dissection involving the descending thoracic aorta is responsible for a substantial proportion of thoracic and thoracoabdominal aortic problems requiring surgical repair.

Although a consensus exists today regarding the need for emergency surgical treatment of essentially all patients with acute type A aortic dissection, the optimal management of patients with aortic dissection involving the descending thoracic aorta—medical only versus catheter interventional and medical versus surgical and medical—remains controversial.¹ Most patients with acute type B dissections are treated medically.²⁻⁷ A complication-specific approach is favored by most authorities, reserving surgical replacement or endovascular stent grafting of the descending thoracic aorta for patients with complicated dissections, including rupture, ischemia of vital

organs, persistent pain, uncontrollable arterial hypertension, or sizable dilation of the false lumen.^{2,4,7} On the other hand, we and other groups have also advocated consideration of early surgical treatment for carefully selected patients with uncomplicated acute type B dissection who are young and are otherwise good surgical candidates, including those with Marfan syndrome or other connective tissue disorders, in an attempt to lower the long-term risk of dissection-related complications and aortic reoperation.⁸⁻¹⁰ Since the late 1990s, emergency thoracic endovascular aortic repair (TEVAR) for patients with complicated acute type B aortic dissection has played a major role (see [Chapter 72](#)), occasionally supplemented by catheter interventional flap fenestration and true lumen bare metal stenting to relieve distal malperfusion.^{10,11}

HISTORICAL NOTE

The first surgical attempt to treat acute aortic dissection complications was described in 1935 by Gurin and associates,¹² who used surgical iliac artery fenestration to correct dissection-related lower extremity ischemia. In 1955, DeBakey and colleagues¹³ initiated the modern era of surgical management of aortic dissection by

introducing graft replacement of the dissected thoracic aorta. Subsequently, DeBakey introduced the use of cardiopulmonary bypass during clamping of the descending thoracic aorta.¹⁴ Wheat and associates,¹⁵ in 1965, recommended medical treatment with use of pharmacologic antihypertensive drugs for aortic dissection involving the descending thoracic aorta. The introduction of percutaneous interventional techniques in the early 1990s (e.g., fenestration of the dissection flap and stenting of aortic branches) to alleviate dissection-induced branch vessel compromise and malperfusion modified the traditional indications for surgical treatment, with more patients now being treated medically and interventionally despite the presence of complications that earlier would have prompted emergency operation.¹⁶ The advent of TEVAR in patients with complicated acute type B aortic dissections since 1999 has been associated with promising results.^{17,18} Although TEVAR is now widely used in patients with acute type B dissection following U.S. Food and Drug Administration (FDA) approval of the Gore C-TAG and Medtronic Valiant stent grafts for acute or chronic dissections in 2013-2014, until the long-term durability and effectiveness of TEVAR are confirmed in randomized prospective trials comparing this therapy with standard medical and surgical therapy, the exact role of this new modality in the treatment of uncomplicated acute type B dissection remains unclear.¹⁰

NOMENCLATURE

As described in [Chapter 70](#), various classification methods have been applied to aortic dissection. During the past 45 years, the Stanford functional approach, based on whether the ascending aorta is involved, regardless of the site of primary intimal tear, has gained broad acceptance. If only the descending thoracic aorta is involved, the dissection is called a Stanford type B, DeBakey type III, University of Alabama “descending,” Massachusetts General Hospital “distal,” or Najafi “posterior” dissection.¹⁹⁻²³ Examples of various types and extents of dissections are illustrated in [Figure 70-1](#) in [Chapter 70](#). This consensus has made it easier to interpret and to compare outcomes of various therapeutic strategies reported from various institutions. Aortic dissections diagnosed within 14 days of the onset of presenting symptoms are arbitrarily termed *acute*, whereas those diagnosed more than 14 days after onset are classified as chronic dissections on the basis of the expected biological behavior of the disease process.^{3,5,7,10,23} The term *subacute* has reemerged in the TEVAR era meaning dissections 14 to 90 days old based on the rationale that the dissection flap still remains moldable and dynamic enough that a stent graft usually can remodel the aorta successfully. This term, however, is too ambiguous to convey meaningful clinical discriminatory information and should not be adopted. Intramural hematoma (IMH) and penetrating aortic ulcers (PAUs) are now recognized as distinct pathologic variants of classic aortic dissection.^{24,25} These lesions are characterized by the absence of an intimal flap dividing the aorta into true and false lumens and more commonly involve the descending thoracic aorta. It is

important to distinguish IMH and PAU from classic type B aortic dissection, but these entities constitute a continuum of pathophysiologic changes that can evolve rapidly from one to the other. Furthermore, management of these lesions can differ in certain clinical circumstances.^{26,27}

EPIDEMIOLOGY AND NATURAL HISTORY

Epidemiology

Acute type B aortic dissection more commonly affects middle-aged to older men. Aortic dissection is seen in all age groups, although the peak incidence is found between the ages of 50 and 69 years.^{28,29} Patients with type B dissections are older than those with type A dissections.²⁹⁻³¹ In the Stanford 30-year experience with aortic dissection, the mean age of patients with acute type B dissection was 64 years, compared with 56 years for those with acute type A dissections.³⁰ The estimated male-to-female ratio is between 2:1 and 3:1.²⁹ The prevalence of arterial hypertension ranges from 45% to 80% and is highest in patients with type B dissections.^{3,5,29-32} Associated atherosclerotic vascular disease is also found more frequently in patients with type B dissections.^{29,31} Between 2% and 4% of patients presenting with acute type B dissections have Marfan syndrome.^{29,30}

The incidence of aortic dissection is estimated to be between 5 and 20 cases per million population per year, which is higher than the incidence of ruptured abdominal aortic aneurysms or ruptured thoracic aortic aneurysms.³³⁻³⁵ In a review of the Swedish national health care registers during a 15-year period, the incidence of aortic dissection increased substantially between 1987 and 2002.³⁶ Approximately two thirds of all acute aortic dissections involve the ascending aorta (Stanford type A), with one third limited to the descending aorta (Stanford type B).^{28,30,31}

Natural History

Untreated, acute aortic dissection can be highly lethal. In the 1967 report by Lindsay and Hurst,³⁴ one third of the patients suffering from acute aortic dissection died within 24 hours, 50% within 48 hours, 80% within 7 days, and 95% within 1 month. In patients presenting with chronic dissection, only 15% were still alive after 5 years. These figures, however, should be interpreted only as approximations because none of the retrospective observational or autopsy investigations was able to capture the true denominator of how many patients sustained a dissection. Patients with dissection involving the descending thoracic aorta (Stanford type B), however, had a somewhat less ominous early prognosis; 75% were alive 1 month after onset. Anagnostopoulos and coworkers,³³ in a large collected series of 963 cases of untreated aortic dissection (type A or B, acute or chronic), reported a cumulative mortality of 70% at 1 week and 90% at 3 months.

Patients with untreated type B dissection usually die of aortic rupture in the left pleural space or distal

malperfusion with or without occlusion of major distal aortic branches resulting in ischemic injury to vital organs.³ An autopsy study by Roberts and Roberts³⁷ of 40 patients with acute or chronic type B dissections illustrated that the dissection or its vascular complications caused at least 84% of deaths in the 31 patients who were treated medically. Some fortunate individuals with acute dissections survive untreated; in almost all these cases, distal reentry sites are found, allowing decompression of the false lumen.^{5,32} The patent false lumen remains prone to progressive expansion over time, resulting in the potential formation of a thoracic or thoracoabdominal false aneurysm.

PATHOPHYSIOLOGY

The typical pathologic lesion found in older adult patients with type B aortic dissection is smooth muscle degeneration within the aortic media, in part a normal manifestation of the aging process.³⁸ These findings are distinct from the elastic tissue medial degeneration of the aorta observed in younger patients presenting with type A dissection, which is more frequently associated with heritable connective tissue disorders.³⁹

The initial event in aortic dissection is tearing of the intima.^{5,39} Type B dissections can infrequently also arise from rupture of an atherosclerotic plaque,⁴⁰ but this usually represents a localized dissecting process that does not propagate and produces a characteristic “mushroom cap” appearance on computed tomography (CT) scans; this is a different process from classic type B dissection, which frequently involves most or all of the descending and abdominal aorta. After a primary intimal tear occurs, blood flow within the aortic wall separates the layers of the media and creates the false channel. Propagation of the dissection occurs within the outer third of the aortic media, usually in an antegrade direction, but it may also propagate proximally, or retrograde, to involve the transverse arch. As in type A aortic dissections, distal reentry sites are usually multiple and commonly are located in regions of sheared-off ostia of arterial branches. Factors influencing dissection propagation include the rate of increase of aortic systolic pressure or aortic dp/dt , aortic diastolic elastic recoil pressure, mean arterial pressure, and aortic wall stiffness and intrinsic integrity.^{5,41,42} In the descending aorta and abdominal aorta, the false lumen often spirals along the left posterolateral wall, with the false lumen frequently incorporating the left renal artery.²⁸ The false lumen ordinarily remains patent, especially if reentry fenestrations are present, but it may occasionally thrombose partially or completely if there is a “non-reentering” false lumen; the pressurized and partially thrombosed false lumen can then extrinsically compromise aortic true lumen blood flow distally. Indeed, most distal malperfusion problems can be traced to a non-reentering false lumen. In the chronic phase of dissection, progressive dilation of the patent false lumen results in overall enlargement of the aorta and formation of a false aneurysm. This usually is a diffuse process involving the entire length of the dissection from the arch to the iliac arteries.

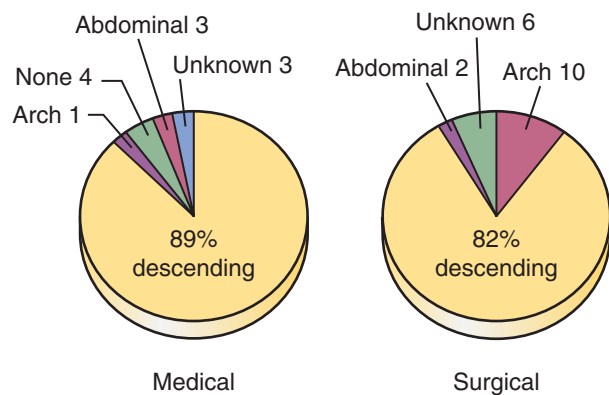


FIGURE 71-1 ■ Site of primary intimal tear in 189 patients with acute type B aortic dissection treated at Stanford between 1963 and 1999, broken down into medical and surgical subgroups. (From Umaña JP, Lai DT, Mitchell RS, et al: Is medical therapy still the optimal treatment strategy for patients with acute type B aortic dissections? *J Thorac Cardiovasc Surg* 124:896–910, 2002.)

For aortic dissections involving the descending thoracic aorta, the primary intimal tear is located in the proximal descending thoracic aorta just beyond the origin of the left subclavian artery in approximately 80% of cases, as illustrated in Figure 71-1.^{1,43} In 10% to 20% of patients, the primary intimal tear is located in the transverse aortic arch, and the dissection extends in an antegrade direction to involve variable lengths of the descending aorta or in a retrograde fashion to involve the ascending aorta. When it propagates backwards across the arch and involves the ascending aorta, the dissection is called a retro-A, type A, or Ruel-Cookey-DeBakey type III-D dissection. In less than 5% of aortic dissections, a distinct primary intimal tear cannot be identified; these dissections are usually confined to the descending thoracic aorta.²⁸ In rare cases, the dissection can be limited to the aortic arch without either antegrade or retrograde propagation (isolated arch dissection). It is also estimated that 2% to 4% of aortic dissections may originate in the abdominal aorta.^{44,45}

IMH originates from spontaneous rupture of the vasa vasorum within the outer third of the aortic media, allowing accumulation of blood within the aortic wall in the absence of a large intimal defect.^{24,27} Alternatively, IMH can follow rupture of an atheromatous plaque through the internal elastic lamina, leading to the formation of a PAU, with subsequent extravasation of blood into the aortic wall.²⁵⁻²⁷ In the past 2 decades, major advances in cardiovascular imaging techniques have led to increasing recognition of IMH with or without associated PAU in patients with acute aortic syndromes. Several investigators reported that these lesions can stabilize with medical therapy, but IMH with or without associated PAU can also rupture or evolve quickly into a classic aortic dissection.^{46,47} It is now recognized that IMH involving the descending aorta (i.e., type B IMH) may have a natural history different from that of classic aortic dissection and a higher propensity for aortic rupture, especially in patients with severe acute symptoms or when the IMH is associated with a deep or large PAU.^{26,27,48}

Aortic branch vessel involvement or thoracoabdominal malperfusion results when the dissection compromises blood flow to important downstream aortic tributaries. As illustrated in [Figure 70-4 of Chapter 70](#), the most common mechanisms producing aortic branch compromise are extrinsic compression of the aortic true lumen by the false lumen and an intimal flap compromising the orifice of the branch artery. As defined by Williams and associates,⁴⁹ static branch compromise is extension of the dissection flap into a branch vessel with subsequent mechanical obstruction of flow; conversely, in dynamic branch compromise, the dissection flap prolapses into the vessel origin or the true lumen is narrowed above it because the bulk of flow is in the aortic false lumen. Compression by the large false lumen can thus result in near-obligation of the true channel (true lumen collapse or “obliteration”).⁵⁰ With extension of the dissection, some aortic tributaries may be spared and continue to be perfused by the true lumen; others may be perfused exclusively from the false lumen after being sheared off and eventually become permanently dependent on flow from the aortic false lumen. Thus, clinical presentation is dependent on which aortic branches are involved and on the severity of compromised perfusion, which can be variable, thus confounding and delaying the correct diagnosis. Simultaneous occurrence of a variety of acute clinical problems without a readily apparent unifying cause should prompt consideration of acute aortic dissection.

CLINICAL MANIFESTATIONS

Patients with acute type B dissection can present with symptoms and physical findings that suggest almost any other acute medical or surgical disease process.^{3,23,32} These numerous, nonspecific manifestations are the main reason that the rapid, correct diagnosis of aortic dissection remains such a formidable clinical challenge.^{7,51} Indeed, aortic dissection occurs more frequently than ruptured abdominal aortic aneurysm, but it is diagnosed correctly less frequently antemortem.^{3,23}

Most commonly, the clinical hallmark of acute type B aortic dissection is the acute onset of severe, lancinating chest or back pain.^{3,5,7,23,32} The initial pain can be in any location, but it usually originates in the interscapular region with later migration to the lower back or abdomen. Pain in acute dissection is thought to be secondary to stretching of the aortic adventitia caused by the dissecting hematoma. Abrupt onset of symptoms and description of sharp, ripping, or tearing pain are also characteristic of acute dissection. Persistence or further migration of pain suggests continuing expansion or distal extension of the dissecting process. In rare cases, acute dissection can be painless; vigilance is essential to recognize other manifestations of aortic dissection in these cases. In a summary from the International Registry of Acute Aortic Dissection (IRAD), 98% of 175 patients with acute type B dissection reported some pain, pain was of sudden onset in 84%, and 63% reported chest pain (anterior in 44%, posterior in 41%) that was significantly different from acute type A dissection (chest pain in 79% and anterior

in 71%).³¹ Back pain was observed in 64% and abdominal pain in 43% of patients with acute type B dissections, much more frequently than in patients with type A dissection.³¹ Moreover, the pain was described as the “worst ever” in 90% of patients, sharp in 68%, and tearing in 52%. Radiating pain was observed in 30% of cases, whereas migration was reported in only 19%.

Despite clinical signs of poor peripheral perfusion, elevated blood pressure is usually observed. In the IRAD report, 70% of patients with acute type B dissection were hypertensive at initial presentation; only 4% were hypotensive and in shock, compared with 25% of patients with acute type A dissection. If the patient is hypotensive, aortic rupture should be suspected. Cardiac tamponade is rare in acute type B dissection; only 2% of patients with acute type B dissection in the 30-year Stanford experience had tamponade, which was thought to be the result of leakage of blood and fluid into the pericardial sac from a large, high-pressure mediastinal hematoma.³⁰

The constellation of other symptoms and signs relates largely to which distal aortic branches are involved in the dissection. Approximately 25% of patients present with symptoms related to aortic branch compromise or develop such symptoms early in the course of their illness⁵²; alternatively, loss of a peripheral pulse may be clinically asymptomatic. In a review of the Stanford experience with peripheral vascular complications of aortic dissection by Fann and colleagues,⁵³ 85 (31%) of 272 patients with all types of dissections sustained at least one peripheral vascular complication, whereas 20% of patients with type B dissections had such complications ([Fig. 71-2](#)). Of the 85 patients with a vascular complication, 18 individuals (21%) suffered two complications, and 7 (8%) had three or more vascular problems. Among the 40 patients with acute type B dissection, no patient presented with a stroke, 3% had acute paraplegia at presentation, 20% sustained loss of one or more peripheral pulses, 8% had impaired renal perfusion demonstrated angiographically, and 5% had compromised visceral perfusion by angiography. The incidence of these complications with the attendant operative mortality rate after surgical graft replacement of the descending thoracic aorta is summarized in [Table 71-1](#). The distribution of specific sites of peripheral pulse loss in these patients is summarized in [Table 71-2](#). Others authors have reported similar figures, with the prevalence of peripheral vascular manifestations ranging from 10% to 30%.^{5,21,52,54,55} As a general rule, morbidity and mortality rates are higher in patients presenting with branch vessel involvement.^{29,52}

The clinical course of peripheral limb ischemia can vary; up to one third of patients may experience spontaneous resolution of the peripheral pulse deficit or a fluctuating course, often because of the reentry of flow into the distal true lumen from the false lumen.⁵⁴ Stroke and transient ischemic attack can complicate acute type A dissection but are seen only rarely in patients with type B dissections. Neurologic findings can vary from minor sensory deficits to frank paraplegia resulting from spinal cord ischemia caused by interruption of intercostal artery blood supply to peripheral ischemic neuropathy.^{32,52} Abdominal pain out of proportion to the physical abdominal findings must be considered potentially to reflect

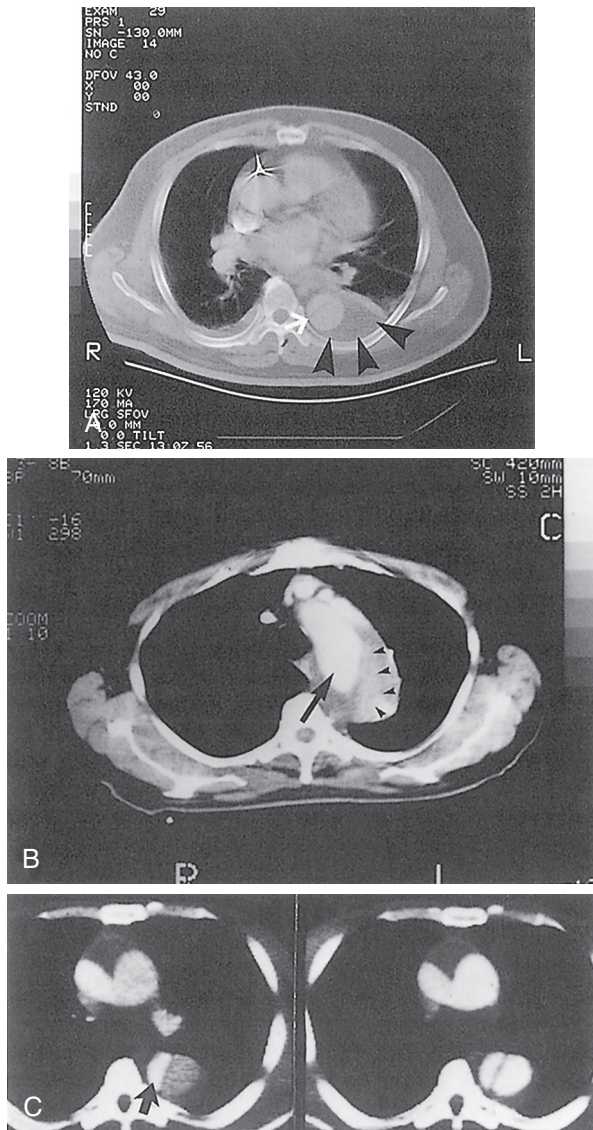


FIGURE 71-2 ■ Examples of diagnostic computed tomography (CT) scans. **A**, The CT scan shows the linear flap (black lucency, white arrow) between the two aortic lumens in the descending thoracic aorta that is characteristic of aortic dissection. In addition, a relatively large hematoma surrounding the aorta is seen (arrowheads), representing recent hemorrhage contained in the posterior mediastinum. Despite this ominous appearance, this patient did well with medical therapy for more than 1 year until progressive enlargement of a localized false aneurysm prompted referral for operation. **B**, CT scan from a different patient with an acute type B dissection illustrating a false aneurysm involving the distal arch and proximal descending thoracic aorta. The false lumen (arrowheads) is partially thrombosed; therefore, it opacifies only faintly compared with the contrast seen in the true lumen (arrow). **C**, Although this patient had a type A dissection (note the deformed true lumen in the large ascending aorta), this CT scan demonstrates differential opacification of the true and false lumens in the descending thoracic aorta. The true lumen (arrow) is completely opacified in the left panel; later in the cardiac cycle (right panel), both true and false lumens are equally opacified. (From Miller DC: Acute dissection of the descending thoracic aorta. *Chest Surg Clin North Am* 2:347–378, 1992.)

TABLE 71-1 Peripheral Vascular Complications and Associated Operative Mortality Rates in a Series of 40 Patients with Complicated Acute Type B Aortic Dissection

Peripheral Vascular Complication	Prevalence (n)	Mortality (n)
Stroke	0% (0)	—
Paraplegia	3% ± 3% (1)	100% (1)
Pulse loss	20% ± 8% (8)	50% ± 18% (4)
Renal ischemia	8% ± 4% (3)	67% ± 28% (2)
Visceral ischemia	5% ± 3% (2)	50% ± 37% (1)

Data from Fann JI, Sarris GE, Mitchell RS, et al: Treatment of patients with aortic dissection presenting with peripheral vascular complications. *Ann Surg* 212:705–713, 1990.

TABLE 71-2 Location of Peripheral Pulse Deficits in 56 of 168 Patients with Acute Type A or Type B Aortic Dissection

Location	Type A (n = 128)	Type B (n = 40)
Right carotid	6	0
Left carotid	6	0
Right arm	25	0
Left arm	10	2
Right leg	21	4
Left leg	14	3
Total	82	9

Data from Fann JI, Sarris GE, Mitchell RS, et al: Treatment of patients with aortic dissection presenting with peripheral vascular complications. *Ann Surg* 212:705–713, 1990.

mesenteric ischemia or infarction, which must be confirmed or ruled out expeditiously.⁵⁴ Oliguria or anuria suggests renal perfusion compromise; flank pain or hematuria caused by renal malperfusion or infarction can mimic symptoms usually associated with ureteral colic or kidney stones.

Physical examination of patients with suspected aortic dissection should include measurement of blood pressure in both upper and lower extremities. A complete evaluation of peripheral pulses is imperative, in addition to a comprehensive motor and sensory neurologic examination. The patient should be reexamined periodically because new vascular or neurologic deficits may come and go. The remainder of the physical examination is often normal.

Most patients with *chronic* type B dissection are asymptomatic. However, progressive enlargement of the aortic false lumen may eventually produce compression, obstruction, or erosion into adjacent thoracic structures, producing symptoms such as chest pain, dyspnea, wheezing, hoarseness, dysphagia, hemoptysis (aortobronchial fistula or erosion into the lung), and hematemesis (aorto-esophageal fistula) and symptoms secondary to compromised flow in an important distal aortic branch.

DIAGNOSTIC MODALITIES

Definitive diagnostic procedures should be performed as expeditiously as possible to confirm the diagnosis of acute type B aortic dissection. Before the widespread availability of newer imaging techniques, the diagnosis was generally made by conventional catheter aortography. Today, much better options include multislice computed tomographic angiography (CTA), transesophageal echocardiography (TEE), and magnetic resonance imaging (MRI). Chest radiography is neither sensitive nor specific. The imaging modality chosen should determine the type of dissection and its extent, the site of the primary intimal tear, and the presence or absence of major aortic branch compromise. More than one imaging study may be necessary to confirm the diagnosis or to identify additional pathoanatomic details; in IRAD, multiple imaging studies were needed in 76% of patients, and an average of 2.2 imaging studies were carried out in patients with acute type B dissection before definitive treatment.^{31,52}

CT scanning has markedly facilitated the rapid and accurate diagnosis of acute aortic dissection. In most cases, a thin-slice spiral CTA with intravenous administration of contrast material can determine rapidly and noninvasively the dissection type (type A or B), as illustrated in Figure 71-2. The extent of dissection, the perfusion status of individual aortic branches, and the size of the true and false lumens in all aortic segments can also be assessed accurately. Identification of two distinct lumens in the descending thoracic aorta separated by an intimal flap confirms the diagnosis of type B aortic dissection.⁵⁶ Other important signs include compression of the true lumen by the false lumen, displaced intimal calcification, thrombosed false lumen, nonopacified crescent-shaped area along the aortic wall (IMH), and ulcer-like projection of contrast material within the aortic wall indicating a PAU.⁵⁷ The presence or absence of pericardial or pleural effusions is also defined. The sensitivity and specificity, respectively, of CTA in making the diagnosis of acute type B aortic dissection are between 82% and 100% and 89% and 100%.^{*} In the 1993 study by Nienaber and coworkers⁵⁹ that prospectively evaluated noninvasive modalities in 110 patients with suspected acute dissection, the sensitivity and specificity of CT scanning were 96% and 89% in patients with type B dissection; the positive and negative predictive values were 80% and 98%, respectively. A drawback associated with CT scanning is the requirement for administration of intravenous contrast material in patients with impaired renal function.

In most centers worldwide, TEE and/or CTA are the diagnostic modalities of choice in patients with suspected type B aortic dissection, and many patients do not require additional corroborative studies.[†] TEE is rapid, convenient, and noninvasive and can be performed in the emergency department, in the intensive care unit, or in the operating room with minimal risk. Undesirable blood

pressure elevation is a potential risk of TEE, mandating adequate sedation of the patient. Multiplanar, phased array TEE with color flow imaging can accurately demonstrate flow in both aortic channels and the flap separating the true and false lumens; real-time three-dimensional TEE imaging can provide spectacular surface-rendered images. The most important finding is identification of an intimal flap, ideally seen in more than one view, oscillating independently of the motion of the aortic wall.^{56,59,61,63} Frequently, the primary intimal tear and secondary fenestrations in the descending thoracic aorta can also be identified. Overall, the sensitivity and specificity of TEE in the evaluation of suspected type B aortic dissection are between 97% and 100% and 94% and 98%, respectively.[‡] Limitations of TEE include dependence on an experienced interpretation of the findings and limited capability to assess abdominal branch vessel involvement and extent of the dissection below the diaphragm; if the patient is very small or very thin, as in Japan, the takeoff of the celiac axis, superior mesenteric artery, and occasionally one or both renal arteries can be visualized with TEE.

Currently, MRI does not play a major diagnostic role in patients with acute dissection because these individuals are often critically ill and connected to various monitoring devices, infusion pumps, or respirators.^{7,32} In the acute setting, the limited 24-hour availability, the relatively long time necessary for image acquisition, and the limited access to the patient during the procedure make MRI much less practical than other diagnostic modalities. Nevertheless, MRI can delineate noninvasively the entire thoracoabdominal aorta and demonstrate the intimal flap, both aortic channels, and involvement of major aortic branches. As with CTA, the most important criterion for the diagnosis of acute aortic dissection with MRI is the identification of two distinct flow lumens separated by an intimal flap.⁵⁶ Many investigators have reported that MRI is associated with high sensitivity and specificity in the evaluation of suspected aortic dissection, both in the range of 95% to 100%.[§] For suspected acute type B dissection, Nienaber and coworkers⁵⁹ observed that MRI had a sensitivity of 97% and a specificity of 100%. Today, magnetic resonance scans are most useful for serial, long-term follow-up of patients with chronic aortic dissections, including postoperative patients and those initially treated medically.

Contrast aortography historically was the “gold standard” in the diagnosis of aortic dissection (Fig. 71-3).⁶⁵ Angiography, however, is invasive, is time-consuming, and necessitates the use of contrast material; moreover, it is not infallible, and the technique carries a risk of morbidity and mortality, but it can provide detailed information about perfusion status of important aortic branches.^{32,56,66} Angiographic diagnosis of acute dissection requires identification of a double lumen or an intimal flap; indirect signs that are suggestive of an acute dissection include compression of the true channel by an expanding false lumen, thickening of the aortic wall,

*References 3, 5, 7, 10, 11, 29, and 56-62.

†References 3, 5, 7, 11, 29, 56, 59, and 63.

‡References 3, 5, 7, 11, 29, 56, and 59-63.

§References 3, 5, 7, 11, 29, 56, and 59-64.

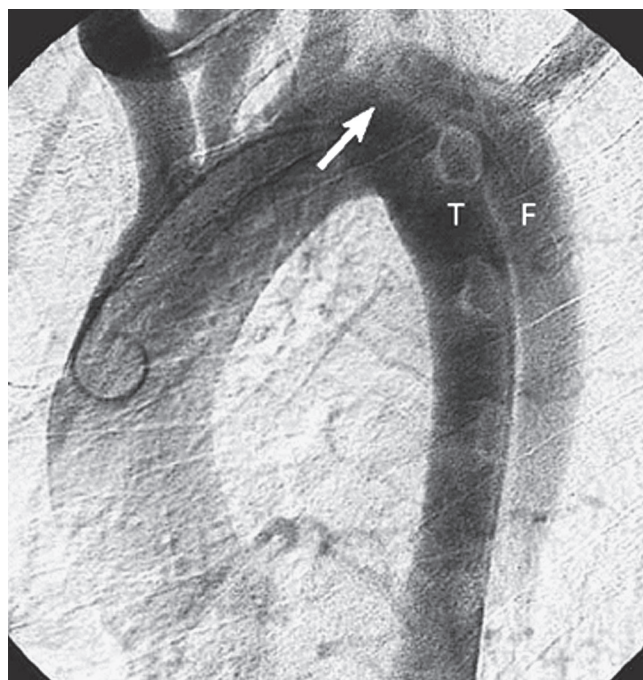


FIGURE 71-3 ■ Aortographic findings in acute type B aortic dissection. The true aortic lumen (T) is extrinsically narrowed by the false lumen (F). The true lumen is characteristically smaller and located medially. Note that the pigtail angiographic catheter has been passed up the true lumen from below. The primary intimal tear (arrow) is located just distal to the left subclavian artery.

ulcer-like projection in the aortic wall (in cases of penetrating atherosclerotic ulcer), and abnormal position of the guidewire or catheter in the aorta.^{26,27,56,65} Biplane angiographic studies of the thoracic aorta are mandatory because single-plane aortography can miss important findings; false-negative results can also occur when the false lumen is thrombosed and in cases of IMH.^{5,27,56} The sensitivity and specificity of aortography in the evaluation of aortic dissection range between 80% and 90% and 85% and 95%, respectively.^{5,7,29,56} Currently, aortography is reserved for patients with acute type B dissection presenting with clinical evidence of malperfusion or those with persistent peripheral vascular complications after proximal aortic repair to delineate the mechanism of aortic branch vessel compromise and guide subsequent appropriate endovascular interventions to restore distal perfusion.^{||}

MANAGEMENT

Strategy

The aim of therapy in patients with aortic dissection is to prevent death and irreversible end-organ damage. As discussed in [Chapter 70](#), almost all patients with acute type A dissection should be considered for emergency surgical repair of the ascending thoracic aorta.^{2,3,5,7} In contrast, the optimal treatment strategy for patients

BOX 71-1 Firm or Relative Indications for Surgical or Endovascular Intervention in Patients with Acute Type B Aortic Dissection

- Persistent pain
- Refractory arterial hypertension
- Progression or expansion of dissection
- Aortic rupture or impending rupture
- Evidence of impaired distal organ perfusion
- Sizable localized false aneurysm
- Connective tissue disorders (Early surgical intervention to be strongly considered)

with acute type B dissection continues to be debated.[¶] In 1965, Wheat and Palmer and colleagues¹⁵ recommended medical “anti-impulse” therapy for acute aortic dissection, and in 1970, Daily and colleagues²⁰ from Stanford concluded that there was no major difference in early outcome between patients treated medically and those treated surgically. The rationale behind medical management is based on three observations: (1) medical therapy prevents early death in most patients^{1,5-7,31,73}; (2) operative mortality for patients with acute type B dissections requiring emergency operations has been relatively high^{6,7,31,43}; and (3) long-term outcome has been similar for patients treated medically or surgically.^{1-3,6,7,73}

Today, most groups favor a complication-specific approach for patients with acute type B dissections ([Box 71-1](#)), reserving surgical or endovascular intervention on the descending aorta for those with rupture, thoracoabdominal malperfusion, impending rupture, or other life-threatening complications. In the past, other “soft” indications included persistent pain and refractory hypertension, but these are too subjective and have been discarded by the FDA in the new registries for TEVAR.^{1-7,10,11,70,71} These are clinical indications and do not include offering asymptomatic patients a semi-elective TEVAR simply because it may help promote aortic remodeling over time, as was the case in the INSTEAD trial.^{74,75} On the other hand, we and some other groups have advocated consideration of early surgical replacement of the descending aorta for selected patients with acute type B dissections who are young and otherwise good operative candidates, irrespective of the presence or absence of complications; this includes predominantly patients with connective tissue disorders such as Marfan syndrome and Loeys-Dietz syndrome.^{7-9,68,76,77} If the operation is successful, these patients theoretically should be at lower risk of sustaining late dissection-related complications or requiring aortic reoperation.

The Stanford aortic dissection classification concept has also been applied to IMH because the prognostic impact of the location and its treatment have been considered comparable to those in patients with a classic aortic dissection.^{27,47,78} It is generally accepted that patients with IMH involving the descending thoracic aorta (type B IMH) can usually be successfully managed conservatively with aggressive blood pressure control in

^{||}References 16, 17, 29, 55, 56, and 67.

[¶]References 1-10, 17, 18, 20, 32, and 68-72.

the absence of disease progression.** Several groups have reported, however, that the prognosis of markedly symptomatic patients with penetrating ulcers located in the descending thoracic aorta and type B IMH coexistent with a deep PAU was worse than the prognosis of those with classic aortic dissection because of a higher incidence of aortic rupture.^{26,27,48} In these cases, early surgical or endovascular treatment should be considered, especially if persistent pain, increasing pleural effusion, and a large, deep PAU are present.

Initial Medical Treatment

As soon as acute aortic dissection is suspected, emergency medical therapy should be initiated and continued while the diagnostic procedures are performed.^{5,7,32} The cornerstone of modern medical therapy, as originally described by Wheat and collaborators, is reduction of mean, peak, and diastolic recoil arterial pressure and the rate of rise of arterial pressure or aortic dP/dt (*not* left ventricular dP/dt) to the lowest acceptable level while adequate cerebral, coronary, and renal perfusion is maintained.^{5,7,14,15,29} The goals of medical treatment are to relieve pain, to control systemic blood pressure, and to limit extension of the dissection. Reasonable targets are a heart rate less than 60 bpm and a systolic blood pressure between 100 and 120 mm Hg.¹⁰ Intensive, continuous monitoring of the patient in an intensive care unit is important, including electrocardiography and insertion of indwelling radial or femoral arterial and central venous lines. A urinary bladder catheter and a pulse oximeter are used. Intravenous beta blockers (e.g., esmolol, metoprolol, labetalol, propranolol) are administered in small boluses or as a continuous intravenous infusion; if needed, an intravenous vasodilator infusion, most commonly sodium nitroprusside, is then added. Labetalol, an α_1 -adrenergic and nonspecific β -adrenergic antagonist, is a good alternative to a combination of agents. Parenteral calcium channel antagonists, such as diltiazem, nifedipine, and nicardipine, that lower arterial blood pressure and left ventricular dP/dt can also be used. It must be remembered that because sodium nitroprusside, angiotensin-converting enzyme inhibitors (e.g., enalapril, lisinopril), and angiotensin receptor blockers are pure arteriolar vasodilators, these agents increase aortic dP/dt; therefore, concomitant administration of a negative inotropic agent is essential. If surgical intervention or percutaneous endovascular treatment is carried out, antihypertensive and negative inotropic therapy is continued during anesthetic induction, intraoperatively, and postoperatively.

Definitive Long-term Medical Management

Whether the patient is initially treated medically or surgically, the intravenous antihypertensive and negative inotropic drugs are gradually transitioned to oral agents during the hospitalization. An oral beta blocker (e.g., labetalol, metoprolol succinate [Toprol-XL], atenolol)

or, if a beta blocker is not tolerated, a calcium channel antagonist like verapamil or nicardipine is preferentially used and continued indefinitely, complemented by an oral angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Recent data from the IRAD investigators suggest that the use of a calcium channel antagonist at discharge from the hospital was associated with improved long-term survival in patients with type B aortic dissection treated medically.⁷⁹ Because it is incorporated into mucopolysaccharides of the media and may weaken the aortic wall,⁷ hydralazine should be avoided, as should any drug that increases aortic dP/dt. Conversely, there is some unpublished evidence (Harry C. Dietz, Johns Hopkins University, personal communication) that in genetic mouse models of the Marfan syndrome, hydralazine has salutary effects on aortic wall remodeling.

OPERATIVE APPROACH

Acute Type B Dissections

The goal of surgical treatment of patients with acute type B aortic dissection is graft replacement of a limited segment of the descending thoracic aorta, including the site of the primary intimal tear.⁷ At Stanford, after induction of general anesthesia, insertion of a double-lumen endobronchial tube, and usually a lumbar intrathecal catheter for cerebrospinal fluid drainage, patients with acute type B dissections are explored through a left posterolateral thoracotomy.^{7,66} Our preference calls for total cardiopulmonary bypass (CPB) by advancing a long right femoral venous catheter into the right atrium from the *right* femoral vein and, if possible, *antegrade* arterial CPB perfusion. This can be accomplished using a short 6-mm vascular graft sewn end to side to the left subclavian or left carotid artery; inserting an arterial cannula into the undissected ascending aorta or arch or into the descending aortic true lumen and advancing it using TEE guidance over a guidewire into the ascending aorta, or into the left ventricular apex and across the aortic valve (Wada and Kazui method of left ventricular apical aortic CPB perfusion); fluoroscopically manipulating a long, small venous cannula (e.g., 15 Fr) over a stiff guidewire up into the undissected ascending aorta or arch via the femoral artery; or, as a last resort, cannulating the femoral artery on the side that is perfused by the aortic true lumen (almost always the one with the reduced or absent pulse).^{80,81} On occasion, if a venous cannula cannot be passed from the femoral vein, an angled venous cannula can be placed through the main pulmonary artery into the right ventricle to provide (or to augment) venous CPB return. Moderate systemic hypothermia (bladder temperature, 25° to 28° C; tympanic membrane temperature, 20° to 22° C) is generally used such that an open proximal anastomosis can be performed in the distal arch during a brief period of hypothermic circulatory arrest. After the open proximal anastomosis is completed, reperfusion to the head and heart is then immediately started using a side limb off the aortic graft or inserting a metal right-angle cannula into the proximal graft. Hypothermic circulatory arrest is also used in almost all cases of chronic type B dissections to facilitate

**References 9-10, 24, 27, 29, 30, 47, and 78.

the proximal anastomosis in the arch, allowing the chronic arch flap to be safely excised along with evacuation of any thrombus in the false lumen. The circulatory arrest times are longer and unpredictable in these chronic cases, and having the left carotid artery cannulated for antegrade selective cerebral perfusion can be useful (the Siena technique popularized by Neri and coworkers).^{82,83} The patient is placed in a steep Trendelenburg position, and uncontrolled venous retroperfusion backward up the venous cannula at 500 to 1000 mL/min is used during hypothermic circulatory arrest to keep the left side of the heart and ascending aorta free of air. Some of this venous retroperfusion trickles back down into the arch through the arch branches. No preliminary proximal or distal aortic dissection is done, and no aortic cross-clamps are applied either proximally or distally. When the pump is turned down, the proximal aorta is opened and transected after mobilization of the phrenic, vagus, and recurrent laryngeal nerves. In acute type B cases, an open proximal anastomosis is performed with a 4-0 BB 54-inch or 5-0 C1 polypropylene suture incorporating a full-thickness aortic cuff (thereby reapproximating the aortic intima and adventitia and obliterating any proximal false lumen) at the distal arch level. An arterial perfusion cannula is then inserted directly into a single side branch of the aortic graft. After arch de-airing, CPB perfusion to the head and the heart is resumed, with care taken to evacuate any air trapped in the heart or ascending aorta. After 5 to 10 minutes of cold CPB reperfusion, systemic warming is started. Proximal intercostal arteries are oversewn. A conservative segment of descending aorta containing the primary intimal tear and the most severe associated injury is replaced with a woven double velour Dacron Hemashield graft. Continuous 4-0 BB or 4-0 SH-1 polypropylene suture and use of deep suture bites—again, with care to incorporate both aortic layers and to obliterate the false lumen in acute dissection cases—is used for the distal anastomosis.⁷ Although we have avoided using Teflon felt for the past 20 years at Stanford, the proximal or distal aorta can be reinforced with strips of Teflon felt or bovine pericardium or, alternatively, by using a small amount of tissue adhesive between the dissected layers, such as BioGlue (CryoLife, Inc., Kenneraw, GA). The proximal cross-clamp is released, air is evacuated, and the anastomoses are checked for hemostasis. After systemic rewarming to a target of 35° to 36° C, CPB is discontinued. Protamine sulfate is administered after all anastomoses are judged to be technically satisfactory with minimal bleeding. Platelets, fresh-frozen plasma, and cryoprecipitate are used if diffuse hemorrhage from suture lines and raw surfaces are evident after a normal activated clotting time is achieved if abnormal coagulation parameters are identified through use of rotational thromboelastography.

Postoperative management of the patient involves intensive monitoring, including serial abdominal, neurologic, and pulse examinations, as well as strict blood pressure control. Cerebrospinal fluid is drained continuously to keep cerebrospinal fluid pressure lower than 10 mm Hg. In patients without spinal cord injury, the drain is removed on the second or third postoperative day. With use of partial CPB (without hypothermic circulatory arrest in that era) and confining the extent of resection to a short aortic segment, the incidence of new

postoperative paraplegia in our earlier experience was only 4% in patients with acute type B dissections.⁴³ We believe that our current method using hypothermic circulatory arrest for an open proximal anastomosis has reduced the incidence of stroke and spinal cord injury.

Management of Peripheral Vascular Complications

The Stanford approach in patients presenting with aortic dissection and ischemic peripheral vascular complications before the advent of endovascular stent grafts (TEVAR) was to proceed initially with surgical repair of the thoracic aorta because central aortic repair usually obviated the need for peripheral revascularization procedures.^{7,53} The operative mortality rate for patients with all types of peripheral vascular compromise was no higher than that for those without such complications; however, visceral ischemia and impaired renal perfusion portended a high risk of death. If persistent mesenteric, renal, or limb ischemia was detected after thoracic aortic repair, surgical fenestration of the distal descending thoracic aorta or suprarenal abdominal aorta or direct revascularization was traditionally attempted as a lifesaving maneuver.^{7,53,54,84} Today, percutaneous endovascular treatment is the preferred initial intervention in cases of postoperative malperfusion and also in high-risk patients with complicated acute type B dissections (see [Chapter 72](#)).¹¹ Endovascular interventions using bare stents in the collapsed true lumen in the aorta or one of its branches or flap fenestration of the aortic dissection flap (to increase flow in the distal true lumen by decompressing the false lumen) can usually reestablish adequate end-organ perfusion in most cases.^{49,85} These endovascular approaches are described in detail in [Chapter 72](#). In the past 2 decades, endovascular stent grafts have been used increasingly in patients with complicated acute type B dissections to cover the primary intimal tear in the thoracic aorta and to restore blood flow in the distal aortic true lumen, which can be “obliterated” or “collapsed”; this successfully relieved distal ischemia in 76% of all compromised aortic branches (and 100% of those with dynamic obstruction).^{17,86}

Endovascular Stent Grafts

Since 1996, endovascular stent grafts have been used in selected patients with acute type B aortic dissections at Stanford.¹⁷ The Stanford University and Mie University combined series showed that endovascular stent graft repair in patients with complicated acute type B dissections was associated with an encouraging early mortality rate of only 16%. The long-term effectiveness and durability of this new therapeutic approach, however, remain unknown. In 2008 and 2010, the Society of Thoracic Surgeons and the American Heart Association published practice guidelines for the management of patients with descending thoracic aortic disease. These guidelines include potential indications for endovascular stent graft treatment based on existing observational studies and opinions of experts.^{10,11,87} Acute type B aortic dissection

^{††}References 10-11, 49, 50, 55, 85, and 86.

with life-threatening complications and acutely symptomatic IMH with or without penetrating ulcer of the descending thoracic aorta were identified as situations in which endovascular stent graft repair seemed justified.^{10,87} Endovascular stent graft coverage of the primary intimal tear, however, is more a temporary resuscitation therapy allowing stabilization of very sick patients rather than a curative procedure; late complications and the need for reintervention are not unusual. Nonetheless, emergency stent grafting can be lifesaving in patients with severe malperfusion even though the therapeutic goal is not to eliminate all blood flow from the false lumen, as is the case in treating thoracic aortic aneurysms. Later sequelae of the dissection can be treated definitively with open surgical repair or additional endovascular interventions if necessary when the patient is not in extremis. Rigorous prospective controlled comparison of this interventional stent graft approach with conventional emergency surgical treatment (for complicated type B dissections) or with medical therapy (for uncomplicated type B dissections) is not yet available. One study, the INSTEAD trial, enrolled 140 patients with uncomplicated subacute or chronic (14 to 52 weeks) type B aortic dissections who were randomized to best medical therapy versus stent graft treatment. All-cause mortality at 2 years was higher in the stent graft limb group, but the difference did not reach statistical significance.⁷⁴ Additionally, freedom from aorta-related mortality and freedom from progressive aortic disease (a composite endpoint for aortic death, conversion, or additional intervention) was comparable between groups. Despite the absence of clinical benefit, thoracic false lumen thrombosis occurred in 91% of the patients in the stent graft group versus 19% of those receiving medical therapy, a highly significant difference. A recent update of INSTEAD reported significantly lower aorta-related mortality and disease progression (a composite endpoint for conversion, additional intervention, or aortic expansion) at 5 years in the stent graft treatment arm.⁷⁵ The ADSORB trial, a second randomized study, compared treatment with a Gore TAG stent graft versus best medical treatment alone in 61 patients with acute (<2 weeks) uncomplicated type B dissections.⁸⁸ The study endpoints had to be changed and the trial ended prematurely because of inadequate patient enrollment rates. There were no differences in clinical outcomes, including death, at 1 year, but false lumen thrombosis in the descending thoracic aorta occurred much more frequently in the TEVAR subgroup than in the medically treated subgroup (57% vs. 3%). Endovascular stent graft treatment of aortic dissection is discussed in detail in [Chapter 72](#).

Chronic Type B Dissections

Surgical intervention for patients with chronic type B dissection is considered when they have symptoms related to the dissection (e.g., pain or symptoms secondary to compression of adjacent anatomic structures, renovascular hypertension [with or without renal dysfunction], mesenteric ischemia, claudication) or if documented expansion of the false lumen occurs. Asymptomatic patients with large chronic aortic dissections (exceeding 55 to 60 mm in diameter) are also offered surgical graft replacement if they are reasonable surgical candidates. In

addition to maximal aortic diameter and symptoms, consideration of other risk factors that modulate the expected risk of aortic rupture, such as increasing age, connective tissue disorders, uncontrolled hypertension, and chronic obstructive pulmonary disease, is also important to determine the optimal timing for operation and to enhance selection of patients.^{89,90}

Open operative surgical graft replacement is conducted similarly to that described before for patients with acute type B aortic dissections, including our CPB perfusion strategy. In these chronic dissection cases, it is even more important whenever feasible to avoid retrograde arterial CPB perfusion from the femoral artery during systemic cooling, as this can blow debris and thrombus from the aortic true or false lumen up into the arch branches and brain or coronary arteries. Furthermore, retrograde femoral arterial CPB perfusion in patients with a chronic dissection is uncontrolled and unpredictable because CPB flow may not necessarily reach all important aortic tributaries, depending on dynamic motion of the dissection flap and local pathoanatomic factors. Deep hypothermic circulatory arrest also makes reattachment of important lower intercostal arteries as Carrel patches safer and helps protect the visceral organs and spinal cord. If the entire thoracoabdominal aorta (Crawford extent II) is being replaced, as is often necessary in young patients with connective tissue disorders and chronic type A or B aortic dissection, we cool the patient to 15° to 20° C (bladder), and CPB rewarming is not begun until all important intercostal arteries have been reimplanted down to the level of the celiac axis. CPB reperfusion is commenced both proximally (with a cannula inserted into a side branch of the proximal graft) and from below with use of either a femoral artery or a cannula in the distal thoracoabdominal aorta graft after completion of the most distal aortic or iliac anastomosis. In chronic dissection cases, we excise the dissection flap in the arch proximally and in the distal descending thoracic aorta. Because the chronic dissection usually extends down into the abdominal aorta, in replacing only the descending thoracic aorta, we frequently use the “elephant trunk” graft technique distally such that if downstream thoracoabdominal aortic replacement should become necessary, the new graft is simply sewn to the dangling elephant trunk graft proximally. It is important in using an elephant trunk graft in patients with aortic dissections to make sure that the dissection flap distally has been excised for a distance exceeding the length of the planned elephant trunk graft to avoid inadvertent trapping of the graft into one lumen or the other.

RESULTS

Comparison of Results of Surgical and Medical Treatment

Historical Perspective

The controversy about the optimal therapy for patients with aortic dissections dates to the 1960s, when DeBakey and colleagues reported results in 179 patients treated surgically with an early mortality rate of 21% and a

5-year survival rate of 50%.⁹¹ DeBakey and colleagues concluded that all patients with aortic dissection should undergo surgical intervention. Importantly, careful inspection of this paper subsequently revealed a skewed patient population; only 38% of the patients had an acute dissection, and most had a DeBakey type III (Stanford type B) dissection. Wheat and Palmer and colleagues¹⁵ then proposed a selective approach to the management of patients with acute dissection, arguing for medical treatment with a combination of agents that decreased arterial blood pressure and also the rate of rise of aortic pressure (aortic dP/dt). In 1970, Daily and colleagues²⁰ introduced the Stanford type A/B dissection classification system and observed no major difference in early outcome in patients with type B dissections treated medically or surgically. In a 1979 Stanford paper, the early results from 11 studies published in the 1970s were analyzed. The overall mortality rate in this era was 33% in medically treated patients (range, 21% to 67%), and the average operative mortality rate for patients with acute type B dissections treated surgically was 36%.⁹² Of course, the patient cohorts differed considerably, which confounded critical comparison of outcomes. Thereafter, the consensus opinion has been that most patients with acute type B dissections should be treated medically, unless life-threatening dissection-related complications are present.^{††}

Contemporary Comparative Studies of Surgical versus Medical Treatment

No prospective controlled trials comparing surgical with medical management of patients with acute type B dissections have been carried out; however, comprehensive comparative retrospective analyses, including a 2002 report by Umaña and associates from Stanford, have been published.^{1,6,39} Strict interpretation of the results of these two treatment modalities is difficult because of a marked disparity in the clinical characteristics of the medical and surgical cohorts, which created a pronounced selection bias. In most series, patients with uncomplicated acute type B dissections are treated medically, whereas those presenting with life-threatening complications or developing complications while being treated medically are treated with TEVAR.

A 1984 report from the Massachusetts General Hospital concluded that early survival in patients presenting with an acute type B dissection was determined primarily by the number and severity of presenting complications due to the dissection, irrespective of mode of treatment.³⁹ In the 1989 combined Stanford and Duke University study, 136 patients with acute type B dissections between 1975 and 1988 were treated medically (63%) or surgically (37%); patients treated medically tended to have more comorbidities or renal disease, whereas those in the surgical cohort were more likely to have aortic rupture or arch involvement.^{6,71} Sequential analyses were performed to adjust for differences in baseline characteristics to separate patients with acute dissections into three

subgroups: all patients (subset I), patients presenting without compelling indications for emergency operation (subset II), and those individuals from subset II who did not have severe comorbidities (subset III). This last cohort represented low-risk, uncomplicated patients who could have been treated either medically or surgically. For all patients, the statistically significant independent determinants of overall mortality were aortic rupture, other dissection-related complications, increasing age, and cardiac disease. Treatment method was not a predictor of outcome in any subset. In the low-risk subset of patients (subset III), moreover, the early mortality rate was similar between the medically and surgically treated patients (16% vs. 9%), as was the long-term survival rate. More recently, a 36-year review of the Stanford experience including 189 patients with acute type B dissections used propensity score analysis to identify subsets of patients treated either medically or surgically who were at similar risks of death. The impact of treatment method on survival, reoperation, and late aortic complications or death was then determined in these more homogeneous samples to neutralize bias.¹ This statistical analysis identified 142 well-matched patients who did not have any compelling emergency surgical indications (111 were treated medically and 31 underwent operation). Long-term survival was similar in the two matched groups. Freedom from aortic reintervention and from late aortic complication or death was also comparable between the medically treated and surgical subsets. In all patients, multivariable analyses did not identify treatment method as a predictor of outcome; instead, patient-related factors and dissection-specific complications determined the prognosis.

Current Results

Early Survival

During the past 30 years, advances in diagnostic imaging modalities, medical critical care, anesthetic expertise, and surgical techniques have allowed clinicians to make the definitive diagnosis more quickly and have improved early survival rate of patients with acute type B aortic dissection treated medically or surgically.⁸⁸ In the 2000 IRAD review of 175 patients with acute type B dissections treated in 12 centers between 1996 and 1998, the 30-day mortality rate was 11% in medically treated patients and 31% in patients who underwent surgery; of course, the two patient cohorts were markedly different.³¹ Similarly, in two more recent IRAD reports focusing on a large cohort of patients with acute type B aortic dissection, it was shown that the early mortality rate of patients treated medically was now lower than 10%; those requiring surgical intervention for acute aortic dissection-related complications, including aortic rupture and shock, had an early mortality rate closer to 30%.^{98,99} Interestingly, in the small group of patients treated with endovascular TEVAR for complicated aortic dissections, in-hospital complications occurred in 20% (compared

^{††}References 2, 3, 10, 19, 32, 51, 66, 73, and 93-95.

⁸⁸References 4, 5, 7, 8, 29, 30, 52, 71, 95-97.

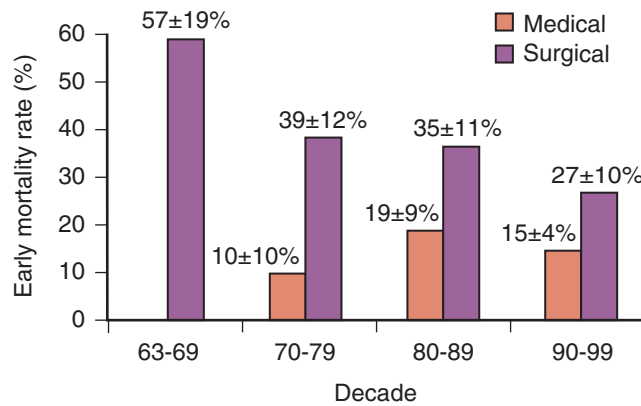


FIGURE 71-4 ■ Early (30-day) mortality rates illustrated as a function of time (decades) and broken down into medical and surgical subgroups in the overall Stanford experience. (From Umaña JP, Lai DT, Mitchell RS, et al: Is medical therapy still the optimal treatment strategy for patients with acute type B aortic dissections? *J Thorac Cardiovasc Surg* 124:896-910, 2002.)

with 40% of the patients treated surgically) and the mortality rate was only 11%, both significantly lower than after surgical treatment.⁹⁹ In the 2002 Stanford paper, the early mortality rate for patients treated medically did not change significantly between 1970 and 1999, ranging from 10% to 19% (Fig. 71-4).¹ On the other hand, the early mortality rate for patients treated surgically decreased from 57% in the 1960s to 27% in the 1990s. Other centers with special expertise in thoracic aortic surgery also demonstrated that early mortality rates closer to 20% can be achieved in the current era in selected patients with acute type B dissections.^{10,100} In an earlier Stanford investigation, multivariable analysis revealed that the independent determinants of operative risk in patients with type B dissections (acute or chronic) were renal or visceral ischemia, aortic rupture, and older age.⁴³ Acute type B dissection caused by an intimal tear located in the arch, whether the patient was treated medically or surgically, was associated with high early mortality rates in a subsequent Duke-Stanford cooperative 1989 report.⁶ In Crawford's surgical experience, the independent risk factors portending operative death were earlier year of operation, surgery within 24 hours of onset of symptoms, and chronic obstructive pulmonary disease.⁹⁵ In the IRAD registry, independent predictors of in-hospital mortality in the overall cohort were hypotension or shock, absence of pain on presentation, and branch vessel involvement; age older than 70 years and hypotension or shock were independent predictors of mortality in the subgroup of patients requiring surgical intervention.^{52,98}

Late Survival

In the 36-year overall Stanford experience, actuarial survival for the entire patient cohort was 71%, 60%, 35%, and 17% at 1 year, 5 years, 10 years, and 15 years, respectively.¹ As illustrated in Figure 71-5A, there was no significant difference in survival between the medical and surgical patients. Multivariable analyses identified shock, visceral ischemia, arch involvement, aortic rupture,

stroke, previous sternotomy, pulmonary disease, and female gender as significant, independent predictors of overall death. In the Baylor series, actuarial survival after surgical repair of type B dissections was 76%, 54%, and 35% at 1 year, 5 years, and 10 years, respectively; independent determinants of late death were earlier year of operation, older age, severe symptoms, higher New York Heart Association functional class, extent of aorta replaced, type of procedure, residual aneurysmal disease, and postoperative complications.⁹⁵ More recent mid-term data from IRAD indicated that 3-year survival of patients discharged alive from the hospital was 78% for those treated medically, 82% with surgical treatment, and 76% with endovascular techniques ($P = NS$).¹⁰⁰ Predictors of late death were female gender, prior aortic aneurysm, history of atherosclerosis, in-hospital renal failure, in-hospital pleural effusion, and hypotension or shock during hospitalization.

Congestive heart failure, renal failure, stroke, and cancer accounted for almost 50% of the late deaths in patients with acute type B dissections in the Stanford series, emphasizing the importance of patient-specific factors in determining their long-term prognosis.¹ Rupture of a contiguous or remote segment of the aorta was responsible for 16% of late deaths in this Stanford series, compared with 29% of late deaths in the 20-year long-term follow-up study from DeBakey and coworkers.²¹ This sobering figure should be amenable to improvement if more diligent patient follow-up imaging surveillance and medical care are provided.

Aortic Reintervention

The actuarial freedom from late aortic reoperation and late aortic-related complications after treatment of acute type B dissection in the overall Stanford experience is illustrated in Figure 71-5B-D. Surprisingly, there was no significant difference in reoperation rate between patients treated medically and those treated surgically.¹ After 5 years, reoperation was necessary in 14% of the medical group and 13% of the surgical patients; at 10 years, reoperation was necessary in 17% of both groups. The only independent predictor of late aortic reoperation was Marfan syndrome, underscoring the fragility of the dissected aorta in these patients. In Crawford's 1990 study analyzing a 33-year experience with surgical management of aortic dissection (type A or B, acute or chronic), 22% of patients required aortic reoperation 10 years later and 88% were free from aortic rupture.⁹⁵ Residual aneurysmal disease, no cardioplegia (probably indicative of improved surgical techniques over time), and preoperative New York Heart Association functional class were the determinants of late aortic rupture; a higher likelihood of reoperation was significantly linked to earlier year of operation, previous proximal aortic procedure, aortic cross-clamp time, and more limited surgical procedures that have been abandoned (e.g., primary repair, aortoplasty, patch repair). In a retrospective analysis of 101 patients with uncomplicated acute type B dissections treated medically, Marui and colleagues^{70,101} from Japan reported that patent false lumen, aortic diameter exceeding 40 mm, and fusiform dilation of the proximal

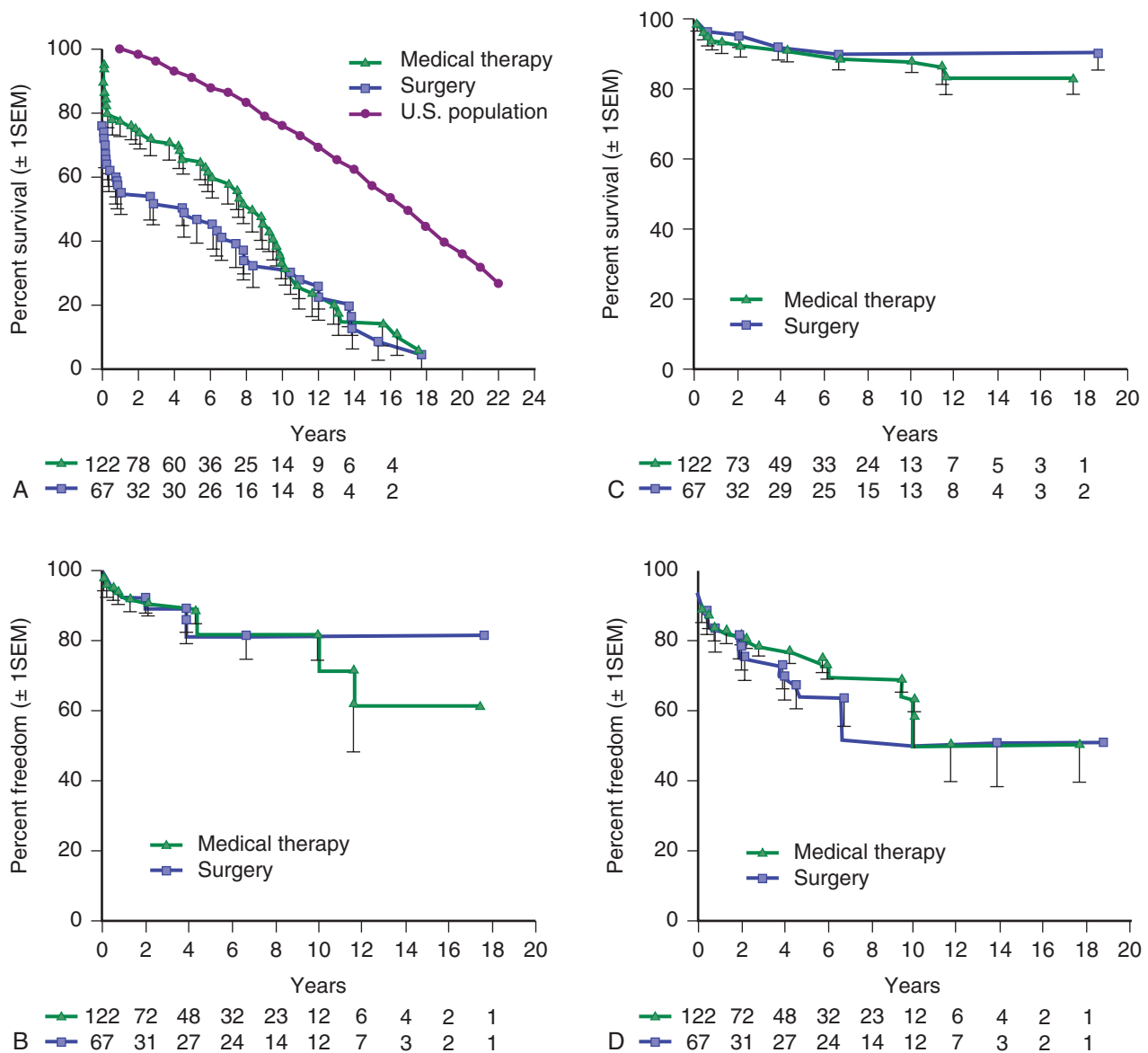


FIGURE 71-5 **A**, Actuarial survival for all patients with acute type B dissections subdivided according to initial treatment method. There was no statistically significant difference in survival between those treated surgically and those treated medically. For perspective, this graph also portrays the survival curve for the age- and gender-matched U.S. population; this indicates that only 35% of patients this age can be expected to be alive 20 years later. **B**, Actuarial freedom from late aortic reoperation (defined as surgical procedures related to the aorta or to complications of the dissection) subdivided according to initial treatment. There was no statistically significant difference between treatment modalities. **C**, Freedom from reoperation for all patients, expressed in actual (or observed cumulative frequency) terms. **D**, Actuarial freedom from late aortic-related complications or death for all 189 patients. (From Umaña JP, Lai DT, Mitchell RS, et al: Is medical therapy still the optimal treatment strategy for patients with acute type B aortic dissections? *J Thorac Cardiovasc Surg* 124:896–910, 2002.)

descending aorta were predictors of late aortic events; these authors recommended that such patients be considered for early surgical intervention.

FOLLOW-UP

In patients with acute type B aortic dissection, whether they were initially treated medically or surgically, an early predischarge CTA or MRI scan is mandatory to rule out early complications and to serve as a baseline reference. During the first few weeks, these patients require close outpatient medical care; attention should be focused on

blood pressure control and cerebral, cardiac, and renal function.^{7,29} Periodic imaging studies of the entire thoracic and abdominal aorta are essential indefinitely to detect aortic complications, such as aneurysmal degeneration of the downstream aortic false lumen, before rupture or death. Attention should also be paid to the patency of the false lumen because it is now known that partial thrombosis of the false lumen (as opposed to patent false lumen or complete thrombosis of the false lumen) is associated with higher mortality than in patients with a patent false lumen.¹⁰² Our protocol calls for the interval between imaging studies to be lengthened gradually from 3 to 6 months during the first year after the

acute event if no worrisome interval changes are detected, then annually thereafter. Lifelong rigorous blood pressure control and negative inotropic therapy are also critically important. In DeBakey and colleagues' 1982 report,²¹ late aneurysmal formation occurred in 45% of patients with poor blood pressure control, compared with 17% of those with well-controlled hypertension. A combination of conventional antihypertensive agents and negative inotropic medications is usually required and needs to be continued indefinitely, even in normotensive patients.⁷⁹ Improvements in the follow-up management of these patients are still needed because mortality rates after discharge from the hospital are still higher than expected (almost one in four patients dying within the first 3 years), irrespective of initial treatment modality.^{1,100}

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ENDOVASCULAR THERAPY FOR THE TREATMENT OF THORACIC AORTIC PATHOLOGIES

Prashanth Vallabhajosyula • Wilson Y. Szeto • Joseph E. Bavaria

CHAPTER OUTLINE

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SUMMARY

The development of thoracic endovascular aortic repair (TEVAR) has dramatically revolutionized the field of cardiovascular surgery. Since Parodi's first description of an intraluminal stent graft device for the treatment of abdominal aortic aneurysms,¹ endovascular device technology has rapidly evolved to treat the multiple pathologies seen in the thoracic aorta. In 1994, Dake first reported the initial Stanford experience with 13 patients undergoing endovascular therapy of descending thoracic aortic aneurysms.² Since then, indications involving off-label use have expanded to include the treatment of aortic dissections, traumatic transections, penetrating atherosclerotic ulcers (PAUs), and intramural hematoma (IMH). Currently, there are four stent graft devices approved by the U.S. Food and Drug Administration (FDA) for the treatment of descending thoracic aortic aneurysms. Questions and concerns remain regarding the appropriate timing, indication of intervention, and durability of

this fast-evolving technology. TEVAR has gained worldwide acceptance in the treatment of pathologies of the descending thoracic aorta (DTA). In the span of a decade, TEVAR has gained on-label FDA approval for the treatment of thoracic aortic aneurysm, PAU, blunt thoracic aortic injury, and type B aortic dissection. This change attests to the rapid evolution and adoption of this technology in treating thoracic aortic pathology.

As TEVAR technology evolves, recent reports have shed light on the utility of endovascular technology in treating ascending aortic and aortic arch pathology—primarily ascending aortic dissection, ascending aorta IMH/PAU, and aortic arch aneurysms in poor open surgical candidates. With improving technology, it is likely that in the future TEVAR will have a defined role in the treatment of ascending aortic and aortic arch pathology. Currently, it has become the gold standard for treatment of descending thoracic aortic pathologies.

DESCENDING THORACIC AORTIC ANEURYSMS

Natural History and Indications for Intervention

Thoracic aortic aneurysms are abnormal dilation of the aorta, characterized by elastin fragmentation and fibrosis, resulting in medial degeneration of the aortic wall.³ These age-related changes likely result in the reduction of aortic integrity and strength. As the population ages, the incidence of thoracic aortic aneurysms appears to be increasing. In a recent Swedish study examining the national health care registry from 1987 to 2002, the incidence of thoracic aortic pathology rose by 52% in men and by 28% in women, reaching 16.3 per 100,000 per year and 9.1 per 100,000 per year, respectively. In the same study, the annual incidence of operations performed on the thoracic aorta increased from 0.8 per 100,000 per year in 1987 to 5.6 per 100,000 per year in 2002 for an overall sevenfold increase. In women, the increase was 15-fold, from 0.2 per 100,000 per year in 1987 to 3.0 per 100,000 per year in 2002.⁴

The natural history of thoracoabdominal aortic aneurysms has been examined in large single-institutional series. Characterized by slow growth over time, aortic aneurysmal degeneration is an indolent pathologic process of aortic dilation leading to potential rupture or dissection. The human aorta grows generally at a rate of about 0.07 cm per year in the ascending aorta, and 0.19 cm per year in the descending thoracoabdominal aorta.⁵ If dissection is present, the thoracoabdominal aorta may grow at a slightly faster rate of 0.28 cm per year.^{6,7}

The major risk in thoracic aortic aneurysms pertains to the catastrophic events of rupture or dissection. The risk of rupture or dissection as a function of maximum aortic diameter has been examined in multiple studies. Clouse and coworkers examined the Olmstead County database and demonstrated that in patients with a maximum aortic diameter measuring 4.0 to 5.9 cm, the risk of rupture was 16% over a period of 5 years. When the maximum aortic diameter is greater than 6.0 cm, the risk of rupture exceeds 30% over the same period of 5 years.⁸ The Yale group have also identified “hinge points” of maximum aortic diameter that represent significant increases in the risk for rupture. In the ascending aorta, this “hinge point” appears to be at 6 cm, with a risk of rupture or dissection at 34% over the lifetime of the patients. In the DTA, the “hinge point” appears to be at 7 cm, with a 43% risk of rupture or dissection.⁶ The annual risk of rupture or dissection as a function of maximum aortic diameter has also been examined. Davies and coauthors⁵ demonstrated that in patients with a maximum aortic diameter of less than 6.0 cm, the yearly rates of rupture, dissection, or death, is less than 8%; however, the annual risk of rupture, dissection, or death dramatically increases to 15.6% when the maximum aortic diameter is greater than or equal to 6.0 cm.

General recommendation for the indication for surgical intervention has been made based on these large

institutional population studies. The decision to intervene surgically must be based on a balance between the risk of surgery or intervention (in the case of TEVAR) versus the risk of rupture or dissection with medical management. The general consensus for conventional open repair is to intervene surgically at a diameter of 5.5 cm for the ascending aorta and a diameter of 6.5 cm for the DTA. Certainly, patients with significant family history of aortic disease or connective tissue disorder such as Marfan syndrome may warrant intervention at a lower threshold of aortic diameter. Furthermore, for patients with symptomatic aneurysmal disease, urgent surgical intervention is recommended regardless of size, because symptoms are an early indicator of impending rupture.

In the era of TEVAR, the perceived lower rates of morbidity and mortality have urged the question: Should the threshold for intervention in the DTA be lowered? With a mortality rate of less than 5% with TEVAR in most centers of excellence,⁹⁻¹² most patients with a descending thoracic aortic diameter greater than 5.5 cm may be considered for endovascular repair (Fig. 72-1). However, the final decision to intervene must be based on previously established surgical dictum: the risk of rupture must outweigh the risk of surgery, regardless of approach.

Device Development

Since the early devices were first described by the Stanford group in 1994,² TEVAR devices have undergone multiple modifications and clinical trials. There are four thoracic endoprotheses currently approved for the treatment of descending thoracic aortic aneurysms. Second- and third-generation devices, as well as disease-specific devices, are currently being investigated.

Gore TAG

The Gore TAG thoracic endoprosthesis (W.L. Gore, Inc., Flagstaff, AZ) was approved by the FDA in March 2005 for the treatment of descending thoracic aortic aneurysms. The first device to be approved, the Gore TAG, is a self-expanding polytetrafluoroethylene endograft comprised of nitinol support. Concern over fracture of the longitudinal support wire led to the revision of the

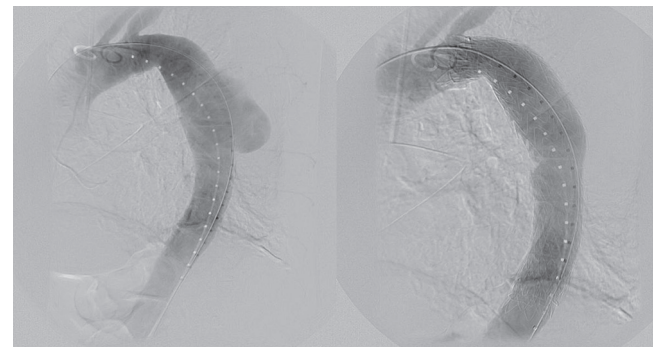


FIGURE 72-1 ■ Angiogram demonstrating endovascular treatment of thoracic aortic aneurysm.

original Gore device to its current Gore TAG endoprosthesis. Unique to this device system is the introducer sheath, which enables the delivery of multiple devices and minimizes traumatic injury to the femoral access vessels. The introducer sheath ranges from an inner diameter of 20 Fr to 24 Fr depending on the size of the Gore TAG devices required for treatment. The Gore TAG endoprosthesis ranges from a minimal diameter of 26 mm to a maximum diameter of 40 mm, with lengths ranging from a minimum of 10 cm to a maximum of 20 cm (Fig. 72-2). The mechanism of deployment involves release of the endograft from a center to peripheral fashion. Thus, precise deployment of the proximal and distal landing zones may be difficult.

In August 2011, Gore Conformable-TAG (C-TAG) device received FDA approval. The C-TAG has essentially replaced the older-generation TAG device. It provides greater flexibility and conformability, with a broad, oversizing window (6%-33%), and is available in straight and tapered forms. The C-TAG is available in a smaller-diameter range than the TAG device (21 mm) and can be placed using an 18 Fr (inner diameter) delivery system. C-TAG is now FDA approved for use in thoracic aortic aneurysm disease, PAU, blunt thoracic aortic injury, and complicated type B dissection.

Medtronic Talent and Valiant Thoracic Endoprosthesis

The Talent Device. Recently approved in June 2008 by the FDA for the treatment of descending thoracic aortic aneurysms, the Talent device is a preloaded stent graft incorporated into a CoilTrac delivery system. It is a stent graft composed of a polyester graft (Dacron) sewn to a self-expanding nitinol wireframe skeleton. Radiopaque markers are sewn to the graft material to aid in visualization during fluoroscopy. The CoilTrac delivery system is

a sheathless, push-rod-based delivery system. Preloaded onto an inner catheter, the Talent device is deployed by pulling back an outer catheter, allowing the device to self-expand and contour to the aorta. A balloon may be used to ensure proper apposition of the graft to the aneurysmal aorta after deployment.

The Talent device is designed as a modular system. Forty-seven different configurations ranging from a diameter of 22 to 46 mm and cover lengths from 112 to 116 mm are available. To accommodate the size differences often found between the proximal and distal portions of the aorta in thoracic aneurysms, tapered grafts are available for better aneurysmal conformability and prevention of junctional endoleaks. Four configuration categories are available: proximal main, proximal extension, distal main, and distal extension (Fig. 72-3). The proximal configurations and the distal extension are offered with a bare-spring design (Free-Flo design). The bare-spring design allows for placement of the device crossing the arch vessels proximally and the celiac artery distally for suprasubclavian and infraceliac fixation, respectively.

The Valiant Device. The Valiant device is designed based on the experience with the Talent device. Similar to the Talent device, the Valiant device is also a preloaded stent graft made of the same polyester graft built onto a self-expanding nitinol skeleton. Modification has been made to improve trackability, conformability, and deployment of the Valiant device. First, device lengths have been increased to a maximum of 230 mm (130 mm for Talent). Because the device is a sheathless system, each piece requires an individual deployment through the access vessel, resulting in repeated exchange in the artery. Longer lengths have been designed to minimize device exchange



FIGURE 72-2 ■ The Gore TAG thoracic endoprosthesis. (Courtesy W.L. Gore, Inc., Flagstaff, AZ.)

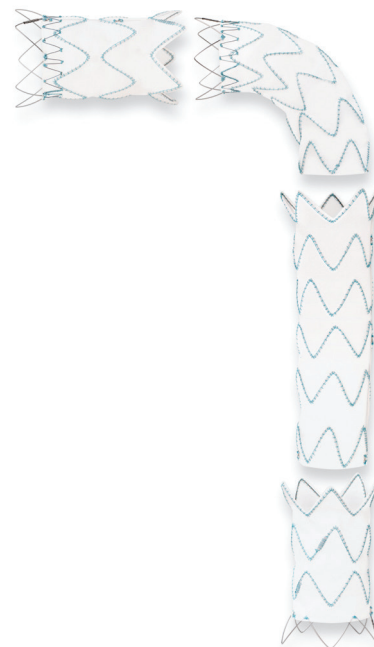


FIGURE 72-3 ■ The Medtronic Talent thoracic endoprosthesis (Medtronic Vascular, Santa Clara, CA).

during deployment. Second, the connecting bar has been removed in the Valiant device for improved conformability, especially in the arch. Third, the number of bare springs at the proximal and distal ends of the device has been increased from 5 to 8 in the Valiant device to improve circumferential force distribution and fixation along the aorta wall. Finally, the Valiant device is introduced in a new delivery system, the Xcelerant Delivery System. First available to physicians in the United States for the AneuRx AAA device, the Xcelerant Delivery System has been modified for the Valiant Device to provide a more comfortable deployment mechanism of the device, especially in tortuous anatomy of the distal arch and thoracic aorta. As opposed to a simple pullback unsheathing mechanism, the deployment of the Xcelerant Delivery System includes a gearing, ratchet-like mechanism in the handle to allow easy deployment. The amount of force required to deploy the device is reduced significantly without compromising the precision of the deployment.

Similar to the Talent device, The Valiant device is a modular design. Eighty-eight different configurations ranging from a diameter of 22 to 46 mm and cover lengths from 110 to 200 mm are available in the Valiant device. Four configurations categories are available: proximal FreeFlo straight component, proximal closed-web straight component, proximal closed-web tapered component, and distal bare-spring straight component. The proximal FreeFlo straight component is designed for the most proximal deployment zone, because the bare springs are designed to allow precise and crossing deployment of the arch vessels. In addition, it is designed as the first piece to be deployed.

In 2012, results of the VALOR II trial were reported for the use of the Valiant endoprosthesis for DTA aneurysm repair.¹³ The pivotal trial was conducted at 24 U.S. sites, assessing 30-day and 12-month outcomes. At 30 days, there were rates of 3.1% mortality, 38.1% major adverse events, 0.6% paraplegia, and 2.5% stroke. At 12 months, aneurysm-related mortality was 4%, with a stent migration rate of 2.9% and an endoleak rate of 13%.

Cook Zenith TX2 Thoracic Endoprosthesis. Recently approved in 2008 by the FDA, the Cook Zenith TX2 thoracic endoprosthesis (Cook, Inc., Bloomington, IN) is designed as a modular system with a specific proximal and distal configuration (Fig. 72-4). The graft consists of stainless steel Z-stents with full-thickness polyester fabric. Similar to the Medtronic delivery system, the Zenith TX2 system does not require a delivery sheath, and it is introduced as a preloaded catheter with triggers. The device sheath has a hydrophilic coating and sizes range from 18 to 22 Fr, depending on the diameter of the endoprosthesis. The diameter of the endoprosthesis ranges from 22 to 42 mm and lengths from 120 mm to 207 mm. The two components are designed to be deployed from a proximal to distal direction, and tapered devices are available.

Deployment of the TX2 is achieved through a trigger system to ensure a controlled deployment. Flushed at the proximal end with barbs to prevent migration and endoleak, the device is deployed by an unsheathing mechanism. To minimize the “wind sock” effect during

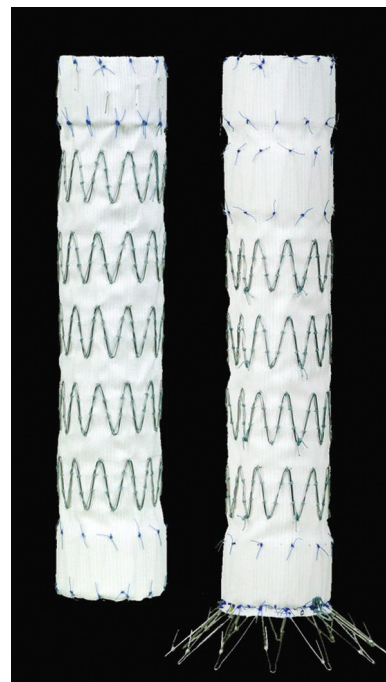


FIGURE 72-4 ■ The Cook ZenithTX2 thoracic endoprosthesis (Cook, Inc., Bloomington, IN).

deployment (thus distal migration), the proximal barb component of the device is not released until the graft is deployed and the trigger released. The distal component is deployed in a similar mechanism. However, in addition to barbs, the distal component also has bare springs at its caudal portion. Proximal and distal extensions are available if additional coverage is necessary.

Bolton Relay Prosthesis. The Bolton Relay graft (Bolton Medical, Inc., Sunrise, FL) is the latest new company to receive FDA approval (in 2012) for TEVAR treatment of DTA aneurysmal pathology. The Relay system features a four-step sheath delivery system for modular delivery (outer diameter 22-26 Fr), with graft lengths ranging from 100 to 250 mm in straight and tapered forms; graft diameters range from 22 to 46 mm, with proximal and distal components. Proximal grafts are available in two types—Relay uncovered graft and Relay NBS covered graft. They feature S-bar (spiral support strut) technology that runs longitudinally along the stent graft, enabling improved support to the entire structure. The Relay system enables proximal capture of stent graft for precise placement, along with a secondary sealing and fixation zone that provides an extra sealing independent of proximal sealing.

Anatomic and Technical Considerations

Anatomic requirements and key technical considerations for successful TEVAR revolve around answering the question of what makes a patient a suitable anatomical candidate for a thoracic aortic stent graft. Initial assessment of a stent graft candidate begins with an extensive preoperative workup and evaluation. Key points of the history and physical examination should include a detailed

neurologic and cardiovascular examination. Distal vascular pulses and preoperative neurologic deficiencies must be documented. Previous abdominal, pelvic, and inguinal surgeries should be noted, because these procedures may demand an alternate access route.

Access

Safe vascular access for thoracic aortic device deployment is the key to thoracic aortic stent grafting. The majority of the morbidity and mortality is a direct result of arterial access complications.^{9,10,12} Extensive preoperative planning with appropriate imaging is mandatory. The “gold standard” for preoperative evaluation is a computed tomography (CT) angiogram that includes the thorax, abdomen, pelvis, and femoral arteries. Fine-cut helical CT scanning with at minimum 3-mm slices is ideal (Fig. 72-5). In patients who cannot receive a CT with contrast, magnetic resonance angiography is an acceptable substitution.

All the thoracic endovascular devices take a long time to reach the descending aorta, are of large caliber to contain the thoracic aortic endoluminal graft, and are relatively stiff to allow “pushability” through the iliofemoral access points and through the abdominal aorta. The management of the delivery of the thoracic aortic stent graft is often the most challenging aspect of the case. Delivery systems of the three currently FDA-approved thoracic endoprostheses will require arterial access size of a minimum of 7.5 to 8.0 mm. Creation of a conduit to the femoral or iliac artery may be necessary to achieve adequate access. Not only the size of the arterial vessels, but also the anatomy of the iliofemoral and abdominal aorta, must be considered when planning the access route. Excessive tortuosity and atherosclerosis with occlusive disease may provide barriers to safe delivery of the endograft. In approximately 20% of patients, retroperitoneal access to the common iliac arteries will be required owing to issues of femoral or external iliac artery size and/or tortuosity.¹⁴



FIGURE 72-5 ■ Computed tomographic angiography of a descending thoracic aortic aneurysm.

Careful review of preoperative studies will indicate which patients will have difficult access. Patients with atherosclerotic occlusive iliac disease may be treated with standard endovascular techniques of balloon angioplasty to reduce the obstruction. Iliac stents should be avoided because of the potential interference of these stents with the thoracic aortic access devices. These procedures on the access vessels should be carried out at least 6 weeks before thoracic aortic stent grafting to allow healing of the iliac arteries post-angioplasty and manipulation. At the completion of the thoracic aortic endografting, iliac stents may be placed if appropriate.

Access to the retroperitoneum allows several options for safe device deployment. The common iliac artery may be used for device deployment. An open surgical conduit can be constructed to allow an end-to-end anastomosis or a side-to-side anastomosis. A 10-mm conduit of synthetic Dacron is commonly used and allows ample size for insertion of all necessary devices. The conduit may be brought through a separate counterincision in the groin to allow better angulation of the relatively long and stiff deployment devices. At the conclusion of the procedure, these conduits may be used to revascularize distal obstructions if needed.

Alternatively, the retroperitoneal iliac vessels, or even the distal aorta, may be accessed using direct sheath insertion. A double purse string of 4-0 Tyron is used to secure the vessel and provide hemostasis with the application of two sets of tourniquets. Direct needle puncture of the artery is followed by dilation and insertion of the device. At completion, the device is removed and the purse string sutures are tied down. Excessive tortuosity of the iliofemoral arteries requires adaptive strategies. The use of external manual manipulation provides a simple method of straightening some of the tortuosity of the aorta and iliac arteries. During fluoroscopy the operator hand can provide gentle force to the tortuous arterial segment to allow straightening and subsequent endovascular access.

In cases of iliac artery tortuosity, advanced endovascular techniques may aid in straightening these segments. The use of stiff wires or buddy wire techniques can provide some degree of straightening of the diseased arteries. In severe cases of tortuosity, brachiofemoral access may be required to perform “body flossing” with an appropriately stiff wire. Typically, a 5 Fr sheath with a long catheter is placed into the aortic arch and then into the descending aorta. A long, stiff wire, such as a 450-cm SS Guidewire (Boston Scientific, Natick, MA), is guided from the brachial artery and retrieved through the femoral artery. Gentle traction on both the brachial and femoral sites will straighten out the tortuosity. Of note, a long catheter must be placed through the brachial artery into the aorta to prevent excessive trauma by the stiff wire along the arch and innominate vessels.

At the completion of the deployment and ballooning of the thoracic stent graft, the entire route of access must be carefully examined to ensure that there has been no injury. The stiff guidewire that was used to position the thoracic endograft should be left in place as the sheaths and remaining endovascular materials are removed. A smaller sheath should be reinserted and a diagnostic

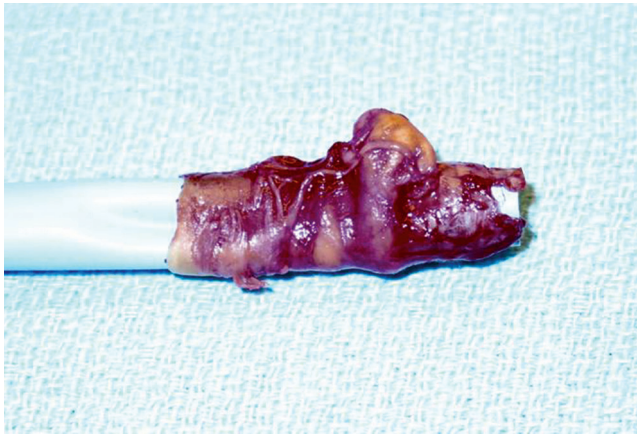


FIGURE 72-6 ■ Iliac artery avulsion after removal of an endovascular delivery system.

aortoiliac arteriogram should be performed to evaluate for thrombus, dissection, or complete avulsion.

The removal of the large sheath, especially when inserted with some force and manipulation, is a particularly dangerous period when injury may occur. There have been numerous reports of successful thoracic endografting with a sheath removed with a complete iliac artery avulsed and attached (Fig. 72-6). At the time of recognition, a stiff wire through this injured artery may be life-saving and allow insertion of an occluding balloon proximally to allow control of a potentially life-threatening bleed. In addition, both blood pressure and heart rate should be carefully monitored during removal and completion of the endovascular procedure for signs of an occult injury.

Landing Zones

The proximal aorta is divided into landing zones as illustrated in Figure 72-7. Unless revascularization is performed, proximal landing in zones 0 and 1 is unacceptable because of the necessary occlusion of the left common carotid artery in zone 1 and the innominate artery in zone 0. Proximal landing in zone 2 is commonly used with either partial or total occlusion of the left subclavian artery. Zone 3 landing is dependent on the exact anatomical neck at the arch. Proximal landing in zone 3 can lead to angulation of the graft, which provides inadequate sealing of the proximal graft along the lesser arch and “bird beaking” or “stove piping” graft placement, which results in a high incidence of Type II endoleaks. Zone 4 landing is usually straightforward because of the lack of angulation and distance from the arch vessels.

The proximal and distal landing zones must be of an appropriate diameter to allow for stent grafting with available devices. In general, devices should be oversized over the diameter of the landing zone between 15% and 20%, depending on the presenting aortic pathology. As has been discussed, the proximal landing zone of the aorta must be carefully examined on preoperative imaging workup. The goal is to create a good “seal” of 15 to 20 mm between the graft and the aortic wall on a disease-free, nontapered, nonangulated portion of the aorta.

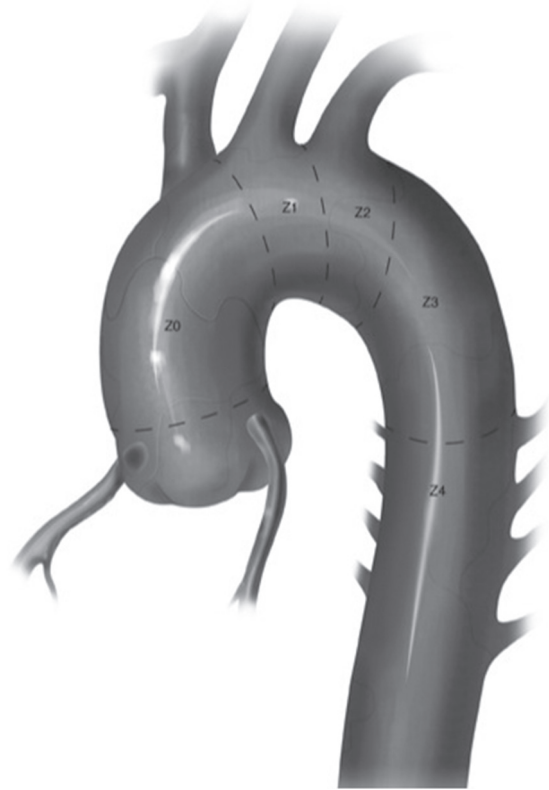


FIGURE 72-7 ■ Classification of landing zones in thoracic aortic endovascular repair. (From Mitchell RS, Ishimaru S, Ehrlich MP, et al: First International Summit on Thoracic Aortic Endografting: roundtable on thoracic aortic dissection as an indication for endografting. *J Endovasc Ther* 9[Suppl 2]:1198–105, 2002.)

There should be adequate length of the proximal landing zone, minimal angulation, minimal tortuosity, and minimal calcification. Angulation of the aortic arch is acceptable if the inner radius is greater than 35 mm and the outer radius is greater than 70 mm. These parameters allow adequate conformation of the aortic stent graft to the arch.

Because zone 2 is often the site of best proximal landing to avoid excessive angulation and tortuosity, the management of the left subclavian artery requires preoperative planning. Some of the possible complications of covering the left subclavian artery include vertebrobasilar artery insufficiency or stroke, left arm ischemia, or ischemia of the heart in patients with a previous left internal mammary artery to left anterior descending coronary artery bypass graft. An evaluation of the right vertebral artery and the adequacy of the circle of Willis is crucial when planning to cover the left subclavian artery. In patients with inadequate collaterals through the circle of Willis, stenotic right vertebral artery, or a dominant left vertebral artery, strong consideration should be made to bypass the left subclavian artery before covering. One option is to transpose the left subclavian artery to the left common carotid artery with oversewing of the proximal left subclavian artery. A second option is to bypass from the left common carotid artery to the left subclavian artery. Either surgical ligation of the proximal

left subclavian at the time of bypass or staged-coil embolization of the proximal left subclavian artery at the time of graft delivery may be used. Bypass of the left subclavian artery may be preferable because it avoids any mediastinal dissection and there is no interruption of antegrade flow to the vertebral artery or internal mammary artery branch vessels.¹⁵

Evaluation of the distal landing zone also requires careful preoperative workup. The distal landing zone should again have 15 to 20 mm of normal aorta with minimal calcification, angulation, and tapering. The celiac artery is the first distal branch vessel that must be avoided. Therefore, the length of the aortic graft must be correctly planned. Enough graft length should cover the aortic pathology while avoiding excessive coverage of the DTA. The goal is to preserve the distal vertebral artery branches and perfusion to the spinal cord.

Results

Multicenter Clinical Trials

The Gore TAG endoprosthesis was approved as a result of the phase 2 U.S. multicenter trial comparing the Gore TAG endoprosthesis (W.L. Gore) to an open surgical control group in the treatment of descending thoracic aortic aneurysms.⁹ Between September 1999 and May 2001, 140 patients with descending thoracic aortic aneurysms were enrolled from 17 sites in the United States. All patients were required to have adequate landing zones of at least 2 cm length of nonaneurysmal aorta distal to the left carotid and proximal to the celiac axis. At the same centers, the open surgical control cohort enrolled 94 patients. Forty-four patients were concurrent controls and 50 were historically and retrospectively acquired by selecting the most recent surgical patients in reverse chronological order.

In the endograft group, statistically significant improvement was seen in the 30-day mortality, incidence of postoperative respiratory failure, renal failure, spinal cord ischemia (SCI), mean intensive care unit, and hospital stay. Thirty-day mortality was 2.1% and 11.7% in the Gore TAG group and the open surgical control group, respectively. SCI was 2.9% in the Gore TAG group versus 13.8% in the control group. However, peripheral vascular complications were significantly higher in the endograft group (14% vs. 4% control group).⁹

The mean duration of follow-up was 25.8 months in the endograft group and 24.9 months in the open control group. Kaplan-Meier 2-year survival was similar between the two groups (78% endograft group vs. 76% control). The incidence of endoleak at 1-year and 2-year follow-up was 6% (6/103) and 9% (7/80), respectively. There were no cases of aneurysm rupture in either group. At 2-year follow up, 45% of the endograft group had aneurysmal regression of 5 mm or greater, 42% had no change, and 13% had aneurysmal progression of 5 mm or greater.⁹ At 5-year follow-up, all-cause mortality remains similar between the two groups (68% endograft group vs. 67% control). Aneurysm-related mortality was lower in the endograft group (2.8%) when compared with the control group (11.7%).¹⁶

The Vascular Talent Thoracic Stent Graft System for the Treatment of Thoracic Aortic Aneurysms (VALOR) trial led to the approval of the Talent endoprosthesis for the treatment of thoracic aortic aneurysms. The Medtronic VALOR trial was a prospective, multicenter, nonrandomized, observational trial evaluating the use of the Medtronic Talent thoracic stent graft system in the treatment of thoracic aortic pathology. The study was conducted from 2003 to 2005 and involved 38 sites. A total of 195 patients were enrolled, with 189 patients identified as retrospective open surgical controls. In the Talent group, the 30-day mortality was 2.1%, with an incidence of paraplegia of 1.5% and stroke of 3.6%. One-year mortality was 16.1% with aneurysm-related mortality of 3.1%. When compared with the surgical control group, the Talent arm demonstrated statistically superior outcome in perioperative mortality (2% vs. 8%, $P < 0.01$), 30-day major adverse events (41% vs. 84.4%, $P < 0.001$), and 12-month aneurysm-related mortality (3.1% vs. 11.6%, $P < 0.002$). In 2012, results were reported from the VALOR II trial, which assessed the Valiant stent graft system for degenerative disease of the DTA.¹³ It was a prospective, nonrandomized, pivotal trial conducted at 24 U.S. sites enrolling 160 patients. The perioperative mortality rate was 3.1%, stroke rate was 2.5%, and paraplegia/paraparesis rate was 2.5%. At 12 months, endoleak rate was 13%, with 4% aneurysm-related mortality. The Valiant device was statistically noninferior to the Talent graft.

Published in 2008, the international controlled clinical trial of the TX2 device is a nonrandomized, controlled, multicenter, international trial comparing the treatment of thoracic aortic aneurysm with the TX2 endoprosthesis versus open repair. Enrollment began in March 2004 and was completed by July 2006. From 42 institutions, a total of 160 patients were enrolled in the endovascular group and 70 patients in the open group. The 30-day survival rate was noninferior for the TX2 group when compared with the control group (98.1% vs. 94.3%). The 30-day cumulative major morbidity scores were significantly lower in the TX2 group when compared with the control group (1.3 vs. 2.9). Although not statistically significant, the incidence of neurologic complications trended in favor of endovascular repair. The incidence of stroke in the TX2 group was 2.5% at 30 days compared with 8.6% in the control group. The incidence of paraplegia in the TX2 group was 1.3% versus 5.7% in the control group. At 12 months' follow-up, aneurysmal growth was seen in 7.1%, endoleak in 3.9%, and device migration in 2.8%. One-year survival estimated from all-cause mortality was similar between the TX2 group (91.6%) and the control group (85.5%). The 1-year survival estimate from aneurysm-related mortality was also similar between the TX2 group (94.2%) and the open surgical control group (88.2%).¹²

In September 2012, the Bolton Relay thoracic stent with Plus delivery system received FDA approval. Current on-label indications for Relay stent graft use in the United States include thoracic aortic aneurysm and PAU. In a study by the RESTORE investigators¹⁷ (multicenter, prospective European trial), outcomes for Relay stent graft treatment of a variety of thoracic aortic pathologies

(aneurysm dissection, PAU, IMH, pseudoaneurysm) were assessed in 304 enrolled patients. Thirty-day mortality was 7.2%, and perioperative stroke and paraplegia rates were 1.6% and 2%, respectively. Two-year freedom from device-related mortality was 95.9%. In a more recent study looking at subgroup analysis in patients treated for traumatic aortic injury, the clinical success with Relay graft was achieved in all 40 cases. Thirty-day mortality was 2.5%, and actuarial 2-year survival was 93.7%.

European Registries

Multicenter experience with TEVAR has also been accumulating in Europe. The Talent Thoracic Registry (TTR) is a database collected from seven European centers. All patients in the registry underwent TEVAR with the Medtronic Talent endoprosthesis between November 1996 and March 2004. The registry involved 457 patients, and the spectrum of pathologies comprised 180 (39.4%) thoracic aortic dissections, 137 (29.9%) atherosclerotic aneurysms, 14 (3%) pseudoaneurysms, 29 (6.35%) penetrating ulcers, 12 (2.6%) IMHs, and 85 (18%) traumatic aneurysms.¹¹ The in-hospital mortality rate was 5%. Technical failure defined as failure to complete an intended stent graft deployment was 2.2%, with a conversion rate to surgery of 2.2%. The in-hospital complication rate was 12.7% and included stroke (3.7%), paraplegia (1.7%), and vascular access issues (3.3%). The mean follow-up was 24 months with 11 late aneurysm-related deaths. Kaplan-Meier overall survival estimate at 1 year was 90.97% and at 5 years was 77.49%. Freedom from reintervention was 92.45% and 70.0% at 1 and 5 years, respectively.¹¹

The results from the European Collaborators on Stent Graft Techniques for Thoracic Aortic Aneurysm and Dissection Repair (EUROSTAR) and United Kingdom Thoracic Endograft Registry were recently published in 2004.¹⁸ This registry included a total of 443 patients (EUROSTAR 340, UK 103) with thoracic aneurysms or dissections in the thoracic aorta who underwent endovascular repair between 1997 and 2003. The patients were recruited from 62 European countries, and the devices deployed included Medtronic Talent, Gore Excluder, and Zenith or Endofit (Endomed). Technical success was achieved in 87% of patients with degenerative aneurysms and 89% with aortic dissection. The 30-day mortality rate in the entire group was 9.3%, with 30-day mortality of 5.3% in the elective aneurysmal group. In the aneurysmal group, neurologic complications included paraplegia (4.0%) and stroke (2.8%). At one-year follow-up, cumulative survival in the degenerative aneurysm group was 80.3%, with 2 (2.1%) aneurysmal-related deaths. The incidence of endoleak at one year was 4.2%, with a reintervention rate of 5.2%.

Complications

Vascular Access

The most common complication associated with TEVAR has been related to vascular access because of the requirement of large-diameter devices. In most series, the access

complication rates can be as much as 22.5%.⁹⁻¹² Complications include vessel disruption, dissection, frank rupture, pseudoaneurysm, arteriovenous fistula, thrombosis, and distal embolic events. Extensive preoperative planning and decisive intraoperative bailout maneuvers are necessary to minimize potentially lethal vascular access complications.

Endoleak

Endoleak is defined as the presence of persistent blood flow into the aneurysm sac after the deployment of an endovascular aortic stent graft device. In earlier series, TEVAR has been associated with an endoleak incidence of 9.6% to 25.9%.⁹⁻¹² Table 72-1 demonstrates the classification of endoleaks associated with endovascular repair of aortic aneurysms.

The presence and the potential development of endoleak during follow-up mandate life-long aortic surveillance with computed tomographic angiography (CTA). Proximal and distal endoleaks (type I) are most commonly the result of inadequate or poor landing zones. Type III, or junctional, endoleaks are likely the result of inadequate overlap of devices, aneurysmal sac expansion, or aortic lengthening over time. In contrast to type II or type IV endoleaks, types I and III endoleaks will likely require further reintervention, either at the time of the primary endografting or at late reintervention during follow-up. Types II and IV endoleaks require strict follow-up and likely will not need further intervention unless symptoms or complications develop.

We recently reviewed the impact of endoleak on our TEVAR experience.¹⁹ Over a 6-year retrospective review period, 105 patients underwent TEVAR with either the Medtronic Talent or the Gore TAG device. Of these 105 patients, 69 patients had sufficient radiographic follow-up to be evaluated. The mean follow-up period was 17.3 months. The total incidence of endoleak was 29%. In these patients, types I, II, and III endoleaks were seen in 40%, 35%, and 20%, respectively. Predictors of endoleaks include more extensive and larger aneurysms at the time of TEVAR, male sex, length of aortic treatment, and increasing number of devices used. The majority of types I and III endoleaks were treated successfully with reintervention, and significant aneurysmal sac regression was seen on follow-up. In contrast, most type II endoleaks were successfully managed with conservative therapy and strict surveillance.

Neurologic Complications

Neurologic complications associated with TEVAR fall within two major areas: stroke and SCI. Stroke is a devastating complication of TEVAR, with an incidence of approximately 3% to 9%.⁹⁻¹² The risks for stroke in TEVAR are likely multifactorial. Arch atheroma burden and embolic events are likely significant risk factors, because endovascular placement of thoracic aortic stent graft often requires multiple wire manipulations in the aortic arch. These manipulations may contribute to increased stroke risk by producing distal emboli. Other risk factors for stroke include history of previous stroke

TABLE 72-1 Classification Scheme for Endoleak and Endotension

Description	
Endoleaks* (Type)	Source of Perigraft Flow
I	Attachment site leaks [†]
A	Proximal end of endograft
B	Distal end of endograft
C	Iliac occluder (plug)
II	Branch leaks [‡] (without attachment site connection)
A	Simple or to-and-fro (from only 1 patent branch)
B	Complex or flow-through (with 2 or more patent branches)
III	Graft defect [§]
A	Junctional leak or modular disconnect
B	Fabric disruption (midgraft hole)
	Minor (<2 mm; e.g., suture holes)
	Major (≥2 mm)
IV	Graft wall (fabric) porosity (<30 days after graft placement)
Endotension [§] (Type)	
A	With no endoleak
B	With sealed endoleak (virtual endoleak)
C	With type I or type III leak
D	With type II leak

*Endoleaks also can be classified on the basis of the time of first detection as: perioperative, within 24 hours of EVAR; early, 1 to 90 days after EVAR; and late, after 90 days. In addition, they can be described as primary, from time of EVAR; secondary, appearing only after not being present at time of EVAR; and delayed, occurring after prior negative computed tomographic scan results. Endoleaks also can be described as persistent, transient or sealed, recurrent, treated successfully, or treated unsuccessfully. Endoleaks and endotension may be associated with AAA enlargement, stability, or shrinkage.

[†]Some type I and type III leaks also may have patent branches opening from AAA sac and providing outflow for leak.

[‡]From lumbar, inferior mesenteric, hypogastric, renal, or other arteries.

[§]Endotension (strict definition) is defined here as increased intrasac pressure after EVAR without visualized endoleak on delayed-contrast computed tomographic scans. In the generic sense, endotension is any elevation of intrasac pressure and occurs with type I, type III, and most type II leaks and endotension in the strict sense.

^{||}Detectable only on opening aneurysm sac.

From Veith FJ, Baum RA, Ohki T, et al: *Nature and significance of endoleaks and endotension: summary of opinions expressed at an international conference. J Vasc Surg* 35:1029–1035, 2002.

and grade V atheroma of the aortic arch, and coverage of the left subclavian artery.²⁰

SCI resulting in paraplegia is an equally devastating complication of thoracic aortic surgery. Endovascular stent graft repair of isolated descending thoracic aortic aneurysms has a reported SCI frequency that ranges from 3.6% to 12.0%, with approximately two-thirds of these cases being permanent deficits.²¹ Endovascular therapy offers several potential advantages in reducing the risk of SCI. These advantages include the avoidance of an aortic crossclamp, fewer episodes of hypotension, less bleeding, and an earlier emergence from general anesthesia to allow detection and treatment of a neurologic deficit.

Conversely, stent grafting may have the disadvantages of requiring more extensive aortic coverage to allow adequate sealing between endoluminal graft and aorta, the inability to reimplant intercostal arteries, and injury to iliofemoral vessels that may provide flow to the anterior spinal artery through the hypogastric and pelvic vascular plexus.

Identified risk factors for SCI after thoracic aortic stent grafting include previous abdominal aortic aneurysm repair (AAA), long segment of thoracic aortic stent graft, mobile atheroma, vascular injury, hemorrhage, and hypotension.^{21–23} The mechanisms that contribute to SCI are multifactorial. The risk of SCI in patients with previous AAA repair may be explained by the destruction of pelvic and hypogastric arterial collateral to the anterior spinal artery. Extended graft coverage, especially in the levels of T6 to T12, compromises the vertebral levels that supply the anterior spinal artery. Hypotension and hemorrhage contribute by decreasing the perfusion pressure to the spinal cord.

Techniques to reduce the risk of SCI include using lumbar cerebrospinal fluid drains and neurocerebral monitoring. The use of a lumbar cerebrospinal fluid drain has been shown in numerous studies to decrease the risk of SCI in open surgical thoracoabdominal aortic aneurysm repairs and endovascular thoracic aortic aneurysm and dissection stent graft repair.^{24,25} The use of neurophysiologic monitoring has been traditionally used to detect intraoperative spinal cord ischemic changes and to allow changes in perfusion management to reverse insults. The use of neurophysiologic monitoring in endovascular treatment of the thoracic aorta has been reported to also allow early detection and intervention to augment spinal cord perfusion pressure to decrease the risk.²⁶

AORTIC DISSECTIONS

Although TEVAR for elective repair of descending thoracic aortic aneurysm has been performed worldwide with increasing frequency, it is the potential role of TEVAR in acute thoracic aortic pathologies such as aortic dissections and traumatic aortic injury that has garnered increasing investigation. Through recent surgical advances, morbidity and mortality with conventional surgical repair have been reduced to acceptable perioperative complication rates. However, mortality for emergent thoracic aortic pathologies remains significant. The minimally invasive nature of TEVAR potentially offers a surgical alternative for this group of high-risk patients. The emerging role of TEVAR in acute aortic dissection will be discussed next.

Natural History and Indications for Intervention

In 1650, Sennertus was the first to describe the process of a tear in the intima of the aorta. However, the term *dissection* was not described until 1802, by Manoir. Until this century, aortic dissection was a postmortem diagnosis. Over the centuries, numerous surgical techniques for aortic dissection have been described with limited clinical

success. It was not until the 1950s, with the development of cardiopulmonary bypass, that surgical repair of aortic dissection became a clinical success.²⁷ Over the last 50 years, techniques to repair ascending aortic dissection have been refined, and surgical intervention has become the preferable therapeutic option.

Classification

Aortic dissection is classified based on the location of the primary tear site and dissection flap. Two classification systems currently exist. The DeBakey system classifies dissection based on the location of the dissection and its extension. Type I dissection begins in the ascending aorta and may involve most of the remaining distal aorta, whereas type II dissection involves only the ascending aorta with no extension beyond the aortic arch. Type III dissection begins distal to the left subclavian artery and involves the proximal thoracic aorta (type IIIa) or further to the iliac arteries (type IIIb). In contrast, the Stanford system classifies dissections into two types. Dissection involving the ascending aorta regardless of its extension is classified as type A. Type B dissection begins distal to the left subclavian artery and involves only the DTA.

Aortic dissection has also been classified based on its timing of presentation. Acute dissection has traditionally been classified as presentation within the first two weeks of the initial symptoms, whereas subacute dissection has been classified as presentation between two weeks and two months. Patients with dissections who present after two months after the initial symptoms are classified as chronic dissection.

Indications for Intervention

Surgical treatment of acute proximal aortic dissection (Stanford type A) has been established as the standard of care, demonstrating significant improvement in survival when compared with medical management. In all but the highest-risk patients, the presence of a dissection in the ascending aorta is in itself an indication for surgery. Current series have demonstrated surgical mortality rates ranging from 9% to 25%.²⁸⁻³⁵ In contrast, medical therapy is associated with a 1-month mortality rate as high as 60%.³⁶ Experience with endovascular repair of acute type A aortic dissection remains limited.³⁷⁻³⁹ Because of these limitations in the current technology, widespread clinical use has not been adopted. However, future development may result in the application of endovascular technique in the ascending aorta.

The management of acute type B aortic dissection remains less well defined. Traditionally, acute type B dissection without complications (i.e., rupture, malperfusion, hemodynamic instability) has been managed successfully with anti-impulse medical therapy, demonstrating low morbidity and mortality rates. According to the International Registry of Acute Aortic Dissection (IRAD),³⁶ uncomplicated type B dissection treated with medical therapy is associated with a mortality rate of 10.7%. In contrast, emergent open surgical repair has historically been associated with significantly higher morbidity and mortality.³⁶

Although medical therapy of uncomplicated type B dissections is associated with good early outcomes, long-term outcome and survival of patients with type B dissection remain disappointing. As much as 20% of patients with type B dissection develop complications (i.e., rupture, malperfusion) requiring surgical intervention.³⁶ Actuarial survival for all patients was 71%, 60%, 35%, and 17%, at 1, 5, 10, and 15 years, respectively, regardless of medical versus surgical therapy.⁴⁰ In most series, 10-year survival regardless of the mode of therapy is between 40% and 50%.⁴⁰⁻⁴³ Furthermore, there appears to be no difference in the freedom from reoperation and freedom from aortic-related complications between the medical and surgical treatment.⁴⁰

The poor long-term outcome of uncomplicated type B dissection is a result of the predisposition of these patients to develop aneurysmal dilation of the thoracoabdominal aorta.⁴⁴ Contemporary series have reported the incidence to be upwards of 80% over a five-year period.^{45,46} Subgroup populations of patients with acute type B aortic dissections also appear to be at risk of poor long-term survival. Predictors of increased long-term mortality include persistent patency with partial thrombosis of the false lumen,^{44,47-49} false lumen diameter greater than 22 mm at the time of initial presentation,⁵⁰ and total aortic diameter greater than 40 mm.⁵¹

Patients with acute type B aortic dissections who present with life-threatening complications including rupture or malperfusion syndrome remain a challenging group to manage. Historically, conventional open surgical therapy in this group of patients has been associated with significant morbidity and mortality, ranging from 30% to 50%.⁵²⁻⁵⁴ Despite improvement in surgical technique, in-hospital mortality remains significant. In the most recent IRAD review, in-hospital mortality in patients undergoing surgical repair of type B aortic dissection was 29.3%. For patients presenting with malperfusion and rupture, the in-hospital mortality rates were 27.8% and 62.5%, respectively.⁵⁴

An alternative surgical option for both acute uncomplicated and complicated type B aortic dissection remains desirable. Many have examined the role of endovascular technique in the acute type B aortic dissection. In uncomplicated cases, the role of TEVAR remains unclear. For patients with complicated type B dissection, the role of TEVAR has emerged as the gold standard, replacing open surgery as the first-line treatment for complicated type B dissection.

Anatomic and Technical Considerations

Endovascular therapy for acute aortic dissection is technically demanding. Some have argued that the current technology is not ideal and that devices designed specifically for dissection are needed.^{55,56} Nonetheless, we emphasize that the complexity involved with endovascular therapy for aortic dissection requires an algorithmic approach that must begin at the primary tear site. Wire access in the true lumen cannot be overemphasized, because deployment of thoracic stent graft devices in the false lumen will have catastrophic consequences. When confirmation of wire access in the true lumen is

needed, intravascular ultrasound has proven to be a valuable tool.

The fundamental principles of endovascular treatment of aortic dissection have major conceptual differences from aneurysmal pathology. The primary goal is coverage of the primary tear site, thus expanding the true lumen and initiating thrombosis and obliteration of the false lumen (Fig. 72-8). Often, the tear site is located in close proximity to the left subclavian artery and coverage is necessary. Despite successful thoracic stent graft therapy, persistent patency of the false lumen may occur because of complex reentry points in the distal thoracoabdominal aorta. In contrast to aneurysmal disease, sizing of the endograft devices should be conservative. The endograft devices should be minimally oversized relative to the diameter of the dissected aorta, generally at most 10%. Aggressive ballooning of the landing zones should also be discouraged.

Particularly in cases with malperfusion syndrome (because the goal of therapy is to restore distal perfusion and correct end-organ ischemia), false-lumen patency may persist despite thoracic aortic endografting. The true lumen may continue to be compressed, thereby resulting in continued malperfusion and end-organ ischemia. Called the PETTICOAT (Provisional Extension to Induce Complete Attachment) concept,⁵⁷ the principle refers to an algorithmic evaluation and treatment of the thoracoabdominal aorta in type B aortic dissection. After coverage of the primary tear site, the status of the true lumen is assessed. If persistent malperfusion is present, deployment of an additional distal device is performed. This evaluation and treatment algorithm is repeated with each adjunct device until distal malperfusion is corrected. In patients with persistent visceral malperfusion despite coverage of the primary tear site, TEVAR in the distal thoracic aorta with adjunct celiac, superior mesenteric artery, or renal bare metal stents should be considered. Subsequently, persistent lower extremity malperfusion may require infrarenal aortic and iliofemoral adjunct procedures including bare metal stents.

For dissections complicated by rupture, coverage of the primary tear site is equally essential. However, the site of rupture must also be addressed with TEVAR. Because of the extent of the dissection and the potential for perfusion of the false lumen through distal complex reentry sites, often the coverage of the entire thoracic aorta from the left subclavian artery to the celiac artery is required. Failure to recognize this concept may result in continued hemorrhage from the rupture site and potentially death.

Results

Uncomplicated Type B Dissection

The rationale for the use of TEVAR in type B dissections is based on the concept that the obliteration, or thrombosis, of the false lumen with an endograft may result in positive aortic remodeling and thus improvement in long-term outcome and survival. Closure of the primary tear site of a type B dissection should promote decompression of the false lumen, with subsequent reestablishment and stabilization of the true lumen of the aorta.

The first use of TEVAR in type B dissections was reported by Dake and coworkers in 1999. The series involved 19 patients undergoing TEVAR for acute aortic dissections; 15 patients had the diagnosis of acute type B aortic dissections. Complete thrombosis of the thoracic aortic false lumen was achieved in 15 patients (79%), with a 30-day mortality rate of 16%. In the follow-up period of 13 months, there was no death.⁵⁸

Many other investigators have reported favorable short-term results with complete and partial obliteration of the false lumen in type B dissections, demonstrating stabilization of the descending aorta in as much as 75% of patients.⁵⁹⁻⁶⁵ Kusagawa and coworkers reported a series of 49 patients with type B dissections (32 acute, 17 chronic). The mean follow-up period ranged from 4 months to 6 years. In the acute dissection group, the average false lumen decreased from an average of 16 mm

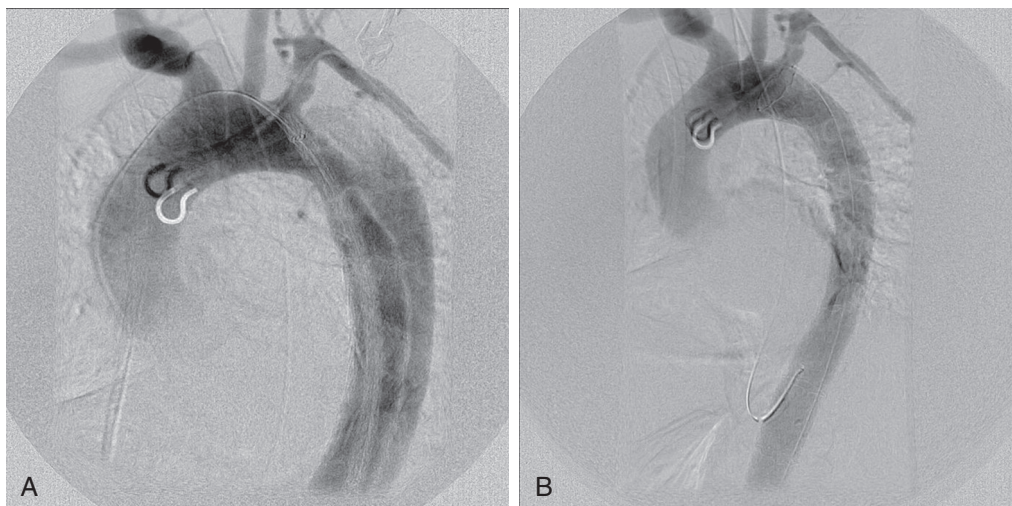


FIGURE 72-8 ■ Angiogram demonstrating endovascular treatment of acute type B aortic dissection. **A**, Positioning of the thoracic endovascular aortic repair (TEVAR) graft in the true lumen of the proximal descending thoracic aorta (DTA) is shown predeployment. **B**, Aortic arch and DTA angiogram post-TEVAR deployment in the true lumen shows loss of filling in the false lumen.

to 3 mm at 2 years after treatment. In 76% of the patients, the false lumen of the thoracic aorta completely disappeared after 2 years. The results were less dramatic in the chronic group.⁵⁹

Dialetto and coworkers reported a series of 56 patients with type B dissections treated either medically ($n = 28$) or with aortic stent grafts ($n = 28$). Follow-up ranged from 1 to 61 months, with 100% follow-up. In-hospital mortality was 10.7% with no incidence of spinal cord ischemia. Follow-up CT scans demonstrated complete thrombosis of the false lumen in 75% of patients treated with TEVAR compared with only 10.7% of patients in the medically treated group. Aneurysmal dilation of the descending aorta was seen in only 3.5% of patients treated with TEVAR compared with 28.5% of patients in the medically treated group.⁶⁰

Eggebrecht and coworkers recently reported a meta-analysis of TEVAR for patients with type B dissections. Thirty-nine studies were included, with a total of 609 patients. The mean follow-up period was 19.5 months. The mean procedural success rate was 98.2%, with a complication rate of 11.1%. The rate of neurologic complications was 2.9%, with stroke at 1.9% and paraplegia at 0.8%. Overall, complications were statistically higher in patients with acute type B dissection (21.7%) when compared with chronic type B dissection (9.1%). The 30-day mortality rate in the acute and chronic dissection groups were 9.8% and 3.2%, respectively. False-lumen thrombosis was seen in 75.5% of patients. Late surgical conversion was required in 2.5% of patients. Endovascular reintervention with TEVAR was necessary in 4.6% of patients. Overall survival by Kaplan-Meier analysis was 90.6%, 89.9%, and 88.8% at 6 months, 1 year, and 2 years, respectively.⁵⁵

The role of TEVAR in acute uncomplicated type B aortic dissection was recently examined in the INvestigation of STent grafts in patients with type B Aortic Dissection (INSTEAD) trial. It was a multicenter, prospective, randomized trial in Europe designed to compare the outcomes of uncomplicated type B dissections treated by (1) TEVAR (Medtronic Talent device) adjunctive to anti-impulse therapy or (2) anti-impulse therapy alone. The study period was 2 years with the primary outcome measure as all-cause mortality. Secondary outcomes included conversions to TEVAR or surgery, false lumen thrombosis, cardiovascular morbidity, rate of aortic dilation, quality of life, and length of intensive care unit and hospital stay. At 1 year, there was no difference in all-cause mortality between the medical (3%) versus the TEVAR (10%) group.⁶⁶ Long-term results of the INSTEAD trial were recently published.⁶⁷ Compared with optimal medical management, TEVAR showed an improved risk of all-cause mortality (6.9% vs. 19.3%, $P = 0.13$) and aorta-specific mortality (6.9% vs. 19.3%, $P = 0.04$) at 5 years. Elective TEVAR rendered improved false-lumen thrombosis in 90.6% of cases ($P < 0.001$).

Recently, outcomes with the management of acute uncomplicated type B dissection with best medical therapy versus best medical therapy with Gore TAG stent graft was assessed. This was a prospective randomized trial (ADSORB trial).⁶⁸ Sixty-one patients were randomized, of which 80% had DeBakey type IIIB dissection.

Although there was no mortality difference at 30 days and 1 year, there was a significantly improved false-lumen thrombosis rate (57% vs. 3%) and false-lumen-diameter reduction ($P < 0.001$) in the best medical therapy + Gore TAG arm. The study concluded that acute uncomplicated type B dissection can be safely treated with stent grafting, with improved aortic remodeling.

In summary, the benefit of TEVAR in acute uncomplicated type B aortic dissection is becoming increasingly evident. Results of TEVAR for the treatment of type B dissection appear promising, demonstrating early evidence of false-lumen thrombosis and aortic remodeling. However, further long-term follow-up data from future trials will be needed before definitive conclusions can be made regarding the impact on aortic remodeling and survival benefit.

Complicated Type B Dissection

Endovascular therapy in the treatment of complicated type B dissections in the acute setting has emerged as a viable surgical alternative, and in some institutions, TEVAR has become the preferred therapy of choice. Duebener and coworkers reported a series of 10 patients with complicated acute type B dissections treated with TEVAR. The mean interval to treatment from the time of diagnosis was 11 hours. Indications for TEVAR were rupture ($n = 2$), malperfusion ($n = 5$), rapid aortic expansion ($n = 1$), and refractory pain ($n = 2$). The primary tear site was covered in 90% of patients, and the early mortality was 20% ($n = 2$). The causes of death in the two patients were aortic disruption distal to the stent graft and hemorrhagic shock after surgical fenestration of the abdominal aorta for persistent malperfusion. The duration of follow-up ranged from 1 to 38 months.⁶⁹

Doss and coworkers reported their experience of 54 patients undergoing emergent surgical management of thoracic aortic diseases, with 28 patients undergoing conventional open surgical technique and 26 patients undergoing TEVAR. The mean age of the patients ranged from 28 to 83 years. Of the 54 patients, the indication for intervention was perforated type B dissection in 14 patients. The mortality rate was 17.8% in the conventional surgical group versus 3.8% in the TEVAR group. Paraplegia rates were 3.6% and 0% in the conventional surgical and the TEVAR groups, respectively.⁷⁰ The same investigators reported their more recent experience with emergent endovascular treatment of acutely perforated type B dissections. In a series of 11 patients over a 10-month period, 7 patients were treated for ruptured aortic aneurysms and 4 for acutely perforated type B dissections. The average interval from diagnosis to treatment was 28 hours. Technical failure (i.e., access failure) occurred in 2 patients. At a mean follow-up of 12 months, there were no cases of paraplegia, stent migration, or endoleaks.⁷¹

Nienaber and coworkers⁷² reported their experience of 11 patients undergoing emergency TEVAR for acute type B dissections complicated by contained ruptures. Emergency TEVAR was successful with no morbidity and stent-graft-related complications. At a mean follow-up of 15 months, there was no mortality. This was

a statistically significant improvement compared with a historic-matched control group of patients undergoing conventional surgical therapy (death, $n = 4$).⁷²

At the University of Pennsylvania, we reviewed our experience with TEVAR for the treatment of acute type B aortic dissection complicated by rupture or malperfusion.⁷³ In our series from 2004 to 2007, 35 patients with acute type B aortic dissection were treated with TEVAR with a technical success rate of 97.1%. The indications for surgery were rupture in 18 patients and malperfusion in 17 patients. Malperfusion involved the mesenteric and renal vasculature in 5 patients, the lower extremity in 3 patients, and both in 9 patients. In addition to thoracic endograft devices, adjunct stent therapy including infrarenal aortic stents, iliofemoral stents, and celiac/mesenteric stents was required in 12 (34.3%) patients. The rate of renal failure (2.8%), CVA (2.8%), permanent spinal cord ischemia (2.8%), vascular access complications (14.2%), and 30-day mortality (2.8%) compare favorably with conventional open repair. Overall one-year survival was 93.4%. The recent IRAD database demonstrates that conventional open repair for acute type B aortic dissection in the current era is still associated with a significant risk of cerebrovascular accident (9.0%), paraplegia (4.5%), visceral ischemia/infarction (6.8%), and acute renal failure (18.3%), all of which were correlated with postoperative death. The overall in-hospital mortality rate was 29.3%, and for patients undergoing surgery within 48 hours, the in-hospital mortality rate was 39.2%.⁵⁴ The dramatic difference in morbidity and mortality between TEVAR and conventional open repair suggests that TEVAR is an effective surgical alternative and supports a new surgical paradigm for the treatment of acute complicated type B aortic dissection. At our institution, TEVAR has emerged as the surgical therapy of choice for the management of acute complicated type B aortic dissection.

PENETRATING ATHEROSCLEROTIC ULCER, INTRAMURAL HEMATOMA, AND BLUNT THORACIC AORTIC INJURY

Historically, PAU with IMH in the DTA has been managed medically. The behavior and clinical management of PAU and IMH in the DTA is not well defined and remains a clinical challenge. Furthermore, the natural history of PAU and IMH remains unclear.⁷⁴⁻⁷⁶ Cho and coworkers⁷⁷ recently reviewed the Mayo Clinic experience with PAU of the DTA over a 25-year period. From 1977 to 2002, 105 patients with PAU of the DTA with ($n = 85$) and without ($n = 20$) IMH were included in the study. The medical group included 76 patients and the surgical group included 29 patients. Thirty-day mortality in the medical group was 4% versus 21% in the surgery group ($P < 0.5$). Defined as conversion to surgery or death, failure of medical therapy was predicted by the presence of rupture at presentation and the era of treatment (before 1990). Aortic diameter, ulcer, or extent of hematoma were not risk factors for medical therapy failure or death.⁷⁷

The introduction of TEVAR has prompted investigators to examine the role of this new technology in descending thoracic aortic PAU and IMH. Jin and coworkers⁷⁸ reported their experience with TEVAR for PAU in the DTA. In their series of 14 patients, the majority of patients was symptomatic and was treated emergently. Endoleaks were present in two patients at completion angiography. With a mean follow-up period of 17.2 months, coverage of PAU was achieved in all patients, with complete resorption of IMH in 2 patients. One patient died of rupture of pseudoaneurysm at one month after surgery. Other investigators have also reported small series of endovascular aortic stent graft therapy for PAU and IMH.⁷⁸⁻⁸¹ Technical success with good short-term follow-up has been demonstrated with low mortality.

In summary, TEVAR for PAU and IMH in the DTA is promising. Endovascular therapy for complicated or symptomatic PAU appears to be indicated. However, more evidence and long-term follow-up are needed to arrive at definitive conclusions. Currently, the TX2, Valiant, and Relay devices have approved on-label indications for PAU treatment in the United States.

Blunt thoracic aortic injury is associated with high mortality, with only 10% of patients arriving to a hospital alive, of which up to 50% die within 24 hours. Endovascular repair of blunt thoracic aortic injury has gained increasing acceptance as the treatment of choice over open surgery. The C-TAG and Valiant endograft devices have received on-label indications by the FDA for the treatment of this condition.

AORTIC ARCH/ASCENDING AORTIC PATHOLOGIES

The introduction of TEVAR has provided an alternative surgical option in patients thought to be at prohibitively high risk for conventional open aortic arch or ascending aortic repair, although the use of endovascular technology in ascending aorta and aortic arch is through off-label use only.

Aortic Arch Endovascular Repair

The arch hybrid repair is essentially a landing zone “0” endovascular repair of the aortic arch and it is guided by two fundamental concepts: (1) brachiocephalic bypass, or revascularization of the great vessels; and (2) construction of optimal proximal and distal landing zones for TEVAR. The arch hybrid repair is especially appealing in patients who are poor candidates for prolonged periods of cardiopulmonary bypass or circulatory arrest—that is, older patients and those with significant comorbidities.

Landing Zones

The principle of anatomic landing zone selection is similar in arch hybrid cases to DTA stent grafting. The hybrid arch concept is an extension of the TEVAR proximal landing zone scheme. Hybrid arch procedures are typically performed with the proximal landing zone in Z0. Therefore, the arch hybrid concept necessitates a

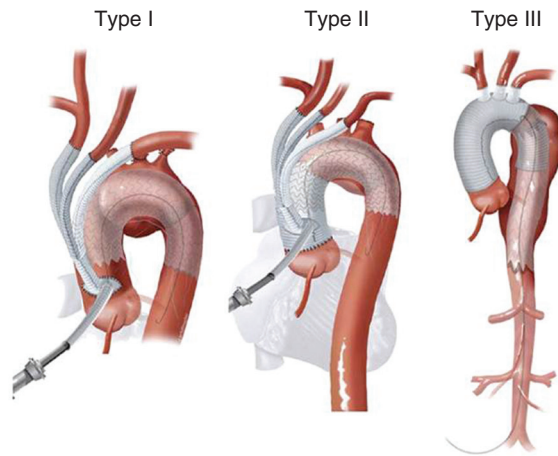


FIGURE 72-9 ■ Arch hybrid classification is shown.

brachiocephalic revascularization procedure to preserve flow through the great vessels.

The hybrid arch repair classification is based on aortic arch aneurysm anatomy and proximal and distal landing zone feasibility. The scheme divides aortic arch aneurysms into three types (Fig. 72-9). The type I arch hybrid is typically done with a classic arch aneurysm, where the ascending and descending thoracic aortas are not aneurysmal or dissected. This anatomy has favorable proximal Z0 and distal Z3/Z4 landing zones, respectively. A type I arch hybrid repair only requires great vessel revascularization with either concomitant antegrade TEVAR stenting or delayed retrograde TEVAR from the iliofemoral vasculature. A type II arch hybrid is an ideal approach in an arch aneurysm without a good Z0 proximal landing zone but has a good distal landing zone in the DTA. Therefore, a type II repair necessitates an open surgical Z0 landing zone reconstruction for proper deployment and seal of the proximal stent graft. Type III arch hybrid repair can be used for even more complex aortopathies such as the mega-aorta syndrome. In this case, the native aorta does not have good proximal or distal landing zones for stent graft deployment. Therefore, a type III repair necessitates an open surgical reconstruction of proximal aorta and arch as a total arch replacement with elephant trunk for stent-graft landing in the DTA. It is important to note that in progression from a type I to a type III arch hybrid repair, the circulatory management options become increasingly complex and therefore must be tailored to patient status and anatomy.

Outcomes

To date there have been no randomized trials evaluating the use of hybrid techniques for the treatment of aortic arch pathology. Several groups have published their single-institution hybrid experience with an in-hospital mortality rate of 0% to 13%, and a permanent stroke rate between 0% and 8%. The incidence of paraplegia was between 0% and 24%.⁸²

Two groups reported their outcomes with type I hybrid arch repair. Both groups report a 0% stroke rate

and one in-hospital death in a total group of 30 patients.^{83,84} Shimamura and colleagues⁸³ reviewed 126 type II hybrids and reported a total stroke rate of 5.6%, a paraplegia rate of 2.3%, and an in-hospital mortality rate of 3.2%. The largest series of type III hybrids, done by Kawaharada and associates,⁸⁴ demonstrated a stroke rate of 3.2%, a paraplegia rate of 0%, and an in-hospital mortality rate of 6.4%.⁸⁴ Although the data reported by these studies are encouraging, they remain limited by the small number of patients treated in their retrospective analysis.

A meta-analysis of 15 studies reporting outcomes for arch hybrid procedures revealed an overall 30-day mortality rate of 8.3%, a stroke rate of 4.4%, a paraplegia rate of 3.9%, and an endoleak rate of 9.2%. A total of 463 patients were included in this analysis.⁸⁵

Ascending Aorta Endovascular Repair

TEVAR is not currently indicated for ascending aortic pathology; however, several centers have described their anecdotal experiences with endografting in the ascending aorta.^{37,86-88} To date, there have been no clinical trials or large series describing outcomes with TEVAR in the ascending aorta. Kolvenbach and colleagues⁸⁹ have described their experience with ascending aorta TEVAR in 11 patients. They report a stroke rate, endoleak rate, and mortality rate of 9%, with a combined mortality and morbidity of 18%. Technical success was achieved in 91% of patients. They concluded that a significant number of their complications were a result of using an endograft that was not designed for unique anatomy of the ascending aorta.

In January 2012, Metcalf and colleagues⁸⁸ described the first case of ascending aorta TEVAR with an endograft designed specifically for the ascending aorta. Their group implanted a Zenith Ascending Dissection device (Cook Medical, Bjaeverskov, Denmark) in a 68-year-old man with an acute type A dissection.⁸⁸ The patient made an uneventful recovery. Currently, several devices are under development for use in clinical trials evaluating the use of TEVAR in the ascending aorta.

SUMMARY

TEVAR has emerged as a viable surgical alternative to the treatment of thoracic aortic pathology. For the treatment of aneurysmal disease, perioperative morbidity and mortality is favorable when compared with conventional open techniques. Midterm outcome and long-term follow-up demonstrate durable results with long-term survival comparable with conventional open repair. Perhaps it is in the setting of acute aortic syndromes that TEVAR may potentially have its greatest impact. Historically associated with significant morbidity and mortality, acute aortic syndromes including traumatic transection, rupture, pseudoaneurysm, and dissection remain major clinical challenges. Although TEVAR is technically more challenging, its results have been favorable in the treatment of acute aortic dissections.

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OCCLUSIVE DISEASE OF THE BRACHIOCEPHALIC VESSELS AND MANAGEMENT OF SIMULTANEOUS SURGICAL CAROTID AND CORONARY DISEASE

Maral Ouzounian • Scott A. LeMaire • Joseph S. Coselli*

CHAPTER OUTLINE

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SUMMARY

Frequently, and in a variety of clinical settings, cardiovascular surgeons encounter occlusive disease involving the branches arising from the aortic arch. As a result of the increasing average life expectancy of human beings, there is a growing subset of older patients who are found to have brachiocephalic occlusive disease incidentally during preoperative evaluation for more routine cardiac surgery. In addition, the widespread use of the internal thoracic

artery (ITA) as the conduit of choice for patients with surgically correctable coronary artery disease has created a subset of patients who, postoperatively, are susceptible to coronary ischemia from occlusive disease involving the subclavian vessels, which produces coronary-subclavian steal syndrome.

Although atherosclerosis is the most common cause of brachiocephalic occlusive disease, other, less common causes of aortic branch occlusive disease, such as Takayasu arteritis and radiation-induced arteritis, can also manifest as occlusion of the aortic arch branch vessels that occasionally requires surgical intervention. Regardless of the cause of intrathoracic brachiocephalic occlusive

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disease, advancements in diagnostic imaging, technical improvements in end-organ protection, the development of endovascular techniques, strategic anesthetic management, and a better understanding of critical care all have enabled cardiovascular surgeons to perform a wide variety of procedures to treat patients with this problem with low operative risk.

Concomitant occlusive disease involving coronary and carotid arteries can pose particular challenges for cardiovascular surgeons, and the ideal treatment strategy for these combined lesions remains controversial. Treatment algorithms for concomitant coronary and carotid occlusive disease have recently expanded with the advent of endovascular techniques. Current strategies for treating patients with this problem include synchronous revascularization, staged procedures, hybrid approaches using endovascular devices, and medical treatment.

OCCLUSIVE DISEASE INVOLVING THE BRACHIOCEPHALIC ARTERIES

Pathophysiology

Atherosclerosis of the aortic arch has been recognized recently as a significant contributor to and an independent predictor of embolic stroke and generalized atherosclerotic disease, and it is the most common cause of intrathoracic brachiocephalic occlusive disease.¹ In addition to its well-known associations with cigarette smoking, peripheral arterial occlusive disease, dyslipidemia, hypertension, male sex, and diabetes mellitus, atheroma has also been associated with elevated levels of fibrinogen and homocysteine.^{2,3} Aortic arch atheroma, first seen early in the patient's adult life, is characterized by gradually increasing severity.⁴ The progression of aortic arch atheroma to brachiocephalic occlusive disease is influenced directly by the presence of aggravating risk factors.

Two important pathologic sequelae directly related to aortic arch plaques are atheroembolism and thromboembolism.⁵ Within the aging aortic arch, a variety of pathophysiologic processes occur: these include calcification, the destruction of smooth muscle and elastic fibers (including the loss of internal elastic lamina), the formation of thrombi, and most importantly, the deposition of atherosclerotic plaques.⁶ The vast majority of occlusive lesions of branching vessels of the arch and of the upper-extremity arterial branches are atherosclerotic in origin, and disease often involves multiple vessels.⁷⁻⁹ In addition, because of the irregular nature of these plaques, embolic phenomena resulting from thrombus deposits—composed of both platelets and fibrin—can occur in nearly a third of such patients. Thrombotic or thromboembolic events predominantly occur in patients with multifocal disease. Embolic phenomena owing to ostial disease of the aortic arch branches are uncommon. A cardiogenic source of embolism must be excluded before emboli can be conclusively attributed to arch branch disease.¹⁰

Inflammatory disorders, such as Takayasu arteritis or polymyalgia rheumatica, are among the less common causes of arch branch occlusive disease. The prototypic vasculitis syndrome that commonly leads to occlusive

disease of the thoracic aorta and its branches is Takayasu arteritis. This disease is characterized by immune-mediated destruction of the medial elastic fibers of the affected vessel, followed by scarring of the media and internal elastic lamina, which causes compensatory intimal proliferation. Takayasu arteritis remains an idiopathic large-vessel vasculitis that generally affects women of reproductive age and predominates in Asians; however, it has been reported in patients of all ethnicities.¹¹ Cardiac failure and cardiomegaly are usually secondary to hypertension and aortic valvular insufficiency. Approximately 60% of patients with Takayasu arteritis require some form of vascular intervention, most commonly involving the coronary arteries, followed by the carotid and upper-extremity arteries.

Additional disorders that can be causative include arteritis stemming from radioactive therapy (for malignancies of the neck or Hodgkin disease), traumatic injuries (e.g., penetrating missile injuries and blunt deceleration injuries), vasospastic disorders, thoracic outlet syndrome, and possibly connective tissue disorders. Radiation therapy can lead to stenosis of the brachiocephalic vessels and induce unpredictable atherosclerotic changes several years after treatment, ultimately resulting in embolic or diminished-flow phenomena.

Clinical Presentation

Clinical manifestations of brachiocephalic occlusive disease (Fig. 73-1) are predominately related to the degree of luminal encroachment in the primary vessel affected and the extent of collateral disease if multiple vascular beds are compromised. Stenosis of aortic arch branches can have direct ischemia-related consequences or lead to steal syndromes in which increases in blood flow to one region result in ischemia in another. Involvement of the innominate artery can lead to anterior, posterior, or combined cerebral symptoms, depending on the amount of collateral flow from the contralateral side via the circle of Willis and the extent of concomitant subclavian or common carotid artery (CCA) involvement. Isolated right-sided steal syndromes can occur, but only if the disease arises in the right subclavian artery and the innominate is relatively spared. In contrast, involvement of the left subclavian artery can result in either upper-extremity claudication or vertebral steal manifesting as vertebrobasilar symptoms, depending on the exact location of the stenotic lesion.

In general, the clinical presentation of patients with brachiocephalic occlusive disease involves either an acute embolic or a chronic stenotic event. Acute embolic symptoms tend to involve cerebral hemispheric events related to anterior circulation and, similar to carotid bifurcation disease, amaurosis fugax. Less often, emboli can affect the upper extremities, usually evidenced by cold or numb hands or fingers. Commonly, stenotic lesions reduce blood flow to upper extremities (and occasionally to lower extremities) and can result in subclavian steal syndrome. Exercise can induce ischemia and cause hand or arm cramping or fatigue (this process is also known as *claudication*); in time, these symptoms can progress to rest pain and possibly to tissue loss.

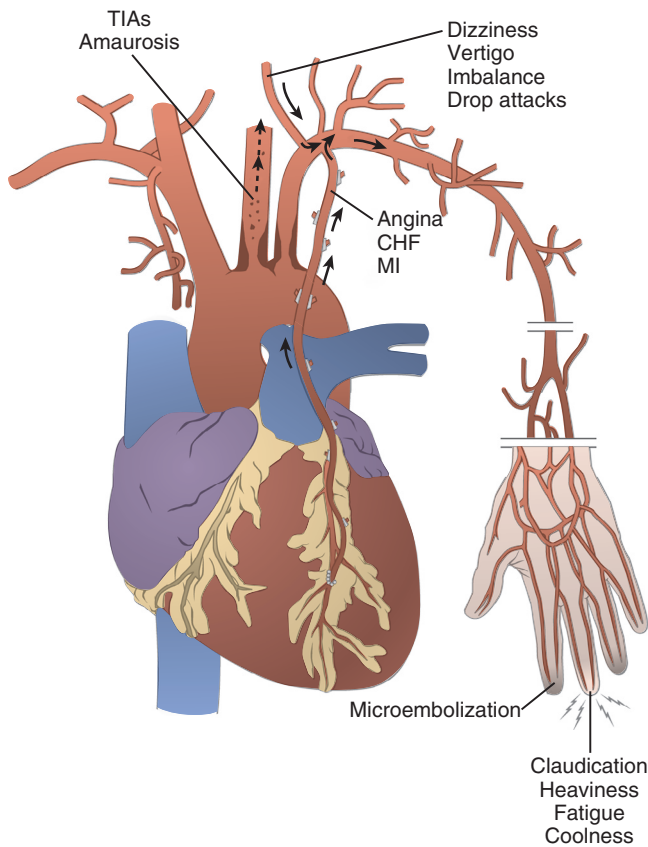


FIGURE 73-1 ■ Common symptoms of occlusive disease involving the brachiocephalic branches. Compromised flow or emboli from common carotid artery lesions can cause a variety of neurologic symptoms, including transient ischemic attacks (TIAs) and amaurosis fugax. Subclavian artery lesions can cause vertebral-basilar insufficiency (including vertebral-subclavian steal), cardiac complications (including angina, myocardial infarction [MI], and congestive heart failure [CHF]) caused by coronary-subclavian steal, and upper-extremity arterial insufficiency or microembolization. (From Takach TJ, Reul GJ Jr, Cooley DA, et al: Myocardial thievery: the coronary-subclavian steal syndrome. *Ann Thorac Surg* 81:386–392, 2006.)

Takayasu arteritis is associated with a broad spectrum of clinical presentations that range from a fairly indolent chronic course to an acute fulminant disease. The initial symptoms most commonly reported by patients are constitutional and include myalgia, arthralgia, and headaches. Vascular symptoms commonly include claudicatory symptoms, carotidynia, and pulseless extremity. The diffuse involvement of major branches of the aorta contributes to an overall diminution of peripheral pulses in these patients, which is why Takayasu arteritis is sometimes referred to as *pulseless disease*. The nonspecific nature of the initial presentation contributes to the delay in the diagnosis of most cases of Takayasu arteritis. The Ueno classification system categorizes the disease into four types according to the extent and location of involvement. Types 1 and 3 are characterized by a disease process that affects the aortic arch and its branches.¹² Stenosis and occlusion are typical of Takayasu arteritis, and the lesions can be either short and segmental or long and diffuse. De novo aneurysms are rare but have been reported in all major branches of the aortic arch.^{13,14} Most aneurysms

arise from sites of previous anastomoses or surgical repair.^{15,16}

The age at presentation for patients with radiation-induced disease primarily depends on the age at which they were exposed to radiation, and is often younger than for those with atherosclerotic occlusive disease. These patients have angiographically atypical lesions that appear diffuse, unlike the focal lesions typical of atherosclerosis.¹⁷ Presentation includes either embolic or flow-limiting symptoms.

Diagnostic Evaluation

Diagnostic imaging, performed after a detailed initial vascular and neurologic examination, plays an important role in determining the appropriate treatment for each patient. A thorough neurologic examination, even in patients with isolated upper-extremity ischemic symptoms, is essential, because such symptoms could potentially be a manifestation of a steal syndrome and concomitant disease elsewhere. Other critical components of a thorough physical examination include measuring the blood pressure in both arms (a systolic difference greater than 20 mm Hg usually suggests proximal occlusive disease) and conducting a detailed pulse examination of the subclavian artery distribution at several locations: the wrist (radial and ulnar arteries), the upper arm and elbow (brachial artery), the armpit (axillary artery), and in the supraclavicular fossa. An absent or weakened pulse found anywhere other than the supraclavicular fossa tends to indicate arterial occlusion. In addition, an Allen test should be performed because the absence of a blush in any section of the hand usually indicates an incomplete palmar arch. Palpation of the infraclavicular and supraclavicular fossae is helpful to identify a subclavian aneurysm or cervical rib. A bruit identified during auscultation of the subclavian artery may indicate thoracic outlet compression of the artery.

The diagnosis of Takayasu arteritis is usually suspected from the patient's history and clinical presentation, and it is supported by the findings of specific serologic tests, tests for inflammatory markers, and angiography.¹⁸ Angiographic studies show a characteristic pattern of stenosis, poststenotic dilation, aneurysm formation, and occlusion with collateral formation. These findings tend to be localized to the aorta and the proximal aspect of its branches.^{19,20} Total body arteriography is an important component of the diagnostic workup of these patients to characterize the full extent of the disease and to provide a baseline for future comparison, because these patients require frequent serial imaging and monitoring for the rest of their lives.

Conventional Imaging Modalities

Digital subtraction angiography offers the opportunity for immediate endovascular intervention if a problem is discovered. As with any intravascular manipulation and imaging technique, the risk of embolic stroke always exists, especially in patients with atherosclerotic disease and plaques.²¹ The development of high-resolution

computed tomographic angiography with reconstructive capabilities has allowed this modality to substitute for digital subtraction angiography in the assessment of the aortic arch branches in specific circumstances. Computed tomography (CT) and magnetic resonance imaging (MRI) provide valuable imaging for assessing the extent of brachiocephalic disease. Contrast-enhanced MRI with reconstruction provides information equivalent to that obtained from conventional CT angiography. Magnetic resonance angiography (MRA), in addition, can yield useful information about occluded vessels reconstituted via collaterals because the imaging process is not contrast dependent. In addition, MRA provides valuable information about factors that affect the risk of embolization and consequent stroke, including the size, extent, and composition of atherosclerotic lesions. We recommend obtaining a preoperative CT angiogram or MRA for all patients who undergo surgical intervention on the branches of the aortic arch; the images serve as a baseline for future comparisons and for assessing the progression of the disease. Lifelong postoperative surveillance imaging and follow-up is an essential component of the care of these patients.²²

Ultrasonography and Emerging Imaging Modalities

Transthoracic echocardiography, although reliable for assessing the ascending aorta, is not ideal for assessing the arch and its branches because of its shallow depth of penetration and because the overlying ribs obscure these vessels. Similarly, transesophageal echocardiography (TEE) is limited in its ability to image the branches of the aortic arch, primarily because of shadowing from the trachea.²³ Intravascular ultrasonography is an emerging technology that may be useful during endovascular interventions.

The advent of transesophageal magnetic coils has made it possible to perform transesophageal MRI (TEMRI).^{24,25} Although TEMRI allows multiplanar reconstruction and provides better quantification of the extent of aortic atherosclerosis, real-time imaging and assessment of plaque mobility are feasible only with the help of TEE. Nonetheless, TEMRI provides a better assessment of the circumferential extent of atherosclerotic involvement than TEE does, and it could become an important option for imaging the supra-aortic great vessels.

Anatomic Considerations in Operative Exposures of Brachiocephalic Vessels

A thorough knowledge of thoracic anatomy is invaluable for the successful exposure of the supra-aortic vessels, and operative success is heavily dependent on good exposure with appropriate proximal and distal control. A median sternotomy provides adequate exposure for all the major arch vessels, including, in most cases, the left subclavian artery. A mini upper sternotomy up to the third or fourth intercostal space provides good exposure for the mid to distal innominate artery. This is useful in situations in which the proximal innominate artery is free of disease

and the aorta does not require clamping for proximal control. A Rummel tourniquet can be used for proximal control in these cases; however, this approach can be challenging to use when innominate artery bypass is necessary or when multiple vessels must be addressed. A full sternotomy is preferred in these circumstances. Extending the median sternotomy incision along the anterior border of the right sternocleidomastoid muscle provides adequate exposure of the bifurcation of the innominate artery and the right CCA. The same incision can be extended over the upper border of the right clavicle if exposure of the more distal aspects of the right subclavian artery is required. The right sternoclavicular joint may need to be dislocated to enhance exposure. Extending the median sternotomy along the anterior border of the left sternocleidomastoid enhances exposure for the left CCA.

The posterior location of the left subclavian artery makes exposure more challenging. When a median sternotomy is performed, it may be necessary to extend the incision over the left clavicle and to dislocate the left sternoclavicular joint for adequate exposure of the intrathoracic course of the left subclavian artery. Isolated left subclavian artery disease can be approached easily via a left posterolateral thoracotomy incision through the fourth intercostal space.

Structures that can interfere with exposure, as well as conduit positioning, are the thymic remnant and the left brachiocephalic vein. The thymus can be split longitudinally or even resected to provide adequate exposure. The brachiocephalic vein can be mobilized as far laterally as necessary so that it may be retracted out of the way to provide better exposure of the proximal arch branches. Ligating the vessel is occasionally necessary to enhance exposure of the left subclavian artery and left CCA. Ligation usually has no significant consequences except for transient left upper-extremity venous congestion. Ligating the brachiocephalic vein is not usually required for bypass procedures; bypass grafts can generally be safely tunneled behind the vein. Attention should be paid to the course of the recurrent laryngeal nerves if the dissection is carried out far laterally into the right subclavian artery and when one is gaining proximal control of the left subclavian artery and the subjacent aorta. The phrenic nerve is vulnerable to injury along its course over the anterior scalene muscle when the sternotomy incisions are extended over the clavicle. In addition, excessive traction in these incisions could jeopardize the functional integrity of the brachial plexus, producing undesirable long-term sequelae.

Cerebral protection is of concern in any operative manipulation involving the innominate artery or the CCAs. During the preoperative evaluation, one should thoroughly ascertain the patient's vascular anatomy, including the patency and size of the vertebral arteries and the completeness of the circle of Willis. Caution should be exercised, as usual, during placement of the proximal clamp and selection of the site for the proximal anastomosis to avoid any area on the aorta with atherosclerotic involvement. Epiaortic ultrasound can be helpful in selecting an ideal clamp site. The robust collateral circulation of the cerebral vasculature allows safe clamping of the innominate artery or proximal CCAs, provided

there is no diffuse or multivessel involvement. Flow through the left CCA should be ensured while the innominate artery is clamped. Similarly, it may be prudent to monitor a right subclavian arterial line when the left CCA is intervened on to ensure that there is flow through the innominate system. Furthermore, it may be helpful to monitor estimated hemispheric perfusion by using near-infrared spectroscopy to perform transcranial oximetry during innominate or left CCA clamping. The strategy for cerebral protection is more complicated in patients with contralateral carotid occlusion or multivessel disease, which occasionally necessitates the use of intraoperative shunts to ensure cerebral protection.

Surprisingly, postoperative neurologic complications are rare, even in patients with multivessel disease. Unless multivessel disease involving one or both carotids is encountered, electroencephalographic monitoring or shunting is usually unnecessary. Cerebral protection is more challenging in patients with a bovine aortic arch configuration, in whom clamping the innominate artery is not an option because this would compromise blood flow through both CCAs; shunting or temporary bypass conduits are essential in this circumstance.

Treatment

In 1958, DeBakey and colleagues²⁶ reported a large series of cases that included a direct transthoracic repair of the supra-aortic trunks—a major feat at that time. Surgical treatment was further advanced by Crawford and coworkers²⁷ with the use of extra-anatomic bypass techniques,

which dramatically decreased the mortality associated with these operations from 22% to 5.6%. Currently, extra-anatomic bypass with synthetic grafts is the most common technique for treating these complex lesions (Fig. 73-2). The use of shunting for cerebral protection when necessary and the recognition of high-risk patients who are likely to benefit from cerebral protective measures have dramatically curtailed the adverse neurologic consequences associated with these procedures. Alternative techniques include direct endarterectomy, endovascular stenting, and transposition.²⁸ In general, direct surgical approaches, such as bypass techniques, are preferred for multivessel and long-segment disease, whereas endovascular techniques are preferred for isolated ostial disease or short-segment disease. Surgical intervention has reportedly produced survival rates of 98% and relieved symptoms in 94% of patients at a mean follow-up of 7.5 years. Crawford and associates²⁷ reported survival rates of 85% at 5 years, 58% at 10 years, and 25% at 15 years. Hybrid and endovascular approaches have been added recently to the surgeon's armamentarium, and they are gradually becoming the preferred treatment modalities for occlusive disease of the supra-aortic trunks, particularly for older patients with significant comorbidity.^{29,30}

Innominate Artery Occlusive Disease

Innominate artery disease is uncommon. It typically involves the ostium or the proximal aspect of the artery and extends along the posterior and lateral walls. Innominate artery occlusion accounts for only 4.7% of cases of

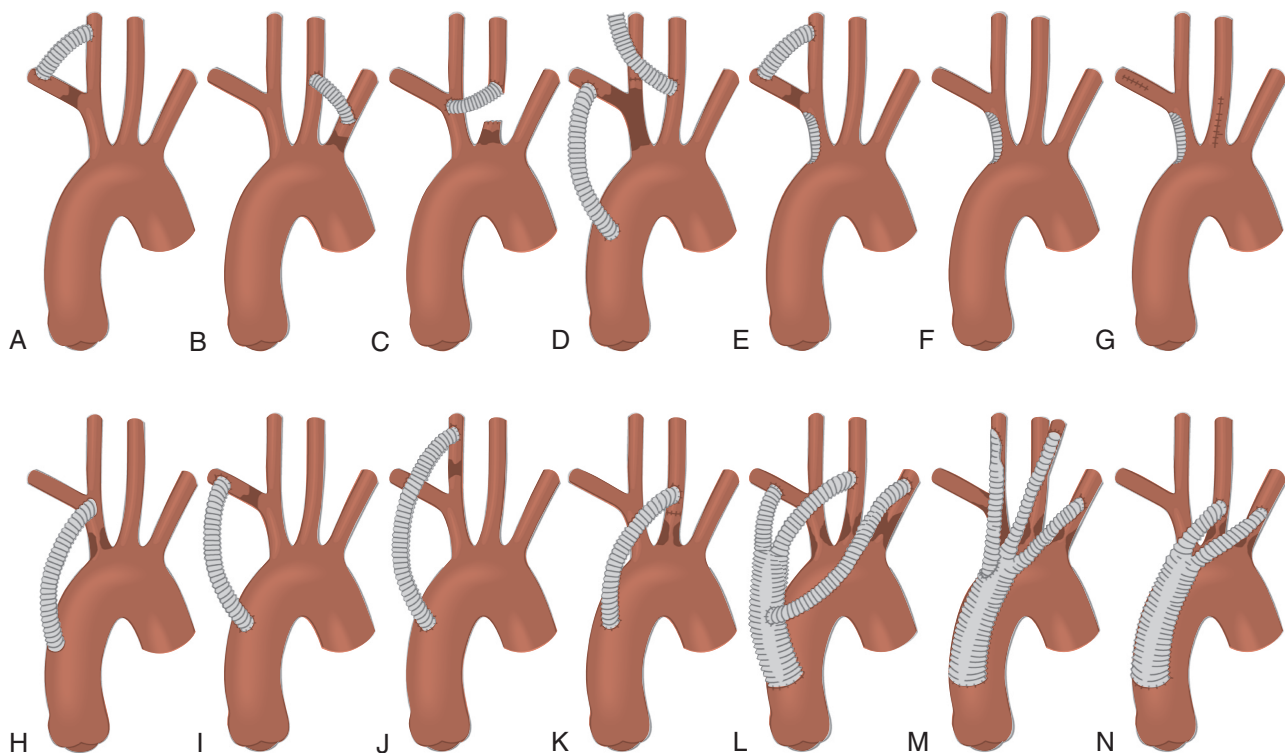


FIGURE 73-2 Options for open surgical reconstruction of the brachiocephalic branches include extra-anatomic bypass procedures (A-E), aorta-to-brachiocephalic artery bypass procedures (D, H-N), and endarterectomies (E-G). (From Takach TJ, Reul GJ Jr, Cooley DA, et al: Concomitant occlusive disease of the coronary arteries and great vessels. *Ann Thorac Surg* 65:79–84, 1998.)

extracranial cerebrovascular disease.³¹ In these cases, the innominate artery is seldom the only vessel requiring revascularization.³² Reul and colleagues³³ found that 60% of patients undergoing revascularization for innominate artery symptoms required intervention in at least one other vessel. Early studies of treatments for innominate atherosclerotic disease favored an extrathoracic approach because of the high morbidity and mortality rates associated with intrathoracic repair.²⁷ Advances in surgical technique and anesthesia, however, produced equivalent results of either extrathoracic or intrathoracic approaches.³⁴ Current clinical indications for treating symptomatic stenosis include transient ischemic attacks (TIAs), stroke, vertebrobasilar insufficiency, subclavian steal syndrome, and upper limb ischemia.

In patients with atheroembolic manifestations, direct operative treatment by excluding the embolic source is an essential element of the treatment strategy for symptom relief. Direct repair or bypass using the transthoracic approach is preferred because it produces less morbidity than using the extrathoracic approach, which is reserved for patients in whom transthoracic repair is contraindicated.^{35,36} Relative contraindications to intrathoracic revascularization include a heavily diseased or calcified arch, previous thoracic surgery, and advanced age or poor medical condition. Extra-anatomic bypass techniques can be used in cases of primary graft infection, in which one would consider routing the graft well away from the preferred primary route. When revascularization of isolated innominate artery disease is contemplated, two transthoracic options exist: endarterectomy and bypass. Recent advances in endovascular treatment also represent a viable treatment strategy.

Innominate Artery Endarterectomy. Endarterectomy for isolated branch disease is reported to have excellent results.³⁶ Relative contraindications include inability to clamp the innominate artery, severe arch atherosclerosis, proximal origin of the left CCA (including a common brachiocephalic trunk), and multivessel disease; a bypass procedure may be preferable in these cases. Whenever possible, endarterectomy should be avoided in patients with Takayasu disease or radiation arteritis, because the transmural inflammatory process complicates the creation of an endarterectomy plane. The endarterectomy proceeds as illustrated in Figure 73-3. Performing intraoperative epiaortic ultrasonography before clamping may be of benefit, because most of these patients have aortic arch atherosclerosis. The vessel can be closed primarily or by patch angioplasty if luminal narrowing is of concern. Long-segment endarterectomies reportedly have been accomplished by extending the arteriotomy or performing separate arteriotomies on the branch vessels.³⁴

Innominate Artery Bypass. Bypass grafting with synthetic prosthetic graft material has produced excellent results and has become the operative procedure of choice. Although the results are comparable to those of endarterectomy, the technical ease of the operation has led surgeons to favor the bypass approach. Bypass techniques are especially well suited for use in cases of Takayasu arteritis, radiation injury, and recurrent atherosclerotic disease.

During the early phases of the development of arterial replacement surgery, operative techniques involved resecting the primary vessel and then placing an interposition graft; this approach was associated with significant

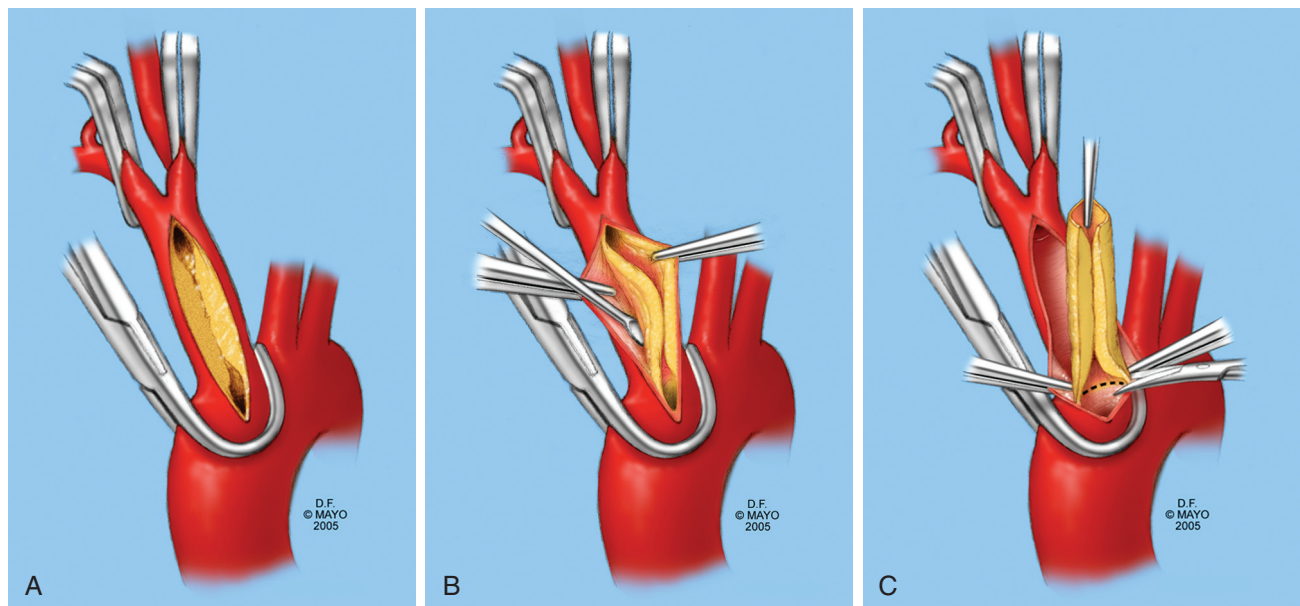


FIGURE 73-3 ■ **A**, After the right common carotid and subclavian arteries are clamped, proximal control of the innominate artery is established with a partial occluding clamp placed on the aortic arch. A longitudinal arteriotomy is created to expose the lesion. **B**, A circumferential endarterectomy plane is developed in the middle of the media. **C**, The endarterectomy is tapered distally to an appropriate endpoint. The lesion is divided proximally (dashed line) near the origin of the innominate artery; if the plaque extends into the arch, the intima is secured with tacking sutures to prevent dissection. The arteriotomy can be closed primarily or with a patch. (From Mozes G, Gloviczki P, Huang Y: Atherosclerotic occlusive disease. In Coselli JS, LeMaire SA, editors: *Aortic arch surgery: principles, strategies and outcomes*. West Sussex, United Kingdom, 2008, Wiley-Blackwell, p 311. Copyright Mayo 2005.)

perioperative morbidity and mortality. The introduction of the bypass technique by Crawford and coworkers³⁷ eliminated unnecessary manipulation and dissection of the diseased native artery while allowing the restoration of antegrade flow in the affected territory. This strategy reduced postoperative morbidity rates and significantly improved results. Late graft patency and patient survival (in those without stroke) appear to be good. Berguer and colleagues³⁵ reported 10-year estimates of $88\% \pm 6\%$ and $81\% \pm 7\%$, respectively. Concomitant coronary artery disease significantly influences both early and late death rates.

As with endarterectomy, epiaortic ultrasound is often useful in selecting the site of the proximal anastomosis and aortic clamping. Typically, an 8- to 10-mm Dacron graft is used to construct the bypass. When there is multivessel disease, a bifurcated or branched graft can be used. If at all possible, the proximal anastomosis should be constructed toward the right lateral aspect of the ascending aorta to avoid potential compression from the sternum or mediastinal contents. As reported by Crawford and colleagues,³⁸ the potential complications of such compression include venous compression and tracheal compromise resulting in death. Care should be taken to construct the bevel with the appropriate orientation to prevent kinking of the graft. The distal anastomosis is constructed in an end-to-side fashion unless the innominate artery is suspected to be the source of embolic disease. In that situation, the surgeon should consider excluding the diseased segment and performing the distal anastomosis in an end-to-end fashion.

Appropriate positioning of the graft is essential to avoid kinking or compression of the graft, which is directly responsible for most eventual failures of this operation. Several maneuvers have been described to create adequate space to accommodate the graft, including ligating the brachiocephalic vein and resecting the innominate artery. Properly gauging the length of the graft avoids leaving a redundant portion of the graft that will be prone to either kinking or traversing anterior to the aorta and being compressed by the sternum. To avoid overestimation, the sternal retractor is released before the graft length is determined. Theoretically, single-branch grafts have the advantage of being less bulky than bifurcated grafts. When bifurcated grafts are used, the common trunk should be left longer, which makes the flow more laminar at the bifurcation of the graft by reducing interference from the high flow of the ascending aorta. In certain circumstances, the lack of intrathoracic domain may preclude proper placement of a bypass graft. These circumstances include a mediastinal reoperation, saphenous vein conduits placed in certain locations during previous coronary artery bypass grafting (CABG) operations, extensive periaortic inflammation, and stents inserted during previous endovascular interventions. Endarterectomy may be preferred to bypass techniques in these circumstances.

Innominate Artery Stenting. Endovascular options for innominate artery disease have been expanding in the past decade. Initial reports had important limitations, including small numbers of patients, short follow-up

periods, and grouping of the data with data from patients with subclavian artery disease, which tends to skew the results.³¹ Only a few studies have examined stenting as a treatment for isolated innominate artery lesions.³⁹⁻⁴² The technical success rate varies from 83% to 96%; stenotic lesions have a higher treatment success rate than total occlusions do. Although early primary and secondary patency rates are excellent ($>95\%$ and $>98\%$, respectively, at up to 2 years), long-term data vary, showing primary patency rates around 70%.

The endovascular approach can be antegrade via the common femoral artery, retrograde via the brachial artery, or a hybrid approach through a retrograde cervical cut-down of the CCA. Innominate artery stenting is particularly useful in treating short-segment disease. In contrast, endovascular stenting should be avoided in long-segment occlusion of brachiocephalic vessels or extensive vessel calcifications because it can increase the risk of complications and poor treatment outcomes, including vessel rupture, catheter-induced cerebral embolization, and vessel occlusion.^{43,44}

The major advantages of endovascular treatment include a reduction in periprocedural morbidity and mortality; the risk of any neurologic deficit ranges from 2% to 4%, while the risk of minor complications hovers at approximately 6%, and the risk of major complications ranges from 1% to 2%.³⁹⁻⁴² Endovascular approaches also offer the benefits of a less invasive approach, a shorter hospital stay, and greater acceptance by patients. The lack of long-term durability data, however, maintains open operation as the first-line treatment for young, otherwise healthy patients who may derive long-term benefit from an open procedure.

Common Carotid Artery Occlusive Disease

Common carotid artery occlusive diseases are usually due to retropropagation of thrombus secondary to occlusion at the carotid bifurcation; less often, these diseases are due to primary ostial disease. There are several approaches to managing carotid bifurcation disease, and any of the techniques could be expanded to include retrograde endarterectomy via transcervical approaches. In patients with CCA occlusion, two key factors must be ascertained before a transcervical or transthoracic approach can be contemplated: (1) the presence or absence of carotid bifurcation disease and (2) whether there is concomitant involvement of the other major branches of the aortic arch.

Common Carotid Artery Bypass. For patients with isolated proximal CCA occlusion and sparing of the carotid bifurcation, a transcervical approach, such as carotid-subclavian bypass or transposition, can be used (Fig. 73-4). It is essential to ensure the patency of the carotid bifurcation and the absence of any proximal subclavian artery disease before this technique is contemplated. In cases of multivessel disease involving the arch branch vessels or common carotid arteries, a transthoracic approach with direct CCA revascularization should be considered. Transthoracic approaches are used selectively in patients with multivessel disease and extensive proximal CCA disease that spares the carotid bifurcation.

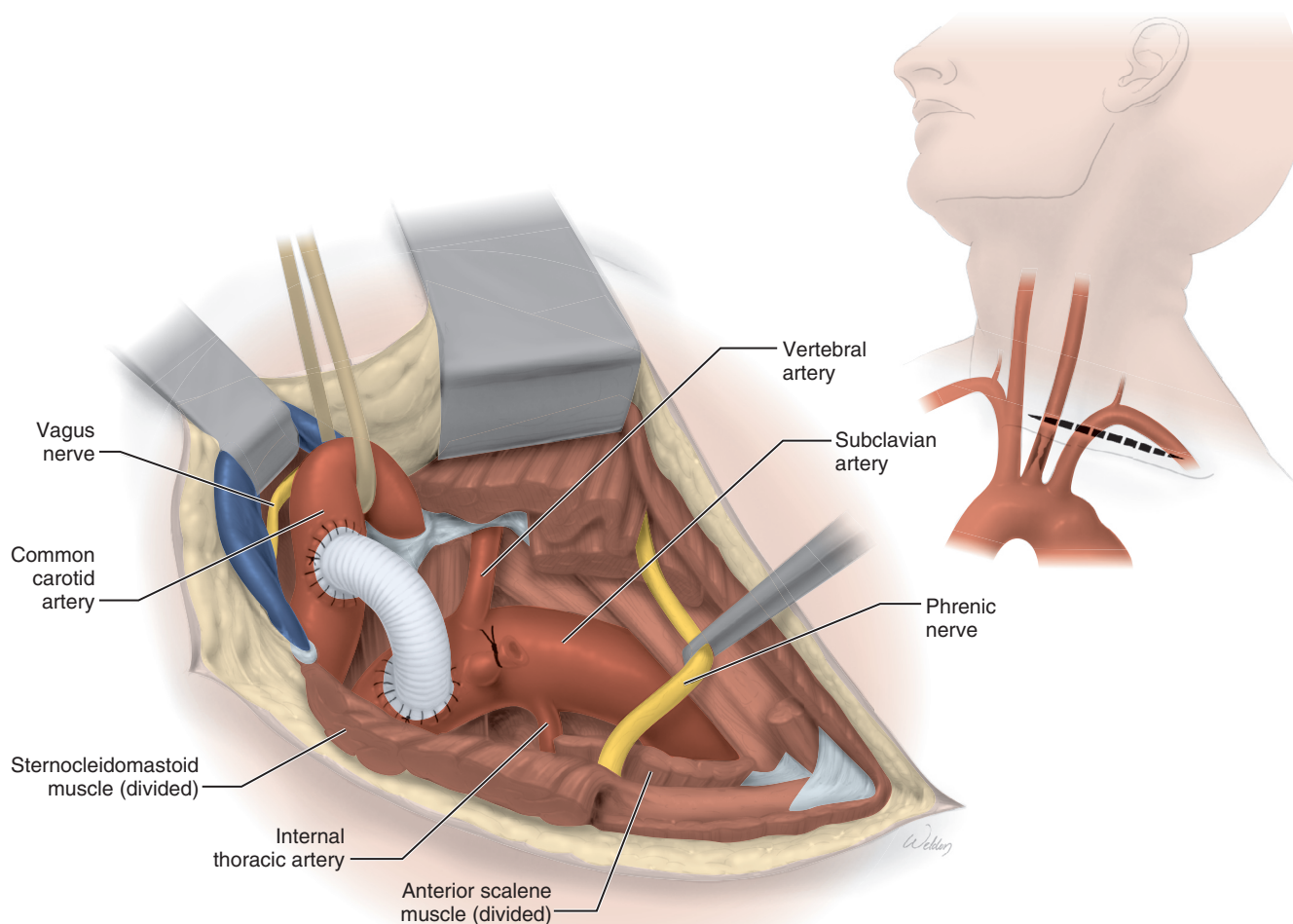


FIGURE 73-4 ■ A left subclavian-to-carotid artery bypass for treatment of common carotid artery stenosis. The procedure is performed through a supraclavicular incision (*inset*) and can be used to treat subclavian artery stenosis. (From Bozinovski J, LeMaire SA, Weldon SA, et al: Hybrid repairs of the aortic arch and proximal descending thoracic aorta. *Op Tech Thorac Cardiovasc Surg* 12:167, 2007, Figure 10. Used with permission. Copyright Elsevier.)

An aorta-to-CCA bypass with a bifurcated tube graft is preferable when both the subclavian and common carotid arteries are involved.

In all cases of CCA reconstruction, preoperative workup should establish the patency of the distal carotid vessels before any operative intervention is undertaken. Most patients who have occluded CCAs also have occluded internal carotid arteries (ICAs). Only rarely, ICA patency exists above a CCA occlusion through collateral flow via the ipsilateral external carotid artery or an aberrant branch of the ICA. Contralateral carotid occlusion, even if asymptomatic, poses a significant additional risk for perioperative stroke in such patients. Although the natural history of asymptomatic proximal CCA occlusion in patients with patent ICAs is unknown, it is likely benign, and surgery is not indicated in these circumstances.⁴⁵ Many surgeons might not consider reestablishing flow in patients with chronic asymptomatic total carotid occlusion, because the incidence of stroke is high during reestablishment of flow, and interventions might not necessarily be beneficial in preventing stroke.

Carotid Endarterectomy with Retrograde Stenting of the Innominate or Left Common Carotid Artery.

In patients with carotid bifurcation disease with retropropagation of the thrombus or concomitant proximal CCA or innominate artery disease, several authors have proposed performing a concomitant transcervical carotid endarterectomy (CEA) with retrograde endarterectomy or angioplasty and stenting.^{46,47} In this treatment approach, CEA is generally done first using local or general anesthesia. Before closing the carotid arteriotomy, the operator inserts a 7-French introducer sheath in retrograde fashion and places a vascular clamp distally to reduce the likelihood of cerebral embolization. After the stent is positioned, the sheath is withdrawn, permitting the arteriotomy incision to be closed. If open exposure of a carotid artery is performed strictly for access to a lesion that involves either the proximal innominate or carotid arteries, an 18-gauge needle and a Bentson wire are often used to cross the lesion, allowing an introducer sheath to be placed and the stent to be positioned. In addition, a stent may be placed in the

proximal innominate artery stent via a right carotid cutdown. To close the arteriotomy, a figure-of-eight suture (typically made with 5-0 polypropylene suture) is placed around the introducer sheath. Another approach involves widening the lumen with patch angioplasty; typically, this is used in cases of diseased vessels or simultaneous bifurcation disease.

A recent meta-analysis by Sfyroeras and colleagues⁴⁸ used data from the largest collection of patients to undergo hybrid treatment for high-grade tandem stenoses of the carotid bifurcation and either the proximal left CCA or the innominate artery. Thirteen studies, which included a total of 133 patients, were identified (proximal lesions were in the ipsilateral CCA in 85 cases and the innominate artery in 48 cases). In the most recent studies, a primary stenting strategy with balloon-expandable stents was most often used. The authors reported a technical success rate of 97%, with low 30-day rates of mortality (0.7%) and stroke (1.5%). Among the 13 studies, mean follow-up ranged from 12 to 36 months; during this time, 5 patients exhibited symptoms of cerebral ischemia, and 17 patients died. Of the 79 patients who received stents, 3 patients (3.7%) developed restenosis, compared with 7 (14%) of the 50 patients treated with angioplasty alone. The authors attributed the low procedural risk to the distal placement of the clamp on the ICA prior to retrograde angioplasty, which reduces the likelihood of cerebral embolization.

Subclavian Artery Occlusive Disease

The left subclavian artery is the arch vessel most commonly occluded by atherosclerosis, even in patients with multifocal disease. The subclavian artery supplies blood to the arm and to the posterior cerebral and cerebellar circulation. Proximal subclavian artery stenosis can result in symptoms originating from either territory because of competition for flow distribution. In patients who have undergone CABG surgery, the presence of a patent ITA graft to the left anterior descending coronary artery (LAD) adds another potentially competing territory. Proximal subclavian artery occlusive disease has various manifestations, including vertebrobasilar insufficiency from posterior cerebral circulatory compromise or from upper-extremity claudication or ischemia, and recurrent heart failure or angina in patients with left ITA-to-LAD grafts (see Fig. 73-1). Intervention is generally not indicated for isolated asymptomatic subclavian stenosis, because isolated proximal artery stenosis is unlikely to cause stroke if the carotid vessels are patent. However, the likelihood of stroke is greater in patients with multivessel disease; therefore, a complete evaluation of the cerebral vasculature is essential, even in patients with symptoms pertaining to the subclavian territory alone. Isolated subclavian artery symptoms, therefore, do not necessarily indicate isolated subclavian artery disease, and patients with such symptoms may require intervention.

Subclavian Artery Bypass. The aim of any treatment strategy for subclavian artery occlusive disease, be it operative bypass or endovascular stenting, is to restore

antegrade flow in both the vertebral and distal subclavian vessels—in essence, to prevent retrograde steal. From an operative perspective, this therapeutic objective can be accomplished with various surgical approaches, which include subclavian-carotid bypass grafting (see Fig. 73-4), subclavian-carotid transposition, vertebral artery transposition to the CCA, and extra-anatomic axillary bypass. In addition, for patients with isolated proximal left subclavian artery occlusive disease, a descending aorta-to-left subclavian artery bypass proximal to the origin of the left vertebral artery may be accomplished with a left thoracotomy approach. These operative strategies have been associated with excellent outcome and a low incidence of symptom recurrence.

Subclavian Artery Stenting. Advancements in endovascular intervention have resulted in remarkable treatment outcomes by providing a less invasive percutaneous approach. Catheter-based primary stenting of the subclavian arteries can be safely performed and produce satisfactory midterm outcomes.^{49,50} In one of the largest series of endovascular repairs of occlusive lesions of the subclavian artery, Sixt and colleagues⁴⁹ reported on 99 patients treated between 1996 and 2004 with mostly (90%) atherosclerotic lesions. The overall primary success rate was 97% (less for total occlusions; 87%), with no neurologic complications and only two access-related complications. The 1-year primary patency rate was 88% for all 97 patients eligible for follow-up, 79% for the patients treated with angioplasty alone, and 89% for the patients treated with stenting ($P = 0.2$).

Routine primary stenting is recommended in most cases because it achieves longer-lasting patency and greater freedom from symptoms of atheroembolism than balloon angioplasty alone. Balloon-expandable stents exert more radial force than nitinol stents do, and they are useful in ostial subclavian lesions because these lesions are usually calcified. A 1- to 2-mm overhang of the stent into the aortic lumen is desirable for ostial lesions. For postvertebral lesions, self-expanding nitinol stents are preferred to balloon-expandable stents because the nitinol stents are more pliable and less likely to be deformed by extrinsic compression.

In patients with coronary-subclavian steal syndrome (CSS), caution is exercised to prevent inadvertent occlusion of the takeoff of a patent left ITA-to-LAD graft when these stents are deployed. If technically feasible, stents should be deployed in a manner that does not compromise the origins of the ITA and vertebral artery. Dietrich and colleagues⁵¹ have shown that CSS can be treated with angioplasty and stenting; rates were 86% for primary patency and 100% for assisted-primary patency after 29 months of follow-up.

Clinical patency is accomplished in more than 80% of patients at 5-year follow up, and 80% of patients are symptom-free for more than 3 years. Complications related to endovascular interventions include stroke, atheroembolism, dissection, and complications related to the access site, such as bleeding, dissection, pseudoaneurysm, stenosis, and thrombosis. Surgery is now typically considered a second-line intervention to be used when endovascular approaches fail.^{52,53}

Multivessel Occlusive Disease

Multivessel involvement is noted in 25% of all cases of intrathoracic aortic arch branch-vessel disease, although reports of some large series note a prevalence in excess of 60%.^{7,27,34} Hence, thorough preoperative diagnostic imaging is necessary, even in patients with isolated symptoms involving a single branch territory. Transsternal aortic branch bypass appears to be the procedure best suited to these situations, and it can be carried out in one of two ways: creating multiple grafts from the aorta to individual vessels, or using branched or bifurcated grafts (see Fig. 73-2). Again, it is essential that aortic manipulation be kept to a minimum, because these patients have significant concomitant aortic arch disease; thus, the best approach may be to place a single-trunk tube graft with branches of appropriate size. The operative challenge in this circumstance is ideally positioning the bulky graft and its branches in an already compromised supra-aortic territory. It is important to position the graft along the greater curvature of the aortic arch and to tailor the length to minimize kinking or compression from surrounding structures.

Takayasu Arteritis

The treatment of Takayasu arteritis involves a combination of immunosuppressive therapy and percutaneous or surgical interventions. The first line of medical therapy remains glucocorticoids; antimetabolites are the second-line drugs in unresponsive cases.^{54,55} Surgical intervention is indicated in patients with symptomatic stenotic lesions or concomitant aneurysm formation. It is important to determine the prognostic stage—determined by using the Ishikawa criteria, which include existing complications, the pattern of the past clinical course, and the erythrocyte sedimentation rate—when considering surgical intervention.⁵⁶ Surgical treatment for patients with Takayasu arteritis might increase survival in those with stage 3 disease, but not in those with stage 1 disease.⁵⁶ Thus, conservative treatment is generally suggested for stage 1 or 2 disease, and most surgeons prudently avoid surgical intervention until the disease has reached a chronic fibro-occlusive stage.

In 1951, Shimizu and Sano⁵⁷ described surgical treatment for occlusive disease of the aortic arch branches in a patient with Takayasu arteritis. The principles of surgical bypass grafting described in the preceding sections apply to most patients, with a few notable exceptions as described here. Several techniques have been used, including endarterectomy with patch angioplasty, resection with interposition grafting, and bypass techniques. Innominate artery stenosis should be dealt with through distal grafting and not endarterectomy. Panarteritis and fibrosis yield an inconsistent plane for endarterectomy, and the adventitia that reconstitutes the vessel is often affected. Moreover, the stenotic lesions affect long segments of the supra-aortic trunk, making bypass procedures technically more feasible.⁵⁸ The disadvantage of bypass procedures, however, is the risk of subsequent pseudoaneurysm formation at the suture lines.

When proximal and distal anastomoses are constructed, sites free of disease should be chosen. Although this practice is not supported by clear scientific evidence, the absence of macroscopic disease is believed by some surgeons to decrease the likelihood of recurrent stenosis or aneurysm formation. Also, most of the involved vessels are surrounded by dense perivascular inflammation, making dissection tedious and potentially dangerous. This problem can be circumvented by planning bypass procedures such that the anastomotic sites are well away from diseased segments. Allowance should be made for progression of the disease, leading to recurrent occlusive disease; therefore, large and generous anastomoses are preferred.^{55,59,60} Subsequent aneurysm formation also needs to be considered in surgical treatment of Takayasu arteritis. Hence, the patients require lifelong follow-up with CT, MRI, or Doppler ultrasonography to monitor for the development of aneurysms. Systemic inflammation or steroid administration has little influence on anastomotic aneurysm formation. Anastomotic aneurysms tend to arise after operations for prior aneurysmal lesions and can develop any time after the initial operation. No specific factor, except the presence of an aneurysmal lesion, seems to predict recurrent aneurysm formation. The cumulative incidence of anastomotic aneurysm at 20 years is reported to be nearly 14%.⁶¹

Although no operative technique has been shown to have significant influence on the postoperative incidence of recurrent disease or aneurysm formation, surgeons prefer to operate on patients with Takayasu arteritis during the quiescent stage of the disease, using felt or bovine pericardial patches and reinforcement sutures to decrease the risk of recurrent aneurysm. Concomitant use of endovascular techniques with medical management has helped to reduce mortality to less than 10% and to improve 10-year graft patency to approximately 70%. Recently, endovascular stenting has been used to treat de novo thoracic aortic aneurysm and stenotic disease secondary to Takayasu arteritis, although the long-term consequences of using this approach remain unknown.⁶²⁻⁶⁴

CORONARY-SUBCLAVIAN STEAL SYNDROME

When a reversal of flow occurs in a previous ITA coronary bypass, myocardial ischemia can occur and result in CSS syndrome (see Fig. 73-1). The resulting ischemic pain can be confused with exertional chest pain of myocardial origin when patients report chest pain from strenuous upper-extremity activity. Often, CSS syndrome occurs in patients with an ipsilateral ITA coronary conduit and proximal subclavian artery stenosis. However, CSS has been reported in cases of inflammatory arteritis involving the proximal subclavian vessels, hemodialysis fistula in the ipsilateral upper extremity, and specific anomalies of the brachiocephalic arteries (dextro-transposition of the left subclavian artery and pulmonary artery).^{65,66}

Clinical manifestations include “silent” ischemia, ischemic cardiomyopathy, generalized heart failure, myocardial infarction (MI), and possibly sudden death. The CSS syndrome can be prevented by identifying patients who

have or may be at risk for developing subclavian artery occlusive disease.⁶⁷ Steal syndrome and myocardial ischemia can develop if substantial subclavian disease is present but untreated before placement of an ipsilateral ITA coronary conduit.⁶⁸ All patients undergoing evaluation before CABG in which the use of ITA grafts is anticipated are examined for ischemia (upper-extremity or cerebrovascular ischemia), bruits (cervical or supraclavicular), and a blood pressure differential of more than 20 mm Hg in the upper extremities. During coronary arteriography, brachiocephalic arteriography should be done in patients with suspected diffuse atherosclerotic vascular disease for better identification of subclavian artery occlusive disease.⁶⁹

In patients with significant brachiocephalic disease who are to undergo CABG surgery, options for preventing CSS include using all-vein conduits, using an ITA conduit once brachiocephalic reconstruction is completed, and using free ITA grafts or radial artery conduits during CABG. In patients who develop CSS after CABG, symptoms can be relieved by aortic-subclavian bypass, carotid-subclavian bypass, transposition of the ITA, or endovascular procedures.⁷⁰

CONCURRENT CAROTID AND CORONARY ARTERY ATHEROSCLEROSIS

Overview

The treatment of patients with multisite arterial disease, specifically those with severe carotid disease who also require CABG, is challenging and controversial.⁷¹⁻⁷³ The current guidelines suggest that carotid revascularization with CEA or carotid artery stenting (CAS) either before or concurrent with CABG surgery is a reasonable strategy in symptomatic patients with substantial carotid stenosis (>80%; class IIa recommendation, level of evidence C).⁷⁴ Furthermore, the safety and efficacy of performing carotid revascularization before or concurrently with surgical coronary revascularization are clear in patients with severe or lesser asymptomatic carotid stenosis (class IIb recommendation, level of evidence C).⁷⁴ It is important to note that these guidelines stem from expert consensus and that there is a general lack of evidence to guide clinical choice. Most experts agree that carotid revascularization is indicated if the lesion is symptomatic, bilateral, or both. However, patients in this population most often have unilateral, asymptomatic disease for which carotid revascularization before or at the time of CABG might not improve clinical outcomes when compared with optimal medical therapy and CABG.⁷⁵⁻⁷⁷

In patients referred for CABG, the prevalence of ≥50% carotid stenosis was between 10% and 22%, and the prevalence of ≥80% carotid stenosis was between 4% and 10%.⁷⁸ The 2011 American CABG guidelines indicate that duplex scanning is a reasonable option in select high-risk patients (patients ≥65 years old and those with left main disease, peripheral artery disease, diabetes, or a history of TIA or stroke, hypertension, or smoking; class IIa, level of evidence C).⁷⁹ The 2011 European peripheral artery disease guidelines recommend carotid duplex

ultrasonography in older patients (patients ≥70 years of age), as well as patients with a history of cerebrovascular disease, carotid bruit, multivessel coronary artery disease, or peripheral artery disease (class I, level of evidence B).⁸⁰

Stroke is a devastating complication of cardiac surgery and is associated with increased major disability and mortality risk and with healthcare costs. Authors from the Cleveland Clinic reported a stroke rate of 1.6% among 45,432 isolated CABG patients.⁸¹ Patients who had a stroke had significantly higher in-hospital mortality (19% vs. 3.7%), as well as poorer long-term outcomes, compared with propensity-matched patients without a neurologic insult.

Risk Factors for Stroke after Cardiac Surgery

Many patient and surgical factors have been identified as independent predictors of postoperative stroke after cardiac surgery, including clinical characteristics, the anatomic features and symptomatic nature of the carotid disease, atherosclerosis of the ascending aorta and transverse arch, and the type of cardiac surgery (Box 73-1). The multifactorial etiology of perioperative stroke partly explains why the neurologic insult can occur in a delayed fashion and on the contralateral side to the carotid lesion.

In the most comprehensive meta-analysis published to date,⁷⁷ 166 studies regarding carotid artery stenosis or occlusion were reviewed. The 30-day incidences of

BOX 73-1 Risk Factors for Stroke after Cardiac Surgery

CLINICAL FACTORS

- Increased age
- History of TIA/stroke
- Peripheral vascular disease
- Atrial fibrillation
- Diabetes
- Hypertension
- Heart failure
- Renal failure

ANATOMIC FACTORS

- Carotid lesion
 - Degree of stenosis
 - Plaque morphology
 - Progressive stenosis
 - Contralateral stenosis/occlusion
- Atherosclerosis of ascending aorta and transverse arch

SURGICAL FACTORS

- Duration of cross-clamp and cardiopulmonary bypass
- On-pump surgery
- Open heart surgery (valve or aortic surgery)
- Redo operation
- Partial clamping of ascending aorta for proximal anastomosis

TIA, Transient ischemic attack

Adapted from Roffi M, Ribichini F, Castriota F, et al: Management of combined severe carotid and coronary artery disease. *Curr Cardiol Rep* 14:125-134, 2012, with permission.

ipsilateral stroke and of any stroke were only 2.0% and 2.9%, respectively, among patients with unilateral, asymptomatic, 50% to 99% carotid stenosis who underwent isolated cardiac surgery without prophylactic carotid revascularization. In asymptomatic patients, these risks did not increase with stenosis severity. In contrast, patients with a history of stroke, TIA, or severe bilateral carotid disease had markedly increased rates of postoperative death and stroke. Additional subanalysis of 26 published reports with a total of 2531 patients showed that when symptomatic patients were also included, patients with 50% to 99% stenosis or occlusion had a 7.4% stroke risk after cardiac surgery; this risk increased to 9.1% in patients with 80% to 99% stenosis or occlusion. The risk of stroke was 6.5% in patients undergoing cardiac surgery with bilateral, asymptomatic, 50% to 99% stenosis, or 50 to 99% stenosis with contralateral occlusion. The risk of death or stroke in such patients was 9.1%. The importance of neurologic symptoms was also shown in an earlier meta-analysis of patients with carotid stenosis who underwent CABG: patients with previous TIA or stroke had a postoperative stroke rate of 8.5%, compared with 2.2% in asymptomatic patients (odds ratio, 3.6).⁸² A few centers have reported no increased stroke by limiting carotid revascularization in CABG patients with asymptomatic carotid stenosis.^{83,84} In a large retrospective study of 4335 patients, the risk of perioperative stroke was significantly increased in the synchronous CEA-CABG group compared with the group that underwent CABG alone (15.1% vs. 0%; $P = 0.004$).⁸⁵

It is generally understood that stroke after cardiac surgery among patients with asymptomatic carotid disease is relatively rare. Furthermore, since the early pivotal randomized trials comparing medical therapy to CEA were performed, contemporary optimal medical therapy has improved considerably. Thus, many argue that if such trials were performed with today's optimal medical therapy (e.g., modern antiplatelet, lipid-lowering, antihypertensive regimens), the previously reported benefit of CEA over medical therapy in asymptomatic patients (5% to 6% vs. 11% to 12%, respectively, for a combined death or stroke rate at 5 years) may be less compelling.⁸⁶⁻⁸⁸ These data call into question the rationale for performing prophylactic carotid revascularization in neurologically asymptomatic patients with unilateral carotid disease. Importantly, among 27,084 patients in the United States who underwent synchronous carotid and coronary revascularization procedures between 2000 and 2004, the vast majority (>95%) had asymptomatic carotid disease.⁸⁹

Surgical Approaches to Concurrent Carotid and Coronary Disease

Strategies to address concomitant, surgically correctable carotid and coronary disease include synchronous CEA and CABG, staged repair with either CEA or CAS followed by CABG, "reverse" staged repair (CABG then CEA or CAS), or no treatment of the carotid disease (CABG alone). The aim of any operative strategy is to minimize the risk of specific major adverse cardiovascular events. The staged and reverse-staged approaches risk

between-stage events such as death, stroke, or MI; this is not entirely unexpected, given that patients might have a severe form of coronary artery disease. Although conducting a carotid intervention before CABG has the advantage of lowering the patient's risk of peri-CABG stroke, the risk of acute MI is still high in the timeframe surrounding the carotid intervention and during the interval between the two interventions. Performing CABG before carotid intervention, on the other hand, could be associated with a high stroke rate. The approach must be individualized to the patient at hand, with careful attention to the symptomatic territory and institutional experience with various strategies. Because no randomized trial has yet compared management strategies for carotid disease at the time of cardiac surgery, the interpretation of available data from observational studies has inherent limitations.

Synchronous Carotid Endarterectomy and Coronary Artery Bypass Grafting

Since the introduction of the concept by Bernhard and colleagues⁹⁰ in 1972, the combined surgical approach has remained a topic of controversy. In the decade from 1992 to 2002, combined CEA-CABG represented only a small portion (1.1%) of all CABG procedures in the United States.⁹¹ In an excellent review of the literature that summarized outcome data from patients ($n = 11,854$) with carotid and coronary disease who underwent synchronous CEA-CABG, Venkatachalam and colleagues⁷² reported an early mortality rate of 5%, a stroke rate of 4%, an MI rate of 3%, and a death, stroke, or MI rate of 10%. Similarly, Timaran and colleagues⁸⁹ reported a mortality rate of 5.2%, a stroke rate of 3.9%, and a death or stroke rate of 8.6% among 26,197 patients who underwent combined CEA-CABG.

Using the Nationwide Inpatient Sample (NIS) database, Gopaldas and colleagues⁹² compared patients who underwent staged repair (CEA before or after CABG during the same admission but not on the same day; $n = 6152$) with patients who underwent synchronous repair (both procedures on the same day; $n = 16,639$). Patients who underwent synchronous CEA-CABG had an in-hospital mortality rate of 4.5%, a stroke rate of 3.9%, and a death or stroke rate of 7.7%. The staged patients had similar mortality (4.2%) but higher morbidity, including more cardiac, wound, respiratory, and renal complications. Among patients who undergo combined procedures, the stroke rate tends to be highest (>10%) in patients who have contralateral carotid occlusion. The presence of neurologic symptoms significantly increases the risk of postoperative death or stroke after combined carotid interventions and coronary bypass (odds ratio, 4.9; $P < 0.001$).⁸⁹

Staged Approach: Carotid Revascularization Followed by Coronary Artery Bypass Grafting

The staged approach involves operative intervention on the diseased carotid vessels followed by myocardial

revascularization, with the obvious theoretical benefit being the reduction of stroke risk during CABG. The risk of MI in the peri-CEA period and during the time interval between the two procedures remains the major drawback of this approach. Takach and colleagues⁹³ reported a low overall stroke rate of 1.9% with the staged approach. In their series, 512 patients underwent intervention for comorbid carotid and coronary disease over a period of 21 years. Before 1986, the incidence of adverse events was greater in patients who underwent combined procedures than in those who had staged interventions (9.4% vs. 2.6%; $P < 0.01$). However, since 1986, both groups have had similar rates of stroke (1.9% vs. 2.0%), death (3.8% vs. 3.0%), and MI (3.8% vs. 5.0%). In this series, approximately 30% of strokes occurred in the contralateral cerebrovascular territory in both the staged and the simultaneous groups. Hemodynamic instability or arrhythmia accompanied 10 of the 15 strokes that occurred during both the synchronous and the staged procedures. Advances in anesthesia, surgical technique, intraoperative monitoring for cerebral ischemia, and myocardial protection have all improved surgical teams' ability to maintain perioperative hemodynamic stability in patients with combined disease. The improvement in neurologic outcomes that occurred after 1986 in patients who underwent combined procedures in this series was attributed to these advances. The risk of stroke was affected by neither the use of a carotid shunt nor the use of patch closure of the carotid arteriotomy. Operative approach (synchronous or staged) was not a predictor of either stroke or death. The staged approach, however, lengthened hospital stay, increased the cost of hospitalization, and raised the risk of acute ischemia and MI in the interval between the CEA and CABG procedures.

Clearly, preventing stroke in patients with coronary disease is a multifactorial problem. Although carotid bifurcation disease may be a major contributing factor for perioperative stroke, it does not directly explain strokes in the contralateral territory, which occur in approximately one third of patients. More than anything else, the presence of carotid bifurcation disease is a marker for generalized atherosclerosis, which by itself increases the risk of hemorrhage, hemodynamic instability, cardiac failure, and atheroemboli. Also, the fact that adverse outcomes are more frequent in patients who undergo combined or staged procedures than in patients who undergo isolated CABG or CEA suggests that patients with concomitant carotid and coronary disease are at greater risk overall and have a poorer physiologic performance status, possibly secondary to diffuse atherosclerosis.

Reverse Staged Approach: Coronary Artery Bypass Grafting Followed by Carotid Endarterectomy

The advantage of the reverse staged approach is that the risk of MI is minimized by intervention on the coronary vessels before a CEA is performed. Unlike the staged approach, in which the elimination of hemodynamically significant carotid stenosis removes only one of the many potential causes of stroke during CABG, a reverse staged

approach essentially eliminates the one major and clearly defined complication of CEA: MI. The meta-analysis by Naylor and colleagues⁹⁴ found that perioperative MI rates were lowest after the reverse staged procedure (0.9%; 95% confidence interval [CI], 0.5-1.4) and were highest in patients who underwent staged CEA-CABG (6.5%; 95% CI, 3.2-9.7). However, patients with reverse staged procedures (CABG-CEA) had a higher risk of ipsilateral stroke (5.8%; 95% CI, 0.0-14.3) and of any stroke (6.3%; 95% CI, 1.0-11.7) than patients with other operative approaches (synchronous or staged).

In a recent randomized trial, 185 patients with asymptomatic unilateral carotid stenosis greater than 70% underwent CEA either early (before or concomitantly with CABG; $n = 94$) or late (1 to 3 months after CABG; $n = 91$).⁹⁵ All patients had general anesthesia, and CEA routinely involved carotid artery shunting. Although early death rates were similar between groups (1.0% vs. 1.1%; $P = 0.98$), there was a significant difference between groups concerning combined 90-day stroke and death rate; this was substantially lower in the early CEA group (1.0% vs. 8.8%; $P = 0.02$). Furthermore, delayed CEA significantly predicted combined stroke and death at 90 days (odds ratio, 14.2; $P = 0.03$). Thus, it was found that CEA before or concomitantly with CABG surgery greatly lowers the risk of stroke.

Carotid Artery Stenting Followed by Coronary Artery Bypass Grafting

Endovascular approaches have pushed the envelope further amidst the controversy surrounding the treatment of patients with combined coronary and carotid disease.⁹⁶ A retrospective study by Timaran and colleagues⁸⁹ of NIS data has provided interesting insights into CAS before CABG. During the 5-year period from 2000 through 2004, 27,084 patients underwent carotid revascularization and CABG during the same hospitalization. Of these patients, 96.7% underwent either staged or synchronous CEA-CABG, and only 3.3% underwent CAS-CABG. Patients who underwent CAS-CABG tended to have fewer major adverse events than did those who underwent CEA-CABG. Specifically, CAS-CABG patients had significantly lower incidences of in-hospital stroke (2.4% vs. 3.9%; $P < 0.001$) and combined stroke and death (6.9% vs. 8.6%; $P < 0.001$) than did CEA-CABG patients; however, the incidence of in-hospital death was similar (5.2% vs. 5.4%) between the two groups. The study, however, did not include separate comparisons either between CAS-CABG and staged CEA-CABG or between CAS-CABG and synchronous CEA-CABG. Unfortunately, typically reported 30-day data were not available in the NIS dataset, and only in-hospital events were captured; thus, major adverse events could be greater than presented. Ziada and colleagues⁹⁷ compared 30-day outcomes between staged CAS-CABG ($n = 56$) and combined CEA-CABG ($n = 112$) groups. Although no significant difference was found for combined death, MI, or stroke ($P = 0.12$), after propensity adjustment, a nearly significant difference was noted for lower stroke or MI rates in the CAS-CABG group.

A prospective, single-center study from Europe examined outcomes in 356 patients who underwent staged CAS followed by CABG.⁹⁸ None of the patients had symptoms of carotid disease in the 4 months preceding CAS, and patients with major neurologic deficits, diffuse common carotid disease, chronic total occlusions, and preocclusive or string sign lesions were excluded. Cardiac surgery occurred with a mean delay of 22 days (range, 14 to 30 days). Despite aspirin and clopidogrel being withheld for 5 days before surgery, there were no cases of carotid stent thrombosis. Following CABG, the 30-day cumulative incidence of death, MI, or stroke was 8.7%. At nearly 3 years' follow-up, the authors reported a remarkable neurologic death rate of 1.1% and a major ipsilateral stroke rate of 1.1%.

As reported by Mas and colleagues,⁹⁹ in patients with isolated yet symptomatic carotid disease (>60% stenosis), CAS produced outcomes inferior to those of the gold standard treatment, CEA. The trial was stopped prematurely when preliminary analyses showed that the incidence of stroke or death was 3.9% after CEA (95% CI, 2.0-7.2) and 9.6% after CAS (95% CI, 6.4-14.0) and that the 30-day incidence of disabling stroke or death was 1.5% after CEA versus 3.4% after CAS. Likewise, the incidence of perioperative stroke was reported to be fivefold higher in symptomatic patients undergoing CAS-CABG than in symptomatic patients undergoing CEA-CABG. However, Versaci and colleagues¹⁰⁰ have supported the feasibility of sequential hybrid CAS immediately followed by CABG; in their 37 patients, the combined incidence of disabling stroke, MI, or death was 8.1%.

The most comprehensive study comparing the three most common surgical strategies for concomitant carotid and coronary artery disease comes from a retrospective review of 350 patients treated at the Cleveland Clinic from 1997 to 2009.¹⁰¹ The majority of patients had asymptomatic disease (81%) and underwent CABG with or without concomitant valve surgery (92%); only 8% of these patients had open heart surgery (OHS) that did not involve CABG (e.g., isolated valve or aortic repair). The study compared three groups: combined carotid endarterectomy and OHS under a single anesthetic (combined CEA-OHS; $n = 195$), staged carotid endarterectomy followed by open heart surgery (staged CEA-OHS; $n = 45$), and staged carotid stenting followed by open heart surgery (CAS-OHS; $n = 110$). In staged CEA-OHS, CEA was performed a median of 14 days before OHS, whereas in the staged CAS-OHS group, patients underwent 3 to 4 weeks of antiplatelet therapy (median interval, 47 days) between CAS and CABG. The authors performed a propensity-adjusted analysis examining the early (up to 1 year) and late (beyond 1 year) risks of the composite endpoint (all-cause death, stroke, and MI). In the early phase, the staged CAS-OHS group's risk of adverse events was similar to that of the combined CEA-OHS group, whereas the staged CEA-OHS group had more adverse events, primarily driven by a higher inter-stage MI rate. Early mortality rates were similar among all three treatment strategies. Beyond 1 year, the staged CAS-OHS group experienced fewer adverse events than either the staged CEA-OHS group (adjusted hazard ratio 0.33; $P = 0.01$) or the combined CEA-OHS group

(adjusted hazard ratio 0.35; $P = 0.003$) did. This late divergence was largely due to increased all-cause mortality in the staged and combined CEA groups. The systematic analysis of all interstage events and the direct comparison of three treatment strategies with a median follow-up of 3.7 years were the strengths of this study. The findings suggest that for patients who require urgent CABG, combined CEA-CABG is the optimal strategy for revascularization. However, for patients with stable angina who could tolerate a few weeks of dual-antiplatelet therapy, staged CAS-CABG may be advantageous. Staged CEA followed by CABG is associated with increased short-term MI and long-term mortality and may not be the optimal approach.

Synchronous Off-Pump Coronary Artery Bypass Grafting and Carotid Endarterectomy

Off-pump CABG has the potential advantage of reducing aortic manipulation, which is a major risk factor for embolic stroke. However, in the largest reported series ($n = 358$), Mishra and colleagues⁶¹ found no significant difference in major adverse cardiovascular events between conventional CABG and off-pump CABG when CEA was performed simultaneously. The difference between off-pump and conventional CABG in terms of stroke rate and outcomes is a separate issue and is beyond the scope of this chapter. Suffice it to say, there is no evidence that this approach to treating concomitant coronary and carotid disease is superior to others that use cardiopulmonary bypass during CABG.

SUMMARY

The surgeon's approach to concurrent severe carotid and coronary artery disease must be individualized to the patient's anatomy, clinical presentation, and comorbid diseases. The clinical challenge is to balance sufficient repair of multisite arterial disease with minimal adverse outcomes, specifically perioperative MI, stroke, and death, including interstage events for staged procedures. In the absence of large-scale randomized trial data, carefully designed retrospective studies provide the best evidence available to guide clinical decision making. The differences in reported outcomes stem from clinical heterogeneity and differences in study design, comparator groups, surgical era, and analytical methods. Experts agree that when significant symptomatic or bilateral carotid artery stenosis is present, whenever possible, carotid revascularization is generally indicated in patients with planned CABG surgery.⁷³ Both the mode (CEA vs. CAS) and the timing (before, during, or after CABG) of carotid revascularization depend largely on the patient's symptoms, as well as on institutional experience. Synchronous, staged, and reverse-staged procedures have each been performed with a low incidence of morbidity and mortality. For patients with unilateral asymptomatic carotid artery stenosis, there might not be a benefit to routine carotid intervention as compared with

contemporary optimal medical therapy and CABG alone. Further studies are needed to elucidate the roles and timing of CEA, CAS, and optimal medical therapy in the management of patients with concomitant severe carotid and coronary artery disease.

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PERCUTANEOUS INTERVENTION ON ABDOMINAL AORTIC AND PERIPHERAL VASCULAR DISEASE

Victor Chien • Elliot L. Chaikof

CHAPTER OUTLINE

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Peripheral arterial occlusive disease (PAD) is a major cause of disability, loss of work, and lifestyle changes. The natural history of PAD is often characterized by slow progression in symptoms over time.¹⁻⁵ However, 70% of patients will remain stable or improve over time, approximately 30% will require an intervention, and 10% will require amputation.⁶ Limb loss is the tragic final outcome of PAD and is associated with a significant degree of disability and a poor overall prognosis.⁷ The aging of the population, continued tobacco abuse, high-fat diets, sedentary lifestyles, and rising prevalence of obesity parallel the increasing prevalence of PAD. The prevalence of PAD in the general population is 3% to 10%, and it is 15% to 20% among patients older than 70 years.⁸ This prevalence probably underestimates the true burden of disease, however, as PAD may be asymptomatic. Because of the rising prevalence of PAD, many cardiovascular specialists have adopted a strategy of “global vascular management” for their patients. In this strategy, the evaluation, care, and intervention plan is more comprehensive in its scope, and it includes the management of vascular disease in all of its manifestations and anatomic locations. This chapter reviews the general aspects of peripheral vascular disease, with particular emphasis on the angiographic and percutaneous interventions after medical evaluation.

PERIPHERAL ANGIOGRAPHY

Indications

The purpose of peripheral angiography is to define the vascular anatomy and to identify significant arterial narrowing that requires revascularization (either percutaneous or surgical). As with any invasive diagnostic test, the risk-benefit ratio should be evaluated before angiography to identify patients who might fully benefit from imaging.⁹⁻¹¹

Lower extremity claudication is classified according to the level of debilitation or restriction of activities. It is important to select the appropriate patient for angiography, given that the morbidity from vascular access might be particularly high among patients with PAD. The most commonly used clinical grading system for PAD is the Rutherford-Becker scale, a 7-point scale from 0, which denotes asymptomatic disease, to 6, which denotes major tissue loss (Table 74-1). In general, patients with Rutherford scale 2 and higher and noninvasive studies that demonstrate evidence of significant disease are likely to benefit from angiography and revascularization. Any patient with symptomatically limiting lower extremity claudication should undergo angiography to fully define the anatomy with a consideration toward revascularization.

TABLE 74-1 Rutherford Scale

Grade	Category	Clinical Description	Objective Criteria
0	0	Asymptomatic	Normal treadmill test
	1	Mild claudication	Ankle pressure after exercise <50 mm Hg but >25 mm Hg less than brachial
I	2	Moderate claudication	More moderate symptoms
	3	Severe claudication	Does not complete treadmill test
II	4	Ischemic rest pain	Ankle pressure after exercise <50 mm Hg
			Resting ankle pressure <60 mm Hg
			Decreased pulse volume recording
III	5	Minor tissue loss	Resting ankle pressure <40 mm Hg
		Nonhealing ulcers	Pulse volume recording moderately decreased
		Major tissue loss	As noted in category 5
	6	Loss above the metatarsal limb no longer salvageable	

Angiography is indicated in patients with threat of limb loss owing to acute thromboembolism. Patients with acute onset of a cool, pulseless extremity after catheterization or trauma require angiography to define the anatomy and site of occlusion in addition to allowing the direct infusion of intra-arterial fibrinolytic therapy or mechanical or rheolytic thrombectomy if necessary.¹²⁻¹⁷

Angiography may be warranted among patients with an abdominal aortic aneurysm or thoracic aneurysm to fully delineate the anatomy, particularly if endovascular repair is considered. However, given current noninvasive imaging techniques, such as magnetic resonance angiography and computed tomographic angiography, it is unlikely that invasive angiography is necessary to define anatomy among patients who are at low surgical risk, in whom an open repair may be most beneficial. Only if invasive angiography answers a particular question (e.g., the angle of the aneurysm neck) that cannot adequately be answered with noninvasive imaging should peripheral catheterization be pursued.

Magnetic resonance angiography may also be useful in the evaluation of coarctation of the aorta. When angiography is needed, anteroposterior (AP) and lateral images are the most useful for patients with coarctation who have not been operated on. Angiography usually confirms the anatomic coarctation, invariably seen just distal to the origin of the left subclavian artery. Further, if the head and neck vessels are imaged with the thoracic aorta, an idea of collateral flows can be inferred as well (i.e., carotid or mammary).

Invasive renal angiography is indicated in patients who have evidence of significant stenosis on noninvasive testing, such as magnetic resonance angiography and Doppler ultrasonography. Other indications include new uncontrolled hypertension in patients younger than 30 years or older than 55 years, refractory hypertension, rising creatinine concentration (specifically after the institution of angiotensin-converting enzyme inhibitor therapy), or unexplained acute pulmonary edema.¹⁸ The prevalence of renovascular hypertension may be as high as 5% in the general population and 30% among patients with coronary artery disease or other PAD.

Because of the multiple-source blood supply to the upper extremity, which is derived principally from the subclavian and vertebral arteries, upper extremity

claudication is rare. Upper extremity claudication symptoms include an inability to perform activities with the affected limb, such as combing hair, brushing teeth, or repeated lifting. Another constellation of symptoms indicating obstructive disease in the upper extremity may come from significant obstruction in the posterior circulation. In this situation, there is a reversal of flow from the vertebral artery in a patient with disease in the ipsilateral vertebral artery, leading to dizziness or difficulties with gait.¹⁹⁻²² Among patients who have undergone coronary artery bypass graft surgery with use of the internal mammary artery, persistent angina and anterior ischemia on noninvasive testing may suggest left subclavian stenosis as the cause of coronary ischemia.^{21,23-27} Therefore, any patient with symptoms of upper extremity claudication, anterior ischemia after coronary artery bypass grafting with the use of the left internal mammary artery, or posterior circulation events and a difference in upper extremity blood pressures should be evaluated for the possibility of subclavian stenosis and undergo evaluation, including angiography.

A critical stenosis of one or both carotid arteries on noninvasive imaging or evidence of transient ischemic attack or stroke and a critical stenosis identified on noninvasive testing is an indication for invasive carotid or cerebral angiography.

Contraindications

The principal contraindications to peripheral angiography are bleeding diathesis, renal failure (true or impending), fever, ongoing infection, and severe anemia (Box 74-1).

Complications

Complications of invasive peripheral angiography primarily involve vascular access site complications, catheter manipulation within atherosclerotic vessels, emboli, clot formation, stroke, myocardial infarction, worsening renal function, or congestive heart failure (Box 74-2). A particularly devastating complication of catheter manipulation within the arterial tree is an atheroembolic event. In its most severe form to the lower extremities, it may cause loss of limb or digits. Likewise, emboli to the renal

BOX 74-1 Relative Contraindications to Catheterization and Angiography

- Bleeding diathesis or inability to take aspirin or adenosine diphosphate inhibitor
- Concurrent febrile illness
- Severe renal insufficiency or anuria without dialysis planned
- Severe allergy to contrast agents
- Severe hypokalemia or digitalis toxicity
- Severe hypertension or ongoing unstable coronary syndrome

BOX 74-2 Possible Complications of Peripheral Catheterization

- Vascular access dissection or perforation: 0.1%-0.2%
- Bleeding or hematoma: 1.5%-2.0%
- Allergic reaction: 0.5%-2.0%
- Vasovagal events: 1.0%-2.0%
- Death: 0.1%-0.2%

circulation can lead to acute renal decompensation or failure requiring dialysis.²⁸⁻³⁰ Pseudoaneurysm or vascular access complications can be as high as 3% in patients with severe peripheral occlusive disease.^{31,32}

General Considerations

There are several important differences in imaging of peripheral vascular structures and coronary arteries. Peripheral angiography commonly uses a larger image intensifier field (14 inches [36 cm]) to encompass larger regions of interest. Digital (not film-based) angiography allows online display of acquired images as well as advanced processing techniques to enhance brightness, contrast, or shift of underlying bone structures to enhance the final image (Fig. 74-1). Frequently, digital subtraction angiography is used. With this imaging method, a baseline background image, referred to as a mask, is obtained immediately before injection of contrast material to digitally subtract bone, calcifications, air, or soft tissues from the final image, leading to the best image quality with the most definition of vascular anatomy. Another advantage of digital subtraction angiography is that it can reduce the volume of contrast material and imaging acquisition time required.

SPECIFIC ANATOMIC IMAGING

Thoracic Aorta

Thoracic aortography is used to define the anatomic relation of the aortic arch and the great vessels, to determine the diameter of the thoracic aorta, to obtain evidence of dissection (Fig. 74-2), and to evaluate for trauma or other vascular injuries. The optimal view of the aortic arch is obtained in the left anterior oblique projection at 30 to 40 degrees oblique. The injection of 30 to 40 mL of

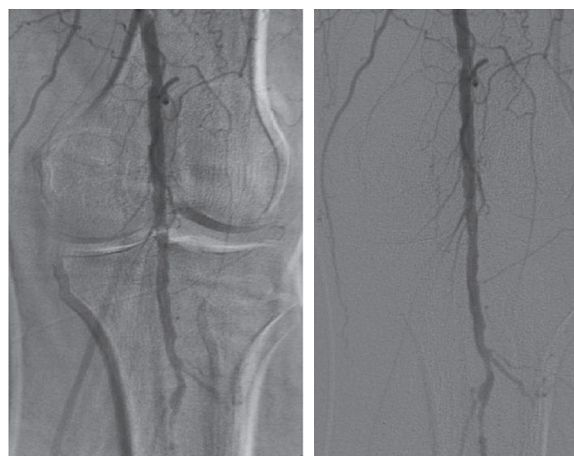


FIGURE 74-1 ■ Digital subtraction angiogram of the popliteal artery with moderate motion of the patient confounding the popliteal evaluation and after “shifting” of the image to re-mask the underlying bone structures for direct angiographic evaluation of the anatomy.

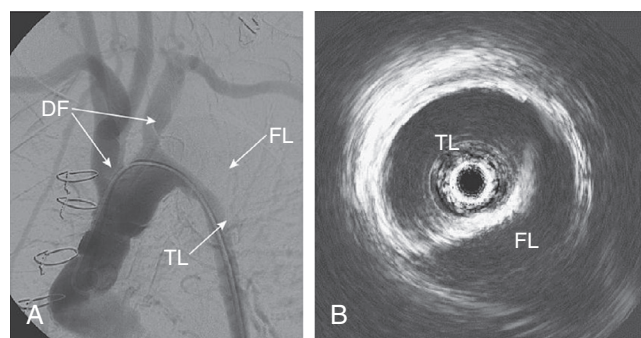


FIGURE 74-2 ■ (A) Angiogram and (B) intravascular ultrasound image of a patient with type A dissection of the aortic arch. The false lumen (FL) and true lumen (TL) are evident in the intravascular ultrasound image. The arrows on the angiogram correlate with the site of the intravascular ultrasound image. DF, Dissection flap.

contrast material at 20 to 30 mL/sec generally opacifies the vessels for adequate imaging. If digital subtraction angiography is used, the patient should be instructed to hold his or her breath to avoid artifacts caused by motion or breathing. The three principal vessels originating from the arch are (1) the brachiocephalic (innominate), leading ultimately to the right subclavian and right carotid arteries; (2) the left common carotid; and (3) the left subclavian artery (Fig. 74-3). The most common normal variant of this anatomy is the so-called bovine arch, in which the left common carotid artery originates from the brachiocephalic trunk. This normal variant occurs in approximately 10% of patients.³²

Abdominal Aorta

The abdominal aorta should be angiographically imaged for evaluation of abdominal aortic aneurysm, dissection, lower extremity claudication, mesenteric ischemia, and renovascular disease. The abdominal aorta begins at the level of the diaphragm. The principal vessels are, in descending order, (1) the celiac artery at the level of L1,

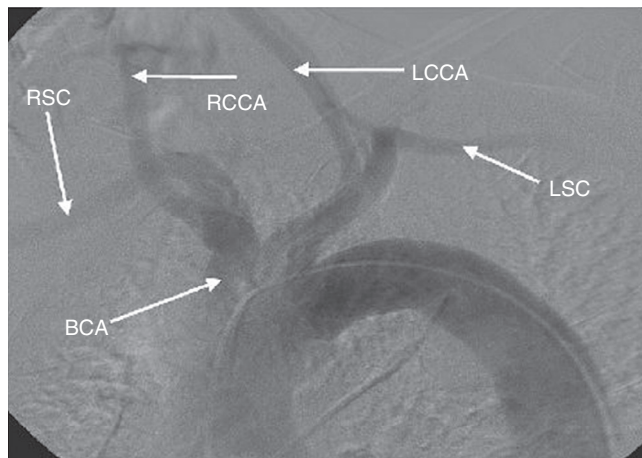


FIGURE 74-3 ■ Digital subtraction angiography of the thoracic arch and great vessels. *BCA*, Brachiocephalic artery; *LCCA*, left common carotid artery; *LSC*, left subclavian artery; *RCCA*, right common carotid artery; *RSC*, right subclavian artery.

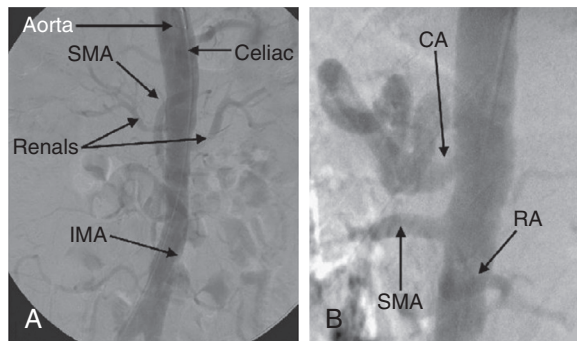


FIGURE 74-4 ■ **A**, Anteroposterior view of digital subtraction angiography of the abdominal aorta and major branches. **B**, Lateral digital subtraction angiography of the abdominal aorta and major branches. *CA*, Celiac artery; *IMA*, inferior mesenteric artery; *RA*, renal artery; *SMA*, superior mesenteric artery.

(2) the superior mesenteric artery at the level of L2-3, (3) the renal arteries at the level of L2-3 just caudal to the superior mesenteric artery, and (4) the inferior mesenteric artery at the level of L4. The abdominal aorta terminates at the bifurcation and the origin of the iliac arteries.

In general, 20 to 40 mL of contrast material injected at 15 to 30 mL/sec will adequately opacify the vessels to define the anatomy. Again, as in the thoracic aorta, it is critical to fully opacify the lumen and the vessels of interest. AP and lateral images (Fig. 74-4) of the abdominal aorta are usually sufficient to delineate all anatomic areas of interest in the abdominal aorta and mesenteric vessels. If selected conduits require further visualization, a soft-tipped catheter can provide selective angiography without requiring large loads of contrast material to fully define the anatomy.

Head and Neck Angiography

The three primary branches emanating from the aortic arch are the brachiocephalic, left common carotid, and

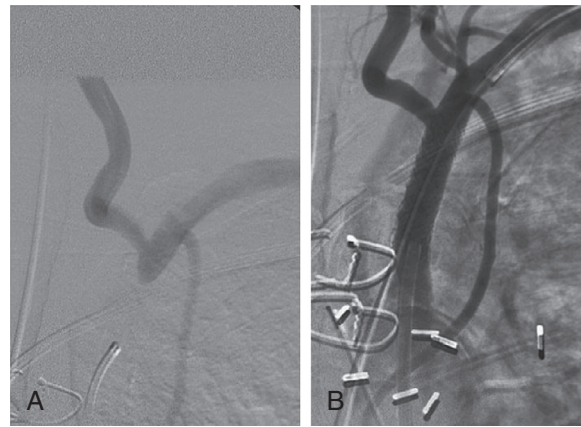


FIGURE 74-5 ■ Digital subtraction angiography of the left subclavian artery before and after intervention. **A**, The left subclavian artery is occluded. **B**, After crossing the left subclavian artery in a retrograde fashion from the left brachial artery, the subclavian is stented, with the final angiographic result noted.

left subclavian arteries. The right subclavian and carotid arteries are the terminal branches of the brachiocephalic trunk. The most common variant of this anatomy is the bovine arch, in which the left carotid and brachiocephalic share a common origin.³²

Subclavian artery disease, stenosis, and occlusion are common.³³ Symptoms are rare because of the dual supply of blood to the upper extremity through the subclavian and vertebral arteries. Upper extremity claudication is rare but is manifested by upper extremity discomfort while engaging in activity with the upper extremity or in activities of daily living. More commonly, subclavian stenosis or occlusion is manifested by either posterior circulation symptoms, such as dizziness and gait instability, which are rare, or anterior ischemia (coronary steal syndrome) in the patient who has been treated with left internal mammary artery coronary bypass grafting (Fig. 74-5).^{23-27,34}

Subclavian artery angiography is optimally performed with both AP and ipsilateral oblique views. Selective angiography can be performed with any straight or slightly angulated catheters. As in the thoracic aorta, nonselective angiography, in general, requires 30 to 40 mL of contrast material injected at 20 to 30 mL/sec to adequately opacify all vessels in the arch. The vessels are usually accessed with the use of the guide wire as a rail, and then the catheter is advanced over the wire. Access to the brachiocephalic, carotid, and subclavian arteries usually requires a counterclockwise movement of the catheter in the ascending aorta for it to engage the vessel of interest. The J-wire is then advanced into the vessel, and ultimately the catheter is advanced over the wire. Once the wire has been removed and the catheter has been flushed, angiography can be performed safely. There is usually some shoulder and neck discomfort with moderate injections of contrast material, and the patient should be forewarned of a sensation of warmth that will follow injections. Discomfort can be minimized, if necessary, with the use of half-diluted contrast material. Excessively vigorous injections should be avoided to

prevent subintimal injection or dye staining into the intima of the subclavian artery.

Atherosclerosis of the subclavian artery is generally proximal at the origin or within the first few millimeters from the aortic origin. The origin of the inferior mesenteric artery is usually spared of atherosclerosis. The origin of the vertebral artery may be involved with atherosclerotic disease, but the need for intervention is low because of the dual blood supply to the posterior circulation that arises from both the contralateral vertebral and ipsilateral carotid arteries with an intact intracerebral circulation.

The carotid arteries generally bifurcate at the level of the fourth cervical vertebra into the internal and external carotid arteries (Fig. 74-6A). The internal carotid usually has no major branches and becomes tortuous below the petrous bone, the so-called carotid siphon. Once the vessel enters the petrous bone, it is considered the intracranial internal carotid artery. On exiting the petrous bone, the internal carotid artery bifurcates early into the anterior and middle cerebral arteries. The external carotid artery has several branches that supply the face.

Carotid atherosclerosis is common.^{35,36} Intervention in the internal carotid artery is performed either percutaneously or surgically. Annually, there are 600,000 strokes in the United States, of which 500,000 are first attacks and 160,000 are fatal. Cerebral occlusive disease encompasses stroke, transient ischemic attack, and posterior circulation (vertebral-basilar) events. Several studies have evaluated the efficacy of various revascularization strategies in preventing future events.³⁷⁻³⁹ The National Heart, Lung, and Blood Institute's Atherosclerosis Risk in Communities study⁴⁰ reported that 83% of all strokes were ischemic, 40% were lacunar, and 14% were thromboembolic. Most patients with extracranial carotid artery disease are asymptomatic.

Risk factors for the presence and progression of carotid artery disease are similar to those of coronary artery disease and include diabetes mellitus, hypertension, hyperlipidemia, and family history. A bruit can aid in identifying patients with carotid stenoses, but the presence of a bruit is neither sensitive nor specific for the detection of clinically meaningful carotid stenosis. For

example, in one study,⁴¹ only 37% of 330 patients referred to a neurology clinic with a cervical bruit had a high-grade carotid artery lesion noted with duplex imaging. A carotid bruit may be associated with subsequent risk of stroke, as the Framingham Heart Study demonstrated that asymptomatic patients with a carotid bruit have twice the risk of stroke.⁴² In addition, a bruit can be a marker of more general cardiovascular risk.⁴³ In asymptomatic patients, risk of stroke was 2.5% if the stenosis was more than 75%. The risk was higher for patients with symptoms (3.3%).⁴⁴⁻⁴⁶

Angiography of the carotid artery is generally performed in the AP and lateral views. Selective angiography should be performed with care to ensure adequate position of the catheter and distance from the bifurcation.

Renal Vascular Imaging

The prevalence of renovascular disease can be as high as 50% in patients with coronary artery disease or other PAD.^{47,48} Renovascular disease is a cause of secondary hypertension in 0.5% to 5% of the general population.^{49,50} Whereas other noninvasive and functional studies such as Doppler ultrasonography, captopril nuclear studies, and magnetic resonance angiography remain useful screening tools, contrast angiography remains the gold standard. The renal arteries have a posterior takeoff from the abdominal aorta. Injection of 15 to 20 mL of contrast material at 30 mL/sec should opacify the intended vessels adequately. An improvement in blood pressure control is one goal of percutaneous revascularization of renal arteries.⁵¹⁻⁵³ Another potential benefit of renal artery revascularization is preservation of renal function.^{48,54-56}

Lower Extremity Angiography

Iliac Vessels

The iliac vessels originate at the termination of the abdominal aorta, usually at the L4-5 level. They remain retroperitoneal throughout their course until they cross the inguinal ligament and become the common femoral artery. The principal bifurcation in the iliac artery is the terminal bifurcation of the common iliac into the internal and external iliac arteries (Fig. 74-7).

Angiography of the iliac arteries is best achieved in the AP and oblique positions (left anterior oblique for the right internal iliac and right anterior oblique for the left internal iliac). The imaging catheter is positioned just above the aortic bifurcation to allow the best opacification of the iliac arteries. In general, 15 to 30 mL of contrast material injected at 20 to 30 mL/sec is sufficient to provide adequate opacification.

In patients with lower extremity claudication, noninvasive testing with ankle-brachial indices by duplex and Doppler imaging is critical. Evaluation with and without exercise, either 5 minutes at 1.5 miles per hour or 40 calf raises is often necessary to provoke symptoms and, more important, to determine the level of stenosis.⁵⁷ Doppler imaging is vital in the evaluation of the lower extremities. Normal flow patterns are triphasic or biphasic (Fig. 74-8). When a critical lesion is present, the waveform becomes

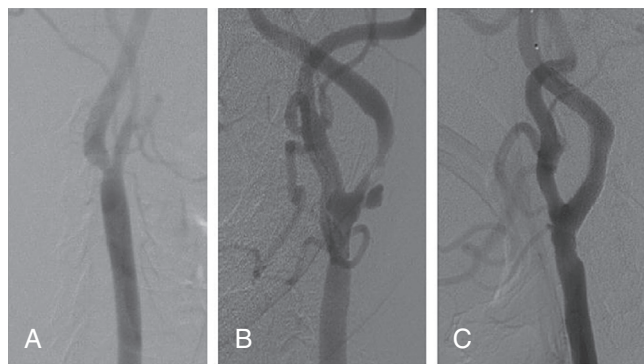


FIGURE 74-6 ■ **A**, Angiogram of a normal carotid and its bifurcation. **B**, Abnormality on an angiogram with an ulcerated left internal carotid artery in a patient several weeks after a transient ischemic attack. **C**, Final angiogram after angioplasty and stenting.

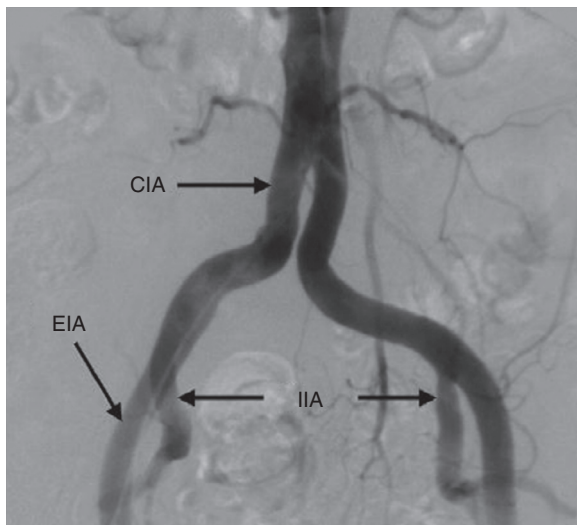


FIGURE 74-7 ■ Digital subtraction angiography in the anteroposterior projection of the terminal abdominal aortic bifurcation. CIA, Common iliac artery; EIA, external iliac artery; IIA, internal iliac artery.

monophasic. Furthermore, during exertion, resting triphasic and biphasic waveforms become monophasic distal to a critical stenosis. The location of the transition in the waveform pattern indicates the level of critical disease and can allow more directed and focused lower extremity angiography. Because the lower extremity arterial tree is relatively superficial, the anatomy can occasionally be directly visualized noninvasively with duplex imaging. Therefore, in some cases, the level and extent of disease may be delineated without vascular access.

Angiographic Technique

Lower extremity angiography can be performed in many ways. There has been an increase in the use of digital angiography and bolus-chase techniques, in which the table stops at various points of the run to mask the image, then returns to the same location and follows the original bolus of contrast material throughout the course. These methods allow a single injection of contrast material and delineation of the anatomy without the need for multiple

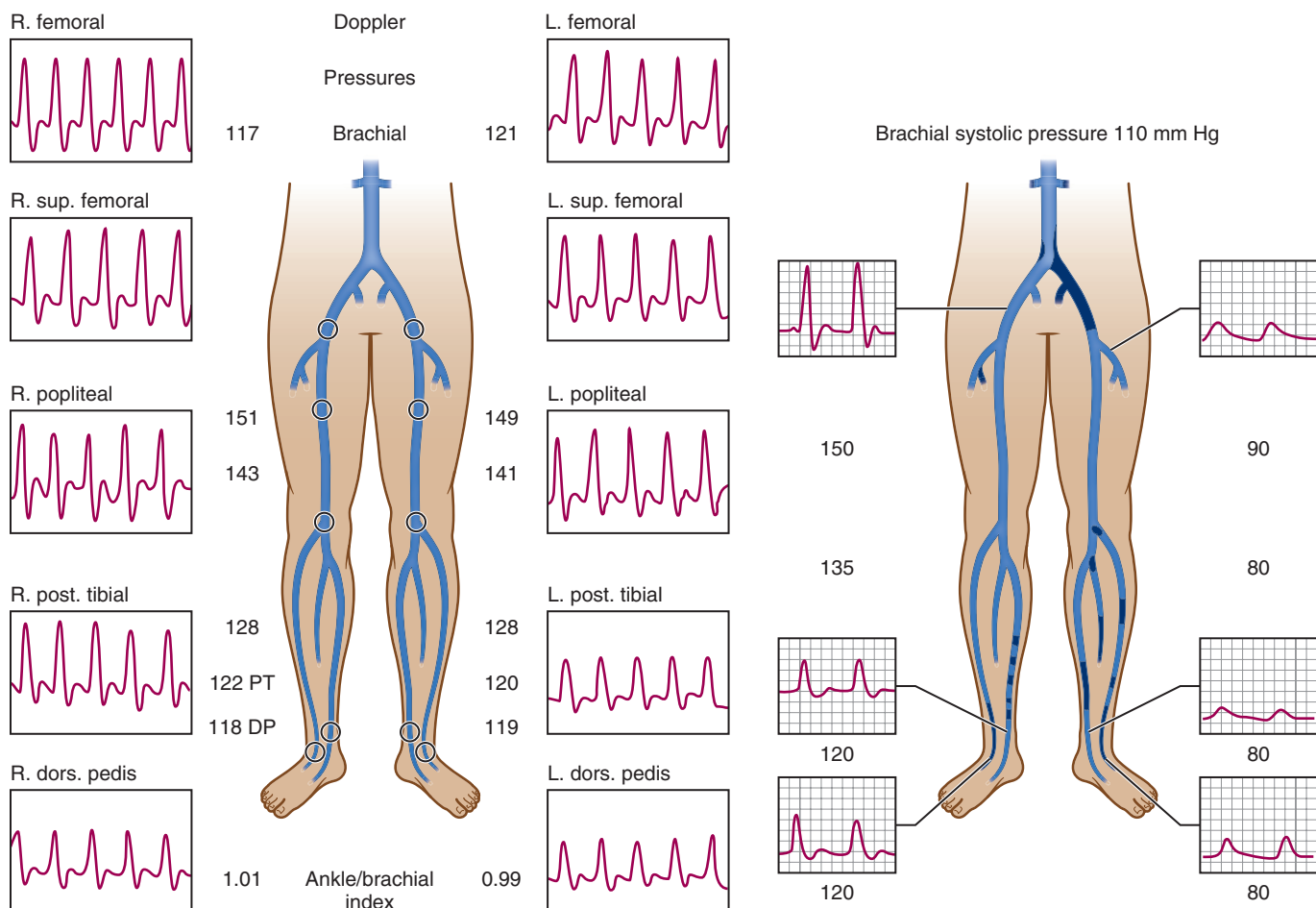


FIGURE 74-8 ■ Doppler waveforms in a normal and an abnormal lower extremity. Note the triphasic waveform in the normal patient and an attenuated, wide-based waveform consistent with a monophasic (abnormal) wave consistent with upstream stenosis or occlusion. L, Left; R, right.

injections. The principal problem with this technique occurs when there is significant motion of the patient from the mask to the contrast bolus-chase and the images are out of register and of poor quality. Small motion from the patient may be digitally shifted in the final angiogram without much difficulty to remove the underlying bone structures and to enhance the final angiographic image (see Fig. 74-1). In general, volumes of contrast material for the lower extremity bolus-chase technique range from 30 to 40 mL at 8 to 10 mL/sec. Other techniques include static images and older cut-film changers. In the static image technique, a focal area is evaluated with a single bolus injection of contrast material of 15 to 30 mL at 8 to 10 mL/sec or by hand injection.

One unique aspect of peripheral angiography is the antegrade puncture of the femoral artery. The common femoral artery is entered as with standard retrograde access, but it is entered in the antegrade direction (in the direction of blood flow to the leg). The entry is less steep (≈ 45 degrees) but should enter the common femoral artery over the femoral head and below the inguinal ligament. This access allows direct intervention for the infrainguinal vessels.

Infrainguinal Vessels

The arterial tree below the inguinal ligament begins with the common femoral artery. This vessel bifurcates early, at the level of the femoral head, into the profunda femoral artery and the superficial femoral artery (Fig. 74-9A). The superficial femoral artery is the principal vessel supplying the lower extremity. It courses anteriorly through the proximal 60% of its length and then begins to course posteriorly, entering the adductor canal (Hunter canal), a musculofascial canal bounded by the sartorius muscle anteriorly, the vastus medialis muscle laterally, and the adductor longus and magnus muscles posteriorly. This canal exits posteriorly, and the artery becomes the popliteal artery as it exits. The popliteal artery then terminates

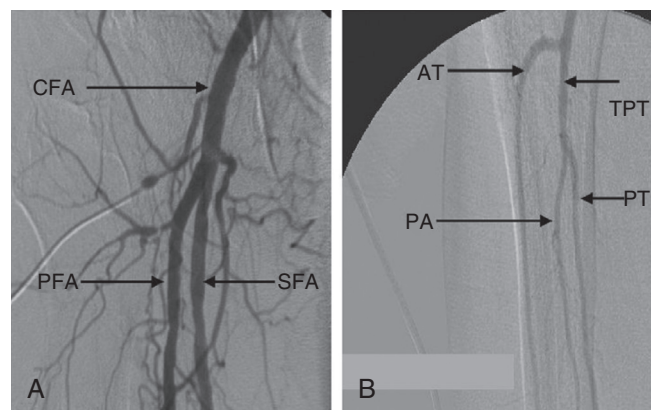


FIGURE 74-9 ■ **A**, Digital subtraction angiography in the anteroposterior projection of the right common femoral artery. **B**, Infrapopliteal digital subtraction angiography in the anteroposterior projection. AT, Anterior tibial artery; CFA, common femoral artery; PA, peroneal artery; PFA, profunda femoral artery; PT, posterior tibial artery; SFA, superficial femoral artery; TPT, tibial-peroneal trunk.

at the level of the tibial plateau into the anterior tibial artery and tibial-peroneal trunk vessels. The tibial-peroneal trunk then terminally bifurcates into the posterior tibial artery and the peroneal artery (see Fig. 74-9B). The posterior tibial and anterior tibial arteries usually are the principal vessels supplying the foot. The posterior tibial artery supplies the medial and lateral plantar vessels, and the anterior tibial artery supplies the dorsalis pedal artery. The distal plantar arteries, along with the dorsalis pedal artery, often communicate to form the plantar arch of the foot.

PERCUTANEOUS INTERVENTION

Thoracic and Abdominal Aorta

Intervention to the thoracic and abdominal aorta is usually performed for dissection, coarctation, or aneurysm and is discussed in full detail elsewhere in this text. Percutaneous intervention with stenting has become the primary method of correction of coarctation.⁵⁸⁻⁷⁰ Success rates for percutaneous interventions are 70% to 80% with a reduction of peak gradient less than 20 mm Hg. Most of the patients are seen within a pediatric population, and as such, adult disease is rarely seen as native coarctation. Percutaneous intervention to postoperative coarctation is feasible and limits the risk of a second open procedure (Fig. 74-10).⁶⁰

In general, there is a greater degree of atherosclerosis in the aorta after it crosses the diaphragm into the abdomen. The consequence of this is either lower extremity claudication or mesenteric ischemia. As disease in the abdominal aorta can lead to lower extremity claudication, it is a possible site of angioplasty and stent implantation

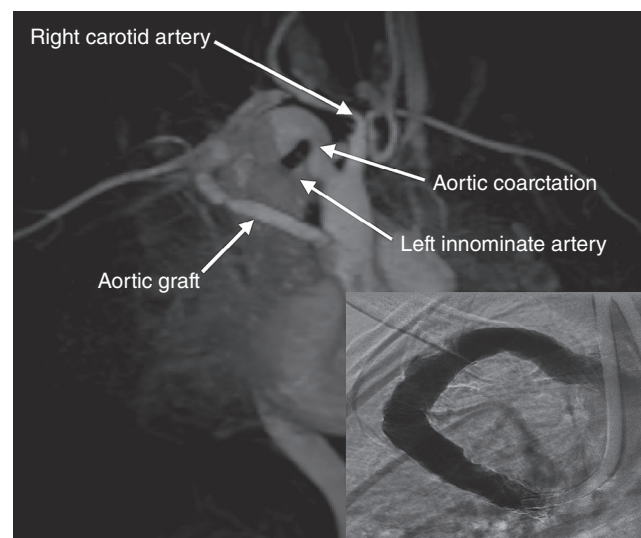


FIGURE 74-10 ■ Magnetic resonance angiographic anteroposterior view of hypoplastic aortic arch with a coarctation. The anatomy of this right-sided arch is as shown with the initial takeoff of the right carotid, then right subclavian (not shown), followed by left brachiocephalic off the descending aorta with intervening aortic-aortic graft. Inset: Completed stenting to the aortic-aortic graft.

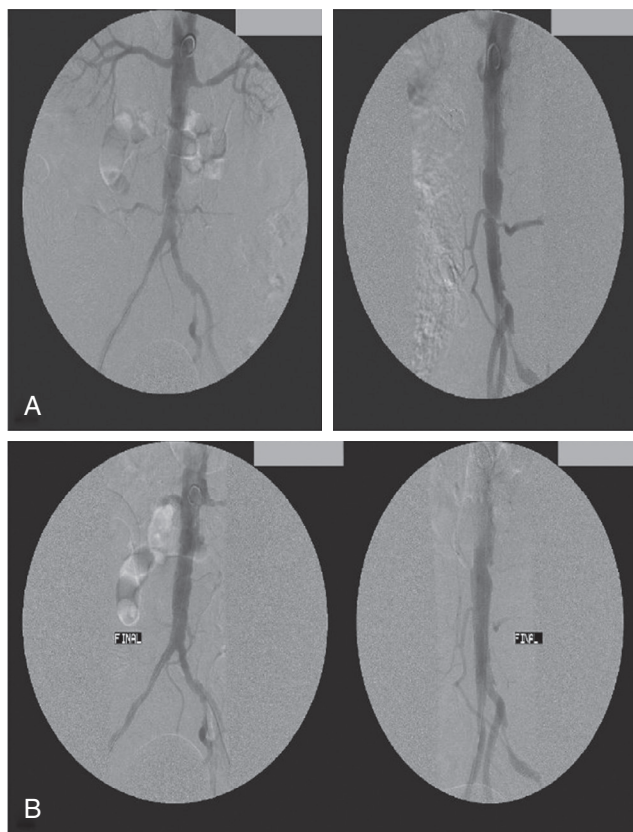


FIGURE 74-11 ■ **A**, Anteroposterior and lateral digital subtraction angiograms of the distal abdominal aorta showing a distal lesion at the level of the inferior mesenteric artery. **B**, A widely patent vessel shown after angioplasty and stenting of the distal abdominal aorta.

(Fig. 74-11). Here, it is important to determine the significance of the lesion and the possibility of intervention. Once the characteristics of the lesion are defined and percutaneous intervention is pursued, the key element is to gain access in each femoral artery. One access point will serve as the primary intervention for the aorta, and the other will then cross the aortic stent, with further intervention to the iliac arteries performed in a “kissing” manner (see Fig. 74-11).

Mesenteric ischemia is somewhat uncommon, given the redundant blood supply to the intestine. If mesenteric ischemia is suspected and revascularization is warranted, a percutaneous procedure may afford less risk to the patient than that from an open surgical procedure. Stenting of the mesenteric vessels is performed usually from the common femoral artery. The long-term restenosis rate is approximately 10% to 15% after several years. Care should be taken in advancing the catheter or other devices through the lesion, because distal embolization can lead to further acute mesenteric ischemia.

Head and Neck Vessels

Whereas some patients have significant stenoses without any signs or symptoms, those patients who are symptomatic face a higher risk of future events.^{37,38} The North American Symptomatic Carotid Endarterectomy Trial

(NASCET) demonstrated that among patients with stroke, the incidence of recurrent ipsilateral stroke at 2 years was 26% for medical therapy as opposed to 9% with carotid endarterectomy (CEA) among patients with a lesion of more than 70% noted by angiography.³⁷ Similarly, the European Carotid Surgery Trial (ECST) demonstrated that in symptomatic patients with all levels of stenosis, patients treated with medical therapy had a 17% rate of stroke compared with 2.8% with surgical revascularization.³⁸ Thus, in symptomatic patients with high-grade stenoses (>70%), CEA appears to be beneficial.

Percutaneous transluminal angioplasty with stenting of the extracranial carotid artery has been performed for more than two decades (see Fig. 74-6B and C).⁷¹ The Global Utilization Report demonstrated the following incidence rates at 30 days: transient ischemic attack, 2.6%; minor stroke, 2.5%; major stroke, 1.4%; and mortality, 0.8%.⁷¹ The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) compared, in a nonrandomized trial, carotid percutaneous transluminal angioplasty and stenting with CEA.⁷² Overall, the combined stroke and mortality rate was similar between groups, at 10% and 9.9% by 30 days. At 3 years, outcomes remained similar.⁷³⁻⁷⁵

There have been two major trials comparing percutaneous techniques with CEA among high-risk⁷⁶ and average-risk patients.⁷⁷ The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study was the first large-scale randomized trial comparing CEA with carotid artery stenting (CAS) with the use of distal protection devices.⁷⁶ SAPPHIRE was designed to test the hypothesis that CAS was not inferior to CEA. High-risk patients were defined as those with clinically significant cardiac disease, severe pulmonary disease, contralateral carotid occlusion or laryngeal nerve palsy, previous radical neck surgery, recurrent stenosis after CEA, or age greater than 80 years. Patients with symptomatic carotid artery disease required a stenosis of at least 50%, and those presenting with asymptomatic carotid disease required stenosis of at least 80%. The surgeons and the interventionists were compelled to agree that the patient was a suitable candidate for either procedure. The primary outcome was a composite of death, stroke, or myocardial infarction within 30 days or death or ipsilateral stroke between 30 days and 1 year. The primary endpoint occurred in 12.2% of patients who underwent CAS and 20.1% of patients who underwent CEA, which demonstrated noninferiority and nearly reached criteria for superiority ($P = 0.053$). Long-term efficacy and safety were evaluated at 3 years with a composite endpoint of death, stroke, or myocardial infarction in 24.6% of patients in the CAS group and 26.9% of patients in the CEA group—a nonsignificant difference.⁷⁸

Several randomized trials have challenged these results. In an attempt to extend the use of CAS to symptomatic patients of average surgical risk, the EVA-3S (Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis) and SPACE (Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy) trials were undertaken.^{77,79}

To be enrolled in EVA-3S, patients had to have had a transient ischemic attack or stroke within the previous 120 days and an ipsilateral carotid stenosis of 60% to 99%.⁷⁷ The primary endpoint was the composite of stroke or death within 30 days after the procedure. The trial was ended prematurely after the enrollment of 527 patients because of safety concerns. Patients who underwent CAS had a 9.6% incidence of the primary endpoint, significantly higher than for patients who underwent CEA (3.9%). A major criticism of the trial was the lack of use of distal protection devices early in the trial, although the incidence of stroke even with the use of protection later in the trial was relatively high (7.9%) and still higher than the incidence among patients undergoing CEA. Furthermore, the use of several distal embolic devices with limited user experience was another significant criticism.

SPACE enrolled 1200 patients with a moderate stroke or transient ischemic attack within the previous 180 days.⁷⁹ The primary outcome—ipsilateral ischemic stroke or death through 30 days—was reached by 6.84% of patients in the CAS group and 6.34% of those in the CEA group, a difference that did not reach statistical significance for noninferiority. A major criticism of this trial was that distal protection devices were not mandated.⁸⁰ Furthermore, operators had limited experience with CAS.

Percutaneous outcomes can be improved with the use of distal protection devices (Fig. 74-12), such as the balloon occlusion GuardWire (PercuSurge, Sunnyvale, Calif.), the filter device AngioGuard (Cordis, Warren, N.J.), or the EPI filter (EPI, Inc., Boston, Mass.). Such distal protection devices have been shown to capture distal emboli that can be liberated with catheter manipulation, balloon inflations, or stenting in the carotid arteries (Fig. 74-13). The major difference is that the balloon occlusion device interrupts flow distally, whereas the

filter devices allow flow to continue but capture the debris.

The more recently completed CREST (Carotid Revascularization Endarterectomy versus Stenting Trial) trial was a large-scale randomized trial comparing traditional CEA with CAS with concurrent use of distal protection devices.⁸¹ The multicenter trial enrolled 2502 patients to assess CAS and CEA for both symptomatic and asymptomatic patients. Symptomatic patients were defined as those that had a transient ischemic attack, amaurosis fugax, or minor nondisabling stroke in the distribution of the study artery within 180 days of randomization, as well as stenosis of the carotid artery greater than 50% by angiography, greater than 70% by ultrasound, or greater than 70% by computed tomographic or magnetic resonance angiography if ultrasound was 50% to 69%. Asymptomatic patients were defined as having carotid stenosis of greater than 60% by angiography, greater than 70% by ultrasound, or greater than 80% by computed tomographic or magnetic resonance angiography if ultrasound was 50% to 69%. Patients with previous disabling stroke or chronic atrial fibrillation were excluded. Results suggested similar short-term and longer-term outcomes between CAS and CEA; however, there was higher stroke risk with CAS and higher myocardial infarction risk with CEA.

Renal Arteries

There are three major clinical trials evaluating the role of renal artery angioplasty or stent implantation among patients with documented renal artery stenosis and difficult-to-control hypertension.

Van Jaarsveld and colleagues⁵³ compared angioplasty alone with medical therapy in the control of hypertension in 106 patients with renal artery stenosis. Inclusion criteria included diastolic blood pressure of 95 mm Hg or higher despite the use of at least two antihypertensive agents, serum creatinine concentration of 1.7 mg/dL or less, and stenosis of 50% or more. More than 40% of patients in the drug therapy group underwent angioplasty in the 12-month follow-up period. Mean blood pressure did not differ significantly between the groups. At 3 months, patients in the angioplasty group were taking significantly fewer antihypertensive drugs, but this difference was not significant at 12 months. More patients in

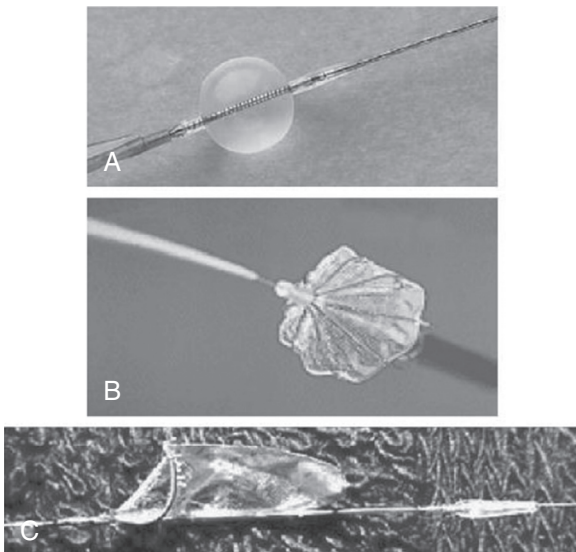


FIGURE 74-12 ■ Distal protection devices. **A**, GuardWire (PercuSurge, Inc., Sunnyvale, Calif.). **B**, AngioGuard (Cordis, Warren, N.J.). **C**, EPI filter (EPI, Inc., Boston, Mass.).

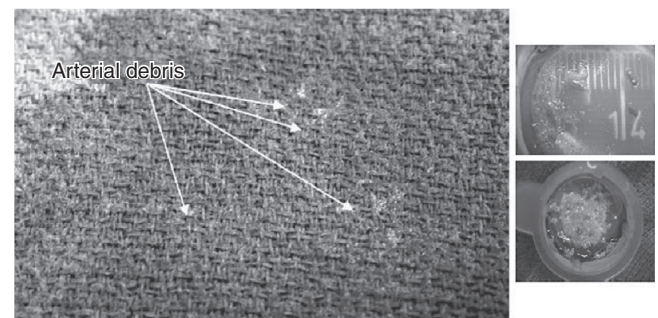


FIGURE 74-13 ■ Distal macroscopic emboli captured with the GuardWire in an ulcerated left internal carotid lesion after predilation with angioplasty before stenting.

the angioplasty group had better blood pressure control, defined as a decrease of 10 mm Hg or more in diastolic blood pressure with no change in medications or a decrease in the number of drugs with no change in diastolic blood pressure. Median serum creatinine concentration was lower in the angioplasty group at 3 months but was not significantly different at 12 months. Major criticisms of the trial include its relatively short follow-up period and the high degree of crossover from the medical therapy group to the angioplasty group, thus limiting the true comparison of the treatment strategies. In addition, although a 50% stenosis was used as an inclusion criterion, pressure gradients across stenotic lesions in the renal vasculature may be more predictive of the pathologic effect of renal artery stenosis than the degree of angiographic stenosis.

A smaller prior study demonstrated a significant reduction in blood pressure compared with medical therapy for bilateral renal artery stenosis but not for unilateral stenosis,⁸² whereas a third study reported a decrease in the number of drugs needed to control hypertension.⁸³

Recent efforts have focused on the development of risk stratification tools to identify patients who would benefit from intervention. A normal resistive index (<80) is associated with a benefit from revascularization, whereas an index greater than 80 is not associated with a benefit from revascularization.⁵⁵ Although assessment of the pressure gradient is critical in selecting appropriate patients for revascularization, the presence of a catheter in a diseased ostium can falsely elevate the gradient. **Figure 74-14** shows a technique to ensure that the pressure gradient is not falsely elevated. As illustrated, when a catheter is placed across a lesion and the pressure difference is measured with the central aortic pressure, the small catheter contributes significantly to the overall gradient, which falsely elevates the true gradient as measured with a pressure wire alone. In this way, more physiologic gradients are measured and may help in revascularizing more appropriate lesions in the renal vasculature.

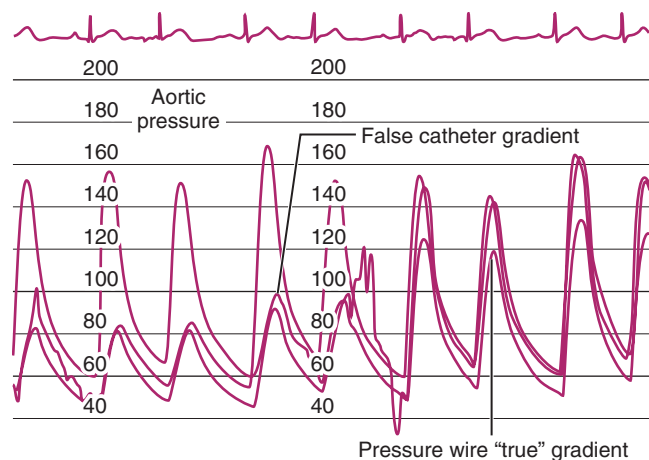


FIGURE 74-14 ■ Pressure measurements across a renal artery lesion with use of a 4 Fr multipurpose catheter and a 0.014-inch PressureWire (St. Jude Medical, Inc., St. Paul, MN) revealing a “false” gradient and a more physiologic gradient after the catheter is removed from the lesion.

The recently completed Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial enrolled 947 patients with atherosclerotic renal artery stenosis and either systolic hypertension while taking two or more antihypertensive drugs or chronic kidney disease. Patients were treated with either medical therapy and renal artery stenting or medical therapy alone. Median follow-up was 43 months. Participants were followed for the occurrence of adverse cardiovascular and renal events with a composite endpoint of death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal replacement therapy. Prior randomized studies, such as the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial⁸⁴ and the Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) trial,⁸⁵ assessed the effect of stenting on kidney function and showed no significant difference, but both have been criticized for enrolling participants without clinically significant stenosis. Furthermore, neither of these studies was specifically designed to detect a benefit with regard to the incidence of clinical events. Nonetheless, the primary conclusion of the CORAL trial suggests that renal artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal artery stenosis and hypertension or chronic kidney disease.

Lower Extremity

Iliac Vessels

Once a lesion is identified on angiography, its functional significance and suitability for intervention can be further assessed with pressure wire measurements. A mean gradient greater than 10 mm Hg at rest or after induction of hyperemia following vasodilation (nitroglycerin or papaverine) is considered significant. The presence of symptoms, abnormal results of noninvasive studies, a significant stenosis on angiography, and a gradient of this magnitude indicate that the lesion is likely to merit revascularization.

Various revascularization techniques are available. Intravascular stenting has been associated with improved long-term patency compared with conventional balloon angioplasty,^{8,86-90} and clinical outcomes after stent placement appear to be similar to long-term outcomes after vascular surgery.^{32,91,92} Results from the STAG (Stents versus Angioplasty for the Treatment of Iliac Artery Occlusions) trial⁹³ was inconclusive regarding a difference in 1-year patency, although a reduction in perioperative complications with primary stenting versus angioplasty was observed. There are multiple stents currently approved for this location, including the Palmaz stent, Boston Scientific Express stent, and SMART stent. Recent studies continue to explore the efficacy of primary stenting for aortoiliac disease.

The advent and evolution of endovascular techniques has led to the use of an endovascular approach to

revascularization in this region when necessary, as with extensive or complex aortoiliac occlusive disease. The multicenter Covered Versus Balloon Expandable Stent Trial⁹⁴ recently suggested that covered stents can provide increased freedom from stenosis compared with bare metal stents at 12 and 18 months; this remains an area that bears further attention, and it will be addressed in the proposed Dutch Iliac Stent (DISCOVER) trial: covered balloon-expandable versus uncovered balloon-expandable stents in the common iliac artery.⁹⁵

Infrainguinal Vessels

Percutaneous interventions to the infrainguinal vessels are acutely successful in most patients, but balloon angioplasty alone remains associated with poor long-term patency.^{8,96-98} Stenting of the superficial femoral artery was not associated with improved patency in two small trials,^{99,100} but the introduction of nitinol stents has led to a significant reduction in restenosis and a significant improvement in walking distance compared with balloon angioplasty with provisional stent implantation in patients with infrainguinal disease.^{101,102} Schillinger and coworkers¹⁰¹ randomized 104 patients with severe claudication or chronic limb ischemia (Rutherford stages 3 to 5), a stenosis of 50% or more, a target lesion length of 3 cm or more, and at least one patent tibioperoneal runoff vessel to balloon angioplasty with provisional stent implantation for residual stenosis of 30% or more or the presence of flow-limiting dissection versus routine nitinol stent implantation. Average lesion length was approximately 13 cm, and 32% of patients in the angioplasty group underwent secondary stent implantation after failed angioplasty. Restenosis, defined as a stenosis of more than 50% on duplex ultrasonography, occurred in 37% of patients in the stent group and 63% of patients in the angioplasty group at 1 year. In addition, patients in the routine stent group were able to walk significantly farther on a treadmill at 6 and 12 months, and the ankle-brachial index was significantly better in the routine stent group at 12 months. The difference in restenosis rate remained significant at 2 years, although reintervention rates and clinical benefit were not significantly different (37.0% among patients undergoing balloon angioplasty and 53.8% among patients who underwent stent implantation; $P = 0.14$).¹⁰²

These results were not reproduced in a larger trial of patients with somewhat shorter lesions (1-10 cm to be enrolled; mean lesion length, 4.5 cm).¹⁰³ Restenosis rates at 12 months were 38.6% in the angioplasty group and 31.7% in the routine stent group, a nonsignificant difference.

In general, lesions in the superficial femoral artery are best treated percutaneously if the lesion is focal and less than 10 cm.¹⁰⁴⁻¹⁰⁶ As the lesion length increases, there is an increase in restenosis after angioplasty alone and, thus, stenting has become the default therapy for these lesion lengths.^{97,104-107} Of particular interest is the use of covered stents, such as the Viabahn stent (W.L. Gore & Associates, Newark, DE). This stent, approved by the U.S. Food and Drug Administration, has a technical success rate greater than 90%. Long-term efficacy was

demonstrated by Saxon and coworkers,¹⁰⁸ who randomized 200 patients with lesions of 13 cm or shorter to Viabahn stent implantation or angioplasty alone. At 12 months, patency rates were 65% in the stent group and 40% in the angioplasty group. Assisted primary vessel patency at 4 years has been reported to be 82%.¹⁰⁹ In a 3-year follow-up to the RESILIENT (Randomized Study Comparing the Edwards Self-Expanding LifeStent versus Angioplasty-alone In LESions INvolving The SFA and/or Proximal Popliteal Artery) trial,^{110,111} the authors sought to evaluate late outcomes of primary nitinol stenting for the treatment of femoropopliteal lesions up to 15 cm long. Nitinol stents were found to have superior short-term patency when compared to balloon angioplasty with 12-month freedom from target lesion revascularization at 87% for the stent group compared with 45% for the angioplasty group ($P < 0.0001$) and no difference in survival at 3 years (90% vs. 92%; $P = 0.71$) or major adverse events (75% vs. 75%; $P = 0.98$). Though Duplex ultrasound was not mandated after the first year of the study, freedom from target lesion revascularization at 3 years was significantly better in the stent group (76% vs. 42%; $P < 0.0001$), as was clinical success (63% vs. 18%; $P < 0.0001$). A recent study exploring the efficacy of primary stenting compared with percutaneous transluminal angiography with provisional stenting in popliteal artery lesions suggested equivalent 1-year patency.¹¹¹

In addition to traditional angioplasty and stent implantation, a number of alternative devices have been used to treat infrainguinal vessels, including atherectomy devices (both directional and rotational), atheroablative devices (e.g., laser), and specialized balloon catheters such as cryoplasty and drug-coated balloons.

The atheroablative technologies include the directional atherectomy catheters. This type of intervention, which was initially designed for use in the coronary circulation, has found a resurgence in the peripheral vasculature. Recently, the SilverHawk device from FoxHollow Technologies (Redwood City, Calif.) has been used in a nonrandomized registry of 84 patients.¹¹² De novo lesions had an 84% patency rate at 12 months and 73% patency at 18 months. Target vessel revascularization was required in 16% of lesions at 12 months.

Excimer laser technology can be used in many different anatomic locations and scenarios, including in-stent restenosis, and it can be used for patients with complex lesions as an adjunctive agent before stent implantation.^{113,114} Cryoplasty is another possible option that has had acute and short-term success in registry studies,¹¹⁵ although more rigorous evaluation with randomized clinical trials in longer lesions remains to be performed.

In superficial femoral artery lesions of moderate length, the use of a paclitaxel-coated balloon can also reduce the incidence of target vessel revascularization.^{116,117} With percutaneous intervention of the infrapopliteal arteries, patency is more difficult to maintain, given the small diameter of the vessels and their dynamic properties at the level of the lower extremity. Research continues with the goal of further elucidating optimal endovascular treatment in the infrainguinal vasculature based on lesion type and location, patient characteristics, and advances in endovascular technology.

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INJURY TO THE HEART AND GREAT VESSELS

Peter I. Tsai • Matthew J. Wall, Jr. • Kenneth L. Mattox

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The heart is a vital organ, with its arch vessels encased in the chest cavity and protected by the manubrium, sternum, and rib cage. Injury to this organ can come from blunt trauma, which includes blunt cardiac injury, more commonly referred to as cardiac contusion, coronary artery injury, atrial/ventricular/valvular rupture, and aortic or arch vessel rupture. Injury can also result from penetrating trauma, with the right ventricle being most commonly injured, and ventricular septal defect being the most common intracardiac injury.

BLUNT CARDIAC INJURY

Historical Perspective

The first recorded cardiac chamber rupture and myocardial contusion were reported after autopsy findings as early as 1679 by Borch (as reported by Osborn¹) and in

1764 by Akenside,² respectively. In 1868, 76 cases reported by Fischer³ described 7 myocardial contusions and 69 traumatic ruptures. Experimental animal work and clinical autopsies by Bright and Beck⁴ have demonstrated that substantially severe forces are responsible for an entire range of cardiac trauma, whereas enormous force is required to rupture the heart. It is also observed that recovery is the general rule, and rupture is the exception. In 1958, a hallmark study by Parmley and colleagues⁵ of a large series of autopsy cases in the Armed Forces Institute of Pathology demonstrated that blunt traumatic heart injury had a 0.1% incidence, with the majority being isolated chamber ruptures (right then left ventricle, followed by right and left atria in decreasing order of occurrence) and some associated with combined aortic ruptures. Myocardial contusion or blunt cardiac injury, although rare, is the most common injury, whereas chamber or aortic rupture is usually fatal.

Mechanism, Pathophysiology, and Incidence

Mechanisms responsible for blunt cardiac injuries can occur from any deliverance of kinetic energy such as blast effect; direct crushing forces through the sternum or rib cage, which can also cause compression of heart against the vertebral column; and traction and torsion from deceleration forces owing to high-speed vehicular collisions and falls from great heights. A sudden rise of blood pressure from compression of the chest can injure the cardiac valves, cause a tear in the ventricular wall or septum, or result in chamber rupture.

These forces result in a continuous spectrum of cardiac injury, ranging from simple contusion to fatal cardiac chamber rupture, including *comotio cordis*, described as sudden cardiac arrest resultant from a sternal blow.⁶ Myocardial contusion, characterized by patchy areas of muscle necrosis and hemorrhagic infiltrate, can also impair ventricular contraction and lead to arrhythmia.

The true incidence of blunt cardiac injury remains expectedly difficult to measure, because the autopsy cases of fatal cardiac chamber rupture do not account for the majority of the blunt trauma cases, which go on to recover.

Clinical Presentation

The rupture of a cardiac chamber, coronary artery, or major intrapericardial vein or artery is usually fatal because of acute tamponade. The few patients who survive do so only because of tears in a cavity under low pressure.⁷⁻⁹ Myocardial contusion induces cardiac failure and arrhythmia that improve with time.¹⁰ Injury to a coronary artery can lead to immediate or delayed myocardial infarction with spasm or dissection of arterial wall.¹¹ Valvular tears resulting in aortic or mitral insufficiency can develop into cardiac failure within a few weeks, whereas tricuspid insufficiency can appear only after several years.¹²⁻¹⁴

Diagnosis

Paramount to an accurate diagnosis is the awareness from the history and physical findings of pain and tenderness over the anterior chest wall (which may be indistinguishable from a classic myocardial infarction), evidence of contusion, ecchymosis, anterior rib fractures, or flail chest.¹⁵ Many patients, however, do not exhibit characteristic symptoms.^{10,16} The presence of complex arrhythmias, subtle findings of a precordial thrill, or presence of a murmur may be all that is present at exam. Cardiac injury can also be reflected with hemodynamic instability marked by refractory hypotension and elevated venous pressure (external jugular vein distention may be absent in cases of severe blood loss) in the presence of cardiogenic shock.

Electrocardiography

Serial 12-lead electrocardiography has traditionally been used to screen patients to detect conduction disturbances resulting from blunt injury; however, there is no

pathognomonic finding that can reliably establish the diagnosis of blunt cardiac injury.¹⁵ Abnormalities range from sinus tachycardia, the most commonly encountered arrhythmia, to supraventricular arrhythmias, such as atrial flutter and atrial fibrillation, ventricular tachycardia, premature ventricular contractions, ventricular fibrillation, right bundle branch block with first-degree heart block or hemiblock, third degree heart block, and T-wave or ST-segment abnormalities.¹⁵ The presence of a normal electrocardiography in a patient who is hemodynamically stable warrants no further investigation.

Cardiac Enzymes and Troponins

The measurement of creatine phosphokinase with myocardial band has been shown to be unreliable,^{10,16-18} except for more specific muscle proteins including troponin (cTnT and cTnI).^{19,20} Combined abnormalities in electrocardiography and serial cTnI levels have been promising in showing increased sensitivity (62% if both positive) and specificity (100% if both negative),²¹ although another study has shown otherwise.²²

Admission electrocardiography and serial troponin levels should be obtained in patients suspected of blunt cardiac injury and followed by transthoracic echocardiography if clinically significant arrhythmias arise.

Two-Dimensional Transthoracic and Transesophageal Echocardiography

Bedside echocardiography has become an important diagnostic tool in trauma patients, detecting abnormalities in the heart (ventricular dyskinesia and valvular dysfunction), thoracic aorta, and presence of pericardial fluid.^{15,23-25} Patients are selected for this modality of examination after demonstration of abnormal electrocardiography and cardiac troponins.

Transthoracic echocardiography cannot be performed in 25% to 30% patients limited by chest wall edema, fractured ribs, and flail chest, whereas transesophageal echocardiography—a more useful adjunct in elucidating periaortic hematoma and other cardiac injuries—is limited by expertise and frequent requirement of intubation, and it cannot be performed in patients with facial or cervical trauma.^{23,24}

Radionuclide Scans

Technetium-99m pyrophosphate, thallium 201, single photon emission computed tomography (SPECT), and multiple gated acquisition scans (MUGA), all use the concept of radioactive substances binding to injured or infarcted sites in the myocardium. However, all have been abandoned secondary to low sensitivity and specificity in the detection of blunt cardiac injury.¹⁵

Spectrum of Blunt Cardiac Injury: Assessment and Management

Pericardial Injury

Blunt rupture of the pericardium can occur from a direct forceful impact to transmitted force from sudden

increased intra-abdominal pressure. Left pericardial tears parallel to the phrenic nerve are most common, followed by diaphragmatic, and right and mediastinal tears.⁷ The heart might eviscerate into the abdominal cavity or herniate through the pericardial sac with torsion of the great vessels. Patients who are stable are worked up and diagnosed with chest radiography, sonography, or computed tomography. Patients who are hemodynamically compromised clinically are treated with immediate surgical intervention (ER thoracotomy), at which time diagnosis is made and the heart is placed back into the pericardial sac, with closure of pericardium, with or without a Gore-Tex patch, to achieve a tension-free repair.

Valvular, Papillary Muscle, Chordae Tendineae, and Septal Injury

Rarely, valvular injuries occur, with the aortic valve being most commonly affected, followed by the mitral valve. Rapid displacement of blood secondary to crushing or compressive forces applied to the thoracic cage during ventricular diastole can lacerate cardiac valve leaflets (most common in the left coronary cusp, followed by the noncoronary cusp), papillary muscles, or chordae tendineae leading to valvular insufficiency.⁵ The classic signs of valvular insufficiency (new murmur, thrill or left ventricular dysfunction with cardiogenic shock, and associated pulmonary edema) may not be immediately recognized, secondary to other concomitant life-threatening injuries. In patients in stable condition, such findings should prompt further diagnostic studies, depending on the clinical status of the patient and prompt repair or replacement as necessary. Septal rupture is also uncommon, and prompt repair is necessary if the patient is symptomatic from significant left-to-right shunt resulting in pulmonary over circulation and right heart dysfunction.

Blunt Coronary Artery Injury

Injuries of the coronary arteries are extremely rare. The proximal right coronary and, more commonly, the left anterior descending artery (because of the location relative to the sternum) become injured with direct compression of sternum to coronary vessel or stretching of the vessel secondary to cardiac torsion, leading to thrombosis or intimal disruption. The result is no different than an acute myocardial infarction. Long-term sequelae of these injuries can also lead to ventricular aneurysm and eventual rupture, ventricular failure, production of emboli, or malignant arrhythmia.⁵

Cardiac Chamber Rupture

Cardiac chamber rupture is relatively uncommon, and only a small percentage of patients survive to reach the hospital.^{7,26,27} Several mechanisms for blunt cardiac rupture have been postulated,⁷ including direct precordial impacts, compression of heart between sternum and vertebral body, transmission of pressure via abdomen into the venous return rupturing particularly the atria, acceleration/deceleration injuries leading to tears of the heart at the attachment sites to the great vessels, blast

effects, and concussive blows thought to be fatal secondary to the production of malignant arrhythmias. Patients usually have persistent hypotension with evidence of pericardial tamponade. Diagnosis of widened mediastinum on chest radiograph or evidence of pericardial fluid from sonographic examination requires prompt intervention in the form of a subxyphoid window. For patients with cardiopulmonary arrest, emergency department (ED) thoracotomy may be the only chance, although the survival rate is dismal.

Myocardial Contusion

The terms *myocardial contusion* and *concussion* should be eliminated in favor of terminology that more precisely describes the injury.²⁸

- Blunt chest injury with electrocardiographic abnormality
- Blunt chest injury with free wall cardiac rupture
- Blunt chest injury with cardiac valve tear
- Blunt chest injury with septal defect
- Blunt chest injury with abnormal cardiac enzymes

We recommend that asymptomatic patients with anterior chest wall injuries not be admitted to the surgical intensive care unit for continuous electrocardiographic monitoring and serial determination of CPK-MB levels or be subjected to further cardiac imaging.

Conclusion

When blunt cardiac injury is suggested secondary to a good history and physical examination, further diagnostic testing with electrocardiographic monitoring and serial enzyme measurements should follow. Sonographic examination can elucidate the presence of pericardial fluid or cardiac or valvular dysfunction that might require prompt surgical intervention.

PENETRATING CARDIAC INJURY

Historical Perspective

In the past, cardiac injury has always resulted in death, as described in the death of Sarpedon from an impalement of a lance to the heart in *The Iliad*.²⁹

In 1761, Morgagni³⁰ described the compressive effects of blood on the heart. Larrey^{31,32} was credited for pioneering the technique of pericardial window. Duval³³ first described the median sternotomy incision, whereas Spangaro³⁴ first described the left anterolateral thoracotomy incision in 1906. In 1926, Beck described the Triad physiology of cardiac tamponade, and later described the repair technique of placing mattress sutures under the coronary vessels to spare ligation.^{35,36}

In 1946, Harken³⁷ described the removal of foreign bodies adjacent to the heart and great vessels. Beal³⁸⁻⁴¹ first described ED thoracotomy and, along with Cooley,⁴⁰ reported the potential benefits for cardiopulmonary bypass in the management of selected intracardiac injuries. Mattox⁴²⁻⁴⁴ further refined and championed ED thoracotomy and cardiorrhaphy, including emergency cardiopulmonary bypass by surgeons.

Incidence

Penetrating cardiac injuries are uncommon and are usually seen only in busy urban trauma centers. The true incidence is difficult to ascertain, as the numbers fluctuate with influence of violent crimes involving firearms or penetrating objects. In 1989, Mattox⁴⁵ reported on a 30-year experience at Ben Taub Hospital in Houston, Texas, of 539 cardiac injuries. Asensio^{46,47} reported a total of 165 cardiac injuries within a 3-year period at LAC/USC Medical Center in Los Angeles, California. Other major trauma centers reported significantly fewer injuries,⁴⁸ which again indicates the rarity.

Etiology

In the civilian arena, the majority of penetrating cardiac injuries results from gunshot wounds and stab wounds, with shotgun and impalement injuries accounting for a small percentage.

In the military arena, most soldiers do not survive the high-velocity automatic rifles encountered in battle. The majority of these patients have sustained injuries from fragments of grenades or shrapnel. Dominguez⁴⁹ described such injuries over a 6-month period in a small series in Baghdad, Iraq.

Clinical Presentation

Most cardiac injuries related to stab wounds are logically based on the trajectory of the insult. This is not so with gunshot wounds, which can injure the heart from precordial and extra-precordial entrance sites.⁵⁰ Hirshberg⁵¹ described 26% associated cardiac injuries in 82 patients presenting with combined thoracoabdominal injuries, whereas Asensio and colleagues⁵² reported 44% incidence of associated penetrating cardiac injuries in his series of 73 patients who sustained thoracoabdominal injuries.

Frank penetrating injuries to the cardiac chambers can lead to acute cardiac tamponade and death, or, similarly, hemorrhage through the lacerated pericardium into the hemithorax, with death as well. Patients that survive such injuries with intact pericardium to prevent fatal exsanguinating hemorrhage, allowing them to reach the trauma center alive, have varying degrees of hemodynamic instability^{46,47} secondary to pericardial tamponade. Interestingly, the Beck triad or Kussmaul sign is present in only 10% of patients⁵⁰ with pericardial tamponade.

Moreno and colleagues,⁵³ in a retrospective study of 100 patients with penetrating cardiac injuries, reported higher survival (77% vs. 11%) in patients with pericardial tamponade, and that right-side chamber injuries confer a higher survival of 79% versus 28% for left-side chamber injuries. Clarke and colleagues,⁵⁴ in a prospective review of 1862 patients over a 3-year period, demonstrated that penetrating thoracic trauma has a high mortality rate of 30% for stab wounds and 52% for gunshot wounds.

Diagnosis

Penetrating injuries, whether by stab wounds or gunshot wounds, should be highly suggestive of potential cardiac

injuries. Hemodynamically stable patients still require routine chest radiography, and a widened mediastinum should elicit caution for further workup. Sonography can determine the presence of pericardial fluid, which is supported by a physical examination that might detect the Beck triad or Kussmaul sign. Evidence of direct trajectory, where the heart is in the path, should require preparation for emergent bedside anterolateral thoracotomy should the patient acutely decompensate clinically.

Subxyphoid Pericardial Window

The reliability of this technique has been proved valuable in ascertaining penetrating cardiac injury.^{55,56} In addition, a transdiaphragmatic pericardial window⁵⁷ has been effectively described in cases of patients sustaining combined thoracoabdominal injuries and cardiac injury needing to be investigated. This technique is also valuable when two-dimensional echocardiography (applied in focused abdominal sonography in trauma) is not available.

Two-Dimensional Echocardiography

Echocardiography has become the gold standard in diagnosis and evaluation of patients with penetrating thoracic injury. It is fast, painless, reproducible, and easily repeated.^{50,57,58} The procedure has 96% accuracy and 97% specificity.⁵⁹ Furthermore, it can be used to delineate intramyocardial foreign bodies versus missiles located within the cardiac chamber.^{60,61}

Management

In patients with penetrating cardiac injury, the majority would have a fatal outcome, no matter the prehospital intervention. In the select group that is still stable enough for transport to the trauma center, time is of utmost importance. This prehospital course is marked by certain surrogate parameters for either improved or dire prognosis.

Under no circumstances should emergency medical personnel delay transport by inserting intravenous lines; this should occur during transport. Concomitant notification of the trauma center to activate the trauma team is also of paramount importance.⁵⁰ Gervin and Fisher⁶² demonstrated a survival advantage if transport to the trauma center was within 9 minutes, whereas all patients with transport time greater than 25 minutes died. Mattox and Feliciano⁶³ found no survivors in 100 patients who received external cardiac compression for more than 3 minutes in the prehospital period. Lorenz and colleagues⁶⁴ noted better survival if patients had systolic blood pressures of 60 mm Hg or greater in the field and upon arrival in the ED. Durham and colleagues⁶⁵ linked prehospital intubation to better tolerance and successful prolongation with prehospital cardiopulmonary resuscitation of less than 5 minutes.

Upon arrival to the ED, the trauma team should be ready to perform advanced trauma life support protocol.⁶⁶ Patients are usually hemodynamically stable at presentation, allowing for expedited yet detailed workup. Another group will be unstable but respond to fluid resuscitation, allowing time to proceed to the operating

room for life-saving surgery. The last group will go into cardiopulmonary arrest requiring ED thoracotomy.^{46,47,50,67} ED thoracotomy, if performed under strict indications for cardiac injuries, has been shown to improve survival rate as much as 31%.⁶⁸ However, patients sustaining multiple cardiac or great vessel gunshot wounds were nearly unsalvageable with ED thoracotomy.⁶⁹

Techniques for Cardiac Injury Repair

Incisions

Median sternotomy, as well as the anterolateral thoracotomy, are the two main incisions of choice. The former is acceptable in patients who are treated for penetrating low anterior chest injuries and who arrive in some degree of hemodynamic instability, but are stable enough for sonographic and chest radiography workup for occult cardiac injuries. The latter is the incision of choice in the management of patients who arrive in extremis. This incision is also used in the ED for emergent resuscitative purposes.^{46,47,50,67,70} The anterolateral thoracotomy can also be extended into the right chest to provide for optimal exposure of the mediastinum and both hemithoracic cavities as necessary.

Adjunct Maneuvers

Exposure of the heart to repair posterior injuries can be accomplished a number of ways. The first step is to place the patient in acute Trendelenburg position, which will optimize the following described strategies for further exposure of the posterior side of the heart. Pledgeted sutures can be placed on the apex of the heart with the sutures cut long, to retract the apex slowly and superiorly to gain access to the posterior injury. A Satinsky clamp can also be used on the right ventricular angle to achieve the same exposure.⁷¹ Sequential placement of folded wet towels behind the heart will gradually lift the heart without causing it to go into arrhythmia and will provide exposure to the posterior injury as well. Stabilizing devices can also be used to provide exposure and steady placement of repair stitches on laceration injuries to the heart without causing further tearing.

Total inflow occlusion of the heart can be performed by placing clamps on the intrapericardial location to isolate and repair injuries at the level of atriocaval junction. The heart will frequently fibrillate, requiring paddle defibrillation and pharmacologic intervention.^{50,70}

Repair of Atrial Injuries

Right atrial injuries can usually be controlled with a Satinsky clamp followed by repair using 4-0 nonpledgeted polypropylene monofilament sutures. The atrium is thin walled and easily torn; therefore, caution and gentle traction aid in repair without further tearing.

Repair of Ventricular Injuries

Blast injuries resulting from gunshots, unlike a stab incision to the ventricle, can make the epicardium and

myocardium more friable and unforgiving with standard suture repair. Coupled with high-pressured bleeding, particularly from a left ventricle injury and tachycardia, the repair can be challenging; 2-0, 3-0, or 4-0 polypropylene with pledgeted sutures should be used and placed in a horizontal mattress fashion. Commercial brand fibrin sealant can be used to reinforce the suture line if necessary.

Coronary Artery Injuries

Direct coronary artery injury can be challenging to repair. Proximal injuries require bypass, especially if there is gross evidence of cardiac ventricular dysfunction. Distal coronary artery injuries, particularly the distal third of the vessel being injured or lacerated, might not require bypass if the heart remains without ventricular dysfunction and tolerates ligation.

Pericoronary artery injuries to the heart with significant bleeding can be managed with horizontal mattress sutures underneath the coronary vessel for safe repair, taking care not to narrow or occlude the coronary artery in the process.^{50,67,72}

Complex and Combined Injuries

Complex and combined injuries can be defined as penetrating cardiac injury in addition to associated thoracic, thoracic-vascular, neck, abdominal, abdominal-vascular, or peripheral vascular injuries. Priority should be given to treatment of injury with the greatest risk of blood loss or being life-threatening.^{50,67,73-75}

Wall and colleagues⁷⁶ described complex cardiac injuries as those beyond lacerations of the myocardium. These injuries often include concomitant coronary artery injuries, cardiac valvular injuries, intracardiac fistulas, and ventricular false aneurysms and coronary sinus injuries. These injuries can be addressed by the cardiac surgeon once the other life-threatening injuries are temporized and addressed.

Conclusion

Penetrating cardiac injury should prompt a comprehensive workup, with a sonographic examination being useful to diagnose the presence of pericardial fluid. Workup can be more extensive in a hemodynamically stable patient with computed tomography (CT) studies. Anterolateral thoracotomy can be used in the emergent setting to cross-clamp the descending aorta and to perform necessary cardiac repairs. Median sternotomy can be used in a patient in stable condition with identified cardiac injuries repaired.

THORACIC AORTA AND ARCH VESSEL INJURIES

Mechanisms and Types of Injury

Penetrating trauma to the thoracic aorta or its arch vessels can lead to immediate exsanguination or a pattern

of injury, much like blunt trauma to the vessels, which can include pseudoaneurysm, partial transection with resultant intimal flap, intimal dissection, thrombosis, and propagation.

Blunt trauma is more interesting from the standpoint that different forces can create injury to the thoracic aorta and its arch vessels. Traction and deceleration forces are classic mechanisms of injury to the thoracic vessels. Vertical deceleration can acutely strain the ascending aorta and innominate artery, as the heart is being displaced caudally and into the left pleural cavity by its natural lay in the mediastinum.^{77,78} Horizontal deceleration acutely strains the aortic isthmus,⁷⁷ whereas sudden extension of the neck or traction at the shoulder will stretch and strain the arch vessels to produce a spectrum of injuries to the vessels including intimal tear, disruption of the media, and complete rupture of the arterial wall.^{77,78} These injuries may again lead to intimal dissection, thrombosis, and propagation or development of pseudoaneurysm.

Natural History

Vessel injuries that involve mural hematoma or limited intimal flap have a benign course and frequently resolve with time.⁷⁹ However, pseudoaneurysms, including small ones, have an insidious course; they tend to expand, compress surrounding structures, and fistulize to surrounding organs, with eventual rupture.^{78,79}

Arch vessel injuries from penetrating or blunt trauma with partial transection bleed and are contained by the local tissues.^{80,81} Avulsions of the arch vessel at the take-off from the arch can bleed into the pericardial or pleural cavity. Acute occlusion of the subclavian artery rarely leads to limb ischemia because of the rich collateral network; however, acute occlusion of the common carotid artery can result in brain ischemia.^{82,83}

Free rupture of the thoracic aorta by penetrating or blunt trauma leads to immediate death in 75% to 90% of cases. Of the few who survive with containment of pseudoaneurysm by the parietal pleura, statistically 8% to 13% will rupture within the first hour of admission, 30% will rupture within 24 hours, and 50% will rupture within 1 week.^{84,85}

Diagnosis

A good history and physical examination will capture many of the injuries of the thoracic vessels. A high-speed head-on collision, fall from great height, ejection from a vehicle, death of another person in the same motor vehicle crash, presence of a seatbelt sign—all should alert one to the possibility of deceleration injury to the thoracic vessels. Penetrating trauma to the base of the neck and chest cavity will lead to the suggestion of injury to the vessels from its trajectory. Gunshot wounds should lead one to suspect any type of injury, which is possible from the ricochet of the bullet on entrance into the chest cavity.

Clinical presentation of arch vessel injury can include cervical or supraclavicular hematoma, bruit, or diminished peripheral pulse.⁸⁰ An aortic isthmus injury can produce decreased blood pressure in the left arm,

although this occurs in only 5% of patients.^{86,87} Brachial plexus injury is usually associated with subclavian artery injury as well.^{81,82} Coma or hemistroke can occur with common carotid injury.^{80,82,84}

Radiographic studies should begin with chest radiography, which in the presence of an injury would typically show a widened mediastinum, blunting of the aortic knob, and enlargement of paratracheal stripe.⁸⁶ Helical CT can detect arterial lesions and has excellent accuracy.⁸⁸ The gold standard is aortic angiography, which provides imaging of the entire thoracic aorta and arch vessels, but this takes time and requires a patient in relatively stable condition.⁸⁷ Transesophageal echocardiography can evaluate the aortic isthmus effectively, but it is less effective in evaluating the distal ascending aorta or arch vessels secondary to interference of the respiratory tract.⁸⁹ There has been a shift in widespread use of CT angiography, and almost complete elimination of aortography and transesophageal echocardiography over the last 10 years.⁹⁰

Assessment and Management

With a normal chest radiograph, the risk of thoracic aortic injury is low; however, if given the history of great fall or deceleration accident, a CT scan would be appropriate. Normal CT results almost certainly rule out injury to the aorta and obviate the need for further investigation. If the mediastinum is enlarged, then the diagnosis of thoracic vessel injury should be determined by angiography because both CT and transesophageal echocardiography can miss certain vascular injuries, especially the arch vessels.⁸⁹

Medical treatment especially aimed at treatment of suspected or identified aortic tear should address prevention of hypertension and pain. Short-acting β -blockers reduce blood pressure, the force of arterial upstroke, and heart rate, with good effect on reducing stress (anti-impulse) on the aortic wall.^{84,91}

Surgery is indicated for repair of most diagnosed thoracic artery lesions.^{87,92} Arch vessels can usually be repaired without circulatory support or arterial shunting. Repair of the aortic isthmus can be done with or without partial circulatory support.⁸⁵ Repair of the ascending aorta and arch usually necessitates full circulatory support with extracorporeal circulation, and possibly with hypothermic circulatory arrest.⁹³

Ascending Aorta and Arch Vessel Injuries

Injuries to ascending aorta or to arch vessels are best repaired by the cardiac surgeon for definitive repair. Isolated ascending aortic injury can be repaired with cardiopulmonary bypass and graft interposition to replace the area of injury. Care should be taken to address intimal dissection—the dissection plane should be obliterated with a combination of felt pledgets and biogluue.

Arch injury can also require circulatory arrest with isolated right subclavian artery (advantage of antegrade cerebral perfusion) or femoral artery cannulation with femoral-atrial venous cannulation bypass to repair the injury with interposition graft successfully.

Descending Thoracic Aortic Injuries

The approach is optimized with a left thoracotomy incision. Identification of the left subclavian artery, left recurrent laryngeal nerve, and left common carotid artery is prudent to allow for safe proximal aortic control, as the aortic clamp is placed between the left common carotid artery and left subclavian artery, avoiding injury to the recurrent laryngeal nerve. Distal aortic control requires a clamp to be placed distal to the area of injury.

Left heart bypass or clamp-and-sew technique can be used to repair the injury, usually with an interposition graft versus primary repair of the injured descending aorta; this carries a significant risk of spinal cord ischemic injury as well.

Recent improvements in technology have allowed the placement of an aortic endograft stent across the injury, which significantly decreases the risk of spinal cord ischemia.⁹⁴ However, long-term follow-up needs to be performed and outcome assessed in the otherwise young, healthy population with descending aortic injury that would have undergone an open repair.

Innominate and Arch Vessel Injuries

The approach to innominate or arch vessel injury is via median sternotomy with or without cardiopulmonary bypass. Debranching repair can be performed with partial aortic cross-clamp to isolate the base of the arch vessel, which can then be divided, with the base oversewn. The distal arch vessel can then be sewn to an interposition graft that is reattached to the ascending aorta with partial aortic cross-clamp as well.

Conclusion

Blunt or penetrating injuries to the chest may involve the thoracic aorta and great vessels. Successful repair is determined by complete proximal and distal control of the injury with or without cardiopulmonary bypass. Interposition graft is usually used, although primary repair is equally optimal if the tissue reapproximates well. Intimal dissection should be checked during repair and then treated. Aortic endograft stent repair is gaining notice, and it should be part of the armamentarium of the surgeon.

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PART F

SURGICAL MANAGEMENT OF VALVULAR HEART DISEASE

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VALVE REPLACEMENT THERAPY: HISTORY, VALVE TYPES, AND OPTIONS

Afshin Ehsan • Gus J. Vlahakes

CHAPTER OUTLINE

THE IDEAL VALVE

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CHOICE OF VALVE REPLACEMENT

THE IDEAL VALVE

Many acceptable substitutes exist today for the replacement of diseased human heart valves. The ideal valvular prosthesis as described by Harken¹ remains the gold standard of cardiac surgery. According to Harken this valve would be durable, with a longevity approaching that of a native valve, thrombogenicity would not be a factor, and therefore no need for supplemental anticoagulation would exist. In addition, this valve would have no inherent gradient, thus allowing unimpeded outflow, and could be implanted with ease while being readily available. Lastly, the valve could grow commensurate with that of the recipient. While the technology of valve prostheses has evolved considerably over the past six decades, this lofty goal has yet to be met.

HISTORY

The first human heart valve operation was a digital valvotomy of a stenotic aortic valve performed by Tuffier in 1914. Cutler, Souttar, Brock, Swan, and Harken refined valvotomies and commissurotomies in the ensuing decades; however, the limited success of these techniques brought to light the need for an effective means of replacing the entire valve. The first step in the evolution of this technology came in 1950 when Hufnagel developed a ball valve that he placed in the descending thoracic aorta of a patient with severe aortic insufficiency.² In 1956, Murray implanted an aortic homograft in the descending thoracic aorta of a patient with severe aortic insufficiency.³ The

introduction of cardiopulmonary bypass opened the era of implanting valve prostheses in their native positions. In 1960, Braunwald and Harken successfully replaced the mitral and aortic valves using valves made of polyurethane.⁴ In 1961 Albert Starr, a surgeon, and Lowell Edwards, an engineer, developed a caged ball valve that resulted in acceptable long-term survival.⁵ Despite their success, the high profile of caged ball valves made implantation in patients with small ventricles and small aortic roots difficult. These valves also had inherently high gradients along with less favorable thromboembolic profiles, making them less desirable as new prostheses were introduced. Edwards Lifesciences (Irvine, CA) discontinued production of the Starr-Edwards valve in 2007.

The next generation of valve prosthesis used a tilting disc that would pivot into an open and close position according to the flow of blood across the valve. Wada was the first to introduce these tilting disc valves in 1966.⁶ The Lillehei-Kaster valve, introduced in 1967, was a hingeless valve with a freely rotating pivoting disc retained by struts. Björk, working with Shiley Laboratories, developed a similar version of a hingeless pivoting disc valve in 1969. Although the hemodynamic profile was improved relative to the caged ball valves, these early pivoting valves were subject to occasional thrombosis. The 60-degree convexoconcave Björk-Shiley valve was prone to catastrophic structural failure secondary to fracture of its welded struts, allowing escape of the occluder disc.⁷

Seeking to improve on the durability and thrombogenicity problems of these early pivoting disc valves, Hall, Woien, Kaster, and the Medtronic Corporation (Minneapolis, MN) introduced the Medtronic-Hall valve in

1977. The valve housing was constructed from one piece of titanium alloy with no introduced welds or bends. The round central disc was made from tungsten-impregnated graphite with a pyrolytic carbon coating, and it had a central hole that allowed the disc to be retained by a curved central guide strut that was part of the housing. Valve washing was improved by a relatively larger minor orifice and a disc that lifted out of the housing and rotated with opening. It had a moderately high profile in the open position and a low transvalvular gradient. Occluder impingement was possible because its position at the equator of the valve housing made it susceptible to obstruction from retained valve elements, sutures cut too long, or pannus. Loss of structural integrity, however, was never reported. The valve could be rotated after implantation to achieve the desired orientation. Several studies reported a low incidence of valve-related morbidity and mortality.^{8,9} Svennevig and colleagues reported a 25-year experience of 816 patients that underwent an aortic valve replacement using the Medtronic-Hall valve.¹⁰ Linearized rates of thrombotic complications, warfarin-related bleeding, and endocarditis were 1.5%, 0.7%, and 0.16% per patient-year, respectively. Valve thrombosis was seen in only four patients. Seventy-nine percent of the patients were in New York Heart Association classes I or II. Despite these outcomes, Medtronic discontinued manufacturing the valve in September of 2009, removing the last of the tilting disc prosthesis available for clinical use.

The next step in the evolution of valve prostheses came in 1977 when St. Jude Medical (Minneapolis, MN) introduced a bileaflet mechanical valve.¹¹ The design has undergone several refinements since its introduction. Its advantage over the caged ball valves or the tilting disc valves are its greater effective orifice area and therefore improved gradients, along with reduced thrombogenicity.

In light of the thrombogenic potential of mechanical valves and the need for lifelong anticoagulation, development of tissue-based valves was undertaken in parallel with mechanical prosthesis. In 1962, Ross reported the use of aortic homografts for aortic valve replacement (AVR) and subsequently developed the Ross procedure, which uses a pulmonary autograft for replacement of the aortic valve.¹² In 1969, Carpentier and Hancock developed the first porcine xenografts,¹³ and Ionescu developed the first glutaraldehyde-preserved bovine pericardial valve in 1971.¹⁴ Limited long-term durability secondary to leaflet calcification and subsequent valve failure plagued the early generation of bioprostheses. Significant progress has been made in improving the durability of these valves through improved fixation strategies and overall valve design. State-of-the-art anticalcification methods are now being used in an effort to improve valve longevity. Given the inherent gradients with stented bioprostheses, stentless xenografts were introduced in 1986, and they have remained an effective option for a tissue-based prosthesis.¹⁵

MORBIDITY AND MORTALITY GUIDELINES FOR VALVE OPERATIONS

Clinical studies are crucial for determining outcomes after cardiac valve operations and precise definitions of

outcomes are critical in comparing valve prostheses. To address this need, the councils of the Society of Thoracic Surgeons (STS) and the American Association of Thoracic Surgery (AATS) formulated the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity. The initial report of this committee was issued in 1988¹⁶ with an update in 1996.¹⁷ The report strictly defines types of morbidity and mortality that can occur after valvular surgery. An understanding of these definitions is crucial for interpreting studies dealing with valvular prostheses.

The guidelines distinguish two types of mortality: hospital mortality and 30-day mortality. *Hospital mortality* refers to death occurring at any time before discharge during a patient's initial hospitalization. Thirty-day mortality, also referred to as *operative mortality*, is death that occurs at any time or place within 30 days of the procedure. There are several precise definitions of valve-related morbidity. *Structural valve deterioration* (SVD) refers to "any change in function of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation."¹⁷ It includes "changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep and suture line disruption of components ... of an operated valve."¹⁷ Thrombotic or infectious causes of valve dysfunction are not included.

Nonstructural dysfunction includes nonthrombotic and noninfectious causes of valvular stenosis or regurgitation that are not intrinsic to the valve itself. "Examples ... include entrapment by pannus, tissue, or suture; paravalvular leak; inappropriate sizing or positioning; residual leak or obstruction from valve implantation or repair; and clinically important hemolytic anemia."¹⁷ Morbid events are often reported as the composite linearized rate, or the number of events divided by the number of patient-years of follow-up (events/patient-years). The composite linearized rate for nonstructural dysfunction of the commonly available mechanical valves is 0.2 to 0.8 (events/patient-years) for the aortic position and 0.3 to 1.4 (events/patient-years) for the mitral position.⁹ Valve thrombosis is defined as thrombus in or about the valve that is not associated with infection and that interferes with valve function or obstructs blood flow through the valve. The composite linearized rate of thrombosis of mechanical valves is 0 to 0.2 (events/patient-years) in the aortic position and 0.4 to 0.8 (events/patient-years) for the mitral position.⁹

Embolism refers to any embolic event not associated with endocarditis that occurs after the immediate perioperative period and after the emergence from anesthesia. Embolic events are further delineated into neurologic events and peripheral embolic events. The composite linearized rate of thromboembolism ranges from 1.4 to 2.5 (events/patient-years) for the aortic position and 1.8 to 3.6 (events/patient-years) for the mitral position.⁹

A bleeding event refers to any clinically significant bleed requiring hospitalization or transfusion or causing death. A patient does not have to be taking an anticoagulant to sustain a bleeding event. Composite linearized rates vary from 0.8 to 2.5 (events/patient-years) for the aortic position and 1.2 to 2.2 (events/patient-years) for the mitral position.⁹

Endocarditis involving an operated valve is designated operated valvular endocarditis. “Morbidity associated with active infection, such as valve-thrombosis, thrombotic embolus, bleeding event, or paravalvular leak, is included under this category and is not included in other categories of morbidity.”¹⁷ Composite linearized rates for prosthetic valve endocarditis range from 0.4 to 0.7 (events/patient-years) for both the aortic and mitral positions.

Consequences of morbid events are also defined by the guidelines. A reoperation is any operation on “a previously operated valve.”¹⁷ The composite linearized rate for reoperation ranges from 0.3 to 1.8 (events/patient-years) for the aortic position and 0.6 to 1.6 (events/patient-years) for the mitral position.⁹

Valve-related mortality is any death after a valve operation caused by a morbid event that is not related to progressive heart failure in patients with functioning valves. Unexplained deaths are just that, and they should be listed as such. Cardiac deaths include valve-related deaths, sudden deaths, and non-valve-related cardiac deaths. *Total deaths* refer to any and all deaths after a valve operation. *Permanent valve-related impairment* refers to any “permanent neurologic or functions deficit” caused by a morbid event.¹⁷

PROSTHETIC HEART VALVES

The following section lists and describes prosthetic heart valves available worldwide. The valves are grouped

according to their structural type (i.e., mechanical vs. bioprosthetic), manufacturer, and design specifications. The order in which they appear in no way delineates a preference by the authors. For a summary of clinically available valves, implantation positions, and sizes please see [Tables 76-1 and 76-2](#).

Mechanical Valves

Bileaflet Prostheses

Medtronic. The Medtronic Open Pivot Mechanical Heart Valve ([Fig. 76-1A](#)) is a bileaflet valve that was originally developed and owned by ATS Medical, Inc. (Minneapolis, MN). The valve is made of a solid pyrolytic carbon orifice and a titanium strengthening band that provides it with added durability. Its unique design eliminates shallow recesses in the hinge area where clots may form. These design features lead to a continuous gentle flow of blood across the valve, resulting in low levels of clotting while helping to prevent damage to blood cells. Furthermore, with the Open Pivot design, the unimpeded flow of blood provides for a continuous passive washing of the valve. Within the Open Pivot Series, there are three subtypes, each geared toward different potential clinical needs. The AP360 is an aortic valve prosthesis with a supra-annular flanged cuff configuration designed for added flexibility and conformability, and it is available in sizes from 16 to 26 mm. The AP valve has a supra-annular compact cuff configuration for ease of suturing and overall conformability. The valve can be placed in either the

TABLE 76-1 Mechanical Valve Choices

Valve Type	Manufacturer	Name	Position	Available Sizes (mm)
Bileaflet	Medtronic	Open Pivot AP360	Aortic	16-26
		Open Pivot AP	Aortic	16-26
			Mitral	16-26
		Open Pivot Standard	Aortic	19-31
			Mitral	25-33
	St. Jude Medical	Masters	Aortic	19-31
			Mitral	19-33
		Masters HP	Aortic	17-27
			Mitral	17-27
		Regent	Aortic	19-27
	Sorin Group	Bicarbon Fitline*	Aortic	19-31
			Mitral	19-33
		Bicarbon Overline*	Aortic	16-24
		Bicarbon Slimline*	Aortic	17-27
		Carbomedics Top Hat	Aortic	19-27
		Carbomedics OptiForm	Mitral	23-33
		Carbomedics Reduced	Aortic	19-29
		Carbomedics Standard	Aortic	19-31
			Mitral	21-33
		Carbomedics Standard	Aortic	16-18
		Pediatrics	Mitral	16, 18, 21
		Carbomedics Orbis*	Aortic	19-31
			Mitral	21-33
On-X		Standard Sewing Ring	Aortic	19-27/29
			Mitral	23-31/33
		Conform-X Sewing Ring	Aortic	19-27/29
			Mitral	25/33
		Anatomic Sewing Ring	Aortic	19-27/29

*Available only outside the United States.

TABLE 76-2 Bioprosthetic Valve Choices

Valve Type	Manufacturer	Name	Position	Available Sizes (mm)
Stented porcine	Medtronic	Hancock II	Aortic	21-29
			Mitral	25-33
		Hancock II Ultra	Aortic	21-29
		Mosaic	Aortic	19-29
	Edwards Lifesciences		Mitral	25-33
		Mosaic Ultra	Aortic	19-29
		Carpentier-Edwards Standard Porcine (2625 and 6625)	Aortic	19-31
			Mitral	25-33
		Carpentier-Edwards S.A.V. Porcine (2650)	Aortic	19-31*
			Mitral [†]	25-33
		Carpentier-Edwards Duraflex Low Pressure Porcine [‡] (6625LP)	Mitral	27-35
		Carpentier-Edwards Duraflex Low Pressure Porcine with Extended Sewing Ring [†] (6625-ESR-LP)	Mitral	27-35
	St. Jude Medical	Epic	Aortic	21-29
			Mitral	25-33
		Epic Supra	Aortic	19-27
		Biocor	Aortic	21-29
			Mitral	25-33
		Biocor Supra	Aortic	19-27
Stented bovine pericardial	Edwards Lifesciences	Carpentier-Edwards PERIMOUNT (2700 and 2700TFX)	Aortic	19-29
		Carpentier-Edwards PERIMOUNT RSR (2800 and 2800TFX)	Aortic	19-29
		Carpentier-Edwards PERIMOUNT Plus (6900P and 6900PTFX)	Mitral	25-33
		Carpentier-Edwards PERIMOUNT Magna (3000 and 3000TFX)	Aortic	19-29
		Carpentier-Edwards PERIMOUNT Magna Ease (3300TFX, 7300TFX)	Aortic	19-29
			Mitral	25-33
	Sorin Group	Mitroflow	Aortic	19-29
		Soprano Armonia [†]	Aortic	19-33
		Pericarbon More [†]	Mitral	19-33
Stentless	St. Jude Medical	Trifecta	Aortic	19-29
	Medtronic	Freestyle	Aortic	19-29
		3f	Aortic	19-29
	Sorin Group	Pericarbon Freedom [†]	Aortic	15-29
		Freedom Solo [†]	Aortic	19-27
	Edwards Lifesciences	Prima Plus	Aortic	21-29
Sutureless bovine pericardial	Medtronic	3f Enable [†]	Aortic	19-29
	Sorin Group	Perceval S [†]	Aortic	S, M, L, XL
	Edwards Lifesciences	Edwards Intuity [†]	Aortic	19-27
Transcatheter	Edwards Lifesciences	Sapien	Aortic	23, 26
		Sapien XT	Aortic	23, 26, 29
	Medtronic	CoreValve	Aortic	23, 26, 29, 31
	St. Jude Medical	Portico [†]	Aortic	25

*Sizes 19, 29, and 31 available only outside the United States.

[†]Available only outside the United States.

[‡]Available only in the United States.

RSR, Reduced sewing ring.

aortic or mitral position and is also available in sizes from 16 to 26 mm. The Standard valve is designed for intra-annular placement and has a generous and compliant cuff. The valve is available in sizes from 19 to 31 mm in the aortic position and 25 to 33 mm in the mitral position. All the Open Pivot valves are rotatable in situ.

Several studies have demonstrated good hemodynamics and an overall low complication rate with these valves.¹⁸⁻²¹ Bernet and colleagues²² reported their outcomes for a series of 1161 patients that received either the SJM valve or the Open Pivot Mechanical Valve. Cumulative survival and freedom from valve-related

mortality at 10 years for the SJM valve and Open Pivot Mechanical Valve were 66% ± 3% versus 68% ± 5% ($P = 0.84$) and 96% ± 1% versus 97% ± 1% ($P = 0.36$), respectively. No structural valve failure was encountered for both valve types. The linearized rates for valve-related adverse events for the SJM valve and Open Pivot Mechanical Valve were, respectively: thromboembolism, 0.9% and 1.1% per patient-year; major bleeding requiring transfusion, 0.3% and 0.5% per patient-year; prosthetic endocarditis, 0.03% and 0.1% per patient-year; paravalvular leak, 0.1% and 0.6% per patient-year.²²



FIGURE 76-1 ■ Mechanical bileaflet valves. **A**, Open Pivot Mechanical Valve. **B**, The Regent mechanical valve. **C**, The Top Hat mechanical valve. **D**, The On-X Heart Valve. (**A**, Courtesy Medtronic, Inc., Minneapolis, MN. **B**, Courtesy St. Jude Medical, Inc., Minneapolis, MN. **C**, Courtesy Sorin Group, Inc., Milan, Italy. **D**, Courtesy On-X Life Technologies, Inc., Austin, TX.)

St. Jude Medical. The St. Jude Medical (SJM) Standard valve prosthesis was approved by the U.S. Food and Drug Administration (FDA) in 1977, and more than 2.3 million valves have been implanted worldwide. The SJM leaflets and ring orifice are constructed with pyrolytic carbon and are highly durable. The 85-degree leaflet opening angle provides improved laminar flow and reduces turbulence. The Hemodynamic Plus (HP) series was developed to address the inherent gradient in smaller valves and the potential for patient-prosthesis mismatch. With the small annulus in mind, the sewing cuff was reduced and redesigned to allow supra-annular placement of the valve, leading to an increased effective orifice area (EOA). The Masters Series was later introduced, providing the ability to rotate the valve to the desired orientation after implantation. The Standard and HP valves are offered only within the Masters Series. The available Standard valve sizes are 19 to 31 mm for the aortic position and 19 to 33 mm for the mitral position, whereas the available HP valve sizes are 17 to 27 mm for both the aortic and mitral positions. The Regent valve (see Fig. 76-1B) is the most recent evolution of the bileaflet design, developed to improve hemodynamic performance. In addition to a supra-annular cuff, the carbon rim was shifted to the supra-annular position. As with the Masters Series it is fully rotatable as well. This redesign allows the valve to achieve an increased EOA and an up to 84%

orifice-to-annulus ratio. The Regent valve is available only for the aortic position and for sizes ranging from 19 to 27 mm.

Several reports have documented the outcomes of the various valve series produced by SJM.²²⁻²⁷ Tool and colleagues²⁸ reported their 25-year experience in which 946 valve recipients were followed prospectively at 12-month intervals from 1979 to 2007. The series included implants using all SJM designs, with the original Standard valve being the most widely used. Among aortic valve recipients, 25-year freedom from reoperation, thromboembolism, bleeding, and endocarditis was $90\% \pm 2\%$, $69\% \pm 5\%$, $67\% \pm 3\%$, and $92\% \pm 3\%$, respectively. Among mitral valve recipients, 25-year freedom from reoperation, thromboembolism, bleeding, and endocarditis was $81\% \pm 10\%$, $52\% \pm 8\%$, $64\% \pm 6\%$, and $97\% \pm 1\%$, respectively. Freedom from valve-related mortality was $66\% \pm 8\%$ and $87 \pm 3\%$ for aortic and mitral valve replacement (MVR), respectively.²⁸

Head-to-head comparisons between the standard and HP designs have also been reported. Vitale and colleagues²⁹ reported results from the Multicenter Study Group for the SJM HP aortic valve prosthesis. This prospective randomized study included 140 patients with 21- and 23-mm-annulus diameters and who received either the SJM Standard valve or the HP valve. Postoperatively and at 6 months, echocardiographic

hemodynamic variables such as ejection fraction, cardiac output, peak gradient, mean gradient, EOA, indexed EOA (iEOA), and performance index were calculated. Decreased peak and mean gradients and increased EOA, iEOA, and performance indexes were found for the HP valve. The authors concluded that use of the HP valve allows implantation of smaller prostheses without patient-prosthesis mismatch (PPM) and with avoidance of the additional morbidity associated with root enlargement procedures.²⁹ Ismeno and colleagues³⁰ similarly reported their results comparing the 19-mm standard and HP valve in the aortic position after 5 years. Those who received the HP valve had statistically better hemodynamics with lower peak and mean gradients and larger EOAs. There was no difference, however, in terms of 5-year survival, late complications, or left ventricular mass reduction between the two groups.³⁰

The Regent valve has also demonstrated good *in vivo* hemodynamics and clinical outcomes. Bach and colleagues³¹ reported the results of a multicenter study from North America and Europe of 361 patients that underwent aortic valve replacement using the Regent valve. The mean gradient at 6 months was 9.7 ± 5.3 mm Hg for the 19-mm valve, with the larger valves having progressively lower gradients. The iEOA was equal to or greater than $1.0 \text{ cm}^2/\text{m}^2$ for all valve sizes and left ventricular mass index decreased significantly between early postoperative ($165.9 \pm 57.1 \text{ g/m}^2$) and 6-month follow-up ($137.9 \pm 41.0 \text{ g/m}^2$; $P < 0.0001$).³¹

Sorin Group. The Sorin Group (Milan, Italy) manufactures two mechanical valve series: the Bicarbon Product Line, developed internally by Sorin, and the CarboMedics Product Line, acquired through the purchase of Sulzer CarboMedics. Within each series there are multiple subtypes geared toward a variety of clinical needs. As a whole, the mechanical valves in their catalog are bileaflet. For Bicarbon, the leaflets are constructed from pyrolytic carbon deposited on a graphite substrate and a housing made of titanium alloy treated with a proprietary Carbofilm coating for enhanced hemo-biocompatibility. For the CarboMedics valve the leaflets are constructed from pyrolytic carbon deposited on a graphite substrate, like those of the Bicarbon valve. The housing of the CarboMedics valve is fabricated from nonsubstrated pure pyrolytic carbon reinforced with a titanium reinforcing ring.

The Bicarbon series features the Fitline valve, which is designed for intra-annular implantation and is available for both aortic and mitral valve replacement. It will fit annular sizes of 19 to 31 mm for the aortic position and 19 to 33 mm for the mitral position. The Bicarbon Overline maintains the same design as the Fitline while improving hemodynamics through its supra-annular seating and 100% orifice-to-annulus ratio. These design features make the valve suitable for small annuli and create the potential benefit of decreasing the need for annulus enlargement. The Overline valve is available only for the aortic position and for 16- to 24-mm sizes. The Bicarbon Slimline is designed for partial supra-annular seating and therefore improved hemodynamics, while maintaining the same design features as the Fitline. The Slimline valve is available only for the aortic position

and for sizes from 17 to 27 mm. All the Bicarbon valves are rotatable *in situ* and are available only outside the United States.

The CarboMedics mechanical valve series has six different valve designs within its portfolio. The Top Hat valve (see Fig. 76-1C) is designed for supra-annular implantation in the aortic position. By virtue of the design, the valve has no ventricular protrusions and leaves no valve components in the annulus. In turn, this design allows for improved seating in a smaller annulus with the advantage of reducing the need for a root enlargement along with a potential 100% orifice to annulus match. The Top Hat is available for sizes ranging from 19 to 27 mm. The OptiForm valve has a symmetrical cuff design that allows the valve to be placed in a supra-annular, intra-annular or subannular position simply by varying suture entry and exit sites. This valve is available for the mitral position only and for sizes from 23 to 33 mm. The Reduced Series valve is an intra-annular valve and was designed primarily for a smaller annulus and root size. The small external diameter and the smaller, pliable cork-shaped sewing cuff allows for improved seating and once again provides the potential advantage of reducing the need for root enlargement. This valve is available for the aortic position only and for sizes from 19 to 29 mm. The Standard valve offers a generous sewing cuff and is available for the aortic and mitral position. Its low-profile pivot design reduces the risk of coronary obstruction for aortic valve replacements and limits protrusion into the atrium for mitral valve replacements, thus reducing potential thrombus formation. The valve is available in sizes from 19 to 31 mm in the aortic position and 21 to 33 mm in the mitral position. The Standard Pediatric valve was designed for small adults or pediatric patients and is available for both the aortic and mitral position. The placement of the aortic valve can be supra- or intra-annular, and the valve available in sizes from 16 to 18 mm. The mitral valve is available in 16 and 18 mm for either supra- or intra-annular placement, while a 21-mm valve is designed for intra-annular placement only. The Orbis valve, available only outside the United States, has a multipurpose cuff design that allows for a variety of implantation techniques. This valve is offered for both aortic and mitral valve replacement and will fit sizes from 19- to 31-mm in the aortic position and 21- to 33-mm in the mitral position. All CarboMedics valves are rotatable *in situ*.

A number of reports have been published demonstrating good clinical outcomes using the Bicarbon and CarboMedics Series.^{32,33} The specific types of Bicarbon or CarboMedics valves used, however, are not detailed in these reports. Azarnoush and colleagues³⁴ reported the 15-year clinical outcomes of the Sorin Bicarbon prosthesis from a multicenter European study where 1704 patients received aortic valve replacement, mitral valve replacement, or both. Actuarial freedom from valve-related deaths at 15 years was 76.4%, and actuarial freedom from thromboembolism, hemorrhage, and endocarditis at 15 years was 88.8%, 77.5%, and 96.8%, respectively. No cases of structural failure were observed.³⁴ Bouchard and colleagues³⁵ reported their 20-year experience with 3297 patients who received a CarboMedics

valve as an aortic valve replacement or mitral valve replacement. At 20 years, freedom from valve-related mortality for AVR and MVR was 78.3% and 74.6%, respectively. Freedom from thromboembolic events, reoperation, and bleeding were 91.6%, 89.2%, and 89.5% for AVR and 88.5%, 80.3%, and 88% for MVR, respectively. Freedom from endocarditis was 97.3% for both AVR and MVR.³⁵ In a direct comparison, Bryan and colleagues²⁴ reported the 10-year follow-up of their prospective randomized trial where 485 patients received either the CarboMedics valve or the SJM mechanical valve in either the aortic position, mitral position or both. Freedom at 10 years from valve-related mortality was 95.0% in the CarboMedics group and 93.0% in the SJM group. Linearized rates per patient-year were 1.1% in the CarboMedics group and 0.8% in the SJM group for thromboembolism; 2.3% in the CarboMedics group and 3.2% in the SJM group for bleeding events; and 0.72% in the CarboMedics group and 0.47% in the SJM group for nonstructural valve dysfunction.²⁴

On-X Life Technologies. The On-X Heart Valve (On-X Life Technologies, Austin, TX; see Fig. 75-1D) is a bileaflet valve constructed completely of pyrolytic carbon. The manufacturer claims that the lack of silicon doping in the valve's carbon construction potentially decreases its thrombogenicity. Its design includes a tall, flared inlet that increases the orifice area and decreases the ability of retained valve tissue to interfere with opening and closing. In addition, the stasis-free pivot design allows the valve to wash itself, and the 90-degree leaflet opening provides improved laminar flow and reduced turbulence. The On-X Heart Valve is available for both aortic and mitral valve replacement. There are three different sewing rings available, each catered to a particular clinical setting. The valve construct within the three sewing rings is the same. The Standard ring is available in sizes from 19 to 27/29 mm in the aortic position and 23 to 31/33 mm in the mitral position. The Conform X model provides a more flexible sewing ring and is available in sizes from 19 to 27/29 mm in the aortic position, whereas for the mitral position it offers one size that is intended to fit an annular size ranging from 25 to 33 mm. The Anatomic sewing ring is designed to fit the contours of the aortic valve annulus and is available in sizes ranging from 19 to 27/29 mm.

Under FDA investigational device exemption, the Prospective Randomized On-X Anticoagulation Clinical Trial (PROACT) has been testing the safety of less aggressive anticoagulation than recommended by the American College of Cardiology and American Heart Association guidelines after implantation of the On-X valve. In the first limb of the PROACT, Puskas and colleagues³⁶ reported their results of 375 patients with elevated risk factors for thromboembolism who underwent an aortic valve replacement. While receiving 81 mg of aspirin daily, patients received either low-dose warfarin with a target international normalized ratio (INR) of 1.5 to 2 or standard warfarin dosing targeting an INR of 2 to 3. The mean INR was 2.50 ± 0.63 for the control group and 1.89 ± 0.49 for the low dose group ($P < 0.0001$). The low-dose group experienced significantly lower

major (1.48% vs. 3.26% per patient-year; $P = 0.047$) and minor (1.32% vs. 3.41% per patient-year; $P = 0.021$) bleeding rates. The incidence of stroke, transient ischemic attack, total neurologic events, and all-cause mortality were similar between the two groups.³⁶ Enrollment for the low-risk aortic and mitral valve replacement arm of the PROACT was completed in 2013.

Bioprosthetic Valves

The inherent clinical benefit of bioprosthetic valves lies with the patient's ability to avoid life-long anticoagulation. Long-term durability, however, remains the Achilles heel of these valves. During the years since the first valve replacement with a porcine xenograft was reported by Binet and colleagues,³⁷ tissue fixation methods have concentrated on improving durability. First-generation bioprosthetic valves were treated with high-pressure (60 to 80 mm Hg) glutaraldehyde fixation; however, it soon became evident that this process led to calcification of the xenograft tissue.¹³ The pathophysiology of calcification is not well understood, but it is believed to be related partly to the affinity of calcium for aldehyde groups that are generated by glutaraldehyde along with the affinity of calcium for collagen in the extracellular matrix of the cells exposed to glutaraldehyde.³⁸ Damage caused by shear stress-induced turbulence is also a contributing factor leading to calcification.³⁹ Amino oleic acid treatment of tissue valves has been shown to prevent calcium from binding to collagen.⁴⁰ Low-pressure and zero-pressure glutaraldehyde fixations have been shown to maintain a more natural collagen alignment and are currently part of the strategies used for bioprosthetic valves. More recently, valve manufacturers have developed proprietary anticalcification strategies for bioprosthetic valves; however, the true efficacy of these treatments has yet to be determined.

Stented Porcine Bioprostheses

Medtronic. The Hancock II is a porcine bioprosthesis that has a record for safety and durability greater than 25 years. The valve is available in sizes ranging from 21 to 29 mm in the aortic position and 25 to 33 mm in the mitral position. The Hancock II Ultra features a reduced sewing cuff designed specifically for supra-annular implantation in a small aortic root, and it is available in sizes ranging from 21 to 29 mm. The valves are treated with sodium dodecyl sulfate (T6), which removes phospholipids in an effort to reduce calcification. A modified fixation process minimizes the septal muscle shelf, thus leading to a larger orifice area and subsequent better hemodynamics. The Cinch Implant System pulls the stent posts centrally and therefore serves as an automated deflection system to assist with suture tying; it further facilitates aortic valve insertion, particularly through a tight sinotubular space, and helps to prevent suture "looping" around stent posts for mitral valve replacement. Several reports have demonstrated good long-term outcomes with the Hancock II.^{41,42} Valfre and colleagues⁴³ reported their experience of 517 patients who received the valve in the aortic or mitral positions. Late freedom

from reoperation was 85.5% and 79.3% at 15 and 20 years, respectively, in the AVR population, whereas in the MVR population it was 73.3% and 52.8%, respectively.⁴³

The Mosaic valve (Fig. 76-2A) is the next generation of porcine bioprosthesis developed by Medtronic. The valve undergoes zero-pressure glutaraldehyde fixation to maintain collagen crimp morphology and leaflet flexibility. The valve also undergoes anticalcification treatment with alpha-amino oleic acid in an effort to reduce leaflet calcification. It has a low-profile semiflexible stent, and its porcine root is predilated in an attempt to maximize valve orifice area. The valve is available in sizes ranging from 19 to 29 mm in the aortic position and 25 to 33 mm in the mitral position. The Mosaic Ultra has a reduced scalloped sewing cuff that conforms to the aortic annulus for complete supra-annular placement and is available in sizes from 19 to 29 mm. The Cinch Implant System is also available for the Mosaic and Mosaic Ultra. Once again multiple groups have reported good durability and safety using this valve.⁴⁴⁻⁴⁷ Twelve-year data on 1029 patients receiving either an AVR or MVR was reported by Jamieson and colleagues.⁴⁶ Freedoms from valve-related mortality were $87.1\% \pm 3.1\%$ for AVR and $82.5\% \pm 7.7\%$ for MVR, whereas freedoms from reoperation were $84.0\% \pm 3.3\%$ for AVR and $82.5\% \pm 7.5\%$ for MVR. Lastly, freedoms from structural valve deterioration by explant reoperation at 12 years for AVR were $93.3\% \pm 2.6\%$ for patients at least 60 years old and $75.9\% \pm 9.3\%$ for patients younger than 60 years. The 15-year compendium of the same cohort published by Medtronic demonstrates continued durability and good clinical outcomes.

Edwards Lifesciences. The Carpentier-Edwards standard porcine valve (see Fig. 76-2B) is a stented bioprosthesis that was introduced in 1975. The leaflets are fixed with glutaraldehyde at moderate pressure (60 mm Hg) and mounted on a flexible cobalt-chromium alloy stent. The septal muscle shelf is sewn onto the stent to prevent obstruction of the valve inlet orifice. In addition, the leaflets receive the proprietary XenoLogiX treatment, which is designed to reduce calcification by extracting up to 95% of leaflet membrane phospholipids. The valve is available for both the aortic (model 2625) and mitral (model 6625) positions, in sizes ranging from 19 to 31 mm and 25 to 33 mm, respectively. The Carpentier-Edwards S.A.V. valve (CE-SAV; model 2650) is the next-generation porcine bioprosthesis that was introduced in 1982 to improve valve durability and transvalvular gradients observed with the Standard design. The valve is constructed using the same flexible cobalt-chromium alloy stent and XenoLogiX-treated leaflets. The glutaraldehyde fixation process, however, was reduced from moderate to low pressure (2 mm Hg). It features a low-profile design to prevent coronary obstruction in the aortic position and to decrease protrusion into the left ventricular outflow tract in the mitral position. The aortic prosthesis is designed for supra-annular placement to improve transvalvular gradients and EOA, and it has a scalloped contour for better anatomic fit. The aortic valve is available in sizes ranging from 19 to 31 mm; however, the 19, 29, and 31 mm sizes are available only outside the United States. The mitral prosthesis (model 6650) is available in sizes ranging from 25 to 33 mm and is available only outside the United States.

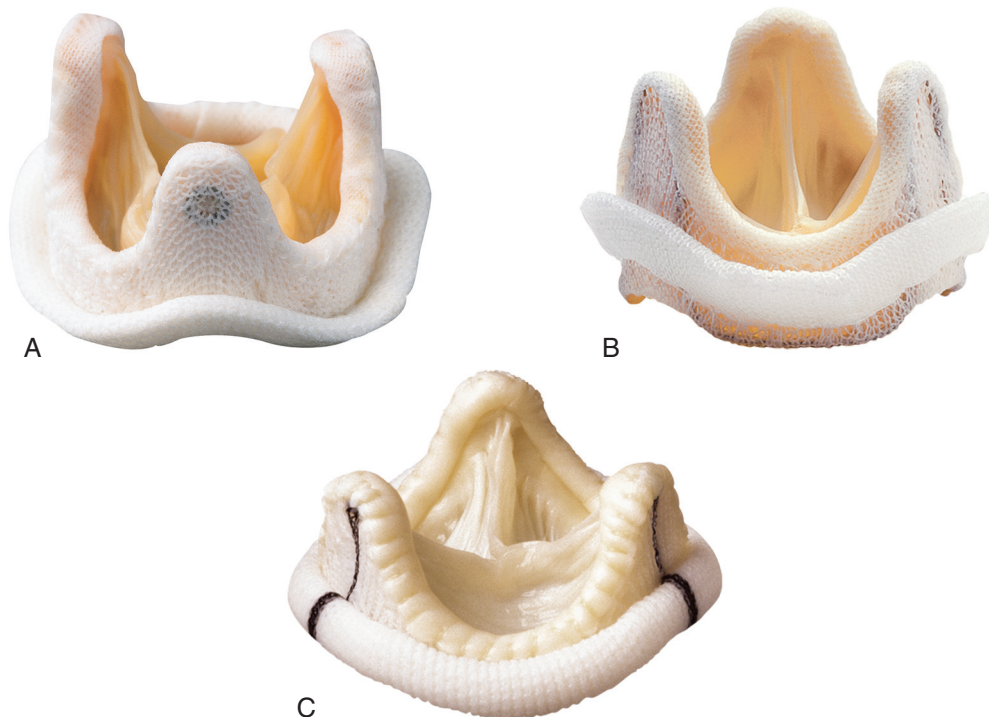


FIGURE 76-2 ■ Stented porcine valves. **A**, Mosaic Bioprosthesis. **B**, The Carpentier-Edwards Standard porcine valve. **C**, The Epic porcine valve. (**A**, Courtesy Medtronic, Inc., Minneapolis, MN. **B**, Courtesy Edwards Lifesciences Corp., Irvine, CA. **C**, Courtesy St. Jude Medical, Inc., Minneapolis, MN.)

The Carpentier-Edwards Duraflex low-pressure mitral porcine valve (model 6625LP) has all the same structural and design features as the CE-SAV mitral valve, and it is available only in the United States. The extended sewing ring model (model 6625-ESR-LP) is designed to offer greater ease of implantation when a larger suture surface is required. This valve is available in sizes ranging from 27 to 35 mm.

Jamieson and colleagues⁴⁸ reported their 20-year experience with the CE-SAV, which included 1823 patients who underwent AVR. Overall actual freedom from reoperation at 18 years was $85.0\% \pm 1.2\%$. Furthermore, the actual freedom from structural valve deterioration at 18 years was $86.4\% \pm 1.2\%$ overall; $90.5\% \pm 1.8\%$ for age 61 to 70 years; and $98.2\% \pm 0.6\%$ for age greater than 70 years.⁴⁸ The only long-term study that evaluated the performance of the porcine mitral valve was by Corbineau and colleagues,⁴⁹ using the Standard valve. Of 139 patients who received the prosthesis, 30 demonstrated structural valve deterioration, with a mean time to onset of 9.0 ± 2.7 years. Although structural valve deterioration was independent of age, the frequency of deterioration was higher in younger recipients. After the age of 65 years, the frequency of structural valve deterioration was no longer variable.⁴⁹

St. Jude Medical. The Biocor valve is a stented porcine bioprosthesis with 20 years of established clinical experience.^{50,51} The valve was acquired by SJM in 1996 and approved by the FDA in 2005. It is available for the aortic and mitral positions in sizes ranging from 21 to 29 mm and 25 to 33 mm, respectively. The design features a flexible stent that adapts easily to the annulus and provides greater ease for knot tying. In addition, its low profile minimizes aortic wall protrusion and reduces left ventricular outflow tract obstruction in the mitral position. The Biocor Supra is designed for supra-annular implantation in the aortic position with the intention of providing better hemodynamics, and it is available in sizes ranging from 19 to 27 mm. The Epic (see Fig. 76-2C) and Epic Supra series use the same valve design as Biocor with the added benefit of receiving the Linx AC Technology, a patented, proprietary anticalcification treatment, designed to improve long-term performance and valve durability. The Epic series was approved by the FDA in 2007, and it is available for the same valve positions and sizes as the Biocor series.

Mykén and colleagues reported their 20-year data of 1712 patients who received the Biocor valve in either the aortic or mitral position. Actuarial freedom from reoperation because of structural valve deterioration was $61.1\% \pm 8.5\%$ and $79.3\% \pm 6.0\%$ after aortic valve replacement and mitral valve replacement, respectively.⁵¹ The results of the FDA regulatory investigation of Epic valve were reported by Jamieson and colleagues,⁵² in which 761 patients received the Epic valve in the aortic position, the mitral position, or both. The actuarial freedom from reoperation at 4 years, because of structural valve deterioration for AVR for age 60 years or less, was $93.3\% \pm 6.4\%$; for ages 61 to 70 years, $98.1\% \pm 1.9\%$; and for older than 70 years, 100% ($P = 0.0006$ for >70 vs. ≤ 60 years). There were no events of structural

deterioration with mitral valve replacement. The actuarial freedom from major thromboembolism for all patients at 4 years was $93.6\% \pm 1.0\%$.⁵²

Stented Bovine Pericardial Bioprostheses

Edwards Lifesciences. The Carpentier-Edwards PERIMOUNT valves are stented bovine pericardial bioprostheses with up to 25 years of demonstrated clinical durability. All PERIMOUNT valves feature a flexible cobalt-chromium alloy stent designed to absorb energy during the cardiac cycle, with three independent symmetrical pericardial leaflets mounted beneath the stent. The leaflets undergo a proprietary stress-free fixation, and they are meticulously matched for thickness and elasticity. The aortic heart valve series consists of the 2700 model, which undergoes XenoLogiX anticalcification treatment, and the 2700TFX model, which undergoes the ThermoFix process, a next generation anticalcification treatment that cross-links unstable glutaraldehyde moieties, in addition to reducing membrane phospholipids. The reduced sewing ring aortic heart valve series consists of the 2800 model and the 2800TFX model. Models 2900 and 2900TFX, available only outside the United States, are identical to models 2800 and 2800TFX, respectively. This series features a reduction in the sewing ring size by 2 to 3 mm, depending on the valve size, and it is designed to facilitate implantation into a smaller aortic root. The two models are distinguished by their anticalcification treatments, with the 2800 receiving the XenoLogiX treatment and the 2800TFX undergoing the ThermoFix process. The Magna aortic heart valve series (3000 and 3000TFX models) further improved the valve design by positioning the stent on top of the sewing ring rather than occupying space within the ring, effectively increasing the EOA and therefore improving valve hemodynamics. Once again, the two models differ only in their anticalcification strategies. Lastly, the Magna Ease aortic heart valve series (3300TFX model) features the same stent placement above the sewing ring, but with a lowered stent base that reduces the overall profile of the valve (Fig. 76-3A). The lower profile maximizes coronary ostia clearance and ease of aortotomy closure. This is the only valve series that is exclusively treated with the ThermoFix anticalcification process. All aortic models are available in sizes ranging from 19 to 29 mm.

A number of reports have documented the long-term safety and durability of the PERIMOUNT valve in the aortic position.^{53,54} Vakil and colleagues⁵⁵ reported the rate of structural valve deterioration, as well as the risk factors influencing this phenomenon for 12,569 patients over a 20-year period. Actuarial rates of explantation for SVD at 10 and 20 years were 2% and 15%, respectively. Younger age ($P < 0.0001$) and higher total cholesterol ($P = 0.002$) were associated with increased risk of explantation for SVD. Smaller valve sizes alone were not associated with increased risk for valvular deterioration; however, higher postoperative peak and mean gradients were significant predictors of SVD ($P < 0.0001$).⁵⁵

The mitral heart valve series features the same design and structural elements as the aortic series. The 6900P model (PERIMOUNT Plus mitral heart valve) and the

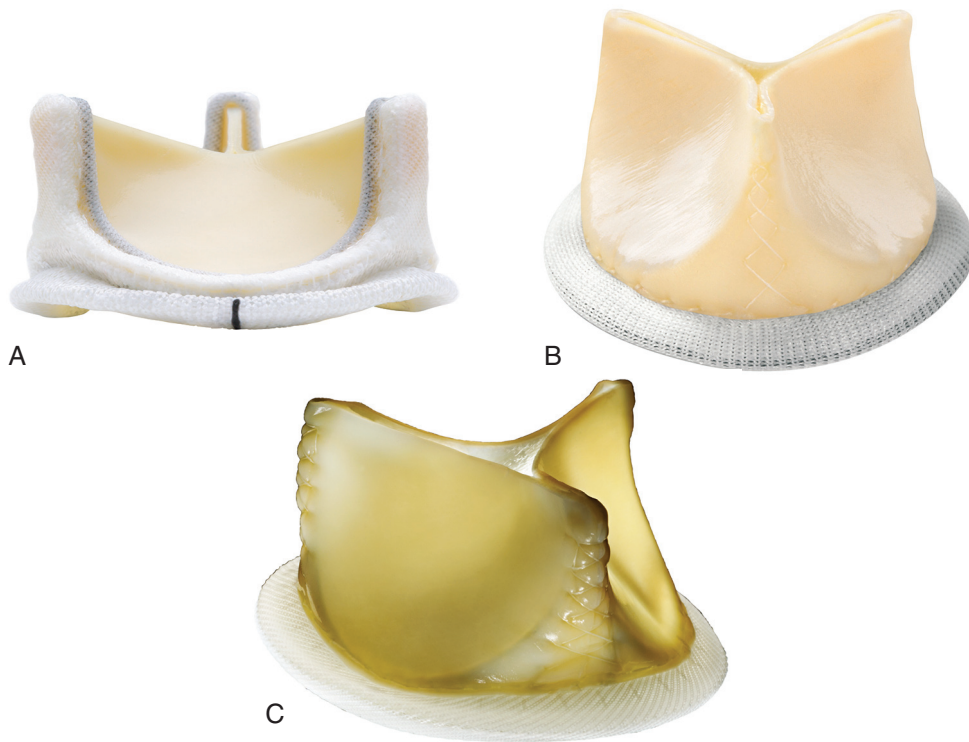


FIGURE 76-3 ■ Stented bovine pericardial valves. **A**, The Carpentier-Edwards PERIMOUNT valve. **B**, The Mitroflow valve. **C**, The Tri-fecta valve. (**A**, Courtesy Edwards Lifesciences Corp., Irvine, CA. **B**, Courtesy Sorin Group, Inc., Milan, Italy. **C**, Courtesy St. Jude Medical, Inc., Minneapolis, MN.)

6900PTFX model differ only in the anticalcification strategies they receive. The Magna Mitral Ease valve (7300TFX) design modifications feature an asymmetric and widened sewing cuff designed to increase the effective suture area and to enhance coaptation between the anterior and posterior aspects of the native mitral annulus. The low-profile design limits projection into the left ventricular outflow tract, and the anatomic sewing ring is designed to tilt the valve away from the left ventricular free wall to reduce the risk of left ventricular free wall abrasion. The Magna Mitral Ease valve exclusively receives the ThermoFix anticalcification treatment. The entire mitral PERIMOUNT valve portfolio includes the Tricentrix holder system, which is intended to prevent inadvertent looping of valve sutures around the stent posts during surgical implantation. All PERIMOUNT mitral valve prostheses are available in sizes ranging from 25 to 33 mm.

Bourguignon and colleagues reported their 20-year outcomes of the PERIMOUNT valve placed in the mitral position in 404 patients. Actuarial freedom from explant because of structural valve deterioration at 20 years was $40.5\% \pm 8.0\%$ (1.9% per valve-year). Competing risk analysis demonstrated an actual risk of explant caused by structural valve dysfunction at 20 years of $25.5\% \pm 2.9\%$. Rates of valve failure were inversely correlated with recipient age, and the expected valve durability was 16.6 years for the entire cohort (11.4, 16.6, and 19.4 years for the patients younger than 60 years, between 60 and 70 years, and older than 70 years, respectively). Actuarial freedom from thromboembolism was $83.9\% \pm 7.6\%$ (0.5% per valve-year), freedom from hemorrhage

was $80.2\% \pm 10.8\%$ (0.7% per valve-year), freedom from endocarditis was $94.8\% \pm 1.4\%$ (0.4% per valve-year), and freedom from structural valve dysfunction was $23.7\% \pm 6.9\%$ (2.3% per valve-year).⁵⁶

Sorin Group. The Mitroflow valve (see Fig. 76-3B) is a stented bovine pericardial bioprosthesis designed for supra-annular implantation in the aortic position. The valve has been available worldwide, except in the United States, since 1982. The current model was introduced in 1991 and was approved by the FDA in 2007.⁵⁷ The valve design features a single pericardial sheet that is mounted around the stent posts, giving it a cylindrical wide leaflet opening for improved hemodynamics. The valve is constructed on a flexible polymer stent that couples maximal flow area with structural strength and resistance to permanent deformation. Its small sewing ring and low profile are designed to ease implantation. The leaflets undergo phospholipid reduction treatment (PRT), a proprietary anticalcification strategy recently approved in the United States. The valve is available in sizes from 19 to 29 mm.

The ISTHMUS investigators reported their results of a multicenter experience with Mitroflow over a 20-year period in which 1591 patients underwent an AVR. Reoperation was required in 96 patients (5.9%), of whom 59 patients (3.7%) had repeated surgery for structural valve degeneration. The actuarial freedom from prosthetic valve degeneration at 18 years was 65.5% (78% in patients older than 70 years) with a linearized rate of 1.4 patients per year (0.8 patients per year in patients older than 70 years). At 18 years, freedom from embolism was 82% (0.9 patients per year), freedom from valve

endocarditis was 89% (0.6 patients per year) and freedom from bleeding episodes was 95% (0.2 patients per year), respectively.⁵⁸

The Soprano Armonia valve is a stented bovine pericardial bioprosthesis designed for supra-annular implantation in the aortic position. It features a soft and easy-fitting sewing ring treated with Carbofilm coating for enhanced hemo-biocompatibility along with a low profile and scalloped stent. The leaflets have a double-sheet design intended to avoid contact between the pericardium and synthetic material. The tissue undergoes postfixation detoxification with homocysteic acid, which neutralizes residues of unbound aldehyde groups, aimed at improving performance in terms of durability, safety, and biocompatibility. The valve is available in sizes ranging from 19 to 33 mm and is clinically approved for use outside the United States only. Fischlein and colleagues⁵⁹ reported the European multicenter study using the Soprano valve in 501 patients at 1 year. Freedom from valve-related death was 98.6%, and actuarial freedoms from thromboembolism, bleeding, endocarditis, and paravalvular leak were 97.1%, 98.9%, 99.1%, and 99.6%, respectively. No events of thrombosis and SVD were observed. They also demonstrated a significant reduction in left ventricular mass, from 211 ± 78.5 g at 1 month to 185 ± 64.7 g at 12 months ($P < 0.0001$).⁵⁹

The Pericarbon More valve is a stented bovine pericardial bioprosthesis designed for placement in the mitral position only. In addition to all the design features and treatments of the Soprano, it has the addition of an anti-looping protection system. The valve is available in sizes ranging from 19 to 33 mm and is clinically approved for use outside the United States only. The largest series using the valve in the mitral position was reported by Caimmi and colleagues.⁶⁰ At a single institution, 78 patients underwent an MVR by the same surgeon using the 29-mm valve. At 12 years, valve-related survival rate was $93.1\% \pm 3.0\%$ while freedom from embolic events was $83.0\% \pm 4.5\%$ and freedom from endocarditis was $98.7\% \pm 1.3\%$. The freedom from primary tissue failure was $56.8\% \pm 6.6\%$ with an $86.3\% \pm 7.5\%$ rate in patients older than 60 years and a $36.8\% \pm 8.2\%$ rate in younger patients.⁶⁰

St. Jude Medical. The Trifecta valve (see Fig. 76-3C) is a stented bovine pericardial bioprosthesis designed for supra-annular implantation in the aortic position that was approved by the FDA in 2011. The valve stent is made from fatigue-resistant, high-strength titanium, designed to reduce stress on the leaflets during the cardiac cycle. The stent posts are covered by porcine pericardium to provide tissue-to-tissue contact between the valve leaflets and stent to reduce leaflet abrasion and potential valve deterioration. The leaflets are from a single sheet of bovine pericardium that is externally mounted to optimize coaptation and maximize flow. Proper leaflet shaping and coaptation are achieved through a proprietary tissue leaflet fixation process. Lastly, the leaflets are treated with the Linx AC Technology aimed toward anticalcification. The valve is available in sizes ranging from 19 to 29 mm.

Results from the global, multicenter, prospective clinical study for Trifecta, in which 1014 patients received

implants at 31 centers, were reported by Bavaria and colleagues.⁶¹ Overall freedom from valve explant was 99.4% at 2 years. At the time of discharge, average mean gradients ranged from 9.3 to 4.1 mm Hg for valve sizes ranging 19 to 29 mm, respectively. There were 27 early thromboembolic events, including 8 (0.8%) strokes, 17 (1.7%) reversible neurologic events, and 2 (0.2%) systemic embolic events. There were no instances of early valve thrombosis, endocarditis, or clinically significant hemolysis. Lastly, there were five late valve explants, including one for structural deterioration and four for endocarditis.⁶¹

Stentless Bioprostheses

The first use of a xenograft stentless valve for aortic valve replacement was in 1986.¹⁵ Because these prostheses have no rigid metal stent, there is little or no inherent gradient across the valve. These valves are supported by the aortic root of the patient once they are implanted by the sub-coronary or inclusion cylinder technique. Certain stentless valves can also be implanted as stand-alone aortic root replacement prosthesis, similar to that of a homograft. Implantation of these valves, however, is more complex and often associated with longer cross-clamp times. These issues, along with the evolution of stented bioprostheses toward decreasing transvalvular gradients, have reduced the popularity of stentless valves in recent years.

Medtronic. The Freestyle valve (Fig. 76-4A) is a stentless porcine bioprosthesis with up to 15 years of demonstrated clinical durability. The valve is a full porcine root that undergoes a proprietary physiologic fixation process that is designed to retain the valve's natural anatomical shape along with alpha-amino oleic acid anticalcification treatment. It can be used as a freestanding aortic root prosthesis, or it can be trimmed and implanted with a subcoronary technique. The valve is available in sizes ranging from 19 to 29 mm. Bach and colleagues⁶² reported their long-term outcomes of a multicenter cohort from North America and Europe where 725 patients were followed for up to 15 years. Freedom from valve-related death at 10 and 15 years was $94.9\% \pm 1.5\%$ and $92.7\% \pm 3.5\%$. Freedom from explant owing to structural valve deterioration was $96.5\% \pm 1.3\%$ and $83.3\% \pm 4.8\%$ at 10 and 15 years, respectively. Increased age was associated with a lower risk of reoperation and explant caused by structural valve deterioration.⁶²

The 3f (form follows function) valve is a stentless bioprosthesis made from three equal equine pericardial leaflets that undergo zero pressure fixation. Its tubular design was aimed to mimic the physiological function of the native aortic valve as closely as possible. The valve is affixed both to the annulus and with sutures at the commissural posts, creating greater valve flexibility and thus facilitating implantation. Given its unique design, the point of maximal stress on the valve is shifted from the commissure to the semilunar "belly" of leaflet. The valve is available in sizes ranging from 19 to 29 mm. Linneweber and colleagues⁶³ reported a 5-year follow-up of 123 patients receiving the 3f valve. There was no severe

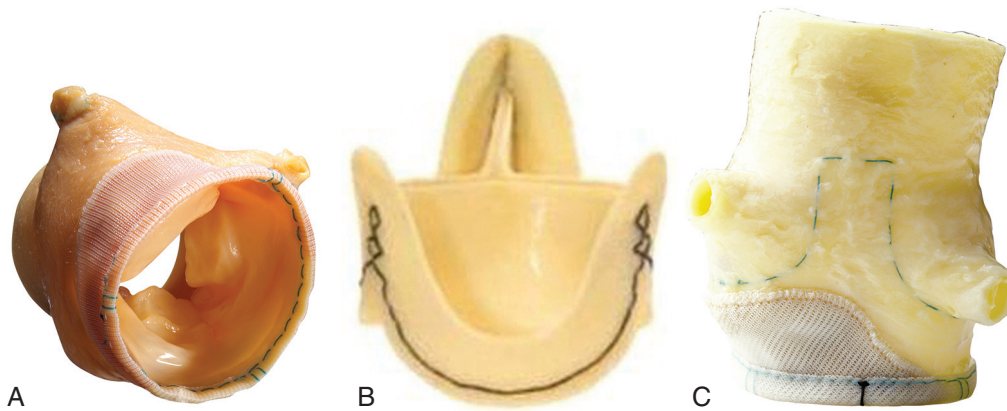


FIGURE 76-4 ■ Stentless valves. **A**, Freestyle Aortic Root Bioprosthesis. **B**, The Freedom Solo valve. **C**, The Prima Plus valve. (**A**, Courtesy Medtronic, Inc., Minneapolis, MN. **B**, Courtesy Sorin Group, Inc., Milan, Italy. **C**, Courtesy Edwards Lifesciences Corp., Irvine, CA.)

structural or nonstructural valve dysfunction identified. Freedom from endocarditis was 100%, and there was minimal paravalvular regurgitation detected in four patients. Collectively, this resulted in a 100% freedom from reoperation. Freedom from severe adverse events was 89%, which included one permanent and three transient neuroembolic events. The mean transvalvular gradients remained low, and the ventricular mass was significantly improved.⁶³

Sorin Group. The Pericarbon Freedom is a stentless bovine pericardial bioprosthesis that undergoes the manufacturer's postfixation detoxification treatment; it is stored in an aldehyde-free solution, thus eliminating the need for rinsing before implantation. It can be used as a freestanding aortic root prosthesis, or it can be trimmed and implanted with a subcoronary technique. The valve is available in sizes ranging from 15 to 29 mm, and is clinically approved for use outside the United States only. Milano and colleagues⁶⁴ reported 10-year outcomes for 85 patients who received the Pericarbon Freedom valve. Actuarial freedom from structural valve deterioration was $96\% \pm 3\%$. Two patients required reoperation because of SVD, one for endocarditis and one for dilation of the sinotubular junction, resulting in an actuarial freedom from reoperation of $93\% \pm 4\%$. Left ventricular mass index decreased from 213 ± 51 gm/m² to 157 ± 43 gm/m² ($P < 0.001$).⁶⁴

The Freedom Solo (see Fig. 76-4B) is a next-generation stentless bovine pericardial bioprosthesis, designed for supra-annular seating aimed at establishing a 100% orifice-to-annulus ratio. The valve is designed for subcoronary implantation only and is available in sizes ranging from 19 to 27 mm. It is currently available only outside the United States, but it is expected to receive FDA approval in the near future. A number of reports have demonstrated low transvalvular gradients after implantation and associated regression of left ventricular mass within several months; however, long-term data on the durability of the valve are not available.^{65,66} There have also been several reports of severe but transient thrombocytopenia in patients that receive the valve,

relative to other available options.^{67,68} The etiology of the thrombocytopenia is unknown.

Edwards Lifesciences. The Edwards Prima Plus valve (see Fig. 76-4C) is a stentless porcine bioprosthesis that undergoes low-pressure fixation and receives XenoLogiX anticalcification treatment. A woven polyester cloth is sewn to the annulus to provide additional support to the first suture line. It can be implanted as a full root replacement or trimmed and placed using a subcoronary technique; however, the approved indication in the United States is for the subcoronary implantation only. The valve is available in sizes ranging from 21 to 29 mm. Auricemma and colleagues⁶⁹ reported their 10-year outcomes in 318 patients who received the Edwards Prima Plus valve. Actuarial freedom from valve reoperation and structural valve deterioration at 10 years were 100% and 64%, respectively. Actuarial freedom from embolic events and endocarditis at 10 years were 84% and 81%, respectively.⁶⁹

Sutureless Valves

Sutureless prosthetic heart valves were initially developed in the 1960s to facilitate valve implantation while reducing ischemic and procedural times. These valves were abandoned, however, because of multiple complications such as paravalvular leaks and valve-related thromboembolic events.⁷⁰ The rapid development of transcatheter technology has fueled a reemergence of the sutureless strategy, once again in an effort to reduce the morbidity and mortality of patients requiring valve replacement. The acceleration of the surgical procedure has the potential to reduce the adverse outcomes seen in higher-risk patients and in those requiring complex multivalve or combined valve and coronary procedures.⁷¹

Medtronic. The 3f Enable (Fig. 76-5A) is a sutureless bioprosthesis constructed with the 3f stentless valve placed over a self-expanding nitinol frame. The inflow flange is covered with polyester fabric and is scalloped to conform to the aortic annulus. Implantation requires a

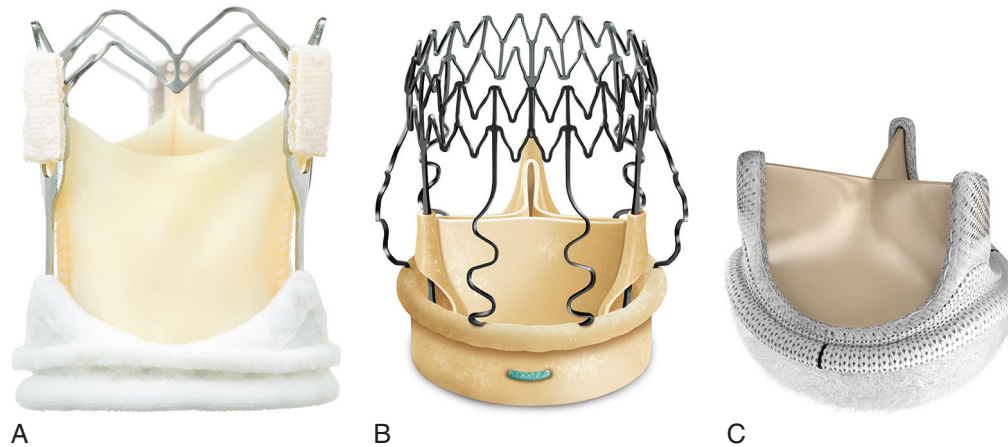


FIGURE 76-5 ■ Sutureless valves. A, The 3f Enable valve. B, The Perceval S valve. C, The Intuity valve. (A, Courtesy Medtronic, Inc., Minneapolis, MN. B, Courtesy Sorin Group, Inc., Milan, Italy. C, Courtesy Edwards Lifesciences Corp., Irvine, CA.)

transverse aortotomy at least 2 cm above the sinotubular junction. As with traditional sutured valves, the leaflets must be excised followed by meticulous débridement of the annulus. A single guiding suture is placed in the nadir of the noncoronary sinus, and the valve commissures need to be aligned to the native valve commissures. The chronic outward force of the nitinol, along with the polyester flange, ensure fixation of the valve and minimize the potential for paravalvular leaks.⁷¹ The valve is contraindicated in bicuspid aortic valves along with irregular or heavily calcified valves. It received CE Mark approval in 2009 and is currently awaiting FDA approval. The valve is available in sizes ranging from 19 to 29 mm. A number of groups have reported their outcomes with the 3f Enable.^{72,73} Eichstaedt and colleagues⁷³ reported their single-center experience of 120 patients with up to 18 months of follow-up. In a population of patients with a mean Society of Thoracic Surgeons risk score of 14.8%, the 30-day mortality was 6.7% overall and 1.4% in stand-alone procedures. Mean and peak transvalvular gradients were 9 mm Hg (4 to 13 mm Hg) and 14 mm Hg (8 to 22 mmHg) at discharge, respectively. In 8 patients (6.7%), permanent pacemaker implantation was necessary. No thromboembolic or bleeding events related to the bioprosthesis were observed.⁷³

Sorin Group. The Perceval S (see Fig. 76-5B) is a stentless, bovine pericardial bioprosthesis attached to a self-expandable nitinol anchoring device, which has the dual role of supporting the valve and providing fixation to the implantation site. The anchoring device is characterized by two ring segments (outflow and inflow ring), three commissural elements supporting the valve, and three pairs of sinusoidal elements providing fixation in the sinuses of Valsalva. The anchoring device is treated with the manufacturer's proprietary Carbofilm coating. In addition to the double-sheet pericardial design, there is a pericardial sealing collar designed to encourage adaptation to the aortic annulus and prevention of paravalvular leaks. The proximal aortotomy should be 3 to 3.5 cm above the valve annulus or 0.5 to 1 cm above the sinotubular junction. The leaflets must be excised; however, the annulus does not require decalcification. Only eccentric

and bulky intra-annular calcium needs to be removed. Guiding sutures are then placed 2 to 3 mm below the nadir of each sinus, maintaining 120 degrees equidistance between each suture. In correspondence to each valve sinus, a buttonhole is provided on the inflow ring, through which the guiding sutures are passed. Before implantation, the prosthesis diameter is reduced to a suitable size and then loaded on the holder. After in situ positioning, the valve is released in two steps. First the inflow ring at the level of the annulus and, when proper positioning is verified, the complete prosthesis is released. Following implantation, a postdilation balloon catheter is inflated inside the prosthesis at the inflow level to improve apposition by modeling the inflow ring on the annulus.⁷¹ The valve is available in small (S), medium (M), large (L), and extra-large (XL) sizes. The valve received CE Mark approval in 2011, and it is expected to receive FDA approval shortly.

Several reports have demonstrated the safety and efficacy of the valve.^{74,75} Rubino and colleagues⁷⁶ reported a multicenter European cohort of 314 patients who underwent AVR using the Perceval S as a standalone procedure or combined with surgical revascularization. The valve was successfully implanted in 99.4% of cases, whereas two patients were converted to a traditional AVR because of severe paravalvular leak. In-hospital mortality was 3.2% and was lower in isolated AVR compared with a combined procedure (1.4% vs. 7.4%; $P = 0.005$). Six patients (1.9%) experienced perioperative stroke, five (1.6%) needed renal replacement therapy, and 25 (8.0%) required pacemaker implantation. Octogenarians and younger patients experienced similar in-hospital outcomes. At 2 years, overall survival was $84.1\% \pm 4.2\%$, whereas freedom from valve-related death was $97.9\% \pm 1.3\%$. Freedom from stroke was $98.9\% \pm 0.8\%$, freedom from endocarditis was $99.1\% \pm 0.6\%$, and freedom from reoperation on the aortic valve was $98.5\% \pm 0.9\%$. Once again, no differences were observed in octogenarians compared with the younger population.⁷⁶

Edwards Lifesciences. The Edwards Intuity (see Fig. 76-5C) is a stentless bovine pericardial bioprosthesis that uses the PERIMOUNT design with a proprietary

balloon-expandable subannular stainless steel frame. The leaflets receive the manufacturer's ThermoFix anticalcification treatment, and the frame is covered with a broad polyester sealing cloth that is expanded slightly below the native aortic valve annulus. Implantation is performed after a traditional aortotomy and excision of the leaflets. Decalcification of the annulus should be performed to where the inner surface of the annulus is smooth. Guiding sutures are placed through the annulus at the nadirs of each sinus and are later secured to the valve. The Intuity received CE Mark approval in 2012, and it is currently being trialed in the United States for future FDA approval. The valve is available in sizes ranging from 19 to 27 mm. The Surgical Treatment of Aortic Stenosis With a Next Generation Surgical Aortic Valve (TRITON) trial reported the 1-year outcomes of 152 patients who underwent AVR using the Edwards Intuity valve. Implantation was successful in 96.1% of patients (146/152), whereas early valve-related mortality was 1.4% and cumulative survival was 92.5% at a mean follow-up of 9.8 ± 5.1 months. Independent core laboratory-adjudicated mean effective orifice area and aortic valve pressure gradient were 1.7 ± 0.2 cm² and 8.8 ± 3.0 mm Hg at 3 months, and 1.7 ± 0.2 cm² and 8.4 ± 3.4 mm Hg at 1 year, respectively.⁷⁷

Transcatheter Valves

Transcatheter valves have created a paradigm shift in the approach to treating valvular heart disease. With the approval of the Edwards Sapien aortic valve and the Medtronic CoreValve, a new generation of valvular therapy was introduced. Approved for nonoperative and high-risk surgical patients with aortic stenosis, these valves have demonstrated significant benefits over medical therapy and comparable outcomes to traditional surgical aortic valve replacement.⁷⁸⁻⁸⁰ SJM has received CE Mark approval for the Portico aortic valve, which is being trialed in the United States for future FDA approval. Transcatheter approaches to mitral, tricuspid, and pulmonary valve replacements are being developed as well, and will likely be clinically available in the near future. As this technology evolves, it will likely reshape the indications for surgical valve replacement while further improving the care of patients with valvular heart disease. A more detailed review of transcatheter valve therapies is presented in [Chapter 79](#).

Homograft Valve Replacement

Homograft valves are harvested from cadaveric donors and cryopreserved until they are ready for use. They are commonly used in congenital cardiac surgery for reconstruction of complex great vessel and semilunar valve anomalies. Currently, the primary indication for a homograft in adult cardiac surgery is as a full root replacement for complicated native aortic valve endocarditis⁸¹ or infected composite aortic root grafts. Initially there was optimism that homograft valves would offer improved durability over conventional bioprosthesis; however, studies have shown that modern biologic valves are equal if not greater in durability.⁸² Subcoronary and inclusion

techniques for implantation were initially described, but these approaches have fallen out of favor. For effective treatment of endocarditis, all infected tissue has to be radically debrided. To that end, the mitral valve curtain and attached septal muscle of the homograft can help in reconstructing the mitral annulus and left ventricular outflow tract. The absence of prosthetic material can offer an advantage that allows complex reconstructions in the presence of an infected field.

CHOICE OF VALVE REPLACEMENT

The choice of valve prosthesis can be a challenging decision faced by both the surgeon and patient. The first and most important step in the process is choosing between a mechanical and bioprosthetic valve. Important factors to consider are the patient's age, life expectancy, preference, indications or contraindications to anticoagulation, and comorbidities. The 2006 American College of Cardiology/American Heart Association (ACC/AHA) and 2007 European guidelines reduced the weight placed on the patient's age and gave greater emphasis to patient preference.^{83,84} The most recent ACC/AHA guidelines further emphasize that the choice of prosthetic valve type should be a shared decision-making process that accounts for the patient's values and preferences, with full disclosure of the indications for and risks of anticoagulant therapy and the potential need for reoperation. A bioprosthetic valve is believed to be reasonable in patients older than 70 years and recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired. Either a bioprosthetic or mechanical valve is considered reasonable in patients between 60 and 70 years old, and a mechanical prosthesis is reasonable for AVR or MVR in patients younger than 60 years who do not have a contraindication to anticoagulation ([Table 76-3](#)).⁸⁵

Another important factor in the selection process is choosing a valve that provides optimal hemodynamic performance. The performance of the valve is determined by the size of the prosthesis that can fit the patient's annulus and by the total cross-sectional area of that prosthesis, or the EOA of the valve, that is available for blood flow. PPM occurs when the EOA of the implanted valve is too small relative to the patient's body surface area. The most widely accepted measure of PPM is the iEOA. In the aortic position, an iEOA greater than 0.85 cm²/m² is considered acceptable. Moderate PPM occurs when the iEOA is between 0.85 and 0.65 cm²/m², whereas severe PPM occurs when the iEOA is less than 0.65 cm²/m². Several reports have demonstrated that PPM after AVR is associated with less improvement in symptoms and functional class, impaired exercise tolerance, less regression of left ventricular hypertrophy, less improvement in coronary flow reserve, more adverse cardiac events, and increased short- and long-term mortality. Moreover, the effect of PPM is more pronounced in younger patients and in those with depressed left ventricular function.⁸⁶

It is important to understand that there are significant discrepancies between the actual dimensions of a valve prosthesis and the labeled prosthesis size when

TABLE 76-3 Summary of Recommendations for Prosthetic Valve Choice from 2014 AHA/ACC Guidelines

Recommendations	COR	LOE
Choice of valve intervention and prosthetic valve type should be a shared decision process.	I	C
A bioprosthesis is recommended in patients of any age for whom anticoagulant therapy is contraindicated, cannot be managed appropriately, or is not desired.	I	C
A mechanical prosthesis is reasonable for AVR or MVR in patients younger than 60 years who do not have a contraindication to anticoagulation.	IIa	B
A bioprosthesis is reasonable in patients older than 70 years.	IIa	B
Either a bioprosthetic or mechanical valve is reasonable in patients between 60 and 70 years old.	IIa	B
Replacement of the aortic valve by a pulmonary autograft (the Ross procedure), when performed by an experienced surgeon, may be considered in young patients when VKA anticoagulation is contraindicated or undesirable.	IIb	C

AVR, Aortic valve replacement; COR, class of recommendation; LOE, level of evidence; MVR, mitral valve replacement; VKA, vitamin K antagonist.

(From Nishimura RA, Otto CM, Bonow RO, et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:e521–643, 2014.)

comparing different models. Therefore, one must be cautious when evaluating the hemodynamic performance of different prosthesis models on the basis of the labeled size. A particular annulus can accommodate a size 21 valve from one manufacturer, whereas the same annulus can accommodate only a size 19 valve from an alternate manufacturer. In general, newer-generation valves have superior performance over older devices, and mechanical prostheses are better when compared with stented bioprostheses. A recent meta-analysis showed that stentless valves provide larger EOAs, reduced transprosthetic gradients, and greater left ventricular mass regression when compared with stented bioprostheses, but at the expense of prolonged cardiopulmonary bypass times. In the end, the choice of valve prosthesis is a multifactorial decision that should be individualized to the needs of each patient, with the intention of achieving an optimal hemodynamic and clinical outcome.⁸⁶

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SURGICAL TREATMENT OF AORTIC VALVE DISEASE

Talal Al-Atassi • Gebrine El Khoury • Munir Boodhwani

CHAPTER OUTLINE

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FUNCTIONAL ANATOMY OF THE AORTIC VALVE

The aortic valve is the last of four cardiac valves through which the blood is pumped before it goes to the rest of the body. It separates the left ventricular outflow tract from the aorta. Its main function is to prevent backward blood flow from the aorta to the left ventricle, while allowing the blood to flow forward during systole with minimal resistance. The normal aortic valve has three semilunar cusps (tricuspid): the left coronary, the right coronary, and the noncoronary cusps. Each cusp is attached below one of the three sinuses of Valsalva, which are slight dilations of the aorta associated with each cusp. These sinuses end at the sinotubular junction, which is the narrowest part of the aortic root. The fibrous skeleton supports the aortic valve and is continuous with the anterior leaflet of the mitral valve.

AORTIC STENOSIS

Epidemiology and Etiology

Isolated aortic stenosis (AS) is more common in men than in women and is found in 2% of people 65 years of age and older. The most common causes of AS include age-related calcific degeneration, bicuspid aortic valve, and rheumatic aortic valve. The distribution of these causes varies across age groups and geographic regions. Age-related degeneration is the most common cause of AS in patients older than 70 years. In contrast, bicuspid aortic valve calcification accounts for most surgical cases in patients younger than 70 years.

Pathophysiology

No appreciable gradient exists across the normal aortic valve during systole. In AS, gradual obstruction of the left

ventricular outflow leads to an increased left ventricular afterload and left ventricular wall stress, elevated left ventricular systolic and diastolic pressures, decreased aortic pressure, and prolonged left ventricular ejection time. Over time, this results in compensatory concentric left ventricular hypertrophy (LVH) to maintain ejection fraction. In patients with chronic severe AS, this compensatory mechanism may become insufficient, leading to gradual dilation and thinning of the left ventricle, and result in a decrease in ejection fraction and in congestive heart failure.

Myocardial oxygen supply and demand is also altered in AS. LVH, increased systolic pressure, and prolonged ejection time result in increased myocardial oxygen demand. Increased diastolic pressure and prolonged systolic ejection time result in decreased diastolic and myocardial perfusion time and hence myocardial oxygen supply. The alteration in myocardial oxygen supply and demand is the underlying mechanism behind myocardial ischemia in patients with AS, even in the absence of coronary artery disease.

Clinical Features

The classic symptoms of AS are angina, exertional syncope, and symptoms of congestive heart failure such as shortness of breath. The mechanisms for angina and congestive heart failure are explained in the previous section. The mechanism for syncope is likely related to the blunting of exercise-induced augmentation in stroke volume as a result of outflow obstruction coupled with exercise-induced peripheral vasodilation. These changes cause a drop in systemic blood pressure leading to cerebral hypoperfusion and syncope.

The classic physical finding is a crescendo-decrescendo systolic ejection murmur heard best at the second right intercostal space, which may variably radiate to the carotid arteries. A palpable thrill may be present in severe cases of AS. Palpation of the arterial pulse may reveal a weak and delayed pulse known as *pulsus parvus et tardus*.

Diagnosis and Grading

Two-dimensional transthoracic echocardiography is the most common modality for the diagnosis and grading of AS (Table 77-1). In most patients, this modality can reliably establish aortic jet velocity, aortic valve peak and mean gradients, and aortic valve area.

Natural History

Without intervention, symptomatic AS has dismal outcomes. Multiple studies consistently reported survivals of 3 years for angina and syncope and 1.5 to 2 years for dyspnea and heart failure.² These findings have driven recommendations for early surgical intervention in patients with symptomatic AS. One third of asymptomatic patients with severe AS will become symptomatic in 2 years with an estimated cardiac death of less than 1% each year to 5% each year.³ Patients with higher grades of AS severity seem to progress at a faster rate than lower grades of AS. After AS becomes moderate, aortic valve

TABLE 77-1 Severity of Aortic Stenosis According to Echocardiographic Criteria

Parameter	Mild	Moderate	Severe
Aortic valve area (cm ²)	1.6-2.5	1.1-1.5	≤1.0
Mean pressure gradient (mm Hg)	<20	20-39	≥40
Aortic jet velocity (m/sec)	2.0-2.9	3.0-3.9	≥4.0

From Nishimura RA, Otto CM, Bonow RO, et al: 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:e521-643, 2014.

area decreases on average by 0.1 cm² per year, the pressure gradient across the valve rises on average by 7 mm Hg per year, and the jet velocity increases by 0.3 m/sec per year.⁴⁻⁷

Indications for Surgery

The class I recommendations for aortic valve replacement (AVR) in patients with AS according to the American College of Cardiology (ACC) and the American Heart Association (AHA)¹ are the following:

1. Symptomatic patients with severe AS
2. Patients with severe AS undergoing concomitant coronary artery bypass graft (CABG) surgery, heart valve surgery, or aortic surgery
3. Patients with severe AS and left ventricular systolic dysfunction (ejection fraction < 50%)

The class IIa recommendations¹ for AVR are the following:

1. Asymptomatic patients with very severe AS (aortic jet velocity ≥ 5.0 m/sec or mean pressure gradient ≥ 60 mm Hg) and low surgical risk
2. Apparently asymptomatic patients with severe AS and an exercise test demonstrating decreased exercise tolerance or a fall in systolic blood pressure
3. Symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (resting valve area ≤ 1.0 cm², aortic jet velocity < 4.0 m/sec or mean pressure gradient < 40 mm Hg, LVEF < 50%, and low-dose dobutamine stress study showing an aortic jet velocity ≥ 4.0 m/sec mean pressure gradient ≥ 40 mm Hg with a valve area ≤ 1.0 cm²)
4. Symptomatic patients with low-flow/low-gradient severe AS with an LVEF ≥ 50%, a calcified aortic valve with significantly reduced leaflet motion, and a valve area ≤ 1.0 cm² only if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms and data recorded when the patient is normotensive (systolic blood pressure < 140 mm Hg) indicate an aortic jet velocity < 4.0 m/sec or mean pressure gradient < 40 mm Hg, and a stroke volume index < 35 mL/m², and an indexed valve area ≤ 0.6 cm²/m².
5. Patients with moderate AS who are undergoing cardiac surgery for another indication.

The class IIb recommendation¹ for AVR is the following:

1. Asymptomatic patients with severe AS if the patient is at low surgical risk and serial testing shows an increase in aortic velocity of ≥ 0.3 m/sec per year.

AORTIC REGURGITATION

Isolated aortic regurgitation is the primary lesion for patients undergoing AVR in only a minority of patients ($\approx 10\%$ to 15%). Aortic valve repair is emerging as an attractive alternative to replacement in selected patients with aortic regurgitation. The details of epidemiology, pathophysiology, diagnosis, and treatment of aortic regurgitation are reviewed in the chapter on aortic valve repair.

AORTIC VALVE REPLACEMENT

Operative Techniques

The traditional and most common approach for an AVR is through a median sternotomy. After exposure of the heart, the patient is heparinized and cannulated. An aortic cannula is placed in the distal ascending aorta, and a two-staged venous cannula is placed in the right atrium. Aortic calcification may preclude safe ascending aortic cannulation, and alternative arterial cannulation, including femoral or axillary cannulation, may be considered. Deep hypothermia and circulatory arrest for management of the heavily calcified ascending aorta have been used, but they carry a significant risk of stroke. Alternate venous cannulation may be used if required for other concomitant procedures. Antegrade cardioplegia is typically used. However, retrograde cardioplegia delivery through the coronary sinus may be useful in the setting of severe aortic regurgitation, coronary disease, or LVH to supplement myocardial protection. A vent is placed through the right superior pulmonary vein. Following initiation of cardiopulmonary bypass and cardioplegic arrest, additional cardioplegia doses may be delivered in a retrograde fashion or directly through the coronary ostia. Patients with AS often have ventricular hypertrophy and may require larger cardioplegia volumes.

The aortotomy is started anteriorly and may be performed in a transverse fashion (in a plane parallel to and approximately 1 cm above the sinotubular junction) or may be an oblique one (starting with a transverse incision above the right coronary, but extending through the sinotubular junction and into the noncoronary sinus). Sufficient distance should be maintained from the right coronary artery to prevent injury during closure.

Retraction sutures are placed in the aortic wall above each commissure, and the distal aorta is retracted cephalad to facilitate exposure (Fig. 77-1). Valve excision is performed one cusp at a time, starting at the commissure between the right and noncoronary cusps and excising the right coronary cusp (Fig. 77-2). Next, the left coronary cusp is excised starting at the commissure between the left and right coronary cusps. The noncoronary cusp is then excised starting at the commissure between the

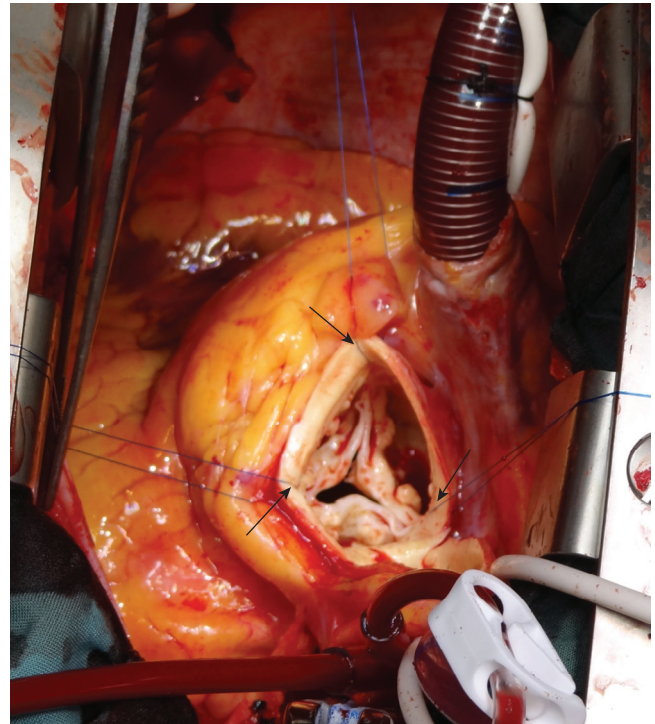


FIGURE 77-1 ■ Aortic valve exposure through a transverse aortotomy aided by three commissural sutures (arrows) and a suture retracting the distal portion of the ascending aorta cephalad.

left and noncoronary cusps. Use of a #11 blade for leaflet excision can permit complete decalcification by cutting around rather than through the calcified regions. Alternatively, after the valve is excised, débridement of calcium from the annulus is performed using forceps and rongeur. After satisfactory decalcification, the aortic root, ascending aorta, and left ventricle are irrigated to remove all free calcium deposits. During irrigation, care should be taken to prevent embolization of calcific debris into the coronary ostia.

Sizing may be performed before or after leaflet excision. In nondilated aortic roots, the sinotubular junction is typically the limiting factor in choosing the largest possible valve. The annulus is measured using commercial valve sizers, and an appropriate-sized valve is used (Fig. 77-3). If the annulus is too small, aortic root enlargement techniques may have to be performed (see next section).

There are two techniques to implant the valve: the continuous and the interrupted suture techniques. The continuous suture technique has fewer knots, which may save time and minimize foreign material left behind. Larger prosthesis may be implanted, as there is less “purse-stringing” effect on the tissues of the aortic root. However, this technique may be problematic if the aortic annulus is fragile or heavily calcified, or if there is suture dehiscence or breakage. The interrupted suture technique (Fig. 77-4) without the use of pledgets is our standard for implantation because it provides the maximum strength for prosthetic attachment, minimizes foreign material, allows placement of the largest possible

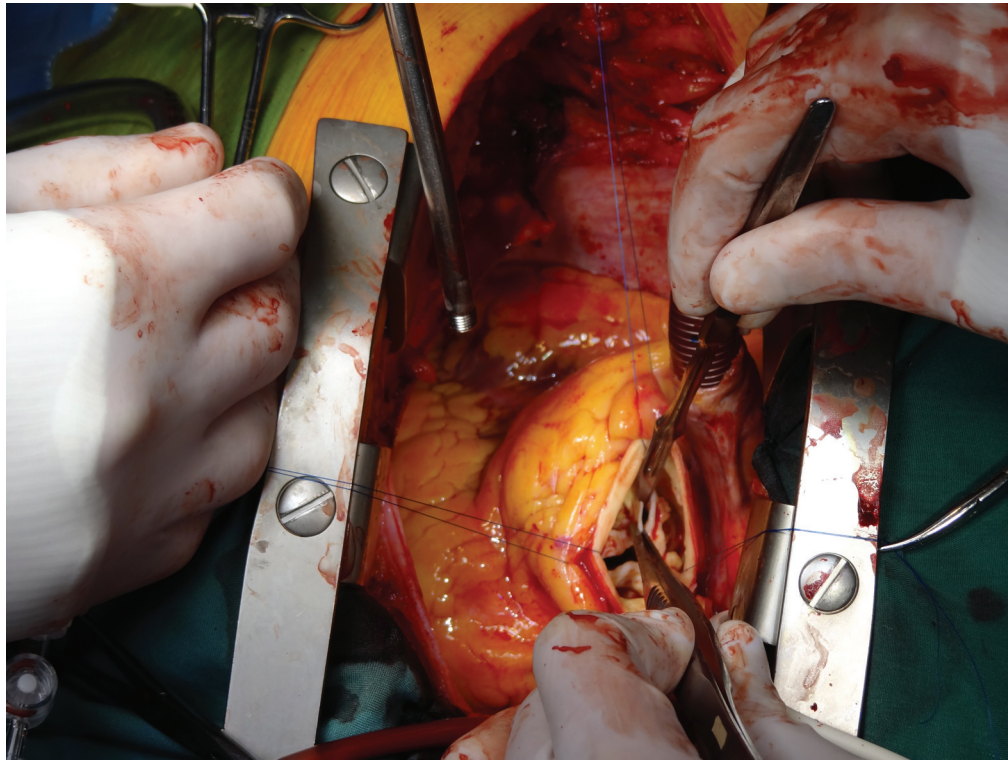


FIGURE 77-2 ■ Sharp excision of the aortic valve is performed using a #11 blade, starting with the right coronary cusp.

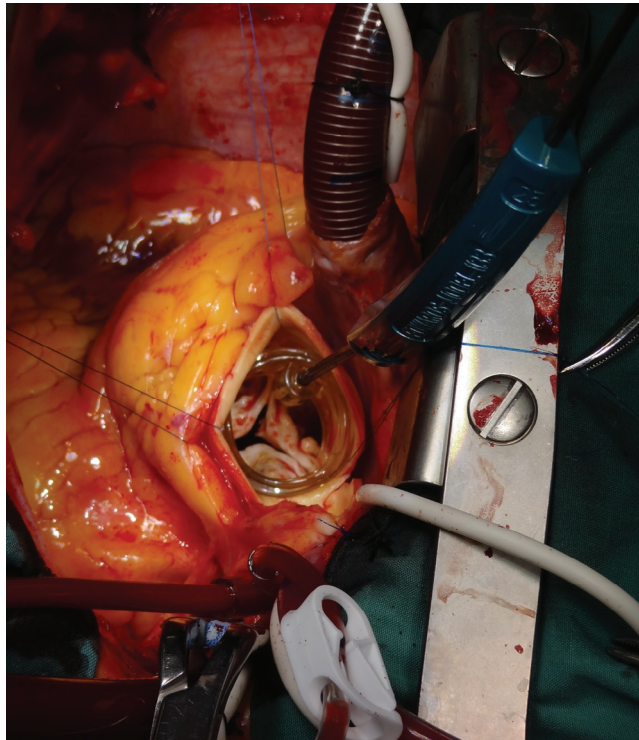


FIGURE 77-3 ■ Sizing of the appropriate aortic valve prosthesis using commercial sizers can be accomplished before (as depicted in this picture) or after valve excision.

prosthesis, and has low risk of paravalvular leak. Alternately colored, double-needle, 2-0 nonabsorbable, braided sutures are passed through the sewing ring of the prosthetic valve, and then through the native aortic annulus, from the ventricular to the aortic side, starting with the left coronary region, followed by the right coronary region, and then the noncoronary region (see [Figs. 77-4](#) and [77-5](#)). The sutures alternate in color (green and white) to simplify identification. Pledgets may be used if the aortic annulus is particularly fragile. The pledgets, using a horizontal mattress technique, are placed below the annulus, allowing the valve to sit above the annulus. The sutures are then passed through the sewing ring of the prosthetic valve, with attention paid to symmetrical spacing around the prosthetic valve. Alternatively, the needles are passed from above to below the annulus, placing the pledgets above and the valve below the annulus. Supra-annular positioning of the valve allows for a larger valve to be used. Great care must be exercised and judicious needle bites taken between the noncoronary and right coronary annuli and near the left coronary annulus because deep bites in these areas may cause heart block and left coronary artery injury, respectively.

After the valve is parachuted down ([Fig. 77-6](#)), all the sutures are then tied systematically starting with the left coronary cusp, followed by the right coronary cusp, and finally the noncoronary cusp ([Fig. 77-7](#)). The aortotomy is then closed in two layers using two running double-needle polypropylene sutures ([Fig. 77-8](#)). If the aortic tissue is thin and friable, Teflon felt or autologous pericardial strips may be used to reinforce the closure.

After the aortotomy is closed, de-airing maneuvers are performed. The aortic root vent is turned on, volume is

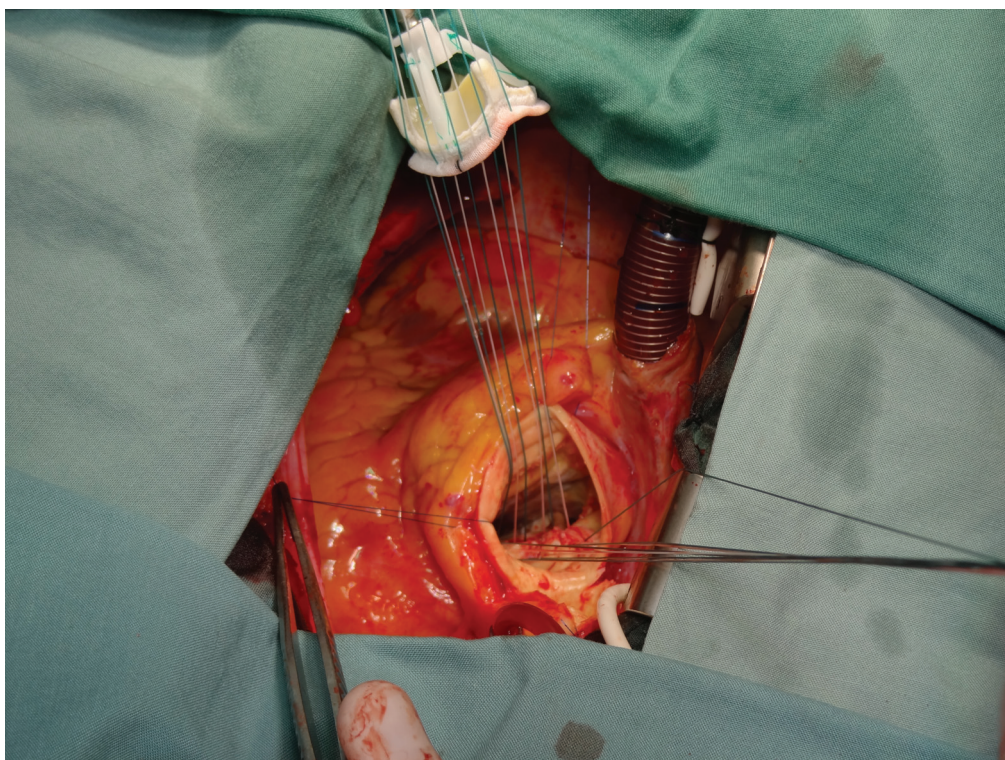


FIGURE 77-4 ■ Alternating green and white valve sutures are systematically passed through the aortic valve annulus and then through the sewing ring of the prosthetic valve traveling from the commissure between the left and right coronary cusps to the commissure between the left coronary and noncoronary cusps.

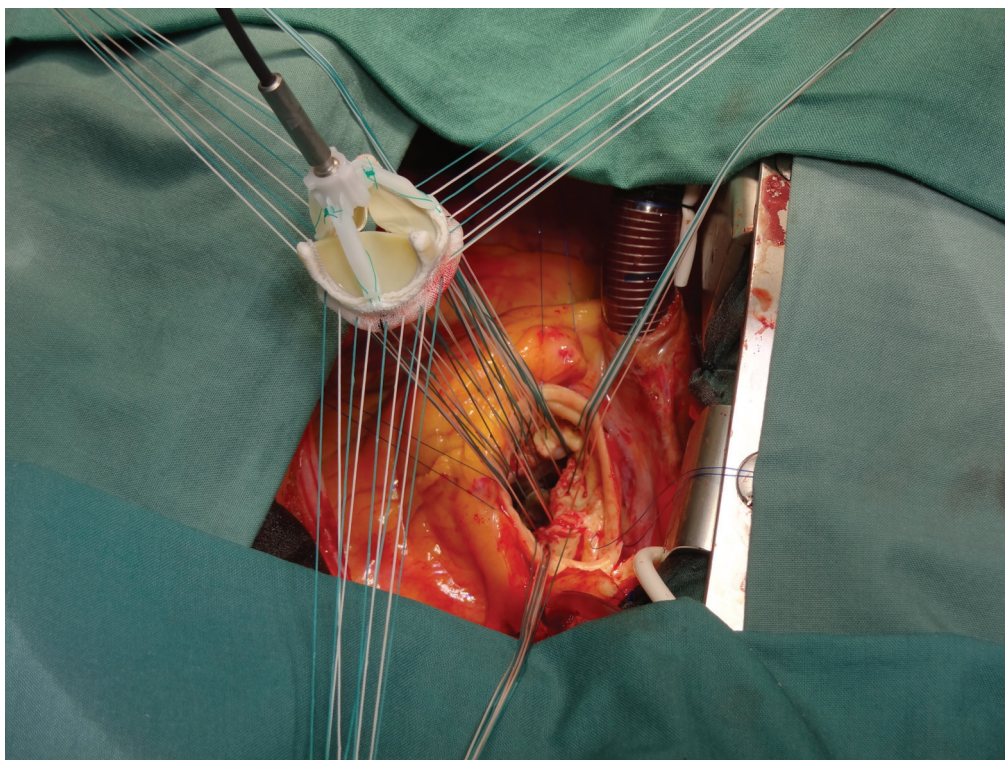


FIGURE 77-5 ■ All valve sutures have been placed around the annulus and through the sewing ring of the valve.

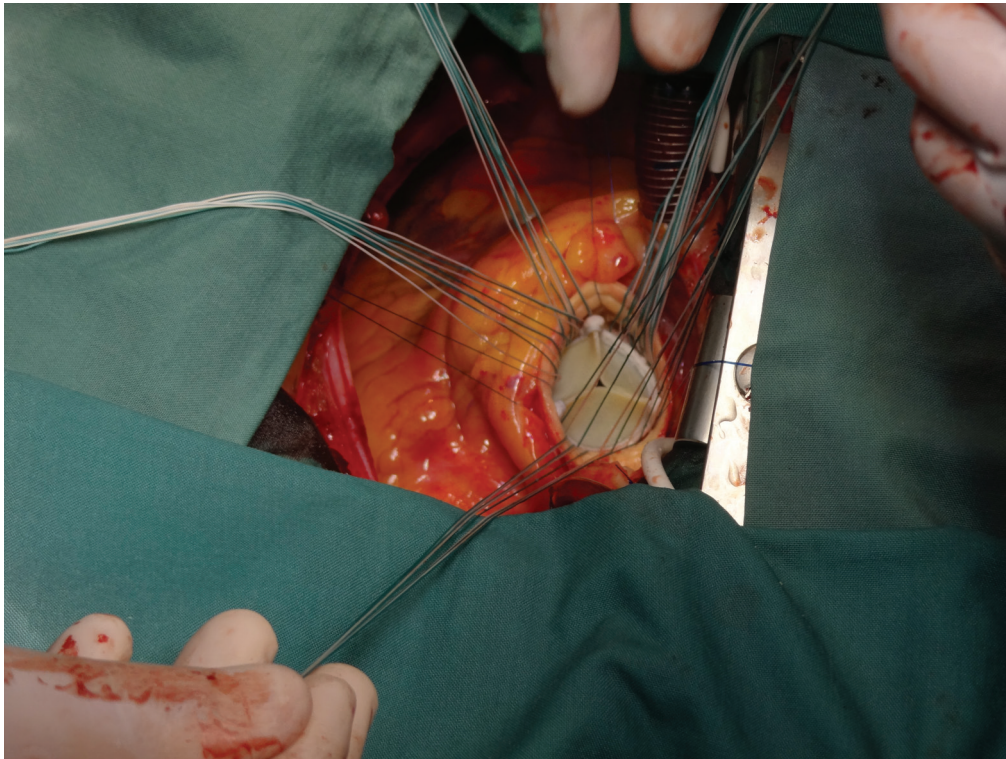


FIGURE 77-6 ■ The prosthetic valve is parachuted down into position by the surgeon who holds one set of valve sutures and the prosthetic valve along with the valve holder. The assistant holds the other two sets of valve sutures. The surgeon and assistant pull on the valve sutures while the surgeon parachutes the valve down into position.

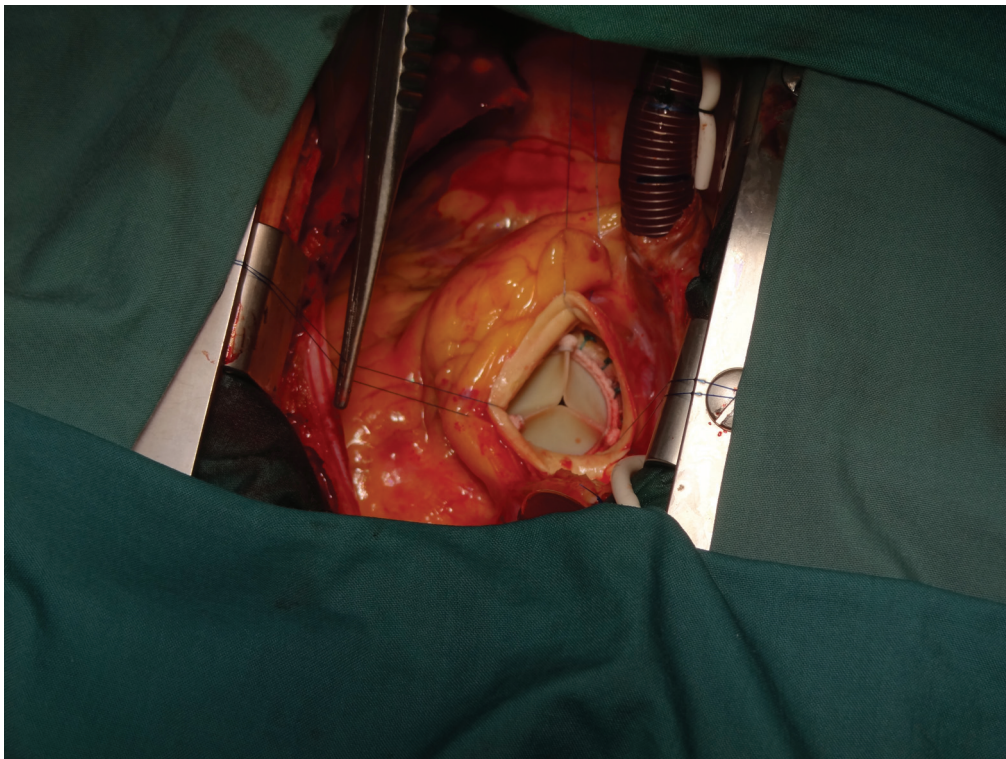


FIGURE 77-7 ■ Picture of prosthetic aortic valve in position after tying all valve sutures systematically beginning with the left coronary cusp, followed by the right coronary cusp, and then the noncoronary cusp.

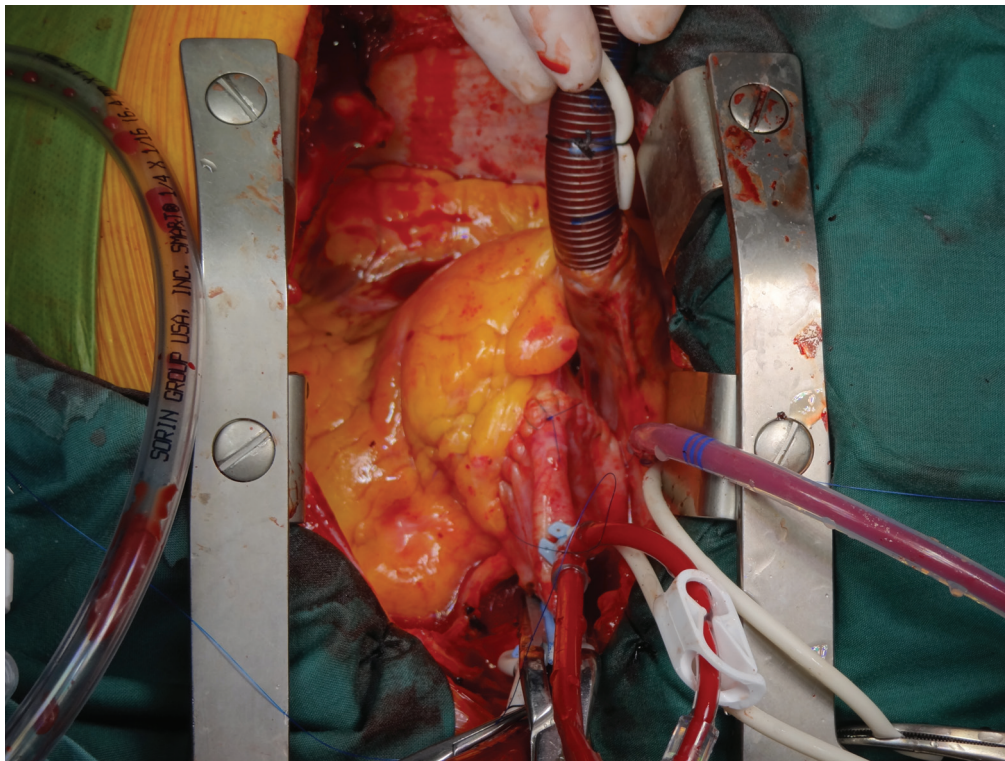


FIGURE 77-8 ■ Closure of the aortotomy can be performed using a one- (depicted in picture) or two-layer technique.

added to the heart, the pulmonary vent is temporarily turned off, the lungs are ventilated, and the left ventricle is gently massaged to displace the intracardiac air into the aortic root vent. After placing the patient in Trendelenburg position, the aortic cross-clamp is removed and the pulmonary vent resumed.

Using transesophageal echocardiography (TEE), paravalvular leak is ruled out, hemodynamic performance of the valve is assessed, and any remaining intracavitary air is detected and removed using additional de-airing maneuvers such as digitally tapping areas found to have a collection of air on TEE or allowing the heart to eject with the aortic root vent on suction. Alternatively, a needle can be used to aspirate the air through the left ventricular apex. All patients undergoing an AVR should receive both atrial and ventricular temporary pacing wires, as there is higher risk of atrioventricular blocks and other arrhythmias following this surgery. The patient is weaned from cardiopulmonary bypass, heparin is reversed with protamine, the cannulae are removed, and the incisions are closed in the usual fashion.

Aortic Root Enlargement

In patients with a small aortic annulus, implanting a small stented bioprosthetic valve or a mechanical valve may leave residual gradient across the aortic valve. Forcing a small prosthetic valve may result in perivalvular leak or disruption of the aorta or left ventricle. Ideally, the patient with a small aortic annulus should be identified preoperatively for optimal planning. However, in some cases precise sizing can only be achieved

intraoperatively. If there is a concern about the possibility of prosthesis-patient mismatch (see later), a root enlargement procedure may be performed. Alternatively, stentless tissue valves or mechanical valves, which have larger effective orifice areas, may be used.

Three different aortic root enlargement techniques have been described. Posterior enlargement of the aortic root (Fig. 77-9) is performed by either the Nicks-Nunez⁸ or the Rittenhouse-Manouguian⁹ technique, whereas anterior enlargement is performed using the Konno-Rastan^{10,11} aortoventriculoplasty technique.

Nicks-Nunez Technique

The Nicks-Nunez method (Fig. 77-10) of aortic root enlargement involves a vertical incision through the commissure between the left coronary and noncoronary cusp and extending down in the interleaflet triangle, followed by patch reconstruction of the aortic root. This method can enlarge the aortic root by 2-3 mm. If larger enlargement is needed, the incision must be extended beyond the interleaflet triangle into the anterior leaflet of the mitral valve and the left atrial roof. After making the incision, either an autologous pericardium or a prosthetic patch is fashioned into a diamond shape. One end of the patch is sewed onto the deep end of the enlarging incision at the level of the aortic-mitral continuity if the incision stopped at the interleaflet triangle. Interrupted pledgeted horizontal mattress sutures are used at the interleaflet triangle and the needles are passed through the sewing ring of the prosthetic valve. The rest of the valve sutures are placed through the aortic annulus as described above.

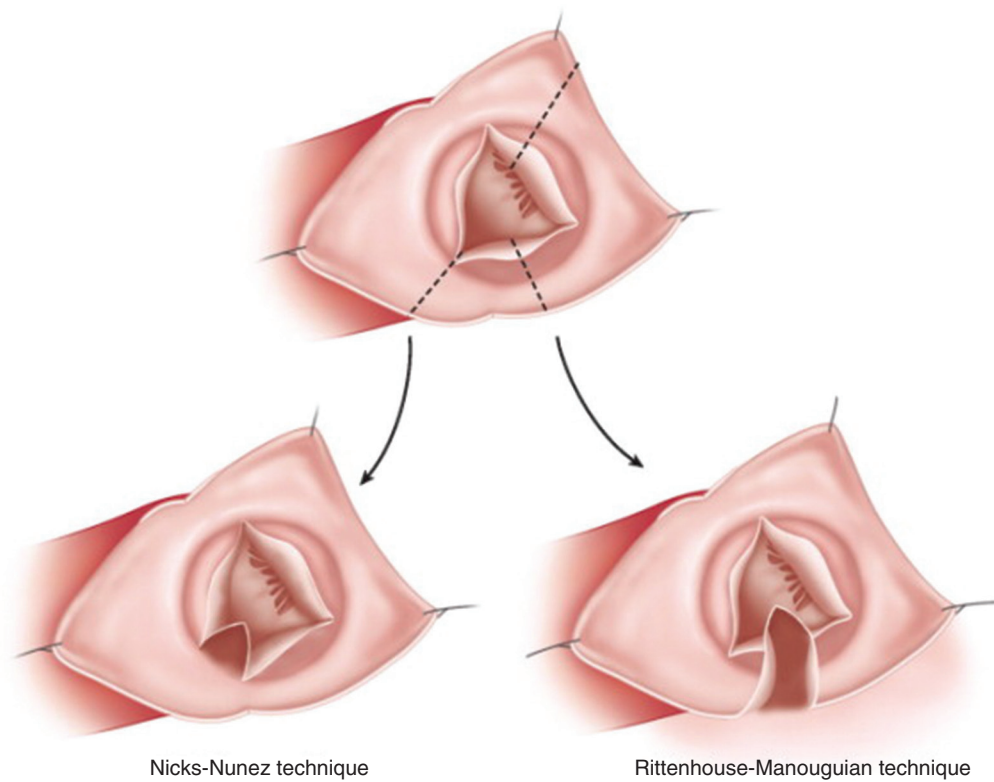


FIGURE 77-9 ■ Posterior enlargement of the aortic root using either the Nicks-Nunez or the Rittenhouse-Manouguian technique.

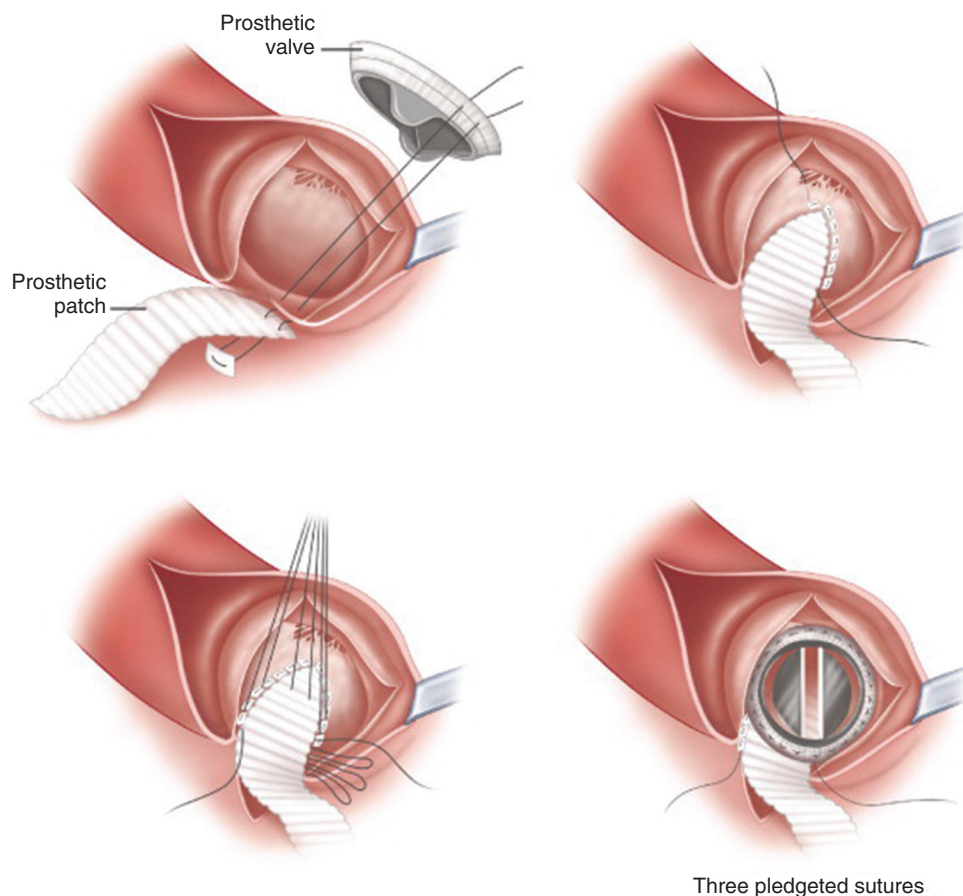


FIGURE 77-10 ■ A diamond-shaped patch of autologous pericardium or prosthetic material is fashioned. One end of the patch is inserted into the distal end of the enlargement using interrupted sutures with pledgets. At the level of the aortic annulus the sutures are passed through the sewing ring of the prosthetic valve. The remainder of the valve sutures are placed through the aortic annulus in a standard fashion.

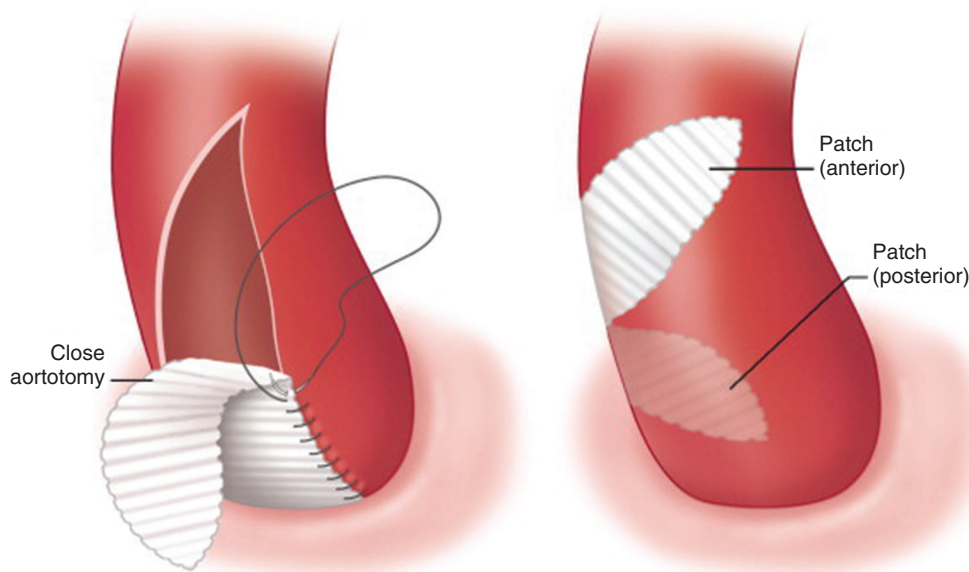


FIGURE 77-11 ■ The diamond patch is then tailored for closure of the aortotomy. If a transverse aortotomy is used, then the patch is transected at the level of the transverse aortotomy and incorporated as part of the anastomosis of the aortic root to the ascending aorta.

If the enlarging incision was extended onto the anterior leaflet of the mitral valve and the left atrium, the diamond-shaped patch is similarly first sewed at the deepest end of the incision, repairing the mitral leaflet. Interrupted sutures without pledgets are used for the mitral leaflet portion. At the level of the annulus, interrupted pledgeted horizontal mattress sutures are passed through the annulus, then the patch, and lastly into the sewing ring of the prosthetic valve. After the valve is tied down, the remaining proximal end of the patch is tailored to close the aortotomy if an oblique incision is used (Fig. 77-11), or cut flat at the level of the transverse aortotomy and incorporated into the anastomosis of the ascending aorta to the aortic root.

Rittenhouse-Manouguian Technique

The Rittenhouse-Manouguian method of aortic root enlargement involves a vertical incision through the middle of the noncoronary sinus extending through the annulus and into the anterior leaflet of the mitral valve. After the incision is made, the patch reconstruction is similar to the Nick-Nunez technique described in the previous paragraph.

Konno-Rastan Technique

The Konno-Rastan method of aortic root enlargement is an anterior root enlargement technique, or aortoven-triculoplasty, whereby a vertical aortotomy is extended into the right coronary sinus left of the right coronary artery, through the aortic annulus near the commissure between the right and left coronary cusps, and into the interventricular septum. A second incision is performed on the right ventricular free wall (Fig. 77-12). After the two incisions are made, a diamond- and a triangle-shaped

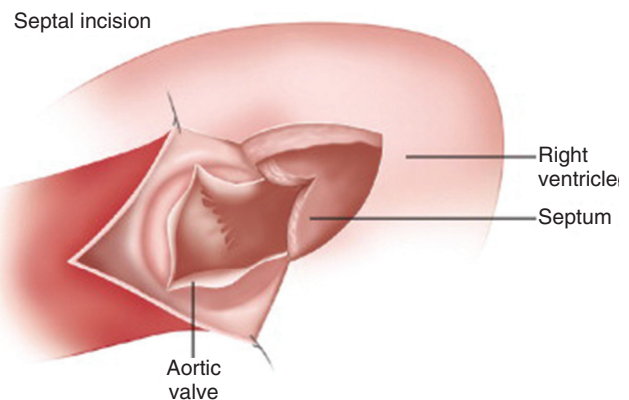


FIGURE 77-12 ■ In the Konno-Rastan method of aortic root enlargement, an incision is made through the right coronary region of the aortic annulus, near the commissure between the left and right coronary cusps. The incision is carried further into the interventricular septum, and a similar incision is made on the right ventricular free wall.

patch are fashioned. One end of the diamond patch is sewed to the deep end of the incision in a continuous fashion to repair the interventricular septum up to the level of the aortic annulus (Fig. 77-13). Then the base of the triangular patch is attached using interrupted pledgeted mattress sutures to the diamond patch at the level of the annulus. The same sutures are also passed through the sewing ring of the prosthetic valve (Fig. 77-14). The rest of the valve sutures are placed through the valve annulus as described above. The triangular patch is then folded to cover the right ventricular outflow tract defect and sewed using continuous running suture. Finally, the left ventricular outflow tract patch is used to close the vertical aortotomy using continuous suture technique (Fig. 77-15).

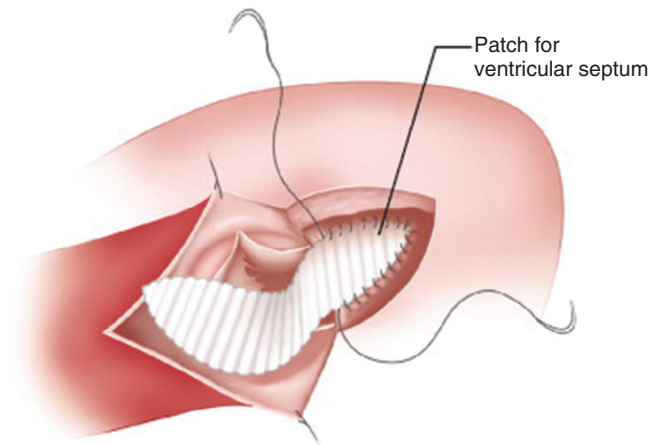


FIGURE 77-13 ■ One end of a diamond patch is sewed to the deep end of the incision in a continuous fashion to repair the inter-ventricular septum up to the level of the aortic annulus.

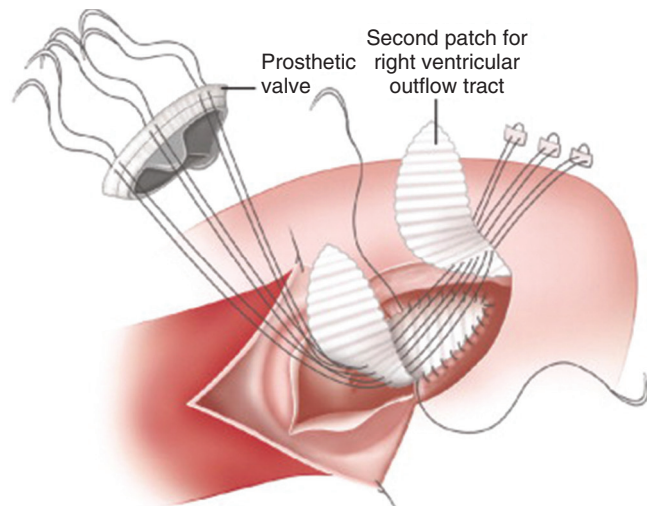


FIGURE 77-14 ■ The base of a triangular patch is attached using interrupted pledgeted mattress sutures to the diamond patch at the level of the annulus. The same sutures are also passed through the sewing ring of the prosthetic valve.

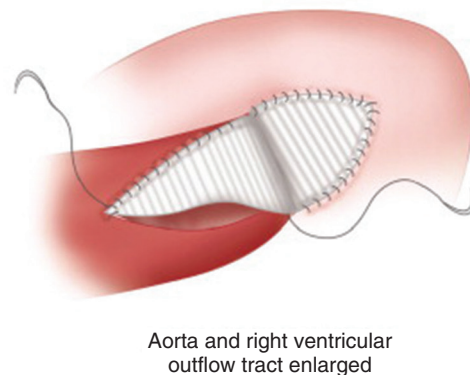
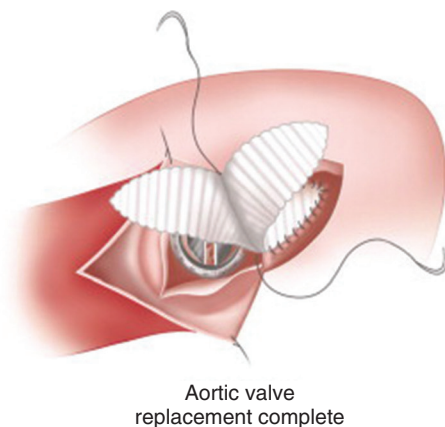


FIGURE 77-15 ■ The triangular patch is then folded to cover the right ventricular outflow tract defect and sewed using continuous running suture. The left ventricular outflow tract patch is finally used to close the vertical aortotomy using continuous suture technique.

SPECIAL CONSIDERATIONS OF POSTOPERATIVE CARE

Postoperative care after AVR is similar to that of other types of cardiac surgery in most regards. However, one important factor to consider is that patients with AS commonly present with LVH, causing decreased left ventricular compliance. Reduction in compliance that occurs during cardiac surgery exacerbates the situation. Therefore, the left ventricle is highly dependent on higher than usual preload for sufficient filling. To that end, filling pressures (central venous pressure) should be kept between 15 and 18 mm Hg with intravenous volume infusions, rather than the usually accepted 8 to 10 mm Hg pressures. Atrial fibrillation, with consequent loss of atrial contractility, is less tolerated in these patients because they are losing up to 20% of their ventricular filling. Rhythm control strategies may be more beneficial in these patients.

OUTCOMES

Early Mortality

Early mortality after AVR is most commonly related to acute cardiac failure, neurologic complications, hemorrhage, and infection. The Society of Thoracic Surgeons (STS) National Database reports a 3.2% 30-day mortality for isolated AVR.¹² When adding CABG, mortality rises to 5.6%.¹³ Although, in the past, isolated reoperative AVR increased the risk of early mortality,^{14,15} it does not appear to do so in the current era.¹⁴ Early mortality has improved with time and continues to do so. In the 1990s early mortality for isolated AVR was approximately 4.3%¹⁵ compared with the more contemporary 3.2%.¹² Similarly, the early mortality of combined AVR and CABG improved significantly with time from 8.0%¹⁵ to 5.6%.¹³ Double valve surgery, including an AVR and either mitral valve or tricuspid valve replacement, raises the operative mortality to 11% to 14%.¹⁶ Triple valve

surgery, including AVR, mitral valve replacement, and tricuspid valve replacement, raises the operative mortality rate to higher than 15%.¹⁶ Risk factors for early mortality include increasing age, higher New York Heart Association (NYHA) functional class, LVH, left ventricular enlargement, presence of aortic regurgitation, renal dysfunction, severe chronic obstructive pulmonary disease (COPD), multiple reoperations, and concomitant CABG or heart valve surgery.¹⁷⁻²¹

Long-Term Survival

Late mortality can be divided into valve-related mortality and non-valve-related cardiac mortality. The former includes deaths caused by structural valve deterioration, nonstructural valve dysfunction, valve thromboembolism, bleeding, valve endocarditis, death related to a reoperation on an operated valve, or sudden and unexpected death in a patient with an operated valve. Non-valve-related mortality comprises other cardiac causes of death, such as progressive heart failure in a patient with a well-functioning prosthetic valve.²² The latter makes up 63% of all deaths in patients with mechanical valves and 59% of all deaths in patients with bioprosthetic valves at 15 years.²³ Although there does not appear to be a survival difference between patients with bioprosthetic and mechanical aortic valves at 10 years,²⁴ structural bioprosthetic valve deterioration leads to a survival benefit for patients with mechanical valves at 15 years follow-up.²³ In contrast, other research has shown that even at 15, 20, and 25 years, there is no survival difference between patients who receive bioprosthetic versus mechanical valves in the aortic position.^{15,21} Risk factors for late mortality include increasing age, higher NYHA functional class, LVH, left ventricular enlargement, left ventricular dysfunction, increased left atrial size, functional mitral regurgitation, atrial fibrillation, ventricular arrhythmia, renal dysfunction, diabetes mellitus, peripheral arterial disease, female gender, smoking, severe COPD, multiple cardiac reoperations, and concomitant CABG or heart valve surgery.^{17-21,25-27}

Early Complications

Neurologic Complications

The joint Society of Thoracic Surgeons/American Association for Thoracic Surgery (STS/AATS) panel subclassified cerebral embolic events into transient ischemic attacks (TIAs), which are fully reversible neurologic events lasting less than 24 hours; reversible ischemic neurologic deficit, which are fully reversible neurologic events lasting between 24 hours and 3 weeks; and strokes, which are nonreversible neurologic deficits lasting longer than 3 weeks.²² The rate of stroke for isolated AVR, according to the STS database, is 1.5%.¹² In high-risk (STS predicted risk of mortality > 10%) and older patients (>80 years old), the risk of stroke rises to between 2% and 4.4%.²⁸⁻³¹ The addition of CABG to the AVR also raises the risk to between 4.9% and 5.8%.^{32,33} Risk factors for early postoperative stroke include low LVEF (<40%), ascending aortic calcification, older than 70 years, female sex, diabetes mellitus, bypass time greater than 120

minutes, a history of stroke, carotid artery disease, and walking less than 300 meters during a 6-minute walk test.³⁴⁻⁴¹ The annual rate of late stroke is 1.3% and 1.4% for bioprosthetic and mechanical valves, respectively. Risk factors for late stroke include female sex, older than 75 years, atrial fibrillation, current or previous smoking, diabetes mellitus, and carotid artery disease.^{42,43} Most postoperative strokes (55% to 76%) occur within the first 24 to 48 hours after surgery, but the high-risk period likely lasts for 3 months after surgery.^{38,44-47} Postoperative stroke is a significant predictor of mortality, raising the mortality rate to 31% for those with early stroke (<24 h) and 14% for those with late stroke (>24 h) compared with the baseline 4.6% mortality rate in one study.³⁸ Although early strokes seem to be related to the operation, late strokes are more influenced by patient- and disease-related factors.⁴⁷

Approximately one third of patients who have undergone cardiac surgery experience postoperative delirium.⁴⁸ Preexisting organic mental disorders, significant prior alcohol consumption, advanced age, intracranial cerebral artery disease, and longer cardiopulmonary bypass time are risk factors for postoperative delirium.^{48,49} Perioperative medications such as opiates and sedatives are known contributors as well.⁴⁹

In one study, postoperative neurocognitive deficits detected on neuropsychiatric testing were identified in 38% of patients at discharge and 19% of patients at 3 months. These changes were not associated with clinically important differences in outcome or in quality of life.⁵⁰

Heart Block and Permanent Pacemaker Implantation

Atrioventricular node block occurs more frequently after heart valve surgery compared with other types of cardiac surgery, with 3% to 8% of patients requiring permanent pacemaker insertion.^{30,51,52} It is rather a unique feature of valve surgery, and it is because of the close proximity of the conduction system to the aortic valve in the area of the membranous septum. Judicious decalcification must be exercised and shallower needle bites must be taken at the level of the commissure between the non-coronary and right coronary cusps. Heart block may be transient because of edema of the tissues around the conduction system. However, if a patient remains pacer-dependent 7 to 10 days postoperatively, we recommend a permanent pacemaker insertion. Predictors of complete heart block and permanent pacemaker insertion include preoperative first-degree atrioventricular block or bundle branch block, postoperative cardiac arrest, combined aortic and mitral valve surgery, and infective endocarditis.⁵² The type of aortic valve prosthesis used was not an important predictor in one study.⁵²

Late Complications

Thromboembolism, Anticoagulation, and Bleeding Complications

Beyond the 3-month period after surgery when the risk of thromboembolism and bleeding is highest, the risk of

thromboembolism is approximately constant. The overall linearized rate of thromboembolism for mechanical aortic valves is quoted as 2 per 100 patient-years and approximately half of that for bioprosthetic aortic valves, according to one report.⁵³ In another report, the rates of thromboembolism are similar among various mechanical valves, ranging between 1.16% and 1.33%,⁵⁴ with one report quoting a lower rate for the On-X bileaflet mechanical valve (On-X Life Technologies Inc., Austin, TX) at 0.6% per year.⁵⁵ The rates are also comparable among different stented bioprosthetic valves, ranging between 0.78% and 1.22% per year.⁵⁴ However, the rate is much lower for allografts with a median of 0.23% per year.⁵⁴ Bleeding rates from anticoagulation appear to be independent of the prosthesis and range from 1% to 2% per year in a recent report.⁵⁴ Fluctuations in the international normalized ratio (INR) seem to be an important risk factor for both thromboembolic and bleeding events.^{56,57} Therefore, close monitoring of the INR to minimize fluctuations may be important to prevent these complications.⁵⁷ New point-of-care home testing may aid in achieving this goal.⁵⁸ Anticoagulation with a minimum target INR of 2.0 to 3.0 for low-risk patients and valves with low thrombogenicity (bileaflet valves) is recommended for mechanical AVR.⁵⁹⁻⁶¹ However, interim results from the first limb of the Prospective Randomized On-X Anticoagulation Clinical Trial (PROACT) suggest that INR may be safely maintained between 1.5 and 2.0 with lower risk of bleeding and without a significant increase in thromboembolism.⁶² The target INR should be 2.5 to 3.5 for patients at high risk for thromboembolism or who receive mechanical valves with high thrombogenicity (disc valves). For bioprosthetic AVR, the bulk of the evidence favors no anticoagulation in patients at low risk for thromboembolism because antiplatelet therapy suffices in this patient population.^{46,63-70} The recommendations are shifting from anticoagulation in the first 3 months followed by antiplatelet therapy thereafter in low-risk patients to only antiplatelet therapy right after surgery.⁵⁹⁻⁶¹ Patients at high risk for thromboembolism should have a different consideration and anticoagulation may be warranted in this group.

Prosthesis thrombosis is a serious but rare complication of AVR that occurs in less than 0.2% of cases per year.⁷¹ It is more common in mechanical valves. Although often ineffective, thrombolysis may be attempted in patients with heart failure caused by valve dysfunction and who are considered too high risk for surgery.⁷² Surgical thrombectomy or re-replacement of the prosthetic valve is usually required and is associated with a high mortality rate of 10% to 15%.^{71,72}

Prosthetic Valve Endocarditis

Prosthetic valve endocarditis (PVE) is a serious complication of AVR and is divided into early PVE if it occurs less than 60 days post implantation and late PVE if it occurs more than 60 days post implantation. The rate of PVE is approximately 0.5% to 1% per year, with a slightly higher rate in the first 6 to 12 months compared to less than 12 months.⁷³⁻⁷⁶ Early PVE is usually a result of perioperative seeding of the prosthetic valve either

intraoperatively or from wound infections or indwelling intravascular catheters postoperatively. Late PVE usually results from noncardiac sources of bacteremia or sometimes from insidious infections with less virulent organisms introduced perioperatively. The microbiological profile of early PVE includes *Staphylococcus aureus*, *S. epidermidis*, gram-negative bacteria, and fungal infections. For late PVE, the microbiological profile resembles that of native endocarditis and includes *Streptococcus* and *Staphylococcus* species. Patients presenting with fever after an AVR should be thoroughly investigated for PVE. Serial blood cultures and transthoracic or transesophageal echocardiography are important components of the diagnostic workup. Surgical indications for the management of PVE include early PVE, valve dysfunction including dehiscence or paravalvular leak, associated heart failure, presence of new conduction defect, abscess, aneurysm or fistula, persistent bacteremia despite maximum and appropriate medical therapy, vegetations larger than 10 mm in size, systemic embolization, all fungal infections, and virulent strains of *S. aureus*, *Serratia marcescens*, and *Pseudomonas aeruginosa*. The timing of surgery has been an area of debate. Sterilization of the valve is ideal before reoperation and is more likely if the vegetation is limited to the leaflets without annular involvement. Strokes from septic emboli are a common occurrence in patients with PVE, and differentiating ischemic stroke from hemorrhagic stroke is important because the former does not adversely affect outcome after reoperation whereas the latter does.⁷⁷ Computed tomography is an important modality in patients with neurologic signs or symptoms of stroke. The outcome following PVE is poor. Early PVE is associated with 30% to 80% mortality, whereas late PVE is associated with 20% to 40% mortality.⁷⁸

Structural Valve Deterioration and Freedom from Reoperation

In the quest for the ideal valve, new valves are constantly being introduced to the market after testing and short-term clinical trials, making the choice between different valves for AVR a challenge. An in-depth discussion of the different valve types is found in Chapter 76. We limit the discussion in this section to structural valve deterioration (SVD) and freedom from reoperation of mechanical and bioprosthetic valves in the aortic position. Third-generation bileaflet mechanical valves have high structural integrity, and SVD is not observed or reported in several large series totaling more than 50,000 patient-years of follow-up.⁷⁹⁻⁸² The durability of these valves is excellent, resulting in a freedom from reoperation of approximately 94% at 10 years⁸² and in one report up to 98% at 25 years after surgery.^{79,83}

Glutaraldehyde-treated biological valves are subject to degenerative changes and calcification with time. Therapies to mitigate these processes help to slow down SVD and include using compounds such as surfactants, alpha oleic acid, and ethanol. The use of bioprosthetic valves has increased dramatically over the past couple of decades, increasing from 42% in 1996 to 82% in 2011.⁸⁴ Although the risk of thromboembolism and anticoagulation-related

bleeding events is lower in bioprosthetic valves, the concern about higher rates of SVD and perhaps higher rates of PVE remains.⁸³ Surgeons must therefore balance between the risks and benefits of various valve choices. There is no convincing evidence to suggest that various second-generation pericardial and porcine bioprostheses differ in longevity; therefore, choice of the valve should depend on surgeon comfort and institutional preferences. Age is an important contributing factor to SVD in patients with bioprosthetic valves. Younger patients seem to have an accelerated rate of SVD probably as a result of a combination of factors, such as calcium metabolism and hemodynamics. In all series, patients older than 70 years have a greater than 90% freedom from reoperation at 15 to 25 years. This rate falls slowly in patients 60 to 70 years old, and precipitously in patients younger than 60 years.⁸⁵⁻⁹⁶ Actuarial freedom from reoperation in these studies probably overestimates the rate of SVD compared with actual freedom. In a recent report, the reoperation rate was 4% at 25 years after bioprosthetic AVR, with 2.6% due to SVD.⁸⁸

Paravalvular Leak and Hemolysis

The continuous suture technique of aortic valve implantation was traditionally thought to be a risk factor for paravalvular leak compared with an interrupted suture technique. However, recent reports show no difference in the rate of paravalvular leak between the two suture techniques.⁹⁷⁻⁹⁹ In the absence of infection, important paravalvular leak in mechanical or bioprosthetic aortic valves is uncommon, although minor leaks may occur.¹⁰⁰ A contemporary report quotes a 0.01% annual rate.⁷⁹ If a paravalvular leak occurs, it can usually be detected in the first few months after surgery.⁷³ There may be an anatomic predisposition in the area extending from the right and noncoronary commissure to one third the distance along the right coronary cusp in one direction and two thirds the distance along the noncoronary cusp in the other direction.¹⁰¹ Minor hemolysis may be managed conservatively, whereas clinically significant hemolysis requires surgical intervention.

Symptomatic Relief

Most surviving patients experience significant functional improvement after an AVR, with 70% to 90% of patients in NYHA functional classes II through IV becoming class I.¹⁰² Even 10 years after surgery, 90% of patients remain in NYHA class I or II.

Left Ventricular Remodeling

Increased left ventricular mass (LVM) is a common occurrence later in patients with aortic valve disease, either through concentric LVH in AS or through left ventricular dilation and eccentric hypertrophy in aortic regurgitation. Increased LVM is a strong negative prognostic factor in aortic valve disease.^{103,104} AVR relieves the left ventricular pressure and volume overload in AS and aortic regurgitation, allowing the left ventricular myocardium to remodel and the LVM to regress. Left

ventricular remodeling occurs in the first 18 months after surgery but can last up to 5 years.¹⁰⁵⁻¹⁰⁷ However, in patients with decreased left ventricular contractility, signifying late-stage aortic valve disease, or reduced exercise capacity preoperatively, remodeling may fail to occur.^{106,108-111} Myocardial gene expression of microRNA-133a (miR-133a) is currently being explored as a potential predictor of left ventricular remodeling in patients with AS, with several reports demonstrating promising results.¹¹²⁻¹¹⁴ Further research may clarify the role of miR-133a in AVR decision making, especially in asymptomatic patients with signs of LVH. The presence of prosthesis-patient mismatch may also hinder LVM regression, as discussed in the next subsection.

Prosthesis-Patient Mismatch

The theoretical goal of an AVR is to reduce the pressure and volume overload on the left ventricle. Although transprosthetic gradients postoperatively should be minimal to allow left ventricular remodeling, high gradients are occasionally seen despite an appropriately functioning valve. The persistence of left ventricular outflow obstruction postoperatively is termed *prosthesis-patient mismatch* (PPM).^{115,116} The parameter that most consistently correlates with postoperative transprosthetic gradients is the effective orifice area (EOA) indexed to the patient's body surface area or, indexed effective orifice area (IEOA).¹¹⁶ The EOA is measured by echocardiography using the continuity equation or by cardiac catheterization using the Gorlin formula. An IEOA of 0.65 to 0.85 cm²/m² is generally defined as moderate PPM, and less than 0.65 cm²/m² is defined as severe PPM. The prevalence of moderate PPM ranges from 20% to 70% and severe PPM ranges from 2% to 11%.¹¹⁵ The significance of PPM is a controversial topic and may depend on the definition of PPM used in various studies. Some studies have shown that PPM does not influence mid-term and long-term survival or left ventricular mass at mid-term follow-up.^{18,117,118} In contrast, other groups have shown that PPM after AVR is associated with less improvement in functional status, less regression of LVH, higher risk of congestive heart failure, and increased long-term mortality.¹¹⁹⁻¹²³ Patients with left ventricular dysfunction, including low-gradient AS, and younger patients (<60 years) who may be more active are particularly susceptible to PPM.^{119,124-127} Several options exist if a surgeon anticipates PPM in a large patient with a small aortic annulus. In young active patients or patients with left ventricular dysfunction (ejection fraction < 50%) choosing prosthetic valves with larger IEOAs according to manufacturer-available user-friendly charts is one option. Aortic root enlargement is another method to allow for the implantation of larger prosthetic valve sizes. However, in older and sedentary patients, the extra risk in performing aortic root enlargement may not be worth the benefit of the extra valve size, and a certain amount of PPM may need to be accepted.¹²⁸

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AORTIC VALVE REPAIR

Munir Boodhwani • Gebrine El Khoury

CHAPTER OUTLINE

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Bicuspid Aortic Valve Repair
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Valve-Related Complications

CONCLUSION

Aortic valve replacement remains the gold standard for the treatment of severe aortic valve disease. However, valve repair is emerging as a feasible and attractive alternative to valve replacement in selected patients. Valve repair can reduce or eliminate the risks of prosthesis-related complications including thromboembolism, endocarditis, anticoagulant-related hemorrhage, and reoperation owing to structural valve deterioration among others. Analogous to the mitral valve, a reconstructive approach to the aortic valve requires a thorough and detailed understanding of three-dimensional valve anatomy, valve function, assessment and classification of pathologic lesions, and treatment of all affected components of the valve. In this chapter, we review the key features of aortic valve insufficiency, aortic valve and root anatomy, an approach to valve assessment and lesion classification, and a demonstration of commonly used reparative techniques for aortic valve repair. Furthermore, we review the outcomes of aortic valve repair in unselected cohorts and in distinct subsets of patients undergoing aortic valve preservation and repair.

AORTIC REGURGITATION

Epidemiology and Etiology

The causes of aortic regurgitation (AR) are numerous and can be attributed to a disturbance in any of the components of the functional unit of the aortic valve (e.g., cusps, sinuses of Valsalva, sinotubular junction, ventriculoaortic junction). In general, the causes can be divided into those that affect the valve cusps (e.g., calcific degeneration, congenitally bicuspid valve, infective endocarditis, rheumatic disease, myxomatous degeneration) and those that affect the aortic root (e.g., aortic dissection, aortitis of various etiologies such as syphilis, connective tissue disorders such as Marfan syndrome).

Pathophysiology

The pathophysiology of AR is dependent on the acuity of onset and duration of the disease process. In acute AR, typically caused by aortic dissection, infective

endocarditis, trauma, or valve prosthesis failure, there is a sudden increase in left ventricular end-diastolic volume because of the regurgitation. Since the left ventricle has limited compliance and does not have time to adapt, the left ventricular end-diastolic pressure (LVEDP) rises rapidly.

In chronic AR, there is a slow and insidious progression of left ventricular (LV) dilation and eccentric hypertrophy because of an increase in left ventricular end-diastolic volume, LVEDP, and wall stress. Dilation of the LV, while maintaining normal systolic function, increases total stroke volume and maintains forward flow.¹ This increase in stroke volume coupled with an increase in LVEDP is associated with the wide pulse pressure typical of chronic AR. Eventually, the hypertrophic response is exhausted, and LVEF drops as afterload increases, leading to heart failure and its associated clinical presentation.^{2,3}

Clinical Features

Patients with acute AR usually exhibit sudden or rapidly progressive cardiovascular collapse, which can be life threatening if not addressed promptly. They often exhibit ischemic symptoms because of the decrease in coronary blood flow and increased myocardial oxygen demand. In contrast, patients with chronic AR are asymptomatic for a long period of time because of the compensatory LV changes discussed earlier. Once the compensatory response is exhausted, the patients start having heart failure symptoms such as exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Patients may also feel palpitations and angina.

The classic murmur of AR is an early diastolic, blowing, decrescendo murmur heard best at the level of the diaphragm at the left sternal border while the patient is sitting, leaning forward, and in deep exhalation. It may become holodiastolic in severe AR, and isometric exercises tend to accentuate the murmur. Classic signs of widened pulse pressure may also be found, including Corrigan or water-hammer pulse, De Musset sign (bobbing of the head with heart beats), Quincke pulse (pulsations of the lip and fingers), Traube sign (pistol shot sounds over the femoral artery), and Müller sign (pulsations of the uvula).

Diagnostic Criteria

Transthoracic echocardiography with Doppler color-flow is the most useful tool for the diagnosis of AR.⁴ The jet width and vena contracta width on Doppler color-flow are used to qualitatively assess the severity of AR, whereas the regurgitant volume, regurgitant fraction, and regurgitant orifice area are used for the quantitative assessment.

Indications for Surgery

Decision making for surgical intervention for aortic valve surgery needs to incorporate the natural history of medically managed disease, the risks associated with surgical intervention, and longer-term risks that might accrue

related to prosthetic valve implantation. The class I recommendations for aortic valve intervention in patients with AR according to the 2014 American College of Cardiology and the American Heart Association⁵ are the following: symptomatic patients with chronic severe AR, asymptomatic patients with chronic severe AR and LV dysfunction (ejection fraction < 50%) at rest, and patients with chronic severe AR who are undergoing concomitant coronary artery bypass grafting, aortic surgery, or other heart valve surgery.

The class IIa recommendation is for patients with asymptomatic AR and normal LV systolic function (ejection fraction > 50%) but with severe LV dilation (end-systolic diameter > 50 mm). The class IIb recommendation is for patients with moderate AR who are undergoing coronary artery bypass grafting, aortic surgery, or other heart valve surgery. Aortic valve intervention may also be reasonable in asymptomatic patients with chronic severe AR, normal LV systolic function, and severe LV dilation (end-diastolic diameter > 65 mm) if the operative risk is low. Other considerations can include evidence of progressive LV dilation, declining exercise tolerance, or abnormal hemodynamic response to exercise.

However, aortic valve repair carries a similar, if not lower, risk of perioperative complication with a low risk of valve-related events over time. Similar to mitral valve repair for mitral regurgitation,⁶ there is some suggestion that aortic valve intervention should be considered earlier in patients in whom aortic valve repair is likely.⁷

Another broad category of patients who undergo aortic valve preservation and repair are those with primary aortic pathology involving the aortic root and/or the ascending aorta and varying degrees of associated aortic valvular disease. In these patients, the primary indication for intervention is driven by aortic size, discussed in the American,⁸ European,⁹ and Canadian Guidelines.¹⁰

From a technical perspective, all patients with primary aortic insufficiency are potentially candidates for repair. However, the success of aortic valve repair is determined largely by the quality of cusp tissue available. Thus, patients with significant leaflet calcification, destruction owing to active endocarditis, or rheumatic involvement are least likely to undergo successful and durable aortic valve repair.¹¹ In contrast, repair has been shown to have good results in patients with bicuspid^{12,13} (and in smaller series, unicuspid,¹⁴ and quadricuspid¹⁵) aortic valves, despite the abnormalities in cusp anatomy. An important limitation to the universal application of aortic valve repair techniques is the lack of surgical expertise and experience in this field; however, this is changing rapidly with increasing interest in aortic valve repair. Patients who are candidates for repair should be referred to centers with appropriate expertise.

AORTIC VALVE ANATOMY AND FUNCTION

The anatomy of the aortic valve and root is familiar to cardiac surgeons.¹⁶ However, there are some features outlined here that are particularly relevant to aortic valve preserving and repair surgery.¹⁷ Like the mitral valve,

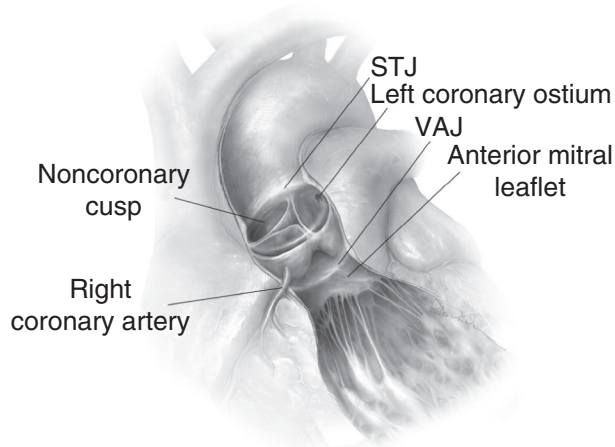


FIGURE 78-1 ■ Anatomy of the aortic valve and the functional aortic annulus. STJ, Sinotubular junction; VAJ, ventriculo-aortic junction.

aortic valve function involves an important interaction between the valve annulus and leaflets. Importantly, however, the annulus of the aortic valve is not a single structure but rather consists of three different components—namely, the sinotubular junction, the ventriculo-aortic junction, and the anatomic crown-shaped annulus, which serves as the insertion point of the aortic valve cusps¹⁸ (Fig. 78-1). These components work together to facilitate normal valve function and together are termed the *functional aortic annulus*. The aortic valve leaflets insert into the aortic annulus proximally at the ventriculo-aortic junction (VAJ) and distally at the sinotubular junction (STJ). In a normal aortic valve, the cusps coapt at the center of the aortic valve orifice with a coaptation height that is approximately at the mid-level between the VAJ and the STJ. The height of the sinuses of Valsalva (from the VAJ to the STJ) corresponds to the external diameter of the STJ, which can be useful to size prostheses for aortic root replacement and to assess cusp geometry after aortic valve repair.

As a functional entity, the aortic valve consists of the functional aortic annulus (FAA), and the valve cusps. The integrity of these two functional components is the basis for good valvular function, and alteration in one of these components is frequently associated with alteration in the other. Thus, a fundamental principle in aortic valve repair is that lesions of the cusps and the FAA should both be addressed at the time of valve repair.

The anatomy of the subvalvular region of the aortic valve and its surrounding structures also has important implications for aortic valve repair¹⁹ (Fig. 78-2). An important observation is that external dissection of the aortic root from its surrounding structures is limited by the membranous septum (at the junction of the noncoronary [NC] and right coronary [RC] cusps) and by ventricular muscle (at the junction of the left coronary [LC] and RC cusps), whereas at all other points, external dissection down to the level of the anatomic valve annulus is possible and necessary when valve-sparing root replacement is performed using the reimplantation technique. Thus, the proximal suture line for the aortic valve

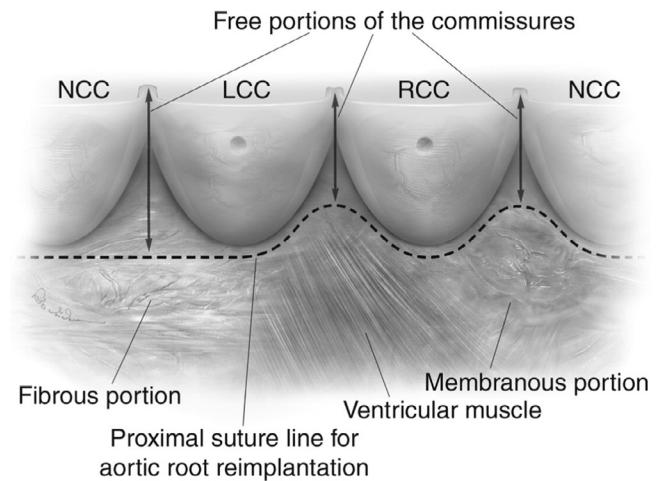


FIGURE 78-2 ■ Anatomy of the subvalvular region of the aortic valve. The dotted line marks the limits of external dissection of the aortic root and the proximal suture line for a valve-sparing root replacement procedure using the reimplantation technique. LCC, Left coronary cusp; NCC, noncoronary cusp; RCC, right coronary cusp.

reimplantation procedure follows these external limitations in a curvilinear fashion.

CLASSIFICATION OF AORTIC INSUFFICIENCY

Until recently, a major limitation to the more generalized application of aortic valve repair techniques was the absence of a common framework for valve assessment to help guide the approach to valve repair. Important lessons in this regard can be learned from the development of mitral valve repair. The Carpentier classification²⁰ of mitral valve insufficiency was responsible, in large part, for the development and generalized dissemination of repair techniques for the mitral valve because it provided a common language for cardiologists, anesthesiologists, and surgeons to communicate about disease mechanisms and pathology. Key characteristics of that classification system were that it encompassed the entire spectrum of disease, it clarified and provided insight into the mechanism of insufficiency, it could be consistently applied using different assessment modalities (i.e., echocardiography and surgical assessment), it guided the repair techniques, and it provided a framework for the assessment of long-term outcome for differing mitral valve pathologies.

Over the past decade, a similar classification of aortic valve insufficiency has been developed with the above characteristics in mind¹¹ (Fig. 78-3). This classification centers on the idea that the aortic valve, much like the mitral valve, consists of two major components: the aortic annulus and the valve leaflets. Contrary to the mitral valve, however, the annulus of the aortic valve is not a single anatomic structure. The functional aortic annulus consists of two separate components, namely the ventriculoaortic junction and the sinotubular junction. As in Carpentier's classification of mitral valve disease,

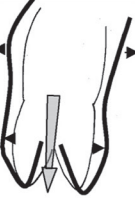
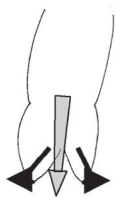
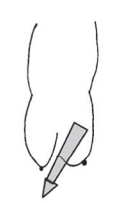
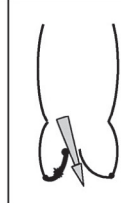
AI Class	Type I Normal cusp motion with FAA dilation or cusp perforation				Type II Cusp prolapse	Type III Cusp restriction
	Ia	Ib	Ic	Id		
Mechanism						
Repair Techniques (Primary)	STJ remodeling <i>Ascending aortic graft</i>	Aortic valve sparing: <i>Reimplantation or Remodeling with SCA</i>	SCA	Patch repair <i>Autologous or bovine pericardium</i>	Prolapse repair <i>Free margin plication Triangular resection Free margin resuspension</i>	Leaflet repair <i>Shaving Decalcification Patch</i>
(Secondary)	SCA		STJ annuloplasty	SCA	SCA	SCA

FIGURE 78-3 ■ Repair-oriented classification of aortic insufficiency. FAA, Functional aortic annulus; SCA, subcommissural annuloplasty; STJ, sinotubular junction.

regurgitation associated with normal leaflet motion is designated as type I. This is largely due to lesions of the functional aortic annulus with type Ia aortic insufficiency (AI) owing to sinotubular junction enlargement and dilation of the ascending aorta, type Ib owing to dilation of the sinuses of Valsalva and the sinotubular junction, type Ic owing to dilation of the ventriculoaortic junction, and lastly type Id owing to cusp perforation without a primary functional aortic annulus lesion. Type II AI is due to leaflet prolapse secondary to excessive cusp tissue or due to commissural disruption. Type III AI is due to leaflet restriction, which can be found in bicuspid, degenerative, or rheumatic valvular disease because of calcification, thickening, and fibrosis of the aortic valve leaflets.

Patients can exhibit either single or multiple lesions contributing to their aortic insufficiency. For example, patients with isolated type Ib AI (owing to dilation of the sinuses of Valsalva) are expected to have a central regurgitant jet. Thus, the presence of a sinus of Valsalva aneurysm with an eccentric AI jet suggests concomitant leaflet prolapse (type II) or restriction (type III). Further assessment of leaflet anatomy can help to better delineate the different mechanisms contributing to AI. Once the mechanism of AI is well understood, the classification system can help to guide the surgeon in the choice of surgical techniques for correction of the pathology.

SURGICAL TECHNIQUES

Exposure and Assessment

Aortic valve repair procedures are generally performed through a median sternotomy. Arterial cannulation is performed distal to any diseased aortic segments, typically in

the distal ascending aorta or aortic arch. Alternatively, axillary artery cannulation may be performed in the setting of aortic arch pathology. A single, two-stage venous cannula is inserted through the right atrial appendage unless alternative cannulation strategies are required to treat coexisting pathology. After cardioplegia, a transverse aortotomy is performed approximately 1 cm above the sinotubular junction starting above the NC sinus and the posterior 2 to 3 cm of aortic wall is left intact. The distal aorta is retracted cephalad. Full-thickness 4-0 polypropylene traction sutures are placed at the three commissures and retracted using clamps, but not tied, to permit a dynamic assessment of valve anatomy. Axial traction is applied (perpendicular to the level of the annular plane) on the commissural traction sutures. This maneuver demonstrates physiologic aortic valve closure position, and the area and height of coaptation is observed. Leaflets are inspected to assess mobility, restriction, calcification, and prolapse. A prolapsing cusp will exhibit a transverse fibrous band at this time, which is also visible on echocardiography¹⁷ (Fig. 78-4).

Interventions on the Aortic Root and Annulus

Type 1 lesions are most frequently due to dilation of the various components of the functional aortic annulus; they can occur in isolation or in association with cusp disease. A type Ia lesion occurs because of a supracoronary ascending aortic aneurysm with concomitant dilation of the STJ. This is corrected by replacing the ascending aorta and remodeling the STJ using a Dacron tube graft. When significant associated AI is present, subcommissural annuloplasty is also performed. Aneurysms of the aortic root (type Ib) are frequently associated with

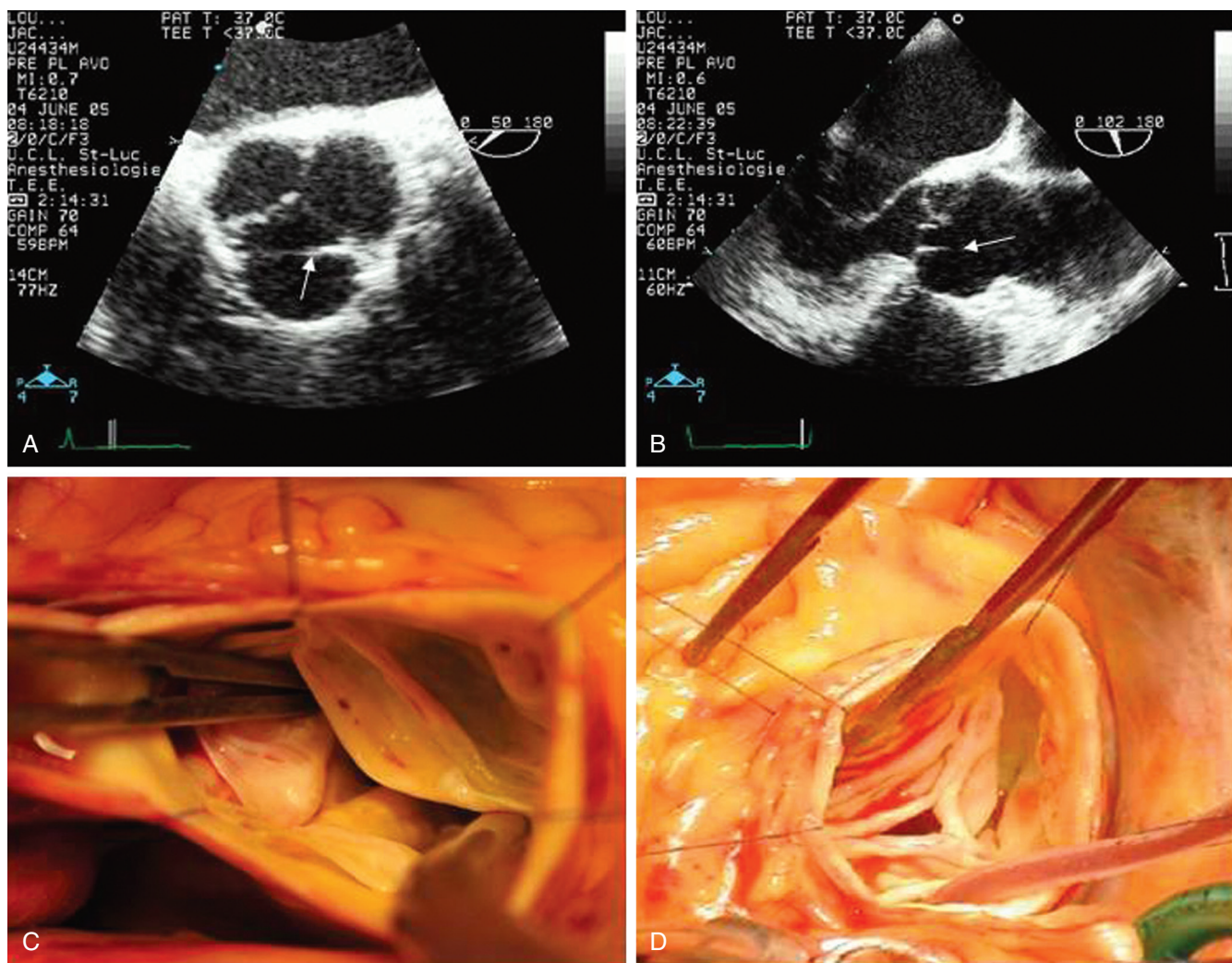


FIGURE 78-4 ■ A and B, A transverse fibrous band is typically visible on echocardiography (arrow) and surgical inspection (C, D) in the setting cusp prolapse in trileaflet aortic valves and may help in the detection and localization of cusp prolapse.

dilation of the STJ and the VAJ. These aneurysms are treated using valve-sparing root replacement, preferentially using the reimplantation technique²¹ because it provides better stabilization of the VAJ. Aortic root remodeling²² can also be used to treat aneurysms of the aortic root, and it is particularly useful when only one or two sinuses are involved or in patients in whom there is no risk of ongoing VAJ dilation.

Subcommissural Annuloplasty

Subcommissural annuloplasty is typically performed at midcommissural height, except at the NC/RC commissure, where it should be performed higher to avoid the membranous septum and conduction tissue (Fig. 78-5). Care should also be taken in this area during tying of the suture, to avoid a tear in the septum. At the other two commissures, the subcommissural annuloplasty can be performed at a lower level if a greater increase in the coaptation surface is desired. A subcommissural annuloplasty reduces the width of the interleaflet triangle, improves cusp coaptation, and can help to stabilize the

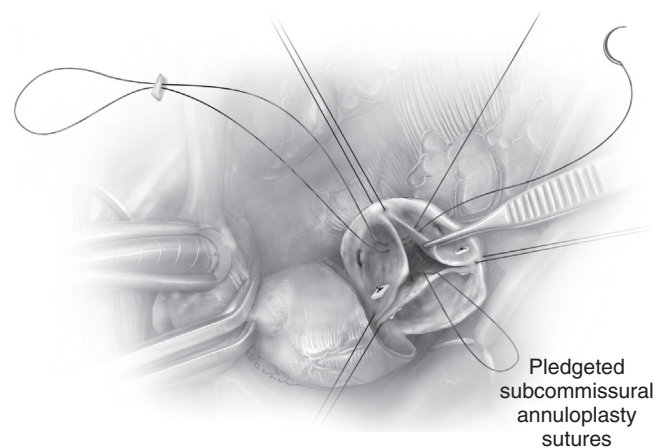


FIGURE 78-5 ■ Subcommissural annuloplasty.

ventriculoaortic junction. In the setting of a bicuspid aortic valve, however, subcommissural is not always sufficient for the prevention of future VAJ dilation.⁴⁹

Valve-Sparing Root Replacement: Reimplantation Technique

A valve-sparing root replacement using the reimplantation technique provides the most stable form of functional aortic annuloplasty. In addition to being used in patients with aortic root aneurysms, this technique can also facilitate aortic valve repair in patients with moderate root dilation in the setting of bicuspid aortic valves. Originally pioneered by David and colleagues, multiple modifications of this procedure have been reported. The important steps of this procedure are described below.²³

Aortic Root Preparation. The key principle is to dissect the aortic root externally as low as possible, given the natural anatomic limitations (i.e., where the root inserts into ventricular muscle). The root dissection is started along the NC sinus and continued towards the LC/NC commissure. In this area, the subannular region of the aortic valve is fibrous and dissection can therefore be

carried to below the level of insertion of the leaflets. Moving toward the RC/NC commissure and along the right sinus and the RC/LC commissure, the dissection is limited by nonfibrous portions of the annulus (Fig. 78-6). The sinuses of Valsalva are then resected leaving approximately 5 mm of aortic wall attached and the coronary buttons are harvested.

Prosthesis Sizing. The three commissural traction sutures are pulled perpendicular to the annular plane with a slight inward motion to ensure good leaflet coaptation. When the leaflets are coapting adequately, a Hagar dilator is used to size the circle that includes the three commissures, and a graft 4 mm larger is chosen as this graft will sit outside the commissural posts. An alternative approach to prosthesis sizing takes advantage of the principle that in a normally functioning aortic valve, the height of the commissure (measured from the base of the interleaflet triangle to the top of the commissure) is equal to external diameter of the sinotubular junction²⁴ (Fig. 78-7). Although various components of the aortic root and the functional aortic annulus may dilate in the setting of root aneurysms, the height of the commissure remains relatively constant. The height of the commissure is most

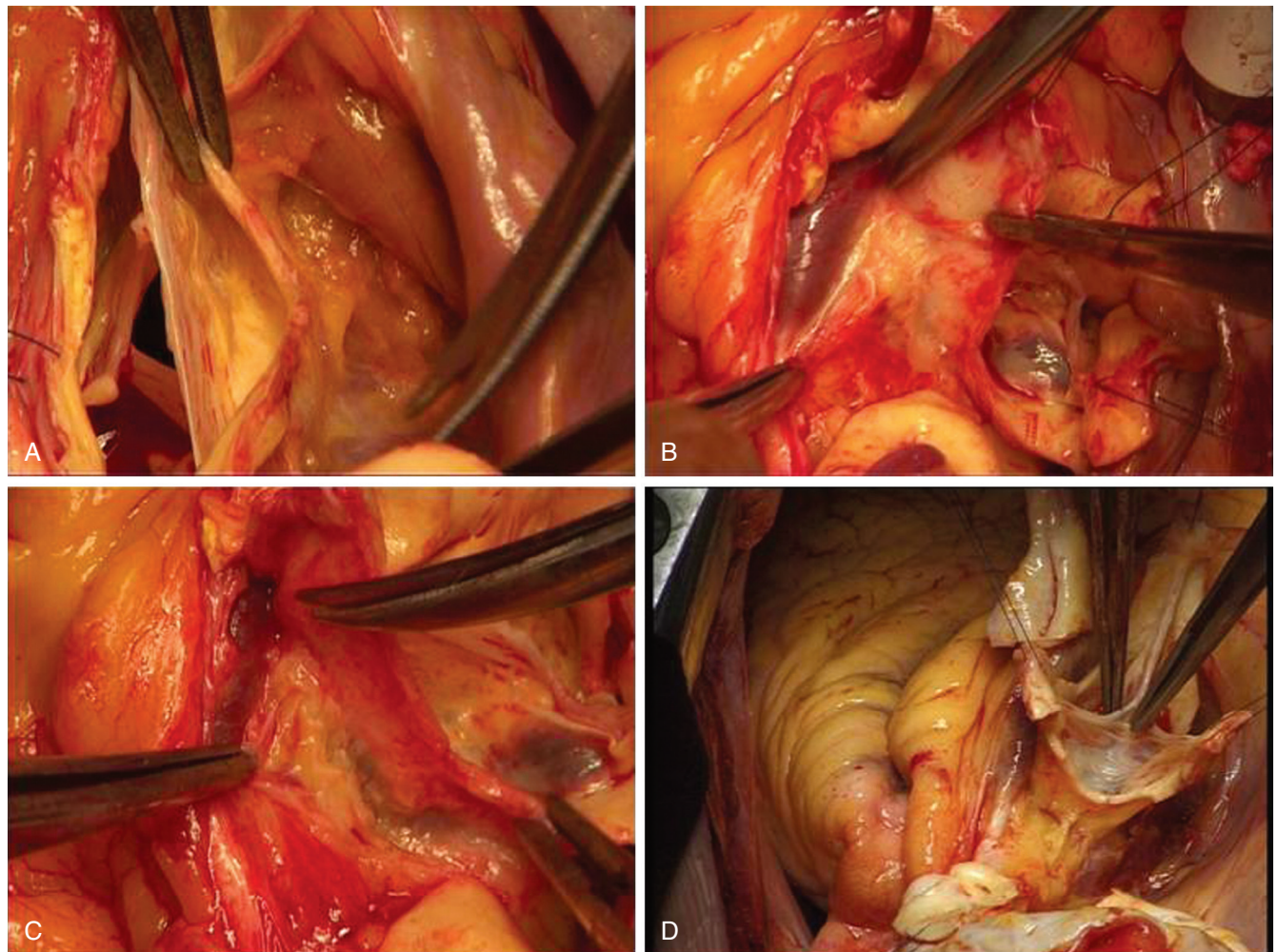


FIGURE 78-6 ■ External dissection for a valve-sparing root replacement procedure using the reimplantation technique.

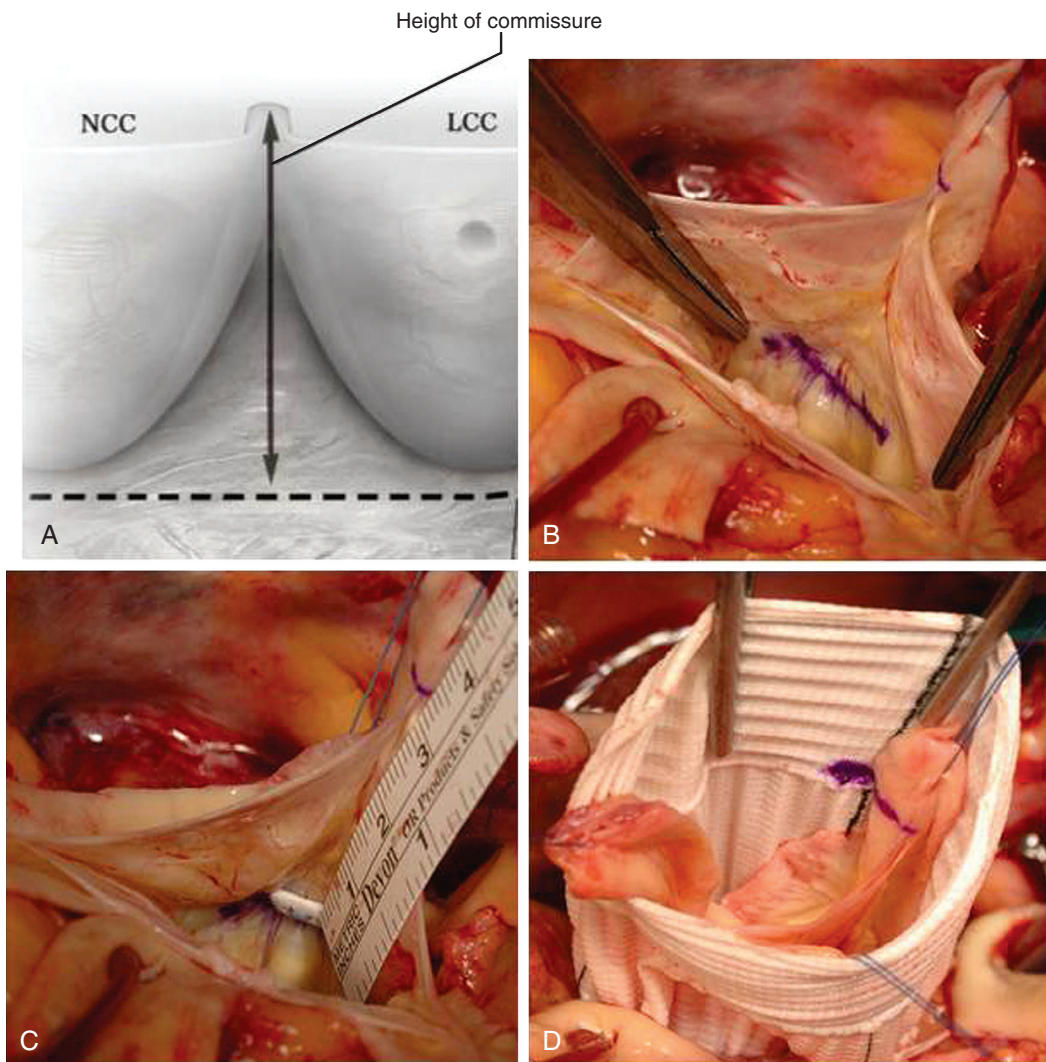


FIGURE 78-7 ■ A novel method for prosthesis sizing when using the reimplantation technique. *LCC*, Left coronary cusp; *NCC*, non-coronary cusp.

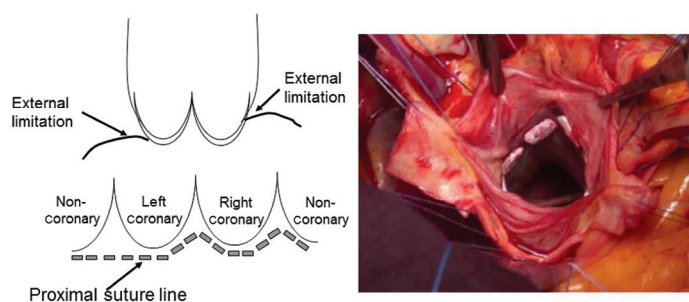


FIGURE 78-8 ■ Proximal suture line for a valve-sparing root replacement procedure using the reimplantation technique.

easily measured at the NC/LC commissure by first drawing a connecting line between the nadirs of the two adjacent cusps (base of interleaflet triangle) and measuring the distance between this line and the top of the commissure. This height corresponds to the diameter of the graft chosen.

Proximal Suture Line. 2-0 Tycron sutures with pledgets are passed from inside to outside the aorta with the pledgets on the inside, starting from the NC/LC

commissure and moving clockwise. Along the fibrous portion of the aortic annulus, these sutures are inserted along the horizontal plane formed by the base of the inter-leaflet triangles. Importantly, however, along the nonfibrous portions of the annulus where the external dissection of the aortic root is limited by muscle, these sutures are inserted along the lowest portion of the freely dissected aortic root, making the proximal suture line slightly higher at the RC/NC and RC/LC commissures compared with the LC/NC commissure (Fig. 78-8).

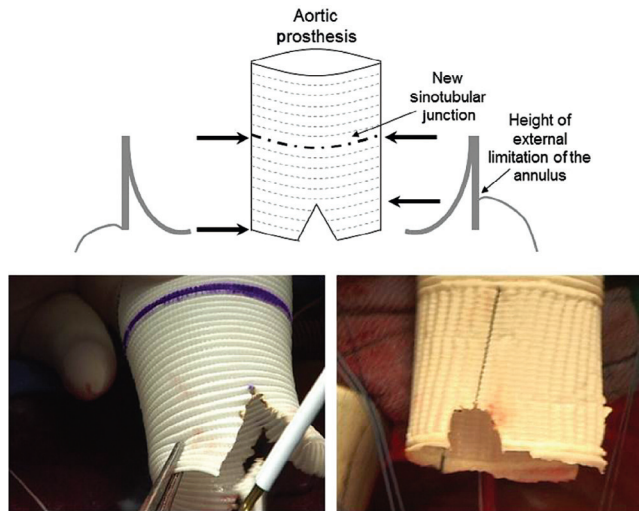


FIGURE 78-9 ■ Tailoring of the prosthesis for the reimplantation technique.

Prosthesis Preparation and Fixation. A Dacron prosthesis with or without built-in neoaortic sinuses can be used. The three commissures are attached to the prosthesis along the same plane—the new sinotubular junction. Because of external limitations of root dissection, the graft has to be tailored. First, the distance from the base of the interleaflet triangle to the top of the commissure is measured at the LC/NC commissure and marked on the graft. Next, at the RC/NC and RC/LC commissures, the distance from the proximal suture to the top of the commissure is measured and used to determine the amount of graft material that needs to be trimmed (Fig. 78-9). The pledgeted sutures are then passed through the base of the prosthesis, respecting the spaces between sutures and the curvilinear contour of the suture line. The commissural traction sutures are pulled up together while tying down the prosthesis to ensure appropriate seating around the aortic annulus.

Valve Reimplantation. The commissures are reimplanted first using 4-0 polypropylene sutures while pulling up on the prosthesis and the native commissure and then tied into place. This running suture line is performed in small regular steps passing the suture from outside the prosthesis to inside and through the aortic wall, staying close to the annulus, and then back out of the prosthesis.

Leaflet Assessment and Repair. After valve reimplantation, it is critical to reexamine the leaflets for any unmasked prolapse, symmetry, and the height and depth of coaptation. Prolapse can be repaired using a variety of techniques described later. Cardioplegia is administered through the distal end of the graft with partial clamping to distend the new aortic root and to assess root pressure and signs of LV dilation. A limited echocardiographic view can be obtained at this time. The cardioplegia solution is then slowly aspirated out of the prosthesis without distorting the leaflets. This gives another visual assessment of the aortic valve in its physiologic closed state as well as the area and height of coaptation. Coronary ostia

are then reimplanted on the graft, and the distal anastomosis is performed at the level of normal aorta.

Alternative Approaches to Aortic Valve Annuloplasty

The reimplantation technique provides the most stable form of annuloplasty of the aortic valve and allows the surgeon to modulate a variety of parameters, including the VAJ, STJ, and cusp and commissural orientation; however, it involves extensive dissection of the aortic valve, root, and surrounding structures, and it necessitates reimplantation of the coronary ostia. In patients with normal-sized aortic roots and dilation of the VAJ, use of the reimplantation procedure for annuloplasty is controversial and can expose the patients to unnecessary risk. Therefore, alternative approaches to annuloplasty of the aortic valve, without root replacement, are currently under development and in various stages of evaluation. External annuloplasty is the most frequently used option using a flexible ring.²⁵ This option is typically used as an adjunct to the remodeling technique for aortic root replacement to provide more VAJ support, but in theory can be used in isolation as well. An important limitation to the external annuloplasty is the inability to place the external ring at the level of the true VAJ because of the limits of external dissection. To overcome this limitation, a number of different internal annuloplasty systems are currently being developed.^{26,27} A suture-based internal VAJ annuloplasty using a large-caliber PTFE suture has also been proposed. However, results of these techniques on long-term valve function are lacking.

Cusp Repair Techniques

Cusp prolapse is the most frequently encountered lesion and is associated with excess length of the free margin, which can be corrected using either central free margin plication or free margin resuspension. When a single cusp is prolapsing, the two nonprolapsing cusps serve as the reference and are used to estimate the required reduction in the free margin length. When two cusps are prolapsing, the third nonprolapsing cusp is used as a reference to indicate the desired height of coaptation. In the rare instance that all the cusps are prolapsing, the goal is to achieve a cusp coaptation height at the midlevel of the sinuses of Valsalva. Alternatively, calipers that permit measurement of effective cusp height can be used.²⁸

Free Margin Plication

The technique for central free margin plication has been described previously²⁹ (Fig. 78-10). A 7-0 polypropylene suture is passed through the center of the two nonprolapsing reference cusps, and gentle axial traction is applied. The prolapsing cusp is gently pulled parallel to the reference cusp, and a 6-0 polypropylene suture is passed through the prolapsing cusp, from the aortic to ventricular side, at the point at which it meets the center of the reference cusp. Next, the direction of traction on the prolapsing cusp is reversed, and the same suture is passed from the ventricular to the aortic side of the cusp

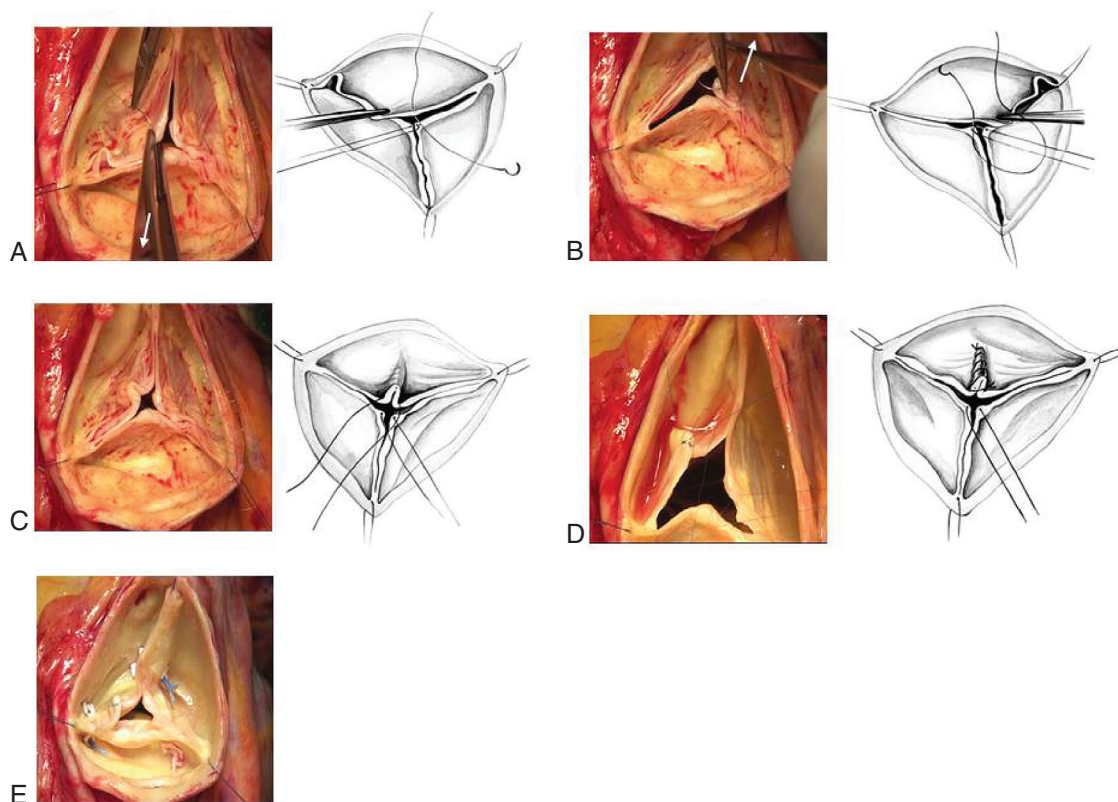


FIGURE 78-10 ■ Free margin plication technique for the correction of cusp prolapse.

where it meets the middle of the reference cusp. The length of cusp free margin between the two ends of this 6-0 suture represents the quantity of excess free margin, which is then plicated by tying this suture with the excess tissue on the aortic side.

The plication is extended by 5 to 10 mm onto the body of the aortic cusp by adding interrupted or running locked 6-0 polypropylene sutures. If there is significant excessive tissue, it can be shaved off using a scalpel or scissors, keeping sufficient tissue to bring the edges together.

Free Margin Resuspension

Excess length of the cusp free margin can also be corrected using resuspension with polytetrafluoroethylene (PTFE) suture^{30,31} (Fig. 78-11). A 7-0 polypropylene suture is first passed through the center (nodule of Arantius) of the two nonprolapsing cusps, which serves as a reference. A 7-0 PTFE suture is passed twice at the top of the commissure. Next, one arm of the suture is passed over the length of the free margin in a running fashion. The suture is locked at the other commissure. A second 7-0 PTFE is then passed in the same fashion along the cusp free margin. The length of the free margin is reduced by applying gentle traction on each branch of the PTFE sutures and applying opposite resistance with a forceps at the middle of the free margin. This maneuver is used to plicate and shorten the free margin until it reaches the same length as the adjacent reference cusp free margin.

The same maneuver is applied for the second half of the free margin. This two-step technique for free margin resuspension allows symmetric and homogenous shortening. When the appropriate amount of free margin shortening is achieved, the two suture ends at each commissure are tied.

This technique can be used in isolation or in combination with other cusp repair techniques, and it is particularly useful in the setting of a fragile free margin with multiple fenestrations or to homogenize the free margin when a pericardial patch is used for cusp augmentation.

Cusp Shaving, Resection, and Patch Use

In contrast to cusp prolapse, management of restrictive cusp pathology owing to localized calcification, inflammatory or rheumatic disease, or bicuspid valve with restrictive raphe (discussed later) can be more challenging. Localized shaving and decalcification of the cusp can be performed, while leaving the cusp surface intact, to improve mobility. When this is not possible or in the setting of endocarditis, localized resection can be performed with the placement of patch material for cusp restoration. The presence of restrictive disease and the use of a patch have both been associated with reduced repair durability.^{13,32} In contrast, pericardial patch closure of fenestrations has been suggested to have acceptable outcomes.³³ The use of newer biomaterials is currently being explored and may help to overcome this limitation.³⁴

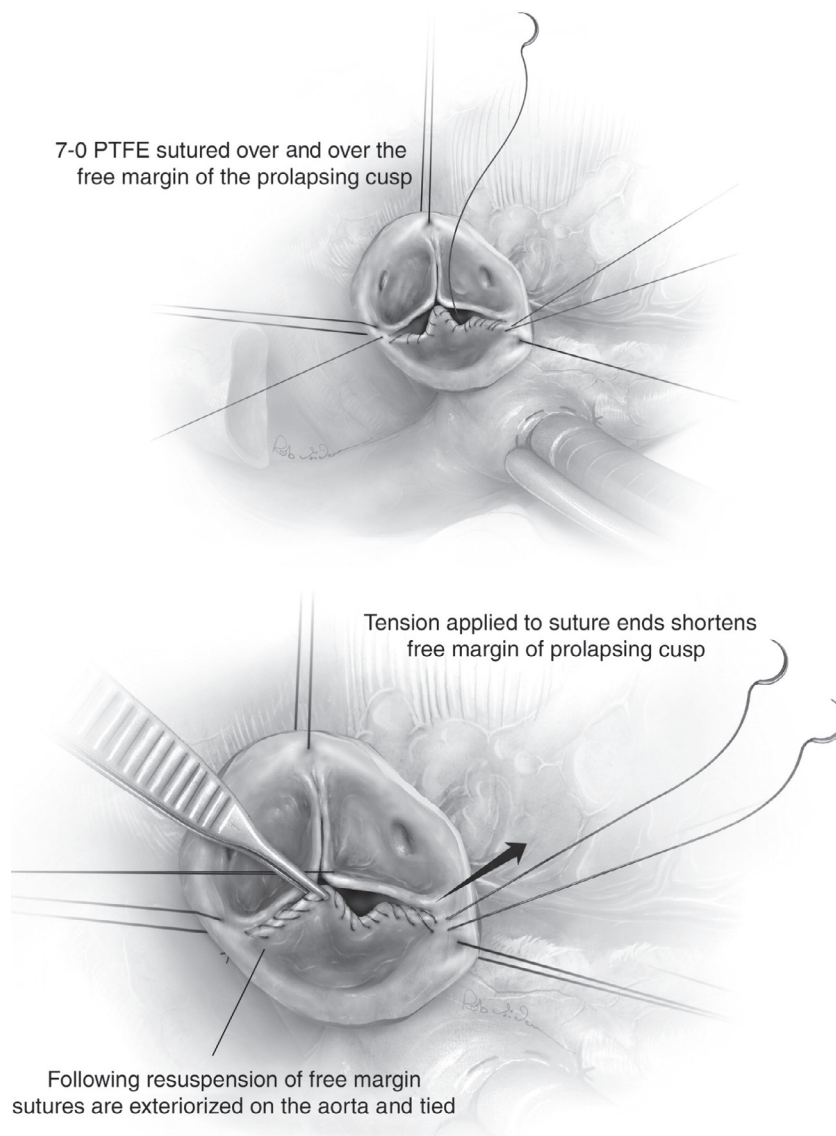


FIGURE 78-11 ■ Free margin resuspension technique using polytetrafluoroethylene (PTFE; Gore-Tex) suture for cusp prolapse correction.

Bicuspid Aortic Valve Repair

Bicuspid aortic valve disease affects not only the valve cusps, but also the functional aortic annulus. Bicuspid aortic valve can be divided into two general types^{13, 35} (Fig. 78-12). Type 0 bicuspid aortic valves do not contain a median raphe, have two symmetric aortic sinuses, two commissures, and a symmetric base of leaflet implantation of the two cusps. This configuration is present in a minority of cases. The mechanism of AI in this setting is usually cusp prolapse of one or both cusps because of the presence of excess cusp tissue.

Type 1 bicuspid aortic valves, which are significantly more prevalent, have a median raphe on the conjoint cusp and an asymmetric distribution of the aortic sinuses, with a large aortic sinus accompanying a large nonconjoint cusp and two smaller cusps fused together with a median raphe. The raphe often attaches to the cusp base in the form of a “pseudocommissure,” which has a height less

than that of the true commissures. The raphe may be restrictive, fibrotic, calcified, or prolapsing. Furthermore, the base of leaflet implantation is typically larger (i.e., occupying a greater proportion of valve circumference) and higher on the conjoint cusp compared to the nonconjoint cusp. The mechanisms of AI in type 1 valves can be due to a rigid and restrictive raphe associated with small fused cusps resulting in a triangular coaptation defect. Alternatively, the raphe may be short and nonrestrictive with well-developed cusps and associated prolapse of the conjoint cusp. Bicuspid valve anatomy can be anywhere along a spectrum between type 0 and type 1. The general algorithm for the repair of bicuspid aortic valves is presented in Figure 78-13.

In type 0 valves, the degree of prolapse is assessed by comparing the prolapsing cusp to the nonprolapsing cusp, similar to trileaflet valves. If both cusps are prolapsing, the goal is to restore the height of coaptation to the midpoint of the sinuses of Valsalva. This can be performed using free

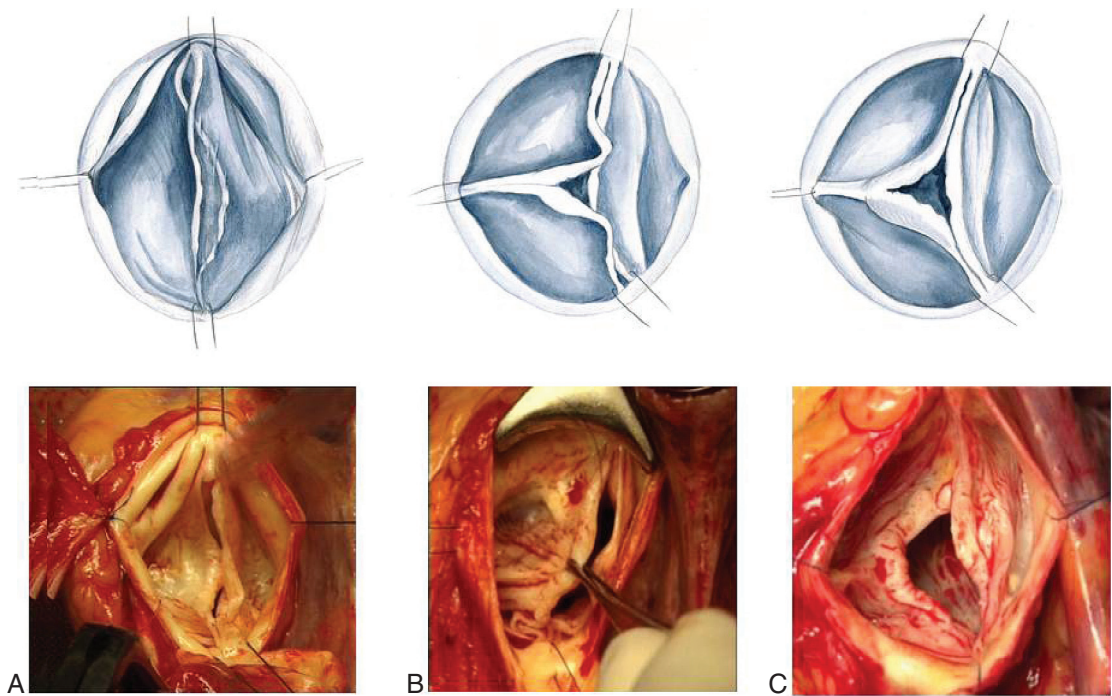


FIGURE 78-12 ■ Cusp anatomy in bicuspid aortic valves.

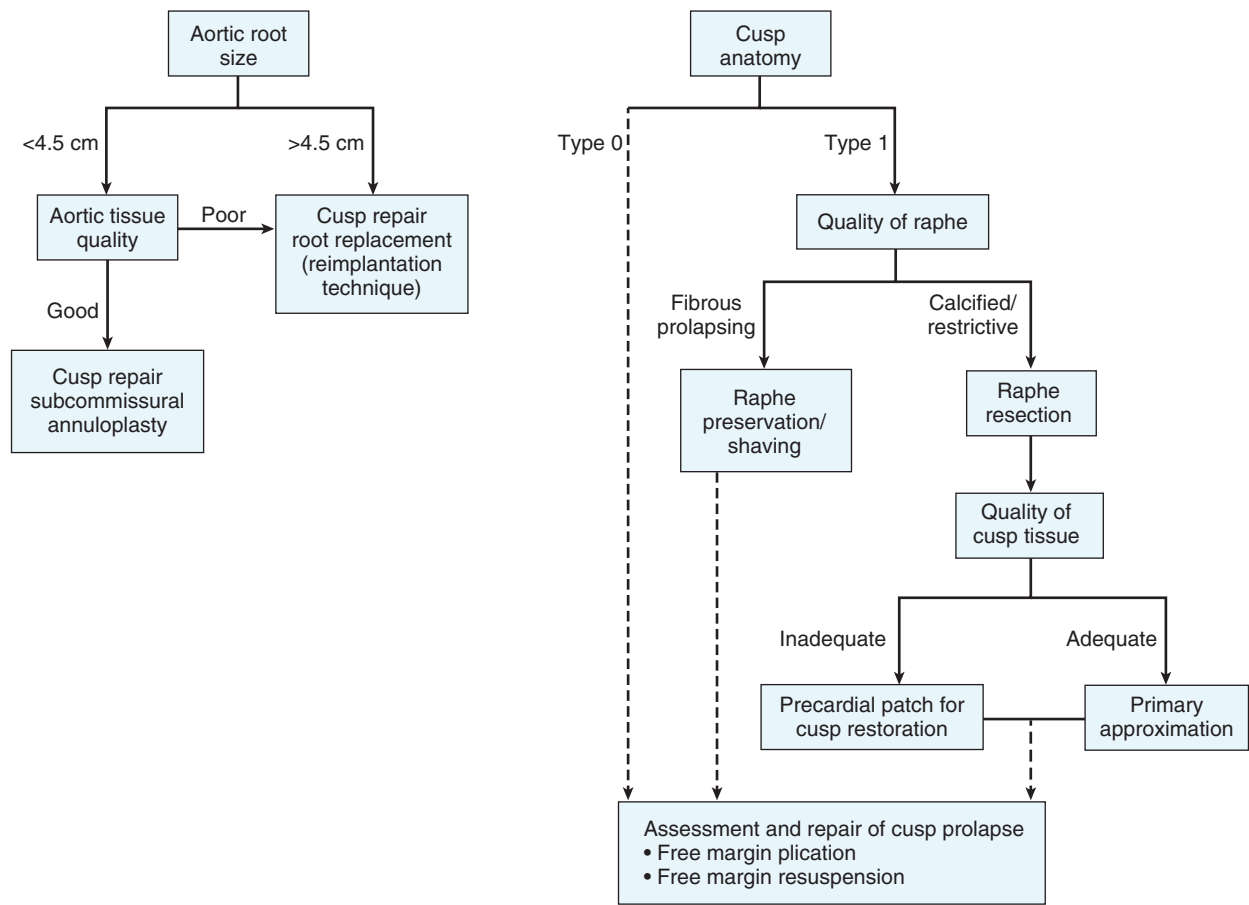


FIGURE 78-13 ■ Algorithm for annulus and cusp management in bicuspid aortic valve repair.

margin plication, free margin resuspension with 7-0 PTFE suture, or both as previously described for trileaflet valves. Thickened, fibrotic areas of the leaflet (typically central aspect of the free margin) are shaved, and localized decalcification is performed if calcium is present.

In type I valves, the median raphe is addressed first. If the raphe is relatively mobile and only mildly thickened and fibrosed, it is preserved and shaved using a combination of a scalpel and scissors (Fig. 78-14). When a severely restrictive or calcified raphe is present, a parsimonious triangular resection of this tissue is performed (Fig. 78-15). Next, the quantity of remaining cusp tissue is assessed by putting the two arms of a 6-0 polypropylene suture on the free margin of the conjoint cusp, on either side of the resected raphe. At this point, lack of cusp

restriction and good valve opening are signs of the presence of adequate cusp tissue. The leaflet edges are reapproximated primarily when adequate cusp tissue is present using running locked or interrupted 6-0 polypropylene sutures. In the absence of adequate tissue, a triangular autologous treated or bovine pericardial patch is used for cusp restoration (Fig. 78-16).

Next, the free margins of both cusps are compared for the presence of any prolapse, which is corrected using free margin plication or resuspension with PTFE.

Unicuspid and Quadricuspid Aortic Valves

Unicuspid and quadricuspid are rare variants of aortic valve anatomy, and both can manifest with either valve

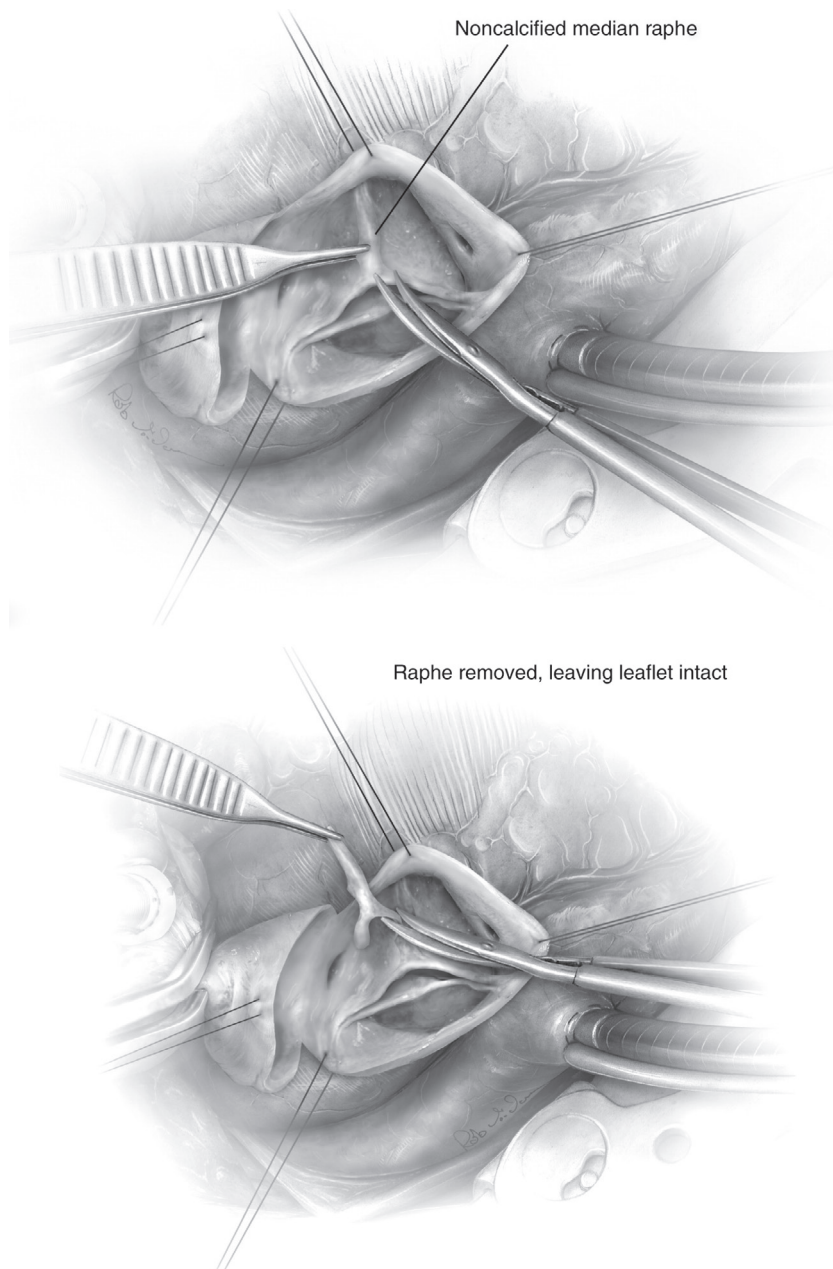


FIGURE 78-14 ■ Shaving of a noncalcified, fibrous raphe.

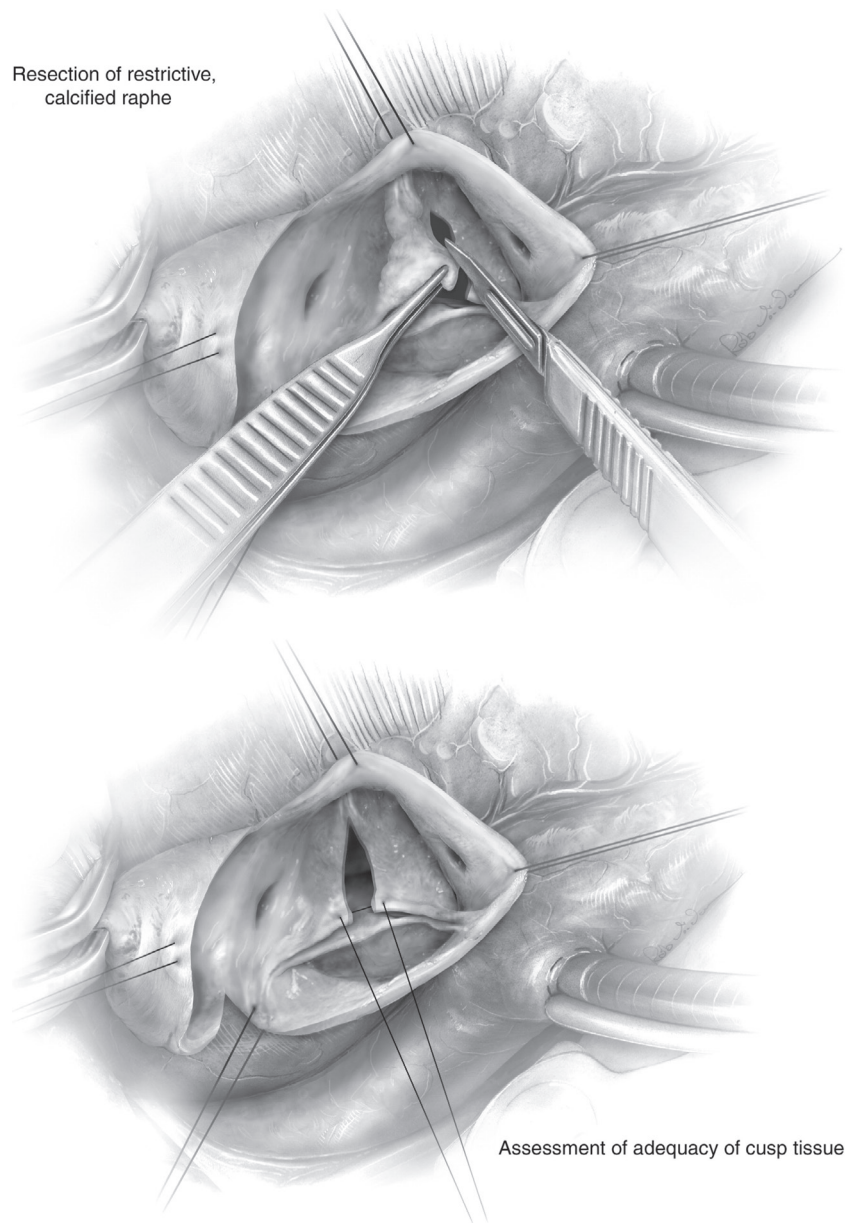


FIGURE 78-15 ■ Resection of a restrictive or calcified raphe (*top*) and assessment of the quantity of available tissue (*bottom*).

stenosis or insufficiency. The most common approach to the repair of the regurgitant unicuspid valve involves bicuspidization by creating a neocommissure using a pericardial patch. Techniques using a single or double patch have been described.^{32,36} These repairs are typically performed in the pediatric or young adult population, and long-term data on valve durability are lacking.

Quadracuspid aortic valves can have a variety of different orientations and may also be associated with aortopathy. Typically, one of the cusps has an additional attachment to the aortic wall and a raphe-like structure that causes cusp restriction. Repair is typically achieved by tricuspoidizing the valve by taking down this attachment and raphe and by repairing the affected cusp. Small

case series using this technique have shown good early results, but long-term data are lacking.^{15,37,38}

INTRAOPERATIVE ECHOCARDIOGRAPHY

In addition to providing important information regarding valve anatomy and mechanism of valve dysfunction, postrepair transesophageal echocardiography is mandatory in patients undergoing aortic valve repair.³⁹ More than trivial to mild residual aortic insufficiency (particularly eccentric jets), coaptation height below the aortic annulus, and coaptation length less than 5 mm have been shown to be important predictors of late repair failure and warrant aortic valve reexploration.⁴⁰

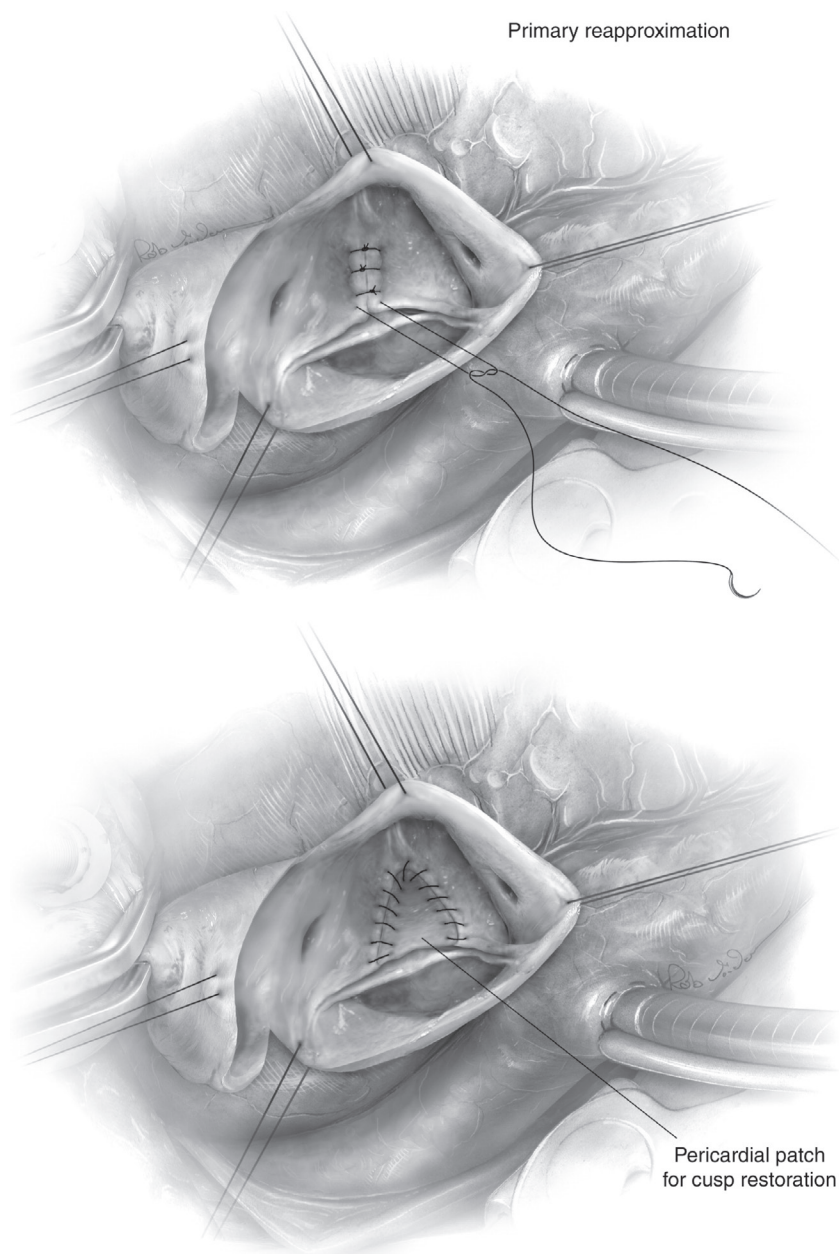


FIGURE 78-16 ■ Primary reapproximation (*top*) or use of pericardial patch for cusp restoration (*bottom*).

OUTCOMES

There are no randomized controlled trials comparing the outcomes of aortic valve repair versus replacement. Data on the durability of aortic valve repair techniques are currently limited to single-center series that are small to moderate in size, with a mean follow-up time of 5 to 10 years. However, data up to 18 to 20 years are emerging in certain subgroups. Important outcome variables include early mortality and morbidity, late freedom from reoperation and recurrent aortic valve insufficiency or stenosis, and the incidence of valve related complications of thromboembolism, bleeding, and endocarditis.

Overall

There are few studies reporting the outcome of unselected patients referred for aortic valve repair surgery. The success rate of valve preservation and repair in this context is rarely reported. Patients with aortic valve repair are typically a heterogeneous group representing the spectrum from young patients with congenital valve disease to older patients with degenerative aortic aneurysms and concomitant AI. As such, outcomes are frequently reported for specific subsets of patients undergoing aortic valve repair.

In a study examining the role of AI classification on surgical techniques and outcome, we evaluated 264 unselected patients undergoing aortic valve repair (mean

age, 54 ± 16 years; 80% male).¹¹ Approximately two thirds of patients were identified as having a single lesion causing AI. Two lesions were identified in 30% and three in 6% of patients. Fifty percent of lesions were type I (normal leaflet motion with FAA dilation or cusp perforation), 35% were type II (leaflet prolapse), and 15% were type III (leaflet restriction). The most common set of multiple lesions were prolapse of aortic valve leaflet in combination with type Ia (STJ dilation) or type Ib (aortic root aneurysm) disease. The classification of AI correctly predicted the surgical technique used in the vast majority of patients (82% to 100%). Overall survival in this cohort was $95\% \pm 3\%$ at 5 years and $87\% \pm 8\%$ at 8 years. Freedom from cardiac death was $95\% \pm 5\%$ at 8 years. Freedom from aortic valve reoperation and replacement at 8 years was $91\% \pm 5\%$ and $93\% \pm 4\%$, respectively. Importantly, classification of AI was also predictive of late outcome with patients with type III (restrictive cusp disease) demonstrating increased late aortic valve reoperation and recurrent AI (Fig. 78-17).

A recent meta-analysis examined the outcome of aortic valve preservation and repair in acute type A dissection and found good valve durability, low risk of valve-related complications, but a significant attrition of patients over time (4.7% per year).⁴¹

Valve-Sparing Aortic Replacement

Outcomes following valve-sparing aortic root replacement have been reported by a number of groups. Results

from large cohorts of patients performed in centers with experience with this technique generally show similar outcomes. David and colleagues⁴² were pioneers of the reimplantation technique and reported their experience in 289 patients, 228 of which underwent the reimplantation technique and 61 underwent the remodeling technique.^{43,44} Early mortality was 1.7%, and 12-year survival was 83%. Late freedom from reoperation at 12 years was 90% with the remodeling technique and 97% with the reimplantation technique ($P = 0.09$). Freedom from recurrent AI at 12 years was 83% after remodeling and 91% after reimplantation ($P = 0.035$). The authors concluded that the reimplantation technique provides more durable outcome.

Schafers and colleagues reported the outcome of the remodeling approach in 274 patients and found that early mortality was 3.6%, freedom from reoperation was 96% at 10 years and freedom from recurrent AI was 87% at 10 years.⁴⁵

Our group has reported outcomes in 164 consecutive patients who underwent valve-sparing aortic root replacement (74% reimplantation, 26% remodeling) specifically examining the effect of presence of preoperative aortic insufficiency on late outcome.⁴⁶ Severe preoperative AI was present in 57% of patients. In this cohort, early mortality was 0.6% and late survival was 88% at 8 years. Freedom from reoperation was 90% at 8 years, and freedom from recurrent AI was 90% at 5 years; both were independent of preoperative AI severity.

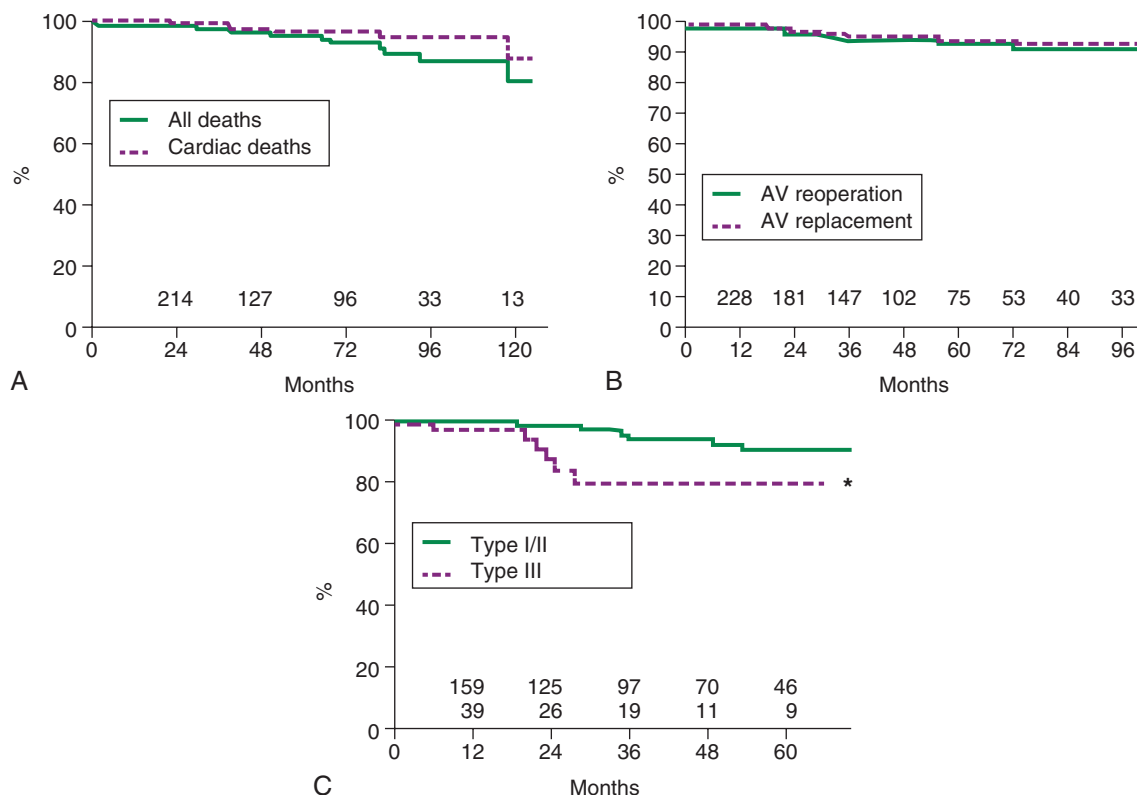


FIGURE 78-17 ■ Survival (A) and freedom (B) from aortic valve (AV) reoperation or replacement in an unselected cohort of patients undergoing aortic valve repair. C, Recurrence of aortic insufficiency (AI) according to lesion type shows increased AI recurrence in patients with type III disease.

Bicuspid Aortic Valve Repair

Unlike the results of valve-sparing aortic root replacement, results of bicuspid aortic valve repair reported in the literature have been highly variable between groups. These differences are largely due to the heterogeneity in the surgical techniques used, particularly the degree of annular stabilization. Schafers and colleagues⁴⁷ performed bicuspid aortic valve repair in 174 patients and found that freedom from reoperation was 97% at 5 years in those undergoing the remodeling approach but only 53% in those not undergoing root replacement.⁴⁷ A more recent update of their experience in 316 patients showed a 10-year survival of 92% and a 10-year freedom from reoperation of 81%. Absence of root replacement and a number of anatomic features of the bicuspid valve, including commissural orientation and VAJ diameter, were predictors of repair failure.¹² Alsoufi and colleagues⁴⁸ reported outcome following bicuspid aortic valve repair in 71 patients. Despite low early and late mortality, freedom from reoperation and recurrent AI at 8 years were 82% and 44%, respectively.

In our cohort of 122 patients undergoing bicuspid aortic valve repair (mean age, 44 years; 80% male, 57%

with associated aortic dilation), there was no early mortality and late survival was 97% at 8 years.¹³ Freedom from late aortic valve reoperation was 98% and 87% at 5 and 8 years, respectively, and freedom from recurrent AI was 94% at 5 years. In our experience, root replacement led to a more durable outcome compared with subcommissural annuloplasty alone (Fig. 78-18). A follow-up study was performed comparing patients undergoing valve-sparing root replacement using the reimplantation technique to all other forms of annular stabilization. Patients were matched for root and annular size and severity of preoperative AI. We found that patients undergoing the reimplantation technique had significantly lower rates of reoperation and recurrent AI.⁴⁹ This confirms the notion that the VAJ in patients with bicuspid aortic valve disease may continue to dilate over time and may cause repair failure.

Trileaflet Aortic Valve Repair

Different techniques can be used to correct cusp prolapse in trileaflet aortic valves. Free margin plication and free margin resuspension are the most commonly used techniques. Studies comparing the two techniques

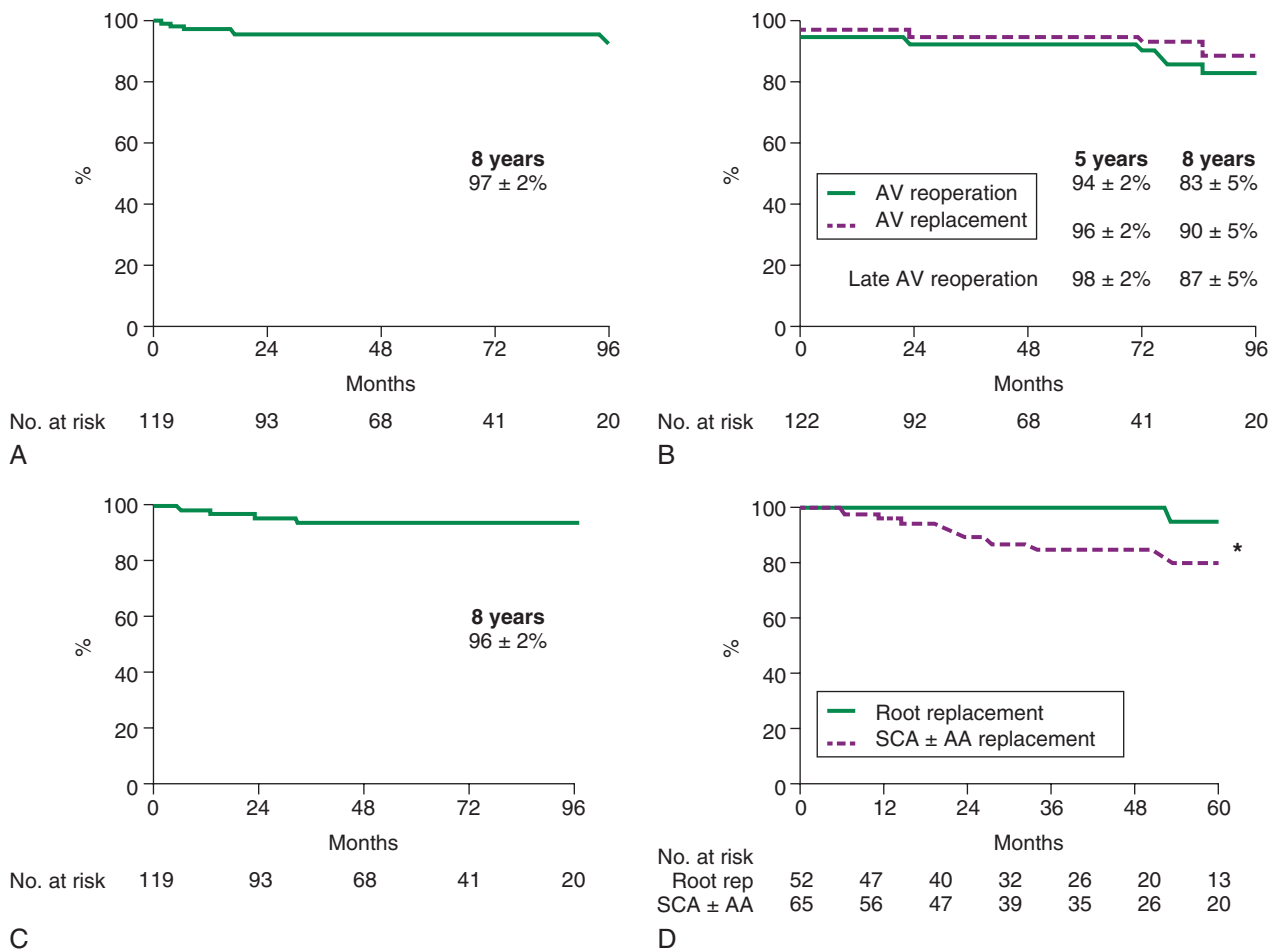


FIGURE 78-18 ■ Survival (**A**) and freedom (**B**) from aortic valve (AV) reoperation or replacement, and (**C**) freedom from thromboembolism and bleeding in patients undergoing bicuspid aortic valve repair. **D**, Patients undergoing valve-sparing aortic root replacement had a higher freedom from recurrent aortic insufficiency than those undergoing subcommissural annuloplasty (SCA) with or without supracoronary ascending aortic (AA) replacement.

demonstrate equivalent durability in terms of freedom from reoperation or recurrent AI.^{31,50} Another important question in the repair of trileaflet aortic valves is the appropriate detection and localization of cusp prolapse. We examined echocardiographic and intraoperative features that could predict the need for cusp prolapse repair in trileaflet aortic valves with or without aortic root pathology. We found that the presence of a preoperative eccentric AI jet, regardless of severity, and the presence of a transverse fibrous band (see Fig. 78-4) were most useful in the detection and correct localization of cusp prolapse.¹⁷

Valve-Related Complications

A consistent finding across all longitudinal studies of aortic valve repair outcome is the low incidence of valve-related events. For prosthetic aortic valve replacements, the rate of thromboembolic events is typically between 1% and 2% per year.^{51,52} For patients with mechanical aortic valves, the rate of anticoagulant related hemorrhage is also 1% to 2% per year. Furthermore, valve thrombosis and prosthetic valve endocarditis are infrequent but devastating complications. In contrast, the combined rate of thromboembolism, bleeding events, and endocarditis following aortic valve repair has been reported in several studies to be less than 0.5% per year.^{11,13,53} This is particularly attractive for young patients who continue to accrue the risk of valve-related events over time.

CONCLUSION

Over the past two decades, important advances have been made in the field of aortic valve repair. These advances include a better understanding of the functional anatomy of the aortic valve, the development of a repair-oriented classification system for aortic insufficiency, the application of valve-sparing techniques to the preservation and repair of regurgitant aortic valves, and the development of cusp repair techniques. New data are available indicating the durability of aortic valve repair up to 10 years. Additional long-term studies and studies comparing aortic valve repair to replacement are needed to better define the role of aortic valve repair in patients with aortic insufficiency.

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TRANSCATHETER AORTIC VALVE REPLACEMENT

Vinod H. Thourani • Sebastian Iturra • Eric L. Sarin

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INTRODUCTION

Aortic stenosis is the most frequent acquired valve disease in older adult patients; consequently, the number of patients requiring treatment increases as the population ages. Current U.S. Census predictions indicate that by 2050 the number of citizens 85 years and older will reach 17.9 million and the number of citizens 65 years and older will reach 83.7 million.¹ Historically, aortic stenosis was treated with surgical aortic valve replacement (SAVR) using cardiopulmonary bypass via either a median sternotomy or minimally invasive techniques. These techniques have produced durable results with low morbidity and acceptable long-term survival rates.²⁻⁵ However, as the older adult population expands, more patients are developing aortic stenosis and multiple medical comorbidities that increase their operative risk. Despite several series demonstrating good clinical outcomes following SAVR in older adult patients,^{2,4,6} many physicians are reluctant to recommend surgery for high surgical risk patients with comorbidities. At least 30% of patients with severe symptomatic aortic stenosis are not treated with

SAVR because of reluctance by referring physicians, patients, or patients' families.⁶ In an attempt to mitigate risk in this frail, older adult population, transcatheter strategies for aortic valve replacement have been developed.⁷ In 2002, Cribier performed the first transcatheter aortic valve replacement (TAVR) through an antegrade approach using the femoral vein and a transseptal puncture technique due to advanced peripheral artery disease in an inoperable patient with severe aortic disease.⁸ In the subsequent decade, it is estimated that more than 60,000 TAVRs were performed worldwide.⁹ The techniques for TAVR have evolved and are currently being performed via retrograde transfemoral (TF), left ventricular transapical (TA), transcending aortic (TAo), transsubclavian (TS), and transcarotid (TC) approaches. This chapter focuses on the indications, preoperative evaluation, operative technique, outcomes, complications, and future of TAVR.

INDICATIONS

The classic indications for an isolated SAVR are symptomatic patients with severe aortic stenosis on transthoracic

echocardiography (TTE), defined as a peak aortic-jet velocity ($V_{\max}$) of at least 4.0 m/sec or mean aortic-valve gradient 40 mm Hg or higher.¹⁰ Typically the aortic valve area (AVA) is 1.0 cm² or less or an AVA index (AVAi) 0.6 cm² or less, but it can be larger secondary to mixed aortic stenosis/aortic regurgitation. The most common symptoms include exertional dyspnea or decreased exercise tolerance, angina, or syncope. In those with symptomatic but low-flow or low-gradient aortic stenosis with a reduced left ventricular ejection fraction, a dobutamine stress echocardiography can be used to ascertain the severity of the valve stenosis. In those patients who are asymptomatic, yet with very severe aortic stenosis ($V_{\max} \geq 5.0$ m/sec or mean aortic-valve gradient ≥ 60 mm Hg), valve replacement is recommended.¹⁰ Currently in the United States, TAVR is indicated in those patients with a life expectancy exceeding 1 year and severe aortic stenosis who are considered either high risk or inoperative by a multidisciplinary heart team, including those with expertise in cardiac surgery, invasive cardiology, echocardiography, cardiac anesthesia, and imaging specialties. Generally, high-risk patients are considered those defined by a Society of Thoracic Surgeons (STS) predicted risk score of mortality (PROM) of 8% or higher or by the presence of coexisting conditions that would be associated with a predicted risk of death by 30 days after surgery of at least 15%.¹¹ Outside the United States, the indications for TAVR are quite varied and are dependent on the institutional and geographic conditions.

PREOPERATIVE EVALUATION AND PLANNING

Patient selection is the key to successful TAVR. The methods of assessment of surgical risk vary but typically include the logistic EuroSCORE and/or the STS risk model. A logistic EuroSCORE higher than 20% and STS score higher than 8% expected mortality is generally accepted as high risk for surgery. Patients with limited life expectancy (<1 year), advanced chronic kidney disease (creatinine > 3.0), preoperative hemodialysis, advanced neurologic disease, and bicuspid aortic valves have been excluded from trials, and experience in these populations is limited but growing.

Pre-TAVR evaluation should seek to answer several questions, including (1) severity of aortic stenosis; (2) iliofemoral vessel size, calcification, and tortuosity; (3) anatomic details of the aortic valve leaflets; (4) annulus, sinotubular, and sinus of Valsalva dimensions; (5) ventricular viability; and (6) extent of coronary artery disease. A combination of imaging techniques may be used to answer these questions. At our institution, to discern these aspects a left heart catheterization, high-definition computed tomography (CT) of the chest, abdomen, and pelvis, and TTE or transesophageal echocardiography (TEE) are used to assess each patient prior to TAVR. Furthermore, objective frailty testing, pulmonary function tests, and carotid duplex ultrasound are performed to assess lung function and carotid stenosis. Severe, hemodynamically significant carotid lesions should be treated prior to TAVR.

Aortic Valve Assessment

A complete echocardiographic assessment is required to assess the aortic valve, most commonly using a TTE. From the parasternal long-axis view, the right and non-coronary cusps are identified, and the annulus is measured between the insertion points of the leaflets (Fig. 79-1). Accurate measurement is essential because this is what determines the size of the valve selected. If calcification, body habitus, or other factors preclude the accurate measurement of the annulus, a TEE ought to be performed. The right and noncoronary artery cusps are identified from the long-axis view at 120 degrees. Measurements of the sinus of Valsalva and sinotubular junction are also obtained from this view. The failure to properly size the annulus may result in a valve too small for the annulus with subsequent perivalvular leak or embolization, whereas a valve too big for the annulus may result in aortic dissection or annular damage. A TEE with three-dimensional reconstruction (Fig. 79-2) can be helpful in determining aortic annulus area and perimeter, which is



FIGURE 79-1 ■ Transthoracic echocardiogram. Parasternal long-axis view measuring the left ventricular outflow tract.

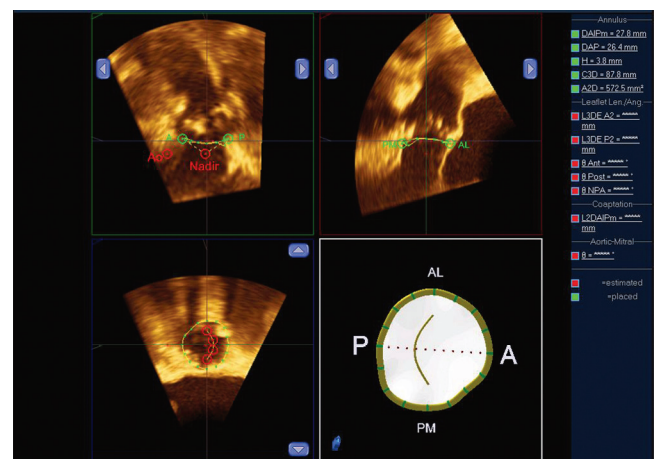


FIGURE 79-2 ■ Transesophageal echocardiogram with three-dimensional reconstruction measuring the aortic annulus area.

particularly useful in patients that were not able to get a three-dimensional CT reconstruction. Sizing of the annulus with supraaortic aortography during balloon aortic valvuloplasty (BAV) may provide additional information when the aortic annulus remains questionable.

All patients should have a CT scan from the aortic valve to the femoral arterial bifurcation. A gated, contrast CT will allow three-dimensional reconstruction, which will show in detail the aortic root anatomy, including the annular, sinotubular, and sinus of Valsalva dimensions, as well as coronary heights above the annulus (Fig. 79-3). Measurement of the annular area or perimeter have supplanted two-dimensional echocardiography in sizing for the appropriate TAVR device and are now the standard of care for assessment of implant size. Each vendor has a sizing chart corresponding to the annular area or perimeter. In those with chronic kidney disease, a three-dimensional TEE as aforementioned is performed to calculate the aortic annulus area and perimeter. This same CT will also delineate aortobifemoral anatomy, details of arterial vessel diameter, and tortuosity and calcification

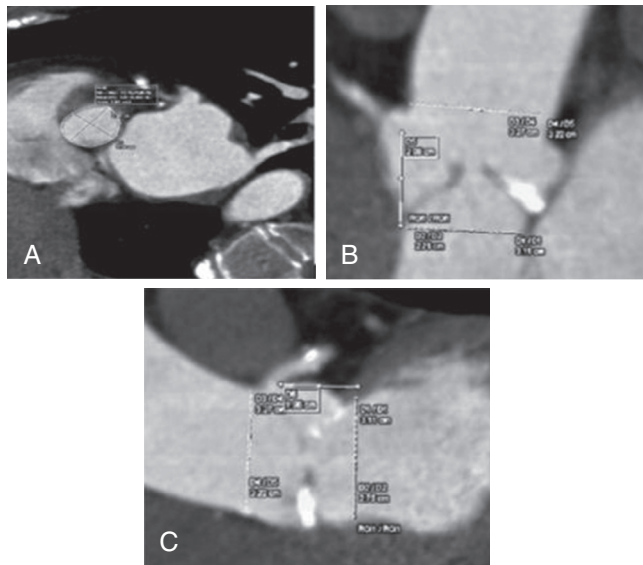


FIGURE 79-3 ■ Cardiac contrast computed tomography with three-dimensional reconstruction measuring the aortic annulus area. **A-C**, Multiple views on computed tomography of the aortic annulus that are required for evaluation of the aortic valve for preoperative TAVR planning.

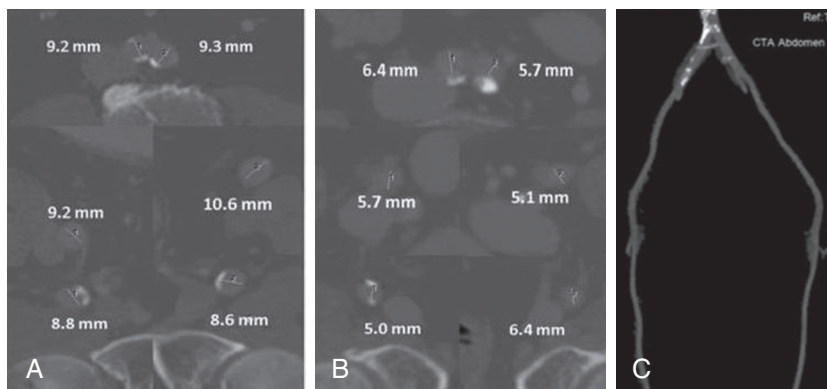


FIGURE 79-4 ■ Contrast computed tomography with three-dimensional reconstruction evaluating the aortoiliac/femoral anatomy. **A**, Anatomy adequate for most transfemoral TAVR valves. **B**, Anatomy not adequate for most transfemoral TAVR valves. **C**, Three-dimensional reconstruction of the iliac and femoral arteries.

(Fig. 79-4). In those with chronic kidney disease, a non-contrast CT and an invasive lower extremity angiogram provide complementary information, allowing for calibrated measurements of arterial diameters and easy detection of very focal stenosis and tortuosity.

Lower Extremity Assessment

Assessment of the lower extremities begins with either a CT scan or lower extremity angiography at the time of cardiac catheterization. Calcification of the large iliac arteries is common but generally does not prevent a femoral artery approach unless the calcification is circumferential and limiting in size. However, calcification in the smaller common femoral arteries is more problematic and may preclude the safe placement of TF systems and should be performed using alternative access techniques. Tortuosity, particularly in the external iliac artery, may complicate the advancement of the sheath. Consequently, moderate calcification in tortuous external iliac arteries (which tend to dive deep into the pelvis) may increase the likelihood of major vascular complications (Fig. 79-5). Tortuous vessels free of significant calcium are often compliant and can usually be straightened by a stiff guidewire. Figure 79-6 is a CT scan representation of severe iliac calcification precluding TF-TAVR.

Other Comorbidity Assessment

Patients with severe coronary artery disease and significant lesions that are amenable to percutaneous coronary intervention can undergo implantation of a bare-metal or drug-eluting stent prior to TAVR. Another potential concern is that the valve may displace a leaflet and cover a coronary ostium when deployed. A sinus of Valsalva that is narrow, a shallow sinus of Valsalva (within 5 mm of the annulus size), a short distance between the annulus and the coronary ostia (<10 mm), and bulky leaflet calcification can increase the risk for coronary obstruction. A sinus of Valsalva greater than 27 mm should accommodate smaller valves, whereas a sinus greater than 29 mm is adequate for all devices.

Alternative Access Considerations

Patients whose preoperative imaging study shows that a TF-TAVR is not advisable need to be evaluated for



FIGURE 79-5 ■ Contrast computed tomography with three-dimensional reconstruction with significant tortuosity of iliac vessels.

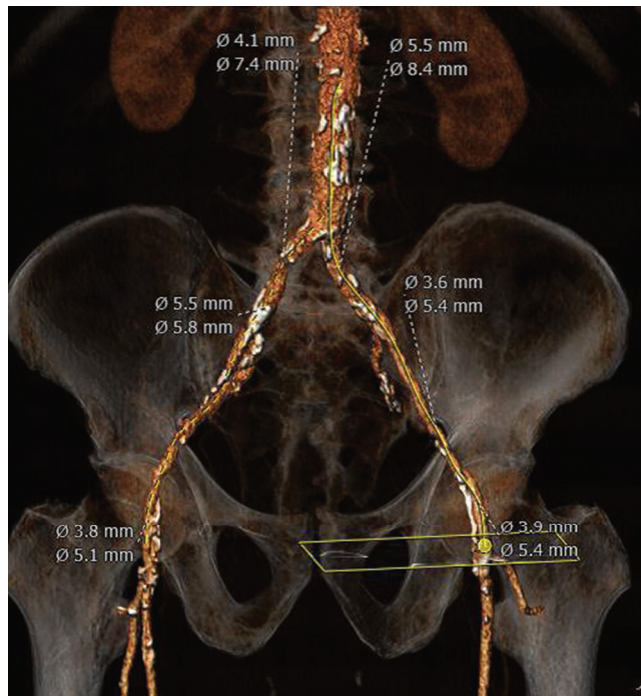


FIGURE 79-6 ■ Contrast computed tomography with three-dimensional reconstruction showing severe iliac-femoral calcifications.

alternative access techniques. A TA approach, via an anterior left mini-thoracotomy, has traditionally been used as the alternative in these patients. However, this approach comes with additional challenges and a different risk set compared with TF-TAVR and may not be appropriate for all patients, particularly those with significant parenchymal lung disease or low ejection fraction secondary to

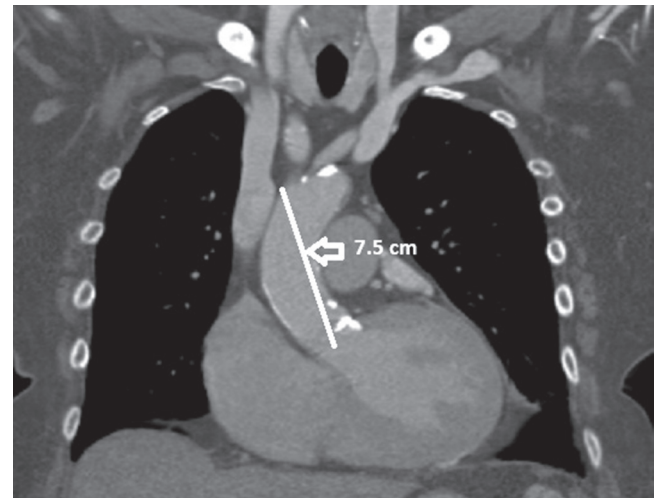


FIGURE 79-7 ■ Contrast computed tomography with three-dimensional reconstruction to evaluate ascending aorta.

the direct cannulation of the left ventricle.¹² TAO is a feasible alternative approach for a TAVR in patients who have not had a previous sternotomy. It is important to evaluate the degree of ascending and aortic arch calcification and the distance from the cannulation (>7 cm) site and the aortic root to ensure adequate deployment of the valve (Fig. 79-7). The transcarotid approach has been used successfully in patients who are not candidates for TF, TA, or TAO.¹³

OPERATIVE TECHNIQUES

Transfemoral TAVR

The TF approach is the least invasive of all TAVR techniques and is the initial procedure of choice by most operators. A 6 Fr sheath is placed in the artery and vein on the nonimplant side. A pigtail catheter is advanced to the aortic valve and aortography is performed to confirm the correct valve plane for valve placement. Through the femoral vein, a temporary pacemaker is advanced to the right ventricular apex for purposes of rapid ventricular pacing. Maintaining consistent pacing capture is essential to safe TAVR. To gain stability and facilitate adequate contact of the pacemaker with the right ventricular myocardium, an 8 Fr Mullins sheath is advanced into the right atrium.

Alignment of the three cusps of the aortic valve is performed via ascending aortic root angiography. This can be performed with the angled pigtail catheter in the right coronary cusp or via power injection with the catheter in the aortic root. The proper aortic plane is identified when all three cusps are visualized at an equal height (Fig. 79-8).

Access to the femoral artery on the implant side is performed using a microneedle under vascular road mapping. The tract is dilated with a 7 Fr sheath and the artery is preclosed with two Perclose devices. Alternatively, a surgical cutdown to obtain femoral access can be performed to insert the sheath. The dilators are placed

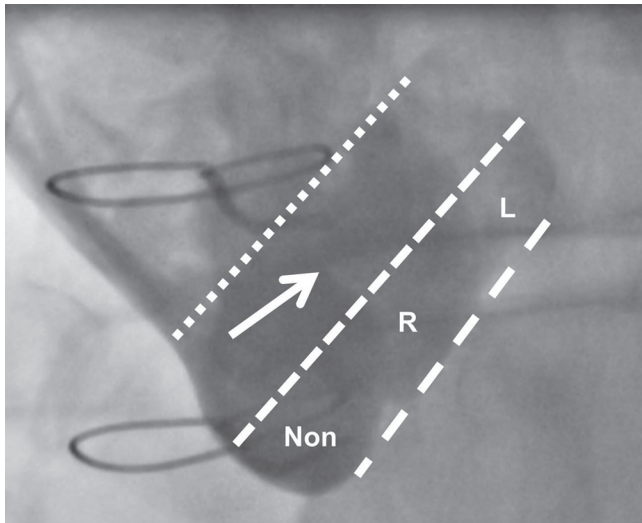


FIGURE 79-8 ■ Aortic root angiogram. Alignment of all three coronary cusps. *L*, Left coronary cusp; *Non*, noncoronary cusp; *R*, right coronary cusp.

and the appropriate sheath is inserted. The patient is heparinized to an activated clotting time (ACT) of longer than 250 seconds. Excessive force should not be applied when passing the dilators to avoid vascular complications during insertion and removal. Next the aortic valve is crossed with an Amplatz left-1 (AL1) catheter. A straight-tipped guidewire or hydrophilic wire is used to cross the aortic valve and advanced into the ventricle. This is exchanged for a 260-cm long, 0.035-inch diameter Amplatz Extra Stiff J guidewire, which has an exaggerated pigtail bend at the proximal end. A BAV is performed under rapid ventricular pacing (generally 180 to 220 beats/min) using a Z-Med 20- or 23-mm balloon catheter.

The appropriate valve delivery system is inserted and advanced to the aortic annulus. Difficulty crossing the aortic valve can occur because the stiff wire can bias to the greater aortic curvature and become lodged in a commissure. Gentle pulling of the wire will allow the delivery system to centralize and cross the valve easier. Excessive force should not be used when crossing because dissection of the aorta can occur. Once the valve has crossed the native valve, the system should not be advanced further because perforation of the left ventricular apex by the nosecone is possible. The proper positioning of the valve is guided by fluoroscopy and echocardiography. The SAPIEN valve, a balloon-expandable valve, is ideally positioned so that its upper margin covers the aortic leaflet tips and the ventricular end covers the aortic annulus or below (Fig. 79-9). When the device is appropriately positioned, the implanting physician should coordinate a long cine-fluoroscopic run with rapid pacing and inflation/deflation of the delivery balloon. We advocate a slow inflation to ensure proper valve position. The balloon should be at maximal inflation for 4 seconds before deflation. It is important that pacing begins before balloon inflation and continues until the balloon is almost completely deflated. Successful rapid pacing with 1:1 ventricular capture at 180 to 220 beats/min lowers the

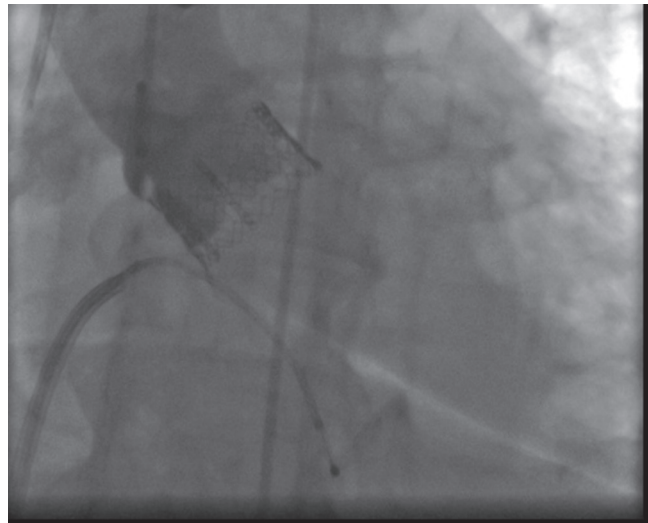


FIGURE 79-9 ■ Fluoroscopy of position of the SAPIEN valve in relation to the aortic annulus and coronary arteries.



FIGURE 79-10 ■ Fluoroscopy of position of the CoreValve in relation to the aortic annulus.

blood pressure below 60 mm Hg and prevents forceful contractions that may move the balloon catheter.

The CoreValve, a self-expanding aortic valve, is positioned by determining its three-tiered design in relationship with the aortic annulus. The inflow portion of the valve is ideally placed 6 mm (one diamond segment of the stent frame) below the point of leaflet attachment. Thus, the portion of the valve with high radial force sits firmly in the annulus, but not so low as to compress the adjacent cardiac conduction system (Fig. 79-10). The uppermost part of the CoreValve rests in the ascending aorta, parallel to the direction of blood flow. The CoreValve system does not commonly require rapid ventricular pacing during deployment.

Following deployment of the aortic valve, proper positioning is assessed with echocardiography. Patency of the coronary arteries is checked, and proper positioning of the device confirmed, with aortography. A valve too low in the ventricle may necessitate the placement of a second valve. Placing the valve too high in the annulus might result in embolization of the device into the ascending aorta or occlusion of the coronary arteries. A trace or mild amount of perivalvular leak is expected after TAVR. If there is more than mild leak around a correctly positioned valve, post-deployment balloon dilation using the balloon on the delivery catheter can further expand the valve and improve the insufficiency.

Transapical TAVR

The transapical TAVR is the second most common TAVR technique and thus far has been used primarily with a balloon-expandable valve. In those patients with severe peripheral vascular disease, the TA approach is an expeditious procedure. This technique is the only antegrade of all approaches with very low stroke rates and the least amount of postoperative paravalvular leaks. Furthermore, the TA procedure is best in those with a prior sternotomy or porcelain aorta. The most serious complication includes left ventricular bleeding, but this is not common. The only relative contraindications to the TA procedure are severe chronic obstructive pulmonary disease (COPD) with a forced expiratory volume (FEV₁) predicted less than 30% or an ejection fraction less than 20%.

The patient is placed supine on the operating room table and femoral artery and vein access is achieved. A femoral transvenous pacer is placed in the right ventricle and a pigtail catheter is placed in the aortic root via the femoral artery. A 4- to 5-cm anterolateral thoracotomy is made in the fifth or sixth intercostal space to expose the left ventricle. Two apical pledgeted 3-0 Prolene purse-string sutures are placed just cephalad to the apex lateral to the left anterior descending artery. The purse-string sutures into the myocardium should be deep stitches but not transmural (Fig. 79-11).

Fluoroscopy is used to position the aortic root and annulus perpendicular to each other, and to align all three aortic cusps in the same plane in a similar fashion as in the TF approach. The left ventricle cavity is accessed

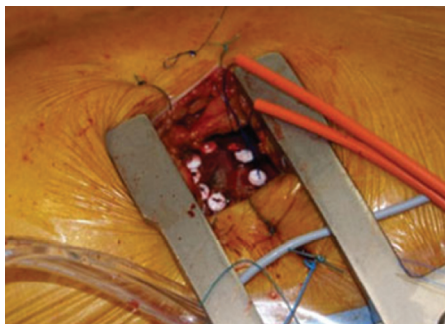


FIGURE 79-11 ■ Transapical transcatheter aortic valve replacement approach. Left thoracotomy with exposure of the apex of the heart with two purse-string sutures.

with a needle, and a 0.035-inch wire is passed into the left ventricle, across the aortic valve, and into the ascending aorta. The wire is maintained in the ascending aorta and not allowed to pass into the right carotid artery. A 7 Fr catheter is placed through the left ventricle apex and across the aortic valve. The 0.035-inch wire is manipulated into the descending aorta using a right Judkins catheter. The 0.035-inch wire is exchanged for a stiff wire (Amplatz Super Stiff; Boston Scientific, Natick, MA) and left in the abdominal aorta. The 7 Fr catheter is exchanged for the appropriate sized delivery sheath, which is positioned 4 cm inside the left ventricle. A BAV is performed with or without rapid ventricular pacing. The balloon is removed and the valve is placed through the left ventricular delivery sheath and positioned across the valve. Positioning, deployment, and post-assessment of the valve are similar to that as aforementioned in the TF-TAVR section. After adequate evaluation, all catheters and wires are removed and the apex sutures are tied down under rapid ventricular pacing. Protamine is administered. If possible, the pericardium is closed over the left ventricular apex surgical site, and a small flexible chest tube is placed in the left pleural space.

Transaortic TAVR

The TAo approach is the third most common TAVR technique and is used in those with balloon- or self-expanding valves. The TAo approach has several theoretical and practical advantages, including avoiding a thoracotomy in patients with poor respiratory function, less postoperative pain, and faster recovery. In addition, the direct aortic cannulation, a procedure with which most cardiac surgeons are comfortable, potentially allows for a more hemostatic closure than in a patient with a fragile left ventricular apex. However, although the TAo approach offers several advantages, it is not appropriate for all patients. TAo-TAVR is contraindicated in patients with porcelain aorta. There are also additional technical challenges when considering the TAo approach in patients with previous sternotomies, prior left internal mammary artery (LIMA) grafts that overlay the aorta, or otherwise hostile mediastinum (e.g., patients with a history of cobalt radiation).

The patient is placed supine on the operating room table with the lower neck exposed to allow for the counter-incision for the delivery sheath. An angled pigtail catheter is placed in the aortic root and a femoral transvenous pacer is placed in the right ventricle. The CT can provide the adequate information of the relationship of the distal ascending aorta to the sternum, the extension of calcification, and the distance from the site of cannulation to the aortic root. This distance should be ideally greater than 7 cm to allow enough space between the delivery system and the free inflation of the balloon during the valve implantation (see Fig. 79-7).

A 5- to 6-cm sternotomy incision is made below the suprasternal notch extending below the angle of Louis at the second intercostal space. A mini-sternotomy is performed using a standard saw, dividing the sternum down to the second intercostal space, where the “J” is completed with a transverse sternotomy. The distal ascending

aorta is exposed and two aortic purse-string sutures are placed at the base of the innominate artery. The patient is heparinized to maintain an ACT greater than 250 seconds. A counter-incision is made in the lower neck through which an 18-gauge needle with a 0.035-inch soft guidewire is passed and used to puncture the aorta through the purse-string sutures (Fig. 79-12). The needle is exchanged for a 7 Fr sheath, and a multipurpose catheter with a straight soft wire is used to cross the valve. This is exchanged for a 260-cm, 0.035-inch Amplatz Extra Stiff J guidewire, which has an exaggerated pigtail bend at the proximal end. The appropriate sheath is placed into the aorta to 2 to 4 cm. A BAV is performed under rapid ventricular pacing. The balloon is removed and the TAVR valve is placed through the delivery sheath and positioned across the stenotic valve. Positioning, deployment, and post-assessment of the valve are similar to that as aforementioned in the TF-TAVR section. After adequate evaluation, all catheters and wires are removed and the aortic sutures are tied down under rapid ventricular pacing. Protamine is administered and generally the pericardium is left open. A small flexible chest tube is placed in the mediastinum and generally the pleural spaces are not opened.

Subclavian TAVR

The transsubclavian approach is the fourth most common TAVR technique and is used primarily in those with a self-expanding valve. Approaching TAVR from the axillary artery presents a few distinct advantages when compared with the other alternative access routes. It remains less invasive compared with the TA or TAO approach because it does not require thoracotomy or limited sternotomy. This makes it appealing for the older, debilitated patient in whom the transfemoral approach is limited by anatomy. Furthermore, in cases of aortic calcification, which would limit the TAO approach, or severe left ventricular or pulmonary dysfunction, which would limit the TA approach, the axillary access route is potentially preferable.

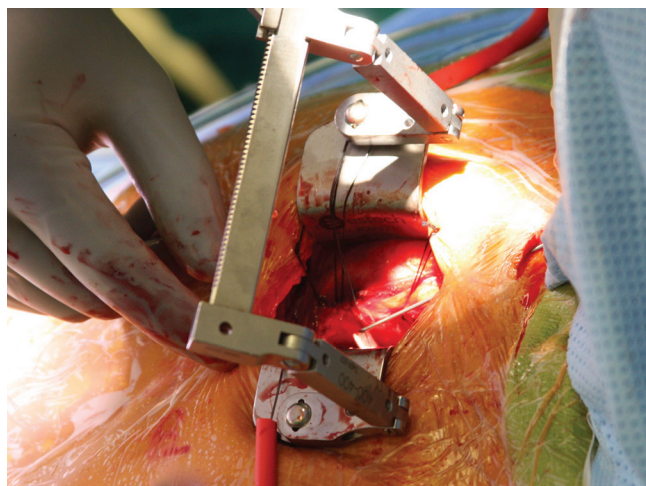


FIGURE 79-12 ■ Transaortic transcatheter aortic valve replacement approach.

Standard femoral artery and vein access is obtained as aforementioned. Surgical cutdown for the left axillary artery is familiar to most cardiac surgeons because it is routinely used as an arterial inflow cannulation site, particularly in the setting of aortic surgery. An oblique incision is made in the deltopectoral groove. The first portion of the axillary artery can be exposed with lateral retraction of the pectoralis minor. Division of the head of pectoralis minor can be performed with minimal morbidity if necessary to obtain optimum exposure. Great care is taken to avoid injury to the medial and lateral cords of the brachial plexus, as they often travel in close association with the artery, particularly in its second portion. The patient is heparinized to maintain an ACT greater than 250 seconds. Use of a synthetic graft in an end-to-side orientation, which is then cannulated with the delivery sheath, is favored by some, whereas others use direct access via a purse-string suture. Using the Seldinger technique, the access site is dilated to accommodate the appropriate caliber delivery sheath for the chosen device. This is advanced over a stiff wire, using fluoroscopic guidance with the tip of the sheath left at the origin of the innominate artery when approached from the left. When approaching from the right, the concern for potential occlusion of the right common carotid artery has led some high-volume centers to position the sheath tip at the origin of the right subclavian artery. Once the sheath is appropriately placed, TAVR deployment proceeds using the usual protocol of the transaortic TAVR. At the conclusion of the procedure, following removal of the delivery sheath, vascular control of the access site is obtained and selective angiography can be used to confirm vessel integrity at the access site.

Transcarotid TAVR

For patients who are not candidates for TF-, TA-, or TAO-TAVR and who have a common carotid artery diameter larger than 8 mm without evidence of stenosis, the TC approach to TAVR can be used.¹³ A 6 Fr sheath is placed in the femoral artery through which an angled pigtail catheter is used for ascending aortography. In the contralateral femoral artery, a 16 Fr Fem-Flex II cannula (Edwards Lifesciences, Irvine, CA) is placed percutaneously. This cannula is connected to perfusion tubing and a 14/15 Sundt carotid bypass shunt (Covidien, Mansfield, MA) (Fig. 79-13). A pacing catheter is placed via the femoral vein. The right common carotid artery is exposed

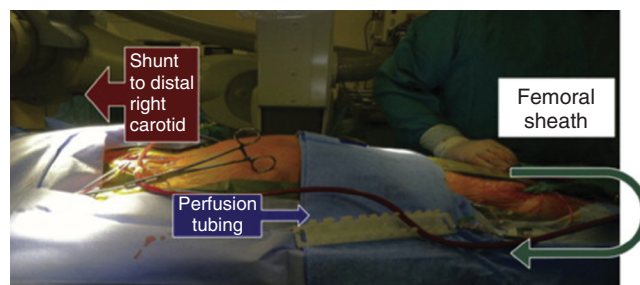


FIGURE 79-13 ■ Transcarotid transcatheter aortic valve replacement approach with visualization of the femoral-carotid shunt.

and after proximal cross-clamping of the common carotid artery, it is opened longitudinally for 2.5 cm. The de-aired bypass shunt is placed in the distal carotid arteriotomy to maintain cerebral perfusion. Cerebral oximetry from the left and right hemispheres is monitored throughout the procedure. Through the proximal arteriotomy, a 0.035-inch J-tipped wire and 7 Fr introducer are placed in the ascending aorta. A multipurpose catheter is then inserted into the ascending aorta and a straight wire is used to cross the native aortic valve. The straight wire is exchanged for an Amplatz Extra Stiff wire, and a Retroflex sheath is introduced into the ascending aorta. Similar to the transfemoral TAVR, a BAV followed by the placement of a valve is performed. Finally, the wires, catheters, and sheath are removed, and the carotid artery is repaired with a bovine pericardial patch.

RESULTS

SAPIEN Valve

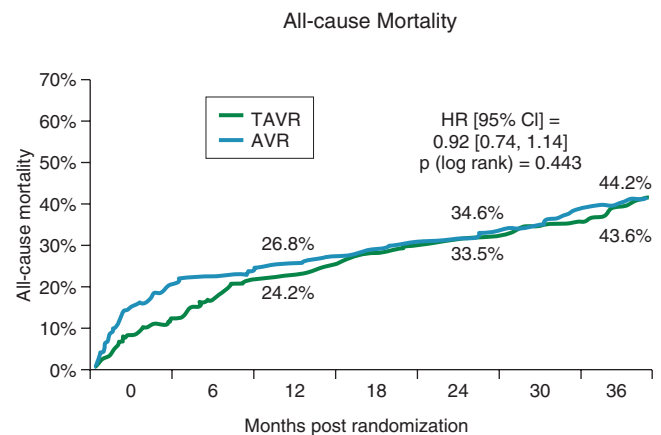
The Placement of Aortic Transcatheter Valves (PARTNER) trial was a landmark and the first randomized study that demonstrated the superiority of TAVR over medical therapy in inoperable patients^{11,14} and the noninferiority of TAVR versus SAVR in high-risk surgical candidates using the balloon-expandable SAPIEN valve.^{15,16} Based on the 1-year outcomes from PARTNER, the SAPIEN valve was approved by the U.S. Food and Drug Administration for use in patients who are not candidates or are at high risk for SAVR.

The results of the randomized, multicenter U.S. PARTNER trial in patients too high-risk for surgery have been published by Leon and colleagues. In this report of 179 patients, the procedural success rate was 96.6%. The AVA and mean gradients across the aortic valve were significantly improved to 1.5 ± 0.5 cm² and 11.1 ± 6.9 mm Hg at 1-year follow-up (preprocedure AVA 0.6 ± 0.2 cm² and mean gradient 44.5 ± 15.7 mm Hg; $P < 0.001$). Mortality was 5.0% and 30.7% at 30 days and 1 year, respectively, following TAVR, establishing its superiority to medical therapy (1-year mortality 49.7%; $P < 0.001$).¹¹

An evaluation of the STS adult cardiac surgery database notes that approximately 6% to 7% of patients presenting for surgical AVR in North America are considered at high risk with an STS score of 8% or higher.^{3,4} At a minimum, this represents a large number of patients who now will have an option for TAVR or SAVR. It is estimated that approximately 30% to 38% of high-risk, older adult patients are not receiving SAVR despite echocardiographic evidence of severe aortic stenosis.^{6,17} The PARTNER trial represents the first randomized trial comparing TAVR with SAVR in high-risk patients. Many physicians have noted that the results may be skewed secondary to the surgical procedure being performed in select university settings. In a multi-institutional study, 159 patients undergoing isolated, primary SAVR with an average STS PROM of $16\% \pm 7\%$ had a 3-year survival of 57% and a median survival of 3.7 years.¹⁸ In a real-world analysis of the STS database, Brennan and coworkers noted a median survival of 2.5 to 2.7 years in high-risk

patients (STS $\geq 10\%$) undergoing SAVR.⁴ Similarly, the SAVR group in the current series has a 55.8% survival at 3 years and a median survival of 3.4 years.

A report by Thourani and colleagues represents the largest series and the first long-term analysis using fully adjudicated outcomes in randomized high-risk patients with aortic stenosis undergoing TAVR with a balloon-expandable valve or surgery (PARTNER trial).¹⁹ At a minimum of 3 years, there was no difference in all-cause and cardiovascular mortality rates between the TAVR and SAVR groups (Fig. 79-14). Strokes were similar between the groups at 3 years, despite increased periprocedural neurologic events in TAVR patients. There was no late (after 30 days) stroke hazard in TAVR compared with SAVR. At 3 years, TAVR hemodynamic performance was maintained with valve gradients and AVAs similar to those of SAVR (Fig. 79-15). In both groups,



Numbers at risk						
TAVR	298	262	243	228	210	188
AVR	351	236	224	209	191	168

FIGURE 79-14 ■ PARTNER trial 3-year analysis: all-cause mortality. AVR, Aortic valve replacement; CI, confidence interval; HR, hazard ratio; TAVR, transcatheter aortic valve replacement.

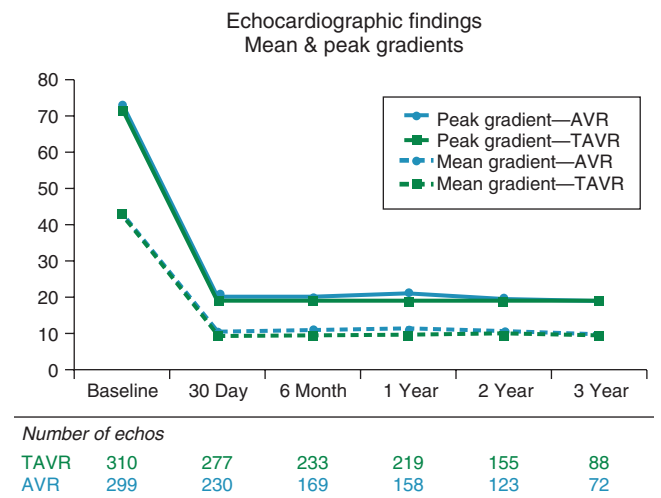


FIGURE 79-15 ■ PARTNER trial 3-year analysis: hemodynamic valve performance by echocardiography. AVR, Aortic valve replacement; TAVR, transcatheter aortic valve replacement.

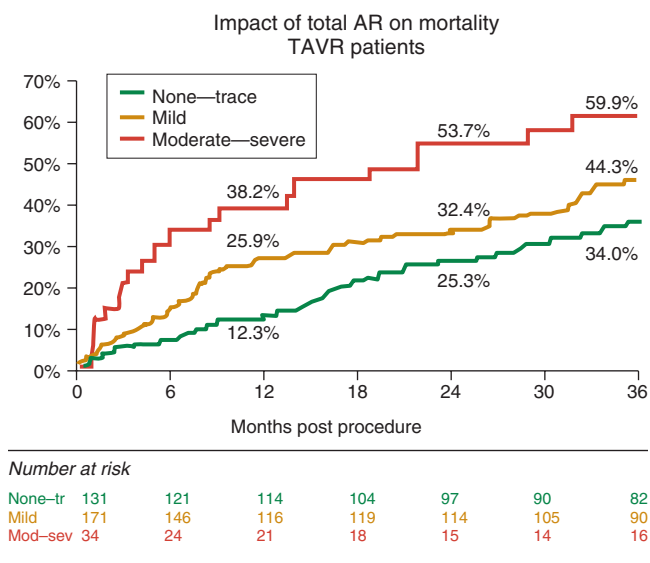


FIGURE 79-16 ■ PARTNER trial 3-year analysis: impact of aortic regurgitation (AR) on mortality. TAVR, Transcatheter aortic valve replacement.

structural valve deterioration was not apparent at the 3-year follow-up. Postprocedural paravalvular aortic regurgitation was frequent after TAVR without important changes during the 3-year follow-up (Fig. 79-16). Of note, and as has been previously reported, even mild postprocedural aortic regurgitation (paravalvular leak [PVL] and total aortic regurgitation) was associated with increased subsequent mortality.¹⁶

Other reports have noted the mid- and long-term TAVR survival rates in Gurvitch and colleagues' study of 70 patients (mean STS score 9.6% and EuroSCORE 31.7%) who underwent successful TAVR with a balloon-expandable valve and who survived 30 days and were followed for a minimum of 3 years.²⁰ The authors noted a survival at 2 and 3 years of 74% and 61%, respectively.²⁰ Correspondingly, the PARTNER series of 348 TAVR patients (mean STS PROM 11.8%) had a 66.5% survival at 2 years and 56.4% survival at 3 years. Similar to the PARTNER series, Gurvitch and colleagues noted no cases of structural valvular deterioration, and only one patient (1.5%) in their series underwent reoperation secondary to endocarditis. In a retrospective, single-center European analysis, Bleiziffer and colleagues reviewed outcomes in 227 patients undergoing TAVR with both balloon-expandable and self-expanding valves for at least 2 years follow-up. In their series, the mean STS PROM was 7% and EuroSCORE 21%, possibly representing a lower risk patient population. They noted a 2-year survival of 66.4%.²¹ In the multicenter UK TAVI Registry of 870 patients undergoing balloon-expandable and self-expanding valve implantation, Moat and colleagues noted a 73.7% all-cause survival at 2 years.²² This figure compares favorably to the 66.5% survival at 2 years in the PARTNER series. However, the UK registry data may not represent a high-risk patient population, with only an average logistic EuroSCORE of 18%.

CoreValve

An early, pioneering series from Grube and colleagues established the self-expanding CoreValve as a viable treatment option for severe aortic stenosis in patients at high risk for morbidity or mortality related to operative intervention (SAVR). Of 25 consecutive patients receiving the CoreValve, 21 (84%) patients were designated procedural successes, and there was a 20% overall mortality.²³ With progressive refinements in technique and device iterations, procedural success improved and the 30-day mortality decreased to 12%. Based on the positive results of these studies and others,^{24,25} CE mark designation for the self-expanding valve was obtained in April 2007.

In the year following obtaining CE mark, 646 patients treated with CoreValve were followed in a multicenter registry. Procedural success was achieved in 97% of patients with a procedural mortality of 1.5%. The incidence of vascular access complications was 1.9% and the 30-day mortality was 8%. A total of 60 patients (9.3%) required placement of a permanent pacemaker. Approximately 70% of the patients had residual aortic insufficiency of grade 1 or 2.²⁶

The introduction of CoreValve to the United States began with a multicenter randomized trial that began in late 2010. The Medtronic CoreValve U.S. pivotal trial adopted a similar trial design to that of the PARTNER trial by targeting aortic stenosis patients at high risk or extreme risk for traditional SAVR. The extreme risk group did not require randomization because the previous findings from the PARTNER study demonstrated a clear survival benefit for TAVR compared with medical therapy. Popma and colleagues reported on 489 patients with a mean STS risk score of 10.3% and mean age of 83 years. The noted all-cause death was 8.4% at 30 days and 24.3% at 1 year. Major stroke was noted at 2.3% at 30 days and 4.3% at 1 year. Major or life-threatening bleeding was noted in 36.7% and the need for permanent pacemaker was 21.6%. The percentage of patients with moderate or severe PVL at discharge was 10.5%. Interestingly, the investigators noted that the severity of PVL diminished over time. In fact, 80% of the patients who had moderate PVL 1 month and survived to 1 year had a reduction in PVL severity.²⁷

In a follow-up study, Adams and associates reported on 795 high-risk patients randomized to either SAVR or TAVR with severe aortic stenosis.²⁸ The mean STS risk score was approximately 7.4% and represented a less sick group than the PARTNER high-risk study, which had a mean STS score of 11.8%.¹⁵ The primary endpoint of all-cause mortality at 1 year illustrated a statistically significant difference between the two groups. Patients undergoing TAVR had a lower all-cause mortality at 1 year (14.2% vs. 19.1%; $P = 0.04$). Permanent pacemaker implantation was higher for CoreValve recipients at 30 days (19.8% vs. 7.1%; $P < 0.001$) and again at 1 year (22.3% vs. 11.3%; $P < 0.001$). Once again, investigators noticed an improvement in paravalvular regurgitation over time. In fact, most of the patients with moderate or severe paravalvular regurgitation at discharge had improved by 1 year to mild or better. Overall the study

represents the first prospectively randomized comparison demonstrating improved survival at 1 year for TAVR compared with SAVR.

The early challenges related to pacemaker implants and PVL have been demonstrated by others. The UK TAVI Registry reported prospectively collected data on TAVR patients implanted up until December 2009.²² Of the 452 CoreValve implants included in the study, 17.3% had moderate to severe aortic insufficiency compared with 9.6% of SAPIEN implants ($P = 0.001$). Furthermore, 24.4% required permanent pacemaker implantation compared with 7.4% of SAPIEN implants ($P < 0.001$). Procedural success was still excellent (98.2%) and 30-day mortality remained acceptable at 5.8%. In the only randomized trial comparing the transfemoral balloon-expandable (SAPIEN XT) and self-expanding (CoreValve) valves, Abdel-Wahab and colleagues randomized 240 patients to receive one of the two valves.²⁹ They noted a significantly lower frequency of residual aortic regurgitation based on intraoperative angiography (41% vs. 18%; $P < 0.001$) and less frequent need for implanting more than one valve in the SAPIEN patients. Cardiovascular and overall mortality at 30 days was similar in both groups. They also noted that the need for a permanent pacemaker was significantly lower in the SAPIEN valve group (17% vs. 38%; $P = 0.001$).

In general, when compared with SAVR, TAVR has been shown in high-risk surgical patient populations to have similar mid-term mortality.^{15,16,19,30,31} An important observation of the aforementioned studies is that despite the relief of aortic stenosis, this high-risk patient cohort continues to have a progressive mortality rate reaching approximately 40% to 45% at 3 years. Although this may be secondary to the inherent comorbidities and age of this patient population, it remains incumbent for health care providers to redefine the most appropriate patients for any therapy or TAVR or SAVR.

TAVR in Patients with Prior SAVR

Tissue prostheses carry a low risk of thromboembolic events (between 0.5% and 1% risk per year without anticoagulation) but have a higher chance of valvular degeneration, requiring the potential need of a repeat surgical intervention at 10 to 15 years from implantation.

Fundamental types of information to determine are the valve type, valve size, and technical technique used in the primary valve surgery. There are numerous types of bioprostheses valves implanted in the aortic position. This could be xenografts (most frequently obtained from bovine pericardial or the porcine aortic valve or root) or homografts. Bioprostheses can also be divided into stented and stentless valves. For each surgical valve to be treated, it requires understanding of the structural and fluoroscopic characteristics for an accurate positioning of the valve in valve (V-in-V). When planning for the adequate sizing for the V-in-V, the important measurement is the true inner diameter of the valve. Other relevant measures include post and leaflet heights, the position of the valves within the aortic root and the relationship with the coronary ostia, and the presence of coronary bypasses.³²

The complications resulting from TAVR in patients with prior SAVR differ from those of standard TAVR. Because the V-in-V is deployed in a fixed structure, it is less frequent to have annular rupture, bleeding complications, paravalvular regurgitation, and new events of conduction abnormalities. There is, however, an increased incidence of valve malpositioning (especially in previous aortic root replacement or stentless valves secondary to the absence of fluoroscopic markers), coronary obstruction (mainly secondary to the displaced leaflets of the failing prosthesis against the coronary ostia), and increase of postoperative aortic prosthesis gradients secondary to underexpansion of the transcatheter valve in a nonexpandable failing prosthesis ring.³³

SPECIFIC PATIENT COMORBIDITIES

With increasing awareness of less invasive techniques available for the treatment of high-risk patients with severe aortic stenosis, there remains controversy over the appropriate therapy regarding SAVR or TAVR. Although this decision may be difficult when based solely on the STS predicted risk of mortality, a more realistic decision-making tool includes the identification of specific patient subgroups that may benefit preferentially from TAVR or SAVR.

Gender

To date, there remains a paucity of studies investigating the impact of gender-related differences following TAVR or SAVR.³⁴⁻³⁷ In an analysis of patients from the PARTNER trial by Williams and coworkers, there was reduced procedural mortality in females undergoing TAVR compared with SAVR (6.8% vs. 13.1%; $P = 0.07$).³⁵ At 2 years, all-cause mortality was significantly lower in females undergoing TAVR (28.2% vs. 38.2%; $P = 0.049$). These investigators also noted that the differences in the reduced late mortality were predominantly in the transfemoral cohort (23.4% vs. 36.9%; $P = 0.02$), whereas there was a less striking benefit in the transapical cohort (37.3% vs. 41.7%; $P = 0.62$). Although procedural mortality also favored TAVR over SAVR in males (6.0% vs. 12.1%; $P = 0.03$), there was no benefit in all-cause mortality at 2 years in the TAVR group (37.7% vs. 32.3%; $P = 0.42$). Moreover, there was no reduction in 2-year mortality in either the transfemoral ($P = 0.86$) or the transapical arms ($P = 0.21$) in males.³⁵ It is plausible that these results suggest that TAVR and, when feasible, the transfemoral route might be the preferred treatment option for older women with symptomatic severe aortic stenosis.

Diabetes Mellitus

Another high-risk patient population presenting with severe aortic stenosis are those with preoperative diabetes mellitus. In 1391 patients undergoing isolated SAVR, Halkos and his colleagues at Emory reported significantly reduced 10-year survival in patients with diabetes (40.5%) compared with those without diabetes (71.2%; $P <$

0.001).³⁸ Only one report thus far has compared outcomes in high-risk diabetic patients undergoing TAVR ($n = 145$) and SAVR ($n = 130$). From a post hoc analysis of the PARTNER trial, Lindman and colleagues noted all-cause mortality at 1 year was 18.0% in TAVR patients and 27.4% in the surgical group ($P = 0.04$).³⁹ In contrast, there was no significant difference in 1-year mortality in nondiabetic patients between groups ($P = 0.48$). These data suggest that TAVR may be the preferred treatment approach for patients with aortic stenosis and diabetes who are at high risk for surgery.

Mitral Regurgitation

The presence of moderate or severe mitral regurgitation (MR) with concomitant aortic stenosis represents a difficult and common patient population. Following isolated SAVR,⁴⁰ but not TAVR,^{41,42} preoperative moderate or severe MR has been associated with worse early and late survival. In a post hoc analysis of the PARTNER trial comparing SAVR and TAVR in those with concomitant MR, Barbanti and coworkers showed that similar changes in left ventricular remodeling and improvement in left ventricular function occur following relief of the aortic stenosis by either SAVR or TAVR.⁴² Correspondingly, improvements in symptoms and functional class were found with both procedures, regardless of the severity of MR. However, in those undergoing SAVR, all-cause mortality at 2 years was higher in those with preoperative moderate or severe MR compared with those with mild or less MR (49.8% vs. 28.1%; $P = 0.04$). In contrast, MR severity at baseline did not affect mortality in TAVR patients (37.0% vs. 32.7%; $P = 0.58$). Unfortunately, current studies have not differentiated the impact of TAVR route (i.e., TF, TA, TAO) on long-term outcomes in this patient population. In select high-risk patients with nondegenerative moderate to severe MR and concomitant severe aortic stenosis, it may be reasonable to consider TAVR as a less invasive mode of therapy.

Renal Dysfunction

A strong association exists between aortic stenosis and renal dysfunction with up to 75% of patients having mild, moderate, or severe renal dysfunction.⁴³ We and others have shown that preoperatively impaired renal function represents a strong independent predictor of adverse short- and long-term outcomes in SAVR and TAVR patients.^{43,44} Recently, Nguyen and colleagues from Emory University compared renal dysfunction within SAVR ($n = 1336$) and TAVR ($n = 343$) patients. They noted an in-hospital mortality in TAVR patients for mild, moderate, and severe renal dysfunction of 3.8%, 2.9%, and 4.4% ($P = 0.89$), respectively. On the contrary, in the SAVR group, worsening renal function was associated with a stepwise increase in short-term mortality, at 2.6%, 4.1%, and 8.9% for mild, moderate, and severe renal dysfunction, respectively. Furthermore, worsening renal function was strongly associated with increased mid- and long-term mortality in the SAVR group, whereas Kaplan-Meier survival estimates for TAVR stratified by renal function do not demonstrate this relationship. In all

patients, the adjusted odds ratio for death was 0.47 when comparing TAVR with SAVR.⁴⁵ In SAVR patients, the adjusted odds ratio for death was 2.6 when comparing severe/dialysis with normal patients. In TAVR patients, the odds ratio was 1.01 when comparing severe/dialysis with normal patients. Although more research and analysis is needed to elucidate the preferential benefit of TAVR in patients with renal dysfunction, it is possible that TAVR mitigates the effect of moderate and severe renal dysfunction on short- and mid-term survival.

COMPLICATIONS

Although TAVR was designed to be a less invasive form of aortic valve replacement for high-risk patients, it still carries many of the same potential complications for open, traditional aortic valve replacement. The Valve Academic Research Consortium-2 (VARC-2) has standardized the endpoint definitions for studies evaluating the use of TAVR, which will lead to improved comparability and interpretability of the study results.⁴⁶ Denoted in this section are the most common complications associated with TAVR.

Acute Hypotension

Acute hypotension during TAVR is not uncommon and may be due to acute aortic insufficiency, left ventricular dysfunction (caused by “stunning” with rapid pacing, ostial coronary occlusion, or other factors), pericardial effusion (typically from right ventricular perforation by the pacing wire or aortic root trauma), arrhythmia, peripheral vascular injury, a “suicide ventricle” (hyperdynamic intraventricular obstruction after unloading by BAV or TAVR), or other factors. Treatment of acute hypotension is dictated by its causes. In the absence of an anesthesiologist, operator-administered boluses of intra-aortic, intraventricular, or intravenous epinephrine or norepinephrine are immediately deliverable and effective temporizing measures. The suicide ventricle, although uncommon, is suggested by high residual gradients, especially dynamic obstruction (worse after a premature beat); can be identified echocardiographically; and is important to differentiate from other causes of acute heart failure: it will be aggravated by diuresis and positive inotropes but can be effectively treated with volume, vasoconstrictors, and negative inotropes.

Stroke

In addition to mortality, one of the most devastating consequences following aortic valve replacement is a new postoperative permanent stroke. Following SAVR in high-risk surgical patients, stroke rates have been reported between 3% and 5%.^{4,5,15,18} The incidence of cerebrovascular events (transient ischemic event or a stroke) during the 30-day period after TAVR ranges from 3% to 7%.⁴⁷ Approximately 50% to 70% of these events occur during, or within 24 hours of, the procedure. In the PARTNER study, an analysis of 30-day and 1-year outcomes, there was an increased periprocedural stroke following TAVR

when compared with SAVR.^{15,48} However, at 2 years and in a more recent study of the PARTNER patients by Thourani and coworkers, there does not appear to be any evidence of a continued increased stroke at the 2- and 3-year follow-up in TAVR patients.^{16,19} In an analysis of the PARTNER trial by Dewey and colleagues, the authors noted improvement in the periprocedural stroke rate from 6.7% in the premarket approval TA-TAVR ($N = 104$) when compared with 2.2% in the nonrandomized continued access TA-TAVR group ($N = 975$).⁴⁹ In a recent meta-analysis, Eggebrecht and associates have shown an overall 30-day stroke/TIA rate was $3.3 \pm 1.8\%$ with most being major strokes ($2.9 \pm 1.8\%$).⁵⁰

Stroke in association with TAVR can occur because of atheroembolism, thromboembolism, cardiogenic shock during the procedure, preexisting cerebral vascular disease, or interaction of these factors. However, catheter manipulation in the ascending aorta is the most likely cause of most strokes observed with TAVR. Predictors of neurologic events were balloon post dilation, valve embolization, and new onset of atrial fibrillation.⁵¹ Major, ischemic stroke may be treated by catheter-based, mechanical embolic retrieval where available. Thrombolysis may also be considered, although the expected benefit may be reduced (particularly with atheroembolism); bleeding risk is typically high because of patient age and morbidity as well as the arteriotomies created for TAVR (if recent). Clinical studies evaluating the most appropriate anticoagulation regimen are also forthcoming.

One of the most recent aspects of stroke prevention includes new cerebroembolic protection devices, which are actively being evaluated and have shown promise in the reduction of embolic debris during TAVR.⁵²⁻⁵⁴ These devices can be categorized in two broad categories: (1) deflectors, which prevent passage of emboli to the cerebrovascular system by redirecting them to the lower half of the body, and (2) retrieval devices, which capture and collect emboli for removal from the systemic circulation.

Among the deflector devices, the Embrella Embolic Deflector (Edwards Lifesciences) and the Triguard (Keystone Heart, Ltd.) have the largest clinical experience to date (Fig. 79-17). Both devices use a nitinol frame that is positioned across the origin of the great vessels in the aortic arch. The Embrella device uses a polyurethane membrane with pore size of $100 \mu\text{m}$ to selectively deflect emboli. The Triguard is a nitinol mesh with a pore size



FIGURE 79-17 ■ Embrella Embolic Deflector (Edwards Lifesciences).

of $140 \mu\text{m}$. The Embrella uses a right radial or brachial approach for deployment, whereas the Triguard is delivered via the femoral artery and covers the entire arch, including the left subclavian artery.

The retrieval system with the most clinical experience to date is the Montage Dual Filter (Claret Medical, Inc.) (Fig. 79-18). The system uses right upper extremity access to place two conical filters with $140\text{-}\mu\text{m}$ polyurethane membranes in the brachiocephalic and left common carotid arteries. At the completion of the procedure, the filters are withdrawn and captured debris is removed from the circulation. A first-in-human series was reported in 2012 detailing use in 40 patients. The series included two generations of the device with improvements in proper placement for the second generation (87%) compared with the first generation device (60%).⁵³ Macroscopic debris was removed from 19 (54%) patients treated; one minor stroke (at 30 days) and two major strokes (at 4 hours, at 27 days) were observed.

Acute Kidney Disease

Significant acute kidney injury (AKI) after TAVR has been reported to be 8%, being an independent predictor of mortality.⁵⁵ The origin of AKI is likely to be multifactorial, involving predisposing conditions such as diabetes mellitus, chronic kidney disease, or peripheral vascular disease, and procedure-related events such as aortic plaque embolism in the renal arteries and hypoperfusion during rapid ventricular pacing. The use of the TA approach has been reported to be an independent predictor of AKI in several studies, probably reflecting underlying comorbidities that predispose these patients to such a complication.

Vascular Complications

Vascular injury at the access site is the most frequent problem with transfemoral TAVR. Major vascular complications occurred in 15% of patients within 30 days of TF-TAVR in the PARTNER trial and were associated

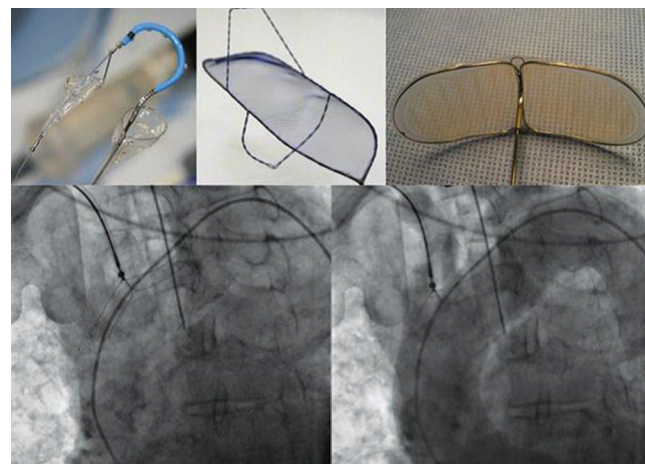


FIGURE 79-18 ■ Montage Dual Filter (Claret Medical, Inc.).

with significantly higher rates of 30-day and 1-year mortality.¹¹ Vascular access site complications are mainly related to the large caliber sheaths used to deliver the valve. The first generation of sheaths (22 to 25 Fr, corresponding to an outer diameter of 9 to 10 mm) was associated with high rates of vascular complications. However, with growing operator experience, improved patient screening and selection, and the smaller diameter of the newer generation of sheaths (18 or 19 Fr, corresponding to an outer diameter of 7.2 to 7.5 mm), the incidence of vascular complication has significantly decreased over time. Within the next few years, we would expect vascular injuries to be below 5%.

Other major vascular complications include thoracic aortic dissection; rupture of the aortic annulus; distal embolization (noncerebral) from a vascular source, requiring surgery or resulting in amputation or irreversible end-organ damage; access-site or access-related injury leading to death, the need for blood transfusion (>4 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage.⁴⁶

Aortoiliac avulsion or perforation may be suspected during arterial dilation and insertion of the delivery sheath, but it may not be clinically manifest until removal of the delivery sheath. If perforation is identified at sheath removal, the sheath should be immediately reinserted (with dilator in place) to help tamponade the bleeding while preparation for more definitive treatment is made. Depending on the site and severity of injury, an aortic occlusion balloon such as the Coda balloon (Cook Medical, Bloomington, Illinois) may be inserted from the contralateral arterial access site. Prolonged balloon tamponade using peripheral angioplasty balloons may be helpful for iliac or femoral perforation, and deployment of covered stents may seal the perforation. Iliofemoral dissection is usually retrograde and does not limit flow, but severe dissections may be flow-limiting or even occlusive. Flow-limiting dissections should be treated with endovascular or surgical repair. Suture-mediated, severe stenosis of the common femoral artery at the access site often responds to gentle balloon dilation, which does not need to completely eliminate the narrowing to be successful: mild to moderate residual narrowing is rarely symptomatic.

Aortic annulus rupture, a rare occurrence, is associated with high mortality. Independent predictors of this complication include valve oversizing and the presence of moderate or severe calcification in the left ventricular outflow tract.⁵⁶ It may present subtly with thickening of the interatrial septum on echocardiography and subsequent development of pericardial effusion. Effusion may be treated with pericardiocentesis, and surgical repair may be considered. Immediate treatment with protamine and blood pressure control are recommended for conservative management.

In the meta-analysis by Genereux and colleagues, the overall incidence of bleeding was 41% (life-threatening, 16%).⁵⁷ Life-threatening bleeding is associated with a 6 to 9 times increase in 30-day mortality after TAVR and was an independent predictor of 1-year mortality. The TA route for TAVR has consistently been reported as an independent predictor of life-threatening bleeding.⁵⁸

Aortic Insufficiency

Acute, moderate, or severe prosthetic aortic regurgitation after TAVR will be paravalvular, transvalvular, or mixed. The 2- and 3-year follow-up of the PARTNER trial using the balloon-expandable valves resulted in significantly worse PVL than SAVR with more than 50% of TAVR patients experiencing at least mild PVL.^{16,19,59} There has been much focus on the effect of aortic regurgitation on survival following TAVR. A number of studies have identified aortic regurgitation higher than grade 2+ to be an independent predictor of short- and long-term mortality.⁶⁰ The direct causal relationship between PVL and mortality still needs to be determined, as does the significant heterogeneity in the assessment of PVL; thus far controversy regarding the use of echocardiography or magnetic resonance imaging continues.⁶¹ The use of cross-sectional CT has improved the accuracy of aortic annular sizing for TAVR and has led to the overall reduction of PVL, displacing two-dimensional TTE as the gold standard for TAVR valve selection.⁶²

Acute transvalvular regurgitation may occur as a result of incomplete valve closure when the valve is deployed in the setting of systemic arterial hypotension and this improves when the blood pressure is increased. The valve also may simply require a brief period of time (minutes) to “warm up” and achieve full leaflet mobility. A third scenario for transvalvular aortic regurgitation is that it may be caused by an overhanging native aortic leaflet, which can prevent closure of the TAVR valve leaflets. In this case, the operator can attempt to close the TAVR valve leaflets by placing an angled-pigtail catheter in each aortic cusp. If this is unsuccessful, another TAVR valve should be deployed just aortic to the initial TAVR valve to adequately displace the native aortic leaflets.

The more common scenario includes that of the paravalvular aortic leak. For patients with more than mild PVL noted during the procedure, the position of the transcatheter heart valve should be assessed. If the valve is malpositioned, a second valve may be implanted in the first valve. However, if the valve is well positioned, dilating the stent-valve with a balloon catheter may expand the valve and fill the annulus more completely. Chronic, moderate, or severe paravalvular aortic regurgitation after TAVR may be treated percutaneously by implantation of a second valve or by implantation of one or more vascular plugs.

Valve Embolization

Valve embolization is most commonly caused by loss of capture during rapid ventricular pacing (leading to ejection of the incompletely deployed valve from the annulus), but it also may be caused by malpositioning or, in rare cases, choosing a valve too small for the annulus. Embolization is best avoided by confirmation of stable pacing and by careful valve positioning prior to and during slow, controlled deployment. In the event of aortic movement during deployment, the valve may be immediately pushed back into the annulus if the deploying operator has maintained pressure on the inflation syringe (to hold the no-longer-crimped valve on the partially inflated balloon)

without further inflation or deflation. If the valve cannot be pushed back across the annulus, then it may be pulled into the arch (and ideally into the descending aorta) before being deployed. If the deployment balloon has been deflated, the valve will be loose on the wire and should be recaptured with the balloon and deployed in a safe location, either just distal to the left subclavian artery or immediately proximal to the common iliac bifurcation. Wire position across the valve must be maintained to prevent the valve from turning and obstructing the aorta. After the embolized valve is secured, a second valve may be implanted in the annulus to complete the TAVR. Valve embolization into the left ventricle is less common and almost always requires surgical intervention.

Coronary Occlusion

Myocardial infarction is a rare yet catastrophic complication during TAVR and occurs in less than 1% of patients.^{11,63} Acute, aorto-ostial coronary occlusion may be treated effectively with immediate percutaneous coronary intervention (PCI) or emergent peripheral cardiopulmonary bypass followed by PCI. Left main coronary artery occlusion is most likely, although right coronary artery obstruction has also been described. Most commonly, patients experience acute hemodynamic compromise with ST-segment elevation suggesting acute myocardial infarct. Percutaneous intervention can be facilitated in high-risk cases by placing a 0.014-inch coronary interventional wire and/or balloon into the coronary artery at risk prior to deployment of the new valve (Fig. 79-19). Prevention remains the mainstay of treatment for this dreadful complication. Coronary artery orifice less than 12 mm as determined by a high-definition CT scan should prompt concern. In such scenarios, performing a BAV with a concomitant root angiogram may discern the potential for main coronary artery occlusion.

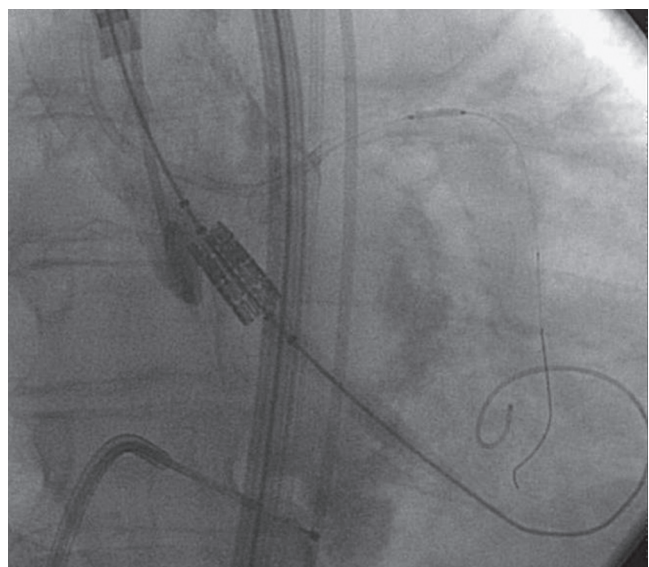


FIGURE 79-19 ■ Left main coronary wire during valve-in-valve deployment.

Conduction Abnormalities

Transcatheter aortic valves intentionally oversize the aortic annulus and are partially placed in a subannular position, bringing them into proximity with the cardiac conduction system as it enters the ventricular septum. The need for a pacemaker post TAVR is infrequent with the Edwards-SAPIEN valve reported at 3.4% in the randomized PARTNER US trial.^{11,15} There remains an important difference in the need for permanent pacemakers after TAVR between the balloon-expandable (6.5%) and self-expanding valves (25.8%).^{64,65}

Complete heart block following TAVR is immediately treated by backup pacing from the temporary pacing wire. The bradyarrhythmia may be transient and the temporary wire may be left in place until the question of need for permanent pacing has been elucidated.

New left bundle branch block (LBBB) occurred in 121 of 1151 (10.5%) patients and persisted in more than half at 6 months to 1 year according to the PARTNER trial data.⁶⁶ New LBBB was not associated with significant differences in 1-year mortality, cardiovascular mortality, repeat hospitalization, stroke, or myocardial infarction. However, it was associated with increased permanent pacemaker implantation during hospitalization (8.3 vs. 2.8%, $P < 0.005$) and from discharge to 1 year (4.7 vs. 1.5%; $P < 0.01$). The ejection fraction failed to improve after TAVR in patients with new LBBB and remained lower at 6 months to 1 year (52.8 vs. 58.1%; $P < 0.001$).⁶⁶

Uncommon Complications

Other uncommon complications reported include tamponade and mitral valve injury. Tamponade can result from cardiac perforation in the right ventricle during placement of the pacemaker and the left ventricle by the stiff wire used for the BAV and TAVR. Large inspiratory drops in systemic arterial pressure (pulsus paradoxus) suggest a hemodynamically significant effusion, which can be confirmed with echocardiography. Treatment with pericardiocentesis is reasonable because the bleeding into the pericardium is often self-limited. If blood loss is substantial, blood may be autotransfused from the pericardium into a systemic vein while preparation is made for surgical exploration. The site of perforation may not be identifiable at surgery.

The mitral valve, including the chordae, may be damaged by guidewires in the left ventricle. Furthermore, the anterior leaflet of the mitral valve can be impinged on by a transcatheter heart valve placed too low in the ventricle. If severe mitral valve damage has occurred, operative interventions are the treatment of choice. Luckily, this is an extremely rare complication.

FUTURE DIRECTIONS

Catheter-based treatment options for patients with structural heart disease are rapidly improving with experience. Although the first randomized trials in North America have only recently been completed, the next generation of TAVR valves has grown immensely around the world.

Devices have been developed to decrease the known TAVR complications, including PVL and embolization. Technology now allows device repositionability and redeployment. The lower profile sheaths and valves will allow more transfemoral access and potentially reduce the need for alternative access devices. Lastly, the use of TAVR in intermediate-risk patients is forthcoming with the completion of the randomized PARTNER 2 intermediate trial with the SAPIEN XT valve and the ongoing SURTAVI trial with the CoreValve system.

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SURGICAL TREATMENT OF THE MITRAL VALVE

Andrew B. Goldstone • Y. Joseph Woo

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ANATOMY

The mitral valve apparatus is composed of the mitral annulus, leaflets, chordae tendineae, papillary muscles, and the left ventricular lateral wall (Fig. 80-1). Chordae tendineae and papillary muscles comprise the subvalvular apparatus.

Annulus

The right fibrous trigone is a dense fibrous area of continuity between the annuli of the mitral, tricuspid, and noncoronary cusp of the aortic valve, as well as the membranous interventricular septum. The left fibrous trigone forms the leftmost border of fibrous continuity between the aortic and mitral valves. The mitral valve leaflets are attached to an ovoid ring, or annulus of fibrous tissue, that extends from the right and left fibrous trigones to form the junction between the left atrium and ventricle. In three-dimensional space, the annulus maintains a hyperbolic paraboloid shape (saddle shape).¹ The mid-anterior and mid-posterior annular segments are highest

(farthest away from the ventricular apex), whereas the anterolateral and posteromedial commissures are lowest. The mitral annulus is thinnest at the insertion site of the posterior leaflet. As this segment is not attached to any rigid cardiac structures, it is the most mobile throughout the cardiac cycle and is the most prone to annular dilation.

Leaflets

The mitral valve has two major leaflets: the larger anterior (aortic) leaflet and the smaller posterior (mural) leaflet. The anterior leaflet is semicircular and is attached to one third of the annular circumference. The leaflet free edge does not have indentations. The anterior leaflet defines the boundary between the inflow and outflow tracts of the left ventricle. The posterior leaflet is quadrangular and is attached to two thirds of the annular circumference. The leaflet typically contains three or more scallops separated by fetal clefts or subcommissures, which develop to variable degrees in each individual.²

The subcommissures of the posterior leaflet permit further division of the mitral valve into eight segments (Fig. 80-2). The three posterior leaflet scallops are anatomically termed *anterolateral* (P1), *middle* (P2), and *posteromedial* (P3) segments. The three corresponding segments of the anterior leaflet are the anterior segment (A1), middle segment (A2), and posterior segment (A3). The anterolateral and posteromedial commissures comprise the remaining two segments. The posteromedial and anterolateral commissures are identified by the axis of the corresponding papillary muscles and the commissural chordae. The distance between the free edge of the commissures and the annulus is approximately 8 mm. As such, during open commissurotomy it is important to maintain this distance to reduce the risk of leaflet tearing and subsequent mitral regurgitation.

The atrial surface of the leaflets is divided into two zones: a marginal rough zone and central smooth zone. The rough zone is the coaptation surface of the valve and is the insertion site of most of the chordae tendineae.

Chordae Tendineae

The chordae tendineae are collagenous leaflet extensions connecting the papillary muscles and the ventricular side of the leaflets (Fig. 80-3). Chordae are classified based on

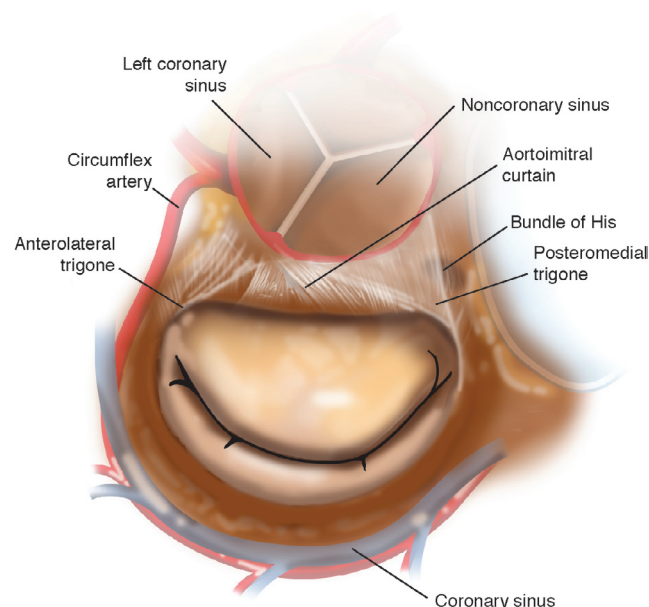


FIGURE 80-1 ■ Surgical anatomy of the mitral valve and other important neighboring structures.

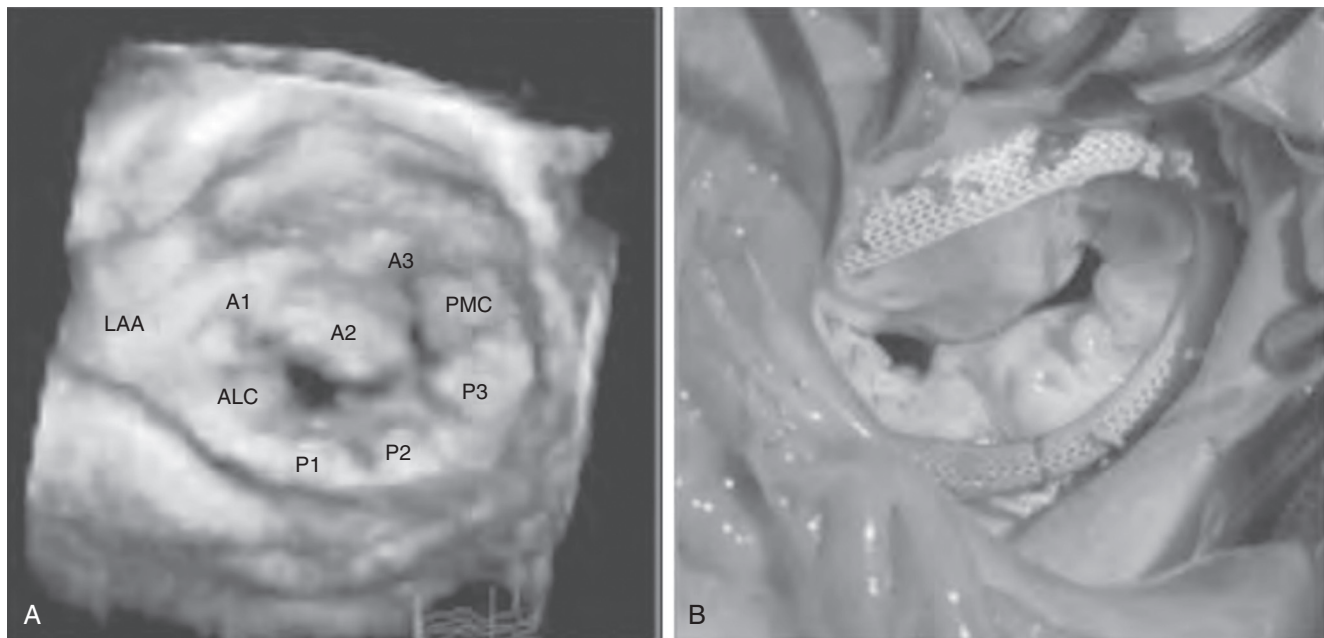


FIGURE 80-2 ■ Segmental anatomy of the mitral valve from the surgical view is demonstrated (A) grossly and (B) with three-dimensional transesophageal echocardiography. (Modified from Debonnaire P, Palmen M, Marsan NA, et al: Contemporary imaging of normal mitral valve anatomy and function. *Curr Opin Cardiol* 27:457, 2012.)



FIGURE 80-3 ■ Subvalvular apparatus. Primary chordae are attached to the free margin of the leaflet, secondary chordae are attached to the ventricular surface of the leaflet body, and tertiary chordae are attached to the ventricular surface of the leaflet base.

the site of insertion on the leaflet. Primary chordae insert on the leaflet free margin and act to prevent leaflet prolapse. Secondary chordae insert on the ventricular surface of the leaflets and reduce excess tension on the leaflet tissue. Tertiary chordae connect the leaflet base to the

mitral annulus and surrounding myocardium. Tertiary chordae are limited to the posterior leaflet of the mitral valve. Often, the diameter of the chordae increases from the leaflet edge to the annulus.

Papillary Muscles and Left Ventricular Wall

Two papillary muscles arise between the middle and apical thirds of the left ventricle. The anterolateral papillary muscle is typically composed of one muscle body while the posteromedial papillary muscle usually arises from two muscle bodies. Each papillary muscle supplies chordae to both leaflets. The anterolateral papillary muscle receives blood from both the left anterior descending artery as well as a diagonal or obtuse marginal branch of the circumflex artery. However, the posteromedial papillary muscle receives blood from only one source: either the circumflex or right coronary artery. Consequently, the posteromedial papillary muscle is more sensitive to myocardial ischemia than the anterolateral papillary muscle. As the lateral wall of the left ventricle supports the base of the papillary muscles, it may also be considered part of the mitral valve apparatus. In fact, the left ventricular lateral wall is integral in the pathogenesis of ischemic mitral regurgitation.

MITRAL STENOSIS

Pathophysiology

In non-diseased adult human hearts, the normal mitral valve area is 4 to 6 cm². Once the mitral valve orifice narrows to less than 2.5 cm², a pressure gradient is necessary to generate blood flow from the left atrium into the

TABLE 80-1 Classification of Mitral Stenosis Severity

Findings	Mild	Moderate	Severe
Specific			
Valve area (cm ²)	>1.5	1.0-1.5	<1.0
Supportive			
Mean gradient (mm Hg)*	<5	5-10	>10
Pulmonary artery pressure (mm Hg)	<30	30-50	>50

*At heart rates between 60 and 80 beats/min and in sinus rhythm.

From Baumgartner H, Hung J, Bermejo J, et al: Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 22:17, 2009.

left ventricle. Based on a semi-quantitative grading system, mitral stenosis is typically classified as mild if the valve area is >1.5 cm², moderate when the valve area is between 1.0 and 1.5 cm², and severe when the valve area is <1.0 cm² or the mean transvalvular pressure gradient exceeds 10 mm Hg (Table 80-1). However, it should be noted that the definition of *severe mitral stenosis* used by the American College of Cardiology/American Heart Association (ACC/AHA) is based on the severity at which symptoms occur as well as the severity at which intervention will improve symptoms (in essence, “severe” in professional society guidelines should be read as “significant”).³ Thus, in the 2014 iteration of the ACC/AHA guidelines, a mitral valve area of 1.5 cm² or less and a mean transvalvular gradient between 5 and 10 mm Hg is considered severe.

The transvalvular gradient results in elevated left atrial and pulmonary venous pressures. Over time, pulmonary artery hypertension develops from a combination of compensatory arterial vasoconstriction, intimal hypertrophy of the pulmonary arterioles and obliterative change, and passive retrograde transmission of the elevated pulmonary venous pressure. Pulmonary edema results when pulmonary venous pressure exceeds plasma oncotic pressure. At rest, mitral stenosis is often asymptomatic; however, any increase in flow across the mitral valve or decrease in duration of diastole results in an increase in the transvalvular pressure gradient. Consequently, dyspnea is typically precipitated by exercise, stress, infection, pregnancy, or rapid atrial fibrillation.

As pulmonary artery pressures rise, both right ventricular end-diastolic pressure and volume increase, resulting in right ventricular dilation and tricuspid regurgitation. Because left ventricular inflow is restricted, left ventricular chamber size or end-diastolic volume is normal or less than normal, and end-diastolic pressure is generally low. Although most patients with mitral stenosis have normal left ventricular dimensions and systolic function, ejection fraction is significantly reduced in a small proportion of patients (generally older adults).⁴ These patients often have severe segmental wall contraction abnormalities of the posterobasal or anterolateral segments likely from papillary muscle fibrosis and immobilization.^{4,5} Diffuse hypokinesis has also been described and is likely due to a chronic low cardiac output state.

Etiology

Although the prevalence of rheumatic disease has markedly decreased in recent decades, particularly in developed nations, it remains the predominant cause of mitral stenosis in the United States and worldwide.⁶ However, only half to two thirds of patients report a definite history of rheumatic fever, with at least a 2:1 female-to-male predominance. Rheumatic valve disease is generally acquired before age 20, and becomes clinically evident one to three decades later.⁷ Nonrheumatic etiologies of mitral stenosis include severe mitral annular calcification (common in older people), congenital mitral valve deformities, carcinoid syndrome, systemic lupus, neoplasm, and prosthetic valve calcification.

Rheumatic heart disease is an insidious fibrotic process that affects all segments of the mitral apparatus, as well as other valves. Mimicry between group A streptococcal antigens and epitopes found on human tissue stimulate autoimmune mediated damage to cardiac tissue.⁶ The mitral valve is the most commonly affected (isolated mitral stenosis is found in 40% of patients), followed by concomitant aortic and mitral valve disease, and least frequently isolated aortic valve disease. Early valvular lesions include: (1) leaflet thickening; (2) chordal thickening, fusion, and shortening; and (3) commissural fusion (Fig. 80-4). Progressive valvulopathy produces a characteristic “fish mouth” single central opening, with restricted leaflet motion during systole and diastole. Chordal thickening and fusion can create a dense fibrotic subvalvular mass that can further obstruct forward flow. Calcification, particularly at the commissural edges and occasionally extending posteriorly into the annulus and subvalvular apparatus, is common late in the disease process and in older patients. These lesions, especially chordal fusion and shortening, often reduce leaflet coaptation by restricting leaflet mobility and thereby yield concomitant mitral regurgitation.

Clinical Characteristics and Diagnosis

The diagnosis of mitral stenosis can be based on medical history, physical examination, electrocardiography, chest radiography, echocardiography, and invasive hemodynamics. As explained previously, patients are most often women and are frequently asymptomatic, although symptoms can include fatigue, dyspnea, hemoptysis (from rupture of dilated bronchial veins), new onset atrial fibrillation, or systemic thromboembolism.

Patients with chronic severe mitral stenosis are often cachectic because of longstanding low cardiac output. In the absence of left ventricular dysfunction, peripheral pulses are normal and the apical impulse is in the standard position on chest palpation. A right ventricular parasternal heave is present in the setting of pulmonary hypertension. Auscultatory findings include a loud S₁, an opening snap, and a diastolic murmur. The diastolic murmur is a low-pitched rumble best heard at the apex. The early diastolic opening snap is generated by sudden tensing of the pliable leaflets during valve opening and is absent later in the disease when the leaflets are immobile. The electrocardiogram may be normal but often

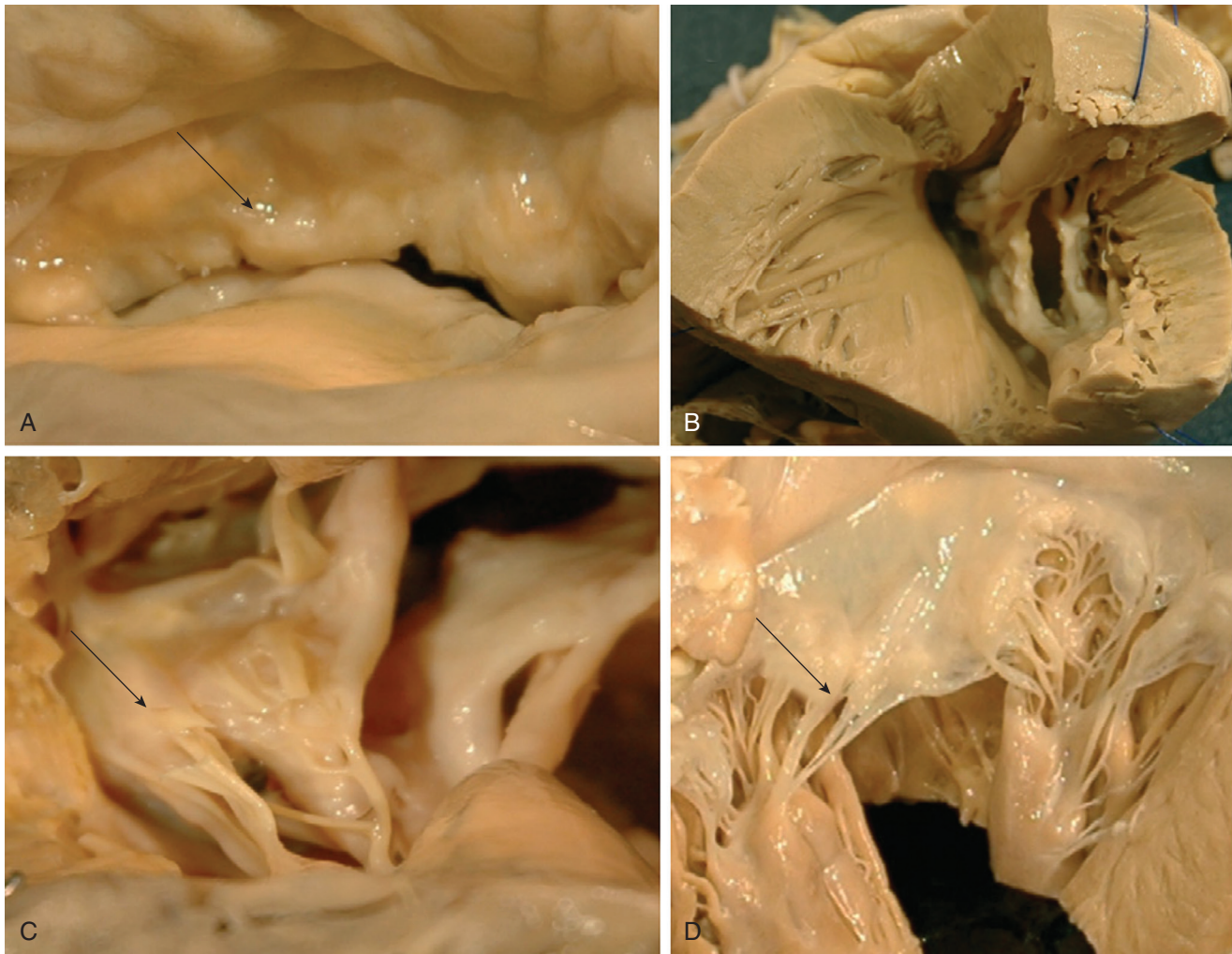


FIGURE 80-4 ■ Pathologic changes of the mitral valve in mitral stenosis. Thickened, rigid, nodular appearance of the mitral valve leaflets as viewed from the atria (**A**) and ventricle (**B**). The commissures are calcified and fused, thereby creating the characteristic “fish mouth”-shaped valve. **B** and **C**, The subvalvular apparatus is thickened, fused, and shortened. **D**, Healthy mitral valve leaflets. (From Chandrashekar Y, Westaby S, Narula J: Mitral stenosis. *Lancet* 374:1273, 2009.)

demonstrates P-wave abnormalities indicative of left atrial enlargement (biphasic P-wave in lead V_1 ; or broad, notched P-wave in lead II), atrial fibrillation, or right ventricular hypertrophy (right-axis deviation, and a tall R-wave in lead V_1). The chest radiograph may be normal; however, a large left atrium is frequently seen. In patients with severe mitral stenosis and pulmonary hypertension, the right atrium and ventricle may also be enlarged.

Echocardiography has become the principle diagnostic method for assessing mitral valve disease. Echocardiography permits evaluation of the morphology, mobility, and extent of calcification of the mitral leaflets, commissures, and subvalvular apparatus. In addition, the severity of mitral stenosis can be assessed by measuring the mitral valve area, the transmitral gradient, left atrial size, and the pulmonary artery pressures (see [Table 80-1](#)). Transthoracic echocardiography also provides a noninvasive evaluation of other valves, as well as right and left ventricular function. Echocardiographic characteristics of the mitral valve apparatus are used to determine candidacy for percutaneous balloon valvuloplasty.

Left-sided heart catheterization is not usually necessary for diagnosis of mitral stenosis, but it can be useful when there is a discrepancy between data from noninvasive assessments. In patients that meet criteria for surgical intervention, cardiac catheterization should be performed to ascertain whether coronary artery disease is present. Right-sided heart catheterization is performed to measure the severity of pulmonary hypertension, and it can be used to determine reversibility after administration of pulmonary vasodilators.

Natural History

Although the average age of index cases of rheumatic fever is approximately 12 years, symptoms do not generally become apparent until 30 years of age.⁷ Once symptoms develop, progression to incapacitating disability occurs over approximately 10 years, and those with more severe symptoms have poorer prognoses ([Fig. 80-5](#)).⁸ As such, the development of symptoms is integral in the treatment decision-making process. In surgically

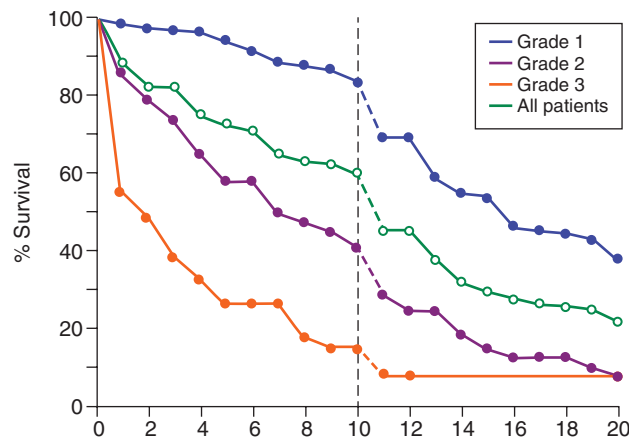


FIGURE 80-5 ■ Survival of patients with surgically untreated mitral stenosis stratified by symptom severity at initial evaluation. *Grade 1*, Asymptomatic; *Grade 2*, mild symptoms; *Grade 3*, moderate or moderately severe symptoms. (From Rowe JC, Bland EF, Sprague HB, et al: The course of mitral stenosis without surgery: ten- and twenty-year perspectives. *Ann Intern Med* 52:741–749, 1960.)

untreated patients with mitral stenosis, the average age of death is between 40 and 50 years.^{8,9}

Various sequelae often develop during the course of surgically untreated mitral stenosis that shorten the interval between symptom onset and death. Left atrial hypertension ultimately distorts atrial cardiomyocyte architecture and predisposes patients to atrial fibrillation. The onset of atrial fibrillation often initiates symptoms because patients with mitral stenosis rely heavily on atrial contraction for ventricular filling, and rapid heart rates reduce the duration of diastole. Consequently, cardiac output declines and left atrial pressure rises. In fact, atrial fibrillation incrementally increases the risk of death in patients with surgically untreated mitral stenosis; 20-year survival was 10% in patients with atrial fibrillation compared with 29% in those in sinus rhythm.¹⁰

Systemic thromboembolism also significantly alters the course of the disease, particularly when it results in stroke. Although most emboli originate in the left atrial appendage or left atrium, atrial fibrillation is not prerequisite for thrombus formation in surgically untreated mitral stenosis. Overall, arterial thromboembolization occurs in at least 10% of surgically untreated patients with mitral stenosis.¹¹

Pulmonary hemorrhage infrequently can develop in even mildly symptomatic patients, but the risk remits after surgical correction of the stenotic valve. Finally, infective endocarditis is uncommon in patients with mitral stenosis.

It is important to emphasize that these data and complicating events correspond to medically treated and surgically untreated patients with mitral stenosis. In fact, progression from initial symptoms to death was likely much shorter before medical therapies such as diuretics were developed. Similarly, surgical treatment has significantly altered the disease course. The increased life expectancy of such patients after surgical correction of mitral stenosis has resulted in the manifestation of late

significant rheumatic aortic valve disease and late secondary tricuspid regurgitation.

Indications for Surgery

Untreated mitral stenosis is associated with a poor prognosis once severe symptoms occur.¹² Percutaneous balloon mitral commissurotomy is the first-line therapy for mitral stenosis in patients with favorable anatomy. This procedure is indicated in symptomatic patients (stage D) with isolated severe mitral stenosis (mitral valve area ≤ 1.5 cm²; Fig. 80-6).³ Left atrial thrombus and greater than mild mitral regurgitation are contraindications to balloon commissurotomy. Percutaneous balloon commissurotomy may also be appropriate in asymptomatic patients with severe mitral stenosis (valve area < 1.0 cm²) and in those with severe mitral stenosis and new onset atrial fibrillation. Finally, balloon commissurotomy can be considered in symptomatic individuals with mitral valve area greater than 1.5 cm² if there is hemodynamic evidence of significant mitral stenosis with exercise (e.g., pulmonary capillary wedge pressure > 25 mm Hg). The Wilkins scoring system grades mitral valve morphology by use of echocardiography (Table 80-2). Four characteristics, graded on a scale from 0 to 4, are assessed: leaflet mobility, leaflet thickening, valve calcification, and extent of subvalvular disease. A total score greater than 8 is predictive of low success with percutaneous balloon mitral commissurotomy.^{13,14} Percutaneous balloon commissurotomy is associated with recurrent mitral stenosis, especially in patients undergoing repeat procedures for recurrence, as well as iatrogenic mitral regurgitation, particularly in patients with high Wilkins scores.¹⁴

Mitral valve surgery is an established therapy for mitral stenosis that predates balloon commissurotomy. Surgical options include commissurotomy (either closed or open, the latter permitting more extensive surgery under direct visualization) or mitral valve replacement. Because of the insidious nature of mitral stenosis and evidence that mitral stenosis does not have longstanding detrimental effects on the left ventricle, surgery should be delayed until the patient has severe, limiting symptoms (New York Heart Association [NYHA] class III or IV).³ Thus, mitral valve surgery is indicated in severely symptomatic patients (NYHA class III or IV) with severe mitral stenosis (mitral valve area ≤ 1.5 cm²) who are not high risk for surgery and who are not candidates for or who have failed previous percutaneous balloon mitral commissurotomy (see Fig. 80-6).³ Concomitant mitral valve surgery is also recommended in patients with severe mitral stenosis undergoing cardiac surgery for other primary indications.

MITRAL REGURGITATION

Pathophysiology

Mitral regurgitation, the retrograde ejection of blood from the left ventricle into the left atrium during systole, may be acute, chronic and compensated, or chronic and

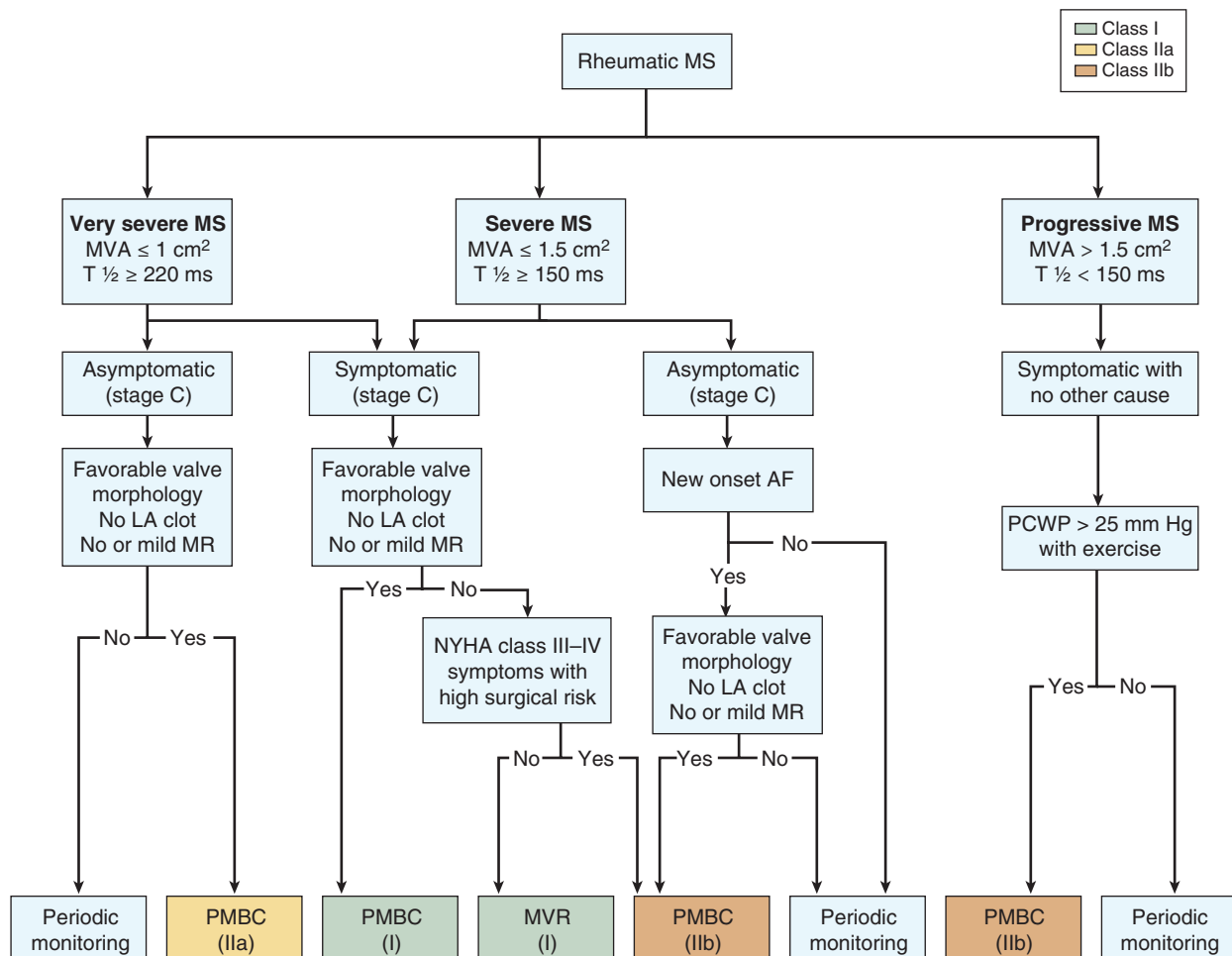


FIGURE 80-6 ■ Indications for intervention for mitral stenosis. AF, Atrial fibrillation; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; T ½, pressure half-time. (From Nishimura RA, Otto CM, Bonow RO, et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:e554, 2014.)

TABLE 80-2 Assessment of the Mitral Valve with the Wilkins Score

Grade	Mobility	Thickening	Calcification	Subvalvular Thickening
1	Highly mobile valve with only leaflet tips restricted	Minimal leaflet thickening (4-5 mm)	Single area of increased echo brightness	Minimal thickening just below the mitral leaflets
2	Leaflet mid and base portions have normal mobility	Midleaflets normal, considerable marginal thickening (5-8 mm)	Scattered areas of brightness confined to leaflet margins	Thickening of chordal structures extending to one-third the chordal length
3	Valve continues to move forward in diastole, mainly from the base	Entire leaflet thickened (5-8 mm)	Brightness extends into mid-portion of leaflets	Thickening extended to distal third of the chords
4	No or minimal forward movement of the leaflets in diastole	Considerable thickening of entire leaflet (>8-10 mm)	Extensive brightness throughout much of the leaflet tissue	Extensive thickening and shortening of all chordal structures that extends to the papillary muscles

Total score is the sum of the four items and ranges between 4 and 16.

Modified from Baumgartner H, Hung J, Bermejo J, et al: Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 22:14, 2009.

decompensated. The new low resistance, regurgitant pathway results in volume overload of the left ventricle at end diastole (increased preload) as well as in a reduction of afterload.¹⁵ Subsequently, a larger volume of blood is ejected from the left ventricle with each contraction. However, the effective forward stroke volume and cardiac output actually decrease because a proportion of the blood volume is ejected retrograde into the left atrium. Volume overload in the left atrium increases left atrial pressure from a normal level of approximately 10 mm Hg to as high as 25 mm Hg. The increased preload ultimately induces ventricular remodeling through eccentric hypertrophy and dilation.¹⁵ A larger ventricular cavity allows for an increase in total stroke volume, thereby maintaining forward stroke volume at near normal levels. This is chronic compensated mitral regurgitation.

Because the annulus is continuous with the left ventricle, annular dilation results from ventricular enlargement. The normal ratio between the anteroposterior and transverse diameters of the mitral annulus is 3:4 in systole. In chronic mitral regurgitation, this ratio is inverted, impairing proper leaflet coaptation and generating regurgitant flow even in the absence of leaflet prolapse. Annular dilation affects the posterior annulus to a greater extent than the anterior annulus.

Similar to ventricular compensation via enlargement, the left atrium dilates to accommodate the volume overload at lower filling pressures.¹⁵ Atrial enlargement increases the risk of atrial arrhythmias, such as atrial fibrillation and consequent mural thrombi from stasis. When mitral regurgitation develops suddenly from chordal rupture, papillary muscle infarction, or leaflet perforation, there is inadequate time for left atrial and

ventricular compensation. Thus, patients with acute mitral regurgitation typically present in a state of acute pulmonary edema and cardiogenic shock.

Ultimately, volume overload and eccentric ventricular hypertrophy impair ventricular performance and prevent effective ventricular contraction; this is chronic decompensated mitral regurgitation. Stroke volume and cardiac output decline as blood preferentially flows retrograde into the lower resistance pathway. Consequently, the pressure in the left atrium and pulmonary vasculature increases. Untreated decompensated mitral regurgitation progresses to irreversible pulmonary hypertension, pulmonary edema, and congestive heart failure. The presence of left ventricular dysfunction portends a worse prognosis regardless of the treatment modality. Although ventricular reverse remodeling can follow surgical correction of mitral regurgitation, it remains evident that normalization of cardiac dimensions is less likely or impossible once the ventricle has enlarged to a certain extent.¹⁶

Functional Classification

A thorough description of valve disease should incorporate the pathophysiologic triad first proposed by Carpentier (Table 80-3).¹⁷ The triad includes etiology (cause of the disease), valve lesions (structural changes resulting from the disease process), and leaflet dysfunction (alterations in leaflet motion resulting from the structural lesion). This classification scheme is emphasized because prognosis is etiology dependent, treatment strategy is determined by the type of valve dysfunction, and different surgical techniques are selected for specific valve lesions.

TABLE 80-3 Pathophysiologic Triad of Mitral Regurgitation

Dysfunction	Lesions	Etiology
Type I		
Normal leaflet motion	Annular dilation	Ischemic cardiomyopathy Dilated cardiomyopathy Permanent atrial fibrillation Endocarditis
	Leaflet perforation	
Type II		
Increased leaflet motion above annular plane (leaflet prolapse)	Chordal elongation or rupture	Degenerative disease Fibroelastic deficiency Barlow's disease Marfan syndrome Endocarditis Rheumatic Trauma
	Papillary muscle elongation or rupture	Ischemic cardiomyopathy Barlow's disease (elongation)
Type IIIa		
Restricted leaflet motion (systole and diastole)	Leaflet thickening or retraction Chordal thickening, retraction, or fusion Commissural fusion	Rheumatic disease Carcinoid heart disease Mitral annular calcification
Type IIIb		
Restricted leaflet motion (systole only)	Papillary muscle displacement Leaflet tethering	Ischemic cardiomyopathy Dilated cardiomyopathy Submitral ventricular aneurysm

The mechanism of mitral regurgitation can be categorized using Carpentier's functional classification (Fig. 80-7).¹⁷ The classification system is compartmentalized according to variations in leaflet motion. In type I dysfunction, leaflet motion is normal and a central mitral regurgitation jet is generated by annular dilation or leaflet perforation. Type II dysfunction describes leaflet prolapse, where the free margin of one or both leaflets rises above the annular plane in systole. Such leaflet dysfunction is most commonly due to chordal elongation or rupture, followed by papillary muscle elongation and rupture. In type III dysfunction leaflet motion is restricted. Leaflet motion restricted during both diastole and systole is classified as type IIIa. Lesions commonly associated with rheumatic valvulitis are most often responsible for type IIIa dysfunction, including (1) leaflet thickening and retraction; (2) chordal thickening, shortening, or fusion; and (3) commissural fusion. As such, coexistent mitral stenosis is not uncommon in the setting of type IIIa mitral regurgitation. Type IIIb dysfunction describes leaflet motion restricted only during systole. Such dysfunction is the result of left ventricular dilation and subsequent leaflet tethering from papillary muscle displacement.

Etiology

Degenerative Disease

Systolic prolapse of a mitral valve leaflet is a relatively common and complex disease process. When severe, mitral prolapse begets significant mitral regurgitation, albeit infrequently (about 10% of patients).¹⁸ Nevertheless, degenerative mitral valve disease is the most common cause of isolated mitral regurgitation in the United States.^{19,20} Pathologic examination of degenerative mitral valves reveals mitral leaflet redundancy and myxomatous leaflet thickening that typically result from collagen replacement by acid mucopolysaccharides.²¹ Mutual support is lost as redundant and elongated leaflets improperly coapt during systole. Consequently, the leaflets extend into the left atrium and the valve is rendered regurgitant. Simultaneously, chordae are placed under abnormal strain. The chordae elongate and may ultimately rupture, generating more regurgitation. Annular dilation and calcification can also arise to varying extents and further contribute to the complexity of the mitral valve dysfunction.

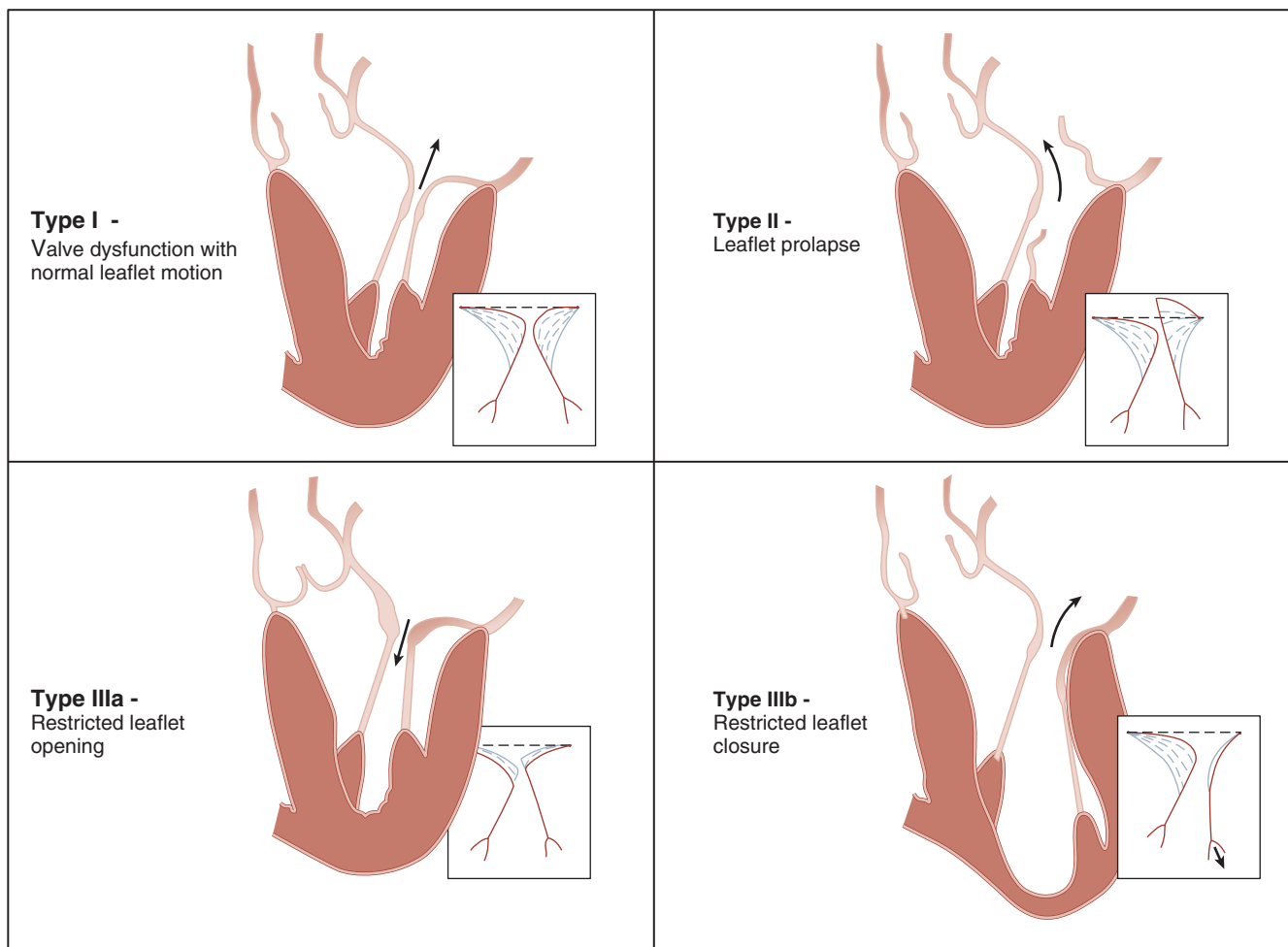


FIGURE 80-7 ■ Carpentier's functional classification of mitral regurgitation: *Type I*, normal leaflet motion; *Type II*, increased leaflet motion resulting in prolapse; *Type III*, restricted leaflet motion; *IIIa*, during diastole and systole; *IIIb*, during systole only. The arrow demonstrates the direction of regurgitant flow in types I, II, and IIIb. In type IIIa, the arrow demonstrates the frequent association with coexistent mitral stenosis. (From Carpentier A, Adams DH, Filsoufi F: *Carpentier's reconstructive valve surgery*, St. Louis, 2010, Elsevier.)

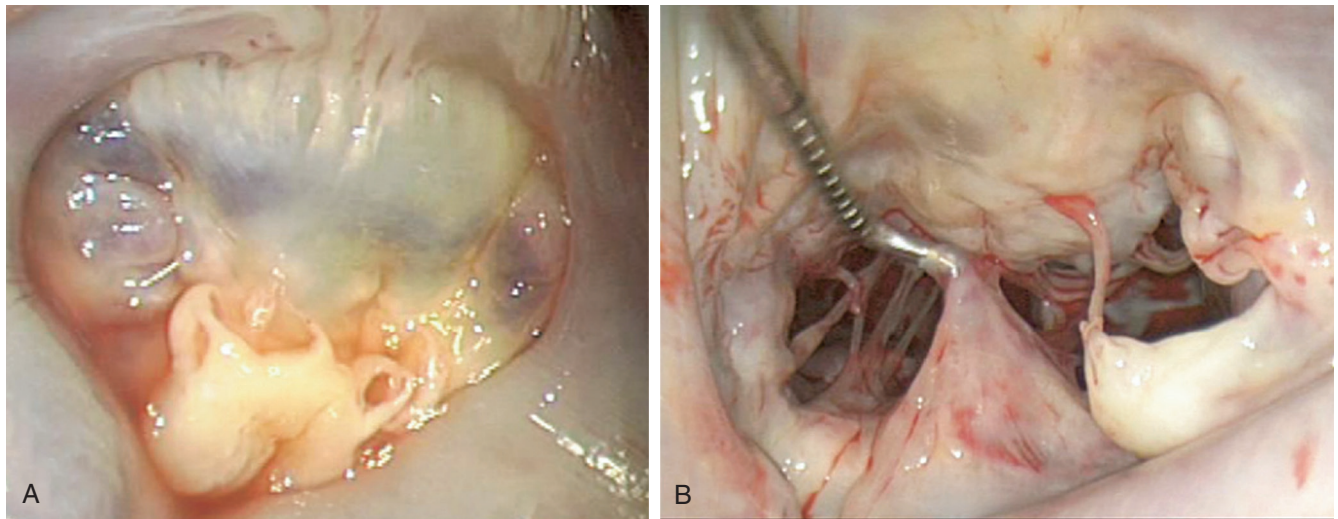


FIGURE 80-8 ■ Surgical lesions in fibroelastic deficiency. **A**, Prolapse of P2 owing to multiple ruptured chordae; the leaflet tissue is thickened compared with other segments. Note the translucency of the anterior leaflet, and normal height and thickness of P1 and P3, in contrast to findings in Barlow's disease (see Fig. 80-9). **B**, Prolapse of P3 with ruptured chord. Note that P3 is thickened, but P2 and P1 are thin and of normal height. (From Anyanwu AC, Adams DH: Etiologic classification of degenerative mitral valve disease: Barlow's disease and fibroelastic deficiency. *Semin Thorac Cardiovasc Surg* 19:94, 2007.)

The spectrum of degenerative mitral valve disease is often subclassified into fibroelastic deficiency and Barlow's disease.²² In fibroelastic deficiency, or idiopathic chordal rupture, a considerable portion of leaflet tissue is unaffected by the myxomatous transformation (Fig. 80-8).²³ Typically, regurgitation is caused by rupture of a single chord that supports the posteromedial portion of the posterior leaflet (P2). Following rupture, the less supported leaflet segment becomes redundant and flail. More extensive posterior chordal rupture may sometimes occur. Patients with fibroelastic deficiency are characteristically older with a short history of mitral regurgitation.

On the opposite end of the degenerative mitral valve disease spectrum, Barlow's disease presents early in life, and most patients have a long history of a systolic murmur. Barlow's disease is characterized by extensive excess leaflet tissue in a dilated annulus (Fig. 80-9).^{21,22} Leaflet tissue is thickened, and there is marked redundancy in multiple segments. In addition, chordae and occasionally papillary muscles are thickened and elongated. Regurgitation is complex and secondary to multi-segment leaflet prolapse. *Forme fruste* valves share morphologic features of Barlow's disease and fibroelastic deficiency: multisegment thickening and prolapse within a smaller valve.

Rheumatic Disease

Progressive leaflet thickening and retraction, as well as chordal shortening and fusion from chronic valvulitis restrict leaflet motion during both diastole and systole, thereby rendering the valve regurgitant (see Fig. 80-4). The anterior leaflet is typically less thickened, and particularly in younger patients, elongated major chordae may allow regurgitation from anterior leaflet prolapse.²⁴ Annular dilation from extensive myocarditis may cause transient mitral regurgitation in the acute rheumatic

process. This mitral regurgitation can spontaneously regress after remission of the pancarditic acute rheumatic process.

Mitral Annular Calcification

Annular calcification is most often seen in older people.²⁵ Although it can occur without apparent disease of the leaflets or chordae, it may be more common in patients with myxomatous degeneration of the mitral leaflets. Calcifying disease of the annulus is a degenerative process that usually involves the posterior circumference of the annulus more than other portions.^{25,26} Annular calcification can extend into the adjacent myocardium of the left ventricle, and it yields mitral regurgitation through restricted motion of the posterior leaflet. Such calcification can substantially complicate mitral repair or replacement.^{25,27}

Infective Endocarditis

Endocarditis is a relatively uncommon cause of isolated mitral regurgitation compared with the frequency in which it is accountable for aortic regurgitation. Mitral valve endocarditis typically occurs in patients with an already structurally abnormal valve because of underlying degenerative or rheumatic valve disease. However, several virulent organisms, such as *Staphylococcus aureus*, may infect nondiseased valves.²⁸ *Staphylococci* and *Streptococci* now account for 80% of cases of endocarditis.^{28,29} Upon infection of a normal or abnormal mitral valve, mitral regurgitation can result from destruction of leaflet cusps, chordae, or both. Because of their spatial interrelatedness, aortic valve endocarditis may directly extend to the mitral valve as vegetations may drop down onto and infect the central portion of the anterior leaflet of the mitral valve (Fig. 80-10).³⁰

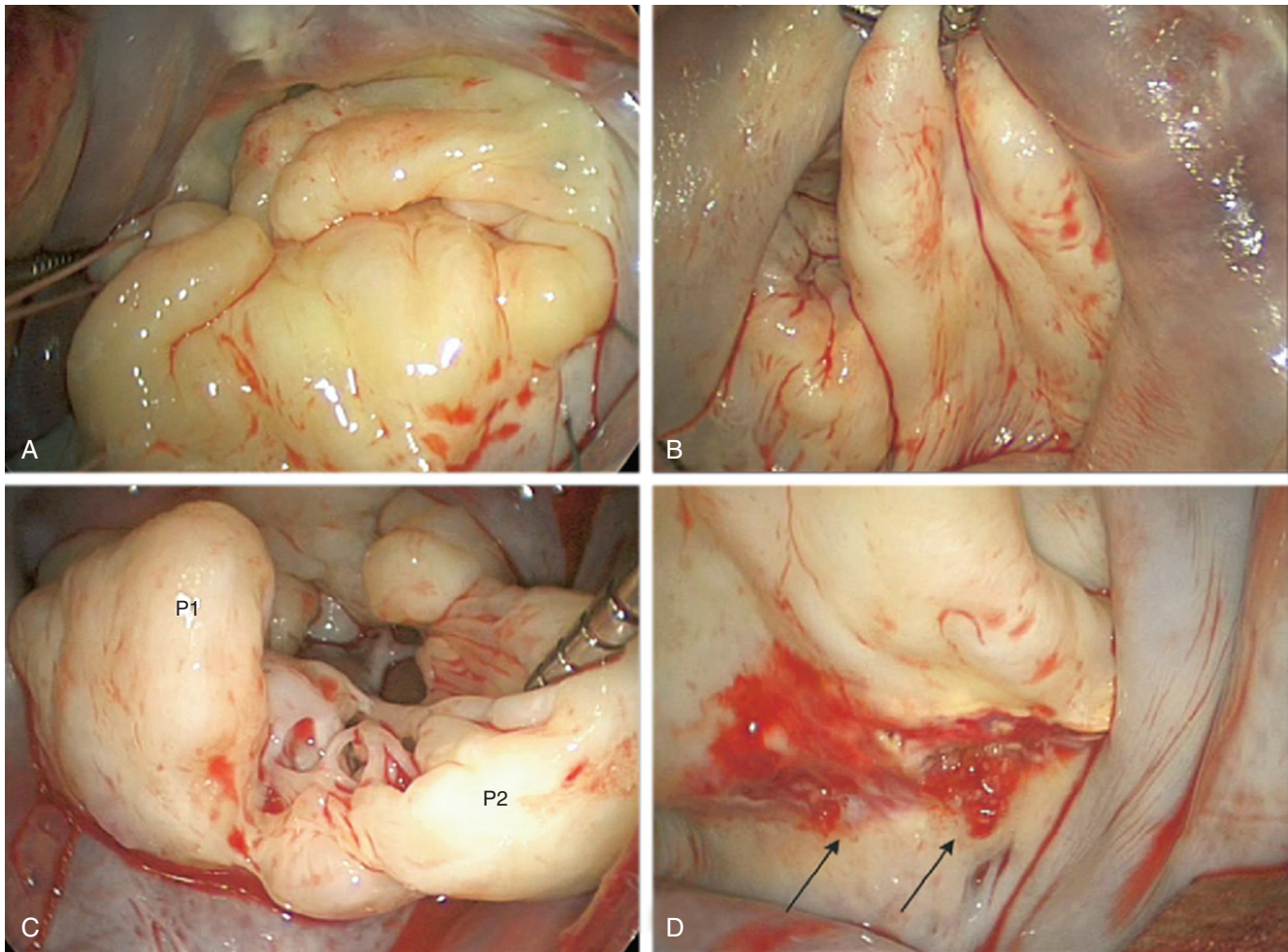


FIGURE 80-9 ■ Surgical lesions in Barlow's disease. **A**, Large valve with redundant, thick, bulky leaflets. **B**, Tall, posterior leaflet with tip rising to anterior annulus. **C**, Calcified anterior papillary muscle with fused, matted chords restricting the P1/P2 junction. **D**, Atrialization of the base of the posterior leaflet. Note the blurring of the atrial-leaflet junction with fissures and microthrombi (arrows). (From Anyanwu AC, Adams DH: Etiologic classification of degenerative mitral valve disease: Barlow's disease and fibroelastic deficiency. *Semin Thorac Cardiovasc Surg* 19:93, 2007.)

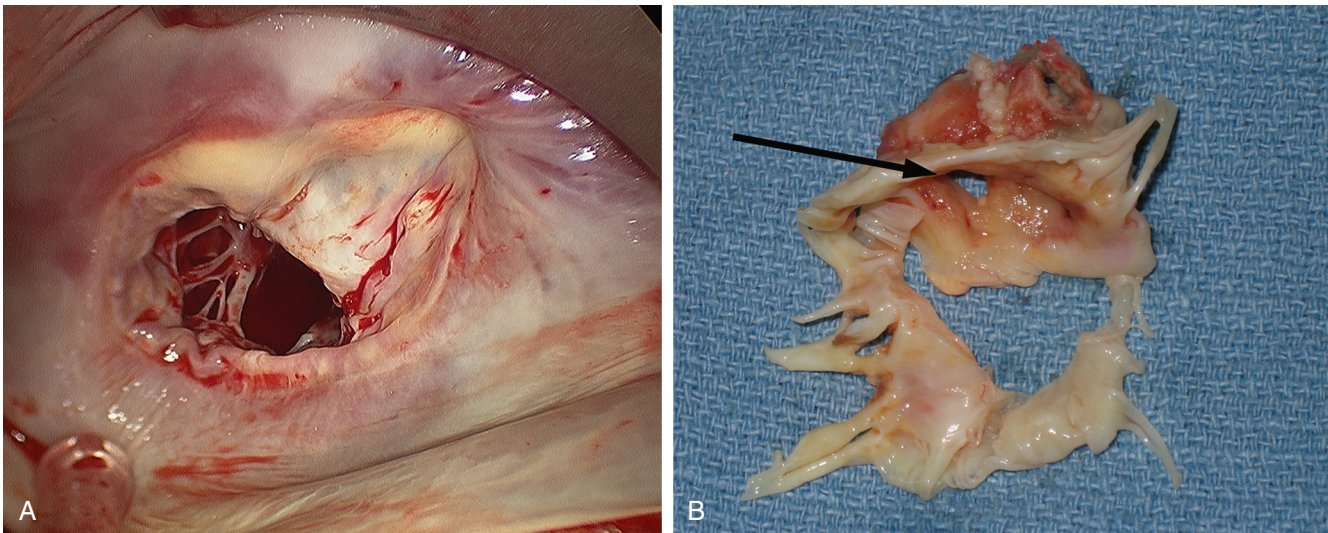


FIGURE 80-10 ■ Surgical lesions in ischemic cardiomyopathy and infective endocarditis. **A**, A dilated annulus with severe posterior leaflet tethering is characteristic of ischemic mitral regurgitation. **B**, Perforation (arrow) of the anterior leaflet of the mitral valve secondary to infective endocarditis.

Ischemic Cardiomyopathy

Left ventricular remodeling after myocardial infarction results in a conversion of the ventricular shape from ellipsoidal to spherical. Consequently, the papillary muscles are displaced, leading to restriction or tethering of posterior leaflet motion during systole (see Fig. 80-10).^{31,32} Leaflet coaptation surface area is compromised, resulting in mitral regurgitation. Furthermore, because of structural continuity between the ventricle and annulus, ventricular dilation leads to annular dilation that may exacerbate mitral regurgitation. Acute mitral regurgitation can result from ischemic papillary muscle dysfunction or rupture.³³ Occasionally, the papillary muscle will not rupture, but will become fibrotic and subsequently elongate, leading to leaflet prolapse.

Dilated Cardiomyopathy and Submitral Left Ventricular Aneurysms

The etiology of this disease is frequently idiopathic; however, known causes include chronic atrial fibrillation, myocarditis, excessive alcohol consumption, and immunologic abnormalities. Similar to ischemic cardiomyopathy, the natural history of the disease is often complicated by functional mitral regurgitation secondary to ventricular remodeling.

Submitral ventricular aneurysms can also result in mitral regurgitation. Such an aneurysm is not due to myocardial ischemia, and it occurs almost exclusively in Africa.³⁴ The aneurysm is generally situated directly beneath the posterior mitral leaflet; therefore, mitral regurgitation develops from aneurysmal distortion of the posterior leaflet.^{34,35}

Clinical Characteristics and Diagnosis

Chronic

Patients with chronic mitral regurgitation are often asymptomatic for years. During this time, left ventricular size can gradually increase and myocardial contractility declines. Ultimately, patients develop exercise intolerance and symptoms consistent with pulmonary venous hypertension. Fluid retention, chronic cardiac failure, and occasionally cardiac cachexia are representative of longstanding untreated disease. Coexistent secondary tricuspid regurgitation is frequently apparent at such late stages of the disease.³⁶

Similar to mitral stenosis, significant mitral regurgitation can generally be diagnosed on the basis of history, physical examination, electrocardiogram, and chest radiograph. On auscultation, a classic pansystolic murmur is appreciable, loudest at the apex, and radiates to the left axilla. However, murmurs may be heard in the parasternal aortic area or infrascapular–posterior cervical area in the setting of eccentric jets from posterior leaflet or anterior leaflet prolapse, respectively. An S₃ may be present because of augmented transmitral flow from volume overload and left ventricular dilation. In addition, lateral displacement of the left ventricular apical impulse from ventricular dilation and parasternal lift from

elevated pulmonary arterial pressures indicate more severe disease.

The electrocardiogram may remain unremarkable despite severe mitral regurgitation; however, evidence of ventricular hypertrophy or left atrial enlargement may also be present. Chest radiography in severe chronic mitral regurgitation may demonstrate left atrial and ventricular dilation (typically greater than in patients with mitral stenosis), and prominent pulmonary vasculature suggests the presence of pulmonary hypertension.

Two-dimensional echocardiography via transthoracic and transesophageal approaches delineate the mechanism and severity of mitral regurgitation (Table 80-4; Fig. 80-11). Echocardiography can also be used to assess left ventricular dimensions and global and regional contractility. Three-dimensional echocardiographic imaging techniques clearly identify leaflet pathology and specific areas of regurgitation within the mitral valve.³⁷ Novel magnetic resonance imaging techniques also accurately characterize anatomic and functional details of mitral valve dysfunction.

Mitral regurgitation can be characterized by left ventriculography. Leaflet prolapse can be visualized, and the degree of regurgitation can be estimated. Quantitative ventriculography permits calculation of regurgitant flow and left ventricular stroke volume, and forward flow can be assessed through measurement of cardiac output.³⁸ Furthermore, left heart catheterization is particularly useful to discern the extent of coronary artery disease, if present.

Acute

Mitral regurgitation can develop acutely because of chordal rupture or infective endocarditis or early in the evolution of acute myocardial infarction. Symptoms and signs are consistent with acute elevation of pulmonary venous pressures and low cardiac output. On auscultation, the murmur of mitral regurgitation is often midsystolic and higher pitched compared with the classic pansystolic murmur of chronic mitral regurgitation. The left atrium and left ventricle are normal in size because of inadequate time for compensation through dilation. Because of acute elevation of pulmonary venous pressure, significant pulmonary edema is often noted on chest radiography.

Natural History

Defining the natural history of mitral regurgitation is problematic because the disease etiology varies, age at onset varies, mitral regurgitation may not worsen for many years, and left ventricular function declines at different rates. It is important to note that left ventricular contractility is not truly assessed by ejection fraction. In fact, in the setting of mitral regurgitation, ventricular contractility often declines despite normal systolic function (ejection fraction) because part of the stroke volume is ejected retrograde into the low pressure left atrium. Ejection fraction does not actually decrease until later in the disease process. Patients with mitral regurgitation can

TABLE 80-4 Specific and Supportive Signs and Quantitative Parameters in Grading Mitral Regurgitation Severity

	Mild	Moderate	Severe
Specific Signs of Severity	Small central jet <4 cm ² or <20% of LA area* Vena contracta width <0.3 cm No or minimal flow convergence†	Signs of MR > mild present, but no criteria for severe MR	Vena contracta width ≥0.7 cm with large central MR jet (area >40% of LA) or with a wall-impinging jet of any size, swirling in LA* Large flow convergence† Systolic reversal in pulmonary veins Prominent flail MV leaflet or ruptured papillary muscle
Supportive Signs of Severity	Systolic dominant flow in pulmonary veins A-wave dominant mitral inflow‡ Soft density, parabolic CW Doppler MR signal Normal LV size§	Intermediate signs and findings	Dense, triangular CW Doppler MR jet E-wave dominant mitral inflow (E>1.2 m/sec)‡ Enlarged LV and LA size¶ (particularly when LV function is normal)
Quantitative Parameters†			
R Vol (mL/beat)	<30	30-44	45-59
RF (%)	<30	30-39	40-49
EROA (cm ²)	<0.20	0.20-0.29	0.30-0.39
			≥60 ≥50 ≥0.40

*At a Nyquist limit of 50-60 cm/sec.

†Minimal and large flow convergence radius <0.4 cm and ≤0.9 cm for central jets, respectively, with a baseline shift at a Nyquist of 40 cm/sec. Cutoffs for eccentric jets are higher and should be angle corrected.

‡Usually above 50 years of age or in conditions of impaired relaxation, in the absence of mitral stenosis or other causes of elevated LA pressure.

§LV size applied only to chronic lesions.

¶In the absence of other etiologies of LV and LA dilation and acute MR.

†Quantitative parameters can help to subclassify the moderate regurgitation group into mild-to-moderate and moderate-to-severe as shown.

CW, Continuous wave; EROA, effective regurgitant orifice area; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; MV, mitral valve; R Vol, regurgitant volume; RF, regurgitant fraction.

From Zoghbi WA, Enriquez-Sarano M, Foster E, et al: Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 16:777-802, 2003.

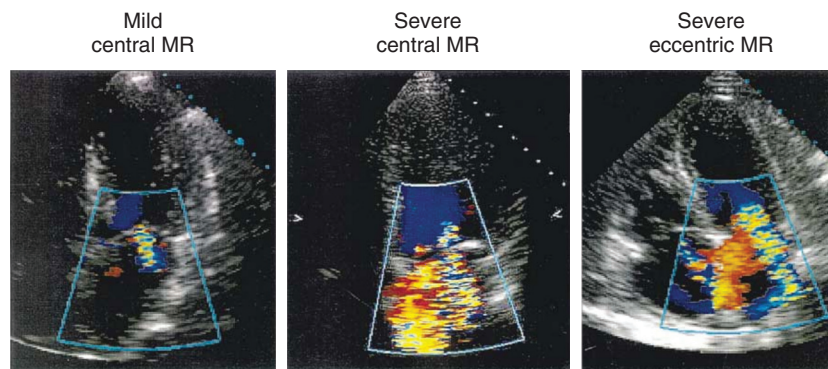


FIGURE 80-11 ■ Examples of color flow recordings of different mitral regurgitation (MR) lesions from the apical window. The case of mild regurgitation has no flow convergence and a small regurgitant jet area, in contrast to that of severe central MR, which shows a prominent flow convergence and large regurgitant jet area. The example with severe eccentric MR has a small jet area impinging on the wall of the left atrium but a large flow convergence and a wide vena contracta. (From Zoghbi WA, Enriquez-Sarano M, Foster E, et al: Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 16:784, 2003.)

also develop secondary tricuspid regurgitation, which also affects natural history.³⁶

Degenerative Disease

Degenerative disease, the most common organic mitral valve disease in the United States, occurs in approximately 2% to 3% of adults.^{19,20} However, many patients do not progress to developing significant regurgitation

requiring intervention. In fact, severe mitral regurgitation requiring valve repair or replacement is uncommon before the age of 50. Although the prevalence increases steeply thereafter, persons with mitral valve prolapse who reach age 70 still only have about a 5% chance of requiring mitral valve surgery.³⁹ Nevertheless, once significant mitral regurgitation develops, the disease progresses similarly to those with ruptured chordae and flail leaflets.

Once a diagnosis of flail leaflet is made, medical management typically is inadequate in improving patient symptoms and survival. Patients with surgically untreated mitral regurgitation because of flail leaflet have mortality rates significantly higher than expected (6.3% yearly).⁴⁰ Severe symptoms portend a worse prognosis as patients even transiently in NYHA class III or IV have much higher mortality rates (34% yearly), although the rate is notable even among those in NYHA class I or II (4% yearly).^{40,41} Essentially, surgery is almost unavoidable within 10 years after the diagnosis and is associated with an improved prognosis in patients with degenerative disease.

Ischemic Cardiomyopathy

The natural history of ischemic mitral regurgitation is covered in [Chapter 92](#). Because ischemic mitral regurgitation is a manifestation of a ventricular disease, it is not surprising that these patients typically have a significantly worse survival than those with degenerative disease.

Rheumatic Disease

Patients with surgically untreated but significant rheumatic mitral regurgitation demonstrate survival similar to those with rheumatic mitral stenosis.^{9,42} Likewise, the survival curves are considerably shorter in particular geographic areas and in certain races: 5-year survival after initial evaluation for rheumatic mitral regurgitation in the United States was 80% compared with 46% in Venezuela.⁴²

Infective Endocarditis

Infection of a previously mildly abnormal mitral valve can generate acute mitral regurgitation. The natural history of such a condition is similar to that of mitral regurgitation caused by chordal rupture. However, the early mortality is significantly higher as death can occur from overwhelming infection and sepsis.

Indications for Surgery

Intervention for patients with primary mitral regurgitation consists of either surgical mitral valve repair or replacement. Mitral valve repair is preferred over replacement if a successful and durable repair can be achieved. Reparability is dependent on valve morphology and surgeon expertise.³

Acute severe mitral regurgitation is an indication for urgent surgery. The indications for surgery in chronic severe mitral regurgitation have evolved during the last decade to reflect incremental improvements in the safety and efficacy of mitral valve repair as well as a better understanding of long-term outcomes in surgically untreated patients. Recommendations by the ACC/AHA for surgical intervention are predicated on symptoms, left ventricular dysfunction, atrial fibrillation, pulmonary hypertension, and valve reparability ([Fig. 80-12](#)).³

Symptoms

The onset of symptoms that results from severe mitral regurgitation worsens prognosis even when left ventricular function appears to be normal. This negative prognostic effect extends even to mild symptoms.⁴³ Thus, an increasing number of clinicians advocate operating earlier in less-symptomatic patients because NYHA functional class has been shown to be an independent predictor of postoperative mortality and left ventricular dysfunction.⁴⁴ Postoperative long-term survival is higher in patients in NYHA class I or II before surgery compared with those in class III or IV, (at 10 years, 76% vs. 48%), and operative mortality is lower (0.5% vs. 5.4%; [Fig. 80-13](#)).⁴³

Left Ventricular Dysfunction and Enlargement

Preoperative left ventricular dysfunction, as assessed by ejection fraction and end-systolic dimension, is one of the strongest predictors of survival, postoperative ventricular function, and functional status after surgery for chronic primary mitral regurgitation.^{43,45-48} Specifically, it has been reported that when the ejection fraction falls below 60%, mortality increases precipitously and prompt surgical referral is critical to outcome ([Fig. 80-14](#)).⁴⁵ Thus, the goal of therapy in mitral regurgitation is to correct it before the onset of left ventricular systolic dysfunction and the subsequent adverse effect on patient outcomes. Ideally, mitral valve surgery should be performed when the patient's left ventricle approaches but has not yet reached the parameters that indicate systolic dysfunction (left ventricular ejection fraction [LVEF] $\leq 60\%$ or left ventricular end-systolic dimension [LVESD] ≥ 40 mm), even if the patient is asymptomatic.³ Because symptoms do not always coincide with left ventricular dysfunction, imaging surveillance is used to plan surgery before ventricular function has severely deteriorated. Further delay, even though symptoms are absent, will lead to greater left ventricular dysfunction and an even worse prognosis. Although it is inadvisable to allow patients' left ventricular function to deteriorate beyond the benchmarks of an LVEF $\leq 60\%$ and/or LVESD ≥ 40 mm, some recovery of left ventricular function can still occur even if these thresholds have been crossed.

Atrial Fibrillation and Pulmonary Hypertension

In nonrheumatic mitral regurgitation, the onset of atrial fibrillation is in part due to enlarging left atrial size, and its presence worsens surgical outcome.^{40,49-51} Furthermore, the longer atrial fibrillation is present, the more likely it is to persist despite intervention. Therefore, it may be reasonable to restore mitral competence by low-risk repair with the hope that the ensuing reduction in left atrial size will help restore and maintain sinus rhythm. The ACC/AHA guidelines advocate surgery in asymptomatic patients with severe mitral regurgitation and new onset atrial fibrillation.³ However, restoration of sinus rhythm following valve surgery is uncertain, and concomitant surgical ablation of atrial fibrillation should be

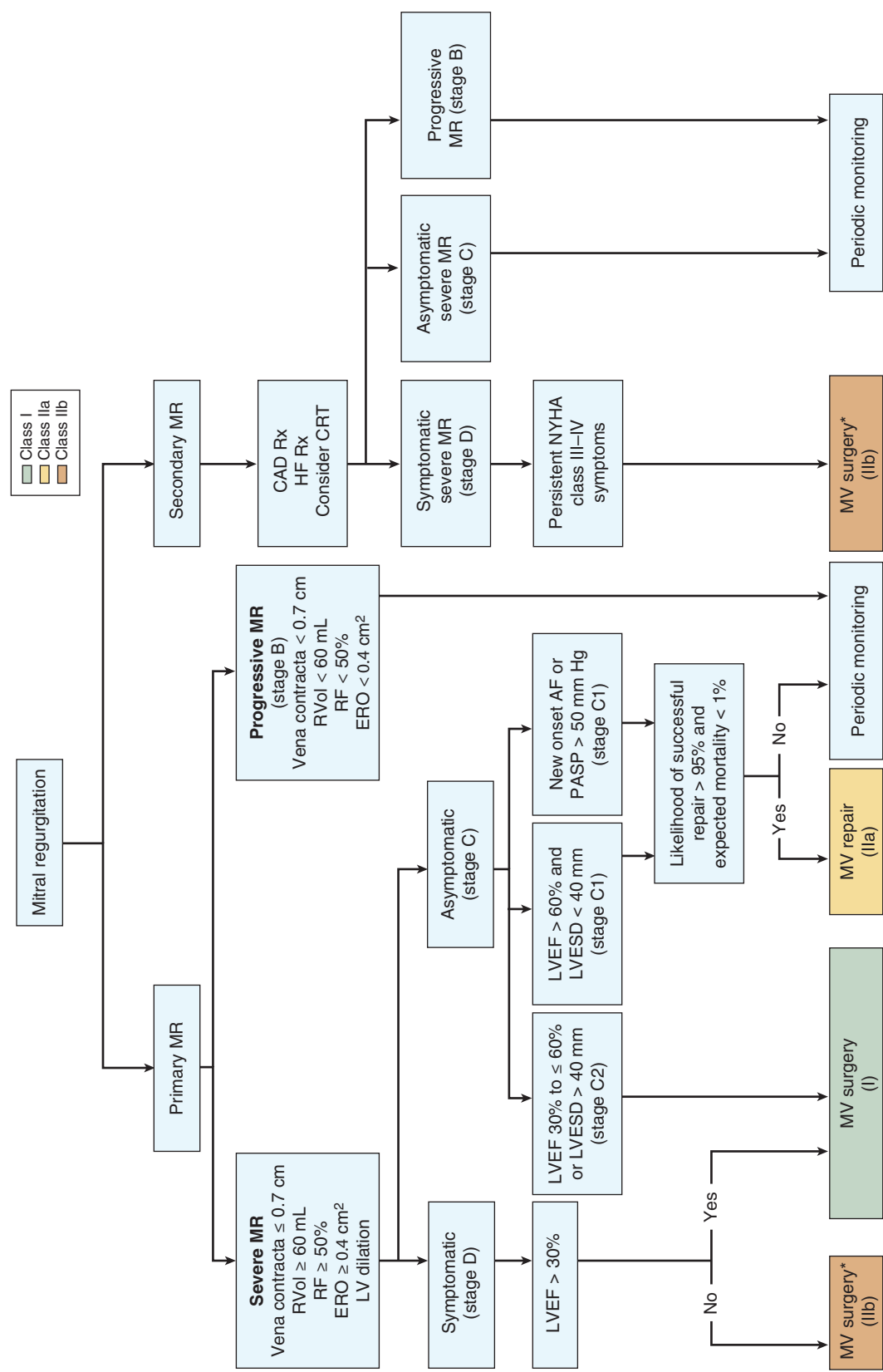


FIGURE 80-12 ■ Indications for surgery for mitral regurgitation. AF, Atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; Rx, therapy. *Mitral valve repair is preferred over MVR when possible. (From Nishimura RA, Otto CM, Bonow RO, et al: 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129:e569, 2014.)

a standard adjunct to patients with a history atrial arrhythmia. This strategy does not apply to rheumatic mitral regurgitation, in which active atrial inflammation can make restoration of sinus rhythm less likely and valve scarring reduces the likelihood of a successful repair. The presence of resting pulmonary arterial hypertension caused by mitral regurgitation is associated with poorer operative and long-term survival after valve surgery.^{46,52,53} Thus, it is reasonable to consider surgery in these asymptomatic patients if resting pulmonary artery systolic pressure exceeds 50 mm Hg and if there is a high likelihood of a successful and durable repair.³

Reparability

Mitral valve repair is preferred over replacement if a successful and durable repair can be achieved. Mitral valve repair is performed at a lower operative mortality rate

than replacement. Although no randomized trials exist for degenerative mitral valve disease, nearly every clinical report has demonstrated that operative risk for repair is approximately half that of replacement. Valve repair not only avoids the risks inherent to prosthetic heart valves, but it better preserves left ventricular function by preserving the subvalvular apparatus. In the case of posterior leaflet prolapse, repair has become sufficiently standardized so that repair is the standard of care. The ACC/AHA guidelines recommend that a successful repair rate of 90% or greater be the expectation of every cardiac surgeon who performs mitral valve procedures.³ Because the probability of successful mitral valve repair is strongly influenced by surgeon-specific mitral procedure volume,⁵⁴ it is recommended that more complex valves be referred to heart teams with particular expertise in this area.³

SURGERY

Anesthesia and Monitoring

Standard monitoring lines are used if the procedure is performed through a median sternotomy. A pulmonary artery catheter should be placed in cases of complex mitral valve surgery and multivalve surgery, as well as in high-risk operative candidates. Carbon dioxide insufflation is routinely used to facilitate deairing and reduce the risk of air embolism following aortic cross-clamp removal. A thorough transesophageal echocardiography study should routinely be performed before the initiation of cardiopulmonary bypass to characterize the mechanism and severity of mitral regurgitation, as well as other valve lesions. Transesophageal echocardiography also permits assessment of left ventricular function, quality of the repair, and extent of deairing. External defibrillator and cardioversion pads are placed in patients undergoing reoperative surgery.

If a right minithoracotomy is planned, the anesthesiologist should place a double-lumen endotracheal tube to permit left lung ventilation and right lung deflation.

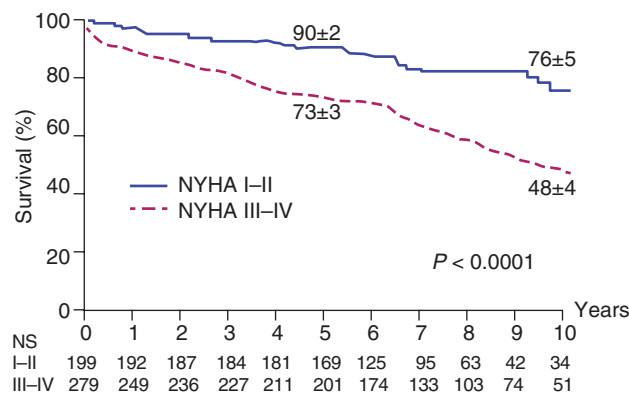


FIGURE 80-13 ■ Overall postoperative survival compared between patients in New York Heart Association (NYHA) class I or II and patients in class III or IV. Numbers at bottom indicate patients at risk. (From Tribouilloy CM, Enriquez-Sarano M, Schaff HV, et al: Impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. *Circulation* 99:402, 1999.)

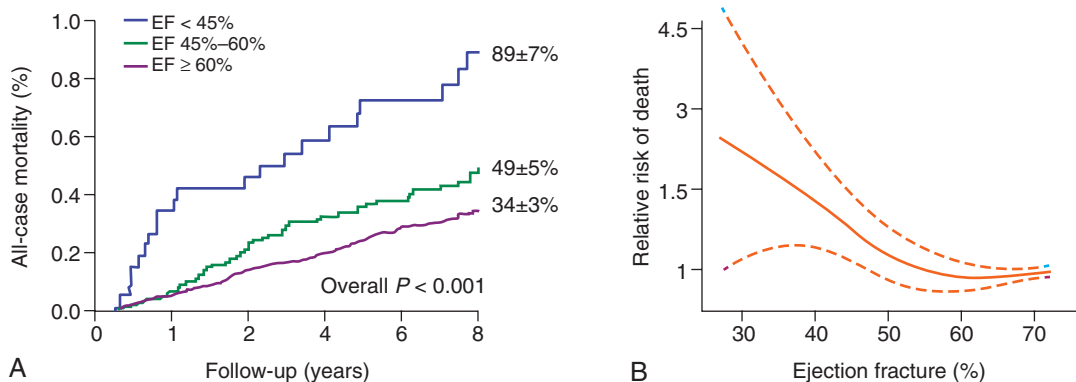


FIGURE 80-14 ■ Impact of preoperative left ventricular dysfunction on survival under conservative management for mitral regurgitation. **A**, All-cause mortality stratified by ejection fraction (EF). **B**, Association between EF and the risk of all-cause death under conservative management. Hazard ratio (solid line) and 95% confidence intervals (dashed lines) were estimated in a Cox multivariable model with ejection fraction represented as a spline function and adjusted for sex, comorbidity index, symptoms, and coronary artery disease. (Modified from Tribouilloy C, Rusinaru D, Grigioni F, et al: Long-term mortality associated with left ventricular dysfunction in mitral regurgitation due to flail leaflets: a multicenter analysis. *Circ Cardiovasc Imaging* 7:366, 2014.)

External defibrillator pads are placed under the right scapula and over the left anterolateral chest. If an endo-aortic balloon occlusion catheter will be used, bilateral radial arterial lines can be placed to facilitate rapid detection of balloon distal migration and innominate artery obstruction. Inadvertent balloon migration is not uncommon, and vascular injuries including aortic dissection have contributed to decreased utilization of this approach. Our institution prefers a transthoracic Chitwood aortic cross clamp and standard antegrade cardioplegia, retrograde cardioplegia, and right superior pulmonary vein venting cannulae placed across the chest wall or directly through the working incision. Thoracic epidural placement is not commonly used, because pain is reportedly mild after minithoracotomy incisions, particularly if rib spreading is avoided.

Surgical Approaches

Median Sternotomy

Median sternotomy is the most common surgical approach in mitral valve surgery.⁵⁵ Because it provides excellent access to all cardiac structures, it remains the surgical approach of choice in patients undergoing multivalve (other than concomitant mitral and tricuspid valve surgery) or combined mitral and coronary bypass grafting surgery. If a median sternotomy is the planned approach for mediastinal entry, then a Sarns 6-mm cannula is placed in the ascending aorta for arterial cannulation. 24 Fr superior vena cava and 28 Fr inferior vena cava metal tip cannulae are preferentially used for bicaval cannulation to maximize exposure and access to the mitral valve via Sondergaard's groove.

Minimally Invasive Approaches

Over the past 20 years, the increasing popularity of less invasive procedures has affected nearly every surgical specialty, including cardiac surgery. Advancements in imaging, surgical instrumentation, and robotic technology have enabled surgeons to perform complex cardiac surgical procedures through small incisions, often eliminating the need for sternotomy or cardiopulmonary bypass.⁵⁶⁻⁵⁹ In addition to benefits of improved cosmesis, minimally invasive mitral valve surgery was pioneered with the intent of reducing morbidity, postoperative pain, blood loss, hospital length of stay, and time to return to normal activity.⁶⁰⁻⁶³

Although initial reports of less invasive mitral valve surgery used parasternal^{61,64} or lower hemisternotomy⁶⁵ approaches for mediastinal access, the right anterolateral minithoracotomy has become the minimally invasive approach of choice for correcting mitral valve disease (Fig. 80-15).^{63,66,67} Compared with lower partial sternotomy, this approach provides a more en face view of the mitral valve and avoids surgery in the xiphisternal region, the area most prone to wound breakdown and infection following sternotomy. The right thoracotomy approach is considerably more resistant to infection because of overlying pectoralis muscle and soft tissue to seal the surgical site.⁶⁸ Robotic and port access mitral valve

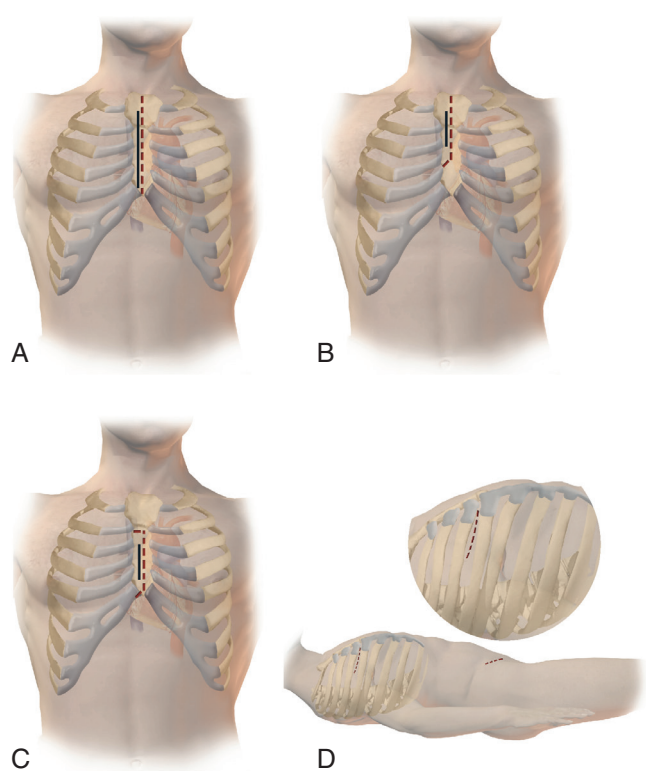


FIGURE 80-15 ■ Surgical incisions. **A**, Conventional median sternotomy. **B**, Upper hemisternotomy. **C**, Lower hemisternotomy. **D**, Right minithoracotomy and groin incision for peripheral cannulation. Solid line represents skin incision and dotted line represents sternotomy.

surgery are thus performed through a 3- to 4-cm incision in the inframammary crease in female patients and just above the nipple in male patients, and the thoracic cavity is entered through the third or fourth interspace. Additional sub-centimeter ports facilitate introduction of a camera, left atrial retractor, suction, and in the case of robotic surgery, working arms (Fig. 80-16). Peripheral cannulation for cardiopulmonary bypass via the femoral arterial and venous vessels as well as the internal jugular vein facilitates smaller working incisions and less clutter of the surgical field. However, the ascending aorta and right atrium can be cannulated directly with the Seldinger technique if a contraindication precludes direct femoral cannulation. Aortic cross-clamping is achieved with a transthoracic Chitwood clamp or endovascularly with an endoaortic balloon occlusion device. Although beating- or fibrillating-heart strategies are used in some centers, concerns for higher stroke rates have led many surgeons to advocate using these techniques with caution.^{55,69} However, this risk is confounded by the nature of the patient for which these strategies must be used, such as patients with prior cardiac surgery, aortic pathology contraindicating cross-clamp application, or severe ventricular dysfunction. As robotic and thoracoscopic port access approaches facilitate all standard resectional and nonresectional valve repair techniques, the procedure of mitral valve repair is akin to the operation performed through conventional sternotomy.^{58,70-72}

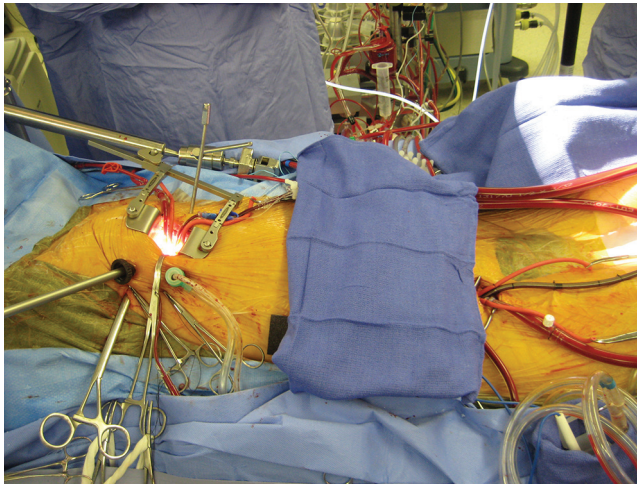


FIGURE 80-16 ■ Exposure and cannulation technique for minimally invasive mitral valve surgery via right anterolateral mini-thoracotomy. (From Goldstone AB, Woo YJ: Minimally invasive surgical treatment of valvular heart disease. *Semin Thorac Cardiovasc Surg* 26:37, 2014.)

Myocardial Management

Cardioplegic arrest is the most commonly used myocardial protection strategy during mitral valve surgery. Alternative techniques, such as beating heart and ventricular fibrillatory arrest, are occasionally used in select patients. Cardioplegic arrest uses cold blood high-potassium cardioplegia solution delivered via intermittent antegrade or combined antegrade and retrograde infusion. Further myocardial protection can be achieved with moderate systemic hypothermia and local hypothermia with topical ice.

Alternative protection strategies should be considered in certain clinical scenarios, such as in patients with severely depressed left ventricular function (beating heart) and severe atherosclerotic disease of the ascending aorta (beating heart or ventricular fibrillatory arrest). These alternative protection strategies are also useful in reoperative mitral valve surgery, when it may be difficult to cross-clamp the ascending aorta and when patent bypass grafts dissuade reoperative median sternotomy.

Operative Sequence in Context of Concomitant Procedures

When performing concomitant procedures, mitral valve surgery is typically performed at a specific juncture in the operation to accommodate anatomic constraints, facilitate operative flow, and avoid potential injury. Examples best illustrate these principles. When performing concomitant coronary bypass, the distal anastomoses are completed before mitral valve intervention. This avoids manipulation and anterior displacement of the heart after placement of a mitral prosthesis, which may beget posterior ventricular wall injury. When performing concomitant aortic valve replacement, the aortic valve leaflets are first resected and the annulus is débrided to avoid potential cutting of mitral annular sutures. The mitral procedure is performed before the aortic valve replacement

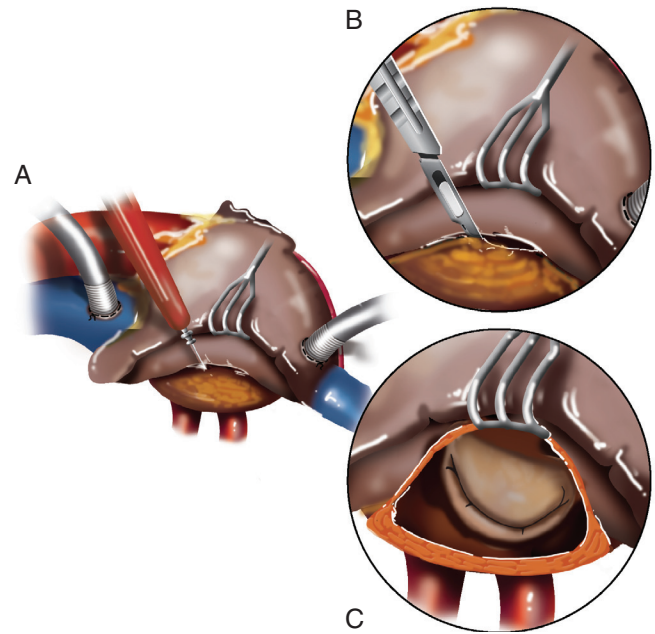


FIGURE 80-17 ■ Interatrial exposure of the mitral valve. **A**, Interatrial groove is dissected to fossa ovalis to expose roof of left atrium. **B**, Left atrium is incised and extended toward the superior and inferior vena cavae. **C**, Anterior retraction of the left atrium to expose the mitral valve.

because the aortic valve prosthesis distorts and obscures the anterior mitral annulus, particularly at the anterolateral commissure. When performing concomitant tricuspid valve surgery, a trans-septal approach is most efficient, and the mitral valve operation is conducted first. The interatrial septum is closed and the tricuspid annuloplasty can then be performed with the cross-clamp removed.

Exposure of the Mitral Valve

Excellent exposure of the mitral valve is essential before any mitral valve intervention. Various techniques have been described, including the interatrial approach through Sondergaard's (or Waterston's) groove, the right atrial trans-septal approach, and the left atrial dome approach.

Interatrial Approach through Sondergaard's Groove

The interatrial approach through Sondergaard's groove is the most commonly employed approach for mitral valve exposure (Fig. 80-17). First, the fatty tissue just anterior to the right superior and right inferior pulmonary veins is dissected, essentially separating the right atrium from the anterior surface of the left atrium. It is important to start this incision on the actual body of the left atrium to avoid any potential involvement of the pulmonary venous ostia. If this incision is extended too medially, the right atrium can be entered accidentally. This issue can be addressed easily with caval tapes or vacuum assisted venous return. Generally, it is not necessary to add additional time to close the inadvertent right atriotomy separately because it can be incorporated in the

left atriotomy closure at completion of the mitral operation. If extensive exposure is necessary, the posterior aspect of the superior vena cava can be dissected from the left atrium to free additional portions of the roof of the left atrium for atriotomy.

Right Atrial Trans-septal Approach

In this approach, bicaval cannulation and caval snaring with tapes are generally helpful. The right atriotomy is initiated and extended posteriorly toward the left atrium (Fig. 80-18). The interatrial septum and fossa ovalis are visualized, and an incision is made in the most posterior aspect toward the patient's right (near the pulmonary veins). Thus, sufficient septal tissue remains not only for retraction of the left atrial roof for exposure of the mitral valve, but also for closure of the atrial septum at the end of the procedure. The septal incision is carried inferiorly down to the end of the fossa ovalis. An incision carried any further will essentially become an extended right atriotomy below the inferior vena cava and should be avoided. Superiorly, the incision is extended beyond the fossa ovalis onto the more muscular portion between the left and right atria near the superior vena cava inlet. Anterior retraction on this left atrial septum results in excellent visualization of the mitral valve because the trans-septal incision is closer to the mitral valve than a standard left atriotomy incision. This incision is particularly useful in the setting of biatrial enlargement often seen in mitral stenosis, as well as in reoperative scenarios in which a previous interatrial groove left atriotomy was performed. It is also a useful approach in patients who have had prior aortic valve replacement, as exposure of the anterolateral commissure can be difficult in this

setting. A variation of this trans-septal incision is the extended trans-septal approach whereby the upper portion of the trans-septal incision is extended over the dome of the left atrium.⁷³ This incision provides outstanding exposure, but is more challenging to properly reapproximate.

Left Atrial Dome Approach

Another less used atriotomy is the isolated left atrial dome approach whereby the roof of the left atrium, in between the aorta and superior vena cava, is incised and retracted. Overall, this incision is smaller given space constraints; however, the direct view of the mitral valve is outstanding. Particular care should be taken during closure of this atrial incision, because bleeding from this incision can be somewhat difficult to repair after weaning from cardiopulmonary bypass, because the incision is obscured by the fully distended aorta and superior vena cava. In most of the aforementioned approaches to the mitral valve, a left atrial vent placed via the right superior pulmonary vein can be positioned with the tip in the left inferior pulmonary vein. An additional suction catheter can be placed from the pericardium into the right inferior pulmonary vein. Typically, one or both of these suction catheters will maintain a completely bloodless operative field and allow perfect visualization of the mitral valve. Two extremely rare and unusual approaches to the mitral valve include a transventricular approach performed in the setting of a left ventricular aneurysm repair⁷⁴ and a transaortic approach performed in the setting of aorto-mitral endocarditis.⁷⁵

Open Commissurotomy

Mitral commissurotomy is indicated in patients with pure mitral stenosis with commissural fusion and preserved leaflet mobility (Fig. 80-19). After left atriotomy, the mitral valve is examined to determine suitability for commissurotomy, and a decision must be made regarding whether the leaflets will be sufficiently pliable after commissurotomy to open adequately at a low left atrial pressure. Ideal valves lack chordal fusion and are not calcified; however, mitral commissurotomy can be performed with acceptable results in less than ideally suited valves.⁷⁶ Yet, advanced commissural calcification, subvalvular fusion, and leaflet retraction may be better treated with valve replacement.

Advanced rheumatic changes can complicate identification of the true commissure locations. Retraction of a stay suture placed in the midportion of the anterior leaflet free edge and another placed similarly in the posterior leaflet helps to identify the commissural groove. Commissurotomy is initiated with sharp dissection along this groove toward the annulus and then toward the center of the valve orifice. It is important to leave a 3-mm ridge of tissue at the commissure to prevent iatrogenic mitral regurgitation. In general, chordae are often more fused beneath the posteromedial commissure. When fused chordae are encountered, they should be fenestrated by removing a triangular wedge of tissue. The incision can be extended to divide the papillary muscle longitudinally

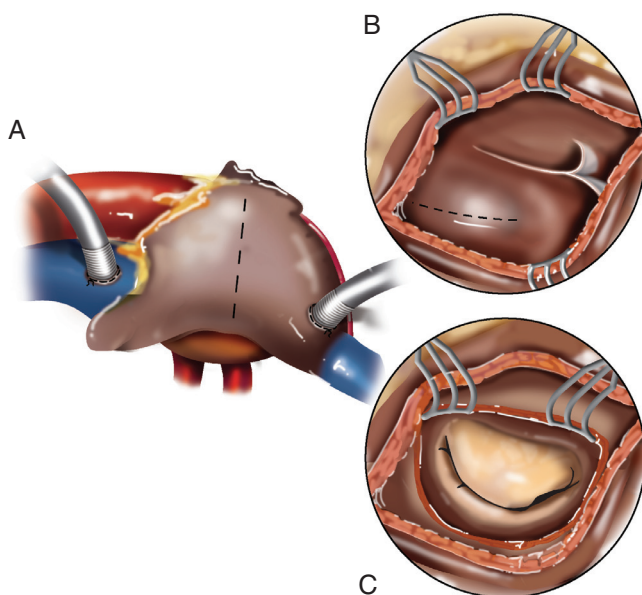


FIGURE 80-18 ■ Trans-septal exposure of the mitral valve. **A**, The right atrium is incised and extended posteriorly. **B**, The septum is incised and extended inferiorly down to the end of the fossa ovalis. **C**, Anterior retraction of the septum exposes the mitral valve.

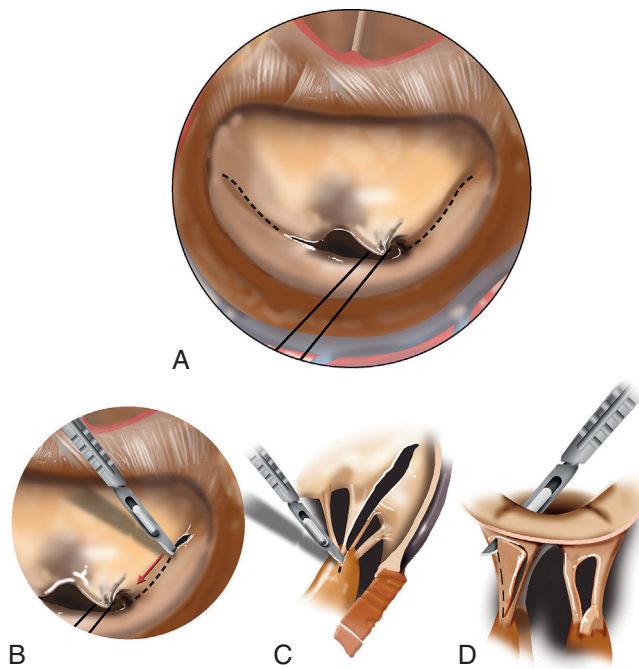


FIGURE 80-19 ■ Open mitral commissurotomy. **A**, Traction on the anterior leaflet delineates the true commissure between the anterior and posterior leaflet. **B**, The fused commissure is incised sharply and extended toward the valve orifice. **C**, The papillary muscle may be split to improve leaflet mobility. **D**, A triangular wedge is removed to fenestrate fused chordae.

to improve mobility. Finally, localized calcium deposits can be removed from the leaflets with a rongeur forceps.

Mitral Valve Repair

Mitral valve repair is the procedure of choice for correcting severe mitral regurgitation.³ Although techniques for repair are numerous, all valve repairs should aim to restore a large surface of leaflet coaptation, preserve leaflet mobility, and restore physiologic annular geometry with a remodeling annuloplasty.¹⁷ Regardless of the techniques being used, a systematic approach to reconstructive surgery should be used that includes a determination of the mechanism of mitral regurgitation via imaging and valve analysis, application of appropriate repair techniques depending on the culprit lesions, and assessment of the repair quality by pressurized saline testing and echocardiography.

Fundamentals of Reconstructive Surgery

Valve Analysis. The mitral valve apparatus should first be carefully examined to confirm the mechanism of regurgitation, evaluate the feasibility of repair, and plan the technical operation. The mitral annulus is inspected to determine the extent of dilation. Segmental valve analysis with a nerve hook can identify areas of leaflet prolapse or restriction.⁷⁷ It should be noted that prolapse of P1 is less common, and the free margin of other valve segments can be compared with P1 to determine severity of prolapse.

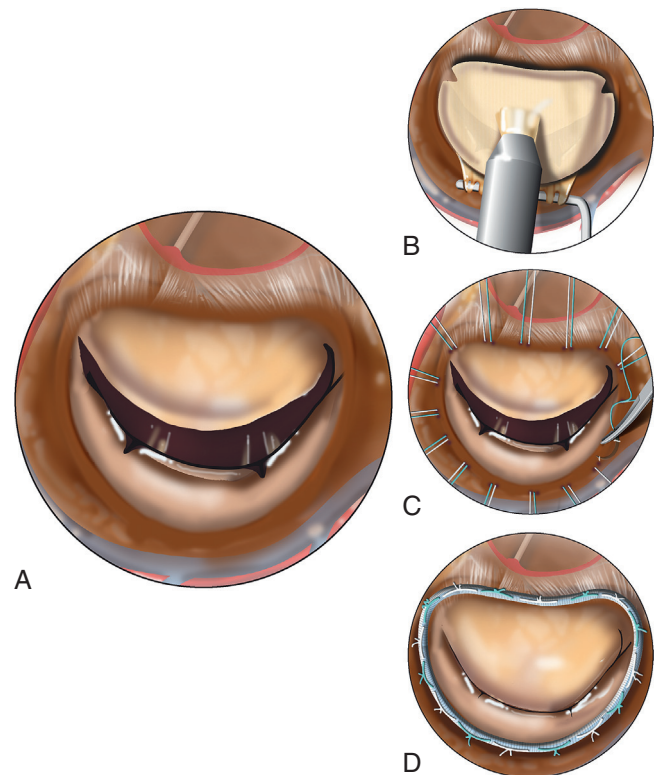


FIGURE 80-20 ■ Remodeling annuloplasty ring implantation. **A**, Dilated annulus with leaflet malcoaptation. **B**, Ring selection is based on measurements of the intercommissural distance and the height of the anterior leaflet. **C**, Sutures are placed circumferentially around the annulus and through the ring. **D**, The annuloplasty ring restores the normal physiologic size ratio and shape of the annulus.

Remodeling Ring Annuloplasty. Regardless of the etiology of valve disease, all patients with chronic mitral regurgitation demonstrate some degree of annular dilation and benefit from a remodeling annuloplasty. As discussed previously, the annulus is weakest along the mural segments and thus typically dilates in the anteroposterior dimension. A remodeling ring annuloplasty restores the normal physiologic size ratio and shape of the annulus, and it improves the surface area of leaflet coaptation. In addition, it improves the longevity of the repair by preventing late annular dilation. Although annular support can be achieved with a posterior band or incomplete ring, the ends of this band must be properly secured in the medial and lateral fibrous trigones to prevent late posteriorly directed annular migration and recurrent mitral regurgitation. Thus, a complete ring with full anterior anchoring typically will more assuredly produce annular remodeling. In most scenarios, annuloplasty sutures are placed first and retracted under tension to improve exposure of the mitral leaflets. Leaflet repair is then conducted (specific techniques to follow; categorized by leaflet pathology), and ring sizing and implantation are performed.

Appropriate ring sizing is based on the intercommissural distance and the surface area of the anterior leaflet (Fig. 80-20). There is usually a strong correlation between the intercommissural distance and the height of the

anterior leaflet. However, if the free edge of the anterior leaflet extends 2 to 4 mm beyond the inferior edge of the selected sizer, a ring that is one size larger should be selected to prevent the risk of systolic anterior motion of the anterior mitral valve leaflet.⁷⁸ Ring sizing also depends on the leaflet repair technique and the amount of functional posterior leaflet tissue that remains. For example, the ring may need to be sized to the mitral orifice area when repairs with artificial neochordae are used.

Simple sutures should be placed circumferentially around the mitral valve and into the mitral annulus (see Fig. 80-20). When placing sutures within the anterior annulus, care should be taken to avoid inadvertent injury to the aortic valve leaflets by taking shallower bites. Similar care should be taken when placing sutures in the area of the anterolateral commissure to avoid iatrogenic injury to the circumflex coronary artery and aortic leaflets. Exposure of the anterolateral trigone region can be improved by exerting traction on the adjacent suture in the posterior annulus. Stretching the commissure in this fashion facilitates proper suture placement. Sutures are then passed through the selected annuloplasty ring. Since the intercommissural distance is equivalent on the anterior annulus and the ring, sutures should be placed evenly through their corresponding places on the ring. However, as the posterior annulus is usually dilated, the spaces of the sutures within the annulus should be greater than their respective spacing on the ring. The ring is then seated to conform the annulus to the shape and size of the prosthetic ring.

Assessment of Repair. The quality of the repair should be evaluated with a saline test after completion of the leaflet repair and again after ring implantation, but before tying the annuloplasty ring sutures so that the surgeon is still free to make additional changes at each stage if corrections are necessary. While the aortic root is vented, saline is injected into the ventricular cavity to prevent air embolism into the coronary arteries. Once air is removed, the aortic root vent is clamped and saline is injected again into the ventricle at a higher pressure. A symmetrical line of coaptation, parallel to the posterior part of the remodeling ring and at a reasonable distance from the left ventricular outflow tract, indicates a successful repair. Asymmetric coaptation lines reveal residual leaflet prolapse or restriction that requires correction prior to separation from cardiopulmonary bypass. A supplemental “ink test” can be performed to further assess the quality of the repair. The valve closure line is traced with a marking pen after pressurizing the ventricle with saline. Saline is aspirated and the leaflet margins are surveyed. Ideal coaptation depth ranges from 4 to 10 mm. A depth less than 4 mm should be corrected by resection of restrictive secondary chordae, cleft closure, or downsizing the annuloplasty ring because shorter coaptation depths suggest limited repair durability. In contrast, depths greater than 10 mm are worrisome for resultant systolic anterior motion, which may warrant further reduction of the height of the posterior leaflet. All valve repairs should be interrogated thoroughly with transesophageal echocardiography after separation from cardiopulmonary bypass.

Valve Repair in Type I Dysfunction

Mitral regurgitation due to type I dysfunction may be due to two aforementioned lesions. Annular dilation is the most common cause, which should be corrected with a complete rigid or semirigid remodeling annuloplasty (see Fig. 80-19).⁷⁹ Type I valve regurgitation may also be secondary to leaflet perforation, commonly seen in infective endocarditis. The management of patching such a lesion is described in further detail later (see [Considerations in Endocarditis](#)).

Valve Repair in Type II Dysfunction

Posterior Leaflet Prolapse. Resection of the prolapsed area or segment has been the conventional technique for repair of posterior leaflet prolapse. However, various nonresecting leaflet repair techniques aimed at preservation of leaflet tissue are well described and increasingly are being adopted.

Quadrangular Resection with or without Sliding Plasty and Triangular Resection. Regardless of the technique chosen, initial placement of annuloplasty sutures helps lift and expose the valve to facilitate repair. When performing the conventional quadrangular resection (Fig. 80-21), stay sutures are placed around normal chordae to delineate the prolapsed area. The prolapsed segment is excised with perpendicular incisions from the leaflet margin toward the annulus to remove a quadrangular section of leaflet tissue. Plication sutures are placed along the posterior annulus in the area of resection. The free edges of the resection gap are then reapproximated with interrupted polypropylene suture to restore leaflet continuity. When the area of prolapse is less extensive, the prolapsing area can be excised with a triangular resection (Fig. 80-22). The free edges of the resection are then reapproximated with polypropylene suture.

In the setting of excessive posterior leaflet tissue, such as in Barlow's disease, it is critical to reduce the height of the posterior leaflet to avoid systolic anterior motion.⁸⁰ Thus, a sliding leaflet plasty technique is performed after initial quadrangular resection (Fig. 80-23). The P1 and P3 segments are detached from the annulus and the gap between the two scallops is then closed with interrupted sutures, taking narrower bites near the free margin and wider bites closer to the annulus. A sliding plasty may also be necessary when a large portion of the posterior leaflet is removed. Interrupted annular plication sutures also facilitate leaflet reapproximation after sliding plasty. However, note that plication of a large segment of the posterior annulus must be avoided because the circumflex artery may kink.

Posterior Ventricular Anchoring Neochordal Remodeling Repair. Minor drawbacks continue to accompany resectional approaches to mitral repair, including irreversibility of leaflet resection, time-consuming leaflet reapproximation with sliding annuloplasty, monoleaflet function, risk for postrepair systolic anterior motion, and potential for dynamic mitral stenosis. Such disadvantages have led to nonresectional paradigms of valve repair, the majority of which are centered on artificial chordal replacement (see [Artificial Neochordae](#) Section). After

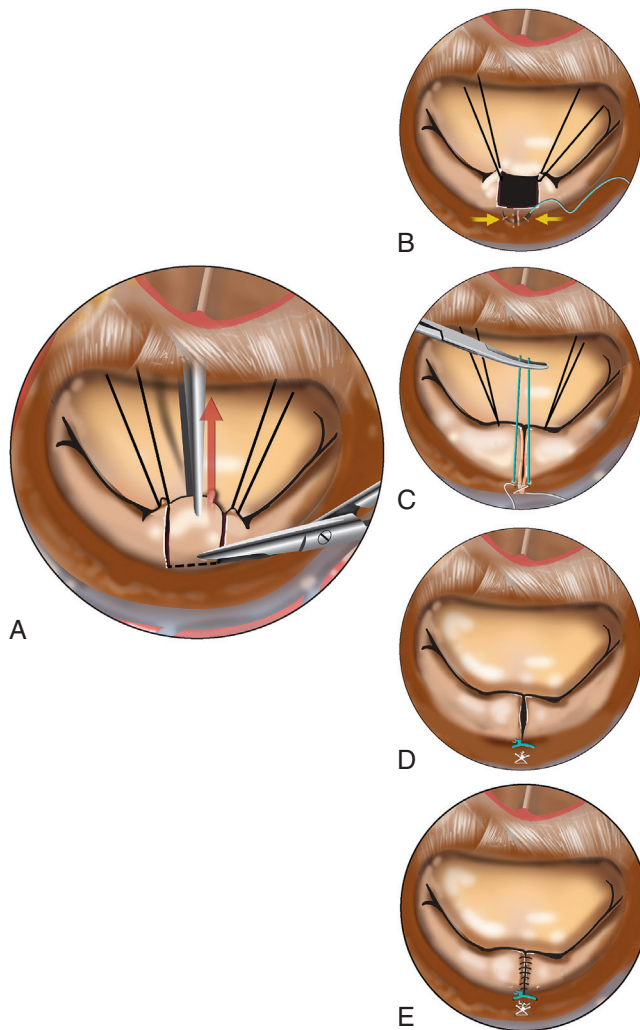


FIGURE 80-21 ■ Posterior leaflet quadrangular resection with annular plication. **A**, The limits of the resection are identified and a quadrangular segment of leaflet tissue is removed. **B-D**, Interrupted annular plication sutures are placed to facilitate gap closure. **E**, The residual defect between P1 and P3 is closed.

less successful attempts with different tissue, Frater and colleagues⁸¹ described the utility of polytetrafluoroethylene (PTFE) for chordal replacement in the setting of diseased or ruptured chordae. Numerous modifications to artificial chordal replacement are well described, including the loop,⁸² loop-in-loop,⁸³ haircut,⁸⁴ and butterfly techniques.⁸⁵ Although neochordal construction circumvents many of the drawbacks of leaflet resection, precise sizing is challenging and maintenance of excess leaflet tissue may risk systolic anterior motion of the mitral valve.

In an effort to develop a mitral valve repair technique that avoids the potential disadvantages of leaflet resection and artificial chordal replacement, while simultaneously facilitating port access approaches by reducing leaflet manipulation and simplifying suture management, we implemented a strategy based on a modified leaflet plication repair.⁸⁶ Single suture imbrication of excess prolapsing leaflet tissue onto the noncoaptation ventricular side of the leaflet effectively creates a smooth coaptation

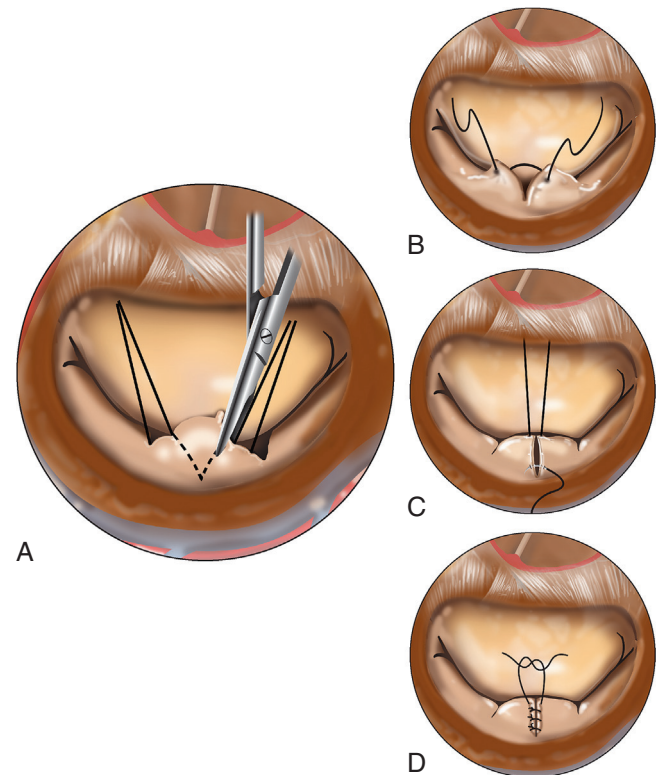


FIGURE 80-22 ■ Posterior leaflet triangular resection. **A**, Stay sutures are passed around nonelongated chordae at the limits of the prolapsed segment and the limits of resection are identified. **B-D**, After resection, the gap is reapproximated with polypropylene suture.

surface without residual prolapse. This technique, however, carries a theoretical risk of basing the repair on potentially diseased native chordae and the potential for the mobile posterior leaflet to advance anteriorly, risking systolic anterior motion. Therefore, we addressed these concerns by further modifying our technique such that a single PTFE suture is used to anchor, support, and remodel the posterior leaflet posteriorly (Fig. 80-24).⁷²

The prolapsed segment is grasped and retracted into the atrium to expose the left ventricular endomyocardium directly below the leaflet. A CV5 PTFE suture is passed into the myocardium approximately 3 to 4 mm deep and loosely tied. The needles are then passed through the margin of the diseased segment at a width of approximately half of the size of the prolapsed region. An inversion plasty is then performed by grasping the leading edge of the diseased segment and inverting it into the left ventricle. The near-apposing leaflet folds are then approximated in a double running fashion with the same PTFE suture that was used to anchor the prolapsed segment. If necessary, additional tissue can be imbricated into the left ventricle using the second half of the PTFE suture.

Posterior ventricular anchoring is not necessary for repair of all cases of posterior leaflet prolapse. If the burden of excess leaflet tissue is not alarming for systolic anterior motion and the subvalvular apparatus does not appear severely diseased, then an isolated inversion plasty may be successfully performed. However, in the setting

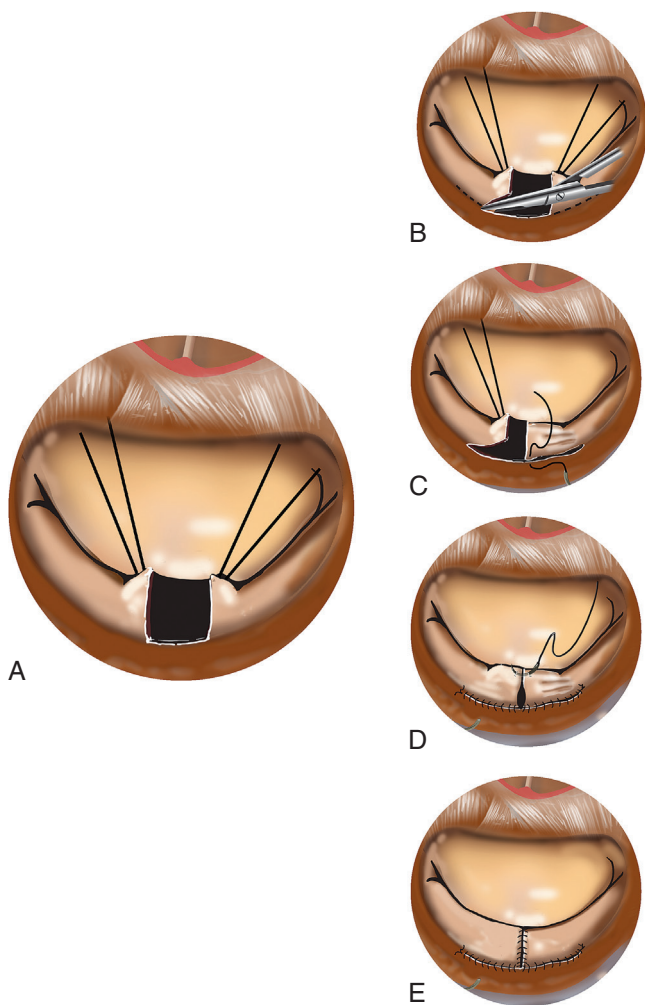


FIGURE 80-23 ■ Posterior leaflet sliding plasty. **A**, After quadrangular resection, the gap between the leaflets is too large to permit direct reapproximation. **B**, P1 and P3 are partially detached from the annulus to permit translocation medially. **C**, P1 and P3 are then reapproximated to the annulus, with greater travel along the annulus than along the leaflet to permit medial translocation. **D** and **E**, The now apposed leaflet remnants are reapproximated with polypropylene suture.

of billowing excess leaflet tissue, multiple torn chordae, or severely elongated chordae, it is prudent to perform a posterior ventricular anchoring repair. This repair minimizes risk for systolic anterior motion and helps to buttress a repair that otherwise would be based on diseased native chordae.

It should be noted that several of the following techniques described for repair of anterior leaflet prolapse can be used on the posterior leaflet, particularly in valves with insufficient leaflet tissue.

Anterior Leaflet Prolapse. Several techniques have been described to correct anterior leaflet prolapse. It is our preference to use chordal techniques instead of resection or papillary muscle techniques. However, these additional repair techniques can maximize the probability of repair.

Triangular Resection. Limited prolapse of the anterior leaflet with excess tissue can be treated with a narrow

triangular resection of the prolapsed area. The free edges are then reapproximated with polypropylene suture.⁸⁸ Of note, large resections of the anterior leaflet greatly reduce coaptation area and increase risk for failure. As such, resections of the anterior leaflet should be small (no greater than 10% of the leaflet surface area).

Chordal Transposition. In the absence of normal secondary anterior leaflet chordae, a posterior leaflet chordal transposition may be performed (Fig. 80-25). This procedure is predicated on the presence of normal marginal posterior leaflet chordae opposite the segment of anterior leaflet prolapse. The segment of the posterior leaflet facing the area of anterior leaflet prolapse is identified. A 3-mm-wide strip of posterior leaflet tissue along the leaflet margin is mobilized with supporting chordae. The width of the strip should approximate the width of the prolapsing area. The papillary muscle to which the chordae are attached is mobilized toward the area of anterior leaflet prolapse by splitting. The posterior leaflet strip is then attached to the free edge of the prolapsing segment. The defect at the posterior leaflet donor site is then closed with interrupted polypropylene sutures.⁷⁸ The primary advantage of this technique is that the difficulty surrounding artificial chordoplasty relating to papillary muscle fixation, neochordal length measurement, and tying is eliminated.

Artificial Neochordae. Artificial chordoplasty is particularly useful when the number of normal chordae is inadequate. The primary difficulty surrounding artificial chordoplasty is adjusting the distance between the tip of the papillary muscle and the prolapsing leaflet edge to the precise length needed. Furthermore, fixing the PTFE suture at the correct length is challenging because the slippery nature of PTFE suture causes knots to slide significantly. Lastly, with suboptimal exposure, visualization of and chordal implantation into the papillary muscles can be challenging. In fact, a multitude of techniques has been proposed to tackle these obstacles.^{78,82,89,90}

In the majority of patients, an adjacent normal, non-prolapsing segment of either the anterior or posterior leaflet provides a reference point for the correct plane of leaflet apposition. The appropriate distance is measured between the correct plane of apposition of a nonprolapsing segment and its corresponding papillary muscle with a measuring device or echocardiography. In the “loop” technique (Fig. 80-26),⁸² using a caliper or measuring device as a template, a PTFE neochord loop is fashioned to this premeasured length by tying a knot over a pledget at the required distance. Each end of the suture is passed again through the pledget twice to stabilize the knot position. The needles are then passed anterior to posterior on the respective papillary muscle and tied over a second pledget. A correct, premeasured PTFE loop is thus secured to the papillary muscle. An additional PTFE suture is then used to fix the premeasured PTFE loop to the prolapsing segment of the mitral leaflet, preferably with the knot facing the ventricular surface. Similar to chordal transfer, multiple artificial neochordae may be required for larger areas of leaflet prolapse, and it is essential that no portion of the leaflet margin greater than 4 mm be left unsupported.⁷⁸

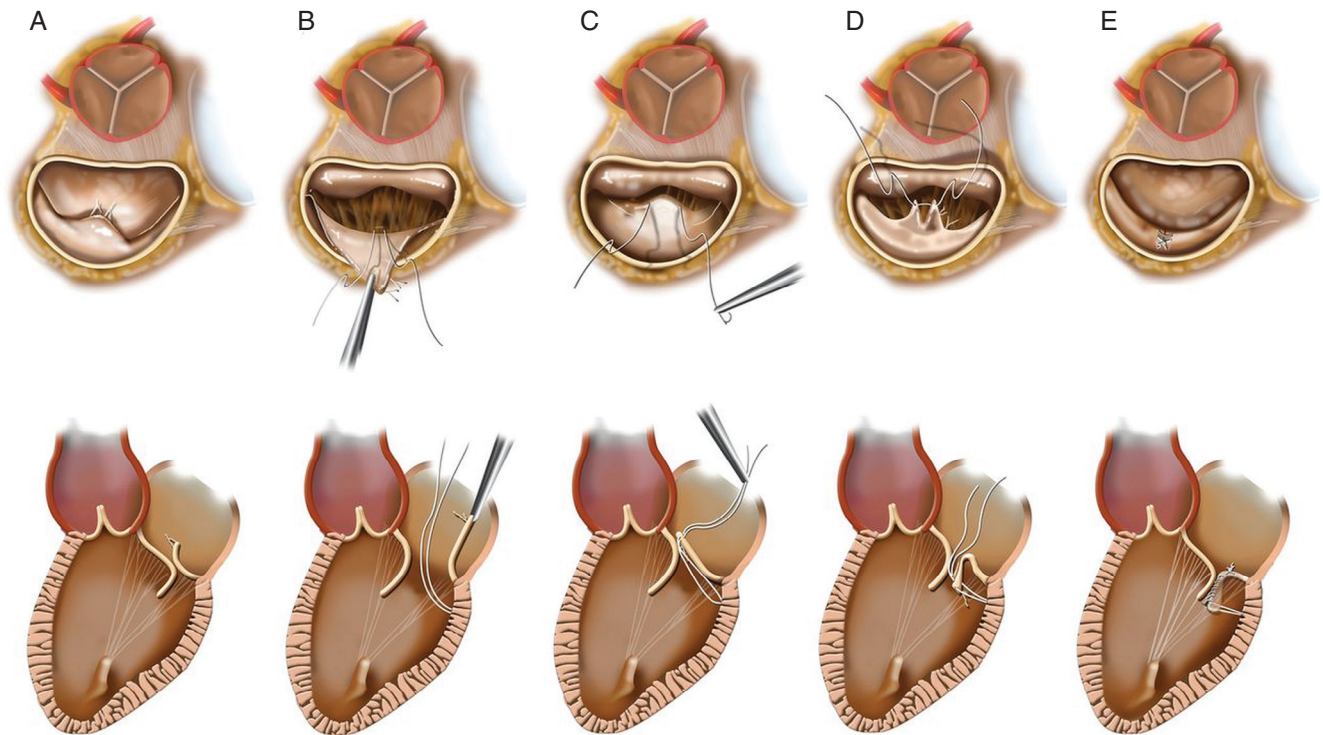


FIGURE 80-24 ■ Posterior ventricular anchoring neochordal repair. **A**, Short- and long-axis drawings depicting degenerative mitral valve disease with posterior leaflet prolapse/flail due to ruptured chordae. **B**, The prolapsed segment is retracted into the left atrium to expose the posterior ventricular wall just beneath the leaflet, and an anchoring CV5 PTFE suture is placed. **C**, The suture is loosely tied and the ends brought through the leading edge of the prolapsed segment. **D**, The margin of the prolapsed segment is inverted into the left ventricle, generating two near-apposing radial folds that are then sutured together. **E**, This eliminates prolapse, yielding a smooth broad coaptation surface. (From Woo YJ, MacArthur JW: Posterior ventricular anchoring neochordal repair of degenerative mitral regurgitation efficiently remodels and repositions posterior leaflet prolapse. *Eur J Cardiothorac Surg* 44:487, 2013.)

Alternatively, a PTFE suture can be passed through the papillary muscle and then through the free margin of the prolapsing segment. Following implantation of the annuloplasty ring, the PTFE suture is tied in the setting of a pressurized ventricle. The knot can then be secured at the appropriate level, where coaptation is restored and the visualized regurgitant flow is eliminated. This free-hand technique is more versatile and less complex, but it requires a degree of judgment and skill for determining the proper chord length and for tying without slipping the knot, thereby overly shortening the neochord.

Double Orifice Edge-to-Edge Repair. Alfieri's edge-to-edge technique effectively creates a double orifice mitral valve and may be used to correct posterior, anterior, or bileaflet prolapse (Fig. 80-27).⁹¹ The prolapsing portion of a leaflet is first identified and then resuspended to the corresponding margin of the opposing leaflet with a figure-of-eight polypropylene suture. The depth of each bite from the leaflet free edge depends on the extent of the leaflet redundancy. For example, in Barlow's disease the desired depth is at least 1 cm, which simultaneously decreases the leaflet height to prevent systolic anterior motion of the mitral valve. When leaflet tissue is thin, additional mattress sutures reinforced with pericardial pledgets can be used to support the suture line. If the prolapsing or flail segment does not involve A2 or P2, the valve will be rendered asymmetric with this repair and the size of the two orifices will differ. The overall mitral valve area is assessed by direct inspection; however, when

in doubt, Hegar dilators can be inserted into each orifice. A total valve area greater than 2.5 cm² is acceptable for average-size patients.⁹²

Commissural Prolapse. Commissural prolapse is effectively treated with resection of the prolapsed area and sliding plasty of the adjacent paracommissural segments (e.g., A1 and P1 sliding plasty for anterolateral commissural prolapse). Additional inverting sutures should be placed in the neocommissure to prevent residual regurgitation. Oftentimes, however, less extensive commissural prolapse can be corrected with a simple inverting suture between the lateral most paracommissural segments. Infrequently, a patient will have commissural prolapse secondary to rupture of a two-headed papillary muscle. In this situation, the prolapse can be corrected with reattachment to the remaining papillary muscle. Furthermore, papillary muscle sliding plasty and shortening are useful options for the correction of extensive commissural and paracommissural prolapse.

Valve Repair in Type IIIa Dysfunction

Repair of type IIIa dysfunction must address leaflet immobility and restriction. Leaflet immobility is primarily related to commissural and chordal fusion. These lesions should be addressed with commissurotomy and chordal fenestration as described previously (see Fig. 80-19).

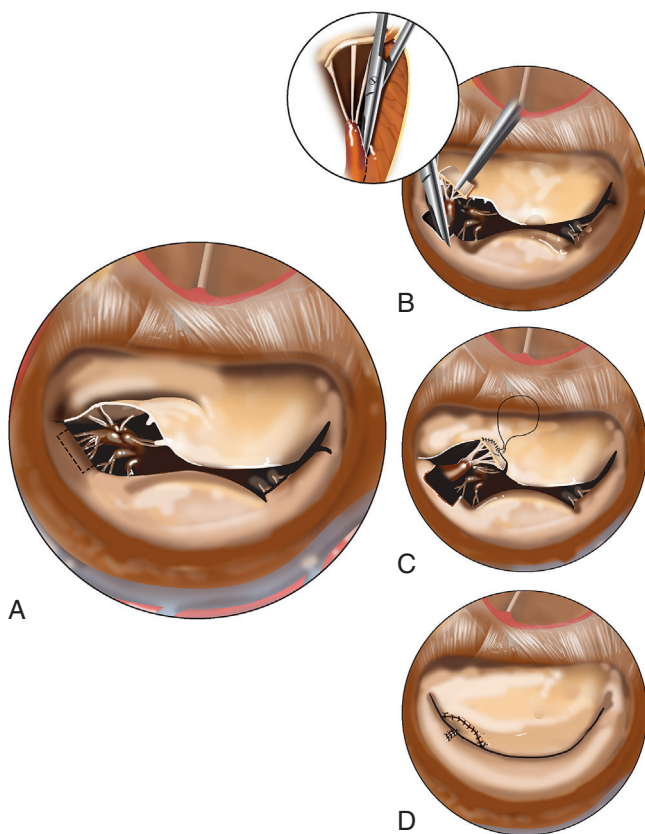


FIGURE 80-25 ■ Chordal transposition. **A**, The segment of the posterior leaflet facing the area of anterior leaflet prolapse is identified. **B**, A strip of posterior leaflet margin tissue is mobilized with its supporting chordae. The corresponding papillary muscle may be split to facilitate transposition. **C**, The posterior leaflet strip is attached to the margin of the prolapsed area on the anterior leaflet. **D**, The residual defect in the posterior leaflet is closed.

The diastolic restriction of leaflet motion characteristic of type IIIa dysfunction can be corrected with leaflet augmentation (Fig. 80-28). For posterior leaflet augmentation, a transverse incision is made 5 mm from the posterior annulus. This incision facilitates excision of fibrotic secondary chordae, but care should be taken to preserve marginal chordae. Autologous or glutaraldehyde-fixed bovine pericardium is then constructed into an elliptical patch. The patch should be sized to increase the height of the posterior leaflet to 15 to 20 mm, leaving a 2-mm margin on the patch for the suture line. The patch is sewn posteriorly from the midline to the annulus and then anteriorly to the leaflet tissue. To account for the new posterior leaflet size, an annuloplasty ring should be chosen that is one size larger than that recommended by standard sizing techniques. The anterior leaflet can also be augmented in a similar fashion; however, a vertical leaflet incision is commonly used.⁷⁸ The patch is sized to the natural gap created by the leaflet incision. Because the anterior leaflet is augmented, an annuloplasty ring should be chosen that is the true size of the new anterior leaflet.

Valve Repair in Type IIIb Dysfunction

Remodeling annuloplasty with an undersized ring is the standard technique to repair type IIIb dysfunction (see Fig. 80-20).⁷⁹ However, the insertion of an undersized prosthetic ring in a severely dilated annulus can cause excessive tension on the sutures, thereby predisposing to ring dehiscence. One can safeguard against this complication by placing multiple sutures around the annulus that overlap. In ischemic mitral regurgitation, this overlapping is particularly important in the area of the posteromedial commissure and P3 segment. In select

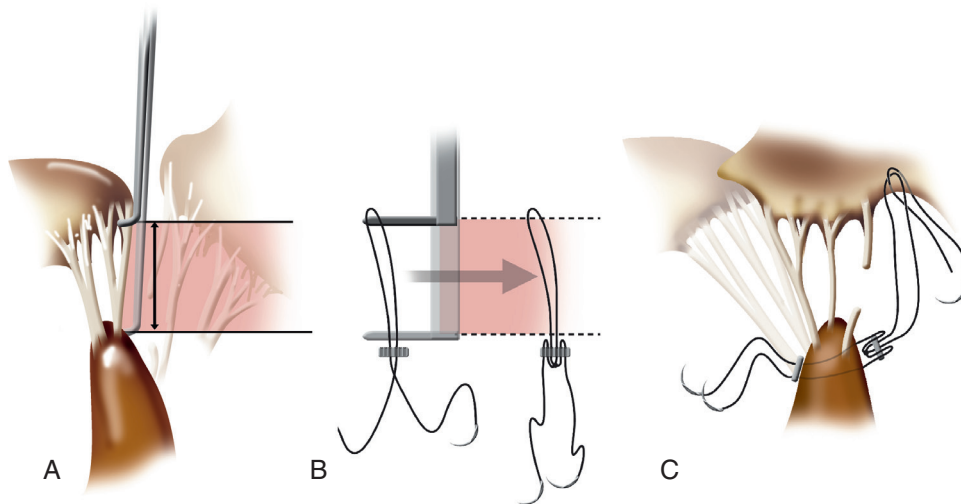


FIGURE 80-26 ■ Artificial chordoplasty using the "loop" technique. **A**, The correct plane of apposition of a nonprolapsing segment and its corresponding papillary muscle with a measuring device. **B**, A polytetrafluoroethylene (PTFE) loop is fashioned to this pre-measured length by tying a knot over a pledget at the required distance. **C**, The needles are then passed anterior to posterior on the respective papillary muscle and tied over a second pledget. An additional PTFE suture is then used to fix the premeasured PTFE loop to the prolapsing segment of the mitral leaflet.

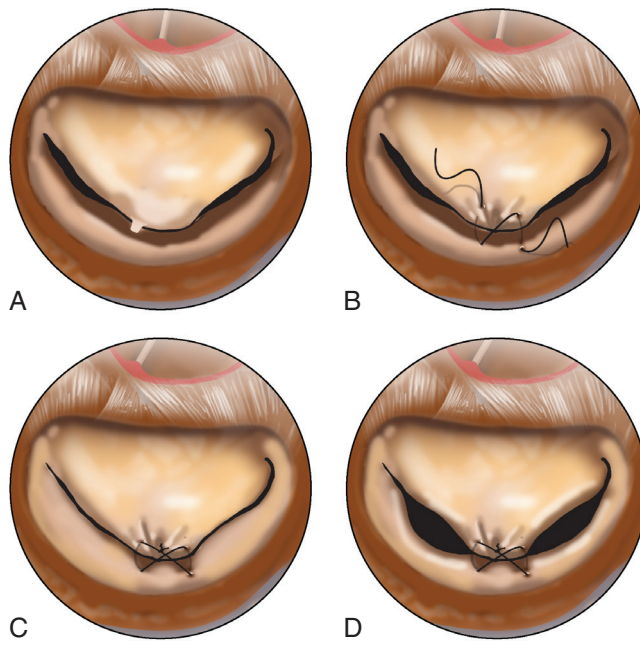


FIGURE 80-27 ■ Double orifice edge-to-edge repair. **A** and **B**, A polypropylene stitch is passed in a figure-of-eight fashion through the midportion of the prolapsing segment (in this case A2) and its opposing nonprolapsing segment (in this case P2) to create a double orifice. **C**, During systole, the valve is no longer regurgitant. **D**, During diastole, the double orifice permits ventricular filling.

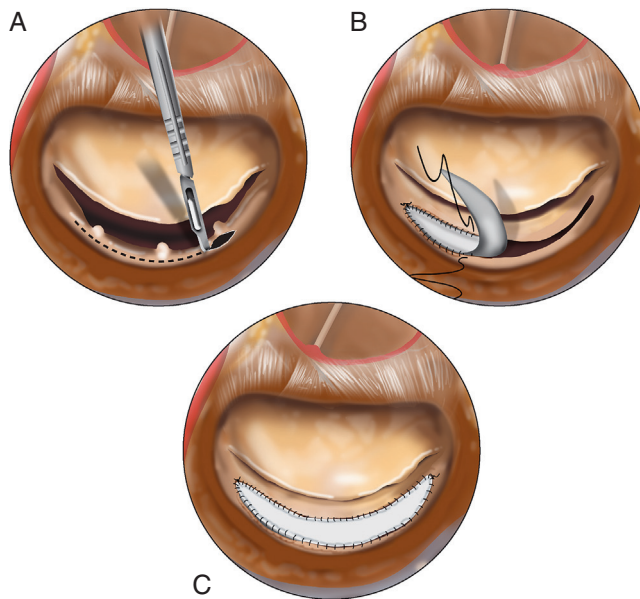


FIGURE 80-28 ■ Pericardial patch leaflet augmentation. **A**, A transverse incision is made in the posterior leaflet 5 mm from the annulus. Fibrotic secondary chordae can be excised through the leaflet incision. **B** and **C**, Pericardium is fashioned into an elliptical patch to increase the posterior leaflet height to 15 to 20 mm. The patch is sewn posteriorly to the annulus and then anteriorly to the leaflet tissue.

patients, posterior leaflet patch augmentation and resection of secondary chordae may be necessary to ensure a more durable repair.

Annular Decalcification and Annular Reconstruction

Annular calcification complicates mitral valve surgery. The risks of atrioventricular disruption, paravalvular leak, and valve dehiscence are all increased in this setting. In general, débridement of calcific foci is obligatory before valve repair or replacement. Annular decalcification is executed by separation of the leaflet from the annulus and en bloc removal of calcium deposits.^{25,93,94} Often, annular reconstruction is required to repair localized atrioventricular disruption following calcium excision. Similarly, débridement of annular abscesses in the treatment of infective endocarditis may necessitate annular reconstruction.

David and colleagues⁹⁵⁻⁹⁷ and Carpentier and colleagues²⁵ have described different techniques for mitral annular reconstruction. In David's technique, mitral annular reconstruction is conducted using autologous or glutaraldehyde-fixed bovine pericardium. The posterior annulus is reconstructed with a semicircular pericardial patch. The patch is usually 2 cm wide but must be wide enough to cover the defect. One of the margins of this strip is sutured to the smooth endocardium of the inflow of the left ventricle, and the other margin is sutured to the posterior left atrial wall with a continuous 3-0 polypropylene suture. The detached posterior leaflet is then reattached to the pericardial patch at the level of the original annulus. In patients with complete destruction of the annulus, a circumferential patch is tailored for annular reconstruction. An annuloplasty ring is then secured to the pericardial patch. Similar techniques use felt.⁹⁴

In Carpentier's technique (Fig. 80-29), the mitral annulus is reconstructed with figure-of-eight atrioventricular mattress sutures to minimize use of foreign material. Braided 2-0 suture is first passed through the atrial edge and then through the ventricular edge, avoiding injury to the circumflex vessels. The suture is passed again in the same fashion and then upward through the atrial tissue to maintain all suture on the atrial side. Ventricular passes should be at least 1 cm wide and involve one third of the thickness of the ventricle to incorporate any fibrous tissue possible. Closure of the atrioventricular junction is facilitated by downward displacement of the atrial edge with forceps. Not only do the figure-of-eight sutures reduce the size of the annulus, but they also displace the surrounding fat and circumflex vessels away from the reconstructed annulus. The free ends of the figure-of-eight mattress sutures are maintained for later insertion of a remodeling annuloplasty ring. The neoatrioventricular junction is further buttressed with a running polyester suture along the line of closure.

Considerations in Endocarditis

The primary goal of any surgery for endocarditis is complete débridement of all infected and necrotic tissue. The

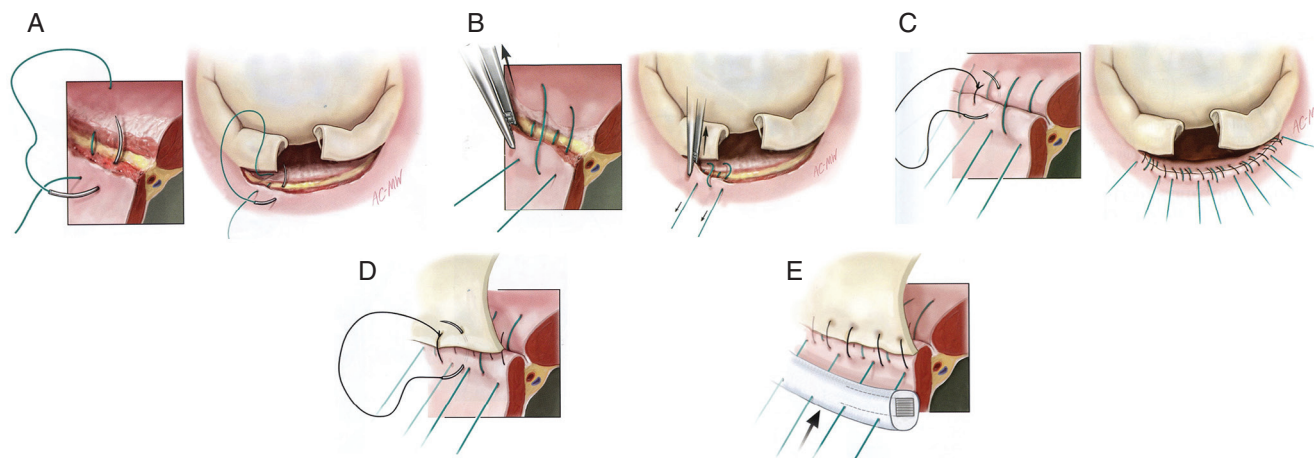


FIGURE 80-29 ■ Annular reconstruction using Carpentier's technique. **A**, Annular débridement results in a defect necessitating reconstruction. A braided 2-0 suture is first passed through the atrial edge and then through the ventricular edge of the defect. **B**, The suture is passed again in the same fashion and then upward through the atrial tissue. Closure of the atrioventricular junction is facilitated by downward displacement of the atrial edge with forceps. **C**, A running suture line further strengthens the neoatrioventricular junction. **D**, The posterior leaflet is reattached to the reconstructed annulus with a running suture. **E**, The free ends of the figure-of-eight mattress sutures are used for annuloplasty ring insertion. (From Carpentier A, Adams DH, Filsoufi F: *Carpentier's reconstructive valve surgery*, St. Louis, 2010, Elsevier.)

feasibility of mitral valve repair depends on the extent of normal tissue remaining after débridement. Extensive leaflet involvement or subvalvular destruction precludes valve repair. However, valve repair is achievable in a majority of cases provided sufficient tissue remains for reconstruction.⁹⁸⁻¹⁰¹ Mitral regurgitation resulting from localized leaflet perforation (typically the anterior leaflet) is amenable to patch repair with autologous pericardium. To address more extensive valve destruction, surgical reconstruction should integrate the many aforementioned techniques in a lesion-specific approach. Although the implantation of a prosthetic ring remains controversial, in the setting of a dilated annulus, a remodeling annuloplasty ring should be implanted routinely.

Systolic Anterior Motion of the Anterior Leaflet

Systolic anterior motion of the mitral valve is a complication after valve repair that results from a discrepancy between the amount of leaflet tissue and the mitral valve orifice area (Fig. 80-30).¹⁰² Effectively, the plane of coaptation is displaced too anteriorly. It is most frequently observed after valve reconstruction when there is excess posterior leaflet tissue and/or an inappropriately undersized annuloplasty ring. It can also result when there is excess anterior mobility of the posterior leaflet, which can occur when artificial chordae are too long. Consequently, the anterior leaflet is displaced toward the left ventricular outflow tract causing both obstruction and late systolic mitral regurgitation. In most instances, systolic anterior motion of the anterior leaflet may be treated non-operatively. Ventricular underfilling is corrected by increasing preload with volume, raising afterload with pure alpha agonists, and slowing the heart rate to increase diastolic duration. Ventricular hypercontractility is addressed by suspending administration of inotropes. In addition, in the setting of asynchrony, ventricular filling

is augmented by atrioventricular pacing. With these maneuvers, most postrepair systolic anterior motion will resolve, and moderate residual ventriculoaortic gradients (<30 mm Hg) usually normalize in weeks to months from left ventricular outflow tract remodeling.¹⁰³

When systolic anterior motion is irreversible, the repair must be re-addressed, and various measures are enacted depending on the causative factor. Chordal length is corrected if believed to be too long. If the posterior leaflet is too tall, excess posterior leaflet tissue is removed with an ovoid leaflet resection at the base of the posterior leaflet. Thus, the height of the posterior leaflet is reduced and the coaptation zone is moved posteriorly. A posterior anchoring neochord can also be inserted. If systolic anterior motion is due to an undersized annuloplasty ring, the ring should be replaced with a larger ring that is appropriately sized to the anterior leaflet.¹⁰⁴

Mitral Valve Replacement

Mitral valve replacement should be performed in patients in whom mitral valve repair is not suitable (e.g., extensive valve destruction from endocarditis, severe leaflet calcification and fibrosis from rheumatic heart disease, or select patients with ischemic cardiomyopathy).⁷⁹ When possible, chordal-sparing mitral valve replacement is the preferred technique because left ventricular function is better preserved (Fig. 80-31).^{105,106}

Typically, the posterior leaflet is left intact and the tissue is used to better support valve replacement sutures. In addition, this strategy automatically preserves the posterior subvalvular apparatus. In contrast, the anterior leaflet must be transferred if it is to be retained. Otherwise, it will be displaced into the left ventricular outflow tract by the valve prosthesis and obstruct outflow. In certain settings (e.g., highly fibrotic, stenotic valve) the anterior leaflet may need to be completely resected. However, whenever possible, the anterior leaflet and its

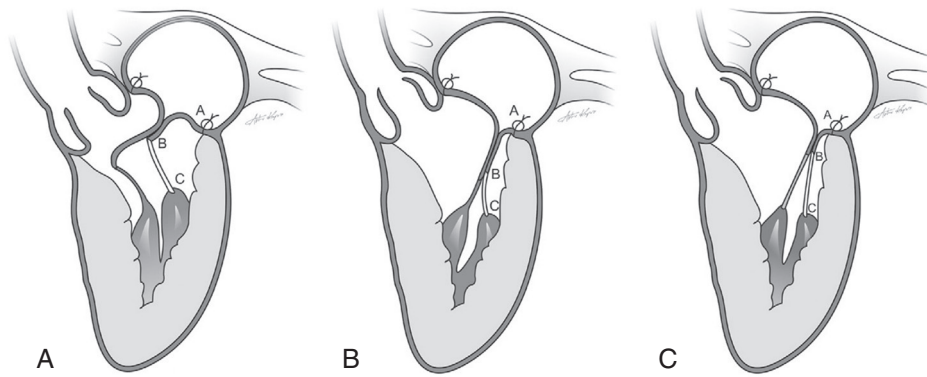


FIGURE 80-30 ■ Systolic anterior motion of the mitral valve and the issue of excess tissue. **A**, Dynamic left ventricular outflow tract obstruction from anterior displacement of the zone of coaptation. **B**, Correction by bringing the coaptation zone posteriorly using shorter artificial chordae. **C**, Correction by moving the coaptation zone posteriorly with a sliding plasty to lower the height of the posterior leaflet. **AB**, Height of the posterior leaflet; **B**, free margin of the posterior leaflet; **BC**, length of the chordae. (From Perier P, Hohenberger W, Lakew F, et al: Toward a new paradigm for the reconstruction of posterior leaflet prolapse: midterm results of the “respect rather than resect” approach. *Ann Thorac Surg* 86:722, 2008.)

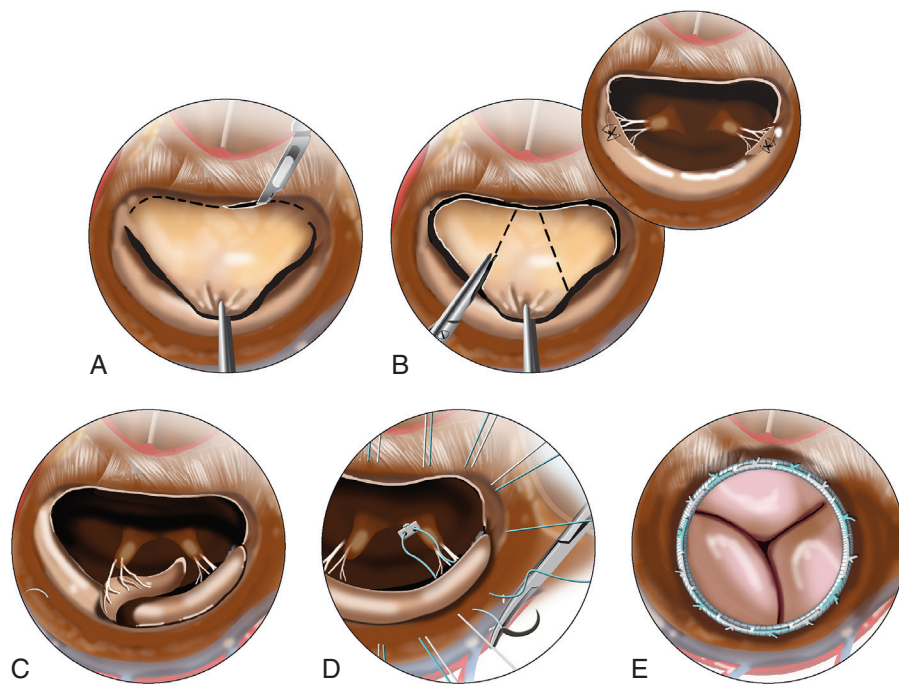


FIGURE 80-31 ■ Chordal-sparing mitral valve replacement. **A**, The anterior leaflet of the mitral valve is detached from the annulus from commissure to commissure. The anterior leaflet chordae can then be spared in two ways: **(B)** excision of the central portion of the leaflet and tacking the remaining segments to their respective 3- and 9-o'clock positions, or **(C)** direct attachment of the anterior leaflet to the posterior annulus from the 5- to 7-o'clock positions. **D**, Horizontal mattress sutures are placed circumferentially around the annulus (supra-annular, noneverting suture placement shown). **E**, Sutures are passed through the sewing ring of the mitral prosthesis and the valve is secured in position.

chordal apparatus should be preserved. The anterior leaflet is incised in a circumferential manner approximately 3 to 4 mm from the mitral valve annulus, and it is detached from commissure to commissure. The chordae to the anterior leaflet can then be preserved in two different manners. One approach is to excise the central portion of the anterior leaflet (which does not contain chordal attachments) and then suture the remaining anterior leaflet segments at their respective 3- and 9-o'clock positions. Alternatively, the detached anterior

leaflet can be attached directly to the posterior annulus, from the 5- to 7-o'clock positions (see Fig. 80-31). In addition to simplicity and rapidity, this technique offers the additional advantage of buttressing the valve replacement sutures in the posterior annulus, which often is extensively calcified. Thus, the anterior leaflet can effectively double as a broad biologic pledget.

Horizontal mattress mitral valve replacement sutures are placed circumferentially around the annulus in an everting (intra-annular) or noneverting (supra-annular)

fashion (see Fig. 80-31). By surrounding the prosthetic valve sewing ring with everted native mitral valve tissue, the intra-annular technique minimizes any possibility of a paravalvular leak. This technique is especially well suited for mechanical valve replacement because it avoids the possibility of leaflet tissue interfering with the hinge mechanism or the leaflet closure edge of a bileaflet mechanical valve. The disadvantage of the intra-annular technique is that smaller valve prostheses will be implanted compared with prostheses placed using a supra-annular technique. A supra-annular technique facilitates the implantation of much larger prostheses, particularly when using a bioprosthetic valve, because the entire sewing ring is secured in the left atrium rather than within the annulus. This supra-annular location also moves more of the valve out of the left ventricular outflow tract and into the atrium. Disadvantages include difficulty visualizing and properly seating pledgets on the ventricular side of the anterior annulus. Hence, sealing the valve sewing ring down onto the annulus when tying the valve sutures is purely by feel as opposed to direct visualization.

If the anterior annulus is exposed suboptimally, it is helpful to begin the leaflet incision but not completely detach the anterior leaflet from the annulus. The leaflet can then be used as a handle. Applying posterior tension on the partially divided leaflet will bring the anterior annulus further into view and facilitate placement of a mitral valve replacement suture. Once the suture is placed, the anterior mitral leaflet incision can be extended in either direction toward the commissures to allow stepwise placement of the remaining mitral valve replacement sutures in the anterior annulus.

Prosthesis Orientation

With a bioprosthetic valve, the three commissures should be oriented at approximately the 1-, 5-, and 9-o'clock positions, and ideally more toward the 1:30, 5:30, and 9:30 positions. This avoids inadvertent placement of a strut directly in the middle of the left ventricular outflow tract (which rests primarily in between the 10- and 1-o'clock positions). This positioning is slightly less important when using a supra-annular technique, because seating the valve above the annulus results in less valve in the left ventricular outflow tract. Orientation of a bileaflet mechanical valve is not as critical given the relatively low profile of the contemporary hinge guards. However, it is ideal to orient the leaflets in the horizontal plane to ensure that the valve guard is not near the left ventricular outflow tract. Far more important than hinge orientation is confirmation that both leaflets move uninterrupted, and that there is no subvalvular tissue interfering with proper valve closure. If interference is encountered, rotating the valve within the housing can be performed easily using the valve holder. Rotation will usually address the issue by repositioning the closing mechanism away from the area of tissue impingement. If interference persists, the culprit tissue can be resected through the valve or retracted away from the valve with a nonpledgeted suture.

A catheter or vent may be placed through the mitral prosthesis to provide left ventricular decompression by

maintaining the mitral prosthetic valve incompetent. The atriotomy is then closed in standard fashion.

Prosthesis Selection

Important considerations in prosthesis selection include the requirement of permanent anticoagulation, durability, and, of course, patient preference. Because of the limited durability of bioprosthetic valves (particularly in younger individuals), recipient age and life expectancy help to guide professional society recommendations. In patients without a contraindication to anticoagulation, the ACC and AHA recommend a mechanical prosthesis for those younger than 60 years, a biologic prosthesis for those over age 70 years, and either prosthesis for those between 60 and 70 years.³ Finally, patients that have contraindications to permanent anticoagulation should receive a biologic prosthesis.

In general, patients younger than 60 years of age at the time of prosthesis implantation have a higher incidence of primary structural valve degeneration and a reoperation rate as high as 40% in patients 50 years of age, 55% in patients 40 years of age, 75% in patients 30 years of age, and 90% in patients 20 years of age.³ Anticoagulation with warfarin carries an acceptable risk in those younger than 60 years, especially in compliant patients who are carefully monitored. Thus, the balance between durability and risk of thromboembolism or bleeding may favor mechanical prosthesis implantation in those younger than 60 years.³

The likelihood of structural valve degeneration 15 to 20 years after biologic prosthesis implantation in patients older than 70 years is approximately 10%.³ In addition, older patients are at higher risk of bleeding complications from permanent anticoagulation. Because the expected number of remaining life years at 70 years of age in men and women is 13.6 and 15.9 years, respectively, the durability of biologic prostheses typically exceeds life expectancy. Therefore, it is reasonable to implant a biologic prosthesis in those older than 70 years to avoid risks of anticoagulation.³

These recommendations are not absolute and are certainly subject to patient preference. Younger patients might not want to make the lifestyle modifications necessary for permanent anticoagulation. In addition, younger women may prefer a biologic prosthesis to facilitate safer pregnancy. With transcatheter mitral valve replacement technology on the horizon, some younger patients may prefer a bioprosthesis with the prospect of rescue valve-in-valve therapy in the future. Thus, prosthesis selection must be individualized to each patient.

RESULTS

There is an increasing need to minimize adverse outcomes in patients with mitral valve disease, particularly given new professional society guidelines advocating surgery in asymptomatic adults. Operative mortality was the principle outcome measure in the early era of mitral valve surgery. However, as current hospital mortality after valve surgery approaches zero, additional

performance variables such as long-term survival, functional status, and reintervention rates have become increasingly important in evaluating modern surgical treatments of mitral valve disease.

Commissurotomy for Mitral Stenosis

Early Mortality and Late Survival

Although mortality in the early experience with closed mitral commissurotomy was high, contemporary outcomes of mortality after either closed or open commissurotomy are low and similar (less than 0.5%).^{76,107} However, in most institutions, percutaneous balloon commissurotomy has essentially replaced surgical commissurotomy for mitral stenosis. Procedural mortality is near zero, and risk of complications such as severe mitral regurgitation or bleeding requiring urgent operation is low. Furthermore, midterm survival in patients with a good hemodynamic result is satisfactory.

Closed, open, and balloon mitral commissurotomy are not curative procedures. As such, survival increasingly deviates from that of an age-, gender-, and ethnicity-matched population over time (Fig. 80-32).^{76,108,109} It should be noted that death typically results from thromboembolism or reoperation and mitral valve replacement, as opposed to consequences of recurrent or residual mitral stenosis or regurgitation.

Morphologic risk factors identified in the aforementioned scoring systems to assess candidacy for balloon commissurotomy likewise impact the risk of recurrent disease and symptoms. As these risk factors also predict need for reintervention, which is typically valve replacement, it is not surprising that morphologic characteristics also predict survival trends. Survival after redo mitral commissurotomy is also acceptable, with 10- and 15-year survival rates of 83% and 63% being reported. However, 31% of hospital survivors required yet another intervention (typically valve replacement), within an average of 8 years.¹¹⁰

Functional Status

In appropriately selected patients, successful commissurotomy significantly improves cardiovascular symptom burden. In fact, greater than 90% of patients are in NYHA functional class I or II within the first 2 years after surgery.^{109,111,112} Symptom burden is directly related to mitral valve orifice area. Initial relief of symptoms is due to the large increase in mitral valve area afforded by commissurotomy. Various reports demonstrate valve area increases by an average of 0.9 to 2.6 cm² after commissurotomy,^{113,114} with open commissurotomy and balloon valvotomy demonstrating superior results compared with those of closed commissurotomy (Fig. 80-33).^{109,115} However, functional status gradually declines from the continued valvulopathic process with resultant reduction in mitral valve orifice area, regardless of whether rheumatic fever reoccurs (Fig. 80-34).¹¹⁶ This phenomenon is evidenced by the correlation between late postoperative mean mitral orifice area and functional class: 2.0 cm² in patients in class I, 1.7 cm² in class II, and 1.6 cm² in class III.¹¹⁷ Risk factors for poor functional status after mitral commissurotomy include older age, higher preoperative functional class, and greater degrees of valve calcification and leaflet immobility.⁷⁶

Mitral Regurgitation after Commissurotomy

Mitral regurgitation is a clear risk of any commissurotomy procedure. Rates of immediate postprocedure mitral regurgitation vary with type of commissurotomy and are lowest for open commissurotomy (2% to 5% for open,¹⁰⁹ 10% for closed,⁷⁶ and 10% for percutaneous balloon¹¹⁸). Although emergency operation for new mitral regurgitation after commissurotomy is rare, surgery may be necessary within a few months. In addition, severity of mitral regurgitation affects the need for mitral valve replacement and survival, with mild mitral regurgitation demonstrating a minimal effect while more severe grades adversely affect both.⁷⁶

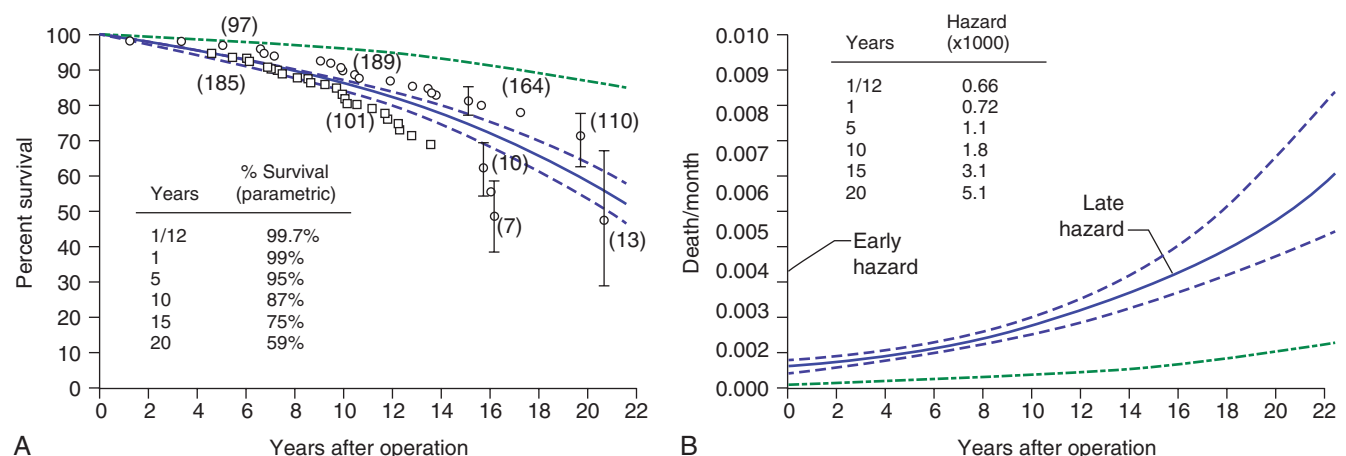


FIGURE 80-32 ■ Survival after surgical mitral commissurotomy. **A**, Actuarial survival analysis with circles representing individual deaths. **B**, Parametric analysis demonstrating the hazard of death after commissurotomy. Dashed dot lines represent an age-, gender-, and race-matched U.S. population. (From Hickey MS, Blackstone EH, Kirklin JW, et al: Outcome probabilities and life history after surgical mitral commissurotomy: implications for balloon commissurotomy. *J Am Coll Cardiol* 17:31, 1991.)

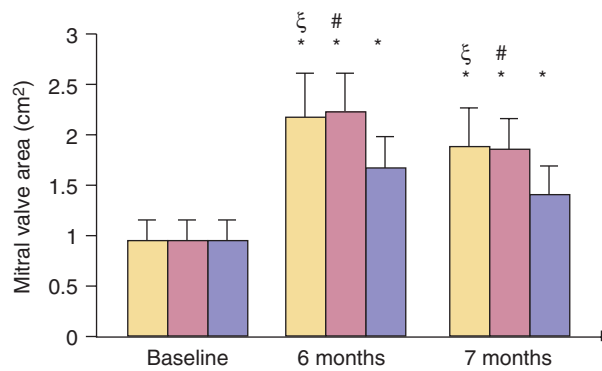


FIGURE 80-33 ■ Mitral valve area after percutaneous balloon (yellow), open (red), and closed (blue) commissurotomy. * $P < 0.001$ compared with baseline. § $P < 0.001$ compared with closed commissurotomy. (From Ben Farhat M, Ayari F, Maatouk F, et al: Percutaneous balloon versus surgical closed and open mitral commissurotomy: seven-year follow-up results of a randomized trial. *Circulation* 97:248, 1998.)

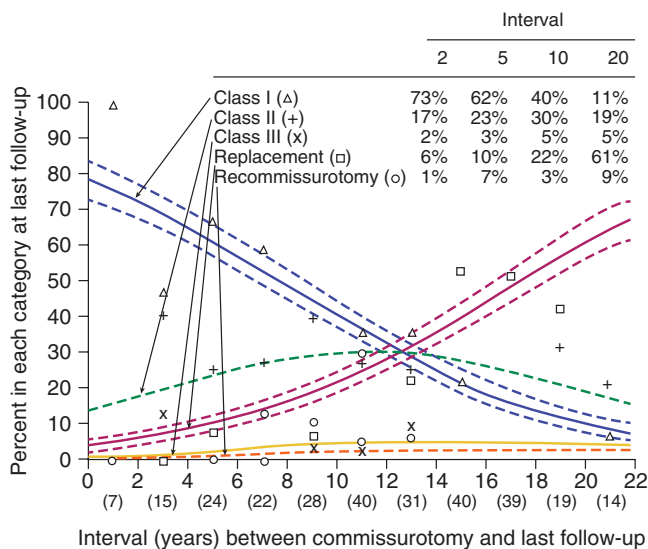


FIGURE 80-34 ■ Functional status after surgical commissurotomy in relation to time since the initial surgery. Note the declining percentage of patients in New York Heart Association class I. In addition, the percentage of patients undergoing mitral valve replacement greatly increases over time. Numbers in parentheses along the x-axis are numbers of patients at each follow-up interval. (From Hickey MS, Blackstone EH, Kirklin JW, et al: Outcome probabilities and life history after surgical mitral commissurotomy: implications for balloon commissurotomy. *J Am Coll Cardiol* 17:34, 1991.)

Reintervention

Because mitral commissurotomy is not a curative procedure, most patients that undergo this procedure require subsequent procedures at some time postoperatively. Most often the subsequent procedure is a mitral valve replacement because worsening leaflet mobility and calcification, as well as progressive subvalvular pathology preclude successful redo commissurotomy. After surgical commissurotomy, valve replacement is performed in approximately 20% of patients within 10 years and 50% within 20 years (see Fig. 80-34).⁷⁶ Similar results are noted in the current era of percutaneous balloon valvotomy, with 60% of patients undergoing repeat intervention within 20 years of the index procedure (76%

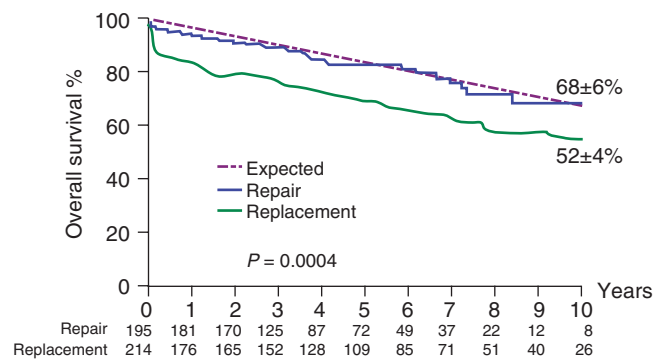


FIGURE 80-35 ■ Comparison of overall survival after mitral valve repair or replacement. The purple dashed dot line represents expected survival of the general population, which is similar to survival after valve repair. (From Enriquez-Sarano M, Schaff HV, Orszulak TA, et al: Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. *Circulation* 91:1022–1028, 1995.)

valve replacement and 24% repeat balloon valvotomy).¹¹⁹ Risk factors for mitral valve replacement after commissurotomy include smaller precommissurotomy valve area, greater leaflet immobility and calcification, greater postprocedure mitral regurgitation, and older age.^{76,119}

Valve Repair for Mitral Regurgitation

Early Mortality and Late Survival

Hospital mortality after isolated mitral valve repair for nonischemic mitral regurgitation is very low. In an analysis of more than 40,000 patients in the Society of Thoracic Surgeons Adult Cardiac Surgery Database, hospital mortality was 1.4% for patients who underwent isolated mitral valve repair between 2007 and 2010.¹²⁰ Furthermore, reference centers have reported hospital mortality rates after mitral valve repair that approach zero.^{63,65,121–125}

Survival over time, inclusive of hospital mortality, of patients with mitral regurgitation who undergo mitral valve repair with or without concomitant procedures is generally better than that of patients undergoing replacement (with the exception of ischemic mitral regurgitation⁷⁹). Contemporary survival data are similar across most centers, with 10-year survival after repair ranging from 68% to 94%,^{63,65,122,126–129} and 20-year survival approaching 50%.^{126,127,130} Variability in survival between reports and improved survival after repair compared with replacement is only partly attributed to the difference in baseline risk profiles of each study population. In the Mayo Clinic experience,^{128,129} operative mortality was 2.6% for mitral repair compared to 10.3% for replacement ($P = 0.002$), and after valve repair late survival (in operative survivors) at 10 years was 69% compared to 58% after replacement ($P = 0.018$). Furthermore, late survival after valve repair did not differ from the expected survival of the general population (Fig. 80-35); however, the two groups differed in their degree of preoperative heart failure and incidence of atrial arrhythmias. To mitigate treatment allocation bias, a number of recent studies have used propensity-score matching to compare outcomes of mitral valve repair and replacement, all of which

corroborate the survival advantage conferred by mitral repair, including in the elderly.¹³¹⁻¹³⁴

Congestive heart failure owing to left ventricular dysfunction is the most common cause of late death after mitral valve repair, and it is best predicted by preoperative left ventricular dysfunction.¹³⁵ Many other variables, such as preoperative symptom burden, cause of valve disease (Fig. 80-36), and age also significantly affect survival.^{43,130,136,137}

Functional Status

After mitral valve repair, symptoms typically resolve and functional capacity is excellent; greater than 90% of surviving patients are reported to be in NYHA functional class I or II 20 years after surgery.^{126,127,137}

Left Ventricular Dysfunction and Remodeling

Beneficial responses of left ventricular performance to mitral valve repair are largely dependent on proper timing of surgery.^{16,45,135,138} In general, mitral valve repair leads to decreased left ventricular strain, regression of left ventricular mass, and decreased left ventricular volume.¹³⁸⁻¹⁴⁰ In fact, in many patients preoperative left ventricular function is preserved. However, even patients with “normal” systolic function preoperatively (ejection fraction > 60%) may develop postoperative left ventricular dysfunction. Quintana and colleagues¹⁴¹ noted that 18.4% of patients had a postrepair ejection fraction of less than 50% despite having “normal” preoperative ventricular function. This ventricular dysfunction failed to recover over 15 years postoperatively in two thirds of those individuals and conferred a 70% increase in the hazard of late death. Similar to other indices of remodeling, ventricular performance is better preserved or improved after mitral valve repair when left ventricular dilation is less severe preoperatively.^{16,139,141} This evidence

strongly supports earlier intervention in asymptomatic patients with progressive left ventricular enlargement.

Residual and Recurrent Mitral Regurgitation

Failure after repair can be classified into three groups: immediate failure (intraoperatively), early failure (<2 years), and late failure (>2 years). Immediate and early failures are typically related to technique, whereas late failure generally is due to continued progression of the valvulopathic process. Analyses of reoperation for failure of mitral valve repair suggest that repair failures are often procedure-related in degenerative disease (usually immediate and early failure) and valve-related in rheumatic disease (usually late failure).¹⁴²⁻¹⁴⁵

The majority of patients have no residual mitral regurgitation immediately after mitral valve repair. In fact, large series from multiple centers report that only 5% of patients demonstrate mild mitral regurgitation prior to hospital discharge, with the remainder having trace or undetectable regurgitation.^{63,146} Intraoperative valve assessment is critical to detect immediate failure. Such failures often are due to suture dehiscence, interscallop leakage, systolic anterior motion of the anterior leaflet, or inadequate surface of coaptation. An unsatisfactory immediate result should prompt re-exploration of the mitral valve and a repeated attempt at effective correction, because residual mitral regurgitation at the end of surgery is directly associated with a high reoperation rate (Fig. 80-37).^{125,129,147,148}

Early failure is defined as new mitral regurgitation after an initially successful repair. Primary causes include absence of a remodeling annuloplasty ring, ring dehiscence from improper sizing or inadequate suture placement, rupture of repaired chordae, or suture line dehiscence on leaflet tissue. Late failure results from progression of underlying disease and typically manifests as new segmental prolapse in patients with degenerative disease or worsening valve and subvalvular fibrosis in patients with rheumatic disease.

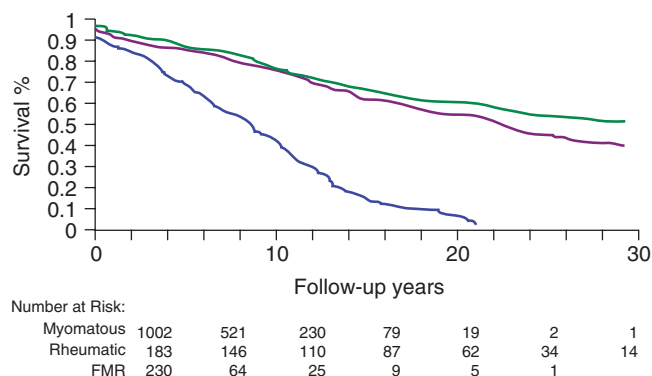


FIGURE 80-36 ■ Overall survival after mitral valve repair stratified by etiology of mitral valve regurgitation. Lines: green, degenerative mitral valve disease; red, rheumatic valve disease; blue, ischemic/nonischemic functional mitral valve disease. FMR, Functional mitral regurgitation. (From DiBardino DJ, ElBardissi AW, McClure RS, et al: Four decades of experience with mitral valve repair: analysis of differential indications, technical evolution, and long-term outcome. *J Thorac Cardiovasc Surg* 139:79, 2010.)

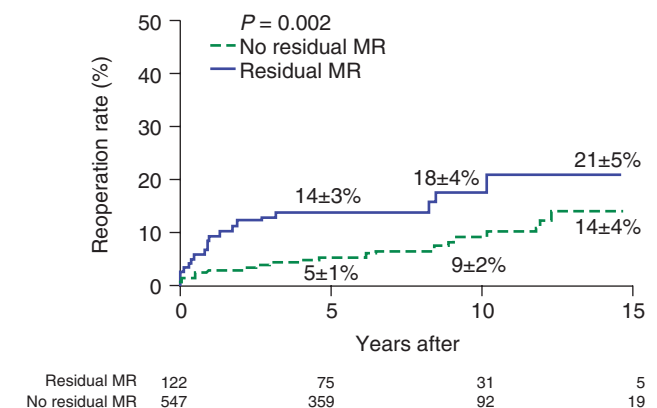


FIGURE 80-37 ■ Reoperation rate after mitral valve repair stratified by the presence of residual mitral regurgitation immediately after repair. MR, Mitral regurgitation. (From Mohty D, Orszulak TA, Schaff HV, et al: Very long-term survival and durability of mitral valve repair for mitral valve prolapse. *Circulation* 104:11-17, 2001.)

Although reoperation rate may underestimate the prevalence of late significant regurgitation, the excellent durability of mitral repair is supported by reports of freedom from reoperation ranging between 80% and 96% at 10- to 20-year follow-up.^{121,125-127,130,149} Although there does not appear to be a definitive relationship between repair technique and recurrent regurgitation, repair failure is clearly influenced by disease etiology and valve lesion (Fig. 80-38). After repair of mitral regurgitation owing to degenerative or rheumatic disease, 20-year freedom from reoperation was 82% and 34%, respectively ($P < 0.001$).¹³⁰ In contrast, greater than 30% of patients randomized to mitral repair with ischemic mitral regurgitation in a multicenter trial demonstrated moderate or severe recurrent regurgitation in just 1 year.⁷⁹

Traditionally, categorization of mitral valves by location of leaflet prolapse (posterior, anterior, or bileaflet) is of prognostic consequence as a number of series document lower repair rates and inferior repair durability for isolated anterior or bileaflet prolapse.^{130,150-153} However, durable repair of anterior leaflet prolapse has improved in the current era, and some report equivalent durability compared to that of posterior leaflet repair.^{154,155} With respect to repair techniques, for complex repairs and those involving the anterior leaflet, chordal replacement is superior to chordal shortening.¹⁵⁶ Yet, a randomized trial of the most common techniques for posterior leaflet prolapse did not reveal an appreciable difference in repair durability between leaflet resection and artificial chordoplasty.¹⁵⁷

Thromboembolic Events

Late thromboembolic complications are uncommon after mitral valve repair, although such patients are rarely anticoagulated for the long term. After an initial high hazard of thromboembolism in the perioperative period, the linearized rates of thromboembolic and bleeding events are as low as 0.2% and 0.1% per patient-year, respectively, over a 20-year period.¹²⁶ David and colleagues¹²⁷ found nearly 90% freedom from thromboembolism within the first 10 years after repair, and greater than 80% freedom after 20 years from the index repair.

Systolic Anterior Motion of the Anterior Leaflet

Systolic anterior motion of the mitral valve is noted immediately postrepair in 5% to 10% of patients with mitral valve prolapse.¹⁵⁸⁻¹⁶⁰ As previously mentioned, this complication that results from anterior displacement of the coaptation zone is limited to patients with degenerative mitral valve disease.¹⁰² However, the incidence of systolic anterior motion appears to have decreased given mechanistic insight and the advent of novel nonresectional leaflet remodeling techniques.^{71,72,161,162} It is important to note that most cases of systolic anterior motion do not require surgical intervention. Grossi and colleagues¹⁵⁸ identified systolic anterior motion in 6.4% of mitral valve repair patients intraoperatively, but all patients were treated medically and gradients resolved in every patient within 1 year.

Infective Endocarditis

Infective endocarditis is extremely rare after mitral valve repair as opposed to replacement. Long-term retrospective studies confirm the low risk of postrepair endocarditis, with 10- to 20-year rates of freedom from endocarditis approaching 100%.^{127,137}

Reoperation

The hazard function of reoperation after mitral valve repair is low and constant, without the rising late hazard phase observed with bioprosthetic valve implantation (Fig. 80-39).¹³⁷ As previously discussed, durability of mitral valve repair is excellent, with freedom from reoperation ranging between 80% and 96% 10- to 20-years after surgery.^{121,125-127,130} Etiology of mitral valve disease, location of leaflet prolapse (posterior vs. anterior), and residual regurgitation at the completion of the initial procedure are the greatest risk factors for recurrent mitral regurgitation and reoperation. However, the type of repair technique appears to have no effect on the prevalence of reoperation.¹⁵⁷ A handful of series have examined reoperations after mitral valve repair. Anyanwu and

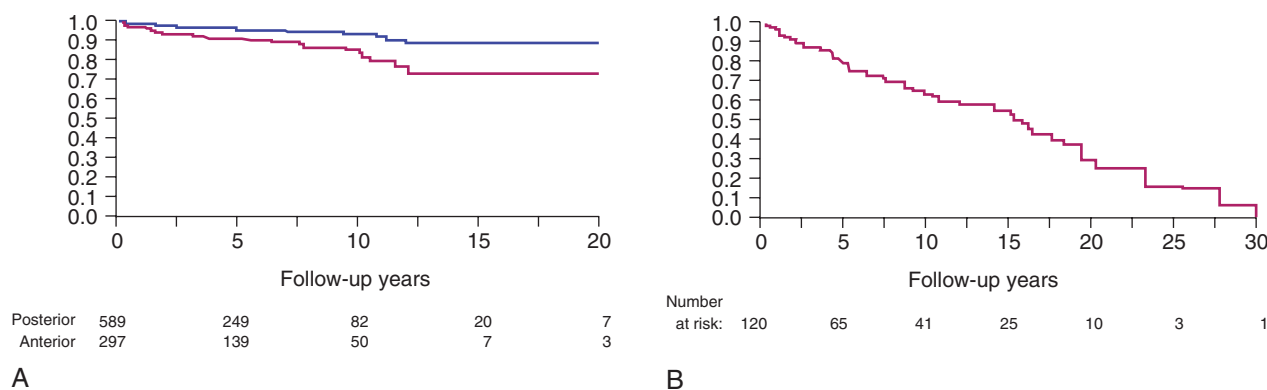


FIGURE 80-38 ■ Reoperation after mitral valve repair for (A) degenerative mitral valve disease stratified by location of leaflet prolapse (posterior, blue line; anterior, red line) and (B) rheumatic mitral valve disease. (From DiBardino DJ, ElBardissi AW, McClure RS, et al: Four decades of experience with mitral valve repair: analysis of differential indications, technical evolution, and long-term outcome. *J Thorac Cardiovasc Surg* 139:79–80, 2010.)

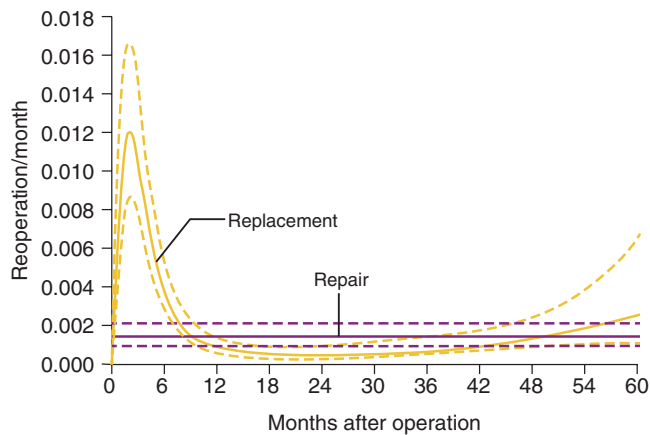


FIGURE 80-39 ■ Hazard functions for mitral valve reoperation in patients with mitral regurgitation who underwent mitral valve repair or replacement. (From Sand ME, Naftel DC, Blackstone EH, et al: A comparison of repair and replacement for mitral valve incompetence. *J Thorac Cardiovasc Surg* 94:208–219, 1987.)

colleagues¹⁴⁵ noted that mode of failure was attributable to progression of original disease in 36%, technical failure in 38%, and new disease in 26% of patients. Feasibility of valve re-repair depends on the primary etiology of valve disease and is successfully accomplished in 36% to 85% of patients.^{144,145,163,164} The advantages of mitral repair over replacement appear to persist during reoperation. In an analysis of the Mayo Clinic's experience of reoperative mitral valve surgery, mitral re-repair independently improved survival compared to replacement.¹⁴⁴

Mitral Valve Replacement

Early Mortality and Late Survival

Hospital mortality after isolated mitral valve replacement for mitral valve disease ranges between 2% and 7% in a number of series.^{79,131,165–168} A recent examination of 24,404 patients from the Society of Thoracic Surgeons Adult Cardiac Surgery Database revealed a hospital mortality of 3.8% following valve replacement for any etiology of mitral valve disease.¹⁶⁹ However, in older adults (>65 years) who are eligible for Medicare, operative mortality after isolated mitral valve replacement is higher (8.9%).¹⁷⁰

Ten-year survival after mitral valve replacement is generally between 50% and 60%, and long-term survival is independent of prosthesis type chosen (mechanical or biologic; Fig. 80-40).^{168,171–175} Concomitant procedures, such as coronary bypass or tricuspid annuloplasty, decrease long-term survival compared with that of isolated mitral valve replacement.^{137,165,176} However, it should be noted that published results of mitral valve replacement have improved,^{177,178} likely from the adoption of chordal sparing valve replacement. Preservation of papillary muscles and normal ventricular geometry minimize risk of midventricular rupture¹⁷⁹ and aid in maintenance of early postoperative cardiac output.¹⁸⁰

Early and late survival after reoperative mitral valve replacement is less than after the index mitral valve

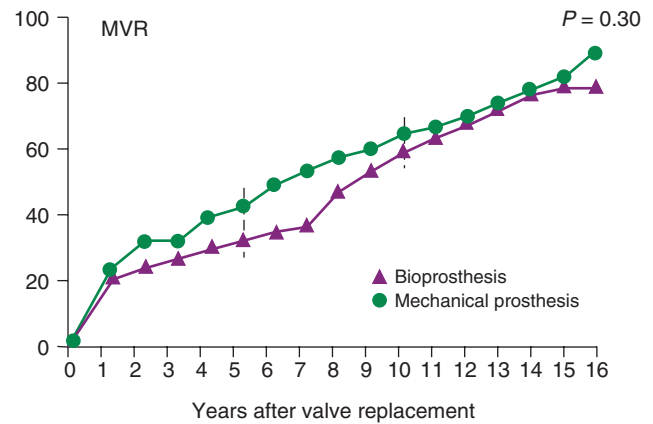


FIGURE 80-40 ■ All-cause mortality after mitral valve replacement (MVR) stratified by prosthesis type (biologic versus mechanical) up to 16 years postoperatively. (From Hammermeister K, Sethi GK, Henderson WG, et al: Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. *J Am Coll Cardiol* 36:1152–1158, 2000.)

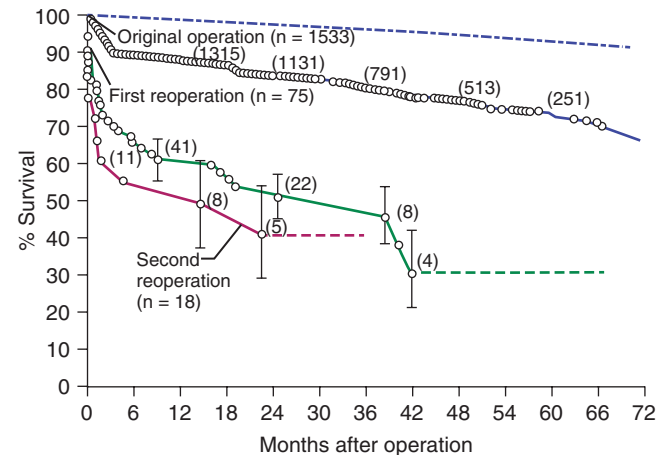


FIGURE 80-41 ■ Actuarial survival after primary valve replacement, first reoperative valve replacement, and second reoperative valve replacement. The purple dashed line represents survival for an age-, sex-, and race-matched general population. (From Blackstone EH, Kirklin JW: Death and other time-related events after valve replacement. *Circulation* 72:755, 1985.)

replacement (Fig. 80-41).^{175,181} This is likely a result of increased technical difficulty inherent to cardiac reoperation, greater functional disability in reoperative patients, and the fact that prosthetic valve endocarditis is a common indication for reoperation. In the current era, however, hospital mortality after reoperative mitral valve replacement has significantly decreased to under 10%.^{182,183}

The most common cause of early and late death after mitral valve replacement is cardiac failure. Modes of late death in operative survivors not owing to cardiac failure include thromboembolism, anticoagulant precipitated hemorrhage, and endocarditis. Unlike patients with acquired aortic valve disease, lethal arrhythmias rarely cause sudden death in patients after mitral valve replacement. Risk factors for premature death include older age (particularly >75 years), left ventricular enlargement and dysfunction, left atrial enlargement, ischemic

cardiomyopathy, significant tricuspid valve disease, severe preoperative functional disability, and failure to preserve the subvalvular apparatus during replacement.¹⁸²

Functional Status

In most patients (>90%), symptoms improve to NYHA functional class II or better. However, patients with more severe chronic disability preoperatively are less likely to gain as much functional improvement. In fact, only half of patients with chronic severe preoperative disability return to NYHA class I after surgery, thereby suggesting that such patients probably harbor a secondary irreversible ventricular cardiomyopathy.

Left Ventricular Dysfunction and Remodeling

In the current era, beneficial responses of ventricular performance are similar to that of repair, though less significant, and largely depend on timing of surgery. Historically, after valve replacement for chronic mitral regurgitation, ejection fraction is at least transiently lower than preoperative values.¹⁸⁴ Although slightly reduced, ejection fraction typically remains within the range of normal when preoperative left ventricular dilation is limited (end-systolic dimension < 5 cm or end-diastolic dimension < 7 cm). When preoperative left ventricular enlargement is severe (end-systolic dimension > 5 cm or end-diastolic dimension > 7 cm), ejection fraction is significantly reduced postoperatively and in some patients may decline even further over time.¹⁸⁴ Ventricular performance and remodeling were significantly improved with the advent of chordal sparing mitral valve replacement. Maintenance of valvular-ventricular interaction preserves systolic performance and leads to beneficial reductions in left ventricular volume and wall stress.^{105,185-187} This has translated into improved survival and global left ventricular function at early and later time points.^{188,189}

Thromboembolic Events

Thromboembolism is one of the more common complications of mitral prostheses, but the incidence is somewhat less in patients with biologic valves (Table 80-5).¹⁹⁰ The incidence of thromboembolism in currently available bileaflet and tilting-disk valves is 1.5% to 2.0% per patient-year. Risk is higher in patients with a large left atrium, intra-atrial clot, or chronic atrial fibrillation. Maintenance of life-long therapeutic anticoagulation, typically with warfarin, is the most important factor influencing the rate of thromboembolism in patients with a mechanical mitral prosthesis. Alternatively, warfarin therapy for 3 months postoperatively and aspirin indefinitely are as effective as long-term warfarin therapy in patients with a biologic mitral prosthesis.¹⁹⁰

Acute Valve Thrombosis

Acute thrombosis of a mitral prosthesis occurs more frequently with a mechanical device than a biologic valve.¹⁹⁰

TABLE 80-5 Incidence of Thromboembolism and Hemorrhagic Events from Anticoagulation for Currently Available Mitral Valve Prostheses

Valve	Thromboembolism (%/pt-year)	Anticoagulant Hemorrhage (%/pt-year)
Mechanical Prostheses		
Starr-Edwards ²³⁰⁻²³²	1.3-6.6	0.6-3.7
Medtronic Hall ²³³⁻²³⁵	1.8-4.2	1.4-3.2
Omniscience ²³⁶⁻²³⁹	0.4-2.5	0.0-2.7
St. Jude ²⁴⁰⁻²⁴³	0.7-3.0	0.3-2.7
Carbomedics ²⁴⁴⁻²⁴⁷	0.5-4.6	0.0-2.8
ATS ^{248,249}	0.5-3.0	0.0-2.3
On-X ²⁵⁰⁻²⁵²	1.5-1.8	0.0-3.1
Biologic Prostheses		
Hancock	1.1-2.4	0.4-1.0
standard ^{253,254}		
Hancock II ²⁵⁵	1.7	1.1
Carpentier	0.8-2.4	0.7-1.2
Edwards		
porcine ^{253,256,257}		
Carpentier	0.6-1.7	0.3-1.2
Edwards		
pericardial ^{258,259}		
Mosaic ^{260,261}	0.2-1.4	0.9-2.0
Biocor ^{262,263}	1.8-2.1	1.1

This complication occurs almost exclusively in the setting of suboptimal anticoagulation. Patients usually present acutely and report a short duration of symptoms (1 to 3 days). Echocardiography is diagnostic, but fluoroscopy may also reveal the diagnosis with evidence of restricted leaflet movement. If the patient is not in cardiogenic shock, acute thrombotic occlusion can be treated with thrombolytic agents.^{191,192} Hemodynamic instability warrants emergency operation, and surgical thrombectomy typically achieves a good result.¹⁹³

Hemorrhagic Events from Anticoagulation

Hemorrhage from anticoagulation usually occurs in the gastrointestinal, urogenital, and central nervous systems, and severity is proportional to the INR. The linearized rate of important hemorrhage has declined, and a recent meta-analysis reported rates of 1% to 2% per year (see Table 80-5).¹⁹⁴ This improvement has coincided with hemodynamic improvements of mitral valve prostheses (Table 80-6) that permit less intense anticoagulation goals (INR required for ball-and-cage valves was 3.5 to 4.5 compared to 2.5 to 3.5 for current mechanical prostheses).

Structural Valve Degeneration

Structural valve degeneration is the principle complication of biologic prostheses in the mitral position. In fact, prosthesis failure accounts for at least two thirds of reoperations in patients with biologic valves.¹⁹⁵ This complication is uncommon in the first 5 years after valve

TABLE 80-6 In Vivo Hemodynamics of Currently Available Prostheses for Mitral Valve Replacement

Valve	Effective Orifice Area (cm ²)					Mean Diastolic Transmitral Gradient (mm Hg)				
	25 mm	27 mm	29 mm	31 mm	33 mm	25 mm	27 mm	29 mm	31 mm	33 mm
Mechanical Prostheses										
Starr-Edwards ^{264,265}		1.4	1.4	1.9			6.3-8.0	6.7-10.0	5.0	
Medtronic Hall ^{266,267}						4.0	3.0-4.3	2.7-3.1	2.0-2.9	2.7
Omnicience ^{236,268,269}	1.7	1.9	1.6-2.2	1.9-2.0	2.0	4.3-9.0	3.6-6.0	3.5-5.1	2.0-6.0	4
St. Jude ^{267,270,271}	2.6	2.5	2.1-2.4	2.8	3.1	3.0	3.3	1.9-3.8	1.5-1.8	1.6-2.5
Carbomedics ^{272,273}		2.1-2.9	2.1-3.0	1.8-3.0		5.3	3.9-4.9	3.3-4.6	3.3-4.6	4.9
Bjork-Shiley ²⁷⁴	2.3	1.8		2.5		2.3-7.0	2.0-6.0		2.3-4.0	
ATS ^{271,275,276}	2.3	2.6-3.0	2.0-2.7	2.0	2.0	7.8	6.0	6.0	4.0	3.0
Biologic Prostheses										
Hancock standard ^{277,278}		1.3-1.5	1.0-2.5	1.0-1.8			7.0-12.0	5.0-7.6	5.0-7.4	
Carpentier Edwards porcine ²⁷⁹⁻²⁸¹		1.7	2.2-3.0	2.5-3.2			6.5-7.0	2.0-7.4	2.6-5.3	
Carpentier Edwards pericardial ²⁵⁸	2.6	2.7	2.6	3.1		4.1	3.0	3.0	3.0	3.1
Mosaic ^{260,261}	1.6-2.6	1.5-1.7	1.8	1.7-2.1	1.9	4.6-5.7	3.8-4.6	4.4	2.7-3.7	3.4
Biocor ²⁶³			3.1	3.3	3.6			6.7	6.2	5.4
Standard Values										
Normal			4-6					0		
Severe stenosis			<1					>12		
Desired value			>1.5					<10		

TABLE 80-7 Freedom from Structural Valve Degeneration Stratified by Biologic Prosthesis and Age

Valve	Age at Implant (yr)	Time Since Primary Mitral Valve Replacement			
		5 years	10 years	15 years	20 years
Hancock standard ²⁵⁴	≤40		68%		
	41-69		84%		
	≥70		84%		
Hancock II ^{197,282}	<65			76%	27%
	≥65			89%	59%
Carpentier Edwards porcine ²⁸³	≤35	79%	51%	0%	
	36-50	99%	64%	10%	
	51-64	98%	73%	26%	
	65-69	98%	67%	40%	
	≥70	100%	92%	75%	
	≤60	100%	78%		
Carpentier Edwards pericardial ^{259,284}	61-70	100%	89%		
	>70	100%	100%		
	≤50		100%	71%	
Biocor ^{263,285}	51-60		100%	90%	
	≥61		100%	100%	

replacement, but begins to increase thereafter with 15-year freedom from structural valve degeneration in earlier biologic valves nearing 40%.¹⁹⁵⁻¹⁹⁷ Rates of biologic valve failure are higher in the mitral position than in the aortic position, and they are significantly higher in younger individuals (<65 years; Table 80-7).¹⁹⁶ Modes of failure include leaflet tear causing prosthetic mitral regurgitation or leaflet calcification causing prosthetic mitral stenosis. The incidence of structural valve degeneration approaches zero for bileaflet, tilting-disk, and ball-and-cage mechanical valves. Mechanical valve dysfunction owing to chronic ingrowth of tissue and

impairment of the closure mechanism is observed infrequently.

Periprosthetic Leakage

Periprosthetic leakage is an uncommon complication following mitral valve replacement that is generally caused by technical errors. In the current era, the incidence of periprosthetic leakage approaches zero in uninfected patients.¹⁹⁸ Preoperative infective endocarditis and mitral annular calcification increase the risk of this complication. It can cause refractory hemolytic anemia in contrast to the

milder hemolysis observed with some mechanical prostheses, particularly tilting-disk valves.¹⁹⁹ Surgery is indicated in all symptomatic patients and in those with minimal symptoms that require transfusion.²⁰⁰ Alternatively, off-label application of transcatheter septal defect closure devices for these leaks has been successful.

Prosthetic Valve Endocarditis

Prosthetic mitral valve endocarditis is significantly less common than prosthetic valve endocarditis in the aortic position.²⁰¹ However, it remains a serious complication that results in the death of more than half of those affected.^{198,202} Prosthetic valve endocarditis that occurs within 6 months of the primary operation is usually due to contamination in the operating theater. Endocarditis that arises later is generally the result of a new bacteremia.

Prosthetic mitral valve endocarditis that occurs early after surgery greatly increases the risk of dehiscence and death. Broad-spectrum antibiotic therapy should be initiated until sensitivities are identified. In most cases, early prosthetic valve replacement is required. Reoperation should only be deferred if there is a superb response to antibiotic therapy without evidence of peripheral embolization or periprosthetic leakage. Yet, the patient must be followed closely to allow for reoperation if clinical status declines. A similar management strategy applies to prosthetic valve endocarditis that presents over 6 months after surgery. These patients have a better likelihood of responding to medical management compared with those who develop endocarditis earlier. However, medical management is less effective when the culprit organism is more virulent, such as *Staphylococcus*.

Reoperation

Reoperation after mitral valve replacement generally is due to periprosthetic leakage and/or infective endocarditis, as well as structural valve degeneration in the case of biologic prostheses. Actuarial freedom from reoperation 5 and 10 years after valve replacement is approximately 95% and 70% to 85%, respectively. However, the hazard functions for reoperation differ greatly between mechanical and biologic prostheses. Because of structural degeneration, biologic prostheses demonstrate a late rise in risk of reoperation (Fig. 80-42).¹⁷⁵ After reoperation, risk of death and reoperation are higher than after the primary operation, and increase with each successive reoperation (see Fig. 80-41).¹⁷⁵

Minimally Invasive Mitral Valve Surgery

A minimally invasive approach to valve surgery must permit performance of a procedure equal or superior to that of the reference standard median sternotomy approach. Therefore, minimally invasive mitral valve surgery must be as safe, effective, and durable as the traditional “open” approach. In addition to benefits of improved cosmesis, minimally invasive mitral valve surgery was pioneered with the intent of reducing morbidity, postoperative pain, blood loss, hospital length of stay, and time to return to normal activity.

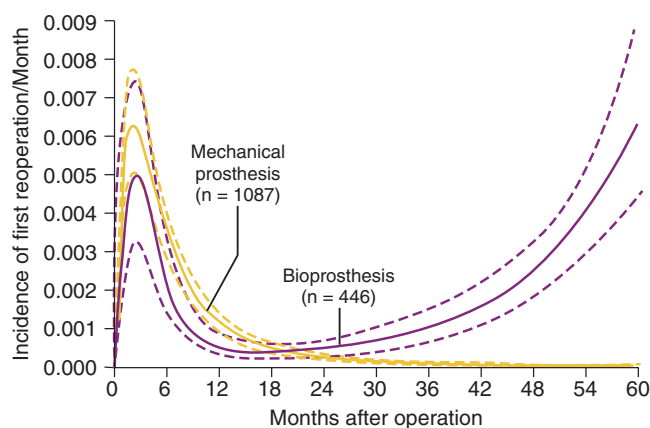


FIGURE 80-42 ■ Hazard of reoperation after mitral valve replacement with a mechanical or biologic prosthesis. While both prosthesis types demonstrate early peaking phases, the hazard function for biologic prostheses also has a late rising phase due to structural valve degeneration. (From Blackstone EH, Kirklin JW: Death and other time-related events after valve replacement. *Circulation* 72:760, 1985.)

Early Mortality and Late Survival

To date, no comparison study has shown a significant difference in operative mortality when comparing minimally invasive mitral valve surgery to that through median sternotomy.^{63,122,203-207} Although reports of initial experiences with port access mitral valve surgery documented mortality rates near 10%,²⁰⁸ recent studies reproducibly demonstrate mortality rates less than 1%, particularly in the case of degenerative mitral valve disease.^{63,122,124,203} Intermediate and long-term results are also encouraging. Propensity score matched comparisons of minimally invasive and sternotomy approaches to mitral valve surgery reveal similar survival up to a decade after surgery.^{63,122,204} In an analysis of 402 well-matched patient pairs at the University of Pennsylvania with mitral regurgitation of any etiology, the 1-, 5-, and 9-year survival was 96%, 96%, and 96%, respectively, after minimally invasive mitral valve repair, and 97%, 92%, and 89%, respectively, following the conventional approach ($P = 0.8$; Fig. 80-43).⁶³

Residual and Recurrent Mitral Regurgitation

Operative approach does not appear to have a significant effect on the likelihood of successful mitral valve repair, with near 100% repair rates achieved for degenerative mitral valve disease through minithoracotomy.⁶³ Durability of the repair is also similar regardless of operative approach. Svensson and colleagues¹²² found that the return of 3+ to 4+ mitral regurgitation after repair at 1 and 5 years were 4% and 5% after minimally invasive surgery, and 6% and 7% after conventional surgery, respectively ($P > 0.1$).¹²²

Postoperative Bleeding and Transfusion

Reductions in postoperative bleeding and transfusion requirements after minimally invasive mitral valve surgery are likely due to smaller incisions and less extensive

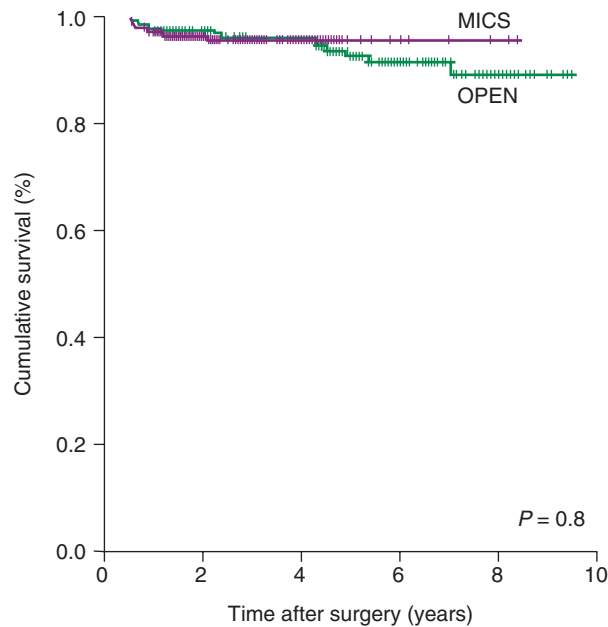


FIGURE 80-43 ■ Actuarial survival after mitral valve repair performed via conventional sternotomy or minithoracotomy in a propensity score-matched cohort. *MICS*, Minithoracotomy approach; *OPEN*, median sternotomy approach. (From Goldstone AB, Atluri P, Szeto WY, et al: Minimally invasive approach provides at least equivalent results for surgical correction of mitral regurgitation: a propensity-matched comparison. *J Thorac Cardiovasc Surg* 145:753, 2013.)

mediastinal dissection.* In a propensity score-matched comparison, Svensson and colleagues documented significantly less mediastinal drainage in patients who underwent mitral valve surgery via partial lower sternotomy.¹²² Others have also demonstrated significant associations between less invasive mitral valve surgery and reduced bleeding and transfusion (12% vs. 20% of patients transfused, $P = 0.04$).⁶³ Finally, three separate meta-analyses reported significant reductions in postoperative bleeding and transfusion requirements when surgery was performed via right minithoracotomy or partial lower sternotomy.^{206,207,213} As blood transfusion is associated with an increase in crude risk of major infection, reduction in transfusion requirement may improve both resource utilization and care quality.²¹⁴

Pulmonary Function

The benefit of minimally invasive approaches to mitral valve surgery on pulmonary function remains uncertain. A number of studies, including meta-analyses, documented reductions in the duration of mechanical ventilation when minimally invasive approaches were utilized.[†] Furthermore, in a study from a mitral valve reference center, a significantly higher proportion of patients were extubated in the operating room (18% vs. 6%; $P < 0.0001$) and postoperative FEV1 was higher.¹²² Yet, other experienced centers have not shown such a benefit.^{63,205}

It remains undetermined whether expedited extubation is actually a consequence of enhanced preservation of mechanical chest wall functionality and pain control, or whether different management protocols drive the divergence in duration of mechanical ventilatory support.

Length of Stay

Less invasive platforms for mitral valve surgery also have been advantageous in terms of shortening intensive care unit (ICU) and hospital length of stay.[‡] In fact, more than half of the studies identified in a meta-analysis by Modi and colleagues²⁰⁶ reported significant reductions in the length of hospital stay. Although the overall meta-analysis failed to demonstrate a significant reduction in length of hospital stay, a recent meta-analysis that focused on surgery mainly via minithoracotomy documented significantly shorter ICU and hospital stays (approximately 1 day shorter) in patients that underwent less invasive mitral valve surgery.²⁰⁷ This benefit has also been observed in higher risk patient populations, including older people²¹⁸ and obese people.²¹⁹

Postoperative Pain and Cosmetic Benefits

Outcomes such as postoperative pain and scar cosmesis are difficult to interpret secondary to their inherent subjectivity. In a survey of 187 patients who underwent thoracoscopic assisted mitral valve repair, 93% of patients were highly satisfied with the procedure and reported mild or no postoperative pain, and 99% of patients believed that their scar was aesthetically pleasing.²²⁰ Vleissis and Bolling²²¹ used patients as their own controls when they interviewed 22 patients who underwent reoperative mitral valve surgery via minithoracotomy after previous median sternotomy. All patients in the study believed that their recovery was more rapid and less painful than after their original sternotomy. A more quantitative evaluation of procedural success is time to return to normal activity. A handful of experienced centers have documented that patients return to normal activity an average of 5 weeks earlier after less invasive mitral valve surgery than after mitral valve surgery via median sternotomy.^{61,215}

Cost

In the current era of health care reform and economics, procedural cost and resource utilization have become increasingly important. Prior to cost analysis studies, hospital and ICU length of stay were used as surrogate measures of procedural cost. Subsequently, multiple groups have equated shorter hospital stays after less invasive mitral valve surgery to cost savings ranging from 7% to 34%.^{61,64,67} Further economic benefit may stem from lower rehabilitation requirements and lower rates of early rehospitalization.^{61,63} In an in-depth economic analysis of cost differences between minimally invasive and sternotomy approaches to mitral valve surgery, Iribarne and

*References 61, 63, 67, 68, 122, 205, 209-212.

†References 67, 124, 205, 207, 210, 213, 215.

‡References 67, 204, 210, 212, 216, 217.

colleagues²²² concluded that minimally invasive mitral valve surgery was both cost effective and cost saving; minimally invasive operations were associated with average savings of greater than \$9000 per patient.

Robotic Technology

It is important to note that robot-assisted port access mitral valve surgery has become increasingly adopted at certain reference centers. Initial experience with robotic technology has been favorable.^{66,223,224} Experienced robotic surgeons have demonstrated that the standard surgical mitral repair techniques are replicated with robot assistance and allow for safe and effective repair of all types of leaflet prolapse.^{66,223} In addition to the benefit of reduced ICU and hospital stays, postoperative survival and durability of mitral valve repair have consistently and reproducibly been comparable to that of the reference standard approach, median sternotomy.^{66,223}

Risks

Despite the many benefits of minimally invasive mitral valve surgery, meta-analyses demonstrate that patients may incur an increased 30-day risk of stroke (relative risk [RR], 1.79; 95% confidence interval [CI], 1.35-2.38), aortic dissection/injury (RR, 5.68; 95% CI, 1.23-26.17), and groin infection (RR, 5.62; 95% CI, 1.26-25.13).²⁰⁷

Learning Curve

Although there is a growing demand for minimally invasive mitral valve surgery, its adoption has not been as widespread as expected. In an analysis of the Society of

Thoracic Surgeons Adult Cardiac Surgery Database, Gammie and colleagues⁵⁵ found that among centers that perform less invasive valve surgery, the median number of minimally invasive mitral valve surgeries performed was only 3, and robotic surgery was only performed in 7.2% of database contributing institutions.⁵⁵ The limited adoption of less invasive mitral valve surgery is likely in part a consequence of the steep learning curve associated with these platforms, particularly robotic cardiac surgery. Chitwood and colleagues²²⁵ demonstrated that rates of repair failure fell from 7% to 4.5% after the first 100 robotic mitral valve procedures. Suri and colleagues²²⁶ noted significant reductions in operative times following the first 50 robotic cases. Most recently, Holzhey and colleagues²²⁷ analyzed 3895 mitral valve surgeries performed via right minithoracotomy by 17 surgeons. With the aid of cumulative sum sequential probability analysis, they concluded that the typical number of operations to overcome the minimally invasive learning curve was between 75 and 125. In addition, more than one minimally invasive operation per week was necessary to sustain acceptable results.²²⁷ Thus, a true learning curve exists for minimally invasive surgery of the mitral valve, and given the heterogeneity of individual learning curves, good mentoring in the initial phase is critical. However, as minimally invasive surgeons must perform the same technical operation through smaller incisions, aptitude in mitral valve surgery via the conventional approach is recommended before transitioning to endoscopic platforms.

Percutaneous Technology

Catheter-based cardiovascular interventions have proven particularly effective in the treatment of coronary artery

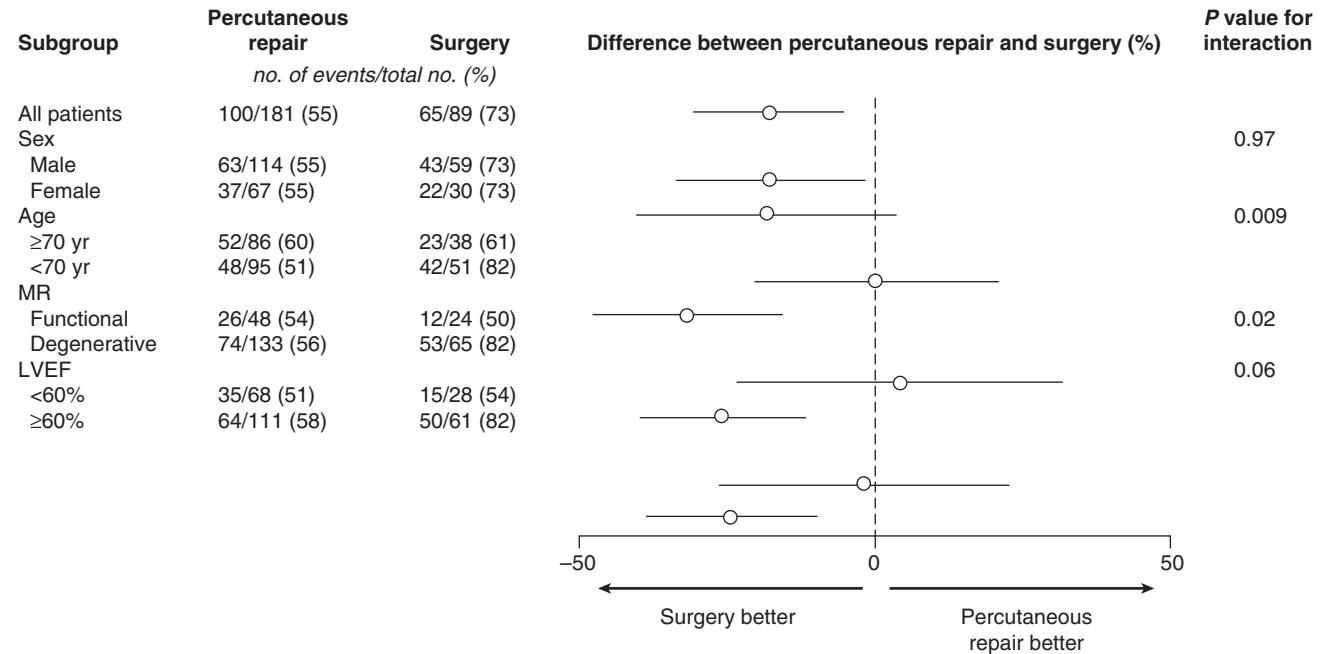


FIGURE 80-44 ■ Differences in rates of freedom from death, mitral valve surgery, or 3+ to 4+ mitral regurgitation between patients who underwent percutaneous repair or conventional mitral valve surgery. Also shown are subgroup analyses for the study cohort. LVEF, Left ventricular ejection fraction; MR, mitral regurgitation. (From Feldman T, Foster E, Glower DD, et al: Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 364:1404, 2011.)

disease. Recently, there has been rapid adoption and implementation of percutaneous treatments for structural heart disease, specifically transcatheter aortic valve replacement. Efforts to recreate the complex surgical techniques of mitral valve repair with catheter-based technologies, however, have been less successful. Alfieri's edge-to-edge technique⁹¹ effectively constructs a double-orifice mitral valve by affixing the anterior and posterior leaflets, but in the contemporary era of mitral valve repair, is generally used as a secondary repair modality. The MitraClip (Abbott Vascular, Abbott Park, IL) replicates the edge-to-edge repair, and is the first catheter-based mitral valve repair system approved for use in the United States. However, initial experience with the device demonstrated poor early and late correction of mitral regurgitation in clinical trials.^{228,229} A phase III comparison of the MitraClip with conventional mitral valve surgery, the EVEREST II trial revealed similar safety outcomes between approaches, but the benefit of reduced blood transfusion requirements was offset by limitations of procedural efficacy (Fig. 80-44).²²⁸ Twenty percent of patients randomized to the MitraClip required salvage with mitral valve surgery due to significant residual mitral regurgitation at 1 year,²²⁸ and approximately 25% needed reoperation at 4 years.²²⁹ Regrettably, salvage mitral valve repair was not possible in nearly half of cases, presumably from physiologic leaflet scarring in response to the clip.²²⁹ Thus, the MitraClip should be reserved for inoperable or prohibitively high-risk patients, as "clip first" strategies may ultimately prevent subsequent mitral valve repair in a significant proportion of patients who may have truly benefitted from the reference standard operation. Additional transcatheter therapies are in earlier stages of development, and they reduce mitral regurgitation via annular reduction or neochordal implantation. As is evident in conventional mitral valve repair, perhaps the most effective and durable transcatheter repair strategy will use more than one repair technique and will be tailored to the cause of the mitral regurgitation. Transcatheter mitral valve replacement devices are likewise in early stages of development and investigation.

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SURGICAL TREATMENT OF TRICUSPID VALVE DISEASES

Carlos A. Mestres • Jose M. Bernal • Jose L. Pomar

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The Controversy: Prophylaxis?

The Research

The tricuspid valve is often ignored by cardiologists and surgeons because of its unique characteristics. It is frequently called “The Forgotten Valve,” and there still is scant information regarding the effects of tricuspid valve diseases on the prognosis of cardiac patients.^{1,2} With the exception of infective endocarditis, primary isolated lesions of the tricuspid valve are rare. There are just a few reports on isolated congenital, rheumatic, tumoral, or ischemic diseases. Frequently, the prominent effect of other valve diseases minimizes its importance. Located at the entrance of the heart, the tricuspid valve, when diseased, produces symptoms that are primarily extracardiac and often silent. The behavior of the tricuspid valve is closely related to the function of the right ventricle; in most cases, tricuspid regurgitation is secondary to right ventricular failure. It follows the dictates of the mitral

valve; resolution of the mitral valve problem is often followed by improvement in the degree of tricuspid regurgitation. As the right heart is a low-pressure system, it is difficult to evaluate its preoperative importance and to assess the value of different surgical techniques. These characteristics often lead cardiologists and surgeons to ignore the tricuspid valve. However, the developments in diagnostic tools, and echocardiography in particular, have increased the awareness of this valve, which has been called the “Cinderella” of all cardiac valves.³

SURGICAL ANATOMY

Situated at the base of the heart, the tricuspid valve separates the right atrium from the right ventricle.

Traditionally, it has been accepted that the tricuspid valve consists of three very thin leaflets attached to the tricuspid valve annulus.

Tricuspid Valve Annulus

Whereas the base of the anterior and posterior leaflets is attached to the free wall of the right ventricle, the septal leaflet is inserted into the base of the interventricular septum. This line of leaflet attachment, known as the tricuspid valve annulus, is more a landmark than an actual fibrous ring. This absence of an encircling fibrotic structure explains the large changes in the tricuspid valve orifice during the cardiac cycle and its easy dilation in disease. The mobility and size of the tricuspid valve orifice are dependent on the transversely oriented myocardial fibers that surround the atrioventricular valves according to the breaking studies on anatomy and function by Torrent-Guasp and colleagues⁴ and Buckberg and colleagues⁵ over the past 15 years.⁵ Tsakiris and associates⁶ found in a canine model that the size of the tricuspid valve orifice changed continuously during the cardiac cycle. The orifice area contracted (from its maximal diastolic size) by 20% to 30%. Tei and associates⁷ confirmed these findings in humans with echocardiography. Hiro and colleagues⁸ and Jouan and colleagues,⁹ working with Duran, analyzed an ovine model for the changes in the normal tricuspid valve orifice during the cardiac cycle as detected by the changes in distance between ultrasound crystals placed around the line of insertion of the leaflets (Fig. 81-1). The tricuspid valve orifice area expands and contracts twice during the cardiac cycle. Orifice contraction begins during the isovolumic relaxation phase of the cardiac cycle and continues through the first half of diastole. Starting with the beginning of isovolumic contraction, a second contraction occurs during ejection, which reduces the tricuspid valve orifice to its minimum area. This contraction corresponds to closure of the valve completed at the end of isovolumic contraction.

The reduction in orifice perimeter is not uniform. The segment of the annulus corresponding to the septal leaflet shortens by 12%, the anterior segment by 15%, and the posterior segment by 17%.⁸ The dilation of the annulus occurs in the anterior and posterior segments, and the dilation of the septal segment is restricted because of the relationship with the cardiac fibrous skeleton.¹⁰ This narrowing of the tricuspid valve orifice is due not only to contraction of its perimeter but, more important, to changes in the shape of the annulus. During contraction, the orifice becomes more elliptical because of displacement of the anteroposterior commissure toward the septum and the bulging of the septum. As in the mitral valve, the “annulus” is not in a single plane. In fact, the tricuspid valve annulus is saddle shaped, with its horn or pommel corresponding to the area of the antero-septal commissure and its cantle to the midpoint of the base of the posterior leaflet (Fig. 81-2). This saddle shape or hyperbolic paraboloid, well known to architects as an ideal design to reduce building tension, has been shown in the mitral valve to significantly reduce peak leaflet stress.¹¹ Furthermore, the increase in the saddle shape during contraction has a “folding” and reducing effect on

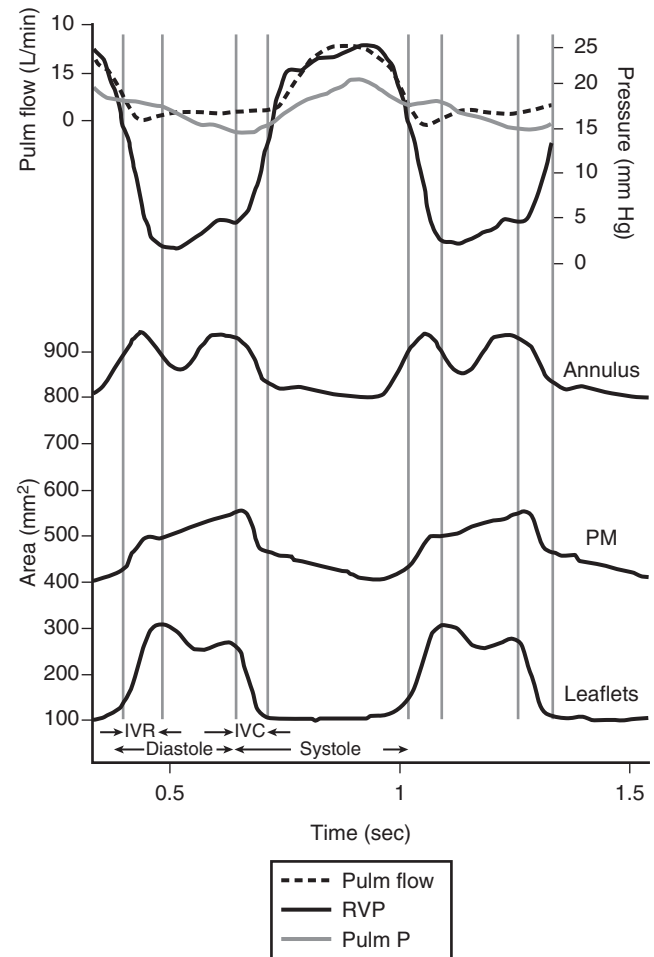
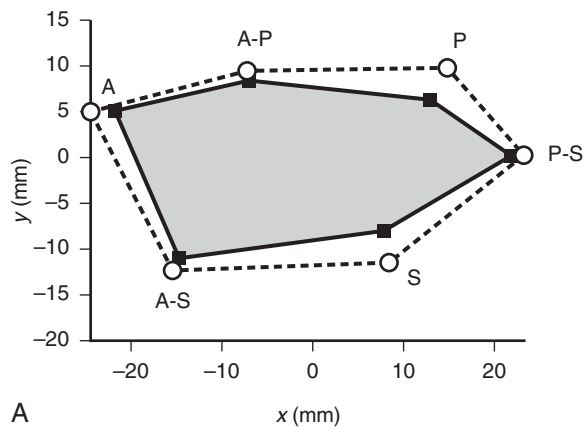


FIGURE 81-1 ■ Changes in the normal tricuspid valve during the cardiac cycle. *Top*, Pressure curves of blood flow in the pulmonary artery (Pulm flow), the right ventricle (RVP), and the pulmonary artery (Pulm P). *Bottom*, Changes in the areas delineated by the ultrasound transducers placed around the tricuspid annulus (Annulus), the tips of the three papillary muscles (PM), and the free edges of the three leaflets (Leaflets) during two cardiac cycles. These recordings allowed the cardiac cycle to be split into diastole, systole, isovolumic contraction (IVC), and isovolumic relaxation (IVR). (Reproduced with permission from Jouan J, Pagel MR, Hiro ME, et al: Further information from a sonometric study of the normal tricuspid valve annulus in sheep: geometric changes during the cardiac cycle. *J Heart Valve Dis* 16:511–518, 2007.)

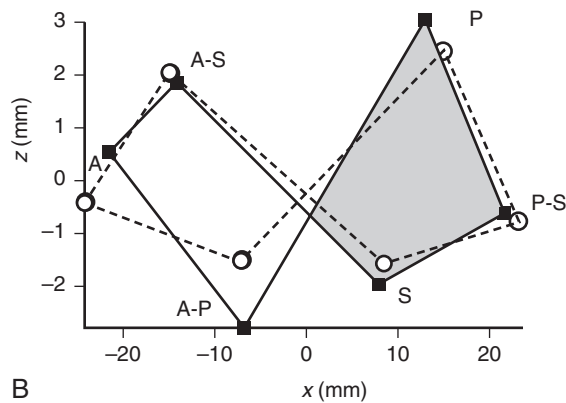
the normal tricuspid valve orifice. In cases of tricuspid regurgitation, besides an increase of tricuspid valve annulus area, there is an increase in planarity or flattening of the normal annulus, which induces leaflet tethering.¹² Rigid structures, such as stented prostheses and rigid annuloplasty rings, destroy this configuration and are likely to have a negative impact on the function of the right ventricle.

Leaflets

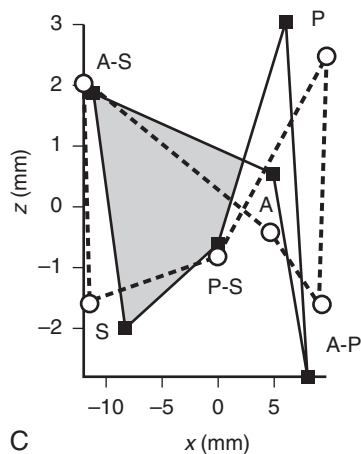
Although the number of tricuspid valve leaflets varies according to author,^{13,14} it is generally accepted that the tricuspid valve consists of three leaflets. These three leaflets are known as *anterior*, *septal*, and *posterior*, and they



A



B



C

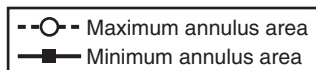
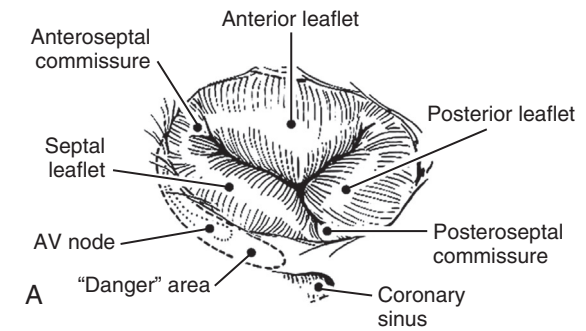
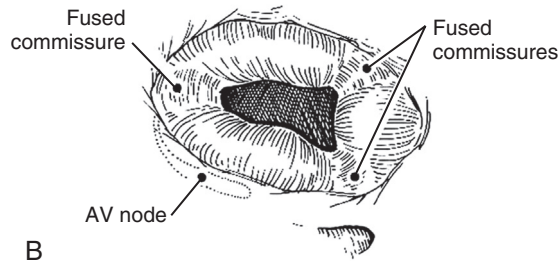


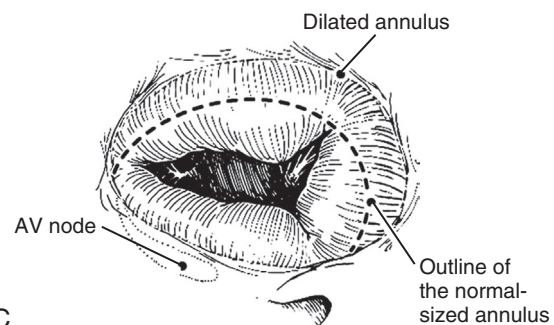
FIGURE 81-2 ■ Geometric changes of the normal tricuspid valve annulus during the cardiac cycle. Orthogonal representations of the tricuspid valve annulus at maximum (dotted line) and minimum (continuous line) area during the cardiac cycle. Circles and squares represent the location of transducers at the mid-point of the bases of the anterior (A), posterior (P), and septal (S) leaflets and at the anteroposterior (A-P), anteroseptal (A-S), and posteroseptal (P-S) commissures. Two relative maxima can be noted in the x-z (B) and y-z (C) planes. P and A-S represent the pommel and the cantle of the tricuspid valve's saddle shape. The representation of the x-y plane is shown in A. (Reproduced with permission from Jouan J, Pagel MR, Hiro ME, et al: Further information from a sonometric study of the normal tricuspid valve annulus in sheep: geometric changes during the cardiac cycle. *J Heart Valve Dis* 16:511–518, 2007.)



A



B



C

FIGURE 81-3 ■ Atrial view of the normal (A), stenotic (B), and insufficient (C) tricuspid valve. AV, Atrioventricular. (Reproduced with permission from Duran CMG: Duran ring annuloplasty of the tricuspid valve. *Oper Tech Thorac Cardiovasc Surg* 8:201–212, 2003.)

are separated by three clefts or commissures named *anteroseptal*, *anteromedial*, and *posteroseptal* (Fig. 81-3A). These clefts do not reach the annulus but delineate small “commissural leaflets.” This is an important surgical point because in cases of fused commissures, their incision should not extend all the way to the annulus; doing so destroys the commissural leaflets. The largest leaflet is the anterior, followed by the posterior, with the septal being the smallest. The excursion of each leaflet (defined as the angle between leaflet free edge and the plane of the annulus) is different.⁹ The excursion of the septal leaflet is significantly smaller than that of the other leaflets. This normal, smaller septal excursion might explain the finding at surgery of a septal leaflet plastered against the septum. This finding, often seen in cases of functional regurgitation, is a sign of severity and is a predictor of a poor result after repair.

Chordae Tendineae and Papillary Muscles

The leaflets are held down by marginal and basal chords that arise from three papillary muscle groups. The

marginal chords are inserted into the leaflets free margin, and the basal chords are inserted into the ventricular surface of the leaflets. Elongation or rupture of the marginal chords results in leaflet prolapse. The basal chords of the tricuspid valve, although far less prominent than the mitral valve basal chords, probably play a similar role in maintaining valvular and ventricular geometry. In most tricuspid valve cases, three papillary muscle groups are found and can be identified as anterior, posterior, and septal. Whereas the anterior and posterior muscles are virtually always present, the septal muscle might be absent in 20% of patients. The anterior papillary muscle is the longest; it most often has a single head and sustains the largest number of chordae.^{15,16} Elegant anatomic studies by Victor and Nayak in hearts harvested at random confirm that every heart has a unique chordal configuration.¹⁷

Terminology

New surgical techniques demand deeper knowledge of the anatomy of the region and, consequently, more precise terminology. A common set of anatomic definitions is needed to report precise preoperative and postoperative echocardiographic information important to both the echocardiographer and the surgeon. Aiming to standardize all anatomic findings, Kumar and colleagues¹⁸ developed a detailed tricuspid valve terminology that parallels previously described mitral valve nomenclature. Although it is based on a surgical, atrial view of the valve, their terminology encompasses all three elements of the tricuspid valve apparatus (i.e., leaflets, chords, and papillary muscles).¹⁶

This alphanumeric system is based on the three papillary muscle groups as defined by the numerals 1 for the antero-septal, 2 for the postero-septal, and 3 for the antero-posterior groups of muscles. Each leaflet is identified with the initial letter of its traditional name: *S*, septal; *A*, anterior; and *P*, posterior. Because the lesion does not often affect the whole leaflet or is limited to the chordae, each leaflet is divided into two areas identified by the papillary origin of the corresponding chords. For instance, the septal leaflet (*S*) is divided into two halves (*S*1 and *S*2), identified by the chords that originate from the antero-septal papillary muscle⁴ or the chords that originate from the postero-septal papillary muscle.⁶ The commissures (*C*) are identified by their papillary origin (1, 2, or 3) as *C*1, *C*2, and *C*3. All chords are identified by their papillary origin and leaflet insertion.

Although it is initially confusing, this nomenclature makes it possible to pinpoint the exact location of a lesion and to describe the surgical maneuvers applied. Its use is particularly significant for reporting of chordal disease and chordal replacement.

Anatomic Relationships

The area corresponding to the antero-septal commissure is close to the aortic root noncoronary sinus of Valsalva (Fig. 81-4). This fact has important surgical implications because placement of anchoring sutures for a tricuspid valve prosthetic device can be difficult at this level if a

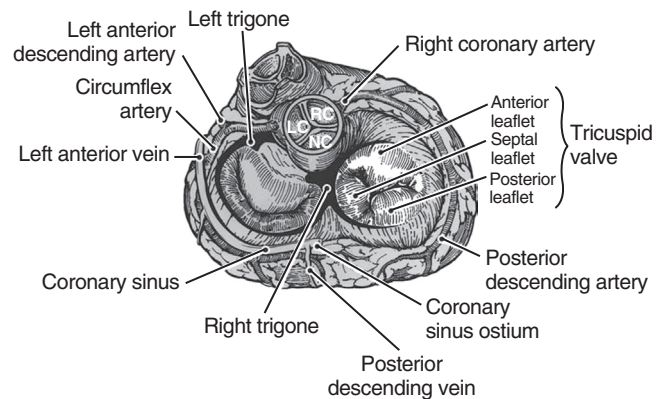


FIGURE 81-4 ■ Base of the heart showing the anatomic relationships of the tricuspid valve. (Reproduced with permission from Duran CMG: Duran ring annuloplasty of the tricuspid valve. *Oper Tech Thorac Cardiovasc Surg* 8:201–212, 2003.)

stented aortic prosthesis is already present. When a concomitant aortic valve replacement is planned, it is preferable to place the tricuspid valve sutures before undertaking the aortic valve replacement, because tears at this level can be difficult to repair. Of course, the experience and expertise of the operating surgeon finally dictates the operative procedure.

The right coronary artery and sinus run parallel to the segment of the annulus corresponding to the right ventricular free wall. Despite this proximity, injury to these vascular structures in performing a valve replacement or annuloplasty is extremely rare. The ostium of the coronary sinus is situated above the postero-septal commissure. Because of its distance from the conducting system (close to the right trigone), it is safe to place a pursestring suture around the ostium of the coronary sinus to hold a retrograde cardioplegia cannula. This simple anchoring technique described by Martinez-Leon and colleagues¹⁹ more than 25 years ago allows for a reliable positioning of the retrograde cannula.

PATHOPHYSIOLOGY

Tricuspid valve lesions have traditionally been classified into two groups: organic and functional. These classifications have an important effect on both the type of surgery performed and its long-term results. Organic lesions are those in which the valve apparatus is macroscopically abnormal (see Fig. 81-3B). Functional lesions are those in which regurgitation occurs in the presence of an apparently normal tricuspid valve apparatus (see Fig. 81-3C).

A different classification, proposed by Carpentier²⁰ in relation to the pathology of the mitral valve, distinguishes three main types of disease according to the mobility of the tricuspid valve leaflets: type I, normal leaflet motion with annular dilation; type II, increased leaflet motion owing to leaflet prolapse that is secondary to chordal rupture or elongation; and type III, reduced leaflet motion due to leaflet thickening, fused commissures, or leaflet tethering.

BOX 81-1 Causes of Organic Tricuspid Valve Disease

Infective endocarditis
 Rheumatic fever
 Degenerative (myxomatous)
 Traumatic damage
 Postinfarction damage
 Carcinoid
 Appetite-suppressant drugs
 Endocardial fibroelastosis
 Lupus erythematosus
 Tumors (myxoma)
 Mediastinal fibrosis

Organic Tricuspid Valve Disease

A variety of etiologic factors can induce organic regurgitation, but still today the most frequent cause of organic tricuspid valve disease in urban populations is infective endocarditis (Box 81-1). Tricuspid valve endocarditis used to be relatively rare, with an incidence of only 5% to 10% of patients with infective endocarditis; however, its frequency dramatically increased with the spread of intravenous drug abuse,^{21,22} with a peak incidence until early in the beginning of the twenty-first century.²³ In this population, the tricuspid valve usually has no preexisting pathologic change. The lesions vary from isolated vegetations to total destruction of the valve, including the annulus. *Staphylococcus aureus* remains the most common organism found in drug addicts, followed by gram-negative organisms and *Candida* species. Fungal infections are also increasing because of longer periods of invasive monitoring of patients with multiorgan failure in intensive care units.²⁴

In the so-called developing world, rheumatic fever is the primary cause of organic valvular heart disease. Typical lesions show varying degrees of leaflet thickening and (most often) commissural fusion. In severe cases, the thickened leaflets become diaphragm-like, with a central circular orifice (see Fig. 81-3B). The subvalvular apparatus is seldom affected, and calcifications are rare. Although tricuspid valve stenosis is the classic lesion, predominant insufficiency is just as common. In a series of 253 patients with rheumatic heart disease who underwent tricuspid valve surgery, Prabhakar and colleagues²⁵ found that organic involvement was present in 45% of the cases and that 45% of them also had annulus dilation. In a classic study of 100 postmortem hearts with rheumatic disease, Gross and Friedberg²⁶ found microscopic evidence of inflammation in the annulus of all four valves (in the acute rheumatic attack). Rheumatic tricuspid valve disease is always associated with rheumatic mitral valve or mitral-aortic valve lesions. The incidence of chronic rheumatic tricuspid valve disease associated with rheumatic mitral valve disease varies widely, from 6% in an echocardiographic study²⁷ to 33% in an anatomic series²⁸ and 11% in the series of Prabhakar and colleagues²⁵ of 1052 patients undergoing rheumatic valvular surgery. In a Mayo Clinic surgical pathology study of excised tricuspid valves at the time of valve replacement,²⁹

postinflammatory etiology was responsible for 53% of the 363 valves studied. However, this frequency had diminished from 79% during the period from 1963 to 1967 to 24% during 1983 through 1987, reflecting the reduction in the incidence of rheumatic fever in the United States as it happened across Europe. Out of these regions, rheumatic heart disease is still a major epidemiologic problem. Leaflet tears and total or partial avulsion of a papillary muscle head occur after closed chest trauma. They are occasionally diagnosed at surgery and only classified postoperatively as traumatic by the patient, who recalls an old accident when prompted by the surgeon.³⁰⁻³² As imaging has greatly improved in the past two decades, traumatic tricuspid regurgitation is better diagnosed and characterized.³³⁻³⁴

An occasional cause of traumatic tricuspid regurgitation is that induced by the bioprobe during a right myocardial biopsy in transplanted patients. Leaflet tears or chordal avulsion results in severe regurgitation that may require urgent surgery.³⁵⁻³⁷

Degenerative tricuspid regurgitation associated with mitral valve prolapse is being increasingly observed. This double valve lesion is particularly frequent in Marfan syndrome as a manifestation of a fibrilopathy that also involves the aortic valve and ascending aorta. The reported frequency of tricuspid valve involvement among patients with mitral valve myxomatous disease ranges between 21% and 52% at all ages.^{12,38-40} Less common causes include organic tricuspid valve lesions secondary to carcinoid syndrome and appetite-suppressant drugs.⁴¹⁻⁴³ In both cases, the leaflets are encased by a fibrous sheath that reduces their mobility, resulting in stenotic and regurgitant lesions. Other rare causes are listed in Box 81-1.⁴⁴⁻⁵³

Functional Tricuspid Regurgitation

Functional tricuspid insufficiency is understood to be exclusively due to annulus dilation and dysfunction (see Fig. 81-3C). The leaflets, chords, and papillary muscles are otherwise normal. Because of the lack of an anatomic fibrous annulus, the tricuspid valve annulus follows the dilation of the right ventricle. The total perimeter of the normal annulus is approximately 100 to 120 mm. In cases of functional tricuspid regurgitation, the circumference of the annulus can reach 150 to 170 mm.⁵⁴⁻⁵⁵ This annulus dilation is nonhomogeneous. In a postmortem study that included normal controls and hearts with rheumatic or myxomatous tricuspid valve disease, Carpentier and colleagues⁵⁶ showed that the anterior and posterior segments of the annulus dilated far more than the septal portion of the annulus (Fig. 81-5). This report, 40 years ago, formed the basis for all annuloplasties that selectively reduce the whole annulus except at the level of the septum. The role of the papillary muscles in this setting is debatable, although it can be considered a correctable influencing factor.⁵⁷

In congestive heart failure, functional tricuspid regurgitation is a predictor of poor survival⁵⁸ and may be an independent risk factor for the development of cardiac cachexia and protein-losing enteropathy.⁵⁹ Cardiac cachexia continues to be a major risk factor in valvular

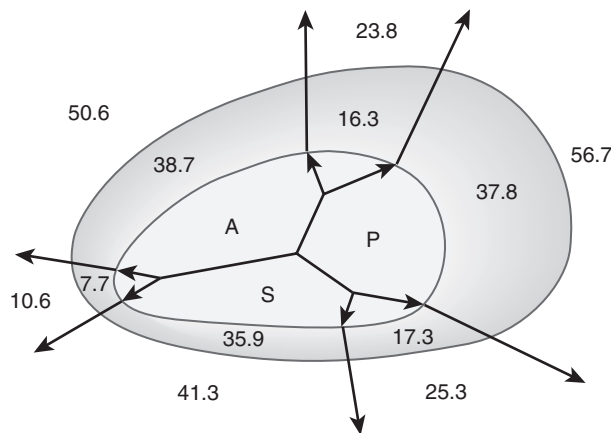


FIGURE 81-5 ■ Diagram of the tricuspid valve annulus showing the normal (inner ellipse) and myxomatous (outer ellipse) valve in centimeters. A, anterior leaflet; P, posterior leaflet; S, septal leaflet. (From Carpentier A, Deloche A, Hanania G, et al: Surgical management of acquired tricuspid valve disease. *J Thorac Cardiovasc Surg* 67:55, 1974, with permission from Excerpta Medica, Inc.)

surgery of any origin.⁶⁰ Koelling and colleagues⁶¹ studied a total of 1436 patients with left ventricular systolic dysfunction (ejection fraction < 35%). Mitral regurgitation was moderate in 30% and severe in 19% of patients. Moderate tricuspid regurgitation was present in 23% and severe in 12% of patients. Patients with severe mitral regurgitation were more likely also to have tricuspid regurgitation. The association is clear and it is confirmed that the severity of tricuspid regurgitation is related to the degree of congestive heart failure.⁶²

Advances in echocardiography have revealed another subvalvular mechanism that applies to both mitral and tricuspid functional regurgitations. Originally observed in functional ischemic mitral regurgitations, this mechanism also applies to the ischemic tricuspid valve and most probably to all functional insufficiencies.⁵⁷ Right or left ventricular remodeling induces a lateral displacement of one or more papillary muscles that apically pulls through the basal chords the body of the corresponding leaflet. The leaflet becomes tethered down, losing its coaptation.^{12,63} Tethering in tricuspid valve regurgitation can currently be treated with valve augmentation.^{64,65}

Functional tricuspid regurgitation is an expression of right ventricular failure with a generalized distortion of ventricular geometry. Although annuloplasty can reduce or abolish functional tricuspid regurgitation by reducing the dilated annulus, it does not address the altered subvalvular geometry. Atrioventricular valve regurgitation is therefore influenced by extravalvular factors. Surgery addresses the myocardial component and is aimed at correcting the geometric distortion.⁶⁶

Right ventricular failure and subsequent functional regurgitation are to play a role in the current era of transcatheter valves. If transcatheter valves aim at reducing surgical risks in patients who are deemed inoperable or carrying a risk which is considered too high, the technology and technique should be able to offer better outcomes. In transcatheter repair of mitral regurgitation using the Mitra-Clip (Abbott Vascular, Abbott Park, IL), outcomes are influenced by the residual baseline degree

of tricuspid regurgitation. This has been pointed out recently by Ohno and colleagues,⁶⁷ confirming that 30-day primary safety endpoint was impaired in the GRASP Registry (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) patients with moderate or severe residual tricuspid endocarditis. Valve regurgitation negatively influenced death and rehospitalization for congestive heart failure at 12 postoperative months; this is in contradistinction with the results after mitral valve surgery. After mitral valve repair or replacement, the risk of progression of tricuspid regurgitation is low, between 3% and 6% up to 5 years postoperatively. The rationale behind a timely operation on the mitral valve encompasses, too, a reduction in progression of tricuspid regurgitation over time.

DIAGNOSIS

The symptoms of the patient with tricuspid valve disease tend to be minimal and overshadowed by the more apparent left-sided symptoms. Because the tricuspid valve is situated at the entrance of the heart, its symptoms are extracardiac. With the exception of advanced cardiomyopathy, it is now uncommon to encounter a patient with the classic symptoms of venous engorgement, such as peripheral edema, hepatomegaly, and ascites. Tricuspid valve disease is mostly silent; the patient mostly complains of asthenia.

The clinical diagnosis of tricuspid valve disease has always been considered difficult. Before the advent of two-dimensional echocardiography⁶⁸ and its application in the operating room through transesophageal probe,⁶⁹ the surgeon used to explore the tricuspid valve digitally through the right atrium and decide whether to treat or to ignore the lesion according to the intensity of the regurgitant jet. This was a common practice three decades ago. This method has been completely abandoned because of its subjectivity and the inability to detect moderate degrees of insufficiency. Right-sided heart catheterization and ventriculography, which were considered the gold standards for the study of all cardiac valves,⁷⁰ have been superseded by two-dimensional color Doppler echocardiography. Because of its noninvasiveness, reliability, and visual impact, two-dimensional Doppler echocardiography is the best tool for determination of the presence, degree, and etiology of tricuspid valve disease. Although transesophageal echocardiography provides invaluable anatomic information at the time of surgery, transthoracic echocardiography remains the most important examination regarding the tricuspid valve. Besides the better window obtained with transthoracic echocardiography, the main reason for its superiority lies in the notorious temporal variability in the degree of tricuspid regurgitation. This is particularly important in functional insufficiencies, in which changes in blood volume secondary to diuretic administration or vascular tone under general anesthesia can severely reduce the degree of regurgitation. Lack of awareness of these facts and exclusive reliance on intraoperative transesophageal echocardiographic examination often result in ignoring significant regurgitations. The advent

of three-dimensional echocardiography is changing the perception of the estimates in tricuspid valve disease, with the understanding of the superiority of two-dimensional echocardiography.

From a surgical point of view, the essential preoperative information includes the following: whether the patient has tricuspid valve disease and whether it is organic, functional, or mixed; quantification of the degree of regurgitation and the direction of the regurgitant jet; pulmonary artery peak and mean pressures; presence and quantification of transvalvular pressure gradients; maximum and minimum tricuspid valve annulus diameter and its systolic shortening; anatomic features of the valve (i.e., leaflet thickness, mobility, billowing of the leaflet body, location of the prolapsing free edge toward the right atrium); and absence of a patent foramen ovale. It is imperative to be aware that underestimation and overestimation of the regurgitant jet area are possible because of changes in gain, filter settings, angle, and distance of the transducer. Experience is required to gain a three-dimensional concept of the direction, location, size, and number of regurgitant jets as the tricuspid annulus is a dynamic multiplanar structure with regional changes.^{71,72} Color Doppler study can even discover minimal regurgitations in 60% to 100% of the normal population, as documented by Yoshida and colleagues⁷³ in normal subjects to set the basis for current understanding. The so-called physiologic regurgitations are useful to evaluate right ventricular and pulmonary pressures.⁷⁴ Contrast echocardiography is a reliable method for detecting tricuspid regurgitation⁷⁵⁻⁷⁷ and a patent foramen ovale.

Semiquantitative evaluation of the severity of tricuspid regurgitation is based on the degree of penetration of the regurgitant jet into the right atrium. A jet that penetrates 2 cm into the right atrium indicates mild regurgitation. A jet that penetrates 3 to 5 cm is considered moderate regurgitation; if it is accompanied by systolic flow reversal of hepatic or caval veins, it is considered severe regurgitation. A more quantitative assessment of the degree of tricuspid regurgitation is performed by the orifice flow acceleration proximal isovelocity surface area radius method. A radius of 1 to 4 mm indicates mild regurgitation; 5 to 8 mm indicates moderate regurgitation; and greater than 9 mm indicates severe regurgitation.⁷⁸⁻⁸⁰ These methods are considered essential in the evaluation of mitral regurgitation, particularly in the intraoperative evaluation of residual regurgitations after repair, and have the same value in the tricuspid valve. Accuracy in determining the actual degree of tricuspid regurgitation is a crucial point in the surgical decision-making process.

Knowledge of the tricuspid valve annulus diameter is important for the surgeon, but its echocardiographic measurement is difficult because the annulus is not circular. As stated, it is a dynamic multiplanar structure with changing regional behavior as clearly depicted by Owais and colleagues.⁷² Small variations in the orientation of the ultrasound beam can provide radically different measurements. The search has been ongoing for a "critical annulus diameter" beyond which the tricuspid valve should not be ignored by the surgeon. Thirty years ago, Ubago and colleagues⁵⁵ suggested 27 mm/m² as the "critical diameter" above which functional regurgitation

always appeared (Fig. 81-6). Using transthoracic echocardiographic examination of 11 consecutive patients with severe clinical tricuspid regurgitation, Come and Riley⁸¹ reported a nonindexed mean diastolic annulus diameter of 51 mm in the four-chamber view and 54 mm in the short-axis view. Among 15 controls, the mean annulus diameter was 34 mm in the four-chamber view and 33 mm in the short-axis view in what is almost a classical contribution. Goldman and colleagues⁷⁵ suggested 30 mm as the cutoff point between absent or mild regurgitation and moderate to severe regurgitation.

A cutoff point must be found beyond which an annuloplasty will fail. Fukuda and associates⁸² in a preoperative and postoperative echocardiographic study of 216 patients with functional tricuspid regurgitation, found that age, tethering height (distance between annulus plane and leaflet coaptation point), and severity of regurgitation were independent parameters predicting residual regurgitation. Preoperative annulus dimension was not associated with outcome of tricuspid valve annuloplasty. In practical terms, it is safe to consider a nonindexed annulus size beyond 40 mm an indication for surgery. When echocardiographic data are not available or are considered unreliable, Dreyfus and colleagues⁸³ suggested using a ruler to measure the maximal stretched orifice from the anteroseptal to anteroposterior commissures. Patients with a dimension greater than or equal to 70 mm (circumference $\pm$ 140 mm, diameter $\pm$ 44 mm) should undergo annuloplasty. All of this forms the basis for the indication for annuloplasty despite some inaccuracy according to the differences among operators.⁸⁴

Preoperative differentiation between organic and functional tricuspid valve disease is also possible and important. Transvalvular gradients, leaflet irregularities, thickening, and doming are clear indications of organic disease. Transvalvular gradients calculated with continuous wave Doppler echocardiography have been shown to correlate well with cardiac catheterization when catheterization was widely used until echocardiography became an established and preferred diagnostic tool.⁸⁵ The normal mean gradient is less than 2 mm Hg, and the end-diastolic gradient is nearly zero. Significant stenosis of the tricuspid valve may be present with a mean gradient of 3 to 5 mm Hg and an end-diastolic gradient of 1 to 3 mm Hg.⁷⁸ Annulus dilation is most often present in both organic and functional lesions, but it is larger in functional regurgitation.^{54,80}

Three-dimensional echocardiography, although preferred for the assessment of the mitral valve, has expanded knowledge of the geometric changes in the normal and diseased tricuspid valve. It is already providing invaluable information on the annulopapillary complex in any valve condition. Accurate assessment is required.^{12,86-88}

INDICATIONS FOR SURGERY

The current consensus is that most diseased tricuspid valves can be repaired easily. Severe lesions are usually treated, but real or erroneously labeled "moderate" lesions are ignored. The problem in the past used to be often related to the absence of a detailed preoperative

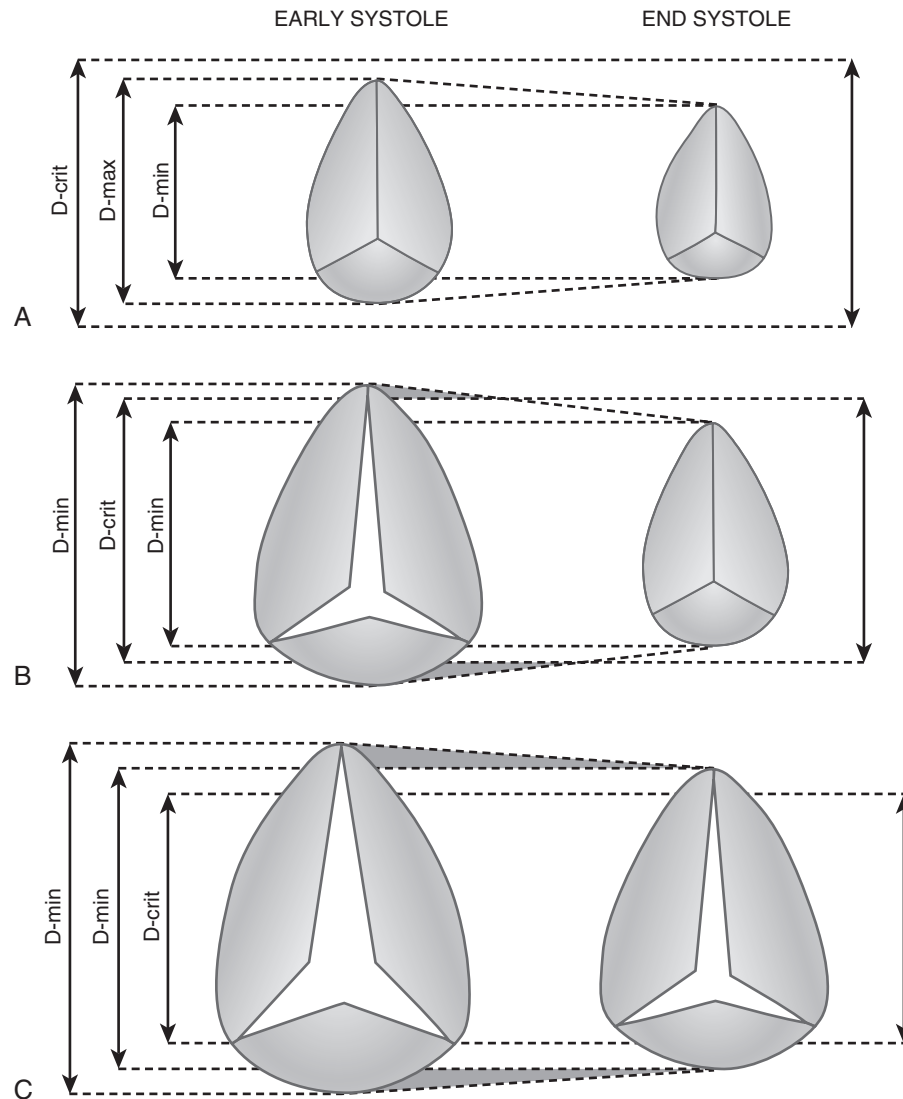


FIGURE 81-6 ■ Diagram of the tricuspid valve. **A**, Patients without regurgitation. Both maximal early systolic (D-max) and minimal late end-systolic (D-min) diameters are below the critical diameter (D-crit) of 27 mm/m². **B**, Patients with mild regurgitation. D-max is larger, but D-min is smaller than D-crit. No cusp apposition occurs during early and mid systole. **C**, Patients with severe regurgitation. D-max and D-min are above D-crit. Pansystolic regurgitation. (From Ubago JL, Figueroa A, Ochoteco A, et al: Analysis of the amount of tricuspid valvular annular dilatation required to produce functional tricuspid regurgitation. *Am J Cardiol* 52:157, 1983, with permission from Excerpta Medica, Inc.)

search for tricuspid valve disease. Intraoperative decision making is unreliable unless the lesion is severe. Preoperative transthoracic echocardiography specifically interrogating the tricuspid valve is an absolute requirement. Current trends in three-dimensional echocardiography result in additional preoperative information per the changing behavior of the tricuspid annulus, which is useful in surgical planning.⁸⁹ The value of intraoperative transesophageal echocardiography cannot be neglected.

Can Tricuspid Valve Disease Be Ignored?

In the early phases of valve surgery, the current knowledge indicated that tricuspid regurgitation in the setting of stenotic valve disease could be solved after mitral valve

replacement.⁹⁰ This conservative approach was based on the assumption of postoperative regression of pulmonary hypertension, which would reduce the tricuspid regurgitation. However, early reports like that of Duran and colleagues⁹¹ stressed the effect of residual tricuspid regurgitation on outcomes and warned on the need for early repair of mitral lesions and tricuspid organic disease, when analyzing 150 patients with mitral valve repair and concomitant tricuspid valve disease. Almost 40 years later, there is agreement that residual noncorrected tricuspid regurgitation is associated with suboptimal or poor outcomes.⁹²⁻⁹⁵ These patients with residual uncorrected regurgitation remain at high risk of cardiac death over the follow-up. Reoperative tricuspid patients requiring valve replacement are clinically in poor condition and increased pulmonary hypertension.^{92,95}

Specific Surgical Indications

The severity of the lesion and its reparability are major drivers for the indication for surgery. As stated, the preoperative clinical condition plays a role in the outcomes, too. Severe lesions demand surgical correction regardless of whether repair or replacement will be performed. Moderate lesions should be treated if repair is expected. This principle emphasizes the importance of a precise and accurate preoperative diagnosis. The advances in imaging have allowed better understanding of tricuspid disease and better surgical planning.

Tricuspid Valve Disease Associated with Left-Sided Valvular Lesions

Previous discussion and accumulated data over time support that tricuspid valve disease associated with left-sided valvular lesions should not be ignored, even if it is mild to moderate ($\geq 2+$). It should be treated at the time of the surgery for the other valves.^{92,93,95}

Organic Lesions

Organic lesions should always be treated.^{91,96} In cases of rheumatic multivalvular disease, ignoring the tricuspid valve lesion on the basis of the small gradient present before surgery is dangerous, because it is likely to become significant postoperatively. This is due to the increase in cardiac output after repair of the left-sided lesions. In addition, the persistence of right ventricular preload will further affect the right ventricle and promote further functional regurgitation.

Traumatic Insufficiencies

Traumatic tricuspid insufficiency of any origin has been increasingly diagnosed because of the development in imaging techniques. This can be due to blunt trauma, defibrillator leads, or endomyocardial biopsies among other causes. Traumatic insufficiencies are virtually always amenable to repair. More than 200 brief reports on traumatic tricuspid regurgitation are currently available, and the vast majority report repairs. In chronic cases, the common finding is a leaflet prolapse because of a fibrotic and elongated papillary muscle head. Repair by plication of the elongated head is not technically complex and is usually successful. Acute tears of a leaflet and avulsion of a chord are treated by resection of the unsupported area with reapproximation of its edges followed by selective reduction of the annulus with an annuloplasty. Polytetrafluoroethylene neochords, following experiences in the mitral valve, have also been attempted in addition to regular repair techniques.⁹⁷

Infective Endocarditis

Right-sided infective endocarditis represents less than 10% of the cases of endocarditis.⁹⁸ Surgery for tricuspid valve is usually not the first option in the setting of infective endocarditis, as more than 95% of the cases are cured with antibiotic therapy. However, in patients with

persistent bacteremia or septic shock, septic pulmonary emboli must be operated. The changing spectrum of the complications of the disease take into account a more aggressive disease.⁹⁹ The rate of successful repair is directly related to the degree of valve destruction. Localized lesion may be easily repaired; a destroyed valve requires replacement.

Functional Tricuspid Regurgitation

Functional tricuspid regurgitation must be treated surgically. The initial conduct dictates repair. The current accumulated information confirms the need for surgery in this setting.⁹⁶ It is clear now that residual tricuspid regurgitation is likely to progress over time, as it has been discussed extensively in the literature and previously in this chapter. Tricuspid annuloplasty, per se, is not an incremental risk factor for mortality and can be performed with the heart beating, according to the experience of the surgeon. Despite the ongoing discussions on whether mild to moderate functional regurgitation needs repair, it sounds appropriate today to perform annuloplasty, especially if there is increased pulmonary artery resistance.^{96,100,101} A maximum valve diameter greater than 40 mm is also an additional indication for repair.

Functional Tricuspid Regurgitation after Heart Transplantation

A special subset of patients with functional tricuspid insufficiency are those with regurgitation that appears after heart transplantation. Possible causes of tricuspid regurgitation after transplantation include distortion of tricuspid valve annulus geometry because of the right atrial anastomosis.¹⁰² It has been shown that the change in surgical technique from biatrial to bicaval anastomosis significantly reduces the incidence of immediate regurgitations, size mismatch of the donor heart, and the pericardial cavity.^{103,104} The bicaval technique results in less tricuspid regurgitation early after transplantation, although long-term outcomes do not show differences in functional capacity in relation with the technique. Patients with moderate or severe tricuspid regurgitation at discharge have an increased mortality during the first five postoperative years.¹⁰⁵

Congestive Heart Failure Secondary to Ischemic or Idiopathic Cardiomyopathy with Mitral Valve Regurgitation

Congestive heart failure secondary to ischemic or idiopathic cardiomyopathy with mitral regurgitation is currently treated by “overcorrection” with an “undersizing” ring annuloplasty.^{106,107} This has proved to be effective in improving clinical condition. Tricuspid valve annuloplasty should be added because tricuspid regurgitation is frequently present. It also avoids the progression of annular dilation. Uncorrected tricuspid regurgitation in patients with cardiomyopathy and mitral regurgitation have worse outcomes. As De Bonis and colleagues¹⁰⁸ demonstrated in an elegant contribution with a somewhat large cohort of 91 patients, tricuspid regurgitation

develops because of progression of the disease or failure of repair. Like in other conditions, the degree of residual tricuspid regurgitation and preoperative right ventricular dysfunction are the predictors for late tricuspid regurgitation. This, therefore, supports an aggressive management of tricuspid regurgitation in this setting.

TRICUSPID VALVE SURGERY

Reconstructive techniques and valve prostheses used in the tricuspid valve are similar to those designed for the mitral position. The evolution of the surgery for atrioventricular valves in the past four decades has mostly relied on the Carpentier^{20,109} and Duran^{110,111} techniques as a reference for repair. Replacement devices have been designed for atrioventricular valves with no specific design differences.

Surgical Approaches to the Tricuspid Valve

The approach to the tricuspid valve is easy because of its anatomic location. It can be visualized through a midsternotomy or a right thoracotomy. Unless an isolated tricuspid valve lesion is contemplated, the type of thoracotomy and incision are dictated by the concomitant surgery on the other valves. A standard or a minimally invasive approach can be used safely.¹¹² To establish cardiopulmonary bypass, separate superior and inferior caval and ascending aorta cannulations are used. The right atrial incision is started close to the appendage and directed toward the posterior aspect of the atrium between the right inferior pulmonary vein and the inferior vena cava (Fig. 81-7). This incision minimizes the problem when an accidental tear of the lower extremity of the incision occurs from excessive retraction. The tricuspid valve surgery can be performed easily in the beating heart; however, a number of surgeons prefer cardioplegic arrest. If retrograde cardioplegia is planned, the coronary sinus is located above the posteroseptal commissure and directly cannulated. To ensure maximal distribution of cardioplegia to the whole heart, a pursestring is placed around the coronary ostium. After the retrograde cannula is in place, the pursestring is tightened, the balloon is inflated, and the catheter is pulled outward until it is arrested by the pursestring. This is an old but simple and effective technique to secure the catheter.^{19,113}

In recent years, the principles of a percutaneous approach to the cardiac valves have been applied to the tricuspid valve. It is likely that percutaneous tricuspid valve repair will become widespread because of the accessibility of the valve and the low-pressure environment of the right heart. There is no preferred approach when simultaneous mitral valve surgery is required. A separate biatrial approach is popular, but transeptal approach from the inferior edge of the fossa ovalis or the most complex transatrial septal incision was described by Guiraudon and colleagues.¹¹⁴

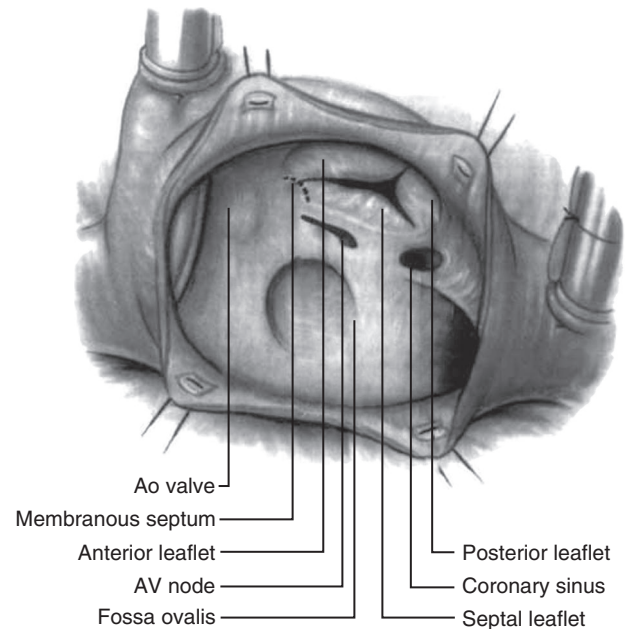


FIGURE 81-7 ■ Surgical view of the tricuspid valve through a standard right atriotomy. The “danger” area corresponding to the atrioventricular (AV) node is located near the anterior half of the base of the septal leaflet. Ao, Aortic. (Reproduced with permission from Duran CMG: *Reoperations on the mitral and tricuspid valves*. In Sabiston DC Jr, Stark J, Pacifico A, et al, editors: *Reoperations in cardiac surgery*, New York, 1989, Springer-Verlag, p 346.)

Tricuspid Valve Commissurotomy

The first closed tricuspid valve commissurotomy was performed in 1952 by Charles Bailey.¹¹⁵ Cardiopulmonary bypass brought more precise techniques like open commissurotomy. Percutaneous balloon dilation has replaced closed commissurotomy, which is based on the principle of splitting the commissures through the distending pressure exercised on the leaflets, although the experience in the tricuspid valve is scant.^{116,117} Tricuspid valve balloon dilation is currently reserved for a small number of patients for whom its minimal invasiveness compensates for its mediocre results. In addition, the low pressure in the right cavities minimizes the importance of the frequent residual gradients and iatrogenic regurgitations. Most tricuspid valve lesions are treated surgically in the setting of advanced mitral valve problems that demand surgery.

In performing an open tricuspid valve commissurotomy, the valve should be inspected carefully because, in severe cases, it can appear as a diaphragm with a central circular orifice and fibrotic edges (see Fig. 81-3B). In these extreme cases, it is difficult to identify the commissures. The subvalvular apparatus is often fairly intact; therefore, a conservative procedure is still possible, although the result may be suboptimal. Valve hooks are placed on either side of the commissure to explore the “fan” chordae always present at the commissures. The incision must ensure that its two edges are supported by chordae. It is often easier to start the incision 4 to 5 mm from the annulus rather than at the edge of the fused

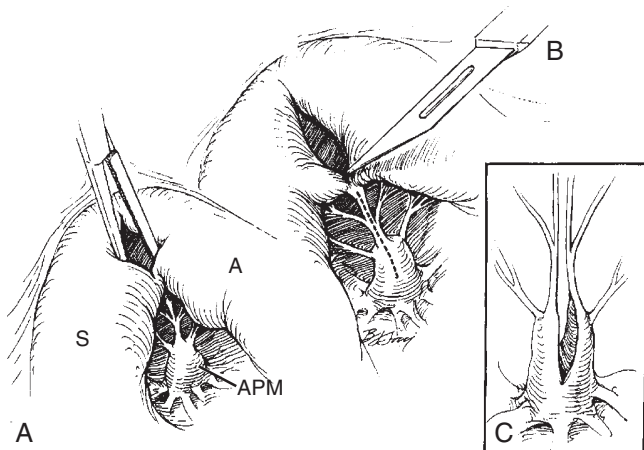


FIGURE 81-8 ■ Tricuspid valve commissurotomy. **A**, Opening of the commissure. **B**, Splitting of fused chordae and papillary muscle. **C**, Split papillary muscle. The anterosseptal commissure is opened distal to the free edge to identify the fused chords. **A**, Anterior leaflet; **APM**, anterior papillary muscle; **S**, septal leaflet. (From Revuelta JM, Garcia-Rinaldi R, Duran CMG: Tricuspid commissurotomy. *Ann Thorac Surg* 39:5:489–491, 1985, with permission from the Society of Thoracic Surgeons.)

leaflets (Fig. 81-8). A better view of the chords will direct the incision toward the free edge. In most cases, two fanlike, thin chords are fused. This incision is then prolonged apically into the papillary muscle for at least 1 cm. The purpose of this essential maneuver is to slow the ongoing fibrotic process and to increase leaflet mobility. At present, these severe forms of commissural fusion are rare in the Western world. Lesser degrees of fusion are frequently present and missed unless the valve is carefully inspected. Often only one or two commissures are affected; the anterosseptal commissure is the most frequently fused. In most cases, a tricuspid annuloplasty must accompany the commissurotomy because of a lack of leaflet tissue or because annular dilation is also present.

Repair Maneuvers

Because most tricuspid valve regurgitations are functional, repair maneuvers other than annuloplasty are less often needed than in mitral valve repair. In acute infective endocarditis, the vegetations must be excised. The vegetation is resected a few millimeters beyond its base in the leaflet. This resection should be in healthy tissue, which is easily identified because of its normal coloration compared with the reddish color of the inflamed area. A triangular resection with its base at the free edge of the leaflet is the best solution. The gap is closed with 5-0 polypropylene sutures. Unless this resection is small, an annuloplasty must follow. Leaflet perforations present in healed endocarditis can be closed with sutures or, if extensive, with a patch of glutaraldehyde-treated autologous pericardium. Fresh autologous pericardium should not be used because it will undergo progressive fibrous retraction. Important tissue destructions can be reconstructed with pericardium supported by polytetrafluoroethylene neochords.⁹⁷

Chordal replacement is not as popular as in the case of the mitral valve. Although papillary muscle and leaflet

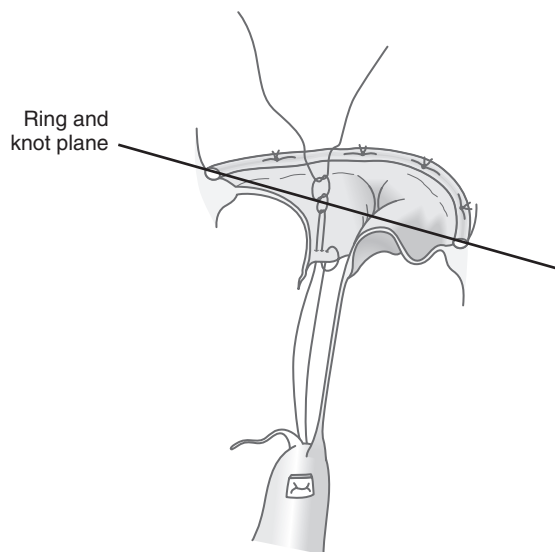


FIGURE 81-9 ■ A simple method to determine the correct length of an artificial neochord. The double-ended suture is anchored to the papillary muscle and passed through the leaflet edge, but not tied. After ring annuloplasty, the suture is tied at the level of the annulus (i.e., the level of the annuloplasty). (Reproduced with permission from Duran CMG, Pekar F: Techniques for ensuring the correct length of new mitral chords. *J Heart Valve Dis* 108:727–735, 1994.)

anchoring of the neochord is not a problem, determination of its appropriate length remains intuitive and based on personal experience, which is globally limited when it comes to the tricuspid valve. Following numerous in vitro approaches to this problem, an easy and simple technique was developed by Duran and Pekar.¹¹⁸ A double-ended, 5-0 Gore-Tex (W. L. Gore and Associates, Flagstaff, AZ) suture is anchored to the papillary muscle and the free edge of the prolapsing leaflet (Fig. 81-9) but not tied. After the annuloplasty ring is placed, the two arms of the Gore-Tex suture are tied at the level of the plane of the annuloplasty. Most failures are due to overcorrection, resulting in a neochord that is too short. To simplify this maneuver, the ring holder incorporates two “guide sutures” that traverse the valve orifice at the level of the annuloplasty. After the ring is in place but still attached to the holder, each arm of the artificial chord is passed on either side of the guiding suture and tied (Fig. 81-10) and the holder is removed. In some cases, a patient may need several neochords arising from the same papillary muscle. Implantation of a new neochord is difficult across the annuloplasty. In these cases, a neopapillary muscle is constructed (Fig. 81-11). A loop of approximately 5 mm is made with a double-ended 2-0 Gore-Tex suture. Each arm of the suture is then anchored to the papillary muscle and secured over pledgets. New artificial chords can then be passed easily through the loop (Fig. 81-12). Because of their simplicity, these techniques have transformed mitral and tricuspid valve repair. The edge-to-edge technique, originally described by Alfieri and his group for mitral valve prolapse,¹¹⁹ has also been applied to the tricuspid valve¹²⁰ to configure a double orifice valve. Leaflet suture approximation techniques including the clover technique have been used on a restricted basis.¹²¹

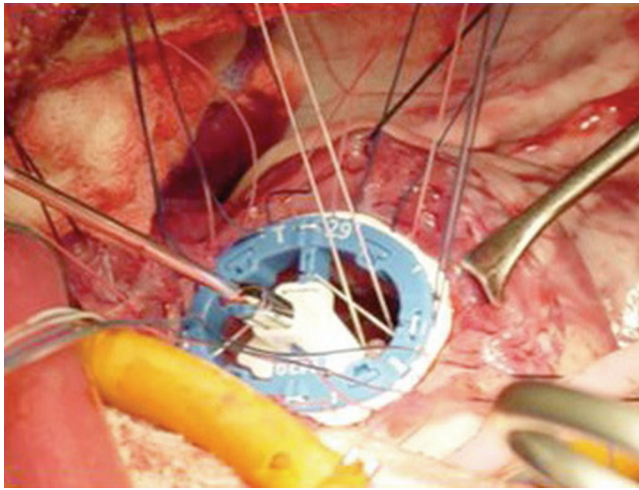


FIGURE 81-10 ■ Intraoperative view: determination of the correct length of the neochord. The annuloplasty ring is already anchored, but the holder is still in place. Each arm of the neochord is placed on either side of the guide and tied at that level. The holder is then removed.

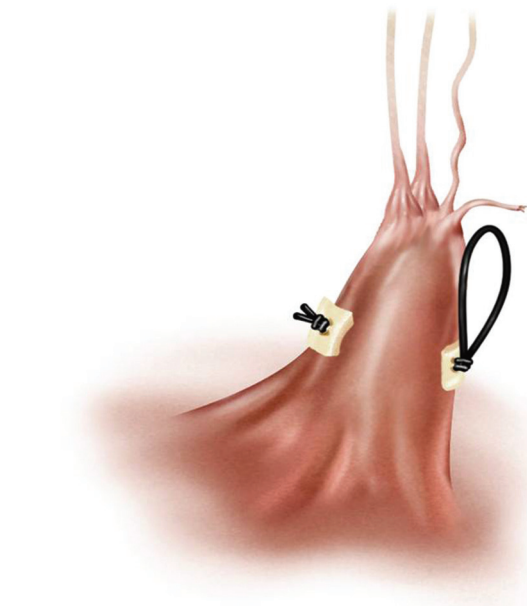


FIGURE 81-11 ■ Neopapillary muscle loop. A 5-mm loop is constructed with 2-0 double-ended Gore-Tex. Each suture's arm is anchored to the medial aspect of the patient's papillary muscle. A number of neochords are passed through the loop.

Tricuspid Valve Annuloplasty

The principle behind tricuspid valve annuloplasty is to selectively reduce the perimeter of the tricuspid valve annulus and, consequently, the size of the tricuspid valve orifice. The lack of leaflet coaptation is compensated by the induced smaller tricuspid valve orifice. The earliest annuloplasties consisted of plication of the annulus at the level of the base of the posterior leaflet. This approach, borrowed from the early mitral valve annuloplasties, was described by Wooller and colleagues¹²² and Kay and colleagues¹²³ (Fig. 81-13). Both have been abandoned

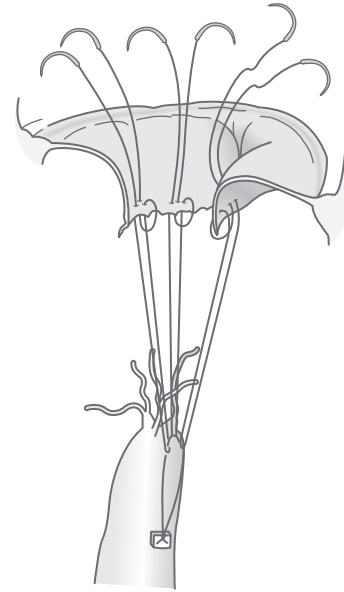


FIGURE 81-12 ■ Multiple neochords anchored by the neopapillary muscle. One loop can sustain all chords corresponding to one papillary muscle. If there is a need to anchor neochords sustained by other papillary muscles, a separate loop must be constructed.

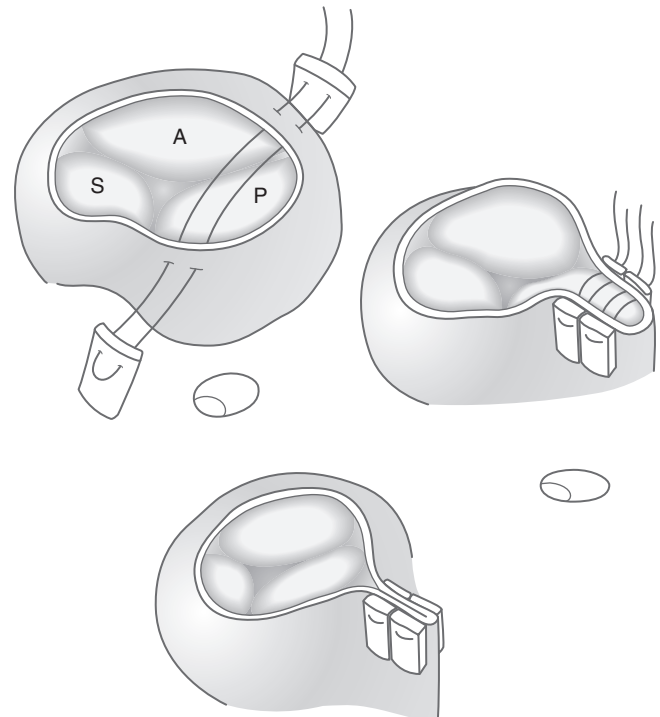


FIGURE 81-13 ■ Tricuspid valve annuloplasty. Posterior annulus plication or Kay procedure. A, Anterior leaflet; P, posterior leaflet; S, septal leaflet. (From Boyd AD, Engelman RM, Isom OW, et al: Tricuspid annuloplasty. Five and one-half years' experience with 78 patients. *J Thorac Cardiovasc Surg* 68:347, 1974, with permission from Excerpta Medica, Inc.)

because of the difficulty in determining the amount of plication necessary and the lack of support for the remaining annulus. Cabrol¹²⁴ and De Vega¹²⁵ independently described a partial encircling suture to narrow the annulus. The extremities of a double suture that runs

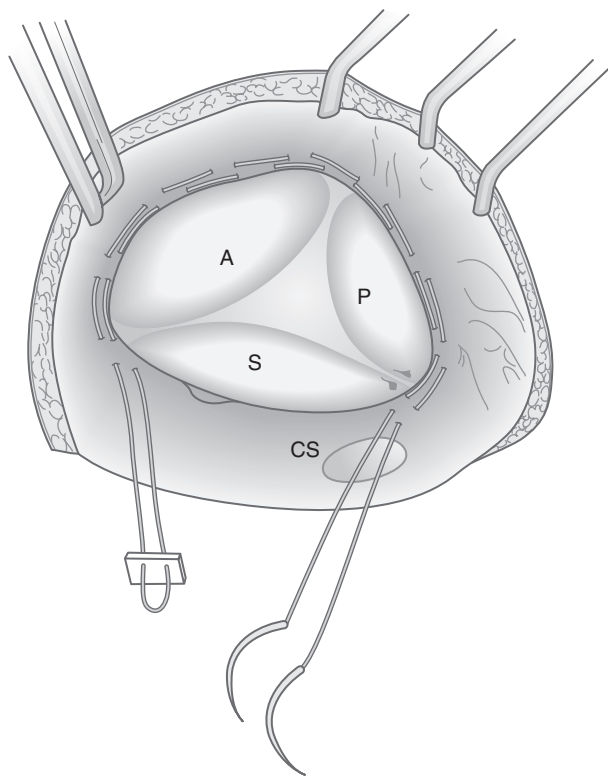


FIGURE 81-14 ■ Tricuspid valve annuloplasty. A de Vega semicircular suture annuloplasty. A, Anterior leaflet; CS, coronary sinus; P, posterior leaflet; S, septal leaflet. (From Imamura E, Ohteki H, Koyanagi H: An improved de Vega tricuspid annuloplasty. *Ann Thorac Surg* 34:710, 1982, with permission from the Society of Thoracic Surgeons.)

along the base of the anterior and posterior leaflets are anchored with pledgets at the anteroseptal and postero-septal commissures (Fig. 81-14). The partial pursestring is tied over an obturator of the desired size. This technique has been popular because of its simplicity and low cost. The De Vega suture-based technique has stood the test of time despite it being heavily criticized because of late recurrence of valve incompetence.^{126,127} The description of Carpentier of a measured rigid prosthetic ring that selectively reduces the annulus opened the era of modern mitral and tricuspid valve annuloplasty.¹⁰⁹ The ring has the systolic shape of the tricuspid valve annulus and is open at the level of the anteroseptal commissure to avoid passing the anchoring sutures close to the conduction system.

As the tricuspid annulus is a dynamic structure with continuous changes in size and shape during the cardiac cycle,^{6,7} a totally flexible and complete ring was developed.¹¹¹ The flexible ring was designed to reduce and selectively reinforce the entire mitral or tricuspid valve annulus with minimal interference in the complex function of the atrioventricular valves. The surgical technique for implantation of a tricuspid valve ring is similar for all types of devices.¹²⁸ Selection of the appropriate ring size is based on the length of the septal segment of the annulus (Fig. 81-15). Large U sutures are placed around the annulus and through the ring (Fig. 81-16). In the septal area, the sutures are passed through the base of the septal

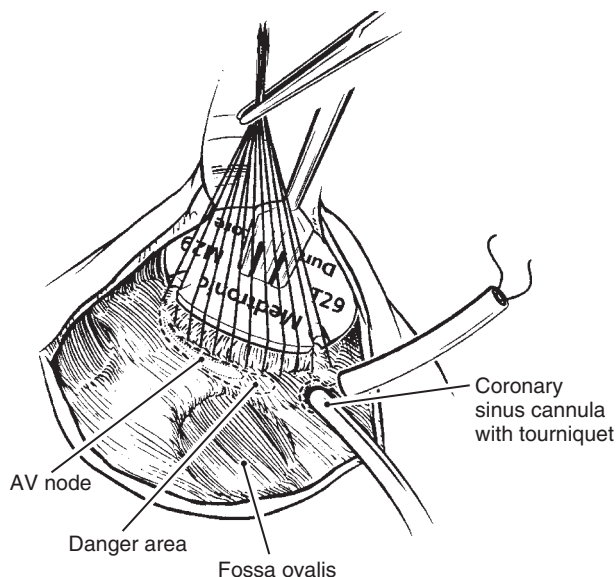


FIGURE 81-15 ■ Tricuspid valve flexible ring annuloplasty: determination of the appropriate ring size by use of the septal annuloplasty anchoring sutures. The length of this segment of the ring and of the septal annulus should be similar. AV, Atrioventricular. (Reproduced with permission from Duran CMG: Duran ring annuloplasty of the tricuspid valve. *Oper Tech Thorac Cardiovasc Surg* 8:201–212, 2003.)

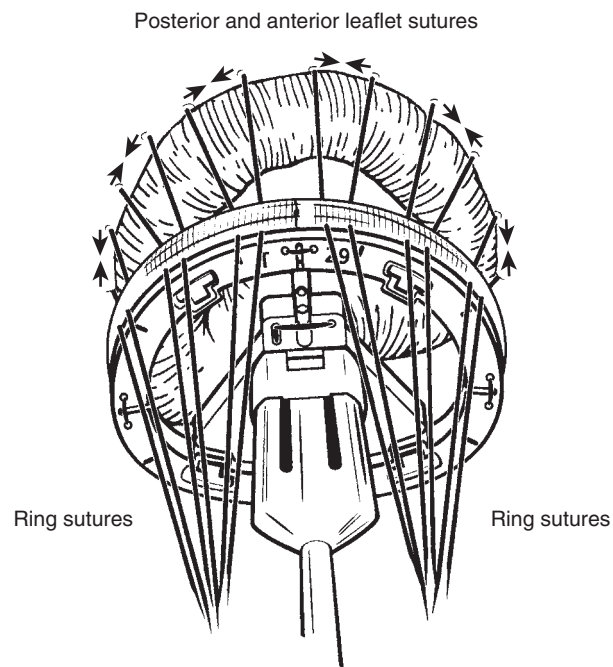


FIGURE 81-16 ■ Tricuspid valve flexible ring annuloplasty: passing of the anterior and posterior annulus sutures through the ring held in the ring holder. Note the selective reduction in the length of this segment of the valve annulus. (Reproduced with permission from Duran CMG: Duran ring annuloplasty of the tricuspid valve. *Oper Tech Thorac Cardiovasc Surg* 8:201–212, 2003.)

leaflet to avoid damaging the conduction system. The ring is brought down and the sutures are tied, reducing the overall perimeter of the tricuspid valve annulus (Fig. 81-17). Open bands that selectively reduce the posterior mitral annulus have been developed and applied to the

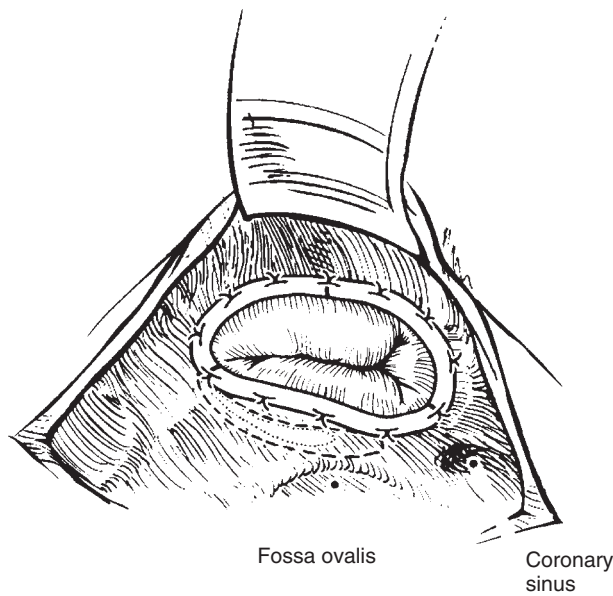


FIGURE 81-17 ■ Tricuspid valve flexible ring annuloplasty: ring in place. The ring sutures have been tied with the ring holder in place, which makes the ring temporarily rigid and therefore avoids plication. (Reproduced with permission from Duran CMG: Duran ring annuloplasty of the tricuspid valve. *Oper Tech Thorac Cardiovasc Surg* 8:201–212, 2003.)

tricuspid valve. In the tricuspid valve, the annulus contention is limited to the base of the anterior and posterior leaflets.¹²⁹ The band designs are based on the assumptions that the intertrigonal distance of the mitral valve and the tricuspid valve septal annulus do not change during the cardiac cycle. However, these areas change continuously in the normal heart¹³⁰ and, more important, also dilate progressively in disease. A partial annuloplasty does not totally protect against further dilation. Although partial annuloplasties are apparently easier to implant than complete rings, they require more expertise (Fig. 81-18).

Tricuspid Valve Replacement

Although the majority of tricuspid valve lesions can be repaired, in some cases the degree of valve destruction is such that it must be excised. The alternatives are excision of the valve without replacement, use of mitral or tricuspid valve homografts, replacement with stented porcine valves or stent-mounted pericardial xenografts, and replacement with a mechanical prosthesis. The epidemic increase in endocarditis caused by drug abuse and the poor rehabilitation of these patients stimulated Arbulu and Holmes¹³¹ to advocate complete excision of the tricuspid valve without replacement. They reported the long-term results of tricuspid valvectomy in 55 patients with mortality of 29% at 13 years after surgery. Although the absence of a tricuspid valve may apparently be well tolerated, the fact that these patients were very young and had normal pulmonary artery pressures must be emphasized.

The expected higher resistance to infection of aortic homografts rekindled an interest in the use of atrioventricular homografts. The first experimental tricuspid

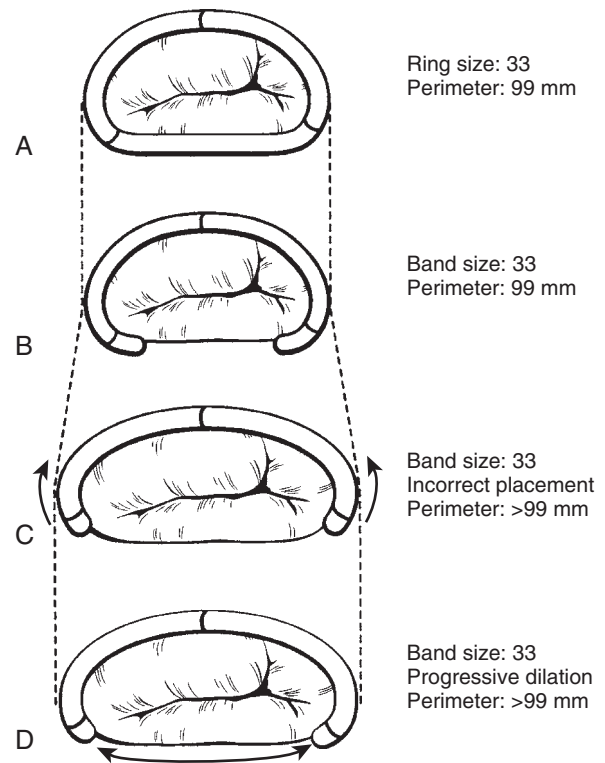


FIGURE 81-18 ■ Tricuspid valve flexible annuloplasties: complete ring versus open band devices. **A**, Ring in place. **B**, Band in place. **C**, Band incorrectly implanted, resulting in a larger tricuspid valve orifice than planned. **D**, Band correctly implanted does not protect against further dilation of the septal annulus. (Reproduced with permission from Duran CMG: Duran ring annuloplasty of the tricuspid valve. *Oper Tech Thorac Cardiovasc Surg* 8:201–212, 2003.)

valve replacements with atrioventricular homografts were performed by Robicksek,¹³² who reported his early results in 1954 and used a homologous tricuspid valve and in 1965 by Hubka and coworkers¹³³ who used a mitral valve homograft. These techniques were followed by isolated, intermittent, and mostly unsuccessful clinical cases until 1993, when we reported successful tricuspid valve replacement with a mitral valve homograft²¹ observed for up to 20 months and di Summa and colleagues¹³⁴ reported the use of a fresh tricuspid valve homograft. Despite satisfactory results over 5 years,^{22,135} the applicability is limited as endocarditis of the tricuspid valve is successfully cured with antibiotic therapy in a large proportion of the cases.⁹⁸

In practice, all tricuspid valve replacements use standard mechanical or stented glutaraldehyde-treated porcine valves or stent-mounted pericardial xenografts. The arguments between the proponents of either alternative are based on the problem of the permanent anticoagulation required with a mechanical prosthesis versus the limited durability of the bioprosthesis. In most cases of tricuspid valve replacement, the entire tricuspid valve apparatus should be retained. Interrupted, pledgeted U sutures are passed along the annulus, incorporating the leaflets. Care must be taken to avoid damaging the atrioventricular node with the septal sutures close to the anteroseptal commissure. In this region, the pledgeted U sutures should be passed at the base of the leaflet,

avoiding myocardial tissue. These riff sutures not only increase the holding power of the stitches but also maintain the continuity between the annulus and papillary muscles, which have been shown in the mitral valve to be essential to ventricular function. The controversy on whether a mechanical or a tissue valve is preferable in the tricuspid position is still active and proponents define the need for anticoagulation and good right ventricular function as preoperative indicators for such an implant.¹³⁶

RESULTS

Annuloplasty

The review of the literature has regularly shown inconsistent results. As the tricuspid valve is a low-pressure system, different degrees of incompetence can be acceptable and well tolerated despite suboptimal results. This was highlighted by Duran and colleagues three decades ago in their elegant review of a series of 150 patients with mitral and tricuspid regurgitation who had preoperative and postoperative hemodynamic evaluations at different intervals extending up to 5 years.⁹¹ All patients had mitral valve repair, and 119 had concomitant tricuspid valve repair; in 31 cases, the tricuspid valve lesion was ignored by the surgeon. Independently of whether the tricuspid valve repair was categorized as “good,” “bad,” or “ignored,” 97% of those with a good mitral valve repair were in functional class I or class II. The quality of the mitral valve repair determined the postoperative cardiac index. At that time and because of these data, strongly emphasizing the need for an early repair of left-sided lesions, these authors were able to conclude that functional TI could be ignored only in patients with predictable and significant reduction in pulmonary vascular resistances and that organic disease of the tricuspid valve must be repaired.

During the 1980s, the superiority of repair over replacement became clearly established. It was shown that repair was possible in most cases including organic lesions. The experience of Prabhakar and colleagues²⁵ with the repair of rheumatic organic lesions with over 90% of patients with satisfactory functional results was encouraging at that time. The absence of valve thrombosis, the unnecessary permanent anticoagulation, and a low reoperation rate have reduced valve replacement to the exceptional case in the case of degenerative or functional disease.^{137,138} The experience of Duran with 306 patients, 92 with proactive tricuspid valve surgery generally indicated in healthier patients yielded in-hospital mortality of 7.5% and actuarial survival rate of 77% at 48 months.¹¹⁰ This relatively low survival at an interval shorter than 5 years indicated that these tricuspid patients were in worse condition than expected. The selection process at that time was negatively influenced by the lack of good imaging of the tricuspid valve preoperatively, intraoperatively, and postoperatively.

These findings favored a more aggressive surgical attitude toward the tricuspid valve, and consequently, earlier indications extended into the lower-risk patients. This attitude has been documented over time with different

devices for tricuspid annuloplasty. The recent experience of Ratschiller and colleagues¹³⁹ is confirmation, although the follow-up for specific devices is still short. The experience over four decades with different techniques of annuloplasty with or without rings or bands confirms that, over time, residual stenosis and regurgitation can become a problem that was documented when early studies showed significant gradients in 50% of patients with a De Vega annular reduction and residual or recurrent regurgitation in 41%.¹⁴⁰ The same occurred with the early types of ring, the Carpentier-Edwards rigid ring (Edwards Lifesciences, Irvine, CA; 48% significant gradients, 31% residual or recurrent regurgitation) when analyzed in early studies¹⁴¹ and the Duran flexible ring (Medtronic, Inc., Minneapolis, MN; 31% significant gradients, 30% residual or recurrent regurgitation).⁵⁴ Technical failures over time, such as ring fracture, were not common although documented.¹⁴² Late factors for ring annuloplasty failure were studied by McCarthy and colleagues¹⁴³ in a large series of 790 patients with functional tricuspid insufficiency; residual or recurrent significant regurgitation graded as 3+ to 4+ was detected in 32% of the patients with the Peri-Guard band (Synovis Life Technologies, St. Paul, MN), 28% with the De Vega suture, 18% with the Cosgrove-Edwards band, and 17% with the Carpentier-Edwards rigid ring. On the other hand, tricuspid regurgitation can develop after successful mitral valve repair for functional ischemic regurgitation, as shown by Matsunaga and colleagues.¹⁴⁴ Almost 50% of patients had significant tricuspid regurgitation at the latest follow-up control after myocardial revascularization and reduction mitral annuloplasty.¹⁴⁴ These results suggested that tricuspid valve reduction annuloplasty might not consistently protect against recurrent functional regurgitation. Functional regurgitation of the atrioventricular valves continues to be a problem, the reason being, as it is currently well known, that cardiomyopathy-induced ischemic disease leads to changes in the right and left ventricular geometry. It is unlikely that the myocardial component can be corrected by any type of prosthetic annuloplasty device of any configuration.² Additional controversy between rigid rings and flexible bands is still active. The lack of controlled studies aiming to shed some light is still a limitation; however, a recent best-evidence topic suggests that although there is relatively less risk of ring dehiscence or fracture in the flexible group, with the rigid ring there is a trend toward a more sustainable and stable postoperative regurgitation.¹⁴⁵

Tricuspid Valve Replacement

Almost 60 years is the interval between the earliest documentation of experimental tricuspid valve replacement and today.¹⁴⁶ It would not be fair to state that things have not changed much when discussing the fate of right atrioventricular valve and orifice in the adult. Cardiac surgery has evolved in a way in which, from a primitive surgical conduct, the current trends are signaling toward a global reduction in the access to the heart following the call of technology.¹⁴⁷ However, the replacement of the tricuspid valve continues to be a challenge for the physicians and

surgeons. As it is clear, the preoperative condition of the patient with tricuspid valve disease dictates outcomes, and these patients usually arrive late and in bad shape predominantly because of right heart failure. Some predictors for failure of repair have been identified in recent years,^{83,148} and the ability of surgeons to achieve a satisfactory anatomic and functional result have rendered tricuspid valve replacement an uncommon operation when compared with mitral or aortic valve replacement in the adult setting.

A number of problems with tricuspid valve replacement are notorious. Despite acceptable results in some series with different types of replacement devices over time,¹⁴⁹⁻¹⁵¹ prosthetic valve dysfunction is a well-recognized condition that carries risk of morbidity and mortality in otherwise usually sick patients.¹⁵² Current data have not been able to show the superiority of a specific prosthetic device.¹⁵³ Speculation about outcomes related to specific factors like gender,¹⁵⁴ among others, has not been confirmed due to the lack of robust data over time.

As tricuspid valve repair is achievable in a large proportion of patients, the published series of tricuspid valve replacement include reduced numbers.¹⁵³ Follow-up has always been a problem in medicine, and it is a key tool to assess the effectiveness of any procedure. There is not an agreed definition of what *long-term* means, and it usually remains a subjective interpretation of time frames depending on what the author wants to report. In cardiothoracic surgery, there has always been an interest in reporting over time. As we enter the sixth decade of valve replacement,¹⁵⁵ we are in a position to analyze actual long-term results of procedures performed by our predecessors. This is the case in valve surgery, which is why we are in need of studies that span a long time, diluting the improvements that have occurred in cardiac surgery. Reports with long follow-up, over two decades, include very different tricuspid valve pathologic processes and often include reoperations.¹⁵⁶ Furthermore, only severe tricuspid valve lesions are treated in poor-risk and evolved patients. Moderate lesions are rarely treated with replacement in current times. The reported hospital mortalities varied between 15% and 25%¹⁵⁶⁻¹⁶⁰ and have not substantially improved in the past 20 years. When isolated tricuspid valve replacement was reported, the hospital mortality went up to 39% in the series of Poveda and colleagues,¹⁶¹ which included patients operated on between 1974 and 1993. When the replacement was subsequent to previous open heart surgery, Hornick and associates¹⁶² reported a hospital mortality of 50% in patients operated on between 1985 and 1993. A more recent experience of 34 patients undergoing isolated tricuspid valve surgery after prior left-sided heart surgery between 1980 and 1997 showed a hospital mortality of 8.8%.¹⁶³ However, at 5 years, the event-free actuarial survival was only 41%. Predictors of poor outcome were the age of the patient, number of previous surgeries, preoperative functional class, congestive heart failure, and pulmonary artery pressure.^{161,162} The published late mortalities were close to 50%¹⁵⁷⁻¹⁵⁹ with survivals of 70% at 3 years for Sanfelippo and colleagues,¹⁶⁴ 47% at 10 years for Thorburn and colleagues,¹⁶⁵ and 41% at 8 years

for Kratz and colleagues.¹⁶⁶ In most series that stretch back to the 1970s, insignificant differences in the overall results are found between mechanical and tissue prostheses for tricuspid valve replacement. Recent series, with or without comparison with tricuspid valve repair, confirm the knowledge that tricuspid valve replacement is associated with long-term cardiac death and valve-related events.¹⁶⁷⁻¹⁶⁹

Standard bioprostheses in the mitral and aortic positions are known to fail because of leaflet tears and calcification, with an incidence of about 25% at 10 years after implantation. There is currently important accumulated information supporting that specific model and tissues have good behavior beyond two decades. Bourguignon and colleagues¹⁷⁰ have recently shown that the actual risk of explant at 20 years of the Carpentier-Edwards pericardial xenograft is 25.5% in a series of over 400 patients followed up to 25 years. Good results have also been reported for other bioprosthesis like the Hancock II, with 20-year freedom from reoperation at 41.4% in mitral patients younger and 61.9% in patients older than 60 years. These can be considered good results.¹⁷¹

However, such complications are rare in the low-pressure pulmonary and tricuspid positions in the adult and children.¹⁷² Ohata and colleagues¹⁷³ reported a comparative study of patients with the Carpentier-Edwards pericardial xenograft in the mitral and in the tricuspid positions. The actuarial freedom from structural deterioration and reoperation at 13 years was 78% for the mitral valve versus 100% for the tricuspid valve. Although these findings would favor the tissue valve, several studies do not show significant differences between mechanical valves and bioprostheses. Carrier and associates¹⁷⁴ in 2003 reported a series of 97 patients with tricuspid valve replacement who were observed for up to 25 years. The overall hospital mortality was 17.5%. Because of their acknowledged preference for the bioprostheses, the authors compared two unequal groups of 81 patients with bioprostheses versus 15 patients with a mechanical valve operated on between 1977 and 2002. No significant differences were found in survival and reoperation rates between the groups. The 5-year actuarial survival was 56% in the bioprosthesis group and 60% in the mechanical group. The freedom from reoperation at 5 years was 97% and 91%, respectively. Describing 435 patients in the U.K. Heart Valve Registry, Ratnatunga and colleagues¹⁷⁵ showed similar survival and reoperation rates of patients with biological and mechanical prostheses. Kaplan and associates¹⁷⁶ also reported similar results among 122 patients averaging 35 years of age at the time of tricuspid valve replacement. Although prosthetic thrombosis and pulmonary embolism occurred in 10 patients, the authors recommended the use of low-profile, bileaflet prostheses. Still, the decision regarding the implantation of a mechanical or tissue valve in the tricuspid position has to be individualized. Songur and colleagues¹⁵³ did not find statistically significant differences over the long-term in their series of 132 patients—one of the largest series. The problem of mechanical valve thrombosis was highlighted by Kawano and colleagues,¹⁷⁷ who reported thrombosis in 6 of 23 patients with a St. Jude Medical valve in their contribution of the year 2000.

Historical series had a proportion of patients dying in whom the actual cause of death was unknown. This might have been due to the lack of postmortem examinations, thus leaving doubts regarding eventual thrombosis.¹⁴⁹ Although thrombosis of a bioprosthesis in the tricuspid position is rare, fibrous pannus formation occurs more often. It leads to progressive stenosis requiring reoperation. Kawachi and associates¹⁷⁸ reported a small series of 23 patients who underwent tricuspid valve replacement with a standard Hancock bioprosthesis. All patients were observed for up to 16 years. The actuarial freedom from structural degeneration was 94% at 10 years. This also occurred in mechanical valves, but only brief reports have been made available.¹⁷⁹ The evolution of imaging techniques has allowed for better visualization of the atrial and ventricular aspects of the valves, thus providing better chances of accurate diagnosis. Three-dimensional echocardiography and more recently multidetector computed tomography have improved our ability to assess atrioventricular prosthetic heart valves.¹⁸⁰

It is difficult to confirm at this point in time if tissue valves are superior to mechanical valves for tricuspid valve replacement. The fact is that there are no large series supporting the superiority of one over the other. The series of Songur includes 123 patients and is one of the largest published recently.¹⁵³ Hemodynamics alone might not be the problem.¹⁸¹ The danger of thrombosis and the need for a stringent anticoagulation regimen when a mechanical valve is used versus the satisfactory performance of tissue valves tilt the balance toward the bioprostheses. History describes our inability to appropriately address atrioventricular valve replacement and especially in the tricuspid position there is a need for more anatomic and, consequently, more physiologic new tricuspid valve prostheses. The underlying message is that patients requiring tricuspid valve replacement are in poor condition preoperatively, and this is the major driver for increased risk and mortality.

KNOWLEDGE AND EVIDENCE

Knowledge

It is clear that the controversy still exists. After many years of experience with the surgical treatment of tricuspid valve diseases, some topics still are difficult to handle. The type of disease is a key component in the discussion. In Westernized countries, functional tricuspid regurgitation seems to be the most frequent diagnosis¹⁰⁰ with valvular regurgitation mostly developing after left-sided valve procedure. The question is whether the degree of regurgitation matters¹⁸² or whether the effect on myocardial function will affect survival.¹⁸³ Kammerlander and colleagues¹⁸⁴ recently analyzed a series of 91 patients who underwent left-sided surgery and found that although late survival was worse in patients with tricuspid regurgitation, right ventricular dysfunction was associated with survival in these patients. Hyllén and colleagues¹⁸⁵ focused on the role of pulmonary hypertension as part of the disease complex also showing poor right ventricular function.

This confirms the need for further study and reinforces our thinking that tricuspid regurgitation of any origin is detrimental to the right ventricle. It is of interest to notice that this also applies to any nonvalvular procedure as well. Transventricular pacing is becoming also a matter of discussion in current times when all types of intracardiac devices for the treatment of malignant arrhythmias and heart failure are implanted in escalating proportions under an increasing number of more or less powerful indications.¹⁸⁶ The effect of regurgitation after single or multiple lead implantation across the tricuspid valve is definitely not known, and more information is needed to update current knowledge.^{187,188}

Organic disease is still a significant problem in non-Westernized countries, and it continues to contribute to the burden of valve disease¹⁸⁹ and cannot be neglected. Once again, the lack of large series may preclude drawing conclusions, but current knowledge indicates that the problem continues to be the worse profile of patients with long-standing tricuspid regurgitation in patients with rheumatic heart disease. Rodríguez-Capitán and colleagues¹⁹⁰ have recently pointed out the problem in another important series of patients with rheumatic involvement. Rheumatic disease involves all valve structures, which is the reason repair rates are much lower than in functional disease. In Westernized countries the incidence of organic disease may be estimated around 15% for patients¹⁹¹ requiring surgery although some series may show higher incidence.¹⁹⁰ As the results of tricuspid surgery are usually less predictable than its mitral counterpart, there are still gaps between the problem, the proposals, the solutions, and the outcomes. In its elegant contribution, Gonzalez-Santos and Arnaiz-Garcia¹⁹¹ have briefly and thoughtfully addressed the problem.

The indications for surgery of tricuspid regurgitation are becoming clear when it comes to the recommendations. The accumulation of information has led to modifications of Practice Guidelines in the past 5 years; however, in the case of tricuspid surgery, we are still missing well-designed controlled studies. Most of the information comes from observational studies, short series, and expert opinion. Current guidelines show some differences, and the most recent confirm that for both primary and functional tricuspid regurgitation in patients requiring left-sided valve surgery, tricuspid surgery is a must as expressed with class I recommendation.^{192,193} The remaining indications still remain in the IIa level.

Finally, from the methodology standpoint, the lack of prospective controlled studies still makes the decision-making process somewhat uncomfortable. It is not that we may not have the ideal tools for analysis, it is the fact that the tricuspid valve has consistently been neglected by many in the community since the days of Braunwald's contribution⁹⁰; this is easily represented by literature data. As we have already pointed out, a quick search through the United States National Library of Medicine using the terms *aortic valve*, *mitral valve*, and *tricuspid valve* yielded the following number of articles with these terms in the title: 13,608 (44.8%), 14,134 (46.6%), and 2625 (8.6%), respectively. When the search was limited to the twenty-first century, the observed results were

7736 (55.0%), 5238 (37.3%), and 1079 (7.7%). By conducting such a brief, quick, and eventually inaccurate search, we understand that less attention has been paid to a valve that has more than functional impact on late outcomes¹⁹⁴; this highlights the difficulties in achieving evidence as to what the best therapeutic options could be. The series of Rodríguez-Capitán and colleagues¹⁹⁰ is an accurate description of a specific environment; the indications are restrictive and limited to patients with advanced or organic valve disease as discussed by Gonzalez-Santos and Arnaiz-Garcia.¹⁹¹ The ultimate fact is that because of the high proportion of patients with organic valve disease or previous surgery, or both, surgery carries a high risk. Outcomes are frequently suboptimal with high mortality rate and poor functional status.

Evidence

There is little scientific evidence available regarding surgery of the tricuspid valve. Currently, the drivers for evidence are controlled studies, systematic reviews, and meta-analyses. Although international databases are filled with all types of articles related to all forms of treatment of the tricuspid valve, the actual number of published methodologically sound articles is scanty. The recent contribution by Parolari and colleagues¹²⁷ has confirmed that when analyzing the short-term outcomes of ring versus suture annuloplasty, there are only two prospective randomized studies separated by almost 30 years.¹⁹⁵⁻¹⁹⁶ The remaining knowledge is reduced to a number of important retrospective studies. When analyzing long-term outcomes, the same authors found no prospective randomized study. Interestingly enough and despite the lack of controlled studies, the median survival at 14 years after ring and non-ring repair was not statistically different among groups. A different topic is residual tricuspid regurgitation. In this case, patients who underwent ring repair performed better than patients with non-ring repair with statistically significant differences favoring prosthetic ring implantation in functional tricuspid regurgitation. In other words and as expressed by Parolari and colleagues,¹²⁷ the patients with non-ring repair had twofold higher risk of recurrent tricuspid regurgitation; this affected late reoperations.

These studies addressed ring versus non-ring repair in functional tricuspid regurgitation. We know that in the so-called Westernized countries, it is rare to find organic disease, which is more typical of rheumatic valvular involvement. The aftermath of literature search is that we still have limited evidence to produce robust conclusions as to which is the better therapy in specific subgroups of patients. It seems then that the meta-analysis of Parolari and colleagues¹²⁷ and the best-evidence topic constructed around the use of ring or non-ring repair in tricuspid regurgitation by Khorsandi and colleagues¹⁹⁷ support the use of ring repair for moderate or severe tricuspid regurgitation. However, there are still a number of unsolved questions as thoughtfully addressed by De Vega in a recent editorial¹⁹⁸ on the long-term results of Guenther and colleagues¹⁹⁹ who presented one of the largest retrospective series of tricuspid repair with 717 patients undergoing both ring and non-ring repair,

concluding also that ring repair is associated with improved survival and lower reoperation rate. The type of disease, the type of patient, the need for reoperation, and its timing may justify a more selective approach to the patient, as proposed by Yilmaz and colleagues from the Mayo Clinic.²⁰⁰

THE FUTURE

In the past 20 years, we have witnessed the booming of minimal access surgery, which is an established approach to the surgical therapy of cardiac disease. Current trends in sick patients are moving toward decreasing the size of the access and the invasiveness of the procedures, aiming at decreasing the effects on physiology.²⁰¹⁻²⁰³ In tricuspid valve surgery, the main drivers for failure are the long-standing disease, the preoperative condition of the patient, and the number of prior operations. They are clearly interrelated.

Cardiac surgery has changed as imaging has greatly improved preoperative diagnosis. The advent of two-dimensional echocardiography and Doppler velocity analysis represented a step forward helping physicians in better understanding heart valve disease.⁶⁸ Atrioventricular valve physiology is better known because of Doppler echocardiography,²⁰⁴ and accurate estimates of valve regurgitation are the consequence of the input given by Doppler analysis and color-mapping. Doppler echocardiography has been shown to have higher sensitivity than contrast echocardiography.²⁰⁵ Color-flow was shown early to be quick and simple in the interpretation of continuous wave Doppler and was an appropriate companion to Doppler, although there were historically some doubts about the investment needed to purchase the equipment.²⁰⁶

Doppler echocardiography and color-flow mapping has become the most useful tool in diagnosis and quality assessment in surgery. We do not understand an operating room without echocardiography. Postoperative evaluation of any cardiac surgical patient heavily relies on echocardiography. The preoperative assessment of valve lesions and ventricular function before the initiation of an operation and the intraoperative evaluation after completion of cardiopulmonary bypass or after off-pump operations are of utmost importance in adult and pediatric cardiac surgery as, of course, information on morphology and function is required for all types of procedures.²⁰⁷⁻²⁰⁸ As we move toward increasing use of technology, monitoring is a key requirement for improving quality.²⁰⁹ Therefore, imaging and technology are going to play an important part in the future of cardiac surgery.

Imaging

Two- and three-dimensional echocardiography and cardiac magnetic resonance are currently the most important imaging techniques for assessment of valve heart disease. The rapid evolution of echocardiography as a diagnostic tool has led to the implementation of newer techniques like strain imaging. Therefore, we are

learning newer definitions, formulas, and calculations from speckle tracking echocardiography.²¹⁰⁻²¹³ As it happened almost three decades ago, the incorporation of these techniques into clinical practice are to revolutionize our knowledge and approach to tricuspid valve disease.

The morphology of the right ventricle is shaped in a crescent and truncated manner, and it has separated inflow and outflow sections. This complex anatomy plays a role in the prognosis of heart disease, the development of functional tricuspid regurgitation, and the interpretation of pulmonary hypertension. It is generally agreed that the variability in the tricuspid annulus diameter plays a role in the indication for tricuspid annular remodeling through annuloplasty. The measurements of the annular diameter at mid-systole and early diastole and right ventricular volumes are part of the surgical strategy.²¹²

It is then time to gain knowledge in the new quantitative methods in two-dimensional and three-dimensional echocardiography. Ongoing research confirms that there are a number of variables that influence diameters in normal volunteers; therefore, this has to be taken seriously in the consideration of diseased individuals for appropriate surgical planning.²¹² The use of different planes of right ventricular analyses is also useful in estimating the clinical effects of pulmonary hypertension. Transverse and longitudinal right ventricular function are reliable markers for cardiac function and high pulmonary artery pressure, respectively.²¹³ Imaging has therefore evolved into a complex field that is continuously developing and influencing surgical practice. The assessment of tricuspid regurgitation is of utmost importance for the surgeon because of the complexity of a nonplanar structure such as the tricuspid valve annulus. Surgical treatment of tricuspid valve disease is still a challenge as per the decision and execution; however, surgeons have higher-quality preoperative information to navigate more accurately through a complex decision-making process.

Newer Technologies, Newer Devices, Newer Philosophies

The accumulated knowledge on tricuspid valve surgery indicates that tricuspid regurgitation secondary to left heart disease is the most common cause of insufficiency of the right atrioventricular valve. The controversy is still alive as to the superiority of ring versus non-ring repair, and it has been addressed in this chapter. According to recent information, it seems that ring repair¹⁹⁹ might have better long-term outcomes regarding survival and freedom from reoperation; the remaining question is whether improving the design of rings might lead to even better outcomes. It is likely that technology comes into aid in the future.

Rings

Three-Dimensional Rings

The tricuspid valve is a nonplanar structure. Rigid rings were initially not design for such geometry, and a number of prior reports are based on rigid rings like the Carpentier-Edwards ring. The aim of newer rings is to

restore the nonplanar geometry of the tricuspid valve annulus. There is scant experience published so far, but the work of Ratschiller and colleagues¹³⁹ with a novel three-dimensional device (Contour 3D, Medtronic, Inc.) sounds attractive. In their experience, the results have been encouraging up to 2 years of follow-up, with a low rate of residual tricuspid regurgitation at hospital discharge, a low reoperation rate, and an excellent early functional outcome. It is evident that the follow-up is still short and extended follow-up is warranted to ascertain eventual superiority over previously tested devices.

The field of three-dimensional rings has still to sustain the test of time. The available experience is limited in time and figures. A previously tested device, such as the MC3 three-dimensional annuloplasty ring (Edwards Lifesciences), has yet to be supported with long-term outcomes, which is mandatory for any device designed to improve valve competency. Although the concept and some devices have been commercially available for some time, no large series have confirmed results over time.²¹⁴⁻²¹⁶ De Bonis and colleagues²¹⁴ analyzed a series of 140 patients and concluded that the three-dimensional ring provides satisfactory early results that remain stable at midterm follow-up. Actuarial survival at 3 years was 94.8%, and the mean follow-up 23 months. Freedom from tricuspid regurgitation >2 was 88%. Annular dilation leading to residual valve insufficiency after ring annuloplasty alone was not the only mechanism involved.²¹⁴ It is also evident that the future has to bring us robust data based on extended observation on these devices.

Biodegradable Annuloplasty

The concept of “vanishing annuloplasty” is definitely not new. Two decades ago, Duran and colleagues²¹⁷ launched what was a new concept at the time after collecting information from animal experiments in sheep in which the authors performed tricuspid suture annuloplasty. The animals were euthanized, and postmortem examinations showed that the suture material had been replaced with fibrous tissue.²¹⁷ These experiments were followed by a clinical series including 25 patients who had no regurgitation 2 years after DeVega annuloplasty with resorbable material.²¹⁸ What happened in these past 20 years? The concept was not embraced by the community, and little information on clinical series is available. The initial concept of a DeVega annuloplasty using resorbable sutures was replaced with an annuloplasty ring using biodegradable materials, as tested in the animal setting by Kalangos and colleagues.²¹⁹ The animal experiments yielded a complete degradation of the biodegradable suture being replaced with fibrous tissue. No safety concerns were raised because of the implant being close to the left circumflex and the great cardiac vein.

However, there is newer interest in this concept of vanishing annuloplasty despite the lack of robust data over time. Little information is available from reports by Myers and colleagues²²⁰ collecting data on both atrioventricular valves. In addition, the main indication in the adult seems to be infection as analyzed by the same authors.²²¹ The Bioring Kalangos annuloplasty ring

(Bioring, Lonay, Switzerland) has been shown to stabilize the native annulus in a variety of conditions also in the clinical setting.^{222, 223} However, the series are small and the average follow-up is less than 10 years.

The revival of the biodegradable annuloplasty is related to newer developments in biomaterials. A number of biological scaffolds are being developed and intended to be replaced by autologous tissue.²²⁴ There is substantial research going on at the moment with biological scaffolds based on extracellular matrix (ECM) that can be obtained from a variety of tissues. The question is whether these scaffolds can be used for annular stabilization under the same rationale that the prior vanishing sutures were used for annuloplasty. The commercially available ECM patches address leaflet tissue reconstruction. As this is an evolving field, the possibility of annular remodeling using these materials cannot be excluded in the future. Speculation is based on the scant experience in different forms of valve therapy with ECM.

Valves and Techniques

Transcatheter valve implantation is the current revolution in the treatment of patients with heart valve disease. The confusing and imprecise term *structural valve disease* seems to be well related to this newer form of therapy of heart valves. It is difficult to understand the pathology, although the medical community is guilty of resorting to phraseology that relies on commercial interests. This has recently been addressed by De Maria in an elegant editorial.²²⁵ That said, the newer developments in valve technology and technique are related to the evolution of the treatment of this structural disease. In cardiac surgery, there is no room for confusing terminology. Current trends in this field are again toward reducing the surgical access and invasiveness by avoiding cardiopulmonary bypass. As we agreed on the usual poor clinical condition of patients with advanced tricuspid disease and the fact that a significant proportion has a number of prior operations, any form of therapy that may complement an appropriately designed medical therapy is welcome. The options for transcatheter valve implantation in the tricuspid position are currently under investigation. It is to be expected that this evolving field will bring advanced solutions for this subgroup of valve patients.

As in the aortic position, there were pioneering efforts such as using balloon dilation of the native tricuspid valve and prosthetic tricuspid implants more than 20 years ago²²⁶⁻²²⁷ that paved the way for future developments. Encouraged by the initial results of valve-in-valve implantation in the aortic position, several authors have jumped into the tricuspid position and tried the valve-in-valve concept. The positive experiences of transcatheter implantation of valves in the pulmonary position were instrumental in addressing the tricuspid position as well. Valve-in-valve seems to be an attractive concept that needs to undergo the test of time. The initial experience reported by Hon and colleagues²²⁸ opened the door to expand transcatheter approach in this group of usually high-risk patients. Roberts and colleagues²²⁹ reported the first short series of implants in congenital and acquired heart disease including 15 cases with a short follow-up of

4 months.²²⁹ They reported one case of early prosthetic valve endocarditis. There is, therefore, accumulated optimism among cardiologists and surgeons, as this is an approach that may help to reduce the risk of surgery in the setting of advanced tricuspid disease. This is definitely an emerging field in cardiology and cardiothoracic surgery. In the past couple of years, a number of reports addressing complex cases have become available. In some cases, isolated tricuspid implants have been attempted, and there are also combined multivalvular implants with good immediate outcomes.²³⁰⁻²³⁴ Current experiences are mostly related to treating patients in poor condition after prior tricuspid valve operations in which there are degenerated tissue valves or perivalvular leaks.²³⁵⁻²⁴⁰ This growing body of information suggests that the future of percutaneous treatment of tricuspid diseases is going to evolve rapidly. The common issue across recent literature is the risk of patients with single or multiple prior interventions and dysfunctional tissue valves. Congenital and acquired disease will be targeted. It is likely that adult patients with previously treated congenital defects will increase the pool of patients that will develop right heart failure or dysfunction of valves or conduits that were implanted to treat the right ventricular outflow tract.

The Melody stented bovine jugular vein conduit (Medtronic, Inc.) and the Edwards Sapien stented pericardial valve (Edwards Lifesciences, Irvine, CA) have been used in the right atrioventricular position. In all these reports, the behavior of the valve seems to be appropriate although the follow-up is still short, with no reports reaching the mark of 5 years. A multicenter French study has been able to collect 71 cases of transcatheter tricuspid valve implantation for failing tissue valves.²⁴¹ Stenotic and regurgitant lesions were treated. The authors stated that there was procedural success in all, although there were two cases of embolization into the right atrium. This raises, of course, some concerns as to the accuracy in definitions and reporting. Another series from the Mayo Clinic has also reported good periprocedural results in 19 patients.²⁴² The periprocedural problems were related to vascular access. This study also lacks short-term follow-up. Most of the short-term information available is related to the hemodynamic behavior of the implant.²⁴³

As there is limited, if any, information on the follow-up after these procedures, it is also to be expected that some problems develop over time. Whisenant and colleagues²⁴⁴ recently reported thrombosis after valve-in-valve implantation. Early valve failure as described by Bentham and colleagues²⁴⁵ and endocarditis raises some concerns about safety and viability that need to be confirmed in the future as follow-up information is accumulated. Prosthetic valve endocarditis after transcatheter valve implantation is emerging as a new entity of difficult diagnosis and treatment that also entails a high risk.²⁴⁶⁻²⁴⁸ As most of the information on transcatheter valve endocarditis is related to the aortic position, some isolated cases in the right atrioventricular position have also been reported in some of the above-mentioned studies.

What seems clear is that the prospects for the development of the transcatheter valve implantation in the right atrioventricular position are good considering the rapidly

increasing number of reports. As in every case of innovation, it is mandatory to collect robust data on the follow-up.

The Controversy: Prophylaxis?

Do we need to be proactive when dealing with trivial or mild tricuspid regurgitation? Do we need to address marginally dilated annuli? There are a number of questions out there with no clear answer. This is a controversy in the subset of patients with functional tricuspid regurgitation. In the case of heart transplantation, it seems appropriate to perform tricuspid annuloplasty in the donor heart because there is information that confirms reduction of mortality and the degree of valve regurgitation. Suture-based annuloplasty has been advocated by Jeevanandam and others.^{249,250} However, this is not very clear in dilated tricuspid annulus undergoing surgery for degenerative mitral regurgitation. The current guidelines give a class IIb recommendation for annuloplasty when there is mild annular dilation without pulmonary hypertension.²⁵¹ Data from Benedetto and colleagues²⁵² suggest that prophylactic tricuspid valve annuloplasty in patients with dilated tricuspid annulus undergoing mitral valve surgery was associated with a reduced rate of tricuspid regurgitation progression, improved right ventricular remodeling, and better functional outcomes. Furthermore, the decision could be facilitated by intraoperative measurements of the indexed tricuspid annular circumference as suggested by Zhu and colleagues²⁵³ over a value of 83 mm/m². Data from Teman and colleagues²⁵⁴ regarding 21 patients who underwent reoperation for functional tricuspid regurgitation also suggest that a more aggressive approach to annuloplasty in primary mitral operations is to be strongly recommended. A recent systematic literature review and meta-analysis concludes on the need to develop specific scores for identification of patients at risk of developing functional tricuspid regurgitation.²⁵⁵

The Research

There is ongoing research related to the tricuspid valve. Part of this research is aimed at developing models to test the newly developed devices, as there is no information that could be extrapolated into the human setting per the follow-up of transcatheter implants. There is nothing new on this, as the early steps toward percutaneous implantation of valves in the atrioventricular positions were taken two decades ago by Boudjemline and colleagues.²⁵⁶ The technological advance in percutaneous valves owing to the massive investment by the manufacturers has prompted an increase in the number of contributions and the evaluation of the concept in different models. Bai and colleagues²⁵⁷ have developed a simple percutaneous model of tricuspid regurgitation in sheep that may help in the assessment of implants. These authors had previously pioneered tricuspid research by implanting homemade pericardial porcine stented valves in sheep, providing tricuspid competence.²⁵⁸ An acute model of tricuspid insufficiency has been created by Lauten and colleagues²⁵⁹ in sheep with the goal of

investigating the effectiveness of valved stents implanted in the vena cavae with good short-term outcomes. There was significant reduction of venous regurgitation and improvement in cardiac output after the implantation of caval stents. The underlying message is that all efforts are directed toward decreasing the risk of surgery in patients with advanced tricuspid disease.

There is also ongoing research related to tricuspid endocarditis. Tricuspid valve endocarditis is cured with antibiotic therapy in more than 95% of the cases, regardless of the pathogen and mode of acquisition.²⁶⁰ Tricuspid valvectomy was a life-saving maneuver in sick patients with addictive behaviors and was documented by Arbulu and colleagues.¹³¹ However, residual massive tricuspid insufficiency led to severe right heart failure that later required valve replacement. As discussed earlier, there were a number of attempts at evaluating mechanical and tissue valves for replacement in this setting, with disappointing results because of valve dysfunction secondary to persistent addiction, although better results were achieved with mitral valve transplantation into the tricuspid position.²¹ The development of biological scaffolds has opened a new field of research. Recently, Gerdisch and colleagues²⁶¹ reported the experience of a number of surgeons with extracellular matrix cylinders in tricuspid valve endocarditis with promising results.²⁶¹ The intriguing and attractive field of scaffolding will definitely be a part of the future in valve research. The aim is to combine an easy implantation and biocompatibility. This feasibility study has proved that ECM can be used for valve replacement. However, recent additional information suggests that a word of caution is mandatory because of unexpected early failure in a given implant.²⁶² Follow-up information and more discussions are warranted.

A highly innovative approach was introduced recently by Bajona and colleagues.²⁶³ Because functional tricuspid regurgitation is characterized by annular dilation and leaflet tethering in a dilated right ventricle, these authors addressed the right ventricle treating tricuspid insufficiency by inserting a catheter-guided, inflatable balloon across the tricuspid valve to eliminate central regurgitation without hemodynamic compromise. The attractive hypothesis is that a screw-in lead with a percutaneous reservoir for balloon volume adjustment will provide added utility. These ex vivo experiments with calf valves have shown promising results regarding hemodynamics. This is also a field to explore, and more developments are expected.

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NATIVE AND PROSTHETIC VALVE ENDOCARDITIS

Amy G. Fiedler • Lawrence S. Lee • Frederick Y. Chen • Lawrence H. Cohn

CHAPTER OUTLINE

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PROSTHETIC VALVE ENDOCARDITIS

SUMMARY

Endocarditis of a patient's native heart valve is defined as *native valve endocarditis* (NVE), and endocarditis of a prosthetic device is termed *prosthetic valve endocarditis* (PVE). The incidence of NVE in developed countries is approximately 1.7 to 7.0 cases out of 100,000 persons per year and is highest in older adults.¹⁻³ NVE typically affects the left heart, with right heart involvement observed in only 5% to 10%.^{3,4} Whereas the overall incidence of NVE and PVE has remained consistent over the past several decades, the causes and risk factors for both NVE and PVE have changed in recent years from rheumatic heart disease to degenerative valve disease, intravenous drug use, intravascular devices, and nosocomial infections predominating.

NATIVE VALVE ENDOCARDITIS

Pathology

Two conditions must be present for the development of almost all cases of NVE: endocardial injury causing a disruption of the valvular endocardial surface, and subsequent infiltration of the injured site by bloodborne microorganisms, typically bacteria.⁵ Endocardial trauma results from degenerative calcific changes, rheumatic disease, mitral valve prolapse, regurgitant jet flow, congenital abnormalities (e.g., bicuspid aortic valve), or iatrogenic causes (e.g., cardiac catheterization). Endocardial injury results in the deposition of platelet-fibrin products, which then serve as a nidus for the attachment of microorganisms. Organisms that cause NVE enter the bloodstream through compromise of the skin, mucosal surfaces, or other sites of focal infection. Common causes for bacteremia or fungemia that predispose to NVE include

intravenous drug use, indwelling catheters, debilitated condition, medical procedures, and even simple events such as tooth brushing and mastication.⁵⁻⁷

In all cases of NVE, complications and symptoms of the infection may be divided into two categories. Systemic manifestations of the disease result from sepsis and embolic phenomena, such as stroke, kidney failure, or fever. In addition, there are sequelae that are the direct results of infection and the location of the infection with respect to any critical myocardial anatomy.

In native *aortic* valve endocarditis, infection may spread into the aortic annulus, destroy the aortic valve, or result in paravalvular abscess formation. Conduction system pathology may result, including heart block, depending on the extent of the infection. Other complications include cardiac fistulas, coronary and systemic embolization of vegetations, stroke, cerebral infarction, and mycotic aneurysms. Large aortic valve vegetations can prolapse into the left ventricular cavity, contact the anterior leaflet of the mitral valve, and cause subsequent double-valve endocarditis. Typically, aortic insufficiency results from aortic valve endocarditis. Untreated cases can lead to destruction of the fibrous trigones and the tissue between the anterior mitral leaflet and the aorta. Heart failure may occur because of volume overload secondary to aortic insufficiency. Fistulas between the aorta and right atrium are also possible.

The most common site of vegetations in native *mitral* valve endocarditis is the mitral valve leaflet near the annulus on the atrial side. Vegetations may be located anywhere on the leaflets or the chordae, and they may occur on the ventricular side as well. Vegetations and debris may destroy part of the ventricular tissue. Complications include invasion into the atrioventricular (AV) groove proper and abscess formation, with severe cases

leading to separation at the AV junction and complete destruction of the fibrous skeleton surrounding the valve.

Native *tricuspid* valve endocarditis usually affects the free margins of the leaflets with relatively infrequent involvement of the annular tissue. Complications of tricuspid NVE include cardiac and pulmonary sequelae as a consequence of valve destruction and embolism. Tricuspid regurgitation with chamber dilation and right heart failure can result, and local extension can cause abscess and fistula formation. Septic pulmonary emboli lead to pulmonary infarction, pulmonary abscess, empyema, and, in rare cases, mycotic aneurysms of the pulmonary arteries.

Microbiology

Endocarditis is caused principally by staphylococci and streptococci. The most common agents are *Staphylococcus aureus* (32%), viridans group streptococci (18%), enterococci (11%), coagulase-negative staphylococci (11%), and *Streptococcus bovis* (7%).^{8,9} Gram-negative bacteria can also cause NVE and are classified into either the HACEK group (fastidious gram-negative bacilli, including *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) or non-HACEK group, with each accounting for approximately 2% of all cases. These organisms require a prolonged incubation period before growth and are often resistant to many antibiotics. Fungal NVE, usually caused by *Candida albicans* or *Aspergillus fumigatus*, is rare but can lead to devastating complications.^{10,11}

The microbiology of NVE differs somewhat depending on specific individual risk factors and demographics. For example, viridans group streptococci is more prevalent in community-acquired endocarditis, whereas the more virulent *S. aureus* is more common in nosocomial cases.^{1-3,8} NVE of the right heart is predominantly a disease of intravenous drug users, and in this population native tricuspid valve endocarditis caused by *S. aureus* is the predominant form of the disease.⁴

Approximately 2% to 7% of NVE cases are deemed “culture-negative endocarditis” when no microorganisms can be cultured from the blood or tissue samples.¹²⁻¹⁵ This occurs more frequently in developing countries, where fastidious or rare organisms are more likely to cause human infection. The most common reasons for culture-negative endocarditis in developed countries are administration of antimicrobial agents before cultures are taken, inadequate microbiological techniques, and infection with highly fastidious bacteria or nonbacterial pathogens (e.g., fungi). In all cases of culture-negative NVE, it is important to ascertain the absence of any underlying undiscovered infection and to initiate aggressive empiric treatment despite the negative culture data.

Diagnosis

Clinical Presentation

The onset of NVE usually begins with fever and malaise. Common physical examination findings include a new

heart murmur or change to an existing heart murmur, petechiae, splenomegaly, clubbing of the digits, splinter hemorrhages, Osler nodes, Janeway lesions, and Roth spots. The latter two are found almost exclusively in acute endocarditis when overwhelming signs of sepsis are displayed early in the clinical course. The virulence of the offending organism affects the severity of symptoms seen, with less virulent organisms such as viridans group streptococcus causing a subacute, protracted clinical course that often can be cured with antibiotics alone.

Laboratory findings include moderate leukocytosis, anemia without reticulocytosis, and hematuria. Blood cultures must be drawn from separate sites and usually help clinicians identify the infective organisms in cases of bacterial NVE. Cultures should be drawn before antibiotics are started.

Imaging Studies

Doppler echocardiography is the single most useful diagnostic modality for documenting endocarditis.¹⁶⁻¹⁹ Transesophageal echocardiography is the preferred study, with a sensitivity and specificity of 95% and 90%, respectively.²⁰ Transthoracic echocardiography is less sensitive for endocarditis but can be used when transesophageal studies are not feasible. Echocardiography can be used to identify vegetations, paravalvular leaks, abscesses, and fistulas. Patients with NVE and concern for metastatic or embolic disease should undergo further imaging with computed tomography (CT) scans of the abdomen and/or head as appropriate. Embolic involvement of the brain can also be investigated with magnetic resonance imaging (MRI).²¹

Duke Criteria

The diagnosis of endocarditis is based on a combination of clinical findings rather than a single test result. Several classification systems for the diagnosis of endocarditis have been published, but the most commonly used is the Duke system.²² First described by Duke University researchers in 1994, this system uses both clinical and pathologic criteria to confirm or reject the diagnosis of infective endocarditis. There are two groups of criteria: “major” (positive blood cultures, positive echocardiographic findings) and “minor” (fever, predisposing conditions, vascular phenomena, immunologic phenomena, equivocal microbiological findings). Based on the number of criteria met, cases are classified into three diagnostic categories: low clinical likelihood of endocarditis, possible endocarditis, and definite endocarditis. Definite endocarditis is diagnosed by documentation of two major criteria, of one major and three minor criteria, or of five minor criteria. Cases are considered possible endocarditis when either one major and one minor criterion or three minor criteria are identified. Most authorities accept a recently modified version of the Duke criteria, as shown in Table 82-1.²³

Management

Aggressive antibiotic therapy is the first and most important intervention in all cases of NVE. Antibiotics should

TABLE 82-1 Modified Duke Criteria for Infective Endocarditis**Major Criteria****Positive Blood Cultures for Infective Endocarditis**

Typical microorganism for infective endocarditis from two separate blood cultures:

Streptococcus viridans, *S. bovis*, HACEK group, *Staphylococcus aureus*, or community-acquired enterococci in the absence of a primary focus, or

Microorganisms consistent with infective endocarditis from a persistently positive blood culture, defined as:

At least two positive blood cultures drawn more than 12 hours apart, or

All of three or most of four or more separate blood cultures, with the first and last drawn at least 1 hour apart

Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer to *C. burnetii* greater than 1:800

Evidence of Endocardial Involvement

Echocardiogram positive for infective endocarditis: TEE recommended in patients with prosthetic valves, rated at least as "possible endocarditis" by clinical criteria, or complicated endocarditis, such as endocarditis with paravalvular abscess; TTE as the first test in other patients as follows:

Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation

Abscess

New partial dehiscence of prosthetic valve

New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

Predisposition: predisposing heart condition or intravenous drug use

Fever: temperature 38° C (100.4° F) or higher

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions

Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor

Microbiological evidence: positive blood culture but does not meet a major criterion as noted above, or serologic evidence of active infection with an organism consistent with infective endocarditis

HACEK, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

From Li JS, Sexton DJ, Mick N, et al: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 30:633–638, 2000.

be started as soon as possible after obtaining blood cultures. Combination broad-spectrum agents should be administered empirically and then adjusted when culture data are available. Surveillance blood cultures and frequent echocardiograms, at least in the first two weeks after initiating treatment, can help to determine and follow the efficacy of therapy. Surgical intervention is indicated in patients who develop worsening symptoms and continued sepsis despite antibiotics. Early surgical

treatment is often required in cases involving virulent organisms such as *S. aureus* and gram-negative bacteria, as these infections will progress rapidly despite antimicrobial therapy. Fungal infection is an absolute indication for surgery.

For the cardiac surgeon, the first management decision is determining the optimal timing for operation. Should operation be undertaken now or after appropriate antibiotic treatment? Most indications for surgical intervention are not absolute, and therefore the decision to operate must be based on each patient's clinical status and assessment of the risks and benefits. In general, the more serious and persistent the symptoms and complications of any particular endocarditis case are, the more likely surgery should be undertaken sooner. Once the decision to operate has been made, expeditious intervention should occur. If an indication for surgery is identified, surgery should not be delayed to complete antibiotic therapy, as this has been associated with increased mortality.^{24–26}

With either mitral or aortic endocarditis, one common indication for immediate surgery is congestive heart failure. Early surgery in such cases is always warranted, as medical therapy alone is usually ineffective and associated with a poor prognosis. Risk factors for early mortality from NVE include New York Heart Association (NYHA) functional class IV heart failure, cardiogenic shock, advanced age, preoperative acute renal failure, paravalvular extension, and staphylococcal infection.^{24–26} In 2006, the American College of Cardiology and the American Heart Association (ACC/AHA) issued guidelines on the management of valvular heart disease, including recommendations on surgical treatment of NVE (Table 82-2).²⁷ In addition to heart failure, the generally accepted indications for surgery are ongoing sepsis, fungal infection, *S. aureus* infection, myocardial abscess, and recurrent systemic embolism. For aortic valve endocarditis, conduction abnormalities are a relative indication for surgery as well.

One subgroup of patients in whom delayed surgery is beneficial, however, is those with evidence of neurologic complications. A thorough neurologic evaluation should be performed in all endocarditis patients, including head CT and/or MRI studies if necessary, to assess for the type and degree of stroke or embolism. Ischemic embolic stroke is more common than hemorrhagic injury, but both are associated with a significant increase in morbidity and mortality.^{28–31} With cardiopulmonary bypass is the risk that an ischemic infarct may be transformed into a hemorrhagic one as a consequence of anticoagulation.²⁹ Thus, if feasible, any surgery should be delayed for 2 weeks after an ischemic stroke and for 4 weeks after a hemorrhagic stroke to reduce the risks of worsening neurologic symptoms and further intracranial hemorrhage.^{21,31–32} This is often a difficult judgment that must weigh the risk of further sepsis and embolization against the hemorrhagic risk of cardiopulmonary bypass anticoagulation. The possibility of mycotic aneurysms should be evaluated with cerebral angiography if clinically suspected and treated before valve surgery with antibiotics; such aneurysms are a contraindication for anticoagulation as well.

TABLE 82-2 2006 ACC/AHA Guidelines for the Management of Valvular Heart Disease

Class I—There is evidence and/or general agreement that surgery is indicated in patients with native valve endocarditis (NVE) with one of the following:

- Valve stenosis or regurgitation leading to heart failure
- Aortic or mitral regurgitation with hemodynamic evidence of elevated left ventricular end-diastolic or atrial pressures such as premature closure of the mitral valve with aortic regurgitation, rapid decelerating mitral regurgitation signal by continuous wave Doppler (v-wave cutoff sign), or moderate to severe pulmonary hypertension
- Infection caused by fungal or other highly resistant organism
- Complications such as heart block, annular or aortic abscess, or destructive penetrating lesions such as fistulas from the sinus of Valsalva to the right or left atrium or right ventricle, mitral leaflet perforation with infective endocarditis of the aortic valve, or infection in annulus fibrosis

Class IIa—The weight of evidence or opinion is in favor of the usefulness of surgery in patients with NVE who develop the following:

- Recurrent emboli and persistent vegetations despite appropriate antibiotic therapy

Class IIb—The weight of evidence or opinion is less well established for the usefulness of surgery in patients with NVE who develop the following:

- Mobile vegetations larger than 10 mm with or without emboli

From Bonow RO, Carabello BA, Chatterjee K, et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol* 48:e1–148, 2006.

Surgical Considerations

The basic tenets of surgery for infective endocarditis are the same as that for débridement surgery of any abscess or infection. The overall principle and goals are meticulous, aggressive débridement with removal of all infected and necrotic tissue, appropriate reconstruction, and the prevention of further contamination. For most cases of NVE, débridement of the infected valvular tissue followed by “simple” valve repair or replacement remains the mainstay of surgical therapy and can yield satisfactory long-term results for patients who otherwise have a dismal prognosis.

Native Aortic Valve Endocarditis

The most commonly used incision in operations for infective endocarditis is the median sternotomy. This permits adequate exposure for planned operation as well as the possibility for extensive reconstruction if necessary. A low transverse or oblique aortotomy is typically used to access the aortic valve. In cases where the extent of infection is limited to the cusps of the valve leaflets, excision of the valve and replacement with a biological or mechanical prosthesis is usually sufficient to eradicate the

infection. There is some debate about the optimal choice of prosthesis in patients with active endocarditis, but the available evidence suggests that bioprosthetic and mechanical valves are comparable in overall effectiveness and rates of recurrent infection for routine endocarditis.³³ If the infection is extensive and a large abscess cavity exists, then the prosthesis of choice is an aortic homograft with root replacement, as this has been shown unequivocally to have a better cure rate.^{38–41}

Involvement of the aortic annulus requires radical resection of all grossly infected areas, leaving a rim of healthy tissue. Any defects must then be reconstructed before implantation of a prosthetic valve. The type of reconstruction depends on the extent of resection performed. Autologous or bovine pericardial patches may be used for smaller and moderate sized defects, whereas Dacron fabric may be suitable for reconstruction of larger areas or the aortic root.^{34–37} If more than 50% of the annulus has been destroyed or there is extensive ventricular-aortic discontinuity, an aortic homograft remains the treatment of choice.^{38–41}

Aortic root abscess presents a particularly challenging problem, as it can be extensive and involve surrounding structures such as the fibrous trigones, interventricular septum, left and right atria, and pulmonary artery.^{34–35,42–44} Again, the most important goal in these cases is meticulous débridement and resection of all infected and necrotic areas, with secondary concern given to reconstruction of defects. These patients will often require replacement of the entire aortic root with reimplantation of the left and right coronary arteries as well as repair of any involved structures. An aortic valve homograft is preferable when there is involvement of the intervalvular fibrosa, not only because of the extent of infection but also because anterior leaflets of the homograft’s mitral valve can be used as a patch for the affected fibrous trigones (Fig. 82-1).^{41–42,44}

Native Mitral Valve Endocarditis

As in surgery for the aortic valve, the median sternotomy is the preferred approach for mitral valve operations. The mitral valve can be accessed via a left atriotomy through the Sondergaard groove or transseptally. Following radical débridement and resection of all infected tissue, the two general reconstructive options available are valve repair and valve replacement. Mitral valve repair is an attractive option as long as adequate resection of all infected tissue does not compromise the durability of valve reconstruction. In cases with extensive destruction, prosthetic valve replacement is performed. In clinical practice, however, virtually all cases of mitral valve endocarditis are treated with valve replacement. Pericardial pledgets are typically used instead of cloth pledgets when suturing the prosthesis to minimize the amount of foreign material implanted in the setting of an active infection.

Mitral valve endocarditis may be caused by vegetations from aortic valve endocarditis prolapsing into the left ventricular cavity and contacting the anterior leaflet of the mitral valve, resulting in “drop lesions” and subsequent double valve endocarditis. If involvement of the mitral valve is limited to a small portion of the anterior

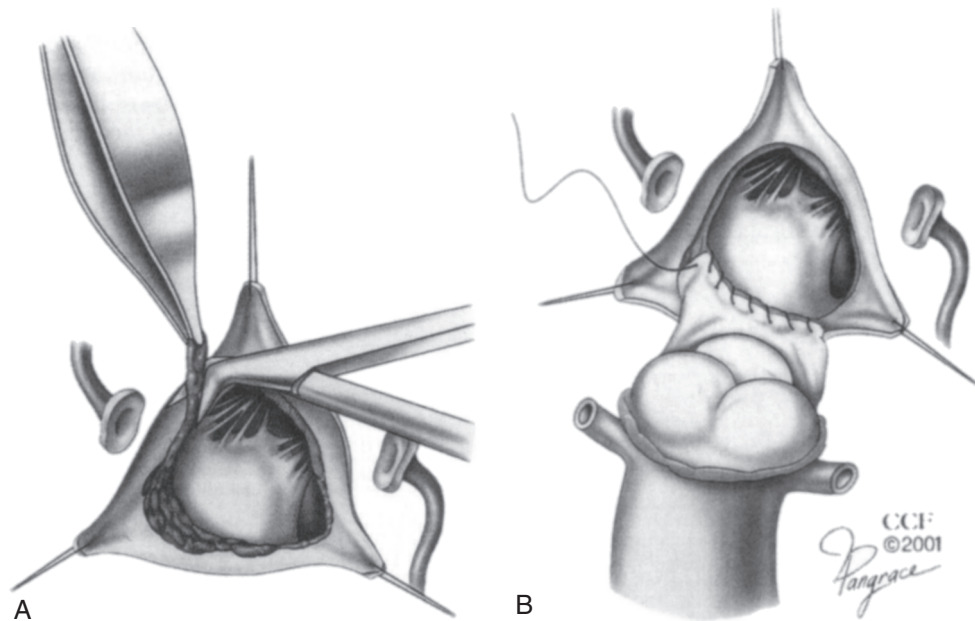


FIGURE 82-1 ■ Aortic root replacement and homograft reconstruction. **A**, The infected tissue is débrided and excised, and the coronary ostia are preserved. **B**, The defect is reconstructed using the mitral valve leaflet of the homograft. (From Sabik JF, Lytle BW, Blackstone EH, et al: Aortic root replacement with cryopreserved allograft for prosthetic valve endocarditis. *Ann Thorac Surg* 74:650–659, 2002.)

leaflet, the affected area can be resected and the defect repaired with an autologous or glutaraldehyde-preserved pericardial patch.⁴⁵⁻⁴⁷ Cases of double valve endocarditis, however, frequently require extensive resection and reconstruction of both aortic and mitral valves. Although pericardial patch repair can be performed to reconstruct the fibrous trigones before valve replacement, in many cases an aortic valve homograft may be a preferable alternative. With the latter, aortic valve and root replacement are performed with the homograft in an anatomic position, and the aortomitral curtain of the homograft is used to reconstruct the base of the native anterior leaflet. If repair is not possible, the mitral valve prosthesis is sutured to the intervalvular fibrosa of the homograft.^{21,38-41,53}

The most frequent site of involvement on the posterior leaflet is the P2 segment. Lesions in this area without concomitant extensive annular destruction are amenable to treatment by quadrangular resection with sliding repair and remodeling annuloplasty. Complex and larger infections that extend into the annulus may necessitate resection of substantial amounts of annular tissue, resulting in sizable defects that require reconstruction of the mitral annulus in addition to valve replacement.

Two different approaches for reconstruction of the mitral annulus have been described by David and Carpentier. The David technique involves the use of autologous or bovine pericardium to reconstruct the annulus (Fig. 82-2).^{43,50-51} A semicircular patch is used to cover the defect, with one side secured to the left ventricular endocardium and the other side sewn to the atrium. The new prosthetic valve is then anchored to the patch. A circular patch can be used in cases where the entire circumference of the annulus must be reconstructed.

The Carpentier technique for mitral annular reconstruction consists of placing figure-of-eight sutures at the atrial and ventricular edges of the defect to close the AV

groove.⁵² With this approach, traction exerted by the sutures reduces the size of the annulus and restores the AV groove without injuring the circumflex vessels. The prosthesis is then secured to the reconstructed annulus. However, if an extensive defect exists in the AV groove because of extensive infection, the David technique is preferable.

Native Tricuspid Valve Endocarditis

Although isolated tricuspid valve surgery can be performed through a right thoracotomy or mid-sternotomy, the median sternotomy is again the most appropriate incision for endocarditis because of the possibility of more extensive surgery. Access to the tricuspid valve is achieved via a right atriotomy made parallel to the AV groove, with care taken to avoid injuring the sinoatrial node and the right coronary artery.

The three main surgical options for tricuspid NVE are total valve excision without valve replacement, valve reconstruction, and valve replacement. Valvectomy without simultaneous replacement avoids the use of any prosthetic material and can be performed in the beating heart, but this often results in massive tricuspid regurgitation and ventricularization of right atrial pressures. Young, otherwise healthy patients may tolerate this hemodynamic alteration, but 20% of patients undergoing this procedure develop right heart failure and require reoperation for implantation of a prosthetic valve.⁶³⁻⁶⁵

Valve replacement with either a biological or a mechanical valve is an option that may be particularly appropriate in cases involving two leaflets or the entire valve. Implantation of a prosthesis, however, obviously exposes the patient to valve-related complications such as thrombosis and recurrent endocarditis. The choice of mechanical versus bioprosthetic valve is debated, but

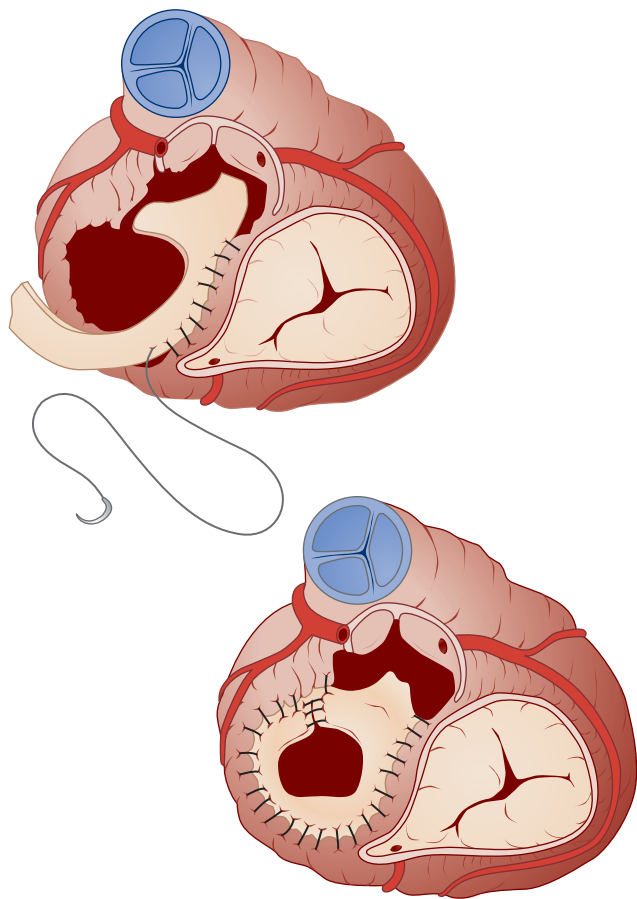


FIGURE 82-2 ■ Large defects in the mitral annulus and central fibrous tissue can be reconstructed using a pericardial patch. (From David TE, Feindel CM: Reconstruction of the mitral annulus. *Circulation* 76:III102–III107, 1987.)

several studies have demonstrated no significant difference in survival and complication rates between these types in the tricuspid position.^{66–68} The overall incidence of recurrent tricuspid valve endocarditis is quite low after valve replacement, but the risk is particularly high in injection drug users and older adults.^{69–71} These two patient populations are associated with the increased risk factors that predisposed them to the development of endocarditis in the first place—intravenous drug use and the presence of foreign bodies such as transvenous pacemaker leads. Valve replacement with a mitral homograft in the tricuspid position has been shown to have promising results, and this may be an option worth considering in patients in whom valve replacement is necessary but who are at high risk for reinfection.^{72–73}

Most cases of native tricuspid valve endocarditis can be successfully treated with valve reconstruction following radical débridement. A number of different approaches have been reported, including posterior leaflet excision (Kay plasty), repair with pericardial patches, commissuroplasty, sliding plasty, and use of artificial chordae.^{74–77} The particular technique applied depends on the amount of reconstruction needed. Repair can be accompanied by annuloplasty to help achieve leaflet coaptation without

excessive tension on the repaired valve, although some surgeons will avoid placing a ring to minimize foreign material. Annuloplasty may be especially helpful in patients with extensive resection and reconstruction. Patients usually tolerate the initial valvular insufficiency after tricuspid repair, and valve competence generally improves over time.⁷⁸

Results

The mortality rate for patients who undergo surgery for NVE has historically been high but has improved significantly over the past several decades. Long-term survival rate is satisfactory, with recent series reporting 15-year survival rates of 50% to 60%.^{54–55} Predictors of poor operative outcome include preoperative shock, paravalvular abscess, left ventricular ejection fraction less than 40%, and infection with *S. aureus*.⁵⁴ Increased age, comorbidities, annular abscess, and acute preoperative myocardial infarction are associated with the development of late complications.⁵⁵ The most frequent postoperative complications for both aortic and mitral NVE include reexploration for bleeding or tamponade, cerebrovascular accident, heart block, new renal failure, sternal infection, atrial and ventricular arrhythmias, valve dehiscence, recurrent endocarditis, and persistent sepsis.

The mortality rate for “simple” cases of native aortic valve endocarditis with involvement limited to the cusps of the aortic valve is reported to be less than 10%, whereas more complex cases carry a significantly higher rate.^{35–37,48–49}

Several studies have demonstrated outstanding results with mitral valve repair in NVE, with lower mortality and higher long-term survival rates when compared to mitral valve replacement.^{56–62} The rate of recurrent infection was also lower with valve repair. The reasons that most likely account for these observations are that foreign material is avoided in the setting of active infection with valve repair and that the sickest patients with the most advanced disease undergo valve replacement rather than repair.

Both tricuspid valve reconstruction and replacement in patients with NVE have been shown to have excellent mid- and long-term results, although the general consensus is to attempt repair if feasible.^{66–68,79,80} The prognosis for patients with NVE involving both the right and left heart is significantly worse when compared to those with isolated right-sided endocarditis, independent of the procedure performed.⁸⁰ This is most likely explained by the fact that patients with right- and left-sided NVE usually have more comorbidities and present with worse preoperative conditions than patients with isolated right heart involvement.

PROSTHETIC VALVE ENDOCARDITIS

Prosthetic heart valves may become infected early on in placement or at any point throughout the lifetime of the valve. In early PVE, it is presumed that the bacteria are introduced at the time of surgery, or via indwelling catheter lines in the immediate perioperative period, which

then migrate to the new device. Risk factors associated with early PVE include but are not limited to infective endocarditis of the native valve, history of intravenous drug abuse, male gender, and a long cardiopulmonary bypass time.⁸¹

Late PVE is classified as PVE occurring more than 12 months after valve placement. The offending organisms and pathogenesis of late PVE more closely resemble what has been described in NVE.⁸² The most common scenario of late PVE involves a transient bacteremia that occurs as a result of direct organism inoculation into the bloodstream, which then localizes onto the prosthetic valve. Dental procedures are a common culprit for bacterial inoculation.

The most common organism responsible for early PVE is *Staphylococcus epidermidis*. Late PVE microorganisms tend to be more similar to those encountered in NVE, such as viridans group streptococci and *S. aureus*.

The clinical signs and symptomatology associated with PVE are similar to those encountered with NVE. The important distinguishing factor between the two is that cardiac complications, such as new and changing murmurs as a result of a paravalvular leak secondary to valve ring dehiscence, and conduction defects from abscess extension into the intraventricular septum are more prevalent in PVE and require urgent if not emergent surgical intervention.

Diagnostic confusion may arise in the immediate postoperative period. Blood cultures that demonstrate staphylococci and yeast likely represent true PVE. Gram-negative bacteremia in an early postoperative patient is statistically more likely to be a result of an indwelling catheter infection, not PVE. In patients with late PVE caused by staphylococci or streptococci, blood cultures are consistently positive if the patient has not been on antimicrobial therapy.

If cardiac complications such as a new or changing murmur arise, indicating the possibility of a paravalvular leak or ring dehiscence, urgent if not emergent operative débridement and replacement are advised. Treatment strategies from an antimicrobial perspective are somewhat more aggressive in PVE than NVE. Therapy should be chosen and tailored based on the identification and susceptibilities of the specific microorganism. If an organism is yet to be identified, vancomycin and gentamicin should be instituted empirically to cover *S. epidermidis*, *S. aureus*, and streptococci. The choice of antibiotics should also consider pathogens standardly encountered at the given hospital. Patients with PVE should be treated for 6 to 8 weeks in most cases, whether or not the valve is removed. If microorganisms are isolated at the time of valve replacement, an additional 6 to 8 weeks of therapy beginning at the time of organism isolation should be instituted.⁸⁴

SUMMARY

NVE and PVE remain significant causes of morbidity and mortality, although recent developments in antimicrobial agents, diagnostic tools, and surgical techniques have improved the prognosis for patients affected by

these diseases. Early detection combined with aggressive antibiotic therapy and early surgical intervention can successfully treat most cases of NVE and PVE. Notable challenges for the cardiac surgeon include the determination of the appropriate timing of operation, removal of all infected tissue, and restoration of physiologic valve function, but sound clinical judgment and meticulous surgical technique can allow for safe and effective surgery.

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ANTICOAGULATION, THROMBOSIS, AND THROMBOEMBOLISM OF PROSTHETIC CARDIAC VALVES

Joseph C. Cleveland, Jr. • Frederick L. Grover

CHAPTER OUTLINE

ARTIFICIAL SURFACES, COAGULATION CASCADES, THROMBOSIS, AND LYSIS

ANTICOAGULATION THERAPY

COMPLICATIONS OF ANTICOAGULATION

Warfarin Sodium

Heparin Sulfate System

Direct Thrombin Inhibitors and Factor Xa Inhibitors

Antiplatelet Agents

PROSTHETIC HEART VALVES

Prosthetic and Mechanical Heart Valves and Thromboembolism

Bioprosthetic Valves and Thromboembolism

Management of Prosthetic Valve Thrombosis

ARTIFICIAL SURFACES, COAGULATION CASCADES, THROMBOSIS, AND LYSIS

Intravascular placement of a foreign body with its non-endothelial surface activates the clotting mechanism, leading to thrombus formation. The exposure of blood to the synthetic surface leads rapidly to deposition of a fine layer of plasma components, mostly protein, followed by platelet deposition. The intrinsic coagulation cascade is initiated along with the extrinsic coagulation cascade: the inflammatory response, including leukocyte activation; the complement system; and fibrinolysis.

Fibrinogen is one of the major plasma proteins, often the first that is deposited on these artificial surfaces. Once the layer of fibrinogen is absorbed onto the surface, platelets can adhere to the fibrinogen. Although surfaces vary greatly in their tendency to promote thrombosis, the reactivity of most materials to blood can be significantly increased if they are first exposed to fibrinogen.¹ Other proteins also are deposited, including fibronectin (a surface protein of many cells), von Willebrand factor (a glycoprotein essential for the adhesion of platelets to subendothelial tissue), thrombospondin (a platelet protein secreted by activated platelets), and factor XII (Hageman factor, the primary activator of the intrinsic coagulation system).

Once platelets attach to the protein layer and spread out on the artificial surface, materials present in the platelet intracellular granules are secreted, including

β -thromboglobulin, which inhibits prostacyclin production; platelet factor 4, which neutralizes heparin sulfate in the endothelium; and serotonin, adenosine triphosphate (ATP), and adenosine diphosphate (ADP). Synthesis of prostaglandins E and F is evident as well, suggesting that endoperoxide metabolism has taken place along with formation of thromboxane A₂ from platelet arachidonic acid. Serotonin, thromboxane A₂, and endoperoxide are potent vasoconstrictors and platelet stimulatory factors.² Finally, platelet aggregation follows platelet adhesion, probably by ADP and serotonin secretion from the adherent platelets. Fibrinogen and thromboxane A₂ are key in this step.

The coagulation cascade is initiated either by reaction of plasma proteins with the artificial surface to form enzymatically active components such as factor XII (intrinsic system) or by introduction of thromboplastin through exposure of subendothelial tissue to the surface (extrinsic system). [Figure 83-1](#) is a schematic diagram of the clotting cascade. Activation of factors XIIa and XIa initiates the intrinsic system, leading to activated factor Xa. Platelets provide the phospholipid surface for this reaction. Activated factor XIIa also initiates the kininogen-kallikrein system, and kallikrein provides positive feedback for the contact activation. Kallikrein cleaves factor XII to convert it to factor XIIa, thereby accelerating contact activation. Bradykinin is also released when kallikrein cleaves high-molecular-weight kininogen. Activated high-molecular-weight kininogen can then bind more prekallikrein and factor XI to the activating surface,

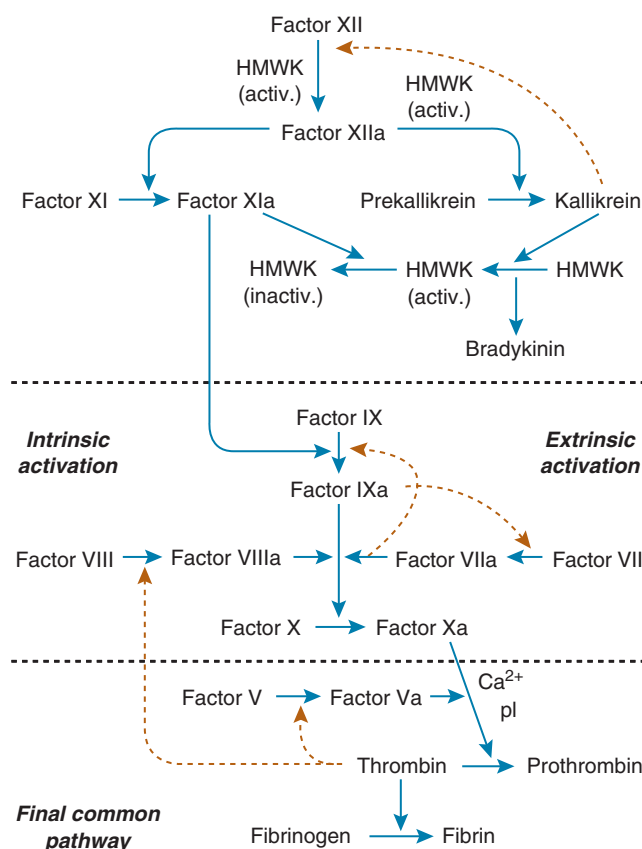
Surface activation

FIGURE 83-1 ■ The coagulation cascade from surface activation to the final common pathway. *HMWK*, High-molecular-weight kininogen; *pl*, phospholipid. (From Ware JA, Lewis J, Salzman EV: Antithrombotic therapy. In Rutherford RB, editor: *Vascular surgery*, ed 3, Philadelphia, 1989, Saunders.)

which further increases the reaction. In the final common pathway, prothrombin is converted to thrombin, and fibrinogen is converted to fibrin. Thrombin recruits more platelets, creating more adhesion and aggregation. A fibrin platelet clot is formed, and thrombosis occurs.

Activation of the clotting cascade on the surface of an artificial device occurs similarly whether it is on the cardiac valve, cardiopulmonary bypass system, vascular graft, extracorporeal membrane oxygenation (ECMO) circuit, mechanical assist device, or vascular catheter. It will produce thrombus formation, and macroscopic and microscopic platelet-fibrin emboli occur commonly as well. Factor XII, kallikrein, and plasmin activate the complement system and activate neutrophils, and kinin formation mediates vasodilation, vascular permeability, and white blood cell migration. Normally, a delicate balance is maintained between these two systems so that uncontrolled clotting or hemorrhage does not occur. The coagulation cascade is initiated, and factor XII and kallikrein initiate clot lysis with conversion of plasminogen to plasmin. Antiplasmins in the circulating blood, particularly α_2 -antiplasmin, rapidly neutralize most of the circulating plasmin; however, plasmin also is incorporated into the clot during clot formation. The fibrin meshwork protects plasmin from antiplasmin once the

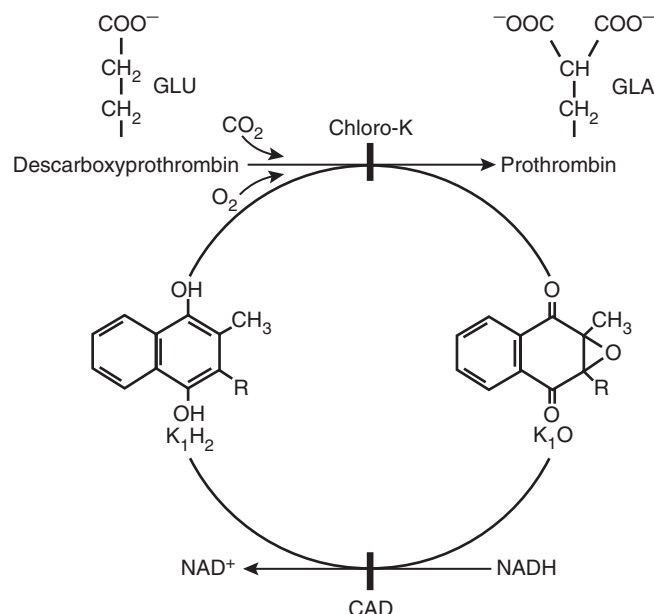


FIGURE 83-2 ■ The vitamin K cycle in the formation of the vitamin K-dependent clotting factors. Vitamin K enters the body and is reduced to vitamin K_1H_2 . K_1H_2 and carboxylase convert vitamin K-dependent clotting factor precursor proteins into active factors; epoxidase converts vitamin K_1H_2 to vitamin K_1 -epoxide (K_1O). Reduced vitamin K_1H_2 is regenerated by reduced nicotinamide adenine dinucleotide (NADH) and is the warfarin-sensitive step. CAD, Coumarin-type anticoagulant drugs. (From O'Reilly RA: Therapeutic modalities for thrombotic disorders: vitamin K antagonists. In Coleman RW, Hirsh J, Marder VJ, et al, editors: *Hemostasis and thrombosis: basic principles and clinical practice*, ed 2, Philadelphia, 1987, Lippincott Williams & Wilkins.)

plasmin is activated to plasmin, allowing fibrin degradation in the clot. In fact, many natural inhibitors offset activated procoagulant protein. Protein C, heparin, antithrombin III, protein S, thrombomodulin, prostacyclin, and plasmin all counter steps in the coagulation cascade.³

ANTICOAGULATION THERAPY

Clinically useful drugs that block the clotting cascade fall into the following primary groups: orally administered vitamin K antagonists; natural anticoagulants, such as the heparin-antithrombin III system; direct thrombin inhibitors, antiplatelet drugs, factor Xa inhibitors; and fibrinolytic agents.

Warfarin sodium remains the most popular orally administered vitamin K antagonist used today in the United States. It blocks the formation of the four vitamin K-dependent clotting factors (prothrombin and factors VII, IX, and X), creating a buildup of their precursors. Warfarin sodium blocks the vitamin K cycle at the regeneration of reduced vitamin K, which is the active form of vitamin K (Fig. 83-2).

Heparin's anticoagulant effect is fairly complex and not completely understood. Heparin sulfate is a glycosaminoglycan that binds to antithrombin III and activates this serine protease inhibitor. Heparin and antithrombin III occur naturally in humans, are secreted by endothelial

cells, and are required to produce their anticoagulant effect. Antithrombin III binds to thrombin and blocks the enzymes of the intrinsic coagulation cascade, including thrombin and factors IXa, Xa, XIa, and XIIa. Both unfractionated heparin and low-molecular-weight heparins work via the previously mentioned mechanisms.

Direct thrombin inhibitors and factor Xa inhibitors have emerged as alternative agents to warfarin for oral anticoagulation. Dabigatran is an orally administered direct thrombin inhibitor, whereas rivaroxaban and apixaban are factor Xa inhibitors. Dabigatran received U.S. Food and Drug Administration (FDA) approval for prevention and treatment of venous thromboembolic disease and treatment of nonvalvular atrial fibrillation based primarily on data from the RE-LY trial.⁴ Several intravenous direct thrombin inhibitors exist, including lepirudin, desirudin, argatroban, and bivalirudin. These agents are used primarily as alternatives to heparin when heparin-induced thrombocytopenia is suspected or confirmed with appropriate diagnostic studies.

Rivaroxaban is an orally administered competitive, direct factor Xa inhibitor. Noteworthy is that this agent is contraindicated in patients with creatinine clearance of less than 15 mL/min or patients on hemodialysis. Rivaroxaban was studied in the ROCKET-AF trial and found to be non-inferior to warfarin in the prevention of stroke in patients with atrial fibrillation.⁵ This agent also was studied for prevention of venous thromboembolism (VTE) during orthopedic surgery and showed efficacy.⁶

The various antiplatelet drugs have different mechanisms of action, making them more or less useful as therapeutic anticoagulation agents. Figure 83-3 is a schematic diagram of the actions of antiplatelet drugs. Aspirin inhibits platelet aggregation by irreversible acetylation of platelet cyclooxygenase, hence blocking the synthesis of prostaglandins and thromboxane A₂. Aspirin prolongs the bleeding time, although variable responses to aspirin's anticoagulant effect exist. Aspirin inhibits platelet aggregation for the life span of the platelet, which is typically 7 to 10 days.

Four adenosine diphosphate P2Y₁₂ (ADP P2Y₁₂) receptor antagonists are FDA approved. These agents reduce platelet aggregation mediated by the binding of fibrinogen to activated glycoprotein (GP) IIb/IIIa receptors on platelets. The thienopyridines are in widespread use as potent antiplatelet agents and are typically used in dual antiplatelet therapy following percutaneous coronary intervention. Clopidogrel in vitro does not affect platelet aggregation. However, in vivo, clopidogrel is metabolized by the liver to several active metabolites—with these metabolites irreversibly inhibiting the P2Y₁₂ platelet receptor. Clopidogrel supplanted ticlopidine principally because ticlopidine is associated with aplastic anemia and thrombotic thrombocytopenic purpura.⁷ The thienopyridine prasugrel converts to active metabolites more efficiently than does clopidogrel; as such, the bleeding risk with this agent is increased compared with other agents in this class. Lastly, ticagrelor is a novel thienopyridine that directly antagonizes the P2Y₁₂ receptor. This drug is also reversible in its inhibition of the receptor. However, it requires twice-daily dosing in contrast with the other thienopyridines. It is presently a Class I

recommendation to discontinue all P2Y₁₂ inhibitors before cardiac surgery. The exact duration in days of discontinuation cannot be specified as the safe interval between discontinuation and cardiac surgery is unknown.⁸ In general, the range for cessation is between 3 and 7 days.

Dipyridamole is a reversible platelet agent, a weak vasodilator, and a weak inhibitor of the enzyme phosphodiesterase, which degrades cyclic adenosine monophosphate (cAMP) to 5'-AMP. With this block, more cAMP is available to inhibit platelet aggregation. Sulfapyrazone appears to reversibly block platelet prostaglandin synthesis and is another fairly weak anticoagulant. At clinical dosages, neither dipyridamole nor sulfapyrazone prolongs the bleeding time.

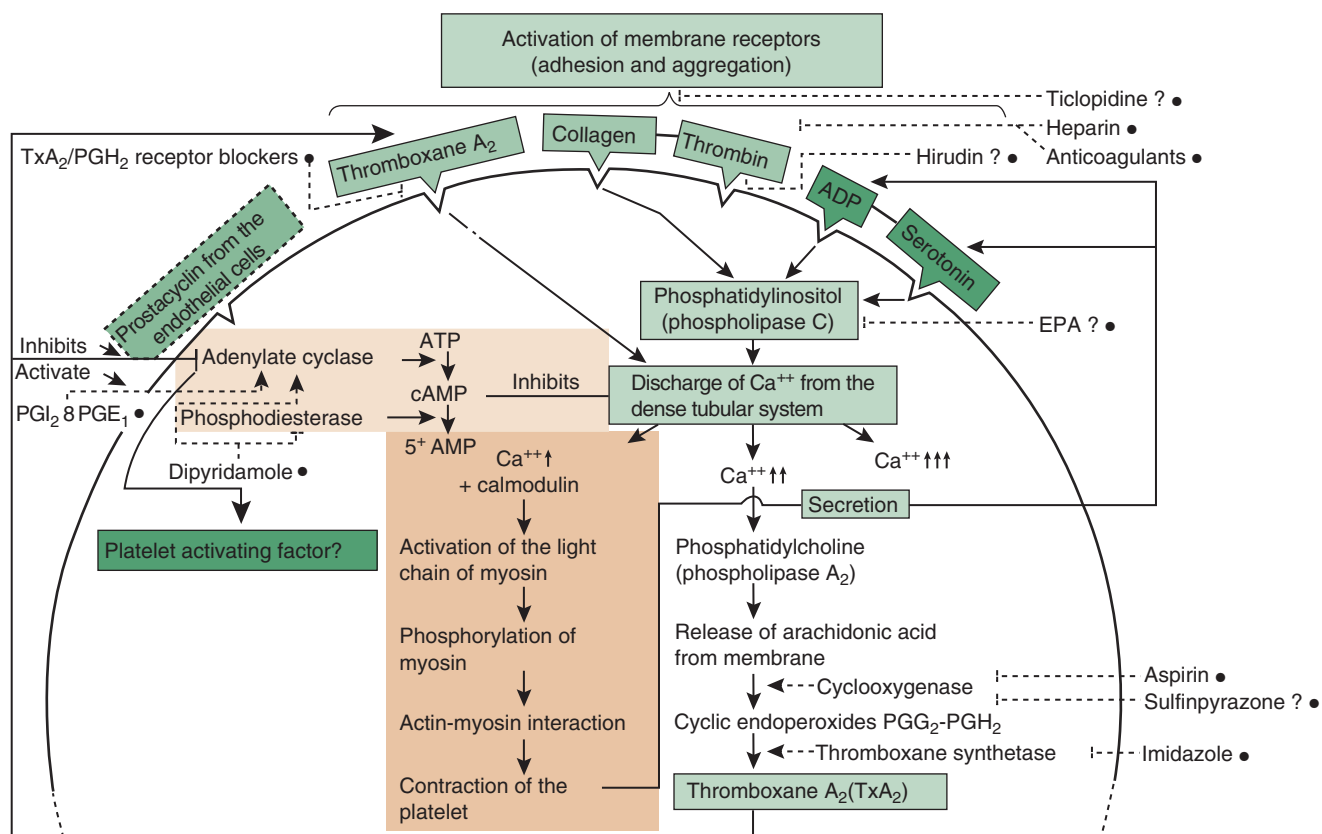
Finally, fibrinolytic therapy has a small but definite place in the management of thrombosis of artificial devices. Streptokinase and urokinase act similarly and induce rapid thrombolysis by activating plasminogen and subsequently forming plasmin. Plasmin causes degradation of the fibrin, reducing thrombus size. Unfortunately, streptokinase and urokinase also induce a generalized plasma proteolytic state as well as local fibrin degradation in the thrombus, and this can lead to uncontrolled hemorrhage. Newer agents (second-generation plasminogen activators) such as recombinant tissue plasminogen activator were developed to prevent induction of this generalized plasma proteolytic state by making these agents fibrin specific. However, this function appears to depend on the dose, and clinical use has not confirmed the decrease in potential for hemorrhage that was hoped for with these drugs.

COMPLICATIONS OF ANTICOAGULATION

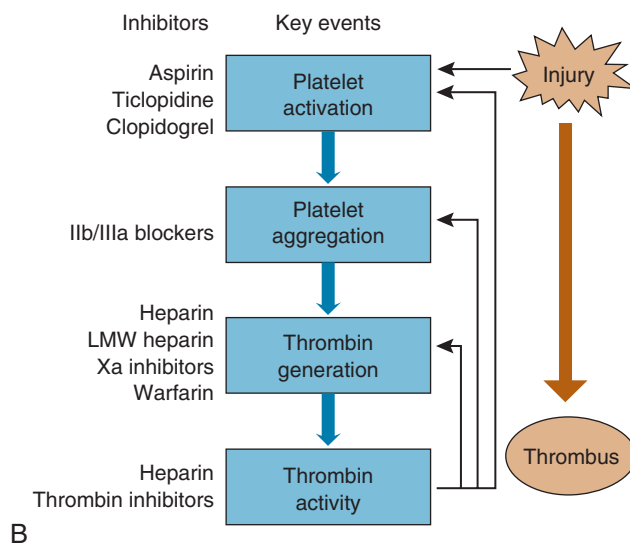
Warfarin Sodium

Bleeding is the most common and most significant complication encountered with the use of warfarin, and therefore close monitoring of the prothrombin time is mandatory. Excessive amounts of warfarin that increase the prothrombin time beyond 2.5 times control and the international normalized ratio (INR) above 5 will increase bleeding complications four to eight times. The gastrointestinal tract is the site of most bleeding complications and is often associated with preexisting disease states, such as peptic ulcer, gastritis, genitourinary lesions, cancer, and hypertension. Indeed, based on the increase in dispensed prescription for warfarin rising by 45% from 1998 to 2004, warfarin is now among the top 10 drugs in the United States with the highest number of serious adverse event reports. Data submitted to the FDA and from a study auditing U.S. death certificates suggest that major bleed frequencies for warfarin are as high as 10% to 16%.⁹

Another significant complication of initial warfarin therapy is skin necrosis. This is secondary to a temporary hypercoagulable state induced in the capillaries when the concentration of protein C (a natural vitamin K-dependent and warfarin sodium-sensitive anticoagulant that circulates in the blood) falls before warfarin's



A



B

FIGURE 83-3 ■ **A**, Presumed sites of action of various platelet inhibitors. Cyclic adenosine monophosphate (cAMP) inhibits calcium (Ca) mobilization from the dense tubular system. *Circles* indicate a platelet inhibitor drug. *Dashed lines* indicate the presumed site of action of the drug. **B**, Key events in thrombosis formation and inhibitors that can prevent specific steps in the process. ATP, Adenosine triphosphate; EPA, eicosapentaenoic acid; LMW, low molecular weight; PG, prostaglandin. (**A**, From Stein B, Fuster V, Israel DH, et al: Platelet inhibitor agents in cardiovascular disease: an update. *J Am Coll Cardiol* 14:813–836, 1989. Reprinted with permission of the American College of Cardiology. **B**, Reprinted with permission from the Institute for Continuing Healthcare Education: *The rationale for extended antithrombotic therapy for patients with post-acute coronary syndromes*.)

inhibition of factors II, IX, and X becomes effective and the desired hypocoagulable state occurs. The activated form of protein C is a powerful inactivator of factors V and VIII. Why this is limited to the skin is unknown.¹⁰ When warfarin is used in pregnant women, it can cause embryopathy in 4% to 8% of fetuses exposed in the first trimester, and exposure to warfarin in the second and third trimesters causes central nervous system abnormalities in 3% of pregnancies. Finally, prematurity, fetal hemorrhage, and stillbirth are increased in infants exposed to warfarin.^{11,12} For these reasons, bioprostheses or allografts should be placed, when possible, in women of childbearing age.

Heparin Sulfate System

Again, the most common complication of heparin therapy is bleeding. Hemorrhagic complications occur in 10% to 20% of patients with normal hemostasis and in up to 50% of patients with thrombocytopenia or uremia.¹³ Thrombocytopenia has been reported in up to 31% of patients and can cause significant morbidity and mortality when it is associated with platelet clumping and thrombosis. Heparin-induced thrombocytopenia (HIT) has become an increasingly recognized and important clinicopathologic syndrome. The frequency of HIT among patients exposed to heparin is highly variable and related to the type of heparin, the patient population, the duration of heparin exposure, and the patient's sex.¹⁴ The immunoglobulin G antibodies form a complex against platelet factor 4/heparin, which binds to the platelet Fc receptor, leading to platelet aggregation and release of prothrombotic microparticles. Cardiac surgery patients are prone to formation of anti-platelet factor 4/heparin antibodies. Accordingly, if the platelet count falls by more than 50% between postoperative days 5 and 14, investigation for HIT antibodies should occur. If HIT is suspected or diagnosed, a direct thrombin inhibitor (lepirudin, bivalirudin, or argatroban) should be initiated and continued until the platelet count normalizes. It is imperative that all sources of heparin be stopped if HIT is suspected. This includes removal of a pulmonary artery catheter if it is heparin coated. If further anticoagulation becomes necessary, such as cardiac reoperation, the surgeon can wait for the antibodies to become undetectable and reuse heparin.¹⁵ However, this may take up to 40 days. Another alternative is to use nonheparin anticoagulants such as danaparoid sodium, lepirudin, and argatroban.¹⁶ Platelet inhibition with glycoprotein IIb/IIIa antagonists followed by unfractionated heparins has also been used successfully.¹⁷

Fractions of heparin that display this effect have the least anticoagulant activity, so the use of low-molecular-weight heparin with high anticoagulant effect and low ability to lead to platelet clumping has become clinically more important.

Direct Thrombin Inhibitors and Factor Xa Inhibitors

Given the widespread adoption of orally available thrombin and Xa inhibitors, clinicians will encounter minor and

occasionally serious, life-threatening bleeding from these agents. The bleeding rates with dabigatran, rivaroxaban, and apixaban reported by various trials are generally 4% to 14%. Management of minor bleeding from these agents usually includes cessation of the agent. The period of time required for cessation of these agents before major procedures is unknown, but a minimum of 5 to 7 days without the drug before a cardiac operation seems prudent. The management of severe, life-threatening bleeding from these agents is challenging because no direct reversal agents are available. In general, to stop major or life-threatening bleeding related to one of these agents, nonactivated prothrombin complex concentrate (PCC) has been recommended.¹⁸

Antiplatelet Agents

Antiplatelet therapy is the mainstay of treatment for coronary artery disease. In some cases, patients require urgent cardiac operations while on these medications. Aspirin does not seem to confer an unduly increased risk for bleeding. The data for clopidogrel suggest that for patients undergoing cardiac surgery within 5 days from the last dose, increased bleeding can be anticipated.¹⁹

The data regarding the newer P2Y₁₂ agents and bleeding after coronary artery bypass graft (CABG) are still emerging. The TRITON-TIMI 38 trial examined prasugrel in comparison with clopidogrel for acute coronary syndromes. Although only 437 patients of 13,608 in this study underwent CABG after receiving either prasugrel or clopidogrel, the rates of minor and major bleeding with prasugrel were 14.1% versus 4.5% in the clopidogrel group.²⁰ Based on these data, it would be prudent to wait 7 days before embarking on a cardiac operation after the last dose of prasugrel if possible. If unable to wait, it is suggested that platelet transfusions can be effective in dealing with bleeding if there has been at least 12 hours between the last dose of prasugrel and the platelet transfusions.²¹ With regard to ticagrelor and bleeding after cardiac surgery, there are insufficient data to base firm decisions. There are little data supporting management of post-CABG bleeding with this agent. It would seem prudent to wait a minimum of 5 days before undergoing cardiac surgical procedures in this group. The latest Society of Thoracic Surgeons Guideline Statement regarding this subject gives credence to the idea of testing platelet inhibition rather than waiting an arbitrary amount of time.⁸

PROSTHETIC HEART VALVES

Edmunds and coworkers^{22,23} and Cohn²⁴ have detailed the need for standardized reporting of thrombotic complications, including uniform definitions; stratification of the data to include the severity of the event, including death; and careful, complete long-term follow-up. Without this standardization, it is difficult to make accurate statements about results, complications, and appropriate anticoagulation therapy. Similarly, it is difficult to compare valves placed in the 1960s and 1970s and their associated complications with valves placed in later decades and their complications.

Through the years, bioengineering advances have led to fewer thrombogenic materials, such as carbon Pyrolite for the St. Jude valve, and a better mechanical valve design has decreased the incidence of valve thrombosis and thromboembolism through greater central flow characteristics. However, more effective anticoagulation has been the most important factor for the decreased incidence of thrombosis in the 1980s and 1990s compared with the 1960s and 1970s, particularly with mechanical valves. Bioprosthetic valves have less inherent thrombogenicity, but this is a result of better central flow characteristics, flexible leaflets, and sinusoidal washout rather than true thromboresistance of the preserved tissue.²⁵ At present, stented porcine xenograft valves and pericardial valves are in use as tissue bioprostheses. The major problem with the pericardial xenograft valves was their durability; both valves developed tearing of the cusps secondary to stress after only a few years of use. The pericardial valves used today are much better and tend to fail by calcification.²⁶

Most prosthetic valves have a sewing ring that is covered with a Dacron or Teflon cloth. When this is exposed to the blood, an adherent layer of thrombus is laid down and serves as a blood-compatible coating. It is initially thin and delicate but later becomes invaded by well-vascularized fibrous tissue. This resists further formation of thrombus. However, if the flow pattern is abnormal, this tissue ingrowth can creep into the orifice from below the valve-sewing ring, forming an obstructive pannus. Finally, allograft aortic valves and pulmonary valved conduits have almost normal platelet survival time and do not form thrombi.

Prosthetic and Mechanical Heart Valves and Thromboembolism

Determining the risk of thromboembolism for patients who undergo mechanical valve replacement is subject to various complex patient- and prosthesis-related factors. A few general principles apply, however. Data from early small case series in which patients were followed who had contraindications to vitamin K antagonists support major thromboembolism rates of 4.0 per 100 patient-years to more than 8.6 per 100 patient-years for total embolic rates.²⁷ The data regarding optimal INR targets for mechanical aortic and mitral valves were derived from retrospective observational studies.²⁸ In general, mechanical valves in the mitral position have roughly 1.5 to 2 times the thromboembolic risk over mechanical valves in the aortic position. Both the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology maintain guideline-supported recommendations for target INR with both mechanical and bioprosthetic valves.^{29,30}

The incidence of all thrombotic complications, including thromboembolic events, for a mechanical aortic prosthesis is approximately 1% to 2% per patient-year, whereas the rate for bioprosthetic valves in the aortic position is approximately half that of the mechanical prostheses.³ The risk of bleeding complication is, however, generally accepted to be higher for mechanical valves in the aortic position versus bioprosthetic valves

because of the use of warfarin anticoagulation. In the two large randomized trials that compared outcomes for patients with either a mechanical or porcine heart valve, both the Edinburgh Heart Trial and the Veterans Affairs Cooperative Trial showed a higher rate of bleeding with mechanical valves.^{31,32}

Bioprosthetic Valves and Thromboembolism

The rate of thromboembolic events for patients with bioprosthetic valves is thought to be highest during the first 90 days after implantation. Specifically, this rate is highest for the first 10 days after aortic valve implantation for the aortic position in patients without warfarin anticoagulation. The thromboembolic rate for a bioprosthetic valve is also high for the mitral position in patients without anticoagulation for days 1 through 10 and for days 11 through 90.³³ Based on these data, it became common practice for patients who received either an aortic or a mitral bioprosthesis to receive 3 months of vitamin K antagonist anticoagulation.

This practice of routinely anticoagulating bioprosthetic valves in the aortic position has been revisited. ElBardissi and colleagues studied 861 patients who underwent bioprosthetic aortic valve replacement. Of these 861 patients, 133 patients (15%) received warfarin anticoagulation and 782 (85%) did not. No difference in thromboembolic events was found between the two groups.³⁴ However, a large Danish registry study recently established a very high thromboembolic rate for patients without warfarin anticoagulation: 7.00 per 100 patient-years versus 2.69 per 100 patient-years in patients treated with warfarin anticoagulation for the first 90 days after bioprosthetic aortic valve replacement.³⁵ Based on current evidence-based guidelines, the 2014 ACC/AHA guidelines suggest that it is a Class IIb recommendation for warfarin administration for 3 months following implantation of a bioprosthetic valve in the aortic position. It should be noted that it remains a IIa recommendation regarding warfarin administration for patients who receive bioprosthetic valves in the mitral position.²⁹

Hammermeister and the Veterans Affairs Cooperative Study on Valvular Heart Disease³² concluded that after 15 years, the rates of survival for patients receiving a mechanical aortic valve replacement were higher than those for patients receiving a bioprosthetic aortic valve replacement. For patients receiving mitral valve replacement, there were no differences in survival rates between patients receiving mechanical valves and those receiving tissue valves. The improved survival rate in the mechanical aortic valve replacement group was offset by a higher rate of bleeding. Structural failure, however, was observed only with the bioprosthetic valves, and bleeding complications were statistically more frequent among patients who received mechanical valves. Hammond and associates,³⁶ in a study of 1012 adult patients who underwent placement of either a mechanical valve or a bioprosthesis with a follow-up of 4814 patient-years, found little direct evidence to strongly support the generalized use of one type of valve over another.

Unfortunately, bioprostheses have a very high failure rate in children, probably because of accelerated calcium metabolism, and there is currently a renewed interest in the use of both fresh and commercially available frozen allograft valves for children and young adults to prevent anticoagulation. The risk of thrombotic or thromboembolic events with use of allograft aortic valves in the subcoronary position, as a free-sewn graft or by root replacement in which a cylinder including the valve is placed by the technique of Ross,³⁷ is almost zero without anticoagulation. Matsuki and coworkers³⁸ reported on 555 consecutive hospital survivors who underwent isolated aortic valve replacement with a free-sewn allograft. The incidence of thromboembolism was 0.034% per patient-year, or 1 patient of the 555 studied. Results with the aortic root replacement in 108 patients described by Okita and associates³⁹ showed no incidence of thromboembolism in 180 patient-years of follow-up. Penta and colleagues⁴⁰ similarly found no incidence of thrombosis or thromboemboli in 140 consecutive patients who underwent homograft replacement of the aortic valve and were observed for a minimum of 10 years. Many of these valves were either fresh or antibiotic-preserved valves. O'Brien and associates⁴¹ reported on a comparison of aortic valve replacements with viable cryopreserved and fresh allograft valves. The freedom from thromboembolism for both groups was 97% at 10 years and 96% at 15 years; the reoperation rate for valve failure was much higher in the group that received the fresh valves. O'Brien initially believed that cryopreserved valves were superior because fibroblastic cell viability is preserved, providing durability. However, recent developments have pointed toward an immunologic basis for valve deterioration with live cells.

The fate of the aortic valve or pulmonary valve used as a conduit to reconstruct the right ventricular outflow tract is not as clear. Bull and associates⁴² described 249 patients who received extracardiac conduits in the right side of the heart. Of the 173 patients who survived 30 days, 72 underwent placement of xenograft conduits of various types, and 4 underwent placement of valveless tubes. The complication and reoperation rates for both valved conduit groups were similar. Calcification of the allograft tube occurred commonly, but the obstruction tended to be at the proximal portion of the conduit where Dacron extensions, which are circumferential, were commonly placed. The development of the neointimal peel in this position led to the obstruction in more than two thirds of patients.

If a noncircumferential proximal hood is used, thrombus and neointimal peel formation is minimal, and obstruction is markedly decreased. Livi and associates⁴³ have shown that the valve of choice for right ventricular outflow tract reconstruction is, in fact, the pulmonary allograft rather than the aortic allograft. Finally, Matsuki and associates⁴⁴ have used the pulmonary autograft valve (the patient's own pulmonary valve) to replace the aortic valve with excellent results (Ross procedure). However, this procedure requires the reconstruction of the right ventricular outflow tract with a pulmonary or aortic allograft, essentially giving the patient disease of two valves rather than the one-valve disease the patient had

originally. Despite this, Matsuki and associates⁴⁴ have shown excellent results with this technique. Finally, the Contegra bovine valved jugular vein seems to be a good alternative for pediatric right ventricular outflow tract reconstruction.

Several general rules make some clinically applicable sense out of these sometimes conflicting data. For children, aortic valve replacement should be carried out either with a mechanical valve, such as the St. Jude bileaflet valve, or with the pulmonary autograft technique to replace the aortic valve as described by Ross in 1967.⁴⁵ This has become the method of choice for aortic valve replacement in children. For mitral valve replacement in children, mechanical valves are required, and these patients should undergo full anticoagulation with warfarin and aspirin. Xenograft bioprostheses should not be used because of the rapid calcification and degeneration that occur with these valves in children. Similar guidelines should be followed for young adults. For women who are of childbearing age or wish to have children, mechanical valves should be strongly discouraged. The complications of anticoagulation, particularly with warfarin sodium and heparin, place the young woman and unborn child at too great a risk. For non-childbearing women and for men younger than 60 years, individual differences in the patients and their desired lifestyle after valve replacement should be strongly considered in choosing the valve. Finally, probably for patients older than 60 years but definitely for those older than 70 years, the use of xenograft bioprostheses (stented or stentless) should be strongly considered in view of the decreased degeneration rate of these valves in older patients and the higher risk of anticoagulation in this population of patients. Guideline-supported recommendations regarding choice of mechanical or bioprosthetic valves support a patient-centered approach to discussing the risks and benefits of prosthetic valve options.²⁹

Management of Prosthetic Valve Thrombosis

All prosthetic valves, including bioprostheses, can develop thrombotic occlusion, but the incidence is higher for the mechanical valve, specifically the caged ball valve and the tilting disc valve. The thrombosis is usually more acute, manifesting as "sudden" valve dysfunction with clinical shock, pulmonary edema, and loss of valve click sounds in mechanical valves and muffled sounds in bioprostheses. The diagnosis is made by fluoroscopy or two-dimensional transthoracic echocardiography, or both. Mortality is high without either fibrinolytic therapy or reoperation. The incidence of this complication is less than 0.3 per 100 patient-years, except for the Omniscience tilting disc valve placed in the mitral position, which has a significantly higher incidence of thrombosis.³

With regard to management of a suspected thrombosis of a left-sided prosthetic heart valve, determination of whether the thrombus is obstructive based on imaging studies is the initial priority. If the thrombus is obstructive and the patient is critically ill, then surgical replacement of the prosthesis is warranted unless the patient is deemed too high risk for operation because of comorbid

conditions. It is arguably difficult to determine which patient or subset of patients is too high risk, because the operative mortality rate approaches 15% and all cases of prosthetic valve thrombosis are therefore “high risk.” Based on the limited data set, the following therapeutic strategies are suggested: thrombolysis is reserved as the initial strategy for patients in NYHA Class I/II heart failure, if surgery is not available (e.g., patient is in a location without cardiac surgery and too unstable to transport), the patient refuses surgery, or if the thrombus is nonobstructive and small (<0.8 cm²). Almost all right-sided prosthetic valve thromboses can be treated with lytic therapy initially, and surgery used if thrombolysis is unsuccessful.⁴⁶

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ROBOTIC AND MINIMALLY INVASIVE MITRAL VALVE SURGERY

Craig M. Jarrett • A. Marc Gillinov • Tomislav Mihaljevic

CHAPTER OUTLINE

ROBOTIC SYSTEMS

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Cardiac surgery has traditionally been performed through a complete median sternotomy, which provides generous operative exposure to all structures in and around the heart. With this approach, complex cardiovascular procedures can be performed safely and effectively. Reductions in incision size and tissue manipulation became possible with the advent of closed-chest cardiopulmonary techniques and advances in instrumentation. Improvements in intracardiac visualization and robotic telemanipulation have pushed the bounds even further.

Today, robotic cardiac surgery, particularly valve surgery, has become standard practice for some surgeons. In this chapter, we describe our experience with robotic mitral valve surgery and other minimally invasive approaches. A number of future systems and novel visualization techniques that might enhance future robotic systems are outlined as well.

ROBOTIC SYSTEMS

Three-dimensional vision and seven degrees of freedom are optimal to manipulate and freely orient objects in a three-dimensional space, such as a body cavity. Consequently, standard endoscopic surgery with only two-dimensional vision and four degrees of freedom reduces accuracy, efficiency, and dexterity of movement. Human motor skill, specifically eye-hand coordination, deteriorates with the indirect observation and manipulation of instruments and tissues in endoscopic surgery. In addition, instrument shaft shear, or drag, necessitates higher manipulation forces by the surgeon, leading to hand muscle fatigue. The surgeon must reverse hand motions in endoscopic surgery because the fixed entry point (fulcrum effect), such as a trocar, makes it a motor skill

set that is nonintuitive to learn. Computer-enhanced systems have been developed to overcome these and other limitations. Through telemanipulation, the surgeon operates from a console with a three-dimensional view of the operative field. The surgeon's movements are reproduced in a scaled proportion by instruments mounted on robotic arms inserted through the chest wall. The robotic arms and "micro-wrist" instruments mimic the human arm and wrist with seven full degrees of freedom. For cardiac surgery, a robotic telemanipulation system, the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA), is currently available, with two different versions.

The da Vinci S Surgical System has three components: a surgeon console, a patient-side cart, and a vision cart. The surgeon console is separated physically from the patient and allows the surgeon to sit ergonomically with his or her head positioned in a three-dimensional vision system, arms at the side, and hands beneath the vision system. This natural eye-hand-instrument alignment replicates the experience of open surgery. The surgeon's analog finger and wrist movements, along with any tremor, are converted to digital signals by sensors in the console. The movements are scaled, whereby movements of the surgeon at the console are larger than movements of the instruments in the patient. The tremors are filtered and smoothed, which removes inherent human tremor with a frequency of 8 to 10 Hertz. This motion scaling and tremor suppression enhance precision at the tissue level. A clutching mechanism at the console, which temporarily disconnects the surgeon's and instruments' movements, enables readjustment of hand positions to maintain optimal ergonomics. The surgeon's movements are transferred to the patient cart digitally, where the instruments move synchronously through one of the four

independent effector arms. For cardiac surgery, the arms are used to control the camera, the surgeon's left and right hands, and the atrial retractor. The vision cart houses the image-processing equipment and a large viewing monitor, which provides the operating room team, including the patient-side assistant, a view of the operative field. The three-dimensional vision system facilitates natural depth perception with high-power magnification (10×) via both 0-degree and 30-degree endoscopes.

The da Vinci *Si* Surgical System, the most recent version, incorporates dual-console capability, enhanced three-dimensional 1080i high-definition visualization, an updated user interface, and improved operating room integration. The dual-console feature supports training and collaboration by allowing two surgeons to sit at separate consoles and easily and quickly take control of the instruments at any time during surgery. Three-dimensional high-definition visualization with capability of 10× magnification increases viewing resolution, providing improved clarity and detail of the anatomic structures. The updated user interface with easy-to-use touchscreen controls simplifies intraoperative system and vision adjustments. Addressing the increasing trend toward operating room integration, vision system components traditionally housed in the vision cart can be installed on an operating room boom, and a multiple-input display allows viewing of up to three video sources, such as the operative field, ultrasound, and electrocardiogram (ECG), at one time.

EVOLUTION OF ROBOTIC CARDIAC SURGERY

Initially, advances in minimally invasive surgery were based on modifications of previously used approaches performed under direct vision. Mini-sternotomies, partial sternotomies, parasternal approaches, and mini-thoracotomies simply reduced the size of the incisions and the degree of tissue manipulation.¹⁻⁴ Advances in cannulation methods and video-optics opened the door for totally endoscopic robotic surgery.

The introduction of Port-Access technology (Cardio-vations, Inc., Ethicon, Somerville, NJ) in 1996 combined a minimally invasive surgical approach (nonsternotomy) with total cardiopulmonary bypass and an arrested heart.^{5,6} The system provides extrathoracic cardiopulmonary bypass with a specialized set of endovascular canulas and catheters to provide antegrade or retrograde cardioplegic arrest, and ventricular decompression. Encouraging results confirmed the feasibility and safety of these techniques and paved the way for the development of less invasive operations. Advances in video-optics started a wave of new endoscopic approaches in general, urologic, gynecologic, and orthopedic surgery. Video assistance in cardiac surgery was first used for closed chest internal mammary artery harvests and congenital heart operations.⁷⁻⁹ In 1996, Carpentier and colleagues performed the first video-assisted mitral valve repair using ventricular fibrillation via a mini-thoracotomy.¹⁰ Soon thereafter, Chitwood and coworkers performed a

video-assisted mitral valve replacement using a microincision, percutaneous transthoracic aortic clamp, and retrograde cardioplegia.¹¹

Cardiac surgery entered the robotic age in 1997 when Mohr first used the AESOP (Intuitive Surgical, Inc., Sunnyvale, CA) voice-activated camera robotic arm in mitral valve surgery. In addition to freeing up the surgeon's hands during surgery, this device allowed for better valve and subvalvular visualization with even smaller incisions.¹² In 1998, Chitwood performed the first video-directed mitral operation in the United States, using the voice-controlled AESOP 3000 robotic arm and a Vista three-dimensional camera (Vista Cardiothoracic Systems, Inc., Westborough, MA).¹¹ The combination of robotic camera control and three-dimensional visualization was an essential step toward the totally endoscopic mitral operations performed today. The first mitral valve repair using an early prototype (the da Vinci articulated intra-cardiac wrist robotic device) of the present da Vinci robot was done by Carpentier and colleagues in 1998.¹³ The first complete repair in North America using the da Vinci system was performed by Chitwood and colleagues in 2000.¹⁴ A 4-cm incision was used for assistant access, but advancements in three-dimensional video and robotic instrumentation progressed to a point where totally endoscopic procedures were feasible. Lange and coworkers performed the first totally endoscopic mitral valve repair using only 1-cm ports with the da Vinci in 2000.¹⁵

In contrast to mitral valve surgery, closed-chest (non-sternotomy) coronary artery bypass surgery could be performed only after the robotic telemanipulation system had been developed. Technically complex maneuvers, such as coronary anastomosis, could not be done with conventional thoracoscopic instruments because dexterity was lacking. Freedom of movement with the "endowrist" instruments, where additional articulation occurs within the patient near the tip of the instrument, was critical in achieving this goal. Early reports of success originated from several centers that were pioneering the effort.¹⁵⁻¹⁸ Although robotic coronary surgery has gained less traction than mitral surgery, today it can be performed safely with reproducible results at dedicated centers.^{19,20}

CLINICAL APPLICATIONS AND PATIENT SELECTION

The da Vinci robot is used for mitral valve repair and single-vessel coronary artery bypass. It is less frequently used for mitral valve commissurotomy and tricuspid valve repair. In our experience, patients are offered robotic mitral valve surgery if they meet strict criteria ([Box 84-1](#)). Patients who have coronary artery disease or other valvular disease that would warrant surgery are excluded. Although tricuspid valve repair and coronary artery bypass graft surgery can be done using a robotic approach, the port placement and patient positioning are different. Mild aortic regurgitation (1+) or greater is also a contraindication because of the inability to reliably arrest the heart with retrograde cardioplegia alone. Patients with a prior sternotomy or right thoracotomy, or who have

BOX 84-1 Robotic Mitral Surgery Exclusion Criteria

- Coronary artery disease or other valvular disease requiring surgery
- Mild (1+) aortic regurgitation or greater
- Prior sternotomy or right thoracotomy
- Significant chest wall deformity that would limit access
- Severely calcified mitral valve annulus
- Aortic, iliac, or femoral atherosclerosis greater than minimal, or femoral vessels less than 7 mm (consider axillary artery cannulation)

significant chest wall deformities that would limit access, are also excluded in our current practice, although there is some early experience with operations on such patients at other centers. Patients with a severely calcified mitral annulus are not candidates because decalcification requires further refinement of instruments and a more reliable means of evacuating any calcium that falls into the ventricle. Lastly, aortic, iliac, or femoral atherosclerosis greater than minimal, and femoral vessel diameter less than 7 mm, are relative contraindications; however, in such cases axillary perfusion may be substituted for femoral artery perfusion.

SURGICAL TECHNIQUES

After induction of general anesthesia, the patient is intubated with a double-lumen endotracheal tube, and a transesophageal echocardiography (TEE) probe is placed. A retrograde coronary sinus catheter is placed via the internal jugular vein and positioned under echocardiographic guidance. Bilateral arterial lines are placed if endoaortic balloon technology is to be used for aortic occlusion and cardioplegia delivery. The patient is positioned with the right chest elevated 30 degrees with a roll caudal to the right scapula and arms tucked at the patient's side.

Subsequent steps should follow a well-defined order to minimize unnecessary morbidity if patient factors preclude a robotic approach and the approach needs to be converted. The femoral vessels are exposed through a small skin incision superior and parallel to the inguinal crease. Once the vessels are deemed appropriate for cannulation (size at least 7 mm and free of atherosclerosis), single left-lung ventilation is established and the robotic ports incisions are made. First, the camera port is placed in the fourth intercostal space 2 to 3 cm lateral to the midclavicular line, and a 30-degree, three-dimensional, high-definition camera is inserted. After inspecting the intrathoracic anatomy and planning the port placement for optimal visualization and repair of the valve, a 2-cm working port is made in the same interspace 2 to 3 cm lateral to the camera port. The left robotic arm port is placed in the third intercostal space 2 to 3 cm medial to the anterior axillary line. The right robotic arm port is placed in the fifth or sixth intercostal space just lateral to the anterior axillary line. The left atrial retractor port is

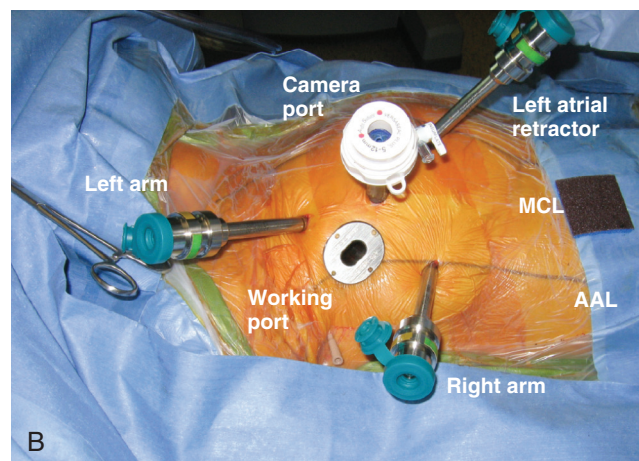
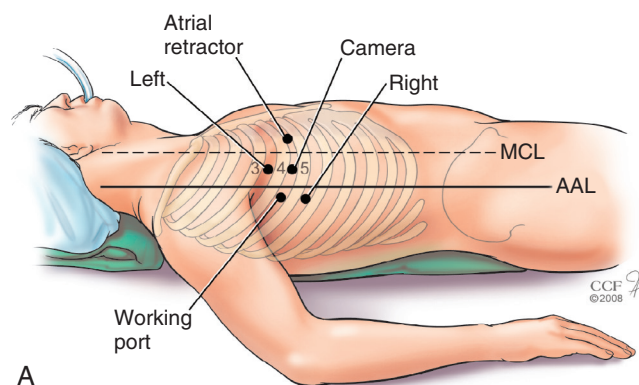


FIGURE 84-1 ■ Schematic (A) and photograph (B) of port placement for robotic mitral valve surgery. AAL, Anterior axillary line; MCL, midclavicular line.

placed through the fourth or fifth intercostal space just medial to the midclavicular line (Fig. 84-1).

A femoral venous cannula (22 or 25 Fr, Edwards Lifesciences, Irvine, CA) is positioned in the superior vena cava (SVC) under echocardiographic guidance, and in most cases a separate SVC cannula (17 Fr) is placed via the internal jugular vein over a wire. Arterial cannulation (19 or 21 Fr) is accomplished via the femoral artery (Fig. 84-2). Cardiopulmonary bypass is established at moderate hypothermia (32° C) and the pericardium is incised 2 to 3 cm anterior to the right phrenic nerve. In patients with a normal sized aorta (less than 4 cm), no evidence of atherosclerosis, and no aortic regurgitation, an aortic endoballoon is used for antegrade cardioplegia. Correct positioning is ensured by TEE and monitoring of bilateral upper extremity pressures. If an endoballoon is contraindicated, a separate antegrade cardioplegia catheter is inserted in the proximal aorta and a transthoracic aortic cross-clamp is positioned in the third intercostal space in the midaxillary line (Fig. 84-3). After cardioplegic arrest, a 3- to 4-cm left atriotomy is made medial to the right superior pulmonary vein, the atrial retractor is inserted in the atrium, and the atriotomy is extended to allow complete exposure of the mitral valve.

The surgeon performs the surgery at the console while the patient-side assistant changes instruments, changes supplies, and retrieves operative materials. Close

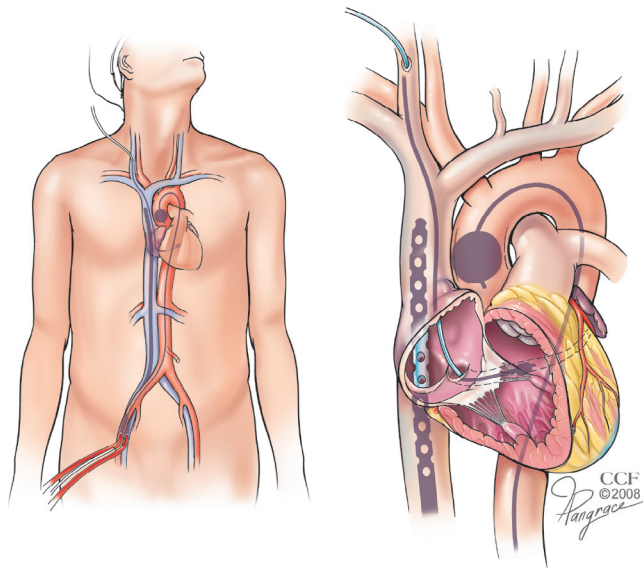


FIGURE 84-2 ■ Overview of cannulation showing femoral venous and arterial cannulas, retrograde coronary sinus catheter, and endoballoon.

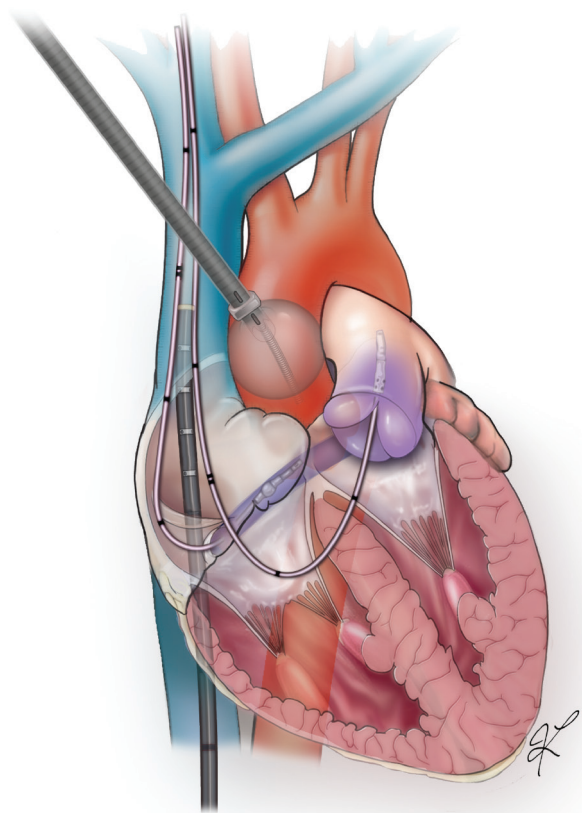


FIGURE 84-3 ■ Transthoracic aortic cross-clamp and direct antegrade cardioplegia catheter.

inspection of the valve will determine what type of repair is required—leaflet resection and artificial chordae are the two most common techniques used to correct leaflet prolapse. Insertion of a partial flexible annuloplasty band using the running technique supports the repair and

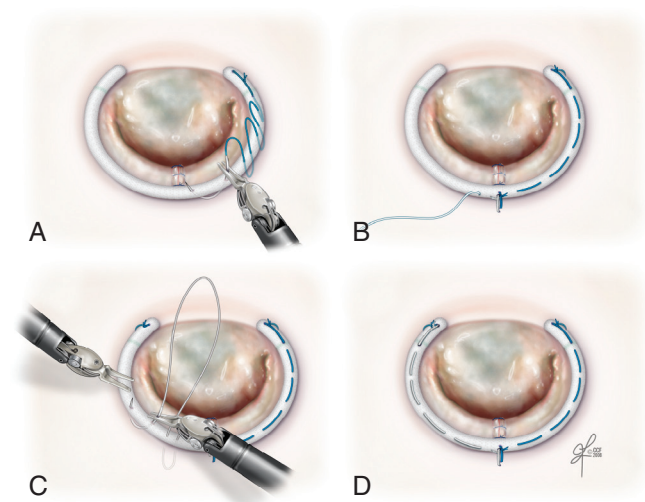


FIGURE 84-4 ■ Schematic diagram of running annuloplasty suture technique using a partial flexible band. **A**, First suture is tied at right trigone and run clockwise to mid-portion of annulus. **B**, Second suture is tied at mid-portion of annulus and tails are tied to first suture. **C**, Second suture is run clockwise to left trigone. **D**, Third suture is tied at left trigone and tails are tied to second suture.

provides annular reduction (Fig. 84-4).²¹ Sutures to complete the repair are tied intracorporeally and retrieved by the patient-side assistant. Competency of the valve is tested by administration of antegrade cardioplegia and saline insufflation. The left atrium is closed using a running polytetrafluoroethylene (PTFE) suture. The robotic arms are removed, and standard de-airing and weaning procedures are performed under TEE. All patients have a transthoracic echocardiogram before discharge.

CLINICAL OUTCOMES

The world experience of robotic mitral valve surgery to date is mostly a collection of retrospective case series. Currently, only one large study exists that compares robotic mitral valve repair with alternative approaches. Nevertheless, surgical results thus far have been encouraging, and short-term outcomes appear similar to outcomes for repair using conventional approaches.

In 2000, Chitwood and colleagues completed the first phase I robotic mitral valve repair trial, which consisted of 10 patients.²² The average total arrest time and total operating room time were 150 minutes and 4.8 hours, respectively. There were no device-related complications and there was one reoperation for bleeding. Average postoperative length of stay was 4 days, and mitral regurgitation was trace or less for all patients at 3-month follow up. Based on these results, an extension of the trial was granted and subsequently reported in 2003 on 38 patients.²³ In this study, total operating room time decreased from 5.1 hours in the first group of 19 patients to 4.4 hours in the second group of 19 patients. Both cross-clamp and bypass times decreased significantly with experience as well. One patient underwent replacement for failed repair.

Mohr and coworkers described their initial experience in 2001 in 17 patients who underwent robotic mitral valve repair.²⁴ Conversion to an alternative approach was necessary in 3 of the 17 cases (17.6%). The average cross-clamp time was 89 ± 18 minutes. Intraoperative mitral regurgitation was trace or less in all but one patient who underwent an immediate endoscopic valve replacement. Another patient had postoperative failure before discharge and required replacement.

A multicenter phase II clinical trial involving 112 patients at 10 institutions was published in 2005.²¹ Total robot, aortic cross-clamp, and cardiopulmonary bypass times were 77.9 ± 0.3 minutes, 2.1 ± 0.1 hours, and 2.8 ± 0.1 hours, respectively. At 1-month echocardiographic follow-up, 9 patients (8%) had 2+ mitral regurgitation, and 6 (5.4%) of these had reoperations (5 replacements and 1 repair). There were no deaths, strokes, or device-related complications.

In 2006, Murphy and colleagues published their results of 127 robotic mitral valve operations.²⁵ Six of the 127 cases (4.7%) were converted to another approach. Of the 121 robotic surgeries, mitral valve repair was completed in 114 patients (94.2%), with the remaining 7 undergoing replacement. Mean aortic occlusion time (with endoaortic balloon) was 102 ± 28 minutes, and mean cardiopulmonary bypass time was 131 ± 34 minutes. Two patients (1.7%) required reoperation on the mitral valve, and there was one hospital death (0.8%). Echocardiographic follow-up was completed in 98 patients with a mean follow-up of 8.4 ± 8.1 months. Mitral regurgitation of trace or less was seen in 95 patients (96.9%).

Our initial results at Cleveland Clinic were published in early 2011.²⁶ From January 2006 to January 2009, 759 patients with degenerative mitral valve disease and posterior leaflet prolapse underwent primary isolated mitral valve surgery by complete sternotomy ($n = 114$), partial sternotomy ($n = 270$), right mini-antrolateral thoracotomy ($n = 114$), or a robotic approach ($n = 261$). Outcomes were compared on an intent-to-treat basis using propensity-score matching. Mitral valve repair was achieved in all patients except 1 patient in the complete sternotomy group. In matched groups, median cardiopulmonary bypass time was 42 minutes longer for robotic than complete sternotomy, 39 minutes longer than partial sternotomy, and 11 minutes longer than right mini-antrolateral thoracotomy ($P < 0.0001$); median myocardial ischemic time was 26 minutes longer than complete sternotomy and partial sternotomy, and 16 minutes longer than right mini-antrolateral thoracotomy ($P < 0.0001$). Quality of mitral valve repair was similar among matched groups ($P = 0.6, 0.2$, and 0.1 , respectively). There were no in-hospital deaths. Neurologic, pulmonary, and renal complications were similar among groups ($P > 0.1$). The robotic group had the lowest occurrences of atrial fibrillation and pleural effusion, contributing to the shortest hospital stay (median 4.2 days), 1.0, 1.6, and 0.9 days shorter than for complete sternotomy, partial sternotomy, and right mini-antrolateral thoracotomy (all $P < 0.001$), respectively.

An early major concern of robotic mitral valve surgery has been the ability to perform complex repairs, such as anterior leaflet or bileaflet repair. Although we began our experience by focusing primarily on posterior leaflet

prolapse, we now feel confident with the robotic approach in patients with anterior or bileaflet prolapse as well. In addition, robotic surgery is offered to patients with mitral valve regurgitation and atrial fibrillation or tricuspid regurgitation.

LIMITATIONS

A significant limitation of contemporary robotic systems is the lack of haptics or tactile feedback. Haptics do for touch what computer graphics do for vision. Although the optics and vision systems have continued to improve dramatically, tactile feedback to the surgeon does not yet exist in robotic surgery. In conventional surgery, almost everything a surgeon does relates to force feedback. The response of tissues to manipulation and the forces applied and given back to the surgeon are essential to identifying pathologic areas, assessing tissue boundaries, and determining the quality of an operation. Currently, surgeons performing robotic surgery assess the force applied to tissue by what they see—how tight tissue appears, how sharp tissue contours are, how subtle color changes are, and so forth. Improving tactile feedback is critical to the continued evolution of robotic technology in minimally invasive surgery.

Another limitation to greater adoption of robotic cardiac surgery is the capital investment required. The cost of \$1.5 million to \$2 million per system (depending on the model, features, service contracts, etc.) plus a per-case cost and additional annual service agreements place it beyond the reach of many institutions. Taking into account these costs, a number of studies have shown higher in-hospital costs for robotic cardiac surgery; this may be shortsighted. In our experience, the per-case cost of robotic surgery is similar to that of conventional surgery when economic outcomes beyond hospital discharge are taken into account.

Longer operative times necessary for robotic mitral valve repair have in part slowed its adoption, although whether or not these longer times affect clinical outcomes remains to be determined. In addition to the setup time for robotic cardiac surgery, a significant portion of time is dedicated to placement of the annuloplasty ring, which is usually anchored with individual mattress sutures that require time-consuming instrument tying. Alternative methods of securing the annuloplasty band, such as a running suture technique or the use of nitinol U-clips (Medtronic, Minneapolis, MN) have shortened operative times and lessened the technical burden of tying a large number of knots endoscopically. In a 2010 report from our institution, a cohort of patients in whom the annuloplasty rings were secured with interrupted sutures ($n = 50$) was compared with a cohort of patients in whom the annuloplasty rings were secured with a running technique ($n = 50$).²¹ Median total procedure (wheels in to wheels out), cardiopulmonary bypass, and aortic occlusion times were significantly decreased by 38, 32, and 19 minutes ($P < 0.01$ in all), respectively, in the running annuloplasty cohort without sacrificing short-term outcomes. In 2007, investigators at Eastern Carolina University reported on a cohort of patients in whom U-clips

were used ($n = 50$) in comparison with a cohort of patients in whom conventional sutures were used ($n = 72$).²⁷ Cardiopulmonary bypass, aortic occlusion, and annuloplasty band placement times were shorter in the U-clip cohort (U-clips versus sutures: 144 ± 50 minutes versus 169 ± 35 minutes, 105 ± 30 minutes versus 132 ± 29 minutes, and 26 ± 5 minutes versus 40 ± 10 minutes, respectively, $P < 0.01$ for all).

Robotic coronary artery bypass surgery continues to be a challenging procedure. The most significant limitation to the success and adoption of robotic bypass surgery is the inability to consistently reproduce a high-quality anastomosis in a timely fashion. Using conventional suture and tying knots adds a significant amount of time to the procedure. Nitinol U-clips (Coalescent Surgical, Inc., Sunnyvale, CA) have been used successfully as an alternative to sutured anastomosis with excellent short-term and mid-term graft patency.^{22,23} Additional alternative methods of creating vascular anastomoses, such as glue or connecting devices, may avert the need to use conventional sutured techniques.^{25,28}

OTHER MINIMALLY INVASIVE APPROACHES

In addition to the robotic approach, many minimally invasive approaches have been described for mitral valve surgery, including the partial sternotomy and right thoracotomy. Common variations of the partial sternotomy include a right-sided partial sternotomy, an upper J incision, a right parasternal incision, and a lower half ministernotomy (T incision).^{1,3,4,17,19,20} Investigators at our institution pioneered the partial upper sternotomy with J incision. Initial results using this approach and an extended transeptal incision were favorable. In our initial experience of 462 cases published in 1999, conversion to a complete sternotomy was necessary in 3%, and there were low rates of wound infection (0.2%), low transfusion requirements, and excellent cosmesis.² In a 2010 report of 590 well-matched patient pairs who underwent conventional minimally invasive surgery versus complete sternotomy, there were cosmetic, blood product use, respiratory, and pain advantages in the minimally invasive cohort with no apparent detriments.⁶ Conventional minimally invasive approaches have since continued to demonstrate improved outcomes and economic benefits over similar surgeries performed through complete sternotomies.³ Given these advantages, mortality and morbidity for robotic and percutaneous mitral valve procedures should be compared with those of conventional minimally invasive approaches rather than with the complete sternotomy.

FUTURE SYSTEMS AND NOVEL VISUALIZATION TECHNIQUES

Technologic advances in cardiac surgery are occurring at a rapid pace. Robotic cardiac surgery has become commonplace for some surgeons. Future incremental modifications and improvements of current systems and

instruments undoubtedly will occur. In addition, novel technology will be developed that will radically change the current paradigm of robotic cardiac surgery and robotic cardiac surgery training.

Current robotic systems are large, take up a lot of space in the operating room, and are cumbersome to move. As technology develops, systems will become smaller, have lower profiles, and be more mobile. Port sizes for the camera and working arms will become even smaller. Further miniaturization may allow for the development of surgical micro-robots, magnetically controlled devices that can be navigated remotely, ingestible cameras, and implantable sensors. Research is currently under way to develop wireless imaging and task-assisting robots that can be placed inside the abdominal cavity during surgery.¹⁵ In addition, investigators at Carnegie Mellon University have described a mobile robotic device that can adhere to the epicardium and navigate to any location in a porcine beating heart model.²⁹

Improving surgical dexterity with haptic feedback is essential to the continued evolution of cardiac surgery, and haptics in robotic surgery is an area of active research. Researchers at Pennsylvania State and Millersville Universities developed a haptic suture simulator that gives a realistic feeling when handling and suturing tissue.⁷ In this simulator, artificial skin deforms relative to the pressure applied to a network of masses and springs through the surgical tool. Specialized software calculates contact forces in the tissue and returns the appropriate forces to the user to simulate the impact of pushing, pulling, cutting, and suturing the skin and underlying tissue. Technology like this could eventually be applied to robotic surgery and allow the surgeon to “feel” the tissue through the robotic arms. The lack of force feedback in current systems makes it possible for the surgeon to inadvertently apply excessive force to the tissue and cause tissue damage. By incorporating haptic feedback into future systems, surgeons will gain a more precise and realistic feel of how tissue is responding to the forces generated by the robotic end-effectors.

Further advancements in visualization will continue to push the field of robotic cardiac surgery forward. In contrast to conventional surgery, the robotic surgeon looks through a vision system rather than directly at the operative field. The three-dimensional display, high definition, and up to 10 $\times$ magnification of the system augment the surgeon's visualization of important structures. In addition, this artificial visualization offers some unique opportunities, such as image stabilization and image overlay. Currently, creation of small-vessel anastomoses on the beating heart is challenging with the robot. Image stabilization systems using a virtual motion compensation scheme are under development with the goal of rendering a motion-stabilized view of the area of interest.¹² Image overlay with the robotic instruments is another unique concept with the robot. Three-dimensional modeling and reconstruction from computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound superimposed with the robotic instruments could provide real-time data acquisition of pathologic characteristics or repair quality. For example, investigators at the University of Western Ontario used real-time three-dimensional

echocardiography as the sole guiding method for atrial septal defect closure in porcine hearts.¹¹ When compared with conventional two-dimensional echocardiography, task completion times were improved by as much as 70%. Investigators at our institution have demonstrated direct endoscopy-guided mitral and tricuspid valve repair in an open-chest, beating-heart bovine model.^{30,31} Using this technique, investigators showed the technical feasibility of beating-heart valve surgery under direct endoscopic imaging. Although the study was performed under open-chest conditions, it is a first step toward closed-chest intracardiac surgery using direct endoscopic visualization. Someday the robotic cardiac surgeon may be able to switch the display and use an alternative imaging source in place of, or in conjunction with, the three-dimensional display to perform beating-heart intracardiac operations.

The future of robotic cardiac surgery is bright. Although years away from full development, it is conceivable that one day a system will exist that will perform fully robotic or automated cardiac surgery. In this scenario, the surgeon will enter all preoperative imaging data on a patient, perform the operation on a virtual simulator, and then transfer the simulation to a robotic telemanipulation system that will perform the operation flawlessly. In addition, a scenario where the operation is planned by software and then performed by a robotic system is imaginable. Although scenarios such as these are years away, existing work has clearly laid the groundwork for automated cardiac surgery.

CONCLUSION

A renaissance in cardiac surgery is under way. Robotic technology is now well established in cardiac surgery and has become standard practice for some surgeons. The success of robotic cardiac surgery is largely the result of advancements in cannulation methods, video optics, instrumentation, and training methods. The development of extrathoracic cardiopulmonary bypass with specialized endovascular cannulas and catheters has allowed for adequate antegrade and retrograde cardioplegic arrest, and ventricular decompression. Enhanced three-dimensional high-definition visualization with the capability of 10× magnification has provided improved clarity and detail of the anastomotic structures. Seven degrees of freedom with the “endo-wrist” instruments, where additional articulation occurs near the tip of the instrument, was critical in improving dexterity in tight spaces. Lastly, the dual-console capability in the newest system allows two surgeons to sit at separate consoles and easily and quickly take control of the instruments at any time during surgery, a situation that helps in training.

Numerous developments must be made in robotic cardiac surgery to increase adoption of robotic technology for coronary revascularization. The creation of robotic coronary vascular anastomoses on a beating heart is technically challenging with current technology, and the inability to consistently reproduce high-quality anastomoses remains a limiting factor in adoption. Improved stabilization devices, automated vascular anastomotic

devices, and the ability to reach all areas of a beating, full heart in a closed chest environment needs to be developed for robotic revascularization surgery to reach its full potential.

Similar to other technologic advances in surgery, robotic cardiac surgery is an evolutionary process. Even the greatest skeptics must concede that substantial progress has been made. In the present era, robotic mitral valve repair has safety and short-term effectiveness profiles similar to those of conventional surgery and has the additional benefits of shorter lengths of stay and faster return to work. Despite enthusiasm, caution cannot be overemphasized because long-term durability of repair has yet to be determined. Any new technology, approach, or technique, including robotic cardiac surgery, must be critically compared with traditional operations, which continue to exhibit long-term success and ever-decreasing rates of morbidity and mortality.

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MANAGEMENT OF CARDIAC ARRHYTHMIAS

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CARDIAC DEVICES FOR THE TREATMENT OF BRADYARRHYTHMIAS AND TACHYARRHYTHMIAS

Adam S. Fein • Lilian P. Joventino • Peter J. Zimetbaum

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- Implantable Cardioverter-Defibrillators

HISTORICAL PERSPECTIVE AND OVERVIEW

Paul Zoll developed the first transcutaneous electronic pacemaker in 1952 for the treatment of life-threatening bradycardia.¹ The first internal pacemaker was implanted in 1958 for the treatment of complete heart block² and in the management of Stokes-Adams seizures.³ Early pacemaker models were simple, fixed-rate devices. Thoracic surgeons performed most early implants by placing epicardial leads directly on the exposed heart; these leads were connected to an abdominally implanted pulse generator. Modern pacemakers have sophisticated microprocessors that apply diagnostic and therapeutic algorithms, which have dramatically increased their versatility.

The development of the implantable cardioverter-defibrillator (ICD) was pioneered by Michel Mirowski.⁴⁻⁶ The initial purpose of the ICD was to provide immediate, automatic defibrillation to ambulatory patients who were victims of a lethal ventricular arrhythmia. Mirowski performed the first human ICD implantation in 1980.⁶ First-generation ICDs were composed of large generators (>200 cm³ volume) implanted in an abdominal pocket with epicardial defibrillator patches. Whereas these early ICDs were capable of only high-energy shocks, current ICDs are small (<40 cm³ volume), yet they contain all the advanced pacing functions of modern pacemakers as well as complex tachycardia treatment options (Figs. 85-1 and 85-2). Despite their diminutive size, newer ICDs have become progressively superior in their sensing, diagnosis, and treatment of arrhythmias. Since the late 1990s, ICDs have emerged as the single most effective lifesaving intervention in the prevention of sudden cardiac death.⁷⁻¹¹

With increased sophistication and miniaturization of pulse generators and the development of the much simpler and safer transvenous approach for implantation of cardiac devices, indications for cardiac pacing as well as for ICDs have dramatically expanded.^{12,13} In addition, the U.S. Food and Drug Administration (FDA) approved the totally subcutaneous ICD in September 2012. It is estimated that approximately 400,000 devices are implanted each year in the United States, and there are more than 3 million patients with implanted cardiac devices currently.

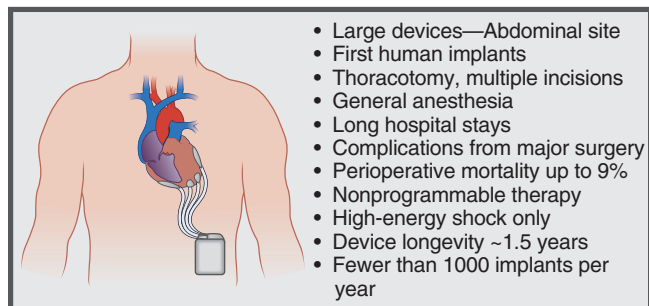


FIGURE 85-1 ■ Implantable cardioverter-defibrillators in 1980. (Courtesy Medtronic, Inc., Minneapolis, MN.)

The remainder of this chapter focuses on the description, implantation techniques, indications, and complications of current implantable cardiac pacemakers and defibrillators.

INDICATIONS FOR IMPLANTATION OF CARDIAC DEVICES

The American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines for device-based therapy of cardiac rhythm abnormalities were updated in 2012.¹⁴

Temporary Pacemakers

Indications

Placement of a temporary pacemaker is indicated whenever hemodynamic compromise is present because of a bradyarrhythmia. Temporary pacemakers should also be placed prophylactically if a high risk for development of hemodynamically intolerated bradycardia is present. Specific guidelines for placement of temporary pacemakers in the setting of acute myocardial infarction exist.¹⁵ Temporary transvenous pacing is indicated in symptomatic sinus bradycardia, sinus pauses of more than 3 seconds, or sinus bradycardia with a heart rate below 40 beats/minute associated with hypotension or hemodynamic compromise, and if unresponsive to a maximum dose (2 mg) of intravenous atropine. Other class I indications for temporary transvenous pacing in acute myocardial infarction include ventricular asystole, alternating left and right bundle branch block, recurrent polymorphic ventricular tachycardia with a heart rate less than 60 beats/minute and prolonged QT, and new bundle branch block or fascicular block and right bundle branch block in the setting of Mobitz II second-degree atrioventricular (AV) block.¹⁵

Venous Access

Table 85-1 summarizes the different sites that can be used for insertion of a temporary pacemaker.¹⁶ The particular patient and the advantages and disadvantages of each site are important factors in the decision of which site to use.

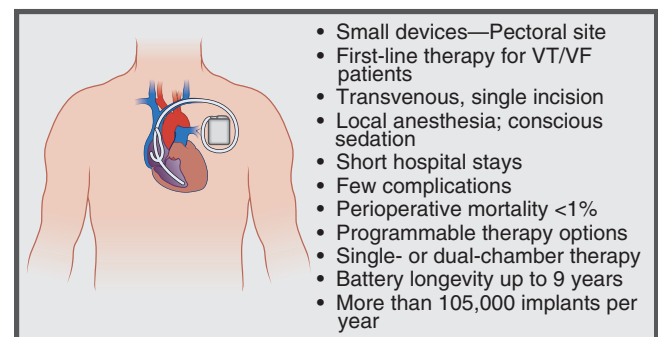


FIGURE 85-2 ■ Implantable cardioverter-defibrillators today. VT/VF, Ventricular tachycardia/ventricular flutter. (Courtesy Medtronic, Inc., Minneapolis, MN.)

TABLE 85-1 Sites for Placement of a Temporary Pacemaker

Site	Advantages	Disadvantages
Femoral vein	Easy access	Leg must remain immobilized High infection risk Fluoroscopy required for proper placement Patient must lie flat
Internal jugular vein	Good site for pacer placement (right better than left)	Risk of pneumothorax, inadvertent carotid artery puncture Patient must lie flat for access; Trendelenburg position preferred to avoid air embolism
Subclavian vein	Good site for pacer placement (left better than right)	Risk of pneumothorax, hemothorax with inadvertent subclavian artery puncture Patient must lie flat for access; Trendelenburg position preferred to avoid air embolism
Antecubital vein (basilic, median basilic, or cephalic)	Access is low risk Good site for pacer placement (left better than right)	Risk of dislodgement; arm must remain immobilized Basilic or median basilic preferred (cephalic has tortuous course to central veins) Fluoroscopy required for pacer placement

From Baim DS, Grossman W, editors: *Grossman's cardiac catheterization, angiography, and intervention*, ed 6, Philadelphia, 2000, Lippincott Williams & Wilkins.

For example, the internal jugular and subclavian veins may be chosen when need for stability and longer pacing requirement is anticipated. If a permanent pacemaker will be required in the future, the temporary pacemaker should be placed through a vein remote from the preferred site for permanent pacemaker implantation. Use of the antecubital veins minimizes bleeding in the coagulopathic patient. However, the risk of cardiac perforation or lead dislodgement is higher if the arm is not kept fully immobilized.

Permanent Pacemakers

Indications

Justifications for permanent pacemaker implantation include alleviation of symptoms and prevention of subsequent morbidity or mortality as a direct result of bradycardia. Bradycardia can result from a variety of disorders of the sinus node, the AV node, the His-Purkinje system, or a combination of these. Sinus node or AV node disease is often not life-threatening but may cause significant symptoms. On the other hand, disease of the His-Purkinje system may be asymptomatic until the development of AV block and its associated severe adverse events.

Symptoms from bradycardia generally result from inadequate cardiac output. Such symptoms may be vague and include fatigue, decreased exercise tolerance, dyspnea

BOX 85-1 Recommendations for Permanent Pacing in Sinus Node Dysfunction

CLASS I

1. Permanent pacemaker implantation is indicated for sinus node dysfunction (SND) with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. (*Level of Evidence: C*)
2. Permanent pacemaker implantation is indicated for symptomatic chronotropic incompetence. (*Level of Evidence: C*)
3. Permanent pacemaker implantation is indicated for symptomatic sinus bradycardia that results from required drug therapy for medical conditions. (*Level of Evidence: C*)

CLASS IIA

1. Permanent pacemaker implantation is reasonable for SND with heart rate less than 40 beats per minute (bpm) when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented. (*Level of Evidence: C*)
2. Permanent pacemaker implantation is reasonable for syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiologic studies. (*Level of Evidence: C*)

CLASS IIB

1. Permanent pacemaker implantation may be considered in minimally symptomatic patients with chronic heart rate less than 40 bpm while awake. (*Level of Evidence: C*)

CLASS III

1. Permanent pacemaker implantation is not indicated for SND in asymptomatic patients. (*Level of Evidence: C*)
2. Permanent pacemaker implantation is not indicated for SND in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia. (*Level of Evidence: C*)
3. Permanent pacemaker implantation is not indicated for SND with symptomatic bradycardia due to nonessential drug therapy. (*Level of Evidence: C*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: *ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices)* developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

on exertion, lightheadedness, dizziness, congestive heart failure, presyncope, and syncope. Patient-triggered ambulatory cardiac monitoring is often helpful in establishing that such nonspecific symptoms are in fact the result of symptomatic bradycardia. Boxes 85-1 through 85-12 summarize the indications for permanent cardiac pacing published by the ACC/AHA Task Force on Practice Guidelines in 2008 and maintained as part of the 2012 focused update.^{12,14}

Text continued on p. 1491

BOX 85-2 Recommendations for Acquired Atrioventricular Block in Adults**CLASS I**

1. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree atrioventricular (AV) block at any anatomic level associated with bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be due to AV block. (*Level of Evidence: C*)
2. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia. (*Level of Evidence: C*)
3. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level in awake, symptom-free patients in sinus rhythm, with documented periods of asystole greater than or equal to 3.0 seconds or any escape rate less than 40 beats per minute (bpm), or with an escape rhythm that is below the AV node. (*Level of Evidence: C*)
4. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level in awake, symptom-free patients with atrial fibrillation (AF) and bradycardia with 1 or more pauses of at least 5 seconds or longer. (*Level of Evidence: C*)
5. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level after catheter ablation of the AV junction. (*Level of Evidence: C*)
6. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with postoperative AV block at any anatomic level associated with postoperative AV block that is not expected to resolve after cardiac surgery. (*Level of Evidence: C*)
7. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy, with or without symptoms. (*Level of Evidence: B*)
8. Permanent pacemaker implantation is indicated for second-degree AV block with associated symptomatic bradycardia regardless of type or site of block. (*Level of Evidence: B*)
9. Permanent pacemaker implantation is indicated for asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of 40 bpm or faster if cardiomegaly or left ventricular (LV) dysfunction is present or if the site of block is below the AV node. (*Level of Evidence: B*)

10. Permanent pacemaker implantation is indicated for second- or third-degree AV block during exercise in the absence of myocardial ischemia. (*Level of Evidence: C*)

CLASS IIA

1. Permanent pacemaker implantation is reasonable for persistent third-degree AV block with an escape rate greater than 40 bpm in asymptomatic adult patients without cardiomegaly. (*Level of Evidence: C*)
2. Permanent pacemaker implantation is reasonable for asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiologic study. (*Level of Evidence: B*)
3. Permanent pacemaker implantation is reasonable for first- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise. (*Level of Evidence: B*)
4. Permanent pacemaker implantation is reasonable for asymptomatic type II second-degree AV block with a narrow QRS. When type II second-degree AV block occurs with a wide QRS, including isolated right bundle branch block, pacing becomes a class I recommendation. (See Section 2.1.3, "Chronic Bifascicular Block.") (*Level of Evidence: B*)

CLASS IIB

1. Permanent pacemaker implantation may be considered for neuromuscular disease such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease. (*Level of Evidence: B*)
2. Permanent pacemaker implantation may be considered for AV block in the setting of drug use and/or drug toxicity when the block is expected to recur even after the drug is withdrawn. (*Level of Evidence: B*)

CLASS III

1. Permanent pacemaker implantation is not indicated for asymptomatic first-degree AV block. (See Section 2.1.3, "Chronic Bifascicular Block.") (*Level of Evidence: B*)
2. Permanent pacemaker implantation is not indicated for asymptomatic type I second-degree AV block at the supra-His (AV node) level or that which is not known to be intra or infra or infra-Hisian. (*Level of Evidence: C*)
3. Permanent pacemaker implantation is not indicated for AV block that is expected to resolve and is unlikely to recur (e.g., drug toxicity, Lyme disease, or transient increases in vagal tone or during hypoxia in sleep apnea syndrome in the absence of symptoms). (*Level of Evidence: B*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

BOX 85-3 Recommendations for Permanent Pacing in Chronic Bifascicular Block**CLASS I**

1. Permanent pacemaker implantation is indicated for advanced second-degree atrioventricular (AV) block or intermittent third-degree AV block. (*Level of Evidence: B*)
2. Permanent pacemaker implantation is indicated for type II second-degree AV block. (*Level of Evidence: B*)
3. Permanent pacemaker implantation is indicated for alternating bundle branch block. (*Level of Evidence: C*)

CLASS IIA

1. Permanent pacemaker implantation is reasonable for syncope not demonstrated to be due to AV block when other likely causes have been excluded, specifically ventricular tachycardia (VT). (*Level of Evidence: B*)
2. Permanent pacemaker implantation is reasonable for an incidental finding at electrophysiologic study of a markedly prolonged HV interval (greater than or equal to 100 milliseconds) in asymptomatic patients. (*Level of Evidence: B*)

3. Permanent pacemaker implantation is reasonable for an incidental finding at electrophysiologic study of pacing-induced infra-His block that is not physiologic. (*Level of Evidence: B*)

CLASS IIB

1. Permanent pacemaker implantation may be considered in the setting of neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with bifascicular block or any fascicular block, with or without symptoms. (*Level of Evidence: C*)

CLASS III

1. Permanent pacemaker implantation is not indicated for fascicular block without AV block or symptoms. (*Level of Evidence: B*)
2. Permanent pacemaker implantation is not indicated for fascicular block with first-degree AV block without symptoms. (*Level of Evidence: B*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1-e62, 2008.

BOX 85-4 Recommendations for Permanent Pacing after the Acute Phase of Myocardial Infarction**CLASS I**

1. Permanent ventricular pacing is indicated for persistent second-degree atrioventricular (AV) block in the His-Purkinje system with alternating bundle branch block or third-degree AV block within or below the His-Purkinje system after ST-segment elevation myocardial infarction (MI). (*Level of Evidence: B*)
2. Permanent ventricular pacing is indicated for transient advanced second- or third-degree infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiologic study may be necessary. (*Level of Evidence: B*)
3. Permanent ventricular pacing is indicated for persistent and symptomatic second- or third-degree AV block. (*Level of Evidence: C*)

CLASS IIB

1. Permanent ventricular pacing may be considered for persistent second- or third-degree AV block at the AV

node level, even in the absence of symptoms. (*Level of Evidence: B*)

CLASS III

1. Permanent ventricular pacing is not indicated for transient AV block in the absence of intraventricular conduction defects. (*Level of Evidence: B*)
2. Permanent ventricular pacing is not indicated for transient AV block in the presence of isolated left anterior fascicular block. (*Level of Evidence: B*)
3. Permanent ventricular pacing is not indicated for new bundle branch block or fascicular block in the absence of AV block. (*Level of Evidence: B*)
4. Permanent ventricular pacing is not indicated for persistent asymptomatic first-degree AV block in the presence of bundle branch or fascicular block. (*Level of Evidence: B*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1-e62, 2008.

BOX 85-5 Recommendations for Permanent Pacing in Hypersensitive Carotid Sinus Syndrome and Neurocardiogenic Syncope**CLASS I**

1. Permanent pacing is indicated for recurrent syncope caused by spontaneously occurring carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole of more than 3 seconds. (*Level of Evidence: C*)

CLASS IIA

1. Permanent pacing is reasonable for syncope without clear, provocative events and with a hypersensitive cardioinhibitory response of 3 seconds or longer. (*Level of Evidence: C*)

CLASS IIB

1. Permanent pacing may be considered for significantly symptomatic neurocardiogenic syncope associated with

bradycardia documented spontaneously or at the time of tilt-table testing. (*Level of Evidence: B*)

CLASS III

1. Permanent pacing is not indicated for a hypersensitive cardioinhibitory response to carotid sinus stimulation without symptoms or with vague symptoms. (*Level of Evidence: C*)
2. Permanent pacing is not indicated for situational vasovagal syncope in which avoidance behavior is effective and preferred. (*Level of Evidence: C*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1-e62, 2008.

BOX 85-6 Recommendations for Pacing after Cardiac Transplantation**CLASS I**

1. Permanent pacing is indicated for persistent inappropriate or symptomatic bradycardia not expected to resolve and for other class I indications for permanent pacing. (*Level of Evidence: C*)

CLASS IIB

1. Permanent pacing may be considered when relative bradycardia is prolonged or recurrent, which limits rehabilitation or discharge after postoperative recovery from cardiac transplantation. (*Level of Evidence: C*)
2. Permanent pacing may be considered for syncope after cardiac transplantation even when bradyarrhythmia has not been documented. (*Level of Evidence: C*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

BOX 85-7 Recommendations for Permanent Pacemakers that Automatically Detect and Pace to Terminate Tachycardias**CLASS IIA**

1. Permanent pacing is reasonable for symptomatic recurrent supraventricular tachycardia (SVT) that is reproducibly terminated by pacing when catheter ablation and/or drugs fail to control the arrhythmia or produce intolerable side effects. (*Level of Evidence: C*)

CLASS III

1. Permanent pacing is not indicated in the presence of an accessory pathway that has the capacity for rapid anterograde conduction. (*Level of Evidence: C*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

BOX 85-8 Recommendations for Pacing to Prevent Tachycardia**CLASS I**

1. Permanent pacing is indicated for sustained pause-dependent ventricular tachycardia (VT), with or without QT prolongation. (*Level of Evidence: C*)

CLASS IIA

1. Permanent pacing is reasonable for high-risk patients with congenital long-QT syndrome. (*Level of Evidence: C*)

CLASS IIB

1. Permanent pacing may be considered for prevention of symptomatic, drug-refractory, recurrent atrial fibrillation (AF) in patients with coexisting sinus node dysfunction (SND). (*Level of Evidence: B*)

CLASS III

1. Permanent pacing is not indicated for frequent or complex ventricular ectopic activity without sustained VT in the absence of the long-QT syndrome. (*Level of Evidence: C*)
2. Permanent pacing is not indicated for torsade de pointes VT due to reversible causes. (*Level of Evidence: A*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

BOX 85-9 Recommendation for Pacing to Prevent Atrial Fibrillation**CLASS III**

1. Permanent pacing is not indicated for the prevention of atrial fibrillation (AF) in patients without any other indication for pacemaker implantation. (*Level of Evidence: B*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

BOX 85-10 Recommendations for Cardiac Resynchronization Therapy in Patients with Severe Systolic Heart Failure**CLASS I**

1. Cardiac resynchronization therapy (CRT) is indicated for patients who have left ventricular ejection fraction (LVEF) less than or equal to 35%, sinus rhythm, left bundle branch block (LBBB) with a QRS duration greater than or equal to 150 msec, and New York Heart Association (NYHA) class II, III, or ambulatory IV symptoms on optimal recommended medical therapy. (*Level of Evidence: A for NYHA class III/IV; Level of Evidence: B for NYHA class II*)

CLASS IIA

1. CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 msec, and NYHA class II, III, or ambulatory IV symptoms on optimal recommended medical therapy. (*Level of Evidence: B*)
2. CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 msec, and NYHA class III/ambulatory class IV symptoms on optimal recommended medical therapy. (*Level of Evidence: A*)
3. CRT can be useful in patients with atrial fibrillation and LVEF less than or equal to 35% on guideline-directed medical therapy (GDMT) if (a) the patient requires ventricular pacing or otherwise meets CRT criteria and (b) atrioventricular (AV) nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT. (*Level of Evidence: B*)

4. CRT can be useful for patients on GDMT who have LVEF less than or equal to 35% and are undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing. (*Level of Evidence: C*)

CLASS IIB

1. CRT may be considered for patients who have LVEF less than or equal to 30%, ischemic etiology of heart failure, sinus rhythm, LBBB with a QRS duration of greater than or equal to 150 msec, and NYHA class I symptoms on optimal medical therapy. (*Level of Evidence: C*)
2. CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120 to 149 msec, and NYHA class III/ambulatory class IV on optimal medical therapy. (*Level of Evidence: B*)
3. CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 msec, and NYHA class II symptoms on optimal medical therapy. (*Level of Evidence: B*)

CLASS III

1. CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration less than 150 msec. (*Level of Evidence: B*)
2. CRT is not indicated for patients whose comorbidities and/or frailty limit survival with good functional capacity to less than 1 year. (*Level of Evidence: C*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

BOX 85-11 Recommendations for Pacing in Patients with Hypertrophic Cardiomyopathy**CLASS I**

1. Permanent pacing is indicated for sinus node dysfunction (SND) or atrioventricular (AV) block in patients with hypertrophic cardiomyopathy (HCM) as described previously (see Section 2.1.1, "Sinus Node Dysfunction," and Section 2.1.2, "Acquired Atrioventricular Block in Adults"). (*Level of Evidence: C*)

(*Level of Evidence: A*) As for class I indications, when risk factors for sudden cardiac death (SCD) are present, consider a DDD implantable cardioverter-defibrillator (ICD) (see Section 3, "Indications for Implantable Cardioverter-Defibrillator Therapy").

CLASS IIB

1. Permanent pacing may be considered in medically refractory symptomatic patients with HCM and significant resting or provoked LV outflow tract obstruction.

CLASS III

1. Permanent pacemaker implantation is not indicated for patients who are asymptomatic or whose symptoms are medically controlled. (*Level of Evidence: C*)
2. Permanent pacemaker implantation is not indicated for symptomatic patients without evidence of LV outflow tract obstruction. (*Level of Evidence: C*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

BOX 85-12 Recommendations for Permanent Pacing in Children, Adolescents, and Patients with Congenital Heart Disease

CLASS I

1. Permanent pacemaker implantation is indicated for advanced second- or third-degree atrioventricular (AV) block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output. (*Level of Evidence: C*)
2. Permanent pacemaker implantation is indicated for sinus node dysfunction (SND) with correlation of symptoms during age-inappropriate bradycardia. The definition of bradycardia varies with the patient's age and expected heart rate. (*Level of Evidence: B*)
3. Permanent pacemaker implantation is indicated for postoperative advanced second- or third-degree AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery. (*Level of Evidence: B*)
4. Permanent pacemaker implantation is indicated for congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction. (*Level of Evidence: B*)
5. Permanent pacemaker implantation is indicated for congenital third-degree AV block in the infant with a ventricular rate less than 55 bpm or with congenital heart disease and a ventricular rate less than 70 bpm. (*Level of Evidence: C*)

CLASS IIA

1. Permanent pacemaker implantation is reasonable for patients with congenital heart disease and sinus bradycardia for the prevention of recurrent episodes of intratrial reentrant tachycardia; SND may be intrinsic or secondary to antiarrhythmic treatment. (*Level of Evidence: C*)
2. Permanent pacemaker implantation is reasonable for congenital third-degree AV block beyond the first year of life with an average heart rate less than 50 bpm, abrupt pauses in ventricular rate that are 2 or 3 times the basic cycle length, or associated with symptoms due to chronotropic incompetence. (*Level of Evidence: B*)
3. Permanent pacemaker implantation is reasonable for sinus bradycardia with complex congenital heart disease with a resting heart rate less than 40 bpm or pauses in ventricular rate longer than 3 seconds. (*Level of Evidence: C*)

4. Permanent pacemaker implantation is reasonable for patients with congenital heart disease and impaired hemodynamics due to sinus bradycardia or loss of AV synchrony. (*Level of Evidence: C*)
5. Permanent pacemaker implantation is reasonable for unexplained syncope in the patient with prior congenital heart surgery complicated by transient complete heart block with residual fascicular block after a careful evaluation to exclude other causes of syncope. (*Level of Evidence: B*)

CLASS IIB

1. Permanent pacemaker implantation may be considered for transient postoperative third-degree AV block that reverts to sinus rhythm with residual bifascicular block. (*Level of Evidence: C*)
2. Permanent pacemaker implantation may be considered for congenital third-degree AV block in asymptomatic children or adolescents with an acceptable rate, a narrow QRS complex, and normal ventricular function. (*Level of Evidence: B*)
3. Permanent pacemaker implantation may be considered for asymptomatic sinus bradycardia after biventricular repair of congenital heart disease with a resting heart rate less than 40 bpm or pauses in ventricular rate longer than 3 seconds. (*Level of Evidence: C*)

CLASS III

1. Permanent pacemaker implantation is not indicated for transient postoperative AV block with return of normal AV conduction in the otherwise asymptomatic patient. (*Level of Evidence: B*)
2. Permanent pacemaker implantation is not indicated for asymptomatic bifascicular block with or without first-degree AV block after surgery for congenital heart disease in the absence of prior transient complete AV block. (*Level of Evidence: C*)
3. Permanent pacemaker implantation is not indicated for asymptomatic type I second-degree AV block. (*Level of Evidence: C*)
4. Permanent pacemaker implantation is not indicated for asymptomatic sinus bradycardia with the longest relative risk interval less than 3 seconds and a minimum heart rate more than 40 bpm. (*Level of Evidence: C*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

Cardiac Resynchronization Therapy (or Biventricular Pacing) for the Treatment of Congestive Heart Failure

The 2012 guidelines updated the formal recommendations (see Box 85-10) for cardiac resynchronization therapy (CRT), or biventricular pacing, as an adjunctive treatment for patients with advanced congestive heart failure.¹⁴ Over the past decade, CRT has emerged as a proven therapy for patients with congestive heart failure (New York Heart Association [NYHA] class >II) caused by systolic dysfunction (left ventricular ejection fraction

≤ 35%) with intraventricular conduction delay, generally of the left bundle branch block type. Patients with QRS duration of more than 150 msec have the strongest clinical response to CRT. There is currently no established role for the use of echocardiographic evidence of mechanical dyssynchrony to select patients for CRT. The 2012 guidelines reflected the growing body of evidence that CRT therapy may benefit patients with milder NYHA I and II symptoms in the setting of pronounced intraventricular conduction delay over 150 msec.^{17,18} Intraventricular conduction delay is present in a large proportion of patients with heart failure, and it is frequently

accompanied by mechanical dyssynchrony. Patients who have benefited from biventricular pacing can have systolic dysfunction as a result of either coronary or non-coronary cardiomyopathies. The therapeutic intent is to improve the mechanical efficiency of the heart by simultaneously activating both ventricles with the use of an implantable pacemaker or pacemaker-defibrillator system. Approximately two thirds of patients who are treated with CRT derive clinical benefit that can be demonstrated by improvement in functional status, quality-of-life scores, and objective measures of exercise capacity, as well as decreases in mortality rate and number of heart failure hospitalizations. In addition, the degree of mitral regurgitation frequently present in the patients treated with CRT often improves, as does left ventricular ejection fraction, with biventricular pacing.

Simultaneous pacing of both ventricles is achieved by pacing the right ventricle from a standard transvenous right ventricular apical lead while the left ventricle is paced by a transvenously placed coronary sinus lead. The preferred location for the coronary sinus lead is within the posterolateral coronary sinus vein, where the activation delay is generally most pronounced because of dyssynchronous activation in the setting of the baseline left bundle branch block type of intraventricular conduction delay. [Figure 85-3](#) illustrates typical lead positions for a biventricular pacing system.

Contraindications

Active infection is a contraindication to placement of permanent pacemaker systems. If the need for pacing is urgent, a temporary transvenous pacemaker should be used. In patients with recurrent or protracted infectious illnesses, temporary placement of a standard (screw-in) pacemaker lead is suggested. The proximal end of the lead is externalized and connected to an external pulse generator, and a sterile dressing is placed over the entry

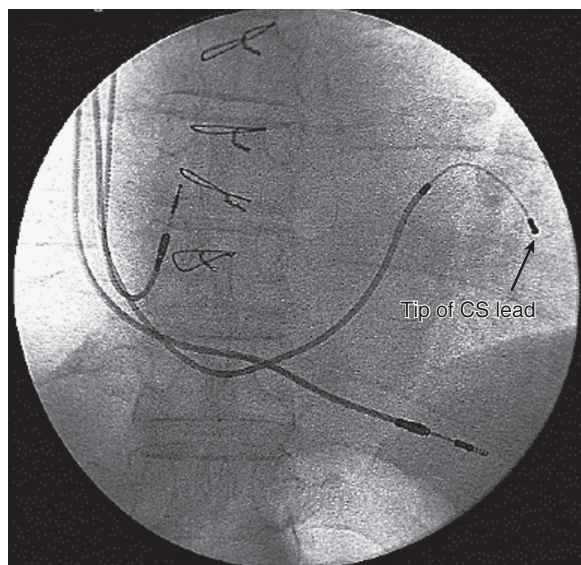


FIGURE 85-3 ■ Fluoroscopic view of a biventricular pacing device. The tip of the coronary sinus (CS) lead is seen within the posterolateral coronary sinus vein.

site. Such temporary systems may be left in place for weeks and may serve as a bridge to implantation of a permanent pacemaker. Alternatively, an epicardial pacing system can be implanted.

Implantable Cardioverter-Defibrillators

Indications

Current ACC/AHA/HRS practice guidelines for ICD therapy are listed in [Boxes 85-13](#) and [85-14](#).¹⁴

A class I indication for ICD therapy is present for patients who survived a cardiac arrest caused by ventricular fibrillation (VF) or hemodynamically significant ventricular tachycardia (VT) not thought to be due to reversible causes. Other class I indications for ICD therapy include spontaneous VT in patients with structural heart disease and syncope of undetermined causes with clinically significant VT or VF induced at electrophysiology study.¹⁴

Several other class I indications for ICD therapy now exist to include the patient population studied in three large clinical trials: MUSTT,⁸ MADIT II,¹⁰ and SCD-HeFT.¹¹ ICD therapy is indicated for patients with left ventricular ejection fraction below 35% (as a result of previous myocardial infarction, who are at least 40 days post myocardial infarction or as a result of nonischemic cardiomyopathy) with functional status consistent with NYHA class II or class III.¹¹ Class I indication for ICD therapy also exists for patients with left ventricular ejection fraction below 30% as a result of previous myocardial infarction (at least 40 days old) who have NYHA class I functional status.¹⁰ In addition, ICD therapy is indicated in patients with left ventricular ejection fraction below 40% as a result of previous myocardial infarction who have nonsustained VT and inducible VT or VF at electrophysiology study.⁸

Other high-risk conditions where ICD therapy is a IIa indication—including arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), hypertrophic cardiomyopathy, long QT syndrome, and Brugada syndrome—have been addressed in the 2012 societal guidelines (see [Box 85-13](#)).

In September 2012, the FDA approved the totally subcutaneous ICD for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant VT, or spontaneous, frequently recurring VT that is reliably terminated with antitachycardia pacing. These devices hold the promise of lifesaving defibrillation without some of the known problems of transvenous systems, including limited vascular access, transvenous lead durability, hazardous lead extractions, and risks of bloodstream infections. There are no current societal guidelines for which patients should be considered for the S-ICD system.

Contraindications to Implantable Cardioverter-Defibrillator Therapy

If VT/VF is a result of a reversible cause such as acute myocardial infarction or serious electrolyte derangements, ICD implantation is not indicated. An ICD is not

BOX 85-13 Recommendations for Implantable Cardioverter-Defibrillators**CLASS I**

1. Implantable cardioverter-defibrillator (ICD) therapy is indicated in patients who are survivors of cardiac arrest due to ventricular fibrillation (VF) or hemodynamically unstable sustained ventricular tachycardia (VT) after evaluation to define the cause of the event and to exclude any completely reversible causes. (*Level of Evidence: A*)
2. ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. (*Level of Evidence: B*)
3. ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study. (*Level of Evidence: B*)
4. ICD therapy is indicated in patients with left ventricular ejection fraction (LVEF) less than 35% due to prior myocardial infarction (MI) who are at least 40 days post MI and are in New York Heart Association (NYHA) functional class II or III. (*Level of Evidence: A*)
5. ICD therapy is indicated in patients with nonischemic dilated cardiomyopathy (DCM) who have an LVEF less than or equal to 35% and who are in NYHA functional class II or III. (*Level of Evidence: B*)
6. ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post MI, have an LVEF less than 30%, and are in NYHA functional class I. (*Level of Evidence: A*)
7. ICD therapy is indicated in patients with nonsustained VT due to prior MI, LVEF less than 40%, and inducible VF or sustained VT at electrophysiologic study. (*Level of Evidence: B*)

CLASS IIA

1. ICD implantation is reasonable for patients with unexplained syncope, significant left ventricular (LV) dysfunction, and nonischemic DCM. (*Level of Evidence: C*)
2. ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function. (*Level of Evidence: C*)
3. ICD implantation is reasonable for patients with HCM who have one or more major risk factors for sudden cardiac death (SCD). (*Level of Evidence: C*)
4. ICD implantation is reasonable for the prevention of SCD in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) who have one or more risk factors for SCD. (*Level of Evidence: C*)
5. ICD implantation is reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta blockers. (*Level of Evidence: B*)
6. ICD implantation is reasonable for nonhospitalized patients awaiting transplantation. (*Level of Evidence: C*)
7. ICD implantation is reasonable for patients with Brugada syndrome who have had syncope. (*Level of Evidence: C*)
8. ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest. (*Level of Evidence: C*)

9. ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta blocker. (*Level of Evidence: C*)
10. ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease. (*Level of Evidence: C*)

CLASS IIB

1. ICD therapy may be considered in patients with nonischemic heart disease who have an LVEF of less than or equal to 35% and who are in NYHA functional class I. (*Level of Evidence: C*)
2. ICD therapy may be considered for patients with long-QT syndrome and risk factors for SCD. (*Level of Evidence: B*)
3. ICD therapy may be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and noninvasive investigations have failed to define a cause. (*Level of Evidence: C*)
4. ICD therapy may be considered in patients with a familial cardiomyopathy associated with sudden death. (*Level of Evidence: C*)
5. ICD therapy may be considered in patients with LV noncompaction. (*Level of Evidence: C*)

CLASS III

1. ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the class I, IIA, and IIB recommendations above. (*Level of Evidence: C*)
2. ICD therapy is not indicated for patients with incessant VT or VF. (*Level of Evidence: C*)
3. ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. (*Level of Evidence: C*)
4. ICD therapy is not indicated for NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D. (*Level of Evidence: C*)
5. ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. (*Level of Evidence: C*)
6. ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, right ventricular (RV) or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). (*Level of Evidence: C*)
7. ICD therapy is not indicated for patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma). (*Level of Evidence: B*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1-e62, 2008.

BOX 85-14 Recommendations for Implantable Cardioverter-Defibrillators in Pediatric Patients and Patients with Congenital Heart Disease

CLASS I

1. Implantable cardioverter-defibrillator (ICD) implantation is indicated in the survivor of cardiac arrest after evaluation to define the cause of the event and to exclude any reversible causes. (*Level of Evidence: B*)
2. ICD implantation is indicated for patients with symptomatic sustained ventricular tachycardia (VT) in association with congenital heart disease who have undergone hemodynamic and electrophysiologic evaluation. Catheter ablation or surgical repair may offer possible alternatives in carefully selected patients. (*Level of Evidence: C*)

CLASS IIA

1. ICD implantation is reasonable for patients with congenital heart disease with recurrent syncope of undetermined origin in the presence of either ventricular dysfunction or inducible ventricular arrhythmias at electrophysiologic study. (*Level of Evidence: B*)

CLASS IIB

1. ICD implantation may be considered for patients with recurrent syncope associated with complex congenital heart disease and advanced systemic ventricular dysfunction when thorough invasive and noninvasive investigations have failed to define a cause. (*Level of Evidence: C*)

CLASS III

1. All class III recommendations found in Section 3, "Indications for Implantable Cardioverter-Defibrillator Therapy," apply to pediatric patients and patients with congenital heart disease, and ICD implantation is not indicated in these patient populations. (*Level of Evidence: C*)

From Epstein AE, DiMarco JP, Ellenbogen KA, et al: ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 51:e1–e62, 2008.

recommended for patients who have a terminal illness and whose life expectancy with an acceptable functional status is less than 12 months.¹⁴ Patients who have severe psychiatric disorders whose illness may be exacerbated by ICD shocks or whose illness may preclude proper ICD follow-up may not be appropriate candidates for ICD implantation. In addition, incessant VT/VF that is refractory to medications is also considered a contraindication to ICD implantation until the arrhythmia is controlled by surgical or catheter ablation.

Similar to implantation of permanent pacemakers, ICD implantation is not recommended in patients with active ongoing infection. Patients with infectious issues who have an indication for ICD therapy can undergo

telemetry monitoring in an acute care or rehabilitation facility until their infection is cleared. Alternatively, a wearable external automated defibrillator is now available for patients who are at high risk for sudden cardiac death as a bridge to permanent ICD therapy. This product is manufactured by ZOLL Medical Corporation (Pittsburgh, PA) and was approved by the FDA in 2002.

BASIC CONCEPTS OF PACING AND ANTITACHYCARDIA THERAPY

Permanent Pacemakers

Pulse Generator

Despite the many variations and designs of modern pacemakers, basic components are similar and include power source (battery), circuitry (output, sensing, telemetry, microprocessor, and memory), metal shell (can), ceramic feedthrough (a piece of wire surrounded by glass or sapphire) to provide an electric connection through the can, outlets through which pacing leads are connected to the header of the pacemaker, and sensors.²⁰ Most pacemaker batteries since 1975 are lithium iodide based. Lithium-based batteries have an ideal energy density that has allowed newer pacemakers to be of small volume yet to possess longer battery life. In addition, as opposed to the original mercury-zinc cells, which develop a sudden decrease in voltage shortly before battery depletion, lithium iodide cells have a predictable and gradual decrease in battery voltage as they approach depletion.¹⁹

At the beginning of life, the lithium iodide battery has a voltage output of approximately 2.8 V. The initial decay is slow until the battery approaches depletion, at which time the battery voltage decays more rapidly. When the battery voltage reaches 2.0 to 2.4 V, the elective replacement indicator is triggered, which may precipitate a change in pacing mode (such as dual-chamber to single-chamber pacing), rate response to nonrate response, or a change in magnet rate behavior.²⁰ Once the elective replacement indicator is triggered, the device has approximately 3 to 6 months before it reaches its end of useful life.

The pulse generator is connected with up to three pacing leads and subsequently implanted into a subcutaneous or submuscular pocket (see implantation techniques). The leads are placed under fluoroscopic guidance at standard right atrial, right ventricular, or in the coronary sinus (for left ventricular pacing) locations. The generator is programmed to sense and pace according to a chosen mode that addresses the individual patient's needs.

Pacemaker Leads

Pacing leads are the direct connection between the pulse generator and the myocardium. The distal end of pacing leads consists of one or two exposed metal electrodes that are linked to the pulse generator by insulated wires.

Leads may be unipolar or bipolar; these distinctions apply to both sensing and pacing functions. Unipolar leads have a single electrode incorporated into the lead

(typically the cathode) and the other electrode (typically the anode) incorporated into the generator. Bipolar leads have both electrodes (the anode and the cathode) incorporated into the distal end of the lead. The difference in electrical potential sensed or created (to produce a pacing stimulus) by a bipolar lead occurs over a few millimeters; the difference in a unipolar lead spans the distance between the tip of the lead and the pulse generator across the chest. Bipolar leads possess significant advantages over their unipolar counterparts: no sensing of musculoskeletal potentials that may inappropriately inhibit pacing, less chance of “cross-talk” between the two leads of dual-chamber devices, less chance of interference with an ICD (ICDs should not be used in conjunction with unipolar leads), and less chance of pacing skeletal muscle. In addition, most generators are compatible with unipolar pacing through a bipolar lead if needed as a result of lead damage or high pacing thresholds.

Leads have fixation mechanisms that may be passive (e.g., tines, talons, and fins) or active (e.g., helical screws), both of which are depicted in Figure 85-4. Passive-fixation leads acquire stability by becoming entrapped in myocardial trabeculations. Active-fixation leads have distal screws that are deployed and penetrate the myocardial wall. Active mechanisms carry a lower risk of dislodgement and provide greater versatility in the choice of implantation sites, because their stability does not depend on the presence of trabeculations. However, active-fixation leads generate a more extensive inflammatory response, which may lead to acute rises in pacing threshold after implantation. Steroid-eluting leads are now available to address the problem of acute rise in capture threshold. Such leads have a reservoir of steroid near the electrode that flows through the porous electrode into the myocardium, thereby reducing the inflammatory response and the rise in pacing threshold.²⁰⁻²²

Pacing

Effective cardiac pacing requires the timed introduction of an electrical impulse, which depolarizes nearby myocardium, leading to propagation of an activation wave front. The term *capture* is used to indicate that successful pacing has occurred.¹⁶ The minimum amount of energy required to produce successful myocardial depolarization and pacing is called the stimulation (or pacing) threshold. The pacing energy threshold is a function of the voltage (denoted in volts) delivered by each electrical impulse and the time duration over which the impulse is delivered (pulse width, denoted in milliseconds). For chronic pacing leads, pacing output is conventionally programmed at twofold the value of the pacing threshold voltage or threefold pacing threshold pulse width, considered the safety margin.

Sensing

Sensing is required for the pacemaker to coordinate pacing with any intrinsic electrical cardiac activity. The earliest pacemakers were not able to sense and paced only in VOO mode (see “Basic Pacing Modes,” later). Pacing leads have a recording electrode and an indifferent

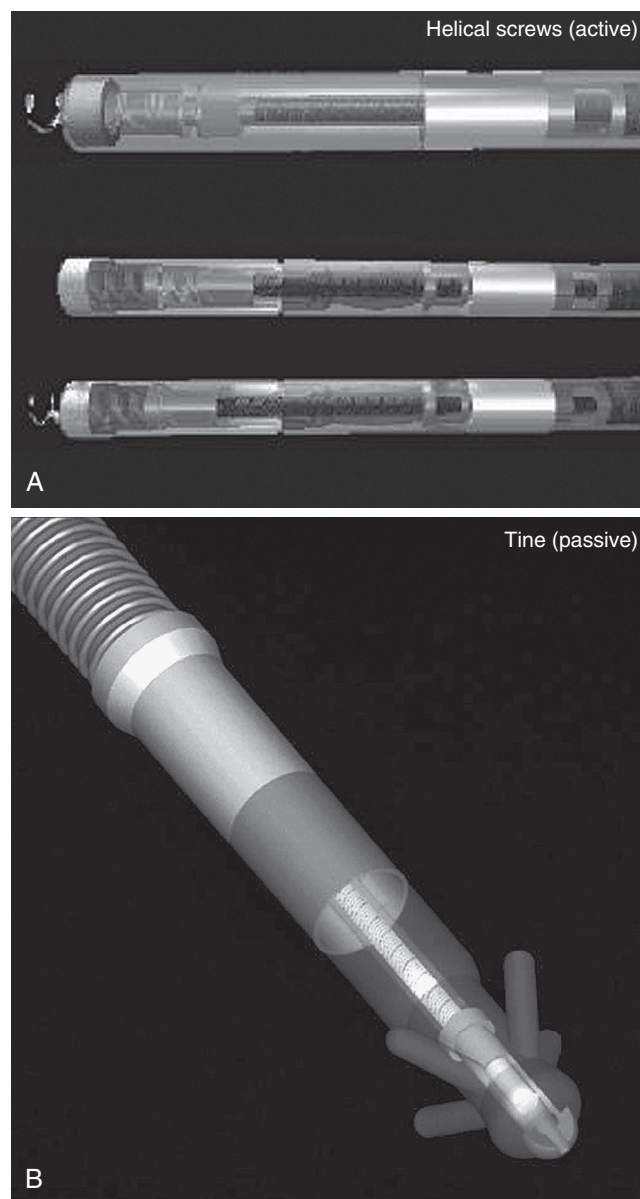


FIGURE 85-4 ■ Fixation mechanisms of pacing leads. **A**, Active fixation (screw) mechanism. **B**, Passive fixation (tines) mechanism. (Courtesy Medtronic, Inc., Minneapolis, MN.)

electrode. As a wave of depolarization approaches the recording electrode and then proceeds away from it, it creates what is called an intrinsic deflection, which is the transition from the approaching to the receding deflection. The slope of the intrinsic deflection is called the slow rate. The pacemaker system has an amplifier that increases the signal from the recording electrode and a band pass filter to delete signals with frequencies too high or too low to represent an intrinsic deflection. The electrogram is “sensed” when the amplitude of the filtered signal exceeds the programmed sensing threshold. When sensing occurs, the programmed timing circuits of the pulse generator are reset. In general, a twofold to threefold sensing safety margin is also incorporated in the pacemaker programming. This allows for reliable sensing of activated myocardium but reduces the incidence of far-field oversensing.

Note that pacing intervals and cycle lengths are expressed in milliseconds, and pacing rates are denoted in beats per minute or pulses per minute. Rate and cycle lengths are inversely related and easily converted into one another: rate in beats per minute (or pulses per minute) may be obtained by dividing 60,000 by the cycle length in milliseconds; conversely, cycle length in milliseconds may be determined by dividing 60,000 by the rate in beats per minute (or pulses per minute).

Basic Pacing Modes

A generic pacemaker code allows the uniform functional classification of all pacing systems.

The first three letters are the most widely used and refer to the pacing and sensing functions of the pacemaker.²⁴ The first position denotes the cardiac chambers that may be *paced*, that is, the atrium (A), ventricle (V), both (D), or none (O). The second position refers to the chambers being *sensed*. The third position is used to indicate the *response the pacemaker has to sensing*, or the action performed by the pacemaker in response to sensing of intrinsic electrical activity. The response to sensing events by the pacemaker may be triggered (T), inhibited (I), both (D), or none (O). In a triggered mode, a sensed event leads to delivery of a pacing stimulus. The triggered mode is used to prevent inappropriate inhibition by an incorrectly sensed event, such as skeletal muscle myopotentials. This function can be lifesaving in patients who are pacemaker dependent. The inhibited mode leads to inhibition of stimulus delivery in the designated chamber after sensing of intrinsic electrical activity. When the sensing response is dual (i.e., triggered and inhibited), pacing in the ventricle or atrium does not occur for a programmable time after intrinsic ventricular activity is sensed (i.e., pacing is inhibited). In addition, when the sensing response is dual, sensing of intrinsic atrial activity leads to inhibition of an atrial pacing stimulus, but it results in triggering of a ventricular pacing stimulus after the programmed AV delay.

The fourth position of the generic pacemaker code denotes the *programmability or rate modulation*. The

possible functions at this position include simple programmable (P), multiprogrammable (M), communicating (C), rate modulation (R), or none (O).²⁴ Simple programmable suggests that the programmability of the pacemaker is limited to certain parameters; multiprogrammable pacemakers are able to program a large number of parameters. The communicating function refers to the ability to exchange signals between the pacemaker and a pacemaker programming device. Rate modulation is the most commonly denoted function in the fourth position. It denotes the capability of the pacemaker to adjust the pacing rate according to a sensor device. Pacemaker manufacturers have designed a variety of sensors that attempt to match the individual's physical activity or metabolic demands by responding to different sources, such as motion, temperature, and chest wall impedance (as an estimate of minute ventilation).

The fifth position in the pacemaker code relates to *antitachycardia therapies*: antitachycardia pacing (P), shock (S), dual (D, shock and pacing), or none (O).²³ Since the advent of ICDs, the fifth position is not generally used in referring to pacing systems.

As a result of emerging data that suggest an increased risk of heart failure hospitalization in patients with high burden of right ventricular pacing, algorithms designed to minimize right ventricular pacing have recently become available in pacemakers and defibrillators.²⁴⁻²⁶ Such algorithms provide pacing in AAI mode but will mode switch to DDD whenever necessary if high-grade AV block occurs. If the AV block is transient, the pacing mode will switch back to AAI. Table 85-2 summarizes the most commonly used pacing modes, including advantages and disadvantages of each one as well as their clinical applications.²³ See Figure 85-5 for an example of DDD pacing mode on a 12-lead electrocardiogram.

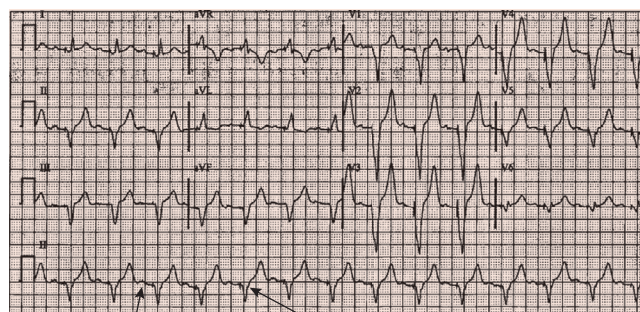
Implantable Cardioverter-Defibrillators

The guidelines for implantation of ICDs are reviewed earlier in this chapter. Despite the ongoing advancement in the development of today's defibrillators, their primary

TABLE 85-2 Commonly Encountered Pacing Modes

Mode	Advantages	Disadvantages	Clinical Uses
AAI(R)	Requires only a single lead Simple	Slow ventricular rates may develop if atrioventricular (AV) block occurs	Sinus node dysfunction without AV node dysfunction
VVI(R)	Requires only a single lead Simple	During pacing, AV synchrony is not preserved	AV block in a patient with atrial fibrillation
DDD(R)	AV synchrony is maintained for patients with sinus node and AV node disease	Requires two leads More complex	Bradycardia caused by sinus node disease or AV node disease
VDD(R)	AV synchrony is maintained for patients with AV node disease One specially designed lead can be used	AV synchrony is lost if the patient develops sinus bradycardia	Bradycardia caused by AV node disease
DDI(R)	AV synchrony is maintained during atrial pacing	AV synchrony is not maintained during atrial sensing	For patients with bradycardia and intermittent atrial tachycardias Not used as a stand-alone pacing mode but as a mode-switching pacing mode

From Wang PJ, et al: *Modes of pacemaker function*. In Kusumoto FM, Goldschlager NF, editors: *Cardiac pacing for the clinician*, Philadelphia, 2001, Lippincott Williams & Wilkins, pp 63–90.



Sensed atrial beat, paced ventricular beat

FIGURE 85-5 ■ Example of DDD pacing mode on a 12-lead electrocardiogram.

goal remains to deliver rapid and effective treatment of ventricular tachyarrhythmias.

Pulse Generator

Most ICD generators are currently implanted in the pectoral region. The pulse generator is composed of a lithium/silver vanadium oxide battery and a capacitor. Whereas in 1989, generator volumes exceeded 200 cm³, current generators are less than 40 cm³.²⁷ Progressively smaller ICD generators have become viable as a result of continued progress in battery and capacitor technology. Essential functions that must be reliably performed by the ICD generator include monitoring of cardiac electrical activity through sense amplifiers, analysis of waveforms for the proper diagnosis of arrhythmias, and delivery of appropriate therapy. The lifetime of the battery depends on the battery capacity, and it is inversely related to the number of shocks and to the percentage of time spent in monitoring and pacing.

In addition to the battery and capacitor, the generator houses the operational circuitry of the device, which is composed of low-power circuits (sensing, pacing, amplifiers, microprocessors) and high-power charging and output circuits.²⁷

Leads

Early defibrillators used high-voltage epicardial (or pericardial) electrode patches for defibrillation. These electrode patches were also responsible for sensing, but frequent problems caused by oversensing prompted the use of a separate sensing lead (epicardial or endocardial). With the development of transvenous defibrillators, electrode patches are now only rarely used.

Currently used endocardial leads are made of high-voltage conductors. At least one conductor is used as the defibrillation coil, which is generally found near the tip of the lead and placed along the posterior right ventricular wall. Some leads have two conductors (or two shocking coils). In such dual-coil leads, the distal coil is in the right ventricle and the proximal coil resides anywhere between the subclavian vein, superior vena cava, and right atrium. Separate single-coil leads may instead be implanted in the right ventricle, superior vena cava, coronary sinus, or a combination of these sites; subcutaneous

tissue arrays may also be used. Leads placed in the right ventricle are required to exhibit sensing and pacing capabilities, whereas such functions are not necessary in leads placed in the superior vena cava or coronary sinus.

In general, defibrillation with use of the pulse generator as one of the electrodes can be achieved by lower energies than defibrillation with a combination of leads. The defibrillation threshold (DFT) is the “lowest clinically obtained energy that can achieve defibrillation.”¹⁶ A combination of any three electrodes may be used, instead of two, in an attempt to lower the DFT.

Endocardial ICD leads perform sensing through a distal electrode at the tip of the lead. The same electrode may also be used for pacing. Unipolar ICD leads (normally placed in the superior vena cava or coronary sinus) have a single high-voltage coil used for defibrillation and are not able to pace or sense. Bipolar ICD leads have two conductors, one of which is used for defibrillation and the other for sensing. Such leads sense intrinsic electrical activity between the tip of the lead and anywhere along the extent of the shocking coil (integrated bipolar sensing). In contrast to true bipolar sensing, integrated bipolar sensing more often leads to oversensing because of noise and far-field artifact as well as to undersensing after high-voltage defibrillation.²⁷ Newer defibrillator leads perform true bipolar sensing between the distal tip of the lead and a ring located approximately 1 cm proximal from the tip. Most recently, “quadripolar” leads are now available that perform true bipolar sensing (between the tip of the lead and the ring, as described earlier) and also incorporate two defibrillation coils. In the subcutaneous ICD system, a subcutaneous electrode with a defibrillation coil is tunneled in the skin parallel to the left sternum.

Tachyarrhythmia Detection

Detection of tachyarrhythmias occurs when the device analyzes recent cycle lengths and R-wave morphologies to classify rhythms and to determine appropriate programmed therapy.²⁷ Because some arrhythmias are unsustained, ICDs must effectively be able to detect the arrhythmia, confirm it before delivering therapy, and redetect the arrhythmia if the delivered therapy was unsuccessful. Current devices may be set to have multiple zones of detection (e.g., VT, fast VT, and VF zones) for which specific therapies can be individually programmed (tiered therapy).

Although arrhythmia detection by current ICDs is reliable, inappropriate shocks may still occur even if the device is functioning properly. Such unnecessary shocks most commonly occur in the setting of atrial fibrillation (or other supraventricular tachycardia) or sinus tachycardia if the ventricular rate falls into one of the detection zones.²⁸ Newer and more sophisticated devices have built-in algorithms or additional detection parameters designed to prevent inappropriate shocks by increasing the specificity of VT detection. For safety reasons, these algorithms are available only in the lowest VT rate cutoff zones and include sudden onset and rate stability criteria as well as a criterion based on electrogram morphology.

Tachyarrhythmia Therapy

Current devices can deliver a range of programmable therapies: high-energy defibrillation shocks, low-energy synchronized cardioversion, and antitachycardia pacing (ATP).

High-Energy Defibrillation. As previously described, the DFT is the lowest clinically obtained energy that can accomplish defibrillation. The patient's autonomic and metabolic state may alter the DFT such that an energy output previously able to achieve defibrillation at a particular time may fail at others. Therefore, after the DFT is determined, a safety margin of at least 7 to 10 J is recommended between the maximum output of the device and the DFT. [Figure 85-6](#) depicts an episode of successful defibrillation of VF by a high-energy therapy delivered by an ICD.

Antiarrhythmic drugs may alter the DFT. Amiodarone commonly raises the DFT, whereas sotalol lowers it.^{29,30} Procainamide and quinidine do not appear to affect DFT.³¹ Physicians can consider DFT testing 3 months after initiation of amiodarone to confirm an acceptable safety margin between the DFT and the programmed high-energy defibrillation output.

Low-Energy Synchronized Cardioversions. Low-energy synchronized cardioversions can be delivered faster (shorter charging time) than high-energy defibrillation and may save device battery. Unlike VF, some VT

can be terminated with very low energy therapies, which may cause less discomfort to the patient. Disadvantages of low-energy synchronized shocks include acceleration of VT to VF, which may delay definitive therapy.

Antitachycardia Pacing. Multiple extra stimuli (with or without addition of premature stimuli to a train of extra stimuli) delivered during tachycardia may interact with the tachycardia circuit and thereby terminate it. ATP can be programmed in today's ICDs, and it is widely used as initial therapy for VT. Similar to low-energy synchronized cardioversions, ATP carries the risk of accelerating VT to VF, in which case a high-voltage shock could be delivered to terminate VF. Advantages of ATP as initial therapy for VT include faster delivery time, less discomfort to the patient, and sparing of device battery (if successful). [Figure 85-7](#) shows an example of successful termination of VT by ATP; [Figure 85-8](#) depicts a failed ATP attempt to terminate VT.

PREOPERATIVE EVALUATION BEFORE IMPLANTATION OF CARDIAC DEVICES

Clinical Considerations

A careful history and physical examination should be performed, with focus on the assessment of prior injury or disease within the planned region for device implantation. A history of prior shoulder or chest injury, surgery,

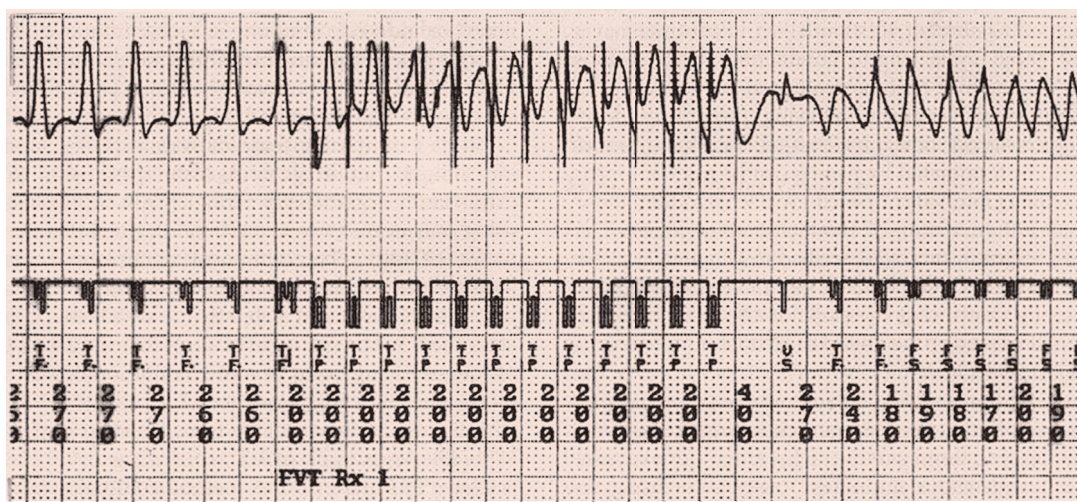


FIGURE 85-8 ■ Failed attempt by antitachycardia pacing to terminate ventricular tachycardia. FVT, Fast ventricular tachycardia.

or radiation therapy may alert the implanting physician of the potential for abnormal venous drainage, which may increase the technical complexity of the implantation. Allergies to medications (including antibiotics, local anesthetic, and intravenous narcotics and benzodiazepines used for conscious sedation) and intravenous contrast material occasionally used for venography should be identified and recorded. It is especially important to recognize and appropriately treat signs and symptoms of active infection before implantation of a permanent cardiac device. Prophylactic antibiotics are administered immediately before and for 72 hours after device implantation. Another essential consideration is the patient's respiratory status. Device implantations generally require that the patient lie flat for the duration of the procedure (up to 2 to 3 hours). Therefore, oxygenation and volume status should be optimized before implantation.

Patients being treated with warfarin or any of the novel oral anticoagulants may remain on anticoagulation therapy during their device implantation. In our institution, it is generally required that the International Normalized Ratio (INR) be less than 3.5 before implantation. We avoid the use of injectable low-molecular-weight heparin or unfractionated heparin bridging around the time of device implantation, because we believe this is associated with greater rates of pocket hematomas.

STANDARD TRANSVENOUS TECHNIQUES FOR IMPLANTATION OF CARDIAC DEVICES

Temporary Transvenous Pacemakers

Percutaneous venous access may be obtained through the internal jugular, subclavian, femoral, or antecubital veins. A lock-down sheath should be introduced in the vein for better lead stability. Fluoroscopy should always be used to guide lead placement when the femoral and antecubital veins are used. The pacing catheter should be advanced to

the right ventricle with care to avoid excessive force that could result in cardiac perforation. The ideal position for the catheter tip is the distal right ventricular septum or inferoapex. The right ventricular free wall and outflow tract should be avoided because of the risk of catheter-induced ectopy and decreased lead stability. After placement of the lead, the sensing and pacing thresholds should be determined. An R wave of 5 mV or more and a pacing threshold of 1 mA or less are adequate. After acceptable placement of the lead has occurred, the sheath should be locked down around the lead. The sheath should then be sutured and the lead secured to the adjacent skin and covered with a dry sterile dressing. A postprocedure chest radiograph should be obtained to confirm lead position and to rule out pneumothorax. At least twice daily, sensing and pacing thresholds should be assessed.

If fluoroscopy is not available, a balloon-tipped catheter should be introduced through the internal jugular or subclavian veins. The distal electrode tip (generally negatively charged) should be connected to one of the precordial leads of a 12-lead electrocardiogram (generally V₁). The limb leads (e.g., lead II) should be recorded and the intracardiac electrogram should be monitored as the balloon-tipped pacing catheter is slowly introduced. When the distal electrode on the tip of the catheter reaches the right atrium, a large atrial electrogram (corresponding to the P wave seen on the limb leads) followed by a smaller ventricular electrogram (corresponding to the QRS on the surface electrocardiogram) should be noted. As the catheter is advanced into the right ventricle, the ventricular electrogram grows larger and the atrial signal becomes smaller. Once the tip of the pacing catheter comes in contact with the myocardium, an injury current (reminiscent of ST elevation) will be recorded immediately after the ventricular electrogram, and the catheter should not be advanced farther. After the pacing catheter is positioned and secured, a 12-lead electrocardiogram should always be obtained to corroborate, on the basis of the morphology of the paced QRS complexes, proper positioning of the catheter.

When asystole (or severe bradycardia) is present, the pacing electrode tips (distal and proximal) should be connected to an active pacing box (or generator) programmed to pace in VVI mode. Paced QRS complexes should emerge once contact of the catheter tip to myocardium occurs.

When temporary atrial (instead of ventricular) or AV sequential pacing is required, a temporary pacing catheter/lead can be placed in the right atrium (active-fixation lead) or in the coronary sinus. The atrial pacing threshold is generally higher in the coronary sinus than in the right atrium.

Duration of temporary pacing should be limited to less than 72 hours to minimize the risk of infection, cardiac perforation, and lead dislodgement. Active-fixation leads connected to an externalized pacemaker generator may be left in place for longer periods.

Permanent Pacemakers

Most permanent transvenous pacemakers are placed in the right or left pectoral region through the cephalic, axillary, or subclavian veins. A peripheral intravenous catheter should be placed on the upper extremity ipsilateral to the planned implant in case venography is necessary to define the anatomy or availability of access. Unless the patient is left-handed or the left side is inaccessible, the left pectoral region is preferable because of greater simplicity of lead placement and manipulation. Prophylactic antibiotics should be administered as described earlier, and the pectoral region should be prepared and draped in sterile fashion.

Cephalic Vein (Cutdown) Approach

Local anesthetic is delivered to the pectoral region. An oblique incision is made over the deltopectoral groove and extended inward by use of blunt dissection. Alternatively, a horizontal incision 2 cm below the clavicle (with its lateral border extending over the deltopectoral groove)

may be chosen. The cephalic vein runs in the deltopectoral groove, which can be identified by the presence of a fatty streak between the pectoralis and deltoid muscles. Once the cephalic vein is identified, it should be dissected free from the surrounding fat and connective tissue. [Figure 85-9](#) illustrates the anatomic location of the subclavian, axillary, and cephalic veins.

A 0 silk suture is placed around the vein (but not tied) proximally and another one distally, and a 5 French (Fr) dilator is placed in the vein. Under fluoroscopic guidance, a guidewire is introduced into the 5 Fr dilator and advanced to the inferior vena cava through the subclavian vein, the superior vena cava, the right atrium, and into the inferior vena cava; the 5 Fr dilator is then removed. Venography may be necessary through the 5 Fr introducer or a peripheral line to establish patency of the vessels or to define the venous anatomy if difficulty in advancing the wire is encountered.

Axillary Vein Approach

The axillary vein can be cannulated through the same cutdown location in the deltopectoral region. The axillary vein is accessed through a single wall puncture technique by landmarks or direct visualization through venography.

Subclavian Vein Approach

The subclavian vein may also be accessed by a single wall puncture technique. The subclavian vein approach is generally the least desirable because of the risk of pneumothorax and the potential risk of crush injury to the pacing leads as they pass between the clavicle and first rib.

Technique

Regardless of the vein used for access, a guidewire is advanced to the inferior vena cava under fluoroscopic

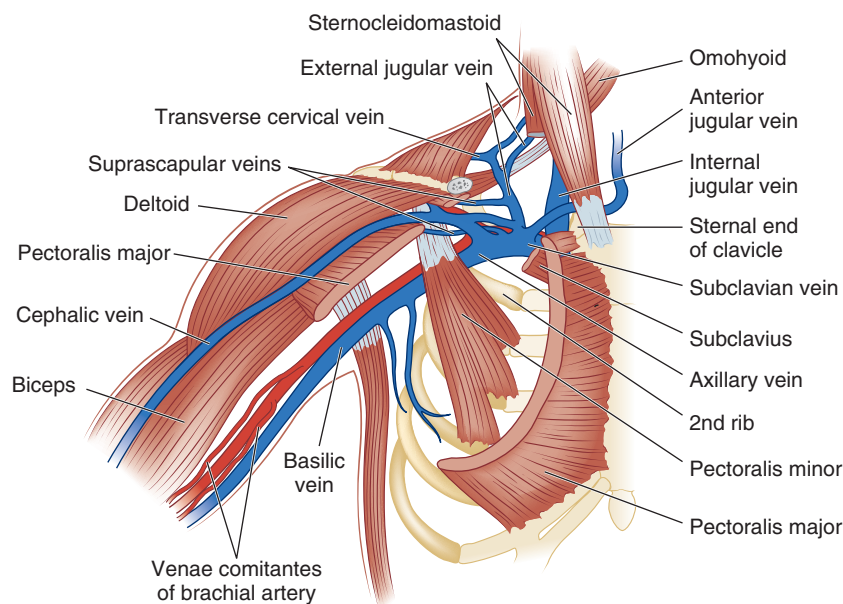


FIGURE 85-9 ■ Anatomic illustration of the subclavian, axillary, and cephalic veins. (Modified from Agur AMR, Lee MJ: Upper limb. In *Grant's atlas of anatomy*, ed 10, Philadelphia, 1999, Lippincott Williams & Wilkins.)

guidance. Once venous access has been secured and the guidewire positioned, sheaths (or introducers) are used for sequential placement of atrial and ventricular leads. While a lead is being placed through the sheath, the patient should be instructed to transiently refrain from talking or breathing to avoid complication by air embolus through the introducer sheath. The fluoroscopic view for optimal placement of the right ventricle lead is generally obtained from the right anterior oblique position. This view allows proper visualization of the full length of the right ventricle (foreshortened in the anteroposterior view). Adequate lead position along the right ventricular inferoseptum and apex should also be confirmed in the left anterior oblique view. Ventricular ectopy may occur during lead placement, but it is generally transient. If there is persistent VT, the lead should be repositioned. If VT continues despite lead repositioning, the rhythm should be terminated by ATP or defibrillation.

Ventricular sensing and pacing thresholds should be checked, and the QRS morphology in lead V₁ should be assessed to confirm that pacing originates from the right ventricle (left bundle branch block morphology should be present in lead V₁). When a right bundle branch block morphology is present in lead V₁, pacing from the left ventricular endocardium (through an atrial or ventricular septal defect), from the coronary sinus, or from the left ventricular epicardium (as a result of cardiac perforation) should be suspected. On occasion, a right bundle branch block morphology will be seen with pacing from the right ventricular septum.

The atrial lead is generally placed in the right atrial appendage if it is present. Use of a curled wire stylet will enable positioning in the right atrial appendage. However, any location in the right atrium is acceptable if it is stable, provided no excessive sensing of the ventricular electrogram is present.

Once acceptable positions for both leads have been obtained, lead stability should be confirmed during coughing and deep breathing exercises. Lead locations should be confirmed from the right anterior oblique and left anterior oblique views. High-output pacing should be performed from both leads to rule out diaphragmatic capture during pacing. Stylets and guidewire should be removed, and proper amount of slack in each lead should be ensured fluoroscopically. After optimal lead positions are confirmed, the leads should be secured to the pectoralis muscle with nonabsorbable suture tied around anchoring sleeves. Final sensing and pacing thresholds should be checked after the leads have been sutured to the pectoralis fascia.

After the leads are secured, local anesthesia is administered to the subcutaneous tissues medial to the deltopectoral groove to create a subcutaneous (or submuscular) pocket for the device generator. The pocket is created by blunt dissection and copiously irrigated. The leads are then connected to the pulse generator according to the indicated positions. The leads are coiled under the generator, and the entire system is implanted into the pocket. Proper sensing and pacing by the device should be confirmed.

The subcutaneous tissues are closed with absorbable suture, and the skin is closed with a subcuticular layer of

absorbable suture or staples. A dry sterile dressing should be placed over the wound.

Implantation of single-chamber devices is done by the same technique except for placement of the second lead. [Figure 85-10](#) depicts a chest radiograph with the expected lead position for a single-chamber transvenous pacemaker.

As discussed previously, the biventricular pacing of both left and right ventricles is appropriate in a particular heart failure patient population. The left ventricle is paced through a passive pacing lead that is advanced through the coronary sinus into a posterolateral vein. If an implanting physician is unable to achieve an optimal location for coronary sinus pacing, an epicardial lead can be placed surgically.

Implantable Cardioverter-Defibrillators

Surgical techniques to implant epicardial patches used in early ICDs are not discussed in this chapter. Instead, this chapter concentrates on the transvenous implantation of current cardioverter-defibrillators.

The left pectoral region is preferred for most ICD implants, whether the patient is right- or left-handed. The coil configuration obtained with a left-sided implant allows a more effective field orientation for defibrillation, when one of the shocking electrodes lies within the pulse generator. The technique used to place modern transvenous ICDs is the same as the technique described to implant transvenous permanent pacemakers (see earlier), although the first transvenous ICDs required abdominal pulse generators because of their large size (transvenous leads were tunneled subcutaneously to the abdomen, where the generator was implanted). Also, subcutaneous patches or arrays were often necessary in early ICDs to achieve acceptable DFT. In [Figure 85-11](#), a postprocedure chest radiograph confirms appropriate lead positions in a dual-chamber transvenous ICD.

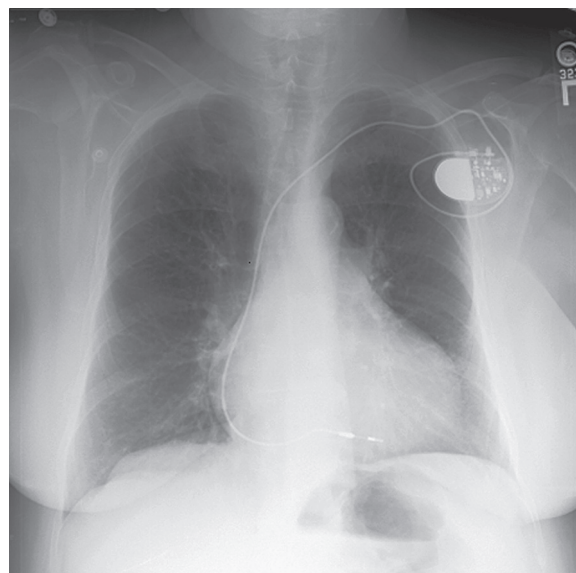


FIGURE 85-1 ■ Posteroanterior chest radiograph showing appropriate lead position for a single-chamber transvenous pacemaker.

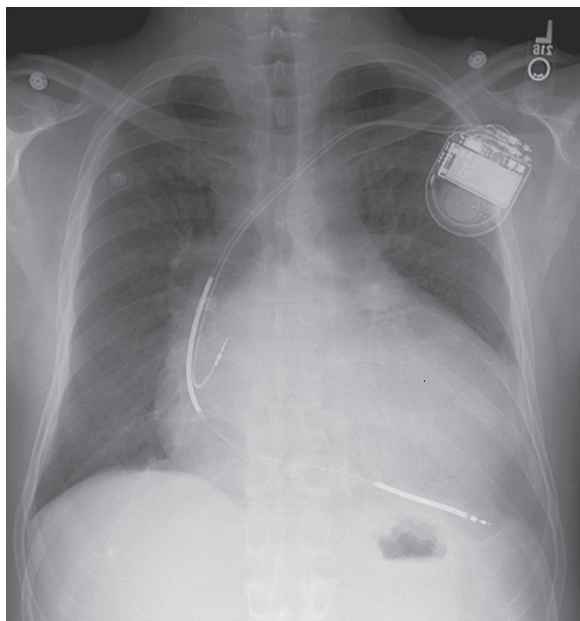


FIGURE 85-11 ■ Posteroanterior chest radiograph showing appropriate lead positions for a dual-chamber transvenous implantable cardioverter-defibrillator.

Recently, the use of a fully subcutaneous ICD has become an option in a selected patient population. In this system, the pulse generator is placed within a pocket created between the fourth and fifth intercostal spaces at the midaxillary line. An electrode is positioned through two subcutaneous tunnels, extending from the pocket to a small xiphoid incision and from the xiphoid to a superior sternal incision.

Defibrillation Threshold Testing

The procedure for any ICD implant can include defibrillation testing to determine the DFT. The prevailing rationale for the routine evaluation of DFTs has been to ensure appropriate sensing of ventricular fibrillation, system integrity, and effective defibrillation. Defibrillation testing is generally performed before wound closure, after the leads are connected to the pulse generator and after the system is implanted into the pocket.

The programmer is used to communicate with the device through a sterile wand placed over the pocket. Recently, wireless devices are available that can communicate with the programmer without physical contact once initial connection with the generator has been established. Before VF induction and ICD testing, some operators deliver a low-energy synchronized shock to allow confirmation of intact connections by checking the high-voltage lead impedance. External defibrillation hands-off pads are also placed and connected to an external biphasic defibrillator in the event of device failure to terminate VF. Testing is generally performed at the least sensitive device setting for detection of VF to ensure an adequate safety margin. After successful testing, the device is programmed at the most sensitive setting for VF detection. VF is most commonly induced by timed

T-wave shocks or by rapid-burst ventricular pacing at 50 Hz.

At our institution, initial testing is performed with a selected energy (10 J lower than the maximum device output) that allows an adequate safety margin between the tested energy and the maximum device output (margin-verification protocol). A second shock with a lower energy is often performed. Before testing, we generally set the second device therapy as a maximum output shock, which is delivered if the first tested energy fails and after VF is redetected. If a high-output shock through the device fails to terminate VF, a 360-J biphasic shock is externally delivered.

Normally, a 5-minute “rest” period is provided between each induction of VF. Other important parameters evaluated during ICD testing include the high-voltage lead impedance and the charge time for delivery of high-voltage therapies. If an adequate DFT is not obtained during testing, addition of extra defibrillation coils (including subcutaneous arrays or patches), reversal of shock polarity, or repositioning of the right ventricle lead may be necessary. A 7- to 10-J safety margin should be incorporated in the final therapy programming of the device. After an acceptable DFT is obtained, the wound is closed as described previously.

Contemporary ICD systems using active cans, pectoralis pulse generators, biphasic waveforms, and intravascular high-voltage leads have considerably lowered the incidence of elevated DFTs. The reliability of current ICD systems has led to recent literature reevaluating the necessity for routine DFT testing at ICD implantation.³²⁻³⁴ As such, observational studies have noted an elimination of DFT testing in one third of initial implants and two thirds of replacements. A study estimates that 5-year survival is expected to be higher in patients who undergo DFT testing at implantation only if the annual risk of a lethal arrhythmia (or the risk of a narrow safety margin) is at least 5%.³² At our institution, we no longer perform routine DFT testing at the time of device implantation or generator change.

POSTIMPLANTATION CARE OF TRANSVENOUS CARDIAC DEVICES

Patients undergoing implantation of electrophysiologic cardiac devices should be observed overnight in the hospital. Continuous telemetry monitoring should be performed during this time to allow early diagnosis and treatment of lead malfunction or dislodgement (the most common complication in the early postoperative period). Bed rest is recommended overnight, and the arm ipsilateral to the implant is placed in a sling for 24 hours. The patient is allowed to move that arm after 24 hours, but lifting of objects weighing more than 5 to 10 pounds and raising the arm above shoulder level should be avoided for 6 weeks after the procedure. A posteroanterior and lateral chest radiograph should be obtained on the morning after implantation to assess adequate lead and generator positions. If the subclavian vein was used for venous access, a portable chest radiograph is required immediately after implantation to rule out

pneumothorax. Anticoagulation with intravenous heparin or low-molecular-weight heparin should be avoided for at least the first 8 hours after implantation. We recommend the continuation of oral anticoagulation of patients through their device implantation if they are already on blood-thinning medication. The use of prophylactic antibiotics should be prescribed as described previously.

The device should be interrogated on the day after implantation to ensure proper device function and to fine-tune the device programming if necessary. The wound should be kept dry for at least 3 days after implantation. A follow-up appointment should be scheduled within 7 to 10 days of discharge for wound check and device reinterrogation. Marked changes in lead impedance and in pacing and sensing thresholds would be identified at that time and could indicate lead dislodgement or malfunction.

COMPLICATIONS OF IMPLANTABLE CARDIAC DEVICES

Serious complications of device implantation occur in less than 2% of patients undergoing the procedure. Procedural complications may be classified as early, which may include intraoperative, perioperative (within 24 hours), or postoperative complications (after 24 hours but within 30 days of the procedure), or late, occurring after 30 days from the procedure.

Examples of early complications are outlined in [Box 85-15](#) and include bleeding, vascular injury, infection, pneumothorax, hemothorax, air embolus, cardiac

perforation or tamponade, rhythm abnormalities, deep venous thrombosis, pulmonary embolism, lead dislodgement, lead fracture or damage, and pocket hematoma. Late complications are also listed in [Box 85-15](#) and may include lead fracture or insulation break, lead dislodgement, pocket skin erosion, infection, migration of generator possibly leading to lead twisting and fracture, and deep venous thrombosis or scarring. [Figure 85-12](#) shows an example of skin erosion with subsequent infection of a device pocket.

EXTRACTION OF CHRONIC LEADS USED IN TRANSVENOUS CARDIAC DEVICES

Overview

Since the introduction of transvenous pacing electrodes in 1958 by Furman and Schwedel,³ techniques to safely remove such leads have been developed and perfected. Earlier techniques focused on the simple use of traction, which can be done safely and without the assistance of specially designed tools only in recently implanted leads (generally, implants less than 1 year old) that have not developed significant fibrosis. For more chronic leads, complications preclude the use of simple traction, and surgical approaches that require sternotomy or thoracotomy were initially the only viable options. Since the mid-1980s,³⁵⁻³⁸ safer transvenous methods for chronic lead extraction have been developed.

Official definitions and guidelines for the practice of transvenously placed lead extractions were published in 2000, and subsequently updated in 2009.^{39,40} The term *lead extraction* is reserved only for the removal of a lead that requires specialized equipment (laser sheath, traction devices, electrosurgical sheaths, rotational threaded tip sheaths, or telescoping sheaths) or from a route other than the implant vein and of any lead implanted for more than 1 year. A complete summary of indications for lead extraction is provided in [Box 85-16](#). Class I indications include serious illness caused by an infected lead, clinical need for a new transvenous cardiac device when all usable veins are obstructed, and malfunctioning, fractured, or

BOX 85-15 Early and Late Complications of Implantable Cardiac Devices

EARLY

- Bleeding
- Infection
- Pneumothorax, hemothorax
- Cardiac perforation
- Superior vena cava perforation
- Lead migration or dislodgement (2%)
- Air embolus
- Venous thrombosis
- Atrial tachyarrhythmias
- Ventricular tachycardia
- Atrioventricular (AV) block by contact injury to the conduction system
- Pocket hematoma

LATE

- Infection of device pocket or leads (2.7%)
- Pocket erosion, wound breakdown
- Lead fracture, insulation damage (0.2%)
- Venous thrombosis
- Chronic pain
- Tricuspid regurgitation
- Left ventricular dysfunction
- Migration of pulse generator
- Twisting or fracture of leads due to manipulation of generator (twiddler syndrome)



FIGURE 85-12 ■ Example of skin erosion and subsequent infection of device pocket. (Courtesy Medtronic, Inc., Minneapolis, MN.)

BOX 85-16 Indications for Lead Removal/Extraction by Transvenous Techniques**INFECTION****Class I**

1. Definite system infection, as evidenced by valvular endocarditis, lead endocarditis, or sepsis
2. Pocket infection as evidenced by pocket abscess, device erosion, skin adherence, or chronic draining sinus
3. Valvular endocarditis without definite involvement of the lead(s) and/or device
4. Occult gram-positive bacteremia (not contaminant)

Class IIa

1. Persistent occult gram-negative bacteremia

Class III

1. Not indicated for a superficial or incisional infection without involvement of the device and/or leads
2. Not indicated to treat chronic bacteremia due to a source other than the cardiovascular implantable electronic device (CIED), when long-term suppressive antibiotics are required

CHRONIC PAIN**Class IIa**

1. Severe chronic pain, at the device or lead insertion site, that causes significant discomfort for the patient

THROMBOSIS AND VENOUS STENOSIS**Class I**

1. Significant thromboembolic events associated with thrombus on a lead or a lead fragment
2. Bilateral subclavian vein or superior vena cava (SVC) occlusion precluding implantation of a needed transvenous lead
3. SVC stenosis or occlusion with limiting symptoms
4. Ipsilateral venous occlusion preventing access to the venous circulation for required placement of an additional lead when there is a contraindication for using the contralateral side (e.g., contralateral AV fistula, shunt or vascular access port, mastectomy)

Class IIa

1. Ipsilateral venous occlusion preventing access to the venous circulation for required placement of an additional lead, when there is no contraindication for using the contralateral side

FUNCTIONAL AND NONFUNCTIONAL LEADS**Class I**

1. Life-threatening arrhythmias secondary to retained leads
2. Lead design failure that poses an immediate threat to the patient if left in place
3. Leads that interfere with the treatment of a malignancy (radiation/reconstructive surgery)

Class IIa

1. Nonfunctional leads that due to design failure pose a threat to the patient that is not immediate or imminent if left in place
2. Nonfunctional lead removal to avoid more than four leads on one side or more than five leads through the SVC
3. Nonfunctional lead removal is reasonable in patients that require specific needed imaging techniques and cannot be imaged due to the presence of the device

Class IIb

1. Functioning leads that due to design failure pose a potential future threat to the patient if left in place
2. Functional leads not being used
3. To permit the implantation of a magnetic resonance imaging (MRI)-compatible system
4. At the time of an indicated device implantation in patients with nonfunctional leads

Class III

1. Not indicated if patient has a life expectancy of less than 1 year
2. Not indicated in patients with known anomalous placement of leads through structures other than normal venous and cardiac structures unless clinical situation compelling

From Love CJ, Wilkoff BL, Byrd CL, et al: Recommendations for extraction of chronically implanted transvenous pacing and defibrillator leads: indications, facilities, training. North American Society of Pacing and Electrophysiology Lead Extraction Conference Faculty. *Pacing Clin Electrophysiol* 23(4 Pt 1):544-551, 2000.

suboptimally positioned leads that pose danger to the patient. Relative contraindications to transvenous lead extraction include lead calcification (detected on radiography) involving the right atrium or the superior vena cava, unavailability of suitable equipment, patient's clinical condition that precludes emergent thoracotomy or less than 1 year survival, or lead placement through unusual routes (e.g., subclavian artery, pericardial space). Because of the potentially serious complications of transvenous lead extractions, physicians properly trained in these techniques and adequately equipped institutions are absolute requirements for the performance of lead extractions.

Data from the U.S. Extraction Database for intravascular extraction of infected or problematic pacemaker

leads from January 1994 to April 1996 were published in 1999.⁴¹ In this series, the success rate was 93% for complete removal of the leads and 5% for partial removal of the leads; 2% failed. Major complications occurred in 1.4% of patients (<1% in centers that performed >300 extractions) and minor complications in 1.7% of patients. Major complications occurred more frequently in women. Predictors of incomplete lead removal or failure included longer implant duration, less experienced operators, ventricular lead location, noninfected leads, and younger age of the patient. Reports using the more modern laser lead extraction technique involving 2561 pacing and defibrillator leads in 1684 patients at 89 sites describe a procedural success rate of 90% with a major complication rate of 1.9% with an in-hospital death rate of 0.8%.⁴²

Tools Used in Chronic Lead Transvenous Extractions

Angiographic Catheters, Snares, Forceps, and Locking Stylets

Angiographic catheters that are commonly used to assist in lead extractions include the angled pigtail catheter, the Judkins right coronary catheter, the multipurpose coronary catheter, and the Amplatz catheter. These catheters are used in combination with common guidewires or tip-deflecting guidewires that loop around or hook onto the pacemaker lead to retrieve it. This approach may also be used to retrieve loose lead ends or free-floating lead remnants. Other tools used include the basket retriever catheter, the Dotter intravascular retriever (helical loop basket) that gets irreversibly entrapped in the lead, and the Dormia basket.

Different types of snares are also available and are used in conjunction with catheters and guidewires to recover and to extract chronic pacemaker leads. Examples of snares include the Curry snare (used to form a wire-loop system), the Amplatz gooseneck snare (loop at a right angle to the guidewire), and the Needle's Eye snare created by Cook Vascular, Inc. (consisting of a hoop-shaped loop and a locking slide threader), which provides a reversible system able to release the seized object. Cook Vascular, Inc., has also developed a "locking stylet" that is efficient in seizing and holding the lead while preventing the lead from stretching or uncoiling as it is being retrieved.⁴³

Forceps (grasping forceps, alligator forceps, and myocardial bicep forceps) have also been used for lead extractions. This stylet intensifies the tensile power of the lead and directs the extraction force to the tip of the lead. The locking system is engaged and released by counterclockwise and clockwise rotation, respectively.

Byrd Dilator Sheaths

These sheaths were marketed by Cook Vascular, Inc., and may be used to assist with extractions performed through the implant vein. They consist of telescoping stainless steel sheaths with metal dilators that are advanced over the lead to sever through the thick fibrous adhesions found at the venous entry site and distal ends of chronic leads. Once entrance to the vein is attained, the metal dilators are exchanged for telescoping flexible plastic sheaths that are able to negotiate the turns.

Excimer Laser Sheaths

Excimer laser sheaths were developed by Charles Byrd and are used in association with the Spectranetics CVX-300 excimer laser system.⁴³ The laser sheath contains a ring of optical fibers at its distal tip able to emit pulses of ultraviolet light that destroy the surrounding fibrous tissues around the lead. Mild countertraction and counterpressure activate the laser. An advantage of the laser system is that tissue vaporization is achieved, as opposed to blunt tissue dissection and shredding. One disadvantage is that the system is not effective against

calcifications, which are often encountered around older leads.

Electrosurgical Dissection Systems

The most recent advancement in lead extraction equipment includes the electrosurgical dissection system developed by Cook Vascular, Inc. Such systems use radio-frequency energy (instead of laser or blunt dissection) to destroy the fibrous endovascular adhesions that anchor device leads to venous walls. The most recent radiofrequency-based system has a dual electrode scheme that performs a bipolar dissection while also functioning as a mechanical dissection sheath. The tip electrode spacing is such that it effectively localizes the disruptive energies to the specific regions interfering with extraction of the lead, as opposed to circumferentially obliterating the endovascular border.

Techniques of Chronic Lead Transvenous Extractions

Transvenous lead extractions should preferably be performed in a setting appropriate for emergent thoracotomy; a cardiothoracic surgeon should be promptly available. Before any transvenous extraction of chronic pacemaker leads, the patient should be prepared in advance for potential thoracotomy. Intra-arterial blood pressure monitoring is recommended. Transthoracic and transesophageal echocardiography and a pericardiocentesis tray should be readily accessible to allow expeditious diagnosis and treatment of possible complications. A temporary pacing wire should be placed through the femoral vein if the patient is pacemaker dependent.

Extraction through the Implant Vein

The generator should be removed and the leads completely freed from adhesions and sutures and dissected down to the venous entry site. If the patient is pacemaker dependent, a temporary pacing wire (normally introduced through the femoral vein) should have been placed ahead of time. The proximal end of the lead, which includes the connector pin, should be cut, and 1 cm of the lead inner coil should be exposed. A coil expander is used to remove any wire burs and to ensure patency of the lead lumen. A locking stylet should then be advanced into the lead inner coil until it reaches the distal tip of the lead. The locking mechanism is activated, and the outer lead insulation should be secured with a tie before introduction of the sheaths. If simple traction is not sufficient to free the lead from the myocardium once the locking stylet is in place, sheaths should be introduced to disrupt fibrous adhesions or scarring. Telescoping stainless steel sheaths (or other available sheaths, including excimer laser sheaths and, most recently, electrosurgical dissection sheaths) should be advanced over the lead down to the venous entry site, where they disrupt the scar tissue surrounding the lead. The sheaths should be advanced down under fluoroscopic guidance to the distal tip of the lead as continuous traction is placed on the locking stylet system. The lead tip may then be pulled

free by counterpressure and countertraction, and the entire lead is extracted. If this method is unsuccessful, another technique (e.g., extraction through the femoral vein) may be used.

Extraction through the Femoral Vein

The femoral vein approach is the preferred technique to extract lead remnants or broken or cut leads that are free-floating in the venous system, heart, or pulmonary artery.⁴³ It may also be used as a primary approach for transvenous extraction of permanent leads, especially if there is concern for pushing infected debris from the original entry site into the circulation. This approach engages angiographic catheters such as the angled pigtail catheter or a variety of snares (see earlier for different types of available snares) to grasp loose lead ends or the deflecting wire and Dotter retriever if no freed ends are available. Traction is applied to pull the lead (or lead remnants) from the heart, and the lead is then withdrawn from the body through the femoral vein sheath.

Complications

Serious complications may occur as a result of transvenous lead extractions. Complications may be intraoperative, perioperative (events that occur or are diagnosed within 24 hours after the procedure), postoperative (events that occur or are diagnosed after 24 hours but within 30 days of the procedure), or late (events that occur or are diagnosed more than 30 days after the procedure date). **Box 85-17** summarizes major and minor complications related to transvenous lead extractions.

MANAGEMENT OF CARDIAC DEVICES DURING AND AFTER SURGERY

Pacemakers

Application of a magnet over a pacemaker inhibits all sensing function of the pacemaker. The previously programmed pacing mode is subsequently transiently changed to DOO, VOO, or AOO until the magnet is removed. The magnet pacing rate varies according to the pacemaker manufacturer. The magnet may be used prophylactically before surgical procedures to avoid inappropriate sensing by the pacer as a result of noise artifact created by cautery. Other procedures during which there is a risk of inhibition of the pacer by inappropriate sensing of noise include electroconvulsive therapy, extracorporeal shockwave lithotripsy, and occasionally electric cardioversions.

Implantable Cardioverter-Defibrillators

Unlike standard pacemakers, defibrillators with backup pacing and pacemaker-defibrillators do not have their sensing function inhibited by a magnet. The magnet does, however, inhibit delivery of any antitachycardia therapy, such as ATP or high-energy defibrillation.

BOX 85-17 Major and Minor Complications Related to Transvenous Lead Extractions

MAJOR COMPLICATIONS

- Death
- Cardiac avulsion or tear requiring thoracotomy, pericardiocentesis, chest tube, or surgical repair
- Vascular avulsion or tear requiring thoracotomy, pericardiocentesis, chest tube, or surgical repair
- Hemothorax or severe bleeding from any source requiring transfusion
- Pneumothorax requiring chest tube drainage
- Pulmonary embolism requiring surgical intervention
- Respiratory arrest
- Septic shock
- Stroke

MINOR COMPLICATIONS

- Pericardial effusion not requiring pericardiocentesis or surgical intervention
- Hemodynamically significant air embolism
- Pulmonary embolism not requiring intervention
- Vascular repair near the implant site or venous entry site
- Arrhythmia requiring cardioversion
- Hematoma at the pocket requiring drainage
- Arm swelling or thrombosis of implant veins resulting in medical intervention
- Sepsis in a previously nonseptic patient with infection
- Pacing system–related infection of a previously noninfected site

OBSERVATION

- Transient hypotension that responds to fluids or minor pharmacologic intervention
- Nonsignificant air embolism
- Small pneumothorax not requiring intervention
- Ectopy not requiring cardioversion
- Arm swelling or thrombosis of implant veins without need for medical intervention
- Pain at cutdown site
- Myocardial avulsion without sequelae
- Migrated lead fragment without sequelae

From Love CJ, Wilkoff BL, Byrd CL, et al: Recommendations for extraction of chronically implanted transvenous pacing and defibrillator leads: indications, facilities, training. North American Society of Pacing and Electrophysiology Lead Extraction Conference Faculty. Pacing Clin Electrophysiol 23(4 Pt 1):544–551, 2000.

Magnet inhibition of antitachycardia therapies prevents delivery of inappropriate ICD therapies during cautery or other procedures that could produce noise erroneously sensed by the lead as VT or VF. Although a magnet is applied to an ICD, causing inhibition of the programmed ICD therapies, the patient should be treated like any patient who does not have an ICD in the event that a tachyarrhythmia occurs. Alternatively, cautery (or other problematic procedures) may be transiently halted and the magnet removed from the ICD to allow implementation and delivery of programmed ICD therapies.

In addition, if a patient is pacemaker dependent, the pacing mode of the ICD should be reprogrammed to DOO, VOO, or AOO (as clinically indicated) before anticipated cautery. Alternatively, a temporary pacing

wire should be placed to avoid inappropriate sensing of noise and subsequent inappropriate inhibition of the pacing function of the ICD. Such inappropriate inhibition of pacing in a pacemaker-dependent patient could be catastrophic if it is not anticipated. After the procedure, the initial ICD parameters should be restored. In general, even if no reprogramming is necessary, ICDs should be interrogated after surgery or a magnet applied to confirm proper functioning and parameter settings.

Of note, some ICD generators are part of a magnet reed switch manufacturer recall and thus have their magnet function permanently turned off. For such generators, ICD therapies should be turned off before surgery expected to require cautery and turned back on after the procedure.

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CATHETER ABLATION OF ARRHYTHMIAS

Ethan R. Ellis • John V. Wylie, Jr. • Mark E. Josephson

CHAPTER OUTLINE

PROCEDURAL TECHNIQUE AND THE ELECTROPHYSIOLOGY STUDY

CARDIAC MAPPING TECHNIQUES

CATHETER ABLATION

SPECIFIC ARRHYTHMIAS

Atrioventricular Nodal Reentrant Tachycardia
Atrial Tachycardia
Atrial Flutter

Accessory Pathway–Mediated Tachycardia
Reentrant Ventricular Tachycardia and
Structural Heart Disease

Idiopathic Ventricular Tachycardia

Atrial Fibrillation

Atrioventricular Junction Ablation

Catheter Ablation of Atrial Fibrillation

Cryoballoon Ablation of Atrial Fibrillation

Over the past 40 years, cardiac electrophysiology has progressed from an esoteric field dedicated to understanding arrhythmia mechanisms to an indispensable modality in the diagnosis and treatment of cardiac arrhythmias. Electrophysiology therapeutics first began with cardiac surgery for the treatment of arrhythmias. After it became clear that invasive surgical strategies could cure arrhythmias, methods for delivery of energy through catheter-based techniques were developed. The advent of catheter ablation has revolutionized the management of patients with tachyarrhythmias. Radiofrequency current has become the energy source of choice for catheter ablation and has made it the first-line therapy for the treatment of many tachycardias.

PROCEDURAL TECHNIQUE AND THE ELECTROPHYSIOLOGY STUDY

The electrophysiology study (EPS) is an indispensable prelude to catheter ablation allowing for the identification of tachycardia mechanism and the most appropriate site for energy delivery. The EPS involves placing electrode catheters in various chambers of the heart for recording, stimulation, mapping, and ablation. Femoral veins and arteries are the most common sites of vascular access used for EPS. Less commonly used sites include the antecubital fossa, subclavian, and jugular veins. Adequate local anesthesia is administered before vascular puncture. A 0.035-inch short J guidewire is placed via the percutaneous Seldinger technique into the femoral vein or artery just below the inguinal ligament. Additional

wires, up to three in a single vein, are placed 5 to 10 mm caudal to the first wire. Double- and triple-headed vascular access devices that can accommodate two or three catheters through a single access sheath are commercially available and are used in some laboratories. Hemostatic sheaths (size 6 Fr to 11 Fr) are placed over the guidewires, up to three in a single vein. If more than three catheters are required, another vein is used, typically the contralateral femoral vein.

For His bundle recordings, the femoral approach allows superior catheter stability. However, catheterization of the coronary sinus (CS) is more readily accomplished via the internal jugular, left subclavian, or left antecubital veins. The lateral antecubital veins that drain into the cephalic vein are avoided because of the right angle at which they enter the axillary vein, making catheter manipulation more difficult. These nonfemoral sites are usually reserved for patients with inaccessible femoral access or difficult CS cannulation despite attempting via the femoral approach with a steerable catheter, but in some laboratories, CS cannulation is routinely performed via the left subclavian vein or right internal jugular vein. Although accessing the CS through a femoral vein is generally more difficult, in experienced hands it can be readily accomplished either via a direct approach, often facilitated by bending the catheter in the hepatic vein to achieve a greater posterior angulation, using a steerable catheter, or more indirectly by forming a catheter loop within the right atrium.

The catheters used in an EPS are either steerable or nonsteerable woven Dacron or synthetic catheters containing electrodes that can be manipulated under

fluoroscopy in the cardiac chambers. Nonsteerable catheters are available in a variety of electrode configurations and preformed curves, but the most common catheters have either 4 or 10 electrodes for pacing and sensing. Steerable catheters have internal tension wires that allow the tip to be deflected up to 180 degrees or more by manipulating a control at the handle. Diagnostic steerable catheters may contain up to 20 electrodes. Catheters used for radiofrequency ablation are all steerable and generally consist of a 3.5- to 10-mm electrode used for ablation and three proximal recording electrodes. A diagnostic EPS typically requires at least three catheter locations: in the high right atrium near the sinus node, at His bundle area across the superior tricuspid valve, and at the right ventricular apex. Depending on the type of study, additional catheters may be placed in the right ventricular outflow tract, CS, anterolateral right atrium, interatrial septum, left atrium, pulmonary veins, and left ventricle.

Accessing the left ventricular cavity is accomplished either via the mitral valve from transseptal left atrial catheterization or via retrograde aortic approach through the arterial system, typically the femoral artery. Although left ventricular catheterization is not a routine part of a diagnostic EPS, it may have importance in patients with ventricular tachycardia and accessory pathway-mediated tachycardia (atrioventricular reciprocating tachycardia). Detailed catheter mapping of the left ventricular endocardium may also have benefit in defining the myocardial substrate in patients with ventricular arrhythmias, depressed ventricular function, history of myocardial infarction, and congestive heart failure.

CARDIAC MAPPING TECHNIQUES

Understanding the mechanism of arrhythmia is vital, before targeting with ablation, to maximize the success of the procedure. Understanding the arrhythmia mechanism can often be achieved with EPS but can be further refined with the use of cardiac mapping techniques. Cardiac mapping allows the identification of temporal and spatial relationships of electrical potentials during atrial and ventricular arrhythmias. The focus of cardiac mapping is generally to identify the origin of a focal arrhythmia or a site of critical conduction for a reentrant arrhythmia. The most common approaches to mapping are simple activation mapping, pace mapping, and electroanatomic activation mapping.

Electrograms acquired during mapping techniques are either bipolar or unipolar. Bipolar electrograms reveal the local electrical activity of the heart between two designated electrodes on the catheter. This typically is over an interelectrode spacing ranging from 1 to 10 mm. Unipolar electrograms reveal the local electrical activity at a single catheter point (usually the distal tip) relative to an electrode placed at a distance from the heart. The advantages of using unipolar mapping are that it gives a more precise measure of local activation and it provides information about the direction of impulse propagation. The advantages of using bipolar mapping include superior signal-to-noise ratio and less contribution from distant electrical activity ("far-field" activity). Frequently,

accurate mapping involves using both bipolar and unipolar electrograms at different points of the study.

Simple activation mapping is achieved by moving a single roving mapping catheter to various points of interest during an arrhythmia, spontaneous or induced, while measuring local activation times relative to a fiducial marker at a second site, such as the onset of the P wave or QRS complex or a stable intracardiac electrogram. Depending on the arrhythmia mechanism, the area of earliest activation is often a reasonable target for ablation of the arrhythmia.

Pace mapping is a mapping technique that can be used when the patient is not in the arrhythmia.¹ It is often used in conjunction with activation mapping as a second confirmatory test to determine the accuracy of the selected site for ablation, but it can be used as a stand-alone mapping technique if the documented clinical arrhythmia cannot be induced during EPS or is not hemodynamically tolerated. Pace mapping entails pacing the suspected target area for ablation at a rate similar to the clinical arrhythmia, and comparing the 12-lead electrocardiogram (ECG) to the ECG of the arrhythmia. A good pace map will have an exact match in 12 out of 12 leads; however, this is often difficult to achieve. When only minor differences in the ECG configuration and amplitude are noted, the spatial resolution of pace mapping can be as good as 5 mm. However, if only assessing for major differences in the 12-lead ECGs, special resolution may be as poor as 15 mm.² In addition to the 12-lead ECG, pace mapping also compares the intracardiac activation sequence seen on the electrophysiology catheters with the sequence observed during the arrhythmia if present or inducible.

Electroanatomic activation mapping relies on the use of specialized three-dimensional electroanatomic systems to assist with intracardiac mapping. The use of these systems can greatly reduce the amount of fluoroscopy time required for a procedure. Most commonly used are the CARTO 3 system (Biosense Webster) and the EnSite NavX system (St. Jude Medical) although the technology of cardiac mapping continues to evolve and newer mapping systems are currently in development. The CARTO 3 mapping system allows three-dimensional electroanatomic mapping using a low-intensity magnetic field and current-based visualization data to provide localization of multiple catheter tips and curves. The system can visualize up to five catheters with and without magnetic sensors but requires the use of compatible Biosense Webster catheters with magnetic sensors for electroanatomic mapping. Biosense Webster mapping catheters have miniature magnetic field sensors at the tip of the catheters, which can determine the location and orientation of the catheter within the magnetic field. With this information, one can create a three-dimensional reconstruction of cardiac chamber geometry. Isochromes of electrical activity can then be overlaid onto this geometry to help define reentrant circuits as well as localize the origin of focal arrhythmias. Additionally, voltage mapping can be performed in sinus rhythm to better delineate the underlying myocardial substrate in any chamber in question. The system has been shown to be highly accurate and reproducible in vitro and in vivo.³

The EnSite NavX mapping system also allows for three-dimensional localization of an intracardiac catheter through the use of three pairs of skin patches that send three independent, alternating, low-power currents through a patient's chest, each with a slightly different frequency. These currents can then be used to calculate different levels of impedances in all three planes corresponding to specific anatomic locations within the chest. Mapping catheter electrodes can then be used to measure different levels of impedance corresponding to specific locations in the heart as they are manipulated within the cardiac chambers. Using these calculated impedance coordinates, the system allows for real-time visualization of the position and motion of up to 64 different electrodes on the ablation catheter as well as other standard intracardiac catheters.⁴ Like CARTO 3, EnSite NavX can create three-dimensional geography of cardiac chambers and superimpose activation isochromes while mapping an arrhythmia or voltage measurements taken during sinus rhythm. However, unlike the CARTO 3 system, the EnSite NavX system does not require proprietary catheters for localization and mapping. EnSite also offers a noncontact mapping option using a 64-pole balloon catheter that generates mathematically derived electrograms and places them on a map of a cardiac chamber defined by a second, roving contact catheter.^{5,6}

CATHETER ABLATION

Catheter-based ablation techniques have been so successful in treating a variety of arrhythmias that they have virtually replaced surgical approaches. In catheter-based ablation, energy is delivered to a precise area of the heart. This is most often performed on the endocardial surface of the heart, although epicardial ablation is possible percutaneously via the subxiphoid approach and is performed routinely at many centers.^{7,8} After mapping techniques are used to identify the area or areas to be targeted for ablation, an ablation catheter is positioned in the desired location and connected to an energy source. Radiofrequency (RF) energy is the modality most commonly used clinically, having replaced direct current (DC) ablation because of superior safety and efficacy. Freezing the target area of the heart through a catheter-based cryoablation system is another method that can be used and is most commonly used in pediatric patients and in ablations performed adjacent to the intrinsic conduction system although cryoablation for atrial fibrillation using a cryoballoon catheter is becoming more common.

RF current is typically delivered in a unipolar configuration from the distal tip of the ablation catheter to a cutaneous grounding patch. The energy is generated as an alternating current with a frequency of 300 to 750 kHz.⁹ These frequencies produce effective heating with negligible muscle stimulation. During RF ablation, the electrical energy is converted to thermal energy by resistive heating. Most of the heating is concentrated at the tip of the catheter secondary to the small surface area of the tip relative to the cutaneous patch. The heat that is generated is transferred to the adjacent cardiac tissue primarily by conduction and to a lesser extent by

radiation, which decreases by the fourth power of the distance from the catheter tip. At steady state the RF lesion size is proportional to the temperature measured at the tissue-catheter interface, as well as proportional to the RF power amplitude.¹⁰

RF ablation results in thermal injury with coagulation necrosis when tissue heating exceeds approximately 50°C for at least 10 seconds.⁹⁻¹² As heat is produced at the catheter-myocardial interface, the impedance drops. A drop of 5 to 10 Ω is a sign of conductive heating to the adjacent tissue. The time to electrophysiologic effect after onset of RF current delivery is often shorter than one would anticipate for a pure thermal mechanism based on the documented rate of tissue temperature rise contiguous to the electrode. This raises the possibility that there is a contribution of a direct electrical effect in addition to the thermal effect of RF.

RF lesion size and power delivery are limited by tissue heating at the catheter-tissue interface on the endocardium. Newer ablation systems use external or internal saline irrigation to cool the catheter tip, which allows greater power delivery and the creation of deeper and larger lesions.¹³ The formation of coagulum may also be decreased with these systems. The catheters typically infuse saline either in a closed system running to the catheter tip or in an open system in which saline flows out small holes at the catheter tip at 17 to 30 mL/min during ablation, similar to irrigated surgical RF ablation devices. Externally irrigated ablation catheters have become the most common catheter used for ablation procedures for the treatment of ventricular tachycardia and atrial fibrillation.^{14,15}

Cryoablation has been used in the surgical treatment of arrhythmias for more than 20 years. Near-transmural lesions can be produced intraoperatively at temperatures of -60°C in the presence of cold cardioplegia. The blood pool presents catheter-based cryoablation systems with a major impediment in achieving adequate temperature. However, a catheter-based closed coolant system has been developed and is in clinical use. The major advantage is the ability to induce a nonpermanent change in tissue conduction, referred to as "ice mapping," followed by a permanent lesion if the ice mapping reveals a desirable location. This method has been used surgically with temperatures of approximately 0°C producing transient loss of electrical function and -60°C producing irreversible damage.¹⁶ A percutaneous approach is complicated by the warming effect of the circulating blood pool, and mean temperatures of -27°C were needed to achieve transient altering of electrical function.¹⁷ However, the temperature required for irreversible damage was similar to that needed in surgery (-58°C). Cryoablation catheters are most commonly used in the pediatric population and in ablations performed near the intrinsic conduction system where the risk of developing complete heart block is elevated. More recently, a cryoablation balloon has been developed which is capable of delivering a circumferential cryoablation lesion at the antrum of the pulmonary veins. This technology has been shown to reduce procedure times for pulmonary vein isolation with similar efficacy and adverse events compared with standard RF ablation.¹⁸⁻²⁰

SPECIFIC ARRHYTHMIAS

Atrioventricular Nodal Reentrant Tachycardia

Atrioventricular nodal reentrant tachycardia (AVNRT) is the most common form of supraventricular tachycardia.^{21,22} Medically, this arrhythmia is often treated with atrioventricular (AV) nodal blocking agents as well as occasionally with antiarrhythmic agents. The ability to cure this arrhythmia with a safe, well tolerated, and highly efficacious catheter ablation has made this a viable option for first-line therapy of AVNRT.²³

The AV node lies within the triangle of Koch, an area confined by the septal leaflet of the tricuspid valve inferiorly, the tendon of Todaro superiorly, and the CS os posteriorly.²⁴ In 1956, Moe and colleagues described physiologic evidence for a dual AV nodal pathway system.²⁵ These pathways were termed “slow” and “fast” based on their conduction time. However, there are no specific anatomic pathways that have been described that correlate with the fast and slow pathways. The functional dissociation of AV conduction into fast and slow pathways provides the substrate most often associated with AVNRT. The fast pathway normally lies at the apex of the triangle of Koch and the slow pathway at the base, near the CS os. However, there is often heterogeneity of atrial activation and these locations are not universal.

“Typical” or “common” AVNRT is usually initiated when a premature atrial impulse blocks in the fast pathway, conducts antegrade over the slow pathway, and then reenters the fast pathway in the retrograde direction (Fig. 86-1). This “slow-fast” AVNRT is responsible for approximately 90% of cases. The “atypical” or

“uncommon” form of AVNRT uses the slow pathway retrograde and fast pathway antegrade. Uncommonly, two relatively slow pathways constitute the reentry circuit (“slow-slow”). Although the terms “slow-fast,” “fast-slow,” and “slow-slow” are commonly used, attempting to classify all AVNRT into these groups is overly simplistic and incomplete given the complexity of AV nodal physiology and the lack of true discrete pathways in its structure.

Initial catheter ablation of AVNRT targeted the fast pathway region in the anterior interatrial septum.²⁶ Ablation at the apex of the triangle of Koch in the region of the fast pathway was more than 90% successful, but it carried an unacceptably high risk of AV block (5% to 10%). Ablation of the slow pathway²⁷ is accomplished via a posterior approach, with the ablation catheter initially positioned near the CS os, at the base of the triangle of Koch (see Fig. 86-1). RF current in the slow pathway region is often accompanied by transient accelerated junctional rhythm with rapid retrograde atrial conduction. This rhythm serves as a marker of a potentially successful ablation. However, rapid junctional tachycardia can be a marker for complete heart block, and ablation should be halted if it is seen.²⁸ Energy delivery should also be stopped if AV block or junctional rhythm with retrograde block is seen. Ablation is performed under continuous fluoroscopic monitoring or three-dimensional electroanatomic mapping to ensure catheter stability. In approximately 40% of cases, dual pathways are still present after ablation, but sustained ANVRT cannot be induced. Single AV nodal complexes (“echo beats”) are observed in three fourths of these patients with dual pathways post ablation, with block always occurring antegradely in the slow pathway. The success rate using a slow

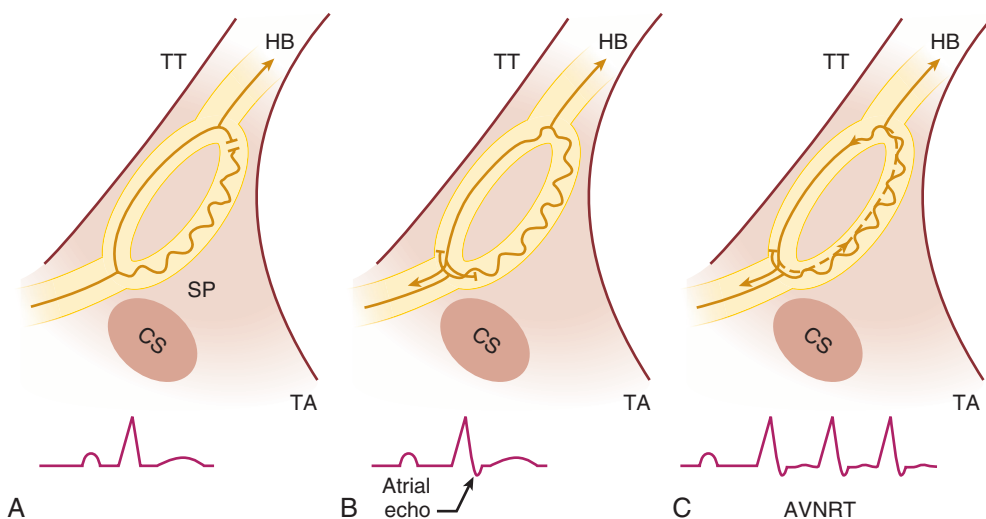


FIGURE 86-1 ■ Mechanism of atrioventricular (AV) nodal reentry. The AV node is shown with two functional pathways: the slow and the fast. The anatomic locations of these pathways are debated and may vary among patients, but their common location is in the triangle of Koch. **A**, During sinus rhythm, the PR interval is short, and conduction occurs down the fast pathway. **B**, A late atrial premature contraction (APC) blocks in the fast pathway and conducts down the slow pathway to the ventricle, resulting in a longer PR interval. The fast pathway recovers the ability to conduct, and retrograde conduction occurs up to the atrium, resulting in an AV nodal echo beat. The slow pathway is refractory, however, so tachycardia does not occur. **C**, A critically timed APC causes more delay in the slow pathway, allowing retrograde conduction up the fast pathway and sequential activation over the slow pathway to initiate typical AV nodal reentrant tachycardia (AVNRT). CS, Coronary sinus; HB, His bundle; SP, slow pathway; TA, tricuspid annulus; TT, tendon of Todaro.

pathway approach is in excess of 95%.²⁹ Slow pathway ablation is preferred to fast pathway because of the equivalent success rate and the much lower risk of complete heart block (1% to 2%).

Atrial Tachycardia

Atrial tachycardias in patients who have never had an ablation or cardiac surgery are usually focal arrhythmias originating in the left or right atria with rates of 100 to 220 beats/min. The mechanism of atrial tachycardias may be automatic or triggered from focal sites or may be microreentrant involving a small area of atrial myocardium. Atrial tachycardias that are incessant and are caused by abnormal automaticity or triggered activity are most amenable to ablation and tend to be resistant to drug therapy.³⁰ Microreentrant atrial tachycardias are frequently easily managed pharmacologically, making ablation second-line therapy. Macroreentrant atrial tachycardias are commonly seen after atrial fibrillation ablation procedures or after cardiac surgeries using atriotomies. These macroreentrant arrhythmias are more common in such scenarios because scarring from previous procedures provides areas of functional block and slow conduction necessary for the initiation of reentry.

Incessant focal atrial tachycardias can occur from various locations in the heart but seem to have a propensity for the crista terminalis, both atrial appendages, the CS, the regions of the mitral and tricuspid annuli, and the pulmonary veins. It is unclear why these structures are prone to develop these rhythms. It has been postulated that regions such as the crista terminalis are sources of automatic atrial tachycardias because of relatively poor cell-to-cell coupling.³¹ Fractionated electrograms at successful ablation sites may be markers of a nonuniform anisotropic substrate because of poor coupling that allows focal automaticity to occur. In adults, atrial tachycardia foci are somewhat more common in the right atrium, and multiple foci are present in 10% to 15% of patients.

Because most incessant atrial tachycardias are focal in origin, the goal of catheter mapping is to find the earliest site of activation (Fig. 86-2). If the tachycardia is not incessant, catecholamine infusion, such as isoproterenol 1 to 10 $\mu\text{g}/\text{min}$ IV or atropine 0.5 to 1.0 mg IV, may be necessary to induce sustained arrhythmia. The initial localization of the arrhythmia focus is made by analysis of the P wave morphology and axis. Catheter mapping is then performed by identifying the site of earliest atrial activation relative to the onset of the P wave. Three-dimensional electroanatomic mapping systems (described earlier) are often used to aid in mapping the atrial activation sequence during tachycardia (Fig. 86-3). Once the catheter is positioned at what appears to be the earliest site of atrial activation, further evidence that it is the correct site of origin can be obtained by pace mapping. In this setting, pace mapping involves pacing at the earliest intracardiac site and comparing the resultant paced P wave morphology with the tachycardia P wave morphology, as well as comparing the sequence of intracardiac atrial activation during pacing and during the tachycardia.³² Pacing with higher output at the proposed site of ablation also helps confirm minimal risk of injury to the

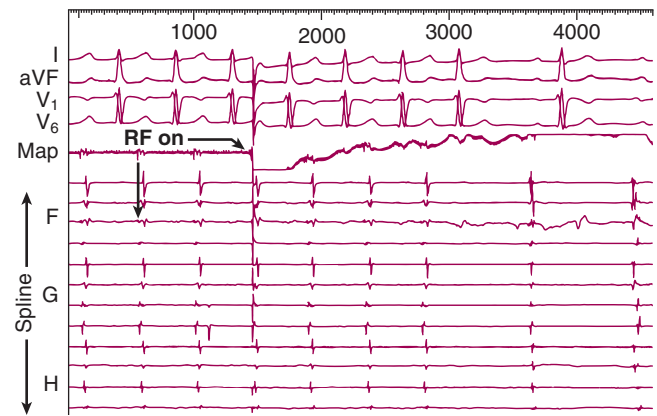


FIGURE 86-2 ■ Ablation of atrial tachycardia. Atrial tachycardia is present. The ablation/mapping catheter is placed at the earliest electrogram recorded on a 64-pole basket catheter (vertical arrow). Radiofrequency (RF) energy delivered at this site terminates the tachycardia. Surface electrocardiogram leads I, aVF, V₁, and V₆ are shown. Map is the ablation catheter signal, and the letters F, G, and H refer to electrodes on the 64-pole basket catheter.

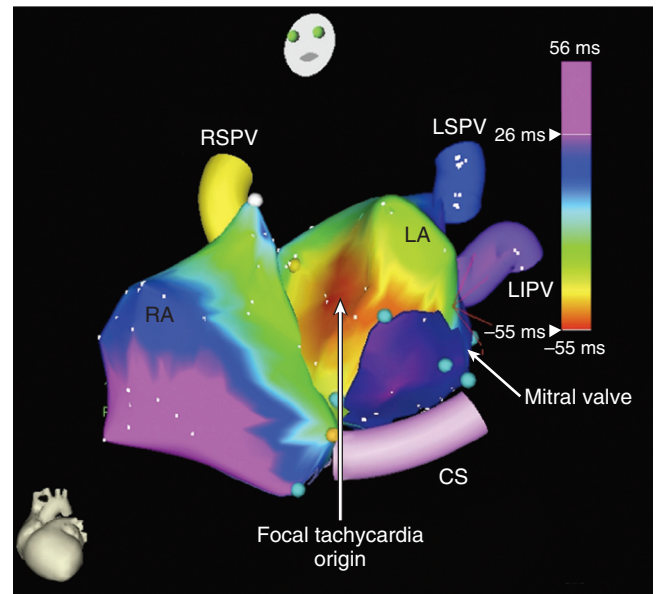


FIGURE 86-3 ■ Three-dimensional electroanatomic activation map depicting a focal atrial tachycardia. Maps of the right atrium (RA) and left atrium (LA) were created using point-by-point mapping with the CARTO system (see text). The color scale at the upper right represents the intracardiac activation timing at each point relative to a fixed reference in the coronary sinus. Red areas are earlier and purple areas are activated latest. Mapping of both the right and the left atrium revealed that the tachycardia was a focal atrial tachycardia originating anterior in the left atrium, near the aortic valve–mitral valve continuity. Ablation at this site successfully terminated the tachycardia. CS, Coronary sinus; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RSPV, right superior pulmonary vein.

surrounding extracardiac structures. This is particularly important in the right atrium with the proximity of the phrenic nerve; however, left phrenic nerve damage has also been reported with ablation in the left atrium.³³ Pacing that results in diaphragmatic stimulation would preclude ablation at that site.

The success rate of atrial tachycardia ablation is variable. For incessant tachyarrhythmias, the success rate approaches 90%, although the recurrence rate may be as high as 25%.^{32,34-36} Because the arrhythmia may not be reliably present or inducible at EPS (factors such as conscious sedation may serve to make them less inducible), a true success rate on an intention-to-treat basis is lower than 90%.

Sinoatrial node reentrant tachycardia represents a distinct entity within the category of atrial tachycardias. Criteria for the diagnosis are consistent atrial activation sequence and P wave morphology in sinus rhythm and tachycardia, consistent initiation and termination with programmed electrical stimulation, and termination of tachycardia with vagal maneuvers or with adenosine.³⁷⁻³⁹ Catheter ablation can be accomplished with good results and a paucity of complications, typically by ablating in the high posterolateral region of the right atrium at the "tail" of the sinus node.⁴⁰ Macroreentrant atrial tachycardias most often arise from the left atrium although they can also be seen in the right atrium. In the right atrium, the most common boundaries used for reentry aside from the cavotricuspid isthmus (discussed in detail in the atrial flutter section) include the CS ostium, the fossa ovalis, or scars from prior surgical incisions. In the left atrium, many left atrial tachycardias circulate around the mitral annulus with the pulmonary veins and the fossa ovalis as posterior boundaries.⁴¹ Scars from prior surgical or ablation procedures can also provide obstacles that lead to atrial tachycardias with large excitable gaps. In macroreentrant atrial tachycardias, electroanatomic mapping systems are often used to identify the macroreentrant circuit, anatomic or functional barriers used by the arrhythmia, gaps in regions of scar, and areas of slow conduction. Successful ablation of macroreentrant arrhythmias may be focal if targeting critical areas of slow conduction or gaps along areas of scar. However, in the case of large anatomic barriers or scars, lines of RF lesions may be required to connect anatomic barriers or scars to one another to interrupt the reentrant circuit.⁴²

Atrial Flutter

Atrial flutter is a rapid atrial arrhythmia with a rate faster than 220 beats/min. Typical isthmus-dependent atrial flutter is a macroreentrant circuit involving the right atrium. The posterior barrier of the circuit is formed by the crista terminalis and its continuation as the eustachian ridge.⁴³ The anterior barrier in typical flutter is the tricuspid annulus.⁴⁴ Typical atrial flutter is either counterclockwise or clockwise, depending on the direction of rotation in the frontal plane around the tricuspid annulus. Although counterclockwise flutter is the more common clinical entity, clockwise flutter can be initiated in most patients with typical atrial flutter.⁴⁵

The 12-lead ECG can give clues to the mechanism of the atrial flutter but sometimes can be ambiguous or misleading. Counterclockwise flutter is characterized by a predominantly negative, sawtooth-like atrial pattern in the inferior leads, with positive atrial deflections in lead V₁ and negative deflections in lead V₆. Clockwise flutter is characterized by a predominantly positive, notched

atrial pattern in the inferior lead, with negative atrial deflections in lead V₁ and positive deflections in lead V₆.

The term *atypical atrial flutter* is generally used to describe an arrhythmia with flutter waves on the 12-lead ECG felt to be inconsistent with an isthmus dependent arrhythmia. However, as noted earlier, the 12-lead ECG can be misleading in the case of atrial flutter, and it is not uncommon to identify an arrhythmia as isthmus-dependent atrial flutter at the time of EPS that terminates with ablation in the cavotricuspid isthmus, despite a 12-lead ECG inconsistent with the classic 12-lead ECG findings described earlier. If an atrial flutter is shown to be non-isthmus dependent, despite the lack of an obvious isoelectric interval on 12-lead ECG, a more appropriate classification would be macroreentrant atrial tachycardia. Further complicating matters, other macroreentrant right atrial tachycardias may have an appearance consistent with typical atrial flutter on surface ECG but may not rely on the cavotricuspid isthmus for reentry. For example, a reentrant circuit around the CS os (termed *intraisthmus reentry*) may have a 12-lead ECG appearance consistent with typical atrial flutter, but it requires a more medial cavotricuspid isthmus ablation beginning anterior to the CS os to facilitate termination.

In a catheter ablation procedure for typical atrial flutter, multielectrode catheters are placed in the CS and in the anterolateral right atrium, around a portion of the tricuspid annulus anterior to the crista terminalis. The catheter around the tricuspid annulus can help determine the direction of rotation, with atrial activation craniocaudal in counterclockwise flutter and caudocranial in clockwise flutter.

Catheter ablation of atrial flutter is dependent on the ability to interrupt the macroreentrant circuit at a critical narrow portion between barriers to conduction, termed the *isthmus*. In both counterclockwise and clockwise flutter, the isthmus targeted for ablation lies anterior to the inferior vena cava (IVC) and eustachian ridge, and posterior to the tricuspid annulus. During flutter, this isthmus is a zone of slow conduction.⁴⁶ Pacing from within this area slightly faster than the tachycardia will help demonstrate if the flutter uses this critical isthmus (i.e., isthmus dependent). If pacing in the isthmus at a rate slightly faster than the tachycardia entrains the tachycardia without alteration of the surface ECG flutter wave morphology and the local post-pacing interval equals the tachycardia cycle length, the tachycardia can be termed *isthmus dependent*. This pacing maneuver proves that the isthmus is a part of the atrial flutter circuit and that ablation in this area will effectively terminate the tachycardia.

Ablation of isthmus-dependent atrial flutter consists of creating a line of block across the right atrial cavotricuspid isthmus. Although this has been described for connecting the CS os to the tricuspid annulus, this approach can be prone to failure because of slow conduction through the eustachian ridge, which is not necessarily a fixed obstacle that produces block.⁴⁷ This can lead to a lower loop of reentry around the IVC, which meets the flutter loop going around the tricuspid annulus in a figure-of-eight manner.⁴⁸ Ablation between the tricuspid annulus and the IVC will eliminate lower loop reentry as

well as isthmus-dependent flutter and is the preferred ablation method.

Ablation is usually performed during atrial flutter. If flutter is not present at baseline, it can be induced with one or two atrial extrastimuli and/or rapid atrial pacing in 90% of atrial flutter patients and 95% of patients with isthmus-dependent flutter.⁴² Ablation can also be performed during pacing from the CS if the patient is not in atrial flutter at the time of the procedure. In patients in flutter, the arrhythmia is typically terminated during RF application in the isthmus; however, termination does not necessarily mean that the line of block is complete. Lack of complete isthmus block has been described in over 50% of cases when RF energy terminates flutter.³¹ To increase the success of the procedure, bidirectional block must be demonstrated.⁴⁹⁻⁵¹ This is demonstrated by pacing the CS catheter, which is medial to the line of isthmus block. When the ablation line is complete, there is no clockwise propagation through the isthmus, and activation is around the tricuspid annulus in a counterclockwise direction. This is seen on the tricuspid annulus catheter as craniocaudal activation during CS pacing. To verify the bidirectional nature of the block, pacing is performed from the lateral tricuspid annulus, lateral to the line of isthmus block. If the line of block is complete, there is no counterclockwise propagation through the isthmus, and activation is around the tricuspid annulus in a clockwise direction. In addition to bidirectional block, at the conclusion of the procedure, split atrial potentials (>100 ms apart) or absence of atrial potentials (electrograms <0.05 mV) may be seen along the ablation line. If bidirectional block is demonstrated, the incidence of atrial flutter recurrence is less than 10%.⁴²

Accessory Pathway–Mediated Tachycardia

Accessory AV connections (“accessory pathways,” “bypass tracts”) are part of a group of physiologic connections producing preexcitation syndromes. This group includes AV connections and nodoventricular, nodofascicular, atriofascicular, and fasciculoventricular connections.⁵²⁻⁵⁴ These pathways appear to represent developmental abnormalities, and it is not surprising that multiple types of accessory pathways may exist in any one patient. AV connections are responsible for the classic Wolff-Parkinson-White syndrome, which is defined as preexcitation seen on an ECG and the presence of an arrhythmia. These connections can conduct antegradely, leading to a preexcited ECG, whereas some may be “concealed” and only conduct retrogradely, from the ventricle to the atrium.

The clinical tachycardia most frequently associated with accessory AV pathways is atrioventricular reciprocating tachycardia (AVRT, or “circus movement tachycardia”). AVRT can be either orthodromic or antidromic. Orthodromic tachycardia results from antegrade conduction down the AV node and retrograde conduction up the accessory pathway. Antidromic tachycardia uses the same circuit but in the opposite direction.

The initial step in an ablation procedure is careful inspection of the 12-lead ECG. Determining the site of

TABLE 86-1 Localizing Accessory Pathways Using ECG Criteria

AP Location (Anatomic Description)	ECG Characteristics of Delta Wave
Left lateral <i>Posterior*</i>	Negative delta waves in leads I and aVL, and positive in inferior leads and precordial leads
Left posterior free wall <i>Inferoposterior</i> <i>Posteroseptal</i> <i>Inferoparaseptal</i>	Positive delta waves in lead I, negative in inferior leads, and positive in right precordial leads Positive delta wave in leads I and aVL and negative in inferior leads (although lead II may be isoelectric or biphasic, the more negative the more leftward the location)
Right free wall <i>Anterior</i>	Negative delta waves in leads V ₁ and V ₂ , positive in I and II, and slightly negative in III
Anteroseptal <i>Superoparaseptal</i>	Positive delta wave in lead I, positive in inferior leads (with lead II greater than III), and precordial leads with primarily negative or biphasic delta waves

*Newer anatomic descriptions for accessory pathway locations are in italics.

AP, Accessory pathway; ECG, electrocardiogram.

an accessory pathway requires either manifest preexcitation (i.e., presence of a delta wave) on the ECG or visible retrograde P waves during orthodromic AVRT. Although complex schema have been proposed, a simpler approach is most prudent because of variability in degree of preexcitation, variability in precordial lead placement, and variations in body shape/size, heart size, and position in the chest.⁵⁵⁻⁵⁸ This approach divides the location of accessory pathways into five regions: anteroseptal, right free wall, posteroseptal, left posterior free wall, and left lateral free wall. Full description of our approach to localizing pathways based on 12-lead ECG is well described elsewhere⁴² and is summarized in Table 86-1. Newer anatomic designations of accessory pathway locations are also provided in this table.⁵⁹

In the past, cardiac surgery was the only option for definitive treatment of accessory pathway–mediated tachycardias, but catheter ablation has replaced surgery as the preferred therapy over the past 20 years. In a catheter ablation procedure, a CS catheter is advanced to the anterolateral mitral annulus to permit mapping of all left-sided pathways except possibly the most anterolateral pathways, and additional catheters are placed in the right atrium and ventricle and adjacent to the His bundle.

Left-sided accessory pathways can use either a transseptal approach or a retrograde aortic approach. Atrial pacing is performed to elicit maximal preexcitation, and the location of the earliest ventricular activation along the CS is noted as the ventricular insertion of the pathway. To identify the atrial insertion, retrograde conduction over the pathway is mapped during ventricular pacing or, preferably, during circus movement tachycardia (to ensure no contribution of retrograde AV nodal conduction), with the site of earliest atrial activation identifying

the atrial insertion. It is important to identify both atrial and ventricular insertions of any accessory pathway when possible, given that slanted pathways are common and ablation at an insertion site may not adequately target the pathway itself. In the setting of concealed pathways, only the atrial insertion can be mapped, although other maneuvers can be used to assess for the presence of a slanted pathway.⁴² If retrograde conduction over the pathway is intermittent or tenuous during the resting sedated state of EPS, isoproterenol can be administered. This can also facilitate initiation of circus movement tachycardia. If rapid retrograde conduction over the AV node during ventricular pacing makes localization difficult, verapamil can be administered to facilitate conduction over the pathway.

After mapping of the accessory pathway, a steerable ablation catheter is then advanced to a position near the accessory pathway. The ventricular insertion of the pathway is best approached via the retrograde aortic approach, whereas the transeptal approach allows easiest access to the atrial insertion site. Success rates of initial attempts at ablation appear to be similar in either approach.⁶⁰ Ablation should target the area between the atrial and ventricular insertions when both can be identified, which is generally near the site of the earliest ventricular activation in manifest pathways and the earliest atrial activation in concealed pathways as the shortest AV and ventriculoatrial (VA) intervals may not be the best target for ablation in slanted pathways. Electrograms recorded at insertion sites of pathways are often fractionated, and occasionally a bypass tract potential can be recorded.

Factors that predict a successful ablation site for a pathway include a stable electrogram, catheter stability and catheter motion in conjunction with the CS catheter, presence of an accessory pathway potential, catheter position at the shortest recorded AV interval (or shortest VA interval if concealed), and activation of the local ventricular electrogram before the onset of the QRS if it is a manifest pathway.

The mapping of right-sided pathways uses similar principles to those used for left-sided pathways. An atrial approach is most commonly used for right-sided accessory pathways. Right atrial pathway ablation can be more complicated because of (1) the presence of a "sack" of atrial myocardium folding over the tricuspid AV ring, which makes catheter manipulation more difficult; (2) possible circumferential tricuspid pathway location versus only approximately 75% of the mitral annulus because of lack of pathways in the region of aortomitral continuity; and (3) lack of an AV groove reference catheter. A multipolar halo catheter can be positioned around the tricuspid annulus to serve as an AV groove reference, but positioning may not always be accurate as it can be difficult to place in a true annular position. When endocardial ablation fails to eliminate accessory pathway conduction, epicardial mapping and ablation can be performed with percutaneous access to the pericardial space.⁶¹ In this procedure, via a subxiphoid approach, a standard sheath is advanced over a wire into the pericardial space and an ablation catheter is manipulated under fluoroscopic guidance for epicardial mapping.⁶²

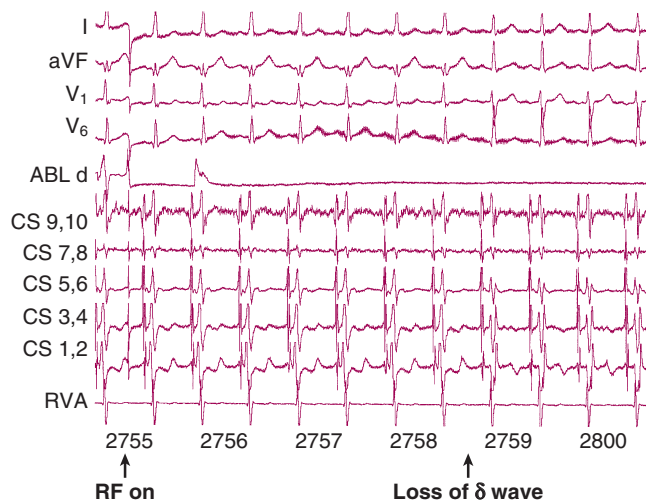


FIGURE 86-4 ■ Ablation in Wolff-Parkinson-White syndrome. Electrocardiogram leads I, aVF, V₁, and V₆ and proximal (CS 9,10) to distal (CS 1,2), and RV apical (RVA) recordings are shown. The bypass tract is a left posterior bypass tract. Radio-frequency (RF) energy produces loss of the delta (δ) wave in 4 seconds (see text).

Coronary angiography is usually required before ablation to ensure ablation is not performed over large epicardial arteries. Pericardial scarring often prohibits this approach in patients who have had cardiac surgery.

After adequately localizing the accessory pathway, RF current is delivered through the distal electrode of the ablation catheter. Successful ablation typically results in loss of accessory pathway conduction within 10 seconds (Fig. 86-4). The patient is then monitored for at least 20 minutes to watch for resumption of accessory pathway conduction, often in the presence of isoproterenol given intravenously. The success rate for catheter ablation of all accessory pathways is greater than 90%.⁶³

Reentrant Ventricular Tachycardia and Structural Heart Disease

Most sustained monomorphic ventricular tachycardia (VT) seen clinically is in patients with coronary artery disease and is most frequently the result of scarred myocardial substrate from a prior myocardial infarction (MI). In this setting, the primary mechanism for VT is reentry. Reentrant circuits are prone to develop secondary to fibrosis from the prior infarction causing disruptions in cellular coupling leading to abnormal paths of conduction as well as zones of slow conduction. Surgical subendocardial resection of these areas has proven curative in selected patients. With the advent of catheter ablation, surgical ablation for VT fell out of favor because of unacceptably high morbidity and mortality rates.⁶⁴⁻⁶⁷ However, these high mortality rates are from surgical series in the 1980s, and one might expect these numbers to be lower today with improved myocardial preservation techniques and additional methods to facilitate the procedure. Thus, surgical therapy for ventricular arrhythmias, particularly in conjunction with coronary artery bypass grafting surgery, is almost certainly an underused procedure

today. Nevertheless, catheter-based VT ablation has supplanted surgical treatment in most cases.

Patients with structural heart disease but no known coronary artery disease or prior MI (such as arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, or non-infarct-related cardiomyopathy) can also present with sustained monomorphic VT related to reentry. As is the case with prior MI, the pathophysiology is generally related to underlying scar and fibrosis. For the purposes of this section, we focus on mapping and ablation of sustained monomorphic VT in the setting of infarct-related cardiomyopathy. However, the approach to mapping and ablation of non-infarct-related VT is generally similar although the most common areas of fibrosis tend to be different, being more often perivalvular or epicardial.

Approximately 95% of patients with a prior MI who present with sustained monomorphic VT will be able to have the clinical arrhythmia induced at EPS. Ideally, to be considered for ablation, the VT should be hemodynamically tolerated, which allows for careful ventricular mapping during the arrhythmia. Substrate mapping during sinus rhythm can identify scarred arrhythmogenic substrate in patients with hemodynamically intolerated VT or in patients in whom VT cannot be induced, which can then be modified with ablation. However, activation and entrainment mapping techniques require hemodynamically tolerated inducible VT. If the rapid rate of a VT is contributing to hemodynamic compromise, administration of agents such as procainamide can slow the VT enough to allow for adequate mapping during VT. Alternatively, vasopressors such as dopamine, norepinephrine, or phenylephrine may be administered to support the patient's blood pressure during an otherwise intolerated VT. A newer alternative involves use of a percutaneous ventricular assist device (pVAD) to maintain adequate perfusion in the setting of rapid VTs or advanced cardiomyopathy. The disadvantages of this strategy are complications inherent in the use of a highly invasive pVAD. However, the potential advantage is that it may allow for induction and mapping of VT, which would be suitable only for a substrate ablation in other circumstances. Further studies are required to determine whether this more invasive strategy translates to improved procedural success rates.^{68,69}

The "site of origin" of the VT is essentially the source of electrical activity producing the VT QRS. Although this is a discrete site in automatic and triggered rhythms, post-MI VT is typically a reentrant rhythm. During reentrant VT, the arrhythmia circuit involves normal myocardium and a protected "isthmus" of scarred myocardial tissue. Because of myocardial scarring and fibrosis, electrical conduction through the isthmus is slow, forming the diastolic interval in the tachycardia circuit.⁷⁰ This isthmus is identified as an area of low voltage on electroanatomic mapping with fractionated electrograms and diastolic potentials seen during tachycardia. The site of origin represents the exit site from the diastolic pathway to the myocardium giving rise to the QRS. The initial step in localization of the VT is examination of the ECG.⁷¹⁻⁷³ Approximately 59% of VTs can be localized with 93% accuracy. Left bundle branch block VT

morphology can be more accurately localized than can right bundle branch block morphology, and VT from a prior inferior MI can be more easily localized than VT from a prior anterior MI.^{42,71,72}

During EPS, once the clinical VT has been induced, an ablation catheter is advanced into the left ventricle after heparinization to an activated clotting time (ACT) of greater than 250 seconds. Either a transseptal or a retrograde aortic approach can be used. Further mapping of the VT is then performed by examination of the electrograms obtained during the VT, as well as their response to pacing during the VT. Stevenson and colleagues have devised a scheme to help understand the various components of the reentry circuit, including the central common pathway or protected isthmus of myocardium that is the target site for ablation.⁷⁰

Regardless of the approach to localizing the protected isthmus, the three major steps are as follows:

1. Activation mapping, consisting of finding the site of early activation closest to mid-diastole. These electrograms frequently are low-amplitude fractionated potentials.
2. Demonstration that this diastolic electrogram has a fixed relationship to the subsequent QRS despite pacing-induced oscillations in the VT cycle length.
3. Performing entrainment mapping to demonstrate an entrained QRS morphology identical to the VT morphology ("concealed entrainment"), with an activation pattern during pacing and after cessation of pacing proving that the site in question is part of the reentry circuit.

If all three criteria are met, there is a greater than 95% chance of terminating the VT with ablation at a single site in the protected isthmus (Fig. 86-5).⁷⁴

Entrainment mapping consists of ventricular pacing at a cycle length slightly shorter than the VT cycle length and seeing if the three previously listed criteria are met.^{70,74-78} Pace mapping, as described earlier for atrial tachycardia, is another method for localizing the VT circuit. In this technique, pacing is performed from candidate sites in the ventricle, and the 12-lead ECG is compared with the VT ECG. An identical match in all 12 leads is considered an ideal pace map. We do not advocate using pace mapping as a primary mapping modality for post-MI VT, however. A pace map that appears similar to the VT would only identify the exit point for the critical isthmus and may be distant from the common pathway ablation target. In addition, pacing during sinus rhythm activates the myocardium in both directions from a protected isthmus, whereas the QRS during reentrant VT is the result of unidirectional activation of the myocardium by the cyclical depolarization front.

When the clinical VT cannot be hemodynamically tolerated after being induced during EPS, consideration can be given to mapping and ablation during sinus rhythm. This technique is known as "substrate ablation" and is similar in principle to the intraoperative surgical ablation techniques used in some centers. Low-amplitude fractionated electrograms and late potentials have been demonstrated in areas of infarction using standard catheter techniques during sinus rhythm.⁷⁹ One study showed

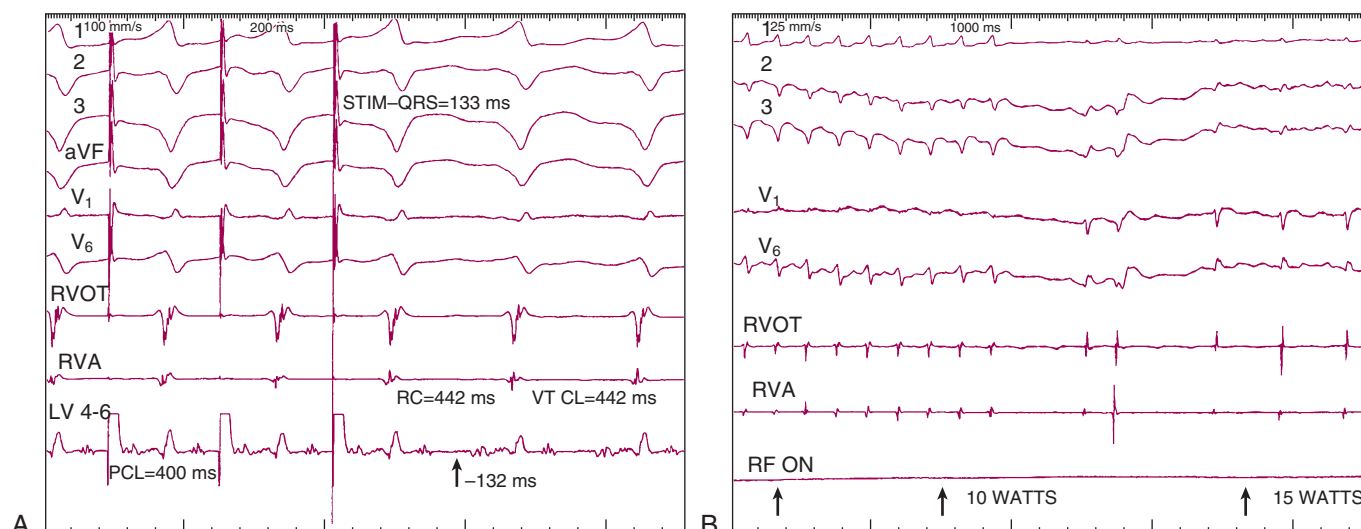


FIGURE 86-5 ■ Mapping and ablation of ventricular tachycardia (VT). **A**, Electrocardiogram leads 1, 2, 3, aVF, V₁, and V₅ are shown during VT with electrograms from the right ventricular outflow tract (RVOT), the right ventricular apex (RVA), and the site of the earliest activity in the left ventricle (LV 4-6). Entrainment of VT from LV 4-6 produces a QRS identical to VT, a stimulus (STIM)-QRS identical to the electrogram to QRS (arrow). **B**, Radiofrequency (RF) application at this site terminates VT. CL, Cycle length; PCL, paced cycle length; RC, return cycle.

that although no specific electrogram characteristic could predict a VT site of origin with adequate specificity, 86% of VTs arose from areas with these abnormal electrograms. Another study showed that the number of abnormal electrograms in cardiac arrest patients (who more often have ventricular fibrillation or polymorphic VT) was smaller compared with the number of patients with sustained monomorphic VT.⁸⁰ Standard catheter techniques do not allow for precise three-dimensional localization of the abnormal electrograms. Endocardial voltage mapping using an electroanatomic mapping system such as CARTO (see earlier) in a chronic infarct model has been shown to more accurately delineate infarcted myocardium than can pathology.^{81,82} Clinically, voltage mapping is used to guide endocardial VT ablation by identifying areas of scar and potential areas of protected isthmuses.⁸¹ Using bipolar voltage mapping, normal endocardial bipolar electrogram voltage using electroanatomic mapping is defined as more than 1.5 mV, based on mapping of controls, and scar is defined as areas with low voltage, less than 0.5 mV. Linear ablation lesions are extended from areas of dense scar to areas of normal voltage myocardium or to anatomic boundaries such as the mitral valve, resulting in a 75% success rate in patients with drug refractory VT that was not hemodynamically tolerated during EPS (Fig. 86-6). A randomized trial showed that prophylactic substrate catheter ablation in patients with a history of VT or ventricular fibrillation was able to reduce the number of implantable cardioverter-defibrillator (ICD) shocks received by patients who had undergone ablation.⁸³ Although ICDs reduce mortality from ventricular arrhythmias, shocks are uncomfortable and are associated with increased subsequent mortality,⁸⁴ and therefore catheter ablation is often considered in patients with ICDs who have received shocks for VT.

Although less commonly performed than endocardial ablation, epicardial ablation of VT is possible both surgically and percutaneously via a subxiphoid approach for

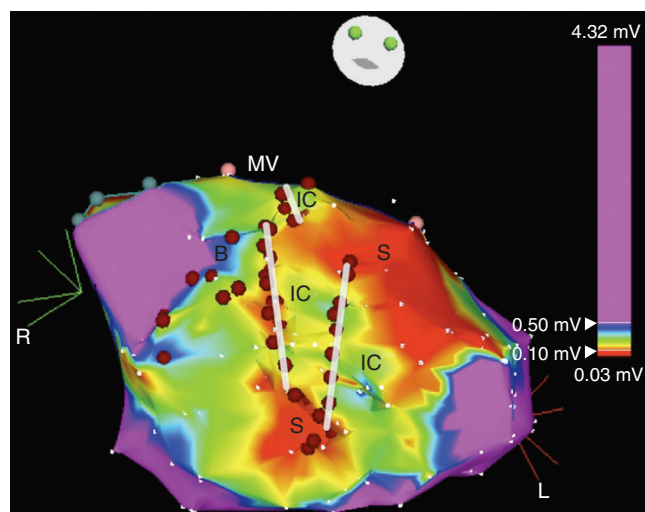


FIGURE 86-6 ■ Substrate ablation of ventricular tachycardia. A three-dimensional electroanatomic CARTO map of the left ventricle is shown in a modified right anterior oblique orientation. The mitral valve (MV) and the septum and part of the anterior and inferior walls are shown. The colors represent electrogram voltage, shown on the scale (right) in a range from 0.1 mV to 0.5 mV. Purple areas are relatively normal myocardium, red areas represent dense scar (S), and between them are areas of viable myocardium with scar. Conduction is slow through these areas, and isthmus channels (IC) can be identified. Red dots represent ablation sites. Note that ablation lines (white lines) extend from areas of scar across the isthmus channel to adjacent areas of scar and from areas of scar to the mitral valve. Additional ablations were also created in the border zone (B) at areas with fractionated electrograms (see text). L, Left; R, right.

access of the pericardial space, often in conjunction with endocardial ablation. This approach is most often used for cardiomyopathies associated with VT of an epicardial origin (non-infarct-related cardiomyopathy, Chagas disease, etc.) or in patients who have refractory VT despite previous endocardial ablation attempts. In some

centers, epicardial ablation is used as a first-line ablation strategy for patients with VT.⁸⁵ Once epicardial access has been obtained, the process of mapping and ablation of VT is similar to that of the endocardial approach. However, catheter manipulation can be more challenging in the epicardium, and coronary angiography before the delivery of RF energy is important to ensure the ablation catheter is a safe distance from the large epicardial coronary arteries. In patients status post coronary artery bypass grafting, localization of bypass grafts is important in order to avoid laceration of grafts during catheter manipulation. Furthermore, in any patients with a history of prior open heart surgery, epicardial scarring and pericardial adhesions can make catheter manipulation in the epicardial space difficult if not impossible. Of note, epicardial ablation has also been used for arrhythmias other than VT, including inappropriate sinus tachycardia, refractory atrial arrhythmias despite previous endocardial ablation, and accessory pathways inaccessible from an endocardial approach.⁸

Idiopathic Ventricular Tachycardia

VT occurs most often in patients with underlying structural heart disease. VT is also seen in patients without known structural heart disease; this is known as idiopathic VT. The most common type of idiopathic VT is caused by triggered activity from delayed afterdepolarizations. It is typically catecholamine dependent, frequently brought on by exertion or emotional stress, and can be terminated by vagal maneuvers, adenosine, calcium channel blockers, or sodium channel blockers. The term *idiopathic VT* is a misnomer because patients with underlying structural disease can also have triggered, focal VTs arising from similar locations and behaving in similar ways to VTs seen in patients without structural disease. With this understanding, it is more appropriate to characterize all VTs based on tachycardia mechanism in addition to underlying substrate.^{85a} For the purposes of this section, we focus on the approach to triggered, focal VTs in patients without underlying structural disease, most commonly referred to as idiopathic VT. These tachycardias most commonly arise from the right ventricular outflow tract (RVOT),^{86,87} coronary cusps, left ventricular outflow tract (LVOT),^{88,89} and mitral annulus,⁹⁰ but have also been reported at other sites in the left and right ventricles.

The characteristic ECG for RVOT VT is a left bundle, inferior axis, with either a right or left axis depending on the location in the outflow tract. For LVOT/coronary cusp VT, the ECG typically has a small r wave in V₁ with early development of a large R wave in the right precordial leads and an inferior axis. These VTs often require catecholamine infusion during EPS for induction. The approach to mapping and ablation for both RVOT and LVOT/coronary cusp VTs is similar.⁹¹⁻⁹⁴ Activation mapping using both bipolar and unipolar electrograms followed by confirmatory pace mapping is the most reliable method for localizing the focal source of these tachycardias. An electroanatomic mapping system is often used to track the timing of catheter points to locate the earliest electrogram relative to the surface ECG and guide

ablation. In the absence of structural heart disease, pace mapping for focal idiopathic VT is a viable modality for localizing the site of origin, unlike in post-MI VT.⁹⁵ Ablation is performed at the earliest identifiable site of ventricular activation or at the site with a pace map identical to that of the clinical tachycardia.

A second and less common variety of idiopathic VT arises from the left ventricle, is reentrant, and is verapamil sensitive.^{93,94,96} The characteristic ECG is right bundle, superior axis, which can be left superior if it is coming from the posterior third of the septum or right superior if it is coming from the apical third. Opinions regarding the optimal approach to ablation vary, but activation mapping of the site of earliest ventricular activation along the septum, followed by pace mapping, is generally a reasonable approach. Some authors advocate targeting presystolic Purkinje potentials or mid-diastolic potentials.^{97,98} Electroanatomic activation mapping and identification of the earliest retrograde Purkinje potentials has also been used to guide ablation.⁹⁹ Entrainment mapping has been reported but is difficult to achieve. Ablation for this type of VT should use as many mapping modalities as possible, with consideration of the Purkinje spike, concealed entrainment if attainable, activation mapping, and confirmatory pace mapping.

Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Catheter ablation for treatment of AF was previously limited to ablation of the AV junction combined with pacemaker implantation in patients refractory to, or intolerant of, pharmacologic therapy. Over the past 15 years, catheter ablation has become a common strategy for decreasing the burden of AF in patients refractory to medical therapy, through elimination of AF triggers and modification of the atrial substrate responsible for the maintenance of AF.

Atrioventricular Junction Ablation

Ablation of the AV junction was the first use of catheter ablation and used DC energy; however, RF energy is superior and is now used for this procedure.^{100,101} This procedure is indicated for patients who have been unable to tolerate medical therapy for AF or in whom it has been ineffective and requires pacemaker implantation before ablation. To perform AV junction ablation, an ablation catheter is advanced beyond the superior aspect of the tricuspid valve, along the ventricular septum, until the maximum amplitude His bundle recording is observed. The catheter is then withdrawn 1 to 2 cm until a large atrial electrogram and occasionally a very small His bundle recording is seen. Ablation is performed in this region until AV block is achieved. This technique targets the distal portion of the AV node and allows for an intact junctional escape pacemaker to persist and provide backup heart rate in the case of pacemaker failure. Occasionally this approach fails and despite ablation of the distal AV node, rapid conduction persists. In these cases, ablation is performed over the His bundle region. In up to 10% of cases, ablation of the His bundle from the left

side is required to achieve effective AV block.¹⁰² After ablation, the patient is commonly monitored in the electrophysiology laboratory during isoproterenol infusion to assess for resumption of conduction. The success rate of this procedure for achieving AV block has been reported to be 97.4%.²⁹

Ablation of the AV junction has been associated with an increased risk of sudden cardiac death, thought to be caused by polymorphic VT related to electrical instability and changes in repolarization caused by the sudden change in heart rate and myocardial activation sequence.¹⁰³⁻¹⁰⁵ These changes may be manifest as QT prolongation and torsades de pointes. As a result, after AV junction ablation, the pacemaker is initially programmed to a lower pacing rate of 80 to 90 beats/min, which is then slowly decreased over several months at follow-up visits.

Catheter Ablation of Atrial Fibrillation

The role of catheter ablation of AF in the management of patients with AF continues to evolve. Haissaguerre and coworkers observed that focal triggers originating in the pulmonary veins may initiate AF; this led to a new catheter-based approach to the treatment of AF.¹⁰⁶ Early procedures used focused catheter ablation of ectopic foci found in pulmonary veins and had limited success. Researchers then proceeded to perform extensive ablation in the pulmonary veins, but this was complicated by pulmonary vein stenosis caused by scarring of the proximal veins.¹⁰⁷ Since that time, multiple newer techniques for isolating the pulmonary veins have been used.

Segmental ostial pulmonary vein isolation is based on the principle that pulmonary vein triggers initiate AF in the left atrium. Ablation is performed around the ostium of each pulmonary vein until conduction block at the left atrium-pulmonary vein border is achieved. The goal of this method is to electrically isolate each vein, thus preventing pulmonary vein triggers from reaching the left atrium to initiate and perpetuate AF.^{108,109} More recently, circumferential left atrial (LA) ablation and wide-area left atrial catheter ablation (WACA) have been used for the treatment of AF. This strategy uses creation of ablation lines that encircle the ostia of all four pulmonary veins, usually in two pairs, one around the left pulmonary veins and one around the right pulmonary veins. These ablation lesions are generally driven by anatomic landmarks and do not require detailed mapping of focal electrical connections between the pulmonary veins and the left atrium, which can simplify the procedure although a greater number of ablation lesions is usually required, resulting in longer procedural times. WACA results in more extensive ablation across a wider area of the left atrium compared with segmental ostial pulmonary vein isolation (PVI), which may provide additional means of preventing AF recurrence including autonomic denervation,¹¹⁰ elimination of AF triggers outside of the pulmonary veins,¹¹¹ and modification of the LA substrate that may facilitate perpetuation of AF.¹¹² In conjunction with ablation around the pulmonary veins, additional ablation lines may be created connecting ablation lines to one another or to anatomic landmarks, such as the mitral

annulus. These additional lines are intended to interrupt potential macroreentrant circuits that could otherwise lead to LA tachycardias.

Small randomized studies that compared segmental ostial PVI with circumferential LA ablation yielded conflicting results. One study found that rates of recurrent symptomatic paroxysmal AF were higher in the segmental ostial PVI group, whereas another study reported that symptomatic recurrences and atrial arrhythmias seen on ambulatory monitoring were significantly greater in the circumferential ablation group.^{113,114} Unfortunately the two studies are not directly comparable because of differences between patient populations and study design. Currently, most physicians believe that a circumferential or WACA approach is superior to a segmental ostial approach. However, there continue to be wide variations in practice patterns. An expert consensus statement recommends that electrical isolation should be the goal of ablation around the pulmonary veins.¹¹⁵ Electrophysiologic criteria for ablation success vary, but the most rigorous operators aim for elimination of electrical signals at the site of ablation and elimination of electrical conduction into the pulmonary veins from the left atrium (entrance block) and from the pulmonary veins to the left atrium (exit block).

Beyond electrical isolation of the pulmonary veins, additional focal ablation in the atria at a variety of different locations has become increasingly popular. It has been postulated that nonpulmonary venous structures entering the atria are alternative triggers of AF, and ablation of regions around the superior vena cava, ligament of Marshall, and CS are performed by many operators as adjunctive therapy to PVI.¹¹⁶ Complex fractionated atrial electrograms (CFAEs) have also been a target of ablation and extensive research. CFAEs are found mostly in areas of slow conduction and it has been postulated that they may be important components of the substrate that allows maintenance of AF. One study reported a high percentage of freedom from arrhythmia following CFAE ablation without PVI in paroxysmal AF patients.¹¹⁷ Beyond the CFAE debate, controversy also remains regarding the benefits of LA substrate modification with additional ablation lines beyond those created to isolate the pulmonary veins. The argument for the creation of additional lines is that RF lesions may create reentrant circuits. LA tachycardias appear to be more common after circumferential PVI as opposed to segmental ostial PVI, which may add weight to this argument because wider ablation lesions may facilitate development of macroreentry.¹¹³ However, an argument against the creation of additional lines is that LA tachycardia following PVI is often treated successfully with reisolation of the pulmonary veins without additional linear ablation lesions.^{117,118}

In practice, AF ablation is now often performed using a stepwise technique.¹¹⁹ Ablation around the pulmonary veins is first performed with the goal of electrical isolation of the veins. Although this technique is often adequate in patients with paroxysmal AF, patients with persistent or chronic AF often require further ablation. Guided by inducibility of AF and conversion of AF during ablation, additional linear lesions may be created. If the patient continues to have inducible AF or remains in AF,

some physicians choose to ablate areas of the left atrium exhibiting CFAEs during LA mapping.^{112,119}

Because catheter ablation of AF is invasive and has procedural risks, it is generally reserved for patients who do not respond to medical therapy with antiarrhythmic drugs.¹²⁰ With the low efficacy of medications and the high success rates of catheter ablation in experienced centers, this procedure is occasionally considered first-line therapy for patients who do not wish to take antiarrhythmic medication. A meta-analysis has demonstrated that the efficacy of catheter ablation is significantly greater than the efficacy of medical therapy.¹²¹ Reported success rates vary widely, ranging from 42% to 88% for patients with paroxysmal AF in studies with adequate follow-up available.^{113,122-124} Success rates for patients with persistent AF are much lower, reported at approximately 50% in most studies, and a recent study of long-standing persistent AF suggested a single procedure success rate as low as 20%.¹²⁵ The complication rate for this procedure is as high as 6%, with tamponade, pulmonary vein stenosis, stroke, and access site complications being the most common adverse outcomes.¹²³ The reasons for this relatively high complication rate include the use of multiple catheters, the transseptal puncture procedure, the need for high-intensity systemic anticoagulation, and the manipulation of catheters and creation of ablation lesions in the left atrium. The most recent American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines on the management of patients with AF make a strong recommendation for RF ablation for patients with symptomatic paroxysmal AF who have failed treatment with an antiarrhythmic drug and a weak recommendation for RF ablation for patients with symptomatic, persistent AF. They make a very weak recommendation for RF ablation for patients with symptomatic paroxysmal AF and significant LA dilation or significant left ventricular dysfunction.¹²⁰

Although specific techniques vary, most operators place standard electrophysiology catheters in the CS and right atrium. Transseptal puncture is then performed. This is accomplished using the standard technique developed 50 years ago.¹²⁶ A long sheath with an inner dilator designed for transseptal access is advanced to the right atrium and placed in the fossa ovalis. Location is confirmed using fluoroscopic landmarks, intracardiac ultrasound, and/or injection of a small amount of contrast dye to "stain" the septum (Fig. 86-7). When location at the fossa ovalis is confirmed, a long needle is advanced from the tip of the dilator until the septum is punctured. Entry into the LA is confirmed by injection of microbubbles seen on intracardiac ultrasound, injection of dye under fluoroscopy, advancement of a wire into the LA or pulmonary vein, and/or direct pressure measurement. Once LA access is achieved with one or two sheaths, an ablation catheter and circular mapping ("lasso") catheter are placed in the left atrium. Systemic anticoagulation with IV heparin is administered throughout LA access with activated clotting times kept between 250 and 400 seconds.

Once LA access is obtained, mapping of the left atrium and pulmonary veins is performed using a three-dimensional electroanatomic mapping system. Recent

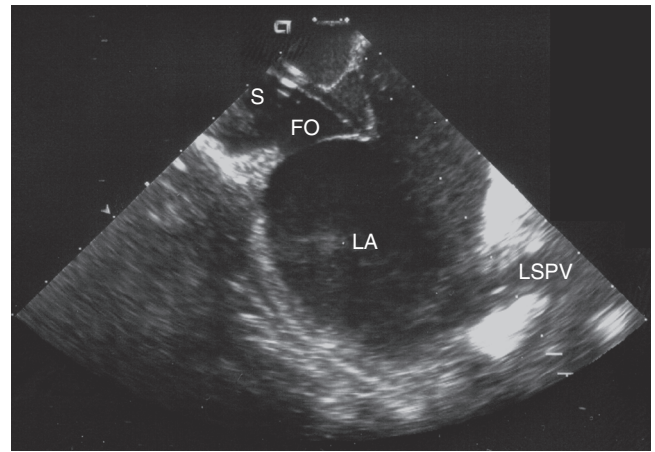


FIGURE 86-7 ■ Intracardiac ultrasound image of transseptal catheterization. The transseptal sheath (S), fossa ovalis (FO), left atrium (LA), and left superior pulmonary vein (LSPV) ostium are shown. The typical "tenting" of the fossa ovalis by the transseptal needle advanced through the sheath confirms appropriate positioning of the needle for puncture of the fossa ovalis.

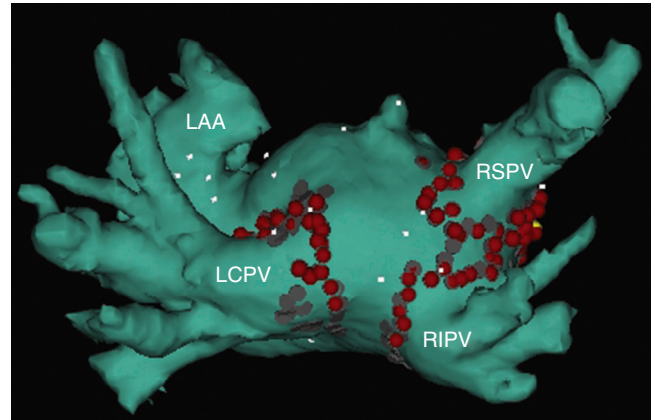


FIGURE 86-8 ■ Three-dimensional electroanatomic map of the left atrium showing integrated information from intracardiac mapping and a previously acquired computed tomography image (CartoMerge, Biosense Webster, Inc.). This patient has a left common pulmonary vein (LCPV) that gives rise to superior and inferior branches, and separate right-sided pulmonary veins. The red and gray circles indicate sites of ablation performed in a circumferential pattern around the pulmonary veins. Bidirectional electrical isolation of all pulmonary veins without additional ablation lines was performed in this patient. LAA, Left atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein.

advances in this technology have allowed the integration of previously acquired computed tomography or magnetic resonance imaging images or real-time tomographic fluoroscopy or intracardiac ultrasound images of the left atrium into the mapping system (Fig. 86-8). Ablation is then performed as described earlier. Manual catheter manipulation remains the most common method, but newer technologies allowing remote magnetic catheter guidance or robotic catheter guidance have been developed and are in limited clinical use.¹²⁷⁻¹²⁹ These technologies show promise for reducing radiation exposure to patient and operator and possibly increasing the safety of the procedure.

Cryoballoon Ablation of Atrial Fibrillation

As mentioned previously, a cryoballoon catheter has been specifically designed for the treatment of AF and is now in use worldwide. The goal of cryoablation for AF using the cryoballoon is electrical isolation of the pulmonary veins. In comparison to RF therapies for AF, cryoballoon functions most like circumferential pulmonary vein isolation: after balloon deployment, cryothermal energy is delivered at the pulmonary vein antrum but does not target other areas beyond the pulmonary veins. To facilitate cryoballoon ablation, a transseptal catheterization is performed using the technique described earlier. After obtaining LA access, a standard transseptal sheath must be upsized to a specialized 12 Fr steerable sheath designed specifically to deliver the cryoballoon, available in two different sizes. Just as with RF ablation, systemic anticoagulation with IV heparin is administered throughout LA access with activated clotting times kept between 250 and 400 seconds. Through the transseptal sheath, the cryoballoon is advanced to the LA and a specialized circumferential mapping ("lasso") catheter is advanced through the cryoballoon and into the targeted pulmonary vein. The cryoballoon is then inflated in the LA and advanced over the lasso catheter until it is positioned into the antrum of the pulmonary vein. Contrast dye is then injected into the pulmonary vein distal to the cryoballoon under fluoroscopy to assess for occlusion. Color Doppler on intracardiac ultrasound is now widely used to assess for pulmonary vein occlusion. Complete occlusion is considered a surrogate for circumferential contact with the cryoballoon. Cryothermal energy is then delivered through the cryoballoon, generally in two applications. Entrance and exit block is then assessed in the same manner as described earlier. Additional cryoballoon applications can be applied as needed. The process is repeated for all major pulmonary veins. If isolation cannot be achieved with the cryoballoon alone, focal ablations can be performed as needed with a cryoablation catheter or standard RF catheter.

The major advantages of cryoballoon ablation for AF are a decrease in procedure time and reduced risk of complications related to RF energy, specifically thrombus formation at the site of lesion creation and cardiac perforation caused by excessive heating or catheter-related trauma. Theoretically, the cryoballoon ablation is also less complex and less dependent on operator dexterity, which is required to create contiguous curvilinear lesions with focal RF ablation. Centers with extensive cryoballoon experience have reported a progressive decline in procedural times, which are generally shorter than average procedural times for RF ablation.¹⁹ Efficacy of cryoballoon ablation for paroxysmal AF has been shown to be similar to results reported for standard RF ablation in nonrandomized and randomized trials.^{18,20,130} For patients with persistent AF, cryoballoon ablation alone has yielded low 1-year procedural success rates, likely related to the knowledge that patients with persistent and permanent AF may require more extensive atrial ablation beyond the pulmonary vein antra to adequately modify their substrate for AF. Combined approaches using cryoballoon ablation and RF ablation for creation of linear

ablation lesions have reported better results in such patients.¹³¹

Complications of cryoballoon ablation appear to differ slightly from those of standard RF ablation. Tamponade and atrioesophageal fistulas have been reported less frequently in cryoballoon ablation. However, phrenic nerve paralysis has been reported with a significantly higher frequency compared with RF ablation, although for most patients, phrenic nerve paralysis is temporary and short-lived.^{19,20} Because of the frequency of this complication, routine use of high output phrenic nerve pacing in the superior vena cava with palpation of the diaphragm during energy application in the right pulmonary veins is routine practice. Pulmonary vein stenosis has also been reported with cryoballoon ablation although most patients were asymptomatic and stenosis was discovered as a result of aggressive postprocedure screening.²⁰

The optimal therapy for AF remains unclear and must be tailored to each patient. Structural heart disease, sleep apnea, aging, and fibrosis all make catheter ablation less likely to be successful. Combination therapy with antiarrhythmic drugs is often required. Many patients with long-standing AF, severe valvular disease, or severely dilated atria have a very low likelihood of success with catheter ablation, and in these patients a strategy of rate control of AF without aggressive attempts to restore sinus rhythm is often indicated. However, many other patients with AF benefit from pulmonary vein isolation with RF energy, cryoballoon ablation, or a combination of the two, and the use of these modalities has become widespread.

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SURGICAL TREATMENT OF CARDIAC ARRHYTHMIAS

Christopher P. Lawrance • Matthew C. Henn • Ralph J. Damiano, Jr.

CHAPTER OUTLINE

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INAPPROPRIATE SINUS TACHYCARDIA

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VENTRICULAR TACHYCARDIA

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Conclusions

Current nonpharmacologic treatments for cardiac arrhythmias include catheter ablation, implantation of pacemakers and cardioverter-defibrillator devices, and surgery. These modalities can be used to treat essentially all supraventricular and ventricular tachyarrhythmias. Although the indications for surgical intervention have narrowed, surgery remains an important treatment option, especially for the most common of all arrhythmias, atrial fibrillation.

ATRIAL FIBRILLATION

Background

Atrial fibrillation (AF) is present in up to 2% of the general population and in approximately 10% of patients

older than 60 years, making it the most common form of sustained cardiac arrhythmia.¹⁻⁵ From 1993 to 2007 the prevalence in Medicare patients 65 years and older has increased 5% each year both because of our aging population and for other reasons that remain poorly defined.⁶ Consequently, there has been a 66% increase in hospital admissions for AF over the past 20 years. It is estimated that AF will affect up to 12 million people in the United States by the year 2050.⁷ Its financial burden is significant, with a global annual cost of \$8705 per patient annually, and \$6 billion in the United States alone.⁸ Although AF is frequently considered to be an innocuous arrhythmia, it can be associated with significant morbidity and mortality because of its three detrimental sequelae: (1) palpitations, which cause the patient discomfort and anxiety; (2) loss of synchronous atrioventricular contraction, which compromises cardiac hemodynamics,

resulting in varying degrees of ventricular dysfunction; and (3) stasis of blood flow in the left atrium, which can result in thromboembolism and stroke.⁹⁻¹³ Separate from the direct cardiac effects, the most feared complications of AF stem from the development of thrombus in the left atrium. These thrombi can embolize and lead to myocardial infarction, acute mesenteric ischemia, and stroke. Stroke, in particular, is three to five times more likely to occur in patients with AF when compared to patients in sinus rhythm.¹⁴ Conversely, 20% to 30% of all acute stroke patients are found to be in AF.¹⁵⁻¹⁷ Antiarrhythmic medications have largely been unsuccessful thus far, with most series showing the efficacy of antiarrhythmic medications to be less than 50%.¹⁸⁻²⁰ Antithrombotic drugs for AF carry with them various complications, including an annual risk of major bleeding up to 3%, rising even higher in older adults.^{17,21,22} AF also independently increases mortality rates. Using data from the Framingham Heart Study, Benjamin and coworkers established the risk factor-adjusted odds ratio for death in men and women with AF as 1.5 and 1.9, respectively.²³

Classification of Atrial Fibrillation

AF can be classified in various ways, but the classification system published jointly by the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society is the most widely used.²⁴ This system defines AF as either paroxysmal or persistent. When a patient has had two or more episodes, AF is considered recurrent. If recurrent AF terminates spontaneously, it is designated paroxysmal, but if it is sustained beyond 7 days, it is termed persistent. Termination by pharmacologic therapy or electrical cardioversion before expected spontaneous termination does not change the designation *persistent*. In a recent consensus statement sponsored by the Heart Rhythm Society, the definition of *permanent* was changed to include only cases in which cardioversion has failed, clarifying that patients with long-standing AF might still be cured by intervention. In those cases, *permanent* has been replaced with the term *long-standing AF* when the duration is more than 1 year.²⁵

Electrophysiology of Atrial Fibrillation

AF is characterized by the irregular activation of the atria and an accompanying irregular ventricular response. Activation of the atria during AF can exhibit two different patterns. One pattern consists of a stable source, either a focal trigger or a small reentrant circuit, with fibrillatory conduction away from the source. The other pattern is characterized by multiple changing sources or reentrant circuits. The specific mechanism may change over time in a particular patient. Work from our laboratory obtained from patients undergoing intraoperative mapping before arrhythmia surgery revealed that the source of AF was not stable in almost half of the patients, even moving from one atrium to the other.²⁶

Four substrates determine whether AF is initiated and sustained: (1) a trigger, usually a premature depolarization or runs of focal ectopic depolarizations; (2) the refractory period of the atria and its magnitude and

spatial distribution; (3) the conduction velocity and its magnitude and anisotropic spread; and (4) the geometry or anatomy, both macroscopic and microscopic. Whatever the pathologic process (e.g., valvular disease, heart failure, ischemia, tachycardia, pericarditis, or inflammation) is, the changes that occur affect one or more of these four factors.²⁷

The surgical treatment of AF is directed at alteration of the geometry and anatomy needed to support AF. Non-reentrant mechanisms, such as abnormal automaticity and triggered activity, are important for the generation of premature beats, which act as a trigger for reentry but may also be involved in maintaining AF. The premature beats interact with the underlying distribution of refractory periods. As the distribution becomes more inhomogeneous, unidirectional block can occur. This is a necessary condition for the initiation of reentry. When unidirectional block occurs, a reentrant arrhythmia will occur only if a critical mass of tissue is present. The critical mass is determined by the tissue geometry, the magnitude of refractory periods, and the conduction velocity. The amount of tissue required to support a reentrant circuit is defined by the equation $WL = CV \times RP$ (wavelength = conduction velocity $\times$ refractory period). If either CV or RP decreases, the amount of tissue needed to sustain AF decreases, and the probability of a patient's having an arrhythmia increases.²⁸ Interventional approaches attempt to alter one of these substrates. However, any treatment strategy has the potential to affect the other substrates that cause AF. For example, incisions or ablations not only affect conduction, but they also alter the geometry of the atria, decrease viable myocardial mass, and can denervate regions of the atria, which alters refractory periods.²⁸

A great deal of emphasis has been placed on the role of the pulmonary veins in the triggering of AF. Paroxysmal AF often originates in the pulmonary veins.²⁹ In humans, the anatomy of the pulmonary veins is variable, with electrically excitable cardiac muscle extending 1 to 4 cm beyond the ostium of the veins.³⁰ Developmental biological studies suggest that pacemaker tissue may be present in the pulmonary veins.³¹ Another potential mechanism of focal activation is afterdepolarization.³² Intraoperative mapping studies have shown ectopic atrial beats originating from the region of the pulmonary veins.²⁷ Biatrial mapping studies by Schmitt and coworkers³³ have shown that the premature beats that trigger AF were located in the pulmonary veins 53% of the time and in the posterior atrium in another 29% of cases.

Successful cure of AF is achieved in some patients by the isolation of the pulmonary veins.²⁹ Furthermore, if triggers of AF were outside the pulmonary veins but other substrates that sustain AF were within the veins, AF would be prevented with pulmonary vein isolation. The failure to cure AF by isolating only the pulmonary veins in some patients, especially those with long-standing AF, suggests that other anatomic triggers or more complicated mechanisms may be involved in these cases. Using intraoperative mapping in patients with mitral valve disease, Nitta and colleagues³⁴ determined that atrial focal activation is one mechanism of AF. Caution should be taken in interpreting various interventional

studies, whether catheter ablation or surgery, as to whether they imply an underlying mechanism involved in a patient's AF. Most intraoperative and catheter mapping systems do not have the spatial resolution within the pulmonary veins to separate reentrant from non-reentrant mechanisms. Therefore, even though "focal" fibrillation may be reported from investigational mapping, this does not rule out reentry as a mechanism underlying the arrhythmia. Claims of cure by pulmonary vein isolation alone must be tempered by the knowledge that the "pulmonary vein isolation" intervention actually incorporates much more than just the pulmonary veins. Commonly, the pulmonary veins, the adjacent atrial muscle, and the muscle in the oblique sinus between the veins are ablated during catheter-based pulmonary vein isolation. This area is more than one third of the left atrium. This large area of ablation substantially reduces the critical mass needed to sustain AF and may incorporate other non-pulmonary vein substrates of AF.

The definitions of paroxysmal, persistent, and long-standing AF do not imply a specific mechanism. Even though clinical results have shown that pulmonary vein isolation is effective 70% to 80% of the time in paroxysmal AF, it is clear that the pulmonary veins are not the only substrate driving AF 20% to 30% of the time.²⁶ Similarly, in persistent AF, pulmonary vein isolation alone is successful in only a small number of patients.²⁵ Human mapping data from our laboratory did not show any significant difference in mechanism between paroxysmal and persistent AF.²⁶ Current diagnostic technologies rarely allow a preoperative delineation of mechanism. However, electrophysiologic studies may allow physicians to identify triggers of AF in some patients.²⁶ Because AF is a complex arrhythmia, mapping requires a high density of closely placed electrodes as well as a sophisticated mapping and signal processing system to define the particular mechanism in an individual patient. In our experience, intraoperative mapping has not been useful in providing real-time information during surgery. The analysis of this complex arrhythmia is time-consuming and difficult. Therefore, the traditional surgical algorithm of obtaining preoperative or intraoperative mapping data and using this information to guide the specific surgical technique, as was done with arrhythmias such as Wolff-Parkinson-White syndrome, has not been feasible for AF. Mapping techniques are currently being developed that may allow interventionalists to customize the lesion set to the specific underlying mechanism.^{26,34-36}

One particularly promising technique is electrocardiographic imaging.³⁷ This technology allows AF to be mapped noninvasively in the awake patient by recording signals from the body surface and solving the inverse equation. This would delineate the mechanism before the proposed intervention and may allow physicians to triage patients to the most effective procedure.

Medical Treatment

Results with medical therapy alone for AF have been disappointing. Antiarrhythmic drugs have had limited long-term efficacy in converting AF to normal sinus rhythm and have significant and sometimes fatal side

effects.³⁸⁻⁴³ The goal of pharmacotherapy is therefore often shifted from *rhythm* to *rate* control, which involves slowing the ventricular response rate to AF, thus avoiding the development of rate-related cardiomyopathy and symptoms such as palpitations. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study^{44,45} showed that management with rhythm control did not have any survival benefit over a rate control strategy in anticoagulated patients with AF.^{46,47} Furthermore, rate control strategy may potentially have advantages over rhythm control, such as a lower risk for adverse side effects.⁴⁶

Rate control alone clearly has disadvantages. Although the ventricular response rate can often be controlled pharmacologically, the atria are still in fibrillation. With persistent AF, two of the three detrimental sequelae associated with AF persist. In patients with baseline cardiac dysfunction, the absence of atrial "kick" often can result in worsening symptoms of congestive heart failure. Most important, patients with AF are at risk for developing thromboembolism, requiring indefinite anticoagulation with warfarin or one of the newer anticoagulants, such as dabigatran, rivaroxaban, or apixaban.⁴⁸ The use of warfarin is associated with a major complication rate of approximately 2% per year.⁴⁹⁻⁵¹ Although these newer anticoagulants decrease the risk of intracerebral hemorrhage without the need for routine coagulation monitoring, they have the same effectiveness as warfarin in the reduction of thromboembolism.⁴⁸

Despite the results from the AFFIRM trial supporting no difference in long-term outcome between rhythm and rate control, there are many clinically meaningful advantages of being in normal sinus rhythm. These advantages include increased exercise tolerance, no need for anticoagulation, decreased palpitations, and prevention of atrial remodeling.^{45,52} Most important, when time-dependent variables were evaluated in the AFFIRM trial, the presence of sinus rhythm was associated with a significantly decreased risk of death (hazard ratio = 0.53; $P < 0.0001$).⁵³ Thus, the AFFIRM trial demonstrated that antiarrhythmic drugs are detrimental and that normal sinus rhythm is beneficial in this population of patients, suggesting a role for nonpharmacologic restoration of sinus rhythm.

Historical Aspects of Surgery for Atrial Fibrillation

Because of the inadequacy of medical therapy for AF, several procedures were developed in the 1980s aimed at treatment of AF. Most of these were abandoned because of their inability to eliminate all three of the detrimental sequelae associated with AF.⁵⁴⁻⁵⁶ Nevertheless, they helped physicians gain fundamental knowledge about the mechanism of AF and laid a foundation for the development of the Cox-Maze procedure and its subsequent iterations. The Cox-Maze procedure is recognized today as the gold standard for surgical cure of AF. The next section briefly describes these various surgical procedures developed in an attempt to cure AF.

Left Atrial Isolation Procedure. In 1980, Dr. James L. Cox and his group developed the left atrial isolation

procedure, which confined AF to the left atrium, thus restoring the remainder of the heart to normal sinus rhythm.⁵⁶ This procedure had the advantage of restoring normal atrioventricular rhythm without requiring a permanent pacemaker. Because the sinoatrial node, atrioventricular node, and internodal conduction pathways are located in the right atrium and interatrial septum, the left atrial isolation procedure did not interfere with normal atrioventricular conduction.

Electrical isolation of the left atrium also unexpectedly restored normal cardiac hemodynamics. This occurred because the right atrium and the right ventricle contracted in synchrony after the procedure, providing a normal right-sided cardiac output that was then delivered to the left side of the heart. Although the left atrium was isolated, the left ventricle adapted immediately to the normal right-sided cardiac output and delivered a normal forward cardiac output.

By confining AF to the left atrium only, the left atrial isolation procedure eliminated two of the three detrimental sequelae of AF: irregular heartbeat and compromised cardiac hemodynamics. However, because the electrically isolated left atrium remained in AF, this procedure did not eliminate the risk of thromboembolism. It also did not address patients in whom the AF originated in the right atrium.

Catheter Ablation of the Atrioventricular Node–His Bundle Complex. In 1982, Scheinman and colleagues⁵⁷ described the catheter fulguration of the His bundle, which controlled the irregular cardiac rhythm associated with AF and other refractory supraventricular arrhythmias. Similar to the left atrial isolation procedure, this procedure electrically isolated the arrhythmia to the atria. However, ablation of the His bundle necessitated implanting a permanent ventricular pacemaker to restore normal ventricular rhythm.

Unfortunately, His bundle ablation eliminated only the irregular heart beat. Both atria still remained in fibrillation, and the vulnerability to thromboembolism was unaffected. Atrioventricular contraction remained desynchronized, compromising cardiac hemodynamics. Despite its drawbacks, this remains a common treatment for medically refractory AF in patients not considered good candidates for a more curative interventional procedure.

Corridor Procedure. In 1985, Guiraudon and associates⁵⁸ introduced the corridor procedure for the treatment of AF. This was an operation that isolated a strip of atrial septum harboring both the sinoatrial node and the atrioventricular node, thereby allowing the sinoatrial node to drive the ventricles. This procedure corrected the irregular heart beat associated with AF, but both atria either remained in fibrillation or developed their own asynchronous intrinsic rhythm because they were isolated from the septal “corridor.” The atria were also isolated from their respective ventricles, thereby precluding the possibility of atrioventricular synchrony. The corridor procedure was abandoned because neither the hemodynamic compromise nor the risk of thromboembolism associated with AF was addressed.

Atrial Transection Procedure. All three surgical procedures developed in the early 1980s had attempted to isolate and to confine AF to a certain region of the atria, stopping it from propagating its effects to the ventricles. None of these procedures was targeted to cure AF.

In 1985, Cox’s group described for the first time a series of experiments that attempted to cure AF in a canine model.⁵⁹ After a number of experiments, it was found that a single long incision across both atria and down into the septum cured AF. This “atrial transection” procedure prevented the induction and maintenance of AF or atrial flutter in canines.⁶⁰ Unfortunately, this procedure was not successful in its clinical application.

Development of the Cox-Maze Procedure

The first successful curative surgical procedure for the treatment of AF was introduced clinically in 1987 by the team led by Dr. James L. Cox at Washington University in St. Louis.⁶⁰⁻⁶² The Cox-Maze procedure was designed to interrupt the macro-reentrant circuits that were thought to be responsible for AF, thereby precluding the ability of the atrium to flutter or fibrillate (Fig. 87-1). In contrast to previous procedures, the Maze procedure successfully restored both atrioventricular synchrony and a regular heart beat, thus decreasing the risk of thromboembolism and stroke.⁶³ The operation involved creating myriad incisions across both the right and left atria. The surgical incisions were placed so that the sinoatrial node could “drive” the propagation of the sinus impulse throughout both atria. It also allowed all of the atrial myocardium to be activated, resulting in preservation of atrial transport function in most patients.⁶⁴

After almost a decade of basic research, the Maze I procedure was introduced in 1987, only to be soon modified to become the Maze II procedure because of late chronotropic incompetence and a high incidence of pacemaker implantations. The Maze II procedure, however, proved to be too technically difficult to perform. It was therefore further modified and renamed the Maze III procedure (Fig. 87-2).^{65,66}

During the 1990s, the Cox-Maze III procedure became the gold standard for the surgical treatment of AF. In a long-term study of patients who had the Cox-Maze procedure, 97% of the patients at late follow-up were free of AF.⁶⁷ Similar results have been reproduced by other institutions around the world.⁶⁸⁻⁷⁰

Surgical Ablation Technology

Despite its proven efficacy, the Cox-Maze III procedure did not gain widespread acceptance. Few cardiac surgeons were willing to add the procedure to coronary revascularization or valve procedures because of its complexity and technical difficulty. In an attempt to simplify the operation, groups around the world have replaced the incisions of the traditional cut-and-sew Cox-Maze III procedure with linear lines of ablation.⁷¹ These linear lines of ablation have been created by use of a variety of energy sources, including radiofrequency energy, microwave, cryoablation, laser, and high-frequency ultrasound.

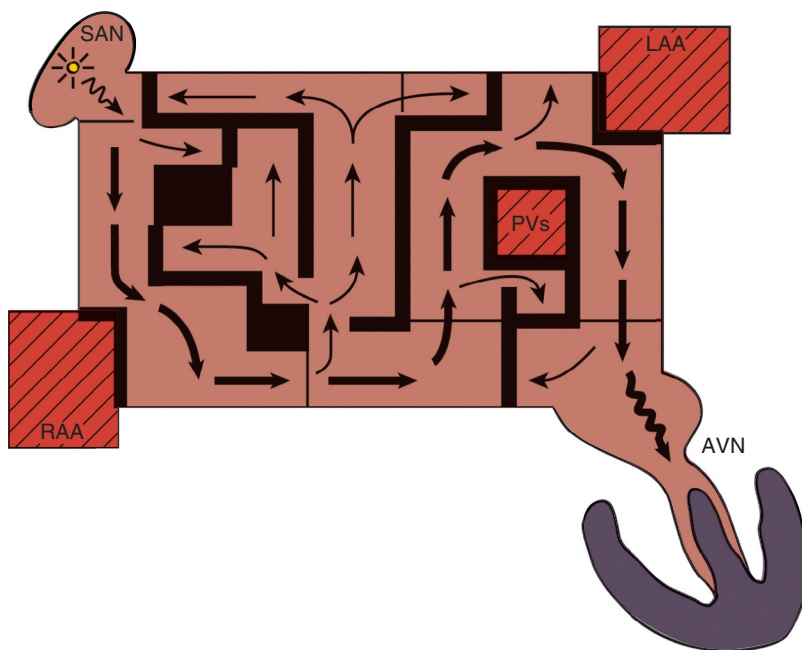


FIGURE 87-1 ■ Original conceptual design of the Cox-Maze procedure for atrial fibrillation. Both atrial appendages were excised, and the pulmonary veins were isolated. AVN, Atrioventricular node; LAA, left atrial appendage; PVs, pulmonary veins; RAA, right atrial appendage; SAN, sinoatrial node. (From Cox JL, Canavan TE, Schuessler RB, et al: The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation. *J Thorac Cardiovasc Surg* 101:406–426, 1991.)

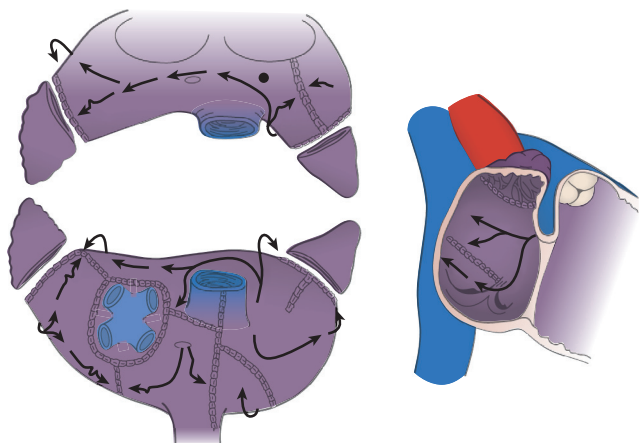


FIGURE 87-2 ■ Two-dimensional drawing depicting the atrial incisions of the Cox-Maze III procedure. (From Cox JL, Boineau JP, Schuessler RB, et al: Modification of the maze procedure for atrial flutter and atrial fibrillation. I. Rationale and surgical results. *J Thorac Cardiovasc Surg* 110:473–484, 1995.)

The development of these new ablation technologies revolutionized the surgical treatment of AF by taking a technically difficult and time-consuming operation and making it relatively easy for most cardiac surgeons to perform. Whereas very few patients (<1%) with AF undergoing cardiac surgery before 2000 underwent a Cox-Maze procedure, a study has shown that more than 40% of patients with AF undergoing cardiac surgery had a concomitant ablation procedure in 2006.^{72,73} Another advantage of ablation technologies is that they have facilitated the development of less invasive operations. A minimally invasive beating heart procedure with high efficacy is the ultimate goal of these efforts. With the availability of easy-to-use ablation devices, numerous groups around the world have introduced new procedures for AF

involving more limited sets of atrial lesions. Some groups are currently performing only the left atrial lesions, whereas others are advocating pulmonary vein isolation alone. Results with these more limited procedures are discussed in a later section.

For ablation technology to reliably replace the incisions in AF surgery, it must meet several criteria. Foremost, it must reliably produce bidirectional conduction block. This is the mechanism by which incisions prevent AF: by blocking macro-reentrant or micro-reentrant circuits, by isolating trigger foci, or by reducing atrial contiguous mass. To do this with certainty, an ablation device must have the capability to reliably make transmural lesions from either the epicardial or the endocardial surface. Experimental work from our laboratory has shown that even gaps as small as 1 mm in ablation lines can conduct fibrillatory wavefronts.⁷⁴

The second crucial characteristic of an ablation device is safety. This requires a precise definition of dose-response curves to limit excessive or inadequate ablation. The surgeon must have knowledge of the effect of the specific ablation technology on surrounding vital cardiac structures, such as the coronary sinus, coronary arteries, and valves. Third, a device should make AF surgery simpler and require less time for it to be performed. This requires features such as rapidity of lesion formation, simplicity of use, and adequacy of length and flexibility. Finally, the device ideally should be adaptable to a minimally invasive approach. This would require the ability to insert the device through small incisions or ports. It would also be beneficial for the device to be capable of creating epicardial transmural lesions on the beating heart.

The current ablation technologies with their advantages and disadvantages are briefly described in this section. At present, there are no microwave, ultrasound, or laser ablation devices on the market and these energy

sources are not discussed. There is still no perfect ablation device. As new devices are introduced in the future, it will be imperative to rigorously examine the effects of the new technology on atrial hemodynamics and electrophysiology.

Radiofrequency Energy

Radiofrequency (RF) energy has been used for cardiac ablation for many years in the electrophysiology laboratory.⁷⁵ It also was one of the first energy sources to be used in the operating room. RF energy can be delivered by either unipolar or bipolar electrodes, and the electrodes can be either dry or irrigated.

There have been numerous unipolar RF devices available for ablation. Estech (San Ramon, CA) has marketed several devices, both dry and irrigated unipolar catheters that are segmented and flexible. These devices can create variable lesion lengths of 10 to 95 mm. The electrodes can be individually selected and temperature controlled. Later iterations have included suction stabilization. The devices are targeted for use in the minimally invasive setting, but they have yet to approach the same degree of transmural ablation that has been achieved with bipolar RF clamps. Both Medtronic and Estech have developed irrigated unipolar RF devices that are used to make point-by-point ablations by dragging the device across tissue to make a linear lesion.

Bipolar RF is similar to unipolar energy except that two electrodes, instead of one, are used to focus the path of energy. This allows faster ablation (usually less than 20 seconds) while focusing destruction to tissue that is within the clamp. With bipolar devices, the electrodes are clamped over the targeted atrial tissue. The first bipolar RF device was introduced by AtriCure, Inc. The Isolator was a specially designed clamp with 1-mm-wide, 5-cm-long electrodes embedded in the jaws of the clamp. The device was unique in that it had an algorithm created to provide a real-time measurement of lesion transmural ablation. The conductance between the electrodes was measured during ablation. When the conductance dropped to a stable minimum level, this correlated well both experimentally and clinically to histologically transmural lesions.⁷⁶⁻⁷⁸ More recent iterations have introduced more uniform clamp strength and a dual electrode design to achieve wider and more consistent lesions.

Other RF ablation devices have been released.^{79,80} The Cobra Adhere and Cobra Adhere XL (Estech, San Ramon, CA) devices are streamlined with suction stabilization for use in minimally invasive procedures, such as port access and thoroscopic approaches. The Cobra Fusion (Estech, San Ramon, CA) includes suction stabilization and has a unique electrode configuration to allow both unipolar and bipolar RF ablation.⁸¹ The Medtronic bipolar devices, the Cardioblate BP2 and Cardioblate LP, have an irrigated, flexible jaw along with an articulating head, with 7-cm-long electrodes. These devices have an algorithm to predict transmural ablation of lesions that has been shown to be effective in experimental and clinical settings.^{82,83}

RF energy uses an alternating current in the range of 100 to 1000 kHz. This frequency is high enough to prevent rapid myocardial depolarization and the

induction of ventricular fibrillation, yet low enough to avoid tissue vaporization and perforation. Resistive heating occurs only within a narrow rim of tissue in direct contact with the electrode, usually less than 1 mm. The deeper tissue heating occurs by passive conduction. With unipolar catheters, the energy is dispersed between the electrode tip and an indifferent electrode, usually the grounding pad applied to the patient. In the bipolar clamp devices, alternating current is generated between two closely approximated electrodes, which results in a more focused ablation. The lesion size depends on the electrode-tissue contact area, the interface temperature, the current and voltage (power), and the duration of delivery. The depth of the lesion can be limited by char formation at the tissue-electrode interface because of the high temperatures (>100°C). To resolve this problem, irrigated catheters have been developed; this reduces char formation by keeping temperatures cooler at the tissue interface. These irrigated catheters have been shown to create larger volume lesions than those created by the dry RF devices.^{84,85}

Dose-response curves for unipolar RF have been described.⁸⁶⁻⁸⁸ Although unipolar RF has been shown to create transmural lesions on the arrested heart in animals with sufficiently long ablation times (60 to 120 seconds), this has not been the case in humans. In one study, after 2-minute endocardial ablations during mitral valve surgery, only 20% of the *in vivo* lesions were transmural.⁸⁷ Epicardial ablation has been even more difficult. Animal studies have consistently shown that unipolar RF is incapable of creating epicardial transmural lesions on the beating heart.^{88,89} Another study in humans resulted in only 7% of lesions being transmural despite electrode temperatures of up to 90°C.⁹⁰ The Cobra Adhere is an epicardial suction-stabilized unipolar RF ablation device. Despite the proposed advantages of epicardial ablation, the Cobra Adhere demonstrated only 40% full-thickness ablation of sectioned ablations after a 2-minute ablation period in animal testing. In particular, the device showed difficulty creating full-thickness lesions in atrial tissue thicker than 3 mm.⁹¹ Bipolar RF ablation, on the other hand, has been shown to be capable of creating reliable transmural lesions on the beating heart in animals with average ablation times between 5 and 10 seconds.^{76,77,92} Newer devices such as the Cobra Fusion have included a combination of both unipolar and bipolar ablation along with the use of proprietary impedance algorithms to determine the amount of time necessary for ablation. Similar animal studies have shown the Cobra Fusion to create transmural lesions in 94% of sectioned lesions.⁸¹

Because RF ablation is a well-developed technology, much is known about its safety profile. Clinical complications of unipolar RF devices have been described, including coronary artery injuries, cerebrovascular accidents, and the devastating complication of esophageal perforation leading to atri-esophageal fistula.⁹³⁻⁹⁶ Use of the bipolar RF devices has eliminated virtually all the collateral damage seen with the unipolar devices, and there have been no clinical complications reported in the literature. Unfortunately, at this time bipolar devices have the drawback of requiring that the tissue be clamped in the jaws of the device to consistently make transmural lesions. This has limited the potential lesion set,

particularly on the beating heart through a minimally invasive epicardial approach, and has required the use of adjunctive unipolar technology to create a complete Cox-Maze lesion set.

Cryoablation

Currently two commercially available sources of cryothermal energy are available. One technology uses nitrous oxide and is manufactured by AtriCure (Cincinnati, OH). The nitrous oxide devices use both rigid reusable and flexible disposable electrodes. More recently, devices using argon were introduced. The technology is now distributed by Medtronic (Minneapolis, MN). This device originally consisted of a disposable flexible catheter that had a 6-cm ablation probe. Newer iterations have included a 10-cm ablation electrode with the addition of a removable clamp. At 1 atmosphere of pressure, nitrous oxide is capable of cooling tissue to -89.5°C ; argon has a minimum temperature of -185.7°C .

The size and depth of cryolesions are determined by numerous factors, including probe temperature, tissue temperature, probe size, duration and number of ablations, and the liquid used as the cooling agent.⁹⁷ With conventional nitrous oxide, 2- to 3-minute ablations have been shown to reliably create transmural lesions on both the right and the left atrium. Because of the heat sink provided by circulating endocardial blood, epicardial cryolesions on the beating heart have not been uniformly transmural.⁹⁸ In one study, investigators were able to create transmural lesions 62% of the time around the pulmonary veins, and two of eight ablations (25%) on the left atrial appendage were transmural.⁹⁸ However, in another study of cryoablation on the beating heart, consistent transmural lesions were created on tissue up to 7 mm thick.⁹⁹ Ablations were performed around the pulmonary veins, and acute electrical isolation was achieved in 13 of 13 animals. Although histologic analysis revealed 89% of sections achieved transmural lesions, none of the box lesions around the pulmonary veins was completely transmural, again emphasizing the drawbacks of cryoablation on the beating heart.

Because of its ease of use and safety profile, cryoablation remains popular for the treatment of AF. A European randomized trial comparing mitral valve surgery alone with mitral valve surgery with left atrial ablations found an increase in cure for AF in the cryoablation group (freedom from AF at 12 months: 43% vs. 73%).¹⁰⁰

Cryoablation has the benefit of preserving the fibrous skeleton of the heart, making this an ideal choice for ablation near valvular tissue. Nitrous oxide cryoablation has had extensive clinical use and has had an excellent safety profile. Although cryothermal energy appears to have no permanent effects on valvular tissue or the coronary sinus, experimental studies have shown late intimal hyperplasia of coronary arteries, and these structures should be avoided.¹⁰¹⁻¹⁰⁴ Doll and colleagues⁹⁸ were able to create mild esophageal lesions with epicardial cryoablation in seven of eight cases.

Cryoablation is unique among the currently available ablation technologies in that it destroys tissue by freezing rather than by heating. The important advantage is its

ability to preserve tissue architecture. The potential disadvantages of cryoablation technology include the relatively long time necessary to create a lesion (1 to 3 minutes) and the difficulty in creating lesions on the beating heart. Furthermore, if blood is frozen during epicardial ablation on the beating heart, it coagulates, creating a potential risk of thromboembolism.

Surgical Indications for Treatment of Atrial Fibrillation

The principal indication for surgery for AF is intolerance of the arrhythmia in patients for whom medical management has failed. Patients with paroxysmal atrial flutter or fibrillation are often more symptomatic than those with persistent or long-standing AF. Major symptoms include dyspnea on exertion, easy fatigability, lethargy, palpitations, and general sense of unease. Before surgery, all patients should have a trial of medical management.

The Heart Rhythm Society created a task force to evaluate indications for catheter and for surgical ablation of AF.^{25,105} The recommendations were developed in partnership with the European Heart Rhythm Association, the European Cardiac Arrhythmia Society, the American College of Cardiology, the American Heart Association, and the Society of Thoracic Surgeons. The task force recommended that programs involved in the stand-alone surgical treatment of AF should develop a team approach to these patients, including electrophysiologists and surgeons, to ensure appropriate patient selection. The consensus of the task force was that the following were appropriate indications for surgical ablation of AF: (1) symptomatic AF patients undergoing other cardiac surgical procedures and (2) selected asymptomatic AF patients undergoing cardiac surgery in whom the ablation can be performed with minimal risk. Stand-alone AF surgery should be considered for symptomatic AF patients who have failed medical management and either prefer a surgical approach, have failed one or more attempts at catheter ablation, or are not candidates for catheter ablation.^{25,105}

Other patients who should be considered for surgery include those who have developed a contraindication to warfarin or who have had a stroke while adequately anticoagulated. The Cox-Maze procedure significantly reduces the risk of stroke in these patients. Approximately 20% of patients who had the original cut-and-sew procedure at our institution had experienced at least one episode of cerebral thromboembolism that resulted in a temporary or permanent neurologic deficit before having the Cox-Maze procedure; less than 2% of patients (6 of 389) had a late neurologic event after surgery (mean follow-up of 6.6 years).¹⁰⁶

Surgical Technique: Cox-Maze Procedure

The final version of the standard cut-and-sew technique to cure AF was the Cox-Maze III procedure.^{60,107-109}

However, few cardiac surgeons performed this operation because of its technical complexity. Most centers have replaced most surgical incisions with linear lines of ablation created by various energy sources. At Washington

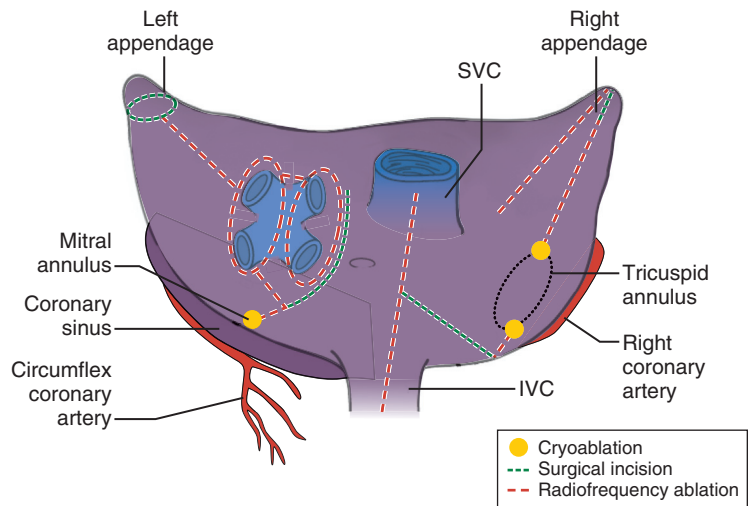


FIGURE 87-3 ■ Cox-Maze IV procedure lesion set. Modifications included independent isolation of pulmonary veins with connecting lesions and no atrial septal incision (originally used for exposure). IVC, Inferior vena cava; SVC, superior vena cava.

University, bipolar RF energy and cryoenergy have been used successfully to replace most surgical incisions of the Cox-Maze III procedure. Our current procedure incorporates most of the lesions of the Cox-Maze III procedure and has been named the Cox-Maze IV (Fig. 87-3).¹¹⁰ Our clinical data have shown that this modified operation has significantly shortened the operative time while maintaining the high success rate of the traditional cut-and-sew Cox-Maze III procedure.¹¹¹

Bipolar RF ablation was chosen for the Cox-Maze IV procedure for several reasons. First, the device allows the on-line determination of lesion transmural by measuring the conductance between the two electrodes.^{76,77,87} Second, the bipolar RF device has short ablation times, with 5- to 6-cm-long transmural ablations performed in 5 to 15 seconds. Third, the lesions are narrow (2 to 3 mm in width), and tissue injury is confined to within the clamp. This eliminates the possibility of unwanted collateral injury.^{94,112-114}

The Cox-Maze IV procedure has three parts: (1) bilateral pulmonary vein isolation, (2) the right atrial lesion set, and (3) the left atrial lesion set with left atrial excision. The operation is often combined with other procedures and is performed through a sternotomy or a minimally invasive (4- to 5-cm) right mini-thoracotomy. The operation is performed using either central or femoral cannulation for cardiopulmonary bypass depending on the operative approach being a sternotomy or mini-thoracotomy, respectively. The standard sternotomy approach is described in the following paragraphs. The mini-thoracotomy approach was previously described by our group.¹¹⁵ All patients receive an intraoperative transesophageal echocardiogram to rule out the presence of left atrial clot and are electrically cardioverted followed by amiodarone infusion if found to be in AF at the time of surgery. It should be noted that each RF ablation line is created by performing two or three ablations with the clamp to ensure transmural.

Pulmonary Vein Isolation

With the patient in a supine position through a median sternotomy, a pericardial cradle is created, and the patient

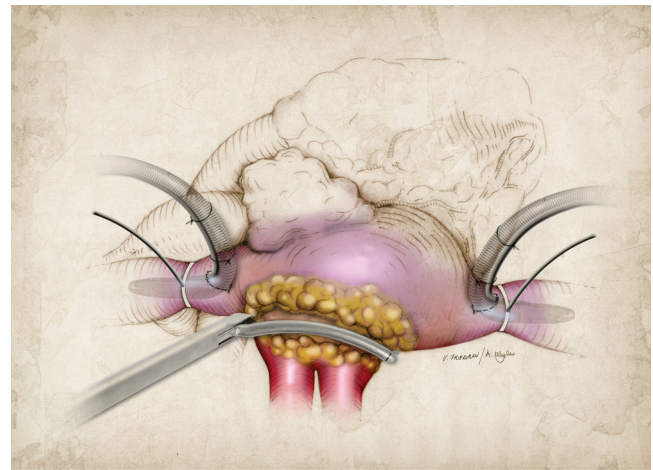


FIGURE 87-4 ■ Right pulmonary vein isolation during Cox-Maze IV procedure. The bipolar radiofrequency device is placed around the right pulmonary veins. The device is clamped on the cuff of atrial tissue surrounding the pulmonary veins.

is centrally cannulated. Normothermic cardiopulmonary bypass is initiated. Both the right (Fig. 87-4) and the left (Fig. 87-5) pulmonary veins are bluntly dissected at their confluences and surrounded with umbilical tapes. If the patient is in AF, he or she is cardioverted at this point. The bipolar RF clamp is passed around the pulmonary veins on each side. Typically three ablations are performed to isolate as large an atrial cuff around the pulmonary veins as possible. Exit block is confirmed by attempting to pace from each pulmonary vein.

Right Atrial Lesion Set

The patient is cooled to 34° C. On the beating heart, a pursestring suture wide enough to accommodate one jaw of the bipolar RF clamp is made at the base of the right atrial appendage. Through this pursestring, an ablation line is created along the free wall of the right atrium down toward the junction of the right atrium and

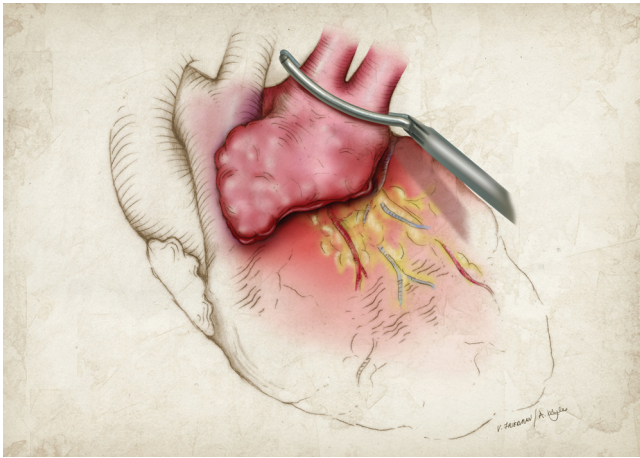


FIGURE 87-5 ■ Left pulmonary vein isolation during Cox-Maze IV procedure. The bipolar radiofrequency device is placed around the left pulmonary veins. The device is clamped on the cuff of atrial tissue surrounding the pulmonary veins. (Modified with permission from AtriCure.)

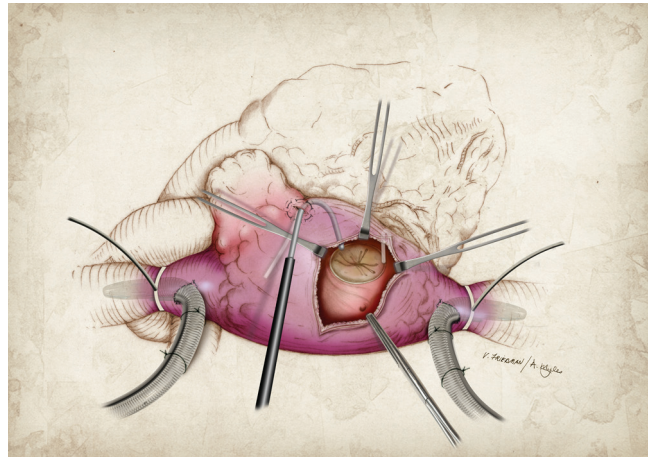


FIGURE 87-7 ■ Endocardial cryoablation through the right atrial pursestring suture to the 10-o'clock position of the tricuspid using a 3-cm linear cryoprobe. (Modified with permission from AtriCure.)

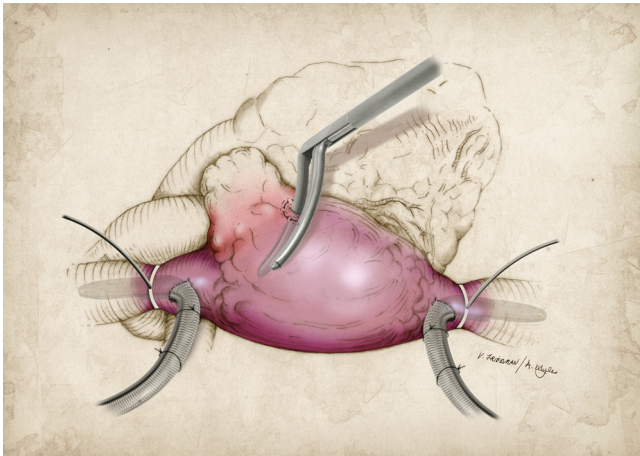


FIGURE 87-6 ■ The right atrial free wall ablation. The bipolar radiofrequency clamp is placed through a pursestring suture in the base of the right atrial appendage and is carried down perpendicularly toward the superior vena cava. (Modified with permission from AtriCure.)

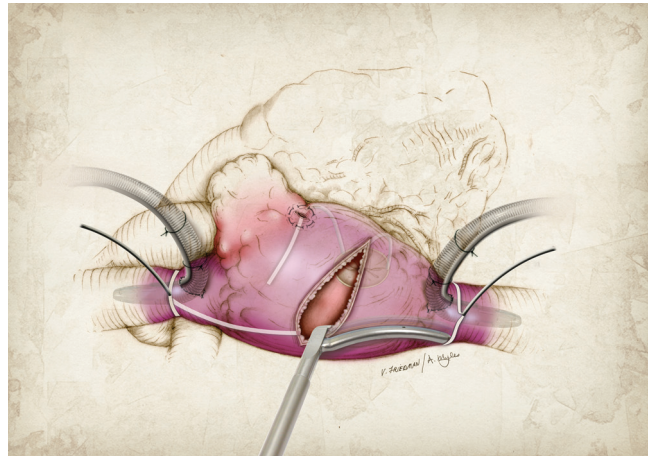


FIGURE 87-8 ■ Bipolar radiofrequency ablation along the superior vena cava and inferior vena cava through the right atriotomy, completing the right atrial lesion set. (Modified with permission from AtriCure.)

superior vena cava (Fig. 87-6). A vertical atriotomy is performed from the intra-atrial septum toward the atrio-ventricular groove, along the free wall of the right atrium at least 2 cm away from the previous RF ablation (Fig. 87-7). Cryoablation is then used for reasons mentioned previously in this chapter because of its ability to ablate without damaging valvular tissue. From the superior aspect of this atriotomy, a 3-cm linear cryoprobe is used to create an endocardial ablation down to the 2-o'clock position of the tricuspid valve. The cryoprobe is then placed through the pursestring suture at the base of the right atrial appendage, and a second linear endocardial ablation is created down toward the 10-o'clock position of the tricuspid valve. A final bipolar RF ablation line is created along the superior vena cava and down the inferior vena cava (Fig. 87-8).

Left Atrial Lesion Set

The aorta is cross-clamped and cold blood cardioplegia is administered. While the patient is under cardioplegic arrest, the left atrial appendage is amputated. Through this incision, one jaw of the RF ablation clamp is inserted and an ablation line is created to the superior left pulmonary vein. The left atrial appendage is oversewn in two layers. A standard left atriotomy is performed, which can be extended superiorly onto the dome of the left atrium and inferiorly around the orifice of the right inferior pulmonary vein. Two separate bipolar RF ablation lines are then created from both the superior and the inferior aspects of the atriotomy incision to the origin of the left superior and inferior pulmonary veins, respectively, thus completing the “box lesion” (Fig. 87-9). A final bipolar RF ablation line is created from the inferior aspect of the

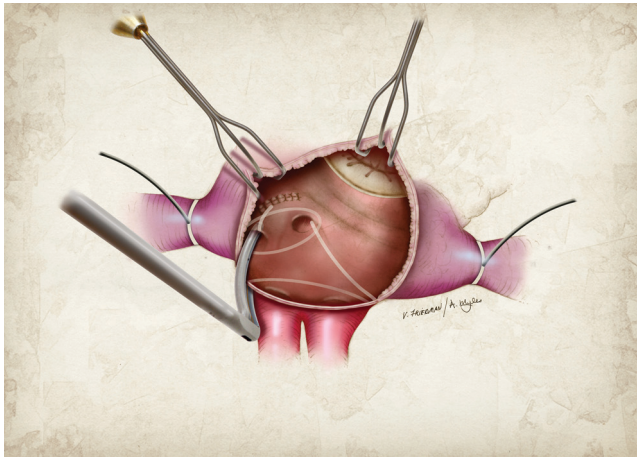


FIGURE 87-9 ■ Completion of left atrial “box lesion” after creating a bipolar radiofrequency ablation line through the amputated atrial appendage to the left superior pulmonary vein and left atriotomy. (Modified with permission from AtriCure.)

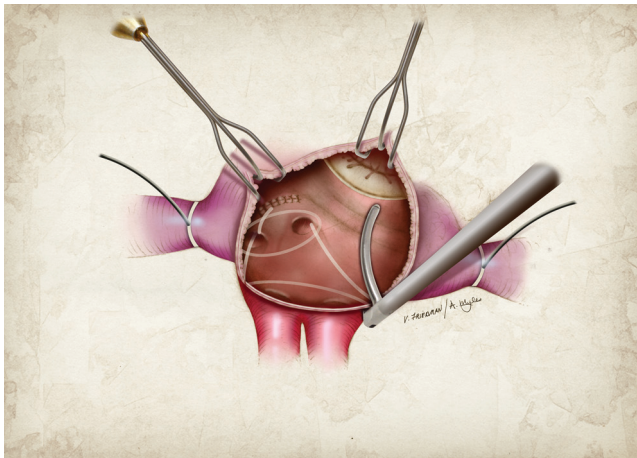


FIGURE 87-10 ■ Bipolar radiofrequency ablation across the floor of the left atrium from the inferior aspect of the atriotomy to the mitral annulus. (Modified with permission from AtriCure.)

atriotomy, across the floor of the left atrium, down to the mitral valve annulus (Fig. 87-10). This ablation line should cross the coronary sinus ideally in the space between the circumflex and right coronary circulations. If the patient has a left dominant circulation, this lesion can be created surgically to identify and spare the circumflex artery, although this is rarely needed. The end of this RF ablation line is marked with methylene blue. This ablation line is connected to the mitral valve annulus by performing an endocardial cryoablation, which overlaps onto the posterior leaflet of the mitral valve. A second epicardial cryoablation is performed simultaneously over the coronary sinus with a linear cryoprobe to complete the left atrial isthmus ablation. This should directly oppose the endocardial cryoablation (Fig. 87-11).

Surgical Results: Cox-Maze Procedure

The long-term results of the Cox-Maze III procedure have been excellent. In our series of 198 consecutive

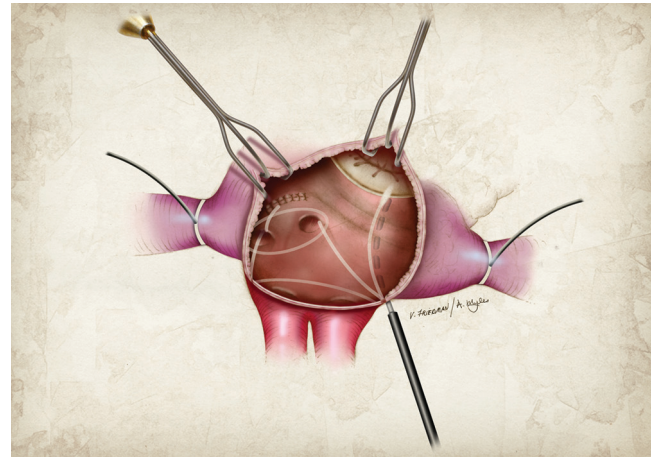


FIGURE 87-11 ■ Epicardial cryoablation over the coronary sinus completing the left atrial isthmus line. Note that this figure does not show simultaneous endocardial ablation over the mitral annulus, which is typically performed. (Modified with permission from AtriCure.)

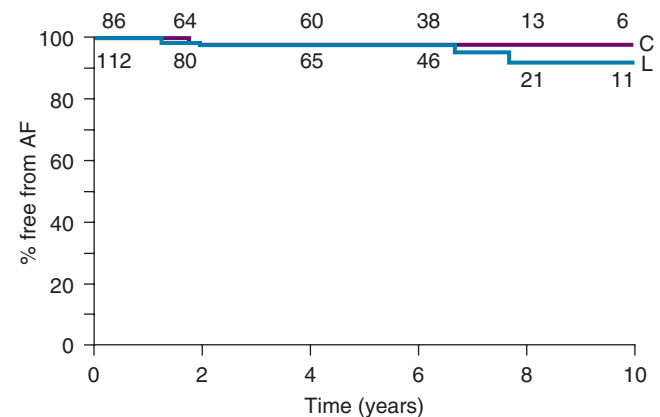


FIGURE 87-12 ■ Kaplan-Meier analysis of freedom from recurrent atrial fibrillation. The numbers on each line indicate the number of patients at risk. There was no difference in the long-term estimate of freedom from atrial fibrillation between the lone Cox-Maze procedure (L) group and the concomitant (C) group ($P = 0.64$). AF, Atrial fibrillation. (From Prasad SM, Maniar HS, Camillo CJ, et al: The Cox Maze III procedure for atrial fibrillation: long-term efficacy in patients undergoing lone versus concomitant procedures. *J Thorac Cardiovasc Surg* 126:1822–1828, 2003.)

patients undergoing surgery, 97% of patients at a mean follow-up of 5.4 years were free from symptomatic AF (Fig. 87-12). There was no difference in cure rates between patients undergoing a lone versus a concomitant procedure. The cure rates off antiarrhythmic medications were 80% and 73%, respectively, in patients undergoing lone and concomitant Cox-Maze procedures at late follow-up.¹¹⁶

Our results using bipolar RF ablation (Cox-Maze IV) have been similarly encouraging. In a prospective, single-center trial from our institution, 91% of patients at 6 months of follow-up were free from AF. The operative mortality was 0%.⁹² More recently, we prospectively evaluated 100 consecutive patients and demonstrated postoperative freedom from AF at 93%, 90%, and 90% at 6, 12, and 24 months, respectively.¹¹⁷ A multicenter

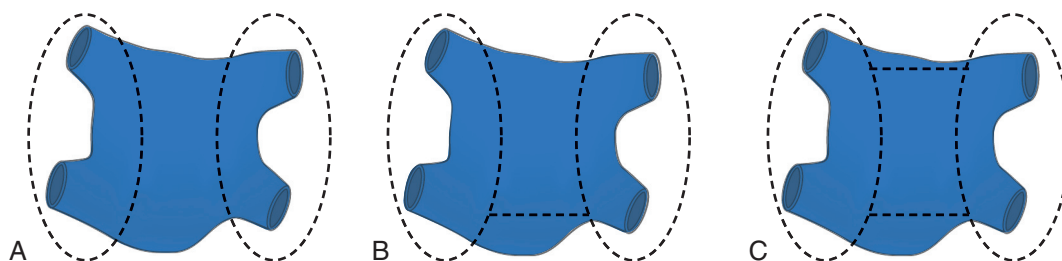


FIGURE 87-13 ■ Pulmonary vein isolation methods. **A**, Left and right pulmonary veins are isolated separately. **B**, Left and right pulmonary veins are isolated separately and then connected with an additional lesion. **C**, Left and right pulmonary veins are isolated separately and connected inferiorly and superiorly, also referred to as a *box lesion*.

trial of the same technology had similar results.¹¹⁸ At 6 months, 96% of patients were in normal sinus rhythm, and there was no operative mortality in this group of 30 patients.⁶³ The modifications with use of bipolar RF have shortened the operation considerably while decreasing the major complication rate. The mean cross-clamp time for patients undergoing a lone Cox-Maze III procedure was 92 ± 26 minutes compared with 41 ± 13 minutes with the Cox-Maze IV.¹¹⁹ The same study demonstrated a major complication rate of 10% in the Cox-Maze III, which was significantly higher than the Cox-Maze IV cohort ($P = 0.004$). Two-year freedom from AF off antiarrhythmics using Holter monitoring was 84%, which was similar to previous reports of the Cox-Maze III documenting an 80% freedom from AF off antiarrhythmics using symptomatic reporting.¹¹⁹

The Cox-Maze IV procedure involves a lesion set around all the pulmonary veins, isolating the entire posterior left atrium by creating a “box” or by a simple connecting lesion between the pulmonary veins with a single ablation (Fig. 87-13). Our group demonstrated that isolation of the entire posterior left atrium by the creation of a box lesion had a significantly lower incidence of early atrial tachyarrhythmias, a higher freedom from AF recurrence at 1 and 3 months, and lower use of antiarrhythmic drugs at 3 and 6 months.¹²⁰ Furthermore, patients receiving a complete box lesion set had significantly higher freedom from AF and freedom from AF off antiarrhythmic drugs at 1 year compared with patients receiving a non-box ablation set (Fig. 87-14).¹¹⁷

The Cox-Maze procedure has also been effective at decreasing the risk of late stroke in this high-risk population of patients. In a report from our institution, 57 of 389 patients (14%) had experienced a neurologic event before surgery. Despite the inherently high risk of stroke in these patients, there were only six neurologic events during long-term follow-up (mean, 6.6 ± 5.0). The long-term stroke rate after the Cox-Maze procedure has been 0.2% per year despite the fact that the majority of patients were able to discontinue anticoagulation.¹⁰⁶

In a series from Japan, the Cox-Maze procedure was found to significantly decrease the incidence of late stroke, even in those patients already receiving anticoagulation for mechanical mitral valves. Patients with chronic AF who had a concomitant Cox-Maze procedure with their mitral valve replacement were 99% stroke free at a follow-up of 8 years, whereas the group with

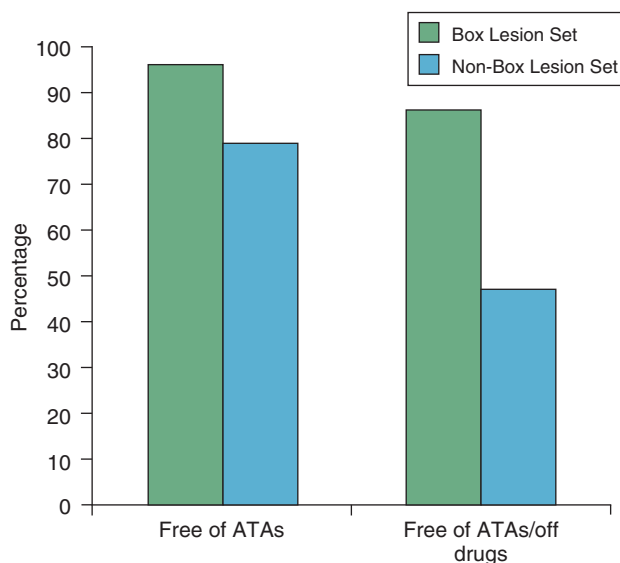


FIGURE 87-14 ■ Freedom from atrial fibrillation on and off antiarrhythmic (ATA) drugs; comparison of box and non-box lesion sets at 12 months. (From Weimar T, Bailey MS, Watanabe Y, et al: The Cox-Maze IV procedure for lone atrial fibrillation: a single center experience in 100 consecutive patients. *J Interv Card Electrophysiol* 31:47–54, 2011.)

mitral valve replacement alone had only an 89% freedom from stroke.¹²¹

Surgical Technique: Other Atrial Fibrillation Procedures

A number of more limited surgical procedures have been proposed for the cure of AF. These procedures generally fall into two groups. The first group comprises those that incorporate only left atrial lesions, and the second group consists of procedures involving pulmonary vein isolation alone with or without ganglion ablation. The left atrial lesion set generally involves pulmonary vein isolation (either as a box or separately with a connecting lesion) and a lesion to the mitral annulus as well as removal of the left atrial appendage. These lesions have been created with many different energy sources, including unipolar and bipolar RF, cryoablation, and microwave.^{93,122–130} The specific technique often depends on the type of device used and has most often been performed on cardiopulmonary bypass.

A number of surgeons have published reports on the technique of pulmonary vein isolation alone for AF.¹³¹⁻¹³⁴ This limited lesion set can be done separately, with a connecting lesion, or as a box lesion (see Fig. 87-13). Various devices have been used to create these lesions, including RF, cryoablation, microwave energy, high-frequency ultrasound, and laser. Pulmonary vein isolation alone is attractive because it can be done without the use of cardiopulmonary bypass and often in a minimally invasive setting. Some investigators have proposed isolation of the pulmonary veins and also ablation of the ganglionic plexi.¹³⁵⁻¹³⁷

Pruitt and colleagues¹³⁸ reported on a minimally invasive technique used on 100 patients. The procedure was accomplished thoracoscopically without cardiopulmonary bypass through use of a unipolar microwave catheter. Wolf and coworkers¹³¹ published a report on a similar technique of bilateral video-assisted thoracoscopic off-pump epicardial pulmonary vein isolation using a bipolar RF clamp. This procedure was performed with two 10-mm ports and one 5- or 6-cm working incision on each side of the thorax. The right-sided pulmonary veins were first isolated while the patient was left side down, and then the patient was repositioned with the opposite side up for the left-sided lesions, including the division of the ligament of Marshall. Finally, the left atrial appendage was resected with an endoscopic stapling device.

A modified version of this approach has been practiced by our group. After double-lumen endotracheal tube intubation, appropriate central venous access, and monitoring (including transesophageal echocardiography to evaluate for left atrial thrombus), the patient is placed left side down with the right arm positioned to expose the right axilla. The third or fourth intercostal space, midaxillary line, scapula, and xiphoid are marked, and the right side of the chest is prepared and draped from the spine to the sternum. A 10- or 12-mm port is placed in the sixth intercostal space approximately 2 cm anterior to the midaxillary line, typically at the level of the xiphoid (Fig. 87-15). Carbon dioxide is insufflated to flood the air space. A 30-degree scope is used to visualize the location of the incision, which is made in the third or fourth intercostal space. A 5-cm muscle-sparing incision is made in the auscultatory triangle. Caution must be exercised in retracting the posterior fat pad to avoid injury to the nerve, artery, and vein located therein. A soft tissue retractor is placed, and the lung is retracted to visualize the right phrenic nerve.

The pericardium is opened anterior and parallel to the phrenic nerve to expose the atriocaval junction. The heart is exposed inferiorly to the diaphragm. Pericardial stay sutures in the lateral edges are anchored posteriorly through the skin. The space between the right pulmonary artery and the right superior pulmonary vein is dissected bluntly. A second 10-mm port is created for direct placement of a specially designed dissector (GlidePath, Atri-Cure). The dissector is introduced lateral to the inferior vena cava and advanced into the oblique sinus and swept medially behind the right pulmonary veins. The superior vena cava is retracted medially to expose the right pulmonary artery. The dissector hinge is engaged, which advances the tip into the space between the right superior

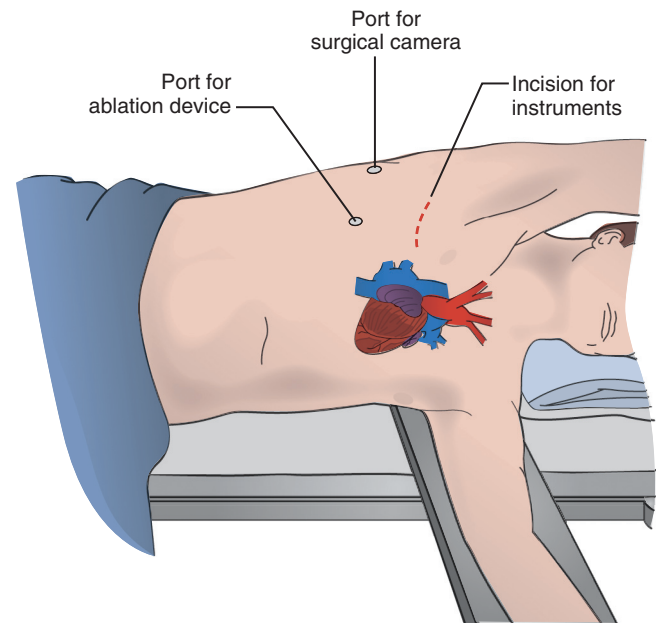


FIGURE 87-15 ■ Incision and port sites for minimally invasive pulmonary vein isolation procedure.

pulmonary vein and the right pulmonary artery. The dissector is articulated in the opposite direction and removed after grasping the GlidePath hood to allow guidance of the bipolar RF clamp into the same space. The plastic hood is attached to the bipolar RF clamp (Isolator, Atri-Cure), and the clamp is closed and inserted into the chest through the same port site. The clamp is then opened and advanced to position the jaws around the pulmonary veins, being guided by the previously placed plastic GlidePath hood. We routinely establish baseline pacing thresholds from each of the pulmonary veins before ablation. Two ablations are performed, the second after a small advancement of the clamp onto the atrium. Each ablation is made after assurance that the clamp is on the atrial cuff and not the pulmonary veins proper.

After ablation, conduction block is confirmed by pacing from each of the pulmonary veins. Additional ablations are created until conduction block is achieved. The clamp is removed, the pericardium is reapproximated, an appropriate drain is placed, and the wound is closed.

The patient is then repositioned with the left side up. The left arm is supported superiorly to expose the axilla. A 10-mm port is placed in the sixth intercostal space in the midaxillary line (slightly more posterior than the port on the right side), and a working incision is made in the third intercostal space under direct visualization. The pericardium is initially opened posterior to the phrenic nerve to expose the left pulmonary artery and then widely opened for device access, with caution exercised to preserve the phrenic nerve. Pericardial stay sutures are placed posteriorly and brought through the skin. The ligament of Marshall is divided by electrocautery, and the space between the left pulmonary artery and left superior pulmonary vein is bluntly dissected. The dissector is introduced through a second 10-mm port placed posterior to the first port. The dissector is positioned into the

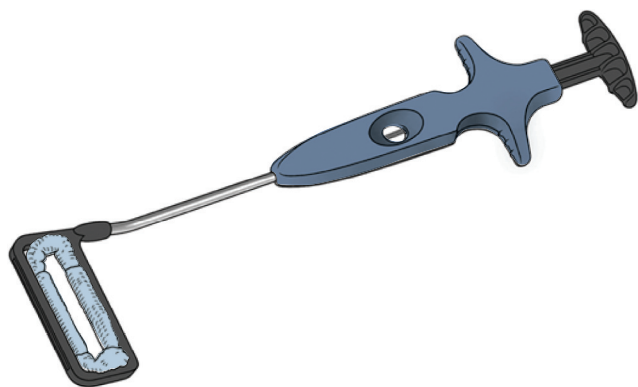


FIGURE 87-16 ■ AtriClip device. (From Emmert MY, Puippe G, Baumüller S, et al: Safe, effective and durable epicardial left atrial appendage clip occlusion in patients with atrial fibrillation undergoing cardiac surgery: first long-term results from a prospective device trial. *Eur J Cardiothorac Surg* 45:126–131, 2014.)

space below the left inferior pulmonary vein and then articulated to swing the tip into the space between the left superior pulmonary vein and the left pulmonary artery. The clamp is similarly brought into the same space by guidance with the plastic hood as on the right side. Ablation of the pulmonary veins is done after baseline pacing thresholds are recorded, with confirmation of conduction block after ablation.

The left atrial appendage is then removed for the reduction of thromboembolic risk. This is done using an atraumatic clip (AtriClip, AtriCure) (Fig. 87-16). This is potentially safer than using a stapler and has better outcomes in terms of completely excluding the left atrial appendage. A multicenter feasibility study demonstrated no adverse events related to the device, and 60 of 61 patients (98.4%) had successful left atrial appendage exclusion, based on results of computed tomography angiography or transesophageal echocardiography, at 3 months.¹³⁹ In a study prospectively evaluating the long-term safety and efficacy of the AtriClip, serial computed tomographic scans showed stable clip positioning without left atrial appendage reperfusion with a follow-up of 3.5 ± 0.5 years. In addition, at 36 months follow-up, no intracardiac thrombi or embolic strokes had occurred.¹⁴⁰

The pericardium is reapproximated with a drain placed, and the left-sided wounds are closed. Patients typically stay in the hospital for 2 or 3 days for drain removal and arrhythmia monitoring.

Surgical Results: Other Atrial Fibrillation Procedures

The performance of only a left atrial lesion set for the treatment of AF is supported by studies showing that most paroxysmal AF originates from around the pulmonary veins and posterior left atrium.^{29,33} However, the surgical treatment of AF by a left atrial lesion set alone has had lower success rates than with the biatrial Cox-Maze lesion set. Intraoperative mapping studies of patients undergoing surgical treatment of AF showed a distinct region of stable dominant frequency, which is indicative of the area of origin of the arrhythmia, in the

left atrium only 30% of the time. The dominant frequency was located in the right atrium 12% of the time. Most important, the location of dominant frequency moved during the recording period in almost half of the patients.²⁶ Therefore, it is not surprising that interventions with limited lesion sets, particularly pulmonary vein isolation alone, do not have the same results as the complete Cox-Maze lesion set.

Surgical pulmonary vein isolation has been shown to be superior to catheter ablation in patients with left atrial dilation and hypertension or where previous catheter ablation has failed. The FAST trial was a multicenter randomized trial that compared 63 patients who received linear antral pulmonary vein isolation by way of catheter ablation and 61 patients who received bipolar RF pulmonary vein isolation and ganglionated plexi ablation. At 1 year, freedom from left atrial arrhythmias greater than 30 seconds evaluated by a 7-day Holter was 66% for surgical ablation and 37% for catheter ablation ($P = 0.002$).¹⁴¹

A well-known complication of performing only the left atrial lesions is postoperative atrial flutter. In a group of 50 patients described by Golovchiner and colleagues from Tel Aviv, 13% of patients experienced postoperative atrial flutter at a follow-up of only 15 months. Left atrial flutter was present in four of six.¹⁴² In a series from Japan, 5 of 24 patients (21%) experienced recurrent atrial flutter or tachycardia after a left-sided procedure with follow-up of 36.9 ± 14.1 months.¹²⁹

The results with left atrial ablation sets have been variable (cure rates 21% to 95%) and are dependent on the precise lesion set, technology used, and patient population. A randomized trial conducted with patients undergoing mitral valve surgery evaluated whether addition of RF ablation on the left atrium was different from mitral valve surgery alone.¹⁴³ Of 101 patients randomized to undergo mitral valve surgery with or without RF ablation, 99 patients eventually met criteria; 45 were evaluated who had RF ablation versus 44 who had valve surgery alone ($P < 0.001$). At 12 months of follow-up, 44% of those undergoing concomitant RF ablation were in sinus rhythm compared with only 5% of those who had mitral valve surgery alone. Although this was significantly better than no ablation at all, this success rate was much lower than has been reported with the Cox-Maze procedure in patients with mitral valve disease.¹⁴⁴

In a meta-analysis of surgical ablative treatments for AF, Barnett and Ad¹⁴⁵ evaluated 69 studies to assess differences in survival and freedom from AF. These studies included multiple types of energy devices and interventions for lone AF as well as concomitant procedures. Compared with control patients, those undergoing surgical ablation had significantly greater freedom from AF at 2 years ($84 \pm 6\%$ vs. $40 \pm 22\%$, $P = 0.001$); freedom from AF at 2 years was also significantly better in patients who had biatrial ablations ($86 \pm 5\%$ vs. $75 \pm 2\%$, $P = 0.001$). These results support a strategy of doing a more complete ablation set (biatrial) when possible, but a more limited lesion set is superior to no intervention for patients with AF.

The results of pulmonary vein isolation alone have been better in patients who have lone AF than in those undergoing concomitant cardiac surgery. In the series by

Wolf and coworkers,¹³¹ 27 patients with AF (18 paroxysmal, 4 persistent, and 5 permanent) underwent video-assisted bilateral pulmonary vein isolation and left atrial appendage exclusion for AF; 91% of patients were free from AF without antiarrhythmias postoperatively. In a more recent series with longer follow-up, Edgerton and coworkers¹⁴⁶ described 57 patients with AF undergoing pulmonary vein isolation plus ablation of the ganglionic plexi. Most patients were observed with prolonged monitoring. In 39 patients with paroxysmal AF, the freedom from AF at 6 months was 82%, and antiarrhythmic medications were discontinued in 74%. In patients with persistent and long-standing AF, the success rate at 6 months was only 56%, and antiarrhythmic medications were discontinued in only 39%.

McClelland and colleagues¹³⁵ described 21 patients undergoing pulmonary vein isolation with ganglionic plexi ablation. Procedural success was defined as freedom from AF and drugs at 1 year. In patients with paroxysmal or persistent AF, 88% of patients had a successful procedure. However, in patients with long-standing AF, only 25% had a successful outcome with pulmonary vein isolation alone.¹³⁶ In our pulmonary vein isolation experience at Washington University with 43 patients, we have had similar results. Patients have been observed with 24-hour Holter monitoring at 3, 6, and 12 months. Our mean follow-up was 24 ± 37 months. In patients with lone paroxysmal AF, the cure rate was 78%, with 67% both free from AF and off antiarrhythmic drugs. However, in patients with persistent or long-standing AF, the cure rate has been only 38%.

The results with endoscopic microwave pulmonary vein isolation have been worse. This is likely because this technology is not capable of creating reliable transmural lesions on the beating heart.¹⁴⁷ In a group of 50 patients of whom the majority had paroxysmal AF, less than half of the patients were free from AF or reintervention at a mean follow-up of only 7.6 months.¹⁴⁸ In a follow-up report that included 100 patients, the late results were even worse. Only 42% of patients were in sinus rhythm at last follow-up. Although totally thoracoscopic surgical ablation with the microwave device was technically feasible, the clinical results were poor, with no demonstrated electrical isolation of the pulmonary veins and poor long-term cure of AF.¹⁴² Because of these poor results, microwave ablation technology is no longer available.

In our experience, the results with pulmonary vein isolation have been worse in patients undergoing concomitant cardiac procedures than in those undergoing AF intervention alone. At Washington University, 23 patients with AF (12 with paroxysmal AF, 11 with permanent AF) underwent pulmonary vein isolation during concomitant mitral valve surgery or coronary revascularization. The average duration of AF in 12 patients was 6.7 ± 14.2 years. At a mean follow-up of 57 ± 37 months, only 50% of patients were free from AF.¹²⁰

In a series reported by Gaita and colleagues,¹²² 105 patients undergoing AF and valve surgery were randomly assigned to three groups: left atrial ablation by two different patterns or pulmonary vein isolation alone. The freedom from AF at last follow-up was only 29% in the pulmonary vein isolation group versus 76% in those who

had more extensive left atrial lesions. In another series, a group of 101 patients underwent pulmonary vein isolation with cryoablation in addition to mitral valve surgery; the freedom from AF at last follow-up was only 53%.¹⁴⁹ Only 25% of patients were able to maintain sinus rhythm without antiarrhythmic drugs. In a study from Japan, 66 patients with chronic AF and mitral valve disease underwent pulmonary vein cryoablation. Normal sinus rhythm was seen in only 61% of patients at late follow-up, and antiarrhythmic drugs were discontinued in 17% of patients.¹³² These reports of pulmonary vein isolation compare unfavorably with the more than 80% freedom from AF at late follow-up seen in mitral valve patients undergoing the Cox-Maze IV procedure at our institution.¹⁵⁰ However, a limited lesion set may have merit in selected patients, as reported results are better than no intervention at all. Certainly, there are groups of patients who are cured with these methods; continued investigation is needed to identify which factors ultimately determine efficacy in each particular group of patients.

Future Surgical Treatments for Atrial Fibrillation

As surgical techniques and technology have advanced, there has been an increasing trend toward the creation of minimally invasive approaches. Increasingly, groups including our own, are performing ablations through smaller incisions with the aid of thoracoscopic video assistance in properly selected patients. Several groups have started performing epicardial ablations with the aid of suction-based RF and cryoablation probes that can be placed through thoracoscopic ports. Historically, these probes do not achieve the same degree of transmural ablation achieved with bipolar RF clamps. Others have attempted to solve this problem using a "hybrid" approach, which uses a combination of endocardial catheter ablations and epicardial ablations with either bipolar RF clamps and/or unipolar RF devices.^{151,152} This approach can be performed in a single stage or as a dual-stage procedure in which the epicardial ablation is performed first, followed at an interval of time by the endocardial catheter ablation. Both the lesion sets and the approaches using a hybrid method vary greatly from institution to institution, and studies evaluating the hybrid procedure generally have a small number of patients. Although these minimally invasive epicardial and hybrid approaches have yet to match the long-term efficacy of the Cox-Maze IV, they hold promise and require continued clinical investigation to determine their precise role. The ideal surgical treatment for AF would consist of a patient-tailored lesion set using devices that consistently achieve 100% transmural ablation through a minimally invasive approach without the need for cardiopulmonary bypass. However, further development in ablation technology and improvements in preoperative diagnostic tests to better determine the mechanisms of AF in each particular patient are desperately needed.

Conclusions

The introduction of ablation devices has revolutionized the surgical treatment of AF, making these curative

procedures available to a wider population of patients. Whereas there have been few randomized trials comparing the different surgical procedures, conclusions can be drawn from the numerous retrospective series that are available after almost 3 decades of surgical experience. In patients with AF undergoing mitral valve procedures, it is recommended that at least a left atrial Cox-Maze lesion set be performed. This adds only 10 to 15 minutes to the cross-clamp time and cures the majority of patients. At our institution, we prefer a biatrial Cox-Maze IV in these patients because success rates of more than 90% have been reproducible in this population of patients.^{144,150}

In patients undergoing coronary artery bypass grafting, the high success rate of the Cox-Maze lesion set has been documented by our group.¹⁵³ In patients with AF having on-pump coronary bypass grafting, it is recommended that a full biatrial lesion set be performed. However, there have been no randomized comparisons of lesion sets in this population. In patients with AF undergoing off-pump coronary bypass grafting, our policy had been to perform pulmonary vein isolation with removal of the left atrial appendage. However, poor results in patients with long-standing AF led us to abandon this approach in that group.

In patients with lone AF, pulmonary vein isolation alone has had good early results in patients with paroxysmal AF. At our institution, this procedure is performed in patients who have paroxysmal AF and a left atrial size of 4 cm or less. In patients with large atria, we prefer a full Cox-Maze lesion set because of the high incidence of non-pulmonary vein triggers in this population.¹⁵⁴

In patients with persistent or long-standing AF, our policy has been to perform a full biatrial Cox-Maze procedure on cardiopulmonary bypass. This is because of the poor results that have been obtained both by us and others with pulmonary vein isolation alone. With the full Cox-Maze IV procedure, success rates in patients with persistent or long-standing AF have been 91% at 1 year, with all antiarrhythmic drugs discontinued in 76% of patients.¹⁵⁰ There has been no difference in our success rates with use of the full lesion set in comparing patients with paroxysmal AF and those with persistent, long-standing AF.

INAPPROPRIATE SINUS TACHYCARDIA

Background and Indications

Inappropriate sinus tachycardia is a rare disorder that is characterized by an abnormally elevated heart rate at rest and an exaggerated rate response with physical activity. To be considered for interventional therapy, a patient's symptoms need to be refractory to dietary modification and medical management. Inappropriate sinus tachycardia was originally described in 1979, but it has only recently been accepted as a medical condition. Patients suffering from this debilitating condition are typically young women. Inappropriate sinus tachycardia is thought to be the result of enhanced automaticity of the sinoatrial node or hypersensitivity to β -adrenergic stimulation. The sinus node impulse may have a multifocal origin, and early activation sites can shift within the sinus node

complex in response to autonomic influences. The first-line treatment is medical therapy with beta blockers or calcium channel blockers.

In patients for whom medical management fails, catheter or surgical ablation is the next therapeutic option. The efficacy of catheter ablation remains controversial. Reported series are small, and there have been a high percentage of failures at long-term follow-up.^{155,156} This has led many centers to abandon a catheter-based approach. Results with surgical intervention have been better but still leave room for improvement.

Surgical Technique: Superior Right Atrial Isolation

At our center, 10 consecutive patients with inappropriate sinus tachycardia have undergone surgery for this arrhythmia. The first seven patients underwent median sternotomy with cardiopulmonary bypass to ablate or to isolate the sinoatrial node; in the last three patients, a minimally invasive technique developed at our institution was performed.¹⁵⁷ In these latter patients, the sinoatrial node was isolated by bipolar RF ablation through a small inframammary incision, without the use of cardiopulmonary bypass (Fig. 87-17). Isolation and ablation of the sinoatrial node are done through a right 6-cm mini-thoracotomy. Intraoperatively, intravenous isoproterenol is administered to create sinus tachycardia with rates of 150 to 180 beats per minute. A large cuff of right atrium adjoining the junction of the superior vena cava is isolated from the body of the right atrium with a bipolar RF ablation device. Three sequential circumferential ablations are performed, and isolation is confirmed with pacing and by observing a significant blunting in response to intravenous administration of isoproterenol. Bipolar pacing above and below the ablation line confirms that the sinoatrial node and surrounding atrium are isolated from the remainder of the heart.

Surgical Results

Two reports with traditional cardiopulmonary bypass demonstrated complications requiring pacemaker placement

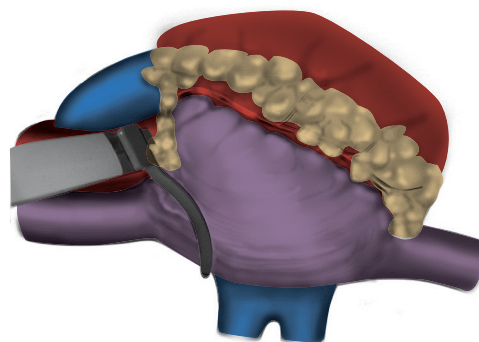


FIGURE 87-17 ■ Position of the bipolar radiofrequency clamp (Isolator, AtriCure) used to isolate the sinoatrial node and surrounding right atrial tissue in the minimally invasive ablation for inappropriate sinus tachycardia. (From Kreisel D, Bailey M, Lindsay B, et al: A minimally invasive surgical treatment for inappropriate sinus tachycardia. *J Thorac Cardiovasc Surg* 130(2):598-599, 2005.)

and development of new supraventricular tachycardia from ectopic foci.^{158,159} In our experience, after a mean follow-up of 7.1 ± 5.7 years, there was no evidence of inappropriate sinus tachycardia recurrence; however, four patients required pacemaker implantation for symptomatic bradycardia and a single patient developed ectopic atrial tachycardia. One patient still experienced palpitations. Four patients experienced complete relief from their cardiac symptoms.¹⁵⁷

Conclusions

Surgical isolation of the sinoatrial node for medically refractory inappropriate sinus tachycardia has acceptable long-term success in preventing recurrence. However, more than half of patients have required pacemaker implantation or have had recurrent symptoms. Less invasive surgical techniques make this a more attractive option for patients with inappropriate sinus tachycardia who have failed medical therapy.

VENTRICULAR TACHYCARDIA

Background

The success of implantable cardioverter-defibrillators (ICDs) and catheter ablation has dramatically diminished the referral of patients with ventricular arrhythmias (ventricular tachycardia) for surgery. However, it is critical that surgeons understand the historically important role of surgery and the present indications for surgical management of ventricular tachycardia. Although ICDs have improved survival by preventing sudden death, they fail to treat the underlying arrhythmogenic substrate. The frequent discharges can impair quality of life.¹⁶⁰ In addition, a population of patients surviving myocardial infarction with ventricular aneurysms, akinetic segments, and ischemic cardiomyopathies develop ventricular arrhythmias and require surgical intervention for treatment of congestive heart failure or coronary artery disease. These patients greatly benefit from concomitant surgery for their ventricular tachycardia.

Historical Aspects of Surgery for Ventricular Tachycardia

In 1961, Estes and Izlar described some patients who underwent successful treatment of ventricular tachycardia with surgical sympathectomy. In the late 1960s, it became apparent that myocardial ischemia initiated many ventricular arrhythmias and that they were related to areas of infarction and scar.¹⁶¹ Two surgical approaches were developed to address this problem: infarctectomy and coronary artery bypass grafting (CABG).^{162,163} Unfortunately, these initial approaches for the surgical treatment of ventricular tachycardia had high mortality rates and relatively poor long-term success. They failed because they were not based on an understanding of the mechanisms involved in ischemic ventricular tachycardia.¹⁶⁴

Improved understanding of these mechanisms during the 1970s led to new surgical approaches. Wellens and

others introduced cardiac mapping techniques that for the first time were able to precisely identify myocardial activation during dysrhythmias.¹⁶⁵⁻¹⁶⁸ Ventricular tachycardia was found to be a reentrant arrhythmia, able to be initiated in the electrophysiology laboratory. It became apparent that ventricular tachycardia often arose from the border zone between infarcted and normal myocardium and that the reentrant circuit was often subendocardial in origin.¹⁶⁹⁻¹⁷³ This led to surgical techniques that were guided by both preoperative and intraoperative electrophysiologic studies.

The first directed surgical cure of refractory ventricular tachycardia was reported in 1975.¹⁶⁷ The patient was a 54-year-old man who presented with refractory ventricular tachycardia after two myocardial infarctions. Epicardial mapping was used to localize the site of earliest epicardial activity to the margin of the aneurysm. Subsequent resection of this area abolished the ventricular tachycardia. In 1978, Guiraudon introduced the encircling endocardial ventriculotomy, an operation designed to isolate the entire border zone from normal myocardium.¹⁷⁴ A near-transmural incision was made from the endocardial surface of the left ventricle down to the epicardial surface (Fig. 87-18). Although this technique met with clinical success, it caused significant ventricular dysfunction. In 1979, Harken and colleagues¹⁷⁵ from the University of Pennsylvania introduced a new technique involving endomyocardial resection directed by intraoperative mapping in 12 patients. They reported 1 operative mortality, with the remaining 11 patients having no recurrent arrhythmias at 1 year. In 1982, Moran¹⁷⁶ modified the endomyocardial resection with an extended resection of all visible scar, which obviated the need for intraoperative mapping (Fig. 87-19). These new procedures resulted in operative mortalities of between 10% and 20%. The success rates improved in some series to

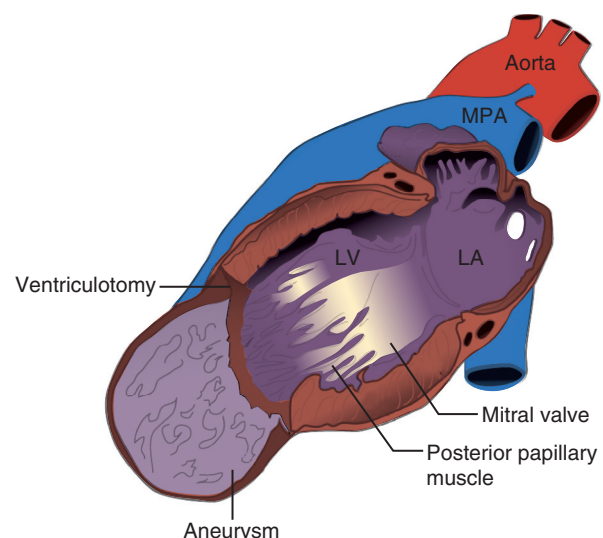


FIGURE 87-18 ■ Encircling endocardial ventriculotomy. LA, Left atrium; LV, left ventricle; MPA, main pulmonary artery. (From Guiraudon G, Fontaine G, Frank R, et al: Encircling endocardial ventriculotomy: a new surgical treatment for life-threatening ventricular tachycardias resistant to medical treatment following myocardial infarction. *Ann Thorac Surg* 26:438-444, 1978.)

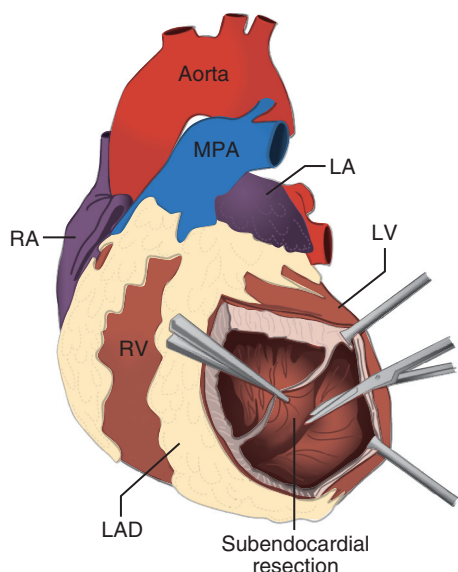


FIGURE 87-19 ■ Endocardial resection procedure. LA, Left atrium; LAD, left anterior descending coronary artery; LV, left ventricle; MPA, main pulmonary artery; RA, right atrium; RV, right ventricle. (From Moran JM, Kehoe RF, Loeb JM, et al: Extended endocardial resection for the treatment of ventricular tachycardia and ventricular fibrillation. *Ann Thorac Surg* 34:538–552, 1982.)

more than 70%, and 5-year survival was approximately 60%.¹⁷⁷⁻¹⁸¹ Subsequently, surgical experience revealed that intraoperative mapping was not necessary to achieve good results if an extended endomyocardial resection was performed. When examining approximately 500 patients having either map-guided or non-guided extended resections, Hargrove and Miller¹⁸² determined that the number of patients whose arrhythmias are inducible at the postoperative electrophysiologic study was not significantly different between groups.

With the introduction of the ICD into clinical practice, referrals of patients for ventricular tachycardia surgery decreased markedly. With a new generation of electrophysiologists and cardiac surgeons who are largely unfamiliar with ventricular tachycardia surgery, many physicians now overlook the role that surgery continues to play in selected patients. The following two subsections discuss indications and techniques for the surgical treatment of ventricular tachycardia in the ICD era.

Surgical Indications for Ventricular Tachycardia

A number of important points need to be emphasized about surgical options for ventricular tachycardia. First, surgical mortality in the ICD era has been significantly lower than that historically reported in the early clinical experience with direct ventricular tachycardia surgery. This is because high-risk patients (i.e., poor left ventricular function, no discrete aneurysm, polymorphic ventricular tachycardia) are no longer referred for surgery but are preferentially treated with ICDs. In a series of patients reported from the University of Virginia and from our institution, the hospital mortality rate was 4.9% and surgical success rates were above 90%.¹⁸³

From 1988 to 2008, the Washington University experience included 74 patients.¹⁸⁴ During the last 10 years of this study period, 11 patients underwent direct ventricular tachycardia surgery with no operative mortality. During this time, the median hospital length of stay was 11 days. Seventy-three percent of patients (8 of 11) had no recurrence of their ventricular tachycardia at a mean follow-up of 5.8 years, and there were no late deaths in this group because of the liberal use of adjunctive ICD therapy. The overall survival of the group during the 20-year study period was excellent, with a 5-year survival of 65%. Thus, in properly selected patients, a low operative mortality rate can be expected, with good late results.

A second important point and an advantage of surgery is that the underlying left ventricular dysfunction can be addressed. This is not the case with catheter ablation, which eliminates only the arrhythmogenic substrate. Furthermore, coronary bypass grafting, left ventricular reconstruction or remodeling, and mitral valve repair can have a significant impact on late survival in appropriate patients.^{185,186} In patients who are referred for surgery for left ventricular dysfunction, it is critical that these patients be offered a concomitant procedure to treat the ventricular tachycardia, when indicated, because of the excellent success rates of preventing recurrent ventricular tachycardia.^{185,186} Surgery can improve the patient's quality of life by decreasing the number of defibrillator shocks.

Finally, ventricular tachycardia surgery can play a role in patients who are receiving frequent discharges from their device. Quality of life of these patients is poor.^{160,187} In patients who have failed catheter ablation or are poor candidates for this procedure, surgery can play an important role if the patients have an appropriate substrate. The different procedures for ventricular tachycardia are discussed in the following section.

Surgical Techniques for Ventricular Tachycardia

Revascularization

Surgical coronary revascularization (CABG) alone has not been highly effective at treating ventricular tachycardia.¹⁸⁸⁻¹⁹⁰ However, evidence suggests that when ischemia is the primary trigger for ventricular arrhythmias, CABG can alter the arrhythmic substrate in selected patients to reduce ventricular arrhythmias.^{191,192} Several groups have documented that 40% to 60% of patients undergoing CABG with a preoperative clinical history of ventricular arrhythmias or fibrillation had no inducible ventricular arrhythmias at postoperative electrophysiologic testing.^{189,190} Lee and colleagues demonstrated that only 25% of patients after CABG and ICD implantation for preoperative ventricular arrhythmias had inducible arrhythmias postoperatively.¹⁹³ However, in most patients with chronic ischemic ventricular tachycardia, the results of CABG have been too unpredictable, and most patients require concomitant ICD therapy. In patients with poor left ventricular function, ICDs play a role even when those patients have no history of ventricular tachycardia. The Multicenter Automatic Defibrillator Implantation

Trial II (MADIT II) found that prophylactic ICD implantation improved survival in patients with prior myocardial infarction and poor left ventricular function (left ventricular ejection fraction < 0.30).¹⁹⁴

In patients with ischemic ventricular tachycardia, the only candidates for CABG alone are patients who have significant coronary artery disease, who have no ventricular dilation or aneurysm, and who suffer from documented exercise- or ischemia-induced ventricular arrhythmias. Postoperative exercise testing and electrophysiologic studies are used to determine whether implantation of an ICD is warranted.

Endocardial Resection

The resection of all visible endocardial scar, a procedure introduced by Harken in 1979, has become the gold standard and the most commonly performed operation for ventricular tachycardia.¹⁷⁵ The amount of ventricular tissue involved or its location near the posterior papillary muscle may limit a complete resection. In these cases, alternative ablation techniques are used either adjunctively or as the sole therapy. Although groups have reported use of energy sources such as laser, RF ablation, and microwave, the most commonly used and well-studied ablation technique is cryoablation. Popularized in the 1980s, the cryoablation probe is applied to the scar and typically cooled to -60°C for 2 or 3 minutes, resulting in lesions 2 to 3 cm in depth.

Although intraoperative mapping has yielded a wealth of information into the mechanisms of ventricular arrhythmias, its clinical practicality and questionable added efficacy to ventricular tachycardia surgery have prevented its widespread adoption. Virtually all surgeons have adopted a technique of resecting all visible endocardial scars without the use of intraoperative mapping.

A retrospective review of 74 patients who underwent an endocardial resection procedure (ERP) with adjunctive cryotherapy for ventricular arrhythmias from 1986

to 2007 was performed at Barnes-Jewish Hospital at Washington University in St. Louis. The mean age was 57 ± 14 years, and 81% of patients were male. One quarter of patients were in New York Heart Association class III or class IV heart failure, and the mean left ventricular ejection fraction was $34\% \pm 9\%$. Ninety-two percent of patients underwent ERP with a concomitant procedure, and 8% underwent ERP alone. The spectrum of procedures included ERP plus left ventricular aneurysm repair (26%), ERP plus CABG (5%), ERP plus CABG plus left ventricular aneurysm repair (46%), and ERP plus left ventricular aneurysm plus other cardiac procedure (15%). The overall operative mortality rate was 15%, with a median intensive care unit length of stay of 4 days and a median hospital length of stay of 12 days. As stated previously, there was no operative mortality during the last 10 years of our experience. Late follow-up was completed in 89% of patients. A Kaplan-Meier survival analysis was performed, and absolute survival for all patients in this series was 74% at 1 year and 65% at 5 years. Eighty-eight percent of the cases were performed during the first decade (1986 to 1996) and the remaining cases during the next decade (1997 to 2007), reflecting the diminishing role of surgical management in this disease. Since 2007, only three additional ERPs have been performed (Fig. 87-20).

Left Ventricular Reconstruction

In 1985, Vincent Dor described a surgical technique to restore the dilated left ventricle in patients with ischemic cardiomyopathy or ventricular aneurysms to its normal elliptical shape by reducing the volume of the ventricle.^{195,196} The Dor procedure uses an endoventricular circular patch to reduce ventricular volume, which subsequently reduces wall tension and ischemia. Good surgical candidates for left ventricular reconstruction typically present with heart failure (left ventricular ejection fraction $< 40\%$), coronary artery disease, large areas of myocardial akinesis (ventricular dilation), or a

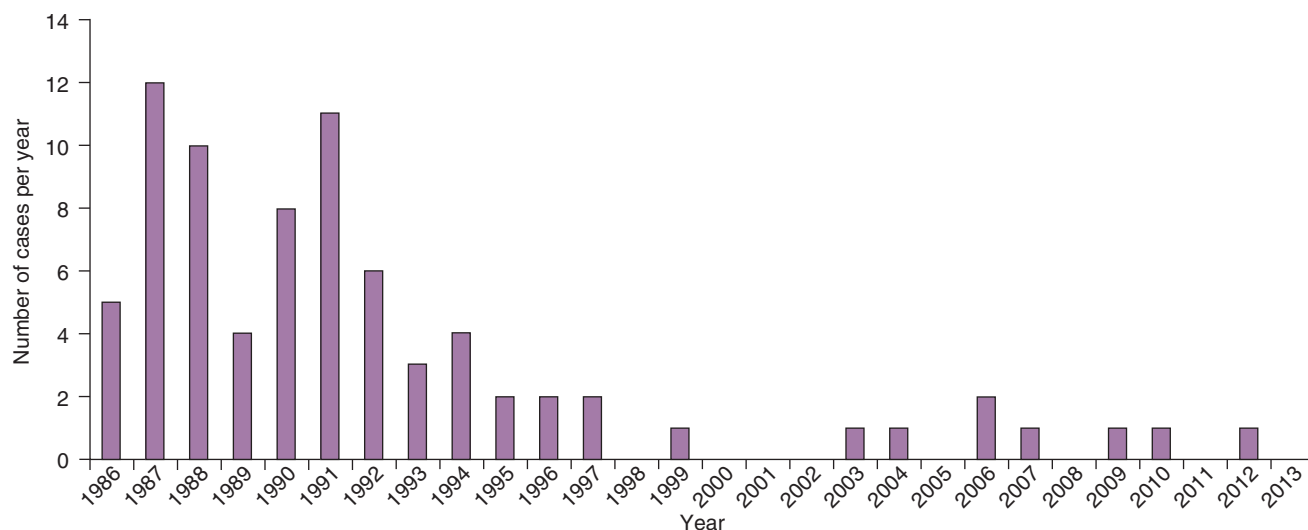


FIGURE 87-20 ■ Washington University School of Medicine/Barnes-Jewish Hospital experience with ventricular tachycardia surgery.

left ventricular aneurysm. These patients commonly have associated ventricular arrhythmias. Currently, Dor emphasizes the importance of complete revascularization (CABG), repair of any mitral disease, and endocardial resection with cryoablation at the same setting. A more complete description of the Dor procedure and its modifications, including technical considerations, can be found in [Chapter 100](#).

In 2004, Maxey and colleagues demonstrated that the Dor procedure restores the left ventricle's geometry, resulting in a mean ejection fraction increase of 12.5%.¹⁹⁷ Ventricular function continues to improve during the patient's lifetime. The RESTORE group experience examined a registry of 1198 postinfarction patients between 1998 and 2003 who underwent left ventricular restoration and found that 5-year freedom from hospital readmission for congestive heart failure was 78%. In addition, 67% of patients were assigned to class III or class IV preoperatively; 85% were assigned to class I or class II postoperatively.¹⁸⁵

Several groups have demonstrated that the triggers for ventricular arrhythmias occur at the scar border zone in patients with ischemic cardiomyopathy.¹⁶⁵⁻¹⁶⁸ Thus, the Dor procedure addresses ventricular arrhythmias by removing the anatomic substrate during resection of the postinfarction scar or aneurysm. In 1994, Dor and associates¹⁹⁶ reported a 90% freedom from inducible ventricular tachycardia at 1 year after endocardial resection and left ventricle reconstruction in 106 patients. In 2004, Mickleborough and colleagues reported long-term outcomes after left ventricular reconstruction and coronary revascularization for patients with hypokinesis or akinesis and coronary artery disease with poor left ventricular function. Results demonstrated that operative survivors had freedom from ventricular tachycardia and sudden death at 1 year, 5 years, and 10 years of 99%, 97%, and 94%, respectively.¹⁹⁸

In spite of the excellent results previously mentioned, the efficacy of left ventricular restoration alone for the treatment of ventricular tachycardia has been controversial. The Cleveland Clinic experience illustrated the relative lack of efficacy of the Dor procedure alone without endocardial resection surgery.¹⁹⁹ In this series, 48 of 113 patients (42%) who had a postoperative electrophysiology study had inducible ventricular tachycardia after the Dor procedure. Furthermore, in patients with an ICD, 15% had either sudden cardiac death or appropriate shocks. With early electrophysiology study, ICD implantation, or both, the overall incidence of sudden cardiac death was less than 1%. In 2004, DiDonato and associates demonstrated in 382 patients that left ventricular restoration with endocardial resection reduced the inducible ventricular tachycardia from 41% to 8%, suggesting that many patients may not need a postoperative ICD.¹⁸⁶

Because of the high lethality of ventricular tachyarrhythmias in patients in whom surgery is not curative, it is generally recommended that all patients after the Dor procedure undergo electrophysiology study or implantation of an ICD if they have had a history of ventricular arrhythmias or inducible ventricular tachycardia preoperatively.

Cardiac Assist Devices and Heart Transplantation

In rare cases, patients present with uncontrolled ventricular arrhythmias refractory to conventional surgical, ICD, or medical therapy. Typically, these patients have an end-stage cardiomyopathy resulting in incessant ventricular tachycardia. If the patients are not amenable to conventional cardiac revascularization or other procedures, these malignant arrhythmias may be effectively palliated with a cardiac assist device, either as a bridge to transplantation or as destination therapy.²⁰⁰⁻²⁰² The cardiac assist device effectively reduces myocardial oxygen demand and can decrease the incidence of ischemia-induced arrhythmias.²⁰³

Conclusions

ICDs and catheter ablation have significantly reduced the role of surgery in the treatment of ventricular arrhythmias. When indicated, however, current surgical techniques can be quite successful. The surgical approach should be individualized to each patient. The current indications for surgery include the following: (1) In patients who have ischemic ventricular tachycardia requiring revascularization and who have poor left ventricular function and no significant wall thinning, the recommended treatment is CABG and ICD placement. If significant wall thinning or a discrete aneurysm is present, ventricular remodeling, extended endomyocardial resection, and cryoablation should be performed. (2) Surgery for ventricular tachycardia should be considered for patients suffering from frequent ICD discharges that are poorly tolerated and have an amenable anatomic substrate. In the presence of frequent ICD shocks with a discrete left ventricular aneurysm or wall thinning, ventricular remodeling, extended endomyocardial resection, and cryoablation should be considered.

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PART H

SURGICAL MANAGEMENT OF CORONARY ARTERY DISEASE AND ITS COMPLICATIONS

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CORONARY ARTERY BYPASS GRAFTING

Talal Al-Atassi • Hadi D. Toeg • Vincent Chan • Marc Ruel

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CONCLUSION

Coronary artery bypass grafting (CABG) is among the most important surgical procedures in the history of medicine. Arguably, no other operation has prolonged more lives, provided more symptom relief, and been more thoroughly investigated. CABG has been the most common procedure of adult cardiac surgery, but its future is increasingly threatened by medical and percutaneous alternatives. However, CABG is evolving with less invasive options, better postoperative care, and refined medical adjuncts. This treatment strategy remains the

most durable means of revascularization for patients with coronary artery disease (CAD) and even more so for patients with diabetes and multivessel CAD. This chapter outlines the history, anatomic considerations, indications, techniques, postoperative care, and results of the modern CABG procedure. Other, complementary chapters in this book cover cardiac anatomy, the coronary circulation, cardiopulmonary bypass, myocardial protection, bypass conduits, off-pump grafting techniques, reoperations, combined procedures, and general postoperative care.

BACKGROUND

History

The initial development of CABG is credited to Dr. Alexis Carrel, who more than a century ago understood the association between angina pectoris and coronary stenosis.¹ In a canine model, Carrel anastomosed a carotid artery segment between the descending thoracic aorta and the left coronary artery. Carrel received the Nobel Prize in Physiology and Medicine for this work in 1912 (Fig. 88-1).¹ Despite this major advance in medical science, the lack of technology to support the heart remained a major hurdle toward the clinical implementation of Carrel's techniques. That surgical roadblock persisted for several decades, until Carrel collaborated with aviator Charles Lindbergh in the 1930s in hopes of developing the world's first heart-lung machine.² Although unsuccessful, their work added to the medical knowledge of the time.

In the late 1940s, Montreal surgeon Arthur Vineberg began implanting the left internal thoracic artery (LITA) onto the anterior myocardial territory in patients with severe angina.³ The Vineberg procedure met with variable success, although many patients experienced symptomatic improvement.⁴ In 1958, Johns Hopkins-trained William Longmire reported on his series of five patients treated with coronary artery endarterectomy, without the use of cardiopulmonary bypass (CPB).⁵ Longmire was likely the first to perform a direct internal thoracic artery (ITA) to coronary artery anastomosis as a consequence of damage to the right coronary artery during one of his endarterectomy procedures.⁶

At approximately the same time, a number of surgeons across the globe were reporting their early experiences

with CABG. In 1962, Sabiston performed the first planned saphenous vein bypass operation at Duke University.⁷ In 1964, Kolesov grafted the LITA to the left anterior descending (LAD) artery, without CPB,⁸ and DeBakey and Garrett reported aortocoronary saphenous vein grafting (SVG).⁹ The world's first CABG program started 3 years later in Cleveland, as Favaloro and Effler began to routinely use reversed saphenous veins for aortocoronary grafting.¹⁰ LITA grafting to the LAD was introduced in the Western world by Green in 1968,¹¹ sequential grafting by Flemming in 1971,¹² bilateral internal thoracic grafting by Kay in 1972,¹³ and the use of radial artery grafts described by Carpentier in 1973 and revived by Acar in 1989.^{14,15}

In the 1970s CABG flourished as the sole therapy for CAD. Several randomized trials—namely, the Coronary Artery Surgery Study (CASS),¹⁶ the Veterans Administration Coronary Artery Bypass Trial,¹⁷ and the European Coronary Artery Bypass Trial¹⁸—were conducted and would lay the foundation for surgical indications. In the modern era of CABG surgery, the prototypical patient is older, has significantly more comorbidities, and is more likely to have undergone percutaneous coronary intervention (PCI) with a drug-eluting stent.¹⁹ However, several multicenter studies comparing CABG with current stent therapy—namely, the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX),²⁰ Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM),²¹ and Coronary Artery Revascularization in Diabetes (CARDia)²² trials—have clearly demonstrated the superiority of CABG when specific patient characteristics, such as diabetes, and coronary anatomy, such as involvement of all three coronary vessels, are taken into account.

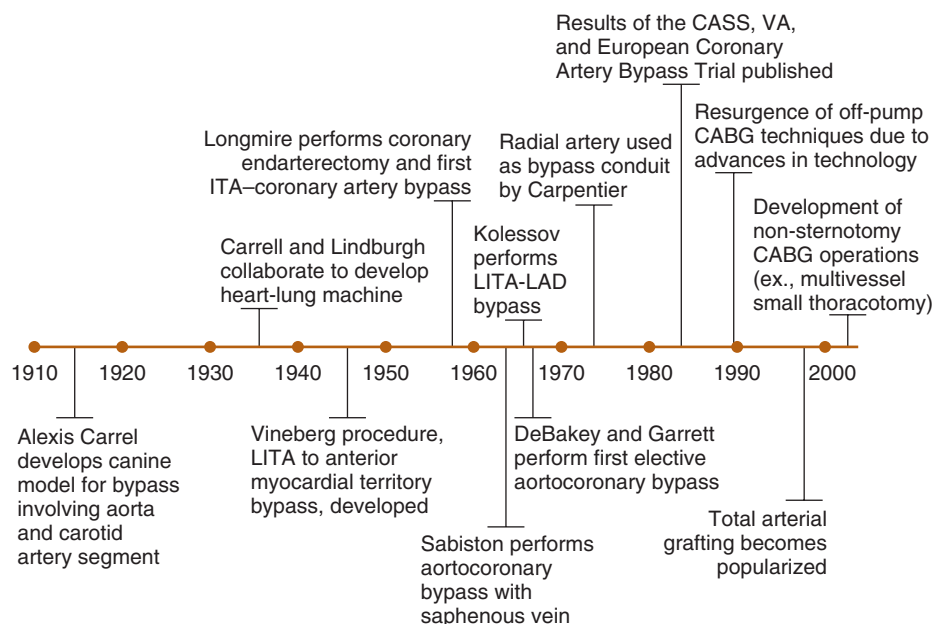


FIGURE 88-1 ■ Advances in the surgical treatment of coronary artery disease. CABG, Coronary artery bypass grafting; CASS, Coronary Artery Surgery Study; ITA, internal thoracic artery; LAD, left anterior descending coronary (artery); LITA, left internal thoracic artery; VA, Veterans Administration Coronary Artery Bypass Surgery Cooperative Study.

Anatomic Considerations

Coronary artery anatomy and size vary widely among individuals. In the absence of CAD, coronary perfusion matches myocardial demand because capillary oxygen extraction is relatively fixed.²³ During exercise, coronary perfusion increases three- to fourfold as a result of vasodilation of coronary arteries and arterioles and from recruitment of additional capillaries.²⁴

In the setting of symptomatic CAD, compensatory physiologic processes are insufficient to provide adequate myocardial perfusion. The effect is either *supply ischemia*, responsible for myocardial infarction (MI) and most episodes of unstable angina, or *demand ischemia*, where coronary blood flow is insufficient during periods of increased myocardial demands from exercise, tachycardia, fever, hypertension, or emotional distress.²⁵ Basal arteriogenesis and collateral formation may be enhanced when new coronary flow patterns and subclinical ischemia develop, but their extent largely depends on the time course of CAD development and is governed by genetic and environmental factors. It is the magnitude of arterial collateralization, of *de novo* arteriolar and capillary development, and dynamic vascular responses that determine the degree of ischemia experienced by a patient. Furthermore, the size and function of the subtended myocardial territory at risk (demand) dictates the degree of ischemia and risk of heart failure in patients with obstructive CAD (supply).

Depending on referral patterns, 40% to 60% of patients who undergo coronary angiography have significant disease involving all three coronary arteries, and 10% to 20% of those patients have stenosis of the left mainstem.²⁶ In patients with single- or double-vessel disease, the most frequently stenosed coronary artery is the right, followed closely by the LAD and least frequently by the circumflex. In some patients, atherosclerosis may be mimicked by myocardial bridging of a coronary artery, which involves a segment of coronary artery completely surrounded by myocardium. Myocardial bridging can result in cardiac ischemia although traditional noninvasive tests are often negative.²⁷

Myocardial hypoperfusion leads to one of four pathophysiologic consequences: stunned myocardium (reversible myocardial dysfunction despite normal/near normal coronary blood flow), hibernating myocardium (reversible myocardial dysfunction with reduced coronary blood flow), nontransmural scar tissue, or transmural scar tissue (irreversible typically nonviable myocardial dysfunction). Patients who describe ischemia on exertion will typically exhibit viable (stunned or hibernating) myocardium, whereas those who describe heart failure symptoms may suffer from irreversible myocardial dysfunction. In addition to clinical evaluation, several contemporary imaging modalities with relatively good sensitivity and specificity are used to further delineate and quantify the proportion of viable myocardium, the most common being nuclear imaging with positron emission tomography (PET) (evaluating viability with glucose uptake of ¹⁸F-fluorodeoxyglucose [FDG]), single photon emission computed tomography (SPECT) (with thallium or technetium radiotracer), dobutamine stress echocardiography (with contrast agents), and dobutamine stress cardiac

magnetic resonance imaging (MRI). With PET, stunned myocardium appears as a hypocontractile segment with normal perfusion and glucose uptake at rest, and hibernating myocardium as a territory with decreased perfusion but preserved glucose uptake.²⁸ Scar tissue, unlikely to benefit from CABG, exhibits both reduced perfusion and glucose uptake, with a milder reduction in nontransmural scars and a severe reduction in transmural scars.

In addition to assessment of angiographically defined stenosis and myocardial viability, technologic advances in interventional cardiology have led to quantitative measurement of coronary blood flow across lesions, and ultra-refined topographic imaging of coronary lesions.^{29,30} Fractional flow reserve values of less than 0.8 (considered significant flow limiting CAD as measured by flow across coronary lesions) has altered management strategies in patients with borderline angiographic CAD resulting in less graft anastomosis at CABG and thus, less on-pump surgery.^{31,32} Alternatively, intravenous ultrasound (IVUS) and optical coherence tomography has improved the resolution and sensitivity of identifying obstructive CAD not traditionally seen on standard angiography.^{31,33} In summary, imaging modalities such as coronary angiography (standard and CT) are obligate adjuncts in defining anatomic coronary artery stenosis and can be further characterized by functional studies such as PET viability, fractional flow reserve, or IVUS. These functional preoperative imaging studies help the cardiac surgeon in determining whether the patient meets indications for CABG and predict the degree of improvement after surgery and outcomes in general.

INDICATIONS FOR OPERATION

The indications for CABG described in this section are based on the 2011 American College of Cardiology/American Heart Association (ACC/AHA) guidelines.³⁴ These updated guidelines include several contemporary multicenter randomized controlled trials comparing CABG to PCI with either first- or second-generation drug-eluting stents, which have become the treatment of choice for PCI.^{35,36} In contrast, previous recommendations were mostly based on historical trials comparing either bare-metal stents or angioplasty alone with CABG.³⁷⁻⁴⁰ With the advancement of less thrombotic stents (i.e., everolimus-eluting stents),⁴¹ minimally invasive CABG options or hybrid operations, and better medical treatment for CAD, it is no surprise that indications for surgical revascularization will be further refined, driven by the constant need to improve patient outcomes.

The pivotal SYNTAX trial randomized 1800 patients with left main or triple-vessel disease to undergo either CABG or PCI (drug-eluting stents).²⁰ The extent of CAD was determined using the SYNTAX score based on severity, location, and extent of coronary stenosis. A low SYNTAX score was defined as less than 22, intermediate as 23 to 32, and high as 33 and above. At 12 months, major adverse cardiac and cerebrovascular events (MACCEs) were significantly higher in the PCI group compared with CABG patients (17.8% vs. 12.4%; $P = 0.002$). This was

mostly accounted for, after post hoc analysis, in patients with higher SYNTAX scores (≥ 33).²⁰ At 3 years, patients with triple-vessel disease and low to intermediate SYNTAX scores (≤ 32) had lower rates of MACCE compared with PCI ($P < 0.004$), whereas patients with left main CAD and SYNTAX scores 33 and higher had lower incidence of MACCE compared with PCI ($P = 0.003$).⁴² Furthermore, because patients with diabetes had higher rates of revascularization in the PCI group compared with CABG, the FREEDOM trial²¹ was conducted to determine whether current PCI therapy (with second-generation drug-eluting stents) or CABG is superior for diabetic patients with multivessel CAD. This randomized controlled trial demonstrated CABG to be superior over PCI in diabetic patients with lower 5-year rates of death and MI; however, stroke rates were slightly higher in CABG patients. Thus, based on the aforementioned historical and latest studies along with the updated ACC/AHA guidelines, the following sections provide detailed anatomic and clinical scenarios for CABG indications.

Clinical Scenarios and CABG Indications

Stable Ischemic Heart Disease

The indications for CABG in the setting of asymptomatic, mild angina, or chronic stable angina are based on the observed survival advantage of CABG over nonsurgical therapy (Table 88-1).^{34,39} Class I indications include the use of CABG to treat significant left main disease ($\geq 50\%$), left main equivalent disease (i.e., proximal stenosis of at least 70% of the proximal LAD and circumflex), triple-vessel disease (especially in patients with left ventricular ejection fraction [LVEF] $< 50\%$ and/or in whom a large area of myocardial ischemia exists), and proximal LAD disease combined with an LVEF between 35% and 50%.³⁴ CABG is also indicated for patients with proximal LAD disease without left ventricular dysfunction, and may be indicated for patients with single- or double-vessel disease not involving the proximal LAD (class IIa).⁴³ Finally, CABG or PCI is indicated in patients with at least one significant coronary artery stenosis with unacceptable angina despite optimal medical therapy (class I) (Table 88-2).^{39,44-46} Recent large studies have demonstrated that stable anginal patients treated with either optimal medical therapy or PCI ($\pm$ CABG) had no significant survival benefit.^{44,47-50} Thus, although these updated guidelines provide a treatment algorithm for CAD patients, the ultimate decision regarding revascularization options should be made between the expert clinician and the well-informed patient.

Acute Coronary Syndromes

Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction. The indication for CABG in patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) is anatomically identical to that in patients with stable ischemic heart disease.⁴³ This includes patients with significant left main or left main equivalent disease, patients with triple-vessel disease, and

TABLE 88-1 Class I and IIa Indications for CABG Surgery

COR	LOE	Clinical or Anatomic Setting
I	A	One or more significant ($>70\%$) coronary artery stenoses amenable to revascularization and unacceptable angina despite best medical therapy (<i>consider PCI as alternative</i>)
I	B	Unprotected left main disease ($>50\%$)
I	B	Triple-vessel disease with or without proximal LAD artery disease
I	B	Survivors of sudden cardiac death with ischemia-mediated ventricular tachycardia
I	B	Double-vessel disease with proximal LAD artery disease
I	B	Emergency CABG after failed PCI in presence of ongoing ischemia or threatened occlusion with substantial myocardium at risk (without impaired coagulation and without a previous sternotomy); surgical repair of a postinfarction mechanical complication (i.e., septal or free wall rupture)
I	B	Emergency CABG in patients with cardiogenic shock, suitable for CABG irrespective of time interval from MI to onset of shock and time from MI to CABG.
I	C	Patients undergoing noncoronary cardiac surgery with left main disease ($>50\%$) or any other CAD ($>70\%$)
I	C	Heart team approach recommended for unprotected left main disease or complex CAD
IIa	B	CABG over PCI in patients with complex triple-vessel CAD (i.e., SYNTAX > 22)
IIa	B	Double-vessel disease without proximal LAD disease with extensive ischemia
IIa	B	Single-vessel proximal LAD disease with LITA for long-term benefit
IIa	B	CAD with left ventricular ejection fraction 35% to 50%
IIa	B	Hybrid (LITA to LAD artery CABG + PCI for non-LAD arteries) for limitation for CABG (unsuitable conduits) or unfavorable LAD artery for PCI

CABG, Coronary artery bypass grafting; CAD, coronary artery disease; COR, class of recommendation; LAD, left anterior descending; LITA, left internal thoracic artery; LOE, level of evidence; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Derived from 2011 AHA/ACC guidelines for CABG.⁴³

patients with ongoing ischemia not responsive to maximal nonsurgical therapy or failed/unfavorable PCI (see Table 88-1). The major difference between anatomically similar patients presenting with unstable angina or NSTEMI compared with stable CAD is that achieving revascularization in an acute coronary syndrome, a potentially life-threatening scenario, creates a stronger motive in preventing death.⁵¹⁻⁵³ The indication for CABG in this setting is further strengthened by the acuity of presentation, degree of ischemia, and benefit of full revascularization.

ST-Segment Elevation (Q Wave) Myocardial Infarction. Primary PCIs and intravenous thrombolytic therapy have supplanted CABG as the first line of therapy

TABLE 88-2 Pertinent History and Physical Examination Elements for CABG

Preoperative Assessment	Possible Implications	Management
History		
Symptoms		
SHORTNESS OF BREATH		
Orthopnea	Left ventricular dysfunction; right ventricular dysfunction; valve disease	Warrants echocardiography to determine cardiac anatomy
Aggravated with activity	Cardiac ischemia	May warrant more urgent surgery depending on severity of symptoms
Chest pain	Cardiac ischemia	Alert anesthesiologist of possible airway difficulty; arrange for CPAP postoperatively
Poor sleep quality/snoring	Sleep apnea	Assess peripheral and central pulses; brachial-ankle index, echocardiography to assess ascending aortic calcification
Claudication	Peripheral vascular disease	Imaging to determine disease in celiac-mesenteric axis; contraindicates gastroepiploic artery use
Postprandial pain	Mesenteric angina	
Past Medical History		
Diabetes mellitus	Poor wound healing; difficult glycemic control perioperatively	Consider skeletonized harvesting for bilateral internal thoracic arteries
Previous sternal irradiation	Internal thoracic artery damage	May contraindicate use of internal thoracic artery
Previous TIA/amaurosis fugax/stroke	Atherosclerotic disease involving arch vessels	Warrants carotid duplex examination and echocardiography; possible need for CT or MRI angiogram to elucidate disease extent
Raynaud phenomenon	Compromised flow in upper extremity precluding radial artery use	May warrant Doppler examination of the forearm; contraindicates radial artery use in most cases
Past Surgical History		
Lower extremity vein stripping	Lack of greater saphenous vein	Choose alternative conduits
Abdominal laparotomy	Possible contraindication to gastroepiploic artery use	Choose alternative conduits
Medications		
Chronic steroid use	Poor wound healing postoperatively; consider steroid withdrawal postoperatively; difficult glycemic control perioperatively	May contraindicate use of bilateral internal thoracic artery use; ensure postoperative steroid administration and glycemic control
Physical		
Asymmetric brachial blood pressure	Atherosclerotic disease involving arch vessels	Warrants carotid and subclavian duplex examination; contraindicates use of pedicled internal thoracic artery grafts on the ipsilateral side of subclavian stenosis
Increased JVP/peripheral edema	Left ventricular dysfunction; valve disease	Warrants echocardiography to determine cardiac anatomy
Auscultation		
Increased P2	Pulmonary hypertension	Warrants echocardiography to determine cardiac anatomy ± CT chest
Murmur	Concomitant valve disease	Chest radiograph; echocardiography to determine cardiac anatomy
Clubbing	Bronchiectasis; chronic pulmonary hypertension; lung malignancy	

CABG, Coronary artery bypass grafting; CPAP, continuous positive airway pressure; CT, computed tomography; JVP, jugular venous pressure; MRI, magnetic resonance imaging; TIA, transient ischemic attack.

for patients in the acute period of ST-segment elevation myocardial infarction (STEMI).³⁴ As a consequence, ongoing ischemia or cardiogenic shock despite maximal nonsurgical therapy, including intra-aortic balloon pump counterpulsation, currently constitute the main indications for emergency CABG in acute STEMI patients (see Table 88-1).³⁴ Other indications for emergency CABG in the setting of STEMI include failed PCI or thrombolysis and demonstration of a large myocardial territory at risk, in combination with an unsuitable anatomy for PCI, left main coronary stenosis, left ventricular failure with severe coronary stenosis outside the initial infarct area, significant valve disease, life-

threatening ventricular arrhythmias believed to be ischemic in origin (left main or triple-vessel CAD), or a mechanical complication of MI such as severe mitral insufficiency, left ventricular wall rupture, or ventricular septal rupture.³⁴

The timing of CABG after an acute coronary syndrome is controversial. Although early surgery may limit the expansion of the infarct, it runs the risk of reperfusion injury that may lead to a hemorrhagic infarct and scar development. In some cases, such as ongoing ischemia and mechanical complications, CABG cannot be delayed and the availability of mechanical support becomes very important. However, data from the New York State

Cardiac Surgery Registry showed that CABG within 6 hours of a nontransmural infarct or within 3 days of a transmural infarct was independently associated with in-hospital mortality. Therefore, CABG should be delayed for at least 6 hours after a nontransmural infarct and 3 days after a transmural infarct when no clear indication for immediate CABG is present.^{55,56}

Spontaneous Coronary Artery Dissection. One rare form of acute coronary syndrome is spontaneous coronary artery dissection (SCAD), which affects 0.1% to 4% of patients with acute coronary syndromes.⁵⁷ SCAD is a nontraumatic, noniatrogenic separation of the coronary arterial wall by intramural hemorrhage leading to compression of the lumen with intramural hematoma. Typical patients presenting with SCAD include females younger than 50 years without traditional cardiovascular risk factors. Causes of SCAD include pregnancy, connective tissue disorders, systemic inflammatory conditions, coronary artery spasm, and precipitating stress events (intense exercise, emotional stress, labor, or cocaine).⁵⁸ Whereas the mainstay of treatment for stable SCAD patients entails beta blockers and antiplatelets, PCI or surgical revascularization should be considered in patients who have ongoing chest pain, show evidence of ischemia, or are hemodynamically unstable despite maximal medical therapy. Specific indications for CABG follow similar anatomic considerations (i.e., left main, left main equivalent, or triple-vessel disease).^{58,59}

Concomitant Noncoronary Cardiac Surgery

Patients undergoing other forms of cardiac surgery such as valvular repair, where coronary angiography demonstrates either a 50% luminal diameter narrowing of the left main artery or a more than 70% narrowing of any other epicardial coronary artery, should undergo concomitant CABG (class I; evidence C). Furthermore, the LITA is a reasonable conduit choice for bypassing the LAD artery (class IIa), and other conduits, mostly vein grafts, can be used to bypass moderately diseased coronary arteries (>50% narrowing) (class IIa).³⁴

Left Ventricular Dysfunction and Heart Failure

CABG is indicated in patients with left ventricular dysfunction (LVEF 35% to 50%; class IIa and LVEF < 35%; class IIb) and left main or left main equivalent disease, and also in the setting of proximal LAD stenosis with double- or triple-vessel disease.⁶⁰⁻⁶² Despite the increased risk of left ventricular dysfunction on perioperative mortality, the long-term results of CABG in patients with mild to moderate left ventricular dysfunction appear favorable.⁶¹⁻⁶³ It is important to note that patients who have poor left ventricular function and/or congestive heart failure (CHF) symptoms must be evaluated for valvular disease and for objective evidence of hibernating myocardium with a perfusion scan. Despite historical studies demonstrating better outcomes with mild to moderate left ventricular dysfunction, results in patients with advanced left ventricular dysfunction (LVEF < 35%)

treated with CABG are more controversial. The Surgical Treatment for Ischemic Heart Failure (STITCH) trial enrolled patients with an LVEF less than 35% with or without myocardial viability.⁶⁴ The primary endpoint of all-cause mortality did not differ in surgically versus medically treated patients at 5 years follow-up. However, several combined secondary endpoints, including death from any cause and heart failure–related hospitalization, were significantly lower in CABG patients. Thus, in efforts to discriminate a difference in survival, the study will be followed for an additional 5 years.

Life-Threatening Ventricular Arrhythmias and Sudden Cardiac Death

Data describing the benefit of CABG as a treatment for ventricular arrhythmias originate from studies involving survivors of out-of-hospital cardiac arrest. CABG is more effective in treating ventricular fibrillation than ventricular tachycardia, as the latter originates from myocardial scar formation. CABG is also particularly useful in the setting of exercise-induced ventricular arrhythmias,^{65,66} and it has been shown to suppress ventricular arrhythmias in the setting of left main or triple-vessel disease. Alternatively, CABG should not be performed on patients with ventricular tachycardia or evidence of scar. All patients should undergo consultation with an electrophysiology specialist for consideration of insertion of an implantable cardioverter-defibrillator (ICD). Patients with depressed left ventricular function, older age, female sex, and extended CPB runs are more prone to developing life-threatening arrhythmias such that temporary mechanical circulatory support may be justified.^{67,68}

Failed Percutaneous Coronary Intervention

Because of improved PCI techniques, stent technologies, and antiplatelet options, failed PCI requiring emergency CABG is rare, with an incidence of 0.4% to 0.8%.^{69,70} Broad indications for CABG after failed PCI include an acute closure of a coronary vessel (or threatened), vessel dissection, perforation, or malfunction of the PCI equipment (i.e., fractured guidewire). Most patients who undergo emergency CABG exhibit an evolving STEMI, triple-vessel disease, left main disease, cardiogenic shock, or a type C coronary arterial lesion (defined as a lesion with any of the following: diffuse lesion [>2 cm length], inability to protect major side branch, excessive tortuosity, degenerated vein grafts, or total occlusions more than 3 months old).^{69,70} As expected, patients who undergo emergency CABG have increased perioperative morbidity and mortality rates. Independent predictors of worse outcomes include advanced age, depressed left ventricular function, cardiogenic shock, absence of angiographic collaterals, and a prolonged time delay for transfer to the operating room.^{71,72} However, if complete revascularization can be achieved without protracted delay, the long-term outcomes in emergency CABG patients after failed PCI mirror those of elective CABG patients.^{70,73-75} Finally, an off-pump CABG approach for patients in whom PCI failed may be associated with less bleeding requiring

reoperation, less renal failure, and less intra-aortic balloon pump usage.^{76,77}

Previous Coronary Artery Bypass Grafting

Operative risk associated with reoperative CABG is greater than that for the primary operation because of the fact that on reentry there may be damage to patent grafts or other cardiac structures, such as the right ventricle or innominate vein. Coronary identification at reoperation is also more difficult. Given the increased risk, the indications for reoperative CABG largely depend on the degree of symptoms, size of the myocardial territory at risk, concomitant valvular disease, and suitability for PCI.⁷⁸ Current guidelines advocate first, PCI in previous CABG patients refractory to medical therapy (class IIa), followed by redo CABG if disabling angina refractory to maximal medical therapy and PCI occurs (class IIb).⁷⁹ Despite the increased risk, advances in current surgical techniques have significantly narrowed the perioperative risk gap between reoperative and primary CABG with studies demonstrating similar long-term outcomes between redo and primary CABG.

In summary, patients undergoing intervention for CAD should be assessed on a case-by-case basis. After clinical, social, and anatomic patient characteristics are taken into account, the use of a heart team is recommended when the choice of revascularization is not apparent. The heart team may take advantage of a hybrid coronary revascularization strategy by performing LITA to LAD artery grafting and PCI of one or more non-LAD arteries. This approach is reasonable in patients with either limitations to traditional CABG (lack of suitable graft conduits, severely calcified aorta) or an unfavorable LAD artery for PCI (tortuous vessel or chronically occluded artery).³⁴

SURGICAL TECHNIQUE

Preoperative Preparation

In most cases, patients are referred to cardiac surgery for CABG with the diagnosis of myocardial ischemia confirmed via noninvasive testing, coronary angiography, or both. Despite this, a detailed and focused history, physical examination (including determining the functional status of the patient), and review of all tests should be performed to confirm the surgical indication, determine the operative risk, and allow for optimal surgical planning (see [Table 88-2](#)).

History and Physical Examination

Attention must be given to a possible misdiagnosis (especially when symptoms appear out of proportion to the angiographic severity of the coronary stenoses), to comorbid conditions, and to the availability of conduits for revascularization. For example, patients with predominant symptoms of dyspnea may have concomitant valvular disease, cardiomyopathy, or pulmonary hypertension that was missed during preoperative evaluation.

On physical examination, this can be determined by the presence of a murmur, an accentuated P2 indicating pulmonary hypertension, signs of cardiomegaly, and subtle cyanosis or clubbing. Symptoms and signs of CHF should be elicited, because the coexistence of CHF may impact preoperative testing, perioperative medical management, intraoperative planning (with respect, in some cases, to the choice of myocardial protection strategy and the selection of conduits), and short- and long-term prognosis after operation.⁸⁰ Patients with previous mediastinal irradiation should undergo preoperative echocardiography to rule out valve disease, pulmonary function testing, computed tomography (CT) of the chest to assess the degree of aortic calcification, and carotid duplex examination. Patients with a history of peptic ulcer disease should be identified and the use of perioperative nonsteroidal anti-inflammatory agents avoided.

The peripheral vascular examination is of utmost importance. Brachial blood pressure should be measured in both arms to determine hemodynamically significant subclavian artery stenosis. A difference of systolic blood pressure more than 20 mm Hg warrants Doppler examination and may necessitate the use of a free ITA graft or alternate conduit if a subclavian stenosis is confirmed.⁸¹ The lower extremities should be examined for the presence of varicose veins and incisions from previous saphenectomy or peripheral vascular procedures. The patient should also be asked whether sclerotherapy was ever performed. Lower extremity arterial disease is associated with a relative mortality risk of approximately fivefold, regardless of the presence of symptoms.⁸² These patients have the highest incidence of aortic calcification and perioperative stroke, and particular attention must be given to the ascending aorta when assessing the preoperative chest x-ray and reviewing the coronary angiogram.⁸³ In cases where a suspicion exists, CT of the chest is indicated. Documentation of peripheral pulses is important if intra-aortic balloon counterpulsation is to be considered and provides a rapid, albeit imperfect, baseline assessment for subsequent comparison if late hemodynamic compromise or tamponade is suspected after the patient has left the intensive care unit.

Absolute contraindications to the use of an ITA include previous damage from penetrating trauma or surgery and documentation of the artery as a major source of collateral perfusion to the mesenteric circulation in cases of chronic aortic thrombosis or to a lower extremity in patients with Leriche syndrome (unless lower extremity revascularization is performed concomitantly).^{84,85} Patients on chronic hemodialysis should have a free rather than an in situ ITA graft performed on the side of their arteriovenous fistula.⁸⁶ Severe obesity, chronic obstructive pulmonary disease (COPD), and diabetes may contraindicate the use of bilateral ITAs, but this is controversial and ultimately depends on individual preferences.⁸⁷ Although conventionally believed to be a relative contraindication to ITA use,⁸⁸ previous thoracic irradiation appears to confer no overt histologic changes relative to nonirradiated controls.⁸⁹ Long-term patency data, however, are scarce; therefore, use of ITA grafts in patients with previous mediastinal irradiation must be evaluated on a case-by-case basis.

Previous upper abdominal surgery or symptoms suggestive of mesenteric angina contraindicate the use of a gastroepiploic artery. Radial artery harvest is avoided in patients with Raynaud syndrome or on the same side in patients who have had recent radial arterial puncture at the time of preoperative coronary catheterization. We prefer to also avoid it, in a side-specific manner, in patients with carpal tunnel syndrome or with a history of previous penetrating trauma involving the wrist or forearm. It is important to both feel for an ulnar pulse and perform the Allen test, using a cutoff of 3 seconds, which has a 100% sensitivity for inadequate collateral hand circulation.⁹⁰ The former is important because, in rare cases, the ulnar artery may sometimes be congenitally absent with an otherwise normal Allen test.⁹¹

Asymptomatic carotid bruits have unreliable predictive accuracy,⁹² but their presence warrants carotid duplex examination if CABG can be performed on an elective basis.⁹³ Perioperative stroke risk is less than 2% in patients with carotid stenoses less than 50%, 10% when stenoses are 50% to 80%, and 11% to 19% in patients with stenoses of more than 80%.⁹⁴ A history of transient ischemic attack or stroke warrants a carotid duplex examination to rule out a carotid stenosis and an echocardiogram to rule out a cardiac embolic source or a patent foramen ovale. If no source is found and symptoms suggestive of vertebrobasilar insufficiency are elicited, MRI angiography of the arch vessels should be performed. Patients who had a recent stroke should ideally delay CABG for a minimum of 4 weeks to limit the risk of further neurologic damage. Combined CABG and carotid endarterectomy is controversial although data suggest that the development of postoperative stroke is related to surgical technique and patient factors rather than operative strategy.⁹⁵ Recent trends suggest that carotid artery angioplasty and stenting with concomitant CABG is emerging as an alternative to combined CABG and carotid endarterectomy.⁹⁶ Preoperative documentation of hemodynamically significant carotid stenoses allows for risk stratification, consideration of a staged procedure preceded by carotid endarterectomy, selection of special intraoperative monitoring, and optimization of blood pressure management perioperatively.

Medications

Aspirin and cardiac medications are continued up to the time of operation, with the exception of digoxin, which is discontinued one day prior to surgery. Warfarin is stopped several days (>5) before surgery in orally anticoagulated elective patients, who are started on low-molecular weight heparin when their international normalized ratio (INR) becomes 2.0 or less; emergent cases are reversed with fresh-frozen plasma, Octaplex, and intravenous vitamin K. Management of the ADP-dependent platelet inhibitors clopidogrel and ticagrelor⁹⁷ varies according to personal preferences; our preferred approach in stable patients is to stop the medication 1 week prior to operation with a minimum of 5 days.^{43,97} Furthermore, prasugrel is typically withheld for at least 7 days before elective CABG. With patients with drug-eluting stents that are within a year of insertion and who will not have their stented coronary segment(s) bypassed,

we prefer to keep them on clopidogrel right up to the day of operation. Patients who have been started on an ACE inhibitor prior to surgical referral should have postoperative serial serum creatinine assessments. If progressive elevation is noted (>25% of baseline), the ACE inhibitor should be stopped to allow the serum creatinine levels to normalize prior to operation.

Laboratory Tests

Complete blood counts, serum chemistries, liver function tests, coagulogram, electrocardiogram (ECG), chest x-ray, and urinalysis are routinely performed. Particular attention is given to a low platelet count (suggestive of possible heparin-induced thrombocytopenia in patients on heparin), an elevated serum creatinine (a strong predictor of increased operative mortality), and the presence of vascular calcification on the chest x-ray. Anterior Q waves with poor R wave progression on the ECG are indicative of transmural myocardial scarring and may warrant echocardiography or preoperative viability testing. Most patients will have undergone preoperative nuclear scintigrams and echocardiography. These are reviewed to determine the functional significance of borderline coronary stenoses and to provide an assessment of valve function, left ventricular systolic wall motion, diastolic function, and right ventricular contractility.

A major improvement in the preoperative evaluation in patients with poor left ventricular function and CHF has been the scintigraphic assessment of myocardial viability. Viability is best assessed with PET; recovery of regional and global left ventricular function after surgical revascularization is correlated with a higher preoperative blood flow and glucose uptake, indicative of less tissue fibrosis and a higher fraction of viable cardiomyocytes in the dysfunctional area (Fig. 88-2).⁹⁸ Results are best if both hibernating myocardium and angina symptoms are present and attributed to a myocardial territory subtended by a graftable vessel with significant proximal stenosis; conversely, patients with no viability, no angina symptoms, and diffuse CAD are less likely to derive a survival benefit compared with medical therapy after CABG. If PET is not available, dobutamine stress echocardiography or MRI may be used to identify reversible myocardial dysfunction; although not as sensitive as PET, dobutamine wall-motion indices are specific in predicting postoperative improvement.⁹⁹

Coronary Angiogram

Coronary angiography is still the fundamental diagnostic tool for describing the surgical anatomy of CAD. As a general rule, vessels 1.5 mm or larger with $\geq 50\%$ to 70% stenosis should be grafted. Consideration is given to smaller vessels if no other target is found in a coronary distribution where myocardial ischemia has been demonstrated on noninvasive testing. With modern techniques of CPB and myocardial protection, incomplete revascularization is rarely justifiable because of its known deleterious effects on short- and long-term outcomes.¹⁰⁰ Failure to bypass a functionally significant and stenosed coronary artery should therefore be exceptional and result from severe comorbidities, from nongraftability, from diffuse

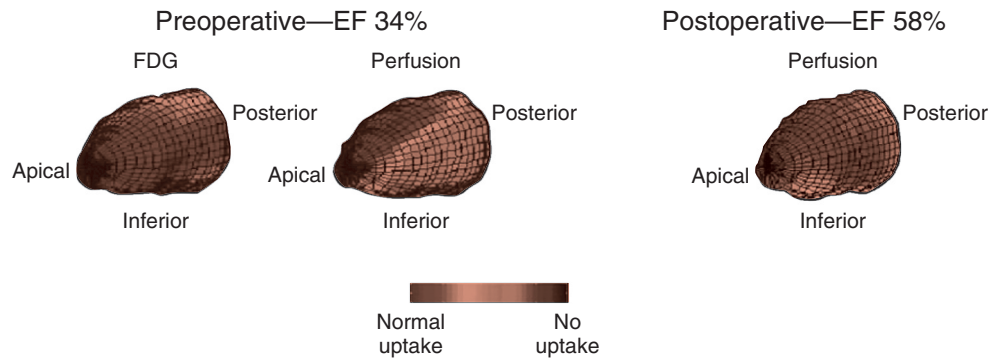


FIGURE 88-2 ■ Myocardial viability assessment. This patient with congestive heart failure symptoms and inferior wall akinesis was evaluated prior to coronary artery bypass grafting (CABG) with ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography and perfusion scintigraphy. Depressed ejection fraction (EF), viable myocytes (indicated by the normal FDG uptake), and the presence of a large posteroinferior perfusion defect were identified preoperatively. After CABG, the perfusion defect disappeared and the EF normalized. (Courtesy Robert S. Beanlands MD, Chief of Cardiology, University of Ottawa Heart Institute).

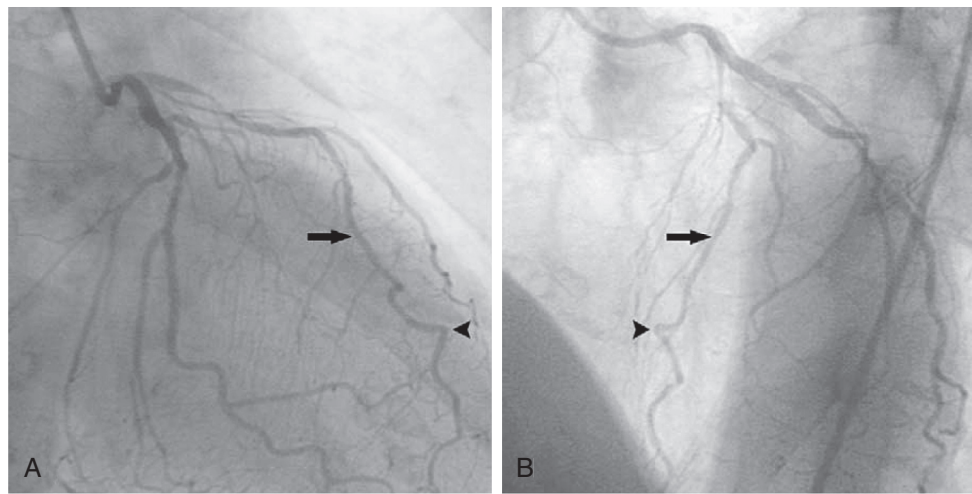


FIGURE 88-3 ■ Intramyocardial left anterior descending artery (LAD). The LAD goes downward (arrows) and, after several centimeters, upward on the angiogram (arrowheads). **A**, Right anterior oblique projection. **B**, Left anterior oblique projection.

aortic and branches calcification with inability to perform Y- or T-grafting, from conduit shortage, or from significant, unexpected intraoperative problems.

An intramyocardial LAD can be a vexing problem. Because LITA-LAD grafting provides a significant survival benefit in CABG patients,¹⁰¹ the failure to graft a stenosed LAD because of its intramyocardial location is clearly suboptimal. However, the situation can be identified preoperatively by seeing the vessel going downward and, after several centimeters, upward on the angiogram or by noticing that the LAD goes straight down to the apex without any curve (Fig. 88-3). Epicardial Doppler or retrograde probing of the LAD after performing a minute arteriotomy at its apical portion (or alternatively on a minor diagonal branch) can be used intraoperatively to identify the LAD at its proximal or mid portion.

Conduit Selection

Internal Thoracic Artery Grafts

The ITA is the preferred conduit for CABG and provides short- and long-term survival benefits in all patient subgroups, including those 75 years of age and older.¹⁰¹⁻¹⁰⁵

The steps in preparing the ITA conduit are described in Figure 88-4. Use of the LITA to graft the LAD (or a main target vessel on the left coronary circulation if the LAD is free of disease) should be performed except in rare circumstances such as preexisting or iatrogenic damage to the LITA, poor flow from severe spasm or dissection, significant ipsilateral subclavian stenosis, demonstrated involvement of the LITA in providing collateral supply to the lower extremity, mediastinal irradiation (if other arterial conduits are available), and emergency CABG with cardiogenic shock.

Bilateral ITAs should be used whenever possible, as this is associated with lower reoperation rates, lower late PCI rates, and possible long-term survival benefits.¹⁰⁶⁻¹¹⁰ Possible contraindications to the use of bilateral ITAs include emergency operation, insulin-dependent diabetes mellitus, obesity, and severe COPD for which the patient requires oral or intravenous glucocorticoid therapy. After decades of debate, use of bilateral ITAs appears not to increase the incidence of deep sternal wound infection except in emergent cases, in patients older than 70 years, and in patients with type I diabetes.^{109,111,112}

Skeletonization of an ITA involves dissection of the ITA without the accompanying periarterial venous and

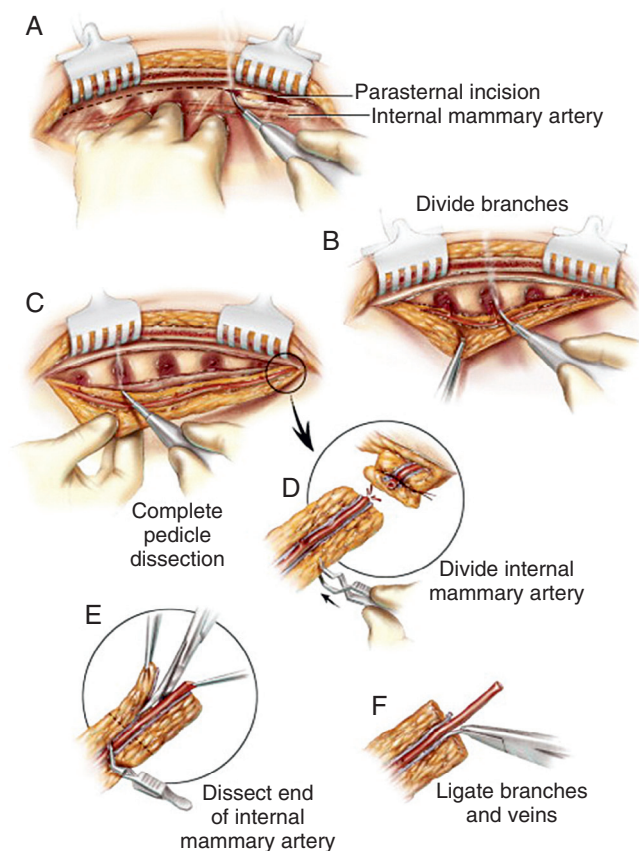


FIGURE 88-4 ■ Preparation of the internal thoracic artery. **A**, After exposure of the posterior surface of the sternum and ribs, electrocautery is used to make an incision along the entire length of the sternum, medial to the internal thoracic artery (ITA). **B**, Cautious tension is applied posteriorly to expose the ITA branches, which are clipped and divided. Blunt dissection is used to mobilize the pedicle in areas with no branches. **C**, After all the branches are clipped, an incision is made lateral to the pedicle to free it from the chest wall along its entire length. **D**, After administration of heparin, the pedicle is divided and the distal end is ligated. Forceful blood flow should be expected from the proximal end. A vascular clamp is applied to the proximal pedicle to control blood flow. **E**, The distal end of the arterial conduit is dissected free from the surrounding venae comitantes and tissue, and **F**, the venae comitantes are clipped. (Adapted from Doty DB, Doty JR, editors: *Cardiac surgery operative technique*, ed 2, Philadelphia, 2012, Saunders, p 409, Figure 36-6.)

fascial tissue. Given that the ITA is a delicate structure, meticulous attention must be paid to avoid artery damage, dissection, or both. Data support the notion that skeletonized ITA use does not impact long-term survival or graft patency, while decreasing sternal wound complications.^{109,113-118} The benefits in vascularity are correlated with decreased sensory deficits to the precordium.¹¹⁹ Patients older than 75 years also appear to benefit from the sternal vascularity benefits of skeletonized ITA use.¹⁰² Excellent results have been reported with the use of skeletonized bilateral ITAs in diabetic patients, and yet some studies showed obese diabetic women had an increased incidence of deep sternal wound infection.^{120,121} Other studies, however, found no association between skeletonized bilateral ITA harvesting in diabetic patients and sternal wound infection.¹²²

Whether a free or pedicled ITA graft is performed makes little difference with respect to patency and endothelial function, provided that a flawless anastomotic technique is used.^{123,124} It is more important to avoid short conduit length, which may invariably lead to angle distortion and resultant compromise in flow and patency. A pedicled ITA graft that appears too short is better cut proximally and repositioned onto the aorta or onto another ITA than left under tension.

In some patients, ITA flow may be very low (i.e., less than 20 mL/min) prior to construction of the anastomosis. This may be because of spasm, small size, or intraoperative injury such as an intimal dissection. If an area of injury is suspected, the ITA should be either converted to a free graft (if long enough) or transected a few millimeters above and below the injury site, the two stumps beveled, and an end-to-end anastomosis performed with 8-0 polypropylene. If no injury is apparent, the ITA in most cases may still be used for grafting, as this does not appear to result in an increased incidence of angiographic string sign or graft occlusion at 1 year postoperatively.¹²⁵ Unrecognized ITA intimal dissections in some cases may spontaneously heal with anticoagulation, antiplatelet therapy, and vasodilators alone.¹²⁶

Radial Artery Grafts

Controversy exists regarding the benefit of the radial artery as an alternative to the saphenous vein. More than five randomized controlled trials to date have compared the use of the radial artery with the saphenous vein as a conduit for CABG.¹²⁷⁻¹³⁴ At 1 year, the radial artery has been found to be equivalent to the saphenous vein in terms of angiographically determined patency.^{127,131,132} At 5 years, however, the radial artery appears to offer either slightly superior or similar patency rates compared with saphenous vein grafts.^{130,132,135} In patients older than 70 years at the time of operation, the use of the radial artery was associated with improved survival at 6 years.¹²⁸ Predictors of lower radial artery graft patency rates when compared with vein grafts include female patients and patients with peripheral vascular disease.¹³⁶ Although radial grafts are highly versatile and can be used for virtually any type of grafting configuration (e.g., aortocoronary, Y, or T), they should not be used to graft coronaries with less than 70% stenosis because of reduced patency and vulnerability for competitive flow physiology.^{137,138}

Intraoperatively, the radial artery may be treated immediately following harvest with a blood/phenoxybenzamine flush (100 mg of phenoxybenzamine mixed in 50 mL of heparinized blood) and left soaking in this mixture for 5 to 30 minutes. Phenoxybenzamine, a non-competitive α_1 -antagonist agent, is nontoxic for endothelial cells and highly effective in preventing acute spasm of the radial artery.^{139,140} In one larger study, phenoxybenzamine was shown to reduce the incidence of perioperative myocardial injury and adverse cardiac events.¹⁴¹ Alternatively, nitroglycerin can be used to dilate the radial artery prior to grafting. The steps in preparing the radial artery conduit are described in Figure 88-5.

Radial artery harvest is contraindicated in the presence of insufficient collateral supply to the hand or Raynaud

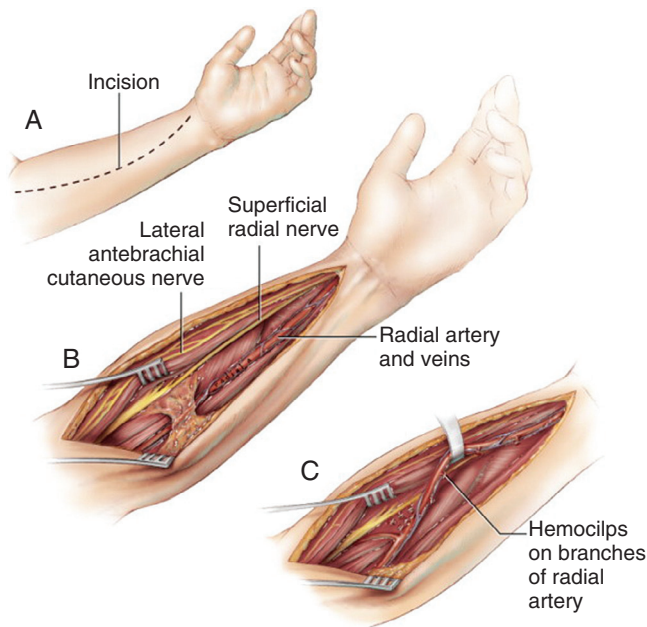


FIGURE 88-5 ■ Open radial artery harvest. **A**, An incision is made in the forearm following the brachioradialis muscle belly. As the dissection is carried deeper, the lateral antebrachial cutaneous nerve will lie lateral to the dissection plane along with the brachioradialis muscle. **B**, The deep fascia of the forearm is opened, exposing the radial artery and veins. The superficial radial nerve also lies lateral to the dissection. **C**, The radial artery and veins are mobilized by clipping branches and using blunt dissection of nonvascular tissue. A vessel loop is used to retract the conduit, avoiding excessive manipulation of the radial artery, which may induce spasm. The dissection is carried out proximally to the recurrent radial artery branch and distally to the fascia enclosing the tendons of the wrist. (Adapted from Doty DB, Doty JR, editors: *Cardiac surgery operative technique*, ed 2, Philadelphia, 2012, Saunders, p 417, Figure 36-9.)

syndrome, in patients with high manual demands such as professional musicians, in the very elderly (who have a high prevalence of radial arteriosclerosis and are unlikely to derive a survival benefit from its preferential use over a vein graft), during emergency operations, and in patients who are likely to require postoperative vasopressors, such as those with very poor left ventricular function. Radial artery use should be expressly discussed during informed patient consent, as the incidence of neurologic complications is approximately 30% and most often consists of decreased thumb strength and sensation abnormality.¹⁴² Diabetes, peripheral vascular disease, elevated creatinine levels, and smoking are associated with an increased incidence of these complications, which resolve with time in most patients.¹⁴³

In efforts to minimize radial artery graft spasm, the predominant cause of early graft failure, the radial artery can be harvested with surrounding perivascular tissues, thereby using an atraumatic “no-touch” technique. Next, replacing mechanical dilation of the free radial artery, pharmacologic dilation with papaverine (or phenoxybenzamine) may enhance nitric oxide production, resulting in decreased endothelial dysfunction. Finally, postoperative radial artery spasm prevention can be considered with either calcium channel blockers or nitrates.¹⁴⁴ Despite little evidence-based literature advocating

calcium channel blocker therapy for the prevention of radial artery graft vasospasm, more than 90% of Canadian surgical centers report routine use of calcium channel blocker prophylaxis lasting from several weeks to 6 months.^{15,145-147}

Endoscopic radial artery harvest gained popularity in the past decade because it provides better cosmesis and less pain compared with open harvesting.¹⁴⁸ Unlike the concern with regard to patency reported in endoscopic vein harvesting, mid-term patency using endoscopic radial artery harvesting seems equivalent to open harvesting.¹⁴⁹

Gastroepiploic Artery Grafts

The gastroepiploic artery is a conduit with a higher propensity for intraoperative problems and a lower postoperative patency than the radial artery. Excellent results have been reported by several groups who have developed an expertise with its routine use with 4- to 5-year patency rates of 86% to 90%.^{87,150-152} To date, there has been one randomized controlled trial comparing the use of the gastroepiploic artery with use of the saphenous vein graft.¹⁵³⁻¹⁵⁵ At 6-month angiographic follow-up, there appeared to be no differences in patency between conduits,¹⁵³ although it appeared the patency of the gastroepiploic artery was more influenced by competitive coronary flow.¹⁵⁴ Despite these encouraging results, several factors make it a difficult conduit to systematically recommend: harvest elicits spasm, kinking and torsion may go unrecognized, and anastomotic problems are more likely the result of the small size of the vessel. One study has suggested that use of the gastroepiploic artery to graft coronaries with only moderate proximal stenosis (70% to 80%) or with poor runoff should be avoided, because this results in decreased patency,¹⁵⁶ whereas another study has suggested that its use as a free graft is also associated with a lower patency than the in situ configuration.¹⁵⁷ Based on this evidence, alternative arterial conduits, or possibly saphenous vein conduits, should be exhausted before considering use of the gastroepiploic artery as the conduit of choice for primary revascularization. Moreover, a recent review emphasized that compared with vein graft patency rates, gastroepiploic artery patency rates were inferior during right coronary artery grafting.¹⁵⁸

Saphenous Vein Grafts

Because of their lower short- and long-term patency compared with ITAs, saphenous veins have not been the conduit of choice for CABG for approximately 20 years.¹⁰¹ Nevertheless, saphenous veins are the most often used and remain useful in several situations. They constitute the most readily available CABG conduit, provide immediate and reliable coronary flow with a low propensity for spasm or severe compromise during low-output states, and constitute a time-honored means of coronary revascularization during emergency procedures or in patients with severe comorbidity and limited life expectancy in whom procedural simplicity, expeditiousness, and reliability are most desirable. Furthermore, current-era

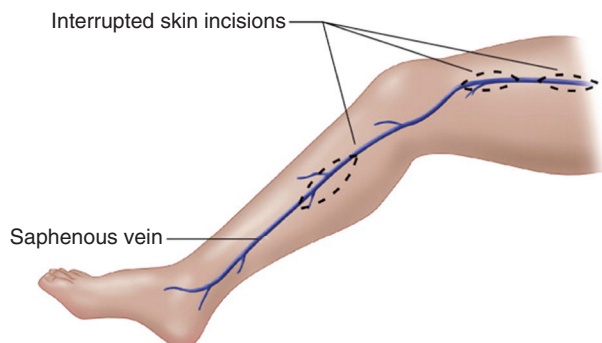


FIGURE 88-6 ■ Interrupted skin incisions to harvest the greater saphenous vein. Compared with a long leg incision, skip incisions provide more cosmesis and lower infection rates while allowing for a direct-vision harvest of the vein. (From Sellke F, Ruel M, editors: *Atlas of cardiac surgical techniques*, Philadelphia, 2009, Saunders.)

antiplatelet and cholesterol medical therapy may improve saphenous vein graft patency beyond that reported in initial CABG series.^{28,159,160} Several groups have demonstrated saphenous vein graft patency rates surpassing radial artery patency rates especially when conduits are grafted to moderately diseased arteries¹⁶¹⁻¹⁶³; furthermore, a recent meta-analysis demonstrated higher side-to-side sequential vein graft patency compared with single vein grafts.¹⁶⁴

A variety of minimally invasive techniques are widely available for retrieval of the saphenous vein. The spectrum of techniques range from skip incisions (Fig. 88-6) to the use of commercially available endoscopic systems.^{165,166} These techniques have been shown to improve patient quality of life and lower harvest site infections.^{167,168} On the opposite end of the spectrum, some centers have advocated the use of pedicled saphenous veins to improve on conduit patency and reduce venospasm.¹⁶⁹ Results from three small randomized controlled trials comparing the no-touch saphenous vein harvesting to conventional harvesting demonstrated superior patency rates at mid-term (18 months) and long-term (8.5 years) follow-up along with improved endothelial integrity.¹⁶⁹⁻¹⁷² With more centers performing this technique, further investigation is needed to elucidate the best method for vein harvesting.

Similar to the radial artery, endoscopic vein harvesting was met with enthusiasm a decade ago as studies showed improved cosmesis and lower infection rates compared with open harvesting.^{173,174} However, excitement was tempered by a large study reporting lower patency rates and higher rates of death, MI, or repeat revascularization at 3 years compared with open harvesting.¹⁷⁵

Other Conduits

The lesser saphenous vein, inferior epigastric artery, and right gastroepiploic artery are three alternative autologous conduits. They are rarely needed for primary revascularization, but they may be useful in patients lacking conduit options. Finally, in rare circumstances, cadaveric cryopreserved saphenous veins, bovine

chemically treated ITAs, or expanded polytetrafluoroethylene grafts can be used.

Operative Preparation

Intraoperative preparation by the anesthesiologist includes upper extremity peripheral intravenous and arterial access (contralateral to the side of radial artery harvest), induction of general anesthesia, endotracheal intubation, central venous access, and occasionally placement of a pulmonary artery catheter. Intravenous antibiotics with gram-positive coverage are administered 30 to 60 minutes prior to the skin incision. Perioperative antibiotic regimens vary on institutional practices, but often include cefuroxime (1.5 g intravenously [IV] every 12 hours) or cefazolin (1 to 2 g IV every 8 hours for 48 hours); in patients with penicillin allergy, vancomycin (1 g IV every 12 hours) is continued for at least two doses until lines and tubes are removed.¹⁷⁶ A nasogastric tube and transesophageal echocardiography probe, if available, are advanced in the esophagus. Baseline measurements of filling pressures, cardiac output, valvular and ventricular function, arterial blood gases, activated clotting time, hematocrit level, and electrolyte levels are obtained prior to the surgical incision.

The patient is prepared and draped, and a limited midline skin incision is made from the manubrium of the sternum to the xiphoid process. If use of a gastroepiploic artery is planned, the median sternotomy skin incision is carried 2 to 3 inches below the xiphoid. Median sternotomy is performed through this incision by slightly mobilizing the subcutaneous fat in the upper portion of the wound away from the pectoralis muscle while an assistant retracts it superiorly and by proceeding from bottom to top of the sternum with the saw. The assistant then starts harvesting the radial artery, saphenous vein, or both. Meticulous hemostasis is ensured at all stages (unless the patient is acutely ischemic or hemodynamically unstable), because this prevents continuous oozing during the remainder of the operation, minimizes the use of the cardiotomy suction with its potential detrimental effects, prevents coagulopathy, and effectively saves time before closure. Our preference is to open the pericardium before harvesting the ITAs, because this does not lengthen the procedure. In addition, this allows not only digital assessment of the aorta and the performance of epiaortic scanning early in the operation (with the planning of alternate cannulation sites and no-touch Y arterial grafting if significant aortic disease is unveiled), but also the identification of target vessels, the estimation of needed conduit length, and the expeditious cannulation if sudden hemodynamic collapse occurs. Epiaortic scanning is useful as a routine adjunct and can detect ascending aortic atherosclerosis in up to 30% of patients undergoing isolated CABG.¹⁷⁷ Contemporary guidelines recommend intraoperative transesophageal or epiaortic scanning of the aorta to detect nonpalpable plaque (class I, evidence B) and reduce the cerebral embolic load (class IIa, evidence B) in patients at high risk of experiencing a perioperative neurologic event.¹⁷⁸ If epiaortic scanning is unavailable, the incidence of perioperative CVA after CABG can still be minimized by routine preoperative

carotid screening, intraoperative transesophageal echocardiography, and a tailored approach to revascularization, thereby avoiding manipulation of the diseased aorta. This includes the use of alternate cannulation sites, fibrillatory arrest, and off-pump revascularization techniques; in a series of more than 6000 CABG patients in whom this approach was used, Trick and coworkers reported a stroke incidence of less than 1%, even in high-risk patients.¹⁷⁹

The ITAs are harvested and are transected distally only after systemic administration of heparin. There are two ways to perform this while minimizing bleeding during harvest of the second ITA: either a partial dose of heparin (e.g., 5000 to 10,000 units) is given at the completion and prior to transaction of the first ITA (with a completion dose administered prior to transaction of the second ITA), or both ITAs are transected at the same time after the second ITA has been harvested and the full dose of heparin given.

Cardiopulmonary Bypass and Cardioplegia

CPB is established with ascending aortic cannulation, right atrial venous cannula drainage, mild hypothermia (32° to 34° C), and alpha-stat pH management. Venting is performed via the proximal ascending aorta by using the antegrade cardioplegia delivery catheter, often at a site to be used later for a proximal anastomosis. Antegrade intermittent cold blood cardioplegia provides adequate myocardial protection for most primary revascularization cases; consideration is given to a combination of antegrade and retrograde routes in severely ischemic patients or when the LAD is obstructed or severely stenotic.¹⁸⁰ Topical cooling makes little difference on myocardial temperature and outcome when combined with antegrade cold blood cardioplegia and has been associated with an increased incidence of postoperative hemidiaphragmatic paresis and pleural effusions.¹⁸¹

Intraoperative transcranial Doppler scanning of the middle cerebral arteries, if available, constitutes a useful adjunct during CPB cases. In our experience, it has helped design minor but effective modifications in cannulation, perfusion, clamping, and venting techniques that have minimized the frequency and overall number of high-intensity transient signals.¹⁸² Use of the cardiomy suction is best avoided because of its potentiation of clotting activation, micelle formation, and microembolism during perfusion. It can be replaced by a cell-saver device during routine cases. Moderate hypothermia and slow rewarming as well as meticulous control of blood glucose levels can also help decrease the incidence of postoperative neurocognitive deficits.^{183,184}

Special Situations

Diffuse Aortic Disease. One of the most formidable technical obstacles that can be encountered during CABG is diffuse disease of the aorta and its branches. Manipulation of a diseased aortic segment may lead to embolization and constitutes the most important risk factor for stroke after CABG.¹⁸⁵ If the aortic disease is focal and does not involve the distal third of the ascending aorta,

the area can usually be avoided during cannulation, clamping, and construction of proximal anastomoses (under single cross-clamping). Multifocal disease, diffuse disease, or disease involving the distal third of the ascending aorta, however, mandates the use of femoral or axillary artery cannulation; the relocation of proximal anastomoses to the proximal ascending aorta, brachiocephalic artery, or descending aorta; the use of hypothermic fibrillation or hypothermic circulatory arrest; and, in some cases, ascending aortic replacement. Fortunately, widespread familiarity with off-pump and Y-grafting techniques has significantly increased the options for managing patients with diffuse aortic disease. In most cases of diffuse aortic disease, an off-pump aortic no-touch CABG operation with bilateral pedicled ITAs or Y or T arterial graft configuration can be performed with acceptably low risk, provided the patient is hemodynamically stable and not acutely ischemic.¹⁸⁶ If refractory hemodynamic instability develops, the patient must be managed with cannulation of the axillary or femoral artery,¹⁸⁷ establishment of CPB, hypothermic fibrillatory arrest during performance of distal anastomoses, and construction of the proximal anastomoses to the innominate artery or to a disease-free area of the ascending aorta using a special, local-control device¹⁸⁸ or during a short period of hypothermic circulatory arrest.⁸³

Preoperative Cardiogenic Shock. Preoperative cardiogenic shock requires immediate establishment of CPB, performed either via femoral cannulation or sternotomy depending on patient characteristics (such as redo operation or a history of previous aortobifemoral grafting) and the surgeon's preferences. If time and hemodynamic status allow, patients should have an intra-aortic balloon counterpulsation pump inserted preoperatively or stabilized with a nondurable percutaneous mechanical circulatory support device such as the Impella 2.5 or 5.0 (Abiomed, Danvers, MA).^{189,190} Combined antegrade and retrograde cardioplegia delivery with warm induction and warm reperfusion techniques can have a net benefit in those patients. Although consideration is given to the use of one ITA graft if the patient is hemodynamically stable, the use of an all-saphenous vein operation is appropriate because of high immediate myocardial demands and anticipated need for postoperative inotropes.¹⁹¹ Revascularization involves the performance of at least one graft to each ischemic myocardial territory.

Medication-Related Coagulation Impairment. Whether the use of antifibrinolytics is mandated in routine CABG cases remains controversial. Recently, the serine protease inhibitor aprotinin has come under scrutiny. Previous reports had suggested that aprotinin may adversely impact renal, myocardial, cerebral, and pulmonary function.¹⁹²⁻¹⁹⁵ In an observational trial involving 3876 patients, Mangano and colleagues found that aprotinin use was associated with an increase in overall mortality at 5 years.¹⁹² Following publication of this study, use of aprotinin dropped precipitously, although some studies have suggested that patients undergoing off-pump CABG may in fact benefit from aprotinin use.^{196,197}

Advances in antiplatelet therapy have revolutionized the management of patients with CAD; however, the antiplatelet effects can also impact postoperative hemostasis.¹⁹⁸ Transfusions of platelets, fresh-frozen plasma, and cryoprecipitate may therefore be needed in these patients. Patients on abciximab may benefit from the routine administration of a single platelet transfusion after protamine administration; this approach appears to decrease the rate of reexploration for bleeding.¹⁹⁹

Previous Tracheostomy. The presence of a tracheal stoma in patients with previous total laryngectomy who require cardiac operations is associated with an increased risk of wound complications, mediastinitis, tracheal injury, or stoma necrosis when a full sternotomy is used. In these patients, a manubrium-sparing sternotomy can be used, where the upper edge of the sternotomy does not extend beyond the top of the third rib. Slow progressive opening of the retractor allows for the operation to be conducted successfully while minimizing the possibility of manubrial fracture, bleeding, and patient discomfort. An alternative approach is to incise the sternum transversely at the second intercostal space and complete the median sternotomy longitudinally down to the xiphoid process.²⁰⁰

Distal Anastomoses

Construction of distal coronary anastomoses begins once the first dose of cardioplegia has been delivered. With current methods of myocardial protection and considering the increased prevalence of diffuse CAD in CABG patients, there is little justification for performing proximal anastomoses first during on-pump CABG. Proximal anastomoses are constructed either sequentially (each distal followed by its proximal under single cross-clamping) or all at once after completion of distal anastomoses. One exception to this approach is during performance of arterial Y- or T-grafting, because the surgeon may complete all proximal conduit anastomoses onto one to two pedicled ITAs prior to the establishment of CPB; this strategy minimizes unnecessary CPB time and allows for the assessment of free flow in each ramus of the configuration prior to distal grafting.

Although the order of revascularization is not of critical importance during on-pump CABG, the first graft performed is usually that to the inferior circulation, followed by the lateral wall, the diagonal system, and the LAD artery. Vessels that are completely occluded and for which a free graft is planned may benefit from construction of the distal anastomosis early in the revascularization sequence to improve cardioplegic delivery to the subtended myocardium.

Many conduit-graft configurations are possible, and the choice is based on the needs of the patient. The pedicled LITA is usually grafted to the LAD, although the pedicled right internal thoracic artery (RITA) can also be used with success and placed in the superior mediastinum to decrease the risk of injury during subsequent sternotomy. The next preferred conduit (i.e., the second ITA, followed by the radial, gastroepiploic artery, and saphenous vein) is kept for the target vessel in decreasing

order of anatomic importance. Poor-quality, diffusely diseased coronary arteries do not necessarily only deserve a vein graft, as the short- and long-term patency of an ITA or radial graft to a diffusely stenotic vessel may be considerably better. Conduit length problems resulting in inappropriate anastomotic tension are almost always solvable by the use of arterial Y-grafts, which are avoided with saphenous veins because differences in conduit size can result in unpredictable flow patterns.

Exposure of the main coronary branches is not problematic during on-pump CABG. The inferior wall may be exposed by packing a small sponge against the inferior vena cava at the right inferior aspect of the oblique sinus. The lateral wall may be exposed by gently twisting and folding the heart on itself in the long axis and placing a sponge underneath to expose the marginal branches. The anterior wall is exposed by a single sponge under the left ventricle.

The most proximal disease-free portion of the coronary artery to be grafted (i.e., immediately after the most distal involvement) is selected for the anastomosis. The epicardium is incised over the area of the coronary artery with a no. 15 blade or a special rounded blade. The anterior surface of the artery is cleared by gentle transverse brushing with the scalpel. Even with cardioplegia, careful inspection of the artery will reveal a thin central line that is red or translucent, indicating the lumen. The anterior wall of the artery is opened longitudinally over this line by caressing gently with the scalpel so as to not damage the posterior wall. Administration of a small amount of cardioplegia to distend the coronary artery lumen may be useful during this step, especially for small (≤ 1 mm) vessels. Occasionally, when the anterior wall of the artery cannot be placed under proper tension, it may be opened by stabbing it with a sharp-pointed scalpel. The blade must enter the artery obliquely and superficially, so as to not penetrate the posterior wall. The incision is enlarged with angled scissors to a length of 4 to 6 mm for end-to-side anastomoses, and 3 to 5 mm for side-to-side anastomoses. The epicardial incision is extended beyond each angle of the arteriotomy to facilitate the anastomosis. The artery may be sized and proximal, and distal patency can be assessed by passing measuring probes into it. Aortic root venting is used only as necessary so as to not introduce an excessive amount of air into the ascending aorta. The distal end of the conduit is incised longitudinally for approximately 20% longer than the coronary arteriotomy; this in conjunction with slightly further spacing of suture bites on the conduit than on the coronary enables the desirable "cobra head" appearance (Fig. 88-7).

Many anastomotic techniques exist, each with advantages and disadvantages. For the sake of reliability under all circumstances, each surgeon should probably limit himself or herself to one main anastomotic technique that is perfectly mastered and can be used with all conduit types, for end-to-side as well as side-to-side anastomoses, and during on-pump as well as off-pump CABG. General principles include the use of 7-0 or 8-0 polypropylene, the use of a no-touch technique in which the intima of the coronary and the conduit are never grabbed, and compulsive attention to the geometric distribution of sutures as the anastomosis is performed, because an

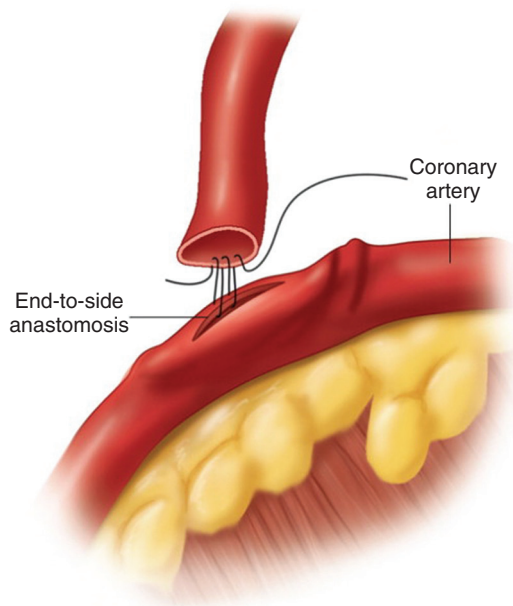


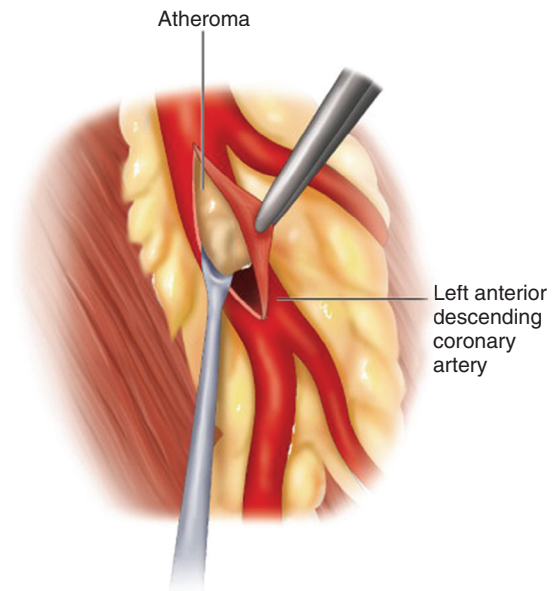
FIGURE 88-7 ■ End-to-side distal anastomosis. After incising the epicardium over the selected coronary artery using a no. 15 blade, an arteriotomy is performed to match the end of the graft. The graft is anastomosed onto the coronary artery using a running 7-0 polypropylene suture. Constant attention is given to the overall anastomosis geometry. (From Sellke F, Ruel M, editors: *Atlas of cardiac surgical techniques*, Philadelphia, 2009, Saunders.)

otherwise adequate but deformed anastomosis may be nonfunctional or prone to thrombosis. Another principle we enforce is that no impediment to native coronary flow should result from construction of an anastomosis, therefore mandating flawless patency at both anastomotic angles so that if for some reason the conduit becomes nonfunctional, native coronary flow will at least be the same as if a bypass graft had not been performed onto this coronary artery.

We prefer to use sequential grafts within a single coronary distribution only (e.g., for two marginal branches of the circumflex system), to avoid possible flow diversion from one myocardial territory to another. Other groups have reported good results using a T-graft configuration that may bridge two or even three myocardial territories.^{186,201} In general, sequential grafts allow for a greater number of arterial anastomoses and, with vein grafts, contribute to an increased long-term patency.^{163,201} Transverse sequential side-to-side anastomoses may be used for saphenous vein grafts with excellent patency rates¹⁶⁴ but are relatively contraindicated with arterial grafts. Perfect orientation of the sequential arterial anastomoses with respect to each other and avoidance of tension or excessive redundancy on the conduit are crucial. Because of the potential to jeopardize revascularization of two or more vessels, any sequential graft that might appear technically unsatisfactory is best redone or replaced with individual grafts.

Coronary Endarterectomy

Coronary endarterectomy is a technique that preceded the invention of CABG.⁵ It is now reserved for select



A



B

FIGURE 88-8 ■ Coronary endarterectomy. **A**, Representative illustration of a large atheroma removed from the left anterior descending artery. **B**, Specimen removed from a completely occluded right coronary artery and subsequently bypassed with a saphenous vein graft. (Courtesy Dr. John Veinot, Department of Pathology, Ottawa Hospital, Ottawa, Ontario, Canada.)

cases of severe diffuse disease where no anastomotic site can be found on a coronary artery that supplies an ischemic and viable myocardial territory (Fig. 88-8). This procedure should not be used because of technical failure to find the true lumen, such as occurs when a diffusely diseased vessel is mistakenly opened into a lateral plaque. Arteries that can be seen on coronary angiography do have a lumen, which can be found despite poor target site selection or extraluminal opening by carefully extending the arteriotomy proximally and distally into the true lumen and performing a long patch angioplasty by using the conduit as an onlay patch. Endarterectomy should also only be used on vessels with high-grade stenoses (>80%). Endarterectomy is combined with an onlay patch angioplasty of the endarterectomized vessel, and a bypass graft is performed using the same conduit. When reserved for carefully selected situations, coronary endarterectomy has been associated with a rate of

perioperative MI of 5% or less, a graft–coronary axis patency of 72% at 30 months, and a good functional outcome that can approach outcomes seen in non-endarterectomized patients.²⁰²⁻²⁰⁴

Sutureless Distal Coronary Connectors

Significant advances have been made with automated coronary connectors and self-closing U-clip distal anastomotic devices. Preliminary reports on the use of these devices in humans describe geometrically adequate anastomoses, excellent immediate graft flows, and good patency at 3- and 6-month angiographic follow-up.²⁰⁵⁻²⁰⁷

Proximal Anastomoses

Most proximal anastomoses are made on the ascending aorta, but alternative sites such as the brachiocephalic artery, axillary artery, and descending aorta can be used in special situations. Y- and T-grafting involves constructing the inflow anastomosis of a free arterial graft to an in situ arterial conduit, using either an end-to-side or a side-to-side configuration. General principles of proximal anastomosis construction include insurance of a perfect graft lie (i.e., without torsion, tension, or excessive redundancy) and the minimization of aortic manipulations.

Although preferences vary, the use of a side-biting tangential clamp is best avoided because of its association with increased cerebral microembolic load and S-100 release during CABG.²⁰⁸ In our experience, several techniques can be used to reduce this embolic load to levels equal or below that of single aortic cross-clamp proximal techniques. These consist of (1) using a tangential side-biting clamp only in the presence of a nondiseased ascending aorta (Fig. 88-9), (2) releasing the cross-clamp and applying the side clamp while the pump is momentarily stopped, (3) irrigating the inside of the aorta after punch holes are made, (4) completely displacing air prior to tying the last proximal anastomosis either by saline instillation or by removal of the bulldog clamp on one of the anastomosed free arterial grafts, which backfills the aorta with blood, and (5) releasing the clamp while the pump is momentarily stopped.

To perform a proximal anastomosis a longitudinal slit, approximately 3 mm in length, is made with a no. 11 blade at the chosen site(s) in the aorta. A punch of either 4.0 (for free arterial grafts) or 4.5 mm (for saphenous vein grafts) in diameter is slipped completely and freely into the aorta through each slit and closed so as to punch out a circular piece of aorta at each site (see Fig. 88-9). Each conduit is irrigated intraluminally and its orientation determined under direct vision, measured so as to not prove too short or redundant once the heart fills (pinching of the venous line to fill the right heart is useful in evaluating this), occluded with a light bulldog clamp, spatulated at its proximal end to a perimeter approximately 20% longer than the aortic punch hole, and connected to the aorta using 6-0 polypropylene. If an arterial conduit appears too short, either it is anastomosed in an end-to-end fashion onto a short segment of saphenous vein, which is itself anastomosed to the aorta, or the

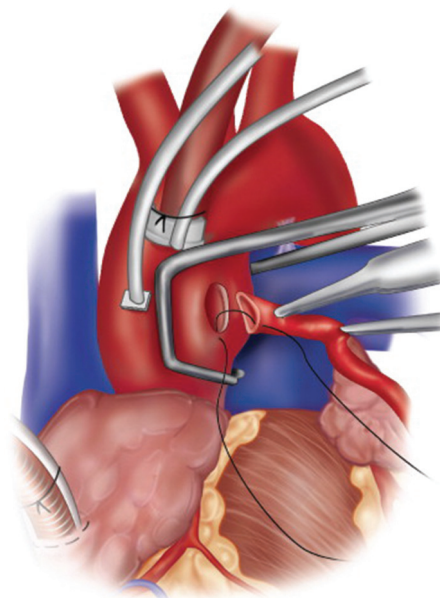


FIGURE 88-9 ■ Proximal anastomosis using a side-biting clamp. With the use of a side-biting clamp and after a small (4- to 4.5-mm) aortotomy is performed, the proximal anastomosis is accomplished with a running 6-0 polypropylene suture. (From Sellke F, Ruel M, editors: *Atlas of cardiac surgical techniques*, Philadelphia, 2009, Saunders.)

arterial graft is anastomosed side-to-side (as a Y-graft) onto another arterial graft.

Sutureless Proximal Coronary Connectors

Commercially available automated proximal aortic connectors have been used successfully by a growing number of groups with good patency rates; however, a prospective randomized controlled trial is needed to explore some concerns regarding early graft closure.²⁰⁹⁻²¹³ Advantages of these connectors include the avoidance of aortic manipulations (except at the anastomotic site) and ease of use, especially for off-pump or robotic-assisted procedures.

Intraoperative Graft Assessment

The high prevalence of small and diffusely diseased target vessels in CABG patients and the increasingly challenging surgical techniques used (such as complex arterial grafting and off-pump procedures) may justify routine graft validation in the operating room. One practice, although subjective, is to gently probe each anastomosis at critical points during construction to ensure proximal, distal, and conduit patency, and rule out a purse-string effect that may insidiously occur if too large or too few bites are taken around the anastomosis, if its geometric configuration is imperfect, or if the assistant pulls excessively on the suture when “following.”

The most widely used modality of objective graft assessment is transit-time flow measurement (TTFM). With this tool, a diastolic-to-systolic perfusion pattern of at least 2 : 1 for grafts constructed to vessels overlying the left ventricle (such as the LAD and circumflex branches)

and a pulsatility index less than 3 are a good predictor of patency, whereas low absolute flow values can be the result of arterial spasm without anastomotic error.^{214,215} Unfortunately, specific cut-off recommendations for graft revision have not been clarified and TTFFM remains imperfect in detecting less than critical stenosis on the graft or at the anastomosis, regardless of the adjunctive use of spectral or fast Fourier transformation analysis.²¹⁶ Other modalities such as high-frequency epicardial echocardiography and power Doppler imaging have been described, but experience is still limited.²¹⁷ Thermal imaging has limited image resolution and is largely unsuitable for off-pump or minimally invasive surgery.²¹⁸

Intraoperative fluorescent cardiac imaging is clinically safe and may prove clinically useful.²¹⁹ This modality uses a 0.5-mL injection of indocyanine green and a portable imaging device to visualize coronary anatomy and grafts during conventional CABG, off-pump coronary artery bypass (OPCAB), or minimally invasive direct coronary artery bypass (MIDCAB). Graft and coronary visualization is very good, but anastomotic resolution needs improvement and overlying fat or muscle can artificially obscure the penetration and detection of indocyanine green (ICG) fluorescence. The modality works best with skeletonized arterial grafts and saphenous vein grafts.

Routine intraoperative completion angiography in the setting of a hybrid operating room has shown, in one study, that up to 12% of bypass grafts may have important angiographic defects that need to be addressed intraoperatively.²²⁰ Further studies are needed to clarify the role of completion angiography in hybrid revascularization.

Weaning from Cardiopulmonary Bypass

Once the proximal anastomoses are completed, each vein graft is de-aired with a 27-gauge needle prior to release of the bulldog clamp. Graft conduits are examined for adequateness of lie and hemostasis at each anastomotic site and side branch while the mean arterial pressure is increased to at least 70 mm of Hg. Distal anastomotic jet bleeding is repaired with a single stitch of 7-0 Prolene; if the toe or heel is involved, repair may compromise the anastomosis, and consideration is given to preparing cardioplegia and reapplying the cross-clamp to redo the anastomosis. It is preferable to spend 10 to 15 extra minutes in redoing an anastomosis that has a significant leak at or near the angle than repairing it with a potential for distortion or occlusion. The epicardium may be used to cover and repair small lateral anastomotic leaks but should not be used near an anastomotic angle.

Preparation of the patient for weaning from CPB involves a routine but thorough assessment of the cardiac, pulmonary, and metabolic systems. The chosen temperature for weaning, a point of current controversy, is reached by slowly rewarming the patient and avoiding hyperthermia.^{183,221} Hematocrit level and metabolic and electrolyte balance are checked and corrected as necessary. The trachea is suctioned and the lungs are reexpanded by hand under direct vision and mechanically ventilated with 100% O₂. Respiratory monitors and alarms are reactivated. The pleural spaces are checked for the presence of fluid or pneumothorax. Atrial and

ventricular epicardial pacing wires are affixed onto the heart and exteriorized on the chest, and heart rhythm and rate are optimized by using synchronized cardioversion or pacing as necessary. Sinus rhythm or atrial pacing at 75 to 95 beats per minute is ideal for weaning, although patients with significant diastolic dysfunction from left ventricular hypertrophy or with incomplete revascularization may benefit from a slower atrial rate in conjunction with a slightly prolonged atrioventricular interval. The ECG is examined for ST-segment changes suggestive of ischemia; if ischemia is present, reassessment and reconstruction of a graft must be considered.

The perfusionist progressively clamps the venous line to provide preload to the ejecting right ventricle, which in turn results in left ventricular preload. Afterload is managed by the anesthesiologist by using either an alpha-agonist agent such as phenylephrine or, in some cases, a direct vasodilator such as nitroprusside. Contractility is assessed by observing left and right ventricular contraction and the evolution of pulmonary arterial pressures during the weaning process, which are reflective of ventricular function, except in cases of pulmonary vascular hypertension. Several adjuncts may be used when weaning is difficult. First, each of the previously described steps is rechecked and corrected as necessary while CPB support is reestablished and a period of reperfusion on the empty beating heart is reinitiated. Second, consideration is given to ischemia or intracoronary air while grafts are reassessed. Third, inotropic support and intra-aortic balloon pump (IABP) are used as necessary. Inotropic and IABP use in nonemergency patients with good left ventricular function preoperatively is abnormal and warrants questioning the adequacy of revascularization (i.e., nonfunctional grafts, plaque or cholesterol embolism during the construction of anastomoses, grafting of wrong coronary vessels or even a coronary vein), and justifies a low threshold for redoing or adding one or several grafts. Further attempts at weaning from CPB are taken after reconsidering the previously mentioned points. If weaning is still unsuccessful after many attempts and clearly related to poor contractility, consideration is given to the use of extracorporeal membrane oxygenation or mechanical ventricular support as a bridge to recovery.

Once the patient is satisfactorily weaned from CPB, the venous cannula is removed and the atrial purse-string suture snared but not tied. The venous line is then sumped with normal saline to return blood to the heart-lung machine reservoir. The aortic line is checked for air that may have migrated from the left ventricle during cardiac ejection, and the perfusionist transfuses aliquots of remaining pump blood according to the directives of the surgeon and anesthesiologist. Excessive right ventricular distention and pulmonary diastolic venous hypertension of more than 22 to 25 mm of Hg are avoided. If these develop and mean arterial pressure is satisfactory, IV nitroglycerine is used as a preload reducer and pulmonary venodilator.

Protamine is administered once stable hemodynamics is achieved and when reestablishment of CPB for support or technical reasons is unlikely to be needed. Chest tubes are inserted in the posterior pericardium, in the anterior

mediastinum, and into each pleural cavity entered. Care is taken at ensuring that chest tubes do not lie in proximity to a graft once the chest is closed: not only could they mechanically compress the graft and lead to distortion and thrombosis, but they may also result in damage if the graft is entrapped into a side-hole of the tube during suction.

After administration of the first dose of protamine, the aortic cannula is removed from the ascending aorta in case of hemodynamic collapse caused by an adverse protamine reaction. Cannulation purse-string sutures are securely tied and reinforced with pledgeted stitches as needed. Hemostasis is checked at each anastomotic site, along each conduit, at all cannulation sites, and on the chest wall. If, despite these measures, blood accumulation is still noted in the pericardium, the left atrial appendage is examined for possible damage caused by the cardiotomy suction during CPB. Radio-opaque markers are left around proximal vein graft anastomoses. The pericardium is partially reapproximated over the anterior left ventricle but not closed to avoid adverse hemodynamic effects. Routine closure of the sternotomy incision concludes the operation.

SPECIAL FEATURES OF POSTOPERATIVE CARE

Early Postoperative Period

Despite unclear evidence, patients with a radial, gastroepiploic, or inferior epigastric artery graft are started on intravenous nitroglycerine or calcium channel blockers as soon as arterial blood pressure parameters allow. Nitroglycerine has been shown to be more effective, less costly, and safer (with a lower incidence of bradycardia and negative inotropy) than intravenous diltiazem.²²² Aspirin (650 mg) is given via suppository within 6 hours of operation and subsequently by mouth at a dose of 100 to 325 mg per day (class I).^{34,223,224} Patients treated concomitantly with clopidogrel are given a slightly lower aspirin dose (81 mg), although no evidence exists for this practice. It is a reasonable alternative to give clopidogrel (75 mg once daily) to patients who cannot tolerate aspirin (class IIa).⁴³ Most patients are extubated within 4 to 6 hours of CABG and discharged from the intensive care unit on the following morning (postoperative day 1). Chest tubes are removed when draining less than 100 mL per 12 hours, when no air leaks, and if the chest x-ray shows no significant residual effusion. Most patients experience surprisingly little postoperative pain, which is managed initially with intravenous narcotics and subsequently with oral codeine or hydromorphone. A short course of nonsteroidal anti-inflammatory drugs is added as an adjuvant in patients with normal renal function and without a history of peptic ulcer or CHF. Beta blockers and other antihypertensive medications are usually restarted at half-dose on the morning following the operation and progressively titrated back to the preoperative dose prior to hospital discharge. Mild to moderate dose statin therapy is now recommended in all patients undergoing CABG, whereas higher doses of statins may be

required to achieve at least a 30% reduction in serum LDL levels. Optimizing glucose control prior to and after surgery with either oral agents or intravenous insulin has reduced the incidence of adverse clinical outcomes. Patients with moderate left ventricular dysfunction (LVEF between 30% and 50%) and normal renal function are started on angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) regardless of symptoms.²²⁵ Our practice is to also start patients with radial or gastroepiploic grafts on daily amlodipine, which is more effective than diltiazem and more specific to the arterial vasculature than nifedipine.^{145,226} Atrial fibrillation prophylaxis varies according to personal surgeon and center preferences²²⁷; our approach consists in maximizing the use of beta blockers early postoperatively. The recent 2011 ACC/AHA guidelines recommend prompt (<24 hours) administration of oral beta blockers to all patients without contraindication to reduce the incidence of postoperative atrial fibrillation (class I).³⁴ Moreover, prophylactic regimens based on the administration of sotalol, amiodarone, and intravenous magnesium have been shown to be effective, although cost-effectiveness remains controversial.²²⁸⁻²³⁰ Patients are discharged home at a median of 5 days postoperatively and in some cases as early as the third postoperative day.

Late Postoperative Period

During the first 3 to 4 weeks after CABG, patients commonly have a poor appetite, insomnia, tiredness, lack of sexual desire, mild neurocognitive deficits, and depressed mood. These phenomena are related to the postoperative state and prove to be transient for most patients; reassurance from the surgeon is often all that is needed. Patients are encouraged to walk progressively as part of convalescence; from a minimum distance of 120 m when discharged from the hospital, patients should progressively increase their daily walking to 1 hour or more by the end of the first postoperative month. Lifting is limited to 3 kg during the first postoperative month, 10 kg during the second month, and 30 kg or less until 6 months after the operation. Structured cardiac rehabilitation programs are a useful adjunct, and patients are encouraged to join as soon as discharged from the hospital. Patients who have a normal convalescence can usually resume driving within 3 weeks of operation and return to work within 2 to 3 months. Patients who have a special occupation in which recurrent cardiac events could put the lives of others at risk (such as bus drivers and pilots) should undergo non-invasive cardiac testing to rule out ischemia prior to resuming work. Despite the invasiveness of CABG, studies looking at the quality of life in patients who participated in the SYNTAX and FREEDOM trials have revealed that quality of life in CABG patients surpasses that of PCI patients after only 6 months.^{231,232}

CABG represents only one of many treatment interventions for patients with CAD, as coronary disease continues to progress. Secondary prevention is essential after CABG: aspirin must be continued, smoking must never be resumed, second-hand smoke must be avoided, exercise must be encouraged, obesity if present must be addressed, lipid profile optimized, and hypertension and

diabetes strictly controlled. These factors have a significant impact on the progression of saphenous vein graft atherosclerosis and, by extension, can also benefit arterial grafts.^{233,234}

Beta blockers are progressively weaned 6 months following uncomplicated CABG in patients with no arrhythmias, no angina, normal ventricular function, and in whom other medications are used for antihypertensive therapy. Amlodipine is discontinued after 1 year in patients with radial or gastroepiploic grafts.²³⁵ Patients with moderate left ventricular dysfunction (LVEF < 40%) should be initiated or continued on ACE inhibitors or ARBs indefinitely, because this is associated with a reduced incidence of cardiac death, acute MI, and clinical heart failure.^{34,225}

RESULTS

Morbidity

The most common complications of CABG are postoperative bleeding, low cardiac output syndrome, MI, neurologic events, renal dysfunction, atrial arrhythmias, and sternal wound infections. Other complications are discussed in detail elsewhere in the book. The definition, incidence, prevention, and treatment of these complications are discussed here.

Postoperative Bleeding and Transfusion

Bleeding after CABG can be attributed to surgical and/or medical causes. Reexploration to control hemorrhage occurs in 2% to 6% of CABG cases²³⁶ and carries a 4.5-fold higher risk of mortality.²³⁷ Predisposing factors for postoperative bleeding and transfusion include advanced age, female gender, lower body weight, preoperative cardiogenic shock, anemia, renal dysfunction (especially dialysis-dependent patients), peripheral vascular disease, poor nutritional status, recent thrombolytic therapy, nonelective cases, repeat operations, and longer CPB times.²³⁷⁻²³⁹ Although this practice is not based on evidence, most surgeons use some variation of the following protocol to guide reexploration: (1) blood drainage from the chest tube more than 400 mL in the first hour after surgery, (2) more than 300 mL/hour in the first 2 hours, (3) more than 200 mL/hour in the first 3 hours, (4) more than 100 mL/hour in the first 4 hours, (5) sudden massive bleeding, (6) signs of cardiac tamponade, and (7) excessive bleeding despite correction of coagulopathy. Surgical causes of bleeding in CABG are usually cannulation purse-string leak, graft anastomosis leak, or bleeding from an ITA branch of stumps.

The medical causes of bleeding can include one or more of the following: depletion of coagulation factors by dilution, activation, and consumption as a result of CPB; quantitative and qualitative platelet abnormalities caused by preoperative antiplatelet medications or renal dysfunction, and the direct effect of CPB; hypothermia, which can impair thromboxane synthesis and suppress platelet aggregation; and residual heparin leading to rebound heparin effect.

Strategies to prevent excessive bleeding after CABG include meticulous surgical technique and hemostasis, prevention or reversal of intraoperative hemodilution, prompt reversal of hypothermia, detection and treatment of residual heparin effect with protamine, blood pressure control, administration of antifibrinolytics, and the use of recombinant activated factor VIIa in severe situations. The latter has been increasingly used in cardiac surgery, but the possibility of bypass graft thrombosis caused by a hypercoagulable milieu remains a theoretical concern.^{240,241}

The incidence of transfusion during primary on-pump CABG ranges from near 0% up to 50% with most centers transfusing approximately 20% of patients.²³⁸ Institution-specific guidelines dictate transfusion thresholds. Preoperative anemia is one of the most important predictors of blood transfusion.²⁴² Studies have shown that both preoperative anemia and perioperative blood transfusions are risk factors for mortality and morbidity including acute kidney injury, wound infections, prolonged ventilation, pulmonary problems, and longer length of stay.²⁴³⁻²⁵⁰ In a large contemporary study of 182,599 patients in the Society of Thoracic Surgery (STS) database,²⁵⁰ preoperative anemia (hematocrit < 33%) had a significant impact on perioperative morbidity and mortality compared to patients with preoperative hematocrit levels higher than 42%. In this study, each 5-point decrease in preoperative hematocrit was associated with 8% higher odds of death, 22% higher odds of postoperative renal failure, and a 10% increase in the risk of deep sternal wound infection. Perioperative blood transfusion was 88.5% in the anemia group compared to 32.5% in the groups with hematocrit levels higher than 42%. Karkouti and associates addressed preoperative anemia with prophylactic transfusion in a pilot trial²⁵¹ and found it did not improve outcomes. This was likely because of the risks of transfusion, which can cancel out the beneficial effects of treating the anemia. Therefore, alternatives to transfusion, such as detecting and managing preoperative anemia from a cause-based approach, must be sought.

Low Cardiac Output Syndrome

Low cardiac output syndrome (LCOS) after CABG is generally defined and accepted as requirement of inotropic medications or IABP insertion to keep systolic blood pressure higher than 90 mm Hg and cardiac index (CI) of more than 2.2 L/min/m² despite optimization of preload, afterload, electrolytes, and blood gas abnormalities for 30 minutes after surgery.²⁵² It occurs in 4% to 14% of isolated CABG cases and carries a 10- to 17-fold increase in mortality and significant increase in morbidity.²⁵²⁻²⁵⁴ Predictors of LCOS include advanced age (>70), female gender, diabetes mellitus, left main and triple-vessel CAD, low ejection fraction (<50%), redo or emergency surgery, recent MI, incomplete revascularization, long CPB time, and poor intraoperative myocardial protection.²⁵²⁻²⁵⁴ Management of LCOS involves thorough assessment of potential causes directed at the modification of correctable causes, such as immediate cardiac and graft catheterization and return to the operating room if necessary. Initially, preload and afterload should

be optimized with appropriate volume infusions and blood pressure control. Contractility may be supported with appropriate inotropic medications. Treating electrolyte and blood gas abnormalities is essential. Hypothermia, if present, must be addressed. An ECG and cardiac enzyme levels must be part of the evaluation to rule out myocardial ischemia or infarction as a culprit. An urgent bedside echocardiogram may be warranted to rule out cardiac tamponade and detect regional wall motion abnormalities if LCOS does not resolve promptly. Evidence supports prophylactic IABP insertion in patients identified preoperatively as at high risk for LCOS.²⁵⁵⁻²⁵⁷ However, IABP may also be inserted postoperatively. In some cases, open chest management may be required for 24 to 48 hours after surgery.²⁵⁸

Perioperative Myocardial Infarction

Perioperative MI occurs in 2% to 10% of first-time CABG cases, depending on the institutional or study definition,^{20,21,259} and carries a higher risk of mortality, morbidity, and reduced long-term quality of life.²⁶⁰⁻²⁶² It may be secondary to graft-related problems or native coronary artery problems. Graft-related problems include kinking and overstretching of the grafts, acute occlusion, technical anastomotic stenosis, or conduit spasm. Causes related to the native circulation include inadequate myocardial protection, incomplete revascularization, and coronary embolization. Insertion of an IABP may be required in these circumstances to minimize myocardial ischemia. Although some elevations in cardiac enzymes are ubiquitous after surgery, elevations in the creatine kinase-myocardial bound (CK-MB) and troponin-I beyond five times the upper normal limit defines a perioperative MI,²⁶³ especially when accompanied by new Q waves or new left bundle branch block on ECG,²⁶⁴ or new regional wall motion abnormalities on transesophageal echocardiography (TEE).²⁶⁵ In a study of 4000 patients by Brener and colleagues,²⁶⁶ elevations of cardiac enzymes above 10 times the upper normal limit was associated with a 30% decrease in survival at 3 years. Inotropes, vasopressors, and the use of an IABP may be helpful in unstable patients; however, cardiac catheterization or reexploration may be needed despite other measures.

Neurologic Events

Neurologic deficit after CABG can be divided into two types: type 1 deficits, which represent major, focal neurologic deficits, stupor, and coma; and type 2 deficits, which are characterized by global deterioration of intellectual function or memory.²⁶⁷ Both types of deficits are likely to be the result of one or a combination of the following: cerebral emboli, hypoperfusion, or inflammation related to CPB. Type I deficits are associated with up to 25% risk of mortality.^{268,269} The incidence of stroke after CABG is between 1.4% and 3.8%.^{270,271} More than half of these occur after surgery, with the remaining occurring intraoperatively.^{272,273} Half of postoperative strokes take place in the first 24 hours after surgery.²⁷⁰ Stroke after CABG carries a mortality of up to 17%, with early (<24 hours) strokes carrying a threefold higher risk of dying

compared with late (>24 hours) strokes.²⁷⁰ Predictors of stroke include advanced age (>70 years), female sex, previous stroke, CHF, atrial fibrillation, diabetes mellitus, hypertension, peripheral vascular disease (including carotid artery disease), renal failure, atherosclerotic aortic disease, and perioperative hypotension or the use of an IABP.^{270,274,275} Although multiple randomized trials did not demonstrate lower prevalence of neurologic injury in off-pump compared with on-pump CABG,²⁷⁶⁻²⁷⁸ one study demonstrated that operative or off-pump techniques that avoided aortic manipulation were associated with fewer intraoperative strokes, which suggests a greater role of aortic manipulation causing stroke compared with CPB exposure.²⁷³ A recent meta-analysis also suggested a significant 30% reduction of stroke in off-pump (1.4%) compared with on-pump CABG (2.1%).²⁷⁹

Type 2 deficits are more difficult to detect and characterize. Delirium occurs in 3% to 50% of patients after CABG, depending on the definition.²⁸⁰ It is generally accepted as a transient disturbance of cognitive function that varies in severity and fluctuates temporally. In addition to causing distress to the patient's family and the health care team, delirium seems to carry long-term consequences such as an increase in mortality.^{281,282} Risk factors of delirium include previous stroke, history of substance abuse, age older than 65 years, perioperative blood transfusion, and perioperative hypotension.²⁸³ Off-pump CABG and preoperative statins may reduce the incidence of postoperative delirium in some cases.^{284,285} Postoperative cognitive dysfunction is common after CABG with an incidence of 30% to 80% at discharge and 20% to 40% six months to 1 year after surgery.^{286,287} It often is difficult to detect, and specialized, targeted testing is needed to reveal the deficits. Despite their common occurrence, they do not seem to be associated with negative long-term consequences.²⁸⁸⁻²⁹⁰

Postoperative Renal Dysfunction

Postoperative renal dysfunction (PRD) is a serious complication of CABG occurring in 7.7% of patients in a large multicenter study, of whom 1.4% required dialysis.²⁹¹ The risk of mortality increases from a baseline of 0.9% to 19% in patients with PRD, and to 63% in patients requiring dialysis. Other studies confirmed these findings²⁹² with one study demonstrating an increased 90-day mortality even with a 50% rise in postoperative creatinine.²⁹³ Furthermore, other groups have shown that PRD is associated with increased rates of cardiovascular events, including the long-term risk of heart failure.^{294,295} Risk factors for PRD, most of which are nonmodifiable, include age older than 70 years, diabetes mellitus, chronic kidney disease, CHF, reoperation, prolonged CPB times, preoperative anemia, perioperative transfusion, and LCOS.^{243,250,291,292} Some propose a more accurate evaluation of renal function through the addition of glomerular filtration rate to serum creatinine after demonstrating the association of occult renal impairment on early and late mortality and cardiovascular events.²⁹⁶ Although off-pump CABG may be associated with a lower incidence of PRD,²⁹⁷ this remains controversial, as some randomized trials have not shown this advantage.^{278,298}

Recombinant human B-type natriuretic peptide given as an infusion during CPB has been evaluated in a randomized trial of 272 patients undergoing CABG.²⁹⁹ Patients receiving the infusion had a significantly lower peak increase in serum creatinine, greater urine output in the initial 24 hours after surgery, shorter length of hospital stay, and lower 180-day mortality. Other studies evaluating human atrial natriuretic peptide have shown similar promising results.^{300,301} Further research will clarify the role of this strategy in protecting the kidneys after cardiac surgery.

Atrial Fibrillation

Postoperative atrial fibrillation (POAF) develops in 20% to 40% of patients undergoing CABG, with a peak incidence on the second and third postoperative days.³⁰²⁻³⁰⁴ It is usually transient and most patients return to sinus rhythm within 2 to 3 days of treatment. However, patients with preoperative atrial fibrillation are unlikely to return to sinus rhythm. The underlying mechanism is not fully understood and is likely multifactorial. A combination of pericardial inflammation, excessive catecholamine production, postoperative autonomic imbalance, interstitial mobilization, volume overload, and alterations in the neurohumoral environment likely contributes to the development of POAF.^{305,306} POAF is associated with a two- to threefold increase in the risk of stroke, increased length of stay, increased cost, and increased mortality.^{302,303,307-309} Predictors for development of atrial fibrillation include advanced age, male sex, smoking, prolonged cross-clamp time, COPD, chronic renal disease, valvular heart disease, atrial enlargement, obesity, prior pericarditis, and withdrawal of beta blockers.^{304,306,310-312}

Treatment of POAF³¹³⁻³¹⁵ begins with correcting electrolyte imbalances, hypoxia, and acidosis. Patients in volume overload may benefit from diuresis when stable hemodynamically. In hemodynamically unstable patients, electrical synchronized cardioversion should be performed. In stable patients, rate or pharmacologic rhythm control strategies should be attempted. Commonly used rate control medications include beta blockers, calcium channel blockers, and digoxin. The latter can be helpful in patients with a depressed left ventricle. Amiodarone is a commonly used medication for pharmacologic rhythm control. Consideration for anticoagulation should be given in patients who remain in atrial fibrillation for 48 hours weighing in the risks of bleeding and thromboembolism.

A recent synthesis from the Cochrane Collaboration, in addition to other reports, looking at preventive strategies for POAF found that beta blockers, sotalol, amiodarone, atrial pacing postoperatively, magnesium, and posterior pericardiotomy reduce the incidence of POAF with variable effectiveness.^{316,317} A recent meta-analysis provides evidence to suggest that preoperative omega-3 supplementation may also decrease the incidence of POAF.³¹⁸

Sternal Wound Infections

Sternal wound infections (SWIs) can be divided into two types: superficial sternal wound infections (SSWIs) and

deep sternal wound infections (DSWIs). The former involves the skin, subcutaneous tissue, and pectoralis fascia and is recognized clinically as the presence of erythema, drainage, fever, or all of these symptoms. The diagnosis of DSWI requires the presence of one of the following: positive culture from mediastinal fluid or tissue; observable mediastinitis during surgery; presence of chest pain, sternal instability, or high-grade fever; and either purulent drainage from the mediastinum or positive blood cultures.³¹⁹ The incidence of SWI is reported to be 0.47% to 8.0% and carries a mortality rate of 0.5% to 9.1%, whereas the incidence of DSWI is 0.22% to 1.97% with a mortality rate of 1.0% to 36%.³²⁰⁻³²²

Microbiologically, *Staphylococcus aureus* and coagulase-negative staphylococci are the most common isolated pathogens.³²³ Reported risk factors for DSWI include advanced age, male sex, COPD, obesity, diabetes mellitus, smoking history, steroid use, renal insufficiency, non-elective surgery, repeat operations, long operative times, reexploration for bleeding, use of bone wax, perioperative transfusion, prolonged hospital stay (>5 days), and the use of bilateral ITAs.^{250,320,324-326} In a recent meta-analysis on this topic,³²⁷ Saso and coworkers concluded that skeletonization of the ITA decreases the risk of all SWIs by 60%, especially in patients with diabetes mellitus, and the advantage is maintained in bilateral ITA harvesting. This is likely because of improved chest perfusion with the skeletonization technique.¹¹⁹ Important steps to prevent SWIs include preoperative showers with chlorhexidine gluconate, prophylactic intranasal mupirocin, hair clipping instead of shaving, intravenous prophylactic antibiotics before skin incision, aggressive perioperative glucose control, skeletonization of the ITA especially when bilateral ITAs are used in obese patients with diabetes or COPD, and strict adherence to sterility.³²⁸⁻³³¹ Although SSWIs may be treated conservatively with antibiotics in most cases, DSWIs commonly require reexploration and débridement of necrotic tissue in the operating room with some cases requiring early vascularized muscle flap coverage.

Mortality

The overall operative mortality of CABG (defined as all in-hospital deaths and all out-of-hospital deaths occurring within 30 days of the procedure) across North American centers that are part of the Society of Thoracic Surgeons database is 3.0%, an improvement since 1990 despite an increase in the mean age of patients (65.1 years), the mean priority status, and the prevalence of comorbid conditions.³³² In the 19,016 patients of the Northern New England Cardiovascular Disease Study Group who received a LITA during CABG, the overall 30-day mortality was 2.4%.³³³ In two contemporary randomized trials, the SYNTAX trial²⁰ and the FREEDOM trial,²¹ the operative mortalities for CABG patients were 3.5% and 1.7%, respectively. These figures are similar to those reported in several other studies.^{111,334}

Predictors of 30-day mortality include high priority of operation, advanced age, female gender, diabetes mellitus, poor left ventricular function (especially in the presence of CHF symptoms), high creatinine level, peripheral

vascular disease, pulmonary disease, and left main CAD.³³⁵ Patients who are younger than 65 and presenting with normal left ventricular function and receiving elective CABG have a 30-day mortality of less than 1%.²⁶⁷

Long-term survival of patients after CABG may depend on the characteristics of the population studied, on the geographic location of the cohort, and on the surgical era, with the impact of secondary prevention programs and arterial revascularization techniques. Most long-term data, however, come from patients who had surgery in the 1970s and 1980s. Long-term vital data of patients enrolled in the CASS registry³³⁶ (who underwent surgery between 1974 and 1979) have shown that survival after CABG in all patients is 96% at 1 year, 90% at 5 years, 74% at 10 years, and 56% at 15 years. Of particular interest in this report, in which arterial grafting was used in only 13% of patients, is that the survival of patients 65 to 70 years or older exceeded that of a matched U.S. population. Sergeant and colleagues³³⁷ reported on 9600 consecutive CABG patients operated on between 1971 and 1993 and found that survival after CABG was 98% at 30 days, 92% at 5 years, 81% at 10 years, 66% at 15 years, and 51% at 20 years. In the final 10-year follow-up of the Bypass Angioplasty Revascularization Investigation (BARI) trial³³⁸ of 914 patients who were randomly assigned to CABG, the survival was 89% at 5 years and 74% at 10 years. The APPROACH registry³³⁹ is a large clinical data collection and outcome monitoring initiative that captured all patients undergoing cardiac catheterization and revascularization in the province of Alberta, Canada, between 1995 and 2000. In 15,392 patients younger than 70 years of age examined in this registry, 4-year adjusted actuarial survival rates for CABG, PCI, and medical therapy were 95.0%, 93.8%, and 90.5%, respectively. Survival rates decreased to 87.3%, 83.9%, and 79.1% for patients 70 to 79 years of age after CABG, PCI, and medical therapy, respectively, and to 77.4%, 71.6%, and 60.3% for patients 80 years of age or older. The SYNTAX trial 5-year follow-up³⁴⁰ reported an all-cause mortality of 11.4% at 5 years for the whole CABG cohort.

Despite the possibility of confounding by indication, evidence suggests that the use of bilateral over single ITA may be associated with improved long-term survival after CABG. Lytle and colleagues reported a risk-adjusted survival of 94%, 84%, and 67% at 5, 10, and 15 postoperative years in 2000 patients who received bilateral ITAs versus 92%, 79%, and 64% in 8100 patients who had a single ITA; an even greater reduction was observed with respect to reoperation rates.¹⁰⁶ Other authors also found that single ITA grafting was a predictor of mortality, late MI, or late reoperation when compared with bilateral ITA grafting (RR = 1.3 [1.1 to 1.6]).^{341,342} A contemporary propensity-matched study demonstrated that bilateral ITAs provided enhanced long-term survival compared with single ITA in patients with normal and reduced LVEF, without increased operative morbidity and mortality.³⁴³ In a meta-analysis of available observational studies, Taggart and colleagues found that the use of bilateral versus single ITA resulted in a hazard ratio for death of 0.81 (95% CI: 0.70, 0.94).³⁴⁴ The benefits of bilateral ITA grafting have also been suggested in the diabetic population.³⁴⁵

Freedom from Cardiac Events

Fundamentally, CABG is performed for two reasons: to improve survival or to alleviate symptoms of angina and prevent nonfatal outcomes such as MI, CHF, and hospitalization. Unfortunately, long-term studies rarely used arterial grafts and lacked structured secondary prevention after CABG. Sergeant and coworkers³⁴⁶ found that the freedom rate from return of angina was 94%, 82%, 61%, and 38% at 1, 5, 10, and 15 years, and that secondary prevention and management of noncardiac comorbidity had the most impact on delaying the return of angina. Freedom from MI was 97%, 94%, 86%, 73%, and 56% at 30 days, 5, 10, 15, and 20 years. Freedom from coronary reintervention, whether PCI or CABG, was 99.7%, 97%, 89%, 72%, and 48% at 30 days, 5, 10, 15, and 20 years. In the BARI trial,³³⁸ freedom from angina was 84% at 5 and 10 years. The freedom from coronary reintervention was 80% at 10 years. In the Arterial Revascularization Therapies Study (ARTS) randomized trial,³⁴⁷ the rates of MI and reintervention at 5 years were 6.4% and 8.8%, respectively. Patients with diabetes mellitus (smaller number) had worse outcomes: their 5-year rates of MI and reintervention were 7.3% and 10.4% compared with 6.3% and 8.4% in patients without diabetes. Arterial grafting probably leads to even better results: in a series of 256 patients³⁴⁸ with triple-vessel disease who received three arterial grafts, the rates for freedom from MI and angina were 97.3% and 85.7% at 7 years, respectively. The SYNTAX trial³⁴⁰ enrolled 1800 patients with triple-vessel or left main CAD across 85 centers. At 5 years, the rates of MI and reintervention were 3.8% and 6.7%, respectively.

Left Ventricular Function

Myocardial ischemia may cause a wide spectrum of myocardial states ranging from viable and functioning, to hibernating, stunned, or scarred and dysfunctional myocardium. The myocardial state and the amount of muscle involved dictates left ventricular function. One of the greatest survival benefits after CABG is in patients with triple-vessel or left main CAD and depressed left ventricular function.^{60,267} If patients exhibit depressed left ventricular function caused by stunned or hibernating myocardium, CABG improves EF by 5% to 18%.^{349,350} These improvements in systolic function appear as early as 2 weeks and endure up to 10 years after surgery, given no cardiovascular events during that time.^{159,351,352} Lack of improvements or deterioration over time is usually related to either incomplete revascularization or graft occlusion. Bax and associates used echocardiography to examine the time course of contractile recovery in stunned and hibernating myocardial PET segments after CABG, and found that 61% of the stunned segments had improved at 3 months, and an additional 9% had improved at 14 months. In contrast, hibernating myocardium segments showed contractile improvement at 3 months in 31% of patients, with a further improvement at 14 months in an additional 61%.¹⁵⁹ Left ventricular diastolic function seems to improve immediately after surgery.³⁵³ Survival of patients with very low LVEF (<20%) range from 59% to 73% at 5 years, with

TABLE 88-3 Reported Conduit Patency in CABG

Conduit	Percentage Patency Based on Duration of Angiographic Follow-up		
	1	5	Late
Saphenous vein graft	84.6% ¹²⁸ 81% ^{*376,425,426} 95% at 6 months ¹⁵³ 94% at 1 yr ³⁷⁷ 98.7% ⁴²⁷	75% ^{*%} ^{*376,425,426} 81% ³⁷⁸ 86.4% ¹³⁰	15 yr: 50% ^{*376,425,426}
Internal thoracic artery			7 yr: 94% ⁴²⁸ 11 yr: 88% ⁴²⁹⁻⁴³² 10-20 yr: 90%-95% ³⁸⁴ 7 yr: 92.5% ³⁹¹
Radial artery	91.8% ¹²⁷	96% at 4 yr ³⁹⁰ 98.3% ¹³⁰ 92.5% ³⁹¹	
Gastroepiploic artery	91% at 6 months ¹⁵³	84% ¹⁵⁰ 63% ¹⁵⁶ 86% ^{151,393,394}	70% ^{151,393,394}

*Patency results published from series in pre-statin and pre-aspirin era.
CABG, Coronary artery bypass grafting.

significant improvements in heart failure and angina class observed among survivors.^{349,352,354-357}

A recent anterior MI with residual wall-motion anomaly is associated with an intramural thrombus in 31% of patients.³⁵⁸ In contrast, this is much less frequent after an inferior or lateral MI. For these reasons, patients with a recent anterior MI (including a perioperative MI) and significant residual anterior or apical wall-motion abnormality should be anticoagulated for 3 to 6 months after CABG.³⁵⁹

Functional Status and Quality of Life

Quality of life after CABG markedly improves in most patients and may correspond to that of a matched control population.³⁶⁰⁻³⁶² Predictors of suboptimal or worsening quality of life include female sex, low socioeconomic status, smoking, diabetes mellitus, hypertension, low ejection fraction, recurrent angina, and nonenrollment into a cardiac rehabilitation program.^{361,363-365} Improvements in quality of life can be observed at 3 months after surgery, and these improvements seem to endure at least up to 12 years after surgery.^{306,364-366} Although advanced age (octa- and nonagenarians) does not preclude improvements in quality of life, they are less pronounced in this group and may not last in the long term.³⁶⁶⁻³⁶⁸ In contrast to the overall improvement in quality of life and functional status, persistent sexual problems are relatively common after CABG and are most prevalent in men, diabetics, patients with hyperlipidemia, and those with preoperative sexual problems.^{369,370} However, men's sexual satisfaction improved, whereas the women's satisfaction decreased 8 years after surgery.³⁶⁹ Twelve years after CABG, patients had similar improvements in quality of life whether they had on-pump or off-pump CABG.³⁷¹ Contemporary data reveal that quality of life in CABG patients may surpass that of PCI patients as early as 6 months after the intervention.^{231,232}

Graft Patency

In comparison with other forms of revascularization such as PCI, OPCAB, MIDCAB, transmyocardial revascular-

ization, or angiogenic therapy, on-pump CABG has a significant advantage in that its long-term procedural outcome has been well characterized. Multiple long-term angiographic studies have described the patency rates of different types of grafts and risk factors associated with their premature closure (Table 88-3). Early closure (i.e., within 2 to 3 months) of any type of graft is usually because of thrombosis, which develops as a result of hemodynamic factors related to poor graft outflow or technical errors.³⁷² Once the early postoperative period is over, vein grafts start developing a disease complex of their own, namely intimal hyperplasia, which is noted in most grafts as early as 1 month after operation^{372,373} and to which the ITA appears immune.³⁷⁴ This process results in a diffuse concentric reduction in vein graft diameter on angiography, which usually matches that of the native coronary vessel by 1 year after implantation. Intimal hyperplasia can be most significant at suture lines and can lead to anastomotic stenosis in up to 20% of vein grafts. The radial and gastroepiploic arteries have a decreased susceptibility to significant intimal hyperplasia compared with vein grafts, which may translate into better long-term freedom from atherosclerosis and patency considering that intimal hyperplasia usually corresponds to sites that later develop graft atherosclerosis.³⁷⁵ Graft atherosclerosis may be observed in vein grafts as early as 3 to 4 years after operation and has a predilection for areas of intimal hyperplasia. It is characterized by a noncapsulated lipid-rich core that is much more friable than native coronary atherosclerosis.

Saphenous Vein Grafts

The early patency rate of saphenous vein grafts improved markedly in the post-aspirin and post-statin era, with long-term patency data not as extensively characterized as older studies in the pre-aspirin and pre-statin era. Fitzgibbon and associates³⁷⁶ found that vein graft patency was 88% early postoperatively, 81% at 1 year, 75% at 5 years, and 50% at 15 years; when stenosed grafts were excluded, the proportion of nondiseased grafts decreased to 40% at 12.5 years. This corresponded to a vein graft

occlusion rate of 2.1% per year after the initial postoperative period. In the current era, vein graft patency has been found to be greater than 95% at 1 year³⁷⁷ and 81% to 86% at 5 years.^{130,378} The way SVG is handled may influence its patency; one study suggested a 94% patency rate at 3 years in no-touch saphenous veins.^{170,379} Some studies demonstrated a higher patency rate in sequential vein grafts compared to individual ones with up to 76% at 7.5 years for sequential vein grafts and 64.5% for individual vein grafts.^{164,380} This is probably a result of higher graft flow as a consequence of improved distal runoff, which may reduce intimal hyperplasia formation. However, another recent trial showed the opposite conclusion, with SVG to multiple distal targets showing higher failure rates at 1 year.³⁸¹ Although postoperative aspirin is the standard of care, adding clopidogrel to aspirin did not provide increased vein graft patency or reduce the frequency of adverse cardiovascular events.^{377,382}

Internal Thoracic Artery Grafts

Late attrition rates of ITA bypass grafts are low because of the fact that ITA grafts rarely develop significant intimal hyperplasia or late atherosclerosis. Furthermore, the ITA has a potential to grow up to 1.4 times its original size to match the diameter of the coronary artery to which it is anastomosed.³⁸³ Improved pharmacologic therapy and structured secondary prevention programs have improved patency rates in the current era. A 2003 report from the Cleveland Clinic demonstrated a 90% to 95% patency rate of the left ITA anastomosed to the LAD 10 to 20 years after surgery.³⁸⁴ Free ITA grafts likely have comparable patency rates as compared with pedicled ITA grafts, provided that a flawless anastomotic technique is used.³⁸⁵ Some studies report³⁸⁶⁻³⁸⁹ similar patency rates of the RITA compared with the LITA, whether anastomosed to the LAD, circumflex, or right coronary artery, with some suggesting that flow through the RITA may be even greater because of handedness.¹¹⁹ Tatoulis and colleagues³⁸⁷ reported a hierarchy of patency of the RITA depending on the coronary territory grafted (highest patency rates to the LAD and lowest to the right coronary territory). The same authors reported a RITA to LAD patency rate of 95% at 10 years and 90% at 15 years, RITA to circumflex artery patency rate of 91% at 10 years, and RITA to RCA patency rate of 84% at 10 years. They conclude that RITA patency rates are equivalent to LITA for identical territories and are always better than radial arteries and saphenous vein grafts.

Radial Artery Grafts

Acar and coworkers,¹⁵ who are responsible for the revival of the radial artery as a bypass conduit, reported a patency of 83% at 5.6 years in 50 of 910 patients who received a radial artery. Iaco and associates³⁹⁰ reported a 96% 4-year patency in selected patients, with no difference in patency whether the radial was anastomosed to the aorta or to the ITA as a Y-graft. Collins and colleagues¹³⁰ reported radial artery patency of 98.3% based on angiographic data from the RSVP randomized

controlled trial. Tatoulis and coworkers³⁹¹ reported 92.5% patency at 5 and at 7 years. Similar to the RITA, they also showed a hierarchy of patency depending on the coronary territory grafted (highest to the LAD and lowest to the right coronary). Other authors have shown that moderate severity of native target stenosis (70% or less) and grafting to the right coronary artery were associated with lower patency rates and when the radial artery is used in a composite T-graft configuration.¹³⁷ Comparing the mid-term (3-year) angiographic outcomes of the radial artery to those of the saphenous vein, a recent meta-analysis of randomized controlled trials revealed a superior complete graft patency of the radial artery compared with the saphenous vein (88.6% vs. 75.8%; $P = 0.005$), although the radial artery was associated with more string signs.³⁹²

Gastroepiploic Artery Grafts

Late results regarding patency of the gastroepiploic artery as a bypass graft are not as favorable as those of the ITA and radial artery. The 5-year angiographic patency was reported by Hirose and colleagues to be 84%,¹⁵⁰ and 86% at 5 years and 70% at 10 years by Suma and associates.^{151,393,394} Factors associated with premature graft closure include technical anastomotic factors and anastomosis to a less critically stenosed coronary artery in a significant proportion of cases. There has been one randomized controlled trial to date comparing the use of the gastroepiploic artery versus the saphenous vein graft.¹⁵⁵ At 6-month angiographic follow-up, there were no differences in patency between conduits, although it appears that gastroepiploic artery patency is more influenced by competitive coronary flow.¹⁵⁴

CABG versus PCI

A detailed analysis comparing the outcomes following CABG and PCI is beyond the scope of this chapter. No doubt, the benefits of both treatment modalities will evolve along with advances in technology and improvements in conjunctive care. Although initially believed to rid in-stent stenosis, drug-eluting stents have been found to be associated with late stent thrombosis.³⁹⁵

At present, 26 randomized clinical trials have compared CABG with PCI (Table 88-4),^{20-22,351,396-417} with most of these studies releasing subgroup analyses and subsequent longer-term follow-up data. Many of these trials were underpowered to show a significant difference in early survival between PCI and CABG. Most of these trials excluded patients with diabetes, poor left ventricular function, and multivessel disease including left main and proximal LAD disease, for which CABG has been shown to be beneficial. However, the most recent trials began including and addressing these patient populations. Another consideration is that because of strict inclusion and exclusion criteria, only approximately 5% of screened patients were enrolled, which has an impact on the external validity of these trials. For trials that presented follow-up data on an original study cohort, no adjustment in the alpha level was made for repeated

TABLE 88-4 Randomized Controlled Trials Comparing PCI and CABG

Trial Name Study Dates	Stent Use/ DES %	Centers/Patient Number	DM %	LVEF < 50%	3VD	Follow-up Duration (Years)	Author Conclusions	Remarks
Left Main Disease								
PRECOMBAT ⁴¹⁷ 2004-2009	Yes	13/600	32%	Mean 61%	41%	2	PCI noninferior to CABG with respect to MACCE.	Noninferiority margin was wide.
Boudriot ⁴¹⁶ 2003-2009	Yes	4/201	36%	Median 65%	14%	1	PCI inferior to CABG at 12 months for unprotected left main disease.	
LE MANS ³⁹⁶ 2001-2004	Yes/35%	7/105	18%	19%	67%	1	LVEF increase at 1 year in PCI group only.	Actual change in LVEF minimal (3.3 ± 6.7 vs. 0.8 ± 0.8).
Proximal LAD								
Lausanne ⁴⁰² 1989-1993	No	1/134	18%		0%	5	No difference in terms of survival or MACE at 2 years. At 5 years, the incidence of non-Q wave MI and need for repeat procedures was higher in the PTCA group.	
Leipzig ⁴⁰⁰ 1997-2001	Yes/0%	1/120	30%		0%	0.5	No difference in terms of survival or MACE; although CABG was superior in terms of angina relief and need for repeat procedures.	CABG performed via MIDCAB.
Groningen ⁴⁰¹ 1997-1999	Yes	1/102	13%		0%	3	Trend toward improvement in MACE-free survival with CABG; CABG superior in angina relief.	CABG performed via OPCAB.
MASS ⁴⁰⁶ 1988-1991	No	1/214	17%	0%	0%	3	Survival and MACE similar between PCI and CABG at 3 years.	
SIMA ⁴⁰⁴	Yes	6/123	11%	0%		10	CABG superior to PCI regarding the primary composite end of all-cause mortality, MI, and the need for additional revascularization.	
Multivessel Disease								
FREEDOM ²¹ 2005-2010	Yes/100%	140/1900	100%	2.5% EF < 40%	83%	5	For patients with diabetes and multivessel disease, CABG is superior to PCI. CABG has significantly lower rates of death and MI at 5 years compared with PCI.	
CARDia ²² 2002-2007	Yes/69%	24/510	100%	28% (65% had EF)	62%	1	Trial did not show PCI to be noninferior to CABG in diabetic patients at 1 year.	
SYNTAX ^{20,340} 2005-2007	Yes/100%	85/1800	35%	1.9% EF < 30%		5	CABG had lower MACCE rates at 1, 3, and 5 years. CABG remains the standard of care for patients with triple-vessel disease or with left main disease and complex lesions. For patients with less complex lesions and left main disease PCI is an acceptable alternative.	
ARTS ⁴¹² 1997-1998		68/1205	17%	0%	32%	5	At 5 years, no difference in mortality between PCI and CABG; MACCE was higher with PCI.	
ARTS II ⁴³³		606 with DES; compared with ARTS I cohort of 1205	26%		55%	1	DES results in decrease in frequency of repeat procedures with no change in survival or MACE.	

Continued

TABLE 88-4 Randomized Controlled Trials Comparing PCI and CABG—cont'd

Trial Name Study Dates	Stent Use/ DES %	Centers/Patient Number	DM %	LVEF < 50%	3VD	Follow-up Duration (Years)	Author Conclusions	Remarks
AWESOME ⁴¹¹ 1995-2000	No	16/454 (only 142 randomized)	37%	45%	68%	3	No difference between CABG and PCI in terms of survival or MACE.	
BARI ^{351,434} 1988-1991	No	18/1792	24%	0%	41%	10	CABG superior in terms of survival, angina relief and need for repeat revascularization at 5 years. At 10 years, survival benefit only remained for patients with DM.	
CABRI ³⁹⁷	No	26/1054	0%	12%	40%	4	No difference between CABG and PCI in terms of MACE or survival.	
EAST ⁴⁰⁷ 1987-1990	No	1/392	23%		40%	8	No difference between CABG and PCI in terms of the primary composite endpoint of death, Q wave MI, and a large ischemic defect identified on thallium scanning at 3 years. No difference was observed in terms of survival at 8 years.	CABG superior in terms of angina relief and angiographically determined revascularization at 3 years.
ERACI ⁴⁰⁹ 1988-1990	No	1/127	11%	0%	45%	3	CABG offered greater freedom from cardiac events and greater angina relief compared with PCI.	
ERACI II ⁴⁰⁸ 1996-1998	Yes/0%	7/450	17%		56%	1	PCI superior to CABG in terms of survival.	
ERACI III ⁴¹⁰ 1996-1998 & 2002-2004	Yes/33%	7/675	18%	50%		1	DES more prone to late stent thrombosis than BMS although no difference in survival was observed.	
GABI ⁴⁰⁵ 1986-1991	No	8/359	10%		18%	1	CABG superior to PCI in terms of angina relief and need for repeat procedures; not survival.	
GABI II ⁴³⁵	Yes	8/313				1	No difference between CABG and PCI conducted.	Used a historical surgical cohort.
MASS II ³⁹ 1995-2000	Yes	2/611	29%		58%	5	CABG superior to PCI with regard to the primary composite endpoint of death, Q wave MI, refractory angina requiring revascularization.	
RITA ³⁹⁶	No	16/1011	6%		12%	6.5	No difference between CABG and PCI in regard to survival or MACE.	
SOS ^{436,437} 1996-1999	Yes/0%	53/988	14%		42%	6	CABG superior to PCI in terms of survival and need for repeat revascularization.	
Toulouse ³⁹⁵	No	1/1152	14%		29%	5	CABG superior to PCI in terms of survival, angina relief, and need for repeat procedures.	

BMS, Bare-metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac and cerebrovascular event; MACE, major adverse cardiac event; MI, myocardial infarction; MIDCAB, minimally invasive direct coronary artery bypass; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; 3VD, triple-vessel disease.

statistical tests. Considering these limitations, a variety of conclusions can be drawn:

1. Although limited data exist comparing unprotected left main stenting (UPLMS) and CABG, UPLMS appears safe in a select patient population. Mid- and long-term results are yet to be established.
2. In the setting of proximal LAD disease, PCI is associated with an increase in the need for repeat revascularization. CABG appears superior in terms of angina relief. Although survival appears similar between CABG and PCI at intermediate follow-up, survival appears superior with CABG in the long term.
3. In patients with triple-vessel disease, CABG provides a survival advantage compared to PCI in patients with intermediate and high baseline SYNTAX scores. CABG is superior to PCI in terms of major adverse cardiac and cerebrovascular events in patients with complex coronary lesions.
4. Diabetic patients derive a survival benefit from CABG, which is maintained over the long term. CABG also reduces the rates of MI compared with PCI.
5. Drug-eluting stents decreased the need for repeat revascularization procedures relative to bare-metal stents; late stent thrombosis with drug-eluting stents does not significantly impact survival compared with bare-metal stents over the long term.

Two contemporary randomized trials were recently completed and contributed further to our understanding of the benefit of PCI with drug-eluting stent versus CABG.^{20,21} The SYNTAX trial²⁰ enrolled 1800 patients with triple-vessel or left main CAD across 85 centers. The primary endpoint of major adverse cardiac or cerebrovascular events at 1 year was higher in the PCI compared with the CABG group (17.8% vs. 12.4%; $P = 0.002$), which was mostly driven by repeat revascularization. The rates of death and MI were similar between the two groups at 1 year, but stroke rates were significantly higher in the CABG group. After 5 years of follow-up, CABG remained superior with regard to the primary outcome. Although the rates of all-cause mortality and stroke were similar between the two groups, the rates of MI, the combination of death or stroke or MI, and cardiac death were all significantly higher in the PCI group. In subgroup analysis, these findings hold true in patients with triple-vessel disease or left main coronary disease and complex lesions (high or intermediate SYNTAX scores for triple-vessel disease and high SYNTAX scores for left main coronary disease). For patients with less complex lesions (low SYNTAX scores for triple-vessel disease and intermediate or low SYNTAX scores for left main coronary disease), PCI may be an acceptable alternative. In triple-vessel disease, the benefit of CABG over PCI with regard to cardiac death was almost twofold ($P = 0.0008$ for intermediate SYNTAX score and $P = 0.0005$ for high SYNTAX score).³⁴⁰

The FREEDOM trial^{20,21} enrolled 1900 patients with diabetes and multivessel coronary disease across 140 centers. CABG was superior to PCI in that it significantly reduced the rates of death from any cause and MI at 5 years at the cost of significantly higher stroke rates in the CABG group. The conclusions did not change across

prespecified subgroups including low, intermediate, and high SYNTAX scores, LVEF <40% and ≥40%.

Although randomization protects against confounding and selection bias, the main problem with randomized studies of CABG versus PCI is generalizability as a result of their nonrepresentativeness and the small proportion of the screened patients who are actually enrolled. The results of seven large registries are more useful for looking at the comparative *effectiveness* of CABG versus PCI in a particular population setting. These registries are the New York State PCI and CABG registries,⁴¹⁸ which compared more than 60,000 patients; the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) registry,³³⁹ which examined approximately 16,000 patients after CABG or PCI; the Northern New England Cardiovascular Disease Study Group Registry,⁴¹⁹ which examined 2766 patients with diabetes; the Duke registry,⁴²⁰ which examined approximately 7000 patients who underwent CABG versus PCI; the DELTA registry,⁴²¹ a multicenter registry evaluating left main coronary artery treatment with PCI versus CABG in 2,775 patients; the CREDO-Kyoto PCI/CABG registry cohort 2, a Japanese registry⁴²² of approximately 16,000 patients with first coronary revascularization; and the CUSTOMIZE registry,⁴²³ which examined approximately 900 patients undergoing PCI versus CABG in unprotected left main disease. Because these studies are observational, the possibility of selection bias (confounding by indication) remains despite accounting for simple confounding via multivariable analyses. Nevertheless, the results of these studies are worth examining and can be summarized as follows:

1. Stenting unprotected left main CAD may be an option in low and intermediate SYNTAX scores and in older adult patients (>75 years old), with the greater risk of repeat revascularization. In high SYNTAX score lesions, CABG remains the gold standard.
2. Three-, four-, and five-year risk-adjusted survival after CABG is superior to PCI for patients with triple-vessel disease in all study participants (regardless of diabetic status or left ventricular function).
3. Patients with high-grade proximal LAD stenosis benefit from CABG over PCI.
4. Superiority of CABG over PCI in diabetic patients is confirmed.
5. There might be an increased benefit of choosing CABG over PCI in older adults; in any case, older adult patients may benefit the most from revascularization over medical therapy for CAD.
6. CABG is superior to PCI with drug-eluting stents in terms of survival, angina relief, and need for repeat procedures.⁴²⁴

CONCLUSION

Coronary artery bypass grafting remains the most durable method of coronary revascularization available today. Its future is exciting and should be directed at further development and research to evaluate the role of routine complete arterial grafting, minimally invasive techniques,

hybrid coronary revascularization strategies, secondary prevention programs, and adjunct pharmacotherapeutic strategies in achieving the ultimate goal of cardiac surgeons: making CABG a near-zero risk, infallible, and permanent method of coronary revascularization.

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OFF-PUMP CORONARY ARTERY BYPASS GRAFTING AND TRANSMYOCARDIAL LASER REVASCULARIZATION

Jatin Anand • Ashraf A. Sabe • William E. Cohn

CHAPTER OUTLINE

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Completely Endoscopic Robotic-Assisted CABG

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TRANSMYOCARDIAL LASER REVASCULARIZATION

Operative Procedure

Clinical Results

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CONCLUSION

In 1967, Sabiston and colleagues reported the first clinically successful coronary artery bypass graft (CABG) operation. Other early pioneers include Favaloro, who is credited with popularizing the use of autogenous saphenous vein, and Kolesov, who performed the first mammary artery to coronary artery anastomosis. Over the next several years, centers around the world began performing CABG procedures in large numbers. Subsequent refinements in cardiopulmonary bypass (CPB), the introduction of cardioplegia, the growing acceptance of the left internal mammary artery graft, and the development of the intra-aortic balloon pump (IABP) resulted in continued improvements in outcomes after CABG. By the early 1990s, more than 350,000 CABG procedures were being performed each year in the United States alone, with routine application in octogenarians, patients with severely impaired ventricular function, and patients with serious noncardiac morbidities.

As results continued to improve, and as mortality and major morbidity rates in the 2% range became

commonplace, many surgeons turned their efforts toward decreasing the invasiveness of CABG and exploring alternative strategies of revascularization. Over the past several years, this effort has produced a number of new technologies, techniques, and variations on traditional CABG—all intended to avoid CPB, minimize aortic manipulation, improve graft patency, and reduce the trauma of surgical access. These variations include multivessel CABG without CPB, single-vessel CABG without CPB via a left mini-thoracotomy, videoscopic single-vessel CABG using surgical robotics, and multivessel CABG via a left mini-thoracotomy using peripheral cannulation and CPB. Other new procedures include transmyocardial revascularization, reoperative CABG through alternative incisions, and grafting strategies and devices that minimize or eliminate aortic manipulation, facilitate construction of the distal anastomosis, and perhaps improve long-term graft patency. This chapter describes these developments, discusses their relative merits, and summarizes current clinical results.

CARDIOPULMONARY BYPASS

The development of the heart-lung machine by Gibbon and its early application by Kirklin initiated the era of open heart surgery, which eventually made CABG possible. CPB and the subsequent introduction of cardioplegia provided a motionless, blood-free surgical field, which enabled the precision and reproducibility necessary for direct coronary anastomosis. Despite the obvious benefits of CPB, however, there is an increasing awareness of its potential deleterious effects. As the formed elements of the blood contact the various components of the heart-lung machine, the blood elements are activated, resulting in a number of hematologic and ultimately systemic changes. Typical sequelae include activation of complement, release of endotoxin, activation of leukocytes, increased expression of adhesion molecules, and release of inflammatory mediators, including cytokines, arachidonic acid metabolites, free radicals, and other components.¹ These sequelae occasionally manifest as coagulopathy, third-space fluid retention, and subtle end-organ dysfunction, including neurocognitive changes. The magnitude of this systemic inflammatory response is generally modest but can be quite severe, especially when the CPB time is prolonged. Furthermore, a small percentage of patients with preoperative end-organ dysfunction sustain significant morbidity when subjected to even a moderate systemic inflammatory response.

Ongoing efforts have been directed at reducing the magnitude of the systemic inflammatory response associated with CPB. These efforts include decreasing the surface area and modifying the surface composition of the CPB circuit to minimize surface activation, reducing hemodilution by decreasing the volume of crystalloid prime needed to institute CPB, avoiding the use of a cardiotomy sucker, and pretreating patients with various anti-inflammatory medications, such as aprotinin.² Despite progress in these areas, performing CABG without CPB remains attractive.

MULTIVESSEL OFF-PUMP CORONARY ARTERY BYPASS

Off-pump coronary artery bypass (OPCAB) grafting is as old as coronary surgery itself. Large case series dating back to the 1970s document its feasibility.³⁻⁵ Nevertheless, OPCAB only recently gained widespread acceptance and entered the mainstream of clinical practice, propelled by a greater awareness of the potential morbidity of CPB and aortic manipulation and facilitated by improvements in surgical tools and techniques. OPCAB is part of the procedural armamentarium of a growing proportion of surgeons worldwide, and it can be performed in virtually any patient requiring coronary revascularization.

The introduction of self-retaining coronary stabilizers and the development of techniques for their use are key factors that have led to resurgent interest in OPCAB. When properly used, coronary stabilizers provide a relatively motionless and blood-free field, similar to that provided by CPB. The subsequent introduction of self-

retaining cardiac positioning devices and the evolution of surgical techniques for rotating the heart enabled precise anastomoses to be constructed on the inferior, posterior, and lateral walls of the beating heart while maintaining adequate hemodynamic values without CPB.

Self-Retaining Coronary Stabilizers

A number of coronary artery stabilizers are available for clinical use. Current stabilizers can be categorized as compression, suction, or capture devices, depending on their design. When used properly, each type provides excellent immobility.

Compression-type stabilizers are generally two-pronged forks that are placed lightly on the epicardial surface so that the prongs are parallel to, and flanking, the coronary artery at the intended anastomotic site. The undersurface of the prongs provides traction to avoid slippage. The fork is attached to the retractor via an articulating arm and can be locked tightly in position once the desired position has been achieved. Generally, the best stability occurs when only light downward force is exerted on the surface of the heart. Paradoxically, an increase in motion occurs when excessive downward force is applied. One should use the exposure techniques described later in this chapter to present the target artery before positioning the stabilizer rather than relying on the stabilizer to retract the heart. Compression-type stabilizers are advantageous in that they may be set up quickly and simply and have an extremely low profile that allows unrestricted access to the coronary artery. For some aspects of the heart, however, compression stabilizers may require slightly more downward pressure to avoid slippage (Fig. 89-1).

Suction-type stabilizers also are generally two-pronged forks attached to the retractor by means of an articulating arm. These stabilizers, however, are constructed with a series of ports on the undersurface of the prongs, which are connected by sterile tubing to a -100 to -300 mm Hg wall-suction unit. The epicardium and epicardial fat that



FIGURE 89-1 ■ Compression-type stabilizers generally have a low profile and a textured bottom surface that improves their ability to grip the epicardium.

flank the vessel are sucked into these ports, allowing the stabilizer to grip the surface of the heart. Thus, less downward force is required at the anastomotic site. Suction stabilizers are set up quickly but require a regulated vacuum line. They have the added advantage of providing traction and countertraction of the fat surrounding the coronary artery, so they are well suited for arteries deep within the fat. Suction stabilizers tend to have a slightly higher profile than compression types, but access to the coronary artery is not generally problematic (Fig. 89-2).

Capture-type stabilizers are usually fenestrated platforms that frame the intended anastomotic site. Silicone elastic tapes are passed deep under the coronary and locked to the platform under tension, pulling the epicardium up against the platform's undersurface (Fig. 89-3A). Like suction, this effect reduces the demand for downward force to prevent slippage. Capture stabilizers, by virtue of their circumferential effect, provide superior anastomotic stability.⁶ Additionally, the silicone elastic tapes compress the coronary against the platform's posterior aspect, providing integrated biplane coronary occlusion (see Fig. 89-3B). Capture stabilizers are arguably more complex to position, however, and require proper spacing and alignment of the silicone elastic tapes to ensure adequate hemostasis. Furthermore, because of their larger size, they may not be well suited for use during construction of tightly spaced sequential anastomoses.

Preventing Hemodynamic Compromise during Multivessel OPCAB

One of the greatest challenges of the early OPCAB procedures was to maintain hemodynamic stability while grafting coronaries on the lateral and posterolateral aspects of the heart. This challenge was greatest in patients with poor ventricular function and marginally compensated ischemia. The problem has been largely eliminated by advances in surgical technique, including placement of deep pericardial retraction sutures, right vertical pericardiotomy and pleurotomy, and right hemisternal elevation, as well as the introduction of cardiac positioning devices and advances in anesthetic management. To understand how these tools and techniques minimize the adverse effects of cardiac manipulation, it is important to understand the causes of potential hemodynamic compromise during OPCAB.

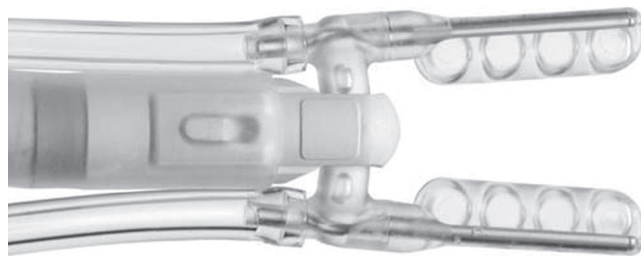


FIGURE 89-2 ■ Suction-type stabilizers use a series of suction cups to grip the epicardium. Although they have a slightly higher profile than compression-type stabilizers, they often require less downward force than compressive footplates.

Left Ventricular Compromise

When a coronary stabilizer is positioned by using excessive downward force, the stabilized aspect of the heart is constrained, leading to diastolic dysfunction and a decreased left ventricular end-diastolic volume (LVEDV), stroke volume, and cardiac output.⁷ Whereas volume loading and Trendelenburg positioning attenuate these effects by elevating left ventricular (LV) filling pressures, recourse to these methods carries a risk of exacerbating intraoperative third-space fluid sequestration and associated morbidity. Similarly, the use of short-acting α -adrenergic agents can effectively maintain perfusion pressure in this setting, but they may be associated with an increased risk of perioperative mesenteric ischemia.⁸ β -Adrenergic agents should similarly be avoided in the setting of yet-to-be-grafted coronary arteries. There are also anecdotal reports of severe mitral regurgitation during exposure of the lateral wall, possibly related to deformation of subvalvular structures in combination with coronary insufficiency. Exposure techniques that minimize or eliminate LV deformation are therefore desirable.

Right Ventricular Compromise

Exposure of the lateral LV wall displaces the heart toward the right, compressing the right ventricle against the pericardium and right side of the sternum. The relatively low pressure in the right ventricle makes that chamber

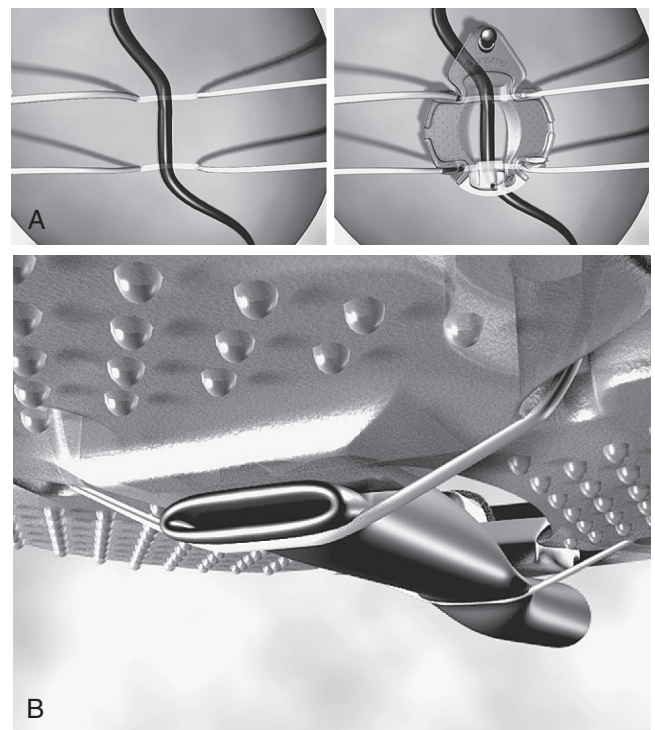


FIGURE 89-3 ■ Capture-type stabilizers use silicone elastic tapes to ensure tight apposition of the textured surface of the footplate and the epicardial surface. This arrangement results in integrated coronary compression. **A**, The surgeon's view of a coronary vessel in a capture-type stabilizer demonstrating spacing of the silicone elastic tapes. **B**, Simulated view of the coronary vessel segment from the underside of the stabilizer.

particularly vulnerable to deformation and reduction of the right ventricular end-diastolic volume (RVEDV).^{9,10} The decreased right ventricular (RV) stroke volume leads to poor LV filling and a decrease in cardiac output. Volume loading and use of the Trendelenburg position can compensate for this effect, as noted in the previous paragraph, but not without potential risk. RV compromise is thought to be the dominant cause in many cases of hemodynamic instability that occurs during exposure of the lateral wall. Various groups have proposed the use of RV assistance as palliation for RV compromise during multivessel OPCAB.^{11,12} Clearly, however, exposure techniques that minimize RV deformation are desirable.

Myocardial Ischemia

Intraoperative myocardial ischemia, secondary to decompensated coronary disease, transient coronary snaring during grafting, or poor perfusion pressure during heart manipulation, is another mechanism that leads to hemodynamic instability. This complication is best prevented by close communication with the anesthesiologist, a revascularization strategy that minimizes myocardial ischemia, and exposure techniques that maintain hemodynamic stability. Whereas each patient should be managed on an individual basis, useful axioms exist. Patients with significant left main stenosis and marginally compensated ischemia may benefit from completion of the left internal mammary artery (LIMA) to left anterior descending (LAD) graft before manipulation of the heart. Similarly, initial revascularization of occluded, collateralized coronary arteries should be carried out before one transiently occludes the vessels that supply collaterals to those arteries. Selective use of intracoronary shunts, aortocoronary shunts, or assisted coronary perfusion devices¹³ can be essential when grafting a moderately stenosed right coronary artery (RCA) proximal to the origin of the posterior descending branch, or when grafting the proximal portion of a moderately stenosed LAD (Fig. 89-4). The judicious use of an intra-aortic balloon pump can occasionally prove invaluable.¹⁴

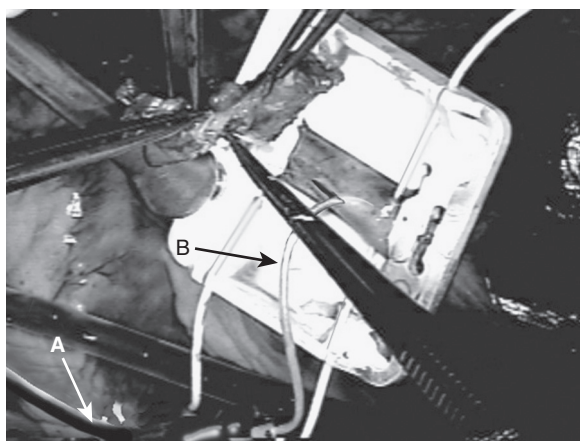


FIGURE 89-4 ■ A small, flexible, olive-tipped shunt inserted in the distal coronary artery (B) is attached to a short extension of IV tubing connected to a small cannula in the ascending aorta (A) to provide uninterrupted blood flow to the distal coronary bed while the anastomosis is constructed.

Exposure Techniques

Depending on the size and shape of the heart and the dimensions of the chest cavity, visualization of the proximal obtuse marginal and posterolateral branches of the circumflex system may be obstructed by the left hemisternum. Although intuitive attempts at improving exposure may involve applying additional rightward force to that aspect of the heart with the stabilizer, this maneuver frequently leads to hemodynamic compromise and paradoxically poor stabilization. Maximal access and stability at the anastomotic site with minimal compromise of cardiac performance is most readily achieved when the stabilizer is applied with little or no pressure; thus, this device should be used only to stabilize the anastomotic field rather than to assist in retracting the heart. In many patients with relatively normal hearts and readily accessible coronaries, little attention to exposure techniques is required. In contrast, during multivessel OPCAB on patients with large, poorly contracting hearts, attention to these techniques is essential. In these patients, exposure of the lateral cardiac wall is best achieved with deep pericardial sutures, a right pleurotomy and pericardiotomy, right hemisternal elevation, or apical suction devices, as described next.

Deep Pericardial Sutures

One of the most important advances in exposure techniques for OPCAB is the use of deep pericardial sutures. First described by Lima,¹⁵ these sutures, when placed under tension, create a ridge of pericardium that supports the base of the lateral left ventricle adjacent to the atrio-ventricular groove and allows the heart to be rotated rightward to assume an “apex up” position (Fig. 89-5). In this subluxed position, the apex of the heart points toward the ceiling and protrudes through the sternotomy incision, often above the plane of the sternal retractor. This generally allows adequate exposure of the lateral and inferior aspects of the left ventricle before the coronary stabilizer is applied.

Placement of deep pericardial sutures may vary among surgeons and according to the patient's anatomy. Generally, one or two 2-0 silk sutures are placed in the

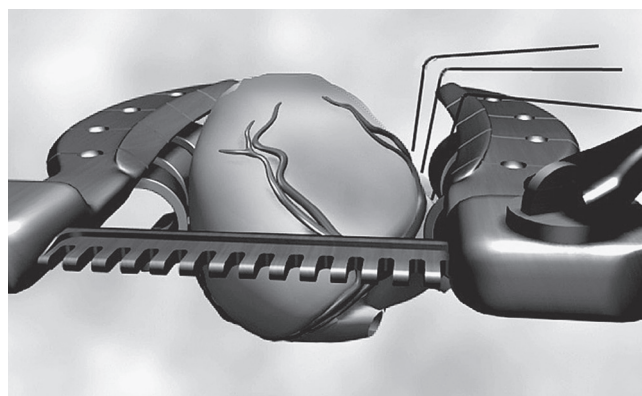


FIGURE 89-5 ■ Deep pericardial sutures secured under tension deliver the heart into an “apex up” position that provides adequate exposure of the lateral wall in many patients.

pericardium posterior to the left phrenic nerve and immediately anterior to one or both left pulmonary veins; one suture is placed deep in the oblique sinus behind the left atrium, and one is placed to the left and posterior to the inferior vena cava (Fig. 89-6). Care must be taken to avoid injury to underlying structures, such as the esophagus and lung.¹⁶ The suture in the oblique sinus is particularly important for obtaining good exposure of the lateral wall near the base of the heart. One commonly used technique consists of placing a single deep pericardial suture in this location, then using that suture to secure the midpoint of a 50-cm gauze strip deep in the oblique sinus. Subsequent traction on the two ends of the strip can be adjusted to optimize exposure of different surfaces of the heart.

Regardless of the technique used, deep pericardial traction sutures generally allow presentation of the lateral, inferior, and even posterior wall of the heart with little change in LV geometry or LVEDV, providing adequate access for multivessel CABG while maintaining hemodynamic stability. In some patients, however, some or all additional maneuvers discussed in the following paragraphs are necessary to accomplish this aim.

Right Pleurotomy and Right Vertical Pericardiotomy

A right pleurotomy and right vertical pericardiotomy are helpful technical adjuncts when lateral wall exposure is difficult. Human pericardium is quite flexible but very inelastic. This inelasticity accounts for the profound hemodynamic effects caused by acute tamponade despite a relatively small volume of intrapericardial fluid. The posterior pericardium, right lateral pericardium, and diaphragmatic pericardium constitute a fixed-volume cusp or pocket. It is into this pocket that the right ventricle is compressed during extreme rightward rotation of the heart. In effect, pressure on the left ventricle results in RV tamponade. Opening the right pleura widely and incising the pericardium will vent the pocket, allowing the heart to herniate into the right pleural space while maintaining the RVEDV.

A right lateral pericardiotomy can be performed by making a right vertical incision that extends from the cut edge of the initial anterior pericardiotomy, 2 cm cephalad and parallel to the diaphragm, down to the level of the inferior vena cava, with care to avoid injuring the right phrenic nerve (Fig. 89-7). The 2-cm rim of pericardium on the diaphragm facilitates closure of the pericardiotomy once grafting is complete. Caution should be exercised in measuring right-sided grafts, as closure of the lateral pericardial incision may affect how they lie. Many surgeons advise closing the lateral pericardiotomy before constructing the proximal anastomosis of a right-sided graft to ensure a tension-free non-kinking graft. In some circumstances, one may also benefit from removing the right pericardiophrenic fat pad, which can be large, and decreasing the tidal volume to provide additional room for the easily deformed right ventricle. These techniques offer some benefit in almost all patients but are extremely valuable in obtaining lateral-wall access in patients with enlarged hearts and marginal hemodynamic stability.

Some surgeons skilled at performing the OPCAB procedure avoid a right pleurotomy and lateral pericardiotomy. These surgeons contend that incising the lateral pericardium and entering an additional body cavity is inconsistent with the objective of decreased invasiveness. Many patients can indeed be treated successfully without this maneuver. In our opinion, however, it facilitates the reproducible performance of a precise anastomosis during multivessel OPCAB. Furthermore, a right pleurotomy neither leaves a scar nor is associated with significant morbidity or additional length of hospital stay.

Right Hemisternal Elevation

In conjunction with the techniques described earlier, asymmetrical right hemisternal elevation can further improve lateral wall exposure. Once the right pericardium and pleura are incised, the right half of the sternum and right blade of the retractor limit rightward displacement of the subluxed apex of the heart. By elevating these structures, the surgeon can cause the apex to clear the posterior aspect of the chest wall. This allows the entire

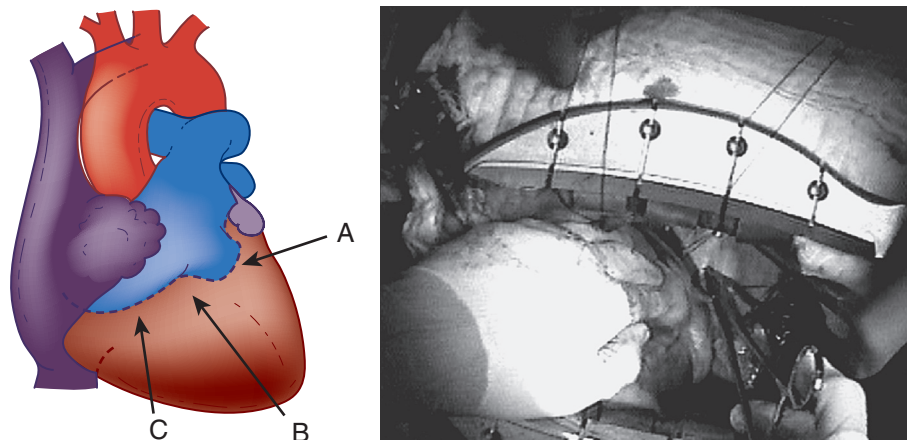


FIGURE 89-6 ■ The diagram shows the approximate locations for the deep pericardial sutures. Most surgeons agree that the suture at B is of greatest importance for lateral wall exposure. The photograph shows operative exposure for placement of the deep pericardial sutures, with the heart reflected up and to the right.

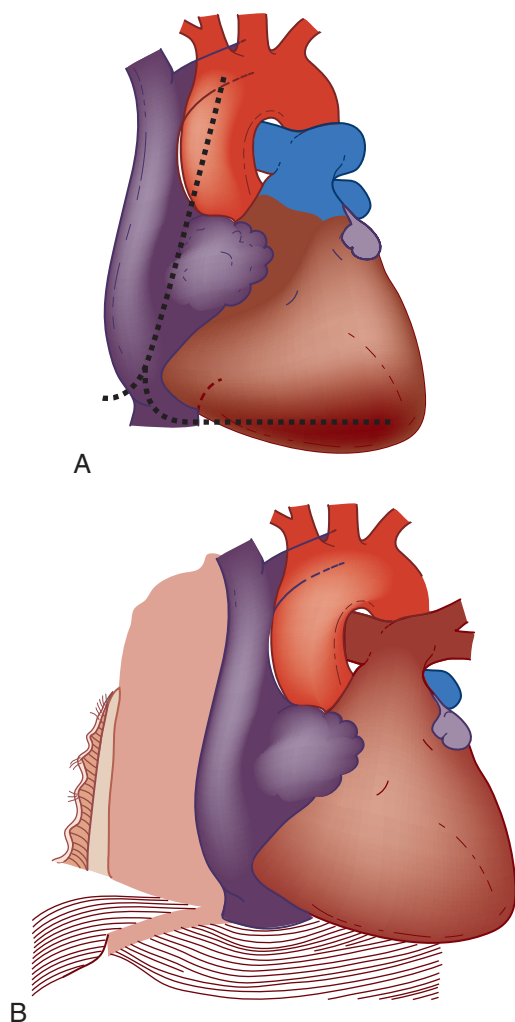


FIGURE 89-7 ■ **A**, An L-shaped pericardiotomy is created to the right of midline with the horizontal component extending to the cardiac apex. The right pleural space is opened widely and the right pericardium is excised almost to the inferior vena cava with care to avoid the right phrenic nerve. **B**, These incisions will vent the pocket, allowing the heart to herniate into the right pleural space to minimize hemodynamic compromise.

heart to rotate into the right pleural space with little change in LV and RV geometry and RVEDV (Fig. 89-8). As a result, the proximal obtuse marginal and posterolateral branches are brought toward the center of the operative field and into the surgeon's view.

Right hemisternal elevation is best carried out as the sternotomy incision is being performed. If anterior traction is applied on the right-sided chest wall when the retractor is first spread, costal microfractures that inevitably form during sternal opening will occur predominantly in the right-sided ribs. The resulting increase in flexibility of the right-sided chest wall will subsequently prevent the need for exaggerated tilting of the sternal retractor, which is often required to overcome the tendency of the left-sided chest wall to rise after internal mammary artery harvest. The diaphragmatic insertion on the inferior aspect of the right hemisternum can also be released to facilitate right hemisternal elevation and create additional room for displacement of the cardiac apex into the right pleural space.

Apical Suction Devices

Self-retaining apical suction retractors have been added to the operative armamentarium of OPCAB surgeons. These tools are used to position the heart for exposure of its lateral and posterior surfaces with little impact on hemodynamic values. The retractors generally consist of a suction cup mounted at the end of an articulating arm that can be locked in position relative to the retractor (Fig. 89-9). The suction cup is placed at or near the apex of the heart and is held in position by a vacuum (300 mm Hg). Pulling the apex away from the base and pivoting the cardiac axis can achieve excellent exposure with little impact on LV geometry and the LVEDV. Although use of these devices adds to the expense of OPCAB, their easy affixation and rapid set-up make them an attractive adjunct for use in challenging cases. In many OPCAB centers, apical suction retractors, in conjunction with a right pleurotomy, vertical pericardiotomy, and sternal tilt, are used in most cases (Fig. 89-10).

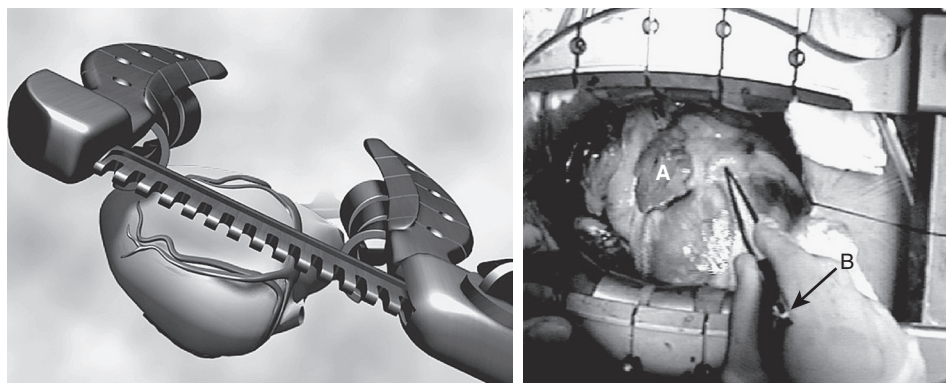


FIGURE 89-8 ■ Tilting the right hemisternum, performing a vertical pericardiotomy, and opening the right pleura often allows the surgeon to position the apex of the heart in the right side of the chest. The cardiac apex (**A**) is deep to the right hemisternum, and the left atrial appendage (**B**) is brought to the center of the operative field. This results in optimum exposure of the lateral wall, especially in patients with cardiomegaly.

Results after OPCAB

The relative merit of OPCAB versus CABG with CPB remains unclear. Few topics in cardiac surgery have given rise to more debate. Since the 1990s, when interest in OPCAB was renewed, researchers have attempted to clarify the ideal role of this treatment modality. Early reports from retrospective, nonrandomized, multicenter series showed lower death and stroke rates, less need for IABP use and postoperative transfusion, and a shorter ventilator time and length of hospital stay for OPCAB than for contemporaneous conventional CABG performed at the same institutions¹⁷⁻²⁴ or recorded in national databases.^{25,26}

These encouraging results led to a number of early prospective, randomized trials, many of which showed no difference between OPCAB and CABG with CPB with regard to mortality, myocardial infarction, or coronary reintervention.²⁷⁻³¹ Early meta-analyses^{32,33} and systematic reviews³⁴ confirmed these results. For years, the use of OPCAB continued to increase. One national, multicenter, observational study showed a peak in 2003, almost one quarter of cases being performed off pump.³⁵ Increasing interest and ongoing international debate continued to drive intense clinical investigation.

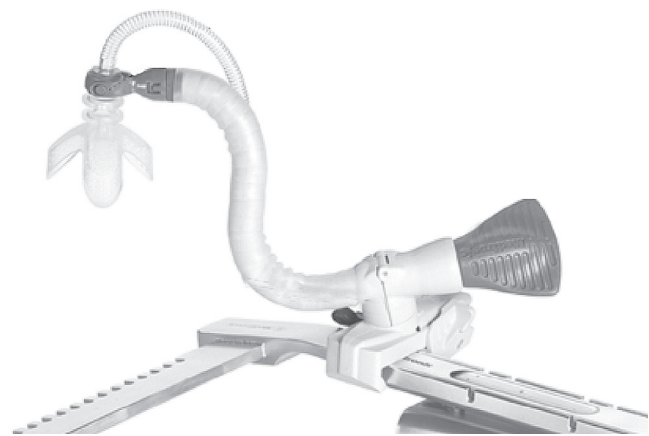


FIGURE 89-9 ■ Apical suction devices allow the surgeon to rapidly position the heart without placement of deep pericardial sutures.

In 2009, the Veterans Affairs Randomized On/Off Bypass (ROOBY) trial investigators reported the first large, multicenter, prospectively randomized study.³⁶ More than 2000 patients were enrolled, and the results sparked intense debate. Patients undergoing OPCAB had a significantly higher rate of the composite endpoint, including all-cause mortality, nonfatal infarction, and repeat revascularization procedures at 1 year. Closer analysis of the follow-up angiography data revealed that OPCAB resulted in lower rates of FitzGibbon A patency and of effective revascularization.³⁷ Furthermore, ineffective revascularization was associated with significantly higher rates of adverse cardiac events.

Shortly after the ROOBY trial results were published, several worldwide groups of investigators began to report their own findings. The German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) study was another prospective, large-cohort, multicenter trial that focused on patients 75 years of age and older.³⁸ Again, more than 2000 subjects were randomized to undergo either OPCAB or CABG with CPB. The investigators reported no significant difference in the composite or individual outcomes of death, stroke, infarction, or new renal-replacement therapy at 30 days or at 1 year.

These trials were subjected to intense debate and criticism. Objectors noted that the trials had enrolled too few patients, thereby lacking sufficient statistical power to detect differences in certain clinical endpoints. The technical expertise of the surgeons who performed OPCAB in these trials was also brought into question. To address these potential limitations, Canadian investigators reported initial data from their multicenter, prospective trial, which randomized almost twice the number of patients to undergo OPCAB or CABG with CPB.

The CABG Off or On Pump Revascularization Study (CORONARY) was more effectively powered than previous trials, and participating surgeons were required to have at least 2 years of experience involving more than 100 procedures performed. At 30 days and 1 year, the CORONARY trial showed no significant differences in the rate of primary composite outcome or its individual components, which included death, nonfatal stroke, nonfatal myocardial infarction, or new renal failure requiring dialysis 30 days after randomization.^{39,40} The OPCAB

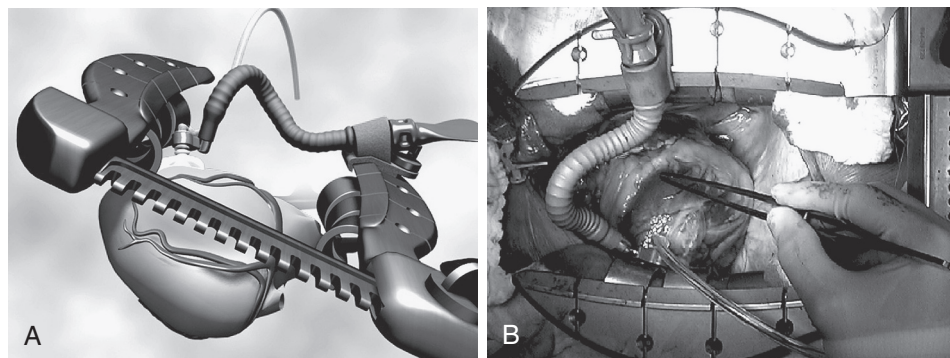


FIGURE 89-10 ■ **A**, An apical suction device, when it is used in conjunction with right hemisternal elevation, a vertical pericardiotomy, and a right pleurotomy, provides optimal exposure of the high lateral wall. **B**, A vein graft constructed without CPB from the descending thoracic aorta to lateral wall vessels through a left thoracotomy avoids some of the technical challenges associated with reoperative CABG in patients with patent mammary artery grafts.

patients had shorter operations and ventilator times, fewer blood-product transfusions, fewer repeat operations for bleeding, and lower rates of respiratory complications and acute kidney injury. However, fewer bypass grafts were completed in the OPCAB group, and the rates of incomplete revascularization were higher. Similar findings regarding fewer numbers of grafts and lower rates of revascularization have been reported in other trials, and these factors are thought to contribute to the inferior long-term outcomes of OPCAB.⁴¹ Five-year follow-up data from the CORONARY trial are anticipated and should provide further evidence for the appropriate use of OPCAB in multivessel CAD.

Although the debate continues, there is still compelling evidence that OPCAB is associated with decreased operative risk in some high-risk groups,^{17,42,43} including older patients, those with a reduced ejection fraction, and those with renal failure.⁴⁴⁻⁴⁷ Several reports have documented that OPCAB is associated with a decreased risk in reoperative patients as well.⁴⁸⁻⁵¹

Because reoperative OPCAB can be performed frequently without dissecting out the ascending aorta or manipulating diseased grafts, it is an attractive approach. However, many surgeons consider the presence of heavily diseased but patent vein grafts a contraindication to OPCAB because of the risk of atheromatous embolization down the grafts while the heart is being repositioned. A tailored left thoracotomy approach has been reported for reoperative grafting of the lateral wall in patients with patent LIMA-to-LAD grafts. Using this exposure, the surgeon can readily construct a graft from the descending thoracic aorta to lateral wall branches while avoiding the technical challenges associated with LIMA-graft mobilization. Long-term patency data are not available for this type of graft. Similarly, lower sternotomy and upper abdominal incisions have been described for constructing grafts to the inferior wall with the right gastroepiploic artery.^{52,53}

Although no consensus as yet exists, it is generally agreed that a well-performed OPCAB procedure is superior to a poorly performed conventional CABG operation and vice versa. Furthermore, there are many patients in whom OPCAB would be technically difficult or inadvisable (because of a deep intramuscular LAD, small diffusely diseased coronaries, need for an extensive endarterectomy, or active ischemia associated with hemodynamic compromise); there are also many patients for whom conventional CABG would pose an unnecessary risk (because of an atheromatous ascending aorta or a systemic disease process that might be exacerbated by CPB). Familiarity with the tools and techniques outlined here and the ability to perform OPCAB when necessary are valuable resources for practicing cardiac surgeons.

Minimizing Aortic Manipulation

Most surgeons agree that OPCAB is ideally suited for revascularization in patients with significant atheroma or calcification of the ascending aorta. In this setting, free grafts constructed from either the right internal mammary artery or the right radial artery can be attached to the side of the in situ LIMA, as described initially by Tector

and colleagues,⁵⁴ and used to perform multivessel OPCAB without manipulating the aorta. Occasionally, the innominate artery can be used as a site for a proximal anastomosis if that artery is free of atheromatous plaque.

Alternatively, free grafts can be attached to a small disease-free area of the aorta with an automated anastomotic device (AAD), which obviates the need for a partial-occlusion clamp (Fig. 89-11). In 2008, the Food and Drug Administration (FDA) cleared these devices for sale in the United States. Although a previous AAD for constructing a clampless proximal anastomosis was approved for U.S. sale in 2001, it was subsequently withdrawn from the market when longer term data suggested that it was associated with decreased graft patency. In contrast, the latest iteration of an AAD for proximal use seems to be associated with equal or improved long-term graft patency when compared to a hand-sewn technique.⁵⁵ Although it is compelling to hope that AADs will improve outcomes by decreasing aortic manipulation, this has yet to be demonstrated in a case-control study. It is clear, however, that the current device allows a widely patent proximal anastomosis to be rapidly constructed without a partial-occlusion aortic clamp; moreover, the AAD can be readily used in patients who have areas of ascending aortic plaque that would make application of a partial-occlusion clamp unwise. The ultimate role of proximal AADs in the evolution of CABG surgery will depend on a number of issues, not least of which are economic ones.

Since 2002, several tools have been available that facilitate construction of a hand-sewn proximal anastomosis between a free graft and the ascending aorta without requiring a traditional partial-occlusion clamp.⁵⁶⁻⁵⁹ Although slightly more labor intensive to use than loading and deploying a proximal AAD, these aortotomy occlusion tools permit construction of a tailored, hand-sewn anastomosis and accommodate a wider range of potential conduits, including radial and free-mammary grafts. These tools require a greater degree of technical facility than does a partial-occlusion clamp, but they decrease aortic manipulation and, like AADs, can be used when aortic plaque would make applying a partial-occlusion clamp ill advised. Using a combination of palpation and epiaortic ultrasonography, the surgeon can frequently identify an appropriate dime-sized area of relatively normal aorta where the occlusion device can be deployed. Although devices of this sort have been shown to liberate fewer gaseous and particulate emboli than do partial-occlusion clamps,⁶⁰ there are no compelling data to show that aortotomy occlusion tools are associated with improved outcomes. Nevertheless, these tools allow OPCAB to be readily performed while avoiding the hazards of cannulation and cross-clamping of the diseased ascending aorta.

Neurocognitive Dysfunction after OPCAB

Numerous published reports have described the new onset of subtle neurocognitive dysfunction (NCD) in some patients after CABG. Depending on the sensitivity of the tests used, the incidence has been reported to be

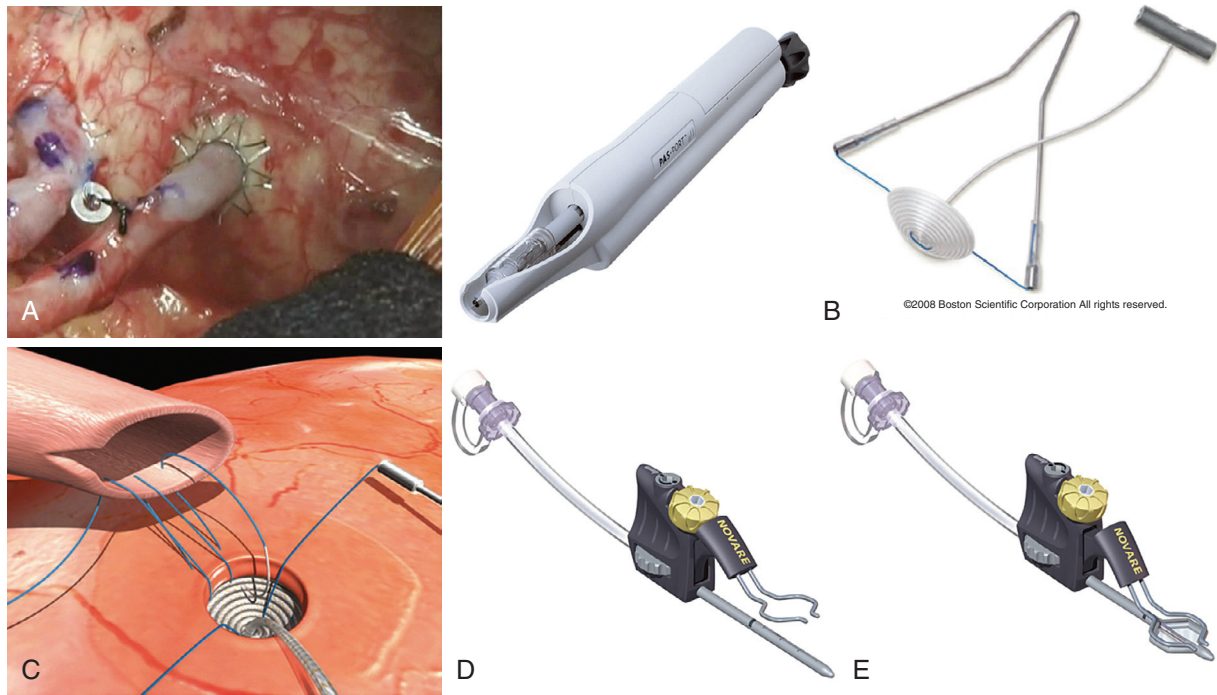


FIGURE 89-11 ■ **A**, An automated device for performing the proximal anastomosis between the ascending aorta and the saphenous vein without a partial-occlusion clamp was approved for clinical use in 2008 after demonstration of intermediate patency equivalent to hand-sewn anastomosis. **B-E**, Tools that facilitate construction of the proximal graft-to-aorta anastomosis without a cross-clamp and automated anastomotic couplers may have an impact on the incidence of neurocognitive deficit after CABG.

5% to 60%. Specific deficits include short-term memory loss, reduced ability to perform simple calculations, and disturbances in personality and mood.⁶¹⁻⁶³ Many CPB-related factors, including a systemic inflammatory response, alterations in cerebral blood flow, and microemboli—either arising from the CPB circuit or related to cannulation and cross-clamping—have been implicated.^{63,64} Several groups have reported that OPCAB is associated with a significantly milder systemic inflammatory response.^{44,65,66} The magnitude of the response, however, has not been shown to correlate with the severity of NCD in individual patients.¹ Furthermore, although a few studies have shown that, compared to conventional CABG with CPB, OPCAB is associated with a reduced incidence of NCD,^{64,67,68} most studies have shown no significant difference.^{31,69-71}

This failure of OPCAB to favorably impact postoperative NCD has been largely attributed to the partial-occluding aortic clamp and to microemboli liberated during its application and removal. Although OPCAB obviates the need to place a perfusion catheter for CPB or a cross-clamp for cardiac arrest, the side-biting partial-occlusion clamp, routinely used at many centers during construction of proximal anastomoses, arguably is equally traumatic.⁷² Avoidance of aortic manipulation by using composite grafts arising from the in situ LIMA and OPCAB has been shown to be an important factor in avoiding postoperative stroke.^{73,74} A number of new devices recently introduced into clinical practice (see earlier) allow proximal anastomoses to be constructed off-pump without application of a partial-occlusion clamp

(see Fig. 89-11). The impact these devices will have on NCD after OPCAB is yet to be determined.

LIMITED-ACCESS CORONARY ARTERY BYPASS

Additional efforts to minimize the invasiveness of CABG have focused on decreasing the trauma of surgical access. Although a median sternotomy is relatively well tolerated, patients must refrain from heavy lifting for 2 to 3 months to allow reunion of the sternum. The incidence of wound complications is low, but sternal wound infections can be life-threatening and generally require repeat operation. Moreover, the musculoskeletal trauma involved in spreading the sternal halves is associated with a small degree of systemic inflammatory response that is synergistic with CPB in causing morbidity.^{75,76} Avoiding a sternotomy is, therefore, an attractive idea.

Minimally Invasive Direct Coronary Artery Bypass (MIDCAB)

In 1995, Benetti and coworkers introduced the MIDCAB procedure,⁷⁷ which was rapidly adopted by multiple centers in the United States and Europe.^{78,79} The procedure is performed through a 7-cm anterior lateral thoracotomy, usually in the fifth intercostal space, and generally consists of a single-vessel off-pump procedure using the LIMA to bypass the LAD. Many early series yielded satisfactory results, including a substantially shorter

length of stay than for standard CABG, as well as decreased resource utilization, a reduced requirement for transfusion, and excellent graft patency.⁷⁸⁻⁸¹ Other reports suggested a reduced incidence of postoperative atrial fibrillation,⁸² but this finding has been refuted.^{14,83} Despite initial enthusiasm, traditional MIDCAB with LIMA harvest under direct vision is currently performed in large numbers in only a few U.S. centers. This decreased utilization is due in part to the technical hurdles involved in harvesting the LIMA under direct visualization through a small anterior lateral thoracotomy.

Several early reports documented successful results with endoscopic LIMA harvest.^{84,85} At many U.S. centers, however, surgeons chose to mobilize the LIMA by using direct visualization through a small thoracotomy to avoid the learning curve associated with videoscopic instrumentation and visualization. Direct harvest is often technically demanding and occasionally results in a LIMA graft of inadequate length. In addition, the vigorous chest-wall retraction required for LIMA exposure results in significant early postoperative pain. Nevertheless, several groups skilled in MIDCAB continue to perform the procedure in large numbers and report excellent results.^{81,86,87}

Hybrid MIDCAB Approach

Several reports have documented the successful application of a hybrid strategy in which a LIMA-to-LAD bypass (MIDCAB) is combined with catheter-based interventions on the circumflex artery and RCA for treating multivessel disease. In one multicenter series, videoscopic mobilization of the LIMA was performed with the aid of a voice-actuated robotic arm used to manipulate the scope (Fig. 89-12).⁸⁸ In this series, the pericardium was opened by using videoscopic techniques before the thoracotomy was performed. In many patients, this facilitated accurate placement of the chest-wall incision, allowing the anastomosis between the LIMA and LAD to be constructed without a rib spreader; only soft tissue



FIGURE 89-12 ■ Videoscopic mobilization of the left internal mammary artery may have a role in the continued evolution of less invasive CABG.

retractors and a specially designed bed-mounted stabilizer were used to expose the anastomotic site through the natural intercostal space (Fig. 89-13).⁸⁹ This approach significantly reduced postoperative pain. This experience generated resurgent interest in the MIDCAB procedure at many centers.

Completely Endoscopic Robotic-Assisted CABG

The literature describes a growing number of series involving completely closed-chest videoscopic LIMA-to-LAD procedures using surgical robots to mobilize the LIMA and to perform the sutured anastomosis, both with CPB^{90,91} and without CPB.^{90,92,93} The robots allow the surgeon to manipulate fully articulating videoscopic instruments by way of master-slave servos and microprocessor control. These instruments allow multiple degrees of freedom and can precisely emulate the surgeon's movements. An easy-to-use control environment, high-resolution displays that provide realistic three-dimensional stereopsis, and high magnification, as well as tremor filtering and motion-scaling options, offer the potential for superhuman precision. This precision compensates somewhat for the absence of tactile feedback. Although the concept is extremely exciting, the routine use of surgical robotics in CABG surgery does not seem imminent. The robots are expensive, and the learning curve for robotic totally endoscopic CABG (TECAB), especially if performed without CPB, is challenging. Surgeons skilled in the procedure can successfully perform only approximately one in three off-pump TECABs in carefully selected patients, resorting to a small MIDCAB incision to perform the anastomosis in the remainder. Future refinements in surgical robotic tools and techniques,

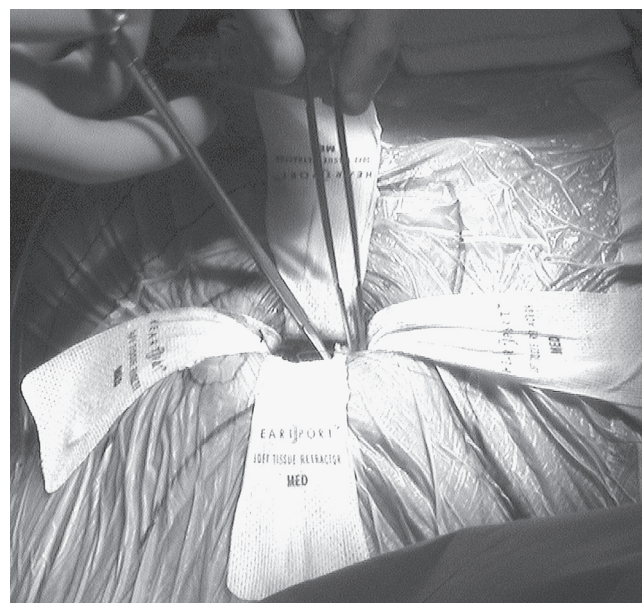


FIGURE 89-13 ■ In one type of less invasive bypass, accurate placement of the chest wall incision often allows the anastomosis between the left internal mammary artery and the left anterior descending artery to be constructed through the natural interspace without placement of a rib spreader.

improvements in automated distal anastomotic devices, and other advances may help determine the ultimate utility of robotics in CABG procedures.

Port-Access CABG

In 1996, Heartport introduced port-access cardiac surgery as a means of decreasing the trauma of surgical access. This strategy uses specialized catheters that are inserted into the femoral artery and vein and allow institution of CPB, balloon endoclamping of the ascending aorta, administration of antegrade cardioplegia, and venting of the ascending aorta. Additional catheters introduced percutaneously into the left jugular vein allow delivery of retrograde cardioplegia into the coronary sinus and venting of the pulmonary artery. A small chest incision can then be tailored for the desired procedure. In the late 1990s, several series of multivessel CABG operations performed through small fifth-intercostal-space thoracotomies were published that showed acceptable results from use of port access for institution of CPB,⁹⁴⁻⁹⁶ but this procedure is not widely used. Decreased enthusiasm is partly due to challenges associated with graft length and lie. Nevertheless, port access has remained an essential component of TECAB in several small series, and it remains an enabling technique in limited-access mitral procedures and atrial-septal defect repair. Advances in surgical robotics and automated distal anastomosis may have an impact on the ultimate role of port-access technology in the evolution of limited-access CABG.

TRANSMYOCARDIAL LASER REVASCULARIZATION

Transmyocardial revascularization (TMR) is an alternative surgical therapy for the treatment of severe coronary artery disease. Currently reserved for patients refractory to medical management, TMR is indicated when complete revascularization cannot be achieved with conventional percutaneous or surgical techniques. In an open TMR procedure, revascularization is achieved with a hand-held laser device that delivers thermal energy to the ventricle, creating 1-mm channels through vaporized myocardium with the aim to improve blood flow.

The efficacy of TMR in relieving symptoms of angina is well documented, and this procedure is no longer considered experimental.^{97,98} Initial positive results led to the approval of TMR by the Food and Drug Administration in 1998, and at least 20,000 procedures, in isolation or combined with CABG, have been performed in the United States.⁹⁹ To date, there remains a lack of long-term, randomized clinical data showing the superiority of isolated TMR over its use as an adjunctive therapy. Indications and long-term benefits remain in question, but ongoing investigations are helping to clarify the ideal use of this technology.

Operative Procedure

Open TMR is performed under general anesthesia and involves the direct application of laser energy to the

epicardial surface of the heart. Preoperative preparation includes chest roentgenography, echocardiography, and a nuclear perfusion scan or dobutamine stress echocardiogram to document hibernating myocardium, as scar tissue does not benefit from TMR.

All patients require intraoperative monitoring with continuous electrocardiography, a Swan-Ganz catheter, an arterial pressure line, and transesophageal echocardiography. A double-lumen endotracheal tube is used to isolate the left lung; this facilitates the procedure in patients who have had previous cardiac surgery and may have pleural or mediastinal adhesions. Skin preparation includes the groin, in case the need arises for IABP insertion. CPB and systemic anticoagulation are not required.

In isolation, TMR can be performed through a left anterior thoracotomy in the fifth intercostal space. After a retractor has been inserted to separate the ribs, the pericardium is opened and the epicardial surface of the heart exposed, with care to avoid previous bypass grafts. Starting near the cardiac base, channels are created in approximately 1-cm increments in a linear fashion, working inferiorly and moving superiorly toward the anterior surface of the heart. This technique prevents expected mild TMR-related bleeding from obstructing the progression of the operation. The number of channels created depends on the size of the ischemic area and of the heart itself. Care must be taken to avoid thinned and dilated myocardium.

TMR is performed with a carbon dioxide (CO₂) or a holmium:yttrium-argon-garnet (Ho:YAG) laser. Both types of lasers rely on thermal energy. The CO₂ laser beam is transmitted through a series of mirrors and lenses, whereas the Ho:YAG laser relies on an optical fiber. The CO₂ device delivers up to 1000 watts of energy, creating 1-mm channels with a 20- to 30-J pulse. By synchronizing the firing of the CO₂ laser with the R wave on the electrocardiogram, one can potentially avoid ventricular arrhythmias. A transmural channel is created by a single 40-msec pulse, which is confirmed on transesophageal echocardiography by the appearance of characteristic changes caused by laser energy dissipating into the blood within the ventricle.

The Ho:YAG laser differs in its method of creating transmyocardial channels. An optical fiber must physically puncture the epicardium before the laser is deployed. The Ho:YAG laser requires 20 to 30 pulses at 2 J to create a single channel, and the pulses are not synchronized to the electrocardiogram, so the arrhythmogenic potential is greater than with the CO₂ laser. The optical fiber must be manually advanced, and successful creation of a transmural channel does not require transesophageal echocardiographic confirmation. After completion of TMR, a chest tube is inserted and the thoracotomy closed. The patient is transferred to the intensive care unit for monitoring.

Clinical Results

Since the first clinical use of open TMR by Mirhoseini and colleagues¹⁰⁰ in 1983, subsequent data have consistently shown a clear and substantial reduction in angina pectoris.¹⁰¹ In multicenter studies comparing TMR to

optimal medical therapy, most TMR patients had at least a two-class reduction in their Canadian Heart Association angina status. Long-term follow-up data have confirmed the persistent relief of symptoms, as well as a possible increase in survival.¹⁰²⁻¹⁰⁴ Combined with CABG in selected patients who have limited options for revascularization therapies, TMR may improve long-term symptomatic relief and does not appear to increase the risk of procedure-related adverse events.^{103,105} TMR has also been used as an adjunct to stem cell therapy, and initial data have been encouraging.^{106,107}

Mechanism

The mechanism by which TMR provides symptomatic relief remains unclear, but three potential contributing effects are recognized: direct perfusion through the channels created by TMR; inflammatory effects resulting in angiogenesis; and sympathetic denervation. Originally, TMR was presumed to provide its benefit via perfusion of the created channels, ultimately affecting nearby capillaries within the myocardium. However, inconsistent reports documenting the long-term patency of these channels have given rise to substantial debate.¹⁰⁸⁻¹¹² Although some positron emission tomography/computed tomography studies have shown evidence of sympathetic denervation,¹¹³ it is difficult to isolate afferent sympathetic nerve fibers, and this mechanism of benefit remains theoretical. Moreover, neovascularization of the myocardium as a nonspecific response to myocardial injury has been demonstrated in previous studies, which have shown upregulation of molecular factors of angiogenesis, such as vascular endothelial growth factor, platelet-derived endothelial growth factor, and fibroblast growth factor.¹¹⁴⁻¹¹⁶ Ongoing research will ultimately help define the role of TMR in clinical practice; meanwhile, this procedure remains a useful tool in the cardiac surgeon's armamentarium.

CONCLUSION

Advances in surgical tools and techniques have given rise to a number of new options in the surgical management of coronary artery disease. Although additional data may be required before the relative merits of these options can be characterized, it is clear that this flexibility will better allow the surgeon to tailor the operative approach to fit the patient. This is especially important given the increased age and comorbidity of patients referred for coronary bypass.

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ROBOTIC AND ALTERNATIVE APPROACHES TO CORONARY ARTERY BYPASS GRAFTING

Stephanie Mick • Suresh Keshavamurthy • Tomislav Mihaljevic • Johannes Bonatti

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ROBOTIC AND ALTERNATIVE APPROACHES TO CORONARY ARTERY BYPASS GRAFTING

The standard approach for coronary artery bypass grafting (CABG) is median sternotomy using cardiopulmonary bypass. However, less invasive approaches, including off-pump CABG and smaller access surgeries with or without robotic assistance, have been developed. This chapter describes less invasive methods of coronary revascularization along with their associated outcomes, with emphasis on robotic CABG. Hybrid coronary revascularization techniques are also considered.

MINIMALLY INVASIVE SURGICAL CORONARY REVASCULARIZATION

Many alternatives to surgical coronary revascularization have been developed in the form of modifications to conventional CABG. These alternatives come under the broad rubric *minimally invasive coronary revascularization*.

It should be noted that when used in the realm of cardiac surgery, this description “minimally invasive” carries more possible meanings than in other surgical specialties. In contrast to other surgical disciplines where the degree of invasiveness of a procedure is primarily defined by the size of access incisions, in cardiac surgery

at least two forms of invasion can be altered. The trauma of physical access can be changed by the use of smaller incisions that involve less (or no) sternal splitting. The physiologic invasiveness can be altered by performing procedures off pump, that is, without the use of cardiopulmonary bypass and cardioplegic arrest. This at least theoretically modifies the degree of physiologic perturbation produced in performing the intervention.

The face of surgical coronary revascularization has been changed by innovations in both of these areas and inventions like the octopus stabilizer, spreaders for mini-thoracotomy approaches, devices for local coronary artery occlusion and shunting, the CO₂ mister-blower, long-shafted thorascopic instrumentation, robotic devices, and minimally invasive extracorporeal circulation have led to a completely different appearance of coronary surgery. Because off-pump coronary artery bypass (OPCAB) grafting is covered in [Chapter 89](#), it will not be covered in depth here; rather, this chapter describes techniques of surgical revascularization using access incisions other than conventional median sternotomy, with or without the use of cardiopulmonary bypass. The degree of revascularization possible with each intervention is discussed as well as some of the literature on the clinical outcomes associated with these approaches, with emphasis on robotically assisted approaches.

Minimally Invasive Direct Coronary Bypass

A minimally invasive direct coronary bypass (MIDCAB) operation (also referred to as single-vessel small thoracotomy direct-vision bypass grafting [SVST]) is a procedure using an anterior, medially placed, mini-thoracotomy incision. The incision is used for both direct-vision left internal mammary artery (LIMA) harvest and creation of an anastomosis of the LIMA to a coronary artery.¹ It is performed off pump and requires the use of a stabilizer placed either directly through the operative incision or through a separate port incision.

Because of the limited access to the lateral and posterior surfaces of the beating heart during this procedure, coronary revascularization using MIDCAB is generally limited to the bypass of the left anterior descending (LAD) artery or its diagonal branches. To allow for takedown of the internal mammary artery (IMA) through this incision, specially designed retractors are available. (In the early development of MIDCAB, rib disarticulation or removal of cartilage was carried out.) The MIDCAB, therefore, essentially amounts to a one-vessel OPCAB to the LAD or its diagonal branches through a small thoracotomy.

Having originally been described in 1965 by Kolessov, the MIDCAB procedure was reintroduced in the mid-1990s. The procedure was adopted at many U.S. and European centers after its reintroduction, and many early series demonstrated decreased hospital lengths of stay relative to conventional CABG, decreased utilization of resources, earlier return to full activity, reduced transfusion requirement, and excellent graft patency.² When compared to a single-vessel OPCAB, data are limited;

however, small studies suggested that durations of mechanical ventilation and total hospital stay were decreased with use of MIDCAB.³

The main downside of this procedure is challenging early postoperative control of pain caused by the chest wall retraction involved in LIMA harvest.¹ Even with the smaller incision, the difficulties with postoperative pain may have contributed to the decrease in popularity of this procedure after its original introduction. Nevertheless, several centers skilled in this approach continue to perform it in large numbers and report excellent results.

For example, in one recent European report, Holzhey and coworkers reported their experience with 1768 MIDCABs between 1996 and 2009.⁴ This Leipzig group reported a 1.75% rate of conversion to sternotomy, 0.8% postoperative mortality rate, and 0.4% perioperative stroke rate. Routine postoperative angiograms showed 95.5% early graft patency, with a short-term target vessel reintervention rate of 3.3%. MIDCAB procedures have also been used successfully in the reoperative arena⁵ with some evidence of decreased operative mortality. The general acceptance of MIDCAB is low, and despite initial enthusiasm, several centers have abandoned the procedure. The significant learning curve for an individual surgeon to reach stable results (additionally requiring continuously high case loads to sustain surgeon skill^{4,6}) and less than optimal graft patency at some centers are probably the main causes for this phenomenon.

Preoperative Considerations

All patients should undergo the complete preoperative workup that is standard for open CABG. The patient's body mass index and body habitus are of worthy of note; obesity is a relative contraindication for MIDCAB because the pressure placed on the wound edges by the retractor during LIMA takedown may cause tissue necrosis and predispose the patient to wound infection. For similar reasons, female patients with large breasts may be at increased risk for wound-related complications.⁷ With regard to preoperative imaging, preoperative assessment of heart position relative to the interspaces on chest x-ray may be helpful in the planning of the access incision.

Technical Details

The patient is positioned supine with the left side up. Optimally single-lung ventilation is used; however, this is not absolutely necessary. If single-lung ventilation is not used, reduction in tidal volume and packing of the lung away from the field can be used. A left submammary incision in the mid-clavicular line in either the fourth or fifth interspace is used^{8,9} ([Fig. 90-1](#)). Review of the heart position relative to the interspaces on preoperative chest x-ray can be helpful in the planning of the access incision. It should be noted that the incision is the lower limit of LIMA takedown; the chest wall caudal to the incision cannot be visualized. Therefore, some physicians preferentially take the fourth interspace approach to obtain maximal conduit length.⁸ This consideration is important in the case of a distal LAD lesion. Some reports have described extensions of the LIMA by a segment of an

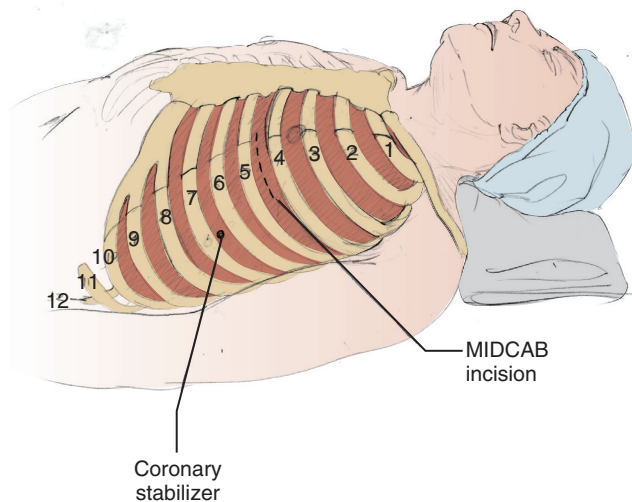


FIGURE 90-1 ■ The limited left anterolateral thoracotomy for minimally invasive direct coronary artery bypass (MIDCAB) is approximately 5 to 7 cm, commencing in the midclavicular line in the fourth intercostal space. Also shown is the port placement for the endostabilizer, which can be used later for insertion of a chest tube. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

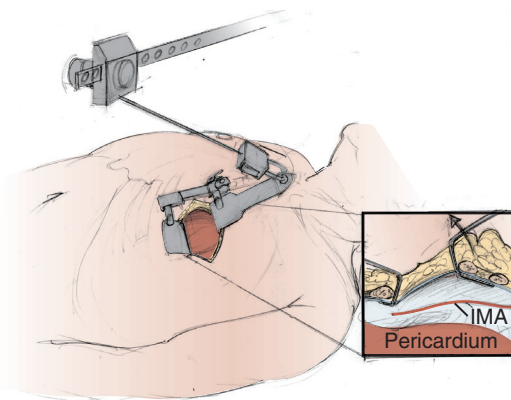


FIGURE 90-2 ■ Specialized retractor setup for left internal mammary artery (IMA) harvest in minimally invasive direct coronary artery bypass (MIDCAB). (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

additional arterial conduit to reach distal LAD targets and to avoid graft tensions.¹⁰

Following incision, a chest wall retractor is inserted for LIMA takedown. In general, retractors used for this purpose (e.g., those made by Medtronic, Inc., Minneapolis, MN) have an elongated superior blade designed to retract the upper ribs away, preventing their acting as a shelf limiting visualization (Fig. 90-2). The pleural fat is dissected away, the endothoracic fascia is exposed and incised with bovie electrocautery, and the LIMA is taken down in skeletonized fashion. It is recommended to locate the LIMA medial to the incision and proceed cephalad to the level of the subclavian vein.⁸ After heparin reaches activated clotting time (ACT) levels of 300 sec, the artery is divided at its distal extreme

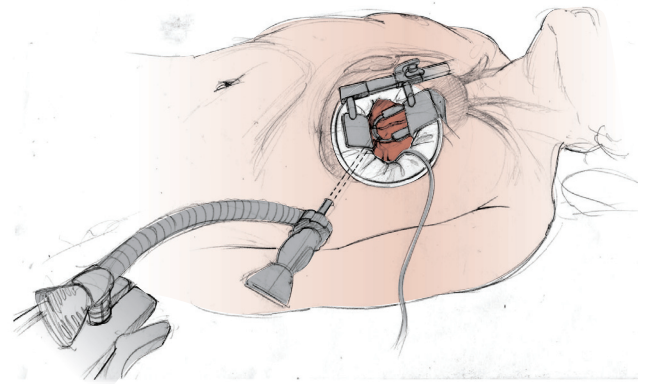


FIGURE 90-3 ■ Endostabilizer has been inserted and left anterior descending artery is exposed for grafting. Note the presence of a soft tissue retractor to optimize visibility. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

and the LIMA retractor is replaced with a standard thoracotomy retractor.

The pericardial fat pad is then removed. The phrenic nerve should be identified and the pericardium incised longitudinally anterior to it to the level of the base of the heart. The apex is identified and the LAD in its position to the right of the apex coursing parallel to the sternum. Care must be taken not to misidentify the diagonal artery as the LAD, which may be the first artery visualized. In contrast to the LAD, the diagonal artery courses parallel to the incision and toward the apex.⁷ Pericardial stay sutures may be useful in positioning the heart.

Once the LAD has been identified, it is stabilized either directly via the incision or using an endostabilizer brought through a separate lateral stab incision (Fig. 90-3). If the latter is used, this incision can also be used later for chest tube placement. Silastic loops are placed proximally and distally if necessary (note that distal snares should be avoided because they can lead to scar lesions and impaired flow), and the artery is exposed. Premedication with lidocaine or other antiarrhythmic can be used before vessel occlusion. Should hemodynamic compromise be encountered following occlusion, a 1.5-mm intracoronary shunt can be used, with the vessel occluders released, while the anastomosis is created. Whether shunted or not, anastomosis creation is performed in the standard fashion with 7-0 Prolene. It is recommended to assess flow with transit time ultrasound.

After heparin reversal and confirmation of hemostasis, the pericardium is loosely reapproximated to prevent heart herniation and adherence of the apex to the intercostal space. Some authors recommend reapproximation using a patch of bovine pericardium for this purpose.⁷ It is important to take care to avoid kinking of the LIMA, particularly as it passes through the pericardium during this process. A nerve block may be achieved by direct infiltration of 0.5% bupivacaine into the posterior intercostal spaces from ribs four to six. A single chest tube is placed in the left chest, the ribs are reapproximated, the pectoral muscle is reapproximated, and the skin is closed in standard fashion.

Postoperative Considerations

Patients can be extubated on the table; however, if patients are left intubated, any double-lumen endotracheal tubes inserted should be exchanged for single-lumen tubes. Aggressive pain management and a strategy of early mobilization should be instituted. If necessary, a thoracic epidural catheter may be used if less invasive pain control methods (narcotics, Lidoderm topical patches, etc.) are not sufficient.⁷ No sternal precautions are required following MIDCAB.

It is recommended to begin aspirin and clopidogrel 6 hours after surgery or once chest tube drainage is minimal⁷; there is some evidence that the use of dual antiplatelet therapy reduces the risk of perioperative myocardial infarction and graft occlusion in off-pump revascularization procedures.¹¹

Thoracoscopic MIDCAB

In an effort to avoid the degree of chest retraction typically involved in the standard MIDCAB procedure, other approaches to LIMA takedown have been developed. In the video-assisted MIDCAB approach (also referred to as “endo-ACAB”), the LIMA is harvested thoracoscopically via small access port incisions. The LIMA-LAD anastomosis is created through a mini-thoracotomy with minimal rib spreading. It should be noted that thoracoscopic LIMA takedown requires chest cavity insufflation, and patients’ ability to tolerate diminished ventilation intraoperatively should be assessed preoperatively.¹

The largest series of thoracoscopic MIDCAB was reported by Vassiliades and colleagues in 2007 who termed this approach *endoscopic atraumatic coronary artery bypass* (endo-ACAB). This group reports a 3.6% conversion to sternotomy or thoracotomy rate, a 1% postoperative mortality rate (to be compared to the STS National Database–predicted 30-day mortality of 2.7%), and a 0.3% stroke rate. These authors report a 96% LIMA-LAD patency rate with a mean follow-up of 18 months. The mean length of stay in the intensive care unit was 11.2 ± 9.9 hours, and in the hospital, 2.4 ± 1.3 days.¹²

Likely because of the advanced thoracoscopic skills necessary for the LIMA takedown in this approach (with an estimated 50-case learning curve required for mastery of the technique¹³), the thoracoscopic MIDCAB has not achieved widespread adoption at this time. However, centers with expertise in the technique have obtained promising results. Robotically assisted MIDCAB represents an alternative to thoracoscopic MIDCAB and is discussed in conjunction with other robotic revascularization techniques later.

Preoperative Considerations

All patients should undergo the complete preoperative workup that is standard for open CABG. The patient’s body mass index and body habitus are worthy of note, as in open MIDCAB. In general, patients with body mass index less than 30 are the most straightforward for those surgeons early in their learning curve. Women with large

breasts can be challenging because port sites may need to pass through the breast itself, or a larger submammary incision may be required. Preoperative spirometry may be helpful in determining the patient’s ability to tolerate the single-lung ventilation (with forced expiratory volume in 1 second [FEV₁] < 1 usually representing the cutoff value).¹⁴

Technical Details

As in an open MIDCAB, the patient is positioned supine on the operating room table with the left side up.

Under single-lung ventilation, three ports are placed in the left midaxillary line in the third, fifth, and seventh interspaces (some physicians recommend the fifth interspace port be placed in the anterior axillary line¹⁵). Standard thoracoscopic instruments can be used. A 30-degree (either 5-mm or 10-mm) thoracoscope is inserted via the fifth space first, and carbon dioxide insufflation is initiated to a target pressure of 8 mm Hg to increase the workspace inside the chest. It should be noted that if hemodynamic compromise is observed (a result of hypertensive pneumothorax, especially in patients with compromised left ventricular function) at this stage, it may be necessary to decrease the rate of insufflation or to evacuate some of the carbon dioxide from the thoracic space. The endoscope should then be inserted and a general view of the intrathoracic space obtained.

Next, a grasper and electrocautery or harmonic scalpel are inserted through the third and seventh interspaces. Following dissection of pleural fat, the endothoracic fascia is visualized. The fascia should be incised approximately 1 cm lateral to the IMA and retracted downward. Using gentle spatulation with the electrocautery or harmonic scalpel to identify the side branches of the IMA, the entire IMA can be harvested from the subclavian vein to the level of the xiphoid process through the cautery or harmonic division of its branches (clips are seldom used) in pedicled fashion.^{7,15} Care should be taken at the level of the first rib to avoid damage to the phrenic nerve and subclavian vein.

The pericardium may be opened and the target vessel identified. Anastomosis creation proceeds in a manner similar to that described for open MIDCAB, with incision placement guided by the thoracoscope. One of the port sites may be used for endostabilizer placement and subsequently the chest tube.

Postoperative Considerations

As in open MIDCAB, patients may be extubated on the table; however, if patients are left intubated, double-lumen endotracheal tubes should be exchanged for single-lumen tubes. Aggressive pain management and a strategy of early mobilization should be instituted. No sternal precautions are necessary. It is recommended to begin aspirin and clopidogrel 6 hours after surgery or once chest tube drainage is in keeping with the evidence that the use of dual antiplatelet therapy reduces the risk of perioperative myocardial infarction and graft occlusion in off-pump revascularization procedures.¹⁶

MULTIVESSEL MINIMALLY INVASIVE PROCEDURES

As described earlier, MIDCABs are generally restricted to the performance of a single LIMA-LAD or LIMA-diagonal bypass. The benefits of this method can be expanded to those patients with multivessel disease by combining MIDCAB with percutaneous coronary intervention (PCI) for lesions on the posterior and lateral surfaces of the heart in a hybrid approach. This hybrid method, however, can be used only when such lesions are amenable to PCI. This has led some physicians to create other minimally invasive alternatives for patients with multivessel disease.

The use of bilateral MIDCABs involving the use of bilateral anterior (medially placed) mini-thoracotomy in conjunction with bilateral direct-vision internal mammary as well as radial artery conduits has been reported¹⁷ but not been evaluated in large studies. The use of bilateral thoracoscopic IMA harvesting followed by right anterior thoracotomy for the bypass of right coronary artery and LAD territories has also been described. It should be noted, however, that in using this technique, bilateral thoracotomies were required to reach posterolateral vessels and it was not possible for the posterior interventricular branch to be bypassed.¹⁸

Techniques involving a single thoracotomy for multivessel disease have also been developed. One procedure, termed the *anterolateral thoracotomy–coronary artery bypass* (ALT-CAB) uses larger left thoracotomy. Through this incision, both the LIMA and the right internal mammary artery (RIMA) can be harvested under direct vision and the greater access to the heart allows all territories to be bypassed. Additionally, central cannulation is possible because of the greater exposure afforded by the larger incision. The procedure has not achieved widespread adoption, but it has been used in selected centers with acceptable results. In a series of 255 patients undergoing this procedure, complete revascularization was achieved in all patients and there were no conversions to cardiopulmonary bypass. The mortality and stroke rates in this series were 1.2% and 0.8%, respectively, with 65.1% of patients discharged within 48 hours of ALT-CAB.¹⁹

The newest non-robotic minimally invasive option for treating multivessel disease, introduced in 2005, is termed *minimally invasive cardiac surgery/coronary artery bypass grafting* (MICS CABG)¹⁸ (sometimes referred to as multivessel small thoracotomy [MVST]).²⁰ This approach uses a more laterally placed thoracotomy than a traditional MIDCAB. A specialized pivoting retractor allows for a full-length LIMA takedown through the thoracotomy, and two port-site incisions allow for the use of an epicardial stabilizer and an apical positioner. As a result of the position of the access incision along with the ability to position the heart with the apical positioner and epicardial stabilizer, all territories of the heart can be bypassed with this technique. The procedure is performed off pump and does not require the use of thoracoscopic or robotic equipment; it essentially amounts to a multivessel OPCAB performed through small incisions.

It should be noted that a limitation of MICS CABG is that right IMA takedown is not possible without use of a larger incision, thoracoscope, or robotic assistance.²¹ However, this limitation may be offset by the use of saphenous vein grafts with proximal anastomoses to the ascending aorta, a technique that has been practiced in selected centers.¹⁸

A dual center series of 450 patients over 3.5 years was reported for the MICS CABG and showed encouraging results. The authors report a 1.3% mortality rate and a 0.4% stroke rate. Complete revascularization was reported in 95% of patients undergoing this technique. No angiographic evidence with respect to graft patency was reported; however, at 19-month mean follow-up, 3% of patients required PCI. A 3.8% conversion to sternotomy was reported, and conversion to on-pump procedure (via peripheral cannulation) was reported in 7.6% of cases. It is interesting to note that the initial report included the entire experience of the institutions with the procedure, including their initial experiences. The authors suggest that this implies that this procedure may be implemented and developed without the occurrence of a significant learning curve with respect to morbidity and mortality. Proponents of this procedure assert that it has a greater availability for all cardiothoracic surgeons because the procedure does not require the costly infrastructure and disposable materials associated with robotic or thoracoscopic procedures.²⁰

Recently, MICS CABG was compared in case-matched fashion to standard OPCAB in a single surgeon's practice. Each group contained 150 patients and was matched with respect to age, gender, left ventricular function, and median number of distal anastomoses. The authors found significantly decreased length of stay (5.4 days vs. 7.2 days OPCAB, $P = 0.02$), wound infection (0 vs. 4% OPCAB, $P = 0.002$), and median time to return to full activity (12 days vs. >5 weeks OPCAB, $P < 0.001$) in favor of MICS CABG over OPCAB. There were no differences in mortality rate or rate of atrial fibrillation between groups, but there was a higher rate of pleural effusion in the MICS CABG group (15% vs. 4%, $P = 0.002$).²² No long-term data on graft patency are available, but early studies suggest excellent short-term patency rate (92% for all grafts, 100% for LIMA grafts at 6 months).²³ Additional data are needed to more fully evaluate this procedure, but it may have potential as a more widely adoptable minimally invasive surgical option for patients with multivessel disease.

Robotically Assisted Revascularization

Robotic surgical systems are telemanipulators in which a surgeon controls micro-instruments remotely from a console. The most widely used system is the da Vinci Si (Intuitive Surgical, Mountain View, CA). The system conveys high-definition three-dimensional imaging to the surgeon at the console and sensors register finger and wrist movements and translate them (tremor-free) into the motion of the micro-instruments in the operative field. The da Vinci robot was approved for cardiac surgery in 2002. Approximately 2000 robotic cardiac operations are performed in the United States per year, most of

which take place in a small number of experienced centers. The number of procedures is increasing modestly but represents a small fraction of the total number of cardiac surgical interventions performed yearly.²⁴

The use of robotics in minimally invasive cardiac surgery was intended to overcome some of the limitations of thoracoscopy. For example, thoracoscopic instruments offer only four degrees of freedom, a level not adequate for the delicacy required by cardiac surgery. The long shafted instruments may be prone to fulcrum effects and shear forces may be exerted at port sites, contributing to postoperative pain from intercostal nerve trauma. In addition, the surgical field images in thoracic surgical systems are presently two-dimensional; this loss of depth perception can impair surgical performance in delicate situations.²⁵

Surgical robotic systems are used in coronary revascularization in various ways, from robotically assisted MIDCAB (robotic IMA harvest with hand-sewn anastomosis using anterior thoracotomy or sternotomy) to totally intrathoracic revascularization (IMA takedown and bypass creation) performed solely through small port site incisions (totally endoscopic coronary artery bypass [TECAB]). TECAB can be performed with or without use of cardiopulmonary bypass and cardioplegic arrest. When cardioplegic arrest is used, the term *arrested heart TECAB* (AH-TECAB) is used. When the heart is not arrested, the procedure is referred to as *beating heart TECAB* (BH-TECAB).

The earliest use of robotic technology (late 1990s to early 2000s) in coronary revascularization recapitulated the role of thoracoscopy in the thoroscopically assisted MIDCAB, described earlier. Namely, robotically assisted IMA harvest was performed followed by single hand-sewn anterior anastomosis through a small thoracotomy in an off-pump fashion. When compared with a single-vessel OPCAB, robotically assisted MIDCAB has been associated with a shorter hospital stay and quicker return to work.²⁶ As with thoroscopically assisted MIDCABs, robotically assisted MIDCABs have also been described as key components of hybrid revascularizations, which are described later.

TECAB may be used for single- or multiple-vessel bypasses (generally using bilateral IMAs in multivessel cases) and represents the least physically invasive means of coronary revascularization. In contrast to other minimally invasive approaches, TECAB does not involve the use of incisions larger than port sites. Both on-pump and off-pump TECABs have been described. First performed in 1998,^{26a} TECAB has been described by proponents as having advantages of minimal surgical trauma and rapid recovery. Scarring is reduced compared with mini-thoracotomy approaches and no rib spreading is involved, resulting in minimal intercostal nerve trauma and less postoperative pain. Series from the early 2000s showed short hospital stays, early return of patients to full activities following TECAB, and rare deep thoracic wound infections, as a result of the minimal exposure of the operative field to the ambient environment. It has been suggested that the obese may benefit more from TECAB with respect to wound complications, as the operative exposure is no different in obese versus non-obese patients using this approach.²⁷

A recent review²⁸ of published series on TECAB found rates of 0.4% all-cause mortality, 0.8% perioperative stroke, 1.8% myocardial infarction, 5.1% new onset atrial fibrillation, 1.2% renal failure, 2.3% early reintervention, and 5.8% revision for bleeding in 360 AH-TECABs. These results compare favorably with conventional approaches with the exception of reoperation for bleeding. The early patency rate was 96.4% (in the 253 patients who had some form of early imaging study). Data on intermediate and long-term follow-up are scarcer in the literature. However, at 5-year follow-up on 62 one-vessel disease patients undergoing TECAB, a survival rate of 95.8%, freedom from MACCE rate of 83.1%, and freedom from angina rate of 91.1% have been reported.²⁹ The longest-term follow-up on graft patency available comes from Currie and colleagues¹⁶ who at 8-year follow-up (using coronary angiography, CTA, and stress myocardial perfusion scintigraphy) found a 92.7% overall patency rate in a mixed on-pump and off-pump population consisting of 82 patients.

Technical Details

Preoperative Evaluation

All patients should undergo the complete preoperative workup that is standard for open CABG. We also recommend that every patient undergo a preoperative CT angiography of chest, abdomen, and pelvis. This allows the surgeon to assess for the size of the heart and its relation to the chest wall, size of the pericardial fat pad, and relation of the IMAs to the target vessels. In our experience, a distance of less than 25 mm from the left heart border to the chest wall can lead to significant technical challenges because of insufficient working space. In addition, the courses (intramyocardial vs. epicardial) of the target vessels should be determined along with the ascending aortic diameter and grade of aortoiliac atherosclerosis. We also recommend spirometry in all patients being considered for TECAB. These values are important not only for determining the patient's ability to tolerate single-lung ventilation during IMA takedown but also for gaining a sense of intrathoracic volume. We have observed an FEV₁ of less than 2.5 liters to be an important cutoff value; under this level, intraoperative technical difficulties (related to space limitations) and postoperative morbidity increase.

The Role of Cardiopulmonary Bypass and Cardioplegic Arrest in TECAB

As mentioned earlier, TECAB can be performed with or without the use of cardiopulmonary bypass. Many patients benefit from beating heart approaches and, ideally, TECAB surgeons should become facile with BH-TECAB. Endoscopic suturing is technically more challenging than in the arrested heart approach, and surgeons are strongly advised to perform on-pump operations with endocardioplegia first. If a BH-TECAB is planned, we recommend prophylactic peripheral cannulation in all cases under all circumstances; the surgeon must be prepared for the worst case scenario of ventricular fibrillation with

the robot docked. Without prior cannulation and the ability to immediately initiate cardiopulmonary bypass, the situation can rapidly grow dire, with potential for great harm to the patient as well as to the TECAB program at the surgeon's institution. Therefore, we reiterate our recommendation to prophylactically cannulate all cases under controlled conditions with connection to the heart-lung machine tubing so that its immediate use can be used. Starting the pump and deflating both lungs can also allow the surgeon to gain significant additional space inside the chest if needed in a BH-TECAB. In some patients, this is the only way to develop adequate space and hemodynamics to access the back wall of the heart.

AH-TECAB requires specific perfusion and cardioplegia skills. Remote access cardiopulmonary bypass and the use of ascending aortic balloon occlusion are technically challenging and require discipline in patient selection. Femoral cannulation and endoballoon should be used only in patients without aortoiliac atherosclerosis (approximately two thirds of patients currently eligible for TECAB fall into this category). Axillary antegrade perfusion and femoral insertion of the endoballoon are the best option for patients with moderate grades of aortoiliac atherosclerosis. Transthoracic clamping and direct aortic root cannulation for cardioplegia are an option but in its early stage of development; challenges associated with this technique include transthoracic puncture of the ascending aorta, insertion of an appropriate catheter, and endoscopic robotic control of bleeding after catheter removal. Surgeons are advised to develop remote access perfusion techniques in other minimally invasive heart surgery before they apply them in TECAB. Introducing both robotic coronary surgery and advanced peripheral heart-lung machine techniques at the same time must be avoided.

With the previously mentioned safety measures in mind, we have found that both AH-TECAB and BH-TECAB are fascinating operations performed at a high level of comfort for the surgeons and their teams.

Technical Considerations in Cannulation

If there is no aortoiliac atherosclerosis on preoperative CT angiography, femorofemoral heart-lung machine perfusion and use of the endoaortic balloon are safe. The femoral vessels are exposed in the groin, usually on the left side. All cannulation maneuvers can be carried out while one team member performs robotic IMA harvest. Arterial and venous cannula placement is carried out under strict transesophageal echocardiography (TEE) guidance with the patient heparinized to an ACT of 300 sec, and additional heparin to an ACT of 480 sec is administered shortly before the initiation bypass. It is of great importance to ensure arterial distal leg perfusion, and we recommend insertion of a distal perfusion cannula into the superficial femoral artery in all cases. A 21 Fr or 23 Fr arterial perfusion cannula with a side arm for the endoballoon catheter is then inserted and connected to the heart-lung machine tubing. Similarly, a 25 Fr venous drainage cannula is brought up into the right atrium and superior vena cava and connected to the heart-lung machine tubing. The aortic endoballoon catheter is inserted into the side arm of the arterial perfusion cannula

and advanced into the aortic root over a guidewire. The catheter is connected to the cardioplegia-vent line of the heart-lung machine, and aortic root pressure and balloon pressure lines are connected to the monitoring devices. Once adequate ACT levels (>480 sec) are confirmed, the heart-lung machine is started slowly. It is important to ensure that adequate venous drainage has been achieved, a drop in systemic perfusion pressure is observed, and lack of ventricular ejection (balloon placement is easier in nonejection conditions) is observed. The surgeon then locates the endoballoon on an adequately visible TEE monitor, inflates the balloon, and immediately injects 6 mg of adenosine into the aortic root. Adenosine induces cardioplegia immediately; this is followed by infusion of antegrade cardioplegia into the aortic root. If a percutaneous retrograde cardioplegia catheter was placed into the coronary sinus, standard protocol of antegrade and retrograde cardioplegia infusion can be followed.

If mild to moderate aortoiliac atherosclerosis is present, we avoid arterial retroperfusion through the femoral artery and instead cannulate the left axillary and use a nonperfusing endoballoon. For anatomic access reasons this is best done before docking of the robotic arms. The vessel is exposed in the left infraclavicular region, clamped and incised after heparinization, and an 8-mm Dacron prosthesis side arm is sutured to the axillary artery. After proper de-airing, the side arm is connected to the heart-lung machine tubing. In these cases, the aortic endoballoon is inserted through a separate 19 Fr cannula in the femoral artery.

In the case that preoperative CT angiography shows significant aortoiliac and general atherosclerosis, forgo endoballoon use and operate on the beating heart with prophylactic peripheral cannulation. The axillary artery is exposed and cannulated as described earlier. The venous drainage cannula is inserted via the femoral vein in percutaneous or open fashion. An ACT level of 300 sec is again used for cannulation. Before starting the anastomosis on the beating heart, the ACT is increased to above 480 sec. Using this strategy, the pump can be started expeditiously at any time point should significant technical difficulties occur.

Procedural Details

Single-lung ventilation and TEE monitoring are mandatory throughout the entire procedure. R2 defibrillator patches are placed with care so that adequate current flow is facilitated and sternotomy can be allowed. An endovent and/or percutaneous retrograde cardioplegia cannula are placed if AH-TECAB is planned.

The patient is placed on the operating table in the supine position with arms tucked and left chest slightly elevated using a subscapular pillow or rolled towel (Fig. 90-4). The patient should be prepped and draped as for open coronary bypass surgery (CABG), with all equipment for conversion to open CABG available in the room.

Correct insertion of the endoscopy ports is a key to the procedure and significantly influences the success of the whole procedure; therefore, port insertion should be performed by the most experienced team member. After

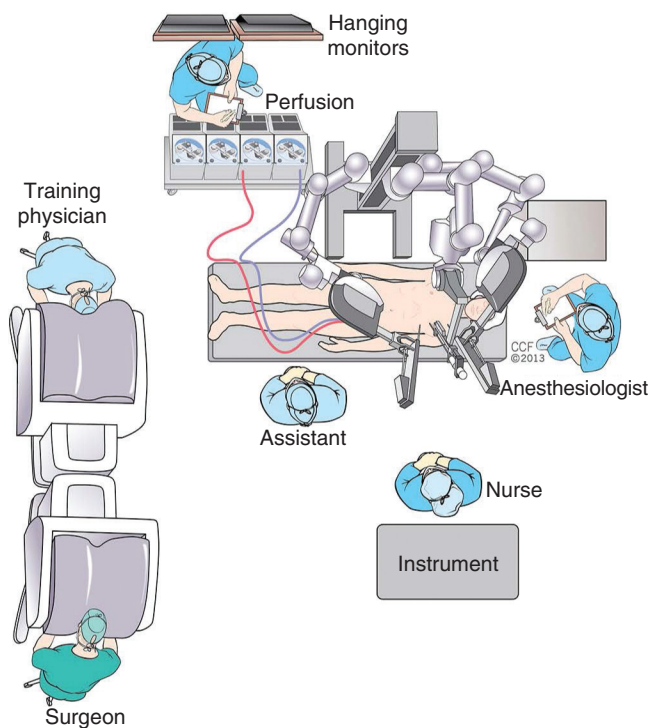


FIGURE 90-4 ■ Operating room setup for totally endoscopic coronary artery bypass (TECAB). (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

deflation of the left lung, a 12.5-mm camera port is used and inserted into the fifth intercostal space in the anterior axillary line. It should be inserted gently and cautiously so as to avoid injury to the heart or mediastinum. Once inserted, CO₂ insufflation at pressures of 8 mm Hg can begin and the angled camera can be inserted. The left and right instrument ports are then placed into the third and seventh intercostal spaces slightly anterior to the camera port under direct videoscopic vision. During this phase, the surgical team should remain aware of the patient's hemodynamics because the increase in intrathoracic pressure may cause hemodynamic compromise. Remaining in communication with the anesthesia team is critical; if hypotension develops during insufflation, the first attempts at correction should be to lower the CO₂ pressure or evacuate intrathoracic CO₂ (via one of the ports) rather than administer fluid or inotrope by anesthesia.

Following port placement, the robotic system is docked (see Fig. 90-4) and the IMA is harvested. This part of the procedure is done with the angled camera view in the up position. The robotic electrocautery spatula and a DeBakey forceps are inserted under videoscopic vision into the right and left ports, respectively. Using low power levels (we use 15 watts) on the electrocautery, the endothoracic fascia is detached from the IMA pedicle. The IMA is harvested in skeletonized fashion. In general, most side branches can be cauterized with clips used only for larger branches. The operator should use the cautery tip for dividing and dissecting the adjacent tissue mechanically, that is, by spatulation rather than tissue-burning maneuvers (Fig. 90-5). After harvesting and heparinization, the conduit is clipped distally, divided, and dropped

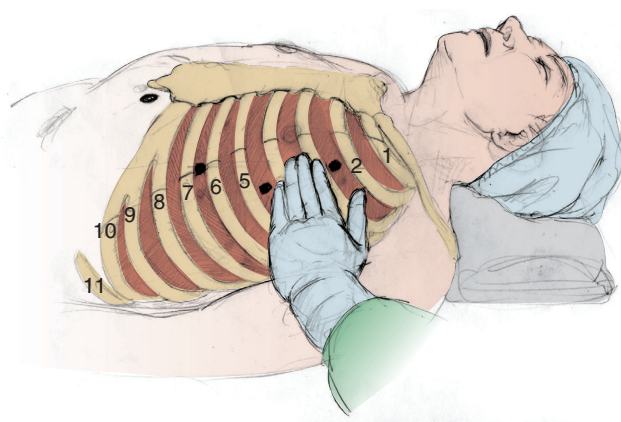


FIGURE 90-5 ■ Patient positioning for totally endoscopic coronary artery bypass (TECAB) with port placement sites. Ports are placed four fingerbreadths apart. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

into the left pleural space to allow autodilation to occur. It should be noted that both the left and the right IMA can be taken down using this technique with the same port and instrument arrangement. To access the right IMA, the retrosternal tissue is divided and the right pleura is entered. When bilateral conduits are used, the right IMA is harvested before the left IMA. Approximately midway through LIMA takedown, we fully heparinize the patient. In keeping with our recommendation for cannulation in all cases, this allows bypass to be started expeditiously at any time point should significant technical difficulties occur as the case proceeds.

A 5-mm assistance port is placed after IMA harvesting in the left parasternal region under scope visualization. This port allows insertion of material needed throughout the procedure such as bulldogs, suture material, Silastic tape, and suction tubing. In our experience, the TECAB procedure became smoother and faster with this trans-thoracic assistance.

Next, the pericardial fat pad is removed and pericardiectomy performed with the angled camera view down. To access the heart, the pericardial fat pad is mobilized using robotic long-tip forceps through the left port and electrocautery at 30 watts on the right and dropped into the left chest. The pericardium is then incised slightly lateral to the right ventricular outflow tract and extended all the way down to the reflection of the pericardium. The pericardial incision is then taken laterally in the caudal and cranial part so that a pericardial flap is created which falls into the left pleural space. Going on-pump before this phase facilitates this phase because both fat pad resection and pericardiectomy are significantly easier with an unloaded heart, especially in obese patients and those with cardiomegaly.

Exposure of Target Vessels

For all work on the coronary targets, the camera should continue to be in the down view position. The LAD can be visualized and accessed without difficulties using the port arrangement described earlier. In BH-TECAB and AH-TECAB cases with lateral target vessels, the LAD can be moved into an easily accessible position using the

robotic endostabilizer brought in through a subcostal port inserted two fingerbreadths left lateral to the xiphoid angle. This subcostal port is docked to the fourth arm of the robotic system.

The endostabilizer can be used for exposure of the circumflex coronary artery system. The operator should steer the endostabilizer gently over the left ventricle. The lateral wall can be lifted and the obtuse marginal branches accessed. In BH-TECAB, this maneuver can lead to hemodynamic compromise and ischemic changes. A supportive cardiopulmonary bypass run should be used to obviate this problem.

The right coronary artery system may also be accessed from the patient's left side. In this case, the endostabilizer is inserted through the left instrument port (change to a 12-mm port is necessary) and the left robotic instrument is inserted through the subcostal port. The acute margin can be lifted so that the posterior descending artery and the posterolateral branch are easily visible and accessible for anastomosis. It should be noted that thus far, this technique has been performed only on the arrested heart. It is important to take care not to injure the right ventricular epimyocardium with the endostabilizer during these maneuvers.

Once the target coronary artery is properly located and exposed, a robotic DeBakey forceps on the left and robotic Pott scissors on the right are used to incise the epicardium. At first, this can be challenging because of the lack of tactile feedback that is part and parcel to robotic work, and care must be used.

The target vessel is then incised using robotic DeBakey forceps on the left and robotic lancet beaver knife on the right, and the arteriotomy is extended with a robotic Pott's scissors (Fig. 90-6). The LIMA is prepared (Fig. 90-7). Bilateral robotic black diamond microforceps are used as needle drivers, and a 7-cm 7-0 double-armed polypropylene suture is used as suturing material. The first stitch is inside-out on the coronary artery, forming the first bite of the first stitch of the back wall of the anastomosis close to the toe. This needle is then "parked" at a distance from the anastomosis in the epicardium, and the anastomosis is continued with the other arm of the stitch, suturing the whole back wall going inside-out on the graft and outside-in on the target vessel (Fig. 90-8). The first three stitches are placed, and the graft is brought

toward the coronary artery wall in typical parachute technique. The operator pulls gently on both suture ends frequently to ensure adequate suture tension. Suturing then continues around the heel of the anastomosis, again suturing the graft inside-out and the target vessel in an outside-in fashion (Fig. 90-9). The needle is then parked in the epicardium and the previously used needle is used to suture the toe and rest of the anterior wall of the anastomosis (Fig. 90-10).

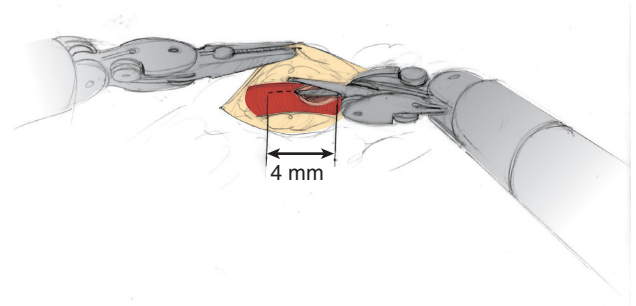


FIGURE 90-7 ■ Exposure of the left anterior descending artery and completion of a 4-mm arteriotomy. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

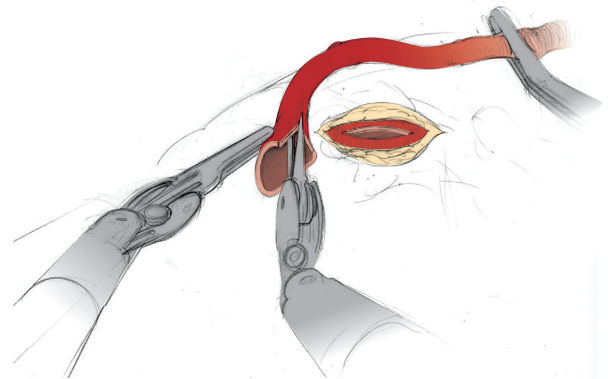


FIGURE 90-8 ■ Preparation of the conduit for grafting. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

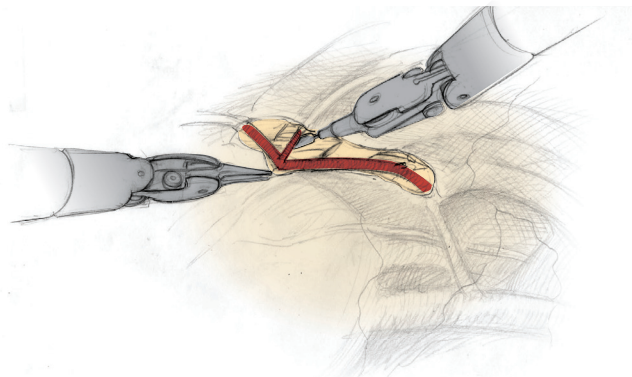


FIGURE 90-6 ■ Robotic left internal mammary artery (LIMA) taken down. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

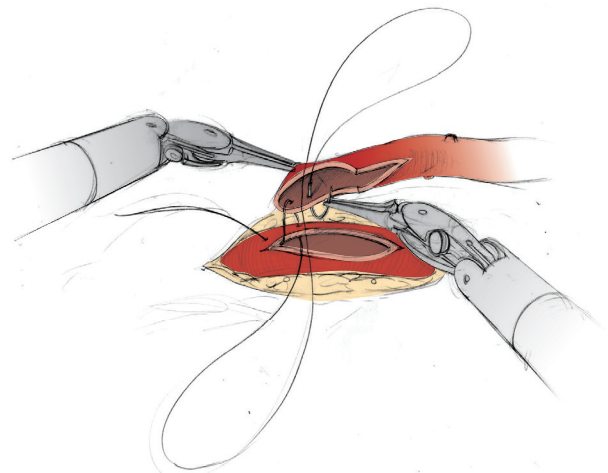


FIGURE 90-9 ■ Technique of anastomosis starting at the "toe." Note inside-out bites on both the coronary artery and the conduit. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

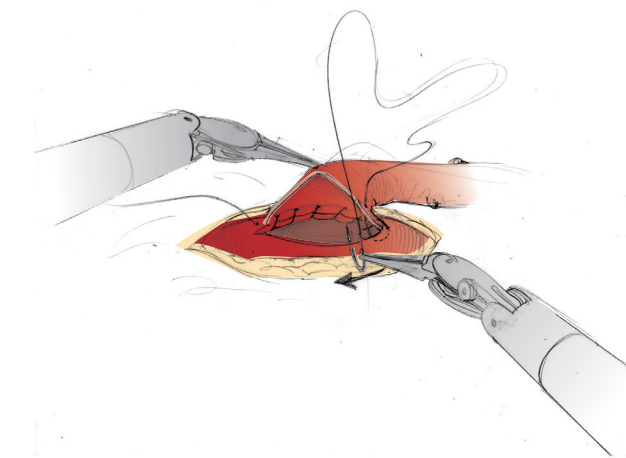


FIGURE 90-10 ■ Progression of totally endoscopic coronary artery bypass (TECAB) anastomosis. Note completion of the “heel” and the direction of suturing. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

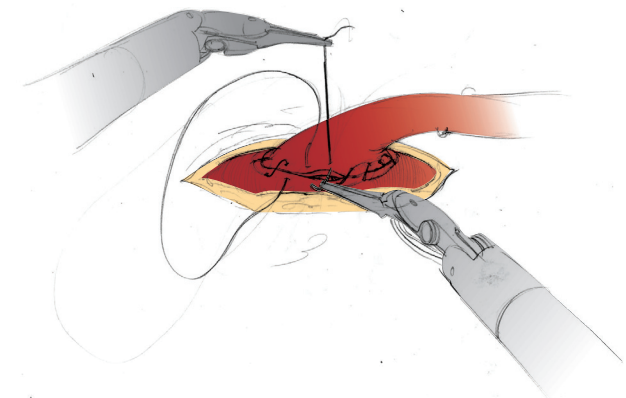


FIGURE 90-11 ■ Completed anastomosis. Note last few bites using the first needle that had previously been “parked.” (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2014. All rights reserved.)

Points on Anastomotic Creation in Arrested Heart TECAB

The coronary artery should be incised with antegrade cardioplegia running to fill the vessel and reduce the risk of back wall injury. Use of Silastic vessel occluding loops can be very helpful in cases of target vessel backflow that prevents a clear view of the anastomotic interior. Gentle probing maneuvers at the toe and heel before completion of the anastomosis can be performed safely (Fig. 90-11). All foreign material should be removed from the chest before the aortic endoballoon is deflated. The heart can become hyperdynamic later, and these maneuvers will be difficult.

Points on Anastomotic Creation in Beating Heart TECAB

Vessel-occluding Silastic tapes should be placed both proximally and distally to the anastomotic site although

usually only the proximal one needs to be occluded. An intraluminal shunt is then inserted into the distal target vessel and advanced into the proximal target vessel. The general suturing pattern is the same as in AH-TECAB; however, all stitches have to be carried out with an extra degree of gentleness to avoid injury to the target vessel wall. The magnified bouncing operative field is challenging until experience has been gained by the surgeon.

Multivessel TECAB

Multivessel TECAB may be achieved using bilateral in situ mammary artery grafts, sequential grafting, or Y-grafts constructed with the contralateral IMA or radial artery. Use of an endoscopically harvested vein graft with proximal anastomosis creation to the left axillary artery has been described.³⁰

Post-Anastomosis Procedures

After completion of the anastomosis, the bulldog clamp on the graft is removed and the anastomosis is inspected. In the robotic setting with high magnification, repair sutures can be placed with excellent visualization if needed. The endostabilizer is removed from the chest and an endoscopic transit time flow probe is brought in for intraoperative flow measurements. Once adequate pump function without signs of myocardial ischemia is ensured, protamine is administered. A tracheal suction tube is brought in through the parasternal assistance port, and residual blood is evacuated from the pleural space. The thoracic cavity is thoroughly inspected and hemostasis is obtained. The robotic system is undocked but all ports are left in place, to be removed under direct video-scopic vision tableside. A chest tube is inserted through the camera porthole with the left lung inflated so as to avoid injuries to the graft during tube insertion.

Postoperative Considerations

Postoperative treatment after TECAB follows the general principles applied in open coronary bypass surgery. Some specifics, however, need to be taken into consideration. Currently no temporary pacing wires that can be placed endoscopically exist; other methods of temporary pacing (e.g., endovenous or transthoracic) are used if necessary. Special attention (neurovascular checks) should be paid to peripheral pulses following cannulation in AH-TECAB. Because of double-lumen tube intubation and single-lung ventilation, respiratory compromise can occur, and the postoperative chest x-ray may show increased rates of atelectasis compared with open surgery and is to be expected. The camera port site is usually the most painful site until the chest tube is removed, and additional pain control is necessary until that time. No sternal precautions are required. In the case of BH-TECAB, we recommend initiation of both aspirin and clopidogrel 6 hours following surgery (or once chest tube drainage is minimal), in keeping with the data suggesting that the use of dual antiplatelet therapy reduces the risk of perioperative myocardial infarction and graft occlusion in off-pump revascularization procedures.¹⁶

HYBRID CORONARY REVASCULARIZATION

Introduction and Definition

Hybrid coronary revascularization (HCR) combines surgical and catheter-based therapies for the treatment of coronary artery disease. Usually, a LIMA graft to the LAD is placed in concert with PCI of non-LAD targets. Generally, the LIMA to LAD graft is performed using a minimally invasive technique (e.g., MIDCAB or TECAB, described in the earlier sections of this chapter). The hybrid concept can be extended to the treatment of combined coronary and valve diseases, such as a minimally invasive valve surgical procedure combined with PCI to coronary lesions with the intention, for example, of converting a high-risk valve/CABG into a lower risk minimally invasive valve procedure, but these applications are not discussed here.

Rationale and Background

The hybrid approach attempts to “bring the best of two worlds” of cardiac surgery and interventional cardiology together by combining the most effective treatment strategies from the two disciplines for the treatment of multivessel coronary artery disease.

It has been well shown that the LIMA to LAD graft is the most effective and durable option for anterior wall revascularization, primarily because of its resistance to thrombosis and atherosclerosis. The LAD supplies the largest area of myocardium (including the anterior wall and septum) of any of the coronary arteries, and the LIMA to LAD graft is known to improve survival, with 5-year patency rates between 92% and 95% and 10-year patency rates between 95% and 98%.³¹ Such proof is lacking for PCI of the LAD. On the contrary, PCI with drug-eluting stents (DESs) offers equal if not better revascularization durability compared with vein and radial artery grafts. One-year saphenous vein graft (SVG) failure rates range between 7% and 30%; 40% to 50% of SVGs will fail or become atherosclerotic by 15 years.³¹

With these factors in mind and in the context of the developing minimally invasive surgical procedures (most particularly suited to the LIMA to LAD anastomosis, such as MIDCAB and TECAB), interest in the potential advantages of hybrid approaches grew beginning in the late 1990s and continuing over the first decade of 2000. Angelini and colleagues reported the first series of six patients, treated with a MIDCAB LIMA to LAD and PTCA or PTCA and stent in 1996. A decade later, a multicenter international trial on the feasibility of coronary hybrid procedures showed the basic feasibility of combining robotic TECAB and PCI.³² Twenty-seven patients requiring double-vessel revascularization were treated with TECAB LIMA-LAD, and PCI to non-LAD targets (bare-metal stent [BMS] or DES). Three-month follow-up angiography showed an excellent LIMA-LAD patency of 96.3% but a lower than expected PCI patency of 66.7%. No deaths or strokes were observed. One

patient suffered a perioperative myocardial infarction. The early reintervention rate, primarily as a result of stent failures, was 29.3%.

Technical and Timing Issues of Hybrid Interventions

Hybrid procedures generally involve a MIDCAB or TECAB surgical procedure for creation of the LIMA to LAD anastomosis along with catheter-based PCI intervention(s). The timing of the surgical procedure in relation to the percutaneous intervention has been a subject of some discussion.

By their nature, all hybrid procedures are staged; only the duration of the staging period and the order in which the procedures are performed can be varied. Two-staged hybrid procedures are those in which PCI and CABG are performed in separate operative locations. The two procedures can be separated by hours, days, or weeks. One-stop procedures are performed in one setting, and the procedures are separated by minutes.³³ In a two-stage hybrid procedure, either the surgical procedure or the percutaneous intervention can be performed first. In a one-stop or simultaneous procedure, the surgical intervention is generally performed first.

The advantages and disadvantages of each approach are discussed next. Each has its theoretical relative merits and drawbacks. At present, there are no data to support any of the approaches above the others; clinicians must weigh the relative merits of each strategy in the context of their practice setting and the clinical scenarios they encounter.

Percutaneous Intervention prior to Surgical Intervention

Performing the percutaneous revascularization before surgical revascularization is associated with several potential advantages. First, the revascularization of the non-LAD targets provides collateral circulation and decreases the risk of ischemia if LAD occlusion is used in the beating heart surgical approach. Second, it allows the interventionalist the opportunity for aggressive multivessel revascularization knowing that if a complication occurs or PCI is not successful, a conventional CABG can be performed at a later time. Most patients who are treated with a “PCI first” approach undergo an acute percutaneous intervention of the culprit lesion for acute coronary syndrome, and the LIMA to LAD graft is placed using a less invasive approach at a later time point.

This approach is associated with a number of disadvantages. It necessitates performing PCI in a setting in which no protection is afforded by a LIMA to LAD graft. Also, unless a third procedure (completion angiogram) is performed after the surgical procedure, no mid-term angiographic imaging of the LIMA-LAD graft is afforded by this sequence of procedures. Most important, the risk of stent thrombosis and need for antiplatelet agents following PCI necessitates either performing the minimally invasive surgical revascularization on clopidogrel (which has been associated with a slightly increased risk of bleeding¹) or maintaining hospital patients on eptifibatide

(Integrilin; Schering-Plough, Kenilworth, NJ) until their surgical intervention.^{1,33}

Surgical Intervention prior to Percutaneous Intervention

Performing PCI after LIMA-LAD grafting makes it possible to avoid antiplatelet-related bleeding complications during the surgical procedure; antiplatelet therapy can be started after surgery and continued long term, in keeping with current recommendations following stent implantation. In addition, the percutaneous interventions can be performed with the protection afforded by the surgical revascularization, allowing interventionalists to more safely approach, for example, left main or diagonal bifurcation lesions.¹ A final benefit to this approach is that it allows for the LIMA-LAD anastomosis to be angiographically evaluated at the time of PCI. However, if there is a complication or failure of the PCI, a second, higher risk operation needs to be performed. This should be a rare occurrence, however, because the incidence of emergent CABG following PCI is less than 1%.¹ Given these considerations, most cardiologists and surgeons who perform two-staged hybrid procedures have adopted this strategy.

At present, the optimal duration of time between the two interventions is unclear. Patients should at least be able to tolerate lying flat on the angiography table, which, because of postoperative respiratory compromise, could take several days. It also seems reasonable to delay PCI until the inflammatory milieu that exists immediately after surgery resolves. This usually requires 3 to 5 days, but patients may need 7 to 10 days of mental and physical recovery following surgery. Ideally, PCI would be performed at the index hospitalization so that the patient would not be discharged without being fully revascularized, but economic issues can make this problematic if long postsurgical recovery periods are required.¹

Simultaneous Procedures

Two-staged procedures involve two teams, logistical challenges, the costs associated with two separate procedures, and possible hospitalization between the procedures. In addition, many patients would simply prefer not to undergo two separate interventions.³³ In centers with hybrid operating rooms where both percutaneous and surgical procedures can be performed, a one-stop procedure can be performed.

In this approach, there is superb monitoring throughout the procedure under general anesthesia, any complications encountered can be resolved in one setting, and a completion angiogram can be done to evaluate the LIMA-LAD graft. Complete revascularization is accomplished before leaving the operating suite, and the patient experiences the emotional and psychological benefit of a complete “fix” in one anesthetic setting.¹ Potential drawbacks include the need for specialized hybrid facilities, increased operative times, and higher cost with inadequate hospital reimbursement. Concerns about performing PCI in the inflammatory milieu created by the surgical

bypass have been raised, and bleeding risk remains a concern because full antiplatelet therapy and incomplete (or no) heparin reversal are practiced after the combined procedure. At this point, the data regarding the effect of clopidogrel on bleeding in patients undergoing hybrid procedure are mixed (with some reporting increased bleeding and others reporting no such increase³⁴⁻³⁶), and the effects of protamine reversal on stent patency are unknown.

The timing of PCI related to TECAB in a hybrid procedure was recently investigated by Srivastava and colleagues.³⁷ The group retrospectively reviewed 238 patients submitted to hybrid treatment over a 10-year period. Most patients (73%) underwent TECAB before PCI. Overall, the authors observed no drastic impact of PCI timing on outcomes, but patients submitted to PCI before or at the same time as TECAB experienced shorter intensive care unit and hospital lengths of stay in comparison with patients who had surgery first. The authors concluded that timing of interventions can be individually tailored to patients' needs.

Current State of Hybrid Revascularization and Recent Information

At the time of this publication, experience with this technique remains limited. No prospective randomized trials on hybrid revascularization have been published, and only three series with triple-digit numbers of patients have been reported.³⁸

The small amount of data available on the subject show a low mortality rate (up to 2%) and a low overall morbidity rate (average of $\approx 4.7\%$ in hospital morbidity across all studies), with shorter hospital and intensive care unit stays than would be expected with conventional CABG.³³ Immediate LIMA to LAD patency rates range from 92% to 100%.³³ With respect to restenosis rates, the data are mixed. Earlier series, which made use of BMSs or angioplasty without stenting, revealed higher 6-month stent restenosis rates so that in the entire experience thus far, these rates range from 2.3% to 23%, with an average of 11% across all of the literature.³³ However, in one series in which only DESs were used in procedures combining MIDCAB and PCI, 97% 1-year patency rates were reported.³⁶

In the largest reported series of robotically assisted hybrid coronary interventions on 226 patients with 5-year follow-up, a 1.3% hospital mortality rate, average hospital stay of 6 days, and a 92.9% 5-year survival rate were found. Five-year freedom from major adverse cardiac and cerebral events was 75.2% and reintervention rates were 2.7% with respect to bypass grafts and 14.2% with respect to PCI targets.³⁸

Given the limited data available to evaluate hybrid revascularization, as well as the evolving nature of both minimally invasive surgical approaches and percutaneous therapies, generalized statements regarding outcomes are difficult to make at this time. Additional studies are needed to fully evaluate this approach.

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RE-DO CORONARY ARTERY BYPASS SURGERY

Bruce W. Lytle

CHAPTER OUTLINE

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THE FUTURE OF CORONARY REOPERATIONS

Reoperations present coronary surgeons with their greatest challenges. Patients undergoing reoperation for bypass grafting are different from those who undergo primary surgery. In addition to the risks of a repeated median sternotomy, their coronary artery and noncardiac atherosclerosis is more advanced, noncardiac comorbidities are more common, ventricular function is more likely to be abnormal, and the vascular pathologic processes that jeopardize myocardium are distinct and varied.¹⁻⁴ All these issues present specific technical challenges.

In addition to the technical difficulties presented by reoperations, decision making is not perfectly straightforward. No major randomized trials have studied patients with prior bypass surgery. In only a few situations do observational studies indicate that reoperative coronary surgery improves prognosis.⁵ For many patients, percutaneous intervention is an appealing prospect, but unfortunately the results of percutaneous treatment of patients with prior surgery have been suboptimal even in the era of drug-coated stents.⁶⁻⁸

The reasons that patients need coronary reoperations have their anatomic bases in an ineffective first operation, bypass graft failure (early or late), progression of atherosclerosis in native coronary arteries, failure of interventional procedures, and combinations of these problems. The relative contributions of these factors have changed with the evolution of bypass surgery and with the evolution of alternative treatments for coronary atherosclerosis. Today, early vein graft failure, although not rare, is rarely an indication for early reoperation. First,

percutaneous interventions are usually available to treat symptomatic patients who experience vein graft failure. Second, as long as an internal thoracic artery (ITA) to left anterior descending (LAD) graft is functioning, sufficient indications for early reoperation are rarely present even if other grafts are imperfect. Early reoperations are usually indicated only in the situation of both ITA and vein graft failure. Late reoperations are usually indicated by a combination of progression of native vessel atherosclerosis and vein graft failure, usually based on the occurrence of vein graft atherosclerosis.

The pathologic changes of vein grafts are important, not only as causes of reoperations but also as causes of events associated with medical or interventional treatment.^{9,10} Early vein graft occlusion is usually associated with intimal disruption and thrombosis. Within 2 to 3 months of surgery, a proliferative intimal fibroplasia develops in most vein grafts. This concentric, diffuse, cellular lesion becomes more fibrous with time, possibly as an adaptive response to arterialization. It usually does not cause stenosis or occlusion. The most recent data indicate an occlusion rate of 6.2% at 1 year after operation. In that study, the use of statins and beta blockers were associated with a decreased risk of intimal fibroplasia (defined by interventional ultrasound) and graft occlusion.¹¹ Within a few years of operation, lipid deposition can occur in association with intimal fibroplasia, and the resulting lesion is termed *vein graft atherosclerosis*. The fully developed lesion of vein graft atherosclerosis is different from native vessel atherosclerosis. Vein graft

atherosclerosis is superficial, nonencapsulated, diffuse, and concentric. It is an extremely friable lesion and is much more prone to embolization than is native vessel atherosclerosis. In addition, clinical studies appear to show that it is more consistently progressive than is true of native vessel atherosclerosis, as vein graft stenoses caused by vein graft atherosclerosis predict a high level of clinical events. Patients with coronary risk factors such as hyperlipidemia and diabetes appeared to experience an increased incidence of vein graft atherosclerosis and graft failure.¹² There is now evidence that treatment with platelet inhibitors and statins decreases the rate of late vein graft failure. However, even with these measures, vein graft atherosclerosis has not been eliminated.

ITA grafts rarely develop atherosclerosis, and the patency rate of ITA grafts, particularly to the LAD coronary artery, exceeds that of vein grafts.¹² The use of ITA to LAD grafts at primary operations clearly decreases the risk of reoperation during the first 10 postoperative years, and the use of both ITA grafts further decreases the risk of reoperation (Fig. 91-1).^{4,13,14} Furthermore, although patent ITA grafts present technical challenges at reoperation, atherosclerotic embolization is not as high a risk as it is for patients with patent but atherosclerotic vein grafts.

For patients undergoing primary bypass surgery, the likelihood of undergoing a reoperation will depend on the length of their life, the severity of the atherogenic diathesis, the effectiveness of the treatment of that diathesis, the details of the primary operation, the alternative therapies available, and the physician's and patient's preferences. A review of patients undergoing primary bypass surgery at the Cleveland Clinic between 1971 and 1974 documented a 25% chance of reoperation by 20 postoperative years.¹⁵ Today we would expect that figure

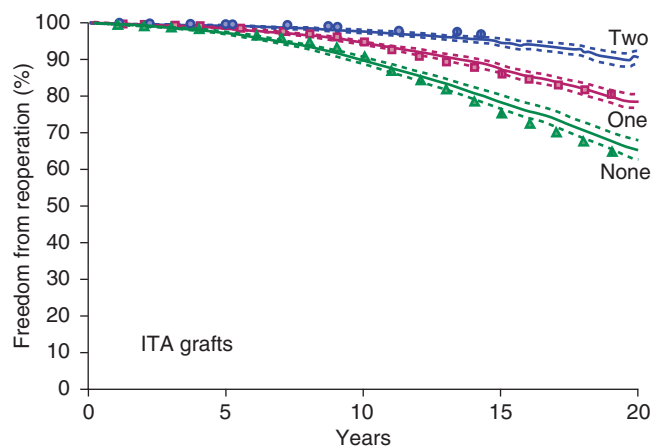


FIGURE 91-1 ■ Predicted freedom from reintervention after primary isolated coronary artery bypass graft stratified by single, double, or no internal thoracic artery (ITA) grafting at primary operation. Solid lines represent parametric estimates enclosed within dashed 68% confidence limits (± 1 SE). (Reprinted with permission from Sabik JF III, Blackstone EH, Gillinov AM, et al: Influence of patient characteristics and arterial grafts on freedom from coronary reoperation. *J Thorac Cardiovasc Surg* 131:90–98, 2006.)

to be much less as the number of isolated coronary reoperations performed has declined. The Society of Thoracic Surgeons database noted 16,091 isolated coronary reoperations reported in 1998, compared with 8820 in 2000 and 5734 in 2009.¹⁶ The reasons for this decline probably include the increased use of ITA grafts at primary operation, better risk factor control producing less progressive vein graft atherosclerosis, and the use of stents to treat vein graft lesions.

INDICATIONS FOR CORONARY REOPERATIONS

The randomized trials of bypass surgery versus medical management or percutaneous coronary intervention did not include patients with previous surgery. Furthermore, patients with previous surgery are extremely heterogeneous, their vascular pathologic processes being multiple and their extent of revascularization not always falling into the categories of single-, double-, and triple-vessel disease. In particular, vein graft atherosclerosis is a more progressive vascular disease, and the presence of vein graft atherosclerosis predicts a particularly unfavorable clinical outcome without repeated surgery. Thus, there is relatively little clarity in terms of the indications for reoperation. Observational studies, however, have provided some important information.

- Early stenoses in vein grafts (<5 years after operation) do not predict unfavorable outcomes if patients are not highly symptomatic.^{5,10} Therefore, an early stenosis in a vein graft is not necessarily an indication for either reoperation or reintervention.
- Patients with early stenoses in vein grafts who are highly symptomatic often exhibit marked improvement after reoperation.⁵
- Late (>5 years after operation) stenoses in vein grafts do predict adverse outcomes when patients are managed medically, particularly if the stenotic vein graft subtends the LAD coronary artery or if multiple vein grafts are involved.^{5,10}
- Late stenoses in vein grafts are more consistently progressive than native vessel stenoses are.¹⁰
- Reoperation can improve the survival rate of patients with late stenoses in vein grafts, particularly if that late stenosis involves a vein graft subtending the LAD coronary artery (Fig. 91-2).⁵
- Patients with late stenoses in vein grafts who do have significant symptoms can usually experience improved symptoms after reoperation.⁵
- Patients with a patent and effective ITA-to-LAD graft who are not highly symptomatic have not been shown to have an improved survival rate with reoperation.⁵

As has been true of patients undergoing primary bypass surgery, functional studies could add to the accuracy of identifying patients who are likely to have unfavorable outcomes without reoperation. Patients who demonstrate ischemia and an impaired exercise capacity are at greater risk for death and cardiac events without reoperation than are those with negative or only mildly positive stress test results.¹⁷

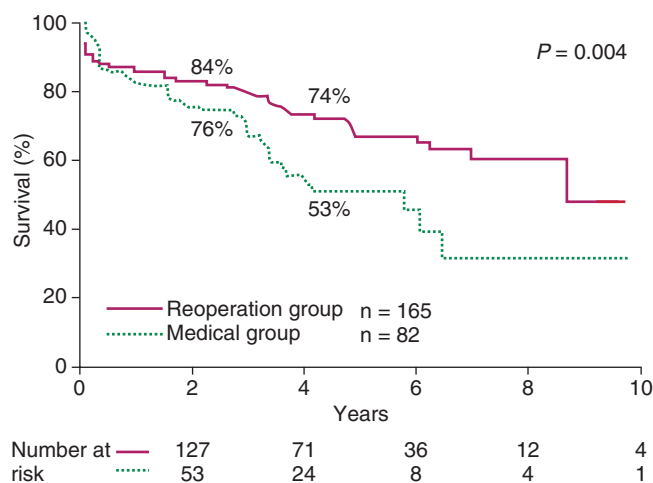


FIGURE 91-2 ■ Comparison of late survival rates for patients with late stenoses of more than 50% in vein grafts subtending the left anterior descending coronary artery shows a distinct survival advantage for patients undergoing reoperation. (Reprinted with permission from Lytle BW, Loop FD, Taylor PC, et al: The effect of coronary reoperation on the survival of patients with stenoses in saphenous vein bypass grafts to coronary arteries. *J Thorac Cardiovasc Surg* 105:605–612, 1993.)

SUMMARY OF CURRENT INDICATIONS FOR TREATMENT OF PATIENTS WITH PREVIOUS BYPASS SURGERY

In the absence of contraindications, all patients with previous bypass surgery should be treated with platelet inhibitors, statin-type drugs, and control of risk factors including hypertension, diabetes, and hyperlipidemia. The indications for more invasive treatment are related to symptom relief and, in some circumstances, improvement of prognosis.

Significant late stenoses in multiple vein grafts or in a vein graft to the LAD coronary artery predict an unfavorable prognosis that can be improved by reoperation; therefore, they constitute a strong indication for repeated surgery. The indications for reoperation in these anatomic situations are particularly strong when they are associated with abnormal left ventricular function, a positive stress test result, and a clear demonstration of myocardium in jeopardy. The presence of multivessel disease jeopardized by native vessel lesions and vein graft disease that includes a proximal LAD lesion also seems to constitute an indication for reoperation for improvement of prognosis. There has not yet been a clear demonstration that reoperation improves the survival rate of patients who have a patent, effective ITA-LAD graft. Severe symptoms of angina combined with severe stenoses in native coronary arteries or grafts subtending areas of viable myocardium constitute good indications for surgery for the purpose of symptom relief.

The availability of percutaneous coronary treatments can be an advantage in the symptomatic treatment of patients with previous bypass surgery. Native vessel disease in particular, when accessible, can be effectively treated with stenting, and in the current era of drug-coated stents, it is often effective. The treatment of vein

graft disease with percutaneous intervention has, unfortunately, not been effective in the long term even with the use of drug-coated stents.^{8,18–20} However, despite those issues, it is still reasonable to use stenting for treatment of symptomatic vein graft disease when large amounts of myocardium are not jeopardized and symptom relief is the goal. There is no evidence that the treatment of vein graft disease with percutaneous intervention achieves any improvement in prognosis in any situation.

Comparisons of surgical and percutaneous treatments for heterogeneous groups of patients with previous bypass surgery have shown roughly equivalent outcomes. However, these studies have been small in number and have not separated patients into subsets based on the vascular pathologic process needing to be treated and prognostic subgroups based on coronary and vein graft anatomy. Therefore, the relative use of reoperation and percutaneous coronary treatment for the anatomic treatment of patients with previous bypass surgery will depend on multiple factors, including the vascular pathologic process producing the ischemia, the general health of the patient and specific contraindications to surgery, the function of the left ventricle, the area of myocardium in jeopardy, and the experience of the surgical and interventional teams.

TECHNICAL ASPECTS OF CORONARY REOPERATIONS

Reoperations are more difficult than primary operations. Some of that difficulty relates to similar but more extreme pathologic processes that are encountered at reoperation, whereas some problems are unique to reoperations. Potential technical problems during coronary reoperations include sternal reentry, aortic atherosclerosis, atherosclerotic vein grafts, patent arterial bypass grafts, diffuse native coronary artery disease, lack of bypass conduits, locating coronary arteries, and myocardial protection. The most common cause of in-hospital death after coronary reoperation is perioperative myocardial infarction. Those myocardial infarctions are often anatomically based; their causes include injury to bypass grafts, atherosclerotic embolization from vein grafts or from the aorta, myocardial devascularization after graft removal, hypoperfusion through new grafts, incomplete revascularization, early graft occlusion, air embolization, technical error, and inadequate myocardial protection. The planning for reoperation and the intraoperative conduct of the procedure must be designed to avoid these anatomic causes of perioperative myocardial infarction.

PREOPERATIVE ASSESSMENT

The first step in reoperative coronary surgery is a complete coronary angiogram that delineates native coronary and graft anatomy. That step is not as easy as it sounds. If bypass grafts are not demonstrated by a preoperative coronary angiogram, it may be that those grafts are occluded, but it is also possible that the angiographer failed to inject them. A copy of the previous operative

note can be important in describing the location of bypass grafts, and it can be helpful to examine old angiograms to identify important coronary arteries and to help understand the previous operative notes. Coronary arteries do not disappear, and a large vessel that was present previously must be accounted for on the current angiogram.

To accomplish symptom relief and improvement of prognosis, there must be a match between graftable coronary arteries and viable myocardium. It is important to establish the state of the myocardium preoperatively by thallium scanning, positron emission tomography, stress echocardiography, or magnetic resonance imaging. Bypass grafts performed to nonviable myocardium do not improve prognosis.

It is important to know which bypass graft conduits will be available. Doppler studies can be used to establish ITA patency, but if the goal of the operation is to use one or both ITAs to bypass important coronary vessels, then it is best to establish their patency with angiography. Venous Doppler studies can be used to assess the presence of greater and lesser saphenous vein grafts, and arterial Doppler studies can assess radial artery status.

Based on studies of intraoperative events, their implication, and the likelihood of rescue once adverse events have occurred, we perform preoperative computed tomographic scanning for all patients undergoing reoperation at the Cleveland Clinic.²¹

MEDIAN STERNOTOMY, CONDUIT PREPARATION, AND CANNULATION

A median sternotomy is the best incision for most coronary reoperations. If computed tomographic scanning demonstrates an increased risk of sternal reentry—those situations including right ventricular enlargement, a patent vein graft to the right coronary artery, an in situ right ITA graft to a left coronary vessel, an in situ left ITA graft that is directly beneath the sternum, aortic enlargement, multiple previous operations, and an injury during a previous sternal incision—we obtain arterial and venous access before reopening the sternotomy (Fig. 91-3). In addition, we prepare the radial artery and saphenous vein segments that are going to be used for bypass grafting before that sternotomy. In difficult situations, cardiopulmonary bypass can be established before a sternotomy is performed, but that is not our usual strategy. We prefer to avoid full heparinization before the dissection and before preparation of the right internal mammary artery. We commonly cut the sternal wires anteriorly but leave them intact posteriorly, and an oscillating saw is used to divide the anterior table of the sternum (see Fig. 91-3). Once that is accomplished, ventilation is stopped, the assistants elevate each side of the sternum with retractors, and the posterior table is divided. We then remove

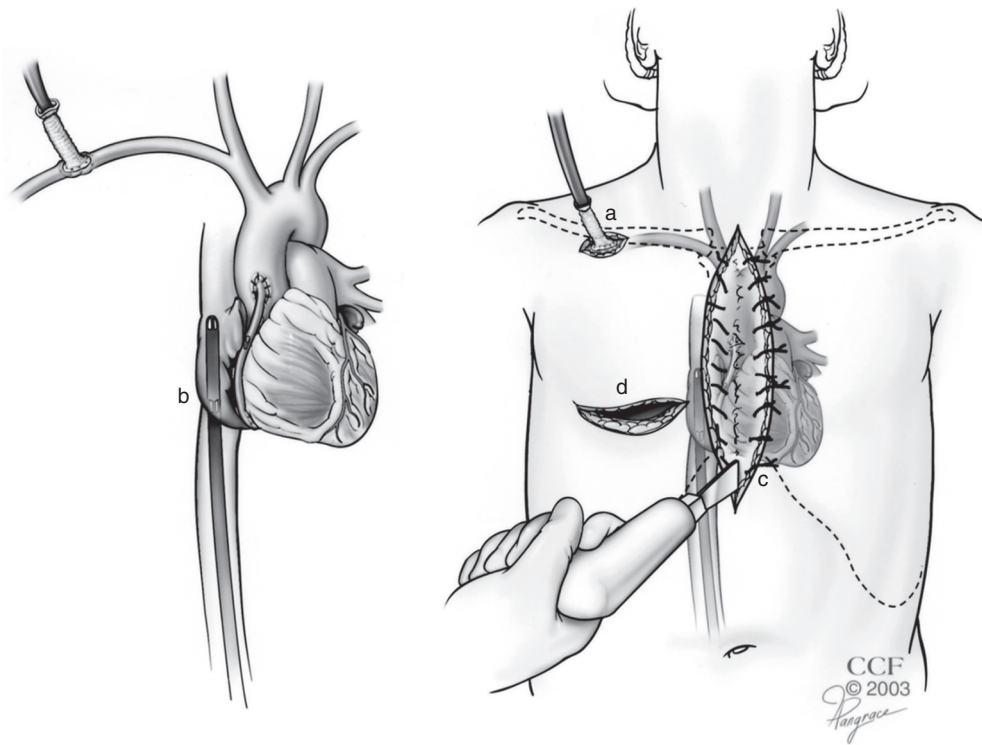


FIGURE 91-3 ■ Strategies for safe sternal reentry during coronary reoperations include (a) axillary artery cannulation for arterial access, (b) femoral venous cannulation to allow institution of cardiopulmonary bypass and to avoid manipulation of an atherosclerotic saphenous vein graft to the right coronary artery, (c) leaving the sternal wires intact posteriorly and using an oscillating saw to reopen the sternum, and (d) a small anterior right thoracotomy to allow safe separation of the right ventricle from the sternum. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2009. All rights reserved.)

the wires once the sternum has been completely divided, because they serve to protect underlying structures. In difficult situations, a small anterolateral right thoracotomy can be performed to facilitate dissection of the heart or the aorta away from the sternum (see Fig. 91-3).

Once the sternum is opened, adhesions are lysed starting at the diaphragmatic level, extending the dissection into the thoracic cavities in a cranial direction. Working from the level of the diaphragm in the cranial direction is the safest approach to avoid graft injury. Superiorly, the innominate vein is freed from the sternum on both sides to prevent a stretch injury. Once the sternum is dissected away from the mediastinal structures, the ITAs are prepared. If there is a patent left ITA graft in place, it is separated from the chest wall. The risk of injury to a patent left ITA graft is established by the location in which the graft is placed at the time of the primary operation. At primary operations, the pericardium should be divided posteriorly and the left ITA is allowed to run posterior into the pericardium. In this location, it is out of danger at reoperation.

Intraoperative echocardiography is used to examine the function of the aortic and mitral valves, intraoperative left ventricular function, and extent of atherosclerosis of the ascending aorta and aortic arch. In the presence of ascending aorta atherosclerosis or lack of room on the ascending aorta, alternative arterial cannulation sites include the axillary artery and the femoral artery. However, for patients undergoing reoperation, the extent of the atherosclerosis really means that the iliofemoral vessels are not ideal for cannulation, and the axillary artery is the preferred site (see Fig. 91-3).

It is important to avoid manipulation of atherosclerotic vein grafts during the dissection of the heart; doing so can result in the embolization of atherosclerotic debris into the distal coronary system and the occurrence of myocardial infarction. This is a specific danger during reoperation, and although a true “no-touch” technique may be difficult to achieve, manipulation of grafts should be minimized.^{1,22,23} To avoid manipulation of an atherosclerotic vein graft to the right coronary artery, it is sometimes wise to cannulate the right atrium through the femoral vein (see Fig. 91-3). When atherosclerotic right-sided grafts are absent, we usually use a two-stage venous cannula through the right atrium into the inferior vena cava for venous cannulation.

When a patent left ITA graft is present, we try to isolate it so that it can be occluded with an atraumatic clamp. This is an aid in myocardial protection as long as we can deliver retrograde cardioplegia. When the location of a patent left ITA graft is not clear, the tissue between the aorta and the left lung is isolated by dissecting posteriorly on the medial aspect of the left lung and on the left lateral aspect of the aorta. We then use an atraumatic clamp across that tissue, which usually includes the left ITA graft.

Once arterial and venous cannulation has been accomplished, we can begin cardiopulmonary bypass and place a retrograde coronary sinus cardioplegia cannula through the right atrium into the coronary sinus. The temperature is then cooled to 34° C, and the aorta is cross-clamped and antegrade cardioplegia is given, followed by

retrograde cardioplegia. Adequacy of the delivery of retrograde cardioplegia is assessed by the pressure in the coronary sinus, the rate of cooling of the heart, and the degree of distention of the cardiac veins. If retrograde cardioplegia delivery is effective, it is used throughout the rest of the case.²² The dissection of the left ventricle is accomplished once the heart has been arrested. This strategy leads to an accurate dissection that is atraumatic to the epicardium and decreases the bleeding as well as the amount of manipulation of any atherosclerotic vein grafts. Furthermore, it aids in the identification and isolation of a patent ITA graft. If we are unable to isolate the ITA graft before aortic cross-clamping, we dissect along the diaphragm to the left side of the apical portion of the LAD coronary artery and then continue proximally to the left of the patent ITA graft. That graft will be included in the strip of pericardium, and it can be clamped.

If it is impossible or dangerous to dissect out and control the left ITA graft, we then decrease the systemic temperature usually to 20° C to achieve cardiac arrest and myocardial protection. We believe, however, that this strategy is inferior to being able to occlude the ITA graft and give retrograde cardioplegia. A study comparing these strategies did not show different outcomes although operative mortality rates were 7% to 8% in both groups.²⁴

Once the heart has been arrested and dissected out, the coronary vessels that are to be grafted are identified. Again, it is important to have a previous operative note and a clear coronary angiogram to help identify these vessels. Previously constructed bypass grafts can be tracked to their point of insertion, which often helps identify vessels, particularly those that are intramyocardial. Intramyocardial vessels often provide the best sites for anastomoses as they have less atherosclerosis than epicardial vessels.

STENOTIC VEIN GRAFTS AND GRAFTING PATTERNS

The management of atherosclerotic but patent or stenotic vein grafts is a major issue during reoperation. Ideally, any atherosclerotic vein graft should be replaced at a reoperation to prevent atherosclerotic embolization at the time of surgery or late progression and graft failure thereafter. However, graft replacement might not be possible because of the lack of bypass conduits. If patent or stenotic saphenous vein grafts (not totally occluded) are removed at the time of operation, it is important to replace them with grafts of equal size and flow to avoid hypoperfusion.²⁵ That usually means replacing stenotic vein grafts with other vein grafts. If only arterial grafts are available, it is usually the best idea to add an arterial graft to the coronary artery and leave the vein graft intact. A concern about the second strategy is that persistent flow through the old saphenous vein graft might create enough competitive flow to produce an atretic arterial graft. That usually does not occur if the vein graft has a stenosis of more than 50%.

When arterial grafts are available, they can often be used effectively during reoperation.¹ If the left ITA has

not been previously used, it usually functions well as an in situ graft. The right ITA is more difficult to use as an in situ graft at reoperation because of limitations in its length, and in most instances it is better used as a “free” graft with a proximal anastomosis to the aorta, a new left ITA graft, or a previously constructed left ITA graft. If there is a previously constructed left ITA graft that is patent, it has often increased in size and is capable of providing good inflow (Fig. 91-4). The use of a patent left ITA graft for a proximal right ITA graft site allows the length of the right ITA to be maximized. Short segments of the left ITA or other arterial grafts can be used to bridge distal LAD stenoses (see Fig. 91-4).

In constructing proximal anastomoses of arterial grafts to the aorta, we try to use the hood of a new or an old vein graft as the anastomotic site, because a direct arterial graft anastomosis to the thickened reoperative aorta can be difficult.

Alternative arterial bypass grafts, such as the radial artery, the gastroepiploic artery, and the inferior epigastric artery, can also have roles during reoperations. The radial artery is a large vessel that can be used as a single graft from the aorta to almost any coronary artery and sometimes as a sequential graft. Early (<5 years) patency studies show a favorable patency rate for radial artery grafts, but only time will tell their ultimate usefulness. The inferior epigastric artery is not a long vessel, but it can be helpful during reoperations as a composite graft. The gastroepiploic artery as an in situ graft can be useful for grafting the posterior descending branch of the right

coronary artery or the distal anterior descending coronary artery.

DIFFERENTLY INVASIVE STRATEGIES FOR REOPERATIVE CORONARY SURGERY

Although most reoperations are best performed through a median sternotomy because of the need to reach multiple regions of the heart, alternative reoperative strategies can provide an advantage in specific situations. Substantial proportions of primary operations are performed without the use of cardiopulmonary bypass, and this off-pump approach is appropriate for some reoperations. A disadvantage of reoperative off-pump surgery lies in the danger of manipulating patent but atherosclerotic vein grafts during dissection of the heart and causing embolization of atherosclerotic debris into coronary arteries. If all grafts are occluded, this is not a risk.

Target vessel revascularization strategies in which limited areas are approached through alternative incisions and off-pump surgery is performed may be effective because the extensive epicardial dissection that can cause embolization is not needed. An increasingly common operation is to graft the circumflex coronary artery through a left thoracotomy with either a radial artery or saphenous vein graft anastomosed to the descending thoracic aorta or subclavian artery and then to the circumflex artery, usually using an off-pump strategy (Fig. 91-5). This approach avoids the risk of damaging a patent left ITA-LAD graft and avoids cardiopulmonary bypass. The disadvantages of this strategy are that intramyocardial circumflex vessels can be difficult to locate, the descending aorta may be atherosclerotic and a difficult site for a proximal anastomosis, and it makes use of the right ITA difficult. When the left ITA is patent to the LAD coronary artery and there is a major circumflex branch available for grafting, it is usually our intent to use the right

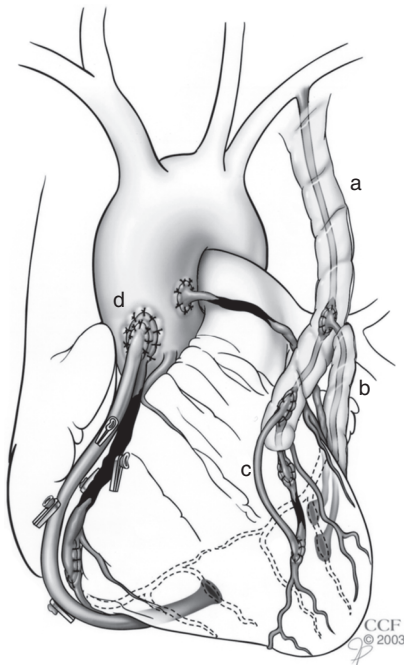


FIGURE 91-4 ■ Multiple grafting strategies are often useful at reoperation. A new or previously placed left internal thoracic artery graft (a) can be used as inflow to maximize the length available for a free right internal thoracic artery graft (b) or a small arterial graft segment (c) used to bridge a distal left anterior descending stenosis. The hood of a previously placed vein graft (d) is often the best location for a new arterial free graft or a vein graft. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2009. All rights reserved.)

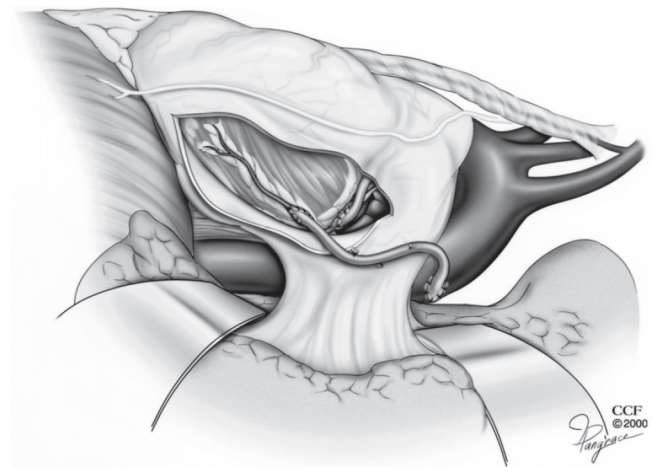


FIGURE 91-5 ■ A left thoracotomy can be used for an off-pump anastomosis of a radial artery or vein graft to the circumflex coronary artery. (Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2009. All rights reserved.)

ITA to graft that circumflex vessel, thus maximizing long-term benefit.

The gastroepiploic artery can be used as an in situ graft to graft the posterior descending branch of the right coronary artery through the diaphragm with a small distal sternotomy or transdiaphragmatic approach or the anterior descending coronary artery through a distal sternotomy or small left thoracotomy. The left ITA can be used to graft the anterior descending coronary artery through a small left thoracotomy (minimally invasive direct coronary artery bypass), and the right ITA can be used to graft the anterior descending artery as an in situ graft through a repeated median sternotomy. These strategies can be useful in specific situations in which the goal is limited revascularization. However, most patients who are reoperative candidates need multiple grafts to multiple vessels.

RESULTS OF CORONARY REOPERATIONS

Coronary reoperations have been associated with higher risks of death and in-hospital complications than primary coronary surgery has.^{1,3,16,23,26-29} Some of the mortality risk appears to be associated with the technical difficulty of the reoperative situation and some with the higher-risk characteristics of reoperative candidates. Studies from institutions with a high level of experience with reoperation have shown that when patient-related characteristics are adjusted for the reoperative situation itself, risk does not appear to be increased, at least in more recent years.²⁶⁻²⁷ On the other hand, studies of broader databases, such as the New York State database, show that reoperation still persists as a specific risk factor in coronary surgery.³ Coronary reoperations are difficult, and it is possible that patients undergoing these procedures at institutions with a high level of experience have better outcomes and that the specific risks of reoperation can be ameliorated with experience.

A query of the Society of Thoracic Surgeons database, which is probably most reflective of widespread practice, shows a decrease in the mortality risk of coronary reoperations from 6.1% in 1998 (542 deaths of 8820 patients) to 4.6% (261 deaths of 5734 patients) in 2009.¹⁶ It is important to note that the absolute numbers of reoperations have decreased, while the proportion classed as urgent increased during that time interval. It is likely that patient selection and acuity classification changed during that interval. The acuity of the operation has always played a defining role in the prediction of hospital mortality and still does. In the Cleveland Clinic series, the risk of hospital mortality for isolated reoperative bypass surgery was 1.7% in 1998 (5 of 291), 1.5% in 2007 (1 of 67), and 1.5% (22 of 1505) during those years cumulatively, whereas urgent reoperations carried a risk of 3.7% (15 of 401) overall. Thus, in any setting, reoperations in situations of increased acuity generate increased risk.

Other factors that increase the risk of coronary reoperations include advanced age, left ventricular dysfunction, and renal failure. In the past, some of the factors specifically associated with the reoperative situation,

including patent ITA grafts and atherosclerotic vein grafts, have been associated with increased risk; however, with the passage of time, the effects of those variables have either decreased or been eliminated. Presumably that has resulted from increased experience and the technical modifications of reoperations, such as the use of retrograde cardioplegia (a factor specifically associated with decreased mortality), minimal manipulation of vein grafts, alternative cannulation sites, and the many other technical modifications used to deal with the reoperative situation.

The late results of reoperation are not as favorable as those after primary procedures. Realistically, reoperations do not make patients as “perfect” as primary operations often do. Few reoperative candidates undergo true complete revascularization, and most have severe native coronary artery disease at the time of their reoperation. It is not surprising, therefore, that anginal symptoms are more common after reoperation than they are after primary bypass surgery. Follow-up of our series of reoperative patients at a mean interval of 72 months after operation showed that 64% of patients were classified as New York Heart Association functional class I, meaning that more than one third had some symptoms.²⁸ It is true that few patients had severe symptoms, but some angina was present in about one third of patients. Other institutions have also noted a high level of angina recurrence after reoperation.

The late survival rates after reoperation are not as good as those documented after primary surgery. Weintraub and colleagues from Emory University documented a 55% 10-year survival rate and more recently noted diabetes to be a specific risk factor decreasing the late survival rate after both reoperation and percutaneous coronary treatment for patients who have had previous bypass surgery.^{2,29} The increased prevalence of diabetes, left ventricular dysfunction, and advanced age in the reoperative population can be expected to correlate with a decrease in late overall survival rates.

MULTIPLE CORONARY REOPERATIONS

Patients with more than one previous bypass operation present incremental problems. A lack of bypass conduits is common, and virtually all patients have highly diffuse native vessel disease. Hospital risks have been increased for patients undergoing third or fourth procedures. In our early experience, we noted an 8% mortality rate of third operations, although more recently the risks for patients younger than 70 years have decreased to 1% to 2%.³⁰ Likewise, the long-term survival rate is not as favorable, although in our most recent follow-up, 84% of patients with multiple previous operations were alive at 5 years and 66% at 10 years after operation.

COMPLEMENTARY END-STAGE REVASCULARIZATION PROCEDURES

Substantial investigations have been directed toward indirect revascularization strategies that might apply to

patients with coronary atherosclerosis so diffuse that neither bypass grafting nor percutaneous coronary treatment will result in complete or effective revascularization. Most patients judged as candidates for these strategies have had previous bypass surgery.

Transmyocardial laser revascularization (TMLR) has been shown with randomized (although not blinded) trials to improve the symptom status of patients receiving only TMLR or TMLR in combination with bypass grafting. We rarely use TMLR in isolation, but we do use it in combination with bypass grafting during reoperation.

THE FUTURE OF CORONARY REOPERATIONS

A huge wave of patients needing coronary reoperations, once feared, has not materialized. However, recurrent ischemic syndromes after bypass surgery are common and are related to time. Despite advances in pharmacologic and interventional therapies for coronary atherosclerosis, many patients still require reoperation, and they present coronary surgeons with their most difficult challenges.

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ISCHEMIC MITRAL REGURGITATION

Anelechi C. Anyanwu • Javier G. Castillo • Amit Arora • David H. Adams

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TYPE II ISCHEMIC MITRAL REGURGITATION

Acute Papillary Muscle Rupture

Chronic Type II Ischemic Mitral Regurgitation

Significant advances have been made in the treatment of ischemic cardiomyopathy; however the presence of mitral regurgitation in this population continues to be a significant risk factor for mortality.¹ This chapter addresses the current concepts regarding the pathophysiology, decision making, and treatment of ischemic mitral regurgitation.

DEFINITION

Carpentier's pathophysiologic triad² is our preferred approach for defining ischemic mitral regurgitation. Most of the clinical literature on ischemic mitral regurgitation remains difficult to interpret because imprecise definitions

are often applied, which leads to marked heterogeneity within and between patient populations. A precise and uniform definition of ischemic mitral regurgitation is critical to the presentation of a relatively homogeneous group of patients for analysis and treatment.³ A strict definition of ischemic regurgitation according to the pathophysiologic triad typically requires the following:

- The *etiology* in this process is ischemic heart disease. This typically requires demonstration of coronary artery atherosclerosis *and* evidence of prior myocardial infarction with regional or global dysfunction or dilation of the left ventricle.
- The primary *lesion* causing regurgitation seen on echocardiography is tethering of the valve leaflets.
- The primary resulting valve *dysfunction* is mitral regurgitation caused by restriction of leaflet motion, which occurs mainly in systole (Carpentier's type IIIB dysfunction).

Although annular dilation often coexists in chronic ischemic regurgitation, this is usually the secondary, rather

than primary, lesion. Ischemic mitral regurgitation with normal unrestricted leaflet motion (Carpentier type I dysfunction) can occur in the setting of a basal infarction, but such cases are infrequent. The infrequently encountered scenario where an infarcted papillary muscle elongates to cause leaflet prolapse (Carpentier type II dysfunction) is a rare form of ischemic mitral regurgitation and is considered briefly at the end of this chapter. When prolapse is seen in patients with ischemic heart disease, the more likely explanation is degenerative, rather than ischemic, etiology. A true type IIIA dysfunction (leaflet restriction in both systole and diastole) is not seen in ischemic mitral regurgitation. If a chronic type II or IIIB dysfunction is seen in a patient with ischemic heart disease, the surgeon must consider nonischemic etiologies: this distinction is important, because the therapy for ischemic mitral regurgitation—a downsized annuloplasty—can be potentially harmful if applied to patients with a type II or IIIA dysfunction if they are misclassified as having ischemic mitral regurgitation (Fig. 92-1).

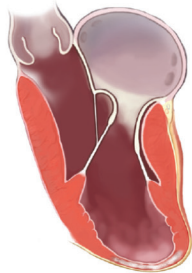
	Type I	Type II	Type IIIB
			
Mechanism	Annular dilation	Leaflet prolapse	Leaflet restriction in systole
Prevalence	Common	Uncommon in acute settings due to early PCI, very rare in chronic scenarios	Most common
Common lesions	Circumferential annular dilation, posterior greater than anterior	Acute papillary muscle rupture (commonly the posterolateral papillary muscle due to single blood supply) or elongation of the papillary muscle due to chronic ischemia	Posterior leaflet restriction and tethering secondary to lateral displacement of the papillary muscles from ventricular remodeling
Surgical techniques	Restrictive ring annuloplasty	Mitral valve replacement Restrictive ring annuloplasty Papillary muscle reattachment (acute) Papillary muscle shortening (chronic) Leaflet resuspension with neochordae	Restrictive rigid ring annuloplasty Mitral valve replacement (severe) Leaflet patch augmentation Chordal cutting (secondary chords) Leaflet resuspension with neochordae (after resection of marginal chords in severe settings) Relocation of papillary muscles

FIGURE 92-1 ■ Carpentier's functional classification in ischemic mitral regurgitation (MR). Type I has normal leaflet motion, and MR is based on annular dilation. Type II dysfunction implies excess leaflet motion with the free edge of the leaflets above the annular plane during systole, which can occur because of papillary muscle rupture (acute infarction) or papillary muscle elongation (chronic). Type IIIB is the most common form of ischemic MR; it results from restricted leaflet motion during systole secondary apical and lateral papillary muscle displacement. *PCI*, Percutaneous coronary intervention.

The majority of patients with ischemic mitral regurgitation have so-called functional ischemic mitral regurgitation from IIIB dysfunction without any leaflet or subvalvular lesions (leaflet tethering occurring because of papillary muscle displacement). Although the term *functional* mitral regurgitation is commonly used to refer to mitral regurgitation without “organic” lesions of the mitral valve, its use should be discouraged, because it is an imprecise term and lacks the mechanistic and therapeutic correlates of the Carpentier functional classification. Furthermore, although it is often assumed that the valve apparatus is normal in functional regurgitation, pathologic studies have shown that these leaflets are thinned out with altered collagen composition compared with autopsy controls.⁴ Secondary mitral valve regurgitation is a more appropriate term because it differentiates mitral regurgitation due to secondary ventricular process, from that due to primary pathology of the valve leaflets or subvalvular apparatus.

A documented clinical history of a myocardial infarction (MI) is not mandatory for the diagnosis of ischemic mitral regurgitation. Although a prior MI is almost always present in these patients, it may be silent in many patients, especially in those with diabetes. In addition, the spectrum of ischemic mitral regurgitation likely includes a small number of patients with large areas of ischemic hibernating myocardium (without substantial infarction), causing papillary muscle displacement and type IIIB mitral regurgitation. However, for practical purposes, in this chapter we will assume (unless otherwise stated) that all patients have infarction-induced ventricular remodeling, as true ischemic mitral regurgitation without underlying infarction is not rare.

The optimal way to evaluate ischemic mitral regurgitation is by semiquantitative or quantitative assessment, preferably by transthoracic echocardiography performed while the patient is awake and not actively ischemic. General anesthesia and even the light sedation required for transesophageal echocardiography (TEE) can unload the ventricle and lead to underestimation of the degree of mitral regurgitation.⁵ In addition, the potential unloading effects of inotropes, vasodilators, and intra-aortic balloon pump can affect the degree of regurgitation. During the past two decades, state-of-the-art techniques for quantifying mitral regurgitation by echocardiography have emerged, and they are particularly useful for patients with ischemic regurgitation. The recommended method to measure the degree of the mitral regurgitation quantitatively is to calculate the regurgitant volume and the effective regurgitant orifice using the flow-convergence proximal isovelocity surface area method. These calculations along with evaluating for hemodynamic consequences of the regurgitation most accurately define the severity of the mitral regurgitation.⁶ The Mayo group has suggested that the thresholds for defining significant mitral regurgitation should be lower (regurgitant volume, ≥ 30 mL; effective regurgitant orifice area, ≥ 20 mm²) in secondary (functional) mitral regurgitation than in primary (organic) mitral regurgitation, given its effect on survival in this group.⁷ Cine ventriculography has been superseded by echocardiography for diagnosis and grading of ischemic mitral regurgitation. The absence of

mitral regurgitation on ventriculography should not be regarded as sufficient to exclude ischemic mitral regurgitation. This is increasingly important in the current era, as many interventionists have moved toward a low-volume injection technique for ventriculography, which is suboptimal for assessing mitral regurgitation.⁸

CLINICAL PRESENTATION

Ischemic mitral regurgitation has traditionally been characterized as acute or chronic. Rarely, some patients develop acute mitral regurgitation during bouts of ischemia; this type disappears with the revascularization or resolution of the ischemia and is not considered in this chapter. Acute mitral regurgitation as a result of papillary muscle rupture after acute myocardial infarction is discussed at the end of this chapter. The vast majority of patients with ischemic regurgitation have a specific propensity to mitral regurgitation because of effects of prior myocardial infarction, effects that are generally permanent and chronic unless they are ameliorated surgically. In many patients, ischemic mitral regurgitation is asymptomatic and is an incidental finding at echocardiography. When regurgitation is severe or long-standing, or when the degree of accompanying left ventricular dysfunction is severe, patients present with symptoms and signs of heart failure.

Patients with type IIIB ischemic mitral regurgitation typically present with one of two clinical scenarios (Fig. 92-2). The first scenario is a patient with symptomatic multivessel coronary artery disease, with or without associated congestive heart failure symptoms, who is referred for surgical or percutaneous revascularization and who is typically noted to have mild to moderate mitral regurgitation on preoperative or intraoperative imaging. The other scenario is a patient with moderate to severe mitral regurgitation and primarily congestive heart failure symptoms, who is referred for mitral valve surgery and who has significant coronary artery disease. Increasingly, patients in the latter group have undergone prior percutaneous or surgical revascularization. Associated coronary artery disease typically involves more than one vessel, but ischemic mitral regurgitation can also occur in the setting of single-vessel disease.

PATHOPHYSIOLOGY

Normal mitral valve function involves a complex, three-dimensional interaction among the leaflets, the annulus, the subvalvular apparatus, and the left ventricle. The mechanism by which myocardial ischemia and infarction perturb this carefully orchestrated process has been the focus of intensive laboratory investigation. Several groups have carefully analyzed the geometric mechanisms of ischemic mitral regurgitation in large animal models using biplane fluoroscopy, sonomicrometry, and two- and three-dimensional echocardiography. Although these studies have several limitations, they provide significant insight into the pathophysiology of ischemic mitral regurgitation and potential treatment modalities.

	Primarily Ischemia	Primarily Heart Failure
		
Mechanism	Posterior leaflet restriction	Leaflet restriction and annular dilation
Severity of MR	Mild to moderate	Moderate to severe
LV dysfunction	Mild to moderate	Moderate to severe
Ejection fraction (%)	30-50	15-40
Indication for surgery	Coronary artery disease	Congestive heart failure

FIGURE 92-2 ■ The two most common and relatively distinct clinical scenarios for patients with ischemic mitral regurgitation. Most patients have primarily ischemic symptoms, and they are noted on evaluation for coronary bypass surgery to have mild to moderate mitral regurgitation. A significant minority, however, primarily have symptoms of congestive heart failure and are noted on evaluation for mitral valve surgery to have significant coronary artery disease. Patients in the latter group tend to have worse left ventricular function. LV, Left ventricular; MR, mitral regurgitation.

The key pathophysiologic components of types I and IIIB ischemic mitral regurgitation include annular changes (dilation, distortion), subvalvular changes (papillary muscle displacement), and ventricular changes (dilation with increased sphericity, and wall motion abnormalities). Figure 92-3 provides an overview of how these components interact to result in poor leaflet coaptation, which is the final common pathway for all types of mitral regurgitation.

Specific Geometric Abnormalities

Annular

Although annular dilation is a common finding in clinical cases of chronic ischemic mitral regurgitation, the degree of dilation is often not severe and does not necessarily correlate with the degree of mitral regurgitation. Dilation of the annulus causes the leaflets to pull apart and hinders adequate leaflet coaptation. Although the posterior portion of the annulus is far more affected by ventricular or atrial enlargement, the anterior annulus has been shown to dilate as well.^{7,9-11} This concept has been demonstrated in both pathologic and imaging studies,^{11,12} which showed that although annular dilation is predominant in the region of the posterior commissure, it is often asymmetrically present throughout the annulus as well. Along with dilation, the annulus also flattens, losing its saddle shape, in ischemic mitral disease.^{10,12} The degree of annular dilation might not be a fundamental component of ischemic mitral regurgitation pathophysiology. Green and colleagues⁸

showed that in an acute sheep model, moderate degrees of annular dilation do not necessarily lead to ischemic mitral regurgitation. Timek and coworkers¹³ noted that the mild degrees of annular dilation that they observed during acute occlusion of the left anterior descending or distal left circumflex did not result in ischemic mitral regurgitation. This study, and several others from the same group, noted the critical role of the septolateral (SL) annular dimension in the pathophysiology and treatment of ischemic mitral regurgitation. The SL dimension—also referred to as the anteroposterior (AP) dimension—is the vertical or short axis of the annular ellipse that extends from the middle of the anterior annulus to the middle of the posterior annulus. The horizontal or long axis of the ellipse is referred to as the *commissure-commissure* (CC) dimension. Studies have shown that in the sheep acute ischemia model, an increase in mitral annular area causes mitral regurgitation only to the extent that it increases the SL dimension. Furthermore, these researchers also demonstrated the importance of the SL dimension by using a cinching device to diminish this dimension abolishing ischemic mitral regurgitation in sheep independent of overall annular circumference.^{14,15} Although the CC dimension does not usually increase significantly with ischemia,¹²⁻¹⁵ it has been shown to change proportionally with the change in the posterior annulus.^{9,11,16} This disproportionate posterior annular dilation accounts for the more significant increase in the SL dimension. In severe cases of ischemic mitral regurgitation, the SL dimension can approach the CC dimension, which results in a circular annulus rather than the normal ellipse.

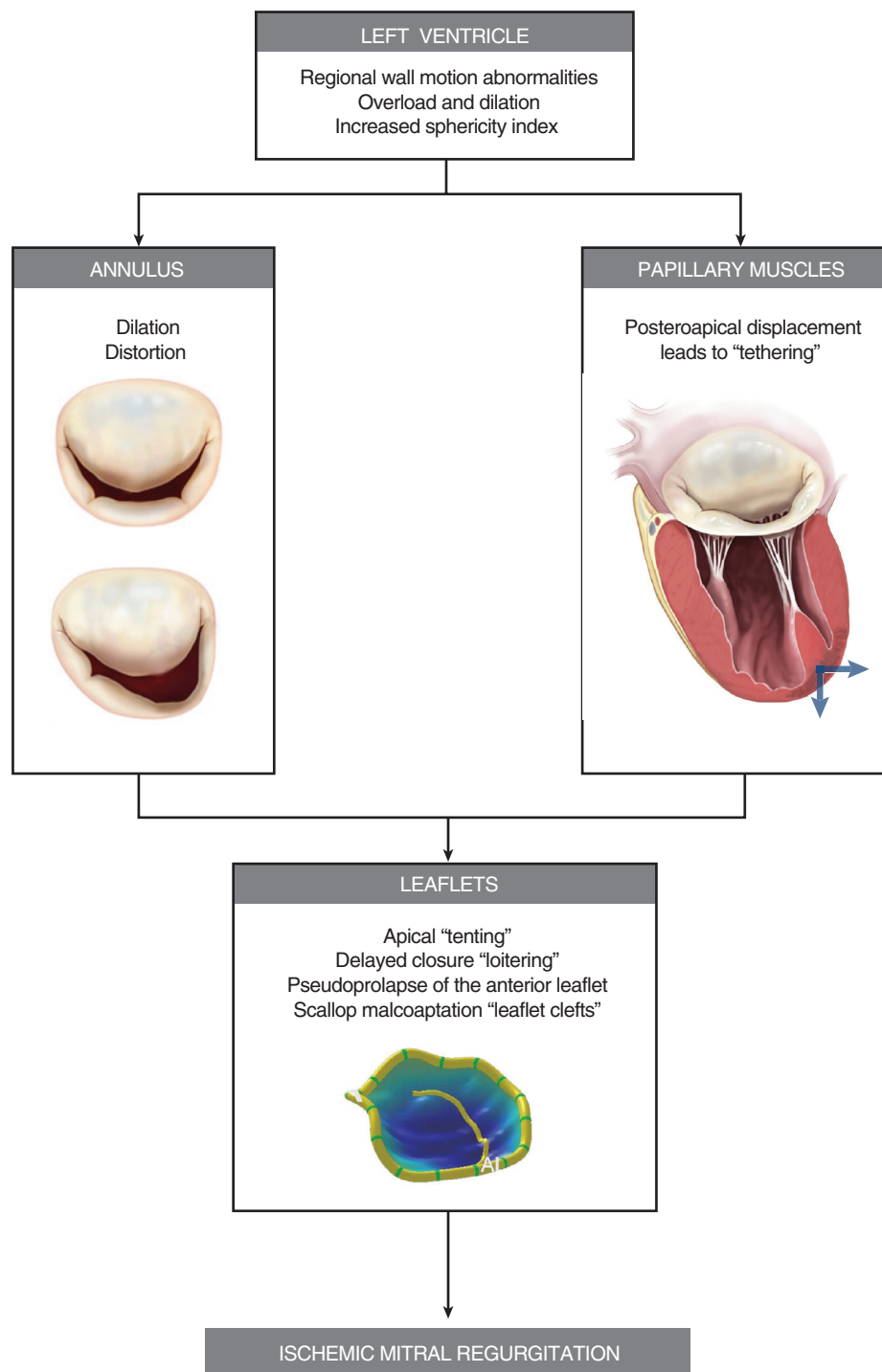


FIGURE 92-3 ■ Pathophysiology of ischemic mitral regurgitation. The interaction among the left ventricle, the papillary muscles, the annulus, and the leaflets leads to poor leaflet coaptation as the final common pathway to mitral regurgitation. The posteroapical displacement of the papillary muscles away from each other (arrows) results in ischemic mitral regurgitation.

Subvalvular

Papillary muscle displacement also plays a critical role in the pathophysiology of ischemic mitral regurgitation. It is important to distinguish this from papillary muscle dysfunction (decreased or disordinated papillary muscle systolic shortening), which had previously been thought to be the primary mechanism for ischemic mitral regurgitation. In fact, papillary muscle dysfunction does not

necessarily result in ischemic mitral regurgitation. Timek and coworkers¹⁷ showed that the decreased shortening of one or both papillary muscles did not correlate with ischemic mitral regurgitation in the sheep. On the contrary, Messas and colleagues¹⁸ demonstrated a paradoxical decrease in ischemic mitral regurgitation with papillary muscle dysfunction.

The primary alteration in papillary muscle geometry leading to ischemic mitral regurgitation is papillary muscle

displacement. The pattern of displacement is actually fairly complex and cannot simply be described as apical tethering. The papillary muscle tips are displaced away from the midseptal (anterior) annulus (i.e., posterolaterally, apically, and away from each other). The tethering distance has been shown experimentally to correlate with the severity of ischemic mitral regurgitation.^{13,17,19} Experimental studies suggest that although displacement of both papillary muscles is probably necessary to induce ischemic mitral regurgitation, displacement of the posteromedial papillary muscle group usually predominates.

Left Ventricular

The initiating insult in ischemic mitral regurgitation is ventricular, specifically myocardial ischemia or infarction with remodeling that leads to regional annular and subvalvular distortion and ultimately poor leaflet coaptation. The independent contribution of global ventricular size and shape to the pathophysiology of ischemic mitral regurgitation is less clear. In an echocardiographic study of 102 patients, Kumanohoso and coworkers²⁰ showed that in comparison to those with anterior infarctions, patients with inferior infarctions had a higher incidence of ischemic mitral regurgitation despite less severe left ventricular dilation and dysfunction; this was directly attributed to more severe posteromedial papillary muscle tethering in the inferior infarction group. Experimental data, however, suggest that regional left ventricular dysfunction does not lead to ischemic mitral regurgitation without some degree of left ventricular dilation.

It appears that the left ventricular sphericity is more important than the actual ventricular volumes or ejection fraction in the pathophysiology of ischemic mitral regurgitation. Using three-dimensional echocardiography, several groups have shown that the mechanism of regurgitation differs according to the region of infarction. Watanabe and colleagues,²¹ for example, found that tethering was more localized and predominant in the medial posterior leaflet in patients with inferior infarction, compared with more widespread tethering of both leaflets in anterior infarction (Fig. 92-4).²¹ This observation confirms the critical role of regional ventricular geometry and function in the pathophysiology of ischemic mitral regurgitation and helps to explain why some patients with only mildly impaired global ventricular function have severe ischemic mitral regurgitation. Song and colleagues²² found that an inferior infarction coexisting with an anterior wall infarct led to a more severe regurgitation, independent of ventricular volume. These observations suggest that geometry of the valve apparatus may be a more important determinant of regurgitation than left ventricular volume or ejection fraction. It is possible, therefore, to have severe ischemic mitral regurgitation in the setting of relatively preserved ventricular function. Tethering is more symmetrical in patients with coexisting inferior and anterior infarction.²²

Leaflet Dysfunction

Papillary muscle tethering leads to apical tenting of the leaflets (restriction of the motion of the free margins of

the leaflets), which prevents the free margins of the leaflets from rising to the plane of the annulus to coapt with one another. Tethering of the secondary chordae can result in an *effet de mouette* deformation of the body of the leaflet, which further impairs coaptation. Leaflet tethering is typically asymmetric in ischemic mitral regurgitation. The posteromedial side of the valve (A3 and P3) has more pronounced restriction when compared with the anterolateral side (A1 and P1).^{23,24} Malcoaptation of the scallops of the posterior leaflet from papillary muscle tethering has also been implicated in the pathogenesis of ischemic mitral regurgitation.²⁵

THERAPEUTIC TARGETS IN ISCHEMIC MITRAL REGURGITATION

Being essentially a ventricular disease caused by coronary stenosis, with effects on the papillary muscle, cords, and leaflet coaptation, ischemic mitral regurgitation lends itself to several therapeutic targets.

Coronary Artery Disease

Coronary artery revascularization is necessary to recruit any hibernating myocardium and thus improve ventricular function. Revascularization can also help to limit future adverse remodeling resulting from continuing ischemia or new infarction. Revascularization alone is not, however, reliable as sole therapy for ischemic mitral regurgitation as the principal cause of the regurgitation, leaflet tethering caused by regional infarction, cannot generally be reversed by revascularization. Correcting ischemia alone has not been reliable at treating the valvular dysfunction, and leaves patients with residual regurgitation and higher rates of worsening regurgitation.^{26,27}

Mitral Annulus

The mitral annulus has been the principal target of surgical therapy for ischemic mitral regurgitation. Bolling and colleagues^{28,29} first popularized downsized annuloplasty to address secondary mitral regurgitation owing to cardiomyopathy in the 1990s. In this group's initial experience, flexible band annuloplasty was used; however, recent data support the use of complete rigid or semirigid downsized annuloplasty in ischemic disease.³⁰⁻³² The restrictive (or downsized or undersized) annuloplasty partly addresses the pathophysiologic derangements seen in ischemic mitral regurgitation. The annuloplasty corrects circumferential annular dilation, whereas downsizing aims to correct the septolateral displacement and thus reduces the tethering distance. Complete rigid or semirigid rings are preferred, as they ensure that the valve remains fixed in the new reduced SL dimension. Asymmetrical rings may be helpful in addressing the asymmetrical tenting seen in inferior infarction. Incomplete annuloplasty with flexible bands may not adequately reduce the SL dimension.

The differences in tethering between anterior and inferior infarctions raises question as to whether characteristics of annuloplasty rings should differ depending on

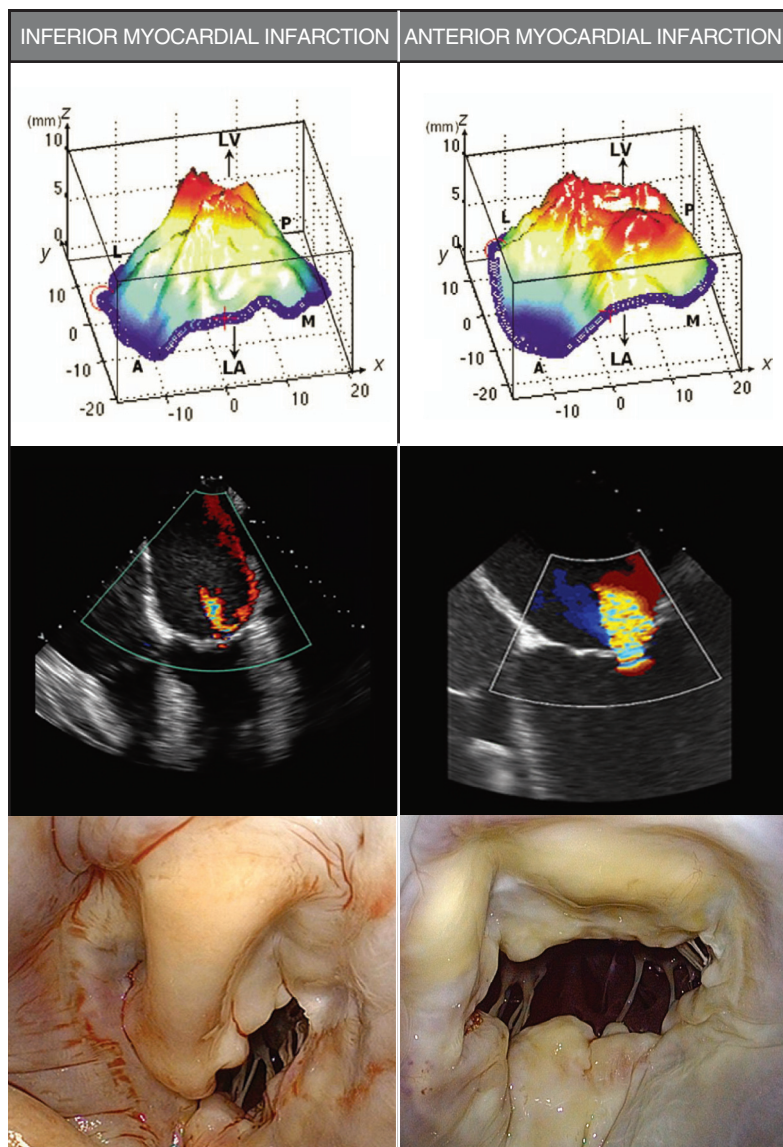


FIGURE 92-4 ■ Tenting and tethering of mitral leaflets into the left ventricle (LV) in patients with ischemic mitral regurgitation. Areas of greatest displacement are shown in *red*. For patients with inferior infarction, tenting of leaflet is more localized with less bulging. For patients with anterior infarction, mitral valve leaflets are widely tethered and bulge toward the LV. The tethered leaflet area is smaller in inferior than in anterior myocardial infarction. A, Anterior; L, lateral; LA, left atrium; M, medial; P, posterior. (Top panels adapted with permission from Watanabe N, Ogasawara Y, Yamaura Y, et al: Geometric differences of the mitral valve tenting between anterior and inferior myocardial infarction with significant ischemic mitral regurgitation: quantitation by novel software system with transthoracic real-time three-dimensional echocardiography. *J Am Soc Echocardiogr* 19:71–75, 2006.)

location of infarction. Lack of emphasis of the annuloplasty on areas of greatest tethering may be responsible for some recurrences after surgical repair. Better understanding of three-dimensional annular geometry can lead to the development of annuloplasty techniques that are tailored to the individual patient based on specific annular geometry and tenting distribution.

Subvalvular Apparatus

Subvalvular approaches aim to reduce leaflet tethering and thus allow better leaflet coaptation. Two broad approaches exist. First, tethering can be ameliorated by division of secondary chordae (Fig. 92-5).³³ Restrictive primary chords can also be divided and replaced with artificial chordae. Second, the tethering distance between the papillary muscle heads and the annular plane can be reduced by using external or internal devices. Several techniques have been developed that relocate the papillary muscles so that they are closer to the annulus (i.e., less displaced), thereby reducing the leaflet tethering.

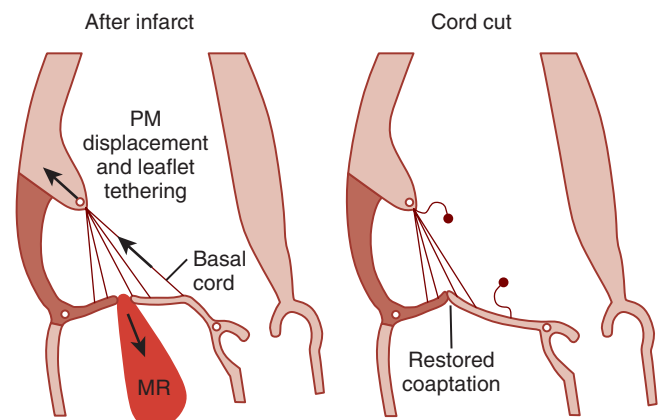


FIGURE 92-5 ■ Distortion of the anterior leaflet resulting from tethering by secondary chordae, causing leaflet retraction and mitral regurgitation (MR). Division of these chordae results in better leaflet mobility and reduction in mitral regurgitation. PM, Papillary muscle. (Reprinted with permission from Messas E, Guerrero JL, Handschumacher MD, et al: Chordal cutting: a new therapeutic approach for ischemic mitral regurgitation. *Circulation* 104:1958–1963, 2001.)

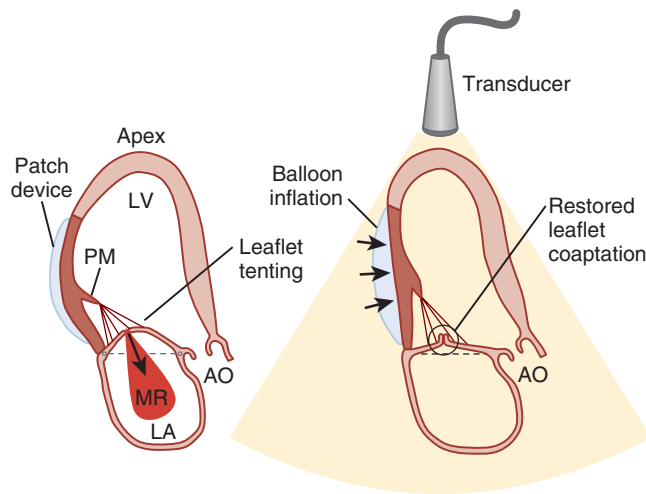


FIGURE 92-6 ■ Patch placement and balloon inflation over infarct region (black) to reposition displaced papillary muscle (PM) toward anterior annulus and relieve tethering and mitral regurgitation (MR) under ultrasound guidance in a beating heart. AO, Aorta; LA, left atrium; LV, left ventricle. (Modified with permission from Hung J, Guerrero JL, Handschumacher MD, et al: Reverse ventricular remodeling reduces ischemic mitral regurgitation: echo-guided device application in the beating heart. *Circulation* 106:2594–2600, 2002.)

External devices designed to reduce tethering by displacing infarcted ventricle have also been investigated. Hung and colleagues^{34,35} used animal studies to evaluate an external device that works by displacing the infarcted ventricular wall that supported the tethered papillary muscle toward the mitral annulus. Use of this device should reduce tethering and resultant regurgitation (Fig. 92-6).^{34,35}

Leaflets

Because the leaflets are not directly involved in the causation of ischemic mitral regurgitation, there is limited scope for surgical intervention on the leaflets. Clefts tend to open up with leaflet tethering, and they may be closed at the time of mitral valve repair. The edge-to-edge leaflet technique has been proposed as an adjunct to annuloplasty,³⁶ but alone it is not as effective a treatment for ischemic mitral regurgitation compared with annuloplasty.³⁷ The edge-to-edge approach, however, is increasingly used with the percutaneous clip technique in patients who are not surgical candidates. There have been techniques for patch augmentation of both the anterior and posterior leaflet with acceptable early results; however, they may be technically challenging.³⁸

Left Ventricle

Operations to restore left ventricular geometry can reduce papillary muscle displacement and result in reduction of mitral regurgitation. This could be achieved by ventricular remodeling procedures (such as the Dor operation) or by localized plication of a lateral wall infarct. Approaches that halt the process of continued

ventricular remodeling can improve durability of ischemic mitral valve repair by limiting further papillary muscle displacement. For example, external ventricular restraint devices wrapped round the ventricle at the time of mitral valve repair have been shown to limit future dilation of the left ventricle³⁹; this eliminates one of the key pathophysiologic mechanisms for recurrent regurgitation after mitral annuloplasty (progressive ventricular remodeling). Injection of polymers into infarcted tissue has been explored experimentally by Hung and colleagues,⁴⁰ who demonstrated that polymer injection supported the infarcted ventricle and stabilized the papillary muscles, thereby resulting in acute reverse remodeling of the ventricle and reduction in papillary muscle displacement and decrease in mitral regurgitation. Finally, injection of myoblasts or stem cells into infarcted tissue is another potential use of the left ventricle as a target, as this could theoretically reduce mitral regurgitation by restoring ventricular function and therefore reducing tethering.⁴¹

The Coapsys device (Myocor, Inc., Maple Grove, MN) was an external compression device, placed without cardiopulmonary bypass, with an intracavitary cord that reshapes the left ventricle. By reshaping the ventricle, Coapsys compressed the mitral annulus and subvalvular apparatus and has been shown to decrease ischemic mitral regurgitation in animal studies.⁴² The RESTOR-MV trial randomized 149 patients with ischemic mitral regurgitation to CABG and conventional on-pump mitral valve repair or CABG with off-pump Coapsys implantation, and it found better survival and fewer adverse events in the Coapsys arm compared with standard surgical repair.⁴³ Unfortunately, the RESTOR-MV study was closed prematurely because of corporate financial issues, and the device did not achieve clinical approval, but the study is a useful demonstration that ventricular reshaping may be effective in ischemic mitral regurgitation.

PREOPERATIVE DECISION MAKING

Preoperative decision making in ischemic mitral regurgitation is complex and challenging. The clinical literature is often contradictory, making it difficult to synthesize and distill the information into concrete and practical clinical recommendations. Many factors must be considered in decision making, including the specific clinical scenario, the negative effects of ischemic mitral regurgitation on medium-term survival, the challenge of the intraoperative assessment of mitral regurgitation severity, the effects of coronary artery bypass grafting (CABG) alone on mitral regurgitation severity, the effects of CABG with or without mitral surgery on survival and late functional status, the additional operative risk of mitral valve surgery at the time of CABG, and the choice of valve repair versus replacement. We believe that the cumulative evidence and experience about these various issues are coalescing into a set of principles that can guide modern surgical decision making for the treatment of this disease (Fig. 92-7).

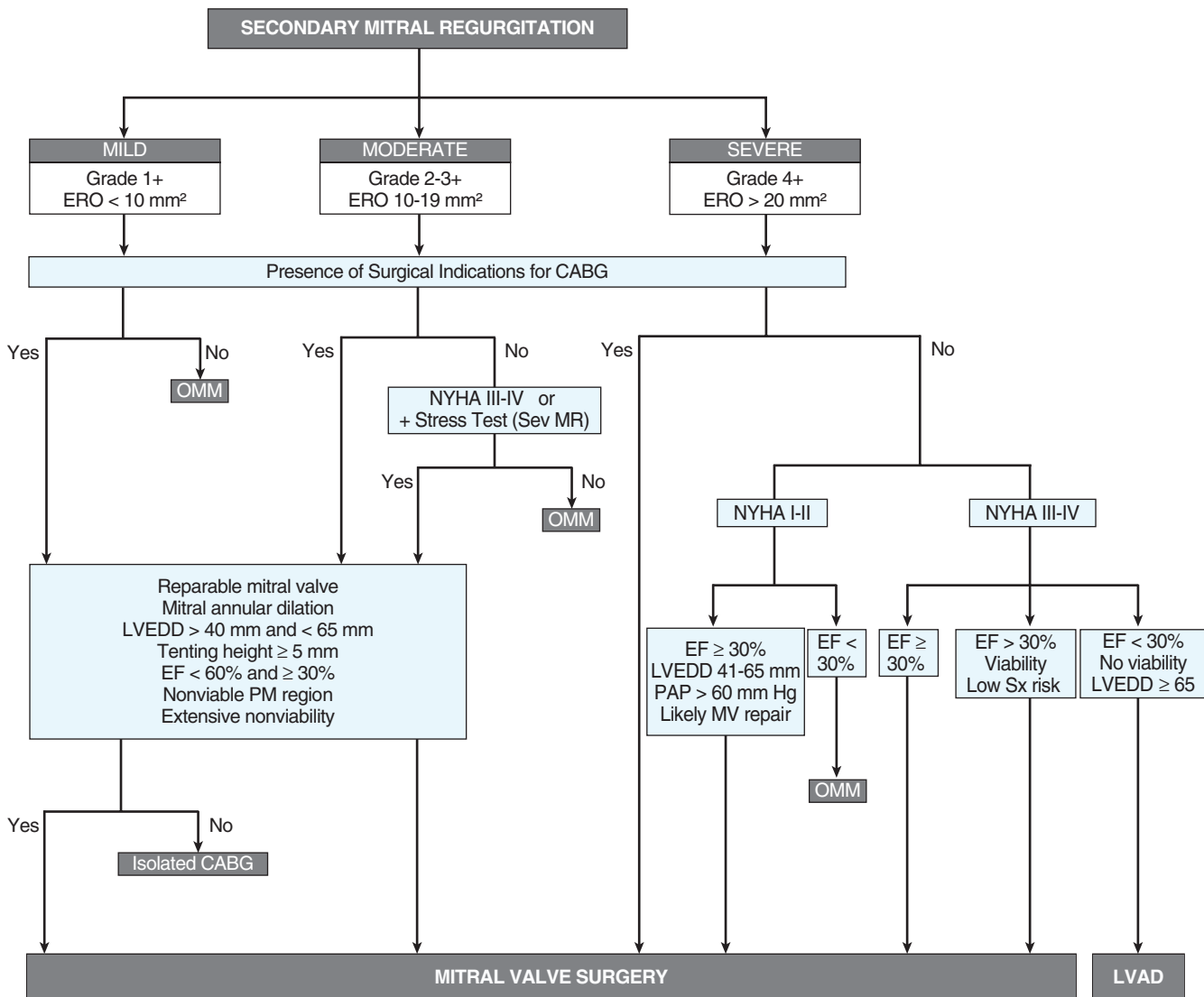


FIGURE 92-7 ■ Decision making algorithm for surgery in patients with secondary mitral regurgitation. CABG, Coronary artery bypass grafting; EF, ejection fraction; ERO, effective regurgitant orifice; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; MR, mitral regurgitation; NYHA, New York Heart Association functional class; OMM, optimal medical management including cardiac resynchronization therapy; PAP, pulmonary artery pressure; PM, papillary muscle; Sx, surgical. (Modified with permission from Crestanello JA: Surgical approach to mitral regurgitation in chronic heart failure: when is it an option? *Curr Heart Fail Rep* 9:40–50, 2012.)

Decision Making in Specific Clinical Scenarios

Severe Ischemic Mitral Regurgitation with Congestive Heart Failure

Patients with severe mitral regurgitation, symptoms of congestive heart failure, or worsening left ventricular function are referred primarily for mitral valve surgery (as opposed to referred for coronary revascularization). The preoperative coronary angiogram typically shows significant coronary artery disease that may or may not have been symptomatic with angina. Patients may have undergone prior surgical or percutaneous revascularization. These patients typically have evidence of prior myocardial infarction and moderate or severe left ventricular

dysfunction. They can be viewed as ischemic cardiomyopathy with associated mitral regurgitation.

It must be stressed that in all these patients the initial therapy is guideline directed heart failure medical management. Medical therapy aims to maintain euvolemia and to reduce cardiac preload and afterload thereby optimizing cardiac performance. In many patients, medical management will result in reduction of severity of regurgitation, with varying degrees of symptom improvement.⁴⁴ Medical therapy includes maximally tolerated doses of diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, aldosterone antagonists, and beta blockers, especially carvedilol. Cardiac resynchronization therapy (CRT) with biventricular pacing should be used in patients with severe ischemic mitral regurgitation who show evidence of dyssynchrony.

Responders to CRT have been shown to have significant reduction in severity of secondary mitral regurgitation.⁴⁵⁻⁴⁷ Consideration for mitral valve surgery for severe ischemic regurgitation in the heart failure patient without primary indication for CABG should, therefore, be undertaken only after confirmation that medical therapy is optimal and CRT has been attempted or is not indicated. In general, surgical therapies are not considered, even if regurgitation remains severe on medical therapy, unless symptoms remain severe (New York Heart Association [NYHA] class III or IV). In selected low-risk patients, however, mitral valve surgery can be considered in NYHA II patients where the ventricle is not severely dysfunctional or remodeled with the hope that intervention can delay or prevent further negative remodeling. (Although there is no direct evidence to support this, randomized trials seem to show reverse left ventricular remodeling at 12 months in patients with moderate mitral regurgitation who undergo mitral valve repair.⁴⁸)

Patients who remain severely symptomatic (NYHA III or IV) despite medical therapy, and who have an ejection fraction over 30%, should be offered mitral valve surgery as the risk is acceptable (provided no major comorbidity) and patients can expect substantial improvement in symptoms. If the ejection fraction is particularly low (<30%), the decision to operate, in the absence of documented ischemia, is similar to the decision that needs to be made for patients with mitral regurgitation as a result of nonischemic cardiomyopathy. Patients with severe ischemic mitral regurgitation with symptoms of congestive heart failure or worsening left ventricular function (or both) can undergo combined mitral valve surgery and CABG as long as the expected operative morbidity and mortality is not prohibitive. For patients who survive and recover from surgery, the expected benefit of surgery would be better control of heart failure with likely improvement of symptoms. However, there is no clear evidence that life expectancy is improved by mitral valve repair in the setting of left ventricular dysfunction, and indeed some data suggest the contrary.⁴⁹ For this reason, advanced therapies for cardiac replacement (transplantation and left ventricular assist device implantation) have been used increasingly as options for treating ischemic mitral regurgitation in the severely dysfunctional and remodeled left ventricle (left ventricular end-diastolic diameter [LVEDD] > 65 mm), particularly where there is limited viability. Young patients with ischemic mitral regurgitation and severe left ventricular dysfunction, with NYHA class III or IV heart failure, should be screened to determine whether they meet indications and criteria for heart transplantation before undertaking mitral valve surgery. Some patients with advanced ischemic cardiomyopathy and ischemic mitral regurgitation, who are not candidates for transplantation, may be suitable for destination left ventricular assist device as an alternative to high risk mitral valve surgery.⁵⁰

An increasingly common scenario is severe mitral regurgitation seen in patients who have undergone prior CABG. Often, this regurgitation had not been addressed at the CABG procedure and has since progressed. These

patients present unique challenge because reoperation in the presence of patent coronary bypass grafts may increase operative risk. Thoughtful consideration for appropriate patient selection and operative strategy is warranted.⁵¹ Reoperative surgery to address ischemic mitral regurgitation is generally recommended only when quality of life is greatly impaired, despite optimal medical therapy (NYHA III or IV).

Mild or Moderate Ischemic Mitral Regurgitation in Patients Undergoing Coronary Artery Bypass Grafting

The other common clinical scenario is that of a patient with symptomatic coronary artery disease who is referred for CABG and who is noted to have mild or moderate mitral regurgitation on preoperative or intraoperative echocardiography. Although the patient may have shortness of breath—as an angina equivalent or symptoms or signs of congestive heart failure (sometimes recognized in retrospect)—myocardial ischemia (an acute coronary syndrome or chronic stable angina) usually dominates the clinical picture and is the primary indication for surgical intervention.

Mild mitral regurgitation usually does not need to be addressed at the time of revascularization.⁵²⁻⁵⁴ If there are indications that the mild regurgitation might not run a benign course (e.g., left ventricular enlargement, substantial infarction or nonviability, pulmonary hypertension, excessive leaflet tenting), then it should be managed as moderate regurgitation.

Although most surgeons agree that severe mitral regurgitation should be corrected at the time of CABG, irrespective of the presenting symptoms, the optimal management of moderate ischemic mitral regurgitation remains controversial. One school of thought favors an aggressive repair strategy for moderate regurgitation, and another is more conservative.

Those favoring a conservative approach argue as follows:

1. Revascularizing ischemic areas will improve regional wall motion and reduce the mitral regurgitation.^{55,56} This benefit of CABG on ischemic mitral regurgitation is seen most in patients who have viable myocardium in the area of revascularization and in patients who do not have dyssynchrony of the papillary muscles.⁵⁷
2. Some historical studies suggested that performing CABG alone does not have a negative effect on long-term survival or functional status, even if some residual mitral regurgitation persists.⁵⁸⁻⁶⁰
3. Mitral valve surgery adds significantly to the operative risk of CABG, with several historical and contemporary series reporting operative mortalities in excess of 10% with combined procedures.^{28,47,61-65}
4. Patients with moderate ischemic mitral regurgitation tend to have relatively small left atria, thereby making mitral valve exposure and repair more difficult.⁵³
5. Mitral valve replacement, if it is necessary, carries the potential burden of prosthesis-related morbidity.

Many other surgeons, however, advocate the more liberal application of mitral valve surgery in patients with moderate ischemic mitral regurgitation undergoing CABG, arguing the following:

1. Chronic ischemic mitral regurgitation is a dynamic condition that is highly dependent on preload and afterload. The preoperative echocardiogram merely represents a brief snapshot of the severity of mitral regurgitation at the time of the study. The fact that many patients with “moderate” mitral regurgitation, or less, present with symptoms of congestive heart failure or enlarged left atria suggests that they probably have frequent episodes of more severe mitral regurgitation.
2. CABG alone does not correct moderate ischemic mitral regurgitation in many patients, especially those with scarring from myocardial infarction and those with annular and ventricular dilation. Patients who do not have viable or hibernating myocardium are less likely to benefit from revascularization alone.^{26,66}
3. Significant residual ischemic mitral regurgitation can, according to several studies, result in late symptoms and decreased long-term survival (discussed later).
4. Mitral annuloplasty is usually technically feasible, and almost always corrects moderate ischemic mitral regurgitation, thereby making mitral valve replacement usually unnecessary (unless the specific preference of the surgeon).²⁶
5. The high operative mortality for combined mitral valve surgery and CABG reported in the literature is outdated and reflects a significant number of patients undergoing mitral valve replacement. Mitral valve repair in the modern era can be performed at the time of CABG, with an operative mortality as low as 2% to 4%.⁶⁷⁻⁷⁰
6. Leaving significant residual mitral regurgitation exposes the patient to a potential need for reoperative mitral valve surgery in the presence of patent coronary grafts, which carries substantial operative risk.⁵¹

Two randomized studies have evaluated the role for mitral valve annuloplasty in moderate ischemic mitral regurgitation. Fattouch and colleagues⁵³ randomized 102 patients to CABG alone or CABG with mitral annuloplasty. This study demonstrated an improvement in NYHA class and a reversal in left ventricular remodeling with the addition of mitral annuloplasty to CABG, but it did not demonstrate a survival advantage.⁵³ More recently the RIME investigators randomized 73 patients undergoing CABG with moderate ischemic mitral regurgitation to CABG alone or CABG and mitral annuloplasty. Compared with patients who had CABG alone, at 12 months patients who had a concurrent mitral valve annuloplasty had superior functional status measured by both the NYHA class and by peak oxygen consumption. Left ventricular reverse remodeling was also greater in patients who had concurrent mitral valve repair.⁴⁸

The summation of best available evidence is in favor of intervening on moderate degrees of regurgitation at the time of CABG,⁷¹ mainly because of benefit in

long-term functional status and left ventricular reverse remodeling. Concurrent mitral annuloplasty should therefore be considered in all patients having coronary artery bypass surgery who have documented moderate or greater mitral regurgitation, unless specific operative or patient-related factors suggest a need for a limited or expeditious operation, or if there is strong basis to believe the mitral regurgitation can reverse with revascularization alone (e.g., good global ventricular function with extensive viability and limited infarction). The recommended surgical intervention for moderate ischemic regurgitation is mitral annuloplasty, as this has been demonstrated in randomized trials to be effective (compared with CABG alone). The efficacy and safety of mitral valve replacement has not been evaluated in the setting of moderate mitral valve regurgitation.

OUTCOMES

There is a growing body of evidence about the negative effects of even modest degrees of ischemic mitral regurgitation on medium-term survival. The modest prognosis of patients with ischemic mitral regurgitation has been documented in a variety of clinical settings, with 3-year survival rates typically being in the range of 50% to 75%, depending on the severity of mitral regurgitation and other patient characteristics.

Effect of Ischemic Mitral Regurgitation on Survival after Myocardial Infarction

Several studies have documented the strong negative effect of mitral regurgitation on survival and occurrence of heart failure after acute myocardial infarction. In their analysis of a subgroup of 727 patients with acute myocardial infarction from the Survival and Ventricular Enlargement (SAVE) trial, Lamas and colleagues⁷² found that even mild mitral regurgitation at the time of presentation was an independent predictor of mortality (relative risk, 2.0), and that this effect could not be attributed to differences in left ventricular function. This finding was reaffirmed in a more recent multicenter retrospective review by Rossi and colleagues (Fig. 92-8).¹ Grigioni and coworkers⁷ found a direct correlation between survival and the severity of mitral regurgitation using quantitative echocardiography done within 6 weeks of myocardial infarction. Aronson and coworkers⁷³ showed similar results reporting on 1190 post-acute myocardial infarction patients with ischemic mitral regurgitation. Within 3 years, 30% of those with moderate or severe regurgitation were hospitalized for heart failure, compared with 5% for those without regurgitation (Fig. 92-9). The 3-year mortality was higher in those with moderate or severe regurgitation (35%) when compared to those without regurgitation (8%; hazard ratio, 5.5). Even mild regurgitation was a risk factor for medium-term mortality (hazard ratio, 2.0). The association between ischemic mitral regurgitation after myocardial infarction and increased mortality and heart failure symptoms is independent of left ventricular function.

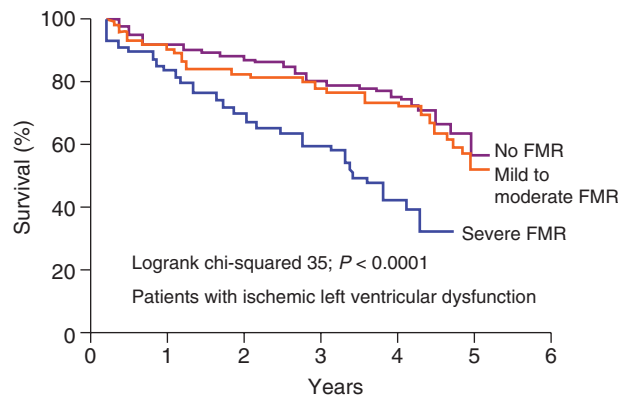


FIGURE 92-8 ■ Midterm effect of functional or secondary mitral regurgitation (FMR) after myocardial infarction. Kaplan-Meier plots showing time to all-cause mortality alone in patients with ischemic left ventricular dysfunction. (Adapted with permission from Rossi A, Dini FL, Faggiano P, et al: Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart* 97:1675–1680, 2011.)

Effect of Ischemic Mitral Regurgitation on Survival after Percutaneous Coronary Intervention

Pastorius and colleagues⁷⁴ examined long-term outcomes in 711 patients with moderate or greater mitral regurgitation at the time of percutaneous coronary intervention (PCI). They found that the presence of moderate or severe mitral regurgitation at that time was associated with a 5-year survival rate of 57%, compared with 97% for those without regurgitation (Fig. 92-10).⁷⁴

Even mild regurgitation was associated with reduced survival (5-year survival rate, 83%). These data corroborate the historical series from Ellis and colleagues,⁷⁵ who demonstrated that patients with moderate to severe mitral regurgitation and ejection fraction less than 40% had a 50% mortality at 3 years despite successful PCI. Kang and colleagues examined a prospective database of 185 patients with significant ischemic mitral regurgitation who underwent surgical CABG (with or without mitral annuloplasty) or PCI. This group showed a longer event-free survival with CABG and mitral annuloplasty compared with PCI (with no mitral valve intervention).⁷⁶ Other data from nonsurgical series also show that uncorrected regurgitation is associated with a poorer long-term survival.⁷⁷ PCI alone should therefore not be considered definitive therapy for patients needing coronary artery disease who have ischemic mitral regurgitation; in patients whose surgical risk is not excessive, the presence of mitral regurgitation should generally be an indication for surgical rather than percutaneous revascularization, provided the surgeon plans to address the mitral insufficiency.

Effect of Ischemic Mitral Regurgitation on Survival after Coronary Artery Bypass Grafting

Two historical studies from the 1980s suggested that preoperative mitral regurgitation is an independent risk

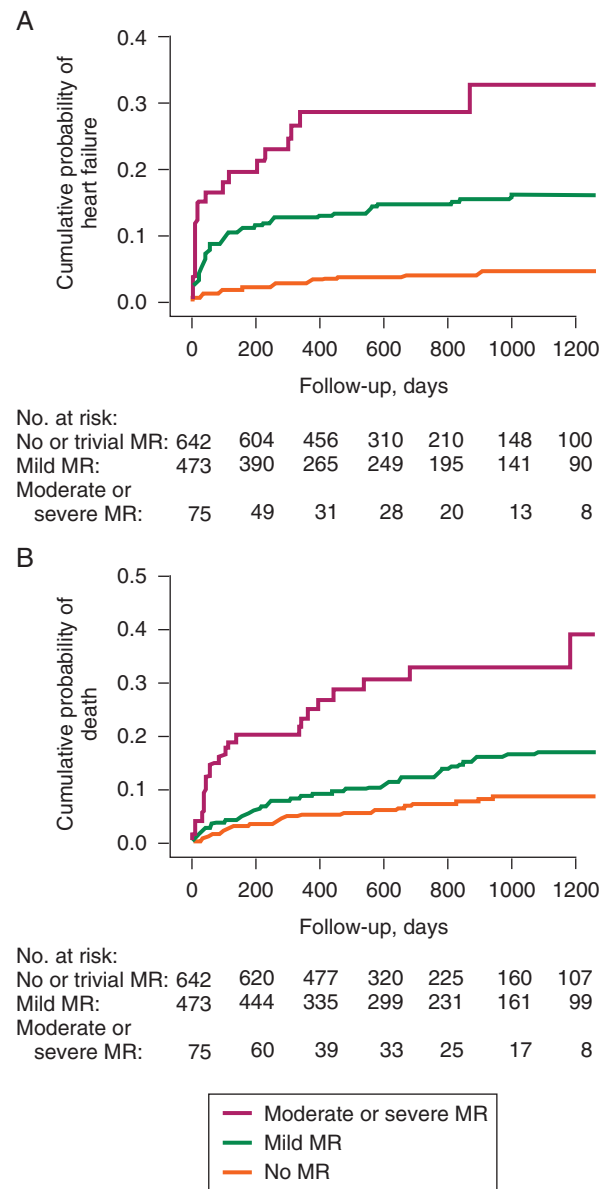


FIGURE 92-9 ■ Short-term effect of ischemic mitral regurgitation (MR) after myocardial infarction. **A**, Cumulative incidence of hospitalization for heart failure treatment. **B**, Cumulative incidence of death. Even patients with mild mitral regurgitation had worse outcomes. (Modified with permission from Aronson D, Goldsher N, Zukermann R, et al: Ischemic mitral regurgitation and risk of heart failure after myocardial infarction. *Arch Intern Med* 166:2362–2368, 2006.)

factor for late death in patients undergoing CABG.^{77,78} Uncorrected mitral regurgitation was an independent risk factor for late death, with a relative risk of 1.5 for each grade of mitral regurgitation. Subsequent studies have demonstrated that CABG alone does not seem to alter the natural history in patients with ischemic mitral regurgitation.^{26,79,80} The detrimental effect on survival of residual regurgitation after CABG, however, seems to be small if global left ventricular function is normal; therefore, it is not unreasonable to apply CABG alone in patients with good ventricular function and moderate

ischemic regurgitation.⁸¹ However, with depressed left ventricular function, studies consistently demonstrate worse survival and quality of life after CABG alone in patients with regurgitation and a severely depressed ventricular function.⁸²⁻⁸⁵ The best available evidence suggests that coronary artery bypass surgery alone does not eliminate the adverse effects of ischemic mitral regurgitation.⁷¹

Coronary Artery Bypass Grafting Alone or with Mitral Valve Intervention

Some have suggested^{85a} that ischemic mitral regurgitation is merely a marker for severe underlying ischemic heart disease and not a direct cause of late death. The body of evidence supporting a direct effect of ischemic mitral regurgitation on late survival is strong. It is particularly compelling because, in many studies, ischemic mitral regurgitation was a predictor of late mortality independent of the usual risk factors (e.g., age, ejection fraction, functional class), which argues against it simply being a confounding variable.

Although the strong effect of ischemic mitral regurgitation on survival supports mitral valve intervention in

many patients with ischemic mitral regurgitation, the decision about whether to intervene in a specific patient can be complex and must take into account multiple factors, including the specific clinical presentation, the presence of comorbid conditions, and the expected operative morbidity and mortality. For purposes of surgical decision making, it is useful to separately consider the two most common clinical scenarios, as noted earlier. Although the detrimental effects of ischemic mitral regurgitation are well known, it is not certain that eliminating mitral regurgitation at the time of CABG improves long-term survival.⁸¹

The severity of mitral regurgitation is of paramount importance when deciding whether to intervene in ischemic mitral regurgitation at the time of CABG. As noted earlier, the evaluation of mitral regurgitation severity should be based on a transthoracic echocardiogram performed in an awake patient. The downgrading of mitral regurgitation by intraoperative TEE has been well documented in the literature. Aklog and colleagues²⁶ showed that 90% of the patients with moderate mitral regurgitation on preoperative echocardiogram had their mitral regurgitation downgraded to mild or less at intraoperative TEE. In nearly one third of these patients, there was no detectable mitral regurgitation on intraoperative TEE (Fig. 92-11). Bach and coworkers⁵ compared preoperative TEE in patients under intravenous conscious sedation with intraoperative TEE in patients under general anesthesia; they noted a significant decrease in the size of the regurgitant jet in patients with “functional” mitral regurgitation, but not in those with flail leaflets. Grewal and colleagues⁸⁶ performed a similar study limited to patients with moderate or severe mitral regurgitation. Half of their patients were downgraded at least one grade, and this effect was again limited to those with functional mitral regurgitation.

The mechanism underlying this phenomenon is almost certainly the unloading effect of general anesthesia, which results in arterial vasodilation and venous vasodilation and decreases afterload and preload, respectively. Although the effects of afterload on mitral regurgitation are generally well recognized, the effects of preload are underappreciated and may in fact be more important. Increased preload results in left atrial, left ventricular, and annular dilation (which can increase leaflet separation)

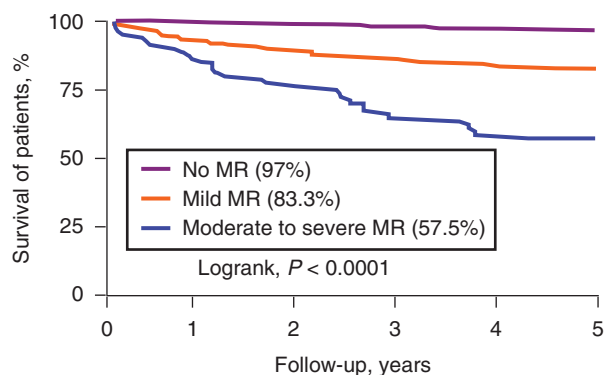


FIGURE 92-10 ■ Influence of severity of mitral regurgitation (MR) on survival after percutaneous coronary revascularization. Presence of moderate or severe MR was associated with substantially poorer 5-year survival. (Reprinted with permission from Pastorius CA, Henry TD, Harris KM: Long-term outcomes of patients with mitral regurgitation undergoing percutaneous coronary intervention. *Am J Cardiol* 100:1218-1223, 2007.)

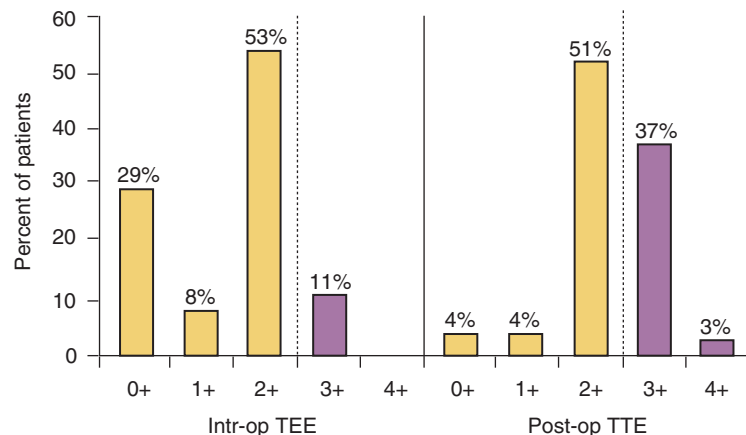


FIGURE 92-11 ■ The effect of coronary artery bypass grafting alone on patients with moderate (3+) ischemic mitral regurgitation (MR). Nearly 90% of patients were downgraded to 2+ MR or less on intraoperative (Intr-op) transesophageal echocardiography (TEE), which indicates that preoperative quantification of MR grade is critical. Although some patients had improvement in MR grade with coronary artery bypass grafting alone, 40% were left with 3 to 4+ MR and only in less than 10% was the MR completely corrected to 0 to 1+. Post-op, Postoperative; TTE, transthoracic echocardiography. (Adapted with permission from Aklog L, Filsoufi F, Flores KQ: Does coronary artery bypass grafting alone correct moderate ischemic mitral regurgitation? *Circulation* 104: 168-175, 2001.)

decrease leaflet coaptation and worsen mitral regurgitation severity. Grewal and coworkers⁸⁶ documented that decreased end-diastolic and end-systolic volumes in patients under general anesthesia support the role of altered loading conditions in this phenomenon.

Although these findings support careful preoperative echocardiography in patients scheduled for CABG with suspected mitral regurgitation, they do not diminish the importance and utility of intraoperative TEE in this setting.⁸⁷ On the contrary, TEE can provide important detailed anatomic information. In addition, intraoperative TEE with provocative testing to increase both preload and afterload may clarify the physiologic importance of the mitral regurgitation and assist with intraoperative decision making if the preoperative assessment is equivocal or unavailable. However, basing the decision not to intervene on (1) a downgraded intraoperative TEE without provocative testing or (2) the residual mitral regurgitation severity on TEE after the bypass graft is performed should be strongly discouraged.

Inadequacy of Coronary Artery Bypass Grafting Alone for Ischemic Mitral Regurgitation

Although earlier data were contradictory, with some studies suggesting that revascularization leads to resolution of ischemic mitral regurgitation^{88,89} and others suggesting that regurgitation usually persists or worsens,^{90,91} most authorities agree that resolution of mitral regurgitation does not predictably occur after coronary artery bypass surgery. Summation of the current literature seems to suggest that although CABG alone can sometimes decrease mitral regurgitation severity (particularly in patients with mild ischemic mitral regurgitation and poor left ventricular function), revascularization has an inconsistent and relatively weak effect on moderate ischemic mitral regurgitation, leaving many patients with moderate or greater mitral regurgitation.

A landmark study in 2001²⁶ was notable for challenging the notion that CABG alone was adequate for ischemic mitral regurgitation. One hundred and thirty-six patients with moderate ischemic mitral regurgitation underwent CABG alone. Among the 68 patients who underwent early postoperative transthoracic echocardiography (see Fig. 92-11), 40% showed no improvement and were left with moderate or severe residual mitral regurgitation. Approximately 50% of patients had some improvement and were left with mild mitral regurgitation. Only a few remaining patients (<10%) had significant improvement, with no more than trace (0 to 1+) mitral regurgitation. The study concluded that CABG alone was not the optimal therapy for many patients with moderate ischemic mitral regurgitation. This study was more recently corroborated by two randomized control trials.^{10,53}

Although CABG alone might not correct ischemic mitral regurgitation, skeptics have argued that residual mitral regurgitation after CABG alone does not itself have an adverse effect on late functional status or survival. The Emory group followed a cohort of 58 patients undergoing CABG alone for moderate mitral regurgita-

tion between 1977 and 1983, and in their most recent update,⁶⁰ 5- and 10-year actuarial survival rates were nearly identical to those of a control group of patients without preoperative mitral regurgitation and who underwent CABG during the same time period. Their patients, however, differ from the patients with typical ischemic mitral regurgitation in most modern series. Specifically, they were relatively young (mean age, 63 years) with normal left ventricular function (mean ejection fraction, 53%) and little or no congestive heart failure (10% in NYHA class III or IV), and nearly a quarter of their patients had nonischemic etiologies such as leaflet prolapse and rheumatic heart disease. However, two large studies from the same era found that mitral regurgitation was an independent risk factor for late death in patients undergoing CABG.^{77,78} The authors recommended the more liberal application of concomitant mitral valve repair for moderate and severe mitral regurgitation.

There is limited information in the literature about the late functional status of patients undergoing CABG alone for moderate ischemic mitral regurgitation. The Emory study reported a trend toward more class III and IV angina (29% vs. 6%) and congestive heart failure (14% vs. 6%) as compared with the case-matched controls. These findings suggest that even if the significant rate of residual mitral regurgitation after CABG alone does not result in decreased long-term survival, it can adversely affect long-term functional status and quality of life. Concomitant mitral valve repair may therefore be justified (if it can be performed with relatively low operative risk) to improve long-term functional status independent of effect on survival.

The inadequacy of CABG alone is further supported by various epidemiologic studies that demonstrate that revascularization by either PCI or CABG is still associated with persistent regurgitation and reduced medium-term survival despite revascularization.^{7,26,77-80}

Effect of Mitral Valve Surgery on Natural History of Ischemic Mitral Regurgitation

There are no randomized trials comparing CABG alone to CABG and mitral valve surgery in the context of severe ischemic mitral regurgitation (the only trials conducted have been for moderate regurgitation). Studies that have attempted direct comparison of these groups are limited, because undocumented patient and surgical factors, or surgeon preferences and bias, often influence the decision to repair or not repair these valves, making it difficult to directly compare groups.⁹² The Cleveland group, using propensity matching to partly balance for selection bias, demonstrated equivalent results with CABG alone compared with CABG and mitral valve repair⁸¹; that study is, however, of limited applicability to current patient cohorts, as many of the surgical procedures undertaken (notably, use of pericardium and flexible bands) have since been superseded and are no longer recommended by most authorities for treatment of ischemic mitral regurgitation. There are numerous reports in the literature on the outcome of mitral valve repair for ischemic mitral regurgitation. These reports are mixed, with some

suggesting it is an effective therapy and others suggesting otherwise. Some reports from the 2000s suggest that mitral valve repair is ineffective for ischemic regurgitation, because many patients were observed to have recurrent regurgitation early after surgery.⁹³⁻⁹⁵ There are, however, flaws in these studies, which we have discussed elsewhere.³ Notably, the surgical techniques were inconsistent, inadequate, or historical; the follow-up was often incomplete; cohorts were heterogeneous; and the methodologic and statistical approaches were sometimes inappropriate (Table 92-1). These limitations make it impossible to draw reliable conclusions from these studies about the efficacy of mitral valve annuloplasty.

Recent papers continue to add to the controversy over whether mitral valve repair is effective for ischemic mitral regurgitation. Although several studies have reported disappointing outcomes with mitral valve repair,⁹⁶ most studies remain limited by critical flaws, thus preventing robust extrapolation.⁹⁷ Common to those studies suggesting ineffectiveness of mitral valve repair is the absence of systematic use of a restrictive annuloplasty using a complete rigid or semirigid ring, as varying proportions of patients in these studies received incomplete flexible rings or pericardium for annuloplasty, which are not recommended for ischemic mitral regurgitation. These flaws can be observed in most studies in the current surgical literature that demonstrate lack of effectiveness of

annuloplasty, compared with CABG, in ischemic mitral regurgitation.⁹⁷

Excellent Midterm Results with Downsized Annuloplasty

The Leiden group has been notable in their work on systematic downsized annuloplasty to treat functional mitral regurgitation.⁶⁶ In a report of 100 consecutive patients who underwent a mitral valve repair for ischemic mitral regurgitation using a semirigid Carpentier Edwards Physio ring annuloplasty (Edwards Lifesciences LLC, Irvine, CA) downsized by two sizes,⁹⁸ echocardiography at mean follow-up of 4.3 years showed that 85% had zero or mild regurgitation, and the 5-year survival rate was 71%. They observed superior outcomes when the preoperative LVEDD was 65 mm or less (Fig. 92-12). This group has also observed sustained reduction in left ventricular end-diastolic diameter at midterm follow-up for patients with LVEDD less than 65 mm at the time of repair.⁹⁹

The Leiden experience^{66,98} has several notable factors that differentiate it from the reports that suggest poor or limited efficacy of annuloplasty for ischemic mitral regurgitation.^{62,65,81,93-96} The immediate postsurgical results suggest that the mitral valve repair was effective because no patients had residual regurgitation leaving the operating room; the patients were all operated in a more recent

TABLE 92-1 Recent Studies Suggesting Limited Efficacy of Restrictive Annuloplasty in Ischemic Mitral Regurgitation

Reference	Main Result	Conclusion	Limitations
Crabtree and colleagues ⁶²	52% survival at 5 years, 28% moderate or severe MR at latest TTE	Questions the benefit of adding annuloplasty to CABG	Use of inadequate technique: 44% of patients received an incomplete (posterior) annuloplasty with a flexible band. Such bands have limited efficacy, as they do not address tethering and dilation in anterior annulus
Gelsomino and colleagues ⁹⁵	Reverse remodeling seen in only 41% of patients	Annuloplasty + CABG is ineffective in a large percentage of patients	Echo follow-up available for only 57% Suboptimal early results: 7% repair failure or residual MR rate Limited revascularization approach: Average of two bypasses per patient suggests incomplete revascularization
Mihaljevic and colleagues ⁸¹	CABG + annuloplasty did not improve long-term functional status or survival compared with CABG alone	Annuloplasty is insufficient to improve long-term clinical outcomes	Historical cohort: Patient inclusion began in 1991, so does not fully reflect recent advances in surgery (e.g., downsized annuloplasty); the current therapy for ischemic regurgitation became routine only in the late 1990s. Unusually high survival rate in CABG-only group: 5-yr survival of 75% not typical in most surgical series Ineffective technique: 15% of propensity-matched patients had annuloplasty with pericardial strips, a technique shown to be ineffective with unacceptably high recurrent MR rate Inadequate technique: 59% of patients received flexible posterior bands, which do not address anterior tethering and dilation.

Adapted from Anyanwu AC, Adams DH: Ischemic mitral regurgitation: recent advances. *Curr Treat Options Cardiovasc Med* 10:529-537, 2008.

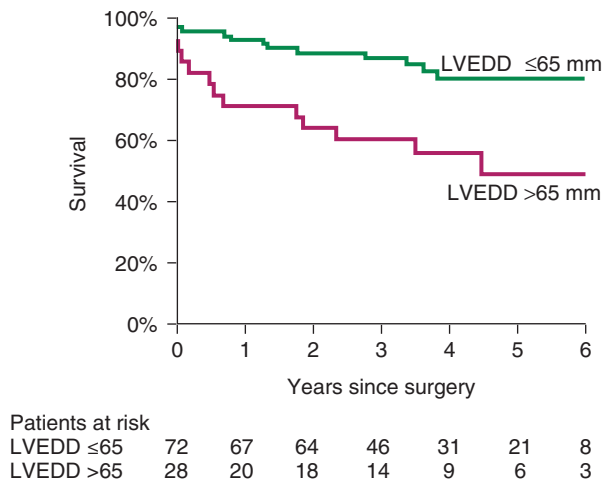


FIGURE 92-12 ■ Actuarial survival rates for two different preoperative left ventricular end-diastolic diameter (LVEDD) cohorts after restrictive annuloplasty, comparing LVEDD greater than 65 mm and LVEDD 65 mm or less (hazard ratio, 3.4; 95% confidence interval, 1.5-7.4; $P = 0.002$). (Adapted with permission from Braun J, van de Veire NR, Klautz RJ, et al: Restrictive mitral annuloplasty cures ischemic mitral regurgitation and heart failure. *Ann Thorac Surg* 85:430-436, 2008.)

era (2000 or after); the annuloplasty was standardized across all patients and always complete, semirigid, and downsized; and echocardiographic follow-up was systematic. Another more contemporary report from Gazoni and colleagues⁶⁹ supports the findings of the Leiden group: in a series of 105 ischemic repairs, a 5-year survival of 84% was observed with a low (6.3%) incidence of recurrent regurgitation on medium-term (>12 months) echocardiography. Geidel and colleagues,⁷⁰ also using predominantly remodeling annuloplasty, were also able to demonstrate excellent medium-term results with restrictive annuloplasty.

Although no good randomized clinical trial has been performed that demonstrates the superiority of complete rigid ring or semirigid annuloplasty over flexible annuloplasty, there is mounting evidence showing significantly improved rates of recurrent regurgitation with minimal incidence of postoperative mitral stenosis in patients receiving complete rings.^{31,32}

Residual Mitral Regurgitation after Ischemic Mitral Valve Repair

Surgical Techniques and Incidence of Residual Mitral Regurgitation

Surgical technique and patient selection are probably the principal determinants of residual mitral regurgitation. With appropriate technique, residual regurgitation (defined as regurgitation other than trivial or mild on leaving the operating room or on predischARGE echocardiography) should be infrequent (<5%) after ischemic mitral repair. Clinical and experimental evidence suggest that any technique other than a complete rigid or semirigid ring is prone to a high incidence of residual regurgitation.⁹³

Suture annuloplasty has a particularly high incidence of residual mitral regurgitation when applied to patients with ischemic mitral regurgitation. Hausmann and coworkers⁶³ reported a 28% incidence of residual mitral regurgitation of at least 2+ with this technique. Von Oppell and colleagues⁴⁷ had a 13% incidence of moderate mitral regurgitation in a series in which most patients underwent suture annuloplasty. Czer and coworkers¹⁰⁰ found that suture annuloplasty failed to decrease mitral regurgitation severity by two grades in 33% of patients. Grossi and coworkers¹⁰¹ noted a significant survival benefit (hazard ratio, 0.29) for ring annuloplasty over suture annuloplasty, with a 5-year survival rate of 74.3% compared with 52.7%, respectively ($P = 0.06$). Although appropriately applied suture annuloplasty can eliminate mitral regurgitation in the short term and it preserves annular contraction, as is well demonstrated in animal studies,^{102,103} these repairs do not seem to be consistently effective and durable in the clinical setting.⁹⁹ Though few groups continue to experience satisfactory results with suture annuloplasty,¹⁰⁴ most surgeons have abandoned the suture method in favor of the more predictable results with ring annuloplasty.

Annuloplasty using a pericardial band has also been shown to be less effective than prosthetic ring annuloplasty, with more than 30% of patients having persisting grade 3+ or 4+ mitral regurgitation after repair.⁹³ The prosthetic ring or band annuloplasty has better results than other techniques, with many groups reporting residual regurgitation rates of less than 10%.

Partial posterior ring annuloplasty has been used in the past because of ease of implantation, especially when there is difficulty exposing the anterior annulus. However, most surgeons prefer a complete ring annuloplasty to address the anterior annulus, which has been shown to dilate in functional mitral regurgitation.¹¹ The initial studies reported by Bolling and colleagues²⁹ described excellent results with a downsized annuloplasty using a flexible ring in ischemic mitral regurgitation. Since those studies, an advantage has been shown using rigid or semirigid ring annuloplasty in this disease process. Tahta and coworkers⁹⁵ showed a 29% (2+ regurgitation or greater) recurrence of mitral regurgitation in 100 patients who underwent CABG and annuloplasty with a flexible Duran ring at 3-year follow-up. This was a considerably higher rate than that seen in series of rigid or semirigid annuloplasty.⁹⁸ Silberman and colleagues³¹ retrospectively compared flexible to semirigid annuloplasty systems. They showed improved hemodynamics, greater reduction in recurrent mitral regurgitation, and a decreased incidence of recurrent regurgitation with the semirigid annuloplasty technique.³¹ Kwon and colleagues³⁰ retrospectively showed an advantage with complete ring annuloplasty when compared with a partial annuloplasty in functional mitral regurgitation (majority of patients were ischemic). Nonflexible rings have been shown to provide better durability in functional disease.³²

Downsizing of prosthetic annuloplasty seems vital in achieving a zero or near zero rate of residual regurgitation. Bolling and colleagues²⁹ were the first to popularize the downsized annuloplasty. They achieved no residual mitral regurgitation in 46 patients undergoing an

annuloplasty alone at the time of CABG, despite using a flexible rather than a rigid annuloplasty. The Leiden group more recently demonstrated zero residual regurgitation rates with the downsized annuloplasty.⁶⁶

Possible Mechanisms of Residual Mitral Regurgitation

A flexible reduction annuloplasty device, such as the Cosgrove-Edwards (Edwards Lifesciences) band or the Duran (Medtronic, Minneapolis, MN) ring, seeks to improve leaflet coaptation by simply decreasing the annular circumference, which indirectly brings the leaflets together. A rigid or semirigid remodeling annuloplasty ring such as the Carpentier-Edwards Classic (Edwards Lifesciences) is designed not only to decrease the annular circumference but, in addition, remodel the systolic annulus back into a kidney shape. This should, in theory, decrease the SL dimension to a greater degree than would a flexible annuloplasty of the same size. This should, in turn, lead to a larger surface of coaptation and less mitral regurgitation. The difference between reduction and remodeling annuloplasty in patients with type IIIB mitral regurgitation is illustrated in Figure 92-13.

Inadequate downsizing or inappropriate sizing may be a potential explanation for residual regurgitation. A true

sized annuloplasty will diminish the mitral regurgitation, but the zone of coaptation might not be sufficient. It has been suggested that the durability of repair is less if the length of the coaptation zone is less than 8 mm. Calafiore and coworkers¹⁰⁵ and Yiu and coworkers¹⁰⁶ have provided evidence that the coaptation depth is important in patients with “functional” mitral regurgitation in the setting of nonischemic cardiomyopathy. Nagasaki and colleagues¹⁰⁷ compared ischemic and nonischemic cardiomyopathy and found that the coaptation depth was the main determinant of severity of regurgitation in the ischemic patients. With appropriate downsizing, the AP dimension is aggressively reduced to bring the restricted posterior leaflet close enough to the anterior leaflet to allow adequate coaptation. Series in which there has been systematic downsizing, especially with a rigid or semirigid ring, report better freedom from recurrent or residual regurgitation compared with series in which there has not been significant downsizing (Fig. 92-14).

Patient Factors Associated with Residual Regurgitation

Patient factors can predispose to residual regurgitation. There are several identified echocardiographic predictors of failure of repair (Box 92-1); these are mainly markers

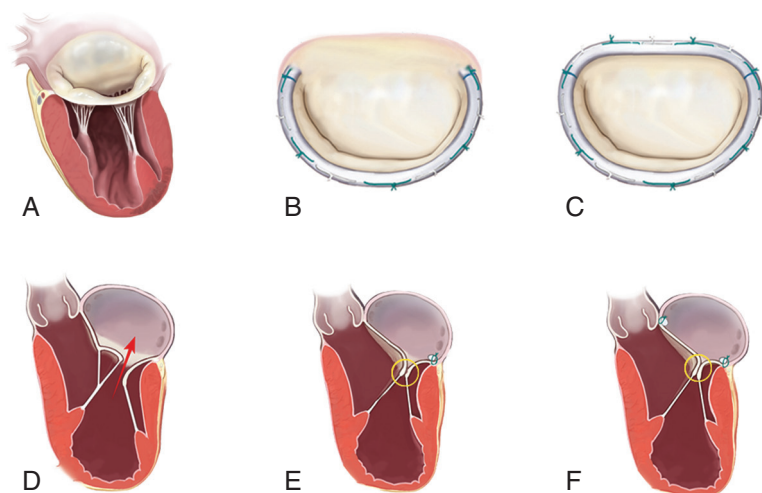


FIGURE 92-13 ■ Unrepaired annulus (A) of a patient with type IIIB mitral regurgitation leading to leaflet tethering. D, Flexible partial-reduction annuloplasty band (B) can reliably reduce the posterior annulus to a specific size, but the degree to which it remodels the annulus and restores coaptation depends on the relative degrees of annular dilation and posterior leaflet restriction. E, Downsized remodeling annuloplasty ring (C) predictably fixes the anteroposterior dimension, which should result in a larger surface of coaptation (F).

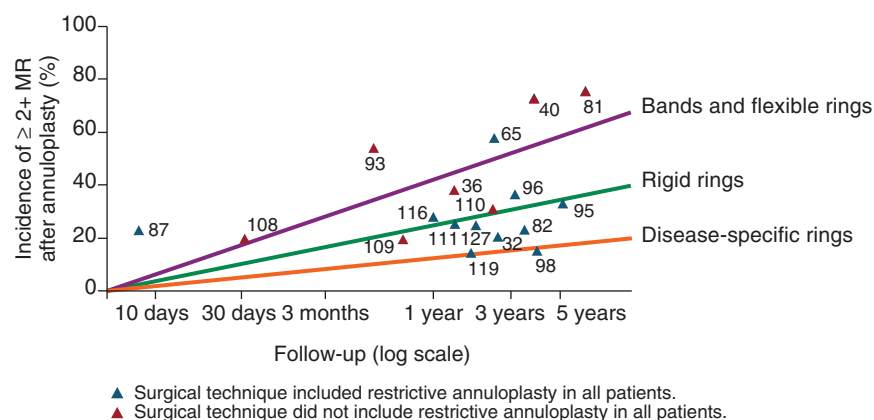


FIGURE 92-14 ■ Incidence of recurrent $\geq 2+$ mitral regurgitation (MR) reported in the literature as a function of time after mitral valve annuloplasty.

BOX 92-1 Predictors of Recurrent Mitral Regurgitation after Mitral Valve Annuloplasty in Patients with Ischemic Mitral Regurgitation

TTE

Indicators of Severe Mitral Valve Tenting

- Systolic tenting area $\geq 2.5 \text{ cm}^2$
- Systolic tenting height $\geq 10 \text{ mm}$
- Posterior mitral leaflet angle ≥ 54 degrees
- Distal anterior mitral leaflet angle ≥ 19 degrees
- Posterior mitral leaflet angle ≥ 45 degrees
- Anterior mitral leaflet tethering angle ≥ 39.5 degrees
- MR jet direction: central or complex

Indicators of Advanced LV Remodeling

- LVESD $> 51 \text{ mm}$
- LVEDD $> 65 \text{ mm}$
- LVESV $\geq 145 \text{ mL}$
- Interpapillary muscle distance $> 20 \text{ mm}$
- Systolic sphericity index ≥ 0.7

Other

- Myocardial performance index ≥ 0.9
- Wall motion score index ≥ 1.5
- Diastolic LV function: restrictive filling

TEE

- Mitral annular diameter in diastole $> 3.7 \text{ cm}$
- Tethering area $> 1.6 \text{ cm}^2$
- MR severity > 3.5

SURGICAL

- Use of flexible ring
- Use of incomplete ring
- Inadequate ring sizing
- Length of leaflet coaptation $< 1.9 \text{ mm/m}^2$ or $< 8 \text{ mm}$
- Residual mitral regurgitation

POSTOPERATIVE

- Absence of early LV remodeling (decrease of LVESV $< 15\%$)
- Residual MR at discharge

LV, Left ventricle; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; LVESV, left ventricle end-systolic volume; MR, mitral regurgitation; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Adapted from Crestanello JA: Surgical approach to mitral regurgitation in chronic heart failure: when is it an option? *Curr Heart Fail Rep* 9:40–50, 2012.

of extreme left ventricular remodeling and/or severe valve tethering.¹⁰⁸ A missed primary lesion can be the cause of residual regurgitation,¹⁰⁹ such as regurgitation through a prominent cleft that is exaggerated after adequate loading of the ventricle is achieved.¹¹⁰ This can be avoided by assuring an adequate zone of coaptation and by closing significant clefts.¹¹¹ Occasionally, residual regurgitation could be due to a coexisting nonischemic etiology, such as degenerative prolapse, calcification, or rheumatic changes.

Incremental Operative Risk of Mitral Valve Surgery (versus Coronary Artery Bypass Grafting Alone) in Ischemic Mitral Regurgitation

A critical piece of information that a surgeon must consider when contemplating concomitant mitral valve surgery for ischemic mitral regurgitation is the additive operative risk of intervening on the mitral valve. A low operative risk would justify a more aggressive approach, given the potential benefit on late outcomes that we have outlined. A high incremental risk would justify a more conservative approach, although it should be kept in mind that the benefit of mitral valve surgery may also be greatest in certain high-risk patient groups (e.g., NYHA classes III and IV heart failure). Leaving the operating room with significant mitral regurgitation can also be most detrimental to the postoperative course of the sicker high-risk patients with poor ventricular function and more comorbidity.

The operative risk for patients undergoing surgery for ischemic mitral regurgitation depends on a number of preoperative factors, most notably age, left ventricular dysfunction, and other cardiac surgical risk factors. Because patient characteristics vary widely among different clinical series, it is difficult to precisely quantify the additional operative risk of mitral valve surgery in a given patient with ischemic mitral regurgitation. Extrapolation from the clinical literature is also challenging, because uniform definitions of ischemic mitral regurgitation have not been used. Some studies include patients with ruptured papillary muscles or with chronic ischemic type II dysfunction, and even degenerative patients with incidental coronary artery disease in cohorts of ischemic mitral regurgitation.

Several historical series have, however, suggested that the presence of ischemic mitral regurgitation does appear to increase the operative risk of CABG alone.* The 3% to 12% mortality rates seen in these studies are higher than those of most contemporary CABG series (generally around 2%).

Although the reported operative mortality for mitral valve replacement at the time of CABG has remained relatively high, the outcomes for mitral valve repair appear to be improving over time, with more recent series reporting operative mortalities of less than 5%.^{67,69,112}

Mitral Valve Repair versus Replacement for Ischemic Mitral Regurgitation

Although mitral valve repair for ischemic mitral regurgitation carries some of the same obvious benefits over replacement that it does for other etiologies (avoiding prosthetic valve-related complications), the higher incidence of repair failure and lower event-free survival with ischemic disease (compared with degenerative and rheumatic cohorts), makes the benefit of repair over replacement less certain when compared with other etiologies.

*References 26, 55, 56, 89, 91, 92.

For this reason, several authors have questioned whether the more effective (in terms of cure of regurgitation) valve replacement should be the preferred option to mitral valve repair (with less certainty of stable long-term freedom from regurgitation), with the hypothesis that the benefits of a more durable fix for the regurgitation would outweigh the incremental risks of a valve replacement. Although valve replacement would yield more durable elimination of regurgitation, there is a higher risk of surgical mortality, late mortality, valve-related morbidity and mortality, and a lesser degree of reverse remodeling with valve replacement.¹¹³⁻¹¹⁵ Historically, the poor results of mitral valve replacement in the setting of advanced ischemic or nonischemic cardiomyopathy led to most surgeons abandoning valve replacement in this setting during the 1980s and 1990s. However, some surgeons later adopted mitral valve replacement, with complete chordal and leaflet preservation, as primary therapy for ischemic mitral regurgitation and reported early results similar to those seen with mitral valve repair.¹¹⁶

Several observational studies have addressed this dilemma. Gillinov and colleagues¹¹⁴ retrospectively analyzed outcomes after repair (remodeling annuloplasty was used in one third of patients, with the remainder receiving a partial flexible band or pericardium for annuloplasty) or replacement in patients with ischemic mitral regurgitation and found that although there was a survival benefit seen with valve repair (5-year survival repair 58% versus 36% for replacement), the highest-risk patients had similar survival rates. The benefit of repair over replacement was diminished in patients with lateral wall motion abnormalities and complex regurgitant jets. This suggested that in some high-risk patients with ischemic mitral regurgitation, a chordal-sparing valve replacement may be an acceptable alternative to repair. Grossi and coworkers¹¹⁷ found better early survival (odds ratio, 0.43), complication-free late survival (odds ratio, 0.5), and a trend toward better overall survival with valve repair.

Most recently, the Cardiothoracic Surgical Trials Network¹¹⁸ conducted a multicenter randomized study enrolling patients with severe ischemic mitral regurgitation to undergo mitral valve annuloplasty or valve replacement (Fig. 92-15). The randomized trial identified no difference in survival, left ventricular remodeling, or quality of life measures at 12 months. However, the group did see a higher occurrence of recurrent mitral regurgitation at 12 months (32.6% with repair, 2.3% with replacement). The authors, however, do not explicitly recommend either valve replacement or repair as the preferred therapy for ischemic regurgitation, and they note that the higher incidence of regurgitation with repair needs to be balanced against (long-term) adverse effects of a prosthetic valve (these were not analyzed in this study). The high rate of recurrence in the repair group is concerning, however, and further analysis will be required to understand the reasons behind such high failure rate (relative to some contemporary series which show much lower early recurrence rate) and to identify surgical and patient predictors of failure.

In another recent analysis, Lorusso and colleagues¹¹⁹ reported results of the Italian, multicenter, retrospective study of ischemic mitral regurgitation patients with a

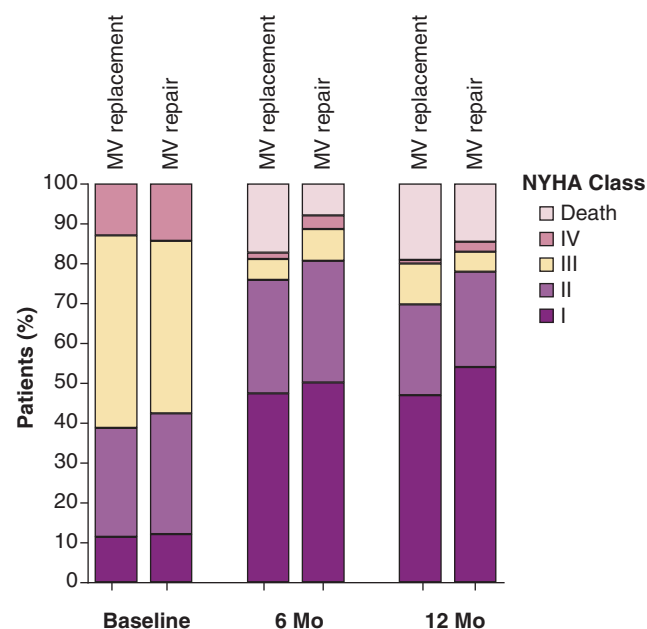


FIGURE 92-15 ■ Rates of New York Heart Association (NYHA) class and death at baseline, 6 months, and 12 months. MV, Mitral valve. (Adapted with permission from Acker MA, Parides MK, Perrault LP: Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med* 370:23–32, 2014.)

reduced ejection fraction. This high risk population was shown to have no benefit with mitral valve repair and, once again, a higher rate of recurrent regurgitation with repair.¹¹⁹

The majority of mitral valve replacements have traditionally been biologic because of the perceived short life expectancy with these patients.¹²⁰ As medical therapy has improved, biologic valve degeneration has been seen with patients who initially underwent an operation for ischemic mitral regurgitation. These high-risk patients may then require a reoperation or reintervention that would entail a higher operative risk than the initial operation.

The decision regarding mitral valve repair or replacement is best made in consideration of individual patient characteristics. Patients with ischemic regurgitation who have echocardiographic findings that increase the risk of recurrent mitral regurgitation or repair failure should be considered for mitral valve replacement. Patients with moderate regurgitation and those with severe regurgitation who have minimal predictors of failure (see Box 92-1) are likely to have durable results with a repair. Patients who have unsatisfactory results with repair on intraoperative TEE should be considered for a second bypass run and valve replacement, because it is well documented that patients with residual regurgitation have poor long-term outcomes.

Overall Recommendations for Ischemic Mitral Regurgitation during Coronary Artery Bypass Grafting

Although most surgeons agree that severe mitral regurgitation should be corrected at the time of CABG, there is no consensus on the management of mild to moderate ischemic mitral regurgitation at the time of CABG. A preponderance of evidence seems to support a

more liberal application of concomitant mitral valve surgery, which can be summarized in the following recommendations.

1. All patients referred for CABG with suspected ischemic mitral regurgitation should undergo careful preoperative transthoracic echocardiography, preferably with quantitative assessment of mitral regurgitation severity while they are not actively ischemic. Those without complete preoperative assessment should undergo careful intraoperative TEE assessment of their mitral valves to determine whether there is an anatomic substrate for ischemic mitral regurgitation. If intraoperative echocardiography shows less mitral regurgitation than expected on the basis of the clinical picture, the patient should receive provocative testing of the degree of mitral regurgitation.
2. Patients with severe ischemic mitral regurgitation should undergo concomitant mitral valve repair. Mitral valve replacement is a reasonable option depending on surgeon preference and expected likelihood of repair durability.
3. Patients with moderate ischemic mitral regurgitation should undergo concomitant mitral valve repair unless preoperative or intraoperative factors suggest that the additional operative morbidity and mortality would be prohibitive (e.g., extensive mitral annular calcification or a strong indication for performing the CABG off pump, such as a heavily diseased ascending aorta).
4. Patients with mild ischemic mitral regurgitation may undergo concomitant mitral valve repair (with caveat similar to that for moderate regurgitation) if history or evaluation is suggestive of periods of greater severity of mitral regurgitation than has been documented. Pointers that suggest the mitral regurgitation may be more severe than appreciated include symptoms of congestive heart failure, enlarged left atrium, enlarged or dysfunctional left ventricle, pulmonary hypertension, and atrial fibrillation. In addition, anatomic findings present on intraoperative TEE should also be considered (e.g., minimal surface of coaptation, severe leaflet tenting coaptation depth, significant annular dilation).

SURGICAL PRINCIPLES

Basic Principles

The basic principles of mitral valve repair for ischemic mitral regurgitation are not fundamentally different from those for degenerative disease. A successful outcome depends on the following:

- Careful review of the preoperative echocardiogram, with particular attention paid to the mechanism of mitral regurgitation, the direction of the mitral regurgitation jets, and specific anatomic abnormalities (e.g., calcification, thickening)
- Good visualization of the entire valve
- Careful segmental valve analysis to confirm the mechanism of mitral regurgitation

- Meticulous suture placement and ring sizing
- Consideration of adjunctive technique, as appropriate

Annuloplasty: Underlying Principles

The significant effects of even mild degrees of ischemic mitral regurgitation on survival should challenge surgeons to make every effort to minimize residual mitral regurgitation after mitral annuloplasty. Careful consideration should be given to choice of annuloplasty method.

The literature does not, in our opinion, support a role for suture or pericardial annuloplasty in this disease. As mentioned previously, the rates of residual mitral regurgitation for these techniques are relatively high. Although the three-dimensional dynamic nature of mitral annulus and its contribution to ventricular function have been well documented, it is unclear what role this plays in pathologic conditions such as ischemic mitral regurgitation. Some laboratory studies suggest that planar fixation of the annulus with a nonflexible ring impairs left ventricular function, whereas others dispute this.²⁸ We suspect, however, that there is a critical role for annular remodeling, specifically in the SL (or AP) dimension in patients with Carpentier-type IIIB dysfunction. As described earlier, a large body of data has been accumulated from several laboratories that describe the mechanisms that contribute to ischemic mitral regurgitation. Several of these studies emphasize the importance of the increased SL dimension in pathophysiology of ischemic mitral regurgitation. It seems, therefore, that the need to remodel the annulus (with a remodeling rigid or semi-rigid ring) far outweighs any benefit of preserving annular motion.

As illustrated in [Figure 92-16](#), a reduction annuloplasty will, to some degree, decrease the SL dimension, improve leaflet coaptation, and correct mitral regurgitation. The extent to which it accomplishes this, however, probably depends on whether the annular dilation or posterior leaflet restriction is the dominant mechanism of mitral regurgitation. If there is predominant annular dilation (type I dysfunction), a flexible band is not an unreasonable option. However, for most patients, where valve tethering is dominant, a complete downsized rigid or semirigid ring should be used for ischemic mitral valve repair.

Asymmetric rings designed specifically for the treatment of ischemic mitral regurgitation can be utilized. For example, the Carpentier-McCarthy-Adams IMR ETlogix ring (Edwards Lifesciences, Irvine CA; see [Fig. 92-16](#)) has a decreased AP diameter (i.e., is pre-downsized); and is asymmetrical, with a narrower dimension at P2-P3, and it has a slight dip at P2-P3 to accommodate the greater posterior leaflet restriction in this region.¹²¹

Valve Exposure

The most common approach to patients with ischemic mitral regurgitation is a full sternotomy with cannulation of the ascending aorta and both venae cava. After completion of bypass grafting, as appropriate, the mitral valve

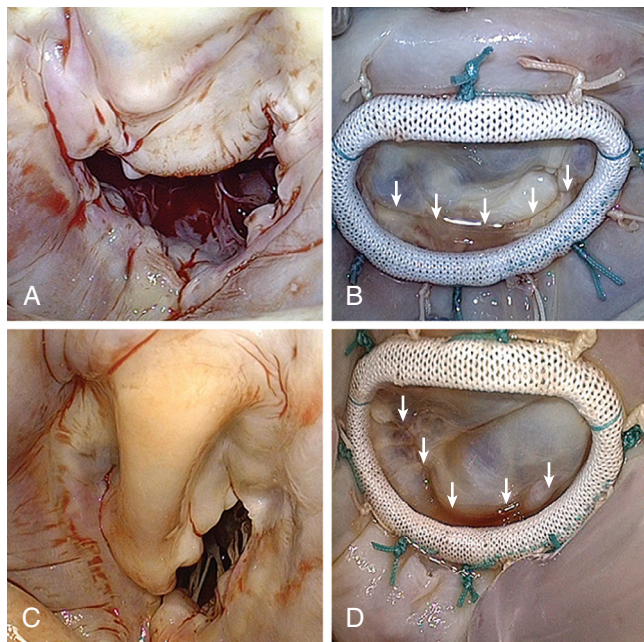


FIGURE 92-16 ■ Symmetrical (A and B) and asymmetrical (C and D) patterns of ischemic mitral regurgitation. Note the difference of coaptation lines (white arrows) after remodeling annuloplasty.

can be exposed either via the interatrial groove or trans-septally. Patients with ischemic mitral regurgitation may have a small left atrial cavity, depending on the acuity of presentation. Despite this, however, excellent exposure of the valve can be obtained with a standard mitral valve retractor system if certain principles are followed. The interatrial approach is most commonly used, and particular attention should be paid to the following: (1) complete dissection of the interatrial groove before atriotomy and (2) posterior extension of the inferior aspect of the atriotomy, with partial detachment of the right lower pulmonary vein. The trans-septal approach may be useful in the setting of a small left atrium or when an aortic prosthesis is present. A thoracotomy approach can be considered in reoperative setting and in primary cases that do not require concurrent CABG (if coronary arteries have been previously stented).

Valve Analysis

Before segmental valve analysis, it may be helpful to place an exposure suture in the posterior annulus at the junction between P1 and P2 to bring the valve apparatus anterior and lateral. Using two hooks, it is then possible to confirm the pathognomonic findings of secondary mitral regurgitation (i.e., posterior or bileaflet tethering, caused by papillary muscle displacement, with otherwise normal leaflets and no evidence of prolapse or fixed restriction; Fig. 92-17A). Associated annular dilation is also commonly present.

Suture Placement

For implanting an annuloplasty ring, 2-0 braided polyester sutures are most commonly used. Because of the

potential for increased tension in the setting of type IIIB dysfunction with associated annular dilation, it is preferable to place the sutures close together along the annulus. We prefer to use crossover sutures (see Fig. 92-17B) to help accommodate and distribute the excessive tension that a restrictive annuloplasty can impose on the annulus. Using the crossover technique, ring dehiscence is rare. The full curve of the needle should be used to encourage deep, wide placement of individual sutures along the annulus. The anterior commissure is usually the most difficult area to expose, and it is usually approached last, after the placement of sutures along the septal, medial, and lateral portions of the annulus to place tension on prior sutures to expose this area of the annulus.

Sizing and Implantation

After sutures are placed around the annulus, standard ring sizers are used to select the appropriate ring. Placing gentle traction on marginal cords in the A2 portion of the anterior leaflet with a hook allows the height and surface area of the anterior leaflet to be measured. An additional measurement to consider is the intercommissural distance.

Because leaflet restriction in ischemic mitral regurgitation results in less leaflet tissue available for coaptation, it is necessary to downsize the complete remodeling ring by one or two sizes to ensure an adequate surface of coaptation after annuloplasty. Systolic anterior motion is almost unknown, despite aggressive downsizing, because the restricted posterior leaflet cannot displace the anterior leaflet into the outflow tract. After a ring is selected (typically a size between 24 and 28 mm), the interrupted sutures are passed through it, with respect paid to the associated geometry of the annulus, crossing over on the prosthetic ring where sutures have been crossed on the annulus. The individual sutures are then tied, thus securing the ring to the annulus.

After the downsized remodeling annuloplasty is completed, a saline test is used to confirm the line of coaptation along the margin of the leaflets. The ink test confirms an adequate surface of coaptation.¹²² The typical appearance of a completed downsized remodeling annuloplasty is shown in Figure 92-16. Nearly the entire orifice is occupied by the anterior leaflet, thereby allowing the entire restricted posterior leaflet to contribute to coaptation.

Adjunctive Procedures

Although the routine use of a remodeling annuloplasty and more aggressive downsizing is likely to minimize the incidence of residual mitral regurgitation after CABG and annuloplasty to well less than 10%, there may be a small group of patients for whom annuloplasty alone is insufficient to correct the mitral regurgitation. A number of adjunctive techniques, applied with the restrictive annuloplasty, can help to eliminate or reduce residual regurgitation in such patients. Some physicians advocate routine use of adjunctive techniques in an expectation that they will yield a more durable repair; however, systematic application of adjunctive techniques has yet to be

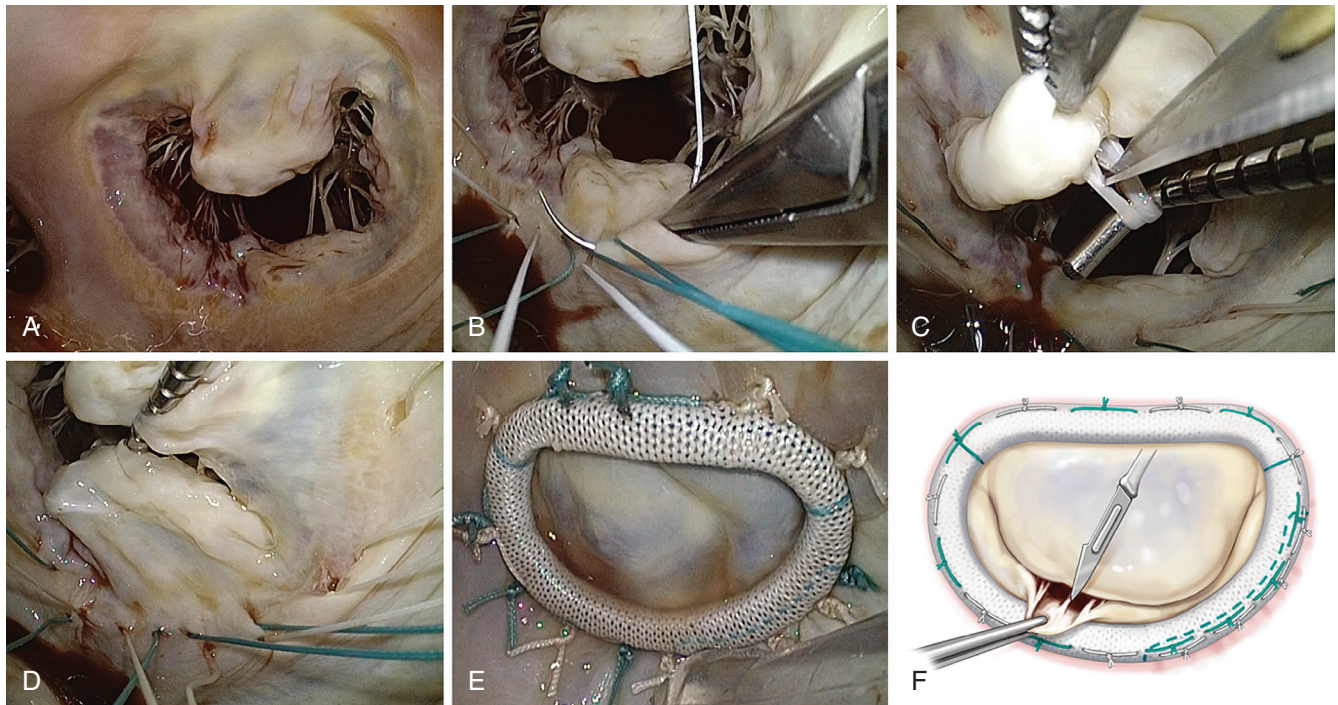


FIGURE 92-17 ■ Surgical approach to ischemic mitral regurgitation in a patient with severe annular dilation symmetric leaflet tethering. **A**, After annular sizing primarily based on the surface area and height of the anterior leaflet, annular sutures are placed. Sutures at the position of the anterior commissure and trigon are placed last, taking advantage of previously placed sutures to expose the area. **B**, Interlocking sutures can be placed along P3 to reinforce the annuloplasty. **C**, Adjunctive techniques in addition to downsized rigid ring annuloplasty include cutting secondary chords to the anterior leaflet. **D**, Closure of leaflet clefts or indentations should be part of the surgical routine when attempting repair to avoid residual leaks because of the lack of tissue. **E**, A full remodeling Carpentier-McCarthy-Adams INR Etlogix ring is placed (disease-specific ring). **F**, Cutting secondary chords of the posterior leaflet can be an option after full repair in patients with generous posterior leaflet tissue.

shown to improve any of the key long-term outcomes (i.e., survival, heart failure, freedom from recurrent regurgitation).

Papillary Muscle Repositioning

Displacement of the papillary muscles is a key component in the pathophysiology of ischemic mitral regurgitation and, in theory, if the distance of displacement is reduced, then mitral regurgitation should be reduced or eliminated because of less leaflet tethering. Reduction in papillary muscle displacement can be achieved by various methods. Kron and coworkers¹²³ initially treated ischemic mitral regurgitation with papillary muscle repositioning using a pledgeted suture attached from the posterior papillary head to the annulus (Fig. 92-18). Rama and colleagues¹²⁴ described suturing the posterior to anterior muscle with autologous pericardial pledgets, whereas Hvass and associates¹²⁵ and Ito and coworkers¹²⁶ used a polytetrafluoroethylene tube to construct a sling around the base of the papillary muscles (see Fig. 92-18). Several variations of these procedures have been described, including some that allow physiologic adjustment of tethering distance on the beating heart.¹²⁷ Although several groups report promising midterm results, it has not been demonstrated that any papillary repositioning techniques result in clinical benefit compared with annuloplasty alone.

Secondary Chordae Cutting

Levine and Schwammenthal demonstrated in animal models that division of secondary mitral valve chordae reduces the degree of tethering in ischemic mitral regurgitation.¹²⁸ Borger and colleagues¹²⁹ reported on a series of 43 patients in whom a downsized annuloplasty was supplemented with dividing secondary chords to the restricted segments of the anterior leaflet, posterior leaflet, and commissures (see Fig. 92-17C and F). They compared these patients to 49 historical and concurrent controls who underwent annuloplasty alone. The authors observed less leaflet tenting and a lower incidence of early recurrent regurgitation in the chordal-cutting group. Application of the chordal-cutting technique was, however, limited to a few surgeons; therefore, differences in surgical skill or expertise may have contributed to the superior outcomes in the chordal-cutting subgroup. The annuloplasty-only group had a higher than expected incidence of early recurrent regurgitation—37% versus 15% in the chordal-cutting group—suggesting technical factors related to inadequate technique could have contributed to worse results in the controls. Chordal cutting can be performed through an aortotomy¹³⁰ and can achieve better reduction in anterior leaflet tenting. Some questions have been raised as to potential deleterious effects of chordal cutting on left ventricular function, but these have yet to be determined.

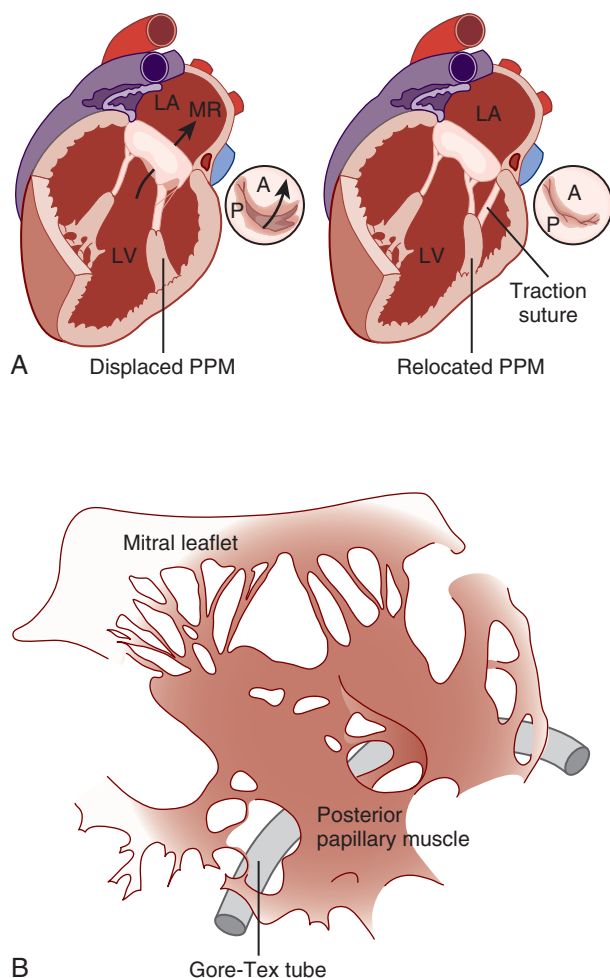


FIGURE 92-18 ■ Approaches to papillary muscle repositioning. **A**, Apical displacement of the posterior papillary muscle (PPM) causing tethering of both leaflets at the medial commissure, producing mitral regurgitation (MR; *left*). Placement of a traction suture relocates the tip of the PPM closer to the annulus, permitting better leaflet coaptation (*right*). **B**, A sling placed around the base of both papillary muscles and tightened reduces displacement of both muscles and thereby also reduces leaflet tethering. A, Anterior mitral leaflet; LA, left atrium; LV, left ventricle; P, posterior mitral leaflet. (Modified with permission from Kron IL, Green GR, Cope JT: Surgical relocation of the posterior papillary muscle in chronic ischemic mitral regurgitation. *Ann Thorac Surg* 74:600–601, 2002; and from Hvass U, Tapia M, Baron F, et al: Papillary muscle sling: a new functional approach to mitral repair in patients with ischemic left ventricular dysfunction and functional mitral regurgitation. *Ann Thorac Surg* 75:809–811, 2003.)

Other Approaches

Poor coaptation of the scallops of the posterior leaflet can occur with leaflet restriction; deep indentations or clefts (P1/P2 or P2/P3; see Fig. 92-17D) should be closed, particularly if a corresponding jet is noted on saline testing. Posterior leaflet patch extension (Fig. 92-19), especially over the P3 scallop, has been used in patients with severe posterior leaflet restriction.¹³¹ Although the edge-to-edge technique is used as an adjunct by some groups,^{36,132} laboratory and clinical data do not provide strong support for its use in surgical repair. Experimental animal work shows that the edge-to-edge repair does not

alter the annular, subvalvular, or leaflet geometric alterations seen in the disease. In vitro laboratory studies suggest that although the edge-to-edge repair can partially reduce regurgitation caused by annular dilation, it is not effective in correcting type IIIB dysfunction associated with papillary muscle displacement.¹³³ Edge-to-edge repair as an adjunct to annuloplasty can exaggerate the risk of mitral stenosis when performed in the context of a downsized annuloplasty. Finally, some surgeons have attempted ventricular solutions to ischemic mitral regurgitation, including plication of left ventricular infarct scar or external device application.¹³⁴

Is Restrictive Annuloplasty Harmful?

Restrictive annuloplasty, the mainstay of current therapy for ischemic mitral regurgitation, invariably results in a valve orifice that is smaller than would be expected for that particular valve, and it also fixes the annulus in a nonphysiologic shape and position. The size 24- to 28-mm rings that are typically used in this disease would be considered small for other pathologies. In theory, therefore, there is a risk of over-narrowing the orifice, resulting in functional mitral stenosis. One clinical study supports this theory. Magne and coworkers¹³⁵ compared 24 patients who underwent successful restrictive annuloplasty with 20 controls who had ischemic heart disease but no mitral regurgitation. They used dobutamine stress echocardiography to evaluate transvalvular gradients and functional capacity.¹³⁵ Compared with controls, patients who had restrictive annuloplasty had higher gradients at rest (13 vs. 4 mm Hg) and stress (19 vs. 6 mm Hg). They noted that the systolic pulmonary artery pressures rose to 58 mm Hg with stress in patients with restrictive annuloplasty (compared with 38 mm Hg in controls). The indexed orifice valve area at peak stress was 1.0 cm²/m² for the restrictive annuloplasty group (compared with 2.4 cm²/m² in control).¹³⁵ These data suggest that restrictive annuloplasty could induce some degree of functional mitral stenosis. The authors, though, did not correlate their findings with symptoms or survival, so it is not clear whether the observed hemodynamics have a bearing on clinical outcome. This study, however, has several limitations that limit the reliability of its findings,¹³⁶ and indeed other studies that have included systematic echocardiography did not observe functional stenosis.⁹⁸ Animal studies highlight other potentially deleterious effects of restrictive annuloplasty, such as inhibition of basal wall thickening¹³⁷ and abolishing of normal annular and leaflet dynamic motion,¹⁰³ but the effects of these changes have not been studied in a clinical setting.

Percutaneous Approaches

Because of the relatively high operative risk and uncertain benefit of mitral valve repair in patients with advanced cardiomyopathy and severe ischemic mitral regurgitation, there has been a surging interest in development of percutaneous approaches to treating ischemic mitral valve regurgitation. Attempts at percutaneous therapy for ischemic mitral regurgitation have largely been directed at either annuloplasty or edge-to-edge approaches.

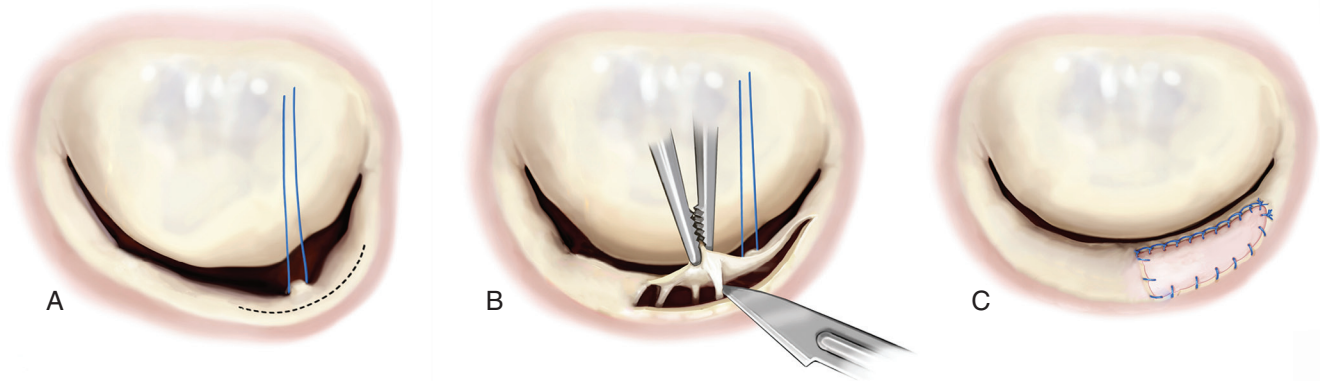


FIGURE 92-19 ■ Posterior leaflet extension with a glutaraldehyde-fixed pericardial patch in patients with ischemic mitral regurgitation. The patch is sutured to the edge of the posterior leaflet defect and the posterior mitral annulus with a running 5-0 polytetrafluoroethylene suture.

Annuloplasty has been fraught with various technical problems, and it is not adequately developed for reproducible and effective application. In a multicenter study of 43 patients with secondary mitral regurgitation, while it was technically feasible to deploy an annuloplasty device in 30 patients, no significant changes were noted in severity of mitral regurgitation, ventricular volumes, or quality of life.¹³⁸ The most used percutaneous device in functional ischemic regurgitation is the MitraClip (Abbott Vascular, Santa Clara, CA), which is a cloth-covered cobalt-chromium device that permanently clips the anterior and posterior leaflets, thereby performing a percutaneous edge-to-edge repair. Studies have demonstrated that the MitraClip can reduce severity of secondary mitral regurgitation in patients with end-stage heart failure with most patients reported to have improved symptoms, reduction in left ventricular size and moderate or less regurgitation at short-term follow-up.^{139,140} The MitraClip, however, does not eliminate regurgitation in many patients (this is expected as has been demonstrated in surgical studies of edge-to-edge), and up to half the patients remain with residual mild or moderate regurgitation. It is not known whether residual regurgitation will have similar long-term negative prognostic effect in patients undergoing percutaneous therapy, as is the case with residual regurgitation after surgical repair. However, considering the severe symptomatic nature of these patients, the rationale for accepting the less perfect edge-to-edge results is that any reduction in mitral valve regurgitation may be worthwhile and potentially beneficial (the same would not hold for surgical repair because the high risk would not justify an incomplete repair). The MitraClip should, however, be reserved for patients who cannot have surgical repair, as the results of ischemic mitral regurgitation repair are superior with surgery than with the MitraClip in terms of long-term freedom from regurgitation and the early survival is similar with both approaches.¹³⁹ Of note, it has not been objectively demonstrated that the reduction in mitral regurgitation grade seen with the MitraClip affects either survival or quality of life compared with optimal guideline-directed medical therapy in patients with advanced heart failure; this is currently the subject of a multicenter randomized trial, Clinical Outcomes

Assessment of the MitraClip Percutaneous Therapy for Extremely High-Surgical-Risk Patients (COAPT), which should report in 2016 to 2018. It is possible that some of the presumed benefit of clip therapy arises from factors such as closer medical supervision and management, patient selection, and placebo effect. Of note, a recent systematic review of 16 studies reporting data on 2980 patients showed that despite a low procedural mortality (4.5% at 30 days), high-risk patients who had successful MitraClip repair still had high early mortality (16.4% at 310 days).¹⁴¹ A single center report of 109 patients with functional regurgitation reported a 3-year survival of 74.5%.¹⁴² It therefore is not clear whether the percutaneous edge-to-edge approach alters the natural history of these patients, as midterm results do not seem to be substantially different from historical controls. Until additional data emerge, therefore, the MitraClip is not considered for primary treatment of severe ischemic mitral regurgitation, except for symptomatic relief in select patients with severe advanced heart failure symptoms who have failed medical therapy and who are not candidates for mitral valve surgery because of excessive risk or presumed futility.

TYPE II ISCHEMIC MITRAL REGURGITATION

Patients with type II (mitral valve prolapse) ischemic mitral valve regurgitation are infrequently encountered in modern clinical practice. Type II ischemic regurgitation can be separated further into acute ischemic mitral valve regurgitation because of papillary muscle rupture or chronic ischemic mitral valve regurgitation secondary to papillary muscle elongation or rupture.

Acute Papillary Muscle Rupture

Historically, acute papillary muscle rupture was observed in up to 5% of patients with transmural myocardial infarction. However, the incidence of acute papillary muscle rupture, and other mechanical complications of acute myocardial infarction, has reduced remarkably in the era of early reperfusion postmyocardial infarction.¹⁴³

The posterior-medial papillary muscle is more susceptible to ischemia because of its dependence on a single vascular supply via a distal branch of either the right coronary or circumflex artery in contrast to the dual blood supply to the anterior muscle from the left anterior descending and diagonal systems. In the setting of acute coronary occlusion, a transmural papillary muscle infarction could potentially lead to muscle necrosis with subsequent rupture of the trunk or one or more of the papillary heads. Usually, the timing of rupture is about 1 week after the initial infarct. Because of the evolution of medical and interventional reperfusion strategies, acute papillary muscle rupture is rare. It must still be considered in the setting of a new systolic murmur and hemodynamic collapse, typically cardiogenic shock, occurring in the first several days after myocardial infarction. Echocardiography is the mainstay for distinguishing the condition from acute ventricular septal defect, free-wall ventricular rupture, or global myocardial dysfunction, which can all produce a similar picture in the setting of transmural myocardial infarction. Lack of a step up in venous oxygen saturation also distinguishes this condition from an acute ventricular septal defect. Once the diagnosis is made, hemodynamic stabilization is usually facilitated by placement of an intra-aortic balloon pump. Surgery should not be delayed, except to optimize hemodynamics and invasive monitoring, because the mainstay of therapy is to correct the embarrassment of massive acute mitral valve regurgitation.

Mitral valve repair with reimplantation of the papillary muscle either into an adjacent nonischemic head or the ventricle can be done, but it is rarely undertaken. One must ensure that the infarcted head itself can hold sutures, usually placed at the insertion of the chordae, and that the reimplantation occurs into an area of viable tissue. Replacement of the chordal apparatus with polytetrafluoroethylene is also feasible, albeit with little known about long-term results in this setting. By far the most common treatment for acute papillary muscle rupture due to myocardial infarction is an expeditious mitral valve replacement. Coronary revascularization is undertaken at the same setting. Surgery carries a high hospital mortality of around 20% in most series.¹⁴⁴⁻¹⁴⁶ Because the burden of coronary disease is low, patients with this condition who survive the initial insult actually have better long-term survival compared with patients with type IIIB ischemic mitral valve regurgitation with long-standing ventricular remodeling and who undergo mitral valve surgery.

The Mayo group¹⁴⁵ analyzed long-term outcomes of 54 patients who had surgery (valve replacement, 41; valve repair, 13) for papillary muscle rupture between 1980 and 2000. As expected, 90% involved the posterior papillary muscle. The overall operative mortality was 18.5%, with most deaths occurring because of low cardiac output or ventricular rupture. Although mitral valve repair was associated with a lower mortality (7.7% vs. 22% for replacement; $P = 0.21$), most repairs were done in the recent era, in which improved outcomes were observed (operative mortality post-1990 was 10%). Patients who had concurrent CABG also had a lower operative mortality. Once patients survived hospitalization, midterm survival was reasonable, with 52% alive and free from heart

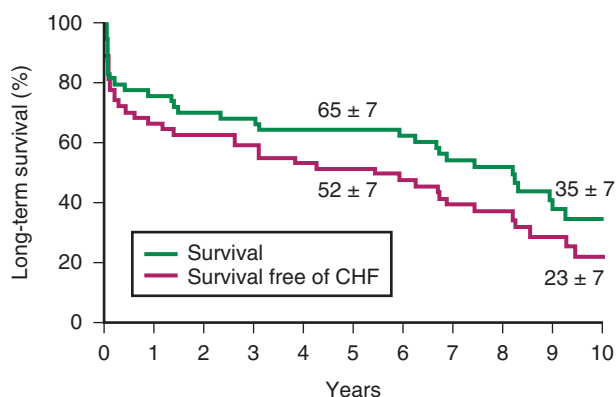


FIGURE 92-20 ■ Overall (including operative mortality) long-term survival (green line) and long-term survival free of congestive heart failure (CHF; red line) after surgery for postinfarct papillary muscle rupture. Numbers indicate the 5- and 10-year survival ($\pm$ standard error). (Reproduced with permission from Russo A, Suri RM, Grigioni F, et al: Clinical outcome after surgical correction of mitral regurgitation due to papillary muscle rupture. *Circulation* 118:1528–1534, 2008.)

failure at 5 years (Fig. 92-20). Six patients developed moderate or greater mitral regurgitation in the follow-up period—four after valve repair, and two after valve replacement.

Chronic Type II Ischemic Mitral Regurgitation

Perhaps even rarer than acute papillary muscle rupture in ischemic mitral valve regurgitation is the occurrence of leaflet prolapse because of elongation, thinning, and fibrosis or rupture of a chronically infarcted papillary muscle. It is usually misdiagnosed preoperatively as degenerative valve disease with chordal elongation with concomitant coronary artery disease. Valve analysis in the operating room generally reveals a fibrotic and thinned-out papillary muscle with normal chords and prolapse of the affected segment owing to elongation of the muscle. The nonprolapsing segments often show a type IIIB restriction. In terms of treatment, chronic type II ischemic regurgitation can usually be treated with valve repair. This lesion condition can be treated like chordal rupture or elongation, as seen in degenerative disease, and it is amenable to a variety of repair techniques. PTFE chordal replacement, chordal transfer, and limited resection and papillary transposition are among repair techniques that can be used to treat this condition. A downsized annuloplasty can also be performed in view of the ischemic etiology and associated type IIIB dysfunction.

Jouan and colleagues¹⁴⁷ reported a series of 44 patients who had surgery for ischemic mitral valve prolapse, of which 66% had chronic mitral regurgitation (more than 60 days after myocardial infarction), whereas the others were operated within 60 days of myocardial infarction. This series included four emergent surgeries. Interestingly, isolated chordal rupture owing to chordal infarction was the postulated mechanism of regurgitation in six patients. The remainders were due to papillary muscle elongation (36%) or rupture (50%). Most of the papillary

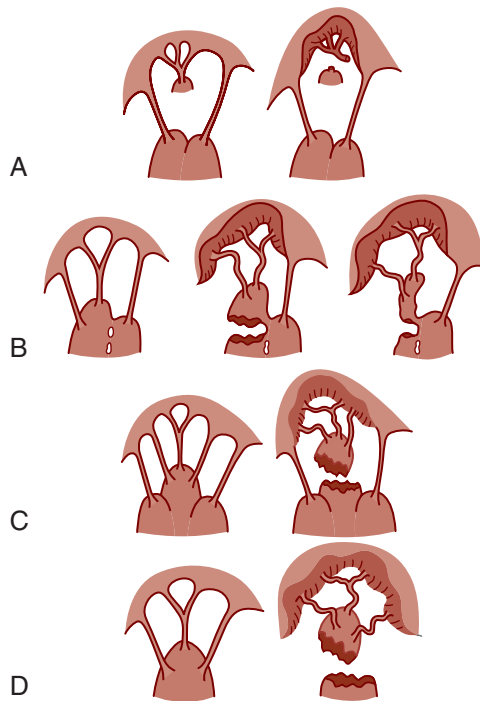


FIGURE 92-21 ■ Classification of papillary muscle rupture according to Jouan and colleagues.¹⁴⁷ **A–C**, Partial rupture, typically present in subacute or chronic fashion. **D**, Classic papillary muscle rupture. Mechanisms of ischemic mitral valve prolapse are shown. **A**, Necrosis of a separate commissural head (inserted close to the annulus) with rupture of the anchorage of the commissural chord. **B**, Necrosis of a single head papillary muscle subdivided in multiple heads with partial rupture. **C**, Necrosis of a fenestrated papillary muscle with detachment of its main insertion: “incomplete” rupture. With time, incomplete rupture mimics papillary muscle elongation. **D**, Single papillary muscle with complete and total rupture.

muscle ruptures were partial or incomplete, thus explaining the subacute or chronic presentation (Fig. 92-21), in contrast to the more dramatic presentation of total rupture (see Fig. 92-21). In addition, all patients had a component of type I or IIIB dysfunction. Mitral valve repair was performed in all but 2 patients. The 5-year survival was 68%, which is comparable to that in type IIIB dysfunction. Repair in the context of ischemic prolapse is expectedly less durable than for prolapse because of degenerative disease, as evident in the 10% actuarial reoperation rate and 30% recurrent moderate or greater mitral regurgitation rate at 5 years, because of greater propensity to recurrence of regurgitation from ongoing ventricular remodeling and from failure of papillary muscle suture techniques when used.

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POSTINFARCTION VENTRICULAR SEPTAL DEFECT AND VENTRICULAR RUPTURE

Sharven Taghavi • Abeel A. Mangi

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SUMMARY

Disruption of the ventricular septum after myocardial infarction is an infrequent event after a full-thickness myocardial infarction. The resulting clinical syndrome can range from an asymptomatic murmur to an extensive left-to-right intracardiac shunt with resulting heart failure and shock. The first approaches to surgical management emphasized delayed repair, which allowed time for fibrosis to occur so that tissue quality at the defect margins was more substantial.^{1,2} Modern approaches recognize that potentially salvageable patients deteriorate during this period of delay. Thus, early surgical intervention is now the accepted treatment.³

HISTORICAL PERSPECTIVE

Postinfarction ventricular septal defect (VSD) was first recognized by Latham at autopsy in 1845.⁴ The first antemortem diagnosis was made in 1923.⁵ In 1956,

Cooley accomplished the first successful surgical repair in a patient who had survived several weeks after septal perforation.⁶ Most patients in the early era were brought to operation a month or longer after surviving acute infarction with the belief that organization of the tissues surrounding the defect would allow a more secure closure.^{1,2} Subsequently, improvements in myocardial protection, the design and refinement of surgical techniques, improved prosthetic materials, and the widespread use of cardiac ultrasonography to permit the earlier diagnosis of VSD have all contributed to making earlier successful repair of this entity a possibility.⁷

INCIDENCE AND DEMOGRAPHICS

Postinfarction VSD complicates 1% to 2% of myocardial infarctions, but it accounts for 5% of deaths after myocardial infarction.^{8,9} The incidence appears to be

declining because of aggressive pharmacologic and interventional management of acute myocardial infarction and better treatment of postinfarction hypertension.¹⁰⁻¹² Postinfarction VSDs occur more frequently in males (male-to-female ratio, 3:2), reflecting the higher incidence of coronary artery disease in men. The average age is 62 years (range, 44 to 81 years). Septal rupture occurs most often after the first acute myocardial infarction.¹³

ETIOLOGY AND PATHOGENESIS

Angiographic evaluation of patients with postinfarction VSD most often reveals a completely occluded culprit coronary artery.⁶ Nearly two thirds of patients have single-vessel disease.¹⁴ There is usually somewhat less extensive disease in other vessels, and less collateralization.¹⁵ Postinfarction VSDs are located most commonly (i.e., in ≈60% of cases) in the anteroapical septum as a result of full-thickness anterior infarction secondary to occlusion of the left anterior descending artery. Twenty percent to 40% of patients with postinfarction VSD have rupture of the posterior septum because of inferoseptal infarction secondary to occlusion of a dominant right or a dominant circumflex coronary artery (Fig. 93-1).¹⁶ Simple rupture, consisting of a direct through-and-through defect, tends to be more common and is usually located anteriorly. Complex rupture with a more serpiginous tract is less common and is usually located inferiorly. Although a single VSD develops in most patients, 5% to 11% of patients may have multiple septal defects.

The myocardial infarction that sets the backdrop for a postinfarction VSD tends to be extensive and has been reported to involve 26% of the free wall on average, compared with only 15% in noncomplicated acute myocardial infarctions.⁸ Postinfarction VSD usually develops

two to four days after acute myocardial infarction, but it has been reported as early as a few hours after acute myocardial infarction and up to two weeks later.^{8,17,18} This time course correlates with histologic findings that show extensive distribution of necrotic myocardium at this time, with relatively sparse vasculogenesis, angiogenesis, or formation of fibrous connective tissue.^{19,20} It has been hypothesized that “slippage” of myocytes during infarct expansion may allow blood to dissect through the necrotic myocardium, where it can enter the right ventricle (or the pericardial space in the setting of rupture of the free wall).^{21,22} Similarly, autodigestion of necrotic myocardium may allow fissures to form, through which blood can subsequently dissect.²³

Left-ventricular free-wall rupture can occur in 4% to 8% of myocardial infarctions^{24,25} and is responsible for 15% of deaths after acute myocardial infarction.²⁶ Free-wall rupture typically occurs one to four days after infarction and is easily diagnosed with echocardiogram.²⁴ Acute rupture is almost always fatal; however, some patients with subacute rupture can be saved, but they require emergent surgical intervention.^{24,26}

PATHOPHYSIOLOGY

The primary determinant of outcome after postinfarction rupture of the ventricular septum is the development of heart failure (left, right, or biventricular), which is a function of both the size of the defect and the magnitude of the myocardial infarction. Left-sided heart failure tends to predominate in anterior VSDs, and right-sided failure predominates in posterior VSDs.²⁷⁻²⁹ The extent of heart failure often cannot be explained solely by postinfarction failure of the ventricle.³⁰ With the opening of a defect in the ventricular septum, a proportion of each left ventricular ejection is diverted from the systemic circulation across the septum into the right ventricle, thereby both compromising forward systemic cardiac output and overloading the pulmonary circulation. The resulting cardiogenic shock can lead to end-organ malperfusion and organ failure, which may be irreversible and fatal. In addition, the normally compliant right ventricle may demonstrate severe diastolic failure after a prolonged left-to-right shunt. The resulting escalation in right ventricular (RV) diastolic pressures can ultimately result in flow reversal across the septum when RV end-diastolic pressures exceed left ventricular end-diastolic pressures³¹ and compound the situation further with systemic hypoxia.

NATURAL HISTORY

Without surgical intervention, one-quarter of patients with postinfarction VSD die within 24 hours. Half will succumb to their illness within the first week, nearly two-thirds will die within two weeks, three-quarters will die within a month, and only 7% will survive longer than one year.^{13,32,33} These data have been confirmed in the recent SHOCK (SHould we emergently revascularize Occluded Coronaries in cardiogenic shock) multicenter trial, in

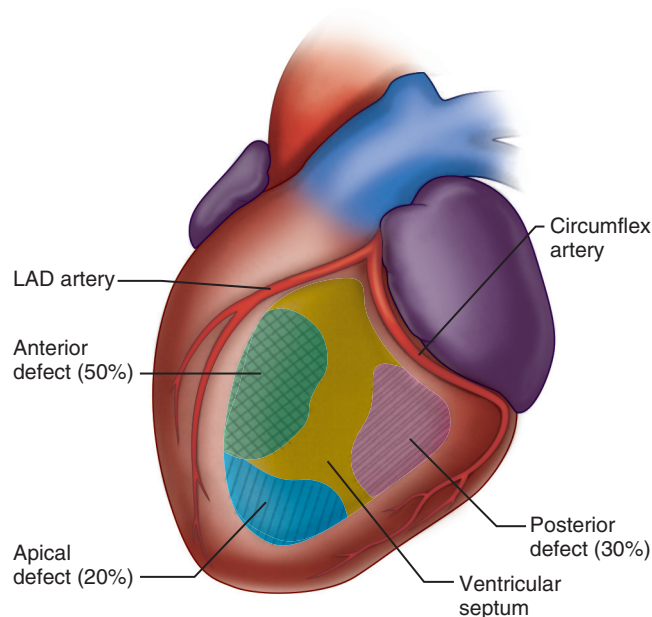


FIGURE 93-1 ■ Distribution of postinfarction ventricular septal defects. LAD, Left anterior descending.

which subgroup analysis of patients who had postinfarction VSD was performed. A total of 55 patients with postinfarction VSD were enrolled in the study a median of 16 hours after infarction and went into shock 7.3 hours thereafter. Of the 24 patients treated medically, only one survived (survival rate, 4%). Of the 31 patients who underwent operation to repair the VSD, 21 underwent concomitant coronary artery bypass grafting. Of these, only six survived (survival rate, 19%). The difference between the groups was statistically significant.³⁴

The historical practice of waiting weeks after postinfarction rupture of the ventricular septum selected out patients with lesser pathology and a relatively mild hemodynamic insult.^{28,35,36} It is clear that attempting to defer early operation in the hopes of maintaining hemodynamic stability deprives many patients of a chance for a successful outcome before irreversible end-organ damage supervenes.^{37,38}

CLINICAL PRESENTATION, PREOPERATIVE MANAGEMENT, AND RISK STRATIFICATION

Presentation

Typically, patients with postinfarction VSD present several days after a myocardial infarction with a harsh new holosystolic murmur that may radiate to the axilla.¹⁸ In more than half of patients, this is associated with recurrent chest pain.⁸ Clinical signs are generally those of right-sided heart failure, and pulmonary edema is rare. The electrocardiographic findings in these patients are the changes seen in antecedent anterior, septal, inferior, or posterior infarction. As much as one third of patients may develop transient atrioventricular conduction block that precedes rupture. Chest roentgenogram is generally nonspecific. Unfortunately, there is no reliable predictor of impending rupture.

This clinical syndrome may resemble acute mitral regurgitation secondary to rupture of a papillary muscle. In fact, both entities may coexist and sometimes can be distinguished only by imaging techniques. On physical examination, the murmur associated with postinfarction VSD is more prominent at the left lateral sternal border, is loud, and is associated with a thrill in more than half of patients. In addition, septal rupture is more commonly associated with anterior infarcts and conduction anomalies, whereas papillary muscle rupture is usually associated with posterior infarction and no conduction anomalies. If the patient is deemed salvageable, immediate placement of intra-aortic balloon pump and early operation are the management strategy of choice.

Diagnosis

The classic technique for distinguishing between acute papillary muscle rupture and postinfarction VSD has been right heart catheterization, during which a greater than 9% step-up in the oxygen saturation between the right atrium and the pulmonary artery is diagnostic of VSD in the appropriate clinical setting.²⁸ Additional

findings, such as an elevated pulmonary-to-systemic flow ratio, which can range from 1.4:1 to 8:1, also verify the presence of the VSD and roughly correlate with size.³⁹ Neither of these techniques accurately localizes the defect. Color-flow Doppler echocardiography can show the size and location of the defect, determine ventricular function, assess pulmonary artery and RV pressures, and exclude concomitant mitral valve disease with sensitivity and specificity approaching 100%.⁴⁰⁻⁴³

Indications for Operation and Preoperative Management

Because the natural history of untreated postinfarction VSD is dismal, the diagnosis of this entity suffices as an indication for operation.³⁸ Patients in cardiogenic shock represent a surgical emergency. Sometimes patients are already in established multisystem organ failure. These patients are unlikely to survive emergent repair and may benefit from a mechanical bridge (e.g., intra-aortic balloon counterpulsation or ventricular assist device) for salvage before corrective surgery. Patients in an intermediate status between shock and stable condition need to have surgical repair within 12 to 24 hours after appropriate preoperative evaluations are completed. A small percentage of patients (<5%) who are completely stable with no clinical compromise can undergo repair on a semi-elective basis.

Preoperative management is directed toward maintaining hemodynamic stability and preventing end-organ damage. Specifically, therapy should be targeted toward reducing systemic vascular resistance (thereby reducing left-to-right shunting), maintaining cardiac output and peripheral perfusion, and maintaining or improving coronary blood flow. All three of these objectives can be accomplished by intra-aortic balloon counterpulsation⁴⁴⁻⁴⁶ or with directed pharmacologic therapy.

Predictors of Risk

Patients with postinfarction VSD comprise a heterogeneous group in which both extremes of risk (i.e., very low risk and very high risk) are possible. For the nonemergent, stable patients, excellent results can be achieved, probability of survival to discharge from the hospital is high, and long-term survival is comparable with that in common cardiac operations. Conversely, patients in extremis tend to have dismal outcomes (Table 93-1).

In various studies, clinical variables have been used to identify the high-risk patient. In several studies, the use of an intra-aortic balloon pump was correlated with increased early mortality⁴⁷; presumably, its use was seen as a marker for disease severity. Other groups have demonstrated that posterior location of the septal rupture is associated with an increased operative mortality,^{28,31,48,49} which may be because the repair is more technically difficult, because the risk of mitral regurgitation is increased, or because RV failure is associated with an RV infarction. Proximal VSDs (closer to the atrioventricular groove) have also been shown to strongly predict early mortality, presumably because they are associated with the largest infarctions.⁵⁰

TABLE 93-1 Preoperative Predictors of Death after Surgical Repair of Postinfarction VSD

Variable	Predictor of Early Death	Predictor of Late Death
Need for preoperative catecholamines	$P = 0.001$	$P = \text{NS}$
Emergent operation	$P < 0.0001$	$P = \text{NS}$
Anterior VSD	$P = 0.04$	$P = \text{NS}$
Age > 65 years	$P = 0.009$	$P = \text{NS}$
Right-sided heart failure	$P = 0.01$	$P = 0.005$
Elevation in blood urea nitrogen	$P = 0.02$	$P = \text{NS}$
Elevation of serum creatinine	$P = \text{NS}$	$P < 0.05$
Previous myocardial infarction	$P = \text{NS}$	$P < 0.05$
Presence of left main coronary disease	$P = \text{NS}$	$P < 0.05$

VSD, Ventral septal defect.

OPERATIVE MANAGEMENT

General Principles

Cardiopulmonary bypass is established with bicaval venous drainage and cannulation of the ascending aorta. The patient is cooled, and cardiac standstill is achieved with blood cardioplegia via the antegrade and retrograde routes. A variety of alternative strategies for myocardial protection are practiced at Massachusetts General Hospital, including continuous warm-blood cardioplegia, fibrillatory arrest, and cold-blood cardioplegia.⁵¹⁻⁵⁴ If myocardial revascularization is to be performed, it should be done before opening the ventricle, to optimize myocardial protection. The general principles of this operation include meticulous attention to myocardial protection, a transinfarct approach to the VSD, thorough trimming of the left ventricular margins of the defect, conservative trimming of the right ventricular margin, close inspection of the papillary muscles and mitral apparatus, a tension-free repair, placement of the patch on the endocardial surface, and buttressing of the repair with Teflon felt to prevent sutures from cutting through the friable muscle.

Infarctectomy

Apical Amputation

The technique of apical amputation was first described by Daggett.³ An incision is made through the infarcted apex of the left ventricle. Débridement of the necrotic myocardium back to healthy muscle results in amputation of the apex of the heart, including the left ventricle, right ventricle, and septum. The remaining apical portions are then reapproximated to the apical septum using a row of interrupted mattress sutures of 0 Tefdek passed sequentially through a buttressing strip of Teflon felt, the left ventricular wall, a second strip of felt, the septum, a third strip of felt, the right ventricular wall, and a fourth strip

of felt. After all of these sutures have been tied, the closure is reinforced with an additional running suture.

Free-Wall Rupture

There have been numerous surgical techniques described for repair of free-wall rupture. Many have advocated closing the defect with infarctectomy and prosthetic patch repair while the patient is on cardiopulmonary bypass.⁵⁵⁻⁵⁸ The use of cardiopulmonary bypass is fraught with difficulty because of the systemic heparinization causing continuous oozing of blood through necrotic myocardium.⁵⁵ For this reason, many clinicians have advocated repair without extracorporeal bypass using an epicardial patch.⁵⁹⁻⁶¹ More recently, the use of a prosthetic patch with surgical glue has been advocated for patients without blowout rupture. The advantage of this technique is that it allows for a simple and expedited repair.⁶²

Anterior Septal Rupture

These defects are approached via a left ventriculotomy through the infarct. If the defect is small, it can be closed by plication with primary closure.⁶³ Most defects are larger and require closure with a Dacron prosthetic patch after débridement of necrotic myocardium. This operation is performed by placing a series of pledgeted interrupted mattress sutures around the perimeter of the defect. Sutures are passed through the septum from right to left along the posterior rim, and they are passed from the epicardium to the endocardium along the anterior rim. Once all the sutures are laid, the patch is inserted and all sutures are pledgeted again and then tied. The edges of the ventriculotomy are then reapproximated in a double-layer closure that is buttressed with Teflon felt or glutaraldehyde-preserved bovine pericardium (Fig. 93-2).

Posteroinferior Septal Rupture

Posterior VSD poses the greatest technical challenge (Fig. 93-3). Simple plication has an extremely high failure rate, and the procedure is often complicated by a reopening of the defect or by catastrophic disruption of the infarctectomy closure. Use of the following technique has been associated with improved operative results. After the establishment of cardiopulmonary bypass, the left heart is vented via the right superior pulmonary vein. The heart is then delivered from the pericardial well as for bypass to the posterior descending coronary artery. The infarct may include both ventricles or may be limited to the left ventricle only. The left ventricle is opened in standard fashion and infarctectomy is performed. The mitral apparatus is inspected, and mitral valve replacement is performed only in the setting of frank papillary muscle infarct. This is performed through a separate left atriotomy. The left ventricle needs to be aggressively débrided, but right ventricular débridement can be limited to only as much tissue as is needed to visualize the VSD. If the posterior septum has simply separated from the free wall, it can be reapproximated primarily in

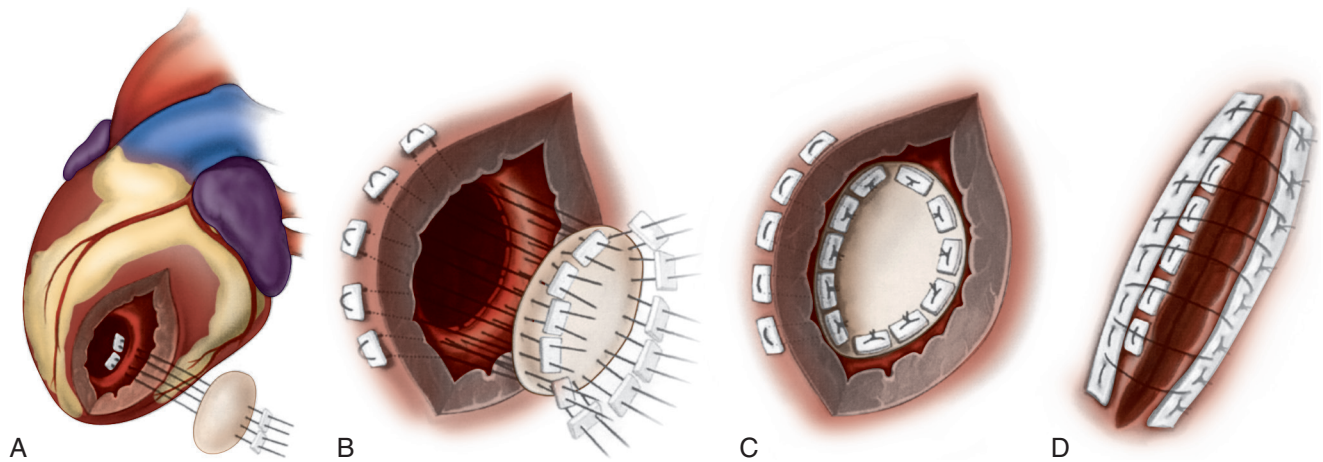


FIGURE 93-2 ■ Technique of repair of anterior postinfarction ventricular septal defect by infarctectomy and patch repair.

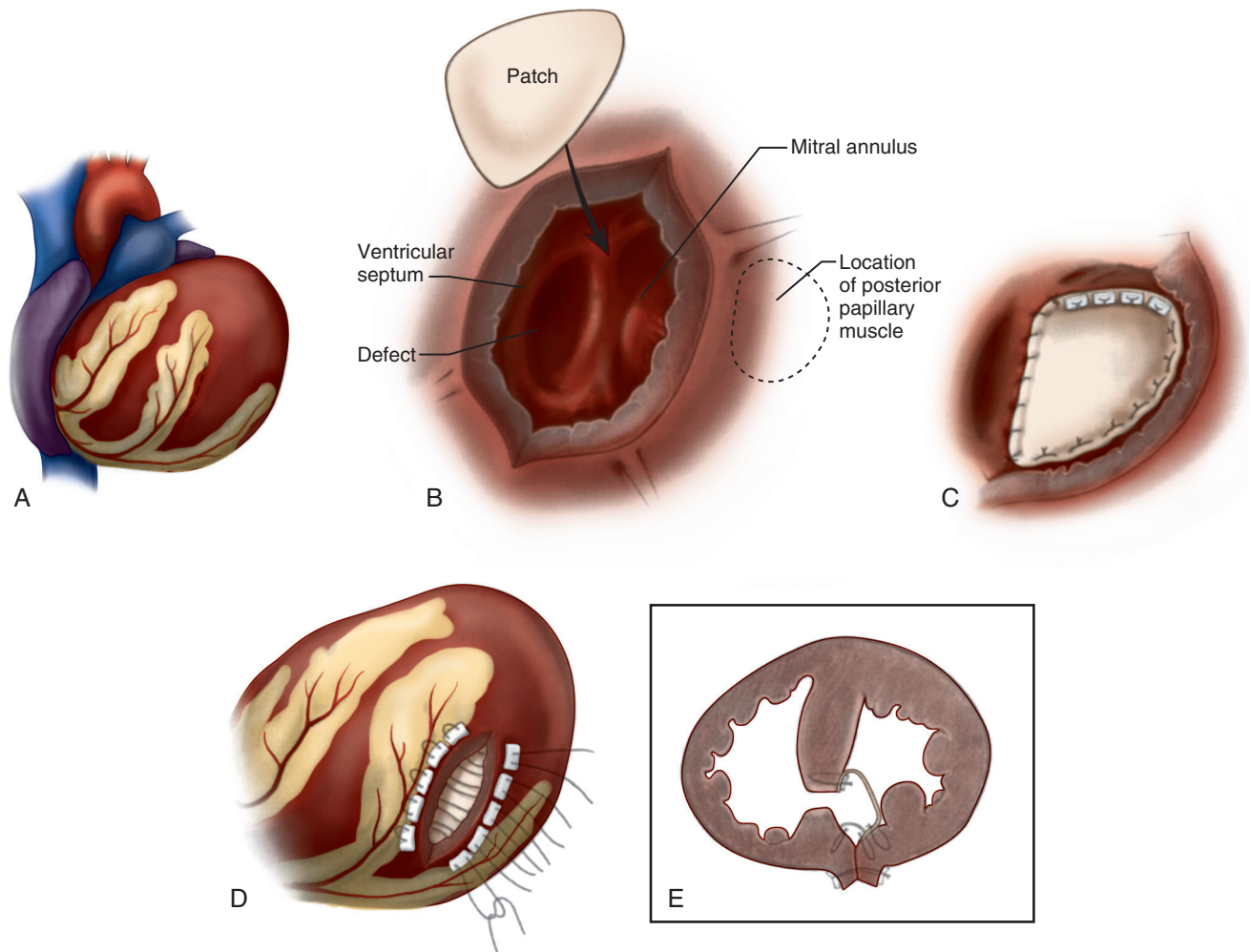


FIGURE 93-3 ■ Technique of repair of posterior postinfarction ventricular septal defect by infarctectomy and patch repair.

a double-layered buttressed closure. Larger defects require patch closure as described earlier. The only difference is that sutures are placed from the right side of the septum and from the epicardial side of the right ventricular free wall. The most important aspect of this operation is to perform a separate patch closure of the

infarctectomy, because primary closure of this large tissue defect with its friable edges under tension has historically resulted in catastrophic disruption. We use a Hemashield Dacron graft (Boston Scientific, Natick, MA) for this purpose and pass sutures through the patch, which is seated on the epicardial surface of the heart, and then

through the margin of the infarctectomy, from the endocardium to the epicardium. Using an appropriately sized patch can result in restoration of normal ventricular geometry.

Infarct Exclusion with Endocardial Patch Repair

The technique of infarct exclusion with endocardial patch repair emphasizes the importance of restoring normal ventricular geometry as an attempt to preserve or restore ventricular function.^{52,53,63-65} The operative strategy is an extrapolation of the technique of Dor and colleagues, ventricular endoaneurysmorrhaphy⁶⁶—which involves intracavitary placement of an endocardial patch to exclude both the septal defect and the infarcted myocardium from the high-pressure zone of the ventricle—while maintaining ventricular geometry, which theoretically enhances ventricular function. Other theoretical benefits of this approach include avoiding resection of the myocardium (which could further compromise ventricular function), and avoiding a suture line in friable muscle (to diminish postoperative bleeding and disruption of the repair).

David and coworkers²⁷ pioneered this technique, which involves exposing the interventricular septum via a left ventriculotomy through the infarcted anterior wall 1 to 2 cm from the left anterior descending coronary artery. Stay sutures are placed in the ventricular wall to aid in exposure of the septal defect. These authors used a glutaraldehyde-fixed bovine pericardial patch for the repair. The patch is tailored to the endocardial shape of the ventricular infarction (generally about 4 × 6 cm) and is then sutured to healthy muscle (on the endocardial surface) surrounding the septal defect with a continuous 3-0 polypropylene suture. The repair is then carried onto the noninfarcted endocardium of the anterolateral ventricular wall with stitches that are approximately 5 to 7 mm deep and 4 to 5 mm apart. The ventriculotomy is then closed over the patch in two layers and is buttressed with two strips of glutaraldehyde-fixed bovine pericardium. In the case of a posterior septal defect, exposure is achieved via a posterior ventriculotomy with the heart elevated as for bypass grafting to the posterior descending artery.

The repair commences with anchoring of the patch to the fibrous annulus of the mitral valve with a 3-0 continuous polypropylene suture starting at a point corresponding to the posteromedial papillary muscle and moving medially toward the septum until the noninfarcted endocardium is reached. The stitch is then transitioned onto the septal endocardium using the technique described earlier. In this area of the repair, the suture should be reinforced with interrupted, pledgeted sutures. The lateral edge of the patch is sutured to the posterior left ventricle along a line corresponding to the medial margin of the base of the posteromedial papillary muscle. These need to be full-thickness stitches, and they should be buttressed with epicardial bovine pericardium or Teflon felt. Again, the ventriculotomy is closed in two layers of full-thickness sutures buttressed with bovine pericardium or Teflon felt.

Intraoperative Management

Coronary Artery Disease

For patients with postinfarction VSD, the value of preoperative coronary artery angiography and coronary revascularization is controversial. Many of these patients have multivessel coronary disease, and bypassing significantly diseased vessels may increase both early and long-term survival.^{27,28,35,64,67,68} Our approach is to perform catheterization when the clinical scenario permits, and to perform concomitant revascularization when indicated. The arguments against simultaneous revascularization are that (1) it provides no additional benefit⁶⁹⁻⁷¹ and (2) it subjects patients to preoperative left-side-of-the-heart catheterization, a time-consuming and potentially dangerous procedure. However, one study has found that concomitant revascularization with VSD repair improves early and long-term survival.⁷² Other groups have proposed selective left heart catheterization and revascularization^{7,73}—avoiding it in patients when a postinfarction VSD is thought to be the result of their first infarction—provided there is no history of angina and no electrocardiographic evidence of previous or ongoing ischemia in another territory.

Weaning from Cardiopulmonary Bypass

We have found routine intraoperative use of a transesophageal echocardiogram to be invaluable for assessing ventricular function, dimensions, residual shunt, and mitral regurgitation when weaning from bypass. For left heart dysfunction, we favor the use of intra-aortic balloon counterpulsation and the use of one of the phosphodiesterase inhibitors, such as milrinone, in the postoperative setting. Strategies to ameliorate right heart failure aim to limit right ventricular afterload while maintaining systemic blood pressure. This can be achieved by right-sided administration of prostaglandin E₁ (0.5 to 2.0 mg/min) with left-sided administration (via a left atrial line) of norepinephrine.⁷⁴ Finally, inhaled nitric oxide (20 to 80 ppm) selectively dilates the pulmonary circuit and may be efficacious in ameliorating right heart failure.⁷⁵ An inability to wean a patient from cardiopulmonary bypass is unusual if the repair has been successful. If there exists the inability to wean from cardiopulmonary bypass, institution of mechanical assist (left ventricular assist device, right ventricular assist device, or extracorporeal membrane oxygenation) may be considered.

Bleeding

When repairing postinfarction VSD, we generally use antifibrinolytic therapy with either aprotinin or ε-aminocaproic acid before commencing cardiopulmonary bypass. Other maneuvers to avoid postpump suture-line bleeding include application of fibrin sealants to the proposed suture line before repair⁷⁶ and the use of biological glues after surgical repair.⁷⁷ As a last-resort measure, Baldwin and Cooley⁷⁸ have used placement of a left ventricular assist device solely as an adjunct to the

repair of friable or damaged myocardium to decrease left ventricular distention, thereby controlling bleeding.

Percutaneous Closure

Successful transcatheter closure of postinfarction ventricular septal rupture, or closure of residual defects after repair, has been reported with increasing frequency. Early experience was with the CardioSEAL device (Nitinol Medical Technologies, Boston, MA), a nitinol double-umbrella prosthesis, which is a transvenous clamshell device.⁷⁹ Use of other catheter devices has also been attempted, including the Amplatzer septal occluder and the Rashkind double umbrella.^{37,80}

The Amplatzer VSD device allows closure of muscular and membranous VSDs, and it can be used for larger postinfarction defects. In a series of seven patients treated with the Amplatzer, the size of the device ranged from 12 to 24 mm, and there was only one death.⁸¹ The use of such devices in an overall treatment strategy is unclear because data suggest that the devices have a high early failure rate. The most attractive role has been its use in the unstable surgical patient, but data on outcomes in this group are difficult to evaluate and not yet well characterized. Catheter approaches appear to be most effective for treating recurrent or residual defects, and we preferentially use them for these conditions.⁸²

Delayed Repair

Sometimes a patient presents with evidence of severe end-organ dysfunction. As was discussed earlier, the risk of repair may be prohibitive in these patients, and consideration should be given to delayed repair. Placement of a ventricular assist device for a defined period of time has the theoretical advantage of allowing reversal of end-organ dysfunction, allowing maturation of the infarct and leading to firmer tissue that could make the closure less prone to technical failure, and permitting recovery of the stunned and energy-depleted myocardium. In our limited experience, this strategy has promise and merits further evaluation. Biventricular support is necessary if instituting left ventricular support results in right-to-left shunting.⁸³

Role of Ventricular Assist Devices

In selected patients, there may be a role for temporary mechanical heart support. The successful use of ventricular assist devices with staged repair of ventricular septal rupture has been described.⁸⁴⁻⁸⁶ Mechanical support may aid in reversing end-organ dysfunction, providing time for maturation of the infarct and leading to firmer tissue. Caution is required, however, because of the potential for high right-to-left shunting across the ventricular septum, which was reported to cause hypoxic brain injury in a patient with postinfarction VSD who was placed on a Heart-Mate left ventricular support device.⁸³ It is preferable that biventricular support be considered when using mechanical assistance in these patients. In addition to shunting, embolization of necrotic debris is possible, with the potential to cause obstruction in support devices.⁸⁷

Postoperative Management

The postoperative care of these patients is similar to that of other patients undergoing extensive intracardiac operations. Early postoperative diuresis is important to decrease the arterial-alveolar gradient induced by the increased extravascular pulmonary fluid associated with cardiopulmonary bypass. A continuous furosemide drip may sometimes be needed. If the patient suffers from renal dysfunction, we favor early institution of continuous venovenous hemofiltration. Intractable postoperative ventricular arrhythmias are treated with intravenous amiodarone.⁸⁸

OUTCOMES

Operative Mortality

Operative mortality (death before discharge or within 30 days of operation) ranges from 30% to 50% (see Table 93-1). David and colleagues²⁷ reported outstanding results with the infarct exclusion technique, with only a 19% early mortality rate. Regardless of technique, the most common cause of death after repair of a postinfarction VSD is low cardiac output (52%). Technical failures such as recurrent or residual VSD are the second most common causes of death (22%). Other causes of death include sepsis (17%), recurrent infarction (9%), cerebrovascular complications (4%), and intractable ventricular arrhythmias.

Long-Term Results

Most series report 5-year actuarial survival between 40% and 60% (Table 93-2).^{28,89-96} In the Massachusetts General Hospital experience, hospital survivors demonstrated 1-, 5-, and 10-year survival rates of 91%, 70%, and 37%, respectively (Fig. 93-4); 75% reported New York Heart Association (NYHA) class I functional status and 12.5% reported class II functional status after surgery.¹⁰ These favorable results have also been reported by other groups. Gaudiani and coworkers reported an 88% 5-year survival

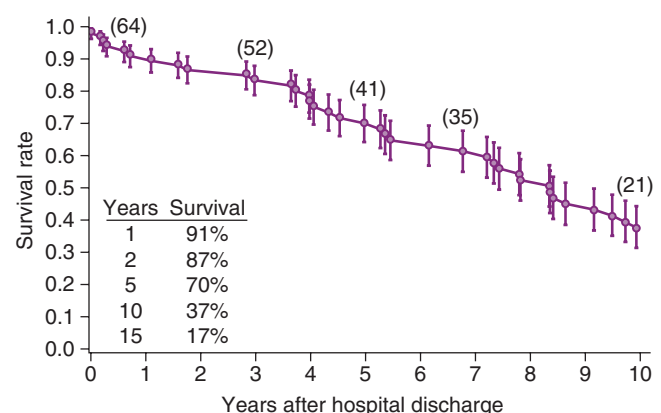


FIGURE 93-4 ■ Postdischarge survival rates after repair of postinfarction ventricular septal defect: The Massachusetts General Hospital experience.

TABLE 93-2 Recent Clinical Experience* with Surgical Repair of Postinfarction Ventricular Septal Defect

Institution	City	Year	Patients (N)	Hospital Mortality (%)	5-year Survival (%)
Massachusetts General Hospital ¹	Boston	2002	114	37	45
University Hospital ⁶³	Zurich	2000	54	26	52 [†]
Glenfield General Hospital ²⁷	Leicester	2000	117	37 (30-day)	46
The Toronto Hospital ²⁴	Toronto	1998	52	19	65 [†]
Southampton General ²⁰	Southampton	1998	179	27	49
MidAmerica Heart Institute ⁴⁶	Kansas City	1997	76	41	41
Green Lane Hospital ³¹	Auckland	1995	35	31 (30-day)	60 [†]
Hôpital Cardiologique du Haut-Lévêque ²⁸	Bordeaux	1991	62	38	44
CHU Henri Mondor ⁵³	Créteil	1991	66	45	44

*Series with fewer than 25 patients and no 5-year follow-up were excluded.

[†]Value estimated from published graphic or tabular data.

rate, with 74% of survivors in NYHA functional class I.⁶⁷ David and colleagues reported a 66% 6-year survival,²⁷ and Davies and associates reported a 5-year survival rate of 69%.⁷³

Recurrent Septal Defects

In 10% to 25% of patients, recurrent or residual VSD may develop,²³ which could result from the reopening of a closed defect, the presence of an overlooked defect, or the development of a new defect in the early postoperative period. Small defects that occur as a result of leaks around the patch are usually asymptomatic and can be controlled with diuretic therapy. Larger defects or those causing symptoms or heart failure should be closed. These attempts may be made first in the catheterization laboratory.

SUMMARY

Although the prevalence of postinfarction VSDs has decreased with modern management of acute myocardial infarction, patients who do come to surgical attention are older and sicker and have complex comorbidities. Surgery is complex and relatively infrequent, and although the results are far better than if the patient had received no treatment at all, morbidity and mortality rates remain high. The use of predictive statistical models can assist us further in helping determine which patients should come to operation early, which patients would be better off temporized with the use of an assist device, and which patients should be turned down or treated percutaneously.

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NONATHEROSCLEROTIC CORONARY ARTERY DISEASE

Neel R. Sodha • Roger J. Laham • Frank W. Sellke

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SUBSTANCE ABUSE

Greater than 95% of patients with myocardial ischemia will have underlying atherosclerotic coronary artery disease as the etiology, with the remaining 5% possessing a range of congenital and acquired lesions. Although these lesions are rare individually, clinicians will inevitably encounter some form of nonatherosclerotic coronary artery disease in their practice.

These disorders can be broadly classified as congenital or acquired. Congenital coronary anomalies occur secondary to atresia, an abnormal origin, or abnormal drainage. Acquired disorders can be secondary to mechanical injury to the coronary artery or result from progressive occlusive disease unrelated to atherosclerosis. Diagnosis may be difficult because these disorders may be asymptomatic or may occur in patient populations in which cardiovascular disease is unsuspected. Given the rarity of certain types of these disorders, management recommendations may be based on limited series or expert opinion.

CORONARY ARTERY ANOMALIES

Anomalous Aortic Origin of Coronary Arteries

Approximately one third of all coronary artery anomalies are an anomalous aortic origin. Although multiple variations have been reported, with each of the three major coronary arteries arising from any of the three sinuses of Valsalva, most are benign. The exceptions to this include the right coronary artery arising from the left aortic sinus, and the left main coronary artery arising from the right aortic sinus, both of which are associated with a risk of sudden death.^{1,2}

The incidence of sudden death associated with a left main coronary artery arising from the right sinus of Valsalva has been reported to be as high as 57% and is most commonly seen with exercise.³ When symptomatic,

patients will present with angina, myocardial infarction, congestive heart failure, or syncope. From its origin in the right sinus of Valsalva, the left main coronary artery may pass anterior to the pulmonary artery, posterior to the aorta, between the great vessels, or through the conal septum. This anatomic position is believed to result in ischemia because of acute angulation resulting in a narrowed coronary orifice, compression of the artery from the adjacent great vessels, and compression by the inter-coronary commissure.^{3,4}

The incidence of sudden death from the right coronary artery arising from the left sinus of Valsalva has been reported to be as high as 25% and, as with the left main coronary artery arising from the right sinus, is often exercise related.^{3,5} When symptomatic, patients will present with angina, myocardial infarction, conduction disturbances, or syncope. The risk of ischemia is felt to result from ostial obstruction or arterial compression by the aortic root during diastole.⁴

The most common variation in anomalous aortic origin of the coronaries is a circumflex arising from the right sinus of Valsalva, or from the right coronary artery (Fig. 94-1). This condition in general does not manifest with symptoms and is diagnosed incidentally. Because the risk of sudden death is minimal, intervention is not needed.

For all anomalous aortic origins of the coronaries, angiography is needed to delineate anatomy and for surgical planning. In the presence of symptoms, surgery is indicated for all patients. For an anomalous left main coronary artery originating from the right sinus of Valsalva, coronary unroofing is recommended regardless of the presence of symptoms and should be performed urgently if symptoms are present. For patients with an anomalous right coronary artery from the left sinus of Valsalva (Fig. 94-2), surgery should be performed for symptoms, but there remains debate about surgery for the asymptomatic patient.⁴ Surgical options include unroofing of the coronary with intimal tacking,⁶ aortic reanastomosis, or patch arterioplasty. Proximal ligation of the anomalous coronary with distal bypass grafting is also used but is limited by durability of bypass grafts.⁴

Coronary unroofing with intimal tacking is the currently favored method for correcting an anomalous aortic origin of the left main coronary artery or right coronary artery from the contralateral sinus. After cardiopulmonary bypass grafting is begun, care must be taken when dissecting the aorta from the main pulmonary artery because the aberrant artery may be injured during this dissection. After establishment of cardioplegic arrest, an oblique aortotomy is generally used, but a “hockey-stick” (vertical followed by oblique) aortotomy may be used if there is uncertainty about the course of the aberrant artery to avoid injury. Upon identifying the abnormal origin, a coronary probe is placed in the artery to confirm its course. With the probe in the arterial lumen, the artery is unroofed, using the probe to prevent inadvertent back wall injury. The edges of the unroofed segment are then tacked to the aortic wall with interrupted fine polypropylene suture, thereby creating a new ostium in a more anatomic position (Fig. 94-3).

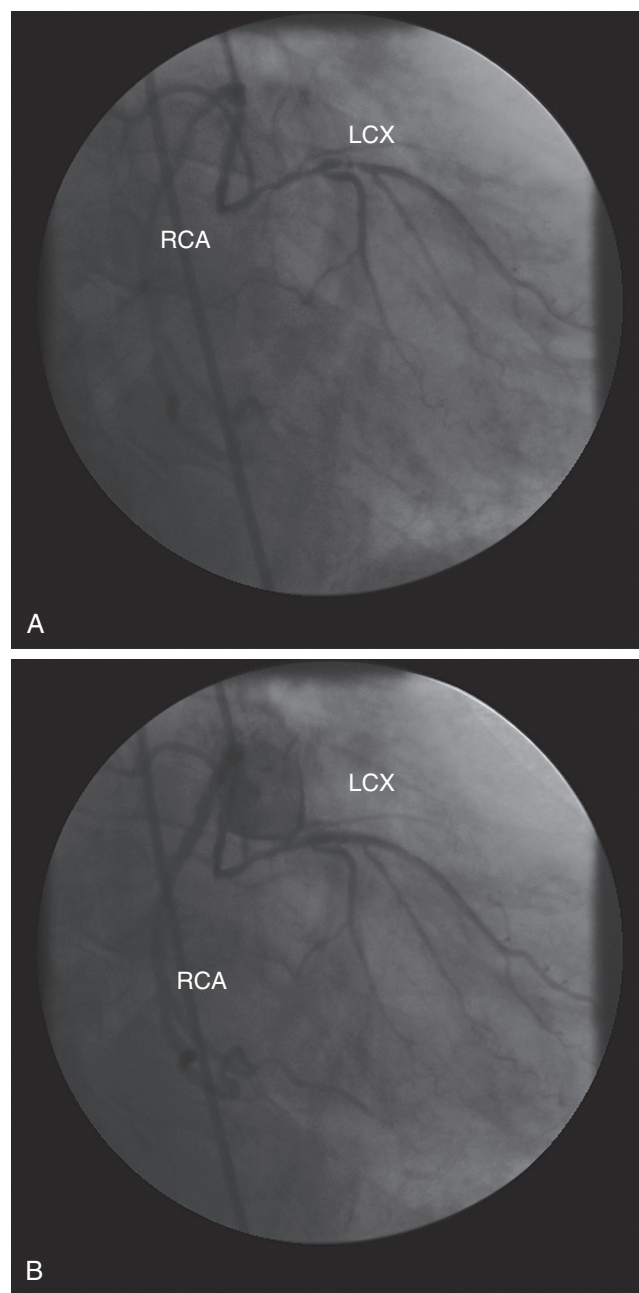


FIGURE 94-1 ■ Anomalous origin of the left circumflex (LCX) from the right coronary artery (RCA) in (A) the shallow right anterior oblique, and (B) the right anterior oblique projections.

Anomalous Pulmonary Origin of Coronary Arteries

Anomalous Left Main Coronary Artery from the Pulmonary Artery

Anomalous left main coronary artery from the pulmonary artery (ALCAPA) has an incidence of 0.25% to 0.5% and remains one of the most common etiologies of myocardial ischemia in pediatric patients.⁷ Symptoms will generally present during infancy unless patients have extensive collateralization from the right coronary

artery, in which case symptoms may not present until adulthood. Because they are dependent upon time of diagnosis, symptoms may be related to angina pectoris or heart failure if extensive myocardial infarction has occurred. Diagnosis can be made with echocardiography

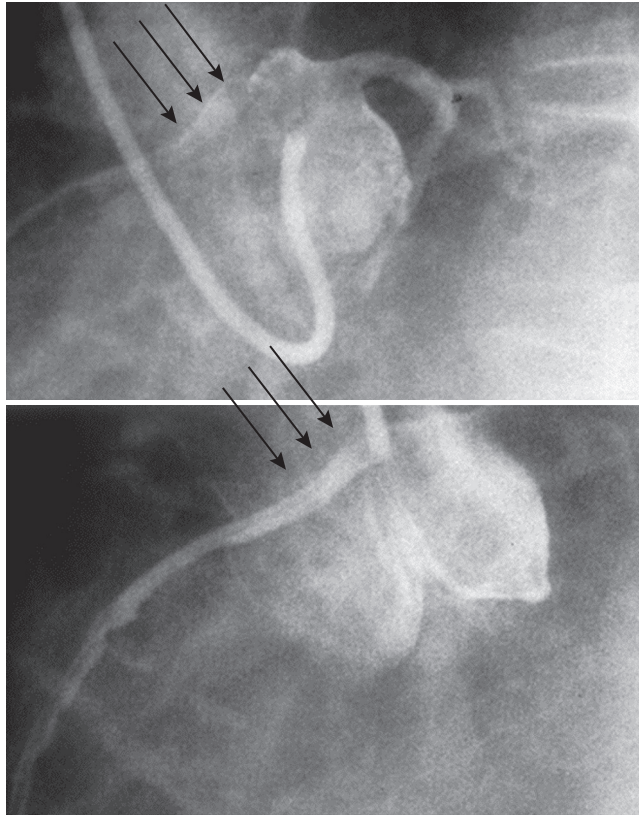


FIGURE 94-2 ■ Anomalous origin of the right coronary artery (arrows) from the left cusp high in the aorta above the left main origin.

with color flow, and if the diagnosis remains in question, magnetic resonance angiography or computed tomographic angiography can be used. Once diagnosis is established, surgical correction should be undertaken because of the risk for infarction and sudden death.⁸ The currently favored surgical approach to correction is that described by Neches,⁹ in which a cuff of pulmonary artery is taken around the coronary and used to reimplant the coronary artery to the aorta. If the anomalous coronary has previously been ligated, or if it cannot be sufficiently mobilized for reimplantation, bypass grafting may be undertaken. Although a certain degree of mitral regurgitation may be present from the prior ischemia, or the ventricular wall may be aneurysmal from prior infarction, most clinicians do not advocate valve repair or aneurysm resection at the time of revascularization because functional improvement is usually seen.⁴

Other Anomalous Pulmonary Origins of Coronary Arteries

As described before, ALCAPA is the most common anomalous pulmonary origin of a coronary artery, with the remainder designated as anomalous pulmonary origins of coronary arteries (APOCA). Anomalous right coronary artery from the pulmonary artery is found in 0.002% of the population and is most commonly discovered before the age of 18.¹⁰ The additional types of APOCA reported include anomalous origin of the circumflex coronary artery from the pulmonary artery and anomalous origin of the right and left coronaries from the pulmonary artery, the latter of which is fatal in the neonatal period. Although patients will commonly present with an asymptomatic murmur, symptoms secondary to myocardial ischemia and heart failure have also been reported.⁴ Diagnosis can be made with echocardiography. When the diagnosis is made, most clinicians

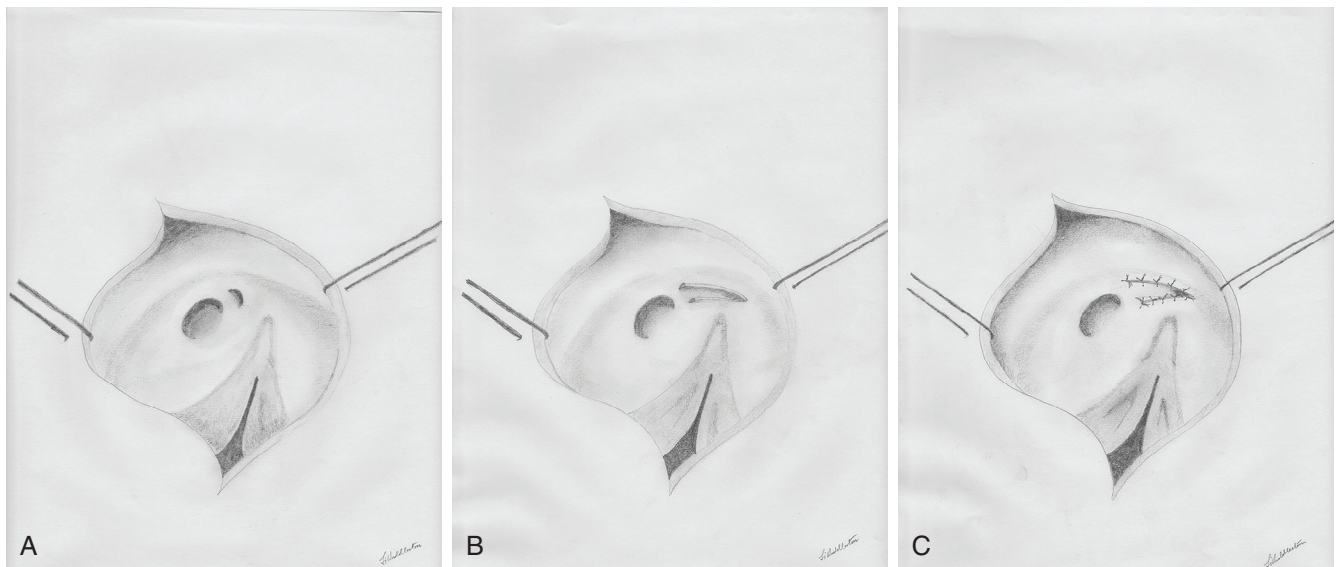


FIGURE 94-3 ■ Anomalous origin of the right coronary artery from the left cusp (A) as seen after aortotomy, (B) unroofing of the anomalous coronary artery, and (C) edge plication for creation of a “neo” ostium. (Courtesy Stephen J. Huddleston, MD, PhD.)

advocate aortic reimplantation of the anomalous coronary because of the risk of sudden death if left uncorrected.^{4,10}

Single Coronary Artery

Single coronary artery is an extremely rare coronary anomaly, with an incidence ranging from 0.002% to 0.06%, and is associated with other congenital heart defects in as much as 40% of patients.¹¹⁻¹³ The anomaly can be classified into three types: type 1 describes a single artery supplying the entire heart, type 2 describes a single artery that divides into a right and left coronary artery, and type 3 covers all other variations. Patients will present either with symptoms related to concomitant congenital defects or with angina. Diagnosis is made with coronary angiography. Although some patients will remain asymptomatic, sudden death has been reported secondary to compression between the great vessels, and concerns over angulation and accelerated atherosclerosis have been reported.¹³ Percutaneous coronary intervention and coronary artery bypass grafting have been used successfully for the treatment of patients with ischemic symptoms, although no guidelines exist for intervention in asymptomatic patients.⁴

Left Main Coronary Artery Atresia

Congenital atresia of the left main coronary artery is quite rare, with only limited case reports found in the literature. The anomaly may present in infancy with rhythm disturbances, syncope, or sudden death, whereas if there is sufficient collateralization from the right coronary artery, patients may not present until adulthood, at which time ischemic symptoms will manifest. Diagnosis is made with echocardiography and coronary angiography, which allow for differentiation from a single coronary artery and ALCAPA. Surgery is recommended at the time of diagnosis and may consist of distal revascularization with coronary artery bypass grafting¹⁴ or reattaching the proximal left main coronary artery to the aortic sinuses.¹⁵

High Takeoff Coronary Ostia

The left main and right coronary arteries generally originate from their respective sinuses of Valsalva below the sinotubular junction. Although the incidence varies significantly between series, the coronary arteries may be located significantly above the sinotubular junction in 0.01% to 0.8% of patients.^{16,17} The origin will generally occur within 1 to 2 cm of the sinotubular junction but has been reported to be as high as 5 cm above the sinotubular junction. The clinical significance of this anomaly remains controversial because cases of sudden death with this condition have been reported in patients with concomitant coronary pathology, which may have been responsible for the mortality.¹⁷ In the asymptomatic patient with an isolated high takeoff coronary in whom an incidental finding is made, observation may be warranted.

Coronary Artery Fistula

Coronary artery fistulae may be congenital or acquired, with an incidence ranging from 0.2% to 0.85%.¹⁸ The fistulae consist of a direct precapillary communication between a major coronary artery and a cardiac chamber, a major vessel, or a vein. When drainage occurs into a cardiac chamber, the term *coronary-cameral fistula* may be used. Currently, approximately two thirds of coronary artery fistulae are congenital and may be associated with additional congenital heart defects in one third of patients.¹⁹ These are thought to develop because of the persistence of sinusoidal connections between the lumens of the tubular heart in early development.²⁰ Acquired fistulae may develop after trauma, coronary angiography or other catheter-based intervention, myocardial biopsy, vasculitis, or cardiac surgery. Most commonly, fistulae will be single in approximately 80% of cases, with multiple fistulae occurring in 10% to 15% of patients, and dual right-left coronary fistulae occurring in less than 10% of patients.²⁰ The left anterior descending and right coronary arteries are the most common sites of origin for fistulae, with the circumflex being an infrequent site.⁴ Drainage runs into the low-pressure right heart or pulmonary artery in greater than 90% of cases but may rarely run into the left atrium or ventricle. Fistulae may be classified as type A or type B based on the system proposed by Sakakibara and colleagues.²¹ In type A fistulae, the coronary artery proximal to the fistula site is dilated, whereas in type B, the coronary is dilated over its entire length, terminating in the right heart. This distinction is of significance clinically because type A fistulae may be ligated on the epicardial surface of the heart, whereas type B should be ligated intracamerally. If fistulae are large, symptoms may appear during childhood, with angina and dyspnea being the most common complaints. Echocardiography is able to identify a fistula, but catheterization is required for surgical planning and obtaining hemodynamic measurements. Although fistulae rarely close spontaneously, intervention (catheter-based or surgical) is favored by most clinicians in younger patients, even if they are asymptomatic, to prevent complications such as ischemia, endocarditis, aneurysm, or pulmonary hypertension.⁴ No consensus exists for the management of asymptomatic older patients with incidentally discovered small fistulae, but observation may be appropriate.²² Successful catheter-based interventions include stenting or coiling and have not been compared with surgical techniques. Surgical techniques are varied and may be performed with or without the use of cardiopulmonary bypass (dependent upon technique). If the coronary artery can be mobilized on the epicardial surface, the fistula may be ligated without the use of cardiopulmonary bypass. Pledgeted mattress sutures may be passed deep into the artery to occlude the fistula without the use of bypass. Internal closure can be performed via arteriotomy if the patient can tolerate temporary proximal and distal occlusion of the coronary artery. Alternatively, the coronary artery may be ligated both proximally and distally with bypass grafting to preserve distal perfusion. Closure can be performed from within

the draining chamber with a purse-string suture or patch, both of which require cardiopulmonary bypass.²⁰

Muscle Bridge

The “epicardial” coronary arteries are normally located superficially on the epicardial surface of the heart, but in certain patients they may course through the myocardium for varying lengths, with the overlying muscle termed a *bridge*. Although there exists debate regarding the contribution of muscle bridges to myocardial ischemia,²³ multiple reports demonstrate ischemia secondary to systolic narrowing of the coronary artery from the overlying muscle.²⁴ In addition to the direct mechanical effects of the bridge, there may be some increase in progression of atherosclerosis proximal to the bridge, which may also contribute to ischemia. The incidence of muscle bridging varies tremendously, from 0.5% to 85%, and is dependent upon the type of study done (angiography versus computed tomography versus autopsy),^{4,24} but muscle bridging with arterial compression is seen in only approximately 0.5% of patients undergoing coronary angiography for evaluation of chest pain.²⁴ If muscle bridging is suspected, coronary angiography with intravascular ultrasonography should be used to confirm the diagnosis (Fig. 94-4). Although some degree of vessel compression is likely benign, reduction of the coronary diameter by greater than 70% during systole and 35% during diastole suggests significant coronary compression.²⁵ Medical management remains the first-line treatment for symptomatic muscle bridging and consists primarily of beta blockade. Via reducing heart rate and prolonging diastole, beta blockers are able to reduce compression and improve flow.²⁶ Calcium channel blockers and nitrates may also provide some relief if vasospasm is a concern.²⁴ For symptoms refractory to medical management, percutaneous coronary intervention with stenting or surgery may be offered. Coronary stenting with drug-eluting stents has demonstrated favorable midterm results, but long-term data are pending.²⁴ Surgical options for failure of medical management include supra-arterial myotomy or coronary artery bypass grafting. Supra-arterial myotomy has yielded good long-term results, but care must be taken to avoid entry into the right ventricle, which may be vulnerable during unroofing.²⁷ As an alternative to myotomy, coronary artery bypass distal to the

muscle bridge may also be considered for patients with atherosclerotic disease proximal to the bridge and in patients with a thick muscle bridge, because this may increase the risk of inadvertent coronary injury or ventricular entry.

Coronary Aneurysms (Coronary Artery Ectasia and Dilating Coronary Atherosclerosis)

Aneurysms of the coronary artery, defined as a diameter 1.5 times the adjacent normal coronary artery, have been reported to occur in 1.5% to 4.9% of the population.^{28,29} Aneurysms are most commonly secondary to underlying atherosclerotic disease but may be congenital or occur secondary to infection, inflammatory disease/vasculitis, or trauma (including iatrogenic trauma after percutaneous intervention). Morphologically, the aneurysms are termed *saccular* or *fusiform*, the latter of which are more commonly seen in patients with atherosclerotic disease. Although fusiform aneurysms are more common, the saccular type is more prone to complications such as rupture or thrombosis. Approximately 50% of coronary artery aneurysms are found in the right coronary artery, with approximately 25% to 50% found in the left anterior descending or left circumflex arteries, and fewer than 10% are found in the left main coronary artery.^{29,30} Diagnosis is generally made during evaluation for ischemic complaints. Although echocardiography may demonstrate the aneurysm, coronary angiography remains the definitive diagnostic modality. There is currently no consensus for the treatment of coronary artery aneurysms among medical management, percutaneous intervention with covered stents, and coronary artery bypass grafting. Medical management entails therapy for the underlying pathology (standard management of atherosclerotic coronary disease, clearance of infection, and immunosuppression in the case of vasculitis). Use of statins to inhibit matrix metalloproteinase activity and use of angiotensin II receptor blockers to inhibit transforming growth factor- β have been tried as adjunct therapy to standard medical management, but no data exist regarding their benefit.³¹ Larger aneurysms may benefit from antiplatelet therapy or formal anticoagulation to reduce the risk of thrombosis and embolization, although size criteria and

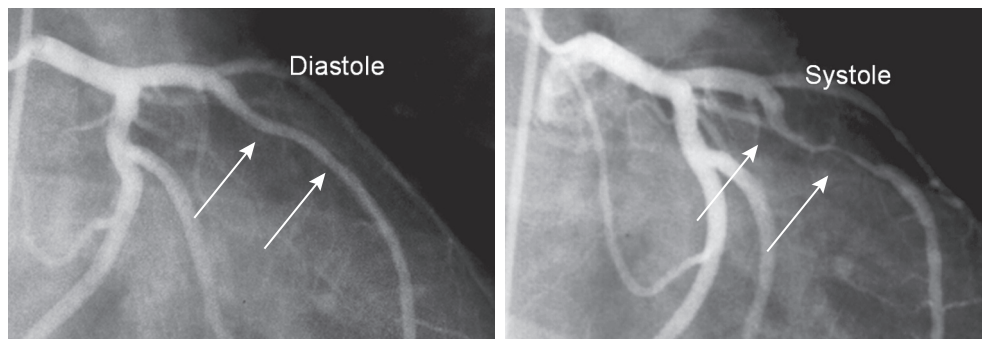


FIGURE 94-4 ■ Muscle bridge (arrows) causing compression during systole.

level of anticoagulation have not yet been determined.³² The successful use of covered stents has been reported (Fig. 94-5), but concerns persist about the risk of stent thrombosis.³¹ Indications for surgical intervention include standard indications for coronary artery bypass grafting, aneurysms near large-branch bifurcations, distal embolization with resulting myocardial ischemia, progressive enlargement, left main coronary artery aneurysms, and size threefold the normal coronary diameter.^{33,34} Methods for the repair of saccular aneurysms include lateral aneurysmorrhaphy, endarterectomy, and thrombectomy. Fusiform aneurysms are surgically managed with conventional distal bypass grafting and aneurysm ligation.

MECHANICAL INJURY TO THE CORONARY ARTERY

Coronary Artery Embolization

The coronary arteries are partially protected from embolic occlusion by the acute angulation of the coronary ostia relative to aortic outflow and by protection from the aortic valve leaflets during systole. Coronary embolization may be iatrogenically induced during catheter-based interventions (transcatheter aortic valve replacement, coronary angiography) or during cardiac surgery (dislodged thrombus, vegetation, calcium, fat, or

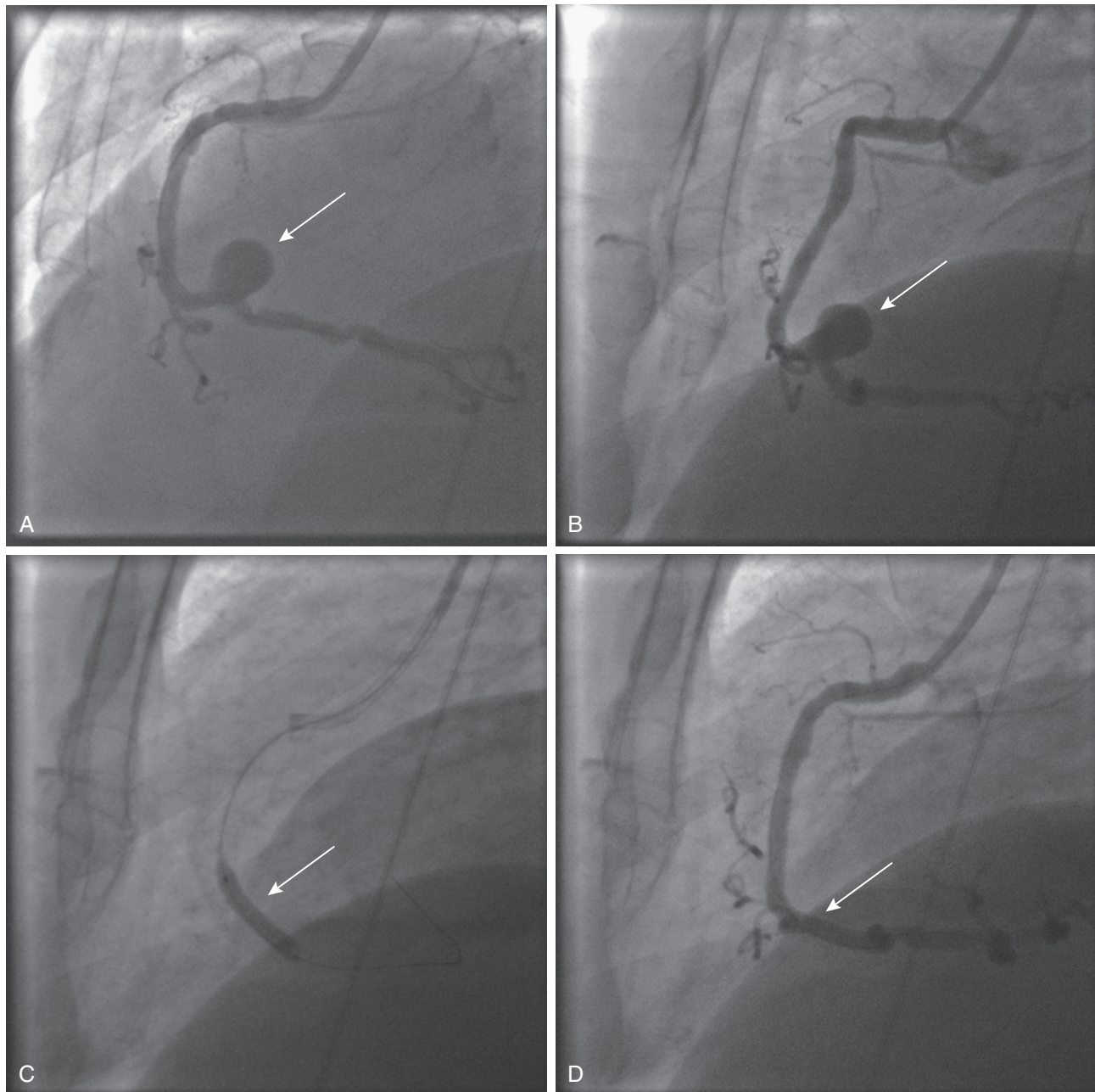


FIGURE 94-5 ■ Right coronary artery pseudoaneurysm (arrow) in (A) the right anterior oblique projection and (B) the left lateral projection. (C) Deployment of a balloon-expandable, covered stent with (D) aneurysm exclusion.

adhesive/hemostatic compounds). Noniatrogenic causes of coronary embolization include intracardiac or valvular thrombus, tumor, vegetation secondary to endocarditis, or paradoxical emboli in the presence of right-to-left shunting. The clinical consequences of coronary embolization are based on size and location. Most commonly, the left anterior descending coronary artery is affected.³⁵ Larger emboli may result in significant myocardial ischemia and require intervention. Coronary angiography will often demonstrate an abrupt cut-off point to contrast flow. Percutaneous attempts to restore flow are the mainstay of therapy during diagnostic angiography with bypass surgery or embolectomy reserved for patients in whom percutaneous attempts are unsuccessful with ongoing significant ischemia. For patients who have coronary embolization during surgery, which is identified in the operating room, attempts at clearance via administration of retrograde flushing via the coronary sinus, embolectomy, or bypass graft may be attempted to relieve ischemia.

Coronary Artery Dissection

Coronary artery dissection is defined as separation of the media of the coronary artery with or without an intimal tear. The resulting hemorrhage in the coronary arterial wall can result in luminal narrowing and subsequent ischemia. A dissection is termed *primary* when it occurs spontaneously, or *secondary* when it is caused by an aortic dissection, trauma, or iatrogenic intervention.³⁶ The dissection can be graded into types A through F based on a National Heart, Lung and Blood Institute classification system.³⁷ Type A includes radiolucent areas within the coronary artery during contrast injection, which do not persist after the clearance of dye. Type B dissections appear as a double lumen separated by a radiolucent area, which resolves after clearance of dye. Type C appears as contrast outside of the coronary lumen, with persistence after dye clearance. Type D appears as a spiral lesion with persistence of contrast dye. Type E appears as persistent filling defects, and type F appears as total vessel occlusion without antegrade flow.

Spontaneous Coronary Artery Dissection

The reported incidence of spontaneous coronary artery dissection varies widely from 0.2% to 1.1% in patients undergoing coronary angiography.^{36,38} The mean age at presentation ranges from 30 to 45 years old, with greater than two thirds of patients being women. Notably, approximately one third of female patients will present in the peripartum period. The left anterior descending coronary artery is most frequently dissected in women, and the right coronary artery in men.³⁹ The underlying etiology may be related to atherosclerosis, peripartum vascular changes, connective tissue disorders, or vasculitis. The diagnosis is most commonly made with conventional coronary angiography with or without the use of intravascular ultrasonography or optical coherence tomography, although computed tomographic angiography is becoming more widely used for diagnosis and follow-up.⁴⁰ Although no specific guidelines exist for the management of spontaneous coronary artery dissection,

medical management (e.g., antithrombotic therapy, anti-ischemic therapy with beta blockers and nitrates), percutaneous coronary intervention, and coronary artery bypass grafting have all been used. In hemodynamically stable patients with no evidence of ongoing ischemia, medical management may be considered.³⁶ In patients with ischemia, the decision to perform percutaneous intervention versus coronary artery bypass grafting should be based on anatomy. Single-vessel dissections may be managed with stenting, if possible. Left main coronary artery and multivessel dissections, as well as failed percutaneous intervention cases, should be managed with conventional coronary artery bypass grafting.^{36,38}

Coronary Artery Trauma

Blunt Trauma

Coronary injury secondary to blunt trauma is rare, accounting for less than 2% of injuries in patients presenting after blunt chest injury.⁴¹ The mechanism of injury may be secondary to aortic dissection with retrograde involvement of the coronary ostia, proximal coronary avulsion (partial or complete) from the aortic root, or intimal injury with resulting coronary dissection or thrombosis. The left anterior descending and right coronary arteries are the most commonly injured. Clinical manifestations are generally immediate with resulting hemodynamic compromise from myocardial ischemia or tamponade, but some injuries may result in delayed thrombosis with late presentation. In clinically unstable patients with bleeding, immediate exploration is warranted with concomitant coronary artery bypass if the injury is proximal, whereas in patients without bleeding, coronary angiography with intervention may be done.^{42,43}

Penetrating Trauma

Owing to their anatomic location, the left anterior descending and right coronary arteries are the most commonly injured after penetrating chest trauma. The immediate clinical manifestation is generally pericardial tamponade. Penetrating injury with hemodynamic compromise or evidence of pericardial fluid will mandate operative exploration. Small coronary artery branches and the distal third of large epicardial coronary arteries may be ligated without inducing significant ventricular dysfunction, but postoperative arrhythmias may occur as a result of focal infarction. For more proximal coronary arterial injuries, intracoronary shunts may be used to gain temporary control of bleeding. Because many penetrating injuries are anterior, off-pump coronary artery bypass techniques with limited heparinization may be done to primarily repair, vein-patch repair, or perform bypass grafting. Standard on-pump techniques can be used as well if exposure is poor or ventricular function is compromised.^{42,43}

Iatrogenic Coronary Artery Trauma

Coronary artery dissection or thrombosis is exceedingly rare after coronary angiography, with rates of less than

0.01%.⁴⁴ These complications can often be managed percutaneously with intracoronary stenting but may require emergent coronary artery bypass grafting if there is resulting ischemia. During cardiac surgery, coronary injuries such as dissection may occur secondary to coronary intubation with handheld cardioplegia cannulae, or use of intracoronary probes. Inadvertent coronary ligation secondary to misplaced sutures during repair of ventricular injuries can occur. Often these injuries will manifest as ventricular dysfunction during separation from cardiopulmonary bypass and necessitate distal bypass grafting.

PROGRESSIVE NONATHEROSCLEROTIC CORONARY OCCLUSIVE DISEASE

Coronary Artery Vasculitis

Polyarteritis Nodosa

Polyarteritis nodosa is a systemic necrotizing vasculitis affecting medium and small arteries. The overall incidence of polyarteritis nodosa is low, with estimates between 0.4 and 2 per million per year.⁴⁵ The vasculitis most commonly affects the kidneys, gastrointestinal tract, skin, joints, and muscles, with symptomatic coronary involvement reported less frequently. The average age of symptom onset ranges from 30 to 50 years, with a predominance in males. Coronary involvement can result in premature atherosclerosis, coronary aneurysm, dissection, or thrombosis.⁴⁶ Medical management of the vasculitis centers on immunosuppression with glucocorticoids and antiplatelet therapy with aspirin. For patients in whom coronary complications develop, the role of surgery versus percutaneous coronary intervention remains to be defined. Most reports indicate that patients are treated with percutaneous intervention initially, with surgery as an option if the former fails. Coronary artery bypass grafting in this patient population is complicated by immunosuppression and concerns with healing, operating during active inflammation, and selection of an appropriate conduit, given concerns of internal mammary artery involvement in some cases of polyarteritis nodosa.^{47,48} Given the generally young age at presentation, some clinicians recommend preoperative imaging of the internal mammary arteries and subsequent use as a conduit if suitable, but they favor avoiding the radial artery as a conduit because of the risk of disease involvement.⁴⁷

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an immune-mediated inflammatory disease with primarily musculoskeletal and mucocutaneous inflammation and predominance in females. When matched against controls with similar risk factors for coronary artery disease, patients with SLE have a threefold higher risk of subclinical coronary artery disease and present at earlier ages, which may be attributable to chronic inflammation, a prothrombotic state, or chronic use of corticosteroids.⁴⁹ When myocardial ischemia is suspected, coronary angiography should be undertaken, with indications for

percutaneous intervention versus coronary artery bypass grafting remaining the same as for patients without SLE. If coronary artery bypass grafting is planned, perioperative consideration of concomitant valvular disease and hypercoagulability should be made. Valvular heart disease is the most common cardiac abnormality seen in patients with SLE, with an incidence of 13% to 100% found in autopsy studies, and is a leading cause of morbidity.⁵⁰ Left-sided valve involvement predominates, and all patients should undergo preoperative echocardiography before revascularization to aid in surgical planning.⁴⁹ Limited case series have reported on the success of coronary artery bypass grafting in patients with SLE and have noted no inflammatory involvement of the left internal mammary artery on pathology specimens, suggesting its suitability for conduit use.^{51,52}

Wegener Granulomatosis

Wegener granulomatosis is a necrotizing vasculitis affecting medium and small vessels, most commonly in the respiratory tract and kidneys. Coronary involvement most commonly manifests as arteritis,⁵³ but clinically significant coronary arterial involvement is extremely rare.⁵⁴

Takayasu Disease

Takayasu arteritis is predominantly a disease found in young Asian women between 10 and 50 years of age and in which the vasculitis affects the aorta and its major branches. The incidence of coronary arterial involvement complicating the arteritis has been reported to be approximately 10%.⁵⁵ Proximal coronary arterial involvement is common, increasing the risk for severe myocardial ischemia.⁵⁶ Reports of percutaneous management of coronary arterial disease have met with limited long-term success,⁵⁷ but use of drug-eluting stents may provide some increase in long-term patency.⁵⁸ Given the limited data on long-term patency rates with percutaneous intervention, and the incidence of left main coronary arterial involvement, coronary artery bypass grafting is often considered a potential initial treatment option. Undertaking coronary artery bypass grafting is complicated by the chronic inflammation of the entire aortic wall, which can lead to morbidity from manipulation, clamping, and creation of proximal anastomoses, as well as subclavian arterial involvement, which can limit usability of the internal mammary arteries.⁵⁹ Successful series have reported using an off-pump technique limiting aortic manipulation and using other arterial conduits such as the gastroepiploic artery.⁵⁹ If the clinical situation allows, surgery should be delayed until inflammation can be controlled with immunosuppressive agents by following serological inflammatory markers. Postoperatively, patients require close long-term follow-up because of the risk of anastomotic aneurysm formation.⁶⁰

Mucocutaneous Lymph Node Syndrome (Kawasaki Disease)

Initially described in 1967, mucocutaneous lymph node syndrome, otherwise known as Kawasaki disease, is a

systemic vasculitis most commonly seen in children that can lead to coronary artery aneurysm formation (Fig. 94-6), thrombosis, or stenosis from scarring. In Japan, the incidence is as high as 175 per 100,000, whereas in the United States, the incidence is 19 per 100,000.⁶¹ Although aneurysms may form in as much as 20% of patients, surgery is relatively uncommon because aneurysms may regress over time.⁶² In Japan, coronary artery bypass grafting is performed in 0.3% to 0.5% of patients diagnosed with Kawasaki disease.^{63,64} The left main coronary artery is the most frequently involved, followed by the left anterior descending artery, the right coronary artery, and the left circumflex artery.⁶⁵ Aneurysm formation may occur within the 6 to 8 weeks after onset of symptoms,

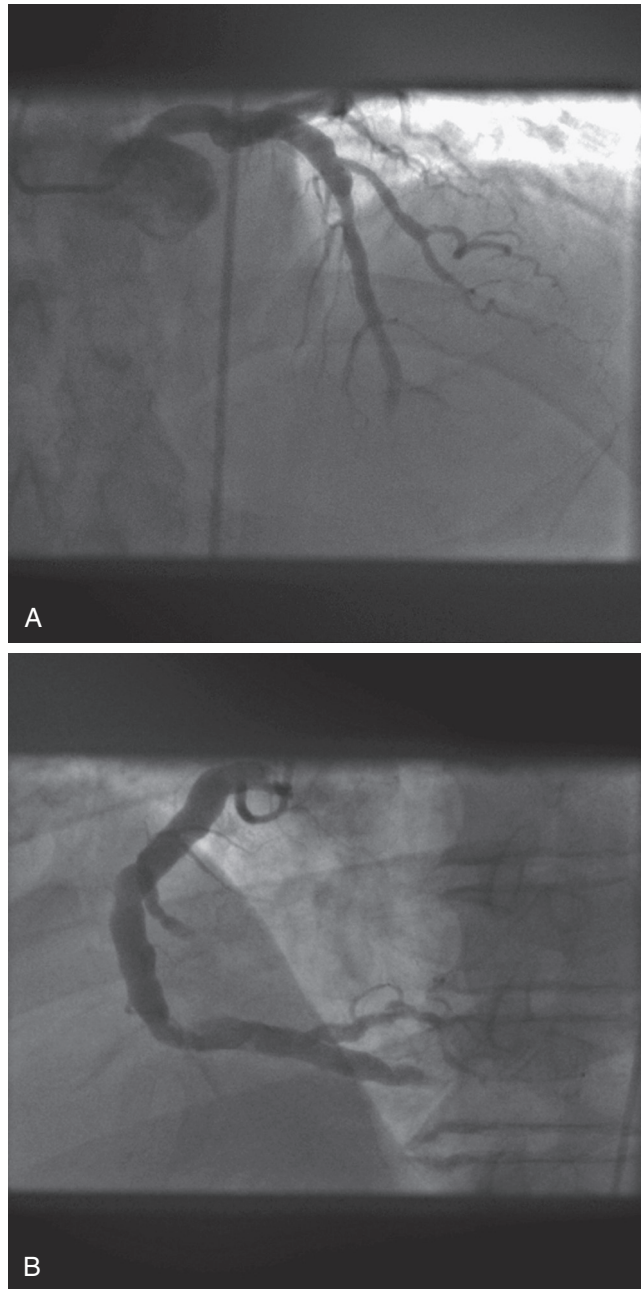


FIGURE 94-6 ■ Coronary dilation in Kawasaki disease seen in (A) the left coronary system and (B) the right coronary system.

and as much as 50% of cases will resolve within 5 years with appropriate medical management, with less than 5% progressing to chronic obstructive coronary artery disease.⁶¹ When intervention is required for ischemia or large aneurysm size, coronary artery bypass grafting is favored over percutaneous coronary intervention because of the long-term patency issues with percutaneous intervention,⁶⁶ and the use of internal mammary artery grafts are favored because of their long-term patency.⁶³

Intimal Proliferation and Fibrosis

Fibrous hyperplasia of the coronary arteries is extremely rare, with only limited case reports published. Disease is most often limited to the intima. Although there is a predominance in females, the etiology remains unknown but is thought to be secondary to genetic, hormonal, or mechanical factors. Fibrous hyperplasia of the coronary arteries can result in sudden death thought to be secondary to arrhythmia.⁶⁷

Ionizing Radiation

Thoracic irradiation is commonly used for the treatment of Hodgkin disease, breast cancer, and certain lung cancers. Patients with a history of thoracic irradiation are at higher risk for the development of atherosclerotic and nonatherosclerotic coronary stenosis secondary to endothelial injury at the time of treatment, and subsequent development of plaques, which may be limited to the intima and independent of cholesterol deposition.^{68,69}

These patients may present at younger ages, often in the second and third decade after treatment. Indications for revascularization in this patient subset are the same as for other patients with obstructive coronary artery disease, but several considerations should be made before percutaneous intervention or coronary artery bypass grafting is considered. Although data are limited for drug-eluting stents, bare metal stenting and balloon angioplasty have been associated with significantly higher rates of restenosis relative to patients without a history of irradiation.⁷⁰ If surgery is planned, consideration should be given to radiation-induced damage to the skin, which may impair healing; mediastinal fibrosis, which may add difficulty to sternal entry; concomitant pericardial disease, which may add difficulty in identifying epicardial coronary arterial targets; and radiation injury to the internal mammary artery, which may preclude its use as a conduit.⁶⁹

Cardiac Transplantation

Cardiac allograft coronary disease secondary to vasculopathy is the leading cause of late mortality in transplant recipients, with greater than 40% of recipients demonstrating coronary disease 8 years after transplantation.⁷¹ Angina is absent secondary to denervation during implantation; therefore, screening is essential for detection. Current screening protocols use coronary angiography with intravascular ultrasonography to establish diagnosis.⁷² The vasculopathy often results in diffuse disease limiting the role for intervention, but in selected cases percutaneous coronary intervention and coronary artery

bypass grafting have been used successfully, but survival benefits remain to be proven.⁷³ Retransplantation remains the only definitive treatment for chronic allograft vasculopathy.⁷²

Extrinsic Coronary Artery Compression

Compression of the epicardial coronary arteries from adjacent structures, tumor, or abscess may result in myocardial ischemia. The most common adjacent structures to cause extrinsic compression are the pulmonary artery in the setting of pulmonary hypertension, and aortic root/sinus of Valsalva aneurysms. Symptoms will most commonly be angina-related. Contrast-enhanced computed tomography of the chest can raise the clinical suspicion of extrinsic coronary artery compression, but coronary catheterization with intravascular ultrasonography has been advocated as the gold standard for diagnosis.⁷⁴ Aneurysm repair and abscess drainage are indicated in the setting of aneurysms and infection, respectively, whereas in the setting of coronary compression secondary to pulmonary arterial hypertension, management options include coronary stenting or bypass grafting.

SUBSTANCE ABUSE

Chest pain has been reported in as much as 40% of patients who present to the emergency department after cocaine use.⁷⁵ A small subset of these patients, ranging from 0.7% to 6%, will have myocardial ischemia and/or infarction.^{76,77} The etiology of the ischemia is multifactorial, secondary to increases in myocardial oxygen demand, vasoconstriction, and increased propensity for thrombosis.⁷⁸ Beyond the acute complications of cocaine use, studies suggest that cocaine users do not have an increased propensity of angiographically significant coronary artery disease when adjustments are made for other atherosclerotic risk factors.⁷⁹

Initial treatment of patients with suspected cocaine-induced ischemia should be similar to all patients with myocardial ischemia. For patients undergoing percutaneous coronary intervention, consideration should be given to the use of bare metal stents over drug-eluting stents secondary to concerns over compliance with antiplatelet agents.⁷⁸ Although there are no specific guidelines for surgical management of cocaine-associated and/or -induced myocardial infarction, coronary artery bypass grafting should be considered in cases of multivessel disease, coronary dissection, or coronary thrombosis not amenable to treatment with percutaneous intervention.

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PART I

SURGICAL MANAGEMENT OF HEART FAILURE

PART OUTLINE

- | | | | |
|-----------|--|------------|---|
| 95 | PERICARDIUM AND CONSTRICTIVE PERICARDITIS | 100 | LEFT VENTRICULAR RESTORATION: SURGICAL TREATMENT OF THE FAILING HEART |
| 96 | SURGICAL MANAGEMENT OF HYPERTROPHIC CARDIOMYOPATHY | 101 | REGENERATIVE CELL-BASED THERAPY FOR THE TREATMENT OF CARDIAC DISEASE |
| 97 | LEFT VENTRICULAR ASSIST DEVICES AND TOTAL ARTIFICIAL HEART | 102 | SURGERY FOR PULMONARY EMBOLISM |
| 98 | HEART TRANSPLANTATION | 103 | TUMORS OF THE HEART |
| 99 | HEART-LUNG TRANSPLANTATION | | |

PERICARDIUM AND CONSTRICTIVE PERICARDITIS

Donald D. Glower

CHAPTER OUTLINE

THE PERICARDIUM

History

Anatomy

Normal Physiology

Pathophysiology

Pericardial Effusion

Cardiac Tamponade

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THE PERICARDIUM

History

The earliest descriptions of the pericardium date back to Hippocrates (460 to 377 BC).¹ Galen (AD 129 to 210) described the protective function of the pericardium and also reported a pericardial effusion in animals. Avenzoar (1091 to 1162) described pericarditis,² and Vesalius (1514 to 1564) carefully documented the anatomy of the pericardium. Jean Riolan (1649) suggested treating pericarditis with trephination of the sternum, and a case of hemopericardium was reported by William Harvey

(1649). The conditions of cardiac tamponade and constrictive pericarditis were described by Richard Lower (1669), John Mayow (1674), and Morgagni (1756). The pathophysiology of constrictive pericarditis was further clarified by Cheevers in 1842.

Kussmaul (1873) noted the association between constrictive pericarditis and decreased intensity of the peripheral pulse (now termed *pulsus paradoxus*). Kussmaul also described inspiratory jugular venous distention, now termed *Kussmaul sign* (as opposed to *normal inspiratory jugular venous collapse*). Pick (1896) reported three patients with constrictive pericarditis and hepatic cirrhosis (a condition now known as *Pick cirrhosis*).

The first successful pericardiotomy was performed by Romero in 1819, and the first pericardiocentesis was performed by Franz Schuh in 1840. Pericardial resection for constrictive pericarditis was proposed by Weill (1895) and Delorme (1898), with pericardiectomy ultimately performed by Rehn (1913) and Sauerbruch (1925). Early surgical treatment of constrictive pericarditis in the United States was reported by Beck (1930), Churchill (1936), and Blalock (1937). Radical pericardiectomy, including excision of thickened epicardium when necessary, was advocated by Holman (1955).

Anatomy

The pericardium is a fibrous sac surrounding the heart and mediastinal great vessels. The outer wall of the pericardial sac consists of an outer fibrosa and an inner serosa.³ Histologically, the fibrosa is fibro-collagenous tissue with elastic fibers oriented along the lines of stress, and the pericardial serosa is composed of mesothelial cells with microvilli and an underlying basal lamina.³

This outer pericardial sac folds onto the heart and great vessels, where the epicardium and outer adventitial layer of the heart and great vessels constitute the visceral lining of the pericardial sac. Laterally, the pericardium forms the medial walls of the pleural spaces. Inferiorly, the pericardium is the superior surface of the central tendon of the diaphragm, and, superiorly, the pericardium blends with the deep cervical fascia. Anteriorly, the pericardium is loosely joined to the xiphoid process and the sternal manubrium by ligamentous structures. Posteriorly and superiorly, the pericardium envelops the great vessels, the venae cavae, and the pulmonary veins. The posterior pericardial space has two developmental

recesses: the transverse sinus separating the great vessels from the pulmonary veins and the oblique sinus separating the left and right pulmonary veins (Fig. 95-1).³

The arterial blood supply and venous drainage of the pericardium come from the pericardiophrenic branches of the internal mammary vessels bilaterally. The lymphatic drainage of the visceral pericardium is the tracheal and bronchial lymph chain, and the parietal pericardium shares lymphatic drainage with the sternum, diaphragm, and mid mediastinum. The pericardium is innervated from the phrenic nerves, with some vagal innervation via the esophageal plexus.³

The pericardium normally contains 15 to 35 mL of serous fluid. Pericardial fluid is a transudate containing less protein but more albumin than serum; therefore, pericardial fluid has a lower osmolality than does plasma.³

Normal Physiology

The pericardium and pericardial fluid minimize friction and energy loss during cardiac motion. While doing so, the normal pericardium and its external attachments maintain cardiac position within the mediastinum in the presence of gravitational or other forces that could impair cardiac filling or function. The pericardium also serves as a barrier, protecting the heart from inflammation or malignancy in adjacent structures.

The normal pericardium has mechanoreceptors connected to phrenic nerve and vagal nerve afferents, which (with stimulation) lower blood pressure, slow heart rate, and contract the spleen in dogs. Pericardial fluid contains prostacyclin, which can affect coronary artery vasomotor tone, and it has fibrinolytic properties that can lyse intra-pericardial clot.

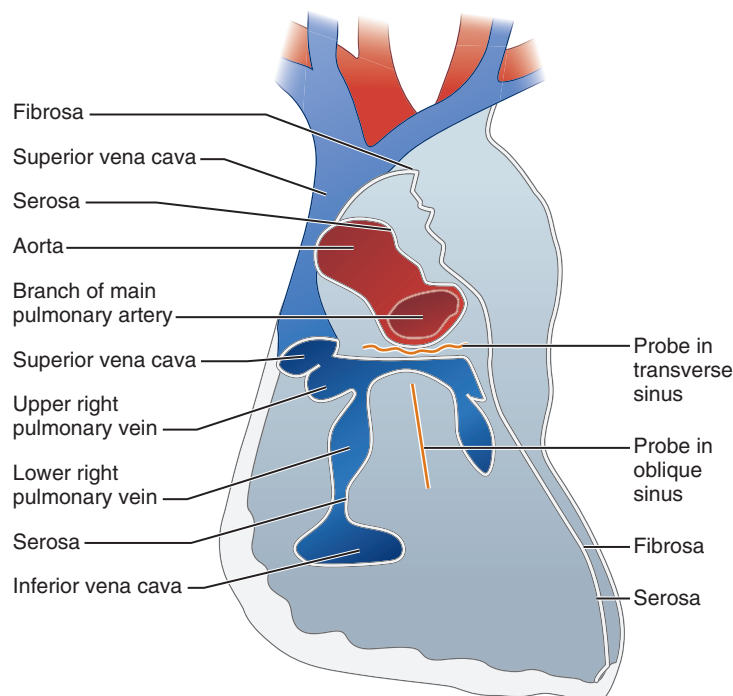


FIGURE 95-1 ■ Anatomy of the posterior pericardial reflections. Note the transverse sinus and the oblique sinus. (From Spodick DH: *The pericardium*, New York, 1997, Marcel Dekker.)

At rest, the normal pericardium probably has little restraining effect on cardiac systolic or diastolic function.⁴ However, under conditions of acute cardiac dilation, the normal pericardium probably increases diastolic stiffness and limits diastolic filling of the left and right ventricles.⁵ Under normal conditions, relatively little interaction between the left and right ventricles is mediated by the pericardium.⁶

Normal pericardial pressure at end expiration is -2 mm Hg. Like pleural pressure, pericardial pressure decreases during inspiration and increases during expiration. As a result, inspiration normally decreases left ventricular stroke volume and decreases aortic blood pressure by less than 10 mm Hg. The mechanisms for these effects do not require an intact pericardium and are similar to the mechanisms of pulsus paradoxus (see later).

Pathophysiology

Pericardial Effusion

Pericardial effusion (>50 to 100 mL) is the simple result of more fluid transuding into the pericardial space than is resorbed. Pericardial effusions requiring drainage typically contain 500 to 700 mL of fluid. Eventually, pericardial pressure rises high enough that resorption matches fluid production. Sustained increases in pericardial pressure over time cause the pericardial sac to stretch (because of material plasticity, or creep) with slippage of pericardial collagen fibers and pericardial thinning. Causes of increased pericardial fluid production include inflammation or infection of the pericardium. Decreased pericardial fluid resorption can result from venous hypertension or lymphatic obstruction. If pericardial effusion increases pericardial pressure sufficiently, cardiac tamponade and pulsus paradoxus can result (see later).

Cardiac Tamponade

Cardiac tamponade has been defined as hemodynamically significant cardiac compression from accumulating pericardial contents that evoke and defeat compensatory mechanisms.³ Cardiac tamponade can result from pericardial fluid, pus, blood, air, or tumor. In a normal pericardium, approximately 200 mL of acute pericardial fluid accumulation can produce tamponade, but larger volumes may be required in chronically enlarged pericardial sacs.

The initial effect of cardiac tamponade is decreased venous return to the right heart resulting from a direct pressure effect and from effectively decreased right atrial and right ventricular diastolic compliance. Decreased right ventricular filling decreases stroke volume and thus cardiac output. Pulmonary venous return to the left heart is decreased by increased left atrial pressure and by decreased right ventricular output. Central venous pressures of 14 to 30 mm Hg are typically associated with cardiac tamponade in euolemic individuals, and lower venous pressures can occur with cardiac tamponade if hypovolemia is also present.

Left ventricular diastolic compliance and diastolic filling are also impaired by cardiac tamponade. Increased

BOX 95-1 Diagnostic Signs of Cardiac Tamponade

PHYSICAL EXAMINATION

- Pulsus paradoxus

PULMONARY ARTERY CATHETER FINDINGS

- Central venous pressure > 14 mm Hg
- Near equalization of central venous, pulmonary artery, and capillary wedge pressures in diastole
- Decreased cardiac output

ECHOCARDIOGRAPHY

- Right atrial compression
- Right ventricular diastolic collapse
- Inferior vena caval dilation
- Inspiratory shift of interventricular septum leftward
- Inspiratory flow velocities: $\uparrow$ tricuspid and pulmonic, $\downarrow$ mitral and aortic

diastolic right ventricular pressure relative to left ventricular diastolic pressure can shift the interventricular septum leftward, thus decreasing preload of the interventricular septum and effectively decreasing left ventricular contractility. By combining these mechanisms, inspiration with cardiac tamponade can decrease systolic blood pressure by greater than 10 mm Hg (see [Pulsus Paradoxus](#), next). Eventually, arterial hypotension and increased intrapericardial pressure can decrease coronary perfusion sufficiently to decrease cardiac contractility caused by global cardiac ischemia.

Diagnostic signs of cardiac tamponade are listed in [Box 95-1](#).

Pulsus Paradoxus

Cardiac tamponade is associated with pulsus paradoxus, which is defined as a fall in systolic blood pressure of greater than 10 mm Hg with inspiration. Pulsus paradoxus is thus an exaggeration of the normal inspiratory decrease in systolic blood pressure because of the same mechanisms (see [Normal Physiology](#), earlier). Although pulsus paradoxus is characteristic of cardiac tamponade, pulsus paradoxus can also be seen in chronic obstructive pulmonary disease, pulmonary embolism, obesity, right heart failure, and ascites, where it occurs by the same mechanisms.⁶ Pulsus paradoxus may be absent in cardiac tamponade with severe left ventricular dysfunction, atrial septal defect, severe aortic regurgitation, or positive pressure breathing.³ Proposed mechanisms of pulsus paradoxus include the following:

- Pooling of blood in the lungs during inspiration
- Increased right ventricular filling during inspiration resulting from lower right ventricular pressure (in turn, right ventricular distention may shift the interventricular septum leftward, thus decreasing septal muscle preload and decreasing left ventricular stroke volume)⁷
- Increased left ventricular afterload (aortic pressure minus pericardial pressure), which decreases left ventricular stroke work⁸

Constrictive Pericarditis

Constrictive pericarditis results when the volume of the pericardial sac itself is sufficiently reduced relative to cardiac volume that cardiac filling is impaired. In constrictive pericarditis, pericardial fluid is generally absent or of normal volume. The wall of the pericardial sac is usually thickened in constrictive pericarditis and may be 3 to 20 mm thick, as opposed to the 1- to 2-mm thickness of normal pericardium (Box 95-2).

Unlike cardiac tamponade, constrictive pericarditis impairs cardiac filling only in late diastole. Thus, early diastolic filling of the right ventricle occurs briefly in constrictive pericarditis until the ventricle suddenly reaches the rigid constraint of the pericardium. The result is the pathognomonic “square root” sign in the right and left ventricular diastolic filling pressure waveforms (Fig. 95-2).

Similarly, in constrictive pericarditis, the central venous pressure tracing has a prominent *y* descent that corresponds to the initial dip of the square root sign of the right and left ventricular tracings. This *y* descent normally results from “diastolic collapse” of the normal venous pressure as rapid atrial filling occurs, and the *y* descent is exaggerated by constrictive pericarditis. Constrictive pericarditis impairs reservoir function and contractile function of the left atrium.⁹ Constrictive pericarditis also selectively impairs contractile function in the left and right ventricular free walls relative to that of the interventricular septum on magnetic resonance imaging.¹⁰

Constrictive pericarditis is associated with inspiratory jugular venous distention (Kussmaul sign; see Fig. 95-2), which is less frequent in cardiac tamponade. Kussmaul sign can also occur in right ventricular failure, restrictive cardiomyopathy, cor pulmonale, and acute pulmonary embolism.

BOX 95-2 Diagnostic Signs of Constrictive Pericarditis

PHYSICAL EXAMINATION

- Kussmaul sign

PULMONARY ARTERY CATHETER FINDINGS

- Central venous pressure > 14 mm Hg
- Near equalization of central venous, pulmonary artery, and capillary wedge pressures in diastole
- Decreased cardiac output
- Square root sign in right and left ventricular pressure tracings
- Prominent *y* descent in central venous pressure tracing

ECHOCARDIOGRAPHY, COMPUTED TOMOGRAPHY, OR MAGNETIC RESONANCE IMAGING

- Impaired right and left ventricular free wall strains relative to septal strain
- Pericardial thickening
- Right ventricular diastolic collapse
- Minimal pericardial fluid

Chronic elevation of venous pressures in constrictive pericarditis can result in hepatic congestion, cardiac cirrhosis, protein-losing enteropathy, and nephrotic syndrome. Chronically, constrictive pericarditis alters the neurohormonal axis with elevations of serum norepinephrine, renin, aldosterone, cortisol, growth hormone, and atrial natriuretic peptide.¹¹

The differential diagnosis of constrictive pericarditis consists primarily of restrictive cardiomyopathy, which can occur simultaneously with constrictive pericarditis.^{5,12} Characteristic histology on myocardial biopsy, pulmonary capillary wedge pressure greater than 5 mm Hg greater than central venous pressure, slower early diastolic filling, and impaired left ventricular systolic function all favor restrictive cardiomyopathy over constrictive pericarditis. Acute volume loading of 500 mL during right heart catheterization accentuates the right-sided pressure findings of constrictive pericarditis and produces smaller changes in restrictive cardiomyopathy.

Diagnosis of Pericardial Disease

History and Symptoms

The presenting symptoms of pericardial disease can include fever, malaise, chest discomfort, shortness of breath, pedal edema, and abdominal distention. Medical history may reveal prior chest trauma, chest irradiation, or exposure to infectious agents such as *Mycobacterium tuberculosis*. The time course of pericardial disease is described as *acute* (<3 months), *chronic* (>3 months), or *recurrent*.⁵

Physical Examination

Physical examination of the patient with pericardial disease may reveal findings of fever, tachycardia, or tachypnea. The peripheral arterial pulse may paradoxically diminish during inspiration (pulsus paradoxus). Inspiratory jugular venous distention may be present (Kussmaul sign). Chest examination may show dullness at the lung bases, muffled cardiac sounds, and a pericardial rub or pericardial knock. A prominent S₃ gallop may be present in constrictive pericarditis. Abdominal examination may demonstrate hepatomegaly or ascites, and pedal edema may be present. The extremities may be cool and constricted in tamponade.

Chest Radiograph

The chest radiograph may show cardiomegaly in pericardial effusion. Pericardial calcification can accompany constrictive pericarditis. Pleural effusion may be present in pericardial effusion, pericardial tamponade, and constrictive pericarditis. Chest radiography may also demonstrate pneumopericardium or mediastinal mass resulting from pericardial cyst.

Electrocardiogram

Pericardial disease can be associated with atrial fibrillation, and the electrocardiogram (ECG) may show

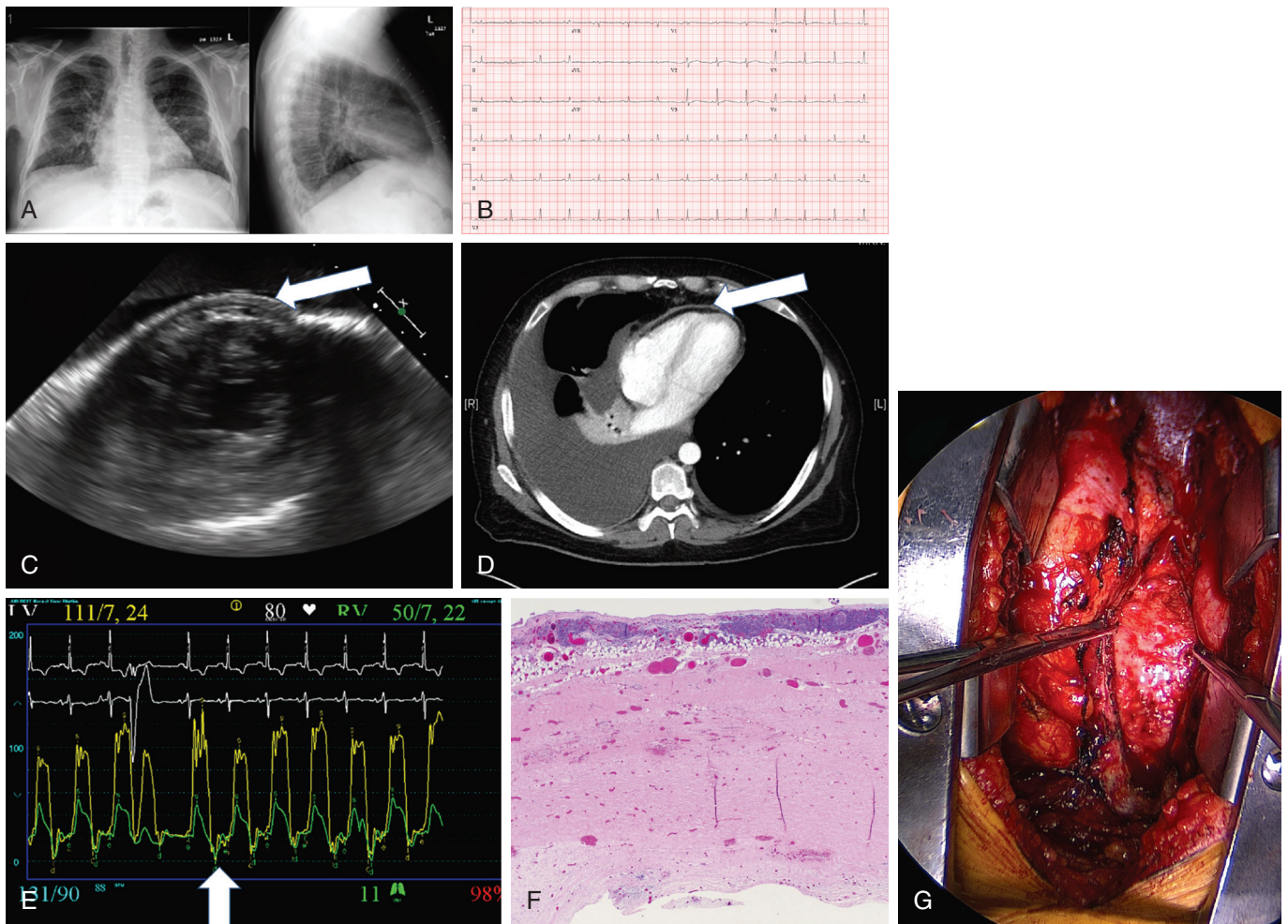


FIGURE 95-2 ■ This patient has constrictive pericarditis. **A**, Chest radiograph with cardiomegaly. **B**, Electrocardiogram with low voltage. **C**, Echocardiogram with pericardial thickening (arrow). **D**, Computed tomographic image showing pericardial thickening (arrow). **E**, Simultaneous right ventricular (green) and left ventricular (yellow) pressure tracings with “square root sign” (arrow) and equalization of diastolic right and left ventricular pressures. **F**, Histology of resected pericardium with marked fibrous thickening and inflammation of the parietal surface (top of picture). **G**, Intraoperative finding of thickened pericardium grasped in clamps.

diminished QRS voltage (see Fig. 95-2). The four stages of ECG changes in acute pericarditis are as follows:

- Stage I—ST elevation in all leads except AVR and V₁
- Stage II—Normal ST segments, but T wave flattening
- Stage III—T wave inversion without Q waves or loss of R wave voltage
- Stage IV—Normalization of T wave

Echocardiography

Echocardiography can easily detect loculated or generalized pericardial effusion. An echo-free pericardial space of less than 10 mm is termed a *small effusion*, whereas circumferential spaces of 10 to 20 mm and greater than 20 mm are considered moderate and large pericardial effusions, respectively.^{5,13} The echocardiogram can also be used to diagnose intrapericardial masses, pericardial cysts, pericardial calcification or thickening, or associated cardiac disease. The echocardiogram can be diagnostic of

cardiac tamponade with findings of end-diastolic right atrial collapse, diastolic right ventricular collapse, and inspiratory interventricular septal shift leftward with increased tricuspid and pulmonic flow velocities and decreased mitral and aortic flow velocities, and dilation of the inferior vena cava (Fig. 95-3).^{13,14}

Computed Tomography

Computed tomography (CT) can demonstrate pericardial effusion, pericardial calcification and thickening, intrapericardial masses, and pericardial cysts (see Fig. 95-2). CT may be more sensitive than magnetic resonance imaging (MRI) in detecting calcification, but it has the disadvantages of requiring intravenous contrast injection and having more motion artifact.¹⁵

Magnetic Resonance Imaging

MRI can demonstrate pericardial effusion, pericardial thickening, intrapericardial masses, pericardial cysts, and

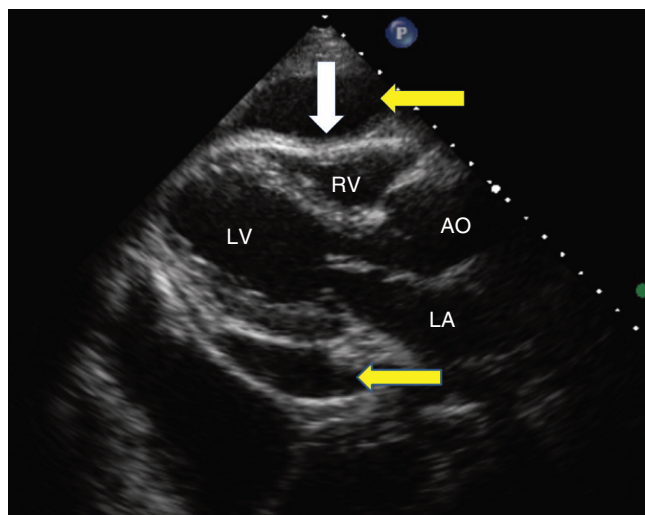


FIGURE 95-3 ■ Two-dimensional echocardiogram (parasternal long-axis view) showing pericardial effusion (yellow arrows) and cardiac tamponade with collapse of the right ventricle (RV) at end-diastole (white arrow). AO, Aorta; LA, left atrium; LV, left ventricle.

even intracardiac disease.¹⁶ Relative to CT, MRI has the advantages of not requiring intravenous contrast injection and of having less motion artifact. MRI may be less sensitive than CT for detecting pericardial calcification. Newer MRI techniques can differentiate restrictive cardiomyopathy from constrictive pericarditis using speckle tracking to compare ventricular free wall strain relative to interventricular septal strain.¹⁰ Pericardial constriction is associated with smaller right ventricular volume and reduced mean trans-tricuspid E:A wave ratios.¹⁷

Cardiac Catheterization

Cardiac fluoroscopy can demonstrate pericardial calcification or abnormally prominent swinging motion of the left ventricle over the cardiac cycle in pericardial effusion. Right heart catheterization can be diagnostic of cardiac tamponade or pericardial constriction (see earlier; see Fig. 95-2). Both tamponade and constriction show equalization and elevation of diastolic pressures in all four chambers of the heart. Physiologic tamponade or constriction with right atrial mean pressure less than 14 mm Hg is unusual. Constriction may be differentiated from tamponade or restrictive cardiomyopathy by the square root sign in the right and left ventricular tracings (see Fig. 95-2), and the findings of cardiac constriction are accentuated by acute 500-mL volume challenge (see **Constrictive Pericarditis**, earlier). Given the noninvasive alternative imaging techniques available today, cardiac catheterization may be reserved for patients where clinical and noninvasive imaging data are inconclusive.¹⁸

Pericardiocentesis

Pericardiocentesis is a means to treat cardiac tamponade rapidly, to prevent tamponade in large effusions, and to obtain pericardial fluid for diagnosis. Contraindications include aortic dissection, coagulopathy, small or loculated

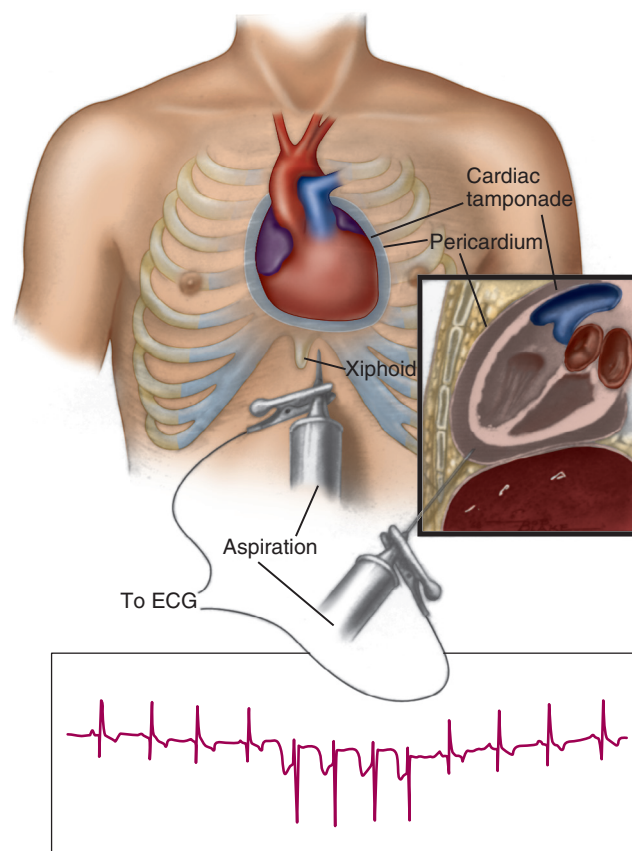


FIGURE 95-4 ■ Technique of subxiphoid pericardiocentesis with electrocardiographic monitoring. Note negative QRS deflection indicating myocardial contact. ECG, Electrocardiogram.

effusions, traumatic hemopericardium, and nonviral infectious pericarditis. Pericardiocentesis is generally performed with the patient supine and with local anesthesia. A long, pericardial needle is inserted into the patient's pericardial space left of the xiphoid, inferior to the left costal margin (Fig. 95-4). The needle is advanced toward the patient's left mid scapula while maintaining aspiration pressure on the needle. Cardiac puncture can be avoided by a combination of echocardiography and monitoring an ECG obtained by an electrode attached to the needle. The needle is withdrawn if the ECG shows sudden negative deflection of the QRS complex, indicating contact with the myocardium.

Once the pericardial space is entered, the needle can be exchanged over a wire for a blunt pericardial catheter. The blunt pericardial catheter can be left in the pericardial space for several days to decrease the rate of recurrent effusion (e.g., from 55% to 24%).¹⁹ Pericardial fluid can be sent to the laboratory for cell count and differential, cytology (possibly including tumor markers), culture (including bacterial, fungal, and mycobacterial), and biochemical examination (e.g., polymerase chain reaction for tuberculosis, pH, specific gravity, lactic dehydrogenase, protein content).³ Peripheral blood can be sent to the laboratory for leukocyte count and erythrocyte sedimentation rate, and for C-reactive protein, serum lactate dehydrogenase, and cardiac isoenzyme values.⁵

Pericardiocentesis is rapid and relatively safe, and it requires little anesthesia. Complication rates vary from 5% to 50% and are increased in smaller effusions, when echocardiographic guidance is not used, and in the presence of coagulopathy.¹⁹ Pericardiocentesis is less effective and less diagnostic in hemopericardium with clot, or in effusion with thick exudate. Most authors believe that pericardiocentesis is optimally used in patients with large anterior effusions and either with tamponade (therapeutic) or a probable infectious or tuberculous etiology (diagnostic).¹⁹ The rate of recurrent effusion and tamponade after successful pericardiocentesis is high (approximately 55%).¹⁹ The incidence of recurrent effusion or tamponade may be decreased by pericardial catheter drainage for 2 to 5 days or surgical drainage.

Pericardial Biopsy

Pericardial biopsy can be performed percutaneously with a pericardioscope or surgically (see [Pericardial Surgical Procedures](#), later).²⁰ Percutaneous pericardial biopsy is performed by dilating a pericardiocentesis needle track to accept an introducer sheath. A biptome can then be placed through the introducer using echocardiographic guidance to obtain pericardial biopsy.²¹ The value and safety of percutaneous pericardial biopsy have not been established.

Pericardial tissue can be examined to diagnose pericarditis, and together with pericardiocentesis it can demonstrate the cause of pericarditis in 30% to 50% of patients. Pericardial tissue may be sent for hematoxylin-eosin and Gram stains, polymerase chain reaction analysis for tuberculosis, and cultures for bacteria, fungus, and tuberculosis. Special stains can be used to detect certain forms of malignancy.

NONCONSTRICTIVE PERICARDITIS

Diagnosis

Using European Society of Cardiology guidelines, pericarditis has been classified as dry, effusive, effusive-constrictive, and constrictive.⁵ The diagnosis of pericarditis requires the pathologic demonstration of pericardial inflammation, scarring, or thickening. Thus certain diagnosis of pericarditis requires pericardial biopsy, generally with surgery to create a subxiphoid or transthoracic pericardial window. The diagnosis of pericarditis can, however, be strongly supported by findings of pericardial effusion or pericardial thickening on echocardiography, CT, or MRI. The diagnosis of pericardial effusion requires only an imaging study demonstrating more fluid than normal (>50 to 100 mL) in the pericardial space.

Etiology and Treatment

Pericardial effusion and pericarditis have a wide variety of causes ([Table 95-1](#)).^{5,22,23} Medical treatment for pericardial effusion should target the etiology of the effusion. Surgical treatment involves either pericardiocentesis or

TABLE 95-1 Frequency of Effusion and Constriction in Pericarditis

Etiology	Effusion (%)	Constriction (%)
Idiopathic	7-30	50-70
Viral	5-25	0
Bacterial	5-10	0-5
Tuberculous	5-10	15
Autoimmune	5-15	1
Type 2 immune or postoperative	5-25	5-60
Malignant	20-50	0
Traumatic or radiation	5-15	9-20
Metabolic or uremic	10-15	0
Surrounding structures	5	1

the creation of a subxiphoid pericardial window or a transpleural pericardial window. Pericardiocentesis or pericardial biopsy can be indicated to determine the cause of the pericarditis and thus define the medical therapy. In a hemodynamically unstable patient, pericardiocentesis is also indicated to treat pericardial tamponade acutely and to achieve hemodynamic stability. Pericardiocentesis can be as effective as pericardial window in achieving diagnosis and draining the pericardial effusion,²⁴ but pericardiocentesis is more likely than pericardial window to require recurrent treatment for recurrent pericardial symptoms.^{19,23,24}

Pericardial window is indicated in any patient with symptomatic pericardial effusion or in whom the cause cannot otherwise be defined. A subxiphoid pericardial window procedure can be performed using local anesthesia; therefore, it is preferable in patients in hemodynamically unstable condition because of tamponade but in whom pericardiocentesis is deemed impractical or unsafe. The transpleural pericardial window is preferable in patients with a good long-term prognosis because of a lower likelihood of recurrent pericardial effusion.²⁵ Pericardiectomy can improve relapse rate without significant increase in mortality for patients with chronic relapsing pericarditis.²⁶

Idiopathic Pericarditis

Idiopathic pericarditis is the diagnosis for 3% to 50% of all patients with pericardial effusion or pericarditis. Management is symptomatic, as it is for viral pericarditis. Symptoms of low-grade pain and fever can be treated with anti-inflammatory agents such as ibuprofen (300 to 800 mg every 6 to 8 hours for days to weeks) along with antiulcer agents. Colchicine 0.5 mg bid for 3 months in addition to ibuprofen or aspirin has been shown in a randomized trial to reduce symptoms, readmission, and hospitalization.^{22,27} More severe or refractory symptoms may respond to prednisone, beginning with 1 to 1.5 mg/kg per day and tapering over the 1- to 3-month course.⁵ Other causes such as infection or uremia need to be excluded before starting steroids. Intrapericardial steroids may be beneficial.³ Pericarditis can produce atrial fibrillation, which may also require treatment. Outcome from acute pericarditis is good, with the most common

complication being recurrent pericarditis.²⁷ Complete pericardiectomy can significantly improve freedom from relapse relative to medical therapy in patients failing medical therapy including steroids.²⁶

Infectious Pericarditis

At least 50% of infectious pericarditis is thought to be viral. The viruses associated with pericarditis include coxsackievirus, cytomegalovirus, echovirus, Epstein-Barr virus, varicella, parvovirus, human immunodeficiency virus, and herpes simplex.⁵ Viral pericarditis is a clinical diagnosis that is frequently made with the assistance of viral serologies. It is often accompanied by myocarditis, which can be documented on myocardial biopsy or indirectly suggested by acute deterioration of ventricular function. Like idiopathic pericarditis, it is usually self-limited. Pericardiocentesis or surgical pericardial drainage with biopsy is performed as needed for diagnosis or treatment of symptoms.

Nonviral infectious pericarditis is usually fatal if untreated, and it has a mortality of 8% to 40% in treated patients.⁵ The most common bacterial organisms causing pericarditis are *Staphylococcus*, *Streptococcus*, and gram-negative organisms in adults and *Haemophilus* or *Staphylococcus* in children. Bacterial pericarditis can occur from bacteremia or from contiguous spread from bacterial infection in the thoracic cavity. Symptoms of fever and chest pain are common. Diagnosis relies on culture or histologic examination of pericardial fluid obtained by either pericardiocentesis or open pericardial drainage.

Bacterial pericarditis requires both appropriate antibiotic treatment and either acute or chronic pericardial drainage. Bacterial pericarditis may respond to a one-time pericardial drainage, with systemic antibiotic therapy for less virulent organisms such as *Streptococcus*. Pericardiectomy may be necessary if initial drainage fails, especially in organisms such as *Haemophilus*.¹⁹ Constrictive pericarditis can develop at a rate of 5% per year after bacterial pericarditis.²² Fungal and staphylococcal pericarditis respond better to more chronic drainage of the pericardium by the subxiphoid or transthoracic approach.

Tuberculous pericarditis can appear with effusion or constriction, or both. Acute tuberculous pericarditis is best treated with intermittent pericardiocentesis. Tube drainage of tuberculous pericarditis is to be avoided to prevent chronic draining sinuses along the tube track. Pericardiectomy or open pericardial drainage (preferably after 1 week of chemotherapy) may be necessary if initial drainage fails, and pericardial constriction results in approximately half of patients with tuberculous pericarditis.²⁸ Amebic or echinococcal pericarditis can require pericardiocentesis or tube drainage depending on the thickness and degree of loculation.²⁹

Autoimmune Pericarditis

Connective tissue or inflammatory diseases such as rheumatoid arthritis, lupus, and systemic sclerosis can produce pericarditis in a minority of patients. The underlying condition should be treated if possible, and pericardiocentesis and pericardial window are reserved for

symptoms refractory to medical treatment or when needed to make a diagnosis.

Type 2 Immune and Postoperative Pericarditis

Type 2 immune pericarditis can occur 5 to 14 days after cardiac injury or operation. Only 10% of patients undergoing cardiac operation have clinically significant postoperative pericarditis, and symptoms are usually self-limited, resolving after 3 to 4 weeks. Intraoperative use of bioabsorbable films may diminish pericardial scarring without the pericardial capsule formation associated with nonabsorbable pericardial substitute material.³⁰ Treatment is similar to that given for idiopathic pericarditis.

Malignant Pericarditis

Malignant involvement of the pericardium is generally metastatic and occurs in approximately 10% to 35% of patients with noncardiac neoplasm. The most common tumors that involve the pericardium are lung (38%), breast (29%), and lymphoma (7%), with 26% being other tumors.³¹⁻³³ Primary malignancies of the pericardium are rare and include mesothelioma (50%), sarcoma, and malignant teratoma. Malignancy of the pericardium generally manifests as cardiac tamponade resulting from malignant pericardial effusion. Pericardial constriction resulting from malignancy is infrequent. Once pericardial effusion is demonstrated by an imaging study, the diagnosis of malignant pericardial effusion can be made by cytologic examination of pericardial effusion in 20% to 30% of cases. Pericardial biopsy doubles the diagnostic yield of pericardiocentesis alone. Pericardiocentesis has had some success, followed by sclerotherapy and also percutaneous balloon pericardiotomy.⁵ The longevity of patients with malignant pericarditis is sufficiently low that subxiphoid drainage and transthoracic drainage have similar success rates.³⁴ Median survival for malignant pericardial effusion requiring surgical intervention is less than 6 to 12 months.^{23,35} Rarely, good long-term results can be obtained with complete excision of localized primary tumors of the pericardium

Traumatic and Radiation-Induced Pericarditis

Only a small fraction of patients receiving mediastinal irradiation develop clinically significant pericarditis. Early pericarditis within 1 to 3 months of initiating mediastinal irradiation is generally self-limited and can be treated symptomatically, as idiopathic pericarditis is treated. Treatment with pericardiocentesis or pericardial window should be reserved for significant refractory symptoms or concern about other causes. A small number of patients may develop constrictive pericarditis, usually 5 to 20 years after irradiation.

Traumatic pericarditis along with hemopericardium and tamponade can result from cardiac intervention such as cardiac catheterization, coronary angioplasty, myocardial biopsy, and balloon valvuloplasty. Pericardiocentesis alone is usually effective if the puncture is isolated to the atria.⁵

Metabolic and Uremic Pericarditis

Metabolic causes of pericarditis include uremia, myxedema, Addison disease, diabetic ketoacidosis, and cholesterol pericarditis. Uremic pericarditis occurs in 20% of patients receiving hemodialysis and in 50% of patients with severe untreated renal disease. Patients may have chronic pericardial thickening that classically looks “shaggy.” Other dialysis patients have less pericardial thickening and significant pericardial effusions because of chronic volume overload.⁵ Therapy for uremic pericarditis is focused on treating tamponade. Intensive hemodialysis may avert tamponade in patients with uremic pericarditis, but pericardial tamponade is most effectively treated by pericardial drainage. Tamponade may respond to pericardiocentesis initially, but the incidence of recurrent tamponade in uremic pericardial effusion is highest with pericardiocentesis alone, better with subxiphoid pericardial window, and lowest with transthoracic pericardial window.¹⁹

Pericarditis from Surrounding Structures

Pericarditis can develop after acute myocardial infarction (Dressler syndrome), aortic dissection, pneumonia, pulmonary infarction, and esophageal disease. Other causes must be excluded. Treatment is focused on the underlying pathology, with care needed to prevent tamponade resulting from myocardial or aortic rupture in patients with larger effusions.⁵

Chylopericardium

Chylopericardium can be idiopathic or follow thoracic surgery. It can be treated with pericardiocentesis or, if recurrent, with subxiphoid or transthoracic pericardial window with or without low thoracic duct ligation.³

Hemopericardium

Hemopericardium can result from trauma, recent mediastinal operation, coagulopathy, cardiac perforation owing to instrumentation, cardiac rupture, or aortic rupture. Acute hemopericardium resulting in cardiac tamponade requires emergent treatment (see [Cardiac Tamponade](#), later). In the absence of cardiac tamponade, the treatment of hemopericardium depends on the underlying disease process. Hemopericardium caused by percutaneous cardiac (especially atrial) puncture in the catheterization laboratory can generally be remedied by placing a pigtail catheter in the pericardial space, reversing anticoagulation, aspirating frequently with the pigtail catheter, and watching for cessation of bleeding.

Hemopericardium caused by surgical diseases such as acute aortic dissection, cardiac or aortic rupture, or penetrating trauma is best treated by tube drainage of the pericardium after surgically correcting the source of the bleeding. Hemopericardium caused by blunt trauma or coagulopathy may require surgical drainage by either the subxiphoid or the transthoracic approach to prevent acute tamponade and late pericardial constriction.

Pneumopericardium

Pneumopericardium is a rare condition that most commonly results from severe chest trauma with associated lung injury, or from spontaneous dissection of air from a ruptured bleb in neonates on positive-pressure ventilation.³⁶ Symptoms are unusual, although tamponade occurs in 37% of patients. Treatment focuses on the underlying disease. Pericardiocentesis or pericardial tube drainage can be effective in patients with tamponade. Mortality is high (58%) because of underlying disease.

CARDIAC TAMPONADE

Etiology

A common cause of acute pericardial tamponade is hemopericardium after recent mediastinal surgery or percutaneous cardiac instrumentation. Other causes include pneumopericardium and hemopericardium resulting from coagulopathy. Approximately half of patients with chronic pericardial effusion present with cardiac tamponade. Malignant effusion and uremic pericarditis are common causes of chronic cardiac tamponade (see [Table 95-1](#)).

Diagnosis

Physical examination may show pulsus paradoxus and jugular venous distention. Cardiac tamponade can be diagnosed using right heart catheterization or echocardiography (see [Table 95-1](#)). For right heart catheterization, cardiac output is typically reduced with elevation of central venous pressure of at least 14 mm Hg, and with equalization of the central venous pressure, pulmonary artery diastolic pressure, and capillary wedge pressure. Echocardiography will show the pericardial space distended with fluid, with right atrial compression or diastolic right ventricular collapse (or both), and inspiratory interventricular septal shift leftward with increased tricuspid and pulmonic flow velocities and decreased mitral and aortic flow velocities (see [Fig. 95-3](#)).¹³ Although 80% of patients have pericardial effusions on echocardiography in the first 3 weeks after heart surgery, a moderate or large pericardial effusion has been associated with a 75% likelihood of developing tamponade.³⁷

Treatment

Cardiac tamponade resulting from hemopericardium within several days after a surgical procedure is almost always managed by returning to the operating room once coagulopathy is corrected. Back in the operating room, the hemopericardium should be evacuated (generally through the original surgical incision) and drains should be left in the pericardial space.

In the absence of a recent cardiac surgical procedure, patients with cardiac tamponade and hemodynamic compromise can usually be stabilized with emergent pericardiocentesis. Depending on the cause of the tamponade, a single pericardiocentesis may be all that is needed.

Otherwise, a pigtail catheter may be left in the pericardium for up to 48 hours, or more definitive pericardial drainage by the subxiphoid or transpleural window may be desirable.

Subxiphoid pericardial window is ideal for many patients with tamponade, because local anesthesia can be used to avoid the hemodynamic embarrassment of general anesthesia in an unstable patient. Transpleural approaches are less suitable for the unstable patient because of intolerance of one-lung anesthesia or pleural insufflation of carbon dioxide. In patients for whom transpleural pericardial window has advantages, an initial pericardiocentesis should be done to relieve tamponade before anesthetic induction for transpleural drainage. Paradoxical hemodynamic instability after relieving pericardial tamponade is associated with poor long-term survival and may be due to underlying ventricular dysfunction.³¹

CONSTRICTIVE PERICARDITIS

Etiology

The most common etiology of constrictive pericarditis in Western countries is idiopathic, with prior cardiac operation and mediastinal irradiation also being common (see [Table 95-1](#)).³⁸⁻⁴⁰ As in earlier decades in the West, tuberculosis in developing countries today is the leading cause of constrictive pericarditis.⁴¹ Pericardial closure at the time of routine cardiac operation can induce some degree of immediate pericardial constriction and decreased cardiac index,⁴² and it probably increases the small but real incidence of late constrictive pericarditis. Although routine pericardial closure at the time of cardiac operation can decrease the risk of sternal reentry, some authors have recommended avoiding pericardial closure in patients with ventricular dysfunction, risk of tamponade, or older age when there is a low likelihood of reoperation.⁴²

Diagnosis

Physical examination may show jugular venous distention and Kussmaul sign. Pericardial thickening with minimal pericardial fluid on echocardiography, CT, or MRI is present in 85% of patients.¹²⁻¹⁴ Pericardial thickening supports the diagnosis, but the pericardium might not be thickened in 15% to 18% of patients with constriction (see [Fig. 95-2](#)). Diagnosis of constrictive pericarditis requires demonstration of the right heart hemodynamics typical of constriction (see [Fig. 95-2](#)). The findings at right heart catheterization include decreased cardiac output, equalization of diastolic right-sided pressures, and the characteristic square root sign with a steep γ descent in right and left ventricular diastolic pressure tracings (see [Box 95-2](#) and [Fig. 95-2](#)). Detection of these findings can be augmented with a 500-mL volume challenge at the time of right heart catheterization.

Treatment

The treatment for pericardial constriction is pericardiectomy (see [Pericardiectomy](#), later). Patients should be

referred before onset of class IV symptoms to minimize postoperative mortality and low cardiac output.³⁸ Approximately 20% of patients with constriction have at least moderate tricuspid regurgitation, which in turn is associated with worse 5-year survival (47% vs. 87%). Significant tricuspid regurgitation in patients undergoing pericardiectomy should prompt consideration of tricuspid operation.⁴³ Rarely, the underlying cause also requires treatment, such as for tuberculous pericarditis.⁴¹ Perioperative mortality can be significantly increased with a Class B or C Child-Pugh score.⁴⁴ Long-term survival in selected patients without myocardial involvement can approach that of the general population.^{39,40,45}

PERICARDIAL CYSTS AND DIVERTICULA

Pericardial cysts and diverticula are usually congenital and occasionally inflammatory in origin, and they represent 10% to 20% of all mediastinal masses.^{46,47} Pericardial cysts and diverticula have a fibrous wall lined with mesothelium, whereas bronchial cysts have bronchial epithelium. Pericardial cysts occur more often in men than in women. Most pericardial cysts and diverticula appear as asymptomatic masses on chest radiography, and one third of patients present with chest pain. Pericardial cysts are found at the right costophrenic angle in 77%, at the left costophrenic angle in 22%, and in other areas (posterior mediastinum, hilar region, right paratracheal region, or aortic arch) in 8%.⁴⁶⁻⁴⁸ Pericardial diverticula communicate with the pericardium and comprise 20% of combined pericardial cysts and diverticula.⁴⁸ Cysts or diverticula found to have low fluid density on CT or MRI need no further workup. Masses with a density higher than that of transudate may need further workup to exclude other pericardial masses ([Fig. 95-5](#)). Cysts or diverticula that need to be removed to exclude malignancy can be approached thoroscopically or via thoracotomy. Even when malignancy is unlikely, some authors have recommended excision of most pericardial cysts to prevent complications of rupture, cardiac compression, or tracheal compression.^{47,48} Percutaneous cyst aspiration and chemical sclerosis may also be feasible and are preferable to surgery for echinococcal cysts.⁵

PERICARDIAL TUMORS

Most pericardial tumors appear with malignant pericardial effusions resulting from malignant metastases from lung, breast, or lymphoma (see [Malignant Pericarditis](#), earlier). Primary pericardial tumors include lipoma, hemangioma, lymphangioma, leiomyoma, neurofibroma, heterotopic thymus or thyroid, teratoma, mesothelioma, thymoma, liposarcoma, angiosarcoma, and synovial sarcoma. Half of all primary pericardial malignancies are mesotheliomas, with angiosarcoma being the next most common primary malignancy. The differential diagnosis includes pericardial cysts and pericardial diverticula (see earlier), which can often be distinguished with CT or MRI.³³

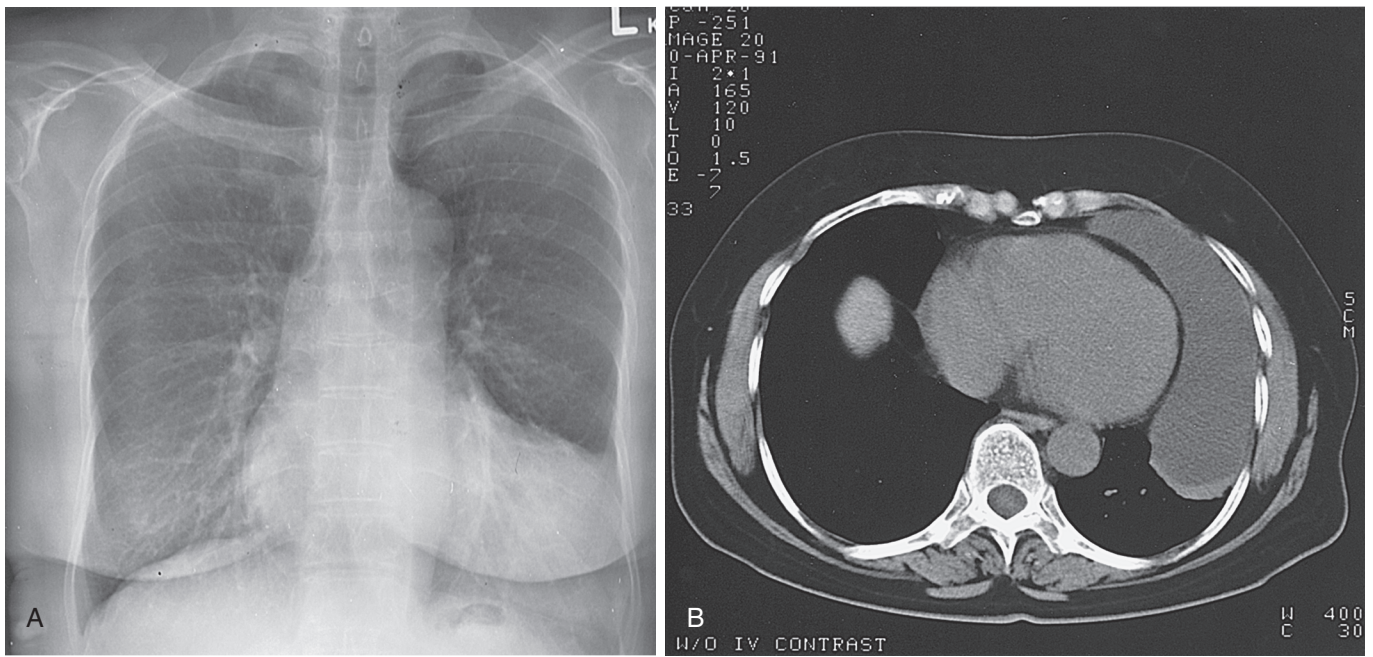


FIGURE 95-5 ■ **A**, Chest radiograph of a patient with a large left-sided pericardial cyst. **B**, Computed tomographic scan of the same patient showing the pericardial cyst extending into the left hemithorax.

Once identified, primary pericardial tumors should be removed if possible. Depending on location and size, either median sternotomy, thoracotomy, or thoracoscopy can be used to approach primary pericardial tumors. Prognosis depends on tumor type and extent. Lipomas, leiomyomas, and heterotopic tissue are generally resectable and have an excellent prognosis. Mesotheliomas almost always spread to contiguous structures in the pericardium, adjacent pleura, and occasionally mediastinal lymph nodes. Mesotheliomas are rarely resectable, and no treatment has been shown to be effective. Survival with pericardial mesothelioma may be 40% at 6 months.⁴⁶

PERICARDIAL DEFECTS

Congenital defects of the pericardium are rare, occurring in 1 in 10,000 autopsies, with a 5:1 male-to-female predominance.⁴⁷ Approximately 30% of patients with pericardial defects have associated cardiac or pulmonary anomalies. The mean age at diagnosis is 20 years. Complete absence of the pericardium is rare but generally asymptomatic.

Partial pericardial defects are left sided in 70% of cases, and they can produce symptoms by compressing the left atrial appendage, allowing cardiac herniation, or even compressing coronary arteries.⁴⁹ Partial pericardial defect can have some risk of death from cardiac herniation, coronary compression, or traumatic aortic dissection.⁵ One third of patients are asymptomatic and are detected by abnormal chest radiograph. Symptoms of partial pericardial defect include sharp, fleeting chest pain that is often positional.⁵⁰ Other symptoms include dyspnea, sweating, syncope, and circulatory collapse.

When there is complete or partial absence of the pericardium, the chest radiograph is always abnormal, with

rotation and leftward displacement of the heart placing the right heart border over the spine. CT and MRI can similarly show displacement and rotation of the heart into the left chest. The presence of a tongue of lung between the pulmonary artery and the aorta is pathognomonic for congenital absence of pericardium.⁵⁰

Complete pericardial absence requires no treatment.⁵⁰ Partial left pericardial defects not overlying the left ventricle may be observed if asymptomatic. Patients with symptoms or partial pericardial defects overlying the left ventricle should be treated surgically to prevent cardiac herniation or compression. Surgical approaches include either sternotomy or thoracoscopy to perform pericardiectomy, repair the pericardial defect with a patch, or amputate the left atrial appendage.⁴⁹

Pericardial rupture can occur as the result of blunt trauma, and it is associated with cardiac injury, cardiac rupture, and cardiac tamponade.⁵¹ Pericardial rupture should be repaired to prevent cardiac herniation, but only after associated cardiac injuries are repaired. Mortality is greater than 50%.⁵

PERICARDIAL SURGICAL PROCEDURES

Subxiphoid Pericardial Window

For patients requiring more extensive pericardial drainage than is possible through pericardiocentesis, the subxiphoid pericardial window is an excellent option that minimizes morbidity, especially in patients who are hemodynamically compromised by cardiac tamponade. The subxiphoid pericardial window provides excellent drainage of the pericardial space, allows placement of large-bore pericardial tubes, and potentially drains the right pleural space. An additional advantage is that the

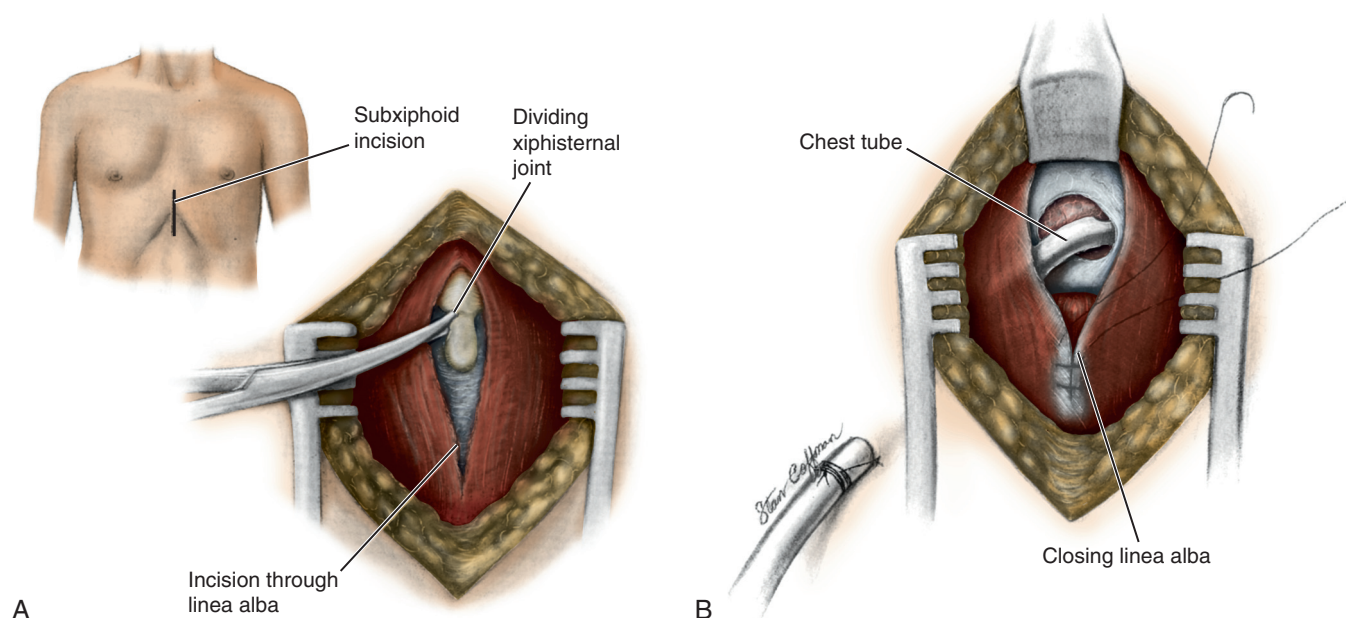


FIGURE 95-6 ■ Technique of subxiphoid pericardial window. **A**, A 7-cm subxiphoid incision is made, the linea alba is opened, and the xiphoid process is excised. **B**, A 2 × 2-cm opening is made in the pericardium, and a tube drain is placed in the pericardial space. (From Glover DD: Pericardial window. In Sabiston DC Jr, editor: *Atlas of cardiothoracic surgery*, Philadelphia, 1995, WB Saunders.)

subxiphoid pericardial window can be created with either local or general anesthesia. Local anesthesia is preferable for patients who are hemodynamically compromised by pericardial tamponade.

After either anesthesia is established, a 6- to 12-cm incision is made in the midline from the cephalad end of the xiphoid to 1 to 2 cm inferior to the xiphoid (Fig. 95-6). The linea alba is divided at the midline, and the xiphoid process is either removed or retracted. With sharp and blunt dissection continuing superiorly and to the patient's left, the pericardium is identified using upward retraction on the sternum and costal cartilages as necessary. Identification of the pericardium can be confirmed by needle aspiration of the pericardium to obtain fluid before making the incision into the pericardial space. When the pericardium is identified, a 4-cm-diameter piece of anterior pericardium is excised. The pericardium and pericardial fluid may be sent for histology and culture. Optionally, the pericardial window can be opened into the right pleural space to drain any right pleural effusion. An angled chest tube can then be placed on the diaphragm in the pericardial space, and an additional chest tube could be placed in the right pleural space. Chest tubes should be brought through the rectus muscle lateral to the incision. The linea alba and remaining incision are then closed.

The mortality directly related to subxiphoid pericardial window is 1% or less, and survival is limited by the underlying disease (50% to 60% survival at 1 year).^{23,24,31} The effectiveness in treating tamponade is nearly 100%, and the diagnostic yield is 40% to 80%.^{24,31} Recurrent effusion or constriction can occur in 9% to 25% of patients,²³ and it may be more likely after transthoracic pericardial resection for patients with benign disease.²³

Pericardioscopy

Pericardioscopy has been performed with general anesthesia using the same technique as subxiphoid pericardial window described earlier. Once the pericardial window has been created, a flexible scope is introduced into the pericardial space.²⁰ The pericardial space is inspected for gross diagnostic purposes, and endoscopically guided biopsy specimens can be obtained. Pericardioscopy combined with pericardiocentesis and subxiphoid pericardial window has been reported to provide a specific diagnosis in 64% of cases, significantly greater than with pericardiocentesis or pericardial window alone.

Transpleural Pericardial Window

A left thoracotomy is generally used to treat hemodynamically stable patients with pericardial effusion and with good long-term prognosis. Thoracotomy may be desired if simultaneous lung biopsy is needed, and chronic pericardial drainage may be more effective than subxiphoid approaches in nonmalignant pericarditis. Thoracotomy is relatively contraindicated in patients with purulent pericarditis to avoid contamination of the pleural space.

A left thoracotomy (as opposed to right thoracotomy) is generally preferred for open transpleural pericardial window because more pericardium is accessible from the left. The patient is placed supine with the left side elevated 30 degrees. General anesthesia is standard, and left lung isolation is optional with either a dual-lumen endotracheal tube or an endobronchial blocker. A 5- to 12-cm submammary incision is made, and the fifth or fourth intercostal space is entered. The lung is retracted

laterally, and the internal mammary artery can generally be spared medially. The left anterior pericardium is opened anterior to the phrenic nerve, taking care not to injure underlying heart and maintaining hemostasis on the pericardial edge with gentle electrocautery. Pericardium can be excised from 1 to 2 cm anterior to the phrenic nerve to the midsternal level. Pericardium posterior to the phrenic nerve can also be excised, although the indications for posterior pericardial resection are unclear. Because left thoracotomy is generally used in patients with good long-term prognosis, studies suggest that at least a 4 × 4-cm piece of pericardium should be excised to prevent recurrent pericardial effusion resulting from adhesions.^{23,25} A pleural drain is left in place, and the thoracotomy is closed in a standard fashion.

Transpleural pericardial window can also be performed using direct or video-assisted thoracoscopy in patients with pericardial effusion without hemodynamic compromise resulting from tamponade. Either the right or the left approach can be used, depending on where the greater pericardial pathology lies, but left thoracoscopy may allow only limited operating space because of the proximity of the distended pericardium to the chest wall. The patient is positioned in a lateral decubitus position (Fig. 95-7). The trocar for the video thoracoscope is initially placed posteriorly, being careful to avoid pericardium, which might extend laterally. Two additional triangulated trocars are then placed for instrumentation. The pericardial window procedure is then performed as in the open transpleural approach just described. An ultrasonic scalpel has been useful for achieving hemostasis on the pericardial edges without the risk of ventricular arrhythmia caused by electrocautery.⁵²

The mortality directly related to transthoracic pericardial window is 1% or less, although operative mortality can be 19% for patients with malignant disease and 5% for those with benign disease.²³ The effectiveness in treating tamponade is nearly 100%, and the diagnostic yield is 40% to 80%.^{19,23} Recurrent effusion or

constriction occurs in 5% of patients, as opposed to 25% with the subxiphoid pericardial window.²³

Transdiaphragmatic Pericardial Window

Transdiaphragmatic pericardial window can be performed using standard laparoscopic techniques or by resecting part of the diaphragm at the time of subxiphoid pericardial window. For the endoscopic approach, a camera is inserted supra-umbilically with trocars in the right and left hypochondria. A 3- to 5-cm-diameter opening in the diaphragm and pericardium is made to drain the pericardium into the peritoneal cavity.⁵³ As with thoracoscopic pericardial window, the ultrasonic scalpel has advantages over electrocautery for minimizing ventricular arrhythmias, smoke, and stimulation of the diaphragm.

Pericardiectomy

Pericardiectomy is usually done through a median sternotomy because of the likelihood of pericardial adhesions that may be dense and because of the bilateral extent of the pericardium. Pericardiectomy is possible through bilateral thoracotomies, and left anterolateral thoracotomy (fifth interspace) has been used to achieve effective pericardiectomy.^{38,43,45}

For sternotomy, a midline incision is made from just inferior to the suprasternal notch to the inferior extent of the xiphoid process (Fig. 95-8). The entire extent of the sternum is divided in the midline with a sternal saw, and the sternum is opened with a sternal retractor. A relatively thin area of anterior pericardium is incised, and a plane between the epicardium and the pericardium is established using sharp dissection. If possible, the pericardium is opened in the midline from the level of the diaphragm to the base of the great vessels. Tradition states that the left ventricle should be freed first to avoid

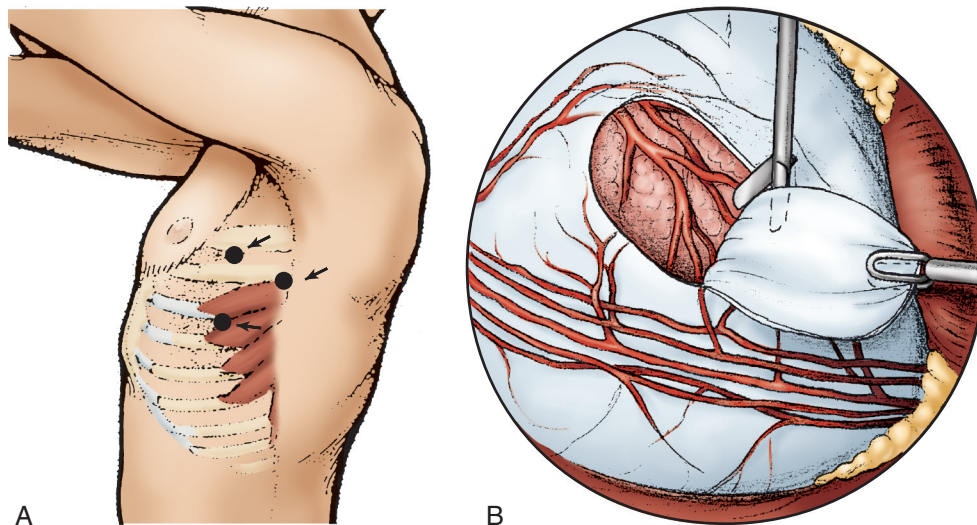


FIGURE 95-7 ■ **A**, Thoracoscopic pericardial window with patient in the right lateral decubitus position. The three trocar sites are shown with the camera placed in the posterior port. **B**, Thoracoscopic view of the pericardial resection. (From Inderbitzi R, Furrer M, Leupi F: Pericardial biopsy and fenestration. *Eur Heart J* 14:135–137, 1993.)

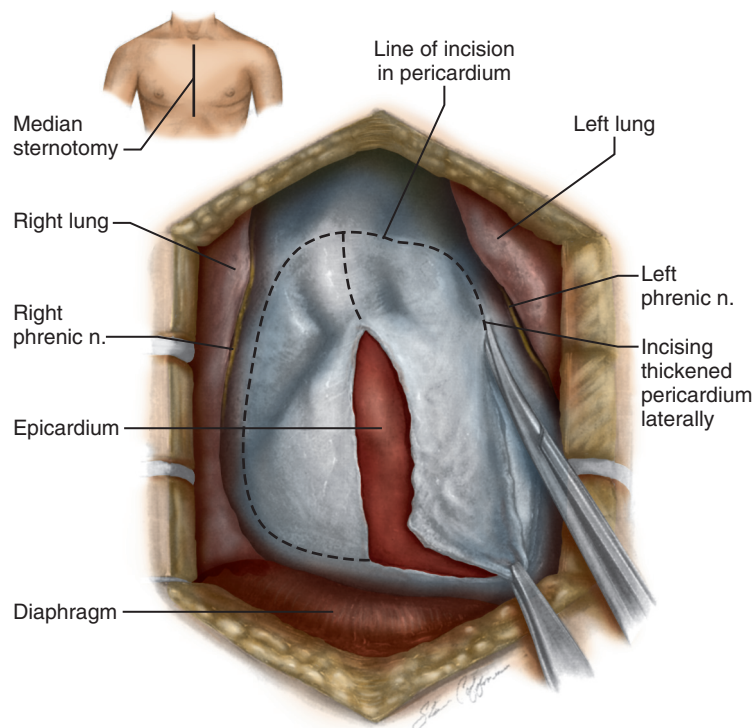


FIGURE 95-8 ■ Technique of pericardiectomy. Median sternotomy is performed, and the pleural spaces are opened bilaterally. The anterior pericardium is excised from the diaphragm inferiorly to the great vessels superiorly and 1 to 2 cm anterior to the phrenic nerves bilaterally. As indicated, the diaphragmatic pericardium and the pericardium posterior to the phrenic nerves can also be excised. Unresectable, thickened epicardium may be scored. (From Glower DD: Pericardiectomy for constrictive pericarditis. In Sabiston DC Jr, editor: *Atlas of cardiothoracic surgery*, Philadelphia, 1995, WB Saunders.)

right ventricular distention, although the frequency of this problem is unclear. The anterior pericardium is freed from 1 to 2 cm anterior to the right phrenic nerve to 1 to 2 cm anterior to the left phrenic nerve laterally, and from the base of the great vessels superiorly on to the diaphragm inferiorly. Occasionally, dense epicardial scar may be impossible to remove without risk of cardiac injury. In that case, the remaining epicardial scar can be carefully incised in a grid pattern of crossing lines 1 to 2 cm apart (waffle procedure), although the effectiveness of this technique is unclear.⁵⁴ Once freed from the epicardium, the pericardium can be excised using low electrocautery to achieve hemostasis. Care should be taken to avoid injury to the phrenic nerves, which may be difficult to identify.

Anterior pericardiectomy (described earlier) can usually be performed without cardiopulmonary bypass, and it provides the majority of the hemodynamic benefit to be obtained in relieving constriction of the right ventricle. Resecting the atrial pericardium may be less important than resecting the ventricular pericardium, making pericardiectomy via left thoracotomy practical in many cases.⁴⁴ However, some authors have advocated excising pericardium posterior to the phrenic nerves on the left or bilaterally to decrease atrial constriction and prevent recurrent constriction.^{38,41,55} Posterior pericardiectomy frequently requires cardiopulmonary bypass because of the cardiac manipulation necessary,³⁸ but with little increase in morbidity.⁴³ Pericardiectomy for constriction provides excellent symptomatic improvement, with 85% of late survivors being New York Heart Association (NYHA) class I and the remainder being class II.³⁸ Operative mortality for pericardiectomy for constriction is 6% to 14%,^{39,56,57} primarily because of persistent low

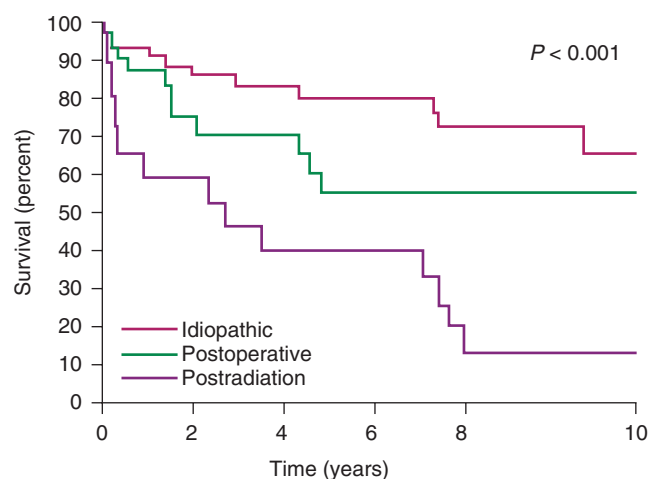


FIGURE 95-9 ■ Survival after pericardiectomy as a function of etiology. (Based on George TJ, Arnaoutakis GJ, Beaty CA, et al: Contemporary etiologies, risk factors, and outcomes after pericardiectomy. *Ann Thorac Surg* 94:445–451, 2012.)

cardiac output (seen in 70% of deaths).^{38,58} Operative mortality is increased by preoperative NYHA class, (being 1% for classes I and II, 10% for class III, and 46% for class IV).³⁸ Child-Pugh score, mediastinal irradiation, age, renal disease, and lack of calcification (Fig. 95-9).^{40,44,57} Normalization of hemodynamics is achieved in 60% of patients,⁷ and normalization of hemodynamics is associated with improved short- and long-term survival.⁴⁵

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SURGICAL MANAGEMENT OF HYPERTROPHIC CARDIOMYOPATHY

Hartzell V. Schaff

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DEFINITION

Hypertrophic cardiomyopathy (HCM), the most common genetic cardiac disease, occurs in approximately 1 in 500 young adults.^{1,2} It is defined as left ventricular (LV) hypertrophy in the absence of an underlying cause, such as systemic hypertension or valvular aortic stenosis.³ In the obstructive form of HCM, septal hypertrophy and abnormal systolic anterior motion of the mitral valve combine to produce left ventricular outflow tract (LVOT) obstruction and variable degrees of mitral valve regurgitation; outflow tract obstruction in HCM is distinct in morphologic appearance and prognosis from congenital membranous subaortic stenosis.⁴ In addition, some patients will have symptoms because of midventricular

obstruction.^{5,6} The condition is important for surgeons because obstruction may occur in more than 70% of patients with HCM,⁷ and transaortic septal myectomy is highly effective in the management of hypertrophic obstructive cardiomyopathy.

HISTORICAL NOTE

The modern description of HCM is credited to Robert Donald Teare, a London pathologist, who in 1958 likened the pathologic findings to “a tumor of the heart” and recognized asymmetrical hypertrophy and myocyte disarray as a familial condition associated with premature and sudden death in young people.⁸ In a subsequent paper in 1960, Teare proposed the term *obstructive*

cardiomyopathy.⁹ In 1957, Brock¹⁰ described a 58-year-old woman with breathlessness, angina, and syncope who was referred with the diagnosis of aortic valve stenosis. At operation, the valve was normal, and subaortic muscular obstruction was found. Despite attempts to relieve this with dilators, the patient had a residual gradient above 90 mm Hg and died postoperatively. An autopsy confirmed muscular subvalvar stenosis 2.5 cm below the aortic valve, but the histology was never defined.

At the same time, Bercu and colleagues¹¹ described the familial occurrence of unexplained ventricular hypertrophy simulating aortic stenosis as “pseudo-aortic stenosis.” Working at the National Institutes of Health, Morrow and Braunwald reported “functional aortic stenosis” and made fundamental contributions to the understanding of clinical and pathophysiologic features of the HCM.¹² The genetic nature of the disease was suggested by Brent and colleagues, who reported two families with “familial muscular subaortic stenosis” compatible with transmission by a mendelian dominant gene.¹³

Hypertrophic obstructive cardiomyopathy (HOCM) was the term applied to the condition by Goodwin,¹⁴ Holman, and others; Braunwald and associates¹⁵ popularized the term *idiopathic hypertrophic subaortic stenosis*. Asymmetrical septal hypertrophy previously was considered to be specific for the disease,^{16,17} but it is now recognized that asymmetrical septal hypertrophy is simply a variant of HCM in which there is a predominance of septal hypertrophy. In current practice, the broad definition, HCM, is generally accepted, recognizing that not all patients have the same distribution of hypertrophy and that LVOT obstruction is not present in all phases of the disease or in all patients.

Surgeons were aware of HCM after Brock's reports and the publication by Kirklin from the Mayo Clinic in 1958.^{10,18,19} Effective treatment of outflow tract obstruction began with a simple myotomy, an incision in the hypertrophied septum as described by Cleveland and others.²⁰⁻²² Subsequently, septal myectomy was used to relieve outflow tract obstruction, and this approach has been favored at our clinic since the earliest reports by Kirklin.¹⁹ Barratt-Boyes and associates advocated excision of the hypertrophied septum through a combined approach with incision in the left ventricle and the aorta.²³ Other approaches to septal myectomy include the left atrial approach with exposure of the hypertrophied septum after division of the anterior leaflet of the mitral valve²⁴; Lillehei used a similar method but detached the base of the mitral leaflet to expose the septum.²⁵ Swan described the use of a corkscrew to excise septal muscle from a limited LV approach,²⁶ and Julian used a curvilinear LV incision that detached the lower part of the free wall of the septum to expose the septal bulge.²⁷

Thickness of the hypertrophied septum can be reduced by shaving the right ventricular side through right ventriculotomy,^{28,29} but this technique is less direct than the transaortic approach. Because systolic anterior motion of the mitral valve is an integral part of the mechanism of LVOT obstruction, excision of the mitral valve and replacement with a low-profile prosthesis, as described by Cooley and coworkers, is an effective method of

relieving outflow tract obstruction.³⁰ This, however, leaves the patient with potential hazards of a prosthetic valve. Rarely, an apicoaortic conduit has been used to relieve complex forms of LVOT obstruction caused by HCM.³¹

All of these earlier methods have been largely replaced by the more predictable and complete transaortic myectomy advocated by Morrow,³² and this is the basis of the extended septal myectomy, the surgical approach we favor that is described here.

CLASSIFICATION

Morphology

Distribution of Hypertrophy

Figure 96-1 shows the variable distribution of LV hypertrophy in patients with HCM. Classically, the anterior basal septum is thickest just cephalad to the anterior leaflet of the mitral valve in its open position. This subaortic obstruction may be accompanied by diffuse ventricular hypertrophy (see Fig. 96-1E), or the hypertrophy may be limited to the septum (asymmetrical septal hypertrophy; see Fig. 96-1B). There may be obstruction in the mid ventricle where hypertrophy of septum leads to contact with the papillary muscles producing obstruction to ejection of blood; in other patients, there may be an apical distribution of hypertrophy (see Fig. 96-1F). The phenotype of the disease and the appearance and severity of hypertrophy do not correlate with genotype; multiple ventricular morphologic appearances may be found in the same family.

Mitral Valve

In the classic form of HOCM, the mitral valve, especially the anterior leaflet of the valve, moves anteriorly during systole. The posterior leaflet closes against the mid- and free-edge third of the anterior leaflet instead of at the free edge as occurs normally. The free edge of the anterior leaflet is then displaced upward and narrows the LVOT. In addition, the anterior displacement of the valve leaflets produces mitral regurgitation of variable degree, which is typically directed posterolaterally.³³ A recent cardiac magnetic resonance imaging study suggested that the length of both the anterior and posterior leaflets of the mitral valve are increased in HCM patients compared to control patients, and the ratio of anterior mitral leaflet length to LVOT diameter of greater than 2.0 was associated with subaortic obstruction.³⁴

Mitral regurgitation is an important pathophysiologic component of HOCM and contributes to the symptoms of dyspnea and fatigability. Apposition of the anterior leaflet to the bulging septum produces a contact lesion, the whitish endocardial scar, which is useful in guiding septal myectomy. The occurrence of systolic anterior motion is often dynamic, and provocative maneuvers such as Valsalva, squatting, exercise, and, in some cases, adrenergic stimulation may be necessary to elicit systolic anterior motion, mitral regurgitation, and LVOT obstruction. The mechanism of systolic anterior motion

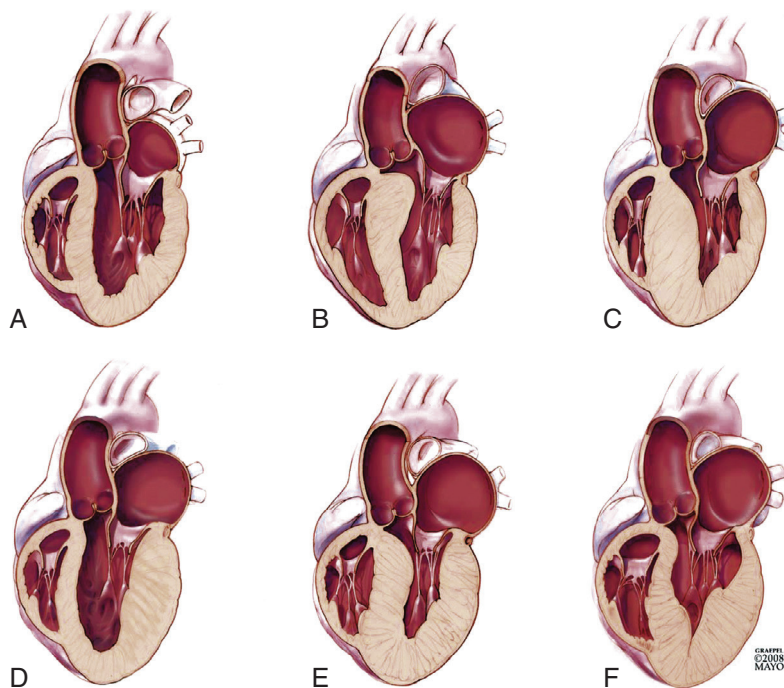


FIGURE 96-1 ■ Morphologic subtypes of hypertrophic cardiomyopathy. Hypertrophy may be localized to the basal septum, as in **B**; diffuse, as in **E**; or predominantly apical, as in **F**. Normal ventricular morphology is shown in **A**. (Adapted and used with permission of Mayo Foundation for Medical Education and Research.)

is debatable, and proposed mechanisms include the Venturi (pull) effect^{35,36} and a drag (push) effect.^{37,38}

Anomalies of papillary muscles are present in 15% to 20% of patients with HCM who undergo myectomy.³⁹ These abnormalities include anomalous papillary muscles, direct insertion of papillary muscles into the anterior mitral valve leaflet (Fig. 96-2), fusion of the papillary muscle to the ventricular septum or LV free wall, and accessory muscles and accessory anomalous chordae (false cords). In most cases, these abnormalities do not complicate myectomy or contribute to outflow tract obstruction; however, in some patients, anomalous papillary muscles, especially those that insert directly into the anterior leaflet, can contribute to outflow tract obstruction.⁴⁰

Right Ventricle

Right ventricular wall thickening has been documented in approximately one third of patients with HCM, and 10% have extreme right ventricular wall hypertrophy (≥ 10 mm).⁴¹ Right ventricular hypertrophy, however, rarely leads to fibrosis as evidenced by hyperenhancement on magnetic resonance imaging, and right ventricular outflow tract obstruction caused by infundibular narrowing is uncommon^{42,43} and mainly limited to cases of HCM manifested in children and young adults.⁴⁴ Right ventricular hypertrophy also occurs as a result of pulmonary hypertension from elevated LV end-diastolic pressure. Indeed, among patients referred for septal myectomy, pulmonary hypertension (right ventricular systolic pressure ≥ 35 mm Hg) was present in approximately half of the patients and severe pulmonary hypertension (right ventricular systolic pressure ≥ 50 mm Hg) was seen in 17% of patients.⁴⁵

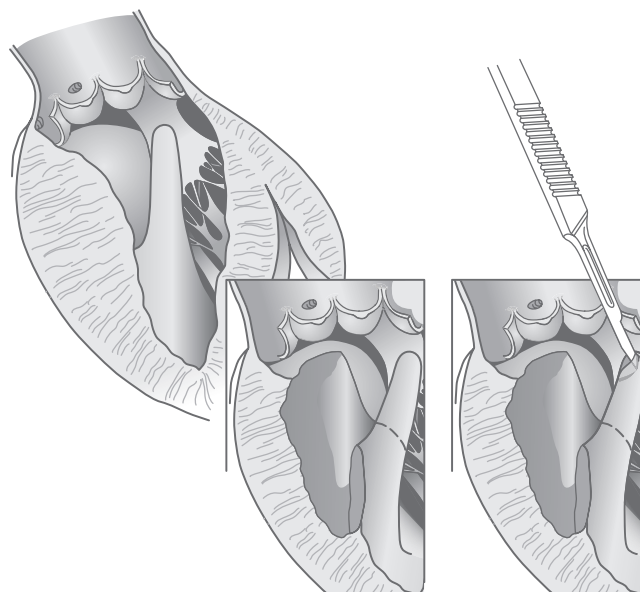


FIGURE 96-2 ■ Anomalous papillary muscles may insert directly into the anterior mitral leaflet and contribute to outflow obstruction. When the anomalous muscle does not support the free edge of the valve, it can be excised. (Adapted and used with permission of Mayo Foundation for Medical Education and Research.)

Aortic Valve

In contrast to congenital membranous subaortic stenosis,⁴⁶ LVOT obstruction in patients with HCM does not directly affect the aortic valve. Aortic valve regurgitation has been observed after transaortic myectomy as a result of iatrogenic injury.⁴⁷

Coronary Arteries

Coronary arteries are larger than normal in patients with HCM, and basal coronary flow is increased in the resting state. Coronary flow reserve, however, is decreased in symptomatic patients with HCM compared with controls, and phasic flow is abnormal with a greater amount of flow during diastole, the presence of flow reversal in systole, and a more rapid deceleration of diastolic blood flow compared with normal patients. Decreased flow reserve is associated with a reduction in coronary resistance, suggesting that the mechanism is not a result of narrowing of intramyocardial small arteries or compression of the microcirculation; indeed, the reduction in coronary flow reserve in patients with HCM may be the result of almost maximal vasodilation of the microcirculation in the basal state. It has been speculated that compression of the microcirculation during systole may be the cause of flow reversal in patients with HCM and the inverse correlation between systolic flow and septal thickness; total coronary blood flow in patients with HCM, however, is preserved and even increased under resting conditions.

Atherosclerotic coronary artery disease is present in approximately 5% to 15% of patients with HCM, depending on the population studied. At the Mayo Clinic, significant coronary artery disease was detected in half of patients who were selected for coronary angiography, and disease was severe in 26%.⁴⁸ Survival of HCM patients with obstructive coronary artery disease is reduced compared with that of HCM patients without coronary artery disease, and survival is also poorer than that of patients without HCM who have comparable coronary artery disease and normal ventricular function.

Muscle bridging of the left anterior descending coronary artery (LAD) is not uncommon, occurring in 15% of patients with HCM undergoing coronary angiography at our clinic.⁴⁹ It is unclear whether bridging of the LAD plays a pathophysiologic role in the disease and associated symptoms of angina. However, for adult patients, risk of death and, in particular, of sudden cardiac death is not increased among patients with HCM with myocardial bridging. In contrast, Yetman and coworkers⁵⁰ reported that among children with HCM, systolic compression of LAD was present in 285 cases and was associated with a greater incidence of chest pain (60% vs. 19%; $P = 0.04$), cardiac arrest with subsequent resuscitation (50% vs. 4%; $P = 0.004$), and ventricular tachycardia (80% vs. 8%; $P < 0.001$). Myocardial ischemia was postulated to be the cause of this poor outcome.

Histopathology

Myocardial Fiber Disarray

A characteristic histologic feature of HCM is myocardial fiber disarray, which consists of short runs of severely hypertrophied fibers interspersed by connective tissue. Myocytes show large, bizarre nuclei with degenerating muscle fibers and fibrosis. It is the disorganized whirling of muscle fibers that is characteristic of HCM. Myocardial disarray is present in the ventricular septum and in

the LV free wall, but it is not pathognomonic for HCM. Fiber disarray may be present in myocardium in any conditions in which there is pressure overload, but the proportion of myocardial disarray is much greater in HCM.^{51,52}

Myocyte disarray has been associated with systolic dysfunction, ventricular dilation, and congestive heart failure.⁵³ It may also be a substrate for ventricular arrhythmias. Disarray has also been greatest in hearts with only a mild degree of LV hypertrophy or with absence of a subaortic mitral valve contact lesion, but there seems to be no direct relationship between myocyte disarray and fibrosis or small vessel disease.⁵⁴

Interstitial Fibrosis

Interstitial fibrosis is an important histologic feature that is present in variable degrees in the ventricle of patients with HCM.^{55,56} It is important not only as a mechanism of diastolic dysfunction but also because fibrosis detected by magnetic resonance imaging has been associated with arrhythmogenesis and risk of sudden cardiac death.^{57,58}

Differential Diagnosis

Other diseases may mimic HCM. Cardiac amyloidosis is an infiltrative disorder of the myocardium that typically produces diastolic dysfunction. Up to 30% of patients with cardiac amyloidosis have prominent subaortic thickening that produces LVOT obstruction. The clinical features and hemodynamics of patients with cardiac amyloidosis are similar to those of patients with LVOT obstruction caused by HCM. The finding of LV granular speckling on echocardiography should raise the suspicion of cardiac amyloid, especially if atrial wall thickness is increased.⁵⁹ Newer techniques of strain and strain rate imaging from speckle tracking may improve discrimination of cardiac amyloidosis from HCM.⁶⁰

Amyloid deposits may be identified incidentally in myectomy specimens of patients with typical features of obstructive HCM, and the mid-term postoperative survival of such patients is similar to that of an age- and sex-matched HCM population without amyloidosis undergoing septal myectomy. In these patients the most common subtype is senile amyloid, which has a good prognosis and rarely leads to multisystem involvement.

Patients with Fabry's disease may present with ventricular hypertrophy and dynamic LVOT obstruction. The mechanism of cardiac hypertrophy is different from that in other infiltrative cardiomyopathies in that it is secondary to increased cardiac muscle mass and infiltration of glycosphingolipids. The disorder caused by α -galactosidase A deficiency can be treated by enzyme replacement therapy, but ventricular hypertrophy and LVOT obstruction may persist and septal myectomy can relieve cardiac-related symptoms.⁵

GENETICS

HCM has a prevalence of 0.2% for phenotypically expressed disease.⁶¹ Approximately 60% to 80% of cases

are familial, and the remainder result from de novo mutations.⁶² HCM is genetically diverse, involving sarcomeric and nonsarcomeric proteins, and hundreds of mutations in more than 15 genes have been identified; indeed, double and compound heterozygosity and homozygosity have been reported.⁶³

Most patients with familial disease have mutations in three protein-encoding genes, β -myosin heavy chain (*MYH7*) in 35% to 50%, myosin-binding protein C (*MYBPC3*) in 15% to 25%, and cardiac troponin T type 2 (*TNNT2*) in 15% to 20%. In current practice, the clinical value of genetic testing is uncertain. Van Driest and colleagues⁶⁴ reported that gene-positive status did not correlate with family history of sudden cardiac death, need for myectomy, or anatomic subtype. Furthermore, specific mutations in HCM are rare; in one study, less than 2% of 293 unrelated patients had putative benign mutations, but serious clinical events developed in these patients, including sudden cardiac death, need for surgical myectomy, and cardiac transplantation.⁶⁵

Other studies suggest that certain mutations are associated with poor prognosis. For example, certain mutations in *TNNT2*, β -tropomyosin (*TPM1*), and *MYH7* may confer increased risk of sudden cardiac death. Olivetto and coworkers reported that identification of myofilament-positive patients through genetic testing predicted a fourfold increase in the risk of the combined endpoint of cardiovascular death, nonfatal stroke, or progression to New York Heart Association (NYHA) class III or class IV symptoms.⁶⁶ Mutations were associated with more severe systolic and diastolic LV dysfunction, and adverse clinical events occurred irrespective of whether the involved myofilament was thin, intermediate, or thick.

A potential benefit of genetic analysis is the preclinical diagnosis in patients with a family history of sudden cardiac death or in those carrying a "malignant" mutation that predisposes them to a severe phenotype. Also, it may be useful to know the precise genetic defect in HCM among asymptomatic family members who carry the mutation and might be at risk of sudden cardiac death.

In addition to variability in clinical course and risk of sudden cardiac death, the phenotype of HCM shows considerable diversity in the severity and distribution of hypertrophy (asymmetrical, concentric, apical), penetrance, and age at onset. This variability may be explained partially by patients who are compound heterozygotes and by the coexistence of other diseases that predispose to hypertrophy.

PATHOPHYSIOLOGY

Diastolic Dysfunction

Diastolic dysfunction with elevation of the LV end-diastolic pressure is the principal pathophysiologic finding in HCM. The resulting increase in left atrial and pulmonary venous pressures accounts for the common symptoms of effort dyspnea and limited aerobic capacity.

With worsening diastolic function, LV filling becomes more dependent on atrial contraction, and occurrence of atrial arrhythmias, especially atrial fibrillation, can cause an acute and profound decrease in cardiac output and worsening of symptoms.⁶⁷

Abnormal myocardial relaxation has been observed in patients with HCM before the development of symptoms. The increased chamber stiffness results primarily from increased wall thickness, but there are other factors of surgical importance that aggravate intrinsic diastolic dysfunction related to LV hypertrophy.

LVOT obstruction has a direct effect of increasing end-diastolic pressure and an indirect effect through the often associated mitral regurgitation. Thus, whereas surgical myectomy has a minimal immediate effect on overall LV mass, symptoms related to diastolic dysfunction are immediately improved when outflow gradients and mitral regurgitation are relieved. A secondary effect of septal myectomy on diastolic function is regression of hypertrophy, as discussed later.

In some patients, concentric ventricular hypertrophy is so severe that muscle mass encroaches on the ventricular cavity and reduces normal cavity size. This is particularly striking in patients with the apical form of HCM, in which the distal third to distal half of the left ventricle may be obliterated (during diastole and systole) by muscle. Surgical remodeling by apical myectomy may increase end-diastolic volume and thus improve diastolic function.

Left Ventricular Outflow Obstruction

Surgical treatment of HCM consists primarily of relief of LVOT obstruction. As discussed before, obstruction results from dynamic narrowing of the subaortic area, which in turn is caused by protrusion of the hypertrophied septum in apposition with the anterior leaflet of the mitral valve. Previously, there was debate on the importance of outflow tract obstruction as a mechanism for symptoms in patients with HCM because of the lability of the finding and the question of catheter entrapment when gradients were measured by invasive catheterization.⁶⁸ It is now recognized that outflow obstruction is much more common than previously thought, correlates importantly with development of symptoms, and may negatively influence long-term survival.

Maron and colleagues documented resting outflow tract gradients of 50 mm Hg or greater in 37% of 320 patients with HCM and, more important, found exercise-induced gradients (mean 80 ± 43 mm Hg) in an additional 106 patients; thus, as many as 70% of patients with HCM who come to clinical evaluation will have significant outflow tract obstruction.⁶⁹ Another important finding in this study was the relative unreliability of the Valsalva maneuver (sensitivity 40%) compared with exercise Doppler echocardiography in detecting these dynamic gradients. Latent obstruction can also be documented during hemodynamic catheterization by isoproterenol challenge, and the technique may be useful in patients who are unable to exercise or in patients in whom reliable Doppler echocardiographic signals cannot be measured.⁷⁰

Mitral Valve Regurgitation

Accelerated blood flow near the hypertrophied basal septum pushes the mitral leaflet at the same time that there may be “suction” forces that contribute to the systolic anterior motion of the mitral valve. Thus, leaflet coaptation is reduced, producing variable degrees of posteriorly directed mitral regurgitation. If the mitral regurgitant jet is directed anteriorly, primary mitral valve disease such as a flail or prolapsing segment should be suspected. As is true with outflow gradients, the degree of mitral regurgitation is often dynamic. Symptomatic patients with moderate or severe degrees of mitral regurgitation associated with HOCM are excellent candidates for operation because the mitral regurgitation and associated symptoms (dyspnea and fatigability) are almost always abolished or significantly improved with adequate septal myectomy.

Intrinsic mitral valve disease may contribute to valvular regurgitation in patients with HOCM. Rupture of chordae with resultant leaflet prolapse can precipitate congestive heart failure, and hemodynamics may worsen if HCM is not recognized and patients are managed medically with afterload reduction.⁷¹

CLINICAL PRESENTATION AND DIAGNOSTIC CRITERIA

Symptoms

Although some children and adolescents present with cardiac limitations, most patients remain asymptomatic until young adulthood or middle age. The onset of symptoms parallels development of outflow tract obstruction, and limitation is gradual, manifested first by fatigability and then by effort dyspnea, angina, and syncope or presyncope. As discussed previously, dyspnea is caused by LV diastolic dysfunction and variable degrees of mitral regurgitation. Autonomic dysfunction, which is present in approximately 25% of patients with HCM, may also contribute to poor exercise capacity; it is manifested by a failure to increase systolic blood pressure by 20 mm Hg during exercise or an actual decline in blood pressure during exertion.

Although obstructive coronary artery disease may coexist, angina is most likely explained by the combination of increased LV wall thickness (increased myocardial oxygen demand) and decreased capillary network (decreased myocardial oxygen supply) in addition to provoking factors such as increased heart rate and increased afterload.

Signs

In HCM patients without obstruction, clinical findings are those of LV hypertrophy. For patients with obstruction, it is important to differentiate dynamic obstruction from fixed obstruction as occurs with valvular aortic stenosis or congenital membranous subaortic stenosis. Auscultation in patients with HOCM reveals the classic crescendo-decrescendo murmur heard best near the left

sternal border, which peaks in mid to late systole and usually ends before the second heart sound. The murmur can radiate across the precordium, but in contrast to valvular aortic stenosis, radiation to the carotid arteries is uncommon. Mitral regurgitation may produce a separate holosystolic murmur audible at the apex. With dynamic outflow obstruction, the carotid pulsation is brisk and bifid. If there is severe hypertrophy, a fourth heart sound may be heard.

Dynamic auscultation can differentiate the murmur of HCM from that of valvular aortic stenosis and mitral regurgitation. Maneuvers such as the Valsalva or stand-squat-stand, which decrease the LV volume, will increase the dynamic gradient and the intensity of the murmur. Other maneuvers to change the intensity of the murmur include leg raising to increase preload and the inhalation of amyl nitrate to decrease afterload and increase heart rate.

Electrocardiography and Chest Radiography

In HCM with obstruction, the electrocardiogram characteristically shows LV hypertrophy with a strain pattern, and Q waves may be present. Electrocardiographic evidence of left atrial enlargement is common, as is a bundle branch block pattern (especially after myectomy). After alcohol septal ablation, a right bundle branch block is commonly observed. With the apical form of HCM, the electrocardiogram shows a distinctive pattern of diffuse symmetrical T wave inversions across the precordium.

Most patients with HCM have normal sinus rhythm, but continuous monitoring will show a high incidence of supraventricular tachycardia (46%), premature ventricular contractions (43%), and nonsustained ventricular tachycardia (26%).⁷² Atrial fibrillation develops in up to a quarter of patients, and onset of atrial fibrillation often precipitates symptoms because of loss of atrial contraction and impaired filling of the left ventricle.

Findings on chest radiography are those of LV hypertrophy and pulmonary venous congestion, and enlargement of the pulmonary artery may be apparent in patients with congestive heart failure.

Echocardiography

Two-dimensional and Doppler echocardiography is the essential tool for the diagnosis of HCM, providing information on ventricular morphology, hemodynamics, and valve function. The most common pattern of hypertrophy is diffuse involvement of the ventricular septum. In patients with HCM, average maximal LV wall thickness is 20 to 22 mm, and in 5% to 10% of patients, LV wall thickness is dramatically increased, measuring 30 to 50 mm.⁷² Morphology of the septum appears to vary according to age, and older patients with HCM often demonstrate a sigmoid configuration.⁷³

The echocardiographic findings of increased wall thickness should prompt a search for other causes, including systemic hypertension (especially in patients on dialysis); valvular aortic stenosis; and infiltrative and glycogen

storage diseases, such as cardiac amyloidosis, Fabry's disease, and Friedreich's ataxia.

On continuous wave Doppler echocardiography, LVOT obstruction is seen as a high-velocity, late-peaking, "dagger-shaped" signal. In patients with low velocity at rest (<3 m/sec), maneuvers such as the Valsalva, inhalation of amyl nitrate, and exercise may demonstrate latent obstruction. Presence and severity of mitral regurgitation can be determined by Doppler color flow imaging. It is important to differentiate the true outflow tract velocity from the mitral regurgitation jet.

Mitral regurgitation that results from systolic anterior motion is eccentric and directed posterolaterally during late systole. A centrally directed jet should suggest a primary leaflet abnormality contributing to valve leakage. Preoperative transesophageal echocardiography is unnecessary in most patients, but intraoperative transesophageal echocardiography is critically important for assessing results of myectomy.⁷⁴

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging is useful in identifying regions of LV hypertrophy not easily recognized by echocardiography, specifically the anterolateral free wall and the apical area.⁷⁵ In addition, magnetic resonance imaging can detect presence and severity of myocardial fibrosis, which appears to be an important risk factor for subsequent ventricular arrhythmias and sudden cardiac death.^{76,77}

Invasive Catheterization

In current practice, cardiac catheterization is rarely necessary for the diagnosis of HCM. Coronary angiography is indicated for patients with symptoms of angina and for patients at risk for coronary artery disease (strong family history, abnormal lipids, older age) who undergo myectomy. A hemodynamic study with isoproterenol provocation can be useful in identifying patients with labile obstruction gradients that cannot be elicited during echocardiography.⁷⁰

NATURAL HISTORY

Symptom Course

The clinical course of HCM is highly variable, and some patients remain free of symptoms and cardiac limitation. In many patients, however, onset of symptoms is associated with development of LVOT obstruction, and it is not clear what causes this in adult patients who have had no gradients until the fourth, fifth, or sixth decade of life. Onset of atrial fibrillation can also precipitate symptoms and predispose to systemic embolism, which occurs in 6% of patients.⁷⁸ Atrial fibrillation is noted in 30% of older patients with HCM.

Infective endocarditis may occur with HCM, and the reported incidence is 1.4 cases per 1000 person-years. The important feature is that in virtually all cases of endocarditis, there is LVOT obstruction. Indeed, among

HCM patients with obstruction, the incidence of endocarditis is 3.8 per 1000 person-years, or a 4% likelihood for development of this complication during 10 years.⁷⁹

Survival

In the general population, survival of patients with HCM is similar to that of individuals without disease, and early reports of high mortality in HCM may be explained by excess numbers of high-risk patients included in studies from tertiary referral centers.⁸⁰⁻⁸² More recent data indicate that the annual mortality rate of patients with HCM is approximately 1%, but there are several important subgroups that have a higher risk of cardiac death; indeed, HCM is the most common cause of sudden death among young athletes.^{7,83,84}

Obstructed versus Nonobstructed Hypertrophic Cardiomyopathy

Until recently, there was uncertainty and debate about the influence of LVOT obstruction on survival of patients with HCM. Convincing studies by Maron and colleagues,⁸⁵ Autore and associates,⁸⁶ and Elliott and coworkers⁸⁷ have demonstrated a strong correlation between resting outflow gradients and late risk of death. In a longitudinal study of 1101 patients with HCM, Maron and colleagues reported that patients with outflow tract obstruction (a basal gradient of at least 30 mm Hg) had a risk of death from HCM or symptom progression that was more than four times that observed among patients without obstruction (Fig. 96-3). The association of outflow tract obstruction on limiting symptoms and death was independent of other clinical variables. Of note, patients with obstruction and mild symptoms (NYHA class II) were more likely to have progression to severe symptoms or to die of heart failure than were asymptomatic patients with cardiomyopathy (Fig. 96-4).⁸⁵

An important clinical question is whether prognosis of asymptomatic HOCM patients with high gradients can be improved by septal reduction. Elliott and coworkers

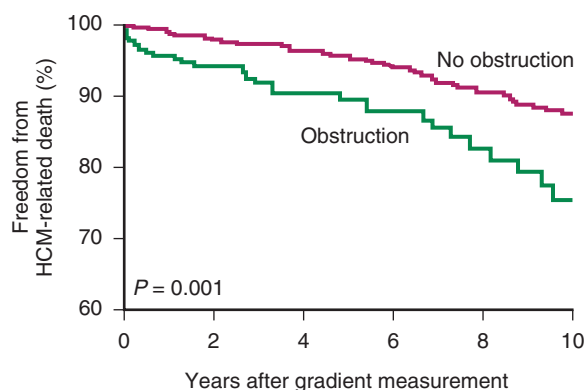


FIGURE 96-3 ■ Survival of patients with hypertrophic cardiomyopathy (HCM) with and without obstruction (≥ 30 mm Hg). This analysis includes only deaths related to HCM. (From Maron MS, Olivetto I, Betocchi S, et al: Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 348:295–303, 2003.)

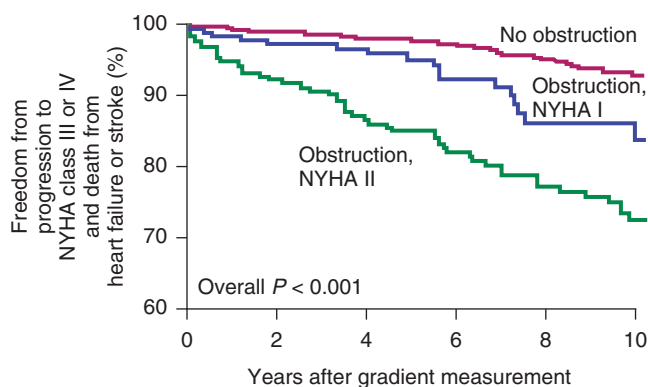


FIGURE 96-4 ■ Probability of progression to severe heart failure, death, or stroke in patients without obstruction and in patients with outflow tract obstruction stratified by presence or absence of symptoms. NYHA, New York Heart Association. (From Maron MS, Olivetto I, Betocchi S, et al: Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 348:295–303, 2003.)

reported that risk of sudden death is relatively low (<0.4% per year) in asymptomatic patients with LVOT obstruction and none of the recognized risk factors for sudden cardiac death, but their study demonstrated reduced survival among patients with LVOT obstruction and nonsustained ventricular tachycardia, abnormal exercise blood pressure response, family history of premature sudden death, unexplained syncope, or severe LV hypertrophy.

The prognosis of patients with latent obstruction is less clear, but a study by Vaglio and colleagues⁸⁸ suggests that the clinical course is similar to that of patients with resting obstruction. In their series, one quarter of patients required invasive therapy for relief of symptoms, and annual mortality was 2%, a rate higher than that reported for patients with HCM and no LVOT obstruction.

Use of Implantable Cardioverter-Defibrillator

Sudden cardiac death is a special concern in HCM, and there is debate about the appropriate use of implantable cardioverter-defibrillators (ICDs) for primary and secondary prevention of sudden cardiac death. In addition to prior cardiac arrest, clinical variables that appear to identify patients at increased risk of arrhythmic events (major risk factors) include nonsustained ventricular tachycardia, massive ventricular hypertrophy (wall thickness > 30 mm), hypotensive response to exercise, family history of sudden cardiac death, and unexplained syncope.⁸⁹ Other findings, such as myocardial bridging in young patients, apical aneurysms, or myocardial fibrosis detected by cardiac magnetic resonance imaging, may also increase risk of sudden death.

Consensus among experts⁹⁰ is that an ICD is strongly warranted for secondary prevention of sudden cardiac death in patients with prior cardiac arrest or sustained and spontaneously occurring ventricular tachycardia and should be considered in patients with multiple clinical risk factors and in selected patients with a single major risk factor, such as a history of sudden cardiac death in a

close relative. For patients who need ICD implantation and are referred for septal myectomy, we prefer to delay device implantation until the third or fourth day postoperatively to avoid the potential for lead dislocation if the ICD is placed immediately preoperatively.

SURGICAL TREATMENT

Indications for Operation

Septal myectomy is, in general, reserved for patients who continue to have limiting symptoms despite medical treatment. Pharmacologic therapy usually begins with β -adrenergic blocking agents, which have a negative inotropic effect and may mitigate latent outflow gradients provoked with exercise. Beta blockers are less effective in reducing resting gradients. The calcium antagonist verapamil has been used for patients with nonobstructive and obstructive HCM. The drug may improve ventricular relaxation and decreased LV contractility, but hemodynamic and electrophysiologic side effects limit long-term use. Disopyramide has negative inotropic effects and is a type Ia antiarrhythmic agent that can improve symptoms by reducing resting gradients. However, this drug also has side effects, including dry mouth and eyes, constipation, and difficulty in micturition. In addition, it increases atrioventricular nodal conduction and thus may increase ventricular rate in patients with atrial fibrillation. Although medications may ameliorate symptoms, drug therapy does not appear to decrease the probability of sudden death. In a study of 173 patients who were taking amiodarone, beta blockers, verapamil, or sotalol for treatment of symptoms, there was no difference in sudden death mortality compared with patients who were receiving no pharmacologic therapy.⁹¹ Thus, ICDs remain the primary therapy for prevention of sudden death in high-risk HOCM patients.

Technique of Operation

Operation is performed through a median sternotomy, and normothermic cardiopulmonary bypass is established in the standard fashion by use of a single, two-staged venous cannula. The aorta is cross-clamped, and cold blood cardioplegia (1000 to 1200 mL) is infused through the aortic needle vent to arrest the heart. Adequate exposure of the subaortic septum is critically important, and several maneuvers facilitate the operation. First, pericardial sutures are used only on the right side to elevate the pericardium toward the surgeon. Next, an oblique aortotomy is made slightly closer to the sinotubular ridge than is usual for aortic valve replacement, and the incision is carried through the midpoint of the noncoronary aortic sinus of Valsalva to a level approximately 1 cm above the valve annulus. The edge of the proximal aorta is held out of the way with small stay sutures, and a cardiectomy sucker is placed through the aortic valve and used to depress the anterior leaflet of the mitral valve to protect it from injury. The right aortic valve cusp is collapsed against the sinus wall, where it will usually stay. A sponge stick is used to depress the right ventricle and to rotate

the septum posteriorly, orienting the LV outflow anteriorly (Fig. 96-5).

A standard no. 10 scalpel blade is used for myectomy; incision in the septum begins just to the right of the nadir of the right aortic sinus (Fig. 96-6). The incision in the septum is made upward and then leftward over to the anterior leaflet of the mitral valve. Scissors are used to complete excision of this initial portion of myocardium. The area of septal excision is then deepened and lengthened toward the apex of the heart, and the hypertrophied septum must be excised beyond endocardial scar (Figs. 96-7 and 96-8). Trabeculations are excised, and the

myectomy site is further enlarged with the use of pituitary rongeurs. Adequate septal myectomy usually yields 3 to 12 g of muscle. Use of the sponge stick to depress the heart posteriorly will improve exposure of the distal extent of the myectomy. The aortotomy is closed, and the operation proceeds as usual.

This technique for more extended myectomy⁹² differs from the standard Morrow operation,³² in which parallel incisions create a trough in the septum that extends up to 3 cm from the aortic valve; wider excision of muscle in the immediate subaortic area improves exposure of the distal extent of the hypertrophied septum, and excision

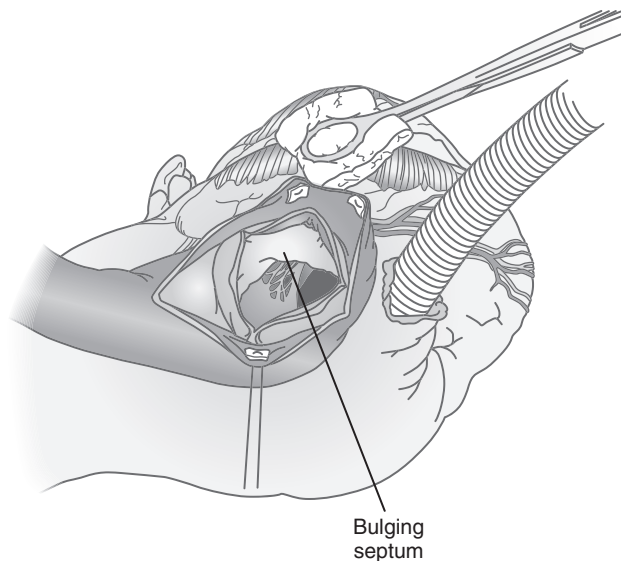


FIGURE 96-5 ■ The subaortic septum is exposed through an oblique aortotomy extended to the base of the noncoronary sinus. The surgeon's view of the septum is improved by depressing and rotating the ventricle posteriorly with a sponge forceps. (Adapted and used with permission of Mayo Foundation for Medical Education and Research.)

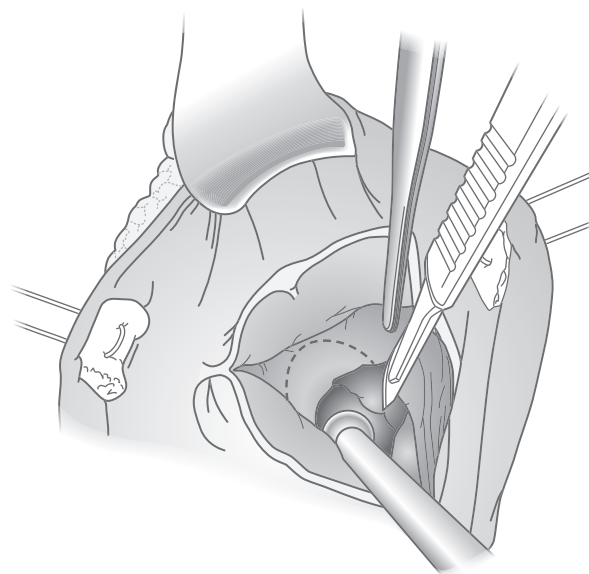


FIGURE 96-6 ■ Septal excision begins just to the right of the nadir of the right aortic sinus and extends leftward toward the anterior leaflet of the mitral valve. After the initial specimen is removed, the area of septal excision should be carried toward the apex of the heart well past the endocardial scar. A wider proximal area of excision improves exposure of the more distal extent of septectomy. (Adapted and used with permission of Mayo Foundation for Medical Education and Research.)

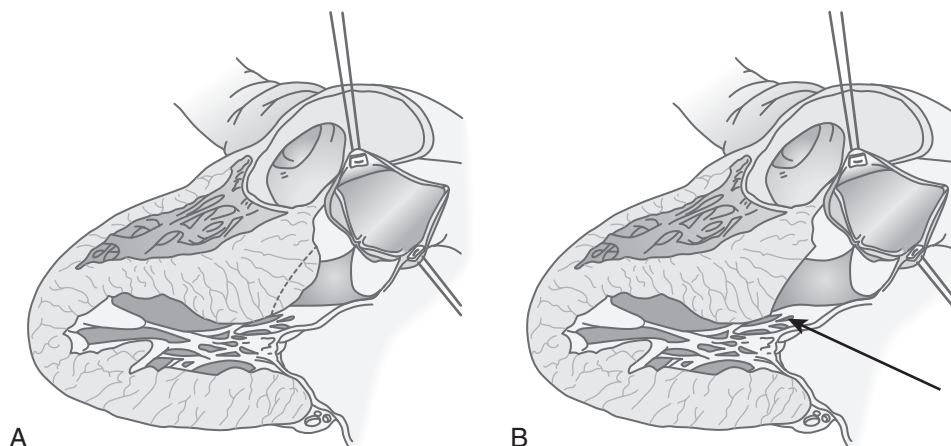


FIGURE 96-7 ■ **A**, A common error in performing septal myectomy is inadequate length (toward the apex) of muscle excision. The bulging septum may appear to be in the immediate subaortic position after initial aortotomy, but if only this portion of the enlarged septum is removed, there may be residual obstruction, as seen by the arrow in **B**. (Adapted and used with permission of Mayo Foundation for Medical Education and Research.)

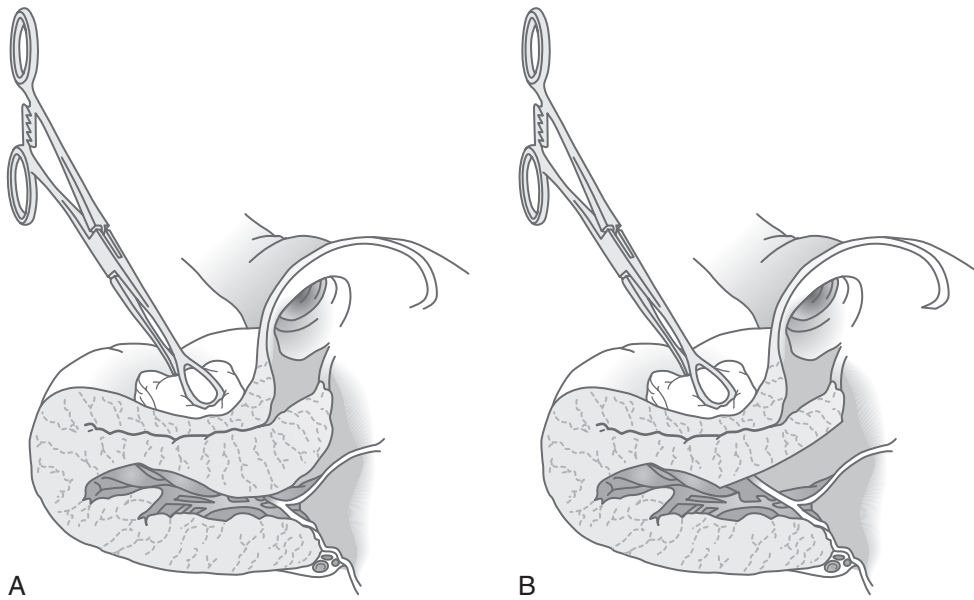


FIGURE 96-8 ■ **A**, Rotation of the ventricle posteriorly improves exposure of the septum and allows the surgeon access to the distal extent of the obstructing segment (**B**). (Adapted and used with permission of Mayo Foundation for Medical Education and Research.)

extends up to 7 cm from the aortic valve. Inadequate myectomy results more often from failure to excise sufficient length of the septum (toward the apex) than from inadequate depth of excision. The methods described have proved adequate for all patients with subaortic obstruction, and maneuvers such as anterior leaflet plication are unnecessary and potentially harmful. Mitral valve replacement is reserved for patients with intrinsic leaflet abnormalities that cannot be repaired. To confirm complete relief of the LVOT obstruction, we routinely measure simultaneous aortic and LV pressure by direct needle puncture before and after myectomy.⁹³ If the resting LVOT gradient is diminished by effects of anesthesia, premature ventricular beats are induced by stimulating the ventricle to elicit the dynamic gradient produced by the Brockenbrough phenomenon; the post-extrasystolic contraction is more forceful because of increased contractility and decreased afterload. The same maneuver is then repeated after myectomy. Transesophageal echocardiography is routinely used.⁷⁴ Intraoperative transesophageal echocardiography can identify residual mitral valve regurgitation, systolic anterior motion, and any septal defects created by excision of septal muscle.

Unroofing of coronary artery bridging is performed in selected cases, particularly young patients and those who have angina preoperatively. After identification of the coronary artery distal to the intramyocardial segment, the anterior surface of the vessel is exposed by sharp dissection that is continued proximally until the LAD reemerges onto the epicardium. The divided myocardium over the artery is usually 3 to 5 mm thick. If the course of the artery is so deep that trabeculations of the right ventricular cavity are entered, pledgeted sutures placed deep into the coronary artery repair the opening into the ventricle. We have combined unroofing of myocardial bridging of the LAD with extended septal

myectomy in more than 36 patients with satisfactory outcomes. Angina is improved, but there is no evidence to suggest that there is a survival benefit secondary to the procedure. Thus, in adult patients, unroofing of a myocardial bridge portion should be considered when a patient undergoes myectomy and has a history of angina.⁹⁴

Postoperative Care

Care of patients after myectomy is similar to care of patients who have had valve replacement for aortic stenosis. Systemic vascular resistance should be maintained at or above the normal range so that LV diastolic filling pressure and coronary perfusion pressure are maintained in the hypertrophied ventricles. Vasodilators are avoided, and continuous infusions of phenylephrine or vasopressin may be useful. It is important to maintain atrioventricular synchrony to maximize LV filling, and atrial pacing is often used. The day after operation, we restart beta-blocking medications at half the preoperative dose but do not routinely restart calcium channel blockers or disopyramide. Atrial fibrillation can be especially deleterious to cardiac output and blood pressure, and early electrical cardioversion may be necessary.

OUTCOMES

Early Results

Mortality

Risk of hospital death after isolated septal myectomy for HOCM is low: less than 1% in experienced centers (Fig. 96-9). Surgical risk may be higher among very elderly patients (particularly those with severe disabling symptoms associated with pulmonary hypertension), patients

with prior myectomy, or those requiring concomitant procedures.

Morbidity

Complications such as complete heart block requiring permanent pacemaker and iatrogenic ventricular septal perforation have become uncommon ($\leq 1\%$ to 2%).⁹⁰ Partial or complete left bundle branch block is a frequent

finding after surgical myectomy but is not associated with adverse sequelae. However, if the patient has complete right bundle branch block preoperatively, interruption of the left bundle after myectomy increases risk of complete heart block. This is particularly important in patients who have had alcohol septal ablation before operation. ElBardissi and coworkers⁹⁵ reported that risk of postoperative pacemaker insertion was 36% in patients who had alcohol septal ablation before myectomy compared with 3% for those without prior intervention.

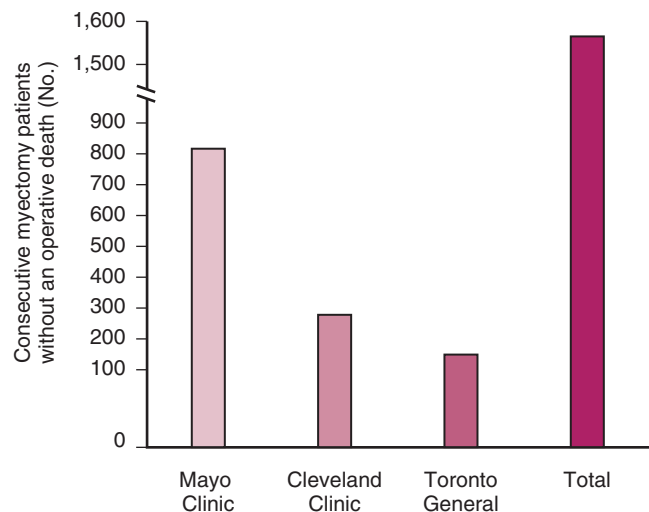


FIGURE 96-9 ■ Operative risk of isolated septal myectomy for hypertrophic cardiomyopathy is less than 1% and approaches zero in centers with broad experience with the procedure. (From Maron BJ: Surgical myectomy remains the primary treatment option for severely symptomatic patients with obstructive hypertrophic cardiomyopathy. *Circulation* 116:196–206, 2007.)

Late Results

Symptom Relief

Improvement in symptoms and exercise capacity after myectomy is highly predictable and durable; more than 90% of severely symptomatic patients have improvement of two or more function classes. Indeed, as illustrated in Figure 96-10, relief of outflow gradients by myectomy is equally effective in improving limitation caused by dyspnea, angina, or syncope.⁹⁶ Importantly, symptomatic benefit of myectomy is directly related to reducing the basal outflow gradient and mitral regurgitation and restoring normal LV systolic and end-diastolic pressures (in more than 90% of patients), which in turn may also favorably influence LV diastolic filling and myocardial ischemia. Relief of the gradient may decrease left atrial size and the subsequent risk for development of atrial fibrillation.

The outcome of patients with latent LVOT obstruction preoperatively is especially instructive. Often operation is withheld in these symptomatic patients because the resting LVOT gradient is less than 30 mm Hg, and

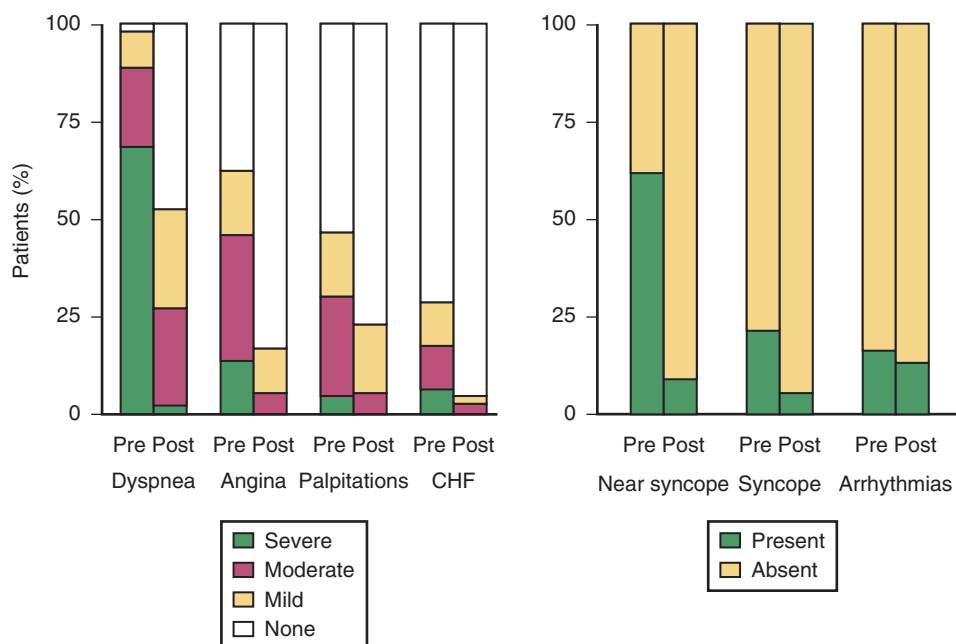


FIGURE 96-10 ■ Symptomatic status of patients with hypertrophic obstructive cardiomyopathy before (Pre) and after (Post) septal myectomy. Relief of obstruction improves angina, dyspnea, and syncope or presyncope. CHF, Congestive heart failure. (From McCully RB, Nishimura RA, Tajik AJ, et al: Extent of clinical improvement after surgical treatment of hypertrophic obstructive cardiomyopathy. *Circulation* 94:467–471, 1996.)

disability is presumed to be caused by diastolic dysfunction. But provocative maneuvers frequently elicit higher gradients and systolic anterior motion (SAM)-related mitral regurgitation that correlate with symptoms. Indeed, in our surgical practice, 30% of patients undergoing septal myectomy have latent obstruction with resting gradients less than 30 mm Hg, and postoperatively, NYHA functional class improves dramatically and to a similar extent as seen in patients with high resting LVOT gradients.⁹⁷

Late recurrence of large resting LV outflow gradients is very uncommon after successful myectomy in either adults or children with HOCM, and this is in contrast to patients who have surgery for relief of congenital membranous subaortic stenosis.⁴⁶ The most common causes of recurrent symptoms and obstruction are limited myectomy at the initial operation, midventricular obstruction, and anomalies of papillary muscles. Most often, inadequate myectomy at initial operation is a result of failure to extend the myectomy far enough toward the apex of the heart.⁹⁸

SURVIVAL

Septal myectomy is usually performed for relief of symptoms, but there is evidence that operation may improve survival of patients with HOCM. In a report by Ommen and coworkers,⁹⁹ late survival of 289 patients with HOCM undergoing septal myectomy was 98%, 96%, and 83% 1 year, 5 years, and 10 years postoperatively, and these survival rates were similar to those of an age- and sex-matched U.S. population and to those of HCM patients without obstruction (Fig. 96-11). In the same study, myectomy patients had superior survival free from all-cause mortality ($P < 0.001$), HCM-related mortality ($P < 0.001$), and sudden cardiac death ($P = 0.003$) compared with those of nonsurgical HCM patients with obstruction (Fig. 96-12), and on multivariable analysis, performance

of myectomy had a strong, independent association with survival (hazard ratio, 0.43; $P < 0.001$).

Studies also suggest mechanisms whereby relief of LVOT gradients might improve survival. The extent of LV hypertrophy is an important determinant of survival in patients with HCM,¹⁰⁰ and successful myectomy results in some regression of LV hypertrophy.^{101,102} Thus, patients with the obstructive form of HCM may have an additive burden of ventricular hypertrophy caused by pressure overload that is relieved by successful myectomy. It is interesting to note that whereas extent of LV hypertrophy is a risk factor for death in natural history studies of HCM, following myectomy, degree of hypertrophy preoperatively does not predict outcome.¹⁰³

Additional insights on improved survival of myectomy patients come from McLeod and associates,¹⁰⁴ who reviewed patients with HCM who had received ICDs. During follow-up (median, 4.5 years), 12 patients (17%) in the nonmyectomy group and only one patient (2%) in the myectomy group had appropriate ICD discharges (Fig. 96-13). The average annualized event rate was 4.3% per year in the nonmyectomy group compared with 0.24% per year after myectomy ($P = 0.004$). Thus, surgical myectomy and relief of outflow gradient is associated with a marked reduction in the incidence of appropriate ICD discharges and risk of sudden cardiac death.

The potential benefit of septal myectomy on patient survival is supported also by postoperative outcome of patients who present with syncope. The presence of syncope despite medical therapy in patients with HCM is considered an indication for surgical myectomy, and Orme and associates^{104a} documented that at median follow-up of approximately 5 years, the recurrence rate of syncope in myectomy patients was 11% compared to 40% in a medically treated group matched for other risk factors. Further, the 10-year survival rate was greater for patients who had undergone surgical myectomy than for the medically treated patients (82% vs. 69%).

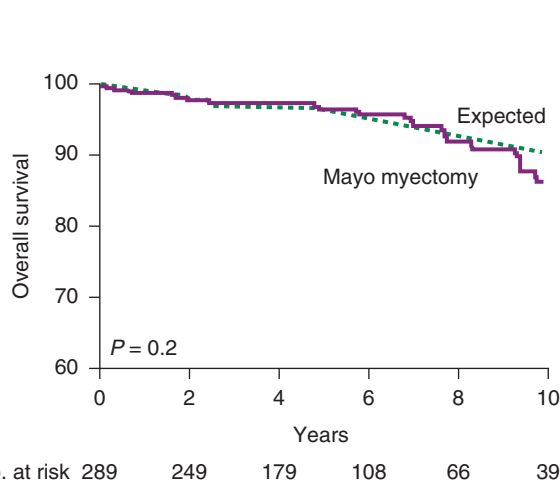


FIGURE 96-11 ■ Survival of patients with hypertrophic obstructive cardiomyopathy after septal myectomy is similar to that of an age- and gender-matched population. (From Ommen SR, Maron BJ, Olivotto I, et al: Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 46:470–476, 2005.)

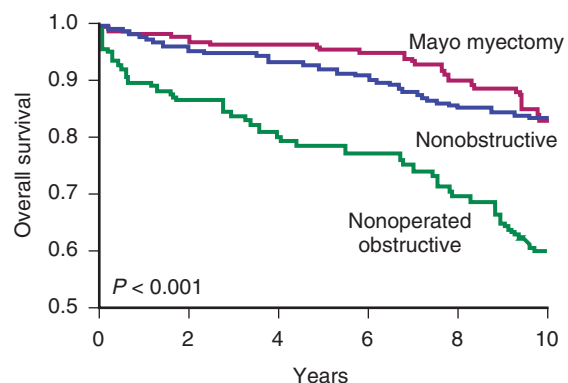


FIGURE 96-12 ■ Survival free from all-cause mortality in three hypertrophic cardiomyopathy patient subgroups: Mayo Clinic surgical myectomy ($n = 289$), nonoperated with obstruction ($n = 228$), and nonobstructive ($n = 820$). Myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, $P < 0.001$; myectomy versus nonobstructive hypertrophic cardiomyopathy, $P = 0.8$. (From Ommen SR, Maron BJ, Olivotto I, et al: Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 46:470–476, 2005.)

COMPARISON TO SEPTAL ARTERY ABLATION

Septal reduction can be achieved by selective infarction of septal branches of the LAD, and the advantages of avoiding surgical incision and hospitalization are obvious. In a review of alcohol septal ablation from 42 published

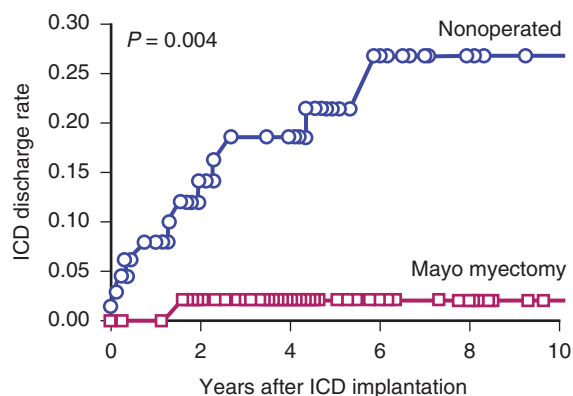


FIGURE 96-13 ■ Implantable cardioverter-defibrillator (ICD) discharge rates among patients with hypertrophic cardiomyopathy who had septal myectomy compared with nonmyectomy patients. Average annualized ICD discharge rates of 0.24% in the myectomy group compared with 4.3% in the nonmyectomy group ($P = 0.004$). (From McLeod CJ, Ommen SR, Ackerman MJ, et al: Surgical septal myectomy decreases the risk for appropriate implantable cardioverter defibrillator discharge in obstructive hypertrophic cardiomyopathy. *Eur Heart J* 28:2583–2588, 2007.)

studies (2959 patients), resting LVOT gradient decreased from 65 mm Hg to 16 mm Hg ($P < 0.001$), basal septal diameter reduced from 21 mm to 14 mm ($P < 0.001$), and hospital mortality was 1.5%.¹⁰⁵ However, the incidence of complete heart block requiring permanent pacemaker was 11%, and other important complications included coronary dissection (1.8%), pericardial effusion (0.6%), ventricular fibrillation (2.2%), stroke (1.1%), new right bundle branch block (46%), and new left bundle branch block (6.5%). Also, symptoms persisted in 11% of patients, re-do alcohol ablation was required in 6.6%, and surgical myectomy was necessary in 2.0%. Thus, whereas this procedure is less invasive, it is not without significant morbidity and mortality.

Because of unfavorable coronary anatomy, some patients with HOCM are not candidates for alcohol septal ablation.¹⁰⁶ Also, concern has been raised about the potential long-term risk of sudden death related to arrhythmogenic substrate from the resulting septal scar. Cardiac magnetic resonance imaging demonstrates that in most patients, alcohol septal ablation causes transmural tissue necrosis, located more inferiorly in the basal septum than myectomy; the infarct usually extends into the right ventricular side of the septum and sometimes spares the basal septum, leading to residual gradients at follow-up (Fig. 96-14).¹⁰⁷ In a nonrandomized comparative study, Sorajja and colleagues¹⁰⁸ reported that in-hospital complication rate is higher with ablation than with myectomy, and that in patients 65 years of age or younger, symptom relief is better after myectomy.

Thus, alcohol septal ablation is an option for patients who may have increased risk for operation, but septal

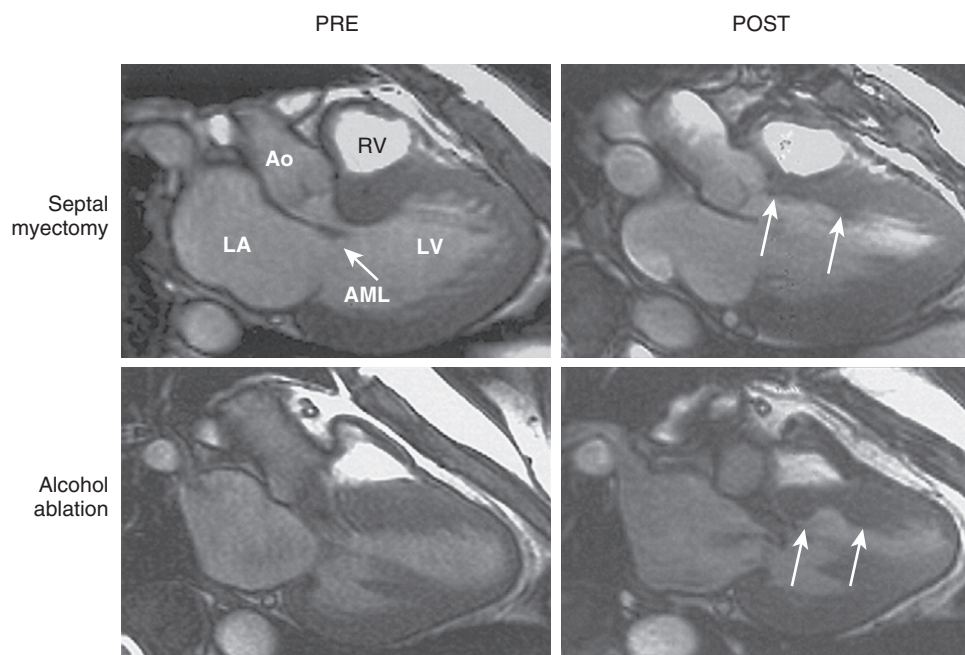


FIGURE 96-14 ■ Cardiac magnetic resonance image after septal myectomy versus septal ablation. *Top panels*, Long-axis views before (Pre) and after (Post) septal myectomy. The portion of basal septum evident in this plane, projecting into the left ventricular (LV) outflow tract, has been excised at myectomy (arrows). *Bottom panels*, Long-axis views before (left) and 5 months after (right) septal ablation. Ablation has spared the most proximal portion of basal septum. AML, Anterior mitral leaflet; Ao, aorta; LA, left atrium; RV, right ventricle. (From Valeti US, Nishimura RA, Holmes DR, et al: Comparison of surgical septal myectomy and alcohol septal ablation with cardiac magnetic resonance imaging in patients with hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 49:350–357, 2007.)

myectomy remains the gold standard for patients with HCM and severe LV outflow obstruction who are refractory to maximal medical therapy.^{61,90}

SPECIAL SUBGROUPS

The preceding discussion has focused on surgical treatment of patients with HCM and subaortic obstruction, and, whereas these patients constitute most of the patients considered for surgical treatment, other HCM patients with different ventricular morphology and pathophysiology may benefit from operation. Midventricular obstruction in HCM is less common than subaortic obstruction, has a different pathophysiologic mechanism, and, in untreated patients, may have a worse prognosis.¹⁰⁹ Unlike subaortic obstruction, related to systolic anterior motion of the mitral valve, midventricular obstruction is caused by systolic narrowing of the mid ventricle with apposition of the septum and papillary muscles. Secondary mitral valve regurgitation is uncommon and is not a part of the pathophysiology of symptoms such as dyspnea, but patients with HCM and midventricular obstruction may develop apical pouches/aneurysms that can lead to ventricular arrhythmias or thromboembolism.^{110,111}

The decision for myectomy in patients with midventricular obstruction is often confounded by uncertainty whether limiting symptoms are due to the intraventricular gradient or to diastolic dysfunction (or both). Also, there is a wide spectrum of phenotypes, and some patients will have both subaortic obstruction (with systolic anterior motion of the mitral leaflets) and midventricular obstruction.

In our experience, midventricular obstruction is most easily exposed through a transapical incision, and the contact lesion that is uniformly present guides excision of the septum.¹¹² Among 51 patients having operation for HCM with midventricular obstruction, a transapical approach was used in 32 patients and a combined transapical and transaortic approach was used in 19 patients. In 13 patients, an apical aneurysm or pouch was repaired at the time of midventricular myectomy. No early deaths or complications related to the apical incision have resulted.

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LEFT VENTRICULAR ASSIST DEVICES AND TOTAL ARTIFICIAL HEART

Koji Takeda • Hiroo Takayama • Yoshifumi Naka

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SynCardia

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Arrhythmia
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SUMMARY

Mechanical circulatory support (MCS) has become the standard of care for patients with refractory, end-stage heart failure.¹⁻⁷ A landmark trial in MCS demonstrated the superiority of a left ventricular assist device (LVAD) over optimal medical therapy with respect to improving survival and quality of life in this subgroup of patients.¹ Over the past decade, there has been a significant evolution in MCS device-related technologies. Devices have undergone substantial modifications in an effort to

improve survival while on support, increase durability, and limit device-related infections, device thrombosis, device malfunction, and perioperative bleeding.³⁻⁵ With improvements in device design yielding devices that can be implanted as destination therapy, the number of durable LVAD implants has dramatically increased in the United States every year (Fig. 97-1).⁶

Current MCS devices can be divided into the following subcategories on the basis of their features:

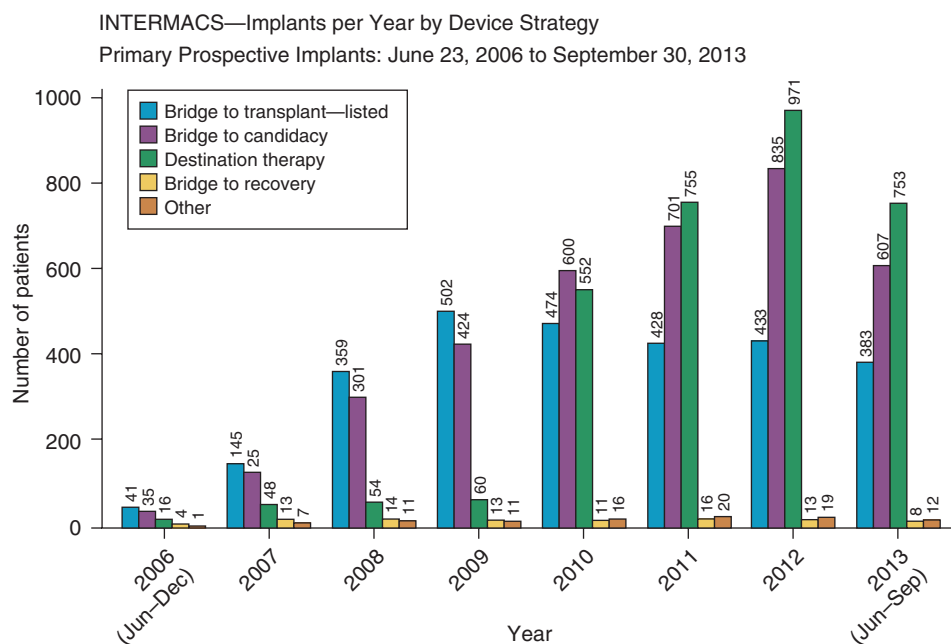


FIGURE 97-1 ■ Number of durable mechanical circulatory support device implants per year by device strategy. (Reproduced with permission from INTERMACS, *Quarterly Statistical Report*, 3rd quarter, 2013.)

short-term versus long-term devices, paracorporeal versus intracorporeal devices, pulsatile versus continuous flow devices, full versus partial support devices, and assist devices versus complete heart replacement (i.e., total artificial heart [TAH]). The indications for implantation of a mechanical device have expanded over time to include acute cardiogenic shock, bridge to transplant (BTT), bridge to candidate (BTC), and destination therapy (DT).^{1,3,6,7} This chapter presents a complete overview of MCS, including a historical perspective, indications for MCS, important factors related to patient selection, types of devices, results using MCS, surgical technique, post-operative management, and complications that occur with MCS.

HISTORICAL PERSPECTIVE

Dr. Michael DeBakey implanted the first mechanical assist device in 1963 in a patient with postcardiotomy shock after an aortic valve replacement. With growing interest in MCS, the Artificial Heart Program was founded in 1964. In 1966, DeBakey reported the first successful bridging to recovery with a ventricular assist device (VAD), also in a patient with postcardiotomy shock. The duration of support in this patient was 10 days.

In 1970, the Artificial Heart Program evolved into the Medical Devices Applications Branch of the National Heart and Lung Institute, with the primary focus of developing short- and long-term VADs as well as a TAH for heart replacement therapy. Dr. Denton Cooley reported the first successful bridging to transplant using MCS in 1978. In 1980, the currently named National Heart Lung and Blood Institute (NHLBI) accepted proposals by Abiomed, Baxter, Thermo Cardiosystems, and

Thoratec to develop VADs and the TAH. The first successful implantation of a heart replacement therapy, a TAH with the Jarvik-7-100, was reported in 1984. However, this device was removed from clinical practice in 1991 because of a relatively high incidence of device-related complications, such as thromboembolic events and infection.

With concurrent advancements in assist device technology, the U.S. Food and Drug Administration (FDA) approved the use of a mechanical assist device as a BTT in 1994—the first of which was HeartMate (Thoratec Corp., Pleasanton, CA), developed by Thermo Cardiosystems. It soon became clear to the cardiac surgery community that implantation of LVADs could salvage patients who were otherwise nonsalvageable and could also improve the quality of life of patients with advanced heart failure.

A major victory for MCS came in 2001 with the results of the REMATCH trial.¹ This prospective, randomized trial of patients with end-stage heart failure who were not eligible for transplantation demonstrated a significant survival advantage for patients who underwent implantation of a mechanical assist device as compared with those receiving optimal medical therapy. The study, however, also highlighted various complications of mechanical support, such as bleeding, infection, stroke, device malfunction, and development of right heart failure, which became a primary focus for device companies and engineers in subsequent years.

The emergence of newer generation VADs with a continuous flow pump driven by a rotary pump represented a further step in this field. A randomized trial demonstrated that a continuous flow pump significantly improved 2-year survival and device-related morbidity as compared with a pulsatile device.³ Since the approval of the continuous flow VADs for both transplant-eligible

(BTT) and transplant-ineligible patients (DT), the number of patients receiving MCS device therapy has been growing rapidly.

As VAD therapy entered the mainstream, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support)—a national registry for patients who are receiving MCS devices—was established in 2006. This registry was devised as a joint effort of the NHLBI, the Centers for Medicare and Medicaid Services (CMS), the FDA, clinicians, scientists, and industry representatives in conjunction with the University of Alabama at Birmingham and the United Network for Organ Sharing (UNOS). Analysis of the data collected is expected to facilitate further improvements in patient evaluation and management.

IMPLANT STRATEGIES FOR MECHANICAL CIRCULATORY SUPPORT

When considering MCS placement, five broad indications can be defined with regard to the clinical intent at the time of implantation. Complex decisions about candidacy for each strategy should be made by an experienced, multidisciplinary team including surgeons and cardiologists. This process is particularly important in ensuring appropriate selection of the patient, timing for device placement, and device to use.

Bridge to Transplant

BTT is a strategy for patients actively listed for heart transplant who would not survive or would develop end-organ dysfunction as a result of low cardiac output before an organ becomes available. While the patient remains on the waiting list, insertion of a durable LVAD can improve survival, functional status, and quality of life.

Destination Therapy

DT is a strategy for patients requiring long-term, lifelong circulatory support who are not eligible for heart transplant because of relative or absolute contraindications.

Bridge to Candidacy

MCS may be used for patients who are not currently listed for heart transplant, with no absolute or a permanent contraindication to transplant. MCS may allow these patients to be eligible for transplant by improving their end-organ function and nutrition, decreasing pulmonary vascular resistance, as well as resolution of comorbidities or lifestyle-related problems (e.g., weight loss, smoking cessation).

Bridge to Decision

In circumstances when a patient is in acute cardiogenic shock, it may not be possible to determine the candidacy for transplant, long-term VADs or myocardial recovery. Additionally, the patient may or may not have multisystem organ failure, and the patient's neurologic status may

or may not be known. A short-term MCS may be used to stabilize the patient's condition and to assess reversibility, as a bridge to more definitive therapies. The next step can be planned while the patient is on the MCS.

Bridge to Recovery

MCS may be used as a temporary circulatory support to unload the ventricle. During this time, MCS use may enhance myocardial recovery from an acute injury enough to wean off the device without the need for transplant.

PATIENT SELECTION

Careful patient selection—a critical element in achieving good clinical results with MCS—requires the evaluation of heart failure severity and the assessment of operative risk and comorbidities.

Common indicators of advanced heart failure for referral for MCS include New York Heart Association (NYHA) class IIIb-IV symptoms, frequent rehospitalizations for heart failure, or unresponsiveness to medical therapies (including neurohormonal antagonists and diuretics), recurrent/refractory ventricular tachyarrhythmia, inotrope dependence, unresponsiveness to cardiac resynchronization therapy, end-organ dysfunction as a result of low cardiac output, peak oxygen consumption less than 14 mL/kg/min, or 6-minute walk distance less than 300 m.⁸ The Seattle Heart Failure Model can be used to estimate a heart failure patient's expected mortality in the next 1 to 2 years and identify patients who might benefit from LVAD support.⁹

The INTERMACS registry classifies heart failure patients into seven clinical profiles based on their signs and symptoms (Table 97-1). These profiles also help to define illness acuity and severity and to assess the operative risk.⁶ The INTERMACS data showed that the proportion of patients in progressive cardiac decompensation (level 2) or cardiogenic shock (level 1) at the time of implantation of a durable LVAD has decreased from approximately 64% before 2011 to slightly less than 54% in 2012. This is because the patients in INTERMACS levels 1 and 2 have a 5% to 8% decrease in 1-year survival rate compared with patients in other INTERMACS levels (Fig. 97-2). Generally, for patients in INTERMACS level 1, placement of a durable VAD is not recommended because these patients are often compromised by end-organ damage, uncertain neurologic status, infection, or major coagulopathy. Therefore, short-term MCS should be applied in these patients as a bridge to decision (BTD) or recovery. Conversely, patients in INTERMACS level 6 or 7 (NYHA class III) are, in general, considered “too well” for MCS placement. Currently, patients in INTERMACS levels 2, 3, or 4 are likely to be appropriate candidates for a durable LVAD implantation.

It is also important to identify those patients with significant right ventricular (RV) dysfunction before LVAD implantation, because RV failure after LVAD implantation can be a fatal complication.¹⁰⁻¹³ The implantation of an LVAD can decrease RV afterload by reducing

TABLE 97-1 INTERMACS Profile Descriptions

Profile 1: Critical Cardiogenic Shock

Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. "Crash and burn."

Profile 2: Progressive Decline

Patient with declining function despite intravenous inotropic support; may be manifest by worsening renal function, nutritional depletion, inability to restore volume balance. "Sliding on inotropes." Also describes declining status in patients unable to tolerate inotropic therapy.

Profile 3: Stable But Inotrope Dependent

Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both) but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction. "Dependent stability."

Profile 4: Resting Symptoms

Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during ADLs. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.

Profile 5: Exertion Intolerant

Comfortable at rest and with ADLs but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may be more at risk than INTERMACS 4 and require definitive intervention.

Profile 6: Exertion Limited

Patient without evidence of fluid overload is comfortable at rest and with ADLs and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment. "Walking wounded."

Profile 7: Advanced NYHA III

A placeholder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.

ADLs, Activities of daily living; NYHA, New York Heart Association.

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pulmonary artery pressures. However, at the same time, increasing cardiac output with an LVAD support may increase systemic venous return to a diseased RV that may not be able to accommodate the additional volume. Furthermore, LV pressure unloading by an LVAD can cause the interventricular septum to shift leftward,

leading to geometric changes in the RV that reduce RV function, exacerbating tricuspid regurgitation. The presence of depressed RV myocardial function can be determined from preoperative hemodynamic indices, including central venous pressure, pulmonary artery pressure, cardiac output, transpulmonary pressure gradient, pulmonary vascular resistance, and RV stroke work index (RVSWI).¹⁰⁻¹³ The RVSWI can be calculated using the following formula: (mean pulmonary artery pressure – mean central venous pressure) × stroke volume ÷ body surface area. Patients with high pulmonary artery pressure and normal central venous pressure (high RVSWI) are at lower risk of postoperative RV failure because the RV is able to generate sufficient pressure. A preoperative echocardiographic assessment of RV function is also important. Attention should be paid to RV dilation, contractility, and degree of tricuspid regurgitation. Numerous studies have attempted to identify the risk factors for the development of RV failure after LVAD placement. The most recent study demonstrated that preoperative predictors of RV failure after implantation of a contemporary continuous flow LVAD included central venous pressure/pulmonary capillary wedge pressure ratio of greater than 0.63, need for preoperative ventilator support, and blood urea nitrogen level greater than 39 mg/dL.¹² Univariate predictors also included RVSWI less than 300 mm Hg × mL/m², central venous pressure greater than 15 mm Hg, and elevated white blood cell count. For patients at a significantly high risk of RV failure, planned biventricular assist device placement should be indicated.¹⁴

Pulmonary hypertension with an elevated pulmonary vascular resistance (>5 wood units) should not be considered an absolute contraindication to MCS. Modern selective pulmonary vasodilators such as sildenafil can reduce pulmonary pressures. In addition, patients who undergo LVAD implantation usually have improved pulmonary vascular resistance.^{15,16} The LVAD can be considered as a BTC in possible transplant candidates with fixed pulmonary hypertension.

Contraindications for device implantation include irreversible end-organ failure, particularly renal failure and hepatic failure, which are uniformly independent predictors of poor outcome.^{6,17-21} Severe, unrecoverable neurologic injury is also a contraindication for device implantation. Systemic sepsis poses a significant risk to patients undergoing LVAD implantation because it can cause a profound refractory vasodilatory state or lead to an increased incidence of device-related infections, such as device endocarditis.^{22,23}

In the pulsatile flow era, numerous studies have identified independent predictors of adverse outcome.^{21,24-26} The common denominator among these independent predictors of mortality is end-organ failure, such as respiratory failure requiring mechanical ventilation, renal failure requiring dialysis, ischemic hepatitis with markedly elevated transaminases, and diffuse coagulopathy resulting from malfunctioning clotting mechanisms. In the revised Columbia screening scale, the following clinical factors were identified as preoperative independent predictors of adverse outcome: mechanical ventilation, prior cardiectomy, prior LVAD implantation, central

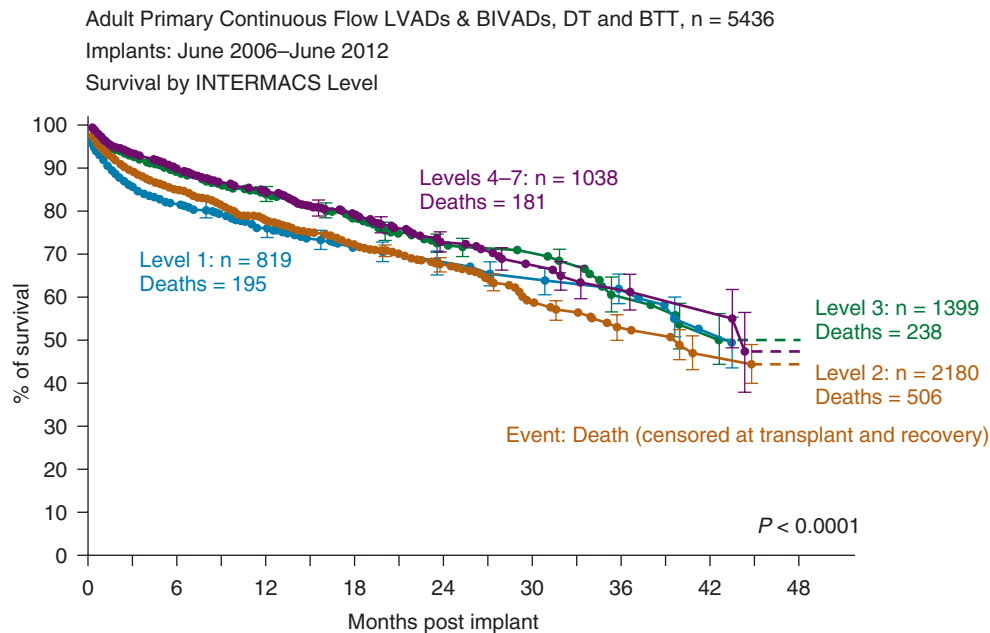


FIGURE 97-2 ■ Survival after durable mechanical circulatory support device implantation by INTERMACS level. *BiVAD*, Biventricular assist device; *BTT*, bridge to transplant; *DT*, destination therapy; *LVAD*, left ventricular assist device. (Reproduced with permission from Kirklin JK, Naftel DC, Kormos RL, et al: Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. *J Heart Lung Transplant* 32:141–156, 2013.)

venous pressure of greater than 15 mm Hg, and prothrombin time of longer than 16 sec.¹⁵ Each factor was given a statistically weighted score, with a score of higher than 5 being associated with a 46% mortality rate and a score of 5 or lower being associated with a 12% mortality rate.

In the continuous flow era, from the analysis of 1122 patients receiving the HeartMate II as a BTT or DT, preoperative predictors of 90-day mortality were older patients, greater degree of hypoalbuminemia, renal dysfunction (higher creatinine), coagulopathy (higher INR), and implant surgery at less experienced centers. Based on the calculated risk score from these factors, mortality rates in the low, medium, and high-risk score groups were 4%, 16%, and 29%, respectively.²⁷ From the INTERMACS registry data, risk factors for mortality included older age, INTERMACS level 1 and 2, DT, renal dysfunction, RV dysfunction, and surgical complexity.⁶

Poor preoperative hepatic function has also been demonstrated to be an independent predictor of mortality after LVAD implantation.^{17,21,24,26} Decreased hepatic synthetic function increases the chance of developing a diffuse coagulopathy intraoperatively and postoperatively, which can cause RV failure secondary to increased transfusion requirements of blood products. The Model of End-stage Liver Disease (MELD) score calculated based on serum bilirubin, creatinine, and INR values is reported to be useful in identifying LVAD candidates at high risk for perioperative bleeding and mortality.^{28,29} Optimization of hemodynamics with reduction of central venous pressure and improvement of cardiac output should be pursued before LVAD implantation to improve hepatic congestion and increase hepatic blood flow.

Severe renal dysfunction was associated with a major reduction in early survival after durable VAD

implantation.^{6,18,20,21,26,27} The incremental effect of worsening renal dysfunction was shown by assigning “moderate” renal dysfunction to patients with a creatinine level greater than 2 mg/dL or blood urea nitrogen level greater than 60 mg/dL, and “severe” renal dysfunction to patients requiring dialysis near the time of device implantation.⁶ Although renal dysfunction caused by low cardiac output or renal vein congestion generally improves after MCS placement, caution should be paid in a patient with severe intrinsic renal disease such as chronic hypertension or diabetes mellitus. Patients with end-stage renal disease requiring dialysis should not be considered for durable LVAD implantation, because of their increased risk of infection.

Preoperative nutrition status assessment is also important.³⁰ Patients with cardiac cachexia are predisposed to poor healing, impaired immunity, and infection, which are generally associated with high mortality.^{26,27} In contrast, obesity is not a contraindication to using a continuous flow LVAD, although patients with a body mass index higher than 35 kg/m² are not eligible for heart transplant.³¹ These devices can provide sufficient cardiac output support to meet the metabolic demands of obese patients.^{32,33}

To assess the patient’s ability to understand VAD care, an investigation of prior psychiatric disorders, history of drug and alcohol abuse, compliance, and cognitive function needs to be conducted. Furthermore, adequate family/caregiver, financial, and environmental support are additional factors for determining potential LVAD candidates.³⁴

Although it is important not to delay durable VAD implantation to the point of significant end-organ dysfunction, it is beneficial to optimize a relatively stable patient preoperatively. This may include hemodynamics

optimization with diuretics, inotropes, short-term MCS (coagulopathy correction) with vitamin K, platelets, or fresh-frozen plasma, and nutrition management. With appropriate patient selection and timing of LVAD implantation, it is possible to achieve excellent results with relatively low associated morbidity and mortality.

TYPES OF DEVICES

Short-Term Mechanical Circulatory Support

Recent innovation of continuous flow technology contributes to the development of various types of short-term MCS, which can be distinguished by the method of placement (i.e., percutaneous or surgical). The current options for percutaneous circulatory support include intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), the Impella, and TandemHeart. Surgical options include the CentriMag (Thoratec, Pleasanton, CA) ventricular support system. Each of these devices is designed for short-term use.

Percutaneous Devices for Short-Term Mechanical Support

Intra-Aortic Balloon Pump. Insertion of an IABP was first reported by Kantrowitz in 1968. It has since become one of the most common forms of mechanical support for the failing heart. It is commonly used for high-risk percutaneous coronary intervention (PCI), acute cardiogenic shock after myocardial infarction (MI), complications after MI such as a ruptured papillary muscle, cardiomyopathy, and preoperative optimization of an MI patient who is awaiting coronary artery bypass grafting (CABG).³⁵ Its mechanism of action involves inflation of the balloon in the descending aorta during diastole, which reduces afterload, increases coronary artery perfusion and pressure, improves myocardial oxygen supply, and decreases myocardial oxygen demand.³⁶ Counterpulsation can be synchronized with either an electrocardiogram or an arterial waveform. Vascular complications of

the IABP include femoral artery rupture, pseudoaneurysm, descending aortic dissection, as well as distal ischemia as a result of impedance of forward flow.³⁷

Extracorporeal Membrane Oxygenation. For patients in circulatory and respiratory failure, ECMO is a viable option. This system uses a centrifugal pump with an oxygenator and a heat exchanger in the circuit, yielding complete cardiopulmonary bypass. A venovenous ECMO is used for respiratory failure with preserved native heart function. To support the failing heart, a venoarterial (VA) ECMO is required (Fig. 97-3). A VA-ECMO system can provide full circulatory support with over 4.5 liter/min flow and rapidly improve tissue oxygenation. The major advantage of this system is the quick and easy percutaneous insertion of inflow and outflow cannulas—generally via the femoral artery and vein. Major disadvantages include infection, bleeding, and complications related to vascular access. Most survival data reported with ECMO have been in the pediatric literature.³⁸ The Extracorporeal Life Support Organization (ELSO) registry has accumulated data on more than 50,000 ECMO cases from more than 220 ECMO centers worldwide, including approximately 2300 cases of adult cardiac failure. In 2012, ELSO reported a survival to discharge rate of 39% for adult cardiac failure.³⁹ No meta-analyses of ECMO or randomized control trials with a mortality endpoint have been published. However, the ECMO system is likely to have the greatest potential for wider clinical use as a short-term MCS in cases such as cardiogenic shock.

TandemHeart. The TandemHeart (CardiacAssist, Inc., Pittsburgh, PA) is another percutaneously inserted device that uses a centrifugal pump. Two cannulas are inserted percutaneously with inflow from the left atrium—via a trans-septal puncture from a catheter entering from the femoral vein to the inferior vena cava to the right atrium and left atrium, and across the interatrial septum—and outflow into the femoral artery (Fig. 97-4). The pump can deliver flow rates up to 5.0 liter/min at a maximum speed of 7500 rpm. The initial clinical experience with this device for patients with high-risk PCI and post-MI cardiogenic shock has been favorable compared with

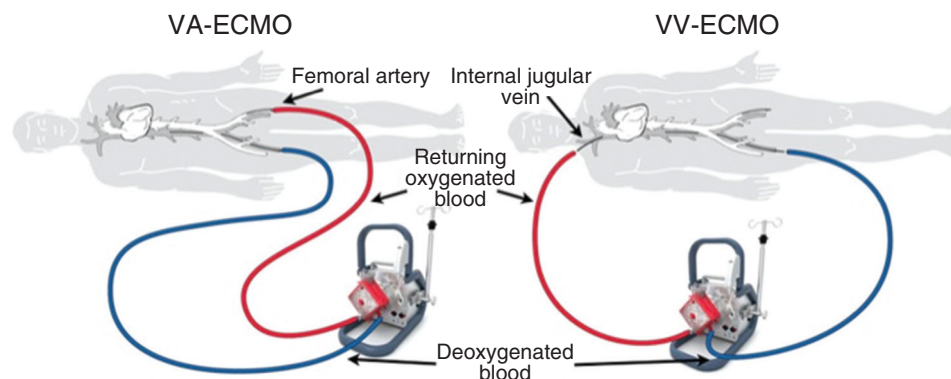


FIGURE 97-3 ■ Extracorporeal membrane oxygenation. ECMO, Extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous. (Reproduced with permission from Cove ME, MacLaren G: Clinical review: mechanical circulatory support for cardiogenic shock complicating acute myocardial infarction. *Crit Care* 14(5):235, 2010.)

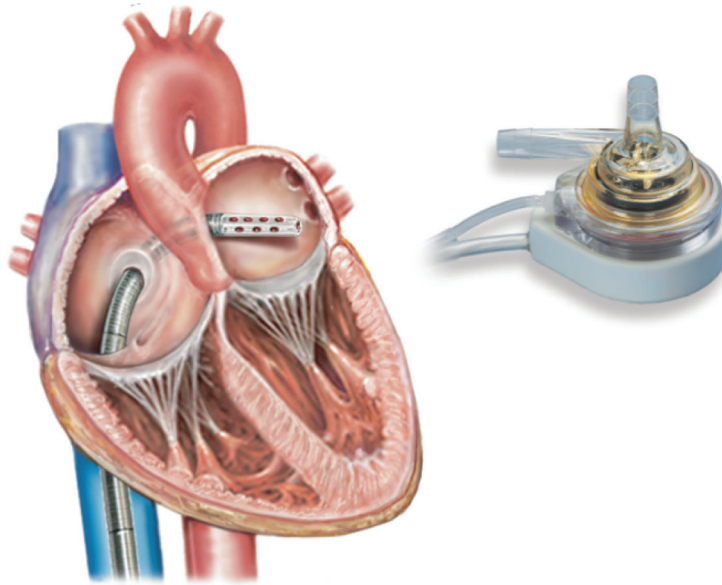


FIGURE 97-4 ■ TandemHeart. (Reproduced with permission from CardiacAssist, Inc.)



FIGURE 97-5 ■ Abiomed Impella family. (Reproduced with permission from Abiomed, Inc.)

IABP.⁴⁰ Subsequent reports demonstrated the TandemHeart circulatory support led to improvement in cardiac index, decrease in pulmonary capillary wedge pressure, and recovery in end-organ function.^{41,42} However, no randomized control trial with a mortality endpoint has been conducted. The popularity of this device may be limited because of its relatively complex mode of insertion requiring trans-septal puncture.

Abiomed Impella. The Impella is an intravascular microaxial rotary pump that can be inserted across the aortic valve to provide forward blood flow from the left ventricle into the ascending aorta. The family of the Impella system includes 2.5, CP, 5.0, LD, and RP (Fig. 97-5).

The Abiomed Impella 5.0/LD—providing flow up to 5 liter/min—is inserted by a cardiac surgeon into the ascending aorta or a peripheral artery, such as the femoral or axillary artery. It is used for acute cardiogenic shock

or postcardiotomy shock. Preliminary reports demonstrated a better survival benefit with implantation of the Impella than with an IABP for patients with postcardiotomy shock.⁴³ A subsequent multicenter prospective trial demonstrated that the use of the Impella 5.0/LD in patients with postcardiotomy shock yielded favorable outcomes.⁴⁴

The Impella 2.5 is a minimally invasive cardiac assist device that is usually inserted by an interventional cardiologist percutaneously through the femoral artery up the descending aorta, across the aortic arch, down the ascending aorta, and across the aortic valve into the left ventricle. This is generally performed under either echocardiographic or fluoroscopic guidance. This device can provide flow up to 2.5 liter/min, giving partial circulatory support, and is relatively easy to implant. Clinical trials, focusing on high-risk PCI and acute MI cases,⁴⁵⁻⁴⁷ have suggested that the Impella 2.5 may provide superior hemodynamic support compared with the IABP. However, similarly to the ECMO and TandemHeart, no conclusive data with mortality as an endpoint are available for the Impella pump family.⁴⁸

The Impella CP has recently become clinically available in the United States. With a maximal flow of 3.5 liter/min, it may overcome the flow limitations of the Impella 2.5.

The Impella RP is specifically designed for RV support and is currently undergoing a clinical trial.

HeartMate Percutaneous Heart Pump. The HeartMate PHP (percutaneous heart pump; Thoratec, Pleasanton, CA) is an investigational device with a catheter-based axial flow pump (Fig. 97-6). Its collapsible elastomeric impeller and nitinol cannula allow for percutaneous insertion. The system can generate 4 to 5 liter/min of flow. It successfully completed the first-in-man phase in 2013 for adjunctive hemodynamic support during a high-risk PCI, with clinical trials planned for 2014.

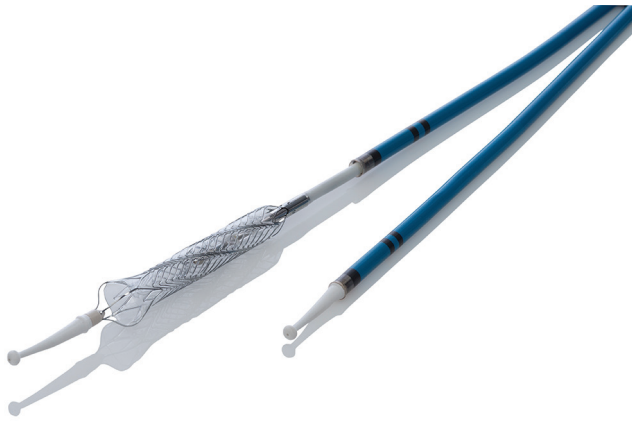


FIGURE 97-6 ■ HeartMate PHP (percutaneous heart pump). In development; not approved for clinical use. (Reproduced with permission from Thoratec Corp.)



FIGURE 97-7 ■ CentriMag. (Reproduced with permission from Thoratec Corp.)

Surgical Devices for Short-Term Mechanical Support

Abiomed BVS 5000 and AB5000. The Abiomed BVS 5000 is a dual-chambered, pneumatically driven, extracorporeal pump that can be used for short-term support as a univentricular or biventricular assist device. The device is capable of flowing up to 6 liter/min. Many series have reported acceptable results with this device.^{49,50}

The Abiomed AB5000—the next-generation device after the BVS 5000—is fully automated and has a vacuum-assisted console. Advantages of this device over its predecessor include allowing patients to be more mobile and extending the duration of device support.

CentriMag. The CentriMag blood pump (Thoratec, Pleasanton, CA) is an extracorporeal centrifugal pump that is FDA approved for up to 6 hours of support time, operating without mechanical bearings or seals.⁵⁰⁻⁵² The system combines the drive, magnetic bearing, and the rotor function into a single unit (Fig. 97-7). The rotor is magnetically levitated, which enables the device to rotate



FIGURE 97-8 ■ HeartMate XVE. (Reproduced with permission from Thoratec Corp.)

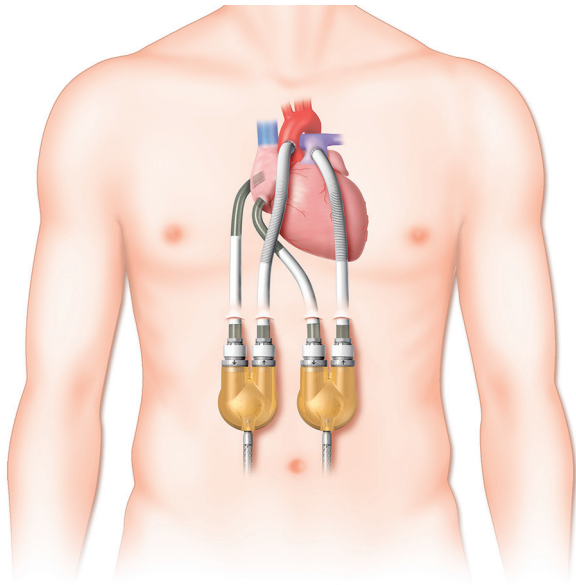
without friction or wear, and eliminates heat production. This serves to minimize trauma to the blood and avoids mechanical failure. Because the rotor surface is uniformly washed, blood stagnation and turbulence in the pump are minimized. Hemolysis is reduced because the mechanical gaps in the pump are wider than 0.6 mm, reducing shear forces. The device can produce flows of up to 10 liter/min with a priming volume of 31 mL.

Implantation of a CentriMag is less technically challenging and faster than implantation of other devices. The cannulas are inserted using techniques similar to those used for routine cannulation in cardiopulmonary bypass. Another particularly useful feature of the device is the ease of adjustment of the device speed and resulting flow. Based on the patient's clinical scenario (i.e., to increase flow during periods of sepsis and decrease flow when attempting to assess weanability from the device), the speed of the device can be increased or decreased simply by pushing a button. This system can provide isolated left ventricular support as an LVAD, isolated right ventricular support as a RVAD, or biventricular support as a full-support biventricular assist device (BiVAD).^{51,52} BiVADs allow decompression of both ventricles, restore hemodynamic stability, provide enhanced peripheral perfusion, and prevent end-organ dysfunction. The CentriMag is a rescue device that can be surgically implanted in patients with acute refractory cardiogenic shock.

Long-Term Mechanical Circulatory Support

Pulsatile Devices

Thoratec HeartMate XVE. The HeartMate XVE LVAD is FDA approved for both BTT and DT (Fig. 97-8). This device has undergone several major transformations. The older version had a pump operated by a pneumatically driven mechanism and contained a large controller console. The newer-generation device is electrically vented and contains a portable console and batteries, giving patients more mobility. Furthermore, the device produces a pulsatile flow with a stroke volume of 83 mL and a maximal flow of 10 liter/min. A large landmark trial of this device has demonstrated superior outcomes compared with optimal medical management.¹



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FIGURE 97-9 ■ Thoratec PVAD (paracorporeal biventricular assist device). (Reproduced with permission from Thoratec Corp.)

However, its long-term use is limited by the high probability of device-related complications.

Thoratec Paracorporeal Ventricular Assist Device.

The Thoratec paracorporeal VAD is a versatile device that has been used extensively for univentricular and biventricular support (Fig. 97-9). The paracorporeal placement of the pumping chamber allows the device to be implanted in patients with body surface areas of less than 1.5 m². The device consists of a polyurethane blood sac contained in a polycarbonate housing, attached to a large pneumatic console, which is used to generate a pulsatile flow with a maximal stroke volume of 65 mL. The device is capable of a flow up to 7.2 liter/min. Tilting disc mechanical valves maintain unidirectional flow. Because the device is placed paracorporeally, less dissection is required. Inflow for the LVAD is from the left atrium or LV apex, with outflow to the ascending aorta. Inflow for the RVAD is from the right atrium or right ventricle, with outflow to the pulmonary artery. The device requires systemic anticoagulation with either heparin or warfarin. With the introduction of the TLC-II portable driver, the system has become less cumbersome for patients and caregivers, improving the patients' mobility and ability to participate in rehabilitation programs.⁵³

Thoratec Intracorporeal Ventricular Assist Device.

The Thoratec intracorporeal VAD, like the paracorporeal VAD, is a versatile device that can provide isolated left, right, or biventricular support. Because it is implantable, it requires more dissection than the paracorporeal VAD. It is the first FDA-approved implantable VAD with biventricular capability for BTT and postcardiotomy shock. A multicenter trial including 39 patients supported with this device reported a success rate of 70% for BTT

and 67% for postcardiotomy recovery, which represents an improvement over historical results for the paracorporeal VAD of 69% for BTT and 48% for postcardiotomy recovery.⁵⁴

Axial Flow Pumps—Second-Generation Devices

Axial flow pumps are continuous flow pumps that operate with a propeller revolving at a set number of revolutions per minute (rpm). Advantages over pulsatile pumps include reduced noise levels and enhanced durability, the latter being attributed to fewer moving parts and contact bearings. The smaller size of these pumps also allows the device to be inserted with less dissection, because the size of the pocket is minimized and sometimes completely eliminated (Fig. 97-10).^{3,7} Disadvantages of an axial flow pump include the lack of a mechanical backup mechanism in the event of major device malfunction, hemolysis as a result of shear forces, and the potential for creating negative intraventricular pressure, with resultant device thrombosis, air embolism, or arrhythmia. Key factors in avoiding the creation of negative intraventricular pressure include preload optimization and perfect LV apical inflow cannula placement.

Several studies have evaluated the potential adverse effects of low-pulsatile continuous flow pumps on end-organ perfusion and function. On the basis of current data, adequate end-organ perfusion and function can be maintained with low-pulsatile continuous blood flow.^{55,56}

After the initial landmark trial showing a significant improvement in the quality of life and survival of patients after implantation of a continuous flow pump as compared with a pulsatile flow device (Fig. 97-11), this group of VADs has become the mainstream for BTT therapy and DT.^{3,7} Since the FDA approval of the HeartMate II device for BTT therapy in 2008 and for DT in 2010, over 98% of all LVADs implanted in the United States were continuous flow pump.⁶

Thoratec HeartMate II. The Thoratec HeartMate II VAD is an axial flow rotary pump constructed of titanium (Fig. 97-12), which can generate flows up to 10 liter/min operating at pump speeds of 6000 to 15,000 rpm. Inflow is via the LV apex, and outflow is via the ascending aorta. The axial flow design eliminates the need for a blood-pumping chamber and volume compensation necessary for volume-displacement LVADs. The pump housing is implanted in the small preperitoneal space and requires only a small pocket. A small percutaneous driveline exits the skin in the right or left upper abdomen. This feature makes the device more suitable for implantation in patients with a smaller body size. Theoretical benefits over previous series of VAD system include a reduced risk of infection, greater patient comfort and quality of life, and greater device durability. Furthermore, it is substantially smaller than the HeartMate XVE and requires a less invasive operative approach. A randomized control trial demonstrated the superiority of the HeartMate II compared with the HeartMate XVE in terms of survival, quality of life, and durability.³ The HeartMate II is approved by the FDA for both BTT therapy and DT.

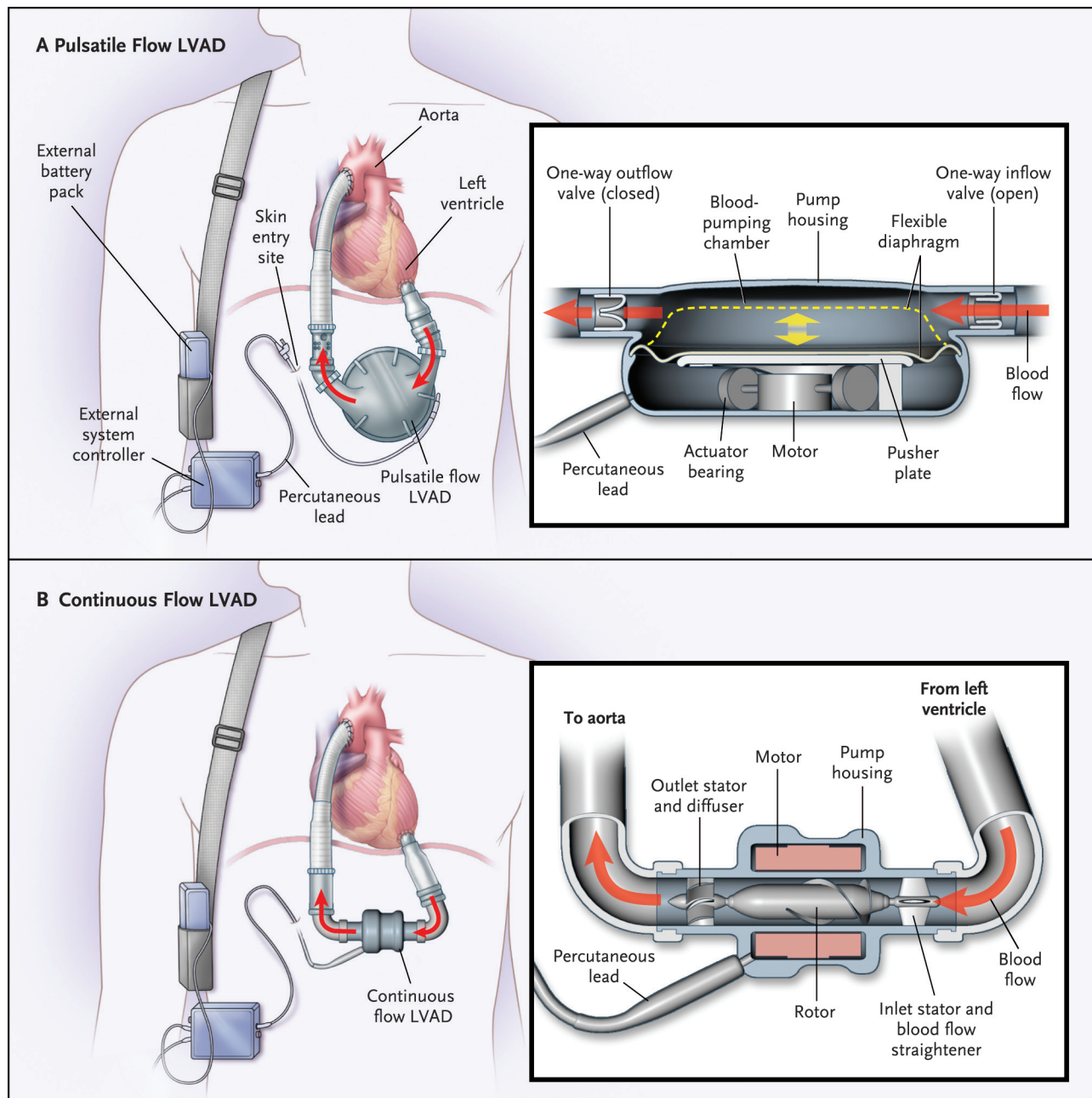


FIGURE 97-10 ■ **A**, Pulsatile flow device. **B**, Continuous flow device. *LVAD*, left ventricular assist device. (Reproduced with permission from Slaughter MS, Rogers JG, Milano CA, et al: Advanced heart failure treated with continuous flow left ventricular assist device. *New Engl J Med* 361(23):2241–2251, 2009.)

The accumulating clinical experience suggests that the pump is associated with a notable improvement in survival. The original HeartMate II BTT trial demonstrated a 1-year overall survival rate of 68%, which has improved to 85% according to more recent data.⁷ In the HeartMate II DT trial, the 2-year survival rate improved from 58% in the early era to 63% in the later era.⁵⁷

Jarvik 2000. The Jarvik 2000 (Jarvik Heart, Inc., New York, NY) is an electromagnetically actuated pump constructed of titanium, measuring 2.5 cm in diameter and weighing 90 g (Fig. 97-13), with a displacement of approximately 30 mL. The titanium impeller blades are

held in place by ceramic bearings. The impeller rotates at speeds of 8000 to 12,000 rpm and can generate a flow of up to 7 liter/min. A unique feature of this device is that the pumping chamber is implanted in the left ventricle. The outflow graft is anastomosed to the descending thoracic aorta. Surgical implantation of the device is typically accomplished through a left thoracotomy.⁵⁸ The pump speed can be adjusted by an external controller dial ranging from 1 to 5. The speed setting of 1 is the slowest, driving the impeller at 8000 rpm and producing a blood flow of 1 to 2 liter/min, whereas the speed setting of 5 is the fastest, driving the impeller at 12,000 rpm and producing a blood flow of 5 to 7 liter/min.⁵⁹

The multiple versions of the Jarvik 2000 device can be differentiated by their energy source. The percutaneous model has a single driveline that exits through the patient's anterior abdominal wall. One version contains skull-mounted pedestals used with cochlear implants: a titanium pedestal is screwed into the skull with a transcutaneous connector that attaches to the power cord. The behind-the-ear cable system may have significant quality-of-life advantages and reduced risk of infection

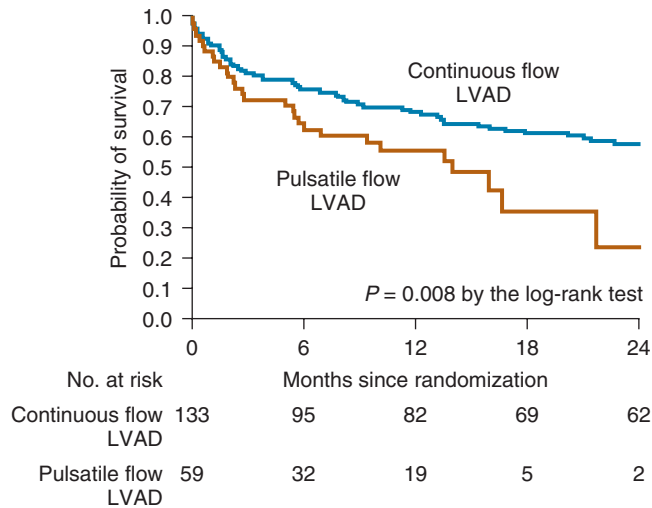


FIGURE 97-11 ■ Survival after continuous versus pulsatile flow left ventricular assist device (LVAD) implant. (Reproduced with permission from Slaughter MS, Rogers JG, Milano CA, et al: Advanced heart failure treated with continuous flow left ventricular assist device. *New Engl J Med* 361(23):2241–2251, 2009.)

compared with the abdominal cables. Furthermore, it enables patients to shower and bathe normally and even go swimming. This system is currently under trial for DT.^{59,60}

MicroMed DeBakey. The MicroMed DeBakey VAD (MicroMed Cardiovascular, Inc., Houston, TX) was developed as a collaborative effort between the Baylor College of Medicine and National Aeronautics and Space Administration engineers. The pump unit for the MicroMed DeBakey VAD is made of titanium, weighs 95 g, and measures only 1.2 inches in diameter and 3 inches in length. The impeller is capable of generating flows up to 10 liter/min. A relatively high number of reports have described stroke and microemboli formation with this device.^{61,62} The child version is approved by the FDA for BTT use in children aged 5 to 16 years.

Newer (Third-) Generation Pumps and Future Devices

Newer-generation devices, so-called third-generation devices, have been designed to address several shortcomings of second-generation axial flow pumps, such as thromboembolic complications and limited device durability. Many of these devices operate on the basis of magnetic levitation technology, in which the rotating propeller is magnetically suspended in a column of blood, obviating the need for contact-bearing moving parts and providing the theoretical benefit of enhanced durability. Continuous flow pumps are generally smaller, can be inserted with only a small device pocket or no pocket at all, are less traumatic, and may have a decreased risk for

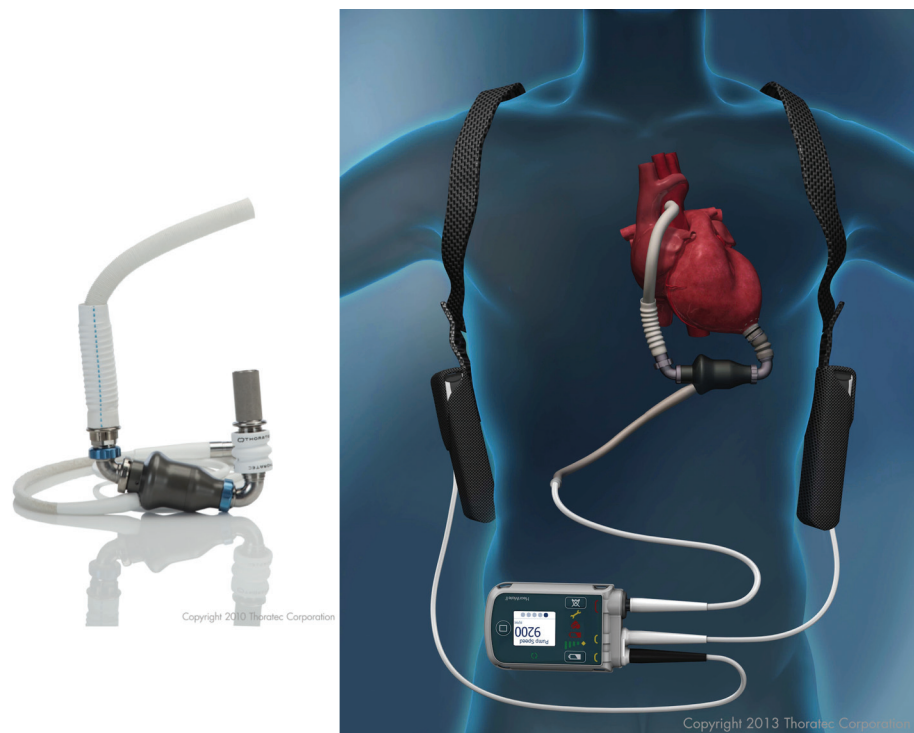


FIGURE 97-12 ■ HeartMate II. (Reproduced with permission from Thoratec Corp.)

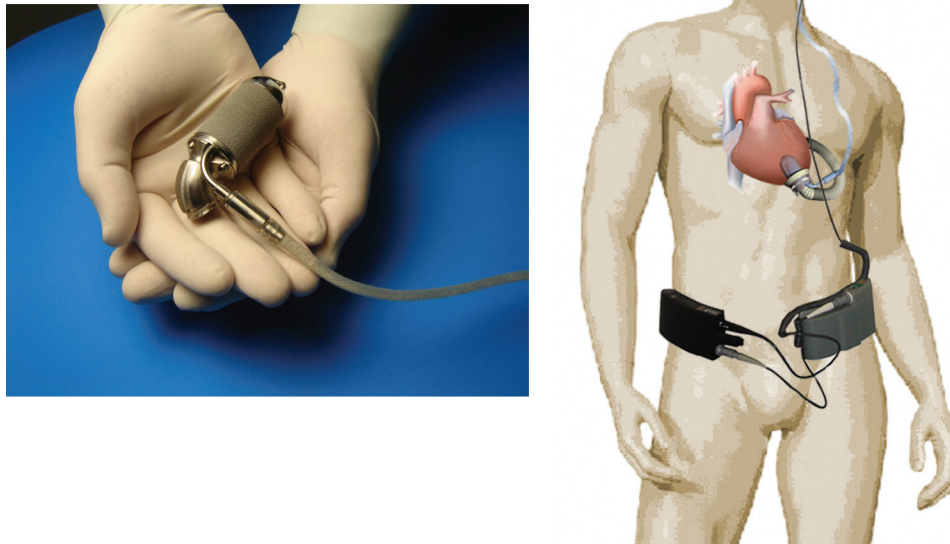


FIGURE 97-13 ■ Jarvik 2000. (Reproduced with permission from Jarvik Heart, Inc.)

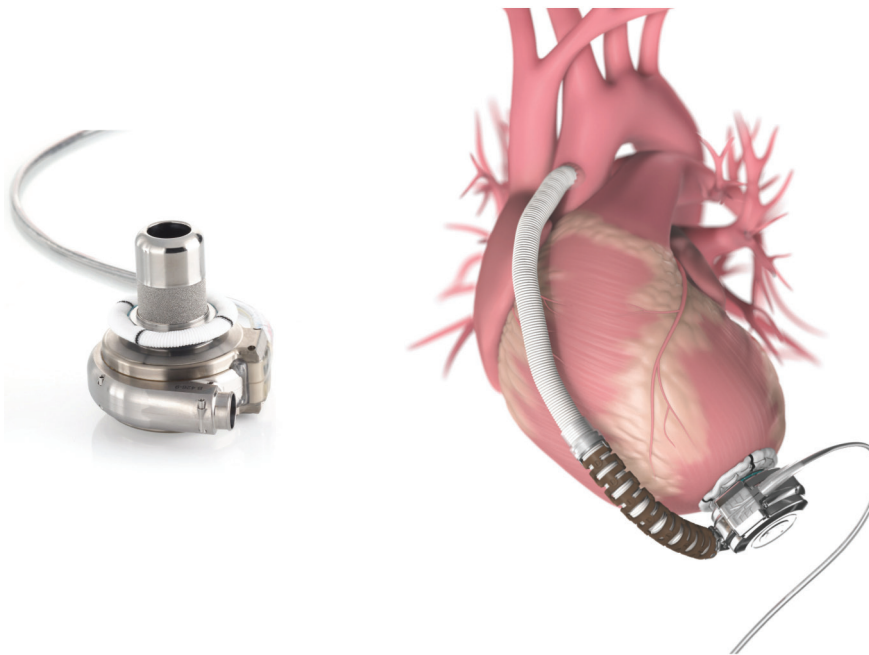


FIGURE 97-14 ■ HeartWare HVAD. (Reproduced with permission from HeartWare, Inc.)

associated infection. Some have been designed to be completely implantable with a transcutaneous energy transfer system. Along with smaller control consoles, these devices allow patients to be readily discharged from the hospital and increase their ability to ambulate. These devices will probably be associated with a significant improvement in quality of life for patients.

HeartWare HVAD. The HeartWare HVAD (HeartWare International, Inc., Framingham, MA) is a centrif-

gal pump with no mechanical bearings (Fig. 97-14), weighing 145 g, with a displaced stroke volume of 45 mL and a flow of up to 10 liter/min at 2000 to 3000 rpm. The inflow cannula is integrated into the left ventricle. The device is implanted in the pericardial space without the need for an abdominal incision. This miniaturized device may be used as a biventricular assist system as well as an LVAD.⁶³ A single, flexible driveline measuring 4.2 mm in diameter exits the anterior abdomen. The device has been tested in several centers throughout

Europe with good results.^{64,65} A clinical trial of BTT demonstrated noninferior 180-day survival to contemporary LVAD registry controls in the United States.⁶⁶ In the study, 127 out of 140 patients (91%) either survived for at least 180 days on the pump or received a heart transplant within that time. The HeartWare LVAD is approved by the FDA for BTT therapy.

The HeartWare MVAD is an investigational device with a continuous axial flow pump, approximately one-third the size of the HVAD.

DuraHeart. The Terumo DuraHeart LVAD (Terumo Heart, Inc., Ann Arbor, MI) uses magnetic levitation technology.⁶⁷ The device can provide a flow of 2 to 8 liter/min at 1200 to 2400 rpm. In case of magnetic failure, the device can levitate the Impella hydrolytically. The pump weighs 540 g and has a diameter of 72 mm and a height of 45 mm. Favorable clinical outcomes as a BTT therapy have been reported in studies conducted in Europe and Japan.^{68,69}

Thoratec HeartMate III. The Thoratec HeartMate III device is also a magnetically suspended centrifugal pump, powered by a magnetically levitated centrifugal impeller (Fig. 97-15). The device can provide a flow of 10 liter/min. This device has the ability to produce a pulsatile flow and has a large gap that may significantly reduce shear stress.⁷⁰ This device is not currently being tested in any clinical trials.

Synergy. The Synergy (HeartWare International, Inc., Framingham, MA) device is a partial-support LVAD that can be placed intravascularly (Fig. 97-16). An inflow cannula is placed through the subclavian vein, into the right atrium, and across the interatrial septum into the left atrium. Outflow is to the subclavian artery. Data from a European trial showed that the partial-support LVAD can provide improvements in hemodynamics and a reduction of heart failure symptoms.⁷¹

Total Artificial Heart

MCS options for patients requiring long-term biventricular support remain limited. TAH currently represents one long-term treatment option for patients requiring biventricular support.⁷² Others include paracorporeal BiVAD and implantable BiVAD.^{53,54} Thus,

despite the enthusiasm of continuous flow pumps, pulsatile technology still has an important role in the treatment of biventricular failure. BiVAD provides biventricular support for the failing native heart, which is left intact. TAH completely replaces the failed ventricles and the four native valves in the orthotopic position. By replacing the failing heart, the TAH can eliminate the native heart complications such as valve dysfunction and arrhythmias.

The TAH is currently approved by the FDA only for BTT. The use of TAH is indicated in transplant candidates at risk of imminent death from nonreversible biventricular failure. Contraindications include transplant ineligibility, absence of biventricular failure, inability to have anticoagulation, and small thoracic cavity size.⁷² According to INTERMACS data, only 2% of current MCS implants are TAH.⁶ A recent large report of 101 patients receiving TAH demonstrated survival to transplantation rate of 68% and 1-year overall survival rate of 77% after transplant.⁷³ Recent retrospective data from Europe showed no difference in survival rate while on support and after transplant between TAH, paracorporeal BiVADs, and implantable BiVADs.⁷⁴ No randomized prospective clinical trials have compared TAH with BiVAD.

SynCardia

The SynCardia TAH (SynCardia Systems, Inc., Tucson, AZ) system is a pneumatic, pulsatile, biventricular device that completely replaces a patient's native ventricles and all valves, while pumping blood to both the pulmonary and the systemic circulation orthotopically (Fig. 97-17). The system consists of the implantable SynCardia TAH and an external console connected via drivelines. It weighs 160 g and displaces 400 mL of volume. It is lined



FIGURE 97-15 ■ HeartMate III. In development; not approved for clinical use. (Reproduced with permission from Thoratec Corp.)



FIGURE 97-16 ■ Synergy. (Reproduced with permission from HeartWare, Inc.)

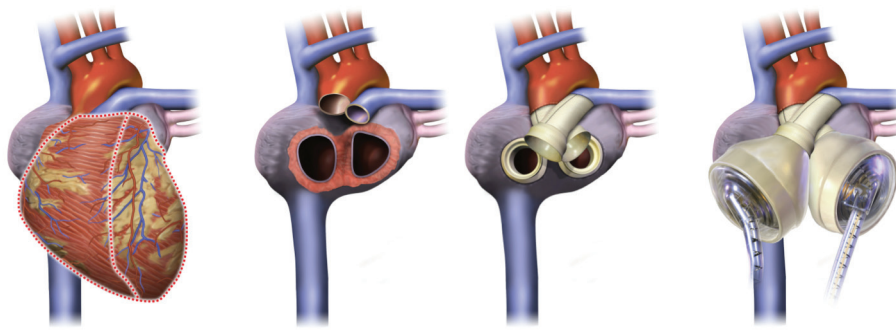


FIGURE 97-17 ■ SynCardia total artificial heart. (Reproduced with permission from SynCardia Systems, Inc.)

with polyurethane and has a four-layer, pneumatically driven diaphragm. Four mechanical Hall valves (Medtronic, Inc.) (two 27-mm inflow, two 25-mm outflow) are mounted on the housing. The diaphragm within the pump is actuated by movement of air from an external console. At maximal stroke volume (70 mL), it delivers a cardiac output of more than 9 liter/min. The artificial ventricles are connected via atrial inflow connectors to the native left and right atrium and to the native aorta and pulmonary artery by the outflow cannulas. The major drawbacks are the complexity of the implant procedure, relatively large device size (body surface area > 1.7 m² and thoracic diameter of at least 10 cm are required), and higher noise level compared with continuous flow pumps. This device is approved by the FDA for BTT therapy. A landmark trial including 81 patients who received SynCardia TAH demonstrated survival to transplantation rate of 79%, 1-year overall survival of 70%, and 1- and 5-year survival rates of 86% and 64% after transplantation, respectively.⁷² The most common adverse events were infection and bleeding.

DEVICE SELECTION

A wide spectrum of MCS devices is available. Important factors that should be considered when selecting a device include the expected duration of support (short- versus long-term support); whether right, left, or biventricular support is required; the patient's neurologic status and overall prognosis; and whether the intent is to bridge the patient to recovery or to transplant, or if the device is to serve as DT. Other important patient-specific factors include the patient's body habitus, blood type, transplant candidacy, and contraindications to anticoagulation. Surgeon preference, level of familiarity, and device availability may also play a role in deciding which device to implant. Moreover, these issues should be raised during multidisciplinary team discussions with experienced surgeons and cardiologists.

INDICATIONS FOR MECHANICAL CIRCULATORY SUPPORT

Major indications for MCS include acute cardiogenic shock after acute MI, postcardiotomy cardiogenic shock, myocarditis, refractory ventricular arrhythmias, acute on

chronic heart failure, and chronic heart failure. Patients can be roughly divided into the following two categories depending on the trajectory of heart failure progression and overall clinical status: (1) patients with acute cardiogenic shock, or (2) patients with chronic advanced heart failure.

Patients in Acute Cardiogenic Shock

Implantation of durable LVADs is associated with poor outcomes in patients with acute cardiogenic shock (INTERMACS level 1) after an acute MI, myocarditis, acute on chronic heart failure, or after cardiectomy.⁶ Generally, transplant eligibility is uncertain in patients with a combination of end-organ failure, uncertain neurologic status, and uncertain social support. Furthermore, the recent IABP-SHOCK II trial suggested that IABP confers no benefit in cardiogenic shock associated with acute MI.^{75,76} Therefore, there is clearly a role for short-term MCS in this population to provide BTD, BTT, or recovery (Fig. 97-18). The current options include the VA-ECMO, Impella, TandemHeart, and CentriMag. Each of these devices seems to be safe, effective, and reliable.^{38-42,44,50-52} They can provide optimal flow to this subset of very-high-risk patients in cardiogenic shock whose predicted mortality rate is almost 100% without mechanical support. In our program, the VA-ECMO or CentriMag BiVAD is preferably used. For patients with unclear neurologic status, profound shock, and severe coagulopathy, the less invasive VA-ECMO is selected. After resuscitation with these short-term devices, the patient's neurologic status, end-organ function, and myocardial function can be evaluated appropriately. Depending on the results, the short-term MCS device is explanted as a transition to each definitive goal (BTD). Ninety patients received either the ECMO or the CentriMag BiVAD through this algorithm for cardiogenic shock. An exchange with an implantable VAD was required in 26% of patients. Other destinations included myocardial recovery in 18% and heart transplantation in 11%. The survival to hospital discharge rate was 49%.⁷⁷

Cardiogenic Shock after Acute Myocardial Infarction

Approximately 6% to 7% of all MI patients develop cardiogenic shock as a complication, with most of these being ST-elevation MIs.⁷⁸ When cardiogenic shock

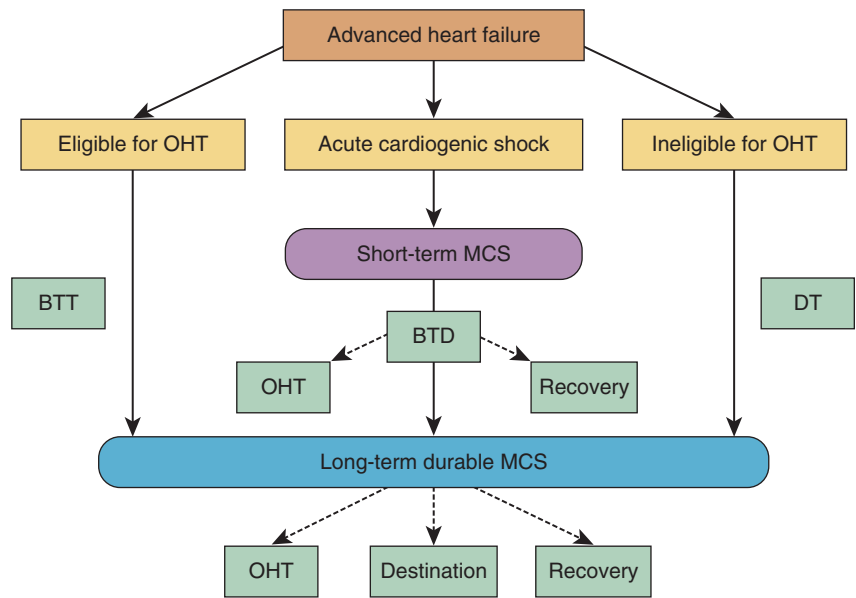


FIGURE 97-18 ■ Patient and device selection flow chart. *BTD*, Bridge to decision; *BTT*, bridge to transplant; *DT*, destination therapy; *MCS*, mechanical circulatory support; *OHT*, orthotopic heart transplantation.

complicates an acute MI, the reported associated mortality rate has traditionally been 85% to 90%.⁷⁹ For patients with refractory cardiogenic shock despite maximal pharmacologic support, the mortality rate approaches 100%.⁸⁰ Moreover, a recent large prospective randomized trial demonstrated that additional IABP treatment did not result in a significant reduction in 30-day mortality rate compared with medical therapy alone.^{75,76} Implantation of a MCS device to provide adequate circulatory support may be the only viable option for survival in these cases. By providing adequate circulatory support, MCS can reverse hypotension while maintaining vital organ perfusion and adequate coronary perfusion pressures.^{42,46-48} The goal of MCS in patients with cardiogenic shock after an acute MI is to bridge the patient to a second procedure, which includes PCI, CABG, CABG plus valve, implantation of a long-term durable LVAD, and explantation of the short-term MCS devices after myocardial recovery.

Cardiogenic Shock after Cardiotomy

Patients in cardiogenic shock after cardiotomy are also best treated with a short-term MCS device. Like the goal of mechanical support in patients after an acute MI, the goal of mechanical support in patients with cardiogenic shock after cardiotomy—irrespective of which mechanical device is used—is to bridge the patient to a second procedure, which includes implantation of a long-term durable LVAD, as well as explantation of the short-term MCS after myocardial recovery.^{44,81,82}

Myocarditis

Acute heart failure and cardiogenic shock from myocarditis are seen typically in a younger patient population. Because the probability of recovery is relatively high in these patients, they should receive a short-term MCS device, such as the ECMO or CentriMag.⁸³ In general, our preference is to implant a biventricular device in

these patients. After normalization of end-organ perfusion and function, myocardial function and recovery are assessed.

Refractory Ventricular Arrhythmias

The subgroup of patients with refractory arrhythmias is heterogeneous. Some do not have significantly reduced cardiac function, whereas others have severely depressed ejection fractions.^{24,25,84} Pharmacologic therapy, such as amiodarone, lidocaine, and beta blockers, failed to control their arrhythmias. Among the patients with reduced LV function, RV function can be either preserved or reduced. These patients can be candidates for both short-term and long-term MCS.

Patients with Chronic Advanced Heart Failure

A progression to chronic heart failure is characteristic of the largest subgroup of patients who receive long-term, durable LVADs. There are two definitive arms depending on transplant eligibility (BTT or DT).^{1,6-8} However, the initial management plan can change over time. For example, comorbidities may improve in a DT patient who was previously ineligible for transplant, making the patient transplant-eligible after LVAD support. Alternatively, a BTT patient may become transplant-ineligible because of device-related complications or progression of comorbidities. Additionally, the INTERMACS registry data demonstrated that 42% of the durable LVAD implants were intended as a BTC.⁶ Thus, in a dynamic clinical situation, it is often difficult to decide between BTT and DT.

Patients Who Are Eligible for Heart Transplantation

Heart transplantation is the optimal treatment for patients with a history of chronic congestive heart failure who

may have additional chronic deterioration or an acute exacerbation. However, the constant shortage of available donors has resulted in an increasing number of patients with longer waiting times on the transplantation lists. The use of a long-term durable LVAD as a BTT has become common in patients who would otherwise not survive or who would develop progressive end-organ dysfunction before an organ becomes available.^{7,31} Dependence on intravenous inotropes (INTERMACS profile level 2 or 3) is traditionally considered the threshold that accelerates consideration of durable VAD therapies in these patients. The BTT strategy is especially reasonable in patients listed for transplant who are expected to have an extended waiting time because of their blood type, large body size, or high degree of allosensitization.

Since the FDA approved the HeartMate II, placement of a continuous flow LVAD such as the HeartMate II or HeartWare has been the mainstream circulatory support therapy for these patients. They are often discharged from the hospital after their VAD is implanted and return at a later date for a transplant.^{7,66} Contemporary, continuous flow, durable LVADs have favorable waiting list outcomes, unless a serious LVAD-related complication occurs.⁸⁵ In addition, the data from the UNOS registry demonstrated that posttransplant graft survival after a bridge with continuous flow durable LVADs was similar to that in patients bridged with inotropes or pulsatile flow LVADs.⁸⁶

Patients Who Are Not Eligible for Heart Transplantation

The REMATCH trial, which randomized 129 non-transplant candidates to optimal medical therapy or mechanical support, demonstrated a 48% reduction in

the risk of death from any cause in the LVAD group compared with the group of patients treated with optimal medical therapy.¹ Based on this result, the FDA approved the use of an LVAD (HeartMate XVE) as a lifelong support therapy (DT). Mortality rate increases to an almost prohibitive value with the onset of end-organ failure—such as renal failure—and in the presence of active infection. In a study of 280 patients who underwent HeartMate XVE LVAD implantation as DT in the post-REMATCH era, the most important determinants of in-hospital mortality were poor nutrition, hematologic abnormalities, markers of end-organ or RV dysfunction, and lack of inotropic support.²⁶ Current requirements for DT are patients with NYHA class IV end-stage ventricular heart failure who are not candidates for heart transplant and who meet all the following conditions: (1) have failed to respond to optimal medical management (including beta blockers and ACE inhibitors, if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; (2) have a left ventricular ejection fraction less than 25%; and (3) have demonstrated functional limitation with a peak oxygen consumption of up to 14 mL/kg/min unless balloon pump or inotrope dependent, or physically unable to perform the test.

Currently, the FDA-approved continuous flow device for DT is the HeartMate II. Since the approval of HeartMate II for DT in 2010, the number of LVADs implanted for lifelong support in transplant-ineligible patients has increased up to 10-fold.⁶ The evolution from pulsatile to continuous flow technology has dramatically improved survival in these patients. A large body of data from the INTERMACS registry demonstrated a 1-year survival rate of 75% (Fig. 97-19).⁸⁷ A subset of their population with no cancer, not in cardiogenic shock, and blood urea

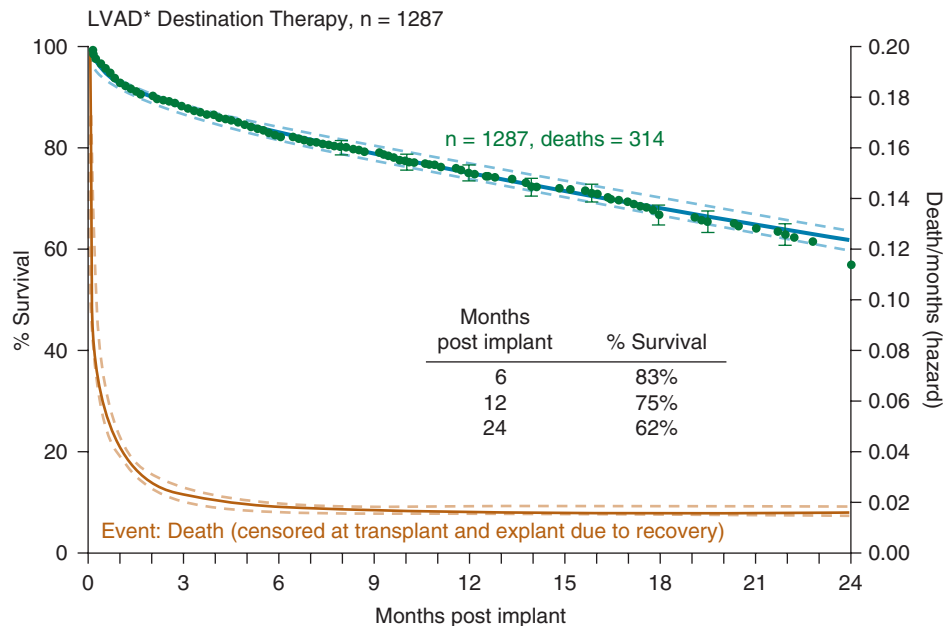


FIGURE 97-19 ■ Survival after left ventricular assist device (LVAD) implant as a destination therapy. (Reproduced with permission from Kirklin JK, Naftel DC, Pagani FD, et al: Long-term mechanical circulatory support [destination therapy]: on track to compete with heart transplantation? *J Thorac Cardiovasc Surg* 144(3):584–603, 2012.)

nitrogen less than 50 mg/dL experienced a 2-year survival rate of 80% or more, which is competitive with heart transplantation.

Given the improvements in technology, as well as in patient selection and care over the past decade, there is a movement to use LVAD therapy in patients who are less ill than those currently eligible for DT. The NHLBI has sponsored the Randomized Evaluation of the VAD intervention before the Inotropic Therapy (REVIVE-IT) trial to test the LVAD therapy in advanced heart failure patients with significant functional impairment who are ineligible for transplant but who have not yet manifested serious consequences of end-stage heart failure, such as end-organ dysfunction, immobility, or cardiac cachexia.⁸⁸

SURGICAL TECHNIQUE USED FOR DURABLE LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION

The technique used for durable LVAD implantation varies depending on the institution and the surgeon. However, the common steps in the operation can be summarized as follows: (1) skin incision; (2) creation of a preperitoneal pocket, if required; (3) mediastinal exposure; (4) cannulation of the aorta and venous system; (5) cardiopulmonary bypass commencement; (6) coring of the LV, placing core sutures on the LV, inserting the inflow core into the LV apex; (7) outflow graft anastomosis to the ascending aorta; (8) de-airing of the device; (9) weaning off cardiopulmonary bypass, actuating LVAD; (10) hemostasis establishment; (11) closing sternotomy.

A vertical midline incision is made beginning just below the sternal notch with variable extension below the xyphoid, depending on the type of device being implanted and the required pocket size based on the device used. A sternotomy is made. A pocket of an appropriate size is created in the preperitoneal space in the upper abdomen. Alternatively, the LVAD pocket can be created between the posterior rectus sheath and the muscle. Careful attention is given to hemostasis during this process. If applicable, a model of the device is used to confirm the appropriate size of the pocket. The driveline is tunneled, exiting the patient via the right upper quadrant. The device is then placed in the preperitoneal pocket.

The patient is fully heparinized. The distal ascending aorta is cannulated at the level of the pericardial reflection. The right atrium is cannulated—unless a tricuspid valve repair or closure of an atrial septal defect is planned, in which case the patient is bicavally cannulated with umbilical tapes and snares placed around the superior and inferior vena cava cannulas.

Cardiopulmonary bypass is then commenced, maintaining normothermia. The LV is decompressed by placing a vent through a stab wound at the LV apex. The LV apex is then cored. Care must be taken when coring to avoid deviation into the septum or the lateral wall. Any prominent trabeculation or thrombus that may impede inflow into the LVAD inflow cannula is excised. Full-thickness 2-0 Tevdek pledget sutures (Genzyme, Fall River, MA) are placed in a horizontal mattress fashion

around the circumference of the LV core. For the fragile myocardium, this suture line is reinforced with a strip of Teflon felt. The sutures are placed through the sewing ring of the inflow cuff, the sewing ring is seated, and the sutures are tied. The cuff is then inserted into the inflow cannula and secured with multiple ties.

The ascending aorta is clamped with a side-biting, partial-occluding clamp. An aortotomy is made, followed by the outflow graft anastomosis using 4-0 Prolene pledget sutures, which involves placement of two mattress sutures buttressed with pledgets in the heel and toe of the graft and corresponding aorta, followed by parachuting of the graft down onto the aorta. BioGlue (CryoLife, Inc., Kennesaw, GA) is applied to the anastomosis just before the clamp is released. The anastomosis is then inspected for bleeding. The outflow graft is clamped.

The de-airing process is then commenced by allowing the heart to fill under mechanical ventilation. The device is de-aired through the outflow housing. The outflow graft is connected to the outflow housing, and a de-airing hole is made in the outflow graft. The cross-clamp is kept on the outflow graft.

With the HeartMate II, the device is started only after the de-airing is completed and the patient is off cardiopulmonary bypass. The device is started at 6000 rpm, the cross-clamp is released, and the device's speed is gradually increased to an adequate rpm level to avoid oversucking of the LV. Throughout this process, the de-airing hole in the outflow graft is kept open.

Chest tubes are inserted. A Gore-Tex pericardial membrane (Gore Medical Products, Flagstaff, AZ) or a CorMatrix (CorMatrix Cardiovascular, Inc., Alpharetta, GA) is sutured to the pericardial edges to minimize reentry injury at reoperation. The sternum is closed in the standard fashion. The abdominal portion of the incision is closed with interrupted sutures, with careful attention to obtain adequate purchase of the fascia and avoid wound dehiscence. The superficial soft tissue and skin are closed in the standard fashion.

In the event of a diffuse coagulopathy with excessive bleeding, the mediastinum is packed with long rolls of gauze and a patch is placed on the skin. The patient is brought back to the operating room after adequate resuscitation and when the coagulopathy has resolved, which generally occurs 24 hours after the initial surgery.

Concomitant Valve Surgery

Preexisting valve pathology is common in patients with heart failure. Patients frequently require concurrent valve procedures at the time of LVAD placement. Patients with mild or more severe aortic insufficiency (AI) should have their native aortic valve repaired or oversewn at the time of VAD implantation. Most cases of AI can be repaired by approximating the raphe of each leaflet.^{89,90} Any patient with a mechanical valve in the aortic position should have the aortic valve oversewn with a patch or replaced with a tissue valve to prevent thromboembolism. Treatment of significant mitral regurgitation (MR) is controversial. The cause of most cases of MR in patients with advanced heart failure is annular enlargement secondary to LV dilation. In general, once the LV is unloaded with the

LVAD, MR will likely improve. However, a recent study demonstrated that approximately one third of the patients continued to have significant MR after LVAD insertion.⁹¹ In addition, concomitant mitral valve repair may result in a greater decrement in pulmonary vascular resistance.⁹² Currently, we prefer to address significant MR. Severe mitral stenosis needs to be repaired at the time of VAD implantation if it significantly interferes with inflow to the device. Moderate to severe tricuspid regurgitation should be considered for repair or replacement to optimize RV function.^{93,94} This is especially important for patients with pulmonary hypertension. Tricuspid valve repair can be performed with annuloplasty repair. If the valve lesions cannot be repaired, a tissue valve is preferred because it has a lower risk of thromboembolism than does a mechanical valve.

Patients who require valve procedures are sicker and have a higher early mortality rate. Furthermore, RV dysfunction is increased in these patients.⁹⁵

Other Concomitant Procedure

Patients with an atrial septal defect or a patent foramen ovale should have these lesions corrected at the time of VAD implantation using standard techniques. Failure to correct these lesions may result in severe hypoxia as a result of right-to-left shunting after the left ventricle is unloaded. Furthermore, any intracardiac thrombus identified in the left atrium or ventricle should be removed before LVAD implantation.

POSTOPERATIVE MANAGEMENT AFTER DURABLE LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION

Early Postoperative Management

Antibiotics are administered preoperatively as prophylaxis for infection and are continued for at least 24 hours after LVAD implantation.

Major effects of a continuous flow LVAD on hemodynamics include increased diastolic pressure and flow. Because a continuous flow pump generates blood flow throughout the entire cardiac cycle, the pulse pressure is greatly reduced. The pulse pressure is influenced by LV contractility, preload, afterload, and pump speed (rpm). An increase in pump speed leads to rising of the diastolic pressure and reduced pulsatility—making it often difficult to palpate the patient's pulse. An arterial catheter is mandatory to monitor blood pressure in the early postoperative period. The mean arterial blood pressure should be maintained between 70 and 80 mm Hg with pressors, because the amount of blood flow through a continuous flow pump is greatly affected by afterload. Vasodilatory hypotension is treated with norepinephrine and arginine vasopressin.⁹⁶

Optimization of RV function is crucial for patients receiving isolated LVAD. RV failure should be aggressively treated with milrinone, dobutamine, epinephrine, and nitric oxide.^{12,13,97} If the optimization of RV function

cannot be achieved by pharmacologic treatments, RVAD support should be considered.

Ventricular and atrial arrhythmias are managed with standard antiarrhythmic agents, such as amiodarone and lidocaine.

Late Postoperative Management

Late postoperative management focuses on encouraging ambulation and rehabilitation as well as patient education about the care and maintenance of the device. After discharge, patients are followed at the outpatient LVAD clinic weekly for the first month after discharge from the hospital and less frequently thereafter. Although continuous flow technology has dramatically improved survival and quality of life, readmission because of bleeding, cardiac difficulties (heart failure and arrhythmia), infections, and thrombosis is common within the first 6 months after discharge.⁹⁸ Comprehensive care from a multidisciplinary medical team, including the patient and caregivers, is mandatory for successful long-term LVAD support.

Anticoagulation

The HeartMate I XVE does not require anticoagulation with heparin or warfarin. In contrast, contemporary continuous flow LVADs such as HeartMate II and HVAD all require anticoagulation with warfarin, as well as antiplatelet therapy with aspirin—and occasionally Persantine—to prevent thromboembolic complications. Intravenous heparin is generally used until the INR reaches target range in the postoperative period. The decision as to when to start anticoagulation and antiplatelet therapies, as well as the dosage, is individualized for each patient based on the device type, risk of thromboembolism, chest tube output, coagulation profile, and treatment plan for the patient.

COMPLICATIONS

Postoperative Bleeding

Bleeding after VAD insertion can be excessive and may result from surgical causes or a diffuse coagulopathy. Significant bleeding can contribute to RV failure, infection, and numerous adverse effects related to multiple blood transfusions. Coagulopathy can result from alterations in the hemostatic system, including dilutional thrombocytopenia and exposure to long-acting antiplatelet or antithrombotic agents. For bleeding caused by a diffuse coagulopathy, platelets, fresh-frozen plasma, or cryoprecipitate may be administered. The decision as to whether to administer these products is based on the profile of INR, partial thromboplastin time, and fibrinogen. Patients with coagulopathy are often hypothermic and should be warmed with heating blankets. A bleeding patient with a rising central venous pressure, downward-trending VAD flows, increasing pressor requirements, and decreasing urine output should be presumed to be experiencing tamponade and should be taken to the operating room immediately for reexploration.

Gastrointestinal Bleeding and Epistaxis

Gastrointestinal (GI) tract bleeding and epistaxis have emerged as major sources of morbidity in patients with continuous flow LVADs.⁹⁹ The bleeding event rate after HeartMate II implantation was 0.67 events per patient-year.¹⁰⁰ Possible mechanisms associated with obligate device anticoagulation include acquired von Willebrand disease, GI tract arteriovenous malformations associated with reduced pulsatility, and impaired platelet aggregation.⁹⁹ The management of bleeding issues is inextricably linked to the risk of thromboembolic events. Considering the individual risks and benefits, careful reduction of anticoagulation and antiplatelet therapy is required for recurrent events.

Infection

Infection, one of the most common complications in LVAD patients, can manifest as a driveline, pocket, blood, or device endocarditis.¹⁰¹ Sepsis occurs in 17% to 28% and driveline infection occurs in 14% to 27% of patients receiving contemporary continuous flow LVADs.^{3-7,57,66} It is important to prophylactically begin antibiotics preoperatively, as previously described, as well as to treat infections aggressively with antibiotics when they do occur. More aggressive treatments including surgical drainage, wound vacuum-assisted closure therapy, and pump exchange may be necessary. The only way to definitively eradicate device endocarditis is to explant the device. Infection is generally not a contraindication to heart transplantation.

Multisystem Organ Failure

Despite effective restoration of adequate cardiac output for tissue perfusion, some patients progress to develop multisystem organ failure—which is related to the preoperative severity of organ dysfunction. Multisystem organ failure often results from a cascade of events, such as bleeding, sepsis, RV failure, and other events.

Thromboembolism

Thromboembolic complications are a major concern in LVAD patients because of the blood-device interface. Thromboembolic events with continuous flow LVADs have been reported to occur in 5% to 8% of cases.^{3-7,57,66} The key factors associated with development of stroke after LVAD implantation are likely to include a previous history of stroke, persistent malnutrition and inflammation, increased severity of heart failure, and postoperative LVAD infections.¹⁰² To avoid conversion to hemorrhagic stroke, anticoagulation and antiplatelet therapies may need to be discontinued.

Right Ventricular Failure

Adequate RV function is essential to achieve sufficient LVAD flow. Significant RV failure is associated with poor outcomes in LVAD recipients. The incidence of RV failure after continuous flow LVAD implantation is

approximately 20%.¹⁰⁻¹³ The proposed underlying mechanisms include intrinsic myocardial dysfunction and insufficient RV afterload reduction.¹⁰⁻¹³ It is important to keep in mind numerous other potential complications after LVAD surgery such as renal failure, infection, and bleeding, which might predispose patients to RV failure. Additionally, patients with a continuous flow pump can develop RV failure from a significant leftward septal shift and distortion of RV geometry caused by LV oversucking. It is therefore critical to avoid setting an excessive pump speed in continuous flow LVAD recipients. Postoperative echocardiography should be performed routinely to monitor RV function, and pump speed should be adjusted to adequate speed levels (rpm).

Signs of RV failure include an elevated central venous pressure (>15 mm Hg), marginal VAD flows of up to 2.2 liter/min/m², low mixed venous oxygen saturation, and decreased urine output. RV failure treatment involves aggressive diuresis and starting or increasing milrinone and/or dobutamine as well as nitric oxide in some cases.⁹¹ When RV failure is refractory to medical management, timely insertion of a RVAD is mandatory before end-organ dysfunction progresses.^{12-14,103}

Arrhythmia

Cardiac arrhythmia, especially ventricular arrhythmia, is also a common issue in the early and late postoperative periods. Although such arrhythmia may not be lethal in the presence of LVAD, it could put patients at risk of RV failure. Adjustment of pump speed under echocardiography may be necessary to evaluate excessive LV unloading or contact between the inflow cannula and LV wall. In addition to implantable cardioverter-defibrillator therapy, interventions aimed at minimizing the risk of recurrent arrhythmias (e.g., antiarrhythmic medication use and catheter ablation) may also be considered.¹⁰⁴

Aortic Insufficiency

The development of de novo AI during a continuous flow LVAD support has been reported. After receiving continuous flow LVAD support for 3 years, 38% of patients are expected to develop at least moderate AI.¹⁰⁵ Significant AI can cause the recycling of blood flow from the LVAD outflow graft into the LV, resulting in decreased forward cardiac output, inadequate ventricular unloading, and increased pump work. This may lead to clinical decompensation requiring surgical correction. Because the non-opening of the aortic valve during continuous flow LVAD support is strongly associated with de novo AI development, optimization of pump speed under echocardiography may be necessary to maintain some pulsatility with intermittent aortic valve opening.¹⁰⁵

Device Malfunction

The severity of a device malfunction varies from minor to fatal. With improvement in device design and engineering, the overall incidence of serious device malfunctions has decreased significantly over time.¹⁰⁶ However, device replacement related to device failure is still

inevitable in some patients. Of the 1128 patients implanted with the HeartMate II, serious device failure requiring pump replacement occurred in 71 (6.4%) patients for the following reasons: percutaneous lead damage (36 events, 3.0%), device thrombosis (25 events, 2.1%), infection (7 events, 0.6%), and miscellaneous other (11 events, 0.9%).¹⁰⁷ Most recently, an unexpected abrupt increase in the device thrombosis rate with the HeartMate II has been reported.¹⁰⁸ In an analysis of 382 patients who underwent implantation of the HeartWare HVAD, pump thrombosis occurred in 8.1% of the cohort.¹⁰⁹ Device thrombosis is caused by various mechanical or nonmechanical factors.¹¹⁰ Close monitoring of lactate dehydrogenase levels and echo-guided ramp studies are useful for early detection of device thrombosis.^{110,111} Pump exchange can be safely performed through a subcostal approach.¹¹²

SUMMARY

MCS represents the standard of care for patients with advanced heart failure from various causes. In addition, MCS may be used as a BTT or a DT and may be the only option for survival in patients with acute cardiogenic shock that is refractory to maximal medical therapy. Tremendous progress has been made over the past 10 years with respect to the evolution of devices, patient selection, surgical techniques, and postoperative management of patients. The limitations of current devices have stimulated research and innovation in an attempt to reduce device size, minimize the invasiveness of the surgical approach, increase device durability, decrease infection, reduce associated thromboembolic complications, and enhance the quality of life of patients with MCS. The outcomes can be expected to improve as the technology continues to evolve.

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HEART TRANSPLANTATION

Peter Chiu • Robert C. Robbins • Richard Ha

CHAPTER OUTLINE

HISTORICAL BACKGROUND

INDICATIONS AND EVALUATION FOR HEART TRANSPLANTATION

Recipient Selection
Allosensitization in the Heart Transplant Recipient
Recipient Management after Listing

ORGAN PROCUREMENT AND PRESERVATION

Donor Selection
Donor Management
Organ Allocation
Donor and Recipient Matching
Donor Operative Technique
Organ Preservation

RECIPIENT OPERATIVE TECHNIQUE

Orthotopic Standard Technique
Orthotopic Bicaval Technique
Orthotopic Total Technique
Heterotopic Technique

RECIPIENT POSTOPERATIVE MANAGEMENT

Clinical Management in the Early Postoperative Period
Maintenance Immunosuppression

COMPLICATIONS

Hyperacute Rejection
Acute Rejection
Acute Cellular Rejection
Treatment of Acute Cellular Rejection
Antibody-Mediated Rejection
Treatment of Antibody-Mediated Rejection
Infection
Cardiac Allograft Vasculopathy
Neoplasm

LONG-TERM RESULTS IN HEART TRANSPLANTATION

SUMMARY

In the span of 5 decades, cardiac transplantation has progressed from an experimental dream to a treatment reality for patients with heart failure.¹ According to the 2013 Registry of the International Society for Heart and Lung Transplantation, 4096 transplants were performed in 2011. The registry captures an estimated 66% of all transplants. Short- and long-term results improved until 2006, after which they remained stable.² Consequently, heart transplantation has continued to be the gold standard for surgical treatment of heart failure. With a rising prevalence of heart failure, it is estimated that more than 25,000 patients annually could benefit from cardiac transplantation.³ Despite this, the limiting factor continues to be the donor organ supply. Therefore, more importance has been placed on expanding the donor pool while developing alternative medical and surgical therapies. These therapies are meant to either bridge the heart failure patient to heart transplantation or serve as a destination therapy.

This chapter reviews the current practice of cardiac transplantation. Importance is placed on donor and recipient selection, recipient management, identifying and managing complications, and long-term results.

HISTORICAL BACKGROUND

The success of heart transplantation can be traced to the 1950s to 1960s, when pioneering achievements in the laboratory eventually translated to clinical usefulness. The earliest attempts at experimental heart transplantation involved heterotopically implanting hearts in animals through vessels in the neck or abdomen. In 1905, Alexis Carrel and Charles Guthrie⁴ revealed that heterotopically transplanted hearts resume spontaneous contraction for several hours. Continued inquiry into the physiologic basis of heart transplantation generated further advancement and interest. This included the important work of Vladimir Demikhov,⁵ in which he implanted both heterotopic and orthotopic hearts in the thorax. The advent of hypothermia and mechanical pump oxygenators in the 1950s made orthotopic heart transplantation (OHT) a stronger possibility. In the 1960s at Stanford University, Richard Lower and Norman Shumway⁶ continuously refined the technique of experimental OHT. Shumway and his team reported survival of up to 3 weeks after the procedure in dogs.⁷ Concurrent with a better understanding of the principles of tissue rejection, critical

immunosuppressive regimens developed. The Stanford group demonstrated long-term allograft survival in dogs when a combination of azathioprine and corticosteroids was administered after transplantation.⁸

In 1964, the first heart to be transplanted into a human recipient was performed by James Hardy⁹ using a chimpanzee donor heart. In 1967, the first human-to-human heart transplant was performed by Christian Barnard in Cape Town, South Africa.¹⁰ The patient, a 57-year-old man with ischemic heart disease, died on postoperative day 18. Soon thereafter, Shumway and the Stanford group performed the first successful cardiac transplant in the United States.¹¹ Additional attempts at cardiac transplantation were made without long-term success, resulting in decreased enthusiasm as the problems of acute rejection and infection became more apparent. Along with Stanford, only a handful of centers worldwide continued performing heart transplants. During this time and over the next decade, the outcomes improved as patient selection criteria were refined and postoperative care advanced. In 1973, Philip Caves and associates¹² introduced percutaneous endomyocardial biopsy, which allowed early diagnosis and treatment of acute rejection. The advancement of immunosuppression, including the use of antithymocyte globulin, offered prophylaxis and treatment for acute rejection.¹³ The introduction of cyclosporine in 1980 was particularly key in the success of cardiac transplantation. Early studies in the United Kingdom by Roy Calne and associates¹⁴ and in the United States by the Stanford group demonstrated its efficacy.¹⁵ Ultimately, combined immunosuppression regimens consisting of cyclosporine or tacrolimus, azathioprine, and prednisone led to long-term patient survival.

The early success of cardiac transplantation played a key role in increasing the number of heart transplant programs worldwide. In turn, the number of transplant procedures performed yearly grew rapidly in the late 1980s and reached its peak by the early 1990s.¹ Ongoing advances in surgical technique, organ preservation, and immunosuppression continue to yield better outcomes in the modern era of heart transplantation.

INDICATIONS AND EVALUATION FOR HEART TRANSPLANTATION

Recipient Selection

Over the years, selection criteria have emerged to identify patients who will benefit most from heart transplantation. The early reports of long-term survival after transplantation validated the effectiveness of transplantation as a treatment for end-stage heart failure such that it is now considered the gold standard for heart failure surgical treatment. The increasing use of ventricular assist devices (VADs) accounts for the decreasing mortality rate of patients on the waiting list, specifically status 1A patients. Because outcomes have improved, recipient selection has become more liberal. The resulting increase in waiting list size has not been matched by an increase in the donor pool. Even with a corresponding liberalization of donor selection criteria, yearly

donor organ allocation numbers 2400 in the United States.² This disparity between the growing demand for organs and a limited donor pool has led to careful reevaluation of recipient selection criteria, as well as exploration of alternative medical and surgical therapies for heart failure. It is clear that organs must be allocated in the most rational and judicious manner possible.

The process of selecting appropriate candidates for cardiac transplantation has become increasingly formalized. Instituting a recipient selection meeting has become standard. Before this meeting occurs, candidates for listing should have their clinical history carefully reviewed and a panel of laboratory and supplementary tests performed (Box 98-1). The process of selecting patients should be as objective as possible. The selection committee should include physicians, nurses, coordinators, dietitians, social workers, and physical therapists.

Common indications include New York Heart Association (NYHA) class III or IV heart failure refractory to maximal medical therapy; debilitating ischemia not amenable to interventional or surgical revascularization; or recurrent, symptomatic ventricular arrhythmias refractory to medical therapy, implantable cardioverter defibrillator (ICD) therapy, and surgical treatment.¹⁶ Asymptomatic patients with severe left ventricular dysfunction alone or patients who are adequately managed with medical therapy should not be considered for transplantation.

For ambulatory patients, important techniques of risk stratification have been developed to identify those at low, moderate, or high risk for mortality while awaiting transplantation. Peak exercise oxygen consumption, or VO_2 , is a measure that correlates well with waiting list mortality.¹⁷ Current International Society for Heart and Lung Transplantation (ISHLT) guidelines suggest that patients who tolerate beta blockade qualify for listing if they have a VO_2 up to 14 mL/kg/min. Those who do not tolerate beta blockade qualify if their VO_2 is up to 12 mL/kg/min.¹⁸ In support of routine repeat cardiopulmonary testing were two previous studies that showed a correlation between increases in peak VO_2 on serial exercise testing and improved survival for listed cardiac transplant patients.^{19,20}

In addition to VO_2 , Aaronson and colleagues²¹ at Columbia University have derived the Heart Failure Survival Score (HFSS) to risk-stratify ambulatory patients awaiting heart transplantation. The HFSS may be particularly useful in patients whose VO_2 is ambiguous.¹⁸ The HFSS has two components. The noninvasive component is composed of seven parameters: diagnosis of ischemic cardiomyopathy, resting heart rate, left ventricular ejection fraction (LVEF), mean blood pressure, peak VO_2 , serum sodium, and presence of intraventricular conduction delay. The invasive component is composed of eight parameters: diagnosis of ischemic cardiomyopathy, resting heart rate, LVEF, mean blood pressure, peak VO_2 , serum sodium, presence of intraventricular conduction delay, and mean pulmonary capillary wedge pressure. Both models can be used to identify a patient's pretransplant mortality risk. Koelling and colleagues²² retrospectively reviewed a database of 524 patients undergoing heart failure evaluation and showed that the HFSS

BOX 98-1 Evaluation of Potential Cardiac Transplant Recipients

PHASE I: ASSESSMENT OF CANDIDACY

General Information

- History and physical examination
- Complete blood cell count with differential and platelet count
- Blood chemistry panel
- Liver function tests
- Renal function panel
- Prothrombin and activated partial thromboplastin time
- Urinalysis
- Chest radiograph
- Pulmonary function test

Assessment of Cardiac Function

- Electrocardiography
- Echocardiography
- Radionuclide ventriculography*
- Right-sided heart catheterization*
- Left-sided heart catheterization*
- Endomyocardial biopsy*
- Peak exercise oxygen consumption (VO₂) testing

Screening Tests

- Stool guaiac (three times)*
- Mammography*
- Prostate specific antigen screening*
- Papanicolaou smear*
- Bone densitometry*
- Carotid duplex*

Infectious Disease Screening

- Hepatitis B surface antigen
- Hepatitis B and hepatitis C virus antibodies
- Human immunodeficiency virus serology
- Human T cell leukemia/lymphoma virus (HTLV-1 and HTLV-2) serology
- Cytomegalovirus IgM and IgG titers
- Toxoplasma serology
- Epstein-Barr virus serology
- Rapid plasma reagin
- Purified protein derivative testing

PHASE 2: PRETRANSPLANT DATA

- Blood type and antibody screening
- HLA-DR typing
- Panel-reactive antibody screening
- 12-hour urine collection for creatinine clearance and total protein

*Performed if indicated by history, age, or physical examination.
HLA, Human leukocyte antigen; Ig, immunoglobulin.

continues to provide important prognostic information in patients with heart failure with or without beta blocker therapy. In addition, the HFSS has been found to be better than VO₂ when applied to all genders and races.²³

Recent advances in medical therapy for patients with heart failure have resulted in improved patient survival rates. In 2001, the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial found that

TABLE 98-1 Underlying Diagnoses of Adult Heart Transplant Recipients 2006–6/2012

Diagnosis	Percentage of Recipients (%)
Cardiomyopathy	54
Coronary artery disease	37
Valvular disease	2.8
Retransplantation	2.5
Congenital heart disease	2.9
Other causes	0.9

From Lund LH, Edwards LB, Kucheryavaya AY, et al: *The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report—2013; focus theme: age*. *J Heart Lung Transplant* 32(10):951–964, 2013.

treating patients with severe heart failure with carvedilol reduced the 1-year mortality rate to 11% compared with a placebo mortality rate of 19%.²⁴ Although no randomized trials comparing heart transplantation with medical therapy have been performed, it is clear that in some cases, medical therapy yields short-term outcomes as good as or better than cardiac transplantation. However, because the greatest mortality risk associated with transplantation occurs in the first year, long-term follow-up is needed to compare late survival in medically treated cohorts with that in transplanted cohorts. Freudenberger and coworkers²⁵ developed a decision analytic model that simulated a randomized clinical trial comparing optimal medical therapy (OMT) with heart transplantation therapy for each individual NYHA class. The authors showed that OMT was superior to heart transplantation for NYHA classes I, II, and III. They also demonstrated life expectancy gains of 113 months, 38 months, and 6 months, respectively. However, heart transplantation was more beneficial than OMT in NYHA class IV patients, with a gain in life expectancy of 26 months.

The most common diagnoses leading to heart transplantation in adults are idiopathic dilated cardiomyopathy and ischemic cardiomyopathy (Table 98-1). Comparison of the 2013 registry of the ISHLT data with the corresponding 2007 registry data reveals new trends. The percentage of recipients with the diagnosis of cardiomyopathy has increased from 48% to 54%. The percentage with coronary artery disease has decreased from 43% to 37%. The diagnosis of valvular, retransplant, and congenital disease has remained relatively stable at 2.8%, 2.5%, and 2.9% respectively. Importantly, survival after transplantation is related to the underlying diagnosis. Risk factors for 1-year mortality include a history of congenital heart disease, prior heart transplant, dialysis, transfusions, ventilator support, and hospitalization. Female donor to male recipient transplants had a higher risk of mortality as well. Five-year mortality risk factors are similar to that of 1-year mortality, but with the added risk of pregnancy, diabetes, and obesity. Finally, at 15 to 20 years, data regarding risk factors for mortality are limited. What is seen is an increased risk with retransplant; however, congenital recipients have better long-term survival than other diagnoses.²

Other studies have shown controversial results. In the United Kingdom, Aziz and colleagues²⁶ performed a retrospective study of 220 heart transplant recipients and compared long-term survival rates of patients with underlying diagnoses of ischemic heart disease and dilated cardiomyopathy. At 5 years, the survival rates were 96% in the dilated cardiomyopathy cohort and 47% in the ischemic heart disease cohort. At 10 years, the survival rates were 92% in the dilated cardiomyopathy cohort and only 29% in the ischemic heart disease cohort. This provocative study suggests that the benefit of transplantation may be greater in patients with dilated cardiomyopathy. The risk of retransplantation for a recipient is also not clear. In one study, cardiac retransplants performed from January 2003 to December 2006 showed improved survival outcomes compared with those in previous eras, with an 82% 1-year survival rate and 75% 3-year survival rate, both similar to rates seen in primary transplant recipients.²⁷ Atluri and coworkers²⁸ conducted a retrospective review of 709 heart transplant patients at the University of Pennsylvania, 15 of whom received retransplants. The authors demonstrated an 86% 1-year survival rate and a 71% 5-year rate for the retransplant recipients, which were similar to the primary transplant patients' survival rates of 90% and 79%, respectively.¹ Revisiting these outcomes using the ISHLT and United Network for Organ Sharing (UNOS) databases will be necessary on a periodic basis to help guide recipient listing decisions. Absolute and relative contraindications to cardiac transplantation are listed in [Box 98-2](#).

BOX 98-2 Recipient Contraindications to Heart Transplantation

ABSOLUTE CONTRAINDICATIONS

- Pulmonary hypertension (PVR > 6 Wood units despite maximal therapy)
- Significant irreversible renal dysfunction (e.g., creatinine clearance < 50 mg/mL/min)
- Significant irreversible hepatic dysfunction (e.g., bilirubin > 3.0 mg/dL)
- Active malignancy

RELATIVE CONTRAINDICATIONS

- Active infection (except in the setting of severe device complication, which is a status 1A criterion)
- Age older than 65 years
- Peripheral vascular disease not amenable to surgical or percutaneous therapy
- Diabetes mellitus with secondary organ damage
- Severe lung disease
- Uncorrected abdominal aortic aneurysm greater than 4 to 6 cm
- Systemic infection with immune suppression risk (human immunodeficiency virus, hepatitis B virus, cytomegalovirus)
- Obesity
- Osteoporosis
- Active peptic ulcer disease
- Substance abuse
- Psychiatric disorder
- Noncompliance with medical care

PVR, Pulmonary vascular resistance.

Noncardiac organ dysfunction plays a large role in recipient selection. Pulmonary hypertension continues to be an absolute contraindication to adult cardiac transplantation. Currently, a pulmonary vascular resistance (PVR) greater than 6 Woods units despite maximal vasodilator therapy is considered an absolute contraindication.¹⁸ The increased PVR presents a large load for the donor right ventricle, which often has mild dysfunction secondary to ischemic time. Those with elevated PVRs benefit more from a combined heart-lung transplant. Further details on heart-lung transplantation can be found in [Chapter 99](#). Renal insufficiency is associated with early mortality after heart transplant, especially if dialysis is instituted either preoperatively or postoperatively.^{29,30} Analysis of the UNOS database by Schaffer and coworkers clearly shows that patients with severe renal failure benefit from heart-kidney transplantation. This benefit is especially strong for those on dialysis.³¹ Hepatic failure also is associated with poor outcomes. As such, combined heart-liver transplants have been accepted as a treatment modality for these patients. Cardiac indications for heart-liver transplants at the time of transplant included restrictive cardiomyopathy (38%), congenital heart disease (21%), idiopathic dilated cardiomyopathy (17%), ischemic cardiomyopathy (8%), and hypertrophic cardiomyopathy (8%). Hepatic indications included cardiac cirrhosis (43%), amyloidosis (28%), hepatitis-induced cirrhosis (10%), metabolic disease (5%), and hemochromatosis (4%). In their analysis of the UNOS database, Schaffer and coworkers noted that the incidence of waiting list mortality was higher in heart-liver candidates, but survival was not different. Further analysis showed that undergoing a heart-liver transplant was associated with enhanced survival compared with undergoing a heart transplant alone.³²

The consideration of heart transplantation for recipients with human immunodeficiency virus (HIV) has been controversial. However, with the advent of effective antiretroviral therapy, a 10-year survival rate of 90% can be expected.³³ To date, there have been a few case studies, the largest of which reported on seven HIV-positive patients who received a heart. The survival rate at 5 years follow-up for this group of patients was 100%.³⁴ Further review of outcomes for this patient population is necessary to ensure equivalent survival to HIV-negative patients. The allocation of donor hearts to recipients with known malignancy is also controversial. The ISHLT listing guidelines published in 2006 indicated that those patients with skin cancer, cancers in remission for 5 years, and low-grade cancer were acceptable for transplant candidacy.¹⁸ Possible candidates for cardiac transplant should have appropriate screening studies performed, including prostate specific antigen, mammographic screening, colonoscopy, and Papanicolaou smear. For those with a known history of malignancy, close cooperation with oncology is required to ascertain the prognosis of the patient and adjunctive management.

Increasingly liberal acceptance of other comorbidities is expanding recipient lists. Diabetes mellitus is increasing in the general population and now constitutes 10% of patients undergoing transplantation.³³ A review of the UNOS database revealed that survival for patients with

uncomplicated diabetes mellitus was similar to that of heart transplant recipients without diabetes.³⁵ Amyloidosis is another disease that has been a relative contraindication to heart transplantation. Our center, as well as others, has adopted protocols to determine which patients with amyloidosis would be eligible for a heart transplant. General exclusion criteria include involvement of more than two organs, creatinine that is elevated above 2.0 mg/dL, and an alkaline phosphatase level higher than 250 U/liter. Patients with significant autonomic instability also should be excluded. The results for this cohort are promising, but further review of data is needed.³³ The age requirement for transplant has also been changing. In the 2013 ISHLT report, the number of patients in the 60- to 69-year-old range and the 70 years and older range has increased in comparison with the 1996-2005 cohort. Survival with increasing age is similar in the first five years, excluding those in the older than 75 years cohort.² The Scientific Registry of Transplant Recipients (SRTR) database confirms that survival in older cohorts is similar to that of younger recipients.³⁶ Patients older than 65 years also have a decreased risk of rejection, likely because of physiologic aging of the immune system. This is reflected in the increased rate of infections and malignancy in this older group.³³

To increase the availability of heart transplantation as an option for older patients, extended criteria cardiac transplantation (ECCT) was started at several centers, most notably by Hillel Laks and colleagues at the University of California, Los Angeles.³⁷ ECCT patients were offered organs that were not normally used for transplantation. The initial results were promising with similar early survival for non-ECCT recipients, but longer term data were needed.³⁸ Comparison between ECCT patients and destination therapy left ventricular assist device (LVAD) patients at Duke University Medical Center revealed similar 1-year survival. However, at 3 years, overall survival was better for the ECCT group.³⁹ A study looking at ECCT in the UNOS database revealed similar 1-year survival of 89% versus 86% for standard criteria versus ECCT. However, at 3 years, there was a significant decrease in survival (66% vs. 77%) for ECCT patients compared with standard criteria patients.⁴⁰ The data appear to argue for liberalized use of ECCT to increase the availability of heart transplantation. Other relative contraindications to transplantation include obesity (body mass index [BMI] > 32), osteoporosis, substance abuse, clear history of medical noncompliance not related to socioeconomic difficulties, and lack of dedicated social support.^{41,42}

In summary, the decision to list a patient for cardiac transplantation requires examination of multiple medical, psychological, and social factors by the selection committee. Because of the scarcity of donor hearts as well as the need for lifelong medical care, the recipient candidate should be selected for optimal success in the context of increasing indications for cardiac transplantation.

Allosensitization in the Heart Transplant Recipient

ABO blood typing is performed on all candidate recipients. In addition, candidate recipients undergo screening

to establish an anti-human leukocyte antigen (anti-HLA) antibody profile. This is referred to as the panel reactive antibody (PRA) test. The PRA is expressed as a percentage of the population against which the recipient has developed antibodies.⁴³ In some centers, a PRA greater than 10% prompts direct testing of a prospective recipient's serum against a prospective donor's lymphocytes.⁴⁴ This is referred to as a crossmatch. A PRA greater than 10% signifies allosensitization. A PRA of greater than 80% indicates a high likelihood that the recipient will have antibodies to a donor.⁴⁵ PRA should be seen as a screening test and not an actual quantitative measurement. Loh and colleagues followed cardiac transplant recipients with a PRA of greater than 25% and showed decreased survival in these patients versus recipients with a PRA of less than 25%.⁴⁶ A PRA greater than 11% was also shown to be a predictor of earlier and more clinically severe rejection when the UCLA Heart Transplant Group retrospectively reviewed pretransplant PRA screens from 311 patients.⁴⁷ Sensitized recipients have a significantly lower 3-year survival compared with those who are not sensitized. This holds true even if the recipient has a negative donor-specific crossmatch.

Newer methods of determining allosensitization in candidate recipients are coming to the forefront. In particular, calculated PRA (cPRA) has emerged as a possibility for traditional PRA calculation. It is derived from HLA frequencies in the 12,000 kidney donors in the United States. It equals the percentage of possible donors that may have one or more HLA antigens that are not compatible with a given recipient. Because it is derived from known crossmatch incompatibility, it may be more accurate than a traditional PRA screening test. Another method of determining possible allosensitization is the virtual crossmatch (VXM). Essentially, the recipient's complete HLA antibody profile is compared with the possible donor's complete HLA antigen profile to determine a match.⁴⁹ To be able to perform it correctly requires a complete identification of the recipient's antibody profile. Although some false negatives and false positives can occur, the use of a VXM strategy can increase the number of transplants for sensitized patients, especially when donors from outside the immediate region are considered. The VXM has a positive predictive value of 79% and a negative predictive value of 92%.⁵⁰ The risk of antibody-mediated rejection in negative VXM transplants is very low.⁵¹

The frequency of PRA testing varies from center to center. However, certain guidelines can be followed. For patients without detectable antibodies, PRA testing should be done every 6 months.⁵² Patients who have demonstrated detectable antibodies should be tested every 3 months.⁵² For patients who have had an infection or blood transfusion, the antibody levels should be checked within 1 to 2 weeks. Patients who have had a VAD placed should have their PRA levels checked every 1 to 2 months.⁵² Outcomes for heart transplant are better associated with lower PRA levels rather than peak levels.⁴³

Managing allosensitization also varies from center to center. To reduce a potential recipient's antibody load, administration of plasmapheresis, intravenous immunoglobulin (IVIG), and immunosuppressive drugs is

pursued.⁵³⁻⁵⁷ A study performed in 1994 first showed the effectiveness of plasmapheresis, reducing a recipient's PRA from 92% to 10%.⁵⁸ Plasmapheresis was continued for at least 2 weeks after transplantation, and the PRA level remained low. At Columbia University, the superiority of IVIG (one to three monthly courses of 2 g/kg, divided in four daily doses) over plasmapheresis (administered as one to two monthly courses, two to three times per week) was shown in terms of greater reduction in IgG anti-HLA class I.⁵⁹ The study also demonstrated that recipients who received one or two courses of IVIG (2 g/kg) had a mean duration of 3.3 months on the cardiac transplantation waiting list as opposed to 7.1 months for those not receiving IVIG therapy. The Columbia group also suggested that IVIG (2 g/kg) had a better safety profile than plasmapheresis based on the fact that plasmapheresis-treated recipients had more systemic infections and episodes of systemic anaphylaxis (defined by hypotension with pressor support requirement). IVIG has the added benefit of protecting from infection.⁶⁰ Itescu and colleagues supplemented IVIG therapy with intravenous cyclophosphamide pulse therapy before cardiac transplantation and as part of a triple immunosuppressive therapy (cyclosporine-based) regimen and demonstrated that this therapy significantly reduced immunologic markers of alloreactivity, prolonged rejection-free intervals, and decreased overall cumulative frequency of rejection.⁵⁴ The authors also concluded that cyclophosphamide was superior to mycophenolate in reducing rejection in sensitized recipients.

Leech and coworkers established that the combination of plasmapheresis and IVIG therapy in presensitized cardiac recipients reduced T cell and B cell PRA levels as well as crossmatch positivity.⁶¹ They concluded that the combined treatment allows a successful outcome in the sensitized cardiac recipient. However, it was noted that there was an increased risk of rejection. Rituximab is increasingly being used in sensitized cardiac transplantation recipients. A chimeric anti-CD20 monoclonal antibody, rituximab decreases B cells and has no effect on plasma cells and, thus, no immediate effect on circulating antibody levels.⁶² It is often used for recipients refractory to other forms of desensitization.⁶³ Guidelines for identification and pretreatment of sensitized patients awaiting cardiac transplantation, as well as for treatment during and after the surgery, are outlined in [Box 98-3](#).

HLA typing of the prospective recipient may be done before transplantation. However, prospective matching of recipient and donor HLA antigens is not routinely performed because it delays the donor operating room time by 4 to 8 hours.

Recipient Management after Listing

During the time in which the patient is awaiting transplantation, optimal medical management should be continued. The patient should be seen by a cardiologist regularly. During this time, the patient should also be enrolled in cardiac rehabilitation. The better the patient's physical state heading into the transplant is, the less likely complications will occur.

As a patient's heart failure becomes more severe, oral medical therapy becomes inadequate. At this time,

BOX 98-3 Identification and Treatment of Sensitized Patients

IDENTIFICATION

- Detailed medical history, including history of previous transplants, blood transfusions, and pregnancies; human leukocyte antigen (HLA) typing for HLA class I (A, B) and class II (DR, DQ) within 3 months prior to listing
- Autoantibody crossmatch without dithiothreitol (DTT)
- Panel-reactive antibody (PRA) using complement-dependent cytotoxicity and solid phase assays (sensitized when PRA > 10%)
- If positive for antibodies against C, DQA, or DP loci, then also type for HLA-C, -DQA, and -DP
- If initial autoantibody results are positive, crossmatch with DTT to identify antibody isotype

PREOPERATIVE TREATMENT FOR PRA GREATER THAN 50%

- Evaluate response to intravenous immunoglobulin (IVIG) with in vitro IVIG inhibition assay
- If patient is hospitalized, adjunctive plasmapheresis should be considered
- IVIG (1 g/kg, with a maximum of 70 g) twice monthly for up to 6 months
- Rituximab administered via central line or peripheral line—first infusion is at 50 mg/hr increasing until a maximum of 400 mg/hr is reached; subsequent infusions at 100 mg/hr increasing to 400 mg/hr as tolerated
- Success of antibody reduction monitored by HLA laboratory (levels obtained before first dose of IVIG and before and after each subsequent IVIG infusion) every 2 weeks
- Post-IVIG testing includes PRA and specificity with and without DTT on full-screen panel (T and B cells) for classes I and II

PERIOPERATIVE AND POSTOPERATIVE TREATMENT OF SENSITIZED PATIENTS

- On bypass: one-volume plasmapheresis, reconstituting with 5% albumin (50%) and fresh-frozen plasma (50%)
- Rabbit antithymocyte globulin (1.5 mg/kg IV): first dose after hemostasis achieved in operating room (OR); repeat dosing on postoperative days (PODs) 2, 3, 5, and 7
- Methylprednisolone (10 mg/kg IV, maximum 500 mg) after hemostasis achieved in OR and 2.5 mg (maximum, 125 mg) IV every 8 hours, three times
- IVIG 2 g/kg (maximum, 140 g) divided into two doses on consecutive days in intensive care unit
- Rituximab as outlined in preoperative section
- Mycophenolate mofetil (1000 mg PO twice in POD 1)
- Oral prednisone (1 mg/kg divided into two doses, POD 2)
- Tacrolimus (0.5 mg PO twice a day, PODs 1 to 5)
- Plasmapheresis POD 7, and every other day for four treatments thereafter

institution of intravenous therapy is necessary. This includes the use of dopamine, dobutamine, or milrinone. Dopamine, a sympathomimetic catecholamine, has both alpha and beta agonist activity and should be used at dosages of less than 5 µg/kg/min; at higher dosages, its arrhythmogenic and renal vasoconstrictive effects predominate. Dobutamine, a β_1 -adrenergic agonist, is most effective at dosages of less than 10 µg/kg/min. Milrinone, a phosphodiesterase inhibitor with inotropic and vasodilator effects, is effective at dosages of up to 0.5 µg/kg/min. Often, a combination of these medications is used. The use of short-term intravenous dobutamine and milrinone has been found to have an adverse effect on survival in the treatment of acute decompensated heart.⁶⁴ As such, the American College of Cardiology Foundation and American Heart Association discourage their routine use in patients with stage D heart failure and patients without evidence of shock or threatened end-organ perfusion. The institution of chronic intravenous inotropic therapy may be reasonable either for patients with cardiogenic shock awaiting definitive therapy or for patients with stage D heart failure, especially those refractory to guideline-directed medical therapy awaiting mechanical circulatory support (MCS) or heart transplantation.⁶⁵

If patients continue to do poorly despite pharmacologic maneuvers, MCS becomes an important option to bridge to transplantation (BTT). MCS devices may be broadly categorized as either short term or long term. Short-term devices include intra-aortic balloon pump (IABP), percutaneous VAD, paracorporeal VAD, and venoarterial extracorporeal membrane oxygenation (VA-ECMO). IABP counterpulsation reduces afterload and augments diastolic coronary perfusion. For this reason, it is especially useful in patients with ischemic cardiomyopathy. These devices can be left in place only for a short period of time (usually several days) and are not effective if left ventricular ejection is severely compromised. There is a risk for infectious complications associated with IABP use, and the 1-year mortality rate is increased in heart transplant recipients who have previously been supported with an IABP.¹

Percutaneous VADs, such as the Impella⁶⁶ and the Tandem Heart,⁶⁷ have been shown to be effective in treating severe cardiogenic shock. However, no data have shown an increase in survival with these devices as primary therapy. Severe, refractory cardiogenic shock can also be treated with VA-ECMO. By virtue of their temporary nature, all short-term devices should be a bridge to recovery, to decision, to transplantation, or to long-term device implantation. Early in the experience, temporary circulatory support was high risk, with a detrimental effect that continued into the posttransplant period. Taylor and associates reported a 238% increase in risk of mortality at 1 year in the 52 patients who underwent BTT between 2002 and 2005.¹ Even with increasing experience—163 patients between 2006 and 2011—the requirement for temporary circulatory support still imparted a 180% increase in the risk of mortality at 1-year post transplantation.²

With the development of improved mechanical assist devices, long-term MCS has become an invaluable tool in the management of end-stage heart failure. The

results of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, which compared 1- and 2-year survival rates of patients with heart failure who were ineligible for transplantation treated with OMT versus LVAD placement, were encouraging.⁶⁸ The investigators found a 25% 1-year survival rate and an 8% 2-year survival rate in the medical therapy group, compared with a 52% 1-year survival rate and a 23% 2-year survival rate in the LVAD group. Based on this study, it was clear that developing a VAD with fewer complications might lead to greater 2-year survival.

In 2007, the Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent (INTrEPID) trial, a prospective nonrandomized study, further validated the survival benefit of LVAD placement versus OMT with survival rates of 46% versus 22% at 6 months and 27% versus 11% at 1 year, respectively.⁶⁹ Patients in the OMT group did not experience any improvement in NYHA functional class, whereas 85% of LVAD patients experienced either minimal or no symptoms. The authors concluded that no further randomized trials should be conducted comparing these two groups because of the overwhelming survival advantage of LVAD versus OMT seen in both REMATCH and INTrEPID trials.

As a follow-up to the REMATCH trial, Slaughter and colleagues evaluated the efficacy of the Heartmate II (Thoratec, Pleasanton, CA) and demonstrated superiority of the continuous flow LVAD as compared with the pulsatile Heartmate XVE. Survival at 2 years in the continuous flow group was 67% compared with 59% in the pulsatile group. Additionally, reoperation because of pump-related complication (device repair, replacement, or explantation including for transplantation) occurred in 24 of 66 patients (36%) receiving a pulsatile device but in only 13 of 134 (10%) of continuous flow LVAD recipients.⁷⁰

Predictably, the effect of LVAD on waiting list survival has been profound. A preliminary study published in 2002 by Aaronson and colleagues⁷¹ retrospectively compared the use of LVADs and high-dose inotropes as BTT in 104 patients at Columbia-Presbyterian Medical Center. Survival to transplantation was 81% in the LVAD group, compared with 64% in the inotrope group. Dardas and coworkers confirmed the benefit of LVAD implantation in an analysis of the Scientific Registry of Transplant Recipients (SRTR) between 2005 and 2010.⁷² Patients who received an LVAD with elective status 1A had a significantly lower cumulative hazard of adverse events (death or delisting because of illness), at 1% within 30 days, compared with medically treated status 1A patients with or without IABP, at 6% within 30 days. Patients with an implanted LVAD who were status 1B also had reduced hazard of adverse events compared with status 1B medically treated patients. On the basis of the low risk of death or illness resulting in delisting among patients with an implantable LVAD, the authors suggested downgrading these patients to a status between 1B and 2. On the other hand, paracorporeal VADs were found to have sustained risk justifying status 1A listing indefinitely.

Wozniak and colleagues reviewed the UNOS database for patients receiving VAD BTT between 1998 and

2012.⁷³ Patients who received any form of ventricular support (either isolated LVAD or biventricular assist device [BiVAD] support) had similar waiting list survival compared with those requiring only inotropic support. However, in patients who received an isolated LVAD, waiting list survival was significantly improved compared with the cohort of medically treated patients including those requiring IABP placement.

Whereas the waiting list outcomes are clear, the effect of LVAD implantation on posttransplantation survival has been controversial. Between 2002 and 2005, pulsatile VAD implantation was associated with a 27% increased relative risk of mortality 1 year post transplantation.¹ This difference in mortality may be attributable to differences among devices, as Russo and colleagues determined in a multivariate analysis of the UNOS database between 2001 and 2006. Patients with extracorporeal VADs had significantly reduced risk-adjusted 90-day graft survival compared with intracorporeal and paracorporeal devices. Posttransplantation survival was similar among patients who were not bridged with a VAD and those receiving either an intracorporeal or a paracorporeal device.⁷⁴

Posttransplant mortality at 4 years among patients bridged to transplantation with a pulsatile LVAD fell significantly as experience developed not only with the operation itself but also with the management of these patients. Those who were bridged to transplantation between 2000 and 2004 were at 30% greater risk of mortality than those who received pulsatile devices between 2004 and 2008. In the latter period, Nativi and associates reported similar outcomes between patients who underwent BTT with pulsatile and continuous-flow devices, and these were not significantly different from patients who did not receive an LVAD.⁷⁵ Contemporary registry data have confirmed this finding with no significant difference in intermediate survival up to 6 years post transplantation among patients who preoperatively had an LVAD, patients who required inotropic support, and patients requiring neither.²

In spite of the benefits of pretransplant implantation on waiting list outcomes and the growing evidence that modern LVADs do not necessarily affect posttransplantation outcomes, the use of LVADs is not without risk. First, patients are exposed to the potential morbidity of device complication; however, this may be acceptable given the improved survival on the waiting list. Of the potential complications that may prompt status 1A listing for heart transplantation (i.e., thromboembolism, device infection, and life-threatening arrhythmia), only infection was associated with worse survival at both 1 year and 10 years post transplantation.⁷⁶

Another potential difficulty with LVAD implantation is the associated increase in PRA.⁷⁷ Although this increase in PRA could be attributable to transfusion of cellular blood products,⁷⁸ the avoidance of leukofiltered cellular blood products has not been shown to be of benefit.^{48,79} LVAD type appears to have an impact on the development of allosensitization related to the interaction between the patient and the device as has been shown in single-institution retrospective studies.^{80,81} The impact of PRA on the subsequent management of patients, includ-

ing the need to reduce HLA antibodies, has been discussed previously.

BiVAD implantation is associated with significantly worse outcomes than LVAD implantation alone.^{82,83} Additionally, there are patients for whom LVAD may be contraindicated (e.g., those with aortic insufficiency, acquired VSD, or right ventricular failure). The total artificial heart was thus conceived as a means to provide biventricular support. In 2004, Copeland and colleagues reported a 79% success rate in BTT, which was superior to historically matched controls.⁸⁴ However, the overall experience with the total artificial heart remains limited, and this remains an area of active investigation.

ORGAN PROCUREMENT AND PRESERVATION

Donor Selection

The selection of donors for cardiac transplantation follows the guidelines outlined in [Box 98-4](#). The regional organ procurement organization is the first group to begin the selection process, at which time information is collected regarding cause of death, body size, ABO blood type, serologies (including human immunodeficiency virus, hepatitis B virus, and hepatitis C virus), and clinical course. A transplant physician then performs a secondary screen. This includes a review of relevant history, baseline electrocardiogram, chest radiograph, laboratory data, echocardiogram, and in some cases cardiac catheterization. The final screen is performed by the procuring surgeon at the donor hospital site.

Potential donors must meet standard requirements for brain death. Donors who died from cardiac causes, have had an acute coronary event, have intractable arrhythmias, or have deleterious structural abnormalities should be excluded.⁸⁵ In addition, donors with a history of severe chest trauma causing severe cardiac contusion with resulting cardiac depression should be excluded. The importance of left ventricular hypertrophy is being reevaluated in light of the shortage of donor organs. Previously, posterior wall (PW) and interventricular

BOX 98-4 Cardiac Donor Selection Criteria

- Age younger than 55 years
- No history of chest trauma or cardiac disease
- No prolonged hypotension or hypoxemia
- Meets hemodynamic criteria:
 - Mean arterial pressure greater than 60 mm Hg
 - Central venous pressure 6 to 10 mm Hg
- Inotropic support less than 10 mg/kg/min (dopamine or dobutamine)
- Normal electrocardiogram
- Normal echocardiogram
- Normal cardiac angiography*
- Negative hepatitis B surface antigen, hepatitis C virus, and HIV serologies

*Performed as indicated by donor age and history.

septal (IVS) thickness was expected to be less than 1.2 cm. In a study by Goland and associates, donors with a thickness of up to 1.7 cm showed no decrease in survival, arguing for more liberal use of hearts with left ventricular hypertrophy.⁸⁶ Donor age younger than 55 years is preferable, although on occasion older donors are considered. Many transplant centers, including Stanford University, have become more flexible regarding the donor age criterion. For all male donors older than 45 years and female donors older than 50 years, cardiac catheterization with coronary angiography should be performed to rule out significant coronary artery disease.⁸⁷ Relative contraindications include positive hepatitis B or C serology, sepsis, history of cancer, or prolonged hypotension or hypoxemia.

Reviewing the 2013 data from the ISHLT registry reveals important trends. The use of donors with diabetes mellitus (3.0%) and hypertension (14%) is increasing. Expansion of the donor pool has been achieved by liberalization of other criteria as well, including increasing ischemic time, mild valvular abnormality, and mild coronary disease.⁸⁸ The use of hearts that have undergone longer arrest and resuscitation has also been noted.⁸⁹ Given this recent liberalization, long-term outcomes with these organs for non-ECCT recipients have not yet been determined. In addition, some data indicate that donor characteristics, such as older age and prolonged ischemic time, may interact synergistically to increase recipient mortality risk.⁹⁰

Donor Management

Meticulous and aggressive hemodynamic management of donors can increase the cardiac donor pool.^{91,92} Because all patients have brain death, they are often hemodynamically unstable as a result of neurogenic shock, excessive fluid losses, and bradycardia.^{93,94} Detailed fluid management is required, with intravascular volume replacement given to maintain a central venous pressure (CVP) between 6 and 10 mm Hg. Whereas excessive use of inotropes or vasoconstrictors is frowned on, the use of low-dose dopamine is associated with improved outcomes after heart transplant.⁹⁵ Intravenous vasopressin can be used to help control diabetes insipidus, which is common in patients with brain death. Ventilator settings should be set with the plan to offer the donor lungs for transplant. The settings should be adjusted to, at most, a fractional inspired oxygen of 40% and a positive end-expiratory pressure of 5 cm H₂O to prevent atelectasis. Although some donor organizations have begun to liberalize transfusion triggers, the outcomes are unclear. As such, a minimal hematocrit of 30% should be maintained. The blood should be cytomegalovirus-negative and leukocyte-filtered blood if possible.⁹⁶

Serial echocardiograms should be pursued in the setting of brain injury. A single echocardiogram may provide initial information but likely is not representative of the true function of the heart. Cardiac dysfunction, as confirmed by echocardiogram, occurs in up to 42% of brain-dead patients, and the correlation between these abnormalities and actual pathologic findings is often poor.^{97,98} Placement of a pulmonary artery catheter is

useful in assessing initial cardiac function and the response to therapy. Typical hemodynamic goals include a mean arterial pressure of greater than 60 mm Hg, a CVP of 6 to 10 mm Hg, and a pulmonary capillary wedge pressure of less than 12 mm Hg.

The Papworth group has reported an increase in organ retrieval of 30% by using an aggressive protocol for donor management.^{99,100} This included placement of a pulmonary artery catheter to guide the process of resuscitating the patient and provision of hormonal therapy, including thyroxine,¹⁰¹ cortisol, antidiuretic hormone, and insulin. Using this protocol, most donors originally deemed unacceptable by strict hemodynamic criteria were converted into acceptable donors. The Crystal City Guidelines outline another management strategy for potential organ donors. The algorithm begins with conventional management; correction of acidosis, hypoxemia, and anemia; and appropriate titration of inotropes to maintain adequate organ perfusion. This is then followed by an initial echocardiogram. If the LVEF is greater than 45%, the heart is suitable for recovery. If the LVEF is less than 45%, hormonal resuscitation and hemodynamic management with a pulmonary artery catheter should be undertaken. The heart will be recovered only if appropriate hemodynamic parameters can be reached.⁸⁷

Organ Allocation

Allocation algorithms have been developed to facilitate organ distribution. In the United States, organ allocation is governed by UNOS. The current heart algorithm takes into account medical urgency, time on the waiting list, and blood type.¹⁰² The waiting list status categories (1A, 1B, 2, and inactive) are defined in Table 98-2. Listing can also be modified by age; for example, adolescent donor hearts are preferably allocated to pediatric recipients. Geographic location also plays an important role in the allocation. Prior to 2006, local thoracic organ allocation was performed before regional allocation. After 2006, thoracic organ allocation by UNOS changed such that regional allocation played a larger role. The policy change allowed for greater regional sharing of organs with a goal of increased allocation to status 1A patients and reduced waiting list mortality. As a result of the change in policy, Schulze and coworkers found an overall increase in waiting list time for status 1A and 1B patients of 17.8 days. However, there was a decrease in waiting list mortality after the change (13.3 vs. 7.9%; $P < 0.001$). At the same time, 2-year posttransplantation survival improved (82.7% vs. 85.4%; $P < 0.001$).¹⁰³

Donor and Recipient Matching

Prospective recipients and donors must be ABO blood type compatible, although not necessarily ABO identical.¹⁰⁴ In the past, differences up to and greater than 20% could be tolerated. For recipients whose PVR remains at the upper limit of acceptable, a donor whose body size is at least equal to that of the recipient should be chosen to decrease the likelihood of acute right-sided heart failure.¹⁰⁵ In the case of patients with normal PVR, the lower limit of an acceptable size match is an area of active

TABLE 98-2 UNOS Medical Urgency Status Categories

Status Level	Category
Status 1A	The candidate is admitted to the transplant hospital that registered the candidate on the waiting list, or an affiliated Veterans Administration (VA) hospital, and the candidate also meets at least one of the requirements: 1. Has one of the following MCS devices in place: TAH, IABP, ECMO. 2. Requires continuous mechanical ventilation. 3. Requires continuous infusion of a single high-dose intravenous inotrope or multiple intravenous inotropes, and requires continuous hemodynamic monitoring of left ventricular filling pressures. 4. A candidate who is at least 18 years old at the time of registration, and may or may not be currently admitted to the transplant hospital, may be assigned adult status 1A if the candidate meets at least one of the following requirements: a. Has one of the following MCS devices in place: LVAD, RVAD, BiVAD.* b. Candidate has MCS and there is medical evidence of significant device-related complications.[†]
Status 1B	At least one of the following devices or therapies in place: 1. LVAD, RVAD, or BiVAD. 2. Continuous infusion of intravenous inotropes.
Status 2	All other actively listed patients.
Inactive	Temporarily unsuitable for transplant. The patient will not receive any heart offers.

*The candidate may be registered as adult status 1A for 30 days at any point after being implanted once an attending physician determines the candidate is medically stable. The 30 days do not have to be consecutive. However, if the candidate undergoes a procedure to receive another device, then the candidate qualifies for a new term of 30 days. Any 30 days granted by the new device would substitute and not supplement any time remaining from the previous adult status 1A classification.

[†]Thromboembolism, device infection, mechanical failure, or life-threatening ventricular arrhythmias. A candidate's sensitization is not an acceptable device-related complication to qualify as adult status 1A.

BiVAD, Biventricular assist device; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; LVAD, left ventricular assist device; MCS, mechanical circulatory support; RVAD, right ventricular assist device; TAH, total artificial heart; UNOS, United Network for Organ Sharing.

From Department of Health and Human Services: *Organ procurement and transplantation network: policies*. Apr 10, 2014.

http://optn.transplant.hrsa.gov/ContentDocuments/OPTN_Policies.pdf#nameddest=Policy_06.

debate. Jayarajan and associates demonstrated that a donor-to-recipient weight ratio as low as 0.6 may be tolerated in gender-matched patients and in male-to-female heart transplants. However, female-to-male heart transplants were found to have increased hazard of mortality and reduced median survival compared with gender-discordant size-matched individuals.¹⁰⁶ In rare situations, small hearts may be heterotopically transplanted into larger recipients, but the outcomes in these cases are significantly worse than size-matched OHT.¹⁰⁷ In patients with an elevated PRA, either a prospective or a virtual crossmatch may be performed with the potential donor.¹⁰⁸ A positive crossmatch portends a high likelihood of hyperacute rejection, and in such cases the donor organ cannot be accepted for that recipient.

Donor Operative Technique

Retrieval of the donor heart typically occurs as part of a multiorgan procurement. In most cases, the cardiothoracic team must work in conjunction with an abdominal team that is procuring the liver and/or kidneys. Communication between the two teams is essential to prevent unnecessary prolongation of ischemic time. This includes agreeing on a start-time for the procuring teams based on the status of the recipient teams. Delays to donor crossclamp may occur if the heart recipient requires a redo sternotomy, especially in the case of a previous LVAD patient who requires explantation. There are minor modifications to the heart procurement technique when either one lung or both lungs are being procured.

A median sternotomy is performed, and the pericardium is opened longitudinally. The heart is carefully inspected for external signs of trauma, infarction, congenital anomalies, and overall right and left ventricular function. The coronary arteries are palpated to evaluate for coronary artery disease. Significant abnormalities preclude use of the donor heart in transplantation. The ascending aorta is dissected from the pulmonary artery and encircled with an umbilical tape. The superior vena cava (SVC) is mobilized to the level of the azygos vein and is then encircled with a single heavy silk tie and snared loosely. The azygos vein is then doubly ligated, but it is not divided.

When the abdominal procurement team has completed their dissection, 30,000 units of intravenous heparin is administered to the donor. A cannula for infusion of cold cardioplegia is inserted into the ascending aorta and secured. If the lungs are being procured, a pulmonoplegia line is inserted through a purse-string stitch and into the main pulmonary artery. Any central venous lines are withdrawn high into the SVC. The SVC is then snared tightly to limit venous return to the heart. The right heart is decompressed, and the donor is exsanguinated by incising the inferior vena cava (IVC) at the diaphragm ensuring enough of a cuff for implantation of both the heart and the liver. Sufficient length on the SVC and IVC will be needed for later bicaval anastomoses. Blood and perfusate from the liver will drain into the right pleural cavity, and suction should be available to keep the field clear. The left side of the heart is decompressed by incising the left inferior pulmonary vein.

Alternatively, if the lungs are also being procured, the left side of the heart is decompressed by amputating the left atrial appendage. As the heart empties, the aortic cross-clamp is placed and cold crystalloid cardioplegia (10 mL/kg) solution is rapidly infused into the aorta ensuring diastolic arrest. It is important to continually observe the left ventricle for distention. Pulmonoplegia solution is also rapidly infused into the pulmonary artery if the lungs are being procured. While the plegia solutions are being delivered, the thoracic organs are topically cooled with several liters of ice-cold slush.

When the infusions are completed and the heart has been appropriately cooled and arrested, the chest is emptied of the cold slush. The heart is rapidly excised by dividing the four pulmonary veins, the IVC, the SVC, the aorta (as high as possible), and the pulmonary arteries. If the lungs are being procured, a short cuff of left atrial tissue may be retained with the pulmonary veins, and the pulmonary artery is divided at the bifurcation of the left and right pulmonary arteries. Once removed from the donor, the heart is examined for debris, including the possibility of an amputated central venous catheter. It is then rinsed in cold saline and sterilely bagged first in cold preservation solution and then in slush. The heart is then placed in a container filled with cold slush and transported in a cooler designated specifically for this purpose. A section of donor pericardium is additionally harvested in the event that it is needed for reconstruction.

Organ Preservation

Several strategies are used for cardiac preservation during organ retrieval and ischemic storage, including the use of hypothermia, cardioplegia, and preservation solutions.¹⁰⁹ Hypothermia at 4° C to 8° C markedly decelerates metabolism and is used during organ retrieval, storage, and transport.¹¹⁰ Cardioplegia is used to arrest electrical activity of the heart.¹¹¹ Adequate decompression of the ventricles during organ retrieval limits injury to the heart during procurement. The heart may be stored in any of a variety of preservation solutions, which can be broadly categorized as intracellular and extracellular types, based on their ionic composition. Intracellular solutions have a moderate to high potassium concentration and little calcium or sodium, whereas extracellular solutions have a high sodium concentration and a low to moderate concentration of potassium.¹¹² In addition to electrolyte constituents, these solutions often contain impermeants and colloids to prevent the development of intracellular edema. Most contain glucose to prevent intracellular acidosis secondary to anaerobic metabolism. Many contain antioxidant additives to protect against reperfusion injury. The possibility of improving donor heart preservation with additives to the preservation solution is being studied, and rho-kinase inhibitor¹¹³ and small interfering RNA¹¹⁴ have been proposed. In rare cases, preservation solutions are used as alternatives to standard cardioplegia during organ procurement.

Cardiac preservation currently is limited to 4 to 6 hours of cold ischemic storage. Longer ischemic periods adversely affect recipient survival.⁵¹ Most notably, in

February 2007, the U.S. Food and Drug Administration (FDA) approved the clinical use of a system developed by TransMedics, Inc., called the Organ Care System (OCS). OCS involves perfusing donor hearts with warm, oxygenated, nutrient-rich blood while maintaining the organ in a beating, functioning state in transit, with the hope that the heart arrives in a healthier and more dynamic state. The recently completed global clinical trial PROCEED II evaluated the safety and performance of the OCS for the preservation of donor hearts during transplantation, but results have not yet been published.¹¹⁵ Several cardiac transplant recipients have received donor hearts that have undergone OCS and have recovered successfully. Long-term results and the comparison between OCS and standard organ preservation methods have yet to be elucidated.

RECIPIENT OPERATIVE TECHNIQUE

Both orthotopic and heterotopic techniques for clinical heart transplantation are performed. Orthotopic transplantation is performed in most cases, whereas heterotopic transplantation is reserved for cases in which the recipient has significant pulmonary hypertension or the donor is notably smaller than the recipient.

For many years, the technique of Lower, Stofer, and Shumway, described in 1961, was the standard.⁶ This technique, often referred to as the biatrial or standard technique, involves excision of the recipient heart at the mid-atrial level and sewing corresponding anastomoses between the donor and recipient left atrium, right atrium, aorta, and pulmonary artery. This technique permits short operative times and avoids potential complications that result from individual caval and pulmonary venous anastomoses, including but not limited to stenosis and thrombosis. Disadvantages of the method include distortion of atrioventricular geometry, which can result in atrial enlargement, atrioventricular valve insufficiency, impaired atrial function, atrial thrombosis, and sinoatrial node dysfunction.^{116,117} Barnard¹¹⁸ introduced an important modification of the technique in 1968: the incision in the donor heart's right atrium was extended from the opening of the IVC into the base of the right atrial appendage, rather than into the SVC, avoiding the region of the sinoatrial node, which may be injured because of its proximity to the right atrial suture line in the classic orthotopic standard technique.

The standard technique is declining in popularity. Newer techniques, including the "bicaval" and "total" techniques, offer the advantage of better preservation of atrial geometry.¹¹⁹⁻¹²¹ In the bicaval technique, the native recipient's right atrium is excised, and separate SVC and IVC anastomoses are made in addition to the left atrial, aortic, and pulmonary artery anastomoses. The total technique uses separate SVC, IVC, aortic, and pulmonary artery anastomoses as with the bicaval technique. However, rather than use a single left atrial anastomosis, the total technique uses separate right and left pulmonary vein anastomoses. The left atrial remnant is divided longitudinally leaving left and right pulmonary vein cuffs, which are then anastomosed to the left and right

pulmonary vein orifices in the donor heart's left atrium. Technical considerations include shortening of the IVC, kinking of the pulmonary artery, and SVC stenosis; an early series from Stanford University reported a 2.4% incidence of SVC stenosis.¹²² The total technique may be associated with additional complications, including bleeding from inaccessible pulmonary vein suture lines and pulmonary vein stenosis.

The bicaval technique is now the most commonly used anastomotic method with 62.0% of recipients undergoing this operation and 34.7% undergoing biatrial anastomosis in 2007 as compared with 2.3% and 97.6% in 1997.^{123,124} The bicaval technique has been increasing in popularity because of the lower incidence of permanent pacemaker implantation, improved tricuspid valve function, and improved right atrial hemodynamics. With respect to mortality benefit, Weiss and coworkers demonstrated using the UNOS database that although gross mortality was higher in patients undergoing biatrial anastomosis at 24% compared with bicaval anastomosis at 18%, this difference was eliminated after controlling for confounders. However, Davies and colleagues were able to show, in a larger cohort, favorable survival for the bicaval technique compared with both biatrial and total orthotopic techniques.¹²⁴⁻¹²⁷

Orthotopic Standard Technique

In the orthotopic standard technique, the recipient is positioned supine on the operating room table. The chest is entered through a median sternotomy, and the pericardium is opened longitudinally. After heparinization, cardiopulmonary bypass (CPB) is initiated via cannulas in the ascending aorta, SVC, and IVC. Snares are placed around the SVC and IVC for total CPB, and the patient is cooled to 28°C.

Once the donor heart has been brought to the operating room, the recipient heart is excised. The aorta is cross-clamped proximal to the aortic cannulation site. The right and left atrial walls, atrial septum, pulmonary artery, and aorta are divided. The pulmonary artery and aorta should be divided just above the semilunar valves (Fig. 98-1A).

The donor heart is prepared for implantation by excising the tissue between the orifices of the four pulmonary veins leaving a single large opening. The right atrium is then opened, beginning from the lateral aspect of the IVC and extending into the base of the right atrial appendage. The heart is carefully examined for any valvular or congenital anomalies.

In the original description of the standard technique, anastomoses were performed in the following order: left atrium, right atrium, pulmonary artery, and aorta. In an attempt to achieve earlier reperfusion, the sequence of anastomoses may be altered. For example, in the case of prolonged ischemic time, the aortic anastomosis can be performed immediately after the left atrial anastomosis allowing the aortic crossclamp to be removed. The original sequence of anastomoses is described as follows.

The anastomosis of the donor and recipient left atria is performed with a double-armed running 3-0 or 4-0 polypropylene suture. The first stitch is placed in the

recipient left atrium at the level of the left superior pulmonary vein and at the base of the donor left atrial appendage. The suture line is continued around the superior and inferior borders of the left atrium and then tied along the interatrial septum. Once this suture line is complete, the left atrial appendage is cannulated with a line of cold saline to facilitate endocardial cooling. In addition, cold saline is continuously infused into the pericardial well to achieve topical cooling.

The two right atria are anastomosed with a double-armed running 4-0 or 5-0 polypropylene suture (see Fig. 98-1B). The first stitch is placed through the midpoint of the donor septum and through the midpoint of the suture line along the atrial septum. The suture line is continued inferiorly first, and then the superior suture line is completed. The two ends of the suture are tied along the right atrial free wall. Once the right atrial anastomosis is completed, systemic rewarming is initiated.

The donor and recipient pulmonary arteries are trimmed to an appropriate length and anastomosed with a running 4-0 polypropylene suture. The donor and recipient aortas are also trimmed and anastomosed with a running 4-0 polypropylene suture (see Fig. 98-1D).

The ascending aorta and pulmonary artery are cleared of air. The SVC and IVC snares are then released, followed by the aortic crossclamp. De-airing is continued as needed. Transesophageal echocardiography aids in de-airing the heart and assessing cardiac function. The line in the left atrial appendage is removed, and the hole is oversewn. Temporary atrial and ventricular wires are placed in the transplanted heart. The heart is then allowed to recover fully. Defibrillation may be necessary. After at least 30 minutes of reperfusion, the patient is gradually weaned from CPB and the cannulas are removed. Intravenous methylprednisolone (500 mg) is administered. Mediastinal drains are placed, as well as pleural chest tubes if the pleura were opened. The chest is then closed in the standard fashion.

Orthotopic Bicaval Technique

In recent years, the bicaval technique for OHT has become the preferred approach at most transplant centers. The bicaval anastomosis was reported in 1991 by Dreyfus and colleagues.¹¹⁹ Several modifications distinguish it from the standard approach. First, the recipient SVC is cannulated just below the innominate vein junction, and the IVC is cannulated at the diaphragm. Recipient cardiectomy is performed as a two-step procedure. In the first step, the heart is transected at the mid-atrial level, the aorta and pulmonary artery are divided, and the heart is removed. In the second step, the posterior walls of both atria are removed; on the right side, the SVC and IVC are transected at their junction with the right atrium, and on the left side, the left atrium is trimmed, leaving a cuff of tissue around the pulmonary vein orifices (Fig. 98-2A). The donor heart's left atrium is trimmed, leaving a single orifice where the pulmonary vein entry sites had been, and the right atrium remains intact (see Fig. 98-2B). In the bicaval approach, the typical sequence of anastomoses is left atria, venae cavae, pulmonary arteries, and aortas. The left atrial, pulmonary artery, and aortic anastomoses

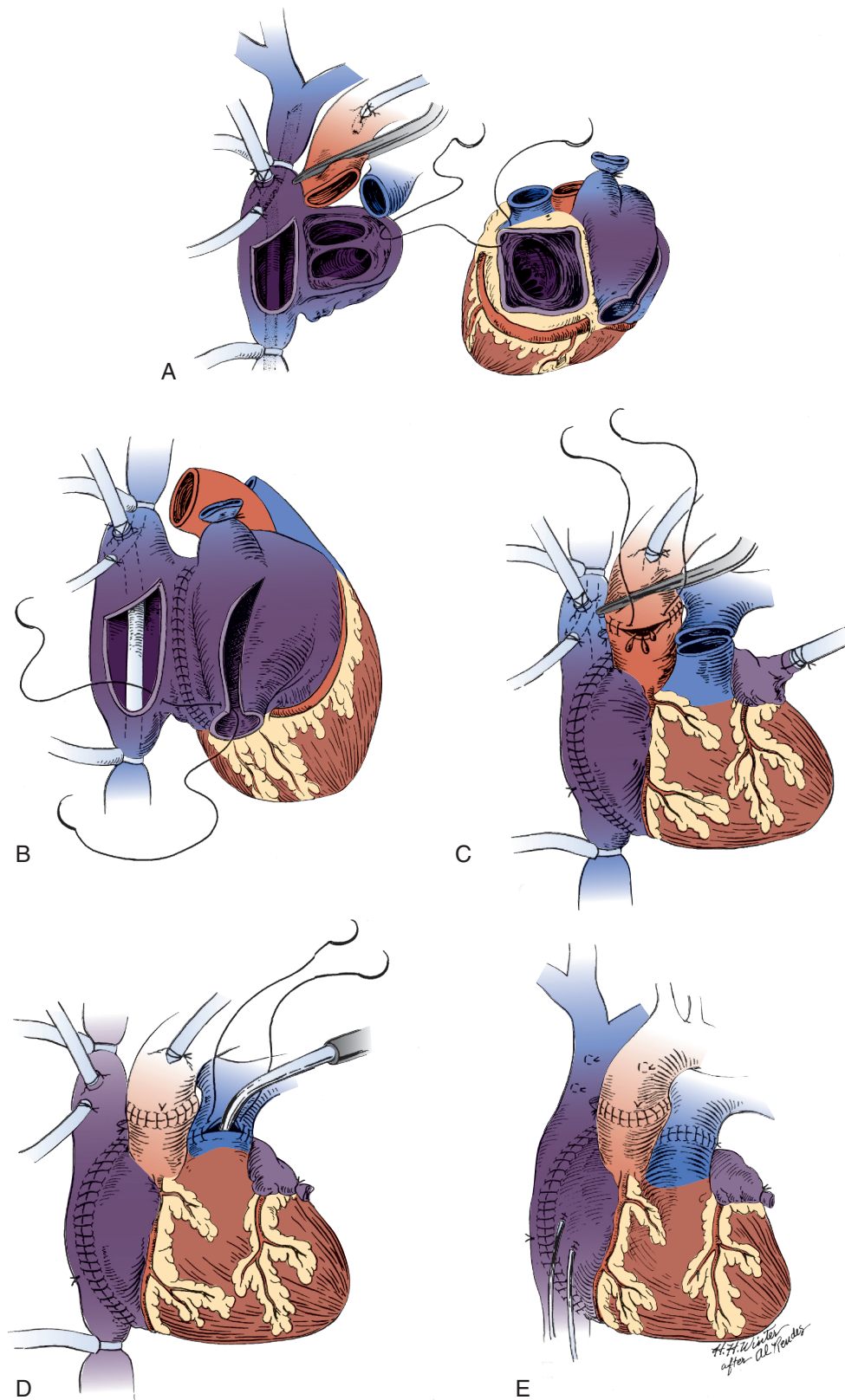


FIGURE 98-1 ■ Biatrial or “standard” technique for orthotopic heart transplantation. **A**, Cannulation technique is similar to that performed in routine cardiac procedures with central cannulation. Tapes have been placed around the superior and inferior venae cavae, and the aorta has been cross-clamped to exclude the heart from the circulation. The recipient’s heart has been excised at the atrioventricular groove. The superior vena cava (SVC) of the donor’s heart has been ligated, and the left atrial anastomosis has been started. **B**, The left atrial anastomosis has been completed. The incision in the right atrium of the donor heart is curved away from the SVC and the adjacent sinoatrial node. The right atrial anastomosis is begun. **C**, The right atrial, pulmonary artery, and aortic anastomoses are completed. The aortic crossclamp is removed, and the patient is weaned from cardiopulmonary bypass. **D** and **E**, When the heart is fully recovered, the bypass cannulas are removed. (From Baumgartner WA, Reitz BA, Oyer PE, et al: Cardiac homotransplantations. *Curr Probl Surg* 16:1–61, 1979.)

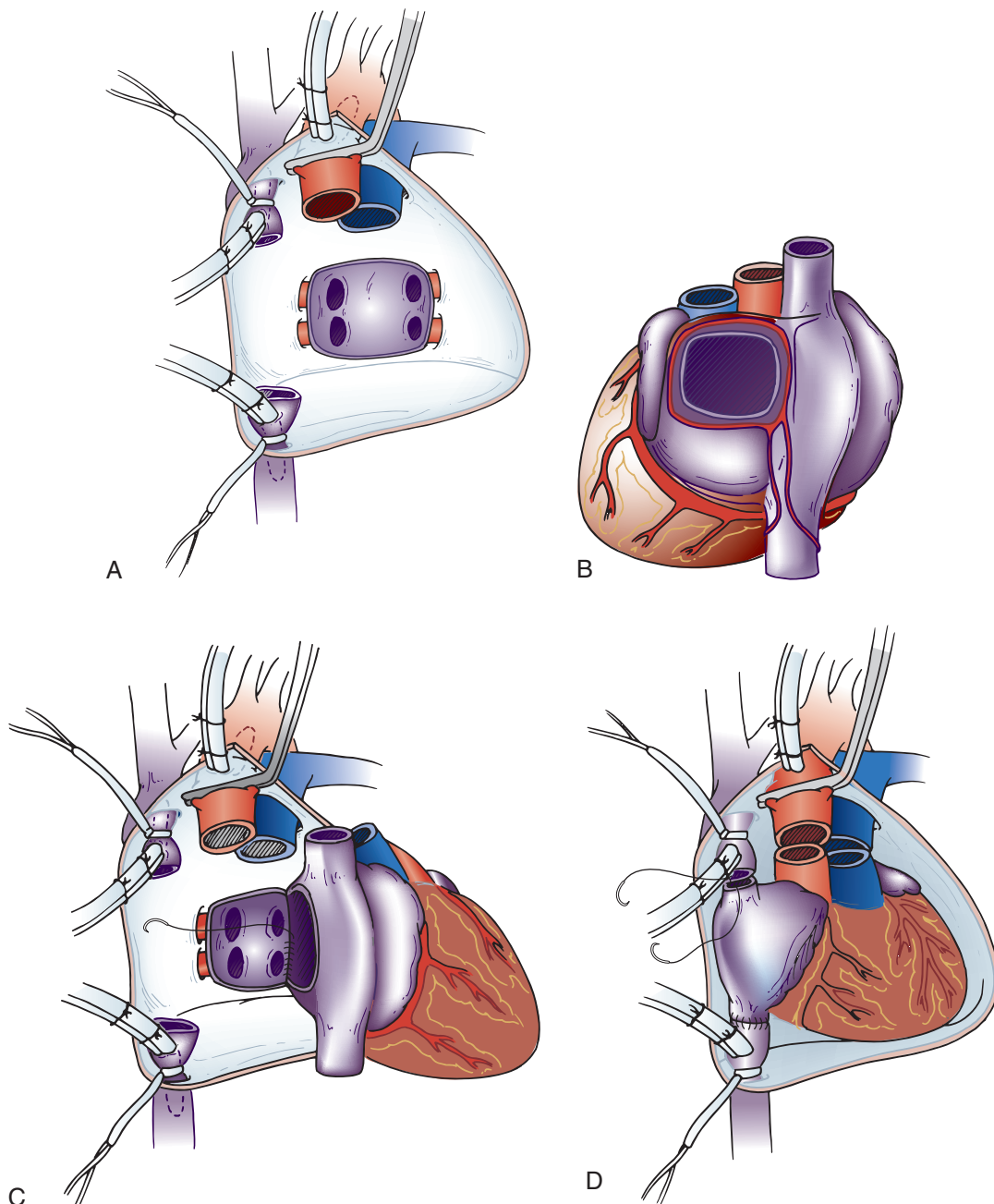


FIGURE 98-2 ■ Bicaaval technique for orthotopic heart transplantation. **A**, Cardiopulmonary bypass is initiated after cannulation of the superior vena cava (SVC), inferior vena cava (IVC), and aorta. The aorta is cross-clamped, and native recipient cardiectomy is performed. A cuff of left atrial tissue is preserved around the four pulmonary vein orifices. **B**, The donor heart is prepared for transplantation. The left atrial tissue surrounding the four pulmonary vein orifices has been excised, leaving a single large orifice. **C**, The left atrial anastomosis is performed. **D**, The IVC anastomosis is completed, and the SVC anastomosis is performed. Once this is completed, the pulmonary artery and aortic anastomoses will be performed.

are performed as described earlier in the standard technique (see Fig. 98-2C). The SVC anastomosis is performed with a running 5-0 polypropylene suture and the IVC anastomosis with running 4-0 polypropylene suture (see Fig. 98-2D).

A further modification to this technique has been practiced at Stanford University by Oyer and associates since 1992, although it was first published in 2001 by Kitamura and colleagues.¹²⁸ The modified bicaaval anastomosis technique for OHT leaves the posterior

portion of the right atrial wall connecting both the SVC and the IVC intact. This modification makes the anastomosis technically easier with respect to proper orientation and eliminates the retraction, tension, or kinking of the venae cavae.

Orthotopic Total Technique

The orthotopic total technique is used at a small number of centers. It is similar to the bicaaval approach except that

during recipient cardiectomy, the left atrial cuff surrounding the pulmonary vein orifices is divided longitudinally into separate right and left pulmonary vein cuffs. Preparation of the donor heart requires separate preparation of the right and left pulmonary veins leaving two orifices on the donor heart's left atrium. Two left atrial anastomoses are fashioned, followed by the bicaval, pulmonary artery, and aortic anastomoses.

Heterotopic Technique

In the heterotopic approach, the donor IVC and right pulmonary veins are ligated, followed by anastomosis of the donor and recipient left atria, SVC, aortas, and pulmonary arteries. SVC and aortic anastomoses are performed in an end-to-side manner, and a short length of graft is used to connect the pulmonary arteries (Fig. 98-3). The heterotopic approach can be used when recipient PVR is markedly elevated given the possibility of acute right-sided heart failure in a donor right ventricle unaccustomed to the pulmonary resistance. In addition, it has been used in cases of donor and recipient size mismatch when medical urgency for transplantation is high.¹⁰⁷ Improvements in mechanical assist devices and a growing experience in their use as BTTs have made the indications for heterotopic heart transplantation almost obsolete.

RECIPIENT POSTOPERATIVE MANAGEMENT

Clinical Management in the Early Postoperative Period

On completion of the transplant, the patient is transported to the intensive care unit. The patient remains mechanically ventilated with continuous monitoring of electrocardiogram, arterial blood pressure, CVP, and pulse oximetry. In most cases, a pulmonary artery catheter is used to further monitor hemodynamics. Temperature, urine output, and mediastinal drain output are monitored as well.

As with other patients undergoing cardiac surgery, dysrhythmias are frequent in the early postoperative period. Junctional rhythms are particularly common after OHT. Because cardiac output of the denervated transplanted heart is primarily rate dependent, the heart rate should be maintained between 90 and 110 beats per minute during the first few postoperative days.¹²⁹ Isoproterenol infusion, theophylline, oral albuterol, and temporary pacing may be used to augment the heart rate. Another option is to place temporary atrial and ventricular pacing leads in the operating suite, allowing for postoperative heart rate adjustment. Less than 5% of patients

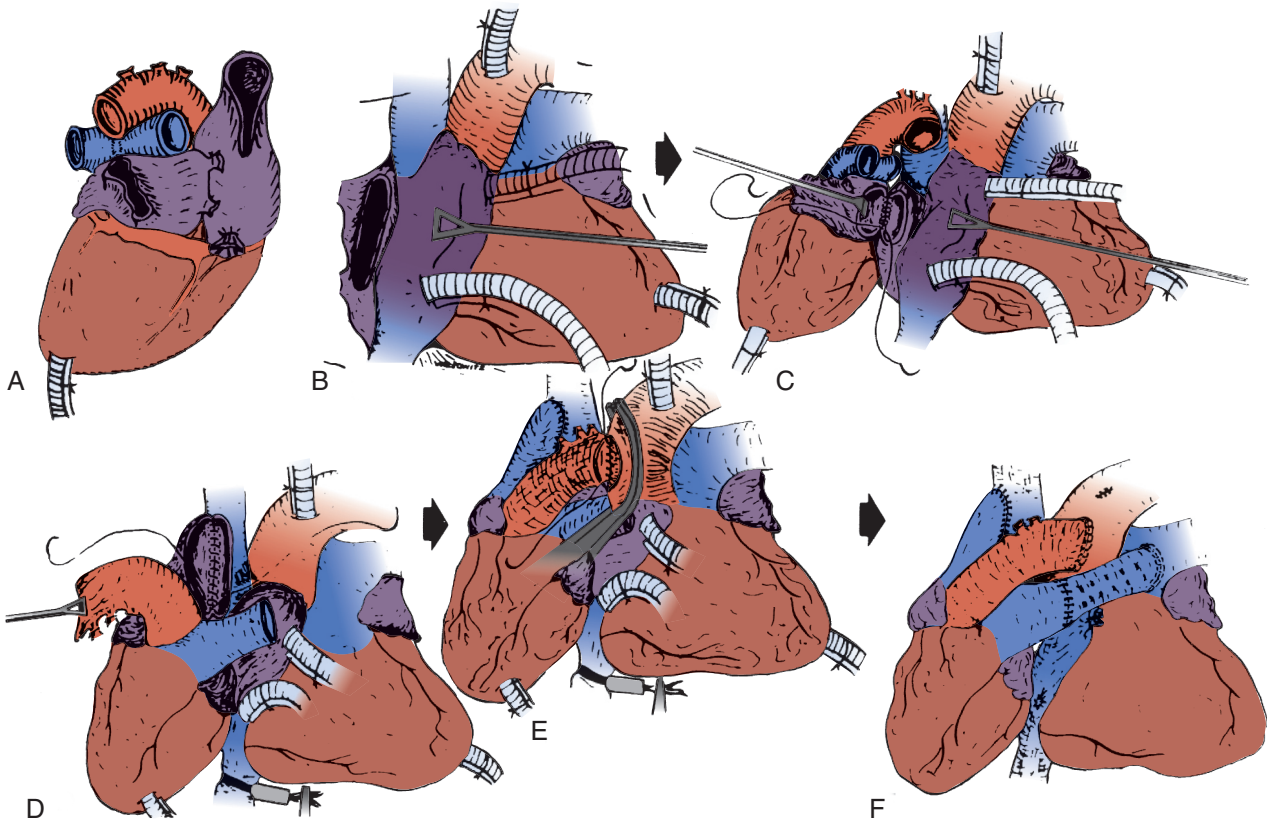


FIGURE 98-3 ■ The heterotopic cardiac transplant. **A**, Posterior view of the donor heart after preparation for anastomosis. **B**, Left atriotomy. **C**, Left atrial anastomosis. **D**, Right atrial anastomosis. **E**, Aortic anastomosis. **F**, Completed anastomoses with a pulmonary-to-pulmonary arterial graft. (**A-E** from Barnard CN, Wolpowitz A: Heterotopic versus orthotopic heart transplantation. *Transplant Proc* 11:309-312, 1979.)

have permanent sinus node dysfunction and require placement of a permanent transvenous pacemaker. The rate of sinus node dysfunction may be reduced when the bicaval technique is used.¹²⁹

In most cases, the postoperative course after transplantation is uncomplicated. The patient is extubated when alert and hemodynamically stable, typically within 6 hours of surgery. The patient is gradually weaned from inotropic support over the first few postoperative days. Invasive catheters are removed as soon as possible to reduce the risk for sepsis, and mediastinal drains are removed when drainage has fallen to less than 200 mL/day. Temporary pacing wires are removed approximately 1 week after transplantation, provided that pacing is not required.

Early complications after transplantation include bleeding, depressed global myocardial performance, and right-sided heart failure. Significant hemorrhage may require surgical reexploration. Depressed global myocardial performance is uncommon but may occur in the setting of prolonged organ ischemia or inadequate preservation.¹³⁰ In such cases, aggressive hemodynamic and ventilatory management is necessary, and support from inotropic agents and vasopressors is needed. Hypovolemia, cardiac tamponade, sepsis, and bradycardia can result in depressed myocardial performance and should be treated expeditiously if they are present.

Right-sided heart failure can occur after transplantation, particularly in recipients who have elevated preoperative PVR.¹³¹ In such cases, the donor right ventricle is unable to work against the elevated PVR and begins to fail within hours after transplantation. Aggressive early management may mitigate the consequences of this complication. Intraoperative transesophageal echocardiography should be performed routinely to assess right ventricular function and evaluate for technical failure such as kinking of the pulmonary artery or anastomotic stenosis. Treatment of right-sided heart failure includes correction of any technical problems, optimization of volume status, medical treatment with inotropes, implementation of pulmonary vasodilators (nitroprusside, inhaled epoprostenol, and inhaled nitric oxide), and avoidance of hypercarbia (goal CO₂, <40 mm Hg). Refractory right-sided heart failure may necessitate placement of a right ventricular assist device.

Maintenance Immunosuppression

In addition to careful monitoring of cardiac function during the immediate postoperative period, much focus is placed on institution of immunosuppression. In most cases, immunosuppression is initiated intraoperatively with intravenous methylprednisolone and continued postoperatively with a combination of intravenous and oral medications. Most centers have adopted triple drug combinations of a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative agent (azathioprine or mycophenolate mofetil [MMF]), and a corticosteroid. Immediately after transplantation, many of these medications are administered intravenously, although some must be delivered via nasogastric tube. Once patients are tolerating oral intake, they can be converted to a completely

oral immunosuppressive regimen. Because the risk for allograft rejection is highest in the first several months after transplantation, immunosuppression is most aggressive during this period. If patients remain free of rejection, immunosuppression is gradually decreased over time. Typical immunosuppressive dosing regimens (early and late) are demonstrated in Box 98-5.

Multidrug immunosuppression targets multiple sites in the immune cascade that lead to allograft rejection.¹³² Calcineurin inhibitors block the activity of calcineurin, a calcium- and calmodulin-dependent phosphatase that is required for early T cell activation and interleukin-2 (IL-2) formation. Antiproliferative agents inhibit lymphocyte replication through a variety of mechanisms. Azathioprine inhibits the *de novo* and salvage pathways for purine biosynthesis. MMF inhibits the *de novo* synthesis of guanine nucleotides. Because activated lymphocytes use the *de novo* pathway predominantly, MMF is thought to have greater selectivity than azathioprine. Corticosteroids inhibit lymphocyte proliferation by inhibiting macrophage production of cytokines, including IL-1 and IL-6.

The drugs in these regimens act synergistically, permitting dosage reduction when used in combination. This helps minimize dosage-dependent toxicity to the transplant recipient. Cyclosporine can cause nephrotoxicity, neurotoxicity, hypertension, hyperlipidemia,

BOX 98-5 Immunosuppression Regimen for Heart Transplant Recipients

PERIOPERATIVELY

- Corticosteroid—methylprednisolone (125 mg IV, every 8 hours for three doses, starting 8 hours after the induction dose in the operating room)

POSTOPERATIVELY

Induction Therapy

- rATG (1 mg/kg, with a maximum of 125 mg, over 6 hours daily for 3 days; premedication with diphenhydramine and acetaminophen, addition of hydrocortisone premedication if timing does not coincide with prednisone or methylprednisolone)

Maintenance Therapy

- Prednisone (20 mg twice daily; taper to baseline dosage by 3 months after transplant)
- Tacrolimus (dosage according to level, with daily trough; beginning dosage, 0.5 mg daily; aim for whole blood level of 12-15 for normal renal function, 8-10 for mild renal insufficiency, 4-6 for severe renal insufficiency)
- Cellcept (1000 mg twice a day, ½ hour before or 2 hours after food)

Alternative Immunosuppressive Agents

- Azathioprine (2 mg/kg PO every night; decrease dosage by half if WBC < 5000 or in the presence of severe renal failure, then titrate for WBC count; hold dosage if WBC < 4000)
- Sirolimus (1 mg PO every day; target level, 5-7)

WBC, White blood cell count.

hirsutism, and gingival hyperplasia. Tacrolimus is also nephrotoxic and neurotoxic and has been associated with glucose intolerance and new-onset diabetes mellitus. Both cyclosporine and tacrolimus are metabolized by the liver and cause upregulation of the cytochrome P450 system. Azathioprine and MMF cause dosage-dependent bone marrow suppression. Corticosteroids are associated with myriad side effects, including poor wound healing, development of cushingoid features, hypertension, diabetes mellitus, osteoporosis, and peptic ulcer disease.

Rapamycin, or sirolimus, is an alternative immunosuppressive agent that has been used successfully in renal and liver transplantation.¹³³ It inhibits mTOR (mammalian target of rapamycin), thereby blocking IL-2 signaling pathways.^{132,134} Rapamycin also inhibits smooth muscle proliferation and has been used in drug-eluting coronary stents to inhibit neointimal hyperplasia. Experimental animal models have shown inhibition of cardiac allograft vasculopathy (CAV) with rapamycin treatment and this has been validated in small, single-institution studies.¹³⁵⁻¹³⁷ A randomized clinical trial performed by Keogh and associates in OHT recipients compared sirolimus with azathioprine in combination with cyclosporine and steroid immunosuppression. Those patients receiving sirolimus showed a significant decrease in acute rejection: 32.4% to 32.8% of sirolimus-treated patients versus 56.8% of azathioprine patients. Sirolimus appeared to also aid in the prevention of CAV at 6 months and up to 2 years.¹³⁸ Additionally, Topilsky and coworkers retrospectively reviewed patients transitioned from a calcineurin inhibitor-based immunosuppressive regimen to a sirolimus-based regimen. In their study, patients receiving sirolimus ended up having lower overall mortality and lower incidence of CAV-related events.¹³⁶

The role of mTOR inhibitors, including sirolimus and everolimus, in the immunosuppressive armamentarium for OHT recipients continues to be controversial, especially regarding calcineurin inhibitor withdrawal and sirolimus conversion in patients with renal impairment. Transition from calcineurin inhibitor to sirolimus in OHT recipients with significant renal dysfunction (requiring hemodialysis) has yielded beneficial results in terms of renal improvement and number of episodes of clinical rejection at 1 year.¹³⁹ On the other hand, evidence shows that mTOR inhibitors may be associated with an increase in wound healing complications. Conflicting data were summarized by a cardiac transplant multidisciplinary committee in 2008, which concluded that calcineurin inhibitor withdrawal in OHT recipients should not be instituted until after the first year of transplantation.¹⁴⁰

Despite the huge advancement of immunosuppressive drug therapy for cardiac transplantation, the specific combination of agents necessary for increased survival, safety profile, and decreased rejection has not been established. Transplant centers' immunosuppressive protocols vary widely, and most existing studies report only short-term findings. Taylor and colleagues¹⁴¹ performed a small prospective randomized multicenter study comparing the efficacy of tacrolimus-based immunosuppression with that of cyclosporine-based immunosuppression. At 1-year follow-up, rejection rates were comparable in both

groups, although the incidence of hypertension and hyperlipidemia was less in the tacrolimus group. A randomized multicenter trial comparing the triple drug regimens of cyclosporine–azathioprine–prednisone and cyclosporine–MMF–prednisone showed improved 1-year survival and greater freedom from rejection in the cyclosporine–MMF–prednisone group.¹⁴² A greater increase in herpes simplex viral infection was found in the cyclosporine–MMF–prednisone group compared with that in the cyclosporine–azathioprine–prednisone group (21% vs. 15%), but no difference in other infectious complications or malignancy was found. In 2006, Kobashigawa and coworkers¹⁴³ conducted a large multicenter randomized trial consisting of 343 OHT recipients who were randomized to receive steroids and either tacrolimus–sirolimus, tacrolimus–MMF, or cyclosporine–MMF. The primary endpoint was incidence of ISHLT grade 3A or greater rejection or hemodynamic compromise requiring therapy within the first 6 months. Secondary endpoints included patient and graft survival at 1 year, rejection incidence, and safety profile. ISHLT grade 3A rejection episodes were diminished in the tacrolimus–MMF group versus the cyclosporine–MMF group at 1 year (23% vs. 36%). At 35%, the tacrolimus–sirolimus group had the lowest incidence of treated rejection episodes of any of the groups. The incidence was 42% in the tacrolimus–MMF group and 59% in the cyclosporine–MMF group. The tacrolimus–MMF group had significantly lower mean serum creatinine compared with the tacrolimus–sirolimus and cyclosporine–MMF groups: 1.3 mg/dL versus 1.5 mg/dL. The triglyceride level (126 mg/dL versus 162 mg/dL in tacrolimus–MMF and 154 mg/dL in cyclosporine–MMF) was also better for the tacrolimus–MMF group. The authors concluded that the combination of steroids, tacrolimus, and MMF may be the most beneficial immunosuppressive regimen in OHT recipients because of fewer rejection episodes and improved side effect profiles.

Along with multidrug immunosuppression regimens, many centers use cytolytic induction therapy to rapidly deplete lymphocytes in heart transplant recipients. This therapy occurs over a 3- to 10-day course, beginning immediately after transplantation. Induction immunosuppressive therapy has declined in popularity to the point that only 47% of heart transplant recipients received it in early 2012.² Currently available induction agents include the following: IL-2 receptor antagonists, such as daclizumab and basiliximab,^{144,145} which are humanized antibodies that effect the destruction of activated T cells expressing the IL-2 receptor on their cell surface; polyclonal antilymphocytic antibodies, for example, antithymocyte globulin (ATG), which is a rabbit or equine polyclonal antibody preparation that results in rapid cytolytic depletion of T cells; and alemtuzumab, a monoclonal antibody directed at CD52.¹⁴⁶ Induction therapy has advantages and disadvantages. Because immunosuppression is immediate, maintenance immunosuppression with other drugs can be delayed. In cases of hemodynamic instability or questionable renal function, this can be advantageous. Initial doses of ATG may be associated with a “cytokine release syndrome,” which manifests with fever, chills, hypotension, and bronchospasm. Patients

receiving this induction agent should be premedicated with acetaminophen, antihistamines, and corticosteroids and should be monitored closely. Because these preparations are raised in animals, patients may develop neutralizing antibodies, making prolonged and repeated courses impossible. Induction therapy with ATG may decrease the incidence of acute rejection in some cases, but in others, it simply delays the time of onset to rejection. Both are associated with a higher incidence of infectious complications and posttransplant lymphoproliferative disorder.¹³² Of note, OKT3 (muromonab-CD3), a mouse monoclonal antibody targeting the CD3 receptor on activated T cells, is no longer available because of a higher incidence of posttransplantation lymphoproliferative disease and side effect profile with no demonstrable benefit over other antibodies.^{147,148}

The experience with IL-2 receptor blockade is more limited, but 1-year follow-up studies have shown a decrease in the frequency and severity of acute rejection and a decrease in development of CAV.^{149,150} Kobashigawa and colleagues¹⁵¹ investigated the safety profile of daclizumab with patients on triple drug therapy consisting of cyclosporine–MMF–steroids from the Scientific Registry of Transplant Recipients. They demonstrated that daclizumab-induced patients had no increased risk for death or infectious death when compared with no induction therapy. Daclizumab-treated recipients also experienced lower rates of acute rejection at 6 and 12 months, with an overall 23% reduction when compared with non-induced patients.

A Cochrane review revealed that IL-2R antagonists were associated with lower incidence of acute rejection compared with no induction therapy. However, polyclonal antibody induction may be associated with a reduced incidence of biopsy-proven severe acute rejection compared with IL-2R antagonists.¹⁵² Long-term prospective studies are needed to determine whether induction with IL-2 receptor antagonists provides a survival benefit and to define patient populations that would benefit most from these therapies.

COMPLICATIONS

Hyperacute Rejection

Hyperacute rejection is a form of humorally mediated rejection. Preformed antibodies in the recipient recognize donor vascular endothelial antigens, resulting in activation of inflammatory and coagulation cascades. Graft vessels thrombose resulting in graft loss. ABO matching of donor and recipient has decreased the rate of hyperacute rejection. For recipients with an elevated PRA, prospective crossmatching of donor lymphocytes with recipient serum has also decreased the rate of hyperacute rejection.

Acute Rejection

The risk for acute rejection is highest during the first few months after transplantation and then persists at a low constant level. Most heart transplant patients experience

at least one episode of acute rejection, and there is a small mortality risk associated with each of these episodes. According to ISHLT data, acute rejection is the cause of death in approximately 11% of patients between 1 and 3 years after transplantation.² In 1994, the Cardiac Transplant Research Database group identified risk factors for recurrent rejection after heart transplantation.¹⁵³ In the first year after transplantation, these risk factors include shorter interval since previous rejection episode, young age, female sex, female donor, positive cytomegalovirus serology, prior infections, and OKT3 induction. After the first year, the dominant risk factors are a greater number of rejection episodes during the first year and the presence of prior cytomegalovirus infections.

The clinical presentation of acute rejection varies widely. Patients may be asymptomatic or may have non-specific clinical signs and symptoms, including fever, anorexia, leukocytosis, and mild hypotension. In rare cases, acute rejection manifests with severe hypotension and circulatory collapse. Because these clinical signs and symptoms lack a high degree of sensitivity or specificity in the diagnosis of acute rejection, the gold standard diagnostic test is a tissue biopsy. Percutaneous endomyocardial biopsy is performed as a part of routine surveillance protocols after heart transplantation. A bioprobe is passed through a sheath in the right internal jugular vein and advanced through the tricuspid valve into the right ventricle, where tissue biopsies are taken. Clinicians should be well versed in tissue sampling, because tricuspid regurgitation, although rare, is a recognized complication. Pathologically, acute rejection can be a focal patchy process, so four to six biopsies should be taken to reduce sampling error.¹⁵⁴ A typical surveillance endomyocardial biopsy protocol includes weekly biopsies for the first 4 weeks after transplantation, biweekly biopsies for the next month, and then monthly biopsies through the sixth month after transplantation. If the patient is free from rejection at 6 months, the frequency of biopsies is reduced to every 3 months.

Because of the cost, invasive nature, and potential for complications associated with endomyocardial biopsy, investigators are now developing alternative noninvasive techniques to monitor cardiac allograft rejection.¹⁵⁵ Emerging and promising techniques include magnetic resonance imaging,¹⁵⁶ wall motion analysis with tissue Doppler imaging,¹⁵⁷ electrical event monitoring with ventricular evoked response amplitude assessment,¹⁵⁸ identification of peripheral blood markers of rejection (e.g., P-selectin, prothrombin fragments, B-type natriuretic peptides, troponin),^{159,160} imaging for necrosis with antimyosin antibody-based scintigraphy,¹⁶¹ and imaging for apoptosis with technetium 99m-labeled annexin V.¹⁶²

Acute Cellular Rejection

The primary process leading to acute rejection is acute cellular rejection, which is T cell mediated. Donor antigen presenting cells (APCs) may be directly recognized by recipient T cells, or donor antigens may cross into the recipient to be taken up by recipient APCs.¹⁶³ The presentation of antigens to T cells via APCs causes conformational changes in the T cell receptor. In the presence of a

TABLE 98-3 ISHLT Standardized Cardiac Biopsy Grading: Acute Cellular Rejection*

Grade	Criteria
Grade 0R [†]	No rejection
Grade 1R, mild	Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage
Grade 2R, moderate	Two or more foci of infiltrate with associated myocyte damage
Grade 3R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis

*The presence or absence of acute antibody-mediated rejection (AMR) may be recorded as AMR 0 or AMR 1, as required.

[†]R denotes revised grade, to avoid confusion with 1990 scheme. ISHLT, International Society for Heart and Lung Transplantation. From Stewart S, Winters GL, Fishbein MC, et al: *Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection*. *J Heart Lung Transplant* 24(11):1710–1720, 2005.

costimulatory molecule, i.e., B7 (CD80 or CD86), on the APC interacting with CD28 on the T cell, promotion of T cell proliferation and cytokine production occurs.¹⁶⁴ Following the sensitization of effector cells, there is a migration of lymphocytes into the allograft with subsequent activation of either the FAS-FAS ligand or perforin/granulysin pathway resulting in myocyte death.¹⁶⁵

A standardized grading system for cardiac acute rejection was developed by the ISHLT Heart Rejection Study Group in 1990. This system graded acute rejection with a score of 0 to 4, with 0 being no rejection and 4 being severe acute rejection. However, with the advent of newer, more effective immunosuppressive regimens and better understanding of transplant immunobiology, a revision of the previous Working Formulation, focused mainly on grade 2 cellular rejection, was approved by the ISHLT board in December 2004.¹⁶⁶ Table 98-3 illustrates this revised ISHLT standardized cardiac biopsy grading system of acute cellular rejection. Briefly, 1990 ISHLT grades 1A, 1B, and 2 combined into 2004 ISHLT grade 1R; 1990 ISHLT grade 3A is now 2004 ISHLT grade 2R; and 1990 ISHLT grades 3B and 4 became 2004 ISHLT grade 3R.

Treatment of Acute Cellular Rejection

When a histologic diagnosis of rejection is made, treatment consists of augmentation of immunosuppression. The degree of augmentation depends on the grade of rejection in addition to symptomatic status (Fig. 98-4). Asymptomatic patients with low grade rejection detected on surveillance biopsy may be managed with adjustments in the patient's regimen, titration to drug levels, and follow-up biopsy. Patients with moderate to severe acute cellular rejection should be treated aggressively even in the absence of symptoms or graft dysfunction.¹²⁹ In the symptomatic patient, prompt institution of therapy is critical independent of the grade of rejection. Options for acute therapy include corticosteroids or ATG.

Modifications to a patient's long-term immunosuppressive regimen may include substituting tacrolimus for

cyclosporine. Similarly, sirolimus or MMF may be substituted for azathioprine. If rejection does not respond to this treatment, an additional pulse of steroids may be given. Acute rejection is rarely refractory to these measures. In such cases, total lymphoid irradiation,¹⁶⁷ plasmapheresis,¹⁶⁸ and conversion of azathioprine to cyclophosphamide or methotrexate have been used.¹⁶⁹

Antibody-Mediated Rejection

Antibody-mediated rejection (AMR), which is a process mediated by donor-specific antibodies (DSAs), has emerged as a major cause of allograft loss. This has led to intense study of evaluation, diagnosis, and treatment. Patients with AMR are more susceptible to developing CAV, and they have a significant mortality rate (17%) in the early posttransplant period.¹⁷⁰ Long-term survival was decreased in recipients with a diagnosis of AMR. Taylor and coworkers¹⁷¹ found that in patients with AMR, allograft 3-year survival was 57%, and the risk for graft loss and dysfunction was approximately twice that in recipients with cellular rejection only.

Acute AMR is estimated to occur in 15% of cardiac recipients. Both the presence of acute AMR and cellular rejection were reported in 23% of biopsy specimens from 587 cardiac recipients. AMR manifests clinically as early as 2 to 7 days if the recipient has been presensitized with donor HLA, or as late as 1 month after transplant, and it may be associated with a rise in DSAs.¹⁷¹ For patients experiencing early AMR, approximately 70% develop allograft dysfunction.¹⁷² If AMR occurs late—several months to years—graft dysfunction is much less common, at 13%.

Generally, the incidence of AMR is increased in transplant recipients with prior sensitization to HLA antigens.¹⁷³ This is not limited to HLA; there is a growing body of evidence that non-HLA autoantibodies may also contribute to AMR.^{174,175} Patients with PRA greater than 10% are at increased risk of AMR.¹⁷⁶ With the increasing number of cardiac retransplants and patients receiving LVAD, the proportion of potential recipients who are sensitized and on the waiting list is expanding. The causes of preformed antibodies are transfusion, previous transplantation, and pregnancy, with pregnancy being a major cause of allosensitization in women.

The development of de novo antibodies occurs in a large proportion of patients,¹⁷⁷ up to 35% in one report with associated decrease in 5-year survival. However, not all autoantibodies will inflict allograft injury. In a process known as “accommodation,” patients may continue to have normal function in the presence of circulating antibodies against donor antigens.

In 2004, the ISHLT assembled an updated version of the grading system for AMR—the Revision of the 1990 Working Formulation for the Standardization of Nomenclature in the Diagnosis of Heart Rejection.¹⁶⁶ In these guidelines, allograft dysfunction and presence of DSAs were requisite criteria for diagnosis of AMR. Wu and colleagues found that patients with asymptomatic AMR developed CAV with greater frequency than did matched controls, suggesting that outcome may be affected in the absence of allograft dysfunction.¹⁷⁸ Moreover, patients

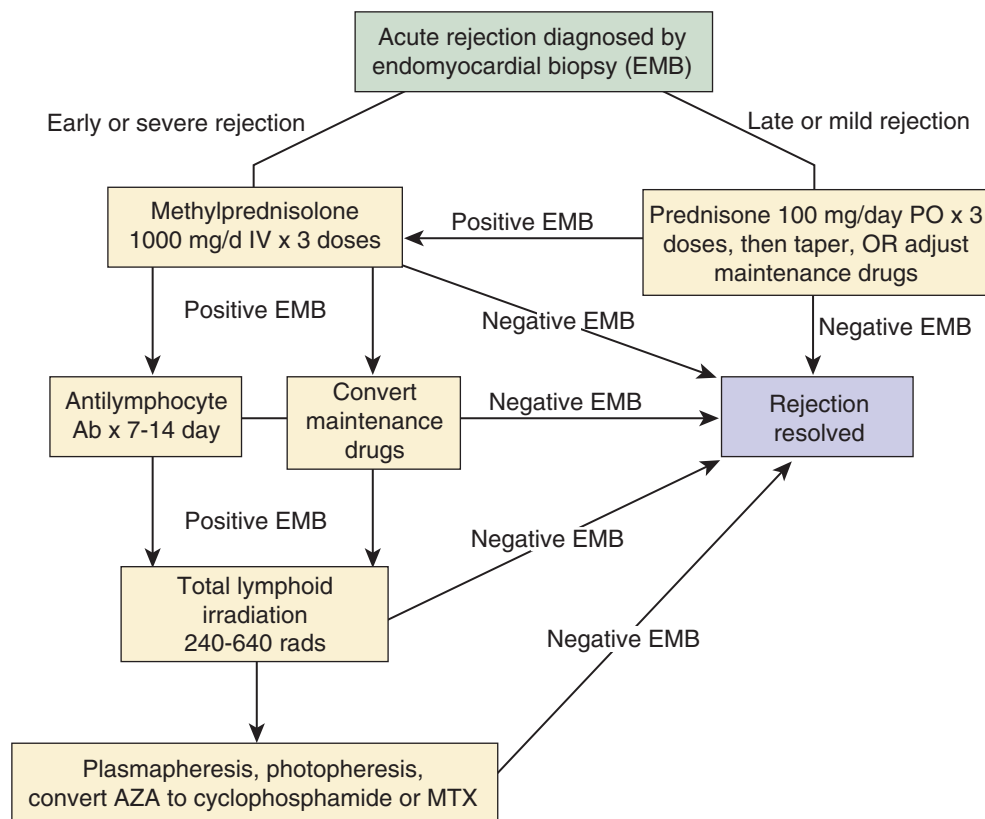


FIGURE 98-4 ■ Treatment algorithm for acute rejection in heart transplant recipients. Ab, Antibody; AZA, azathioprine; MTX, methotrexate.

with asymptomatic AMR may be at greater risk for cardiovascular mortality than cellular rejection.¹⁷⁹ Based on this evidence, a consensus conference on AMR was convened in 2010 with the recommendation that the diagnosis be based on histopathology and immunopathology rather than relying on clinical presentation and serologic studies. In 2013, the ISHLT published a statement standardizing the diagnosis of AMR incorporating the recommendations from the 2010 consensus conference¹⁷⁶ (Table 98-4).

Treatment of Antibody-Mediated Rejection

Although the exact treatment regimens for recipients with AMR vary between transplant centers, the principles on which it is based are the same: aggressive hemodynamic management along with augmentation of the immunosuppressive regimen to maximize the effort against circulating DSAs and lessen B cell activity. Plasmapheresis, steroid therapy, rituximab, ATG, bortezomib, and IVIG are used in a variety of combinations.¹⁷⁶ Figure 98-5 shows a proposed algorithm for the treatment of AMR in cardiac recipients.

Infection

An inherent complication of immunosuppression is increased risk for infection. In the first three years after transplantation, infection is the cause of death in 12% to

29% of patients.² The pathogens involved vary depending on the time after transplantation. Early infections in the first month after transplantation are commonly caused by bacteria and often manifest as pneumonia or urinary tract infections.¹⁸⁰ Typical pathogens include *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus*. Whereas infectious episodes are decreasing in frequency overall, the proportion of infections caused by gram-positive organisms is increasing.¹⁸¹ The use of perioperative antibiotics and early removal of invasive catheters may aid in the prevention of perioperative infections. Late infections are typically caused by opportunistic pathogens, fungi, and viruses. However, the risk of infection decreases over time as immunosuppressive therapy is generally tapered.¹⁸² The proportion of mortality attributable to infection is only 11% to 12% greater than 3 years out from heart transplantation.²

Cytomegalovirus (CMV) is the most common and clinically significant viral pathogen in heart transplant recipients.¹⁸³ It may cause a variety of syndromes and has been implicated as a trigger for accelerated CAV. Heart transplant recipients are at high risk for CMV infection because cell-mediated immunity, which is necessary to combat CMV, is impaired by conventional immunosuppressive drugs. CMV infection may manifest either as primary infection or as reactivation of a latent infection. Primary CMV infection may develop in seronegative recipients receiving a heart from a CMV seropositive donor. In such cases, donor leukocytes or the allograft itself may harbor CMV and transmit it to the recipient.

TABLE 98-4 ISHLT Standardized Cardiac Biopsy Grading: Acute Antibody-Mediated Rejection (AMR)

Grade	Definition	Substrates
pAMR 0	Negative for pathologic AMR	Histologic and immunopathologic studies are both negative.
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are negative.
pAMR 1 (I+)	Immunopathologic AMR alone	Histologic findings are negative and immunopathologic findings are positive (CD68+ and/or C4d+).
pAMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present.
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema and immunopathologic findings are present. These cases may be associated with profound hemodynamic dysfunction and poor clinical outcomes.

ISHLT, International Society for Heart and Lung Transplantation.

From Berry GJ, Burke MM, Andersen C, et al: The 2013 International Society for Heart and Lung Transplantation working formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. *J Heart Lung Transplant* 32(12):1147–1162, 2013.

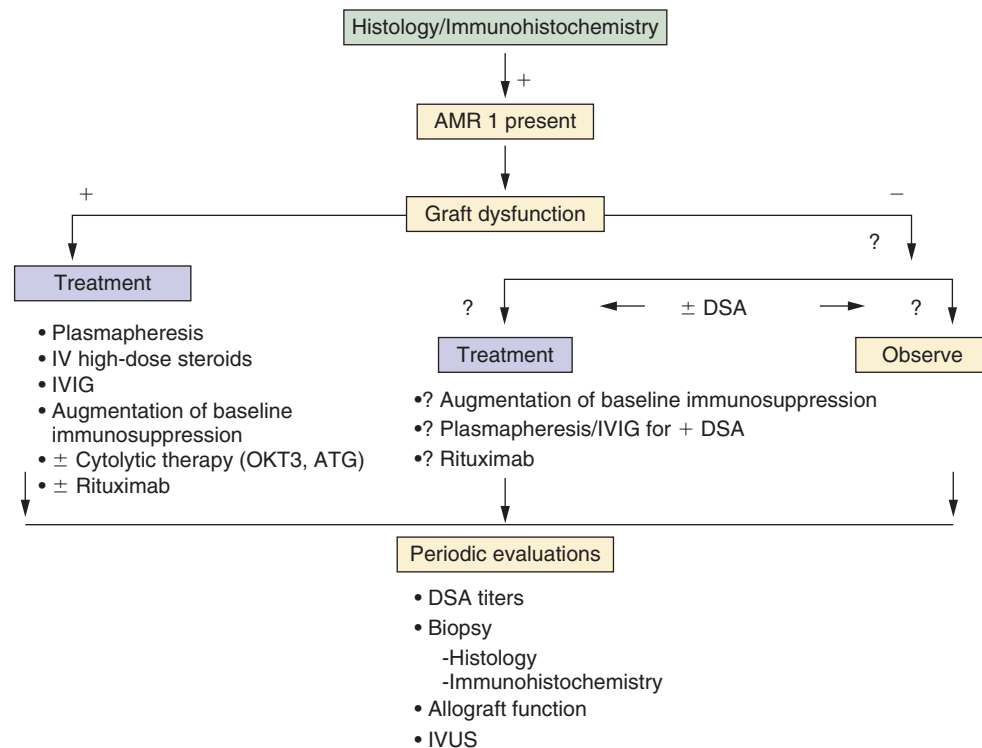


FIGURE 98-5 ■ Algorithm for treatment of antibody-mediated rejection (AMR) in cardiac transplant recipients. ATG, Antithymocyte globulin; DSA, donor-specific antibody; IV, intravenous; IVIG, intravenous immunoglobulin; IVUS, intravascular ultrasound. (From Uber WE, Self SE, Van Bakel AB, et al: Acute antibody-mediated rejection following heart transplantation. *Am J Transplant* 7(9):2064–2074, 2007.)

Reactivation of latent CMV may occur in seropositive recipients. The risk for CMV infection in different populations of cardiac transplant recipients is illustrated in Table 98-5. The seronegative recipient of a heart from a seropositive donor and those being treated for acute rejection with antilymphocyte antibody preparations are at highest risk.

CMV infection can manifest as a mononucleosis-like syndrome, or it may be tissue invasive. The most common sites for tissue invasion are the lung, liver, and gastrointestinal tract. Less common sites include the retina and skin. Diagnosis is made by measurement of viral load with either quantitative polymerase chain reaction or

antigenemia assays; by direct culture of the virus from blood, urine, or tissue specimens; or by observation of characteristic histologic changes (enlarged cells containing nuclear inclusion bodies). A combination of intravenous ganciclovir and hyperimmune globulin is used to treat CMV infection.¹⁸³

Several populations of cardiac transplant patients benefit from prophylactic treatment against CMV infection. Serologically mismatched patients (seronegative recipient of heart from seropositive donor) are treated with a combination of ganciclovir and hyperimmune globulin for weeks to months after transplantation.^{183,184} Often, seropositive recipients are also treated with a

TABLE 98-5 Risk of Cytomegalovirus (CMV) Disease in Populations of Cardiac Transplant Recipients

Donor CMV Serotype Status	Recipient CMV Serotype Status	Antilymphocyte Antibody Therapy	Incidence of Disease (%)
Positive	Negative	—	50-75
Positive or negative	Positive	No	10-15
Positive or negative	Positive	Induction	≈25
		Antirejection	50-75
Negative	Negative	—	≈0*

*In donor negative/recipient negative transplants, CMV disease is uncommonly seen under two circumstances: transfusion of viable leukocyte containing blood products from a seropositive donor or acquisition of virus in the community through intimate person-to-person contact.

From Rubin RH: Prevention and treatment of cytomegalovirus disease in heart transplant patients. *J Heart Lung Transplant* 19(8):731–735, 2000.

course of ganciclovir to prevent reactivation infection. Some groups have shown that administration of intravenous ganciclovir when antilymphocyte antibody therapy is used to treat rejection reduces the risk for CMV disease to baseline levels.

Protozoal pathogens that can appear after heart transplantation include *Pneumocystis carinii* and *Toxoplasma gondii*. Pulmonary infection with *P. carinii* can be prevented by routine postoperative prophylaxis with trimethoprim sulfamethoxazole or aerosolized pentamidine (for sulfa-allergic patients). Toxoplasmosis may occur in serologically mismatched patients (e.g., *T. gondii*-seronegative recipient of heart from *T. gondii*-seropositive donor) but may be prevented by prophylaxis with atovaquone.^{181,185}

Invasive fungal infections are uncommon after cardiac transplantation, but when they occur, they cause significant morbidity and mortality. Fungal pathogens include *Candida albicans* and *Aspergillus*. Treatment consists of fluconazole, itraconazole, or amphotericin B.

Cardiac Allograft Vasculopathy

The long-term success of cardiac transplantation is limited to some extent by the development of CAV. The mechanism of injury leading to CAV is poorly described. The recipient immune response to the donor heart results in endothelial injury mediated by recipient APCs and direct recognition of donor MHC.^{163,186,187} The process of T cell activation produces a cascade of events that increases leukocyte adhesion to vessel walls and stimulates vascular remodeling.⁵⁰ The end result is the development of intimal fibromuscular hyperplasia, atherosclerosis, or vasculitis, which results in a histopathologic appearance similar to atherosclerotic disease in the nontransplanted patient.⁴³ However, CAV differs from atherosclerosis in extent and tempo. The disease process results in diffuse concentric narrowing of both epicardial and intramyocardial vessels. In addition, disease can appear within weeks of transplantation in spite of rigorous screening for coronary disease.¹⁸⁸

Analyzing data in the Cardiac Transplant Research Database, Costanzo and colleagues reported that at 5 years, angiographically evident CAV was present in 42% of transplant patients with 7% having severe disease. Risk factors for the development of CAV in this study included

older donor age,¹⁸⁹ donor history of hypertension, donor male sex, recipient male sex, and recipient black race.¹⁹⁰ Additional risks include recipient factors such as post-transplantation hyperlipidemia, hypertension, and diabetes, and donor factors including explosive method of death and intracranial hemorrhage.^{191,192} Aziz and coworkers stratified the incidence of CAV by underlying patient diagnosis and correlated a primary diagnosis of ischemic cardiomyopathy with an increased incidence of CAV.²⁶

Significant CAV results in diminished coronary artery blood flow and may lead to arrhythmias, myocardial infarction, sudden death, or impaired left ventricular function with congestive heart failure. It is unusual for patients with severe CAV to have classic anginal symptoms, because the cardiac graft is denervated. Between 10% and 12% of late deaths after heart transplantation are attributable to CAV.² Because of the significant morbidity and mortality associated with CAV, screening for CAV occurs at most transplant programs. Yearly coronary angiography is recommended, although it lacks sensitivity and typically underestimates the presence of disease. Dobutamine stress echocardiography also may be used for routine screening.¹⁹³ Intracoronary ultrasound, when available, is a more sensitive procedure that provides information about intimal area, lumen area, and plaque morphology.^{194,195}

Treatment for CAV is limited. Because of the diffuse nature of the disease, patients are rarely candidates for coronary artery bypass grafting. Focal stenoses have been treated with angioplasty and stenting, but there is a high rate of restenosis.¹⁹⁶ Ultimately, severe progressive disease may require retransplantation. Because treatment options are limited, prevention of CAV is essential. Risk factor modification, including control of hyperlipidemia, hypertension, and hyperglycemia, may limit development of the disease. At-risk patients should receive routine prophylaxis against CMV.

Neoplasm

The incidence of neoplasia is higher in transplant recipients than in the general population. This is undoubtedly a consequence of chronic immunosuppression. Moreover, because immunosuppressive regimens are particularly aggressive in thoracic organ transplantation, these patients develop malignancies more often than renal and

liver transplant recipients.¹⁹⁷ The ISHLT reports that between 28% and 32% of heart transplant recipients develop malignancies by the tenth year after transplantation.^{1,2} Of these, most are skin cancers (squamous cell carcinoma and basal cell carcinoma)¹⁹⁸ and B cell lymphoproliferative disorders. B cell lymphoproliferative disorders cause the greatest degree of morbidity and mortality. They represent a spectrum of diseases ranging from cellular hyperplasia to true lymphomas, and more than 95% are associated with Epstein-Barr virus infection.¹⁹⁷ The mainstay of treatment for posttransplant lymphoproliferative disorder is reduction of immunosuppression and antiviral therapy.¹⁹⁹ Chemotherapy, radiotherapy, and immunotherapy have been used successfully in some cases. Other malignancies that occur at higher frequency in the transplant population include Kaposi sarcoma, carcinoma in situ of the cervix, and carcinoma of the vulva and anus. The incidence of solid organ tumors common in the general population (i.e., carcinoma of the lung, breast, colon and rectum, and prostate) is not higher in the transplant population.²⁰⁰

LONG-TERM RESULTS IN HEART TRANSPLANTATION

Long-term outcomes in heart transplantation have improved considerably in the past several decades, and median survival for all patients since 1982 is now 11 years (Fig. 98-6). Risk factors for 1-year mortality reported in the 2013 ISHLT registry include preoperative temporary circulatory support, chronic device therapy, total artificial heart, dialysis dependence, previous transfusions, gender mismatch, ventilator dependence prior to transplantation, and diagnosis.² Additionally, low preoperative albumin,²⁰¹ renal insufficiency not requiring dialysis,³¹ race, heart failure causes,²⁰² and poor preoperative clinical status may contribute to poor postoperative outcomes.²⁰³ Aside from recipient factors, annual heart transplant center volume has been shown to affect 30-day and 1-year mortality.²⁰⁴ Rather than a strict reflection of procedural success, annual volume appears to be a proxy for the aggregate of human factors and health systems.

Significant risk factors for late mortality include both pretransplantation recipient and posttransplanta-

tion characteristics. Elevated PRA, HLA mismatch, ventilator dependence, temporary circulatory support,² recipient age younger than 55 years, recipient history of diabetes, and race all contributed to late mortality, suggesting that recipient selection continues to be a key component in the determination of posttransplantation survival.²⁰⁵ After transplantation, an increasing burden of rejection episodes and more frequent infectious complications affect longevity.²⁰⁶ Annual heart transplant center volume has been an area of increasing interest. Increasing transplant center volume confers a protective effect on survival at 1, 5, and 15 years post transplantation. Performing nine or more transplants per year has been shown to be a significant inflection point for the determination of long-term success.²⁰⁵

Approximately 40% of patients are hospitalized in the first year after transplant, often for treatment of rejection or infection. By the second year after transplant, only 20% are hospitalized. The vast majority, approximately 90%, report good functional status after transplantation as reflected by a Karnofsky score of 80% to 100%. However, only 35% of working-age (25 years to 60 years old) heart transplant recipients were working at 1 year and 46% at 3 years after transplantation.²

SUMMARY

The history of heart transplantation is a remarkable one. Its development has exemplified the paradigm of surgical translational research that drives so many new therapies today. It remains the gold standard for surgical treatment of late-stage heart failure, even in the presence of emerging and exciting technologies. Although heart transplantation is still limited by the number of donor hearts available, liberalization of donor selection criteria as well as novel methods of preservation and resuscitation of donor hearts will likely increase the donor pool. Continued improvement in developing immunosuppressive therapies as well as postoperative care is decreasing mortality, complications, and hospital length of stay. The surgical principles that define the operative course of heart transplantation will likely remain the same as future possibilities such as stem cell-derived hearts appear.

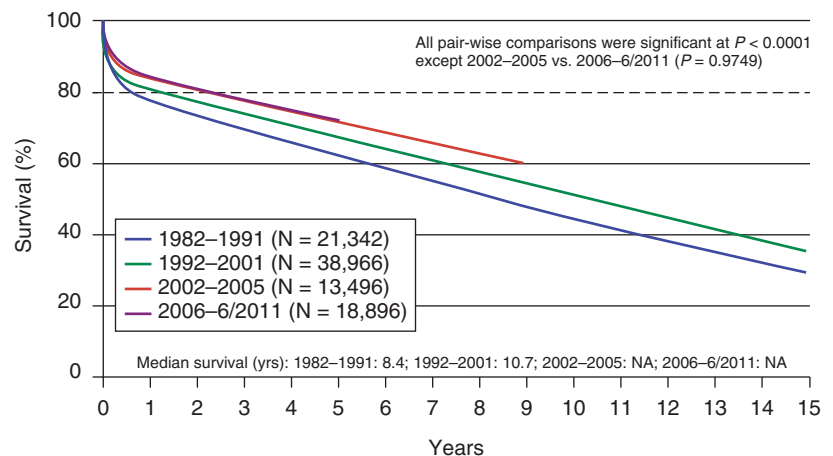


FIGURE 98-6 ■ Kaplan-Meier long-term survival by era (adult recipients). (From Lund LH, Edwards LB, Kucheryavaya AY, et al: The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report—2013; focus theme: age. *J Heart Lung Transplant* 32[10]:951–964, 2013.)

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HEART–LUNG TRANSPLANTATION

Steve K. Singh • Hari R. Mallidi

CHAPTER OUTLINE

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The clinical realization of heart–lung transplantation evolved through much earlier experimental developments in the laboratory. Alexis Carrel¹ (Fig. 99-1) and later Demikhov² and Marcus and associates³ performed experiments that explored the possibility of using heart–lung transplantation to replace diseased organs. When heart transplantation was first performed in 1968, Cooley, Lillehei, and Barnard all performed human heart–lung transplants, but patient survival time was short. Progress in the laboratory translated to the clinical application of the first successful human heart–lung transplant performed at Stanford in 1981.⁴ Since the time that these initial clinical transplantations were performed, combined heart–lung transplantation and isolated lung transplantation have undergone dramatic changes in all aspects, including indications, operative technique, and postoperative management. This chapter reviews the state-of-the-art and current issues in the field of heart–lung transplantation.

INDICATIONS FOR HEART–LUNG TRANSPLANTATION

Over time, with the increased technical success of isolated single- (SLT) or double-lung transplantation (DLT), the indications for combined heart–lung transplantation have narrowed. The primary reason for heart–lung

transplantation is irreversible dysfunction of both organ systems. The primary underlying defect could be cardiac in origin, such as congenital heart disease with irreversible end-stage cardiomyopathy and secondary pulmonary hypertension—also known as *Eisenmenger syndrome*. Alternatively, the primary defect could be pulmonary dysfunction, leading to irreversible heart disease over time. In general, the cardiac dysfunction is severe right-sided heart failure secondary to chronically elevated pulmonary arterial pressure—or *cor pulmonale*.

Another group of patients who have combined heart and lung disease has two separate disease processes that may not be related, such as a patient with a heavy smoking history who has severe emphysema and end-stage ischemic cardiomyopathy. These patients are rarely considered for heart–lung transplantation. However, experience with patients who have separate disease processes in the lungs and the heart has suggested that combined heart–lung transplantation is not a good treatment option and is associated with poor postoperative results and diminished long-term survival rates.

Recipient Diagnosis

The diagnostic profile of heart–lung transplant recipients reported to the Registry of the International Society for Heart and Lung Transplantation (ISHLT) from 1990 through 2007 is depicted in Figure 99-2.⁵ Pulmonary

hypertension secondary to congenital heart disease is the most frequent diagnosis, found in 33.9% of individuals who require heart–lung transplantation.⁵ Cardiac lesions that can result in secondary pulmonary hypertension include atrial and ventricular septal defects, patent ductus arteriosus, truncus arteriosus, and other complex congenital anomalies, including univentricular heart



FIGURE 99-1 ■ Alexis Carrel described the first heart–lung transplantation in a feline model in 1907. This experiment and numerous other observations predicted the eventual benefit of organ transplantation. For these outstanding accomplishments, Carrel received the Nobel Prize in 1912.

with pulmonary atresia and hypoplastic left heart syndrome. Pulmonary hypertension secondary to congenital heart disease varies prognostically when compared with primary pulmonary hypertension (PPH). Despite comparable levels of pulmonary arterial pressures, individuals with Eisenmenger syndrome have lower right atrial pressures, a better cardiac index, and an overall better prognosis than patients with pulmonary hypertension without congenital heart disease.⁶ Therefore, hemodynamic variables are less reliable in this group as an indicator for transplantation than is the presence of progressive symptoms (discussed later). Significant hemodynamic derangements in patients may be effectively managed with medical therapy, thus delaying transplantation.

Secondary pulmonary hypertension with complex, irreparable cardiac defects must be treated with heart–lung transplantation. In a recent study, patients with Eisenmenger syndrome caused by a ventricular septal defect or multiple congenital anomalies had a highly significant survival advantage when a heart–lung transplantation was performed as opposed to cardiac repair combined with lung transplantation.⁷ However, patients with simple cardiac defects, such as atrial septal defects, should be considered for repair of the cardiac defect combined with single or bilateral lung transplantation. Lung transplantation with intracardiac repair has evolved as a viable alternative to heart–lung transplantation for several reasons. First, right ventricular function improves after lung transplantation as a result of the normalization of pulmonary vascular resistance.⁸ In addition, there is a shortage of donor hearts. Furthermore, denervation and graft coronary artery disease associated with cardiac transplantation is avoided.

Primary pulmonary hypertension associated with irreversible right ventricular failure is the second most

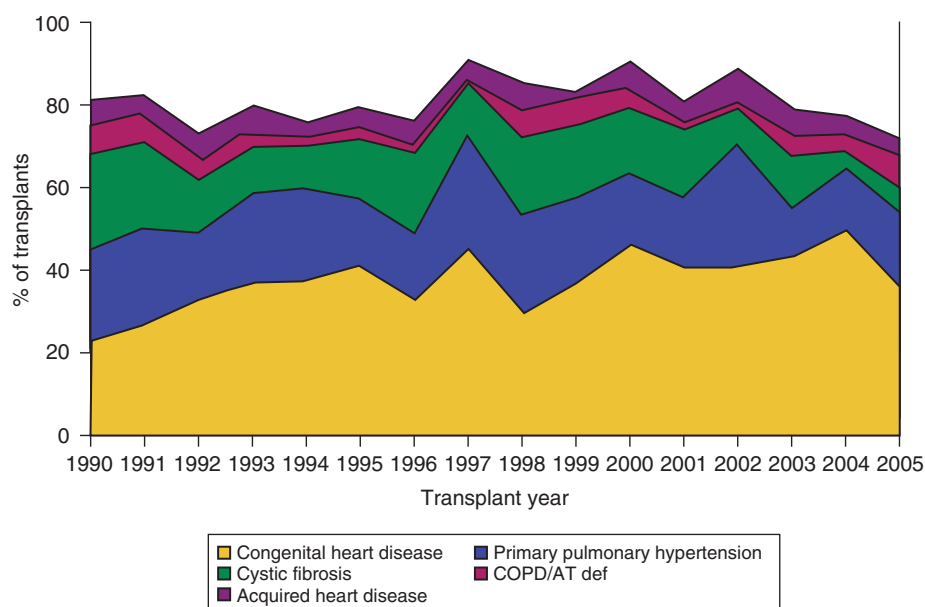


FIGURE 99-2 ■ Indications for heart–lung transplantation from 1990 to 2005. AT def, Antitrypsin deficiency; COPD, chronic obstructive pulmonary disease. (Modified from Trulock EP, Christie JD, Edwards LB, et al: The Registry of the International Society of Heart and Lung Transplantation: Twenty-Fourth Official Adult Lung and Heart-Lung Transplant Report—2007. *J Heart Lung Transplant* 26:782–795, 2007.)

common indication for heart-lung transplantation, with 24% of recipients having this diagnosis.⁵ In contrast to secondary pulmonary hypertension from congenital heart disease, abnormal hemodynamic parameters are closely related to increased mortality.⁹ Therefore, patients with PPH should be promptly referred to a transplant pulmonologist for initiation of intravenous (IV) pulmonary vasodilators. If severe right ventricular failure persists despite aggressive medical therapy, heart-lung transplantation may be indicated.

The role of heart-lung transplantation in the setting of PPH has also evolved over the past several years. Individuals with pulmonary vascular disease and improved right ventricular function after initiation of medical therapy may also be treated effectively with either SLT or DLT. In the setting of PPH, DLT results in both greater hemodynamic improvement and a shorter duration of postoperative mechanical ventilation than does SLT,¹⁰ and it is the preferred operation in most transplantation centers. Furthermore, comparable survival rates were noted in patients with PPH after heart-lung transplantation and after DLT.¹¹ Because DLT decreases the use of scarce donor hearts, a trend has recently emerged in favor of DLT for patients with PPH. This trend has resulted in a decrease in the number of heart-lung transplants for PPH during the past 10 years. The subsets of patients who have fixed pulmonary vascular resistance that is not responsive to vasodilators, and who have irreversible right-sided heart dysfunction, are still candidates for heart-lung transplantation.

The remainder of heart-lung transplantations are performed for a variety of disorders that result in end-stage pulmonary failure and irreversible cardiac failure. These include individuals with septic lung disease, such as cystic fibrosis and bronchiectasis; ischemic and restrictive cardiomyopathies with intercurrent end-stage lung disease; or acquired pulmonary vascular disease. Primary parenchymal lung disease, such as idiopathic pulmonary fibrosis, desquamative interstitial pneumonitis, and lymphangioleiomyomatosis, may occur with severe right-sided heart failure and may also be a reason for heart-lung transplantation.

The introduction of the "domino" transplantation procedure renewed interest in heart-lung transplantation for septic lung disease. In this procedure, the recipient of a heart-lung transplant served as a heart donor for a second recipient, thus maintaining donor organ allocation.^{12,13} Recent studies have demonstrated equivalent survival rates in recipients of domino heart grafts and in recipients of cadaveric heart grafts. However, this procedure is rarely performed, and bilateral lung transplantation remains the procedure of choice for most septic or parenchymal lung disease.

The distribution of preoperative diagnoses managed with heart-lung transplantation at Stanford from 1981 to the present has been as follows: Eisenmenger syndrome, 44%; PPH, 23%; cystic fibrosis, 12%; complex congenital heart disease, 12%; α_1 -antitrypsin deficiency, 2%; cardiomyopathy with pulmonary hypertension, 2%; failure of SLT, 1%; congenital bronchiectasis, less than 1%; pulmonary lymphangioleiomyomatosis, less than 1%; and other diagnoses, 3%.¹⁴

Recipient Selection Criteria

The selection of appropriate candidates for heart-lung transplantation is of paramount importance for success of the procedure. Any patient with end-stage cardiopulmonary disease with the capacity for full rehabilitation is a potential candidate for heart-lung transplantation. Suitable candidates should have a life expectancy of less than 2 years and generally have marked persistent functional disability, with a New York Heart Association (NYHA) class designation of III or IV. Patients must otherwise be in good general health without other serious systemic illness. The occurrence of life-threatening complications, such as severe right-sided congestive heart failure with liver dysfunction, massive hemoptysis, or multiple syncopal episodes, suggests a poor prognosis and the need to list a patient as a candidate for heart-lung transplantation.

Recipients of heart-lung transplants generally are younger than heart transplant recipients, with 44% being between the ages of 35 and 49 years, and only 15% being older than 60 years.⁵ It must be determined that the patient and the family are emotionally prepared for transplantation. Each patient must be assessed for the presence of adequate emotional and psychosocial support to withstand the rigorous and intrusive medical regimen that will continue throughout their remaining life. Heart-lung transplantation has become more common as a therapeutic option for complex congenital heart disease in infants and children.^{15,16} These recipients also must be carefully evaluated, and they should have an extremely strong family support network to cope with the complex regimen and the frequent medical follow-up.

The risk for mortality while a patient is on the waitlist must be balanced with the 1-year mortality risk after transplantation to determine the ideal time to activate someone on the transplant waitlist. The individual's disease process should be severe enough to warrant heart-lung transplantation, yet the patient must be well enough to survive the long wait until the transplantation occurs, and well enough to survive the surgical procedure itself.¹⁷ The underlying disease determines the appropriate window. Survival with or without transplantation varies by disease process and by the patient's overall physical condition. Identification of a critical turning point in a patient's disease that signals an accelerated decline is the key to appropriate referral for transplantation. Pulmonary and cardiac clinical signs that can be used to gauge the appropriateness of listing include changes in the rate of decline in exercise capacity or pulmonary function, increasing frequency of infectious complications, increasing number and duration of hospitalizations, and increasing supplemental oxygen requirements. Other signs include increasing requirements for diuretics and increased hepatomegaly and bilirubin levels. Hyperbilirubinemia has been shown to be a marker for poor postoperative outcome in patients with pulmonary hypertension and right ventricular dysfunction. Patients with chronic bilirubin levels greater than 2.1 mg/dL who are undergoing heart-lung transplantation have been demonstrated to have significantly worse postoperative mortality (58%).¹⁸ The rate of perioperative complications,

including coagulopathy, hepatic encephalopathy, poor wound healing, and impaired clearance of cyclosporine with resultant nephrotoxicity, were also significantly increased after heart–lung transplantation in such patients.¹⁹

Heart–lung transplantation should be undertaken before multisystem organ failure and severe malnutrition ensue. Although patients await a suitable donor, many become increasingly debilitated. Every opportunity to optimize a patient's physical strength and nutritional status should be aggressively pursued.²⁰ Good physical performance before transplantation has been associated with improved postoperative recovery. Therefore, patients should be referred for physical therapy early in an effort to improve their functional status and optimize their recovery potential.

In the past, most centers considered conditions associated with extensive adhesions, such as previous thoracotomy or sternotomy, septic lung disease, and previous chemical or surgical pleurodesis, an absolute contraindication to heart–lung transplantation. Historically, patients with these conditions had increased morbidity and short-term mortality resulting primarily from excessive blood loss and pulmonary issues associated with massive transfusions of blood products. The introduction of antifibrinolytic therapy (aprotinin) in thoracic organ transplantation has provided improved outcomes for this group of patients.²¹ However, with increasing evidence that this drug is associated with worse survival and a higher risk for renal and neurologic complications after isolated coronary artery bypass surgery, its use in North American surgical programs has diminished markedly. Heart–lung transplantation in patients with previous surgery may remain one indication for its continued use.²² Current alternative antifibrinolytic options include aminocaproic acid and tranexamic acid. We now routinely accept patients with previous cardiac or thoracic surgery for heart–lung transplantation, and they represent a significant proportion of patients on the current waiting list.

In patients selected for transplantation, routine pretransplantation screening is performed for ABO blood group, the presence of preformed antibodies, human leukocyte antigen (HLA) and reaction of degeneration tissue types, and titers of antibodies against cytomegalovirus, herpes simplex virus, and toxoplasmosis. ABO compatibilities are strictly adhered to because isolated episodes of hyperacute rejection have been observed in patients in which transplantations were performed across ABO barriers. In addition to ABO compatibility, donor–recipient matching is also based on body size. In practice, matching donor and recipient height seems to be the most reproducible method for selecting the appropriate donor lung size. In general, the dimensions of the donor lungs should not be greater than 4 cm greater than those in the recipient. Other investigators have proposed that the simplest method of matching donor-to-recipient lung size is to use the respective predicted total lung capacity values.^{23,24}

Once an appropriate donor–recipient match is made, the recipient is screened for preformed antibodies against a panel of 50 random donors. A percent reactive antibody (PRA) level greater than 25% prompts a prospective

specific crossmatch between the donor and recipient. A positive crossmatch indicates the presence of anti-donor circulating antibodies in the recipient, and the organ cannot be accepted for transplantation. Despite several retrospective studies that reveal improved graft survival with HLA matching,^{25–27} prospective HLA matching is not feasible given the short ischemic times tolerated. Furthermore, in a recent multicenter study, HLA matching for lung transplantation did not have a large effect on clinical outcome, including the development of obliterative bronchiolitis (OB).²⁸

Recent data suggest that the presence of an elevated PRA level is associated with both early and late mortality.²⁹ In addition, elevated PRA levels have been shown to be associated with an increased incidence of acute rejection in both lung and heart transplantation patients, with an increased incidence of graft vascular disease in heart transplantation patients, and with an increased occurrence of accelerated bronchiolitis in lung transplantation patients.^{30,31} Methods to decrease the patient's PRA level and to avoid antibody production by virtual, or, when time allows, prospective crossmatching, have decreased the negative effects of high baseline PRA levels on late survival.³²

Many heart–lung transplant patients, especially in the pediatric population, have undergone previous cardiac surgery and are extremely sensitized when they present for heart–lung transplantation. Specific protocols using immunoglobulin, plasmapheresis, and rituximab have been shown to decrease the PRA levels in potential organ recipients. In addition, posttransplant treatment initiated in the operating room with plasma exchange, plasmapheresis, weekly immunoglobulin injections, and monitoring for the development of donor-specific antibodies has minimized the risk for hyperacute rejection in this population.³³ The current desensitization protocol being used at Stanford is shown in [Box 99-1](#).

TREATMENT OF PATIENTS AWAITING TRANSPLANTATION

The average waiting period for a heart–lung block is greater than 18 months; therefore, treatment of recipients after they have been listed is a critical aspect of the preoperative plan. Routine medical care, including clinical surveillance, optimization of cardiopulmonary function, and management of disease-specific and age-specific issues, should be addressed during this time. General considerations in the pretransplantation period include appropriate surveillance protocols and screening for malignancies such as prostate, breast, and colon cancer. Other issues that should be addressed include appropriate prophylaxis for thromboembolism with warfarin³⁴ and aggressive maximization of bone density, because osteoporosis is increasingly recognized as a clinical problem for patients who are receiving long-term steroid therapy.³⁵ Nutrition and high-intensity pulmonary rehabilitation should be optimized. Finally, psychosocial issues need to be addressed with referral for supportive counseling, support groups, and other training means to help each patient cope with the upcoming challenges.

BOX 99-1 Treating the Highly Sensitized Heart-Lung Transplant Patient

WEEK 1

- IVIG $\times$ 2 consecutive days; each dose, 1 g/kg at 100 mL/hr

WEEK 2

- Rituximab, 375 mg/m² IV

WEEK 3

- Rituximab, 375 mg/m² IV

WEEK 4

- IVIG $\times$ 2 consecutive days; each dose, 1 g/kg dose at 100 mL/hr
- Monthly IVIG treatment thereafter until transplantation

TRANSPLANT MANAGEMENT

- PRA level > 50% and complement fixation (C1q) absent:
 - Plasmapheresis in the operating room when patient is on cardiopulmonary bypass
 - Immediate retrospective crossmatch
- PRA level > 50% and complement fixation (C1q) present:
 - Prospective crossmatch before transplantation

IV, Intravenously; IVIG, intravenous immune globulin; PRA, percent reactive antibody.

Disease-specific issues in patients awaiting heart-lung transplantation need to be addressed. These patients require optimal treatment of heart failure with standard therapeutic measures such as sodium restriction, aggressive diuresis, and vasodilators. Afterload reduction with nitrates, hydralazine, and angiotensin-converting enzyme inhibitors prolongs survival in patients awaiting transplantation.³⁶ In patients with PPH, supplemental oxygen is recommended to avoid hypoxic pulmonary vasoconstriction. Indications for outpatient oxygen therapy include an arterial partial pressure of oxygen (Pao₂) of 55 mm Hg or less (or arterial oxygen saturation [Sao₂] < 88% on room air) at rest, during physical exertion, or while asleep.³⁷ The prognosis of patients with PPH is determined by hemodynamic variables, and the following parameters are associated with a poor outcome: increased mean pulmonary artery pressure (mPAP > 85 mm Hg; median survival, 12 months), increased mean right atrial pressure (RAP > 20 mm Hg; median survival, 1 month), and decreased cardiac index (CI < 2.0 L/min/m²; median survival, 17 months).⁹ In addition to supplemental oxygen therapy, initiation of pulmonary vasodilator therapy improves hemodynamics and survival in patients awaiting transplantation. Epoprostenol is a short-acting prostaglandin, normally released by the endothelium, that vasodilates the pulmonary vascular bed and inhibits platelet aggregation. Continuous infusion of epoprostenol (Flolan; GlaxoSmithKline, London, UK) has been demonstrated to significantly improve pulmonary hemodynamics, exercise capacity, and survival in patients with NYHA classes III and IV heart failure.^{38,39} Patients may

BOX 99-2 Heart-Lung Donor Selection Criteria

- Age <40 years
- Smoking history <20 pack-years
- Arterial PO₂ of 140 mm Hg on an FiO₂ of 40%, or 350 mm Hg on an FiO₂ of 100%
- Normal chest radiograph
- Sputum free of bacteria, fungus, or significant numbers of white blood cells on Gram and fungal staining
- Bronchoscopy showing absence of purulent secretions or signs of aspiration
- Absence of thoracic trauma
- Human immunodeficiency virus (HIV)–negative status

then wait longer for transplantation. Despite improvements in pulmonary hemodynamics and survival, diseases often progress or tachyphylaxis develops. Therefore, patients need to be followed closely and returned to the active transplant list if any clinical deterioration is noted. In patients who have right ventricular failure while awaiting transplantation, the creation of an interatrial shunt to decompress the pressure-overloaded ventricle may need to be considered.⁴⁰

Patients with cystic fibrosis awaiting heart-lung transplantation have special needs. Pulmonary hygiene is of critical importance, because greater than 80% of patients are chronically colonized with *Pseudomonas aeruginosa*.⁴¹ Pulmonary clearance techniques, institution of bronchodilators, and initiation of antibiotics in the setting of acute infection are lifelong requirements. Prophylactic antibiotics are not routinely given because of the development of multiresistant organisms.⁴² Sinus disease and lower respiratory tract infections are risks in most patients with cystic fibrosis. Bilateral maxillary sinus anastomies performed in the pretransplantation period have resulted in fewer infectious complications in the posttransplant period.⁴³ In addition to infectious issues, other associated risk factors such as malnutrition secondary to malabsorption, pancreatic insufficiency, and diabetes mellitus must be properly addressed.

SELECTION AND MANAGEMENT OF DONORS

The satisfactory criteria for heart-lung blocks are similar to those for hearts and lungs separately (Box 99-2). The lungs are the most delicate solid organ, with frequent parenchymal damage and neurogenic edema occurring after brain death, as well as the increased risk for aspiration. These factors result in only 20% to 30% of multi-organ donors having lungs suitable for donation. Preliminary donor evaluation includes a detailed history, review of electrocardiogram and echocardiogram, chest radiograph, and arterial blood gas analysis. A donor age of less than 40 years is preferred. However, potential donors aged 40 to 50 years are considered at most transplant centers, provided they have normal cardiopulmonary functioning and a normal coronary arteriogram. Acceptance criteria also include no significant lung

contusion or history of aspiration or sepsis. There should be no history of prior cardiac or pulmonary surgery. A donor chest radiograph must be clear with no signs of pathology. An arterial blood gas analysis should reveal an arterial oxygen tension level of greater than 350 mm Hg on a fractional inspired oxygen concentration (FiO_2) of 100%, and 100 mm Hg on an FiO_2 of 30%. Lung compliance is estimated by measuring peak inspiratory pressures, which should not exceed 30 cm H_2O . Tracheobronchial infection must be excluded with chest radiography, Gram stain of sputum, and bronchoscopy.

On arrival at the donor hospital, the retrieval team assesses the chest radiograph, recent arterial blood gas analyses, and hemodynamic parameters to confirm that there has been no deterioration in oxygenation or cardiac function. If possible, the bronchoscopic examination is repeated to ensure that there are no mucopurulent secretions suggestive of infection or aspiration, as in tracheobronchitis. The final assessment includes visual and manual intraoperative assessment of the heart and lungs, confirming normal lung parenchyma with no palpable masses or evidence of contusion.

Because of growing waiting lists and increased mortality before a transplant is received, most centers have expanded their donor acceptance criteria with the increased use of so-called marginal donors.⁴⁴ Thoracic trauma with a resultant pneumothorax is not a contraindication, provided there is not a continuous air leak. Furthermore, lungs that are mildly contused can also be used, provided ongoing bleeding is not noted on bronchoscopy and/or there is no major atelectasis. Patients with prolonged intubation and ventilation (>70 hours), once thought to be a contraindication, should also be considered. As noted previously, older donors also are being considered, provided that pulmonary functional parameters are normal and no significant coronary artery disease is detected. Donor infection with hepatitis C virus is an evolving area in cardiopulmonary transplantation. Hepatitis C–negative recipients have an increased risk for acquiring hepatitis, but the effect on patient survival remains unclear.⁴⁵ Absolute contraindications include severe coronary or structural heart disease, prolonged cardiac arrest, active malignancy (sometimes excluding primary brain cancers such as astrocytoma and skin cancers), smoking history of greater than five pack-years, and positive human immunodeficiency virus (HIV) status.

Donor management after a declaration of brain death is a critical area in which there are opportunities for significantly improving the number and quality of potential donors. Aggressive management strategies implemented by organ procurement organizations have made “unacceptable” lungs, defined as a Pao_2 -to- FiO_2 ratio of less than 150, acceptable for transplant.⁴⁶ Donors with unacceptable lungs were treated with invasive monitoring, methylprednisolone, fluid restriction, inotropic agents, bronchoscopy, and diuresis. The resultant “acceptable” organs were successfully transplanted without compromise of either 30-day or 1-year graft survival.⁴⁶ The major goal in the initial management of these donors is the maintenance of hemodynamic stability and pulmonary function. Patients who have suffered an acute brain injury are usually hypovolemic, and appropriate fluid

resuscitation is the initial step. Complicating factors include the development of diabetes insipidus, which should be treated with a vasopressin infusion (0.1 to 0.4 U/hr).⁴⁷ Fluid administration is guided by the central venous pressure, keeping in mind that a central venous pressure greater than 8 mm Hg has been demonstrated to be an independent risk factor for the development of lung dysfunction.⁴⁸ Inotropic agents such as dopamine or phenylephrine are instituted to maintain perfusion pressure after intravascular volume has been repleted. The donor is not hyperventilated after brain death is declared, and a pH of 7.40 is the goal, thus avoiding pulmonary vasoconstriction. Positive end-expiratory pressure of 5 is maintained to prevent atelectasis, and higher levels are avoided because of their deleterious effect on cardiac output.

The pathophysiology of brain death and its deleterious effect on the cardiovascular system have been well described.⁴⁹ The resultant endocrine and metabolic derangements are a potential area of intervention in the marginal donor with hemodynamic instability. Hormonal therapy, including triiodothyronine (T_3), cortisol, insulin, and vasopressin, has been shown to have beneficial effects on the hemodynamic profile of marginal donors.⁵⁰ Physiologic resuscitation, guided by a better understanding of the pathophysiology of brain death, ultimately leads to an increase in the number and quality of heart–lung donors.

HEART–LUNG PRESERVATION

The goal of optimal heart–lung preservation is to ameliorate the effect of ischemia–reperfusion (IR) injury on the allograft. In early heart–lung transplantations, donor transportation to the transplant center with on-site procurement was considered essential because of a lack of confidence in lung-preservation techniques. As with heart transplantation, better preservation techniques would expand the pool of available donors and would make donation more acceptable to referring hospitals and donors’ families.

Minimization of IR injury ultimately results in optimization of allograft function in the posttransplantation period. Nonspecific graft failure, which most likely represents IR injury, remains a significant cause of perioperative morbidity and possibly mortality.⁵¹ Reperfusion injury may predispose the transplant recipient to an increased risk for acute rejection secondary to the upregulation of histocompatibility class II antigens.⁵² Understanding the pathophysiology of IR injury allows the implementation of strategies aimed at preserving function, minimizing injury, and prolonging allograft and patient survival.

The result of inadequate preservation is activation of the inflammatory cascade, resulting in pulmonary endothelial injury and increased capillary permeability. The resulting pulmonary interstitial and alveolar edema leads to diminished airway compliance, poor gas exchange, and increased pulmonary vascular resistance. Numerous recent studies have elucidated the role of the neutrophil and its interaction with the pulmonary endothelium in

the pathogenesis of IR injury.⁵³⁻⁵⁵ Reperfusion injury is caused in part by a complex interplay between leukocyte activation and the subsequent release of inflammatory mediators and cytokines, which leads to pulmonary endothelial injury.

Since the early 1980s, various methods have been developed to provide adequate heart-lung preservation. These methods have varied from simple graft excision and cold storage to sophisticated autoperfusion with donor blood and a working heart-lung preparation. Today, only two methods are actively used: (1) perfusion with pulmonoplegia solutions and cold storage and (2) perfusion with cold donor blood. Both methods include the use of pulmonary vasodilators. Pulmonary artery flush, the most widely adopted method of allograft preservation,⁵⁶ allows the rapid cooling of both lungs, resulting in a significant improvement in allograft function noted after both the infusion time (4 minutes) and total volume (60 mL/kg) are increased.⁵⁷ To counteract the reflex pulmonary vasoconstriction arising from preservation solutions, donors are pretreated with prostaglandins. These selective pulmonary vasodilators, alprostadil in North America and epoprostenol in Europe, improve the distribution of the pulmonary arterial flush and thus improve lung preservation. Recently, the role of retrograde flush through the left atrium has been advanced because of the improved distribution of the flush in a porcine model.^{58,59}

The two types of crystalloid pulmonary artery flush solutions, intracellular and extracellular, are both designed to counteract the cellular swelling that results from graft ischemia and hypothermia. The intracellular solutions, Euro-Collins (EC) and University of Wisconsin, are composed of electrolytes that mimic the intracellular environment. The extracellular solutions include the Wallwork solution, which uses donor blood, and low-potassium dextran (Perfadex; XVIVO Perfusion AB, Gothenburg, Sweden). The most commonly used preservation solution is EC crystalloid solution, which has been modified with magnesium sulfate and 50% dextrose. A recent study has demonstrated that lung procurement with low-potassium dextran resulted in a significantly decreased incidence and severity of reperfusion injury with improved allograft function, as well as improved survival, when compared with EC.⁶⁰ The addition of a retrograde flush for isolated lung transplantation has resulted in improved posttransplant lung function.⁶¹ This retrograde flush technique can be safely used in combined heart-lung transplantation by making a small left atrial incision, flushing the preservation solution retrograde via the veins, and collecting the effluent in the proximal pulmonary artery, where a separate small incision is made. In contrast, the use of Celsior solution as a lung-preservation solution resulted in lethal posttransplant outcomes in a porcine model of lung transplantation.⁶²

Recent investigations in the laboratory and clinic have demonstrated improvements in allograft preservation after the modification of pulmonary arterial flush solutions. The focus has been to intervene at the level of the leukocyte-endothelial interaction in an effort to preserve the function of the pulmonary endothelial cell. The

impact of toxic inflammatory mediators elaborated by the leukocyte has been reduced by techniques such as leukocyte filtration,⁶³ introduction of monoclonal antibodies directed against anti-intercellular adhesion molecules and selectins,^{53,55,64} and vascular immunotargeting strategies.⁵⁴ Furthermore, treatments aimed at preserving pulmonary endothelial function by restoring endothelium-derived mediators, such as nitric oxide (NO) and prostacyclin, have been shown to improve allograft pulmonary function.⁶⁵⁻⁶⁸ Instead of focusing on the preservation solutions or additives, others have focused their attention on the development of continuous organ perfusion systems. The TransMedics Organ Care System is an organ perfusion system that preserves organs by using a warm-blood perfusion of the organ during storage. The system has been approved for use in Europe for donor heart procurement and in late-stage clinical trial protocols in the United States.

OPERATIVE TECHNIQUE FOR DONOR HEART-LUNG REMOVAL

In the early days of heart-lung transplantation, the donor was transported to the recipient hospital, and in an adjacent operating room, the recipient heart-lung block was excised simultaneously with donor organ preparation. Long-distance procurement is now the rule as a result of improvements in donor selection, donor management, and preservation techniques. Numerous procurement teams work together, and optimal communication is essential.

The donor operation is performed via a median sternotomy (Fig. 99-3). The pericardium is opened vertically and laterally on the diaphragm, and a pericardial cradle is created. Both pleural spaces are then opened, followed by the inspection of both lungs and pleural spaces. In cases of trauma, cardiac and pulmonary contusions are immediately ruled out. The pulmonary ligaments are then divided inferiorly by using electrocautery. The ascending aorta and aortic arch are dissected free and encircled with tapes. The superior and inferior venae cavae are then dissected free and also encircled with tapes. The azygos and innominate veins are ligated and divided, which affords excellent exposure to the proximal trachea. The tissue overlying the proximal trachea is incised vertically and encircled with a tape. Dissection of the distal trachea is kept to a minimum to avoid injury to the peribronchial vessels at the carina.

The patient is administered 300 U/kg of IV heparin, and the aorta and pulmonary artery are cannulated. Approximately 15 minutes before applying the aortic crossclamp, prostaglandin E₁ (PGE₁) is infused IV, initially at a rate of 20 ng/kg per minute and gradually increasing to a target rate of 100 ng/kg per minute. During PGE₁ infusion, the mean arterial blood pressure should be maintained at greater than 55 mm Hg. Inflow occlusion is accomplished by ligating the superior vena cava distally to avoid damage to the sinoatrial node. The inferior vena cava is clamped with a straight Potts clamp. The heart is allowed to empty, and the aortic crossclamp is applied. Cold crystalloid cardioplegia (10 mL/kg) is

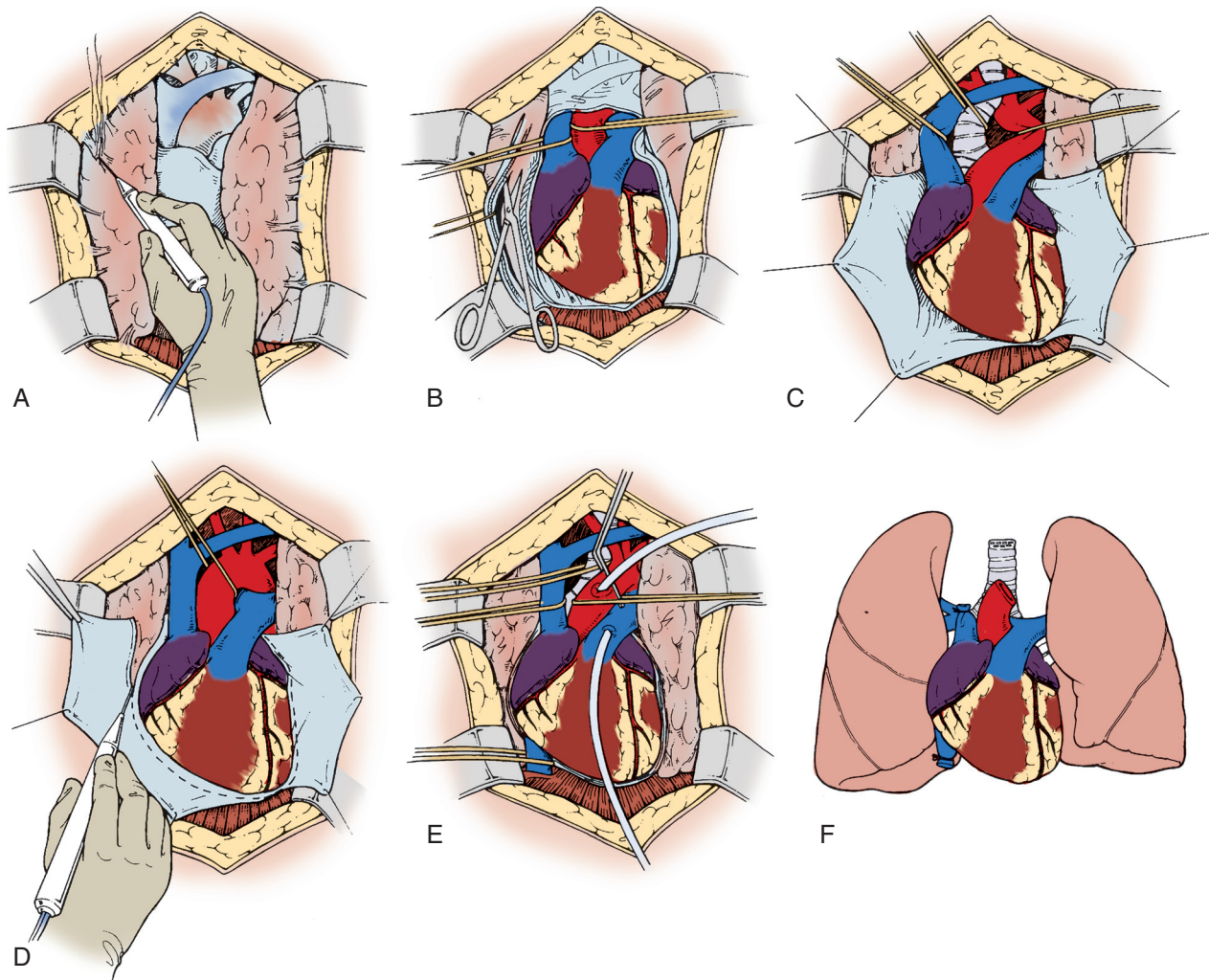


FIGURE 99-3 ■ The donor operation. **A**, Through a median sternotomy, adhesions are lysed and the pulmonary ligaments are divided inferiorly. **B**, The pericardium is opened and cradled, followed by dissection of the ascending aorta, venae cavae, pulmonary artery, and trachea. **C**, Tapes are placed around the aorta, venae cavae, and trachea. **D**, The entire anterior pericardium is excised back to each hilum. **E**, Cardioplegia and pulmonoplegia solutions are infused simultaneously into the aorta and main pulmonary artery after aortic crossclamping. Application of topical cold Physiosol follows immediately. **F**, The venae cavae and aorta are divided, and the heart–lung block is dissected free from the esophagus and posterior hilar attachments. After the trachea is stapled and divided at the highest point possible, the entire heart–lung block is removed from the chest. (From Yuh DD, Robbins RC, Reitz BA: Transplantation of the heart and lungs. In Edmunds LH, editor: *Cardiac Surgery in the Adult*, New York, 1997, McGraw-Hill, pp 1451–1475.)

administered via the aortic root. The inferior vena cava is incised, and the left atrial appendage is amputated immediately after initiating the pulmonoplegia. Adequate venting should be ensured and cardiac distention avoided. Pulmonoplegia with an EC solution at 4°C is rapidly infused at a rate of 15 mL/kg per minute for 4 minutes. During the administration of cold cardioplegia and pulmonary perfusate, copious amounts of cold topical saline are immediately poured over the heart and lungs. The lungs are ventilated with half-normal tidal volumes of room air while the dissection is completed, separating the heart–lung block from the posterior mediastinum, from inferior to superior. The lungs are inflated to a tidal volume of three-fourths normal, and the trachea is stapled with a TA-55 stapler and divided. The aorta is then divided, and the heart–lung block is removed, wrapped with sterile towels, and immersed in ice-cold saline at 4°C in preparation for transport (see Fig. 99-3).

Clinically, we have used grafts preserved for up to 6 hours with successful implantation and outcome.

OPERATIVE PROCEDURE

The operation to replace the heart and lungs is one of the most fascinating and challenging procedures for cardiothoracic surgeons. The anatomy that is encountered and the areas of the thorax that are dissected are not otherwise commonly seen. Careful attention to details can simplify the procedure in even the most challenging patients.

Patients with PPH with end-stage right ventricular failure are usually the ideal candidates for heart–lung transplantation. These patients generally have not had previous cardiac or thoracic surgery and do not have large mediastinal collaterals from cyanosis. Conversely, patients

with congenital heart disease and pulmonary atresia, or Eisenmenger syndrome and cyanosis, may have large mediastinal bronchial collaterals that require careful ligation. The most challenging aspect of the procedure is to remove the heart and lungs without injury to the phrenic, recurrent laryngeal, and vagus nerves. Careful attention to hemostasis is necessary before implantation of the graft, because exposure of many of the areas of dissection is difficult.

The recipient procedure for heart-lung transplantation has evolved over the past decade, with two major changes often used: the conversion from atrial cuff to bicaval anastomoses, and the positioning of the pulmonary hila anterior to the phrenic nerve pedicle. The right atrial cuff anastomosis was initially proposed in heart-lung transplantation to facilitate cannulation for cardiopulmonary bypass and eliminate the possibility of stenoses at the vena caval anastomoses. As in the transplantation of the heart alone, asynchronous contraction of both atrial cuffs is associated with an increased incidence of atrioventricular valve regurgitation. A demonstrated clinical benefit of caval anastomosis is fewer postoperative arrhythmias.⁶⁹ Because the pulmonary hila are positioned anterior to the phrenic nerve pedicle, less posterior mediastinal dissection is required, resulting in decreased rates of phrenic and vagus nerve injury.⁷⁰ Another advantage to this technique is that it allows for easier inspection of the posterior mediastinum for bleeding by rotation of the heart-lung block anteriorly and medially while the patient is still on cardiopulmonary bypass.

With careful attention to detail in the posterior mediastinal dissection and during the creation of the windows in the pericardium, the placement of the lungs posterior to the phrenic nerves can be performed safely. The primary advantage to this approach is seen in the reoperation setting. The placement of the donor lungs posterior to the phrenic nerves results in maintenance of the normal anatomic relationships, which facilitates the dissection at the time of repeat transplantation.

The patient is prepared for operation with the usual monitoring lines. After the induction of general anesthesia, the chest and both groins are prepared and draped in a sterile manner. A standard median sternotomy incision is made, and both pleural spaces are opened anteriorly (Fig. 99-4). A portion of the pericardium is removed anteriorly, avoiding the phrenic nerves. The ascending aorta and both venae cavae are dissected free and encircled with tapes. After fully heparinizing the recipient, the high ascending aorta and both venae cavae are cannulated separately, cardiopulmonary bypass is instituted, and the patient is cooled to 28°C. The aorta is cross-clamped, and a small amount of cardioplegia may be given to induce cardiac arrest.

First, the heart is excised as in heart transplantation. Next, the lungs are removed sequentially. The right and left bronchi are skeletonized, and a stapling device (TA 30, 4.8 mm) is used to occlude them. Cutting the bronchus distally allows the lung to be removed easily and avoids contamination from the open bronchus.

The native main pulmonary artery remnant is then removed. A portion of the pulmonary artery is left intact adjacent to the underside of the aorta in the region of the

ligamentum arteriosum, which minimizes damage to the recurrent laryngeal nerve. The final step in preparing the recipient is to open the pericardium at the superior part of the pericardial space just anterior to the right and left bronchi, allowing dissection back to the carina. The stapled ends of the right and left bronchi are grasped, and dissection is carried up to the level of the distal trachea. In this area, it is important to stay directly on the bronchus, use electrocautery if possible, and avoid injury to the vagus nerve as it passes posterior to the bronchus and anterior to the esophagus. The vascular lymph nodes in this area may be very large, particularly in patients with cystic fibrosis. Bronchial vessels are individually identified and ligated or clipped. Patients with secondary pulmonary hypertension from congenital heart disease have large mediastinal bronchial collaterals that must be carefully ligated. Hemostasis is imperative in this area of dissection because exposure to this region is difficult after transplantation of the heart-lung block. The chest wall also is carefully inspected, and electrocautery or an argon beam coagulator is used. After absolute hemostasis is ensured, the donor heart-lung graft is prepared for implantation.

The donor heart-lung block is removed from its sterile container and brought to the operative field in a basin of cold saline solution. The donor trachea is excised several rings above the carina, and the superior tracheal segment, with the clamp attached, is then removed from the field. The tracheobronchial tree is aspirated with a sucker that is later discarded. At the same time, a sample to be cultured is taken directly from the trachea. The trachea is trimmed back so that only one complete cartilaginous ring is left just above the carina. A syringe full of normal saline is used to irrigate the bronchi and visualize them for retained secretions or any foreign body that might have been aspirated by the donor.

The heart-lung graft is then lowered into the chest with the lung hila anterior to the phrenic nerve pedicles (see Fig. 99-4). A cold saline solution and gauze pads soaked in cold saline are placed over the lung and heart to maintain hypothermia during implantation. The recipient trachea is opened one cartilaginous ring above the carina, and all the adventitial peritracheal tissue that is adjacent to the superior tracheal segment is left in place. Small bronchial vessels may require a Liga clip or suture; use of electrocautery at the cut edge of the trachea should be avoided. The tracheal anastomosis is performed with a running suture of 3-0 polypropylene, starting on the left side of the trachea and completing the posterior row from the inside. The same suture is continued anteriorly from outside the trachea. There should be a fairly close size match between donor and recipient, but any disparity can generally be accommodated by the flexible membranous part of the trachea. These bites usually go around at least one cartilaginous ring, and the donor trachea slightly invaginates the recipient trachea in most cases. When the tracheal anastomosis is complete, the chest is irrigated with several liters of ice-cold saline solution to cool the graft and to help remove any contamination from the trachea.

The recipient inferior vena cava is then anastomosed to the donor inferior vena cava by using a running 4-0

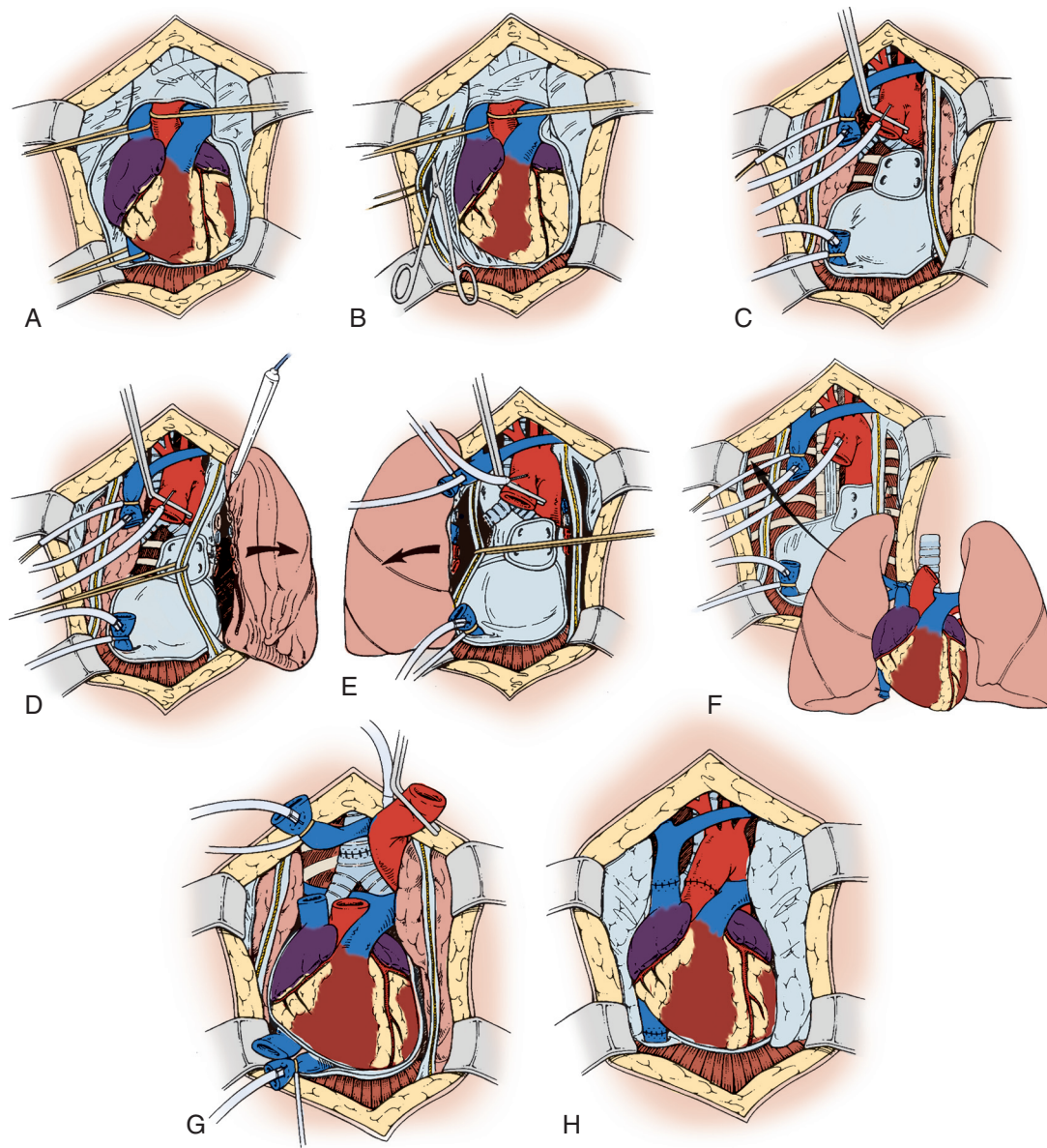


FIGURE 99-4 ■ The recipient operation. **A**, Through a median sternotomy, the anterior pericardium is partially removed, and the ascending aorta and both venae cavae are dissected and encircled with tapes. **B**, The right phrenic nerve is carefully separated from the right hilum. **C**, Cannulation for cardiopulmonary bypass consists of a cannula in the high ascending aorta and separate vena caval cannulas. Once the patient is on cardiopulmonary bypass, the native heart is excised in a manner similar to that used for standard cardiac transplantation. **D-E**, Left and right pneumonectomies are performed by dividing the respective inferior pulmonary ligament, pulmonary artery and veins, and main-stem bronchus. **F**, The heart-lung block is lowered into the chest, placing the hila anterior to each respective phrenic nerve pedicle. **G**, The tracheal anastomosis is performed with a continuous 3-0 polypropylene suture. **H**, The caval and aortic anastomoses are performed with a continuous 4-0 polypropylene suture. (From Yuh DD, Robbins RC, Reitz BA: Transplantation of the heart and lungs. In Edmunds LH, editor: *Cardiac Surgery in the Adult*, New York, 1997, McGraw-Hill, pp 1451–1475.)

polypropylene suture. At this point, the patient is rewarmed toward 37°C, and the superior vena caval and aortic anastomoses are performed in an end-to-end fashion by using a continuous 4-0 polypropylene suture (see Fig. 99-4). After completion of the aortic anastomosis, the patient is placed in a slightly head-down position, the ascending aorta and pulmonary artery are aspirated for air, and the caval tapes and the aortic crossclamp are removed. A leukocyte filter in the cardiopulmonary bypass circuit is opened 10 to 20 minutes before the aortic unclamping. The tracheal tube is aspirated by

using sterile technique, and ventilation is resumed with room air. The left atrial opening at the appendage is repaired. When the patient's body temperature is almost normal and heart and lung function are satisfactory, cardiopulmonary bypass is discontinued and decannulation is performed routinely. The inspired concentration of oxygen is increased as required. Temporary pacing wires are applied to the donor right atrium and ventricle and brought out through the skin below the incision. Right-angled chest tubes are placed in the right and left pleural spaces, and a straight chest tube is placed in the

mediastinum. Methylprednisolone (500 mg) is given to the recipient after heparin reversal with protamine sulfate.

The posterior mediastinum is then inspected for bleeding by carefully rotating the heart-lung block anteriorly and medially while the anesthesiologist uses hand ventilation. This maneuver is facilitated by using the most recent modification, in which the pulmonary hila are placed anterior to the phrenic nerves. Large amounts of warm saline solution at 37°C are used to irrigate both pleural spaces and the mediastinum. When hemostasis is satisfactory, the sternum is closed routinely with multiple stainless steel sternal wires.

POSTOPERATIVE MANAGEMENT

Intensive Care Unit

The immediate postoperative management of the patient undergoing heart-lung transplant is similar to that of any patient after cardiac surgery. Patients are allowed to awaken early in the postoperative course and are monitored closely for hemodynamic stability and bleeding. Endotracheal tube suctioning is performed when appropriate, and the patient is weaned from the ventilator in a routine manner. When the patient is alert and hemodynamically stable and blood gases and ventilatory mechanics are satisfactory, the patient is extubated. Strict attention is paid to fluid balance, and a vigorous diuresis is encouraged in most patients. As soon as possible, the patient is allowed to sit in a chair and begin ambulation. A physical therapist works with the patient to facilitate rapid rehabilitation.

Several points must be kept in mind when treating heart-lung transplant patients in the immediate postoperative period. Early graft dysfunction, manifested by progressive hypoxemia and hypercapnia, can be present in up to 10% to 15% of patients.⁵¹ The proposed etiology is IR injury in the transplanted lung. This injury results in increased pulmonary capillary permeability, alveolar edema, impaired pulmonary compliance, and increased pulmonary vascular resistance with right ventricular dysfunction. Graft dysfunction can progress rapidly, and early treatment is essential. Initiation of pulmonary vasodilators such as alprostadil or inhaled NO may be necessary. Inhaled NO has been demonstrated to decrease the intrapulmonary shunt, optimizing ventilation-perfusion matching after lung transplantation.⁷¹ In another study, inhaled NO administered in the setting of lung allograft dysfunction doubled the ratio of arterial oxygen tension to inspired oxygen fraction (P_{aO_2} to F_{iO_2}) within 1 hour of administration.⁵¹ Furthermore, significant reductions in airway complications, duration of mechanical ventilation, and mortality were noted.⁵¹ In cases of persistent, severe pulmonary graft dysfunction refractory to all intervention, extracorporeal membrane oxygenation has been used successfully to stabilize gas exchange in several patients.⁷²

Immunosuppression

The immunosuppression regimen for heart-lung transfer recipients includes induction therapy with polyclonal

TABLE 99-1 Early Induction Immunosuppressive Therapy after Heart-Lung Transplantation

Immunosuppressive Agent	Dosage
Methylprednisolone	500 mg IV after administration of protamine in the OR 125 mg IV every 8 hours for 3 doses
Rabbit antithymocyte globulin	1.5 mg/kg IV on POD 1, 2, 3, 5, and 7
Daclizumab	1 mg/kg (first dose in OR, then every 14 days on POD 14, 28, 42, and 56)

IV, Intravenously; OR, operating room; POD, postoperative days.

TABLE 99-2 Early Immunosuppression Therapy after Heart-Lung Transplantation

Immunosuppressive Agent	Dose
Tacrolimus	Start with 1 mg orally twice a day on POD 1
0-6 mo	12-15 ng/mL
7-12 mo	10-15 ng/mL
>12 mo	8-10 ng/mL
If sirolimus added	5-7 ng/mL
Mycophenolate mofetil	Start at 500 mg twice a day on POD 1; adjust to white cell count >4 and side effects
Prednisone	
Induction	Hold 8 days, then start at 0.6 mg/kg, divided doses
No induction	Start on POD 1 at 0.6 mg/kg, divided doses

POD, Postoperative day.

rabbit antithymocyte globulin (RATG) and maintenance therapy with tacrolimus, mycophenolate mofetil, and prednisone. Standard protocol is depicted in [Tables 99-1](#) and [99-2](#).

Induction therapy is used on the basis of data showing that it decreases the incidence of early acute rejection, chronic rejection, and OB.^{73,74} Induction therapy is initiated with RATG (1.5 mg/kg IV) on postoperative days (POD) 1, 2, 3, 5, and 7 (see [Table 99-1](#)). If the patient is hemodynamically unstable or allograft function is compromised from reperfusion injury, RATG dosing is delayed for several days. From 1987 to 1993, induction therapy at some centers was switched from RATG to OKT3, the murine monoclonal antibody directed specifically against the T cell (CD3) receptor. However, the use of OKT3 was later shown to be associated with a greater incidence of acute pulmonary allograft rejection, postoperative infection, and OB when compared with RATG.⁷⁵ These findings resulted in a return to using the polyclonal anti-T cell antibody for induction therapy. More recently, there has been a switch to using the interleukin (IL)-2 receptor blocker daclizumab for induction therapy, or to using no induction therapy, especially in patients with significant posttransplant IR injury.

Methylprednisolone (500 mg IV) is administered intraoperatively and continued postoperatively at a dose of 125 mg IV every 8 hours for three doses. If induction therapy is used, maintenance prednisone is withheld for 1 week. Steroids are then restarted on POD 8 with a daily divided oral dose of 0.6 mg/kg prednisone, which is gradually tapered over the next 3 to 4 weeks to 0.1 to 0.2 mg/kg per day. The risk for airway complications after transplantation is not adversely affected by the use of postoperative steroids.⁷⁶ If induction immunotherapy is not used, then prednisone is started after the IV dosing is completed at a dose of 0.6 mg/kg per day in divided doses, with gradual tapering down to a maintenance dosage of 0.1 mg/kg per day.

In addition to steroids, maintenance immunosuppressive therapy includes mycophenolate mofetil and tacrolimus. Mycophenolate mofetil is initiated on POD 1, starting at a dosage of 500 mg twice daily. The dosage is titrated to maintain a leukocyte count greater than 4000/mm³ and to avoid significant side effects. Tacrolimus is also initiated on POD 1 and titrated slowly based on trough levels, with the goal of achieving therapeutic levels on POD 5. This strategy avoids high serum levels and prevents nephrotoxicity. Patients who are unable to tolerate oral intake secondary to prolonged intubation or malabsorption are administered one third of the calculated total dosage IV in a continuous manner.

Although this immunosuppressive regimen has served heart–lung transplantation well, high rates of acute allograft rejection, infection, and chronic rejection, primarily manifested as OB, still exist. The quest for more efficacious and less toxic immunosuppressive regimens is a continual investigative challenge. Starting in approximately 2005, there was a shift from the use of cyclosporine to tacrolimus that was based on studies suggesting that the incidence of OB syndrome was lower with the use of tacrolimus.⁷⁷ Mycophenolate mofetil has been shown to have antiproliferative effects on T and B cells by inhibiting *de novo* purine biosynthesis, with improved efficacy and reduced toxicity.⁷⁸ An added advantage of using mycophenolate mofetil is the selective expansion of regulatory T cells, which may lead to better host tolerance of the transplanted organ.⁷⁹ In addition, newer T cell–inhibitory agents, such as sirolimus (rapamycin), which specifically blocks smooth muscle cell proliferation, can potentially prevent both acute rejection and the manifestations of chronic rejection, also with less toxic side effects.^{80,81}

COMPLICATIONS

Acute Rejection

The fine balance between adequate immunosuppression and the risk for infection and rejection remains one of the most difficult problems in heart–lung transplantation, as with any lung transplantation. The detection of acute rejection is rare in the first postoperative week, and the majority of episodes occur within the first year after transplantation. The diagnosis of acute rejection in the early posttransplantation period is usually based on

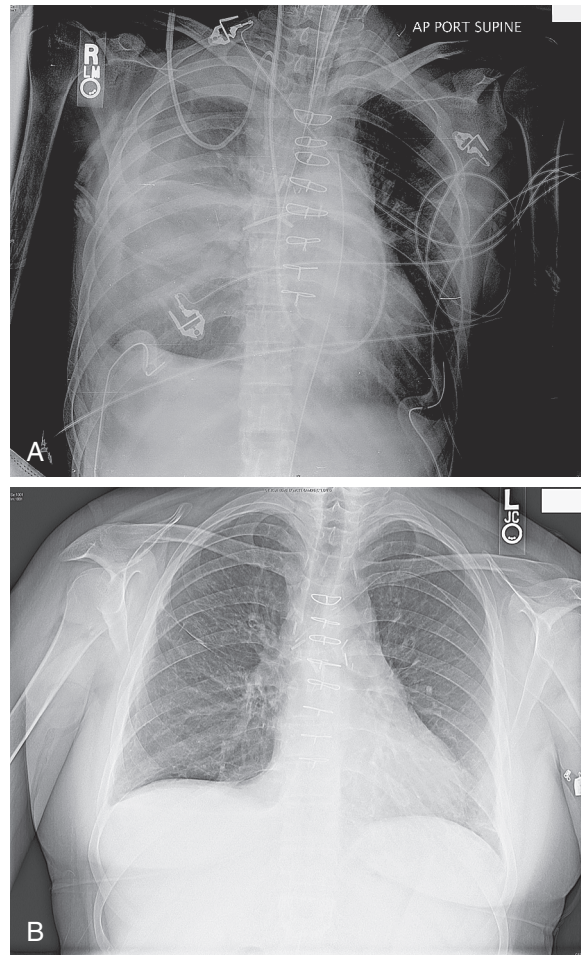


FIGURE 99-5 ■ Acute and resolving lung rejection. **A**, Chest radiograph illustrates bilateral infiltrates characteristic of acute pulmonary rejection. **B**, Follow-up chest radiograph after pulsed methylprednisolone treatment of acute rejection demonstrates resolution of infiltrates.

clinical parameters manifested by lung allograft dysfunction. Signs of acute rejection include dyspnea, low-grade fever, impaired oxygenation and ventilatory parameters (including a diminished forced expiratory volume in 1 second [FEV₁]), and diffuse interstitial infiltrates on chest radiograph (Fig. 99-5).⁸² Acute cellular rejection during the first month is associated with an infiltrate seen on the chest radiograph in 75% of cases. After the first month, however, the chest film is normal or without change in 80% of patients.^{83,84} The role of other modalities such as spirometry, computed tomography (CT), and bronchoscopy with transbronchial biopsy (TBB) become increasingly important.

Acute allograft rejection in the early postoperative period is the single most significant risk factor for the development of subsequent OB, so the role of surveillance modalities in detecting and treating early rejection become critical in preventing chronic rejection and improving survival rates. Spirometric surveillance has been shown to be a reasonable screening tool for acute rejection. FEV₁ and forced expiratory flow rate at 25% to 75% of vital capacity (FEF_{25%-75%}) were noted to

be decreased during episodes of acute rejection, with FEF_{25%-75%} being the best parameter to distinguish acute rejection from infection.⁸⁵ Because of some lack of sensitivity and specificity of spirometric surveillance, however, TBB remains the gold standard for the detection of rejection.

In heart-lung transplantation, the simultaneous rejection of both the heart and lung is rare,⁸⁶ and endomyocardial biopsy does not help diagnose acute lung rejection.⁸⁷ Furthermore, histologic assessment by using TBB is superior to cardiac biopsies because cardiac rejection is very rare without lung rejection, and thus the need for routine endomyocardial biopsies has been eliminated.⁸⁸ Surveillance bronchoscopy with TBB in heart-lung recipients is routinely performed at 2 and 4 weeks after transplantation, and then at 2, 3, 6, and 12 months thereafter, or as clinically indicated. At least five TBB specimens that contain lung parenchyma are necessary to obtain an adequate quantity of specimen. TBBs performed in the setting of clinical symptoms were positive for rejection or infection in 72% of cases.⁸⁶ The yield for surveillance biopsies after 1 year in asymptomatic patients, however, is very low.⁸⁹ Late postoperative biopsies are therefore guided by clinical parameters, and any deterioration in pulmonary function leads to further evaluation.

Rejection episodes occurring within the first 3 months, or those graded as moderate or severe, are treated with IV methylprednisolone at a dose of 1000 mg/day for 3 consecutive days, followed by an increased oral maintenance dose of 0.6 mg/kg per day, tapered to 0.2 mg/kg per day over 3 to 4 weeks. Both the chest radiograph appearance and clinical symptoms usually improve rapidly after the initiation of pulsed steroid therapy. In milder cases of rejection, or in cases occurring after 3 months, treatment consists of increased oral prednisone, followed by a gradually tapered dose over 3 to 4 weeks. Patients with steroid-resistant or persistent allograft rejection are treated with either monoclonal (OKT3) or polyclonal (RATG) antilymphocyte therapy. Other potential treatments in refractory and recurrent cases include switching to rapamycin, methotrexate, total lymphoid irradiation, or extracorporeal photochemotherapy.⁹⁰⁻⁹³

Infection

Infectious complications remain a significant cause of morbidity and mortality in heart-lung recipients. The spectrum of potential pathogens is extensive, yet some common patterns can be appreciated. Bacterial infections are most prevalent early in the postoperative period, with the highest incidence noted in the first month after heart-lung transplantation.⁹⁴ Bacterial infections can manifest as pneumonia, mediastinitis, line sepsis, urinary tract infections, and skin infections. Gram-negative bacilli are the most common bacterial pathogens. Late after transplant, opportunistic pathogens such as viral, fungal, and protozoal species are more common.

Cytomegalovirus (CMV) is the most common viral pathogen in heart-lung transplants. CMV has been associated with pneumonitis in as much as 50% of patients and is associated with an increased incidence of chronic

rejection manifested as accelerated graft coronary artery disease and OB.^{95,96} In addition to pneumonia, CMV infection can have presenting symptoms such as leukopenia and fever, gastroenteritis, hepatitis, and retinitis. CMV events occur within the first 12 months, with the majority appearing within the first 3 months. Individuals at the greatest risk for serious infections are seronegative recipients (R⁻) receiving a heart-lung block from a seropositive donor (D⁺). The incidence of serious infections in these patients is 90%, which falls to 10% when recipient and donor are CMV-negative. The diagnosis of CMV disease (symptomatic) or CMV infection (without symptoms) is established by several means: seroconversion from anti-CMV immunoglobulin M (IgM) negative to positive; a fourfold rise in CMV IgG antibody titers; positive viral cultures from urine, blood, or dimercaprol (bronchoalveolar lavage); or CMV inclusion bodies on transbronchial biopsy.

Most transplant centers perform transplants across CMV serologic barriers, implementing prophylactic measures in high-risk patients (D⁺R⁻). These patients receive prophylaxis with CMV hyperimmunoglobulin (CytoGam; CSL Behring, King of Prussia, PA) in addition to ganciclovir (DHPG).⁹⁷ This combination regimen resulted in a significant decrease in both CMV disease and CMV infection when compared with DHPG alone.⁹⁸ Standard protocol is to administer DHPG at 5 mg/kg IV twice per day for 14 days, then at 6 mg/kg once per day for 20 days. After DHPG, valganciclovir (Valcyte; Genentech, South San Francisco, CA) (900 mg) is initiated for 6 weeks after transplant. CytoGam is given at a dosage of 150 mg/kg IV within the first 72 hours after transplantation and then continued at a dosage of 100 mg/kg at 2, 4, 6, and 8 weeks, followed by 50 mg/kg at weeks 12 and 16 after transplant.

Fungal organisms are the least common pathogens, yet these infections are associated with the greatest mortality. The risk of fungal infections after lung, heart-lung, and heart transplantation can be significantly lowered by prophylaxis with aerosolized amphotericin B.⁹⁹ Inhaled treatments with amphotericin B have been shown to decrease the rate of fungal infections at 3 months from 0.8% to 0.2%, and the incidence fell twofold at 12 months when compared with a group that did not receive the inhaled treatment.⁹⁹ Bronchodilators are administered prophylactically before treatment to reduce bronchospasm. Fungal infections, diagnosed by sputum culture or CT-guided needle aspirate, are aggressively treated with intravenous amphotericin B administration.

Pneumocystis jiroveci pneumonia has been effectively prevented in heart-lung recipients since the initiation of prophylaxis with the combination of sulfamethoxazole and trimethoprim.¹⁰⁰ The dosages of sulfamethoxazole and trimethoprim are 800 mg and 160 mg, respectively, twice daily, 3 days per week, adjusting the dosage for renal insufficiency. If patients have a sulfur allergy or leukopenia develops, inhaled pentamidine (300 mg) is initiated once a month. *Toxoplasma gondii*-negative recipients receiving a transplant from a seropositive donor are treated with a 6-week course of pyrimethamine (25 mg) every day and leucovorin (10 mg) every day. In addition, long-term prophylaxis typically includes clotrimazole

(Mycelex Troches) for the prevention of mucosal candidal infections.

Chronic Rejection—Obliterative Bronchiolitis

The main cause of long-term morbidity and mortality after heart–lung transplantation is chronic rejection, primarily manifested as OB. The clinical diagnoses of bronchiolitis obliterans syndrome (BOS) and the pathologic diagnoses of OB were defined in the working formulation by the ISHLT.¹⁰¹ BOS does not require a histologic diagnosis; it is defined as a deterioration of graft function secondary to progressive airways disease. Other potential etiologies such as acute rejection and infection must be excluded before a diagnosis of BOS is reached. The clinical manifestations of BOS include a dry cough and progressive dyspnea. Interstitial pulmonary infiltrates are seen on the chest radiograph, and an obstructive pattern is seen in pulmonary function tests. BOS can be staged on the basis of the deterioration of FEV₁.¹⁰¹ OB, on the other hand, is a histologic diagnosis based on the presence of eosinophilic fibrous scarring of the membranous and respiratory bronchioles, with partial or complete obliteration of the lumen.¹⁰²

The overall incidence of BOS or OB at 5 years after heart–lung transplantation, as reported by the ISHLT Registry, is approximately 48% (Fig. 99-6).⁵ Significant risk factors associated with the development of OB include the frequency and severity of acute rejection, as well as the appearance of lymphocytic bronchiolitis on TBB.⁷³ Furthermore, organizing pneumonia, as well as CMV infection, significantly potentiates the effects of acute rejection.

A growing body of evidence supports the hypothesis that OB is an immunologically mediated process. In addition to its association with acute rejection, the disease is most commonly found in patients with the greatest degree of HLA mismatch.¹⁹ Patients with OB have an increased number of mismatched major histocompatibility complex (MHC) class II antigens,¹⁰³ immunologic mediators such as IL-2 and IL-6 in bronchioalveolar

lavage fluid,¹⁰⁴ and a predominance of CD8⁺ cytotoxic and suppressor cells on TBB.¹⁰⁵ CMV infection may have a stimulatory effect on the immune system that enhances the viral injury.¹⁰⁶ CMV prophylaxis with ganciclovir has been demonstrated to delay the onset of OB.¹⁰⁷ In addition to its immunologic stimulus, CMV also has a direct stimulatory effect on the smooth muscle cells of the airways, as well as indirectly via the elaboration of growth factors and mitogenic mediators.¹⁰⁸ Better control of the immune response, prevention of acute rejection, and reducing CMV infection are the best therapies for preventing the incidence of BOS or OB.

For long-term surveillance, patients are provided with a portable spirometer so that expiratory flow can be checked frequently between clinic visits.^{109,110} If there is any interval decrease or any signs of respiratory tract infection, the patient is instructed to contact the transplant center or primary care physician so that pulmonary function tests can be performed. Any subsequent alteration in FEV₁ 25%-75% prompts further evaluation with bronchoscopy and bronchoalveolar lavage, and TBB. After infection has been ruled out, augmentation of immunosuppression is the current mode of therapy. If acute rejection is seen with the TBB, pulsed-dose steroids are started (methylprednisolone, 1 g IV for 3 days). In the setting of augmented immunosuppression, CMV prophylaxis is begun, with ganciclovir and fungal prophylaxis combined with inhaled amphotericin B.

Despite stabilization of pulmonary function with augmented immunosuppression, relapse rates are greater than 50%, and mortality is significant.^{111,112} The actuarial survival curves for heart–lung transplant patients are quite different for patients with BOS/OB and those without BOS/OB (Fig. 99-7). Markedly better survival rates were also demonstrated in patients with BOS stage 1 than in those with BOS stages 2 or 3.¹¹¹ The main cause of death is usually respiratory failure secondary to a superimposed pneumonia. Retransplantation often remains the only therapeutic option, although the results of retransplantation in patients who have developed

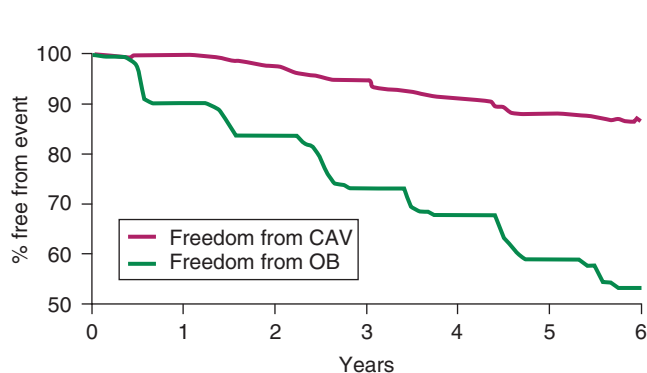


FIGURE 99-6 ■ Freedom from obliterative bronchiolitis (OB) and cardiac allograft vasculopathy (CAV), or accelerated graft coronary disease, after heart–lung transplantation. (Modified from Trulock EP, Christie JD, Edwards LB, et al: The Registry of the International Society of Heart and Lung Transplantation: Twenty-Fourth Official Adult Lung and Heart-Lung Transplant Report—2007. *J Heart Lung Transplant* 26:782–795, 2007.)

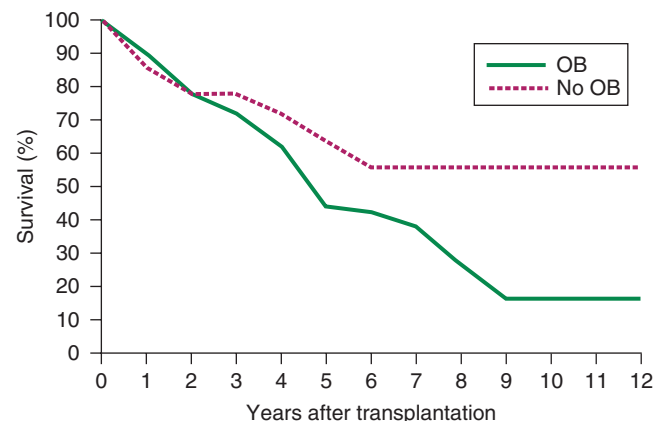


FIGURE 99-7 ■ Effect of obliterative bronchiolitis (OB) on patient survival rate after lung and heart–lung transplantations. (Modified from Reichenspurner H, Giris R, Robbins RC, et al: Stanford experience with obliterative bronchiolitis after lung and heart–lung transplantation. *Ann Thorac Surg* 62:1467–1472, 1996.)

end-stage OB are poor, with an actuarial survival rate of only 25% at 1 and 3 years after transplantation.¹¹³

Chronic Rejection—Graft Coronary Artery Disease

Very few heart-lung recipients who survive the first year will die as a result of graft coronary artery disease.^{114,115} The incidence of cardiac allograft rejection in heart-lung recipients is low.⁸⁷ The incidence of angiographically detectable coronary artery disease was only 11% at 5 years after heart-lung transplantation,¹¹⁴ which is similar to the data from the ISHLT Registry (see Fig. 99-6).⁵ This is in contrast to heart-only transplant recipients, of whom as many as 50% develop significant angiographic disease by 5 years; this is the major cause of mortality and retransplantation in these patients. A recent study using intracoronary ultrasonography confirmed the low incidence of transplant coronary artery disease in heart-lung recipients when compared with the heart-alone recipient group.¹¹⁶ When the lungs and heart are both transplanted, the lungs are more immunologically active. This observation was confirmed in an animal model, in which hearts that were transplanted in combination with lungs or spleen displayed an impressive reduction in myocardial rejection; this phenomenon is termed the *combi-effect*.¹¹⁷

Complications of Immunosuppression

There are several side effects resulting from long-term immunosuppression. Cyclosporine causes nephrotoxicity, hypertension, hepatotoxicity, hirsutism, and gingival hyperplasia, and it is associated with an increased incidence of lymphoma. Azathioprine causes a generalized bone marrow depression manifested as leukopenia, thrombocytopenia, and anemia. Long-term use of steroids causes hypertension, diabetes, osteoporosis, and impaired wound healing. Induction therapy with either RATG or OKT3 can cause significant hemodynamic instability and respiratory compromise manifested as fever, hypotension, and bronchospasm. Patients are therefore premedicated with corticosteroids, acetaminophen, and antihistamines before the administration of immunosuppressive agents.

One of the more troubling consequences of heart-lung transplantation is the development of posttransplant lymphoproliferative disorder (PTLD).¹¹⁸ This is characterized by lymphadenopathy and often a diffuse lymphocytic infiltrate on TBB.¹¹⁹ The treatment is immediate reduction in the intensity of the immunosuppression. The disease has essentially two forms: malignant and nonmalignant. Early onset of PTLD (<12 months after transplantation) is typically benign and resolves rapidly after reduced immunosuppression. Conversely, late PTLD is associated with a 70% to 80% mortality rate and typically resists reduction by immunotherapy or traditional chemotherapy.¹²⁰

Additional Complications

Airway complications have become rare after heart-lung and lung transplantation as the result of improvements

in surgical technique and postoperative management. The risk for a major airway complication after heart-lung transplantation is approximately half of that after a single-lung transplantation, with a reported incidence as low as 3.8%.¹²¹ The incidence of airway complications is unrelated to steroid use in the preoperative or postoperative period.⁷⁶ Furthermore, no significant correlation could be identified with the ischemic interval, anastomotic wrapping, or date of first rejection episode.¹²²

Abdominal complications after heart-lung transplantation remain a significant source of morbidity and mortality.¹²³ The prevalence of symptomatic gastroparesis after heart-lung transplantation is high, probably as a result of vagotomy at the time of removal of the heart-lung block.¹²⁴ Gastroparesis with gastric distention can lead to gastroesophageal reflux with subsequent aspiration. Episodes of aspiration and the resultant inflammatory response can result in significant lung allograft dysfunction. Furthermore, whether this allograft injury predisposes the patient to an increased risk for BOS or OB remains to be determined.¹²⁵ Laparoscopic antireflux surgery should also be considered in patients with severe reflux disease after heart-lung transplantation, because pulmonary function and reflux symptoms have been shown to significantly improve with this treatment.¹²⁶

PHYSIOLOGY OF THE TRANSPLANTED LUNG

Standard measure of pulmonary function indicates that long-term function of the transplanted heart and lungs is well maintained. Integrated cardiopulmonary function with exercise is also largely intact.^{127,128} Some debate has centered on a bronchial hyper-responsiveness to a methacholine challenge.¹²⁹ There does appear to be an associated decrease in mucociliary clearance, which may be a contributing factor to the serious and repeated infections seen in heart-lung recipients.¹³⁰ In the absence of OB and severe recurrent infection, the function of the transplanted heart and lungs is conducive to an excellent quality of life.¹²⁷

LATE RESULTS

A retrospective review of all 174 patients with end-stage cardiopulmonary disease who underwent heart-lung transplantation at Stanford University between the time of the first landmark operation in 1981 to 2000 revealed that 40% of these patients were still alive, with a 5-year actuarial survival rate of 49% (Fig. 99-8). This record compares closely with the worldwide experience with heart-lung transplantation, as reported by the ISHLT Registry, and is similar to that for patients receiving double-lung transplantation alone (Fig. 99-9).⁵ A review of the experience at Stanford from 1991 to 2002 reveals improved survival when compared with the preceding decade.¹⁴

Causes of mortality after heart-lung transplantation differ over time after surgery. Early deaths, occurring less than 1 month after surgery, are most often the result of

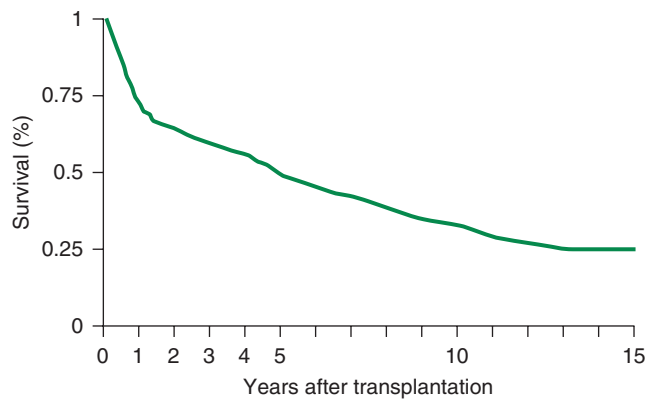


FIGURE 99-8 ■ Actuarial survival of patients who underwent heart-lung transplantation at Stanford University, 1981 to 2000.

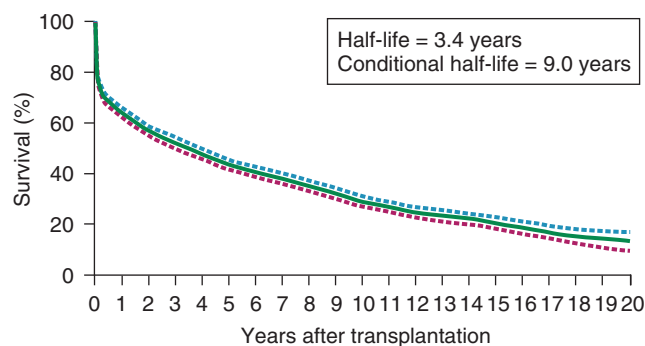


FIGURE 99-9 ■ Heart-lung transplantation actuarial survival based on data from the International Society for Heart and Lung Transplantation (ISHLT) Registry. Half-life is time to 50% survival; conditional half-life is time to 50% survival of hospital survivors. (Modified from Trulock EP, Christie JD, Edwards LB, et al: The Registry of the International Society of Heart and Lung Transplantation: Twenty-Fourth Official Adult Lung and Heart-Lung Transplant Report—2007. *J Heart Lung Transplant* 26:782–795, 2007.)

infection (36% of overall deaths), hemorrhage (8% to 20%), acute respiratory disease syndrome (4%), and non-specific graft failure (7% to 9%).^{14,114} Acute rejection of the heart-lung graft is fairly uncommon, resulting in mortality in less than 2% of patients. Almost all rejection events in these patients occur within the first 3 months, with a linearized rejection rate twice as high for the lung (0.7 events per 100 days) when compared with the heart (0.35 events per 100 days). The most common cause of death after the immediate postoperative phase is OB. The overall prevalence of OB in patients surviving heart-lung transplantation longer than 3 months was 64%, with an overall mortality greater than 70% after 5 years of follow-up.¹¹¹ Additional causes of late death include infection, malignancy, and coronary artery disease. The incidence and severity of transplant coronary artery disease are significantly less when compared with those of the heart transplantation population.¹³¹ However, this complication remains an important cause of late death in heart-lung recipients.¹¹⁴

The long-term functional results after heart-lung transplantation are encouraging. Most recipients are able

to resume an active lifestyle without the need for supplemental oxygen, and they demonstrate significant increases in exercise capacity after transplantation.^{128,132} Pulmonary function as measured by spirometry is also markedly improved after heart-lung transplantation.¹²⁸ The functional benefits of heart-lung transplantation are particularly evident when considering that this subgroup of patients would otherwise have a life expectancy of less than 2 years, despite maximal medical and nontransplantation surgical therapy.

FUTURE DEVELOPMENTS

Imperfections remain in the use of heart-lung transplantation for definitive treatment of end-stage cardiopulmonary disease. Significant improvements in selective immunosuppression and the development of precise immunotolerance are required before heart-lung transplantation can restore normal heart and lung function without significant long-term morbidity and mortality. The development of new immunosuppressive agents, the use of genetic engineering to formulate new humanized monoclonal antibodies, and the field of pharmacogenomics provide continued hope for an improved outlook for heart-lung transplant recipients. Novel approaches such as ex vivo gene therapy, the induction of immunotolerance, and xenotransplantation are promising areas of continual investigation.

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LEFT VENTRICULAR RESTORATION: SURGICAL TREATMENT OF THE FAILING HEART

Lorenzo Menicanti • Serenella Castelveccchio

In memory of Professor Marisa Di Donato.

CHAPTER OUTLINE

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Left Ventricular Geometric Abnormalities in Ischemic and Nonischemic Ventricles
Rationale for Reshaping Cardiac Architecture
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SURGICAL VENTRICULAR RESTORATION FOR ISCHEMIC CARDIOMYOPATHY

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OUTCOMES

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Coronary Artery Bypass Surgery with or without Surgical Ventricular Restoration: Insights into the STICH Trial
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SUMMARY

In response to the increasing health, economic, and social impacts of heart failure, clinicians are investigating new surgical therapies that do not involve heart transplantation. Heart failure affects about 5 million patients in the United States, and more than 250,000 die annually. Nearly 70% of patients with heart failure have coronary artery disease, and nearly all have had a myocardial infarction (MI).¹ In part, the increase in the prevalence and incidence of heart failure results from improved diagnosis and treatment of cardiac disease (especially ischemic disease), but another factor is the aging of the population.² Despite improvements in medical treatment since the 1960s and the introduction of potent new drugs, the prognosis for patients affected by heart failure remains extremely poor.^{3,4} However, with recent advances in surgical therapy for cardiac disease, new surgical options can be offered to some of these patients as an alternative to medical therapy. Some conventional drug therapies have

not shown any significant improvement in the survival of patients with heart failure.⁵⁻⁸

After a diagnosis of heart failure, the 5-year mortality rate is still 60% for men and 45% for women, despite improvements in its medical management.⁹ Currently, improvements in surgery technology and in surgeons' skills have broadened the indications for cardiac surgery. Historically, patients with severe congestive heart failure (CHF) were listed for heart transplantation, and although this is a very effective therapy for end-stage heart failure, the limited number of donor organs remains a crucial problem.¹⁰ Indeed, the Registry of the International Society for Heart and Lung Transplantation shows that the number of heart transplant centers worldwide has dropped from 248 in 1995 to 201 in 2005.¹¹

Until recently, surgical management was directed toward the underlying pathology of coronary disease and the secondary mitral insufficiency that evolves as the

heart dilates, but surgeons do not systematically approach the ventricle. Surgical ventricular restoration (SVR), the topic of this chapter, was launched by Dor and colleagues¹² and represents a relatively novel surgical approach that aims to restore (i.e., bring back to normal) the dilated, distorted left ventricular (LV) cavity to improve function. It requires knowledge of the remodeling infrastructure, of the structural changes that lead to geometric abnormalities, and of the role of compensatory, remote muscle and stretching mechanisms that lead to electrical instabilities.¹³

SVR is more than a single procedure, because it includes coronary grafting and mitral repair when needed, and thus it has the potential to treat the three components of the disease: the ventricle, the vessels, and the valve ("triple V" as defined by Buckberg^{14,15}).

PATHOPHYSIOLOGY OF HEART FAILURE

Left Ventricular Remodeling

In dilated cardiomyopathy (a common cause of heart failure), a primary determinant of the disease process is LV remodeling. The underlying causes of dilated cardiomyopathy are diverse, and the origin may be nonischemic or ischemic.

LV remodeling is a complex, dynamic, and time-dependent phenomenon that involves molecular, cellular, interstitial, and genome-expression changes that manifest clinically as changes in the size, shape, and function of the heart after cardiac injury.¹⁶ The process can evolve slowly or rapidly after the myocardial injury, and it contributes importantly in the progression to end-stage CHF. Box 100-1 summarizes the principal changes that occur in LV remodeling. The extracellular matrix participates in the altered ventricular geometry after MI. Cardiologists and cardiac surgeons traditionally viewed the extracellular matrix as an inert collection of structural macromolecules that serve as a scaffold for cells. However, a large body of evidence supports a central role for the extracellular matrix in the control of numerous cellular functions¹⁷ and supports the idea that the extent of LV

remodeling is a critical determinant of clinical outcome after MI.

Current working models for heart failure include the cardiorenal model (excessive salt and water retention), the hemodynamic model (pump failure and excessive vasoconstriction), and the neurohormonal model (overexpression of biologically active molecules capable of exerting unfavorable effects on the heart and circulation). Each of these may be necessary but not entirely sufficient to explain all the causes of disease progression in the failing heart. After the myocardial insult and the initial decline in pumping capacity, a variety of compensatory mechanisms are evoked to restore cardiovascular function and normal homeostasis. Adrenergic, renin-angiotensin, and cytokine systems are activated systemically and locally in the myocardium in response to reduced cardiac output.^{18,19} A variety of circulating and tissue proteins and peptides (e.g., norepinephrine, angiotensin II, endothelin, aldosterone, tumor necrosis factor, interleukins) are generated in an initial adapting response. However, chronic overexpression of these biologically active molecules may fundamentally alter gene expression, changing protein synthesis in both myocytes and fibroblasts.

The biomechanical model for heart failure described by Mann and Bristow helps to explain the progression of heart failure independent of the neurohormonal status of the patient.²⁰ In fact, current medical therapy, acting against neurohormonal activation, tends to slow progression but fails to arrest the process of remodeling. In addition, many types of neurohormonal inhibition proved to be ineffective or even harmful in patients with heart failure.²¹

To explain the failure of neurohormonal antagonism, Mann and Bristow focus on LV size and geometric abnormalities as being responsible for progression of the disease. Geometric changes lead to structural abnormalities of the myocytes and of the myocardium, which worsen cardiac function and increase neurohormonal activation; this may make the cardiovascular system less responsive to normal homeostatic control mechanisms.²⁰

Left Ventricular Geometric Abnormalities in Ischemic and Nonischemic Ventricles

The determinants of LV geometry are shape, volume, and cardiac mass, and these three components may be altered by cardiac disease, which can be primarily degenerative, valvular, or ischemic in origin. Ischemic cardiomyopathy leads to a sequence of structural changes to compensate for the increased load produced from the nonfunctional akinetic or dyskinetic regions.²²

In anterior myocardial infarction, the LV apex is primarily involved, so regional changes affect the anterior, septal, and inferoseptal ventricular components. Globally, the elongation and widening of the ventricle occur proportionally to maintain a constant ratio (i.e., a constant *sphericity index*, or short ratio to long axis). However, when patients develop secondary mitral insufficiency, the

BOX 100-1 Left Ventricular Remodeling

MYOCARDIAL CHANGES

- Myocyte loss
- Necrosis
- Apoptosis

ALTERATIONS IN EXTRACELLULAR MATRIX

- Matrix degradation
- Replacement fibrosis

ALTERATIONS IN LV CHAMBER GEOMETRY

- LV dilation
- Increased LV sphericity
- LV wall thinning
- Mitral valve insufficiency

LV, Left ventricular.

sphericity index is abnormal and the ventricle is more spherical. In the absence of mitral regurgitation (MR), therefore, the sphericity index fails to detect shape abnormalities in anterior postinfarction cardiomyopathy. The *conicity index* has been proposed to assess the conical shape of the apex and its changes after MI (Fig. 100-1).²³ Another important shape change that occurs after an anterior MI is the displacement of the papillary muscles laterally and toward the apex, which produces tethering of the posterior mitral leaflet and mitral restriction.

Alternatively, shape changes after an inferior MI are different²⁴: the short axis is widened more than the long axis is elongated, which leads to an increase in the sphericity index and accounts for the more frequent occurrence and the more severe degree of MR. Table 100-1 compares the geometric abnormalities that occur in anterior and inferior myocardial infarctions.²⁵

Nonischemic dilated cardiomyopathy exhibits a more spherical shape than ischemic cardiomyopathy: the short axis is enlarged, MR is more frequently involved, and wall motion is severely and diffusely hypokinetic. Pump function is markedly reduced and there are apparently no regional differences in contractility. However, biopsy studies show nonhomogeneous disease in many patients, with the amount of scarring and fibrosis ranging from 4% to 60% between the free wall and the septum, which may account for the failure of some types of surgery, such as the Batista operation, to reduce the ventricular cavity in patients with nonischemic dilated cardiomyopathy.^{26,27}

Rationale for Reshaping Cardiac Architecture

Figure 100-2 shows the spiral arrangement of myocardial fibers as reported in a very old anatomy atlas. Studies^{28,29} established that fiber orientation was a function of transmural location, with fiber direction being predominantly longitudinal in the endocardial region, transitioning into a circumferential direction in the midwall, and becoming longitudinal again over the epicardial surface. Such an alignment of fibers in double layers (left- and right-handed from the base to the apex) forms a double helix. These layers are not aligned parallel to one another;

rather, the myofiber sheets diverge within the LV wall, creating angulations with respect to the plane of the epicardial surface. These fiber angulations serve to resist deformation and to maintain the distribution of tension within normal limits at the three levels: longitudinal, radial, and circumferential. Moreover, this architecture gives to the heart a form resembling a geometric ellipsoid, which favors the direction of flow toward the aorta. When angulations are deformed by fiber disruption, fibrosis, or scarring of myocardial tissue, the shape of the ventricle loses its characteristics and its functionality (following the strict relationship between form and function). For a given fiber contractile status, the ejection fraction (EF) changes according to the shape of the ventricle, being low in a spherical ventricle (sphericity index, toward 1) and high in an elliptical shape (sphericity index, toward 0). In fact, macroscopic anatomic alterations can affect wall tension, which, according to the Laplace law, is directly proportional to LV pressure and chamber radius and inversely proportional to wall thickness. In animal models of myocardial damage or after MI in humans, ventricular remodeling alters the major determinants of wall stress,^{30,31} and functional impairment has been reported in the remote zones of dilated LV with geometric abnormalities.³² When the ischemic systolic dysfunction is superimposed on the use of preload to

TABLE 100-1 **Geometric Differences According to Site of Myocardial Infarction**

	Inferior	Anterior	P value
Diastolic diameter (mm)	69 ± 10	63 ± 9	0.009
Systolic diameter (mm)	57 ± 12	50 ± 11	0.009
Septum thickness in diastole (mm)	12.8 ± 3	10.5 ± 3	0.001
Posterior thickening (%)	16 ± 15	32 ± 23	0.008
Left ventricular mass index (gm/m ²)	217 ± 51	165 ± 39	0.000
Left atrium size (mm)	48 ± 8	44 ± 7	0.008
Mitral regurgitation present (%)	87	69	0.04
Mitral regurgitation grade	2.9 ± 1.1	2.0 ± 1.1	0.0003

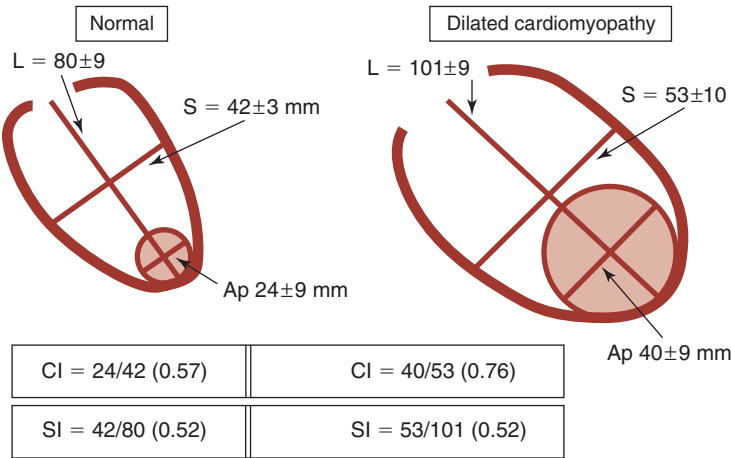


FIGURE 100-1 ■ Geometric measures in normal and dilated cardiomyopathy. Sphericity index (SI) is calculated as the short- to long-axis ratio (S/L), and conicity index (CI) as the apical to short-axis ratio (Ap/S). Apical diameter is determined by using the diameter of the sphere that best fits the apex. Note that the SI has the same value in normal subjects and in patients with dilated cardiomyopathy, because the elongation of the ventricle is proportional to the increase in width, so the ratio remains stable, whereas the CI is markedly abnormal in the patients.

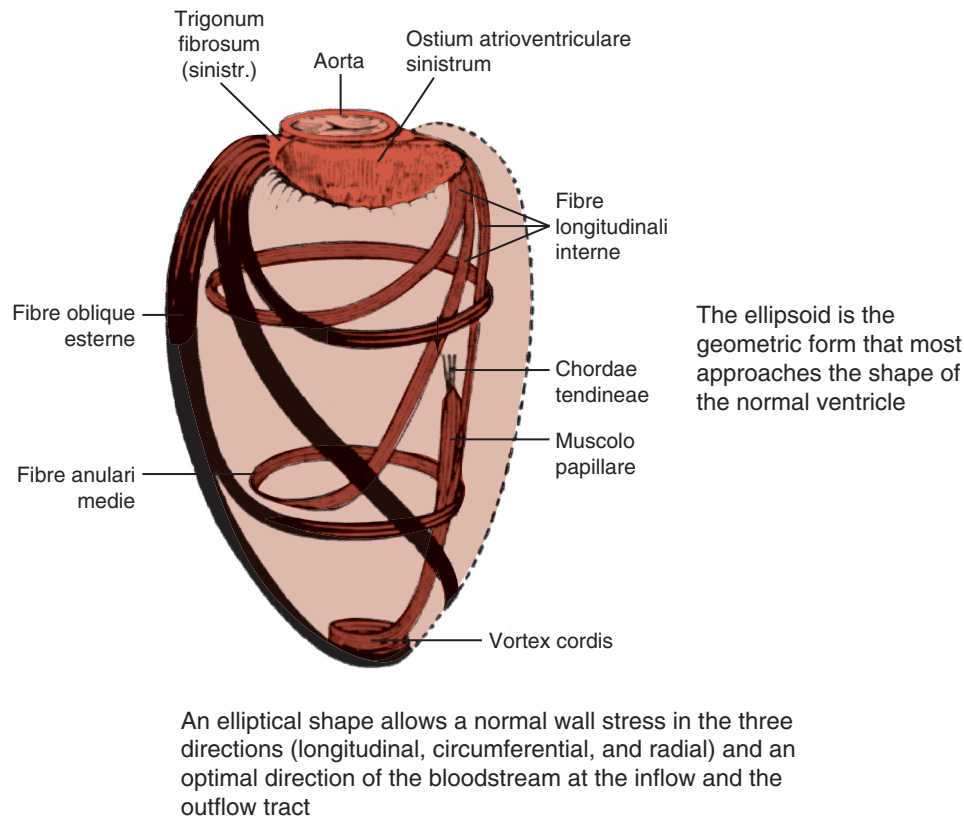


FIGURE 100-2 ■ The three-dimensional architecture of the heart. From an eighteenth-century atlas of anatomy. (From Benninghoff-Goertler: *Atlas of anatomy*, vol II, Padova, Italy, 1996, Piccin Editore.)

improve cardiac output during exercise, the ventricle can be further dilated because of its inability to eject blood, starting a cycle that further deteriorates LV function. In addition, LV end-diastolic pressure can increase in the presence of reduced myocardial compliance (resulting from tissue stiffening), which tends to resist deformation, whereas increased stiffness leads to decreased systolic function.

A further increase in end-diastolic and end-systolic volumes (ESVs) leads to an adverse prognosis.³³ As part of the GUSTO (Global Utilization of Streptokinase and t-PA for Occluded Arteries) trial, Migrino and associates³³ evaluated ESV at 90 to 180 minutes into reperfusion during acute MI. They demonstrated that in successfully reperfused patients after MI, an increase in ESV beyond 40 mL/m² worsens prognosis in terms of both development of heart failure and mortality. A post-MI ESV index equal to or greater than 60 mL/m² carries a 1-year mortality rate of up to 30%. In the SAVE (Survival and Ventricular Enlargement) trial, left ventricular size was a strong independent risk factor for mortality after 2 years.³⁴

Even after coronary artery bypass surgery, patients with large ventricles have a worse prognosis. Yamaguchi and coworkers³⁵ identified LV ESV index greater than 100 mL/m² as an independent risk factor for the development of CHF in ischemic cardiomyopathy. These reports helped cardiac surgeons focus on the importance of reconstruction of the left ventricle in ischemic cardiomyopathy.

Left Ventricular Aneurysm or Ischemic Dilated Cardiomyopathy?

Left ventricular aneurysm was first described in the eighteenth century.³⁶ In 1816, Cruveilhier³⁷ attributed ventricular aneurysm to myocardial fibrosis, although its association with coronary thrombosis was not generally appreciated until a century later. It was not until Tennant and Wiggers showed paradoxical motion in acutely ischemic myocardium that the physiologic implications of ventricular injury became apparent.³⁸ Subsequently, Murray described systolic paradoxical expansion of acutely infarcted myocardium and correlated this with diminished cardiac output and falling blood pressure.³⁹ In 1967, Klein and coworkers⁴⁰ published a hemodynamic study on LV aneurysm that became a milestone in the field of mechanics and energetics of the left ventricle after an ischemic injury. Gorlin and coauthors were the first to state that when approximately 20% to 25% of left ventricular area is inactivated by any pathologic process, the degree that the myofiber must shorten to maintain stroke volume exceeds physiologic limits, and cardiac enlargement (Starling mechanism) must ensue to maintain adequate ejection of blood. With this concept, they anticipated the concept of LV remodeling and described the way MI relates to the genesis of aneurysm. Furthermore, they described that the aneurysm can be either dyskinetic (i.e., paradoxical expansion resulting during systole) or akinetic (i.e., myocardial fibrosis, calcification within the scar, thickened overlying pericardium, mural

thrombosis, and endocardial thickening may rigidify the aneurysm wall and prevent its expansion).

Gorlin offered the following definition:

An aneurysm is identified by a left ventricular angiogram as any akinetic or dyskinetic segment of myocardium. An akinetic segment is defined as a segment that appears to have no motion during systole, whereas a dyskinetic segment appears to bulge paradoxically during systole. Intraoperatively, an aneurysm is identified as a circumscribed area of scar, which is thin, often adherent to the pericardium and which may or may not bulge paradoxically during systole. The aneurysmal segment is easily outlined by looking for the area that puckers and collapses when the left ventricle is vented.

This cineangiographic and surgical definition of ventricular aneurysm is compatible with the pathologic definition: "A localized outpouching of the cavity of a cardiac chamber, with or without outward bulging of the external surface."⁴¹

Early revascularization, with either thrombolysis or primary percutaneous transluminal coronary angioplasty, has beneficial effects on infarct size and LV function and therefore has profoundly changed the picture of MI and its sequelae.⁴²⁻⁴⁴ However, even with early mechanical relief of the coronary occlusion, unfavorable global LV remodeling may occur. Bolognese and coauthors demonstrated that almost 30% of patients with excellent infarct-related artery patency at 6 months continue to undergo

LV remodeling.^{45,46} In patients with an anterior MI, this occurs more frequently when myocardial contrast echocardiography demonstrates a higher incidence of microvascular dysfunction. Figure 100-3 shows the progression of an anterior MI toward ischemic dilated cardiomyopathy in one of our patients. Figure 100-4 shows two of the shape abnormalities that may occur after successful early recanalization for anterior MI as analyzed by the centerline method.⁴⁷⁻⁴⁹ Thus, an acute MI, either anterior or inferior, may result in any of four types of shape abnormalities (Fig. 100-5).⁵⁰ This classification is incomplete because it does not take into account abnormalities occurring at the septum or at the lateral wall. However,

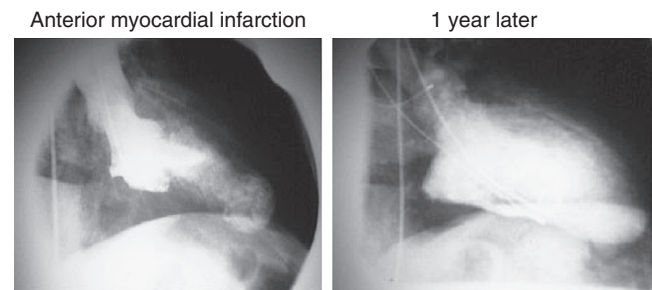


FIGURE 100-3 ■ Left ventricle (LV) angiography, 30-degree right anterior oblique projection. *Left*, Early after myocardial infarction, systolic frame. Note the small apical aneurysm. The left anterior descending artery was successfully reperfused. *Right*, The LV angiogram 1 year later showed marked end-systolic volume dilation of the ventricle, and the patient had symptoms of heart failure.

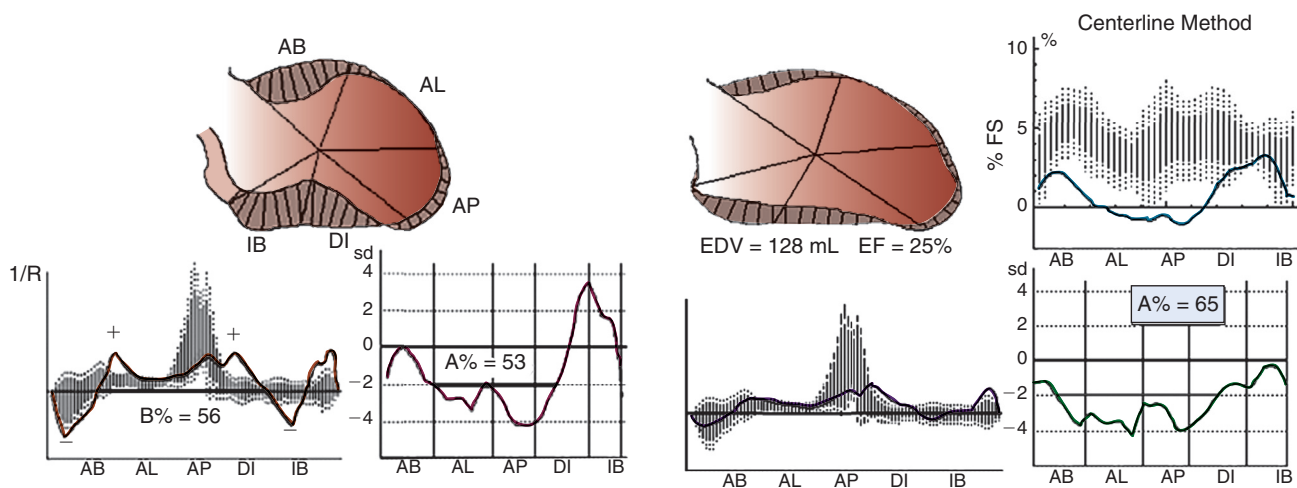


FIGURE 100-4 ■ Left ventricular (LV) curvature and regional wall motion analyses in two patients after an anterior myocardial infarction was successfully reperfused. LV shape on the left represents the true aneurysm, with the classic neck at the border between thickening and nonthickening myocardium. LV shape on the right represents the true dilated ischemic cardiomyopathy, without borders between thickening and nonthickening myocardium. Graphs below each silhouette represent the curvature analysis (*left*) and the centerline analysis (*right*). Curvature values, expressed as the reciprocal of the radius ($1/R$) on the ordinate, are measured from the aortic to the mitral plane around the ventricular perimeter. Shadowing indicates standard deviation of normal motion; the line indicates wall motion in the patient. The curvature of the apex is greater in the normal heart and reduced in the patient. Note the sharp variation of curvature values from negative (–) to positive (+) and from + to – in the patient on the left. Curvature values in the patient on the right are extremely reduced without variations (neither negative nor positive)—that is, the curvature is flattened all along the perimeter. Centerline analysis: regional wall motion of 45 chords around the LV perimeter is quantified. A%, Extent of asynergy; AB, anterobasal region; AL, anterolateral region; AP, apical region; B%, extent of curvature abnormalities; DI, diaphragmatic region; EDV, end-diastolic volume; EF, ejection fraction; FS, fractional shortening; IB, inferobasal. (From Baroni M, Barletta G: Digital curvature estimation for left ventricular shape analysis. *Image Vis Comp* 10:485–494, 1992; and Sheehan FH, Stewart DK, Dodge HT, et al: Variability in the measurement of regional left ventricular wall from contrast angiograms. *Circulation* 68:550–559, 1983.)

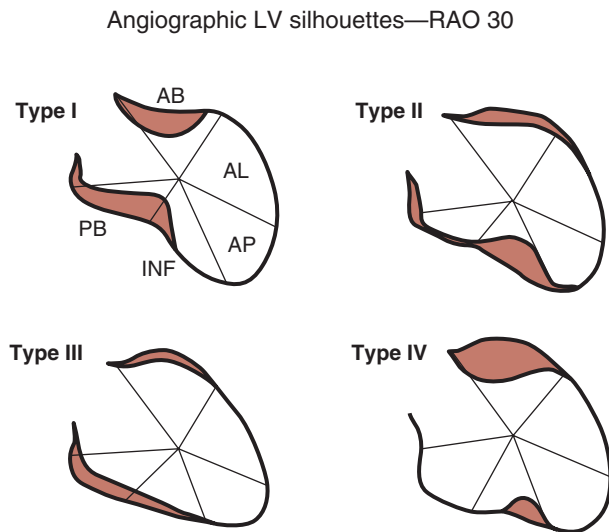


FIGURE 100-5 ■ Silhouettes of left ventricle (LV) shape abnormalities after myocardial infarction. Diagrams represent evaluation by angiography in 30-degree right anterior oblique projection. *Type 1*: LV shape is geometrically delimited by two systolic “borders” between thickening and nonthickening myocardium; the classic neck of the true aneurysm is evident. *Type 2*: The shape is characterized by only one border between thickening and nonthickening myocardium, not two borders as in type 1. *Type 3*: LV systolic shape is without borders (i.e., the curvature is flattened along the overall perimeter of the ventricle). *Type 4*: Double-site myocardial infarction (anterior and inferior). AB, Anterobasal region; AL, anterolateral region; AP, apical region; INF, inferior; PB, posterobasal region; RAO, right anterior oblique projection.

it is useful for assessing treatment results, especially after volume reduction surgery, when the results after repair of a true aneurysm look profoundly different from the results after surgery for types 2, 3, or 4. [Figure 100-6](#) shows an echocardiographic study from four patients with three types of shape abnormalities. Apical four-chamber and two-chamber views are shown.

Left Ventricular Aneurysmectomy

The first successful surgical correction of an LV aneurysm occurred in 1957.⁵¹ Denton Cooley described the technique of open resection and simple closure on cardiopulmonary bypass in 1958.⁵² This technique was the standard of the profession for the next 30 years. In 1968, Favaloro and colleagues⁵³ reported on a series of 130 patients who underwent resection for LV aneurysm, with a hospital mortality of 13%.

In 1979, Grondin and associates⁵⁴ reported on a series of 40 patients with aneurysms who were medically treated. They divided the group into those with and those without symptoms. After 10 years, survival was 90% in asymptomatic patients but only 46% in patients who were symptomatic at the time of diagnosis. The causes of death were predominantly CHF, thromboembolism, and arrhythmias. They suggested that mortality depended on aneurysm size, with large aneurysms conferring a higher risk. These reports implied that medical management resulted in improved survival, and they fostered a reluctance to use surgery to treat this disease. As recently

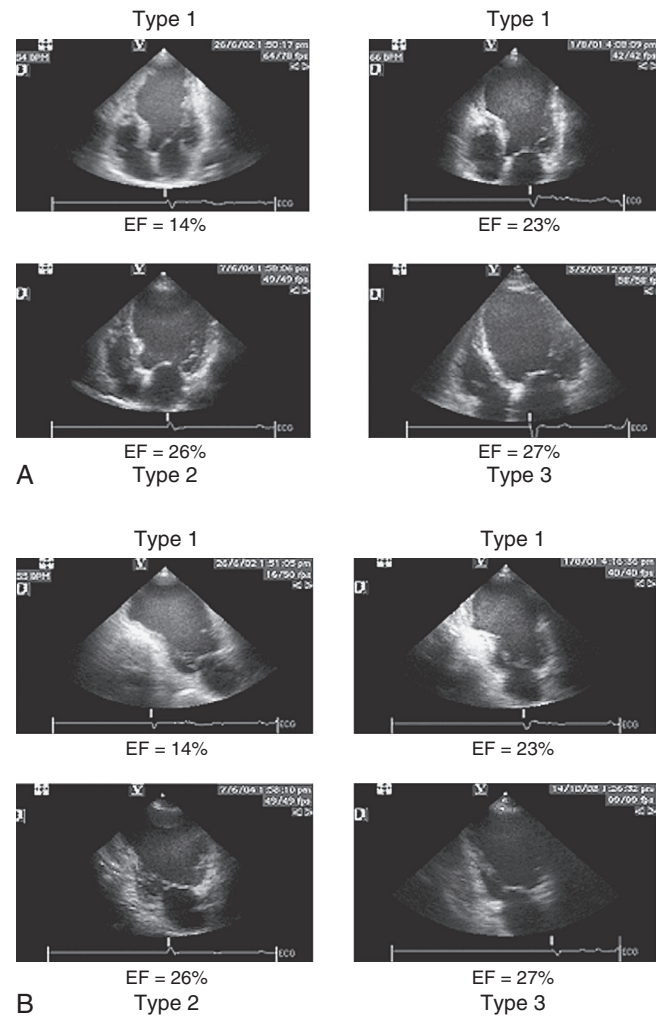


FIGURE 100-6 ■ Echocardiographic four-chamber (**A**) and two-chamber (**B**) views are shown in four patients after an anterior myocardial infarction. All patients have marked left ventricular dilation with low ejection fraction (EF), but the shapes are definitely different. Types 1, 2, and 3 are shown.

as 1983, Cohen and coworkers⁵⁵ recommended that aneurysms be resected only after maximal medical management (for heart failure, angina pectoris, recurrent thromboembolism refractory to anticoagulation, and refractory ventricular tachycardia) had failed.

In 1985, the concept of surgical repair of the LV aneurysm was altered. Newer techniques described by Jatene⁵⁶ involved excluding the dyskinetic scar when performing a circular endoventricular suture, and Dor and colleagues¹² began using an endoventricular patch to rebuild a failing ventricle after extended endocardectomy for ventricular tachycardia. The concept was to reduce the LV size and reconstruct a more elliptical cavity, treating the dilation in all its components (anterior, apical, and septal), as opposed to performing a linear resection^{57,58} of the aneurysm, which left untouched a septal dilation and created a distortion of the residual chamber. The concept of excluding all diseased tissue from the cavity was a fundamental improvement.¹² With this change in technique, a reduction was seen in hospital mortality as well as in late mortality. Dor and coworkers demonstrated that the technique is

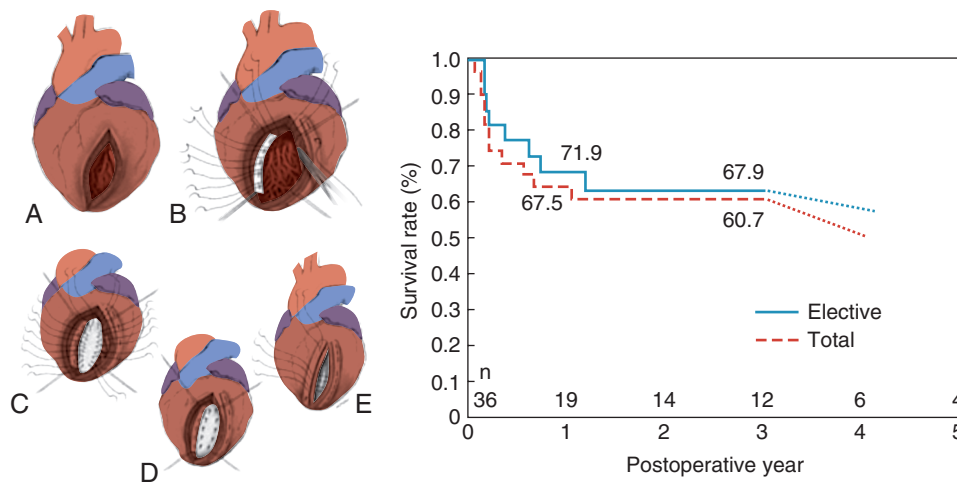


FIGURE 100-7 ■ Left, Septal anterior ventricular exclusion (SAVE) procedure, with steps A to E. See text for explanation. Right, Survival rates after the SAVE procedure were slightly higher when the surgery was elective. The number of patients (*n*) surviving at each follow-up year is shown above the abscissa. (With permission from Suma H, Isomura T, Horii T, et al: Septal anterior ventricular exclusion procedure for idiopathic dilated cardiomyopathy. *Ann Thorac Surg* 82:1344–1348, 2006.)

applicable not only to dyskinetic but also to akinetic areas. As a consequence, the indications and patient selection for volume reduction surgery have changed.⁵⁹

DIAGNOSIS AND PATIENT SELECTION FOR SURGERY

Nonischemic Cardiomyopathy

LV reconstruction for dilated cardiomyopathy (the Batista procedure, or partial left ventriculectomy) has been abandoned, primarily because of unacceptable perioperative mortality and morbidity.²⁷ One reason for its failure was that the pathology of the whole chamber was assumed to be uniform and homogeneous. However, there is evidence that the disease is nonhomogeneous, and that the septal and lateral walls differ in scarring and fibrosis.^{60,61} Thus, in the Batista operation, if a minimally diseased lateral wall was excised and a very fibrotic septum was retained, postoperative LV function was adversely affected, even if the left ventricle was properly downsized.

Therefore, Suma and colleagues⁶¹ suggested an intraoperative echocardiographic evaluation to assess the regional contractile response to preload reduction, to aid site selection, and to improve surgical results. In the intraoperative echocardiography-guided volume reduction test, the initiation of partial cardiopulmonary bypass decompresses the dilated (stretched) chamber and induces functional changes of left ventricular wall motion and thickness. Identification of wall motion changes means that the most diseased region can be selected for exclusion, leaving the more viable muscle to resume function after restoration. This idea comes from experience in restoring the ischemic left ventricle, when the scar is evident and can be excluded. However, the concept of nonhomogeneity in nonischemic cardiomyopathy is new. Suma reports that if intraoperative echocardiography shows that the septum is the weakest part, the septal anterior ventricle is excluded. Septal anterior ventricular

exclusion (SAVE) was introduced by Suma and colleagues^{26,60,61} and called *pacopexy* by Buckberg and coauthors⁶² in recognition of the contributions of Francisco (Paco) Torrent-Guasp, whose ingenious anatomic concepts defined the helical ventricular myocardial band and furthered our understanding of the relationship between structure and function.^{14,63} To make an elliptical ventricle, a long and narrow endoventricular patch is placed along the septum with interrupted mattress sutures so that the septum and a part of the anterior wall are excluded (Fig. 100-7). In patients with nonischemic dilated cardiomyopathy and advanced New York Heart Association (NYHA) class, results in terms of survival rate are promising.

When intraoperative echocardiography shows that the weakest part is the lateral wall, Suma and coworkers⁶¹ perform a partial left ventriculoplasty (Fig. 100-8).

Asynergic Areas

Appropriate candidates for LV reconstruction have suffered an MI, have a dilated left ventricle, and have an asynergic area (either dyskinetic or akinetic) of 35% or more of the ventricular perimeter. These patients have symptoms of heart failure, angina, or intractable ventricular arrhythmias.

The left ventricle should be evaluated carefully with coronary angiography (ventricular angiography in right and left anterior oblique projections), by a complete echocardiographic study (four- and two-chamber views, and parasternal long- and short-axis views), or by a magnetic resonance imaging (MRI) study. The objectives of these imaging techniques are to assess parameters for patient selection (Box 100-2), treatment planning, and follow-up.

Patients with either akinetic or dyskinetic scar may benefit from SVR, and it is the *extent* of asynergy rather than the *type* of asynergy that is related to outcome after the surgery.⁶⁴ The region to be surgically excluded should be carefully evaluated for wall motion and thickening.

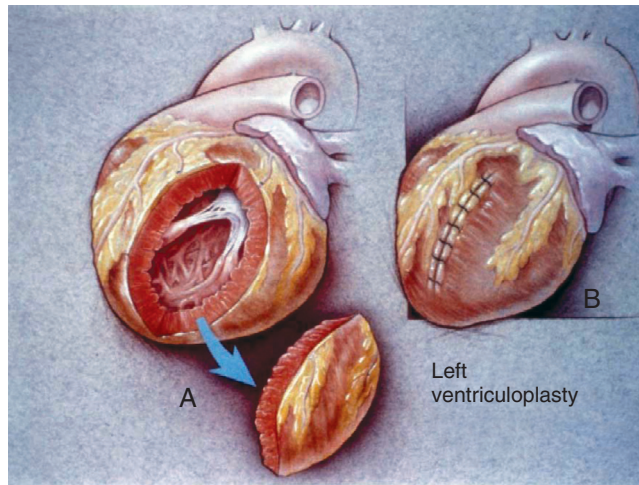


FIGURE 100-8 ■ Left ventriculoplasty, or Batista operation. **A**, Lateral partial ventriculectomy. **B**, Closure of the ventriculotomy.

BOX 100-2 Parameters for Patient Selection

- Internal dimensions of the ventricle
- Ventricular volumes (both in diastole and in systole)
- Ejection fraction
- Thickness and thickening of the wall
- Extent of asynergic area
- Status of the remote regions
- Presence or absence of viability
- Presence or absence of mitral regurgitation
- Mitral annulus size and left atrium size
- Right ventricular function

Wall motion assessment can be accomplished by LV angiography, echocardiography, or nuclear scintigraphy, but MRI provides a more accurate determination of LV volumes and EF, because it shows the epicardial and endocardial border from the base to the apex in a three-dimensional view.

LV angiography is a planar technique that shows at most two projections along the ventricle. It does not show the epicardial border, so it does not help in a calculation of thickening. However, application of the centerline method to LV angiography resulted in a reliable quantitative assessment of regional wall motion⁴⁹ with clear definition of asynergy. Echocardiography allows visualization of both the endocardial and the epicardial borders, so wall thickening and wall motion can be assessed. However, an echocardiographic method that precisely defines regional wall motion is not available. Therefore, wall motion is measured by the wall motion score index,⁶⁵ which results from a qualitative (thus subjective) evaluation of motion and is expressed by a number derived from the sum of the degree of asynergy at 16 different segments (normal, 1; hypokinetic, 2; akinetic, 3; dyskinetic, 4; aneurysmal, 5).

Echocardiography has several other limitations: (1) the LV apex is not adequately seen when the ventricle is enlarged (e.g., in dilated cardiomyopathy); (2) the endocardial border is often not clearly seen, which

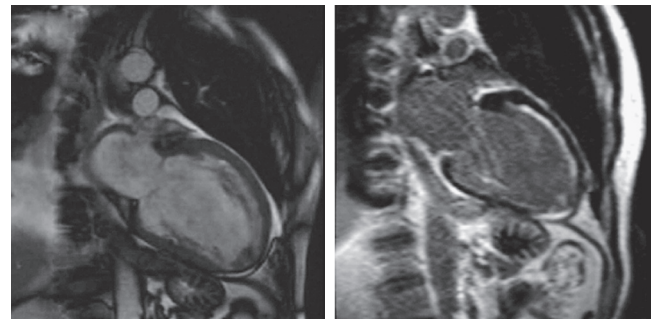


FIGURE 100-9 ■ Cardiac magnetic resonance images with late gadolinium enhancement. *Left*, Normal subject, without myocardial scar. *Right*, An example of extensive transmural myocardial scar in a patient who will undergo surgical left ventricular restoration. The two-chamber view is shown. Note the bright myocardium extending from the basal anterior region to the apex and inferoapical region.

accounts for intraobserver and interobserver variability in measuring LV volumes and EF; and (3) many patients have comorbidities (e.g., obstructive pulmonary disease, obesity) that make the echocardiography images suboptimal.

Nuclear scintigraphic methods display endocardial border motion in planar views (with radionuclide angiography, labeling the blood pool) or the myocardium, including endocardial and epicardial visualization with gated single-photon-emission computed tomography. However, such studies require the use of radioactive tracers and are not available in all cardiac centers. Also, cardiovascular MRI is not available everywhere, and some patients have contraindications to the study (e.g., claustrophobia, presence of implantable cardioverter-defibrillator). However, it allows a most comprehensive evaluation with highly accurate and reproducible measurements in a single session.⁶⁶ The greatest usefulness of cardiovascular MRI is in the detection of myocardial scar with late gadolinium enhancement. Myocardial scar tends to accumulate a significantly higher concentration of gadolinium than normal myocardium. Ten to 20 minutes after infusion, scarred regions appear very bright, whereas normal myocardium appears dark, at typical imaging times. [Figure 100-9](#) shows a patient with extensive scarring in the anterior and apical territory. A predictor of myocardial viability is the ratio of the thickness of tissue exhibiting late contrast enhancement in a segment to the total LV wall thickness in that segment. Segments with nearly transmural extent of late contrast enhancement are highly unlikely to have recovery of function after revascularization.⁶⁷

Commercially available software dedicated to LV function analysis now provides a semi-automated assessment of regional wall motion, the extent of normal and abnormal contracting myocardium, and the percentage of scarred tissue ([Fig. 100-10](#)). This allows a prediction of myocardial viability without a need for pharmacologic stress. Cardiovascular MRI also allows quantification of regional deformation by radionuclide tagging and calculation of strain and strain rate, which can be particularly useful for examining the remote regions and the apical twisting and untwisting.⁶⁸ Torsion and twisting and

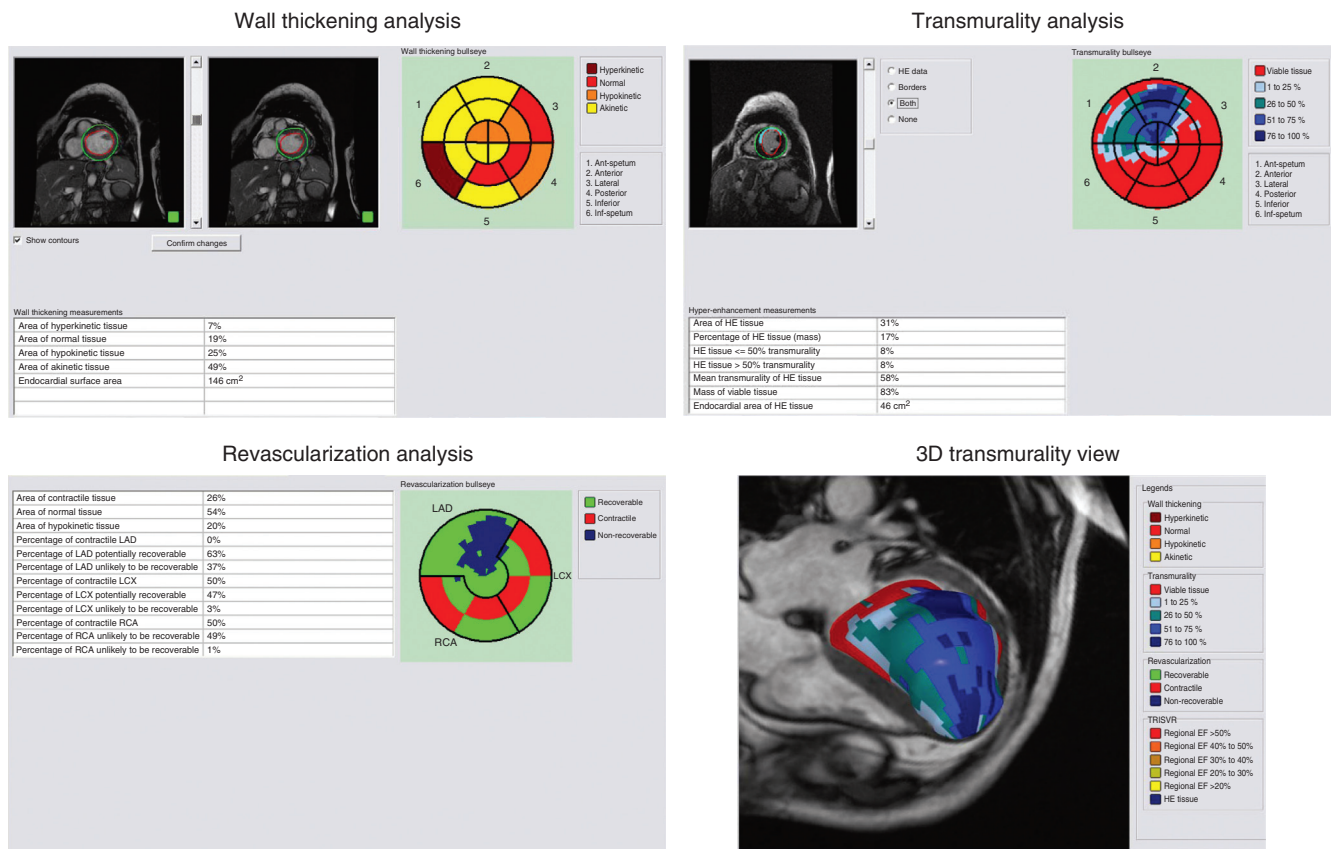


FIGURE 100-10 ■ Analysis of cardiac function using MARISA software (Magnetic Resonance Imaging System Analysis [Chase Medical, Richardson, Texas]). *Top left*, Wall motion analysis quantified as normal, hyperkinesia, hypokinesia, and akinesia. The percentage distribution of asynergy is calculated. *Top right*, Assessment of scar transmurality with late gadolinium enhancement. The extent of the transmurality from 0% to 100% is color coded, and the percentage of scarred tissue is calculated. *Bottom left*, Analysis of viability: the green area represents potentially viable myocardium that may improve with revascularization; the blue area represents the transmural, nonviable scar. *Bottom right*, Three-dimensional reconstruction of the left ventricle superimposed on the four-chamber view. The extent of the scar as evaluated by late gadolinium enhancement is shown.

untwisting movements of the apex (as opposed to the base) greatly contribute to blood ejection and to maintaining a good pump function; these mechanisms are reduced or even lost after an anterior MI, resulting in further impairment in cardiac function. Cardiovascular MRI tagging, however, is not routinely performed in clinical practice but is confined to research studies because the data analysis is laborious and time consuming and requires intensive computation. With the development of a tissue Doppler imaging technique and the two-dimensional “speckles” or endocardial border tracking analysis,^{69,70} it is easier to measure systolic and diastolic deformation either longitudinally or radially. Vector direction gives the clockwise and counterclockwise directions of contraction, which is particularly useful for assessing torsional mechanics at the apical level. An analysis of untwisting also provides information on diastolic function, at least on rapid filling.

Status of Remote Regions

The quantification of remote regions is performed to determine whether a patient is a candidate for an SVR procedure, and these regions are often not evaluated by

conventional imaging studies. After an anterior MI, remote regions may show hypokinesia or even akinesia resulting from critical coronary disease in the right or left circumflex coronary artery (hibernating myocardium), or remote myocardium may be dysfunctional in the absence of coronary stenosis because of the high local tension that reduces shortening. Several years ago, we demonstrated³² that SVR induced an improvement in remote nonischemic regions in patients with anterior infarction; in that study, we excluded patients with significant stenosis in the right and left coronary arteries. Nowadays, with cardiovascular MRI, we can predict the recovery of function in ischemic, hibernating areas that will benefit from concomitant coronary artery bypass grafting (CABG), and we can also predict whether dysfunctional, nonischemic segments may recover after volume reduction. Therefore, we propose a term other than *hibernating* or *stunned* for dysfunctional nonischemic myocardium in dilated cardiomyopathy—*exhausted myocardium*—which implies recovery of function if the hemodynamic burden that imposes a high wall tension is relieved by SVR.

On the other hand, the detection of scar in remote regions by late gadolinium enhancement may predict an unsatisfactory pump improvement and a higher mortality

rate after SVR. A significant scarring in a myocardial segment precludes, in fact, the likelihood of postoperative contractile recovery of that segment.

In summary, extensive preoperative imaging studies are necessary for selecting patients, planning treatment, and evaluating the results of SVR. Cardiovascular MRI is the best option, because it provides the surgeon with all the necessary information for planning an effective, comprehensive surgery tailored to the individual patient, and all the information can be obtained in a single examination taking less than 1 hour.

Finally, cardiologists, radiologists, and surgeons must collaborate to improve knowledge about patient selection and to achieve an optimal surgical outcome.

SURGICAL VENTRICULAR RESTORATION FOR ISCHEMIC CARDIOMYOPATHY

Left ventricular reconstruction by endoventricular circular patch plasty repair was described and proposed by Dor and colleagues in 1984¹² for rebuilding the left ventricle after an MI, either during the acute phase (surgical treatment of septal rupture or refractory ventricular arrhythmias according to the Harken technique⁷¹) or in patients with chronic MI and with LV asynergy (akinesia or dyskinesia) to exclude all the akinetic nonresectable areas (e.g., septum and posterior wall). In addition, a complete coronary revascularization is achieved and mitral repair or replacement is performed if needed.⁷²

The term *surgical ventricular restoration* includes operative methods that reduce LV volume and restore ventricular elliptical shape. The concept of reducing wall stress through the surgical restoration of LV cavity size and geometry is the guiding principle behind this innovative technique.

Since the first description by Dor and colleagues,¹² the procedure has been adopted by many surgeons, but it is not widely used because surgeons have been unwilling to incise and exclude the akinetic normal-appearing segments often encountered after early reperfusion. Instead, CABG is performed, and the nonfunctioning akinetic muscle containing deeper scar is left undisturbed.⁷³

The technique has not been standardized, and surgeons use essentially four variations of LV reconstruction to exclude the septum. These include a linear closure by

Jatene,⁵⁶ a modified linear closure by Mickleborough,⁷⁴ a circular closure with a patch by Dor and Menicanti,⁷⁵ and a double cerclage closure without a patch by McCarthy.⁷⁶ All of these techniques involve an incision into the diseased anterior wall, an exclusion of the entire diseased segment, and a reduction in ventricular cavity size. In the majority of patients, reconstruction is done on the anterior portion of the left ventricle. However, reconstruction has also been performed on the posterior wall after circumflex or right coronary artery occlusion. Most of these patients undergo concomitant coronary artery bypass, and many also undergo mitral valve repair.

Surgical Details of Anterior Surgical Ventricular Restoration

Surgical LV restoration as performed since 2001 by our group at the San Donato Hospital in Italy is conducted on the arrested heart with antegrade crystalloid or cold-blood cardioplegia. CABG is first performed, as completely as possible, almost always on the left anterior descending coronary artery, to preserve the upper part of the septum and to guarantee complete revascularization. The ventricle is opened at the middle of the scar on the anterior wall, with an incision parallel to the left anterior descending artery, starting from the midportion and proceeding toward the apex. The internal part of the cavity is examined, and thrombi are removed if present. The mitral valve is repaired, when necessary, through the ventricular opening with a double-armed stitch at the posterior annulus, from trigone to trigone, and the mitral orifice is undersized with a 26-mm valve sizer.⁷⁷

In July 2001, we introduced the Mannequin (Chase Medical, Richardson, TX), which we fill with 50 to 60 mL of saline per square meter of the patient's body surface area to optimize the size and shape of the new ventricle. This TRISVR technique is a refinement of the Dor technique that introduced a sizer device in 1998, which allows standardization of the procedure. The device is inserted into the LV cavity after an incision is created (Fig. 100-11) and then carefully inflated with saline when it is seated properly in the cavity, to avoid the risk of inflating the device when it is in the mitral valve. The new apex will be placed at the apex of the Mannequin, and this is the starting point for the 2/0 endoventricular circular suture. The suture is carried

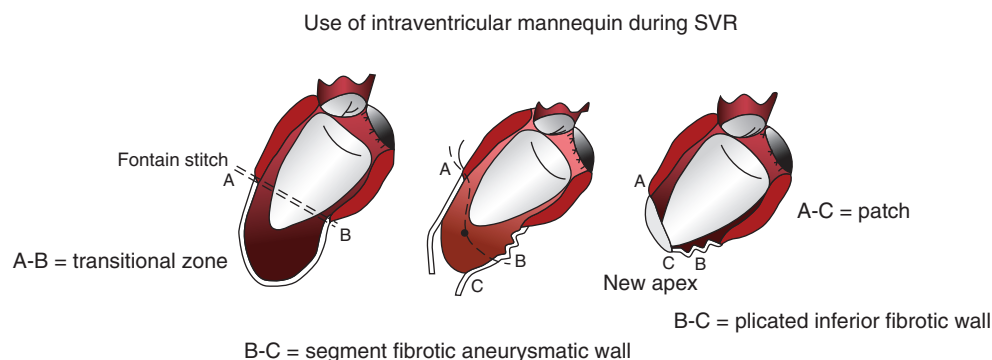


FIGURE 100-11 ■ The use of the intraventricular mannequin during surgical left ventricle reconstruction. SVR, Surgical ventricular restoration.

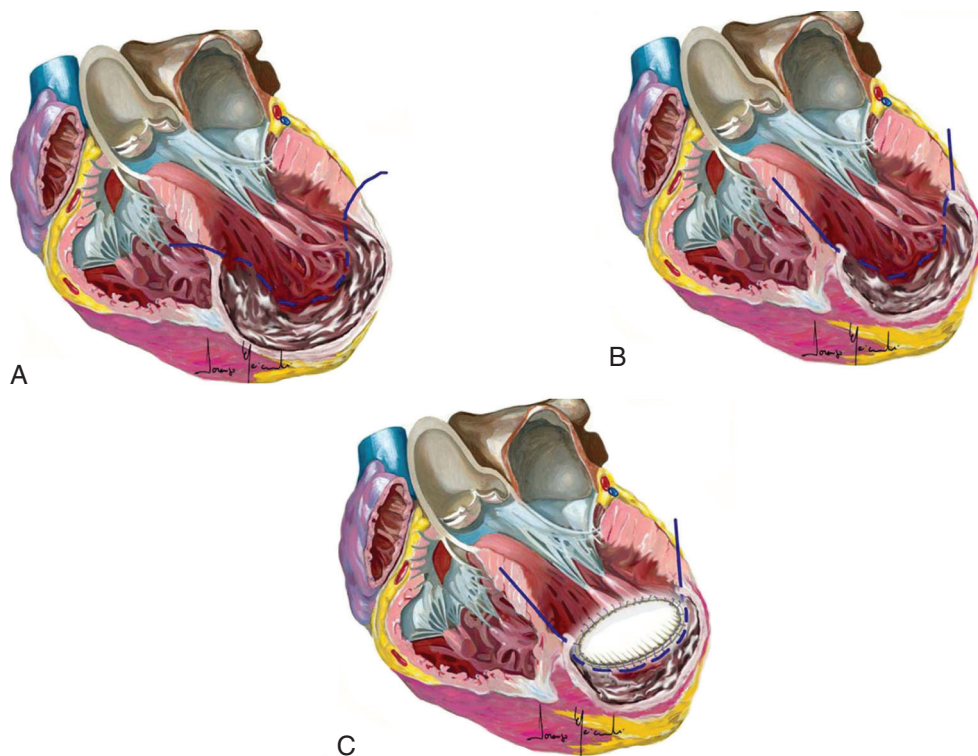


FIGURE 100-12 ■ Sequence of a suboptimal endoventricular suture. **A**, Suturing is done on a plane parallel to the mitral valve. **B**, The suture is tightened. **C**, The patch is inserted, and its resultant position is parallel to the mitral valve.

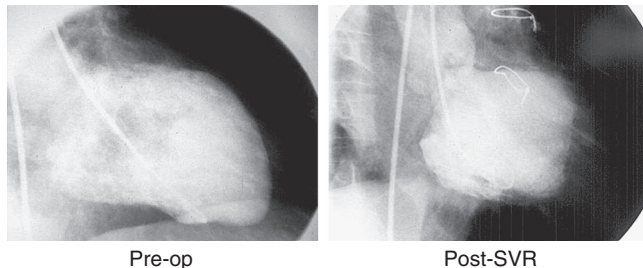


FIGURE 100-13 ■ Angiography preoperatively (Pre-op) and postoperatively after surgical left ventricular reconstruction (Post-SVR). *Left*, Before surgery. *Right*, After surgery. Note the spherical left ventricular chamber achieved after surgery.

deep toward the septum and up toward the aortic outflow tract on an oblique plane to reconstruct an elliptical shape, not a spherical chamber. The suture is then brought toward the lateral wall, and back to the apex, and tightened on the Mannequin. The plane of the closure should not be parallel to the mitral valve (Fig. 100-12). If the closure plane is parallel to the mitral valve, the result is a spherical chamber (Fig. 100-13). The shape of the device is appositely conical with a physiologic short-to-long-axis ratio to reconstruct a more physiologic, elliptical shape. After positioning the new apex, the surgeon places the circular stitches at the transitional zone (between the scarred and the sound tissue). When the ventricle is not very enlarged, the Mannequin reduces the risk of creating a residual cavity that is too small. It is also useful when the infarcted region is not clearly demarcated, as occurs in dilated cardiomyopathy (type III silhouette [see Fig. 100-5], as described by our group).⁵⁰ In this circumstance, the transitional zone between

BOX 100-3 Surgical Pitfalls

- Incorrect indications
- Incomplete revascularization
- Embolism
- Cavity dimension: too large or too small
- Cavity shape: spherical or distorted

scarred and nonscarred myocardium is not well defined, and the Mannequin allows rebuilding of the ventricle in an elliptical way with a proper residual size. Box 100-3 shows surgical pitfalls during SVR.

The use of the Mannequin is a refinement of the technique introduced by Dor in 1998 using a toy balloon. The size of the device is chosen by multiplying the body surface area of the patient by 50 or 60 mL. This choice is empirical: we prefer to leave a residual chamber with a normal volume (52 ± 13 mL/m² in a series of 52 normal subjects from our echocardiography laboratory).²³

The technique used by Menicanti is shown in Figure 100-14. In some circumstances, the inferoapical region is dilated after an anterior MI because of left dominance of the anterior descending artery. When the device is in place during reconstruction, a gap between the transitional zone and the position of the new apex is evident; in such cases, we thread a direct suture from inside to reduce the inferior dilation and to lift up the new apex, bringing the lateral wall toward the septum (Fig. 100-15). Usually, this suture runs for 1 to 1.5 cm. In chronic anterior MI, the LV apex, in addition to being enlarged, is also shifted inferiorly and posteriorly (Fig. 100-16), and this alters the direction of flow toward the aorta. Thus,

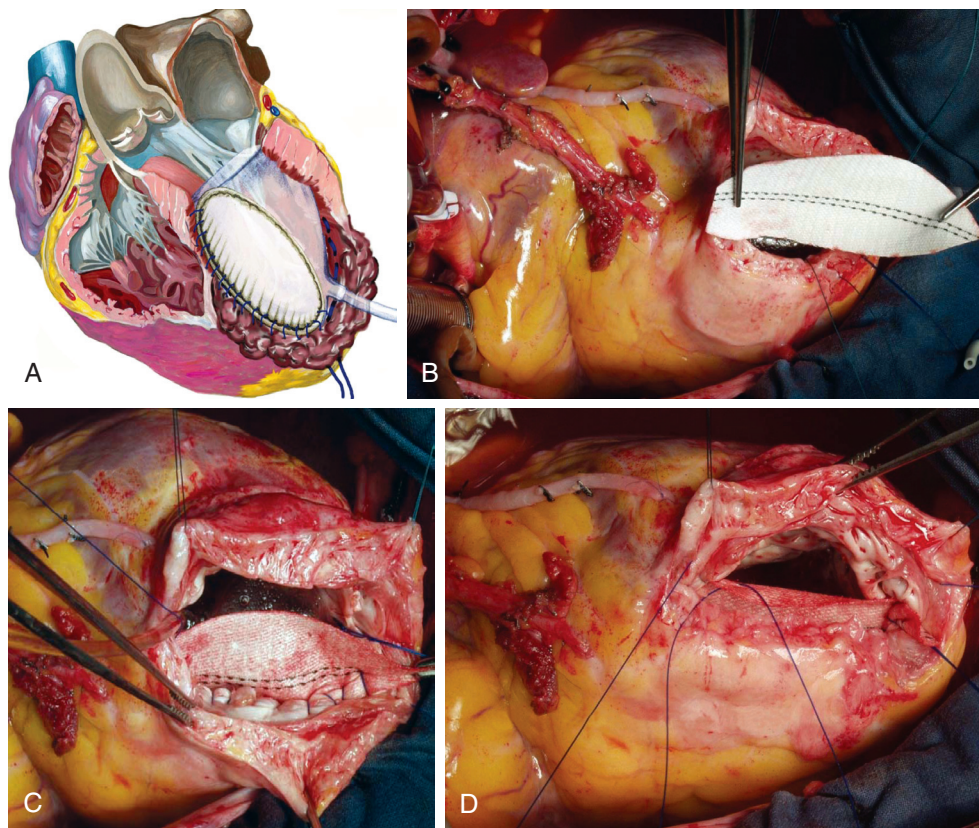


FIGURE 100-14 ■ **A**, Schematic representation of surgical left ventricular reconstruction as performed by Menicanti. The device is inserted in the correct position, and the patch is sutured when the device is in place and parallel to the septum (i.e., oblique to the aorta). In photographs from the operating room (**B-D**), mammary anastomosis to the left anterior descending artery is completed, as is the venous sequential graft. **B**, The Dacron patch is prepared with an elliptical shape and appropriate size. **C**, The patch is trimmed during the suturing. **D**, Suturing of the completed patch.

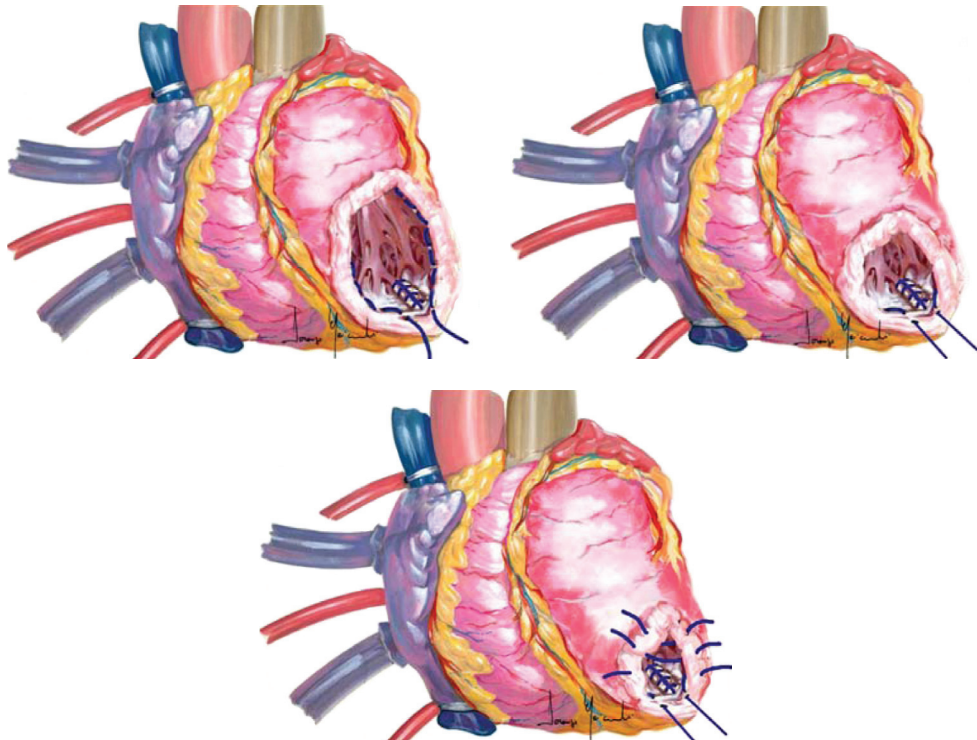


FIGURE 100-15 ■ To reduce the inferior wall dilation, a direct suture is brought from inside. In this way, the lateral wall is approximated to the septum, and the new apex is lifted up to a more anterior position.

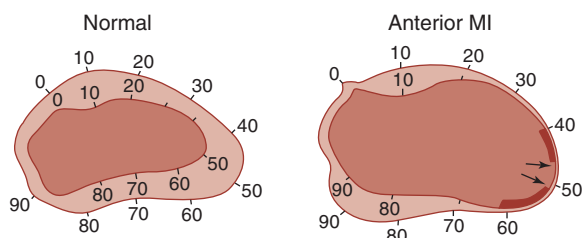


FIGURE 100-16 ■ The shape of the left ventricle, obtained by Fourier analysis of curvature as seen by 30-degree right anterior oblique angiography. Reconstructed silhouettes are averages for normal subjects and for patients with anterior myocardial infarction (MI). The apex in the patient silhouette is enlarged (less conical) and shifted downward and toward the mitral plane in both systole (inner line) and diastole (outer line). Numbers refer to the 90 chords as identified by the centerline.⁴⁹ (From Baroni M, Barletta G: Digital curvature estimation for left ventricular shape analysis. *Image Vis Comp* 10:485-494, 1992.)

it is very important for the surgeon to give the apex a conical form in an anterior position, because this reestablishes the correct blood vortex at the apex and a more physiologic direction of flow.

The Mannequin is then removed and the opening of the ventricle is closed with a direct suture if it is less than 3 cm, or it is closed with an elliptical synthetic patch if it is greater than 3 cm. The suture attaching the patch is continuous and conducted in an everting manner, starting from the deeper septal part of the opening, going toward the apex, and then up again toward the lateral wall.

Mitral Valve Repair during Surgical Ventricular Restoration

We have adopted a new surgical technique to repair the mitral valve during SVR with CABG. Because our technique reduces the dimensions of the mitral annulus, we avoid an atrial approach to the annulus and access it through the same ventricular incision that is used to perform SVR (Figs. 100-17 and 100-18). After the LV cavity is opened, each papillary muscle head is identified, and the mitral valve leaflets and chords are evaluated. The posteromedial fibrous trigone is visualized, and a pledgeted 2/0 polyester suture is placed from the ventricular side to the atrial side. The two arms of this suture progress with a running stitch toward the anteromedial trigone, carrying it to a few millimeters from the mitral annulus with biting sutures into atrial and ventricular muscle. The suture arms pass through the anterolateral trigone, and a second pledget is inserted. The entire posterior annulus becomes completely bounded by this suture. To undersize the mitral annulus and avoid valve constriction, a 26-mm sizer is introduced into the mitral orifice, and the suture is tied against the second pledget.

We analyzed the shapes of the left ventricle in a series of patients with MR undergoing SVR and compared them with a series of patients without MR. Quantitative shape analysis showed a flattening of the inferior curvature in patients with MR (Fig. 100-19), as well as reduced regional fractional shortening by centerline analysis. Patients with MR also had a less concave systolic inferior

Mitral valve repair by endoventricular approach

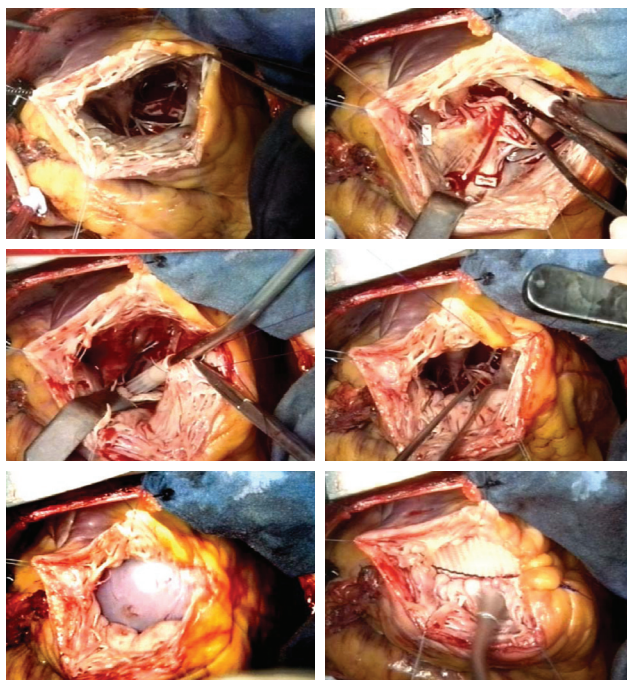


FIGURE 100-17 ■ Intraoperative mitral valve repair via the ventricular approach. Note the orientation of the patch at the end of the procedure: it is placed very deep into the septum and oblique to the aorta.

segment. Furthermore, overall shape differed significantly, with more spherical chambers in patients with MR than in those without (Table 100-2). Between July 2001 and April 2008 at the San Donato Hospital, 116 of 458 patients undergoing SVR with CABG had an associated mitral repair. Operative cardiac mortality was 12.9% (15/116), significantly higher than the 4.7% mortality without mitral repair (16/342). Figure 100-20 shows geometric features of the mitral valve before and after surgery. We focused on anterior infarctions to avoid the changes in the submitral apparatus that occur with inferior infarction, and because LV shape changes that occur in anterior infarctions are the primary determinants of functional MR in patients with severe heart failure. Increased sphericity plays a central role in the development of functional MR, because it progressively widens the LV transverse diameter; our findings (see Table 100-2) confirm this causation.

The decision for valve repair is based on preoperative measurements of ventricular volume, annular size, and the degree of MR. Formerly, we repaired moderate or severe MR (grade 3 or 4+) and mild MR (grade 2+) if the annulus was dilated (>38 mm). In a recent series of patients with mild MR treated with SVR but without mitral repair,⁷⁸ the outcome was excellent in terms of improvement in function and survival. Thus, successful surgical treatment of functional MR depends on reestablishing normal leaflet coaptation by changing the architecture of the mitral annulus or of the ventricular wall, or both. Consequently, surgical interventions include coronary revascularization, reducing mitral annulus, and restoring LV shape to reduce tethering and

ventricular volume. The mitral annulus can be reduced with a prosthetic ring via the atrial approach or by annular suture of the posterior ring via a ventricular approach.⁷⁷ Downsizing the ring is essential to optimize the extent of coaptation, as emphasized by Bolling and colleagues.⁷⁹

Surgical Details of Posterior Surgical Ventricular Restoration

Limited data are available on surgical repair for LV dilation resulting from inferior MI.⁸⁰ Changes in LV

geometry vary with the site of coronary occlusion—for example, the classic posterior aneurysm with a bulging of inferior wall and good contraction in the remaining cavity, or global dilation of the LV chamber with regional wall dysfunction at the inferior and posterobasal region. Although both conditions can lead to secondary MR, it happens more frequently in the global dilation because of the enlargement of the transverse diameter and the globular shape. Surgery for the posterior aneurysm generally involves a patch to close the neck of dilation, but the treatment of global dilation of the inferoposterior wall is more complex, especially because of the relationship between the scar and the dilation with respect to the papillary muscles.

A very short incision is made in the scar, or where a depression is evident during venting. Through this incision, the position of papillary muscles is carefully checked. After an inferior MI, there are two possibilities: (1) the dilation is mainly between the two papillary muscles or (2) the dilation is between the posteromedial papillary muscle and the septum, which is deeply involved (Fig. 100-21). We use two techniques for LV dilation after an inferior MI. The first, shown on the left in Figure 100-22, begins with opening the scarred wall at the level of the scar or at the level of the collapsed area, parallel to the posterior descending artery. A continuous 2/0 Prolene suture reapproximates the two papillary muscles

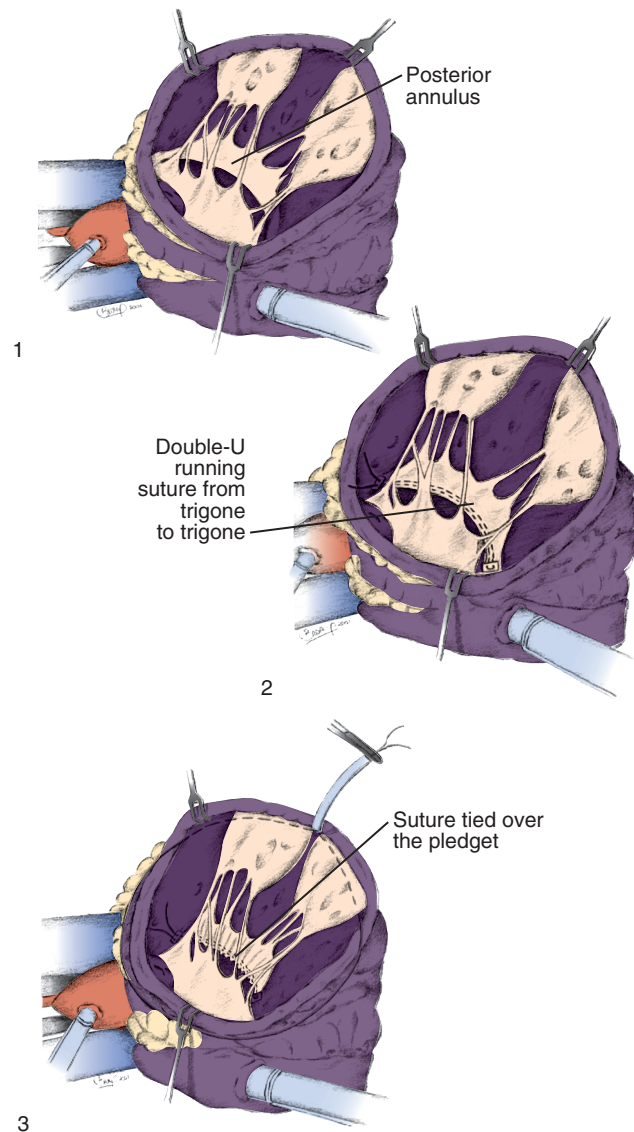
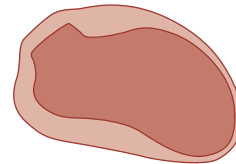


FIGURE 100-18 ■ Schematic representation of mitral repair through a ventricular opening.

No mitral regurgitation



Mitral regurgitation

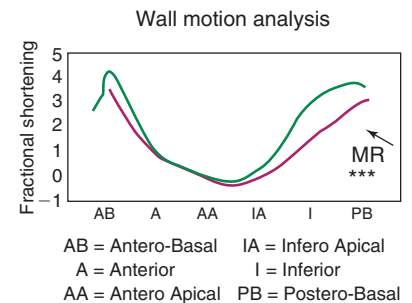
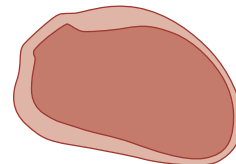


FIGURE 100-19 ■ Reconstructed left ventricle shapes by Fourier analysis. The inferior curvature is flattened in patients with mitral regurgitation (MR), and regional wall motion (as evaluated by the centerline method) is reduced in these patients at the inferior and posterobasal regions. *** $P = 0.001$. (From Sheehan FH, Stewart DK, Dodge HT, et al: Variability in the measurement of regional left ventricular wall from contrast angiograms. *Circulation* 68:550–559, 1983.)

TABLE 100-2 Relationship between Left Ventricular Sphericity and Degree of Mitral Regurgitation

	No MR	MR Grade 1 to 2+	MR Grade 3 to 4+	ANOVA
Sphericity index: diastole	0.49 ± 0.08	0.55 ± 0.09	0.60 ± 0.10	0.0001
Sphericity index: systole	0.40 ± 0.09	0.47 ± 0.11	0.54 ± 0.11	0.0001

ANOVA, Analysis of variance; MR, mitral regurgitation.

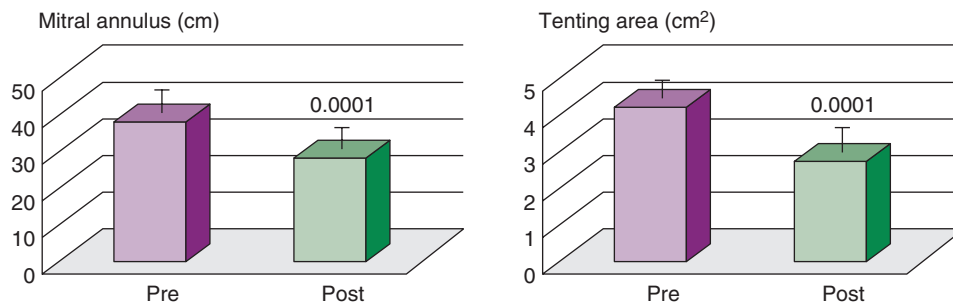


FIGURE 100-20 ■ Improvements in mitral geometry seen after surgical left ventricular reconstruction plus mitral repair. Improvements in size of annulus and tenting area after surgery; $P = 0.0001$.

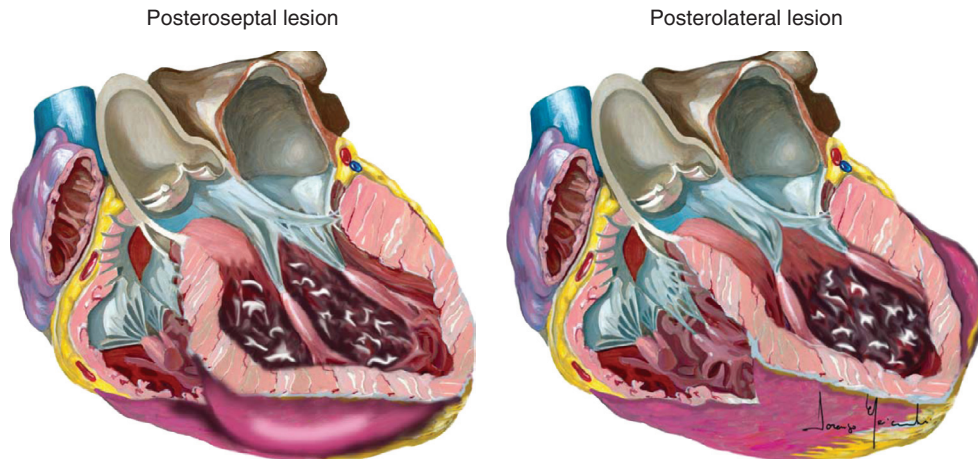


FIGURE 100-21 ■ Two types of lesions occur after inferior myocardial infarction, as recognized by the position of the papillary muscles after the incision at the posterior scar. *Right*, The dilation is between the two papillary muscles. *Left*, The dilation is between the posteromedial papillary muscle and the septum.

and excludes the entire dilated zone. The suture is started at the beginning of the dilation (sometimes just at the mitral annulus) and continues toward the apex. In the second procedure (see Fig. 100-22, on the right), the wall is opened, and then the continuous suture is brought past the posteromedial papillary muscle, bringing the posterior wall against the septum. In this way, when MR is determined only by the displacement of the posteromedial papillary muscle, mitral insufficiency is repaired. Our results from about 125 patients who received posterior SVR show a significant decrease in end-diastolic and ESV and an improvement in EF and clinical status. Operative mortality rate is higher than in anterior SVR (7.2%) and survival rate is significantly lower.⁷⁷

OUTCOMES

Many groups have found the results of SVR to be favorable and consistent.^{15,59,81-104} In Table 100-3, a summary of the best-evidence studies, we have recorded the number of patients enrolled, the number of associated mitral procedures, the operative (30-day) mortality, and improvements in ESV and EF. Follow-up is also reported, when available.

The largest reported series (from the RESTORE group, a team of cardiologists and surgeons from 12 centers on four continents¹⁰²) and, more recently, a

single-center experience from Menicanti and associates⁹⁸ reported on SVR for 1198 and 1161 patients with anterior MI, respectively, and demonstrated that SVR improves symptoms and long-term survival in patients with ischemic cardiomyopathy and severe heart failure. The beneficial effects of SVR in improving cardiac function and in reducing LV volume, ventricular arrhythmias, and MR has been largely accepted.^{59,72,85-89,92,95,97} A reduction in mechanical intraventricular dyssynchrony has also been demonstrated.¹⁰⁵⁻¹⁰⁷

The RESTORE group (Reconstructive Endoventricular Surgery returning Torsion, Original Radius and Elliptical shape to the left ventricle), organized by Gerald Buckberg in 1998, is the first international team to find evidence that for patients with CHF, rebuilding the heart by addressing a geometric solution (to bring back to normal the shape and size of the damaged ventricle) is an effective method to treat ischemic dilated cardiomyopathy.¹⁰⁸

Data reported in the literature are in close agreement: SVR results in a significant acute improvement of systolic function, significant acute reduction of mechanical dyssynchrony, and significant reduction in wall stress. Although data are more limited for changes in diastolic function, these changes are comparable with the changes in patients with preserved LV function who undergo elective CABG.^{109,110} The acute beneficial effects on systolic function are largely maintained in the long term, and

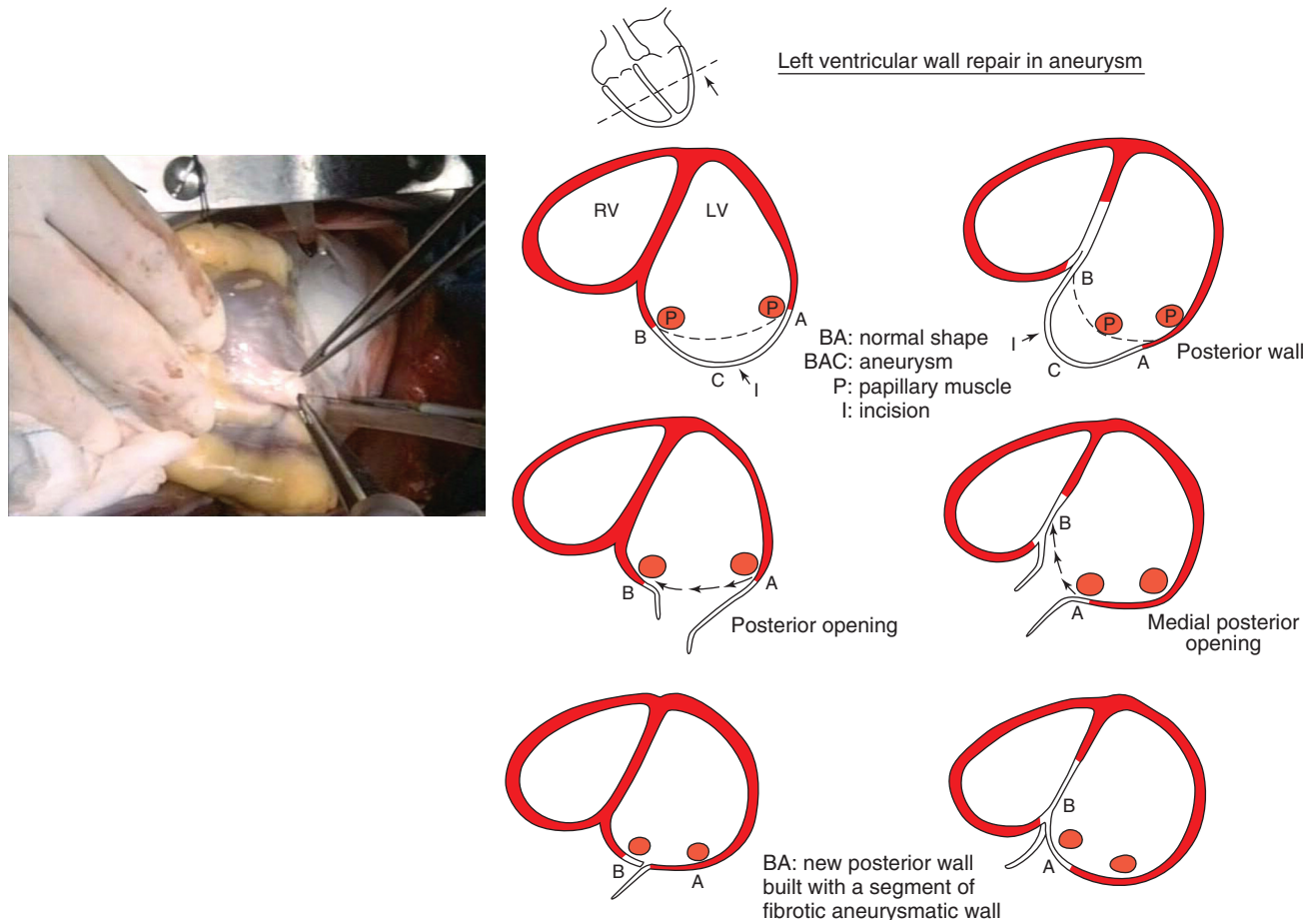


FIGURE 100-22 ■ Two techniques of posterior repair of the left ventricle of a patient with an aneurysm. The image shows the posterior wall of the ventricle. The diagrams show the two techniques, from top to bottom on the left, and from top to bottom on the right. *Left*, After the opening of the scarred wall, the base of the papillary muscles is identified, and the dilation is observed to be mainly between the two papillary muscles. A 2/0 Prolene suture is started at the beginning of the dilation (sometimes at the mitral annulus) and continues toward the apex, excluding all the damaged tissue from the cavity. *Right*, After the wall is opened, a continuous suture is threaded past the posteromedial papillary muscle, bringing the posterior wall against the septum. In this way, when mitral regurgitation results from the displacement of the posteromedial papillary muscle, mitral insufficiency is repaired. LV, Left ventricle; RV, right ventricle.

SVR induces a significant reverse-remodeling associated with clinical improvement and improved survival. Interestingly, the entity of EF improvement and of LV volume reduction is uniform in all the reported series, varying from +6 to +15 (absolute points) for EF, and from 30% to 45% reduction for LV ESV (see Table 100-3). Also, survival rates appear uniform among different studies, being an average of nearly 80% at 5 years and 60% at 10 years. Survival rates in patients with advanced NYHA functional class are particularly gratifying, being 88% at 3 years in NYHA class 3 and 68% in NYHA class 4, as reported by Williams and associates,⁸⁴ and 50% at 5 and 10 years, as reported by Menicanti and colleagues (Fig. 100-23).⁹⁸ Moreover, the rate of rehospitalization for heart failure is reported to be low.^{98,102} These results are similar to those reported at 6 months after heart transplantation, and a study from Cotrufo and coworkers showed no differences in mortality, clinical improvement, and survival rate between a comparable group of patients with dilated ischemic cardiomyopathy who underwent either SVR or heart transplantation.¹¹¹

Surgical Ventricular Restoration and Diastolic Function

Data on diastolic function after SVR are limited. Experimental studies and theoretical considerations suggest that SVR induces diastolic dysfunction.¹¹² The effect of SVR on diastolic function was recently the focus of two studies by Tulner and colleagues.^{104,106} The effects of SVR on ventricular function and the related effects of diastolic dysfunction on outcome after SVR have not been well studied until recently. However, a study by Tulner and colleagues¹⁰⁶ (and see the accompanying editorial by Burkoff and Wechsler¹¹²) was the first in which the diastolic pressure-volume relationship was measured in patients before and after SVR. They showed that diastolic compliance appears to be reduced early after SVR, leading to a reduction in stroke volume. These effects may result from postoperative edema, because pulmonary pressures late after SVR are significantly reduced.

The factor most likely to affect diastolic function is the size of the residual LV cavity. Excessive volume

TABLE 100-3 Best-Evidence Studies of Surgical Left Ventricular Reconstruction

Author	Patients (N)	Mitral Valve Procedures (N)	Early Mortality (%)	ESV (mL/m ²) (Change)	EF Change (Absolute Points)	Follow-Up (% Survival)
Sartipy ⁹⁵	101	29	7.9	N/A	27 ± 9 to 33 ± 7 (+6)	120 mo (1 yr, 88%; 5 yr, 65%; 10 yr, 57%) 24 mo (95%)
Maxey ⁹⁵	95 (56 with SVR vs. 39 CABG alone)	14	0	N/A	22 ± 11 to 32 ± 9 (+10)	
Mickleborough ⁸⁶	285	6 (3 replacements)	2.8	N/A	Not reported	120 mo (1 yr, 95%; 5 yr, 82%; 10 yr, 62%) 5 yr (69%)
Athanasuleas ¹⁰²	1198	22% repairs 1% replacements	5.3	80 ± 51 to 57 ± 34 (-46%)	29 ± 11 to 39 ± 12 (+10)	
Multicenter Registry	870	61/388 (16%) not reported in the overall series	7.3	N/A	Not reported (+10 to +15)	N/A
Di Donato ⁸⁷	207	N/A	8.1	112 ± 64 to 46 ± 26	35 ± 13 to 48 ± 12	60 mo (1 yr, 98%; 5 yr, 82%)
Cirillo ⁹⁸	69	12/69 (17.3%) (1 replacement)	4.3	100 ± 35 to 68 ± 15 (-32%)	32 ± 4 to 44 ± 7 (+12)	24 mo (92%)
Menicanti ⁹⁸	1161	90/488 (18%) not reported in the overall series (2 replacements)	4.7	145 ± 64 to 88 ± 40 (mL) (-39%)	33 ± 9 to 40 ± 10 (+7)	120 mo (62% at 10 yr)
Ribeiro ¹⁰⁰	137 (significant MR excluded) 34 patients, CABG alone	None	2.6	107 ± 19 to 63 ± 17 (-41%)	34 ± 6 to 44 ± 5 (+10)	24 mo (95%)
Yamaguchi ⁸¹	48 patients (CABG vs. CABG + SVR)	11/48 (23%)	?	112 ± 21 to 94 ± 28 in CABG alone 137 ± 24 to 65 ± 19 in CABG + SVR	21 ± 6 to 28 ± 7 in CABG alone 24 ± 7 to 42 ± 9 in CABG + SVR (+18)	5 yr: (53% ± 11% in CABG alone; 90 ± 10 in CABG + SVR)
O'Neill ⁸³	220	108/220 (49%)	1.0	120 ± 46 to 77 ± 26 (-36%)	21 ± 7 to 25 ± 9 (+4)	60 mo (1yr, 92%; 3 yr, 90%; 5 yr, 80%)
Conte ⁹¹	78	17 repairs (22%) 6 replacements (7.7%)	7.7	116 ± 59 to 66 ± 23 (-43%)	23 ± 9 to 29 ± 10 (+6) Patients in NYHA IV	36 mo (88% NYHA III; 68% NYHA IV)
Hernandez ¹⁰³	731	Not reported	9.4	N/A	N/A	N/A
Multicenter Registry (STS)						

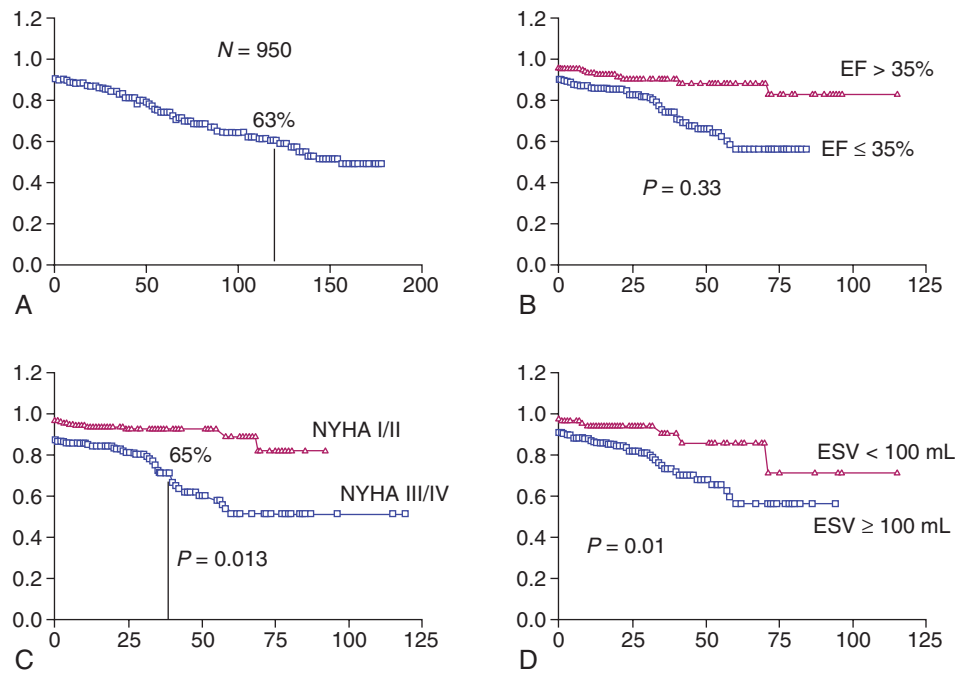


FIGURE 100-23 ■ Kaplan-Meier survival curve in a large series of patients from the San Donato Hospital in Italy. **A**, Survival in the overall population. **B**, Survival by ejection fraction (EF) ≤35%. **C**, Survival by New York Heart Association (NYHA) functional class. **D**, Survival by end-systolic volume (ESV) ≥100 mL.

reduction probably causes diastolic compliance to shift farther to the left on the pressure–volume curve than end-systolic elastance, thereby producing diastolic heart failure. This may have been the genesis of the unsatisfactory results obtained with standard linear aneurysm repair.¹¹³ With the introduction of sizing devices for LV reconstruction, the risk of leaving a too-small residual cavity is almost absent, but there is currently no objective evidence to support the selection of a particular postoperative size.

In an earlier paper,¹⁰⁵ we reported changes in diastolic function after SVR in a series of 30 patients evaluated by pressure–volume loops. We found significant improvement early after surgery in filling pressure and in parameters of diastolic function (peak filling rate, time to peak filling rate, and tau) (Fig. 100-24), as well as in diastolic pressure–volume curves (Fig. 100-25).

In a recent paper, we reported that end-stage or restrictive diastolic dysfunction (i.e., the ratio of early to late diastolic filling is >2) was associated with early mortality in 254 patients undergoing SVR.⁹⁸ Our group also made an interesting observation in regard to the relationship between diastolic worsening (defined as an increase of at least one class level of diastolic filling pattern) and the preoperative LV shape: patients with nonaneurysmal lesions and a higher sphericity index tended to have a higher rate of worsening of diastolic function.¹¹⁴ Furthermore, we have analyzed time-course changes in diastolic function after SVR and found that at follow-up (average time from surgery, 8 months), the majority of patients did not have significant changes in diastolic function, but 20% developed a restrictive pattern. Figure 100-26 compares the preoperative characteristics of patients who developed diastolic restriction and the characteristics of

those who did not. Larger LV diameters, greater left atrium size, increased sphericity index of the LV chamber, and lower EF were significantly associated with the development of diastolic dysfunction.²⁵

Surgical Ventricular Restoration and Left Ventricular Dyssynchrony

Left ventricular dyssynchrony has been recognized as a condition leading to LV dysfunction, both in ischemic and nonischemic dilated cardiomyopathy. Cardiac resynchronization therapy (CRT) is a treatment option in symptomatic patients with end-stage heart failure and LV mechanical dyssynchrony. Current indications for CRT in patients with drug refractory end-stage heart failure are NYHA class III–IV symptoms, LV EF less than 35%, QRS duration greater than 120 msec, and a left bundle branch block configuration. Large randomized, placebo-controlled studies have demonstrated the beneficial effects of CRT on symptoms, exercise capacity, and quality of life.^{115,116} Despite these beneficial effects, however, a consistent number of patients (almost 50%) do not benefit from CRT. The reasons are related to difficulties in defining asynchrony and to the presence of scarred regions that cannot respond to therapy.¹¹⁷ In patients with end-stage heart failure, LV mechanical dyssynchrony, whether interventricular or intraventricular, is related to electrical, structural, and morphologic features.^{118,119}

We tested the capacity of geometric rebuilding by SVR to restore a more synchronous contractile pattern without the use of an exogenous pacing input.¹⁰⁵ Thirty patients (58 ± 8 years old) undergoing SVR at the

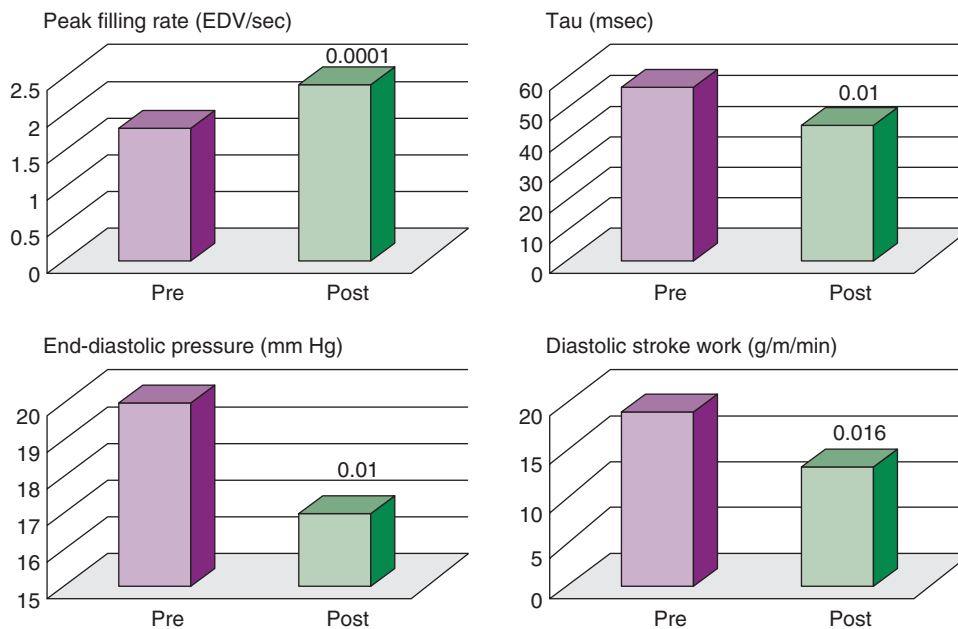


FIGURE 100-24 ■ Predischage changes in diastolic parameters induced by surgical ventricular restoration. The improvement was significant for all parameters. EDV, End-diastolic volume

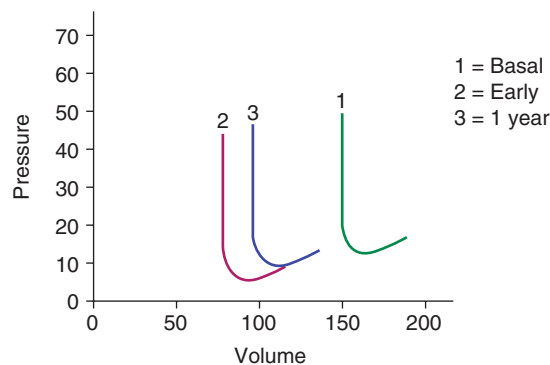


FIGURE 100-25 ■ End-diastolic pressure–volume curves obtained preoperatively (1), early postoperatively (2), and after 1 year (3) in a series of patients undergoing surgical ventricular restoration. Values are means. Note the marked left shift of the curve on the abscissa and the reduction of end-diastolic pressure. At 1 year, the curve shifts to the right, but it remains significantly improved with respect to the baseline (personal unpublished observations).

Cardiothoracic Centre of Monaco were prospectively evaluated with a protocol that used simultaneous measurements of ventricular volume and pressure to construct pressure–volume (P/V) and pressure–length (P/L) loops. Mean QRS duration was normal (100 ± 17 msec). Preoperative LV contraction was highly asynchronous. Endocardial time motion was either early or delayed at the end-systolic phase, yielding P/L loops with abnormalities in morphology and orientation. Postoperatively, SVR resulted in a leftward shifting of P/V loops and an increased area; endocardial time motion and P/L loops almost normalized (Fig. 100-27). The hemodynamic consequences of SVR included improved EF, reduced end-diastolic and ESVs, more rapid peak filling rate, and improved mechanical efficiency resulting in

mechanical intraventricular resynchronization that improved LV performance. This SVR-induced resynchronization has been confirmed in other studies.^{107,109}

The observed intraventricular dyssynchrony stems from asynchrony of the component parts of the LV chamber (structural nonhomogeneity). SVR accomplishes exclusion of scarred and thinned myocardium contiguous to normal, nearly normal, or ischemic tissue (Fig. 100-28).

Surgical Ventricular Restoration and Ventricular Arrhythmias

Another field in which SVR has demonstrated efficacy is that of ventricular arrhythmias (VAs). Complex, malignant VA frequently occurs in patients with ischemic dilated cardiomyopathy and may be responsible for sudden death in this population. Myocardial tissue heterogeneity increases susceptibility to ventricular arrhythmia, and this heterogeneity can be indexed by cardiac MRI.¹²⁰ The presence of infarcted tissue or scar forms the substrate for malignant reentrant arrhythmias,¹²¹ and MRI can, in principle, detect such a substrate because of its ability to delineate necrotic myocardium at all stages of infarct healing.¹²²

Infarcts can have marked spatial heterogeneity, with areas of necrosis interspersed with bundles of viable myocytes, particularly in the border zones and periphery of the infarct.¹²³ Tissue heterogeneity in these regions may create areas of slow conduction that generate the substrate for the development of lethal reentrant arrhythmias.¹²⁴ Increased mechanical loading of the heart, as occurs in dilated cardiomyopathy, is often associated with arrhythmias, the so-called stretch-induced arrhythmias. The alteration of the cardiac mechanical properties developing early in heart failure is accompanied by action

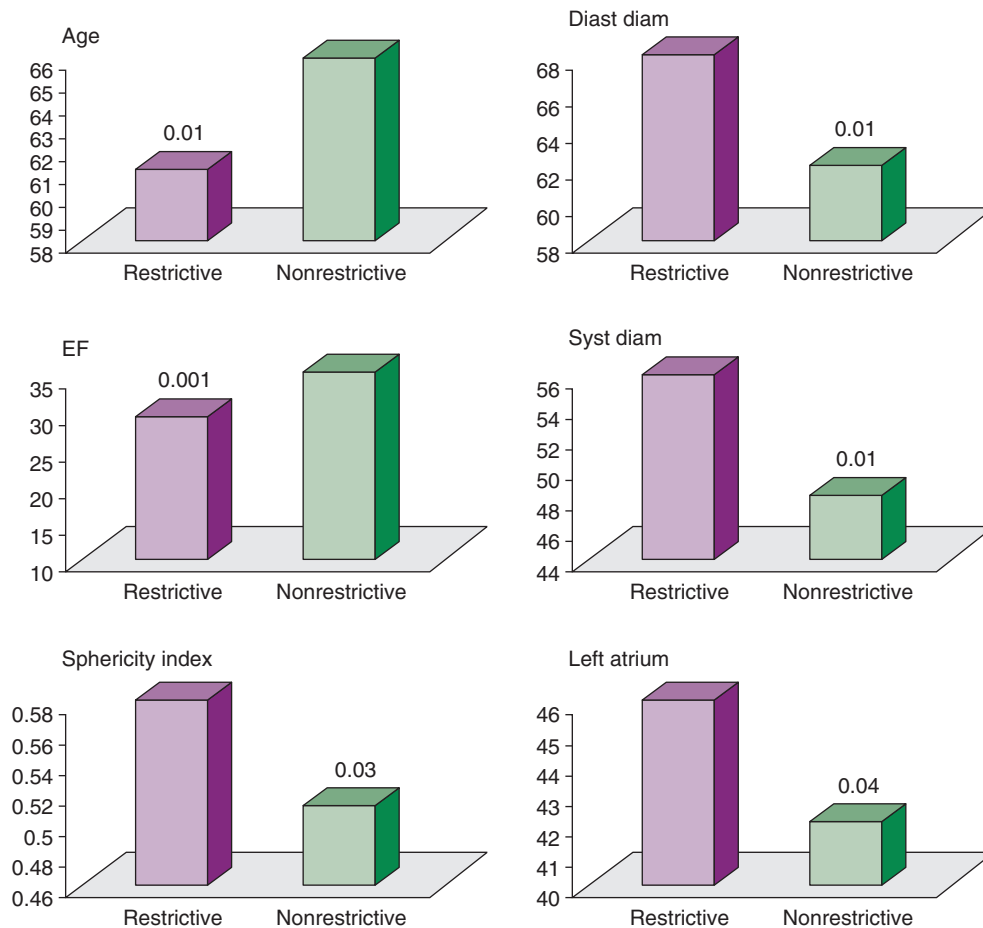


FIGURE 100-26 ■ Preoperative characteristics of patients who developed diastolic restriction after surgical ventricular restoration. Left ventricle (LV) diameters, left atrium size, sphericity index of the LV chamber, and ejection fraction (EF) were significantly worse in those who did not develop restriction. *Diast*, Diastolic; *Syst*, systolic. (Data presented by the authors at a meeting of the European Association for Cardiothoracic Surgery, Barcelona, Spain, September 2008.)

potential lengthening, which is modulated by an acute stretch. The stretch induces a mechano-electric feedback that is the common pathway responsible for the induction of VAs.¹²⁵

Di Donato, Dor, and associates¹²⁶ described a large series of patients with spontaneous or inducible ventricular tachycardia and compared them with patients who did not have arrhythmias. The study group included 87 patients with clinical documented ventricular arrhythmias and inducible or noninducible ventricular tachycardia (“spontaneous”), 105 patients with no clinical arrhythmia but with inducible arrhythmia in an electrophysiologic study (“inducible”), and 190 patients without clinical or inducible ventricular tachycardia (“no arrhythmia”).

A preoperative ESV index helped define the potential for preoperative arrhythmias. For the “spontaneous” patients, it was greater than 120 mL/m²; for the “inducible” patients, it was greater than 100 mL/m²; and for the “no arrhythmia” patients, it was less than 100 mL/m². SVR induced a significant reduction in inducible ventricular tachycardia—from 41% preoperatively to 7% at early study, and it was still 7% 1 year later (Fig. 100-29). Cardiac mortality was low at 5 years and not significantly

different between the spontaneous and the nonspontaneous groups (Fig. 100-30).

For this series of patients, Dor added extended non-guided endocardectomy and cryoablation at the transitional zone in patients with spontaneous and inducible arrhythmias, and to address a chamber size and shape factor during the SVR, he included in the procedure the following: resection of scar (a trigger of arrhythmias), septal exclusion, and cavity reduction by endoventricular patch (to reduce stretch), while supplementing the procedure with coronary grafting (to relieve ischemia) and mitral repair (to reduce wall tension), when needed. Dor’s success in antiarrhythmic management is supported by others who also perform cryosurgery,^{86,94} but no single factor can be identified to account for the high electrical success rate in these patients and for the low incidence of sudden death. A reasonable interpretation of these findings is that SVR addresses all the components that may activate ventricular arrhythmias (electrical and mechanistic volume-related cause), and that ventricular rebuilding deals effectively with the functional reentry circuit that can produce ventricular arrhythmias and simultaneously slows progression of heart failure in patients with dilated heart CHF.

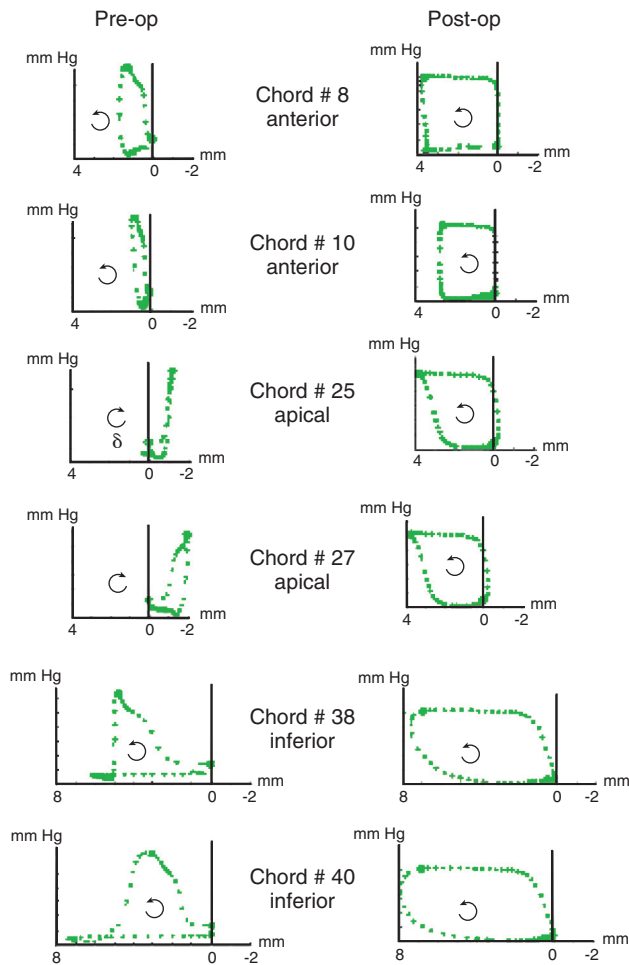


FIGURE 100-27 ■ Pressure-length (P/L) loops constructed at the 45 chords of the ventricular perimeter (identified by the center-line method) are reported at different regions before and after surgery in a single patient. Note the abnormalities in size, shape, and orientation of the P/L loops before surgery (Pre-op) and the improvement after surgery (Post-op). P/L loops after surgery almost normalized, with squared shapes caused by rectilinear isometric phases.

Coronary Artery Bypass Surgery

Coronary bypass surgery is an important treatment for ischemic cardiomyopathy, but there is no evidence that the bypass procedure is superior to optimal medical therapy in patients with ischemic heart failure. Before the STICH trial, evidence of the benefit of surgical revascularization in patients with LV dysfunction and coronary artery disease was reported in old studies. The Veterans Affairs Cooperative Study of Coronary Bypass Surgery demonstrated a survival advantage for patients with impaired ventricular function who underwent revascularization compared with those who were medically treated.^{127,128} In the Coronary Artery Surgery Study, patients with mild or moderately impaired ventricular function had an improved survival after CABG compared with those who were medically treated.¹²⁹ Unfortunately, few patients with severe LV impairment were included. A second Veterans Affairs trial in patients with unstable angina also demonstrated a survival advantage in patients with abnormal LV function who underwent bypass surgery.¹³⁰ The results of these studies have been further supported by data from the SOLVD (Studies of Left Ventricular Dysfunction) studies and other reports.¹³¹

Despite this information, surgeons were reluctant to operate on patients with poor ventricular function, because it usually translated into poor surgical outcome. Fortunately, this has changed, because the outcome after CABG in the setting of severe LV dysfunction has improved significantly. Perioperative mortality in more recent series has decreased and now approaches 2% to 8% in many institutions. Late survival, angina status, and NYHA class have improved in follow-up periods. However, LV dysfunction remains a major marker of increased morbidity and mortality after CABG. Patients with an EF of less than 20% are four times more likely to develop low cardiac output syndrome compared with patients with normal EF. In the CABG Patch trial, patients with preoperative CHF had twice the perioperative mortality than did patients with normal ventricular function.¹³²

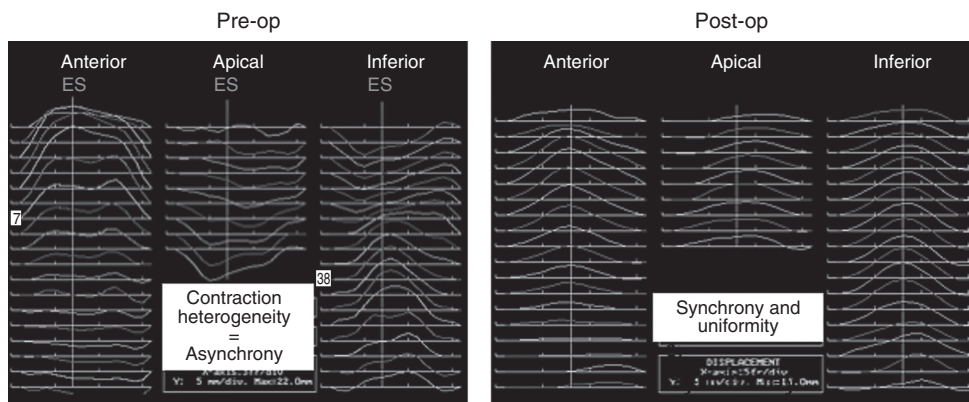


FIGURE 100-28 ■ Endocardial time-motion at 45 chords (identified by the centerline method) at three regions is shown before and after surgical ventricular restoration in one patient. After surgery, almost all segments reach the end-systolic phase synchronously, whereas almost none did so preoperatively despite a normal duration of QRS. This behavior reflects intraventricular dyssynchrony. ES, End-systolic phase.

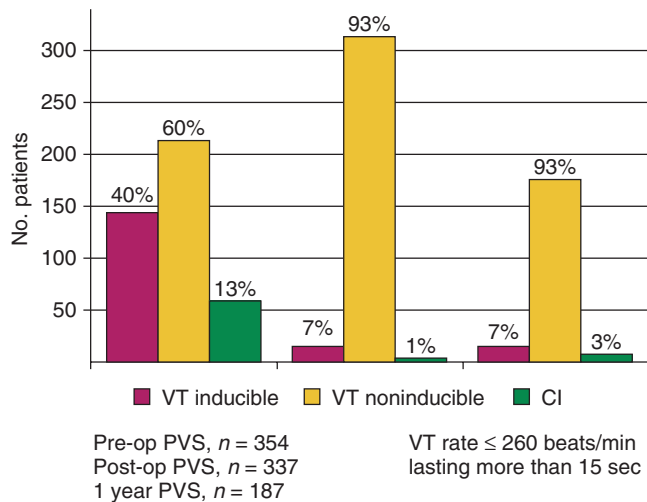


FIGURE 100-29 Inducible ventricular tachycardia (VT) at electrophysiologic study before and after surgical ventricular restoration in a large population treated at the Cardiothoracic Centre of Monaco. The electrophysiologic protocol was not aggressive (up to two extra stimuli at two different cycle lengths) and was the same at the three tests. VT is no longer inducible in a significantly high proportion of patients, both at discharge and after 1 year (only 7% are still inducible postoperatively). CI, Confidence interval; PVS, programmed ventricular stimulation.

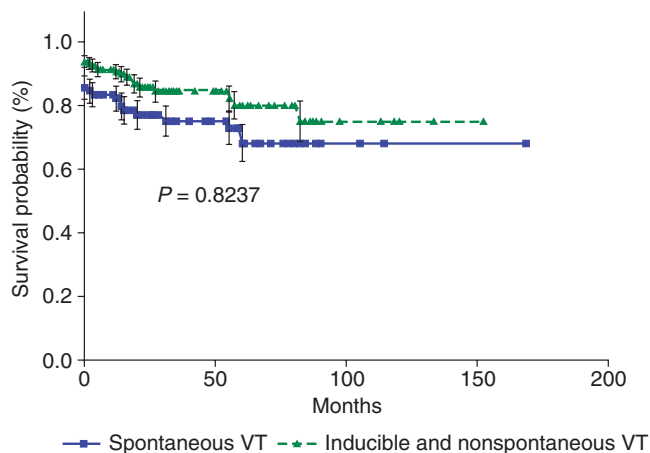


FIGURE 100-30 Kaplan-Meier survival curves in patients with spontaneous ventricular tachycardia (VT) and without ventricular arrhythmias who underwent surgical ventricular restoration. No significant difference was observed.

Coronary Artery Bypass Surgery with or without Surgical Ventricular Restoration: Insights into the STICH Trial

The STICH trial was designed to verify two hypotheses on a large population of patients affected by ischemic CHF and LV systolic dysfunction who were randomly assigned to receive medical therapy alone or combined with CABG (Hypothesis 1) and CABG alone or CABG plus SVR (Hypothesis 2).¹³³

The results of Hypothesis 2 showed that SVR combined with CABG had no impact over CABG alone on

mortality, heart failure hospitalizations, exercise tolerance, or quality of life.¹³⁴

Several major limitations of the STICH trial have already been noted,¹³⁵ including: (1) patient inclusion bias (i.e., many patients whose primary surgeons considered SVR to be clinically indicated were not randomized, characterized, or studied); and (2) the average reduction of ESV in the SVR group was much smaller than planned (raising serious questions about whether the procedure was performed properly in a majority of cases). Based on that, our group analyzed the impact on survival of a residual left ventricular end-systolic volume index (LVESVI) of greater than or less than 60 mL/m². We showed that LVESVI after SVR affects the probability of death, being significantly higher in patients who remain with a postoperative LVESVI of greater than 60 mL/m².¹³⁶ We hypothesized that the lack of additional improvement in terms of survival in the SVR group observed in the STICH trial might be a result of the inadequate volume reduction, which left the patients in the two arms at identical risk. Witkowski and colleagues confirmed this observation showing that a residual post-surgical LVESVI of at least 60 mL/m² was independently associated with a fivefold increase of death and rehospitalization for heart failure at 2 years' follow-up after SVR.¹³⁷ Furthermore, a more recent analysis of the STICH trial data showed that SVR combined with CABG conferred a survival benefit compared with bypass alone with the achievement of a postoperative end-systolic volume index of 70 mL/m or less.¹³⁸ In the meantime, the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) recognized the merit of SVR, which has been included as a surgical option combined with CABG in selected heart failure patients with a scar in the LAD territory and a baseline LVESVI greater than or equal to 60 mL/m² (Class of Recommendation IIb; level of evidence B).¹³⁹

The results of Hypothesis 1 (1212 patients with an ejection fraction of 35% or less and coronary artery disease amenable to CABG randomly assigned to medical therapy alone or medical therapy plus CABG) were not far different.¹⁴⁰ No difference was observed in the primary end point of death for any cause; however, cardiovascular deaths were reduced compared with medical therapy alone.

It has been observed that the trial, in spite of the acronym, was a study of ischemic heart disease rather than heart failure per se. However, although it is true that only 37% of patients had severe heart failure symptoms (NYHA functional class III and IV), it should be outlined that only 4.7% had severe symptoms (Canadian Cardiovascular Society [CCS] angina class III-IV) and as much as 37% had no angina plus another 15% in CCS I. Therefore, the randomized population was extremely heterogeneous. Furthermore, data on LV volumes were not reported, except for the substudy on myocardial viability (601 patients) showing an LVESVI of 92 ± 39 mL/m². According to these baseline characteristics, the results of Hypothesis 1 were not surprising: in the literature, no benefit of any type of revascularization in patients with

no angina and enlarged dysfunctional left ventricles has been reported.

Along with the results of the Hypothesis 1 group, data obtained in a substudy of patients randomized to medical therapy with or without CABG after the assessment of myocardial viability were reported.¹⁴¹ There was no significant interaction between viability status (assessed using single-photon-emission computed tomography, dobutamine echocardiography, or both) and treatment assignment with respect to mortality ($P = 0.53$). These results differ markedly from results of previous retrospective studies and meta-analyses, suggesting that assessment of myocardial viability alone should not be the deciding factor in selecting the best therapy for these patients. Future prospective studies need to be designed to determine the role of cardiac imaging in clinical decision making.

Mitral Repair

Ischemic MR conveys an adverse prognosis, doubling the mortality seen in patients after an MI, in those with chronic heart failure, and after surgical or catheter revascularization.¹⁴²⁻¹⁴⁷ It is common, and it increases mortality even when it is mild,¹⁴³⁻¹⁴⁵ with a graded relationship between severity and reduced survival. Currently, it is not clear whether the poorer outcomes in this group depend on the valvular dysfunction or whether it is merely a surrogate marker of extensive comorbidities, particularly the amount of ventricular dysfunction.

The term *functional MR* broadly denotes abnormal function of normal leaflets in the context of impaired ventricular function; it typically occurs in globally dilated and hypokinetic ventricles or with segmental damage that affects valve closure. It occurs in roughly 20% to 25% of patients followed after MI^{143,145,148,149} and in 50% of those with CHF.¹⁵⁰ The mechanism of MR in end-stage heart failure is multifactorial. Briefly, it is related to changes in LV geometry, with a subsequent displacement of the subvalvular apparatus, annular dilation, and restrictive leaflet motion (class IIIb according to Carpentier's classification),¹⁵¹ which results in coaptation failure.

Recent advances in noninvasive Doppler echocardiography allow reliable assessment of regurgitant volume^{152,153} and of the orifice of MR by combined methods.^{154,155}

Since the turn of the century, laboratory and clinical studies¹⁵⁶ have helped to elucidate the mechanisms that underlie ischemic MR, using several different imaging modalities. These studies have demonstrated that the two key anatomic elements contributing to the development of MR are annular remodeling and disruption of the dynamic anatomic relationship between the subvalvular apparatus and the mitral annulus, which is manifested as systolic tethering of the leaflets into the LV cavity. The extent to which each of these two elements contributes to valvular incompetence varies substantially among individual patients.¹⁵⁷

Although several indices of annular remodeling, including mitral annular area, intercommissural width, and septolateral annular diameter, are readily quantified by standard two-dimensional echocardiographic techniques, methods for quantifying leaflet tethering have not

been standardized. Descriptive geometric indicators derived from single-plane measurements made from two-dimensional echocardiographic studies, such as tenting height and area, have been proposed.¹⁵⁸ Tenting is characterized by insufficient systolic leaflet body displacement toward the annulus, with coaptation limited to leaflet tips, resulting in MR. Unfortunately, these measurements are inherently inaccurate because of the high variability of scanning planes and regional variation in both mitral annular shape and leaflet tenting that develop in conjunction with postinfarction LV remodeling. Recently, three-dimensional echocardiography has been applied to the evaluation of mitral valve morphology and may play a valuable role in the assessment of patients undergoing mitral repair surgery.^{159,160}

The clinical significance of functional MR is frequently underrated because of low murmur intensity and mismatch between severe symptoms and unimpressive regurgitant volume and effective regurgitant orifice. Nevertheless, functional MR is a major component of LV dysfunction, causing pulmonary hypertension and LV volume overload, which in turn potentiates LV remodeling, a major determinant of the outcome of LV dysfunction. Mild and moderate functional mitral insufficiency are also associated with significantly decreased survival in patients undergoing CABG, but whether correction of moderate functional MR at the time of CABG improves outcome has yet to be determined.

Previously, surgical treatment of MR was avoided in patients with heart failure and severe pump dysfunction because of concerns about operative risk and perioperative complications. More recently, with improvement in surgical techniques, surgical mitral annuloplasty for MR in the setting of heart failure has become a more popular treatment option. Bolling and associates have demonstrated the feasibility of mitral valve repair in patients with heart failure by downsizing the annulus using a flexible ring.^{79,161} Their initial results in 48 patients who underwent restrictive mitral annuloplasty showed an early mortality rate of approximately 5% with 1- and 2-year survival rates of 82% and 71%, respectively. Several recent studies have confirmed that early mortality is low (between 5% and 7%); heart failure symptoms, LV size, and EF improve; and intermediate outcome is favorable.^{162,163} However, several studies in patients treated with mitral annuloplasty demonstrated a high recurrence rate (30%) of MR after the 6-month follow-up.^{164,165} In contrast to these results, Bax and coworkers¹⁶⁶ reported no recurrence of MR, and Szalay and associates¹⁶³ reported a recurrence rate of 3% with a mean MR grade of 0.6 at 1-year follow-up. The low recurrence rate in these latter studies may be associated with a more truly restrictive annuloplasty performed in these patients. Of note, the paper by Bax and colleagues showed reverse remodeling at follow-up, especially in patients with an LV end-diastolic diameter of less than 65 mm. However, no randomized clinical trial has yet demonstrated that surgical correction of MR by mitral annuloplasty improves survival or leads to reverse remodeling. Wu and associates demonstrated that there is no clearly demonstrable survival benefit conferred by mitral annuloplasty for significant MR in patients with chronic heart failure.¹⁶⁷

Currently, the use of a stringent restrictive ring, two sizes smaller than the measured size, is advocated to achieve a better leaflet coaptation and possibly to prevent recurrence of MR and promote reverse remodeling.¹⁶¹

There are concerns that correction of MR might decrease LV systolic function as a result of afterload increase caused by closure of a low-resistance runoff into the left atrium. In addition, it has been suggested that undersizing the mitral annulus might affect LV contractility because of increased mechanical tension on the base of the heart.¹⁶⁸ Moreover, according to some authors, restrictive mitral repair might impair diastolic filling, but Bolling and Dion demonstrated that undersizing the annulus leads to acute beneficial geometric changes of the base of the LV, which reduces volume and stress.^{79,166}

Mitral surgery is proposed in selected patients to improve cardiac function. However, often in patients with a dilated heart and severe MR, the simple correction of the mitral valve might not be sufficient to improve LV function and reverse LV remodeling. Functional MR is a ventricle disease, and a procedure on the left ventricle should be added whenever possible, especially in ischemic dilated cardiomyopathy. However, if MR is mild, SVR can be used to reduce it by improving LV function and geometry, without surgical valve correction.⁷⁸

Different techniques were reported for reducing the mitral annulus. Kay and colleagues¹⁶⁹ reported mitral plasty with reduction of the posterior annulus without a ring, and Carpentier¹⁷⁰ used a rigid ring. A flexible ring could be also used. Menicanti and associates⁷⁷ reported that the transventricular approach for MR with LV reconstruction could be performed without a prosthetic ring, and that the results were favorable. Bolling and coworkers⁷⁹ used undersized circumferential rings to reduce the annulus in patients with severe MR associated with dilated cardiomyopathy. Isomura and coworkers used noncircumferential flexible rings initially and then changed the technique to use the circumferential semi-rigid rings (Carpentier-Edwards physio-ring) of a smaller size (undersized ring, 26 or 28 mm).¹⁷¹

SVR with or without an intraventricular patch is the second key component of mitral repair. Because reducing ventricular volume decreases wall stress and enhances remote regional wall motion,³² we hypothesize that SVR-related improvement of inferior wall motion is a component of MR reduction. This enhancement, together with reduced papillary muscle width, helps reduce stress and improve remote motion.

However, although our understanding of ischemic MR evolves and the technologies used to manage these patients continue to be refined, the higher rates of recurrent MR after repair have led some to consider valve replacement instead of repair. Evidence for repair or replacement was limited until the released results from the first multicenter, randomized trial, which showed no significant difference in LV reverse remodeling or survival at 12 months between patients who underwent mitral valve repair and those who underwent mitral valve replacement.¹⁷² Replacement provided a more durable correction of MR, but there was no significant between-group difference in clinical outcomes. A longer follow-up is needed to confirm the findings of this trial.

SUMMARY

In the current clinical practice, the choice to add SVR to CABG should be based on a careful evaluation of patients, including symptoms (heart failure symptoms should be predominant over angina); measurements of the LV volumes; careful assessment of mitral valve, including geometry and MR severity; and assessment of the transmural extent of myocardial scar tissue and viability of regions remote from the scar, and it should be performed only in centers with a high level of surgical expertise. Further clarifications of (1) ventricular properties associated with better hemodynamic effects of SVR and (2) links between hemodynamic effects and clinical outcomes could help define appropriate patient selection criteria.

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REGENERATIVE CELL-BASED THERAPY FOR THE TREATMENT OF CARDIAC DISEASE

Nick J.R. Blackburn • Aleksandra Ostojic • Erik J. Suuronen • Frank W. Sellke • Marc Ruel

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SUMMARY

Heart failure (HF) is a burgeoning disease. Recently published American Heart Association projections indicate that its prevalence will increase by 46% from 2012 to 2030 resulting in approximately 8 million people with HF in the United States alone.¹⁻⁴ Ischemic heart disease is the major contributor to HF and despite best practices and management strategies, many patients are left with significant disability. Events such as myocardial infarction can result in the irreparable loss of viable cardiac mass and in this and many other clinical scenarios, save for transplantation, no therapies currently exist to remedy lost myocardium. Considering the shortage of donor hearts, a rationale to develop regenerative stem cell based therapies is provided.

Thousands of clinicians and investigators worldwide are working toward harnessing the properties of adult stem or progenitor cells to treat injury in tissues and organs that have limited intrinsic capacity for repair and regeneration, such as the brain and the heart. Yet, achieving cellular cardiomyoplasty remains elusive. As a basic definition, cell therapy for regeneration is the therapeutic use of a cell population to promote growth and repair of diseased and / or damaged tissue to restore anatomy and function. The focus tends to be, typically, in settings where this does not occur appreciably such as myocardial infarction and traumatic brain or spinal cord injury. In the setting of ischemic cardiomyopathies, the goal of stem cell therapy would, preferably, be a combination of

promoting the growth of new or existing blood vessels to improve tissue perfusion, and the growth of new cardiomyocytes within the damaged myocardium. Since its inception, cell therapy has achieved the most success in facilitating new blood vessel formation via either angiogenesis or vasculogenesis. Unfortunately, it has been somewhat more difficult to restore lost cardiomyocytes. Although we are likely still decades away from completely regenerating the diseased myocardium, recent evidence indicates that we are at least a little farther ahead. The aim of this chapter is to familiarize readers with the field of cell therapy for cardiac regeneration. Despite many deserving preclinical and clinical studies, unfortunately this review will not be comprehensive, because of length restrictions. Instead, only those cell types with the most promise and best available evidence will be discussed. The clinical focus will be acute MI where the loss of cardiomyocytes is a hallmark of this disorder; however, stem cell use in other clinical entities will also be briefly touched upon. Methods of administration will be covered, as well as the principal mechanisms of action that have been identified. Finally, a brief section will outline some of the current challenges facing the field and possible future directions. At the end of this chapter readers will be familiar with the field of cell therapy for cardiac repair and for those interested references are provided.

DELIVERY METHODS FOR CELL TRANSPLANTATION

Stem cell products for the injured heart can be administered through several methods—some more invasive than others—and each presenting with unique advantages and disadvantages (Table 101-1). Generally, stem cells can be infused intravenously or via patent coronary arteries supplying the ischemic region of the heart, or stem cells can be injected directly into the ventricular wall via a percutaneous transendocardial or a surgical transepicardial approach (Fig. 101-1).

TABLE 101-1 Administration Models

Routes	Advantages	Disadvantages
Intravenous injection	Simplest	Few migrate into the target
Intracoronary injection	Can be administered into patent artery, higher cell homing versus intravenous infusion, low risk of arrhythmia	Unsuitable for larger stem cells, hinder cellular transmigration, exacerbation of atherosclerosis
Intramyocardial injection	Most reliable under direct visualization; highest cell dose	Invasive, potential for cell “clumping”

Intravenous Infusion

Intravenous infusion is the simplest method of cell administration. Given this delivery strategy is nonspecific, it relies heavily on proper homing of the infused cells to the ischemic myocardium. Thus, the disadvantage of this method is that a low percentage of the infused cells home it to the intended target.⁵ Cells can also become trapped in other organs, particularly in lymphoid tissues, so that an additional small proportion of cells enters the coronary circulation and migrates into ischemic myocardium.^{6,7} This is particularly disadvantageous with pluripotent cells increasing the opportunity for off-site proliferation. In addition, with larger cell types, such as mesenchymal stem cells (MSCs) or skeletal myoblasts, microembolization can occur because these cells may be incapable of penetrating beyond a given capillary bed, making them unlikely to reach their target.

Intracoronary Infusion

Infusing stem cells via a patent coronary artery can be performed at the time of selective coronary angiography, and it is well-suited for the specific delivery of cells to the ischemic territory of the myocardium. The obvious advantage of intracoronary infusion is that cells can travel directly into myocardial regions in which nutrient-rich blood flow and oxygen supply are preserved, ensuring a favorable environment for the survival of cells, a prerequisite for stable engraftment.^{8,9} Indeed, in a study performed by Hofmann and colleagues,⁶ homing of unselected bone marrow cells to the infarct region was apparent only after intracoronary delivery but not after intravenous infusion. One disadvantage; however, is that high coronary flow after stem cell injection can prevent low-affinity adhesion to the myocardial capillaries, thus hindering cellular transmigration into the infarcted zone. Another disadvantage to delivering stem cells in this fashion to a potentially diseased segment of the coronary artery is that the combination of stem cells and the pro-angiogenic milieu of the plaque may serve to exacerbate macrovascular and microvascular disease. Similar to intravenous delivery, intracoronary infusion of cells might not be suitable for certain types of larger stem cells, such as skeletal myoblasts and MSCs, which can be prone to embolization. Despite some of these limitations, intracoronary injection of stem cells has been the preferred method of delivery in most clinical studies thus far.

Intramyocardial Injection

Intramyocardial injections constitute an invasive approach to delivering therapeutic cell products compared with the other methods mentioned. This approach is performed by delivering cell suspensions into target myocardial areas via direct injection during minimally invasive thoracoscopic or open procedures.¹⁰ It can be the preferred method of delivery particularly when there is a lack of patent coronary arteries supplying the ischemic region or when the procedure is performed in tandem with mechanical revascularization. The surgical injection process is simple and can be performed under direct

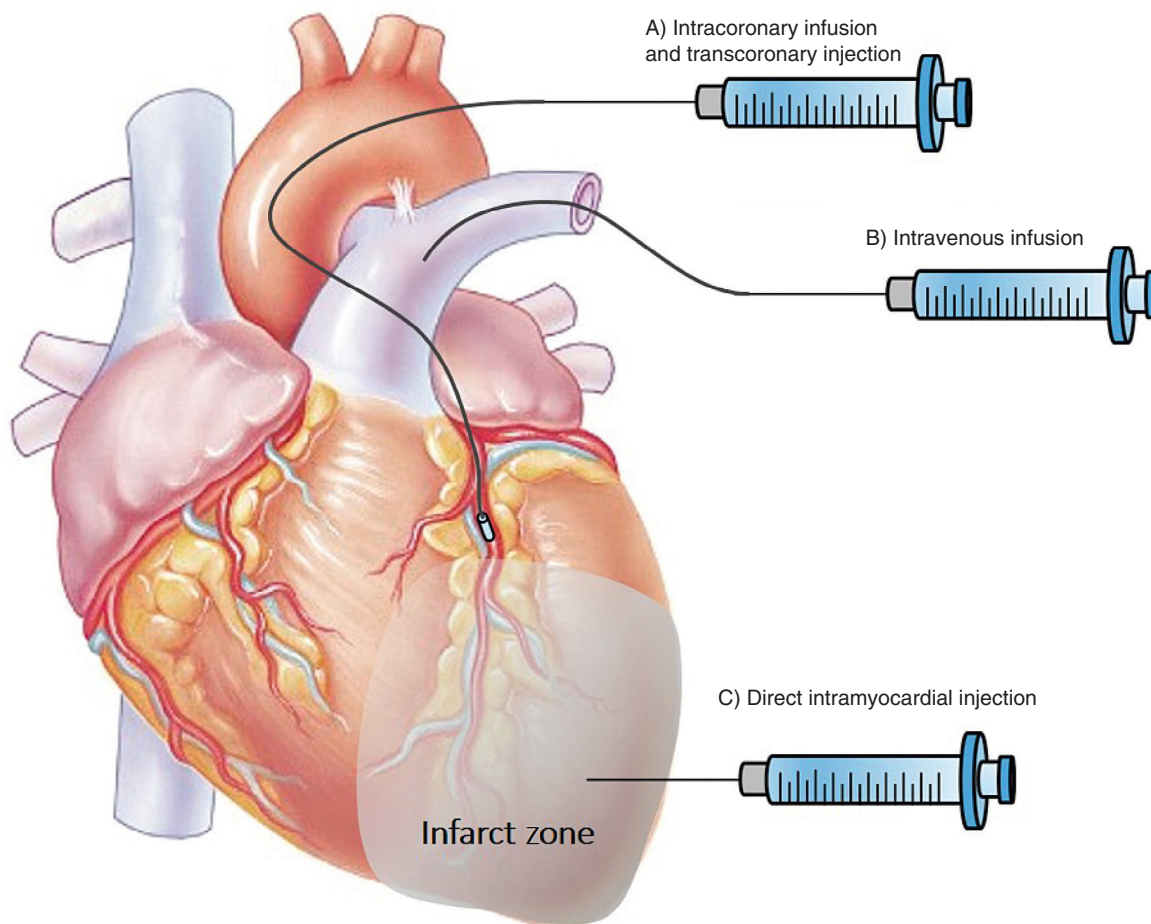


FIGURE 101-1 ■ Delivery routes for transplanted cells for the treatment of ischemic heart disease.

visualization, allowing evaluation by inspection of the potential target zones. As an alternative to user-based visualization of cell injection, electromechanical mapping (e.g., using the NOGA system) can serve to improve the reliability of surgical transeptal injections, or assist transcatheter injections as a percutaneous procedure.¹¹ Multiple injections of concentrated cell suspensions at minimal volumes appear preferable to less frequent, larger volume injection. This method is feasible and potentially the most reliable in ensuring stem cells reach the intended or injured areas of the myocardium.⁸ Regardless, it is still difficult to predict the survival and function of progenitor cells injected into uniformly necrotic tissue, and the ischemic or necrotic area may prove too hostile to ensure proper cell engraftment and survival.

There are disadvantages to intramyocardial injections. Some nonspecific delivery can occur often because of cell leakage during injection. Moreover, cell clumping can prevent uniform cell distribution in the target area. This method of delivering stem cells may also be inappropriate in situations of diffuse disease such as nonischemic dilated cardiomyopathy where focal deposits of directly injected cells might be poorly matched to the underlying pathophysiology.¹²

Summary

The optimal route for administering stem cells has yet to be determined, although the method of choice will likely be specific depending on a number of factors such as the cell product, patient clinical characteristics, and disease setting. In more acutely ischemic scenarios such as acute myocardial infarction (AMI), the release of chemotactic stimuli into the peripheral circulation, in response to the ischemic injury, may favor homing of intravenous or intracoronary infused cells. However, in situations in which these signals have been abated, as may be the case for chronic ischemia or old scar, injection of the cells directly into the cardiac muscle may produce a more favorable outcome.¹³ To date, most trials report a low frequency of complications regardless of route of administration associated with cell base therapies supporting the safety of any of these approaches.¹⁴

ADULT STEM OR PROGENITOR CELLS FOR CARDIAC CELL THERAPY

A number of adult stem or progenitor cell types have been investigated for the treatment of heart disease

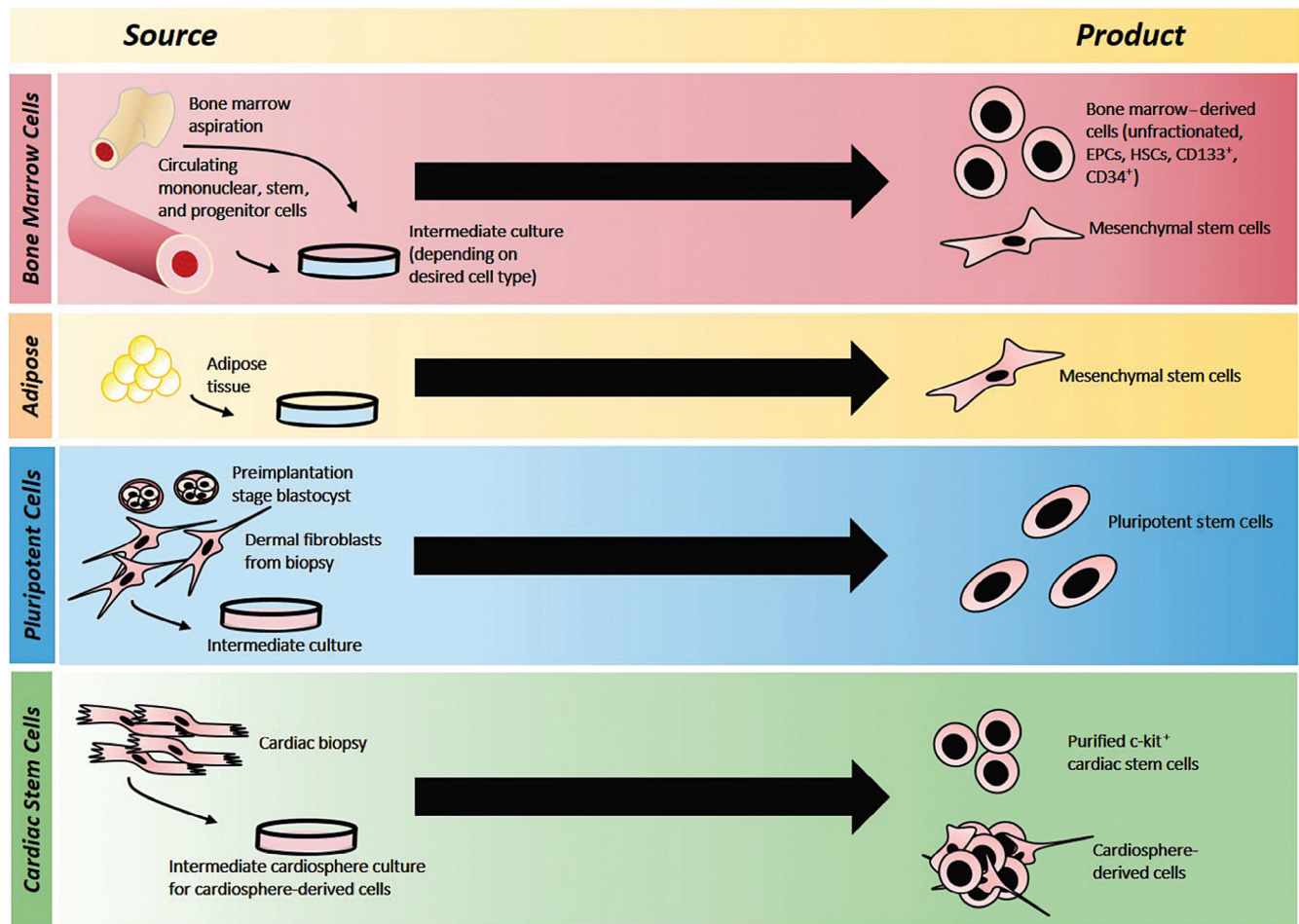


FIGURE 101-2 ■ Cell types currently undergoing clinical trial and emerging cell types. EPC, Endothelial progenitor cell; HSC, hematopoietic stem cell.

(Fig. 101-2). They have been procured from the bone marrow (bone marrow–derived mononuclear cells [BMCs]), the peripheral circulation, adipose tissue, skeletal muscle, or cardiac muscle biopsy specimens. Pluripotent cells such as the embryonic stem cell (ESC) or the inducible pluripotent stem cell (iPSC) have also received much attention. Most have been investigated extensively in preclinical models, and some in the clinical arena. Some emerging cell types, such as the iPSC, have not yet reached clinical trial. The most pertinent cell types, either for emerging relevance or historical importance, are discussed in the following sections, and a summary is provided in Table 101-2. No consensus has been reached on the ideal cell type; however, some candidates appear more promising than others. If the ideal cell type does exist, it should fulfill most if not all the following criteria¹⁶⁶:

1. Stem cells should be safe. In other words, they should not form tumors, predispose patients to fatal arrhythmias, or elicit immune reactions.
2. Stem cells should improve heart function, quality of life, and mortality.
3. Stem cell harvest and culture methods should be clinically feasible and not cost-prohibitive.
4. Stem cells should be available as a standard, “off-the-shelf” product.

5. Stem cell use should not be controversial or ethically ambiguous.

The following sections will cover the predominant cell types emphasizing clinical data. For emerging cell products that have not yet reached clinical trial, animal studies instead will be the focus. A summary of select clinical trials is provided in Table 101-3 (note that this table is not exhaustive, but is provided as an example).

Bone Marrow–Derived Cells

The bone marrow hosts a myriad of cell populations, including hematopoietic and nonhematopoietic cells and progenitors. Interest in autologous BMCs for the treatment of ischemic cardiac syndromes was first stimulated by the discovery of the putative endothelial progenitor cell (EPC) by Asahara and colleagues in 1997.¹⁵ These EPCs, originally from the bone marrow, were found to circulate in the peripheral blood homing to sites of tissue ischemia to participate in postnatal vasculogenesis.¹⁵ Since then, cells derived from the bone marrow have been the preferred cell type in both preclinical and clinical cardiac cell therapy studies. BMCs can be harvested via either bone marrow aspiration or peripheral blood apheresis followed by isolation of the

TABLE 101-2 Cell Types

Cell Type	Phenotypic Markers	Advantages	Disadvantages
Skeletal myoblasts	CD56, Desmin	Easily harvested and expanded; good survival rates; differentiate into myotubes	Poor differentiation into cardiomyocytes; high risk for arrhythmias
Embryonic stem cells	CD133, Oct 4, SSEA-3/4, Sox	Differentiate into cardiomyocytes, endothelial cells, and smooth muscle cells	Ethical challenges, tumorigenicity, ectopic differentiation, immunogenicity
Bone marrow–derived stem cells			
Hematopoietic stem cells	CD34, CD133, CD45, Sca-1, c-kit	Improve cardiac function, promote angiogenesis	Mechanistically, may only reconstitute peripheral blood leukocytes
Endothelial stem cells	CD34, CD133, VEGFR2, CD144, Sca-1	Increase blood vessel formation, prevent cardiomyocyte apoptosis	Variable efficacy
Mesenchymal stem cells	CD106, c-kit	Have reduced immunogenicity (at least initially), easy to expand and maintain ex vivo; robust secretome	Large cell type
Adipose tissue–derived cells		Less expensive, less invasive to harvest, and potentially available in great quantities	Isolation needs to be optimized for clinical use
Side population cells	CD45, CD59, CD43, CD49d, CD31, and integrin markers	Differentiate into cardiomyocytes and endothelial cells	Little if any preclinical data
Inducible pluripotent cells	Oct4, Sox2, Klf4, c-Myc, Lin28, Nanog (introduced)		Yet to be tested
Cardiac stem cells	c-kit, Sca-1, isl 1	May generate cardiomyocytes; strong paracrine repertoire	Very low numbers, isolation difficult; limited clinical experience

mononuclear cell fraction by density-gradient ultracentrifugation. Upon isolation of the mononuclear fraction, BMCs can either be kept unfractionated or be further purified to isolate subpopulations identified by specific surface antigenic expression. In some cases, depending on desired cell type, fractionated BMCs may require further ex vivo expansion in culture.⁸ The subpopulations of BMCs that have been studied in the context as cardiac regenerative therapies includes hematopoietic stem cells (HSCs), EPCs, MSCs, and purified CD133⁺ or CD34⁺ cells (see Fig. 101-2). Bone marrow products have gained much favor from investigators mainly because of their ease of procurement and expansion in culture, and they tend to possess a relatively high concentration of adult progenitors.⁸

Unfractionated Bone Marrow Cells

The capacity for unselected or unfractionated BMCs to promote cardiac repair has been controversial,¹⁶⁻¹⁸ yet they remain the most thoroughly investigated cell type in clinical trial.¹⁹ Their popularity is driven largely by practical reasons. For example, BMCs are (1) derived from straightforward harvest protocols, (2) do not require complex or prolonged ex vivo management, and (3) contain a small niche of stem and progenitor cells despite representing a heterogeneous population.¹⁹ BMCs have been investigated in AMI, chronic ICM, and HF, but for the sake of brevity the following section will focus on trials of AMI. Readers interested in the results of BMC therapy in other clinical settings can consult several excellent reviews.^{10,19}

The safety and feasibility of BMC therapy was established from early, small trials of AMI such as the “Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction” (TOPCARE-AMI).²⁰⁻²² The demonstration that cell therapy may be safe, and possibly effective, prompted further inquiry into mid-sized, double-blind, randomized trials such as the “Reinfusion of Enriched Progenitor Cells and Infarct Remodelling in Acute Myocardial Infarction” (REPAIR-AMI) and the “BOne marrow transfer to enhance ST-elevation infarct regeneration” (BOOST) trials.^{23,24} Initial follow-up analysis from both the REPAIR-AMI and BOOST trials reported benefits associated with BMC therapy.^{23,24} BMCs were infused 3-7 days after successful reperfusion and were associated with superior cardiac function (5.5%-6.7% improved left ventricular ejection fraction [LVEF]) compared with placebo at 6 months postintervention.^{23,24} In addition, cell therapy was not associated with an increased risk for adverse clinical events.²⁴⁻²⁶ Substudies of both trials were subsequently released by trial investigators with equally promising results. For example, patients receiving BMCs in BOOST demonstrated improvements in diastolic function,²⁷ whereas there was a reduction in a prespecified cumulative end-point of death, MI, or necessity for revascularization at 1-year follow-up of the REPAIR-AMI.²⁶ Several other trials also support the benefit of BMC therapy in patients with AMI. Trials by Assmus and colleagues,²⁸ Cao and colleagues,²⁹ Yousef and colleagues,³⁰ and the “FINish stem CELL study” (FINCELL) reported positive benefits associated with BMC therapy including improved global ventricular function, a reduction in

TABLE 101-3 Select Clinical Trial Results

Study	Cell Therapy Patient	Cell Type and Cell Number	Route	Follow-up	Results
TOPCARE-AMI ^{20,22}	AMI (n = 29)	2.1×10^8 BMCs	IC	1 yr	LVEF↑; perfusion↑; remodeling↓
BOOST ^{24,27,32,33}	AMI (n = 30)	1.6×10^7 CPCs	IC	5 yr	LVEF↑ (6 months only), no change vs. control at 5 years
Fernandez-Aviles et al ²¹	AMI (n = 30)	2.4×10^9 BMCs	IC	11 mo	LVEF↑; ESV↓
MAGIC ⁵²	AMI (n = 20)	7.8×10^7 BMCs	IC	6 mo	LVEF↑; ESV↓; regional perfusion↑
Choi et al ¹⁸⁶	AMI (n = 10)	1.5×10^9 G-CSF-mobilized cells	IC	6 mo	LVEF↑
Ge et al ¹⁸⁷	AMI (n = 10)	2×10^9 G-CSF-mobilized cells	N/A	6 mo	LVEF↑
Strauer et al ¹⁸⁸	AMI (n = 10)	4×10^7 BMC	IC	6 mo	LVEF↑; perfusion↑
Chen et al ¹⁸⁹	AMI (n = 10)	2.8×10^7 BMCs	IC	3 mo	Infarct size↓; LV perfusion↑
	AMI (n = 34)	$4.8-6 \times 10^{10}$ BMCs	IC	6 mo	LVEF↑; perfusion↑; wall motion↑
REPAIR-AMI ^{23,26,28,190}	AMI (n = 102)	BMCs (50 mL bone marrow)	IC	1 yr	LVEF↑; infarct size↓; ↓remodeling
Janssens et al ¹⁹¹	AMI (n = 33)	3×10^8 BMSCs	IC	4 mo	Infarct size↓; regional systolic function↑
Li et al ¹⁹²	AMI (n = 35)	7.3×10^7 PBSCs	IC	6 mo	LVEF↑; wall motion↑
ASTAMI ^{34,36-38}	AMI (n = 50)	BMCs (50 mL bone marrow)	IC	6 mo	No benefit
TOPCARE-CHD ^{64,193}	CMI (n = 28)	2.1×10^8 BMCs	IC	3 mo	Wall motion↑
	CMI (n = 24)	2.2×10^7 CPCs	IC	3 mo	Wall motion↑
Katritsis et al ¹⁹⁴	CMI (n = 11)	$2-4 \times 10^6$ BMCs and EPCs	IC	4 mo	Perfusion defects↓; infarct size↓
Perin et al ¹⁹⁵	HF (n = 14)	3×10^7 BMCs	IM	4 mo	LVEF↑; regional perfusion↑
Stamm et al ^{196,197}	CMI (n = 20)	5×10^6 AC133 ⁺ BMCs	IM	6 mo	LVEF↑; perfusion↑
Ahmadi et al ¹⁹⁸	ICM (n = 19)	N/A	IM	6 mo	WMSI↓
Hendrikx et al ¹⁹⁹	CMI (n = 10)	6×10^7 BMCs	IM	4 mo	LVEF↑; systolic thickening↑; Defect score↓
Losordo et al ⁷⁵	RA (n = 18)	$5-50 \times 10^4$ CD34 ⁺ cells/kg	IM	6 mo	Exercise tolerance↑; perfusion↑
Mocini et al ²⁰⁰	ICM (n = 18)	2.9×10^8 BMCs	IM	3 mo	LVEF↑; wall motion↑
Tse et al ²⁰¹	ICM (n = 8)	BMCs (from 40 mL bone marrow)	IM	3 mo	LVEF↑; wall motion↑
G-CSF-STEMI ⁸⁵	AMI (n = 44)	G-CSF mobilized cells	N/A	1 yr	↑Perfusion 1 week and 1 month post treatment
STEMMI ^{86,87}	AMI (n = 78)	G-CSF mobilized cells	N/A	6 mo	No improvement, some inverse association between circulating mesenchymal cells and systolic recovery
REVIVAL-2 ⁸⁸	AMI (n = 56)	G-CSF mobilized cells	N/A	4-6 mo	No improvement
FINCELL ³¹	AMI (n = 40)	BMCs (360×10^6)	IC	6 mo	↑LVEF
Cao et al ²⁹	AMI (n = 41)	BMCs (5×10^7)	IC	4 yr	↑LVEF
Hare et al ⁸⁹	AMI (n = 53)	Allogeneic MSCs ($0.5-5 \times 10^6$ cell/kg)	IC	6 mo	↑LVEF and global symptom score in patients with anterior MI
REGENT ⁷⁴	AMI (n = 80)	BMCs or CD34 ⁺ CXCR4 ⁺ selected cells (1.78×10^8 cells; 1.90×10^6 cells)	IC	6 mo	↑LVEF in patients with baseline EF < 37%
BALANCE ³⁰	AMI (n = 62)	BMCs (6.1×10^7 cells)	IC	5 yr	↑contractility; ↑hemodynamic status; ↑exercise capacity; ↓mortality
SCPIO ^{127,132}	HF (n = 16)	c-kit ⁺ CSCs (1×10^6 cells)	IC	1 yr	↑LVEF; ↓infarct size
HEBE ¹⁶⁷	AMI (n = 200)	BMCs or PBMCs ($\approx 290 \times 10^6$)	IC	4 mo	No improvements
Losordo et al ⁷⁶	RA (n = 167)	CD34 ⁺ selected BMCs ($1-5 \times 10^5$ cells/kg)	NOGA IM	1 yr	↓weekly angina frequency; ↑exercise tolerance
Quyynmi et al ²⁰²	AMI (n = 16)	CD34 ⁺ selected BMCs (10×10^6 cells)	IC	6 mo	↑perfusion; ↑LVEF; ↓infarct size
BONAMI et al ³⁵	AMI (n = 49)	BMCs (98×10^6 cells)	IC	3 mo	↑myocardial viability; ↓non-viable segments
Williams et al ²⁰³	ICM (n = 8)	BMCs or MSCs ($100-200 \times 10^6$ cells)	IM	1 yr	↑regional contractility; ↓end-diastolic volumes; ↓infarct sizes
Chih et al ²⁰⁴	RA (n = 18)	G-CSF mobilized cells	N/A	42 wk	No improvements

Continued

TABLE 101-3 Select Clinical Trial Results—cont'd

Study	Cell Therapy Patient	Cell Type and Cell Number	Route	Follow-up	Results
POSEIDON ⁹⁰	ICM (n = 5)	Allogeneic and autologous MSCs (20-, 100-, 200- × 10 ⁶ cells)	IC	1 yr	↑functional capacity; ↑quality of life; ↓ventricular remodeling
TAC-HFT ²⁰⁵	ICM (n = 65)	MSCs and BMCs	IC	1 yr	↓MLHFQ both cell types ↑6MWT; ↑regional function; ↓infarct sizes MSCs only
CADUCEUS ¹²⁸	AMI (n = 31)	CDCs (25 × 10 ⁶ cells)	IC	6 mo	↓scar mass; ↑viable heart mass; ↑regional contractility; ↑regional systolic wall thickening
Perin et al ⁴⁷	HF (n = 10)	ALDH+ BMCs (2.27 × 10 ⁶)	NOGA IM	6 mo	↓LV end-systolic volume
SWISS-AMI ⁴²	AMI (n = 200)	BMCs	IC	4 mo	No improvements
TIME ⁴¹	AMI (n = 65)	BMCs (150 × 10 ⁶ cells)	IC	1 yr	No improvements

AMI, Acute myocardial infarction; BMC, bone marrow–derived mononuclear cell; CDC, cardiosphere derived cells; CMI, chronic myocardial infarction; CPC, circulating progenitor cell; CTO, chronic total occlusion; EF, ejection fraction; EPC, endothelial progenitor cell; ESV, end-systolic volume; G-CSF, granulocyte colony-stimulating factor; HF, heart failure; IC, intracoronary; IM, intramyocardial; LV, left ventricular; MSC, mesenchymal stem cell; RA, refractory angina pectoris.

morbidity and mortality, and a neutral effect on severe adverse reactions, including arrhythmias and restenosis of the stented coronary artery.²⁸⁻³¹

Unfortunately, despite the positive early experience with BMCs in patients, other trials have not been so promising. Moreover, follow-up from some of the earlier, positive trials were beginning to release disappointing long-term results. For example, the 2-year results of the REPAIR-AMI could not conclusively associate BMC therapy with improved morbidity and mortality²⁸; in BOOST, whereas the difference in LVEF improvement between cell therapy and placebo were significant at 6-month follow-up, the effect was not sustained at 18 months.^{24,32} A subgroup of patients with pronounced transmural infarcts may have benefited from cell therapy, although this was required to be tested prospectively in a randomized trial. Regardless, the lack of beneficial effects associated with BMCs in BOOST was sustained in the 5-year results.³³ Examples of results from recent trials include the “BONE marrow in Acute Myocardial Infarction” (BONAMI), which have been mixed, and those from the “Autologous Stem-Cell Transplantation in Acute Myocardial Infarction” (ASTAMI) trial, which were altogether negative.^{34,35} Aside from a small improvement in exercise time, ASTAMI did not associate BMCs with improvements in global LV function, or ventricular remodelling.^{34,36-38}

Before reaching clinical trial, many elements such as cell dose, frequency, or time of delivery had not been systematically determined for stem cell therapies. In some trials, such as the REPAIR-AMI, only until patients were stratified based on time of delivery after reperfused MI did some suggestion arise that timing of delivery influenced the efficacy of the therapy. This prespecified subgroup analysis associated later cell delivery (about 7 days after reperfused MI) with more pronounced benefits.²³ Thus, several recent trials including the TIME, late-TIME, and SWISS-AMI sought to test this hypothesis comparing the time of delivery between cells delivered early, mid, or late postinfarction.³⁹⁻⁴² Unfortunately, results from all three trials did not associate beneficial

effects with BMC therapy for AMI, consistent with the BOOST and ASTAMI trials, regardless of when cells were delivered after AMI.³⁹⁻⁴² Results from the TIME trial may, however, require careful scrutiny as cells were procured from a novel, convenient extraction method that had not been previously validated in bioactivity assays or animals models as opposed to the already well-supported and published methods for isolation.

Establishing a concrete position on the efficacy of BMC therapy for AMI has so far been difficult and results from recent trials such as TIME, late-TIME, or SWISS-AMI have not been able to answer this question conclusively. The outlook for BMC therapy is less than optimistic. Given the conflicting evidence and emerging alternatives, favor may lean toward products with well-demonstrated capacity to produce improvements in global LV function, mortality, and quality of life. Moreover, although some cumulative evidence from recent meta-analyses suggests that BMCs are associated with modest improvements in LV function (2%–4% LVEF), the question remains of whether these improvements are clinically meaningful.^{43,44} The upcoming European large, phase 3 “Effect of Intracoronary Reinfusion of Bone Marrow–derived Mononuclear Cells on All-Cause Mortality in Acute Myocardial Infarction” (BAMI) trial (NCT01569178) will probably represent the final consensus of BMCs in cardiac cell therapy in AMI.

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are a subset of BMCs that are multipotent and self-renewing and from which all blood cell types are derived. They are possibly the first stem cell therapeutic investigated in patients dating back from early trials of bone marrow transplantation for fatal leukemias.⁴⁵ Their use can be potentially curative for genetic blood disorders such as thalassemia and immune deficiency, or malignancies such as leukemia.⁴⁵ The prevailing hypothesis is that HSCs give rise to two lineage restricted progenitor cell types, including myeloid progenitors and lymphoid progenitors that, in turn, supply

the number of lymphocytic and granulocytic cells, macrophages, platelets, and erythrocytes found in the blood. However, specific identification and classification of HSCs has been difficult largely because of the limitations of current imaging and lineage tracing methods.⁴⁶ Generally, HSCs are identified by a lack of hematopoietic or myeloid lineage (lin) markers and, depending on the report, the presence of a number of antigenic surface markers such as CD34, CD38, CD90, CD133, CD105, CD45, and c-kit (CD117) or other markers such as the presence of aldehyde dehydrogenase.^{47,48} Their use as a cardiac regenerative cell product was stimulated by early studies indicating that lin⁻, c-kit⁺ HSCs could restore necrotic myocardium by transdifferentiating into all the major cardiac cell types (cardiomyocyte, endothelial cell, and smooth muscle cell) conferring salutary effects.^{49,50} Unfortunately, this notion was met with sharp criticism and conflicting data.^{16,17} Subsequent evidence instead indicates that HSCs are, in fact, not cardiomyogenic but adopt mature hematopoietic fates in ischemic myocardium.^{16,17,51} Whether the benefits of HSCs are derived from an ability to restore damaged myocardium or from a separate, possibly paracrine, mechanism remains a topic of intense debate.⁵⁰

Consensus on what combination of surface, cytosolic, or functional markers define the HSC is lacking, thus making direct comparisons between trials difficult. Given this loose definition of HSCs, some of the trials discussed in the following section might apply equally to other BMC products, and vice versa. The MAGIC trial assessed the feasibility and efficacy of HSC infusion in patients with MI and who underwent coronary stenting.⁵² Granulocyte colony-stimulating factor (G-CSF), a well-established stem-cell mobilizer, was administered to mobilize bone marrow-derived HSCs into the peripheral blood 4 days before apheresis and cell procurement.⁵² This trial involved three separate arms including the HSC group, a control group (not placebo), and patients receiving G-CSF alone.⁵² At 6 months after infusion, patients treated with HSCs showed significant improvements in exercise capacity (450 vs. 578 seconds), myocardial perfusion (perfusion defect, 11.6% vs. 5.3%), and systolic function (LVEF, 48.7% vs. 55.1%). Although no adverse events occurred because of cell infusion combined with G-CSF, enrollment of the G-CSF cohort was eventually discontinued because of high rates of in-stent restenosis, highlighting a potential safety concern and cautioning future trials using G-CSF administration as a strategy for endogenous stem cell mobilization.⁵² Recent trials, though, such as Perin and colleagues⁴⁷ have not reported any significant adverse cardiovascular or cerebrovascular events associated with HSC infusion in similarly high-risk patient cohorts with advanced ischemic heart failure and CAD ineligible for PCI or surgical revascularization.⁴⁷ The difference, perhaps, is that Perin and colleagues⁴⁷ elected to aspirate bone marrow from the iliac crest as opposed to administering G-CSF. In their trial, HSCs were then purified based on the presence of cytosolic ADH, constituting a population of primitive Lin⁻CD34⁺CD38⁻ cells. When administered to patients with advanced ischemic heart failure ADH⁺ HSCs were associated with a significant decrease in

left-ventricular end-systolic volume and a trend toward maximal oxygen consumption at 6 months.⁴⁷ It is difficult to draw meaningful conclusions given that only 20 patients were enrolled in the study. Overall, HSCs appear to be beneficial for the treatment of ischemic cardiomyopathies, but larger, randomized, controlled trials are required to confirm early results.

Endothelial Progenitor Cells

Before the characterization of a circulating EPC in 1997 by Asahara and colleagues,¹⁵ vasculogenesis, the process of de novo blood vessel development, was believed to be limited to the embryonic development of vasculature from endothelial cell progenitors or angioblasts. Now it is understood that a subset of bone marrow cells, possibly the putative EPC, mobilizes from the bone marrow to the peripheral circulation ultimately reaching sites of tissue injury or ischemia to participate in postnatal vasculogenesis.^{13,15,53,54} Circulating EPC levels have also been recognized as possibly providing clinical information on atherosclerotic burden and future cardiovascular risk.^{55,56} Despite the significant attention that has been devoted to studying EPC biology, consensus on an unambiguous definition of the EPC is still lacking and, likewise, the success of many studies has been hindered by the absence of such a definition. EPCs were first characterized as a population of cells that were CD34⁺, VEGFR2⁺, and adherent to fibronectin (Fig. 101-3A).¹⁵ Today, they are either broadly identified as the mononuclear cells adherent to fibronectin or by cell surface expression that may or may not include CD31, FLK-1 (VEGFR2), CD34, CD133 (AC133), c-kit, and other endothelial markers including VE-cadherin.⁵⁷ The criteria that distinguish an HSC from an EPC, and vice versa, may seem unclear given they seem to share many of the same surface antigenic markers.⁵⁷ As a cell therapy product, however, EPCs are distinguished from HSCs based on specific ex vivo culture requirements. Separate techniques exist to produce what can be referred to as the *early* or *late* EPC. Both early and late EPCs first require isolating the mononuclear cell fraction from the peripheral circulation, and early EPCs are generated

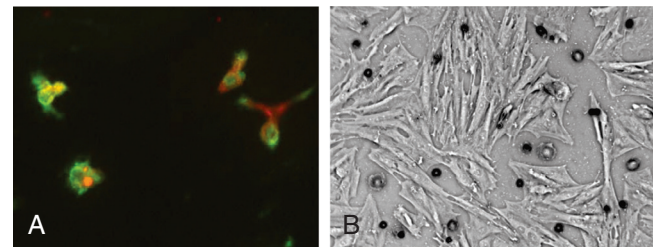


FIGURE 101-3 ■ Endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs) in culture. **A**, EPCs from the peripheral blood mononuclear cell layer, cultured on fibronectin for 4 days. Adherent cells (CD34⁺, VEGFR-2⁺) typically take up the markers lectin and Dil-Oxidized Low Density Lipoprotein. **B**, MSCs cultured from human bone marrow yielding a population of adherent MSCs that characteristically express the antigens CD29 and CD44 but are negative for the hematopoietic cell marker CD45.

through subsequent culture on fibronectin for 3 to 7 days, whereas late EPCs are produced via culture for greater than 14 days on collagen type I.^{55,58} For a more detailed discussion on the characterization of EPC phenotypes or potential diagnostic use of circulating EPCs, interested readers are referred to an excellent review by Fadini and colleagues.⁵⁵

In preclinical animal models of ischemic cardiomyopathy EPC transplantation prevented cardiac myocyte apoptosis, resulted in increased blood vessel formation, decreased infarct size, and improved function.^{59,60} The capacity for human EPCs to transdifferentiate into cardiomyocytes has also been reported,⁶¹ but not all studies support this conclusion.⁶² Instead, recent evidence suggests that human early EPCs may be proangiogenic, enacting their salutary properties through paracrine mechanisms. The proangiogenic effects of late EPCs, instead, is thought to be via direct incorporation into the vasculature.^{55,63}

Considering the attention EPCs have received in preclinical animal models of myocardial ischemia, there is comparatively little experience with their use in patients. This is likely owing to pragmatic considerations and investigator preference for unfractionated or sorted BMC products neither requiring ex vivo culture. EPC cell therapy has been explored in several settings, including AMI and chronic ischemic heart disease. As a therapy delivered shortly after reperfused AMI, the small TOPCARE-AMI trial reported that EPC transplant was safe, feasible, and potentially beneficial.²⁰ EPCs were infused approximately 4 to 5 days after MI and were associated with improved LVEF ($51.6 \pm 9.6\%$ to $60.1 \pm 8.6\%$), improved regional wall motion in the infarct zone, and profound reduction in end-systolic left-ventricular volumes at 4-month follow-up,²⁰ with benefits persisting in the final 1-year follow-up.²² Indeed, contrasting results were released by the same group in a similar trial assessing EPC cell therapy for the treatment of chronic ischemic heart disease.⁶⁴ The randomized, controlled TOPCARE-CHD trial assessed the efficacy of BMC, EPC, or placebo treatment later after MI in patients who had a myocardial infarction at least 3 months before enrollment and a well-demarcated region of left ventricular dysfunction.²⁰ Cells were infused into the vessel supplying the most dyskinetic area of the ventricle, and the results of this study contradict those of TOPCARE-AMI, as EPC delivery was significantly inferior to BMC therapy in terms of improving global left ventricular function.⁶⁴ The absolute improvement witnessed with BMC therapy, similar to their experience in AMI, was modest. BMC therapy was associated with an increase in approximately 2.9 percentage points according to left ventricular angiography and 4.8 percentage points according to MRI.⁶⁴ The precise mechanisms underlying the benefit of BMC therapy were not investigated in the trial, and it remains unclear as to why EPCs proved inferior in this setting. A higher number of progenitors isolated from the bone marrow aspiration may account for this discrepancy. Moreover, given that patients with CHD have been shown to have pronounced EPC dysfunction, limited cell recruitment and action at the site of injury may have also contributed.⁶⁵

Fractionated CD34⁺ Bone Marrow Cells

As an alternative to heterogeneous cell products, in recent years focus has shifted to BMCs isolated based on CD34 expression given their potent proangiogenic properties.⁶⁶ CD34 is believed to be a cell-to-cell adhesion factor expressed in some cell types, including hematopoietic cells, endothelial cells, muscle satellite cells, hair follicle stem cells, and fibrocytes.⁶⁷ The function of CD34 remains largely unknown, although in HSCs some evidence suggests that CD34 alters engraftment potential and other properties, such as cell adhesion and migration.^{67,68} Peripheral blood CD34⁺ cells have been shown to transdifferentiate into most of the major cardiac lineages,⁶⁹ including endothelial cells,^{15,70} vascular smooth muscle cells,⁶⁹ and cardiomyocytes,⁷¹ principally via cell fusion.⁷² CD34⁺ cells purified from peripheral blood BMCs have been shown to exhibit superior efficacy and safety for therapeutic neovascularization after MI compared with total mononuclear cells in rodent studies.^{59,60,73} They have also been shown to exhibit superior efficacy for preserving integrity and function following MI compared with unselected mononuclear cells with an equivalent number of CD34⁺ cells,⁷³ suggesting that a purified CD34⁺ cell product might possess greater therapeutic potential than a mixed mononuclear cell population.

The REGENT trial investigated the therapeutic potential of fractionated CD34⁺ mononuclear cells for the treatment of significant systolic dysfunction (LVEF < 37%) secondary to reperfused anterior MI.⁷⁴ Two hundred patients were randomized to intracoronary infusion of CD34⁺CXCR4⁺ purified cells, total mononuclear cells, or a control group receiving no therapy at all (no placebo) and were followed for 6 months.⁷⁴ Similar to REPAIR-MI, both the purified CD34⁺CXCR4⁺ and BMC therapies were associated with a trend in modest improvement ($\approx 3\%$) in systolic function.⁷⁴ Unfortunately, the study was plagued by a high dropout rate in the control cohort, probably because of the open-label design, which may have potentially accounted for some results not reaching statistical significance. Nonetheless, for patients who received CD34⁺ cell therapy, a clear trend for better outcomes was evident in patients with a baseline ejection fraction (EF) below the median (<37%) compared to those whose baseline EF was above the median. In addition, a low baseline EF (<37%) was an independent predictor for pronounced benefits in terms of cardiac function.⁷⁴ This pattern is consistent with the results reported in REPAIR-AMI.²³ The authors also highlighted that the use of a relatively small number of CD34⁺CXCR4⁺ cells was associated with a similar trend in functional improvement as the use of 100 times more total mononuclear cells, similar to the results published by Kawamoto and colleagues in rats.^{73,74} The mechanisms that could account for these benefits were not explored, but it is unlikely that it was a result of de novo cardiomyocytes. Instead, recent laboratory evidence indicates that CD34⁺ cells secrete exosomes that have independent angiogenic activity, potentially accounting for a significant component of the paracrine effect of these cells.⁶⁶

Indeed, the hallmark of ischemic cardiomyopathies, such as myocardial infarction, is the loss of myocardium.

In this scenario, cell therapy may be a futile endeavor if no meaningful restoration of myocardium can be accomplished. Moreover, the data supporting the cardiomyogenic potential of CD34⁺ purified cells is less than convincing. However, in situations in which instead neovascularization may be preferred, CD34⁺ cells could offer some benefit. Early evidence for the feasibility, safety, and benefit of purified CD34⁺ cells mobilized by G-CSF administration in 24 patients with refractory angina was provided by Losordo and colleagues⁷⁵ in a pilot phase I/IIa randomized trial. Follow-up was performed in a larger double-blind, randomized phase II trial in 167 patients.⁷⁶ CD34⁺ purified cells, or an equal volume of diluent (placebo), were injected with an electromechanical (NOGA) mapping injection catheter. Low-dose CD34⁺ therapy improved both weekly angina frequency and exercise tolerance measures.⁷⁶ Mortality was not different between control and cell therapy cohorts at 12 months, although cell mobilization and collection procedures were associated with elevations in cardiac enzymes that will require follow-up in future studies.⁷⁶

CD34⁺ purified cells might represent a natural progression from unfractionated BMC therapies, and a more standard product compared with HSC- or EPC-based therapies based on their properties and preclinical results. However, cumulative evidence reviewed in a recent meta-analysis of BMC trials suggests that, overall, CD34⁺ purified cell therapy might not offer meaningful benefits in the settings of acute MI or chronic HF, possibly because of a lack of clinically relevant cardiomyogenic potential.⁴³ Given their potent proangiogenic paracrine properties, CD34⁺ cells could offer potential in settings where neovascularization in itself could offer substantial benefits, such as refractory angina or chronic ischemic cardiomyopathy.

Mesenchymal Stem Cells

Mesenchymal stem cells are stromal cells found within the bone marrow or adipose tissue and can be expanded via ex vivo culture (see Fig. 101-3B).⁷⁷ Similar to other bone marrow cell types, they are loosely defined based on surface expression and culture characteristics which include adherence to plastic in cell culture and the surface antigen expression of CD105⁺/CD90⁺/CD73⁺/CD34[−]/CD45[−]/CD11b[−] or CD14[−]/CD19[−] or CD79[−] α /HLA-DR1[−].⁷⁸ MSCs have been identified as promising candidates because of their relative ease of procurement, multilineage differentiation potential, robust secretome, antiapoptotic, immunomodulatory properties.^{55,81,83,84} They have also been shown to be capable of activating resident cardiac stem cells.^{51,77,79,80} Given their immune-privileged status, they may serve as ideal allograft candidates, although the long-term benefits as allogeneic products have been challenged.⁸¹ Some authors contend that MSCs can adopt cardiomyocyte-like phenotypes when injected into both healthy and infarcted myocardium; however, these results have been scrutinized, and others attribute these observations as either MSC fusion with resident cardiomyocytes or nonexistent altogether.^{79,82,83}

Purified human-derived MSCs have been shown to attenuate contractile dysfunction and to prevent adverse

remodeling in rodent and swine models of myocardial infarction.⁸²⁻⁸⁴ In contrast with the classical method of collecting cells and deploying via infusion or injection, initial clinical attempts at harnessing MSCs assessed pharmacologic mobilization of the cells from the bone marrow using G-CSF. Assessing G-CSF mobilized cells soon after AMI, results from the “G-CSF ST-segment Elevation Myocardial Infarction” (G-CSF STEMI), “STEM cells in Myocardial Infarction” (STEMMI), and “Regenerate Vital Myocardium by Vigorous Activation of Bone Marrow Stem Cells” (REVIVAL-2) trials showed that G-CSF administration did not result in improved systolic function compared with placebo.⁸⁵⁻⁸⁸ A substudy of the STEMMI trial sought to describe the cells mobilized by G-CSF administration and to determine the association, if any, between plasma concentration of these cell types and changes in left ventricular systolic function.⁸⁶ The authors associated an inverse relationship between circulating MSCs and systolic functional improvement following G-CSF administration after MI.⁸⁶ This relationship was left relatively unexplored, but it could be a consequence of several mechanisms. It may be that reduced circulating MSCs is a reflection of increased homing to the infarcted myocardium, or given the large size of MSCs their increased concentration in the circulation may contribute to further microembolization and infarction.

MSCs are one of the few cell types to date that may offer a true “off-the-shelf” product given their potential immune-privileged status.⁷⁸ Hare and colleagues⁸⁹ assessed the safety of this type of allogeneic product in a double-blind, randomized, dose-ranging trial of 53 patients with reperfused MI. The primary end-point of the study was safety, whereas efficacy measured by ejection fraction and ventricular volumes constituted exploratory, secondary end-points. Safety profiles were similar between the allogeneic MSC product (Prochymal; Osiris Therapeutics Inc., Baltimore, MD) and placebo treatments.⁸⁹ Patients receiving MSCs experienced fewer episodes of ventricular tachycardia and improved pulmonary forced expiratory volumes.⁸⁹ In terms of efficacy, MSCs were associated with improved global symptom score and ejection fraction.⁸⁹ These results highlight some potential advantages of MSCs versus other BMC products. For example, the product used in this trial was a readily available allogeneic product prepared from healthy donors, circumventing any potential issues with patient clinical condition on cell potency. It also obviates the need for an invasive and highly painful bone marrow aspiration. Results from the recent POSEIDON trial reinforce some of these benefits.⁹⁰ POSEIDON was a small, randomized, pilot trial that compared the safety and efficacy of autologous or allograft MSC transcatheter delivery in patients with chronic ischemic LV dysfunction secondary to MI.⁹⁰ The primary end-point was safety measured by incidence of severe adverse reactions.⁹⁰ None of the cell products reached the predefined stopping point for incident severe adverse reactions, supporting the low immunogenicity of MSCs. In terms of secondary end-points, reflecting efficacy, the combined results appear encouraging. Autologous, but not allogeneic, therapy resulted in improvements in the

6-minute walk test and Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores.⁹⁰ Moreover, both cohorts demonstrated improvements in New York Heart Association (NYHA) class.⁹⁰ Both were associated with reduced early enhancement defect, a measure of infarct size, end-systolic volumes, and sphericity.⁹⁰ In addition, patients having received allogeneic therapy demonstrated improved end-diastolic volumes.⁹⁰ Changes in EF were not apparent from the aggregate results, although a trend for an inverse dose-response relationship was observed. Increases in EF and pronounced changes in ventricular geometry were evident in patients receiving a lower dose of MSCs.⁹⁰ The results are promising but will require substantiation in several follow-up trials given the small sample size, open-label design, and lack of a placebo-controlled group.⁹⁰

MSCs are an exciting candidate as the field of cell therapy progresses. Given their potent paracrine properties and immune privilege, they may truly offer the potential for an off-the-shelf product. A major knowledge gap that remains before the potential for these cells can be fully realized is the mechanisms underpinning observed benefits. Nevertheless, given their purported benefits and considerable secretome, MSCs appear to be promising as cardiac cell therapy evolves.

Summary of Bone Marrow Cell-Derived Products

Establishing a firm position on the benefits of BMC-based cell therapies is challenging. Several recent meta-analyses agree that BMC cell therapy could offer modest short-term functional improvements at 6 to 12 months, with a trend indicating that these benefits may also persist long term in patients with AMI.^{43,44} Some effects on left ventricular end-systolic volume, recurrent AMI, readmission for heart failure, unstable angina, or chest pain were also associated.^{43,44} Given the high degree of trial variability in elements—such as the time of delivery following MI or reperfusion, cell type, cell dose, method of administration, imaging modalities to assess function, and clinical hard end-points—conclusions are difficult to draw. Moreover, many of the recent, larger trials failed to demonstrate benefits.⁹¹ Even so, the question remains of whether modest improvements in cardiac function are clinically relevant.⁴³ Several of the aforementioned BMC cell types may be suitable for some clinical scenarios, although they likely do not represent the ideal candidate for regenerating lost myocardium.

Pluripotent Cells

The two cell types that may possess the most potential are the ESCs and their manmade counterparts—the inducible pluripotent stem cells (iPSCs)—although the neoplastic risk associated with pluripotent cells may preclude their use in patients. ESCs also remain a controversial cell type given their stage of harvest. ESCs are obtained from the inner cell mass of a preimplantation-stage blastocyst.⁹² They were first successfully isolated in 1998,⁹² and since have been differentiated into cardiomyocytes *ex vivo*.^{93,94} Undifferentiated human ESCs express the stem cell markers Oct4, stage-specific mouse

embryonic antigen (SSEA)3/4, TRA-1-60, and TRA-1-81.⁹⁵ ESC-derived cardiomyocytes exhibit proper morphology with organized sarcomeres and express cardiac specific transcription factors such as Nkx2.5, GATA-4, and MEF2C, although they lack a true, mature phenotype.^{96,97,98} Transplanted ESC-derived cardiomyocytes have been shown to produce functional improvements in several rodent infarct models.⁹⁸⁻¹⁰¹ To date, only one pre-clinical large animal study, performed by Ménard and colleagues,¹⁰² has been conducted to evaluate the cardiomyogenic potential of ESCs for myocardial ischemia. Ménard and colleagues¹⁰² delivered cardiac-committed murine ESCs 2 weeks after MI into the host myocardium of immunosuppressed or immunocompetent sheep. The ESCs engrafted and functionally colonized the scar area, with new cardiomyocytes resulting in modest improvements in cardiac function.¹⁰² ESCs represent the ultimate example of the candidate cell for cell therapy as they fulfill all the criteria of a stem cell: clonality, self-renewal, and pluripotency. However, given they can be driven to virtually any cell type they are also a significant neoplastic risk.¹⁰³ ESCs will also necessarily be allografts posing a risk for graft rejection. The benefits reported by Ménard and colleagues¹⁰² occurred without teratoma formation or graft rejection, regardless of whether the sheep were administered immunosuppression. Others, though, have published contrasting results.¹⁰¹⁻¹⁰⁴ Future methodological breakthroughs may serve to significantly reduce the risk of graft rejection or neoplasticity, although it is contentious whether these risks can be eliminated completely. The modern clinical trial is a stringent and risk-adverse environment, each becoming more and more difficult to achieve regulatory approval.^{3,45} Graft rejection and teratoma formation for ESC therapy, even in one patient, would constitute an unacceptable outcome. It is also doubtful that the controversy surrounding ESC use in the clinic will subside—at least anytime soon. Therefore, it is unlikely, at least for the foreseeable future, that ESCs will ever be used in the clinic.

The iPSC was the focus of the 2012 Nobel Prize in Physiology or Medicine.¹⁰⁵ They were first generated from adult mouse somatic cells using a collection of transcription factors known as *Yamanaka factors*, named after the senior author who led the discovery.¹⁰⁶ The first human iPSCs were generated in 2007 and have since successfully produced cardiomyocytes *in vitro*.¹⁰⁷⁻¹⁰⁹ The iPSC has garnered significant attention in disease modeling,¹¹⁰ and, unsurprisingly, many investigators agree that the iPSC holds tremendous promise for cardiac regenerative medicine.¹¹⁰ At the time of writing this chapter, no clinical trials were in progress relating to iPSC use for cardiac regenerative purposes; however, several animal studies have been published offering promising early results. Canine- and porcine-derived predifferentiated iPSC-endothelial cells were shown to restore cardiac function and to reduce infarct sizes in murine models of myocardial infarction.^{111,112} iPSCs could constitute a viable autologous cell therapeutic, particularly since they obviate the legal and ethical concerns traditionally associated with ESCs. Moreover, as iPSC reprogramming technology improves they may constitute the ideal cell type for personalized medicine. It may be possible one day to design patient- or disease-specific iPSCs in an

effort to cater to specific clinical needs and patient characteristics. Currently, translation of iPSC based therapies into the clinic is premature. For one, similar to ESCs the methods required to produce iPSCs are known to be oncogenic.¹¹³ New techniques have done much in addressing this issue including the use of small molecules or synthetically modified mRNA.^{114,115} Predifferentiating iPSCs to the desired cell type, such as cardiomyocytes or endothelial cells, may be a possible alternative if contaminating undifferentiated iPSCs could be eliminated, or at least significantly minimized.¹¹⁶ Regardless, these efforts may be futile because the process of reprogramming somatic cells can induce genetic or epigenetic aberrations that may prove irreconcilable technically and incompatible clinically.¹¹³ Ultimately, new methods would need to be verified rigorously first to ensure the absence of a neoplastic risk before the first patient could be treated. Should the risk of tumor formation be addressed, the lack of methods to produce standardized cell products with sufficient yield is another obstacle that may also preclude their clinical use.¹¹⁷ The efficiency of generating iPSCs is low, and there is significant variability in yield with current methods and technology.^{113,117} Nevertheless, the results from early studies into the potential therapeutic benefits of iPSC-derived products certainly warrant further investigation.

Cardiac Stem and Progenitor Cells

The premise that the adult human heart is a postmitotic organ was the dominant view for much of the twentieth century. Observations of possible cardiomyocyte turnover in the adult human heart emerged as early as 1960, although what might constitute the most direct evidence was provided recently in 2009 by Bergman and colleagues.¹¹⁸ Taking advantage of the rise in atmospheric ¹⁴C from Cold War-era nuclear bomb testing that ended in 1963, they approximated that cardiomyocytes renew at 0.45% to 1% per year, gradually declining as one ages.¹¹⁸ Although the actual rate of turnover remains unclear, this evidence firmly established some capacity for myocyte turnover in the heart; however, many fundamental questions persist regarding the heart's ability to self-renew.^{98,119} The source of this capacity was potentially answered by Beltrami and colleagues¹²⁰ in 2003 who identified a niche of stemlike cells existing within the heart of mammals. These putative "cardiac stem cells" were negative for hematopoietic cell lineage markers and positive for stem cell marker c-kit, and they were clonogenic, could self-renew, and were multipotent.¹²⁰ They were capable of differentiating into cardiomyocytes, smooth muscle cells, and endothelial cells.¹²⁰ In addition, when injected into the ischemic rat heart, these cells or their clonal progeny were shown to develop blood carrying vessels and myocytes with features characteristic of younger cells.¹²⁰ Given these properties, the putative "cardiac stem cell" (CSC) may represent the best candidate cell type for cardiac cell therapy.

Since the results released by Beltrami and colleagues, CSC contribution to postnatal cardiomyogenesis has gained support.^{121,122} However, these reports conflict with the firmly established evidence that cardiomyocyte renewal in animals that display considerable cardiac

regenerative potential (e.g., amphibians, zebrafish) occurs via the proliferation of preexisting myocytes and not from the influence of stem cells.⁹⁸ Indeed, contrasting evidence was provided by Senyo and colleagues,¹²³ reporting that either during normal cardiac homeostasis or in response to injury cardiomyocyte renewal in mice occurs by the division of preexisting cardiomyocytes and is not mediated by a stem cell niche. Others, however, provide compelling evidence that c-kit⁺ cardiac stem cells are necessary and sufficient for complete functional and anatomic recovery during diffuse cardiac injury with patent coronary circulation.¹²⁴ These seemingly contradictory observations may be reconciled with the hypothesis that ischemic injury depletes tissue stem cells, possibly including CSCs.¹²³⁻¹²⁶

Despite the uncertainty revolving around the cardiomyogenic potential of CSCs *in situ*, many researchers and clinicians have pursued using this population therapeutically. To date, several methods have been developed to isolate and expand this population *ex vivo* for therapeutic purposes including purified c-kit⁺ cells, cardiosphere-derived cells (CDCs), Sca1⁺ CSCs, side population cells, and islet-1⁺ cells. In this review, we will focus on the CDCs and purified cardiac c-kit⁺ cells (i.e., CSCs), which are the best studied and are the only populations in which there are ongoing clinical trials.^{10,127,128}

C-kit⁺ Cardiac Stem Cells

Cardiac stem cells isolated and purified based on c-kit surface expression are the best characterized in terms of preclinical animal models of cardiovascular disease. Human CSCs injected early after permanent coronary occlusion in immunodeficient mice and immunosuppressed rat hearts were shown to restore some contractile function to the infarcted area of the ventricle, improve ventricular performance, and alleviate some chamber dilation.¹²² In addition, hearts explanted from both animal groups demonstrated chimerism and the coexistence of human and rodent cells together within the infarcted myocardium.¹²² Rota and colleagues¹²⁹ assessed CSC delivery in a model of chronic HF secondary to ischemia where the isolation and injection of CSCs may be more clinically feasible and have shown that injecting CSCs into the border zone of a 20-day-old infarct in rats preserved left ventricular function, successfully replaced a portion of the myocardium, and mitigated some ventricular remodeling.¹²⁹ CSC transdifferentiation into cardiomyocytes has been offered to explain the positive effects of CSC transplantation.¹²⁹ However, others, such as Tang and colleagues,¹³⁰ report that CSC integration with the myocardium could not account completely for the benefits. In their study, GFP⁺ CSCs only occupied 2.6% and 1.1% of the risk and noninfarcted regions, respectively¹³⁰; therefore, a paracrine mechanism likely explains the discrepancy. The beneficial effects of CSC therapy have been replicated in large animal models as well.¹³¹ For example, Bolli and colleagues¹³¹ administered CSCs 3 to 4 months after reperfused MI in swine via the infarcted artery. Swine receiving CSC therapy had significantly greater LV ejection fraction, maximum LV dP/dt, and lower LV end-diastolic pressures at 1 month after treatment.¹³¹ Together, these studies provide proof of

concept that c-kit⁺-selected CSC transplantation may offer functional benefits and may be also capable of promoting some degree of myocardial regeneration during ischemic injury.¹²²

The “Stem Cells Infusion with Patients with Ischemic cardiomyopathy” (SCIPIO) (Clinicaltrials.gov, no. NCT00474461) phase I trial is the only trial at the time of this writing assessing autologous c-kit⁺ lineage-negative CSC therapy for the treatment of an ischemic cardiomyopathy.¹²⁷ Results from the 2-year follow-up of SCIPIO were not available at the time of compiling this chapter, although interim results have been published.^{127,132} SCIPIO is a phase I, open-label, single-center trial assessing CSCs in patients with heart failure secondary to ischemic disease. The open-label design was chosen given that blinding the control cohort would have required cardiac catheterization with placebo infusion.¹²⁷ Patient inclusion criteria included previous myocardial infarction, LVEF less than 40%, and undergoing CABG. CSCs were administered approximately 3 months after CABG being delivered to the proximal coronary artery or graft supplying the infarcted region of the ventricle. Overall, from the interim results, patients that completed the 12-month follow-up had an absolute increase in LVEF of 12.3 points, whereas no improvement was apparent in patients in the control cohort.¹²⁷ The mean LVEF of all patients before treatment was approximately 30%. In addition, the NYHA functional class decreased in all 16 patients receiving CSC treatment from a mean of 2.19 to 1.63 after 4 months and patient responses to the MLHFQ, from 46.44 to 26.69. No changes were reported in the NYHA or the MLHFQ for control patients. CSC collection in the operating room appears not to interfere with standard procedures or outcomes,¹³² and harvest was successful despite the severity of disease, comorbidities, and likely feasible for most patients undergoing CABG. The procedure did not prolong cardiopulmonary bypass time, aortic cross-clamp time, or total surgical time.¹³² In summary, the use of autologous c-kit⁺ CSCs holds much promise, likely deriving from the fact that these cells may represent a cardiac specific stem cell niche responsible for cardiomyocyte homeostasis. Thus far, phase I clinical trial results agree with the preclinical animal models, and the procedure of harvesting and CSC infusion appears to be safe warranting further study in phase II trials.

Cardiosphere-Derived Cells

Cardiosphere-derived cells represent a heterogeneous ex vivo outgrowth cell product derived from cultured cardiac biopsies.¹³³⁻¹³⁵ This subpopulation was first reported by Messina and colleagues¹³⁴ in 2004. The term *cardiosphere* was coined from the observation that ventricular or atrial tissue biopsy subcultures would produce emigrating cells that formed spherical aggregates.¹³⁴ These aggregates contained, among a number of cell types, cardiac progenitors and when injected into the infarcted rat myocardium would produce functional benefits and some histological recovery.¹³⁴ Since its original description, the CDC method has been refined to include endomyocardial biopsy specimens.¹³⁵ Phenotypically, these cells express a wide array of surface antigens, including those

that mark endothelial cells (KDR human; FLK1 and CD31 mouse), embryonic and stem cells (SSEA-1, abcg2, CD34, c-kit, sca-1), and mesenchymal stem cells (CD105, CD90). In rodent models, when injected shortly after experimental infarction, CDCs were associated with improved LVEF and hemodynamic parameters, as well as reduced infarct sizes and increased percentage of viable myocardium.¹³³⁻¹³⁶ In swine, CDCs harvested from endomyocardial biopsy specimens infused 1 month after MI were associated with a reduction in relative infarct sizes compared with control at 8 weeks after treatment.¹³⁷ CDCs were also associated with improved hemodynamic parameters such as higher dP/dt maximum and lower dP/dt minimum, and no instances of infarction related to cell infusion was reported.¹³⁷ However, CDC infusion did not reduce final infarct size, improve LV mass, or improve contractile function of the ventricle.¹³⁷ Allogeneic CDC transplant has also been documented as being safe and relatively non-immunogenic in pre-clinical models.¹³⁶ Transplantation without immunosuppression appears safe and functional results are consistent with previous studies.¹³⁶

The CDC method for isolating CSCs has been sharply criticized with claims that cardiospheres represent primarily a culture of fibroblasts and other cardiac cell contamination,¹³⁸ but this view is not universal as others have shown that adult cardiac stem cells can be grown directly from myocardial biopsies.¹³⁹ The promising preclinical results warranted investigation in a phase I clinical trial. To date, three clinical trials are complete or ongoing studying the use of CDCs for cardiac regeneration; these include “CARDiosphere-Derived aUTologous Stem Cells to Reverse ventricUlar dysfunction” (CADUCEUS) trial (NCT008933602), the “AutoLogous Human CARDiac-Derived Stem Cell to Treat Ischemic cARDiomyopathy” (ALCADIA; NCT00981006), and the “Allogeneic Heart Stem Cells to Achieve Myocardial Regeneration” (ALLSTAR; NCT01458405) trials. The CADUCEUS study involves the use of CDC products from septal endomyocardial biopsy specimens, the ALCADIA trial will be assessing bFGF slow release concomitant with CDC therapy, while ALLSTAR will assess allogeneic CDC transplant. At the time of this writing, both ALLSTAR and ALCADIA are in the process of recruiting patients, and results were only available for the CADUCEUS trial.¹²⁸ The CADUCEUS trial assessed CDC therapy for patients with recent myocardial infarction (≤ 4 weeks) and significant left ventricular dysfunction (LVEF $\geq 25\%$, $\leq 45\%$). Patients were randomly assigned to a treatment group, and those receiving CDC therapy were administered the product (≤ 90 days after myocardial infarction) via over-the-wire angioplasty catheter in the infarct-related artery.¹²⁸ The primary endpoint was safety 6 months after infusion, including ventricular tachycardia, fibrillation, sudden unexpected death, and MI after infusion.¹²⁸ Efficacy was assessed in terms of the NYHA class, MLHFQ, 6-min walk test, and MRI. CDC therapy did not produce complications within 24 hours of infusion. Overall, CDC therapy seems safe, with 24% of patients in the CDC group having experienced serious adverse events compared to 13% in the placebo, but conclusions are difficult to draw given the

low number of patients included in the study. There were no differences reported in NYHA, or MLHFQ scores. Patients receiving CDC at 1 year increased walked distance compared with controls. No differences in LVEF were reported; however, MRI non-gadolinium-enhanced tissue in CDC patients showed reduced scar mass, increased viable heart mass, regional contractility, and regional systolic wall thickening. There were no benefits in terms of end-diastolic volume, end-systolic volume, and LVEF by 6 months. The lack of benefit in terms of global cardiac function, particularly LVEF, is consistent with the large-animal model published by Johnston and colleagues.¹³⁷

Overall, CDCs are a heterogeneous population of cells that can be derived from several available subculture methods of atrial, ventricular, or endomyocardial biopsy specimens. Some controversy exists as to the cardiomyogenic potential of this product, but there appears to be more proponents than critics. Unfortunately, the clinical effects of CDC therapy are somewhat mixed. Results from the CADUCEUS study did not confirm meaningful effects on cardiac function or clinical status in patients treated with CDCs. Overall, CDCs represent an alternative method to the lineage-negative c-kit⁺-purified CSC, although based on available evidence further assessment of clinical outcomes is required.

Combination Products

The clinical experience with most of the cell populations studied thus far have unarguably not met with expectations motivated by preceding preclinical results. A number of laboratories have investigated combining different cell types in the effort of taking advantage of complementary modes of action and possible synergistic effects. Some examples follow.

Early and late EPCs appear to promote neovascularization through separate modes of actions. Early-EPCs seem to be proangiogenic on account of a paracrine mechanism, whereas late EPCs tend to integrate directly within the microvasculature.⁵⁸ Given these separate yet complementary mechanisms of action, Yoon and colleagues¹⁴⁰ demonstrated that infusing a combination of early and late EPCs promotes a synergistic effect on neovascularization. Similarly, Latham and colleagues¹⁴¹ cotransplanted CDCs with early EPCs 1 week post-MI in mice. In vitro both cell types promoted equivalent vascular networks, whereas the cell types had distinct cytokine profiles. Each offered similar functional benefits when transplanted alone, though when transplanted together offered a complementary effect on function superior to the benefits of either cell type individually.¹⁴¹ In swine with reperfused MI, Williams and colleagues¹⁴² reported that combined transplantation of MSCs and CSCs reduced infarct sizes twofold greater in combination than either cell alone, and the combination therapy restored cardiac functional parameters, such as EF, to baseline. These studies represent a growing body of evidence that begs the question as to whether the future of cell therapy will need to rely on novel strategies, such as multiple cell sources, to achieve the desired clinical outcome.¹⁴⁰

POTENTIAL MECHANISMS OF ACTION FOR CELL-BASED REGENERATIVE THERAPIES

Our experience so far with cell-based regenerative therapies is that they are safe, feasible, and potentially beneficial for a number of clinical settings, including AMI, chronic ischemic cardiomyopathy, refractory angina, and heart failure. However, a major gap that persists is understanding the mechanisms underpinning their benefits. The following sections will describe our current understanding of the mechanisms of action of cell based therapeutics in cardiac regenerative medicine. A schematic representation of the major proposed mechanisms of action of transplanted cells is shown in [Figure 101-4](#).

Transdifferentiation and Cell Fusion of Transplanted Cells

The initial hope with cell-based therapies was that it would provide a means of regenerating previously lost myocardium through transdifferentiation to cardiomyocytes. It also may appear to be the most obvious justification to explain the salutary effects of cell therapies; however, with the evidence that is available to date, it does not appear to be the major mechanism, if providing any contribution at all. For example, the transdifferentiation of bone marrow cells, including CD34⁺ selected cells,^{73,75,76,160} has equally as many critics^{16,17} as there are supporters.^{49,143} Instead, the concept of BMC cell-fusion with resident cardiomyocytes has been proposed, but again this has also been contested.^{144,145} Initially, MSCs appeared to participate in cardiomyogenic phenomena as well, although now their benefits are believed to be derived primarily from their robust secretome.* CSCs have been reported to produce all major cardiac lineages,^{120,126,129,130,149} yet some reports deem this process insufficient to account for the improvement in cardiac function.¹³⁰ The evidence supporting the cardiomyogenic potential of CDCs is somewhat less nebulous, reported as either quite minimal¹⁵⁰ or nonexistent altogether.¹³⁶

It is possible that transplanted cell therapies have been able to regenerate cardiomyocytes within damaged myocardium. How much is occurring and the overall contribution to the functional effects are the questions that remain. Most reports to date agree that if any cardiomyogenesis occurs, it is certainly disproportionate with the magnitude of the benefits. Instead, other mechanisms are more likely.

Neovascularization from Transplanted Cells

Many of the cell types discussed have been demonstrated to offer some capacity to contribute to the formation of new blood vessels within the myocardium including BMCs, CSCs, MSCs, and CD34⁺ cells ([Fig. 101-5](#)).^{15,73,149,151} Neovascularization may prove beneficial in

*References 77, 78, 80, 82, 84, 146-148.

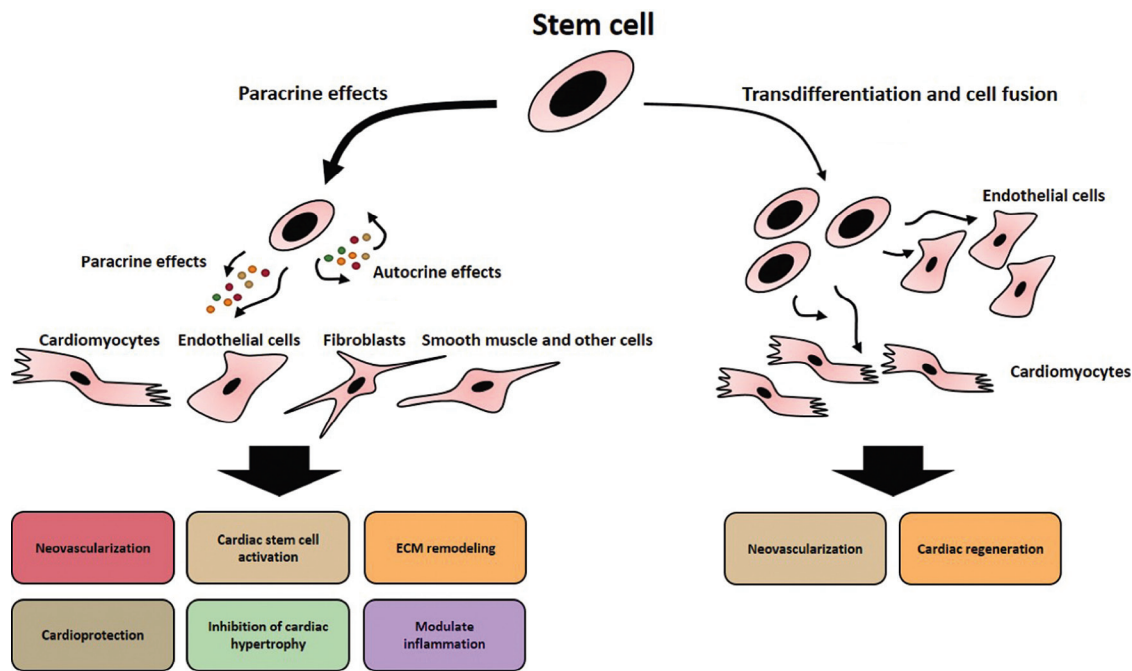


FIGURE 101-4 ■ Proposed mechanisms of action for transplanted stem cells. Transplanted stem cells were originally thought to participate in cardiac repair via direct transdifferentiation (*right side, thin arrow*). We now understand the contribution of cell fusion and transdifferentiation of stem cells to cardiomyocytes and neovascularization to occur very minimally, if at all (denoted by *thin arrow*). Instead the predominant hypothesis is that transplanted stem cells influence the behavior and survival of resident cells through paracrine effects (*left side, thick arrow*). Transplanted stem cells can release soluble growth factors, angiogenic cytokines, and microRNA that together serve to promote neovascularization, activate resident cardiac stem cells, favorably alter extracellular matrix (ECM) remodeling, confer cardioprotection, inhibit cardiac hypertrophy, and modulate inflammation. Intervening on these processes may ameliorate this emerging cardiac therapeutic modality.

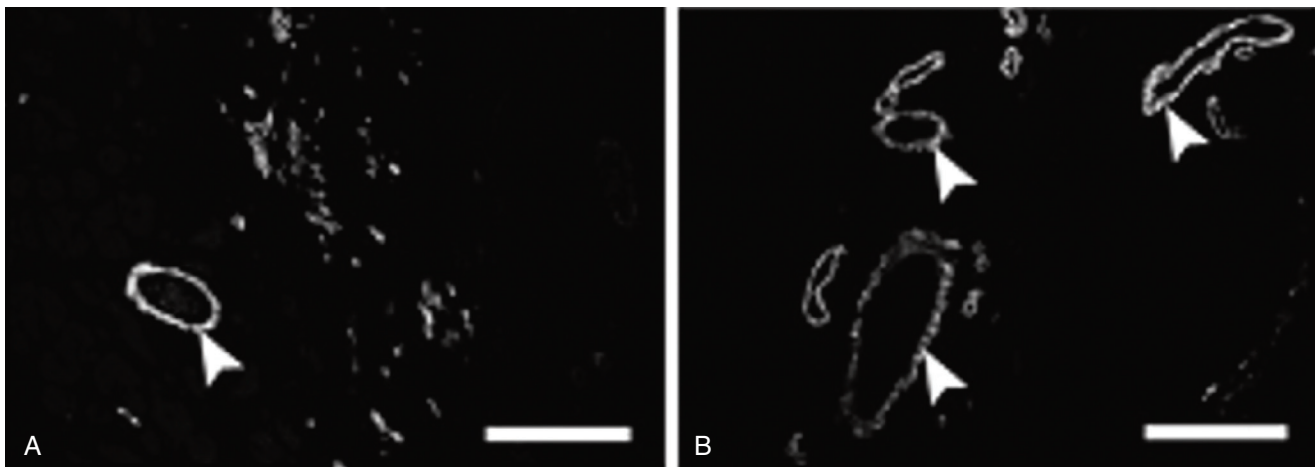


FIGURE 101-5 ■ Transplanted cell contribution to neovascularization. Transplanted endothelial progenitor cells (**A**) and mesenchymal stem cells (**B**) contributing to the formation of capillaries within muscle fibers. Arrows indicate positive α -smooth muscle acting staining in arterioles. Scale bar = 150 μ m.

settings where the region of interest may constitute ischemic, but viable, myocardium. However, the benefits of increasing blood vessel density are less clear in many clinical scenarios. For example, in a scar from an old MI or during acute reperfused MI, it is hard to imagine how increased vascular density would be advantageous. Perhaps settings such as refractory angina or chronic ischemic cardiomyopathy are examples of when benefits may be potentially derived from increased vessel density, but this is not the case with all clinical scenarios.

The Paracrine Hypothesis

Paracrine effects is the reigning hypothesis to explain the benefits associated with transplanted cells. *Paracrine* refers to the capacity of transplanted cells to release signal and growth factors (cytokines, chemokines, exosomes, microparticles, and microRNAs) into the extracellular milieu affecting the behavior and survival of neighboring cells.^{146,151,152} Examples of the reparative processes associated with paracrine effects include neovascularization,

cardioprotection, modulating inflammation, inhibiting remodeling, antihypertrophic responses, and activation of resident cardiac stem cells.

Neovascularization

The ability to promote neovascularization for most cell types is a result of the release of various chemokines (SDF-1a),^{153,154} proteins (e.g., VEGF, bFGF, IGF-1),^{155,156} and microRNAs, potentially through exosomes.^{66,157,158} The cardioprotective benefits associated with c-kit⁺ cells from the bone marrow after MI is a result of the modulation of the angiogenic cytokine milieu.¹⁵⁹ Reestablishing blood supply in some situations could salvage ischemic myocardium in diseases such as chronic ischemic cardiomyopathy, though as discussed, this mechanism likely does not account for benefits in patients without residual or persistent ischemia.

Cardioprotective

Paracrine-mediated cardiomyocyte salvage in an ischemic environment is an effect of transplanted cells.^{146,151} For example, the functional benefits associated with MSCs appear to occur despite the lack of any evidence of their long-term engraftment within the myocardium.⁸⁴ A number of reports indicate that some of these benefits stem from antiapoptotic effects of secreted factors on cardiomyocytes and endothelial cells.^{77,84,160} Cytoprotective paracrine effects seem to underpin a number of other candidates of cell therapy, including IPSC derived endothelial cells,¹¹² BMCs,^{60,158} EPCs,¹⁵² and cardiac-derived stem cells.¹⁵⁰ The release of IGF-1 and subsequent inhibition of miR-34a processing from transplanted BMCs was recently shown to contribute to the paracrine protective effect of this cell type.¹⁵⁸

Modulation of Inflammation

Chronic, unabridged inflammation is a major determinant of the severity of disease in ischemic cardiomyopathies.¹⁶¹ Injected cells, such as MSCs, can act as guardians of inflammation attenuating the local inflammatory response by releasing signaling molecules within the environment.⁸⁰ Transplanted MSCs into ischemic zones have been shown to decrease proinflammatory cytokines, such as TNF- α , IL-1 α , and IL-6.¹⁴⁶ This may be, in part, mediated by the secretion of anti-inflammatory protein TSG-6.¹⁶² Intravenously infused MSCs after MI in mice were shown to embolize to the lungs, secrete TSG-6, and improve cardiac function and reduce infarct sizes.¹⁶²

Extracellular Matrix Remodeling

The effect of the extracellular matrix (ECM) on proper functioning of the heart cannot be overstated. The stability and dynamic equilibrium of the ECM with cardiomyocytes ensures proper alignment and prevents overstretching of myocytes.¹⁶³ It is also equally important in secondary roles, such as ensuring proper functional and electrical behavior of the myocardium and vasomotor reactivity of coronary microvasculature.¹⁶³ In pathologic

scenarios, such as myocardial infarction, impaired remodeling of the ECM plays a substantial role in LV dilation and dysfunction, and morbidity and mortality.¹⁶⁴ At the molecular level, an imbalance in matrix metalloproteinases (MMPs) and tissue-inhibitors of MMPs (TIMPs) production favors this impaired remodeling.¹⁶⁴ Paracrine factors released by transplanted cells may serve favorably to influence the outcome of ECM remodeling post-injury. For example, MSCs have been shown to decrease postinfarct fibrosis.¹⁴⁶ In a rat model of dilated cardiomyopathy, transplanted MSCs decreased MMP-2 and MMP-9 expression, leading to reduced fibrosis and improved function.¹⁶⁵ Rota and colleagues¹²⁹ demonstrated that transplanted CSCs increased MMP-2, MMP-9, and MMP-14, while decreasing TIMP-4 levels in a model of HF secondary to MI in rats.

Inhibition of Hypertrophy

Stem cells therapies have been shown to reduce the hypertrophic response of cardiomyocytes in models of ischemic heart failure.^{129,130} It is uncertain, however, whether this is secondary to reduced cardiac stress and improved function or whether it constitutes a principal, paracrine function of transplanted cells.

Activation of Resident Cardiac Stem Cells

Endogenous cardiac stem cells are considered to play an important role in cardiac homeostasis, particularly in the turnover of resident cardiomyocytes.¹²⁴ Some cell types have been shown to activate endogenous CSCs. For example, Loffredo and colleagues⁵¹ demonstrated that c-kit⁺ bone marrow cell stimulation of endogenous CSC cardiogenic activity was a critical mechanism of the therapy. The authors also reported that this function was limited to c-kit⁺ BMCs and not MSCs, although others have shown similar results with MSC therapy.^{82,148} The contribution of activated endogenous CSCs also has been shown to be significant with CSC-based cell therapy.¹³⁰

CURRENT CHALLENGES AND FUTURE DIRECTIONS FOR CARDIAC REGENERATIVE MEDICINE

As we move forward in translating new cell therapies into the clinic, we must approach the next steps with careful optimism as many challenges and obstacles remain.¹⁶⁶ Indeed, recent successes in the laboratory and the convergence of different fields, such as tissue engineering, provides exciting opportunities as we work toward finally achieving our goal of cellular cardiomyoplasty. The early experience with stem cell therapy was largely positive, particularly with BMCs. However, since these initial pilot trials ensuing results have contradicted early reports and recent, larger trials have not been able to resolve the controversy reporting positive,³¹ somewhat positive,⁷⁴ mixed,³⁵ and negative findings.^{167,168} Other cell types have been equally controversial, and providing an explanation is difficult. Likely the answer is multifactorial and cumulative. The inconsistency in reported outcomes for stem

cells may arise from clinical factors such as patient clinical characteristics and definitions of efficacy, or other elements such as the limited engraftment or survival of transplanted cells and their dysfunction.¹⁶⁶

Patient Clinical Characteristics

Cumulative evidence from BMC therapy supports modest improvements in clinical parameters such as left ventricular function. These benefits appear to be comparable to current interventions such as primary PCI, mechanical revascularization, or pharmacologic therapy. Unlike BMC therapy, conventional treatments have proven survival outcomes and a well-established routine in clinical practice.¹⁶⁹ Thus, cell therapy may prove unnecessary and equally lack any benefit for some or most patients. In many of the discussed trials, patient cohorts comprised a relatively healthy patient population with reperfused AMI and minor dysfunction ($\geq 50\%$ LVEF) also treated with contemporary medical therapy. Given the comparatively minor dysfunction in these patients, it is possible that they were not those who could derive the most benefit from stem cell therapy. Interestingly, in trials in which patients were stratified based on clinical characteristics (e.g., severe cardiac dysfunction), the greatest benefits appeared to occur in the sickest patients (low baseline EF).^{26,31,74} The implications for future investigations and cardiac therapy altogether are that potentially cell therapy is maximized in those who can possibly derive the greatest benefit—the very ill.

Measures of Efficacy

The prevailing surrogate marker to assess benefits derived from cell therapy has been cardiac left ventricular function, specifically LVEF. Indeed, it is possible that improvements in EF might not be best suited for our definition of efficacy, as EF can be dependent on neurohumoral influences, ventricular geometry, or load. Other metrics of improvement, such as changes in geometry, scar size, perfusion, and viable myocardium measured with modern imaging modalities (e.g., cardiac MRI or PET), may be more appropriate along with other clinically relevant metrics, such as mortality.

Transplanted Cell Dysfunction and Ex Vivo Cell Priming

Clinical trial results have obviously not been as compelling as the preclinical evidence that originally inspired their use in patients. One possible explanation is that, often, many clinical parameters are not recapitulated in animal models. For example, in contrast to preclinical rodent studies in which both donors and recipients are often healthy, young animals, patients are far from healthy and often suffer from other comorbidities. Thus, donor cells from preclinical animal studies are likely poor approximations of the clinical autologous products. For example, BMCs have been shown to be impaired functionally in the setting of diabetes, previous MI, and heart failure, and because of on-pump coronary bypass.^{56,170,171} CSC function and survival, equally, appear to be impaired

by diabetes.¹⁷² In mice, recent MI impairs donor BMC therapeutic efficacy because of a high inflammatory state in the donor bone marrow.¹⁷⁰ As the proper functioning of autologous cells appears to depend on individual patient characteristics, several investigators have sought to use novel methods, such as priming cells *ex vivo*, to circumvent these potential limitations.¹⁹ For example, our group developed a collagen I-based biomaterial matrix as a substrate to improve the potency of cultured early EPCs.¹⁷³ This culture method resulted in a higher proportion of CD34⁺ and CD133⁺ EPC progenitors and improved their capacity to direct *de novo* neovascularization compared with the traditional method of culture on fibronectin.¹⁷³ Other examples include Noiseux and colleagues,⁸³ who showed that over-expressing Akt in MSCs improves transplanted cell retention and engraftment. The Akt-MSCs were superior at reducing infarct sizes and improving cardiac function.⁸³ Overexpressing endothelial nitric oxide synthase (eNOS) in transplanted cells is an example of priming cells that is currently under clinical investigation.^{19,174} Reduced eNOS expression and nitric oxide (NO) production have been implicated in both endothelial dysfunction¹⁷⁵ and in impaired progenitor cell function.^{174,176} Pretreating BMCs *ex vivo* with an eNOS enhancer was demonstrated to rescue this dysfunction and improve their therapeutic efficacy in preclinical studies.¹⁷⁷ The Enhanced Angiogenic Cell Therapy in Acute Myocardial Infarction (ENACT-AMI; NCT00936819)¹⁷⁴ trial will be the first of its kind to assess transgenic, enhanced stem cells. Autologous early EPCs will be transfected with human eNOS to improve their angiogenic potency and cells will be delivered in patients with significant LV dysfunction after MI.¹⁷⁴ The trial is actively recruiting patients, and the first patient was treated in September 2013 in Ottawa, Canada.

Autologous versus Allogeneic Cells

The vast majority of clinical trials for cell therapy have investigated autologous products and depending on individual patient clinical features autologous cells may be suboptimal.¹⁶⁶ This source of cell therapy is obviously attractive as it circumvents challenges involved in allograft surgeries such as immunologic graft rejection.¹⁶⁶ On the other hand, allogeneic products could be advantageous as “off-the-shelf” products obviating the surgical pragmatic concerns of procuring and culturing patient-derived cells, particularly if they are to be infused soon after AMI. They could be highly standardized and produced in large numbers.¹⁶⁶ In turn, this could ensure the cost-efficient, timely and safe access to a cell therapy product. Immune rejection is an obvious concern, as is the potential for eventual immune tolerance. MSCs may be promising candidates as evidenced by the POSEIDON and Prochymal trials^{89,90} given their purported immune-privilege.⁸⁰

Cell Engraftment and Biomaterials

Unfortunately, whether cells have been autologous or allogeneic therapies retention and engraftment continues impede optimal performance.¹⁷⁸ Regardless of delivery method, cell type or method used to assess cell retention

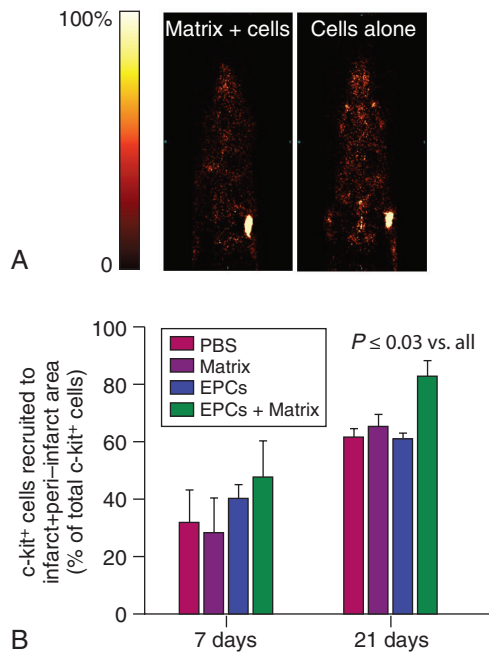


FIGURE 101-6 ■ Stem cell therapy transplanted with collagen-based biomaterial matrix can synergize to improve cell engraftment and functional benefits. **A**, Small animal positron emission tomographic images at 150 minutes after endothelial progenitor cell (EPC) injection into the ischemic hind limb muscle. Images of transplanted ¹⁸F-FDG-labeled EPCs delivered with the matrix showed significantly higher retention compared with the cells injected alone. **B**, C-kit⁺ cell recruitment is greater in EPCs + matrix-treated MI hearts at 1 and 3 weeks after treatment. PBS, Phosphate-buffered saline.

and survival, generally, only a small fraction of transplanted cells are retained within the myocardium over the short term.¹⁷⁸ Over the long term, the loss of transplanted cells is cumulative as attrition worsens.¹⁷⁸ Our group and others have investigated merging principles from tissue engineering and cell therapy to improve the engraftment, retention, and survival of transplanted cells.^{179,180} Suuronen and colleagues¹⁸⁰ assessed the efficacy of CD133⁺ EPCs delivered in a collagen I-based injectable hydrogel matrix in rat ischemic hindlimb. Transplanting cells within the biomaterial improved their retention greater than twofold (Fig. 101-6A), and rats receiving the combined therapy had greater arteriole and capillary densities in the ischemic hind limb compared with cells delivered alone.^{180,181} More recently, we demonstrated that delivering early EPCs with the hydrogel matrix improved transplanted cell engraftment and the recruitment of endogenous c-kit⁺ cells (see Fig. 101-6B), and synergized to improve viability, perfusion, and function of infarcted myocardium.¹⁸² Other investigators from our institute demonstrated that CSCs encapsulated within matrix-enriched capsules delivered in a murine MI model improved the long-term retention of cells and also resulted in greater functional recovery and reduced infarct sizes.¹⁷⁹

In Situ Cell Therapy

The mainstay of current cell therapies has been a workflow of cells that (1) are procured from a donor

(autologous or allogeneic), (2) are or are not further purified and/or primed, and (3) are delivered either via direct injection or intravenous or intracoronary infusion. This process may still hold some clinical potential, but it is costly, labor intensive, and relatively inefficient at promoting cardiac regeneration, if at all. Emerging advances in cell reprogramming may offer new opportunities, including in situ cell therapy. Several authors demonstrated that fibroblasts migrating to and populating the infarcted region of the heart may be reprogrammed into cardiomyocyte-like cells or inducible cardiomyocyte-like cells using a technique similar to the one required to produce iPSCs.^{98,183,184} The efficiency of this procedure is low, with only 7% to 15% of cardiac fibroblasts converted to cardiomyocyte-like cells, but resulted in profound reductions in scar size and improvements in cardiac function.^{183,184} Optimizing the efficacy and safety of this process are obvious requirements for translating them into the clinic; nevertheless, it provides an exciting alternative to the currently accepted paradigm of ex vivo cell therapy. Other groups have investigated similar methods at promoting cardiac regeneration in situ.¹⁸⁵ Eulalio and colleagues¹⁸⁵ demonstrated that administration of select microRNAs markedly stimulated cardiomyocyte proliferation in the border zone and resulted in almost complete anatomic and functional recovery. MicroRNAs may constitute another novel method for in situ cell therapy.

SUMMARY

We are currently in an exciting phase of cardiac cell therapy. Although early forays have not exactly measured up to our initial expectations, we are definitely wiser for it. As we move forward in trying to find the optimal therapy to regenerate the injured heart several pressing issues require addressing. First, we need to return to the laboratory to further understand regenerative mechanisms and how they may be mediated up to improve the efficiency of current and future therapies. Second, an iterative and systematic process of identifying the optimal cell type, dose, and delivery method is required and needs to be substantiated by well-designed, large-multicenter trials for each clinical entity. Moreover, these effects need to be followed up with sufficient power to prove benefits as well as safety. It is possible that BMCs will likely be forgotten as alternatives emerge with proven abilities to repair injured myocardium. Further still, ex vivo cell therapy may die out and lose favor with clinicians and investigators as tissue engineering or in situ methods evolve. It is difficult to predict which cell type or technology might ultimately prevail in our pursuit of a cardiac regenerative therapy, though given that the need for such a therapy will not likely subside anytime soon, the pursuit will continue passionately until we can finally mend a broken heart.

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SURGERY FOR PULMONARY EMBOLISM

Patricia A. Thistlethwaite • Michael Madani • Stuart W. Jamieson

CHAPTER OUTLINE

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SUMMARY

Pulmonary thromboembolism is a significant cause of morbidity and mortality in the United States and worldwide. The estimated incidence of acute pulmonary embolism is approximately 63 per 100,000 patients in the United States, based on clinical and radiographic data.¹ Acute pulmonary embolism is the cause of approximately 235,000 deaths per year based on autopsy data. Acute pulmonary embolism occurs half as often as acute myocardial infarction and is three times as common as cerebrovascular accident. It is the third most common cause of death (after heart disease and cancer).² Estimates of the incidence of acute pulmonary embolism, however, are generally thought to be low, because in 70% to 80% of patients in whom the primary cause of death was pulmonary embolism, the diagnosis was unsuspected premortem.^{3,4}

Of patients who survive an acute pulmonary embolic event, approximately 3.8% will go on to develop chronic pulmonary hypertension (PH).⁵ Once PH develops, the prognosis is poor, and this prognosis is worsened in the absence of intracardiac shunt. Patients with PH caused by pulmonary emboli fall into a higher risk category than those with Eisenmenger syndrome, and they encounter a higher mortality rate. In fact, once the mean pulmonary pressure in patients with thromboembolic disease exceeds 50 mm Hg, the 3-year mortality rate approaches 90%.⁶ Despite an improved understanding of pathogenesis, diagnosis, and management, pulmonary emboli and their long-term sequelae remain frequent and often fatal disorders.

Pulmonary embolism was first described by Laennec in 1819.⁷ It was he who related the condition to deep

venous thrombosis, and Virchow⁸ later associated the three factors predisposing to venous thrombosis as stasis, hypercoagulability, and vessel wall injury. Virchow distinguished two types of thrombus in the pulmonary arteries of such patients: the embolus that arose as thrombus in a systemic vein and the thrombus that occurred in situ within the pulmonary arteries distal to the occluding embolus as a result of the stagnant blood flow in that segment. To prove that pulmonary emboli arose from the peripheral venous circulation, Virchow inserted pieces of rubber or venous thrombi recovered from humans at autopsy into the jugular or femoral veins of dogs. When the animals were sacrificed, the foreign embolic material was found in the pulmonary arteries. Although pulmonary embolism can be caused by tumors, septic emboli, and foreign bodies, the overwhelming occurrence of pulmonary embolism is due to venous thromboembolism.⁹

ACUTE PULMONARY THROMBOEMBOLIC DISEASE

Clinical Points

The majority of pulmonary thromboembolic episodes are silent, and it is not until the amount of embolic material is substantial that the patient becomes symptomatic. After an acute, major thromboembolic episode, approximately 15% to 20% of patients die within 48 hours.¹⁰ Most of the remaining patients resolve the emboli substantially by a variety of mechanisms. Therefore, it is in

the subgroup of patients who have a sudden fatal outcome ($\approx 100,000$ annually) that invasive therapy for acute pulmonary embolism might be considered.

Although the role of surgical therapy for the PH resulting from chronic pulmonary emboli is now well established, the appropriate treatment for acute pulmonary embolism remains unclear. There are several reasons for this. Many patients die of massive pulmonary embolism in the terminal phases of another illness, which would make aggressive therapy inappropriate. For patients in whom invasive therapy is potentially indicated, there is substantial difficulty in defining which patients will respond to anticoagulation therapy for an acute massive pulmonary embolism in the limited amount of time available for diagnosis and treatment before death occurs.

The hemodynamic response to a large, sudden pulmonary embolus relates to a variety of factors, most notably the size of the embolus, the degree of obstruction that it produced in the pulmonary vascular bed, and the underlying function of the lung that remains perfused. The degree of vascular obstruction is related to the number of segmental arteries that are occluded and to prior pulmonary vascular capacitance. Thus, the hemodynamic consequences of acute pulmonary embolism are also a reflection of factors, such as the age of the patient and any possible previous thromboembolic events. The pre-existing status of the right ventricle that governs the forward flow of blood is also significant in determining the hemodynamic response to pulmonary embolism. Right ventricular function is affected by factors such as the degree of right ventricular hypertrophy or dilation, tricuspid valve regurgitation, and the presence of coronary artery disease.

In addition to the mechanical factor of pulmonary artery obstruction, there are reflex and hormonal factors that can increase pulmonary vascular resistance (PVR) at the time of acute pulmonary embolism. Humoral factors, specifically serotonin, adenosine diphosphate, platelet-derived growth factor, and thromboxane, are released from platelets attached to the thrombi,^{11,12} whereas platelet-activating factor and leukotrienes are secreted by neutrophils.¹³ Anoxia and tissue ischemia downstream from emboli inhibit endothelium-derived relaxing factor production and enhance release of superoxide anions by activated neutrophils.¹⁴ The combination of these humoral effects contributes to enhanced pulmonary vasoconstriction. Thus, some patients with a relatively small embolus may have an exaggerated response to the degree of pulmonary vascular obstruction.

In patients without preexisting cardiac or pulmonary disease, an obstruction of less than 20% of the pulmonary vascular bed results in minimal hemodynamic consequences. It is only when the acute pulmonary obstruction exceeds 50% to 60% of the pulmonary vascular bed that cardiac and pulmonary compensatory mechanisms are overcome and cardiac output begins to fall.¹⁵ Right ventricular failure occurs, which is accompanied by systemic hypotension as the amount of blood reaching the left ventricle decreases. The dilated right ventricle causes a shift of the ventricular septum to the left, further compromising left ventricular filling. Although patients with

chronic pulmonary artery obstruction can have high pulmonary artery pressure levels that reflect the degree of obstruction, in acute pulmonary embolism the previously normal right ventricle cannot generate these pressures. Therefore, in acute massive pulmonary embolism, pulmonary artery pressures may be normal, and a pulmonary artery systolic pressure of 30–40 mm Hg may represent severe PH.

Acute pulmonary embolism usually presents suddenly. Symptoms and signs vary with the extent of blockage, the magnitude of humoral response, and the preembolus reserve of the cardiac and pulmonary systems of the patient.¹⁶ The clinical diagnosis is often missed or falsely made. Most pulmonary emboli occur without sufficient clinical findings to suggest the diagnosis, and in an autopsy series of proven emboli, only 16% to 38% of patients received a diagnosis while still alive.¹⁷ The acute disease is conveniently stratified into low-risk, submassive, or massive embolism on the basis of hemodynamic stability, arterial blood gases, and lung scan or angiographic assessment of the percentage of blocked pulmonary arteries.^{18,19}

For patients with minor pulmonary embolism, physical examination may reveal tachycardia, rales, low-grade fever, and sometimes a pleural rub. Heart sounds and systemic blood pressure are often normal; sometimes the pulmonary second sound is increased. Less than one third of patients with acute pulmonary embolism have concurrent evidence of clinical deep venous thrombosis.¹⁷ Room air arterial blood gases indicate a PaO_2 between 65 and 80 torr and a normal PaCO_2 of approximately 35 torr.²⁰ Pulmonary angiograms typically show less than 30% occlusion of the pulmonary arterial vasculature. Recent studies suggest that normotensive patients who have normal biomarker levels (Brain Natriuretic peptide [BNP], N-terminal pro-BNP, Troponin I, Troponin T) and have no RV dysfunction on echocardiographic imaging have short-term mortality rates approaching 1%.^{21,22,23}

Submassive pulmonary embolism is defined as an acute pulmonary embolism without systemic hypotension (systolic blood pressure > 90 mm Hg) but with either right ventricular dysfunction or myocardial necrosis.¹⁹ This form of embolism is associated with dyspnea, tachypnea, dull chest pain, and some degree of cardiovascular changes manifested by tachycardia, mild to moderate hypotension, and elevation of central venous pressure.²⁰ Some patients may have syncope rather than dyspnea or chest pain. In contrast to massive pulmonary embolism, patients with submassive embolism (at least two lobar pulmonary arteries obstructed) are usually hemodynamically stable and have adequate cardiac output.²⁴ Room air blood gases reveal moderate hypoxia, with a PaO_2 between 50 and 60 torr, and mild hypocarbia, with a PaCO_2 no more than 30 torr.²⁰ Echocardiograms may show right ventricular dilation. Pulmonary angiograms indicate that 30% to 50% of the pulmonary vasculature is blocked; however, in patients with preexisting cardiopulmonary disorders, a lesser degree of vascular obstruction may produce similar symptoms.

Massive pulmonary embolism is life threatening and is defined as a pulmonary embolism that causes

hemodynamic instability, requiring inotropic support.²⁴ It is usually associated with occlusion of more than 50% of the pulmonary vasculature, but it can occur with much smaller occlusions, particularly in patients with preexisting cardiac or pulmonary disease. The diagnosis is clinical, not anatomical. Patients develop acute dyspnea, tachypnea, tachycardia, and diaphoresis and may lose consciousness. Both hypotension and low cardiac output (<1.8 L/min/m²) are present. Cardiac arrest can occur. Neck veins are distended, central venous pressure is elevated, and a right ventricular impulse may be present. Room air blood gases show severe hypoxia ($\text{PaO}_2 < 50$ torr), hypocarbia ($\text{PaCO}_2 < 30$ torr), and acidosis.²⁰ Urine output falls, and peripheral pulses and perfusion are poor.

The clinical diagnosis of submassive or massive pulmonary embolism is unreliable and is incorrect in 70% to 80% of patients who have subsequent angiography.²⁵ The differentiation between submassive or massive pulmonary embolism and acute myocardial infarction, aortic dissection, septic shock, and other catastrophic states can be difficult and costly in time. Although plain chest radiography, electrocardiogram, and insertion of a bedside Swan-Ganz catheter may add confirmatory information, they will not necessarily prove the diagnosis. Routine laboratory test results are usually normal.

The most common electrocardiographic abnormalities of acute pulmonary embolism are tachycardia and nonspecific ST and T wave changes. The major value of the electrocardiogram is the exclusion of a myocardial infarction. A minority of patients with massive embolism may show evidence of cor pulmonale, right axis deviation, or right bundle branch block.¹⁷ Chest radiography may show oligemia (Westermarck sign) or linear atelectasis (Fleischner lines), both of which are nonspecific findings. Ventilation-perfusion (V/Q) scans can provide confirmatory evidence, but these studies can be unreliable because pneumonia, atelectasis, previous pulmonary emboli, and other conditions can cause a mismatch in ventilation and perfusion that mimics positive results.²⁶

In general, negative V/Q scans exclude the diagnosis of clinically significant pulmonary embolism. V/Q scans are usually interpreted as high, intermediate, or low probability of pulmonary embolism to emphasize the lack of specificity but high sensitivity of the test.²⁷ Magnetic resonance angiography is an excellent noninvasive method for the diagnosis of pulmonary emboli, and it provides specific information regarding flow within the pulmonary vasculature.²⁸ Unfortunately, this method is expensive, time consuming, and not widely available. Like catheter-based pulmonary angiography, it is generally not suitable for hemodynamically unstable patients. Transthoracic echocardiography or transesophageal echocardiography with color flow Doppler mapping can provide reliable information about the presence or absence of major thrombi obstructing the main pulmonary artery; however, these techniques are usually inadequate for visualization of the lobar vessels, where the embolic material is often localized. More than 80% of patients with clinically significant pulmonary embolism have abnormalities of right ventricular volume or contractility, often associated with acute tricuspid regurgitation.²⁹ In a subset of patients, abnormal flow patterns can

be discerned in major pulmonary arteries during transesophageal echocardiography.³⁰

Prophylaxis

Although prophylactic measures should be considered and used for all patients undergoing major surgery or who have prolonged immobility, certain other patients also fall into a potentially high-risk group for pulmonary embolism. These patients include those with previous embolism, malignancy, cardiac failure, obesity, or advanced age.³¹ The prevalence of deep venous thrombosis of the thigh or pelvis, its strong association with pulmonary embolism, and the identification of the associated risk factors listed earlier provide the basis and rationale for prophylactic anticoagulation for the prevention of acute pulmonary embolism. Simple measures such as compression stockings probably should be prescribed more often and should be used in most nonambulating patients in the hospital. Intermittent pneumatic compression devices are more cumbersome, but also effective. These compression devices are available for the calf or the whole leg. They can provide a range of compression pressures, inflation and deflation duration, and sequential or nonsequential inflation, although a clear difference between these variations has not been demonstrated. Both compression stockings with a compression pressure of 30 to 40 mm Hg at the ankle and pneumatic compression devices reduce the incidence of deep venous thrombosis after general surgery to approximately 40% of control patients.³² Multiple studies have shown that low-dose subcutaneous heparin or low-molecular-weight heparin given once a day reduces the incidence of deep venous thrombosis^{33,34} with a concomitant reduction in the incidence of pulmonary embolism. This reduction in thrombosis has not been associated with an excessive risk of bleeding.³³ Recent studies suggest that of patients who have deep venous thrombosis diagnosed in the hospital without pulmonary embolism, the probability of clinically diagnosed pulmonary embolism within the next 12 months is 1.7%.³⁵ If pulmonary embolism occurs, the probability of recurrent pulmonary embolism is 6%.³⁵

Supportive and Thrombolytic Therapy

The majority of patients who die of pulmonary embolism do so within 2 hours of the initial acute event, before the diagnosis can be firmly established and before effective therapy can be instituted. Once the diagnosis is made, however, treatment will be either medical (supportive and thrombolytic therapy) or surgical (Fig. 102-1).

Oxygen should be administered to alleviate hypoxic pulmonary vasoconstriction, and it is likely that a severely affected patient will require intubation and ventilatory support. Pharmacologic agents, including cardiovascular pressors and vasoactive agents, can be used to stabilize the patient's hemodynamics. Once the circulation has been stabilized, arterial and central venous catheters are placed to monitor cardiac output and pulmonary arterial oxygen saturation. There is debate as to whether pulmonary artery catheters, although obviously helpful in management, should be used in the setting of acute pulmonary

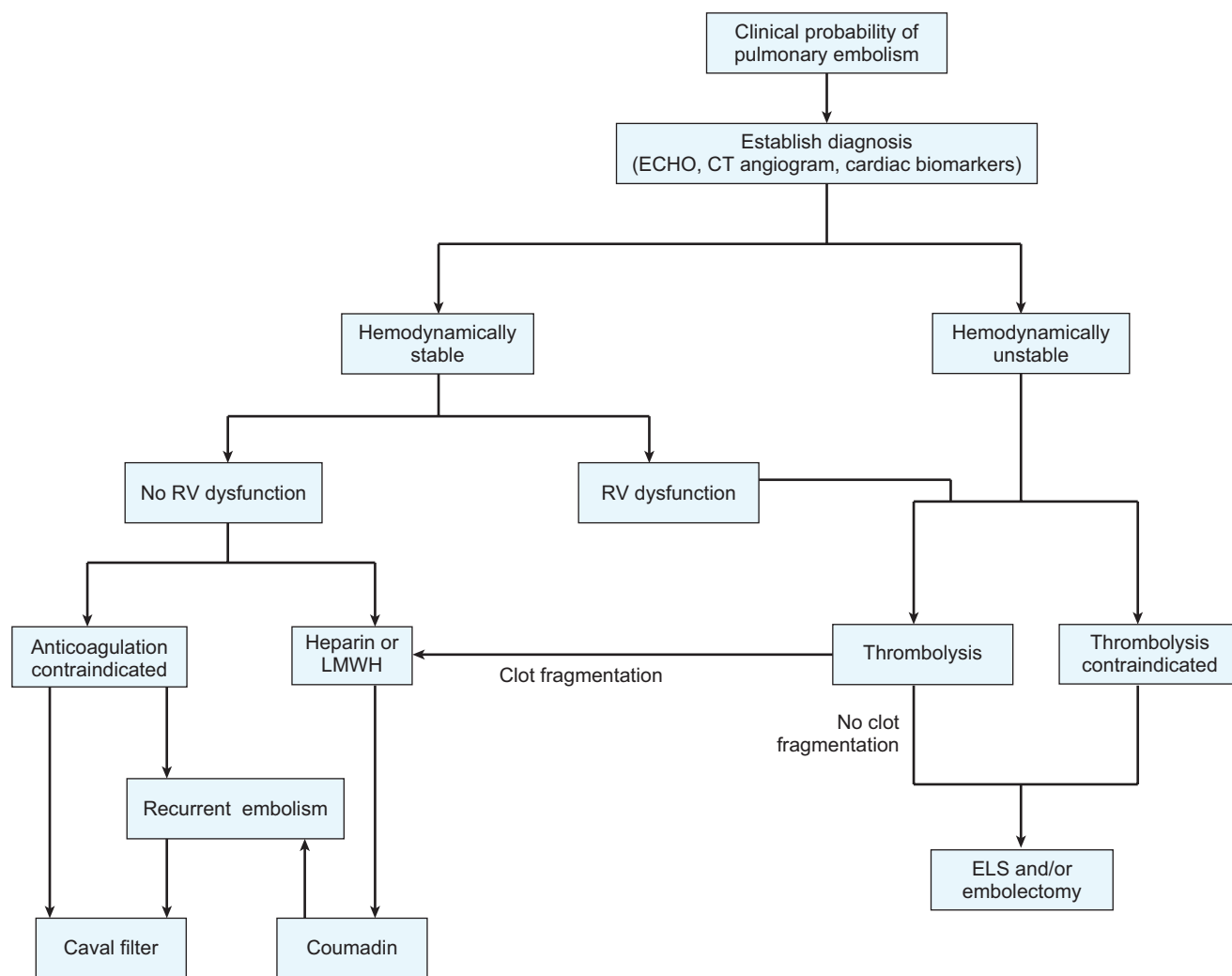


FIGURE 102-1 ■ Acute pulmonary embolism treatment scheme. *CT*, Computed tomography; *ECHO*, echocardiography; *ELS*, extracorporeal life support; *LMWH*, low-molecular-weight heparin; *RV*, right ventricle.

embolism, because of the risk of dislodging further thromboembolic material. The electrocardiogram is monitored, a Foley catheter is inserted for accurate recording of urine output, and blood gas levels are obtained. Patients with objectively confirmed pulmonary embolism and no contraindications for anticoagulation should receive prompt anticoagulant therapy with subcutaneous low-molecular-weight heparin, intravenous or subcutaneous unfractionated heparin, or subcutaneous fondaparinux (an inhibitor of activated factor Xa).^{19,36} For patients with suspected or confirmed heparin-induced thrombocytopenia, a non-heparin-based anticoagulant, such as lepirudin, argatroban, or bivalirudin should be used.³⁷ Although each of these individual therapies prevents propagation and formation of new thromboemboli, they rarely dissolve the existing clot. In most cases, the patient's intrinsic fibrinolytic system will lyse fresh thrombi over a period of days to weeks.³⁸ Intravenous heparin is monitored by measurement of activated partial thromboplastin times, which are maintained between 51 and 70 seconds (roughly twice that of controls) every 6 to 8 hours. The platelet count should be measured every 2 to 3 days to detect the presence of heparin-induced

thrombocytopenia. Prothrombin times are also obtained at baseline to prepare for anticoagulation with warfarin later.

Although warfarin is typically used for long-term anticoagulation after acute pulmonary embolism, several new oral anticoagulants have recently come on the market that do not require laboratory monitoring of anticoagulation (Table 102-1). They include factor Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa), as well as the direct factor IIa (thrombin) inhibitor dabigatran (Pradaxa). All these drugs except edoxaban have been approved by the U.S. Food and Drug Administration (FDA) for the long-term treatment of deep venous thrombosis with or without pulmonary embolism, with edoxaban currently undergoing FDA scrutiny. To date, there are no known clinically validated reversal agents for rivaroxaban, apixaban, edoxaban, or dabigatran. Based on the strength of available evidence and current American College of Chest Physicians Evidence-Based Guidelines, warfarin continues to be a monitorable, reversible, and effective agent in patients with venous thromboembolism and acute pulmonary embolism, and it should remain the first-line option for

TABLE 102-1 Pharmacologic Characteristics of Direct Oral Anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Trade name	Pradaxa	Xarelto	Eliquis	Savaysa
Approved by the FDA for treatment of PE	Yes	Yes	Yes	No
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Onset of action	2 h	2.5-4 h	3 h	1-5 h
Half-life	12-14 h	9-13 h	8-11 h	8-10 h
Renal clearance (%)	80	60	25	35
Metabolism	P-gp	P-gp/CYP3A4	P-gp/CYP3A4	P-gp/CYP3A4
Dosing	b.i.d.	b.i.d., qd	b.i.d.	b.i.d., qd

CYP, Cytochrome P450 3A4; PE, pulmonary embolism; P-gp, P-glycoprotein.

long-term (3-6 month) treatment of pulmonary embolism.³⁹ However, the factor Xa inhibitors rivaroxaban and apixaban, as well as the direct thrombin inhibitor dabigatran, are each viable alternatives in patients with less than optimal INR control (targeted therapeutic range < 60%) or in whom warfarin monitoring and management is not possible.⁴⁰ Three months of warfarin anticoagulation is recommended for patients with a first-episode deep venous thrombosis related to a major reversible risk factor (i.e., recent surgery or trauma).^{41,42} Six months of warfarin anticoagulation is recommended for patients who have recurrent or unprovoked deep venous thrombosis with or without pulmonary embolism as prophylaxis against recurrent disease.^{43,44}

The natural history of the clot in survivors of acute embolic events is fragmentation and progressive lysis. It therefore follows that the addition of streptokinase, urokinase, or recombinant tissue plasminogen activator improves survival by increasing the rate of lysis of fresh thrombi in the pulmonary arterial tree. Thromboembolytic agents dissolve thrombi by activating plasminogen to plasmin. Plasmin, when in proximity to a thrombus, degrades fibrin to soluble peptides. Circulating plasmin also degrades soluble fibrinogen and, to variable degrees, factors II, V, and VIII. In addition, increased concentrations of fibrin and fibrinogen degradation products contribute to coagulopathy by both inhibiting the conversion of fibrinogen to fibrin and interfering with fibrin polymerization. The thromboembolytic agents currently approved by the FDA for the treatment of acute pulmonary embolism are streptokinase, urokinase, recombinant tissue plasminogen activator (alteplase), and tissue plasminogen activator.⁴⁵ Some new agents (so-called second-generation thrombolytics) such as reteplase, saruplase, staphylokinase, tenecteplase, and anistreplase are undergoing clinical testing.⁴⁶

Although thrombolytic therapy has been shown to increase the rate of lysis of fresh pulmonary clots more than that of heparin alone,⁴⁷ there has been little difference measured in the amount of residual thrombus between the two treatments in early studies using small cohorts of patients.^{48,49} However, four registries (MAPPET, ICOPER, RIETE, EMPEROR) comparing thrombolytic agents with intravenous (IV) heparin in acute pulmonary embolism have been large enough to detect a significant difference in the most important endpoint—mortality, particularly in patients with massive pulmonary embolism, presenting with hypotension.⁵⁰⁻⁵⁵

More recent experience suggests a trend toward better results with thrombolytic therapy because of a more rapid diminution in right ventricular afterload and dysfunction.^{56,57} Thus, thrombolytic therapy should also be considered in normotensive patients with evidence of severe right ventricular dysfunction on echocardiography. Compared with heparin therapy alone, thrombolytic agents carry a higher risk of bleeding problems, with up to 20% of patients experiencing a significant bleeding complication.^{58,59} In general, thrombolytic therapy is contraindicated in patients with intracranial hemorrhage, fresh surgical wounds, anemia, recent stroke, peptic ulcer, or bleeding dyscrasias.

Percutaneous Treatments

Percutaneous techniques to recanalize complete and partial occlusions in the pulmonary trunk or major pulmonary arteries are potentially life saving in selected patients with massive or submassive pulmonary embolism.⁶⁰ Transcatheter procedures can be performed as an alternative to thrombolysis when there are contraindications or when emergency surgical embolectomy is unavailable or contraindicated. Catheter interventions can also be performed when thrombolysis has failed to improve hemodynamics in the acute setting. The goals of catheter-based therapy include rapidly reducing pulmonary artery pressure, increasing systemic perfusion, and facilitating RV recovery.⁶¹⁻⁶³

There are three general categories of percutaneous intervention for removing emboli and decreasing thrombus burden: aspiration thrombectomy, thrombus fragmentation, and rheolytic thrombectomy. For aspiration thrombectomy, a device is used that consists of a small terminal cup attached to a flexible catheter.⁶¹ Syringe suction is applied to the cup as a thrombus is engaged. The catheter and clot are removed en masse through the venotomy site, and this process can be repeated multiple times. Thrombus fragmentation has been performed with balloon angioplasty,⁶⁴ a pigtail rotational catheter,⁴⁵ or a more advanced fragmentation device (the Amplatz catheter with an impeller housed in a capsule at the tip) driven by a compact air turbine that homogenizes thrombus by maceration and fragmentation. A metal capsule protects the vessel from the rotating impeller.⁶⁵ A third technique, the rheolytic thrombectomy technique, uses a dual-lumen catheter: one small lumen for delivery of pulsatile pressurized saline and a larger effluent or exhaust

lumen to drain the thrombus. High-velocity saline jets are injected toward the effluent lumen. This produces an area of low pressure at the tip of the catheter (Venturi effect), thereby fragmenting the thrombus and allowing it to be evacuated through the effluent lumen.^{63,66}

Recently, a new technique of suction thrombectomy with extracorporeal venovenous support (AngioVac, Angiodynamics, Latham, NY) has been described for the removal of proximal pulmonary emboli.⁶⁷ With this technique, a drainage cannula with a balloon-actuated, expandable, funnel-shaped distal tip is introduced through a femoral or right internal jugular vein and advanced under fluoroscopy to the site of embolism. The cannula is connected in circuit with an extracorporeal circulation pump attached to a second cannula inserted into the contralateral femoral vein. Venovenous bypass is instituted, and particulate matter suctioned through the inflow cannula is trapped within filters in the circuit, allowing for reinfusion of blood that is free of gross debris. This hybrid procedure is typically performed in an operating room, with thoracic surgeon and cardiologist present.⁶⁸ Successful catheter extraction of thrombus with clinically significant reduction in pulmonary arterial pressure for each of the above methods varies between 75% and 88%, with the best results achieved for proximal and main pulmonary artery embolism.^{69,70}

Acute Pulmonary Embolectomy

When contraindications preclude thrombolysis, emergency pulmonary thromboembolectomy is indicated for suitable patients with either life-threatening circulatory insufficiency from massive pulmonary embolism or submassive pulmonary embolism.⁷¹ The decision to proceed with catheter-based versus surgical embolectomy requires interdisciplinary teamwork, discussion that involves the surgeon and interventionalist, and an assessment of the local expertise. If a patient has been taken directly to the operating room without a definitive diagnosis, transesophageal or epicardial echocardiography and color Doppler mapping can confirm or refute the diagnosis in the operating room.⁷² The primary difficulty with the broad application of operative embolectomy is that it is almost impossible to determine which patients will die without intervention. An emergency pulmonary embolectomy is most feasible (because of time) and most successful in patients who ultimately may not require it, which makes it difficult to establish the efficacy of this operation. To date, no randomized trial has evaluated surgical embolectomy in patients with acute pulmonary embolism. Indications for acute surgical intervention include the following: (1) critical hemodynamic condition, with the patient deemed unlikely to survive; (2) definitive diagnosis of pulmonary embolism in the main or lobar pulmonary arteries with compromise of oxygen gas exchange; (3) unstable patients in whom thrombolytic or anticoagulation therapy is absolutely contraindicated; and (4) the presence of a large clot trapped within the right atrium or ventricle.

Acute pulmonary embolectomy was first described by Trendelenburg in 1908⁷³ using pulmonary artery and aortic occlusion, through a transthoracic approach. There

were no surviving patients. Sharp⁷⁴ performed the first successful open embolectomy, using cardiopulmonary bypass.

For pulmonary embolectomy, a median sternotomy incision is used and cardiopulmonary bypass is instituted. The procedure is best performed on a warm, beating heart, without aortic cross-clamping, cardioplegia, or fibrillatory arrest. Occluding tapes are placed around the superior and inferior vena cavae. Two polypropylene sutures are placed in the mid-pulmonary artery for traction. A longitudinal incision is made between these sutures in the main pulmonary artery trunk 1 to 2 cm distal to the valve. If necessary, the incision can be extended directly into the left pulmonary artery. Extraction is limited to directly visible emboli, which can be accomplished to the level of the lobar and segmental arteries. Fresh clot removal from subsegmental arteries may be attempted, but is often surgically difficult because of the soft, sticky, often fragmental nature of peripheral pulmonary emboli. The emboli are extracted using forceps, suction, and balloon catheters. The right pulmonary artery also can be exposed and opened between the aorta and superior vena cava to allow better exposure in segmental vessels, if necessary. A sterile pediatric bronchoscope can be used to visualize emboli in tertiary or quaternary pulmonary vessels, so that they can be cleared with balloon embolectomy or suction. After cleaning the pulmonary arterial tree lumina, the pleural spaces can be entered, and the lungs are manually compressed to dislodge small distally lodged clots, which can then be suctioned out. The pulmonary arteriotomy is then closed with a 6-0 polypropylene suture. After restarting the heart, the patient is weaned from bypass, decannulated, and closed. The aim of this operation is to remove most of the embolic material, and no attempt is made to perform an endarterectomy.

As a corollary to this operation, some groups recommend either placement of an inferior vena caval filter or caval clipping before chest closure. Greenfield has recommended placement of an inferior vena caval filter under direct visualization before closing the chest.⁷⁵ Historically, some European surgeons clipped or plicated the intrapericardial vena cava at the end of the embolectomy to prevent migration of lower body clot into the pulmonary circulation; however, this procedure is associated with stasis in the venous system in the lower body and leg swelling.⁷⁶ In most centers that offer emergency pulmonary thromboembolectomy, no caval procedure is performed in the perioperative period, and recurrent deep venous thrombosis or pulmonary embolism are treated by anticoagulation with warfarin for 6 months.⁷⁷ Percutaneously placed filters are recommended only for patients with contraindications to anticoagulation or for patients with recurrent pulmonary embolism on therapeutic anticoagulation. The cone-shaped Greenfield filter is the most widely used permanent filter in the United States, and it is associated with a lifetime recurrent embolism rate of 5% and a lifetime patency rate of 97%.^{78,79} The advent of retrievable inferior vena caval (IVC) filters appears to have lowered thresholds for IVC filter placement in the United States; however, there are few data to support or refute this claim.^{19,80} Late

complications of permanent and retrievable filters include recurrent deep venous thrombosis (21%), IVC thrombosis (2% to 10%), and IVC penetration (0.3%).⁸¹ IVC filter fractures have also been reported.⁸²

Extracorporeal Life Support

The wider availability of long-term mechanical perfusion (termed *extracorporeal life support* [ELS]) using peripheral vessel cannulation to stabilize the circulation offers another approach to life-threatening pulmonary embolism. Most pulmonary emboli, even those that are massive, will dissolve with time. ELS can be instituted outside the operating room setting and can be implemented with rapidity in institutions where preparation for its emergency use has been made. With a trained team, needed equipment, and associated supplies readily available, ELS can be implemented within 15 to 30 minutes.⁸³ For hemodynamic support during the period of a life-threatening pulmonary embolism, venoarterial extracorporeal support can be instituted and maintained for a period up to several weeks, if necessary.⁸⁴

This procedure begins with an IV heparin bolus of 1 mg/kg, followed by percutaneous or surgical cut-down of the femoral artery and femoral or internal jugular veins. If pulses are absent or weak, a larger incision is usually faster; however, because patients need heparin and have possibly received fibrinolytic drugs, a minimal wound is preferred. The tip of the venous catheter is advanced into the right atrium to obtain a flow rate of 2.5–4.0 liters/min using an emergency pump-oxygenator circuit primed with crystalloid.⁸⁵ The perfusion circuit consists of IV or arterial access tubes, a centrifugal pump, and a membrane oxygenator.⁸⁶ An electromagnetic flowmeter is placed on the arterial line, and an arterial filter is not applied. While the patient is receiving ELS, heparin is infused to maintain the activated clotting time between

150 and 180 seconds. In the initial hours after institution of ELS, activated clotting times are measured every 30 minutes, followed by every hour thereafter until decannulation. During the period of ELS support, thrombolytic drugs may be instilled directly into the pulmonary artery via a Swan-Ganz catheter to aid in clot lysis. ELS support can provide critical support to bridge an unstable patient to surgical embolectomy.⁸⁷

Once oxygenation has been stabilized and PVR has normalized, the patient is decannulated, and the cannulation sites are surgically closed. ELS is usually discontinued in the operating room because vessels should be sutured closed due to the need for heparin and long-term anticoagulation.

Results of Surgical Embolectomy for Acute Pulmonary Embolism

Mortality rates for emergency pulmonary embolectomy vary widely, between 0% and 62% (Table 102-2).^{88–108} It is difficult to compare these retrospective studies because of the difference in time in which the operations were performed, the preoperative hemodynamic state of the patient populations, and the variation in treatment plans. In general, greater surgical mortality was encountered if a patient had a preoperative cardiac arrest or required ELS support. For example, the mortality in patients who have suffered a cardiac arrest is reported in multiple series from 27% to 64% (see Table 102-2), while the mortality in patients who have not suffered cardiac arrest is reported to be between 6% and 44%. Consequently, although some groups report low mortality rates, this may be attributable to the selection of less ill patients as candidates for surgery. In patients in whom ELS is instituted during preoperative cardiac resuscitation, subsequent operative mortality ranges between 44% and 57%.^{43,85} Thus, the outcome depends largely on the

TABLE 102-2 Surgical Pulmonary Embolectomy Series (1994–2014) with More Than 20 Patients: Comparative Mortality

References	Date	No. of Patients (N)	Preoperative Cardiac Arrest	Mortality in Patients with Preoperative Cardiac Arrest	Total Mortality
Stulz ⁸⁸	1994	50	31/50 (62%)	19/31 (61%)	23/50 (46%)
Jakob ⁸⁹	1995	25	13/25 (52%)	4/13 (31%)	6/25 (24%)
Doerge ⁹⁰	1996	36	14/36 (39%)	8/14 (57%)	9/36 (25%)
Doerge ⁹²	1999	41	14/41 (34%)	9/14 (64%)	12/41 (29%)
Ullmann ⁹¹	1999	40	19/40 (48%)	12/19 (63%)	14/40 (35%)
Aklog ⁹³	2002	29	1/29 (3%)	—	3/29 (10%)
Leacche ⁹⁴	2005	47	6/47 (11%)	2/6 (33%)	3/47 (6%)
Spagnolo ⁹⁵	2006	21	2/21 (10%)	0/2 (0%)	0/21 (0%)
Digonnet ⁹⁶	2007	21	6/21 (29%)	4/6 (67%)	13/21 (62%)
Kadner ⁹⁷	2008	25	8/25 (32%)	—	2/25 (8%)
Sádaba ⁹⁸	2008	20	—	—	2/20 (10%)
Vohra ⁹⁹	2010	21	9/21 (43%)	—	4/21 (19%)
Medvedev ¹⁰¹	2011	27	—	—	0/29 (0%)
Zarrabi ¹⁰⁰	2011	30	3/30 (10%)	—	2/30 (7%)
Lehnert ¹⁰³	2012	33	1/33 (3%)	—	2/33 (6%)
Takahashi ¹⁰⁴	2012	24	11/24 (46%)	3/11 (27%)	3/24 (13%)
Taniguchi ¹⁰²	2012	32	3/32 (9%)	1/3 (33%)	6/32 (20%)
Aymard ¹⁰⁵	2013	28	—	—	1/28 (4%)
Wu ¹⁰⁶	2013	25	8/25 (32%)	4/8 (50%)	5/25 (20%)
Zarrabi ¹⁰⁷	2013	30	—	—	4/30 (13%)
Worku ¹⁰⁸	2014	20	3/20 (15%)	—	1/20 (5%)

preoperative condition of the patient. Primary causes of death include brain damage, cardiac failure, uncontrollable bleeding, and sepsis. Recurrent embolism after surgery is uncommon,⁹⁶ and approximately 80% of those who survive surgery maintain normal pulmonary artery pressures and exercise tolerance. In these patients, postoperative angiograms are normal or show obstruction in less than 10% of vessels. A minority of patients who have obstruction in more than 40% of pulmonary vessels after surgery have experienced reduced pulmonary function and exercise tolerance.¹⁰⁹

CHRONIC PULMONARY THROMBOEMBOLIC DISEASE

Incidence and Natural History

The natural history of pulmonary embolism is generally total embolic resolution, or resolution leaving minimal residua, with restoration of a normal hemodynamic status. However, for unknown reasons, embolic resolution is incomplete in a small subset of patients. If the acute emboli are not lysed in 1 to 2 weeks, the embolic material becomes attached to the pulmonary arterial wall at the main pulmonary artery, lobar, segmental, or subsegmental levels.¹¹⁰ With time, the initial embolic material progressively becomes converted into connective and elastic tissue filled with endothelial and smooth muscle precursor cells as well as macrophages.^{111,112} Often, visualization of the pulmonary arteries by angiography a few weeks after unresolved pulmonary embolism reveals vessel narrowing at the site of embolic incorporation. In some patients, recanalization of some of the pulmonary arterial branches occurs, with the formation of fibrous tissue in the form of bands and webs.¹¹³ By a mechanism that is poorly understood, this chronic obstructive disease can lead to a small vessel (precapillary) arteriolar vasculopathy characterized by excessive vascular and inflammatory cell proliferation around small arterioles in the pulmonary circulation.¹¹⁴ These pulmonary microvascular changes resemble the arteriopathy observed in World Health Organization Group 1.1 or idiopathic pulmonary arterial hypertension and are gaining increased recognition as contributors to disease progression in chronic thromboembolic PH.¹¹⁵ Precapillary arteriolar vasculopathy is mostly seen in the remaining open vessels, which are subjected to long exposure at high flow. Pulmonary hypertension results when the capacitance of the remaining open bed cannot absorb the cardiac output, either because of the degree of primary obstruction by thromboembolic material and adjacent remodeling or because of the combination of a proximal obstruction and secondary small-vessel vasculopathy. The importance of pulmonary arteriolar remodeling in the development of chronic thromboembolic PH is supported by the following observations: (1) there is often a lack of correlation between elevated pulmonary arterial pressure and the degree of angiographic pulmonary vascular bed obstruction, (2) PH can progress in the absence of recurrent thromboembolism, and (3) total PVR is still significantly higher in chronic thromboembolic PH patients than in acute

pulmonary embolism patients with a similar degree of proximal vascular bed obstruction.^{116,117}

The incidence of PH caused by chronic pulmonary embolism is even more difficult to determine than that of acute pulmonary embolism. There are more than 500,000 survivors of symptomatic episodes of acute pulmonary embolism per year.¹¹⁸ The incidence of chronic thrombotic occlusion or stenosis in the population depends on which percentage of patients fails to resolve acute embolic material. One estimate is that chronic thromboembolic disease develops in only 3.8% of patients with a clinically recognized acute pulmonary embolism.⁵ If these figures are correct and only patients with symptomatic acute pulmonary emboli are counted, approximately 19,000 individuals would progress to chronic thromboembolic PH in the United States each year. However, because many (if not most) patients with a diagnosis of chronic thromboembolic disease have no antecedent history of acute embolism, the true incidence of this disorder is probably much higher.

Regardless of the exact incidence, it is clear that acute embolism and its chronic relation, fixed chronic thromboembolic occlusive disease, are much more common than is generally appreciated and are seriously underdiagnosed. In 1963, Houk and colleagues¹¹⁹ reviewed the literature of 240 cases of chronic thromboembolic obstruction of major pulmonary arteries, but found that only six cases were diagnosed correctly before death. Calculations extrapolated from mortality rates and the random incidence of major thrombotic occlusion found at autopsy supported the postulate that more than 100,000 people in the United States currently have PH that could be relieved by operation. An autopsy analysis of 13,216 patients showed pulmonary thromboembolism in 5.5% of autopsies and up to 31.3% in older patients.¹²⁰

Chronic thromboembolic PH is a disease characterized by initial thromboembolism to the pulmonary arterial tree that does not resolve itself. Whether this is due to an endothelial insult, preexisting prothrombotic state, or endothelial or smooth muscle progenitor cell trapping and remodeling is the subject of debate. No clear etiology has been defined for the majority of patients who develop chronic thromboembolic PH. Lupus anticoagulant may be detected in approximately 10% of chronic thromboembolic patients,¹²¹ and 20% carry anticardiolipin antibodies, lupus anticoagulant, or both.¹²² A recent study has demonstrated that the plasma level of factor VIII, a protein that is associated with both primary and recurrent venous thromboembolism, is elevated in 39% of patients with chronic thromboembolic PH.¹²³ Other hematologic abnormalities observed in chronic thromboembolic PH include increased resistance to thrombolysis¹²⁴ and decreased thrombomodulin levels.¹²⁵ Analyses of plasma proteins in patients with chronic thromboembolic disease have shown that fibrin from these patients is resistant to thrombolysis *in vitro*.¹²⁶ In addition, in a previous pathology series, 15% of patients had an underlying autoimmune or hematologic disorder (e.g., polycythemia vera).¹²⁷ Finally, non-O blood group types are significantly more common in patients with chronic thromboembolic PH compared to patients with idiopathic pulmonary arterial

hypertension¹²⁸ and compared with the general American and European populations (<http://www.redcross.org>).

Case reports and small series have suggested links between chronic thromboembolism and previous splenectomy, thyroid replacement therapy, permanent intravenous catheters, and ventriculoatrial shunts for the treatment of hydrocephalus or chronic inflammatory conditions, such as osteomyelitis or inflammatory bowel disease. In addition to these observations, associations with sickle cell disease, hereditary stomatocytosis, the Klippel-Trenaunay syndrome, and malignancy have been described.¹²⁹ However, the vast majority of cases of chronic thromboembolic PH are not linked with a specific coagulation defect or underlying medical condition as described earlier.

Without surgical intervention, the survival of patients with chronic thromboembolic PH is poor and is inversely related to the degree of PH at the time of diagnosis. Riedel colleagues⁶ found a 5-year survival rate of 30% among patients with a mean pulmonary artery pressure greater than 40 mm Hg at the time of diagnosis and 10% in those whose pressure exceeded 50 mm Hg. In another study, a mean pulmonary artery pressure as low as 30 mm Hg was identified as a threshold for poor prognosis.¹³⁰

Clinical Manifestations

Patients with chronic thromboembolic PH usually have subtle or nonspecific presenting symptoms. The most common symptoms are progressive exertional dyspnea and exercise intolerance.¹³¹ These symptoms are a result of elevated dead space ventilation and a limitation in cardiac output from obstruction of the pulmonary vascular bed. As the disease progresses, additional symptoms such as edema, chest pain, lightheadedness, and syncope may develop. Early in the course of thromboembolic disease, physical findings may be limited to an accentuated P2, which can be overlooked easily during the physical examination. Nonspecific chest pains occur in approximately 50% of patients with more severe PH. Hemoptysis can occur in all forms of PH and probably results from abnormally dilated vessels distended by increased intravascular pressures. Peripheral edema, early satiety, and epigastric or right upper quadrant fullness or pain can develop as the right side of the heart fails and cor pulmonale develops.

Physical signs of PH include a jugular venous pulse that is characterized by a large A wave. As the right side of the heart fails, the V wave becomes predominant. The right ventricle is usually palpable near the lower left sternal border, and pulmonary valve closure may be audible in the second intercostal space. Patients with advanced disease may be hypoxic and cyanotic. Clubbing is an uncommon finding. As the right side of the heart fails, a right atrial gallop may be auscultated, and tricuspid insufficiency develops. Because of the large pressure gradient across the tricuspid valve in PH, the murmur is high-pitched and might not exhibit respiratory variation. These findings differ from those usually observed in tricuspid valvular disease. A murmur of pulmonic regurgitation also may be detected, and a specific auscultatory

finding is a flow murmur at the back—thought to result from stenosed pulmonary vessels.¹³²

Diagnostic Evaluation of Chronic Thromboembolic Pulmonary Hypertension

Pulmonary vascular disease always must be considered in the differential diagnosis of unexplained dyspnea. The diagnostic evaluation serves three purposes: to establish the presence and severity of PH; to determine its etiology; and, if thromboembolic disease is present, to determine whether it is surgically correctible (Fig. 102-2).

Chest radiography is often unrevealing in the early stages of chronic thromboembolic PH. As the disease progresses, several radiographic abnormalities may be found. These abnormalities include peripheral lung opacities suggestive of scarring from previous infarction, cardiomegaly with dilation and hypertrophy of the right-sided chambers, and dilation of the central pulmonary arteries. Pulmonary function tests are often obtained in the evaluation of dyspnea, and they serve to exclude the presence of obstructive airways or parenchymal lung disease. There are no characteristic spirometric changes that are diagnostic of chronic thromboembolic PH. Single-breath diffusing capacity for carbon monoxide (DLCO) may be moderately reduced, and it has been reported that 20% of patients have a mild to moderate restrictive defect caused by parenchymal scarring.¹³³ Arterial blood oxygen levels may be normal even in the setting of significant PH. Most patients, however, experience a decline in PO₂ with exertion.

Transthoracic echocardiography is the first study to provide objective evidence of the presence of PH. An estimate of pulmonary artery pressure can be provided by Doppler evaluation of the tricuspid regurgitant envelope. Additional echocardiographic findings vary depending on the stage of the disease, and they include right ventricular enlargement, leftward displacement of the interventricular septum, and encroachment of the enlarged right ventricle on the left ventricular cavity with abnormal systolic and diastolic function of the left ventricle.¹³⁴ Contrast echocardiography may demonstrate a persistent foramen ovale, which is the result of high right atrial pressures opening the previously closed intraatrial communication. Once the diagnosis of PH has been established, distinguishing between major-vessel obstruction and small-vessel pulmonary vascular disease is the next critical step.

Radioisotope ventilation-perfusion (V/Q) lung scanning is the essential test for establishing the diagnosis of unresolved pulmonary thromboembolism. A normal ventilation-perfusion scan excludes the diagnosis of chronic thromboembolic PH. The V/Q scan typically demonstrates one or more mismatched segmental defects caused by obstructive thromboembolism. This is in contrast to the normal or "mottled" perfusion scan seen in patients with primary PH or other small-vessel forms of PH.¹³⁵ It is important to note that V/Q scanning can underestimate the magnitude of perfusion defects with chronic thromboembolic PH, as partial recanalization of

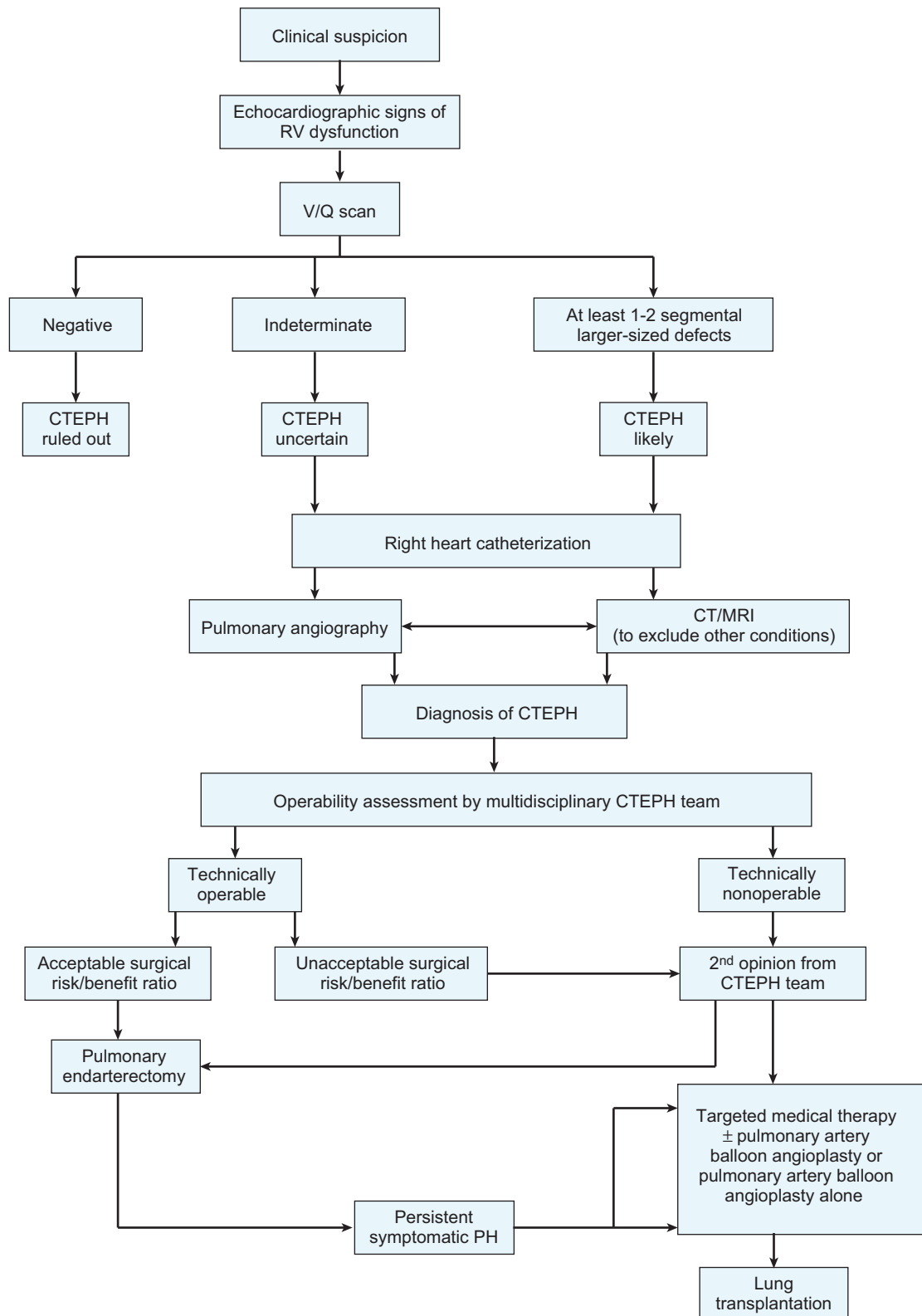


FIGURE 102-2 ■ Chronic thromboembolic pulmonary hypertension treatment scheme. *CT*, Computed tomography; *CTEPH*, chronic thromboembolic pulmonary hypertension; *MRI*, magnetic resonance imaging; *PH*, pulmonary hypertension; *RV*, right ventricular; *V/Q*, ventilation-perfusion.

the vessel lumen can occur, resulting in some perfusion though with significant obstruction to flow.¹³⁶

Cardiac catheterization provides essential information in the evaluation of patients with suspected thromboembolic PH. Right ventricular catheterization allows for the quantification of the severity of PH and assessment of cardiac function. Measurement of oxygen saturations in the vena cava, right ventricular chambers, and the pulmonary artery may document previously undetected left-to-right shunting. Coronary angiography and left-sided heart catheterization provide additional information about patients at risk for coronary artery or valvular disease and establish baseline measurements for cardiac output and left ventricular function. This information is crucial in the preoperative risk assessment of patients deemed candidates for pulmonary endarterectomy.

Pulmonary angiography is the gold standard for defining pulmonary vascular anatomy and is performed to identify whether chronic thromboembolic obstruction is present, to determine its location and surgical accessibility, and to rule out other diagnostic possibilities. In angiographic imaging, thrombi appear as unusual filling defects, pouches, webs, or bands, or completely thrombosed vessels that may resemble congenital absence of a vessel. Organized material along a vascular wall produces a scalloped or serrated luminal edge.¹³⁷ Despite concerns regarding the safety of performing pulmonary angiography in patients with PH, with careful monitoring, pulmonary angiography can be performed safely even in patients with severe PH.¹³⁸ Biplane imaging is preferred, offering the advantage of lateral views that provide greater anatomical detail compared with the overlapped and obscured vessel images often seen with the anterior-posterior view. Maturation, organization, and recanalization of clot produces angiographic patterns of the following: (1) pouch defects, (2) webs or bands, (3) intimal irregularities, (4) abrupt narrowing of major vessels, and (5) obstruction of main, lobar, or segmental pulmonary vessels.¹³⁹

In approximately 20% of cases, the differential diagnosis between idiopathic pulmonary arterial hypertension and distal small-vessel pulmonary thromboembolic disease is difficult to establish. In these patients, pulmonary angioscopy often may be helpful. The pulmonary angioscope is a diagnostic fiberoptic device that was developed to visualize the intima of central pulmonary arteries. It is inserted through a vascular sheath inserted in a central vein and passed through the right side of the heart into the pulmonary artery under fluoroscopic guidance. Inflation of a latex balloon affixed to the tip of the angioscope results in obstruction of blood flow in the artery and permits visualization of the arterial intima. The classic appearance of chronic pulmonary thromboembolic disease by angioscopy consists of intimal irregularity and scarring, with webbing of the vessel lumina.¹⁴⁰ The presence of embolic disease, occlusion of vessels, or the presence of gross thrombotic material also is diagnostic. In addition, percutaneous interventional approaches using intravascular ultrasound and optical coherence tomography have provided high-resolution, real-time imaging of vascular obstructions of chronic thromboembolic PH *in vivo*.¹⁴¹

More recently, multidetector computed tomography (CT) pulmonary angiography, helical CT scanning,¹⁴² single photon emission CT scanning,¹⁴³ and magnetic resonance angiography¹⁴⁴ have been used to screen patients with suspected thromboembolic disease. Although promising, none of these techniques yet provide the resolution of pulmonary angiography, particularly in visualizing thromboembolic disease in the segmental and subsegmental vessels. Features of chronic thromboembolic disease seen by these modalities include evidence of organized thrombus lining the pulmonary vessels in an eccentric fashion, enlargement of the right ventricle and central pulmonary arteries, variation in size of lobar arteries (relatively smaller in affected segments compared with uninvolved areas), and parenchymal changes compatible with pulmonary infarction. It is important to note that recent advances such as dual-energy CT,¹⁴⁵ cone-beam CT, electrocardiograph-gated 320-row area detector CT, and lung perfusion magnetic resonance imaging may change paradigms in pulmonary vascular imaging in the future.

Surgical Selection

Although previous attempts had been made, Allison and colleagues¹⁴⁶ performed the first successful pulmonary thromboendarterectomy through a sternotomy using surface hypothermia in a patient with a 12-day history of pulmonary embolism, but only fresh clots were removed and an endarterectomy was not performed. Since then, there have been many occasional surgical reports of the surgical treatment of chronic pulmonary thromboembolism,¹⁴⁷ but by far the greatest surgical experience in pulmonary endarterectomy has been at the University of California, San Diego (UCSD),^{148,149} where more than 3200 operations have been performed.

The three major reasons for considering a patient for pulmonary endarterectomy are hemodynamic, respiratory, and prophylactic. The hemodynamic goal is to prevent or ameliorate right ventricular compromise caused by PH. The respiratory objective is to improve function by the removal of a large, ventilated but unperfused physiologic dead space. The prophylactic goals are to prevent progressive right ventricular dysfunction, retrograde extension of the clot, and the prevention of secondary vasculopathic changes in the remaining patent vessels. Pulmonary endarterectomy is considered in patients who are symptomatic and have evidence of hemodynamic or ventilatory impairment at rest or with exercise. Patients undergoing surgery usually exhibit a preoperative PVR greater than 300 dyn·s/cm⁻⁵, typically in the range of 800 to 1200 dyn·s/cm⁻⁵.¹⁵⁰ Although most patients have a pulmonary artery pressure that is less than systemic, the hypertrophy of the right ventricle that occurs over time makes PH possible at suprasystemic levels. Therefore, many patients have a level of PVR in excess of 1000 dyn·s/cm⁻⁵ and suprasystemic pulmonary artery pressures. There is no upper limit of PVR level, pulmonary artery pressure, or degree of right ventricular dysfunction that excludes patients from operation. For those with milder PH, the decision to operate is based on individual circumstances. Some patients elect to

undergo surgery at this early stage of disease because of dissatisfaction with their exercise limitation or concerns about clinical deterioration in the future.

Those who choose not to pursue surgical intervention at early stages of the disease require close monitoring for progression of PH. Because of the changes that can occur, especially in the remaining patent (unaffected by clot or obstruction) pulmonary vascular bed subjected to the higher pressures and flow, pulmonary endarterectomy is usually offered to symptomatic and asymptomatic patients whenever their angiograms demonstrate significant thromboembolic disease.¹³⁹

Guiding Principles of the Operation

There are several guiding principles of the operation: (1) the endarterectomy must be bilateral, and therefore the approach is through a median sternotomy; (2) identification of the correct dissection plan is crucial; (3) perfect visualization is essential by use of circulatory arrest, usually limited to 20 minutes for each side; and (4) a complete endarterectomy is essential. The operation must be bilateral because, for PH to be a major factor, both pulmonary arteries usually are substantially involved. The only reasonable approach to both pulmonary arteries is through a median sternotomy. Historically, there were reports of unilateral operation, and occasionally this is still performed through a thoracotomy.¹⁵¹ However, the unilateral approach ignores disease on the contralateral side, subjects the patient to hemodynamic jeopardy during the clamping of the pulmonary artery, and does not allow good visibility because of the continued presence of bronchial blood flow. In addition, collateral channels develop in chronic thromboembolic PH not only through the bronchial arteries, but also from diaphragmatic, intercostal, and pleural vessels. The dissection of the lung in the pleural space via a median sternotomy, apart from bilateral access, avoids entry into the pleural cavities and allows for the ready institution of cardiopulmonary bypass.

Cardiopulmonary bypass is essential to ensure cardiovascular stability when the operation is performed and to cool the patient to allow circulatory arrest. Excellent visibility is required, in a bloodless field, to define an adequate endarterectomy plane and then follow the pulmonary endarterectomy specimen deep into the subsegmental vessels. Because of the copious bronchial blood flow usually present in these cases, periods of circulatory arrest are necessary to ensure visibility.¹⁵² There have been recent reports of the performance of this operation without circulatory arrest.^{153,154} However, it should be emphasized that although endarterectomy is possible without circulatory arrest, a complete endarterectomy is not.¹⁵⁵ The circulatory arrest portions of the case are limited to the most distal portion of the endarterectomy process, deep in the subsegmental vasculature, and they are usually limited to 20 minutes for each side with restoration of flow in between.

A true endarterectomy in the plane of the media must be accomplished. It is essential to appreciate that the removal of visible thrombus is largely incidental to this operation. Indeed, in many patients, no free thrombus is

present; and on initial direct examination, the pulmonary vascular bed may appear normal. The early literature on this procedure indicates that thrombectomy often was performed without endarterectomy, and in these cases the pulmonary artery pressures did not improve, often resulting in death.

An IVC filter is always placed before surgery unless an obvious upper extremity or cardiac (e.g., intraventricular pacing wire, ventriculoatrial shunt) source is present. In the latter case, removal of any foreign material is undertaken, with alternative sites used, as with replacement of intravascular pacing leads with epicardial electrodes. Patients are treated with warfarin until the time of surgery, and this treatment is continued throughout the patient's life after surgery.

Pulmonary Endarterectomy: Surgical Technique

The technique for pulmonary endarterectomy has largely been developed by Dr. Stuart Jamieson at UCSD.¹⁵⁶ After a median sternotomy incision is made, the pericardium is incised longitudinally and attached to the wound edges. Typically the right side of the heart is enlarged, with a tense right atrium and a variable degree of tricuspid regurgitation. There is usually severe right ventricular hypertrophy, and, with critical degrees of obstruction, the patient's condition may become unstable with manipulation of the heart. Anticoagulation is achieved with the use of heparin sodium (400 U/kg, IV) administered to prolong the activated clotting time beyond 400 seconds. Full cardiopulmonary bypass is instituted with high ascending aortic cannulation and two caval cannulas. These cannulas must be inserted into the superior and inferior venae cavae sufficiently to enable subsequent opening of the right atrium. The heart is emptied on bypass, and a temporary pulmonary artery vent is placed in the midline of the main pulmonary artery, 1 cm distal to the pulmonary valve. This marks the beginning of the left pulmonary arteriotomy.

After cardiopulmonary bypass is initiated, surface cooling with both a head jacket and a cooling blanket on the operating room table is begun. The blood is cooled with the pump oxygenator. During cooling, a 10° C gradient between arterial blood and bladder or rectal temperature is maintained.¹⁵⁷ Cooling generally takes 45 minutes to 1 hour. When ventricular fibrillation occurs, an additional vent is placed in the left atrium through the right superior pulmonary vein. This prevents the occurrence of atrial and ventricular distention resulting from the large amount of bronchial arterial blood flow that is common with these patients. It is most convenient for the primary surgeon to stand initially on the patient's left side. During the cooling period, some preliminary dissection can be performed, with full mobilization of the right pulmonary artery from the ascending aorta. All dissection of the pulmonary arteries takes place intrapericardially, and neither pleural cavity is entered. An incision is then made in the right pulmonary artery from beneath the ascending aorta under the superior vena cava and entering the lower lobe branch of the pulmonary artery just after the takeoff of the middle lobe artery.

Any loose thrombus, if present, is removed. The endarterectomy cannot be performed in the presence of thrombus because it obscures the plane and prevents collapse of the endarterectomized specimen, hindering distal exposure. It is important to recognize that, first, an embolectomy without subsequent endarterectomy is ineffective and, second, in most patients with chronic thromboembolic hypertension, direct examination of the pulmonary vascular bed at operation generally shows no obvious embolic material. Therefore, to the inexperienced or cursory glance, the pulmonary vascular bed might appear normal, even in patients with severe chronic embolic PH. If the bronchial circulation is not excessive, the endarterectomy plane can be found during this early dissection. However, although a small amount of dissection can be performed before the initiation of circulatory arrest, it is unwise to proceed unless perfect visibility is obtained, because the development of a correct plane is essential.

When the patient's temperature reaches 20° C, the aorta is cross-clamped and a single dose of cold cardioplegic solution is administered. Additional myocardial protection is obtained with the use of a cooling jacket wrapped around the heart. The entire procedure is now performed with a single aortic cross-clamp period with no further administration of cardioplegic solution. A modified cerebellar retractor is placed between the aorta and the superior vena cava. When back bleeding from bronchial collaterals obscures direct vision of the pulmonary vascular bed, thiopental is administered (500 mg to 1 g) until the electroencephalogram becomes isoelectric. Circulatory arrest is then initiated, and the patient undergoes exsanguination. It is rare that one 20-minute period for each side is exceeded. Although retrograde cerebral perfusion has been advocated for total circulatory arrest in other procedures, it is not helpful in this operation because it does not allow a completely bloodless field, and, with the short arrest times that can be achieved, it is not necessary.

Any loose thrombotic debris encountered is removed. Next, a microtome knife is used to develop the endarterectomy plane posteriorly within the media of the vessel. Dissection in the correct plane is critical because if the plane is too deep, then the pulmonary artery may perforate, with fatal results, and if the dissection plane is not deep enough, then inadequate amounts of the partially resorbed thromboembolic material will be removed. Once the plane is correctly developed, a full-thickness layer is left in the region of the incision to ease subsequent repair. For the endarterectomy, gentle traction with forceps while sweeping the outer vessel wall layer away results in the progressive withdrawal of the endarterectomy specimen. The procedure is primarily performed with a long miniature sucker with a rounded tip.¹³⁹ As each lobar branch appears, it is grasped individually and the specimen is withdrawn until each segmental vessel branches again. Each of these subsegmental specimens is then extracted. Removal of each lobar and then segmental branch makes subsequent distal dissection easier. If a large mass of endarterectomized tissue begins to obscure visibility, it is excised. The entire specimen can thus be removed for a length of approximately 20 cm. The distal-most portion endarterectomy is

performed with an eversion technique. Perforation at the level of the subsegmental vessels will become completely inaccessible later, so care must be taken to remain in the plane of the media for endarterectomy. Clear visualization in a completely bloodless field provided by circulatory arrest is therefore essential during development of the distal surgical plane. It is important that each subsegmental branch is followed and freed individually until it ends in a "tail," beyond which there is no further obstruction. Residual material should never be cut free; the entire specimen should "tail off" and come free spontaneously. Once the right-sided endarterectomy is completed, circulation is restarted and the arteriotomy is repaired with a continuous 6-0 polypropylene suture. The hemostatic nature of this closure is aided by the nature of the initial dissection, with the full thickness of the pulmonary artery being preserved immediately adjacent to the incision.

After completion of the repair of the right arteriotomy, the surgeon moves to the patient's right side. The pulmonary vent catheter is withdrawn, and an arteriotomy is made from the site of the pulmonary vent hole laterally to the pericardial reflection, avoiding entry into the left pleural space. Additional lateral dissection does not enhance intraluminal visibility, can endanger the left phrenic nerve, and makes subsequent repair of the left pulmonary artery more difficult. The left-sided dissection is virtually analogous in all respects to that accomplished on the right. The duration of circulatory arrest intervals during the performance of the left-sided dissection also is subject to the same restriction as the right. After the completion of the endarterectomy, cardiopulmonary bypass is reinstituted and warming is commenced. Methylprednisolone (500 mg IV) and mannitol (12.5 g IV) are administered, and during warming a 10° C temperature gradient is maintained between the perfusate and body temperature. If the systemic vascular resistance level is high, nitroprusside is administered to promote vasodilation and warming. The rewarming period generally takes approximately 90 minutes, but varies according to the body mass of the patient.

When the pulmonary arteriotomy has been repaired, the pulmonary artery vent is replaced at the top of the incision. The right atrium is then opened and examined unless a negative "bubble" test result before cardiopulmonary bypass reveals no persistent foramen ovale on transesophageal echocardiography. Otherwise, any intraatrial communication (present in ≈20% of patients) is closed at this point. Although tricuspid valve regurgitation is invariable in these patients and is often severe, tricuspid valve repair is not performed. Right ventricular remodeling occurs within a few days, with the return of tricuspid competence.¹⁵⁸ If other cardiac procedures are required, such as coronary artery or mitral or aortic valve surgery, these are conveniently performed during the systemic rewarming period.¹⁵⁹ Myocardial cooling is discontinued once all cardiac procedures have been concluded. The left atrial vent is removed, and the vent site is repaired. Air is evacuated from the heart, and the aortic cross-clamp is removed.

When the patient has rewarmed, cardiopulmonary bypass is discontinued. Dopamine hydrochloride is

routinely administered at renal doses, and other inotropic agents and vasodilators are titrated as necessary to sustain acceptable hemodynamics. The cardiac output is generally high, with a low systemic vascular resistance. Temporary atrial and ventricular epicardial pacing wires are placed. Despite the duration of extracorporeal circulation, hemostasis is readily achieved, and the administration of platelets or coagulation factors is generally unnecessary. Wound closure is routine. A vigorous diuresis is usual for the next few hours, also the result of the previous systemic hypothermia. All patients are subjected to a maintained diuresis with the goal of reaching the patient's preoperative weight within 24 hours. Extubation is usually performed on the first postoperative day.

Thromboembolic Disease Classification and Prediction of Surgical Outcome

Four major types of pulmonary occlusive disease, based on anatomy and location of thrombus and vessel wall pathology, have been described.¹³⁹ This intraoperative classification of disease allows for the prediction of patient outcome after pulmonary endarterectomy.¹⁶⁰

1. Type 1 disease ($\approx 11\%$ of cases of thromboembolic PH; Fig. 102-3): fresh thrombus in the main or lobar pulmonary arteries. In this situation, major vessel clot is present and visible on the opening of the pulmonary arteries. This clot usually reflects main or lobar pulmonary vessel wall disease, with stasis, and fresh propagation of clot into the major pulmonary vessels.
2. Type 2 disease ($\approx 43\%$ of cases; Fig. 102-4): intimal thickening and fibrosis with or without organized thrombus proximal to segmental arteries. In these cases, only thickened intima can be seen, occasionally with webs in the main or lobar arteries.

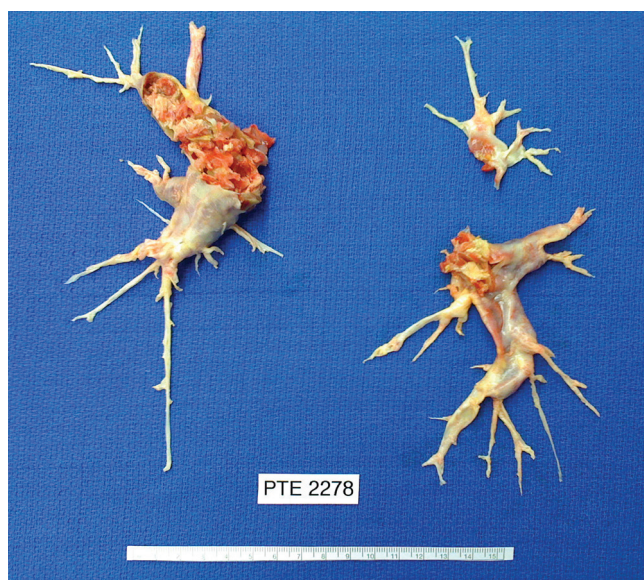


FIGURE 102-3 ■ Surgical specimen removed from right and left pulmonary arteries. Evidence of fresh thrombus indicates type 1 disease.

3. Type 3 disease ($\approx 42\%$ of cases; Fig. 102-5): fibrosis, intimal webbing, and thickening with or without organized thrombus within distal segmental and subsegmental arteries only. This type of disease presents the most challenging surgical situation. No occlusion of vessels can be seen initially. The endarterectomy plane must be raised individually in each segmental and subsegmental branch. Type 3 disease is most often associated with presumed repetitive thrombi from indwelling catheters or ventriculoatrial shunts and sometimes represents “burned out” disease, in which most of the embolic material has been reabsorbed.
4. Type 4 disease (less than 4% of cases): microscopic distal arteriolar vasculopathy without visible thromboembolic disease. Type 4 disease does not



FIGURE 102-4 ■ Surgical specimen removed from the right and left pulmonary arteries indicates type 2 disease.

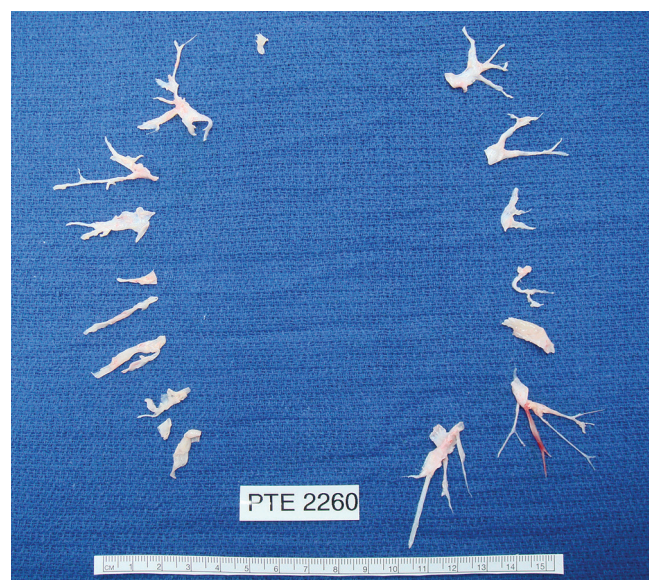


FIGURE 102-5 ■ Surgical specimen removed from right and left pulmonary arteries. In this patient with type 3 disease, the dissection plane was raised at each segmental level.

represent classic chronic thromboembolic PH and is inoperable. In this entity, there is intrinsic small-vessel disease, although secondary thrombus can occur because of stasis. Small-vessel disease may be unrelated to thromboembolic events (primary PH) or can occur in relation to thromboembolic hypertension because of a high-flow or high-pressure state in previously unaffected vessels similar to the generation of Eisenmenger syndrome.

We have noticed, in the last several hundred patients, an increase in the number of patients with type 3 disease (currently, $\approx 42\%$ of cases) and a decrease in the number of patients with Type 1 (currently, $\approx 11\%$ of cases) disease. Whether this reflects referral bias (i.e., difficult cases are preferentially sent to UCSD), increased recognition and diagnosis of thromboembolic PH, or a change in the presenting spectrum of disease is unclear. Nonetheless, despite seeing an increase in patients with more distal, surgically challenging disease, excellent hemodynamic and survival outcomes have been achieved at our institution.

Results of Pulmonary Endarterectomy Surgery

Although pulmonary endarterectomy is performed at several major cardiovascular centers throughout the

world, the majority of experience with this operation has been at the UCSD, where the technique of this operation was pioneered and refined. More than 3200 pulmonary endarterectomy operations have been performed at UCSD since 1970, whereas the entire reported literature on this operation (exclusive of UCSD) is approximately 2000 cases; 2400 cases have been completed at UCSD since 1997. The mean patient age of the last 1000 patients undergoing operation was 51.6 years, with a range of 8.9 to 84.8 years. There is a slight male predominance, reflecting either disease predilection, surgical bias, or both. In 40% of cases, at least one additional cardiac procedure was performed at the time of operation. Most commonly, the adjunct procedure was closure of a persistent foramen ovale or atrial septal defect (18.9%) or coronary artery bypass grafting (7.9%).¹⁵⁹

With this operation, a reduction in pulmonary pressures and resistance to normal levels and corresponding improvement in pulmonary blood flow and cardiac output are generally immediate and sustained.^{161,162} These changes are permanent.¹⁶³ Table 102-3 lists the most current statistics for the last 1000 patients who underwent pulmonary endarterectomy at UCSD with respect to hemodynamic improvement. Table 102-4 presents results for the same patient group stratified for thromboembolic disease classification group. Whereas before the operation more than 82.6% of the patients were in New

TABLE 102-3 UCSD Pulmonary Endarterectomy Recent Hemodynamic Results*

Variable	All Patients (N = 1000)	PTE Patients (n = 882)	PTE-CABG Patients (n = 79)	PTE-Value Patients (n = 39)
Mean decrease in PAS (mm Hg)	34.7 $\pm$ 18.8	35.2 $\pm$ 18.3	35.7 $\pm$ 22.3	18.3 $\pm$ 16.9
Mean decrease in PAD (mm Hg)	10.6 $\pm$ 8.8	10.9 $\pm$ 8.8	8.7 $\pm$ 9.8	7.9 $\pm$ 7.2
Mean decrease in PVR (dyn·s/cm ⁻⁵)	448.5 $\pm$ 345.6	455.5 $\pm$ 350.7	413.5 $\pm$ 303.3	345.5 $\pm$ 286.4
Mean increase in CO (L/min)	1.1 $\pm$ 1.5	1.1 $\pm$ 1.5	1.1 $\pm$ 1.2	1.5 $\pm$ 1.7
Mean decrease in tricuspid regurgitant velocity (m/sec)	1.2 $\pm$ 0.9	1.2 $\pm$ 0.9	1.1 $\pm$ 0.7	0.6 $\pm$ 0.9

*Data are shown as means $\pm$ standard deviation.

CABG, Coronary artery bypass grafting; CO, cardiac output; PAD, pulmonary artery diastolic pressure; PAS, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; UCSD, University of California, San Diego.

TABLE 102-4 UCSD Thromboembolic Disease Classification: Pulmonary Endarterectomy Hemodynamic Results*

Variable	All Patients (N = 1000, 100%)	Type 1 (n = 112, 11.2%)	Type 2 (n = 425, 42.5%)	Type 3 (n = 417, 41.7%)	Type 4 (n = 46, 4.6%)
PVR (dyn·sec/cm ⁻⁵)	692 $\pm$ 382.7 241.0 $\pm$ 131.7	832.8 $\pm$ 463.6 226.6 $\pm$ 109.4	667.4 $\pm$ 353.8 208.7 $\pm$ 108.2	673.2 $\pm$ 382.1 258.8 $\pm$ 132.1	747.8 $\pm$ 367.5 410.8 $\pm$ 200.1
CO (L/min)	4.5 $\pm$ 1.4 5.6 $\pm$ 1.5	4.0 $\pm$ 1.4 5.4 $\pm$ 1.2	4.5 $\pm$ 1.3 5.8 $\pm$ 1.5	4.5 $\pm$ 1.5 5.5 $\pm$ 1.5	4.2 $\pm$ 1.6 4.8 $\pm$ 1.4
Systolic PA Pressure (mm Hg)	74.6 $\pm$ 20.2 40.1 $\pm$ 13.3	76.2 $\pm$ 18.4 38.4 $\pm$ 11.3	75.1 $\pm$ 19.8 37.5 $\pm$ 11.6	73.7 $\pm$ 21.3 41.7 $\pm$ 14.0	74.1 $\pm$ 17.1 52.6 $\pm$ 15.9
Diastolic PA pressure (mm Hg)	27.0 $\pm$ 9.1 16.3 $\pm$ 5.7	29.0 $\pm$ 8.9 15.8 $\pm$ 4.9	27.0 $\pm$ 9.0 15.6 $\pm$ 5.5	26.4 $\pm$ 9.2 16.8 $\pm$ 5.7	27.1 $\pm$ 9.7 20.5 $\pm$ 6.3
Mean PA pressure (mm Hg)	44.8 $\pm$ 11.9 25.0 $\pm$ 7.7	46.2 $\pm$ 11.4 24.2 $\pm$ 6.7	44.9 $\pm$ 11.6 23.5 $\pm$ 6.9	44.2 $\pm$ 12.6 25.9 $\pm$ 8.1	44.9 $\pm$ 10.2 32.0 $\pm$ 8.5
Mortality (%)	15 (1.5%)	4 (3.6%)	5 (1.2%)	5 (1.2%)	1 (2.2%)

*Data are shown mean $\pm$ standard deviation or number (percentage). Upper numbers of each pair are preoperative values, and lower numbers are postoperative values obtained just prior to removal of the Swan-Ganz catheter.

CO, Cardiac output; PA, pulmonary artery; PVR, pulmonary vascular resistance.

York Heart Association (NYHA) functional class III or IV in this series, at 1 year after operation, 87.6% of patients were reclassified as NYHA functional class I or II. In addition, echocardiographic studies have demonstrated that, with the elimination of chronic pressure overload, right ventricular geometry rapidly reverts toward normal.^{164,165} Right atrial and right ventricular hypertrophy and dilation regresses. Tricuspid valve function returns to normal within a few days as a result of restoration of tricuspid annular geometry after the remodeling of the right ventricle; therefore, tricuspid valve repair is not performed with this operation.¹⁵⁸

Centers from around the world are now presenting results of surgical series of pulmonary endarterectomy operations. Table 102-5 summarizes the survival and hemodynamic outcome after pulmonary endarterectomy from this growing body of surgical experience.^{149,153,154,163,165-187}

Severe reperfusion injury is the single most frequent complication after pulmonary endarterectomy, historically occurring in approximately 15% of patients, but now in a much smaller percentage of our patients ($\approx 5\%$). Of patients with reperfusion injury, the majority resolve the problem with a short period of ventilatory support and aggressive diuresis. A minority of patients with severe lung reperfusion injury require prolonged periods

of ventilatory support, whereas extreme cases require venovenous extracorporeal support for oxygenation and blood carbon dioxide removal.¹⁸⁸ Neurologic complications from circulatory arrest have mostly been eliminated by shorter circulatory arrest periods and the use of a direct cooling jacket placed around the head, which provides even cooling to the surface of the cranium. Stroke rates for the last 1000 pulmonary endarterectomy patients at UCSD is 0.2%. In the last 1000 pulmonary endarterectomy patients at UCSD, reexploration for bleeding occurred at a rate of 2.8%, and 33.9% of patients required intraoperative or postoperative blood transfusion. Despite an average duration of surgery of 6.2 hours, wound infection occurred in only 0.6% of patients.

The single greatest risk factor for operation remains the severity of pulmonary vascular resistance and the ability to lower it to a normal range at operation. Patients with high pulmonary vascular resistance with minimal vascular obstruction on angiogram (Type 4 small vessel vasculopathy indistinguishable from idiopathic pulmonary arterial hypertension) have the worst prognosis, and surgery does not correct PH in this population. Arteriolar-capillary vasculopathy without larger vessel thromboembolic disease was not influenced by blind endarterectomy of the proximal pulmonary arterial tree. The majority of early deaths after this operation are in this subgroup, and

TABLE 102-5 Pulmonary Endarterectomy Series of More Than 50 patients: 2008-2014

References	Date	Dates of Study	Patients (N)	Periop Deaths (N)	Preop Mean PA Pressure (mm Hg)	Postop Mean PA Pressure (mm Hg)	Preop Mean PVR (dyn·s/cm ⁵)	Postop Mean PVR (dyn·s/cm ⁵)
Condliffe ¹⁶⁹	2008	2001-2006	236	37	48	27	1091	464
Corsico ¹⁶⁸	2008	1994-2006	157	18	48	24	1140	327
Freed ¹⁶⁷	2008	1997-2006	229	0	47	25	800	244
Thistlethwaite ¹⁶⁶	2008	NR	1100	52	46	28	859	290
Thomson ¹⁵³	2008	2003-2006	150	22	52	29	740	336
Saouti ¹⁷¹	2009	1998-2007	72	5	42	22	572	NR
Skoro-Sajer ¹⁷⁰	2009	1994-2006	62	NR	48	NR	746	383
Gan ¹⁷³	2010	1989-2007	360	16	81	NR	19*	NR
Kunihara ¹⁷²	2010	1995-2006	219	6	48	24	800 [†]	300 [†]
de Perrot ¹⁷⁸	2011	2005-2011	58	3	45	24	965	383
Freed ¹⁷⁷	2011	1997-2007	314	0	48	26	805	301
Kunihara ¹⁷⁶	2011	1995-2009	279	31	47	26 [†]	872	350 [†]
Schölzel ¹⁷⁵	2011	2000-2009	74	5	41	25	521	NR
Surie ¹⁶⁵	2011	NR	73	6	42	24	808	419
van der Plas ¹⁷⁴	2011	2003-2009	96	10	41	25	768	422
Ishida ¹⁶³	2012	1990-2010	77	11	47	25	868	313
Madani ¹⁴⁹	2012	1999-2006	1000	NR	46	29	861	294
		2006-2010	500	NR	46	26	719	253
Morsolini ¹⁵⁴	2012	1994-2011	347	35	45	25	999	439
Surie ¹⁷⁹	2012	NR	73	5	40	23	714	410
Nishimura ¹⁸²	2013	1986-2010	195	NR	43	NR	792	NR
Ross ¹⁸¹	2013	1999-2012	91	NR	43	20	753	182
Sato ¹⁸⁰	2013	2001-2010	60	NR	49	22	998	269
Berman ¹⁸⁷	2014	NR	72	0	48	26	698	265
Ghio ¹⁸⁶	2014	1994-2012	296	0	44	23	925	303
Schölzel ¹⁸⁵	2014	2004-2009	52	5	40	NR	971	NR
Skoro-Sajer ¹⁸⁴	2014	1994-2010	110	5	NR	NR	770	368
Wietska ¹⁸³	2014	1998-2008	66	6	50	25	752	176

*Recorded as Woods units.

[†]Numbers were estimated from graph data in references.

NR, Not recorded; PA, pulmonary artery; Periop, perioperative; Postop, postoperative; Preop, preoperative; PVR, pulmonary vascular resistance.

efforts are directed at better determining who these patients are in the preoperative setting to avoid unnecessary operation.

In the UCSD experience, overall perioperative mortality was 5.4% for the entire cohort of patients, encompassing a span of more than 30 years. In the last 1000 cases, surgical mortality for pulmonary endarterectomy was 1.5%. This reflects the learning curve for safely performing this operation and the refinements in surgical technique that enhance patient outcome.

A survey of surviving patients who underwent pulmonary endarterectomy between 1970 and 1995 at UCSD has formally evaluated long-term outcome from this operation.¹⁸⁹ Questionnaires were mailed to 420 patients who had surgery more than 1 year prior, and responses were obtained from 308 patients. Survival, functional status, quality of life, and the subsequent use of medical assistance were assessed. Survival after pulmonary endarterectomy was found to be 75% at 6 years or more. This survival exceeds single- or double-lung transplant survival for thromboembolic PH. Ninety-three percent of the patients were found to be in NYHA class I or II, compared with approximately 95% of the patients being in NYHA class III or IV preoperatively. Of the working population, 62% of patients who were unemployed before operation returned to work. Patients who had undergone pulmonary endarterectomy scored several quality of life components slightly lower than normal individuals, but significantly higher than the patients before operation. Only 10% of patients used oxygen after surgery. In response to the question "How do you feel about the quality of your life since your surgery?" 77% replied much improved, and 20% replied improved. These data appear to confirm that pulmonary endarterectomy offers substantial improvement in survival, function, and quality of life.

Alternative Therapies for Chronic Thromboembolic Pulmonary Hypertension

There are patients with chronic thromboembolic PH who are not surgical candidates, because they are either (1) technically nonoperable, or (2) technically operable but have an unacceptable surgical risk. Determination of operable candidacy should be done by a center with expertise with pulmonary endarterectomy. Candidates that are deemed poor surgical candidates may be evaluated for the option of either balloon angioplasty of the pulmonary vasculature¹⁹⁰ or medical management with riociguat,¹⁹¹ the only drug currently approved by the FDA for the treatment of chronic thromboembolic PH.

In 2001, Feinstein and colleagues¹⁹² published a series of 18 patients with inoperable chronic thromboembolic PH who underwent balloon dilation of the pulmonary arteries, with variable results. More recently, Japanese investigators refined pulmonary artery balloon angioplasty by using smaller balloons, by limiting the number of balloon inflations per session to two pulmonary vascular segments, and by the use of intravascular ultrasound.^{193,194,195} An average of 4.8 sessions is needed per

patient, and severe reperfusion edema was seen in 2% of patients. Although pulmonary artery balloon angioplasty remains largely experimental in the United States, it is rapidly gaining attention for use in nonoperable patients, such as those who have incurable malignancy or are too frail to survive operation.

Recently, riociguat, a new class of oral drug and stimulator of guanylate cyclase, met the primary and secondary endpoints (increased 6-minute walk distance, improvement in World Health Organization functional class, hemodynamics, biomarkers, and quality of life) of a phase 3, multicenter, randomized, double-blind, placebo-controlled study of 261 patients with adjudicated inoperable chronic thromboembolic PH or persistent PH after pulmonary endarterectomy.¹⁹⁶ This drug was approved by the FDA in October 2013 for the treatment of inoperable chronic thromboembolic PH and persistent PH following pulmonary endarterectomy. It is important to note that pulmonary endarterectomy remains the gold standard treatment of chronic thromboembolic PH, and it is curative of this disease. Only patients deemed inoperable by an experienced pulmonary endarterectomy team or those that have residual PH after pulmonary endarterectomy should be offered riociguat.

SUMMARY

Pulmonary hypertension owing to chronic pulmonary emboli is a condition that is underrecognized and carries a poor prognosis. Pulmonary endarterectomy is considered the best treatment for chronic thromboembolic PH. The only curative therapeutic alternative to pulmonary endarterectomy is lung transplantation and heart-lung transplantation. The advantages of pulmonary endarterectomy include a lower operative mortality, better long-term results with respect to survival and quality of life, and the avoidance of chronic immunosuppressive treatment and allograft rejection. Currently, mortality rates for pulmonary endarterectomy are 1.5%, and the operation allows for sustained clinical benefit. These results make it the treatment of choice over transplantation for thromboembolic disease to the lung both in the short and long term.

Although pulmonary endarterectomy is a technically demanding operation, excellent results can be achieved. Improvements in operative technique developed over the past four decades allow pulmonary endarterectomy to be offered to patients with an acceptable mortality rate and anticipation of clinical improvement. With the increasing recognition of patients who have thromboembolic PH and the realization that pulmonary endarterectomy is a safe and effective operation for this condition, it is anticipated that this will be an expanding area of surgical therapy in the future.

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TUMORS OF THE HEART

Oz M. Shapira • Michael J. Reardon

CHAPTER OUTLINE

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SECONDARY METASTATIC TUMORS

Neoplastic involvement of the heart can be divided into primary cardiac tumors arising in the heart and secondary cardiac tumors that have metastasized to the heart. Primary cardiac tumors can be further stratified into benign and malignant tumors. Secondary involvement of the heart is relatively common, with 10% to 20% of patients dying of disseminated cancer having metastatic involvement of the heart or pericardium.^{1,2} Surgical resection is seldom possible or advisable for these tumors, and surgical intervention is usually limited to drainage of malignant pericardial effusions, diagnostic biopsies, or both. There are uncommon cases of metastatic disease limited to the heart for which resection is reasonable.³

Primary tumors of the heart are uncommon but not rare. In unselected autopsy series, the incidence of primary cardiac neoplasm ranges between 0.0017% and 0.19%.⁴⁻⁸ Approximately 75% of primary cardiac tumors are benign and 25% are malignant.^{2,9} Approximately 50% of the benign tumors are myxomas, and approximately 75% of the malignant tumors are sarcomas.^{2,9} The clinical incidence of these tumors is approximately 1 in 500 cardiac surgical cases and, with the exception of myxomas, most surgeons will rarely encounter primary cardiac tumors. The purpose of this chapter is to summarize useful information for the evaluation and management of patients with primary and secondary cardiac tumors and to provide a reference for additional study on these subjects.

HISTORICAL BACKGROUND

Cardiac tumors were a postmortem diagnosis until the first antemortem diagnosis of a cardiac tumor was made in 1934 when Barnes diagnosed a cardiac sarcoma using

electrocardiography and biopsy of a metastatic lymph node.¹⁰ In 1936, Beck successfully resected a teratoma external to the right ventricle,¹¹ and Mauer removed a left ventricular lipoma in 1951.¹² Treatment of cardiac tumors was profoundly influenced by two events: the introduction of cardiopulmonary bypass in 1953 by John Gibbon allowing safe and reproducible approach to the cardiac chambers and the introduction of cardiac echocardiography allowing safe and noninvasive diagnosis of an intracardiac mass. The first echocardiographic diagnosis of an intracardiac tumor was made in 1959.¹³ A large right atrial myxoma was removed by Bahnson in 1952 using caval inflow occlusion but the patient expired 24 days later.¹⁴ Crafoord in Sweden first successfully removed a left atrial myxoma in 1954 using cardiopulmonary bypass,¹⁵ and Kay in Los Angeles first removed a left ventricular myxoma in 1959.¹⁶ By 1964, 60 atrial myxomas had been removed successfully with a steady increase because of increasing safety of cardiopulmonary bypass and increased use of echocardiography for detection.¹⁷ Operations are currently routinely performed on the vast majority of patients with atrial myxoma with minimal mortality.^{9,18} Primary malignant tumors, however, continue to represent a challenge.

PRIMARY BENIGN TUMORS

Myxomas

Definition, Incidence, and Prevalence

Myxomas are the most common primary cardiac tumors. They are benign. Although they have been reported in both sexes and in all age groups, they most often occur

in women in the third to sixth decade of life. Myxomas are usually sporadic, but at least 7% occur as part of an autosomal dominant syndrome. In the latter situation, the myxoma is a component of a larger syndrome referred to as the *Carney complex*.⁶ In the Carney complex, myxomas are associated with spotty pigmentation of the skin and endocrine hyperactivity. Myxomas that arise as part of the Carney complex affect both sexes equally and at any age. They arise as single or multiple lesions in all chambers of the heart, and tend to recur after surgical excision.⁷

Morphology

Arising from the endocardium, myxomas usually extend into a cardiac chamber. They are generally polypoid, pedunculated lesions with a smooth surface that may be covered with thrombus. The tumors range in size from 1 to 15 cm, but they are most commonly about 5 cm in diameter with a weight of approximately 70 g.^{8,19-21} Myxomas are thought to arise from pluripotent mesenchymal cells. Histologically, they consist of a matrix of acid mucopolysaccharide.²² The cells are polygonal or spindle-shaped and may form capillary-like channels that can communicate with arteries and veins located at the base of the tumor.²⁰

Myxomas most commonly occur in the atria. Approximately 75% arise in the left atrium, and 15% to 20% arise in the right atrium.²⁰ Most left atrial myxomas are located on the border of the fossa ovalis, but they can originate from any place on the atrial wall. The remaining myxomas are located in the ventricles. Myxomas arising from cardiac valves are rare (Fig. 103-1).

Clinical Characteristics

Patients with myxomas can have a variety of symptoms. In the sporadic form, classic findings include emboli, congestive heart failure caused by obstruction of cardiac blood flow, and constitutional symptoms. These sequelae are related to the location, size, and mobility of the tumor.

Because most myxomas arise in the left atrium, systemic embolization is common, occurring in 30% to 50% of cases.²³⁻²⁵ Left ventricular myxomas have an even higher propensity to embolize.^{26,27} Right atrial myxomas rarely display clinical manifestations of emboli. Embolic material from myxomas can compromise blood flow to any organ, but the brain is most commonly affected. Myxoma should be included in the differential diagnosis of any systemic embolic event, and any embolic material removed should undergo histologic evaluation.

Patients with myxomas can also display signs and symptoms related to cardiac obstruction. Typically, the findings are related to the tumor's ability to impede filling of the ventricles; in such instances, signs and symptoms may mimic those of mitral or tricuspid valve stenosis. Less commonly, the tumors impede atrioventricular (AV) valve leaflet coaptation, causing valvular regurgitation. Much less frequently, ventricular tumors obstruct ventricular outflow and cause findings similar to those of aortic or pulmonic stenosis. Constitutional symptoms

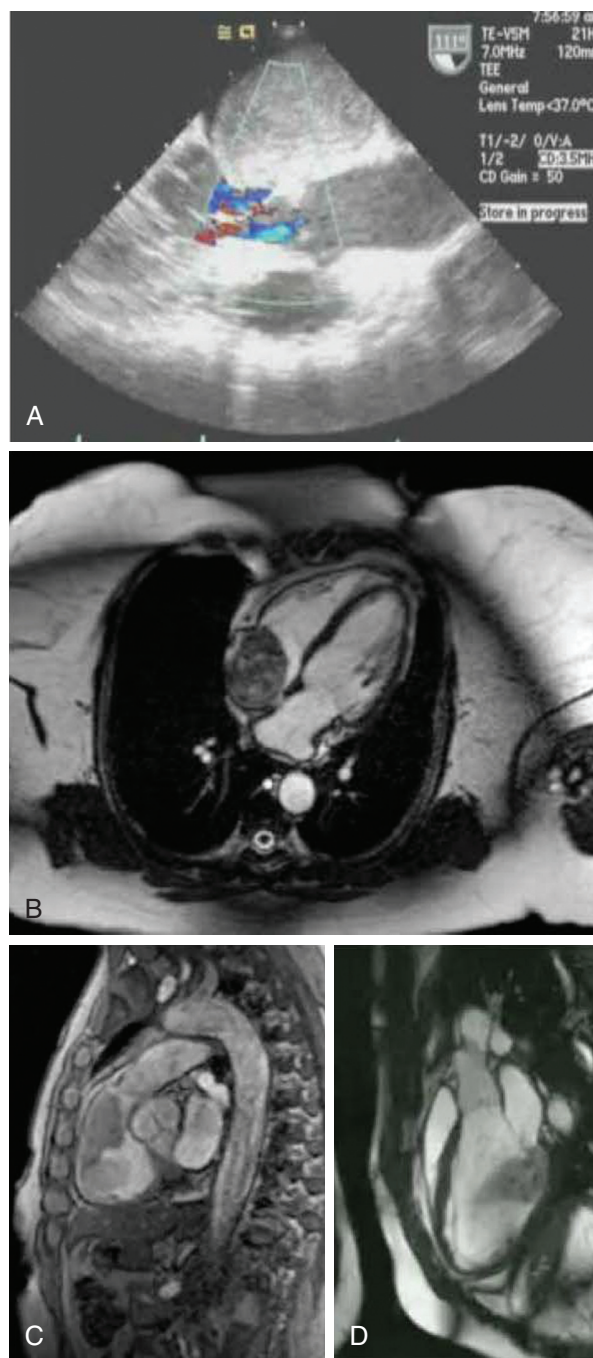


FIGURE 103-1 ■ Myxomas of the heart. **A**, Echocardiography of giant left atrial myxoma. **B**, Magnetic resonance imaging of right atrial myxoma. **C**, Magnetic resonance imaging of right ventricular myxoma. **D**, Magnetic resonance imaging of left ventricular myxoma.

include fever, malaise, rash, weight loss, and myalgia. Abnormal laboratory values, including elevated erythrocyte sedimentation rate, anemia, thrombocytopenia, and an elevated C-reactive protein, are common. These constitutional symptoms and laboratory findings are not related to tumor size or location. Many patients with myxomas are however asymptomatic. The myxoma may be detected by routine screening echocardiography performed for other indications. Asymptomatic myxomas

should be excised to prevent emboli, valvular dysfunction, or constitutional symptoms.

Diagnosis

Echocardiography is the imaging modality of choice for diagnosis of myxomas. Tumor location and characteristics can be delineated by two-dimensional transthoracic echocardiography. Transesophageal echo and three-dimensional echocardiography can be used to characterize the tumor further.^{28,29} The echocardiographic appearance of myxomas is usually distinctive, but other causes of intracardiac masses must be included in the differential diagnosis. In cases of diagnostic uncertainty, magnetic resonance imaging (MRI) and computed tomography (CT) may be helpful. Final diagnosis is confirmed by pathologic examination.

Management

Surgical resection is the mainstay of treatment. The intracardiac mass is excised after establishing cardiopulmonary bypass and cardioplegic arrest. Bicaval cannulation is used for venous return. Great care must be taken to minimize manipulation of the heart before cross-clamping the aorta to reduce the risk of intraoperative tumor embolization. A variety of approaches are available for resection of left atrial tumors. In the absence of other cardiac disease, a minimally invasive or robotically assisted operation can be used to speed postoperative recovery. Intracardiac exposure is generally achieved through a lateral, longitudinal incision in the left atrium. When visualization is difficult, additional incisions in the right atrium and septum are made.

The tumor is resected en bloc. Tumors that arise from a relatively well-defined pedicle can be excised without full-thickness excision of a button of atrial wall. However, many surgeons prefer to excise a portion of the atrial wall, especially if the tumor arises from the interatrial septum or it is a broad-based tumor. Tumors of the ventricle may be resected without full-thickness excision of a portion of ventricular wall. Tumors arising from an AV valve can usually be resected without the need for valve replacement. Regardless of the site of origin, the AV valve in proximity to the tumor should be inspected for evidence of damage.

The results of surgical excision are good, with a low risk of morbidity and mortality (0% to 3%).^{9,30,31} Recurrence of atrial myxomas is infrequent. Sporadic myxomas recur in 1% to 3% of patients at an average of 2.5 years after surgery.³² The risk of recurrence of familial myxomas ranges from 12% to 20%.^{32,33} Therefore, regular echocardiographic follow-up is recommended in the latter group. When myxomas recur, they should be resected.

Lipomas

Lipomas are well-encapsulated tumors consisting of mature fat cells that can occur anywhere in the heart, but also are found in the pericardium, subendocardium, subepicardium, or intra-atrial septum.²⁰ They can also occur at any age and have no sex predilection. Lipomas are slow

growing and can attain considerable size before producing obstructive or arrhythmic symptoms. Many are asymptomatic and are discovered incidentally on routine chest roentgenogram, echocardiogram, or at surgery or autopsy.^{34,35} Subepicardial and parietal lipomas tend to compress the heart and may be associated with pericardial effusion. Subendocardial tumors can produce chamber obstruction. The right atrium and left ventricle are sites most often affected. Lipomas lying within the myocardium or septum can produce arrhythmias or conduction abnormalities.³⁶ Large tumors that produce severe symptoms should be resected. Smaller, asymptomatic tumors encountered unexpectedly during cardiac operation should be removed if excision can be performed without adding risk to the primary procedure. These tumors are not known to recur.

Lipomatous Hypertrophy of the Interatrial Septum

Nonencapsulated hypertrophy of the fat within the atrial septum is known as *lipomatous hypertrophy*.²⁰ This abnormality is more common than cardiac lipoma and is usually encountered in older, obese, or female patients as an incidental finding during a variety of cardiac imaging procedures.³⁷ Various arrhythmias and conduction disturbances have been attributed to its presence.³⁸⁻⁴⁰ The main problem posed is differentiation from a cardiac neoplasm when the lesion is discovered on echocardiography.⁴¹ After the demonstration of a mass by echocardiography, the typical T1 and T2 signal intensity of fat on MRI can usually establish a diagnosis (Fig. 103-2).^{42,43} Arrhythmias or heart block are considered by some as an indication for resection, but there is lack of data as to the long-term benefits from resection.⁴⁴

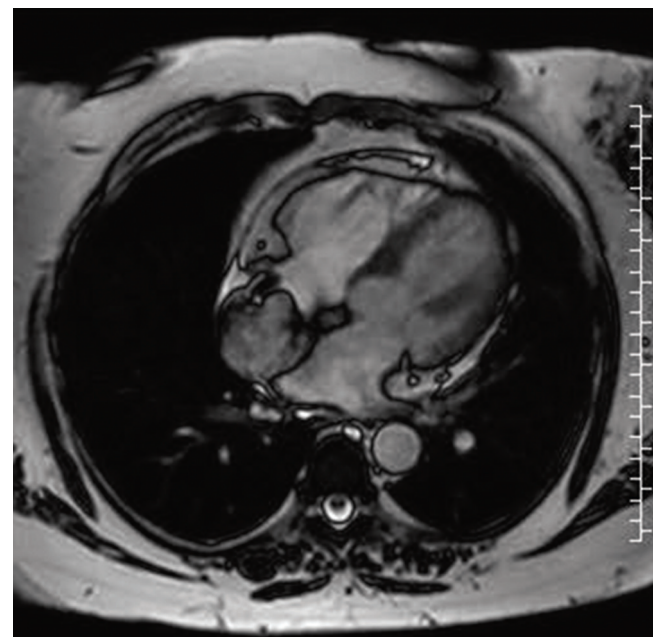


FIGURE 103-2 ■ Lipomatous hypertrophy.

Papillary Fibroelastoma of the Heart Valves

Papillary fibroelastomas are tumors that arise characteristically from the cardiac valves or adjacent endocardium.⁴⁵ Grossly, tumors are described as resembling sea anemones with frondlike projections. The AV and semilunar valves are affected with equal frequency. Ventricular fibroelastomas that occur on the left side have a high risk of stroke.⁴⁶ Papillary fibroelastomas were formerly thought to be innocuous because they were incidental findings at an autopsy. It is now known that they are capable of producing obstruction of flow, particularly coronary ostial flow, and they can embolize to the brain and produce stroke.^{46,47} They are usually asymptomatic until a critical event occurs. Now they are found more often because of the more frequent use of echocardiography. Papillary fibroelastomas of the cardiac valve should be resected whenever diagnosed because of their known tendency to produce life-threatening complications. These tumors can often be resected using minimally invasive techniques (Fig. 103-3).⁴⁶ Valve repair rather than replacement should follow the resection of these benign tumors whenever technically feasible, using conservative margins of resection. Cytomegalovirus has been recovered in these tumors, suggesting the possibility of viral induction of the tumor and chronic viral endocarditis.⁴⁴

Rhabdomyoma

Rhabdomyoma is the most frequently occurring cardiac tumor in children. It usually manifests during the first few days after birth. It is thought to be a myocardial hamartoma rather than a true neoplasm.⁴⁸ Although rhabdomyoma appears sporadically, it is associated strongly with tuberous sclerosis, a hereditary disorder

characterized by hamartomas in various organs, epilepsy, mental deficiency, and sebaceous adenomas. Fifty percent of patients with tuberous sclerosis have rhabdomyoma, but more than 50% of patients with rhabdomyoma have or will develop tuberous sclerosis.^{49,50} The exceptional patient is one with a solitary, single rhabdomyoma who does not have or develop tuberous sclerosis.

More than 90% of rhabdomyomas are multiple and occur with approximately equal frequency in both ventricles.⁵¹ The atrium is involved in fewer than 30% of patients. Pathologically, these tumors are firm, gray, and nodular and tend to project into the ventricular cavity. Micrographs show double normal-sized myocytes filled with glycogen and containing hyperchromatic nuclei and eosinophilic staining cytoplasmic granules.^{20,49} Scattered bundles of myofibrils can be seen within cells by electron microscopy.⁵¹

The most common presentation is heart failure caused by tumor obstruction of cardiac chambers or valvular orifice flow. Clinical findings can mimic valvular or subvalvular stenosis. Arrhythmias, particularly ventricular tachycardia and sudden death, can be a presenting symptom.⁴⁹ Atrial tumors can produce atrial arrhythmias.⁴⁹ The diagnosis is suggested by clinical features of tuberous sclerosis and is made by echocardiography. Rarely, no intramyocardial tumor is found in a patient with ventricular arrhythmias, and the site of rhabdomyoma is located by electrophysiologic study.⁴⁹

Early operation is recommended in patients who do not have tuberous sclerosis before 1 year of age.⁵⁰ The tumor is usually removed easily in early infancy, and some can be enucleated.⁵⁰ Unfortunately, symptomatic tumors often are both multiple and extensive, particularly in patients with tuberous sclerosis who unfortunately have a dismal long-term outlook. In such circumstances, surgery offers little benefit.

Fibroma

Fibromas are the second most common benign cardiac tumor, with over 83% occurring in children. These tumors are solitary, occur exclusively within the ventricle and the ventricular septum, and affect the sexes equally (Fig. 103-4). Fewer than 100 tumors have been reported, and most are diagnosed by the age of 2 years. These tumors are not associated with other disease, nor are they inherited. Fibromas are nonencapsulated, firm, nodular, gray-white tumors that can become bulky. They are composed of elongated fibroblasts in broad spiral bands and whirls mixed with collagen and elastin fibers. Calcium deposits or bone can occur within the tumor and occasionally are seen on radiographs.

The majority of fibromas produce symptoms through chamber obstruction, interference with contraction, or arrhythmias. Depending on size and location, such a tumor can interfere with valve function, obstruct flow paths, or cause sudden death from conduction disturbances in up to 25% of patients.⁵⁰ Intracardiac calcification on chest radiographs suggests the diagnosis, which is confirmed by echocardiogram.

Surgical excision is successful in some patients, particularly if the tumor is localized, does not involve vital

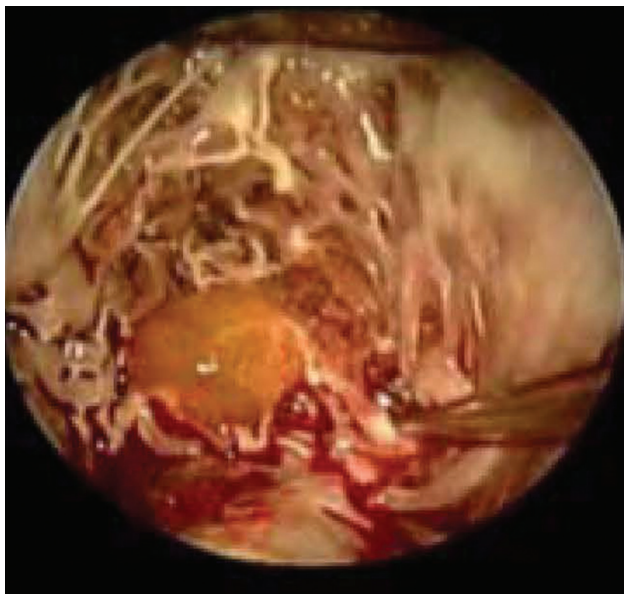


FIGURE 103-3 ■ Fibroelastoma seen through minimally invasive thoracoscopic approach.

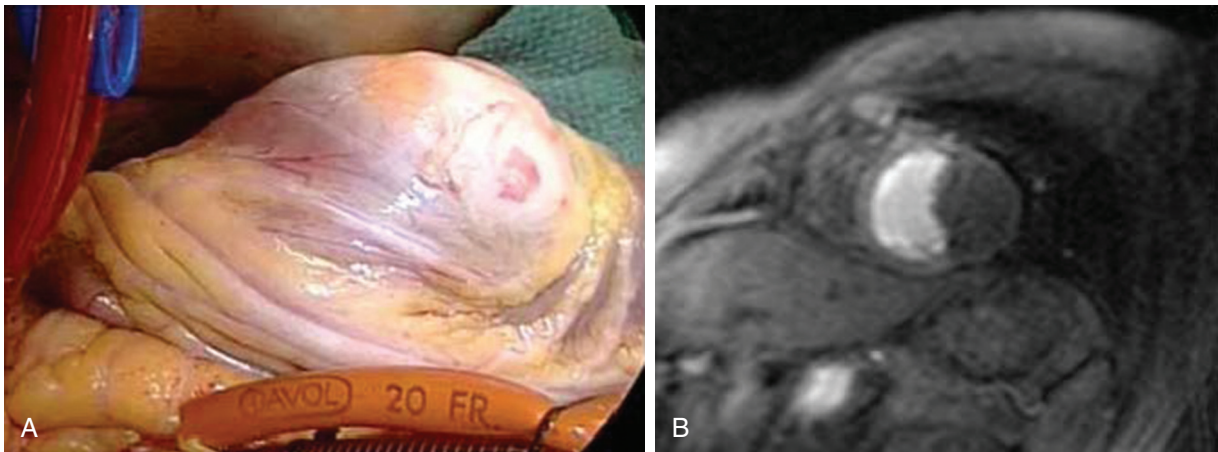


FIGURE 103-4 ■ Fibroma. **A**, Heart showing left ventricular fibroma. **B**, Cardiac magnetic resonance imaging showing left ventricular fibroma.

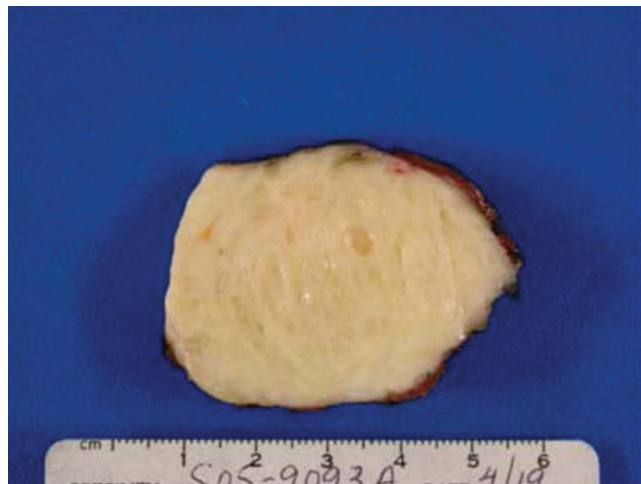


FIGURE 103-5 ■ Resected fibroma.

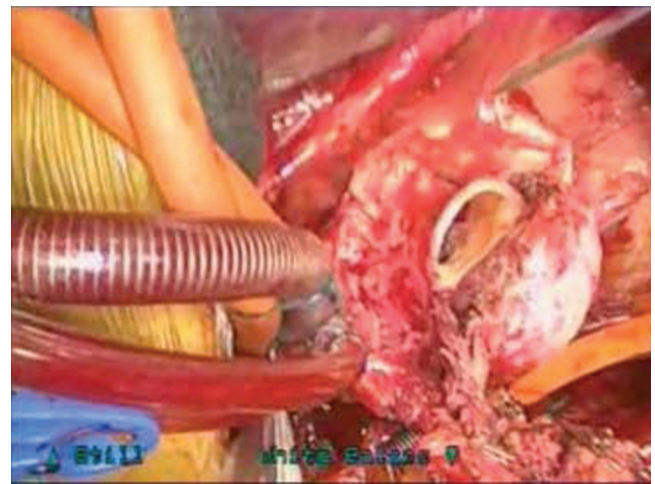


FIGURE 103-6 ■ Paraganglioma of the aortic root

structures, and can be enucleated (Fig. 103-5).⁵² However, it is not always possible to completely remove the tumor, and partial removal is only palliative, although some patients have survived many years.^{53,54} Operative mortality can be high in infants. Most cases involve adolescents and adults.⁵² Successful, complete excision is curative.⁵² Children with extensive fibromas have been treated with cardiac transplantation.⁵³

Paraganglioma

Cardiac paragangliomas arise from chromaffin cells of the sympathetic nervous system and can produce excess amounts of catecholamines, particularly norepinephrine, but usually are not hormonally active. Approximately 90% of hormonally active paragangliomas are in the adrenal glands and are referred to as *pheochromocytomas*. Fewer than 2% arise in the chest and are referred to as *hormonally active cardiac paragangliomas*, with the term *pheochromocytoma* being restricted to the adrenals. Only 32 cardiac paragangliomas had been reported by 1991.⁵⁵ The tumor predominantly affects young and middle-aged adults with an equal distribution between the sexes.

Approximately 60% of tumors occur in the roof of the left atrium. The remainder involve the interatrial septum or anterior surface of the heart.⁵⁶ The tumor is reddish-brown, soft, lobular, and consists of nests of chromatin cells (Fig. 103-6).

Hormonally active patients usually present with symptoms of uncontrolled hypertension or are found to have elevated urinary catecholamines. The tumor is usually located by scintigraphy using ¹³¹I-metaiodobenzylguanidine^{57,58} and CT scan or MRI.^{57,58} Occasionally, cardiac catheterization with differential blood chamber sampling is necessary. Because these tumors are vascular and may be near major coronary arteries, coronary arteriograms are advisable and percutaneous biopsy should be avoided.

After the tumor is located, it should be removed, using cardiopulmonary bypass with cardioplegic arrest. Hormonally active patients require preanesthetic alpha and beta blockade, and careful intraoperative and immediate postoperative monitoring. Most tumors are extremely vascular and uncontrolled operative hemorrhage has occurred.⁵⁸ Resection may require removal of the atrial or ventricular wall, or both, or a segment of a major coronary artery.⁵⁹ Explantation of the heart to allow

resection of a large left atrial paraganglioma has been attempted by Cooley and colleagues⁶⁰ and accomplished by Reardon.⁵⁹ Transplantation has been performed for nonresectable tumor. Complete excision produces cure.⁵⁹

Hemangioma

Hemangiomas of the heart are rare (24 clinical cases reported), affect all ages, and can occur anywhere within the heart.⁶¹⁻⁶³ These vascular tumors are composed of capillaries or cavernous vascular channels. Patients usually develop dyspnea, occasional arrhythmias, or signs of right heart failure.⁶⁴ Diagnosis is difficult and chest roentgenography may be abnormal, but is not specific. Echocardiography or cardiac catheterization usually but not always establishes a diagnosis of cardiac tumor by showing an intracavity filling defect.⁶⁵ CT scan and MRI should be done. Axial T2-weighted MRI should show a high signal mass caused by vascularity.⁶⁶ Coronary angiography typically shows a tumor blush and maps the blood supply to the tumor.

The tumors can be resected in asymptomatic patients, and cardiopulmonary bypass is recommended. Meticulous ligation of feeding vessels is required to prevent postoperative residual arteriovenous fistulas or intracavity communications. Partial resections have produced long-term benefits.⁶¹ Tumors rarely resolve spontaneously.⁶⁷

PRIMARY MALIGNANT TUMORS

Sarcomas

Primary cardiac malignancy is uncommon, with only 21 surgically treated cases noted in a 25-year surgical experience from 1964 to 1989, combining the experience of two large institutions, the Texas Heart Institute and the M.D. Anderson Cancer Center in Houston, Texas.⁶⁸ Even in busy centers, primary cardiac malignancy continues to challenge the diagnostic ability and surgical skills of thoracic surgeons. Our current primary cardiac sarcoma database included more than 200 patients seen over 15 years, and surgical results have begun to improve.^{9,69-74} Approximately 25% of primary cardiac tumors are malignant, and of these approximately 75% are sarcomas.⁷⁵ McAllister's survey of cardiac tumors found the most common to be angiosarcomas (31%), rhabdomyosarcomas (21%), malignant mesotheliomas (15%), and fibrosarcomas (11%).²⁰

Primary malignant cardiac tumors arise sporadically showing no inherited linkage. Although they may span the entire age spectrum, they usually occur in adults over 40 years of age. The patients usually present with symptoms of congestive heart failure, pleuritic chest pain, malaise, anorexia, and weight loss.^{76,77} The most common symptom has been dyspnea.⁷⁸ Some develop refractory arrhythmias, syncope, pericardial effusion, and tamponade.⁶⁸ The primary approach to primary cardiac sarcoma is complete surgical resection which is often a challenge. Our approach to primary cardiac sarcoma is to classify them according to location rather than cell type.

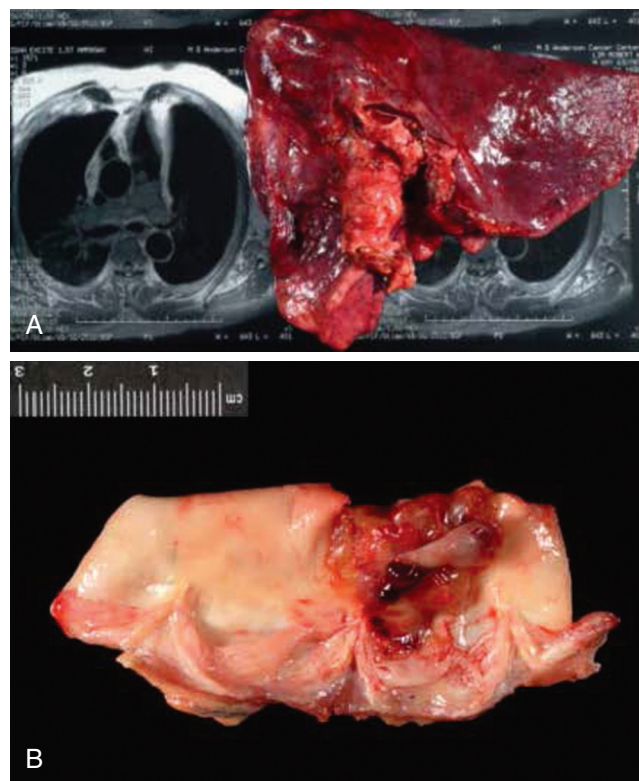


FIGURE 103-7 ■ Pulmonary artery sarcoma. **A**, Pulmonary artery sarcoma overlying computed tomographic scan. **B**, Pulmonary artery sarcoma starting at pulmonary valve.

Location generally determines presenting symptomatology and potential surgical approaches. We divide our cases into right heart, left heart, and pulmonary artery sarcomas.^{69,79}

Pulmonary artery sarcomas often present late with pulmonary artery obstruction and can be mistaken for chronic pulmonary emboli. Cardiac MR will show tissue perfusion and allow differentiation as a tumor. These tumors arise in the dorsal pulmonary artery and often involve the valve (Fig. 103-7). Complete resection rather than endarterectomy should be performed to allow maximum survival.⁷² Left heart sarcoma often presents with left heart obstruction and congestive heart failure. Surgical resection can be challenging because of the location of the posterior left atrium. We have used cardiac autotransplantation to allow full exposure, aggressive resection, and accurate reconstruction of the heart (Fig. 103-8).^{70,73,75,80} Right heart sarcomas tend to be more bulky and infiltrative and less often appear with heart failure. Our experience has been that survival is markedly affected by achieving an R0 resection, which occurs in only about one third of cases. We recommend biopsy and neoadjuvant therapy to allow shrinkage of these large and bulky tumors to improve the R0 resection rate, and we are completing a protocol of this approach (Fig. 103-9).⁷⁴ These tumors are all aggressive, and we recommend postresection chemotherapy even when R0 resection is achieved. Surgical resection and overall care of these patients is complex and is best done in centers of excellence with multidisciplinary cardiac tumor teams.

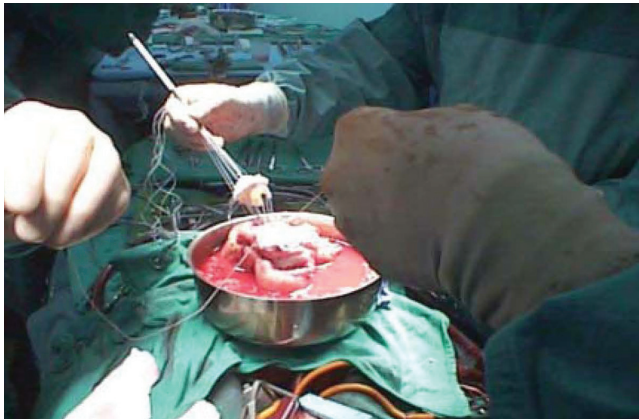


FIGURE 103-8 ■ Cardiac autotransplantation.

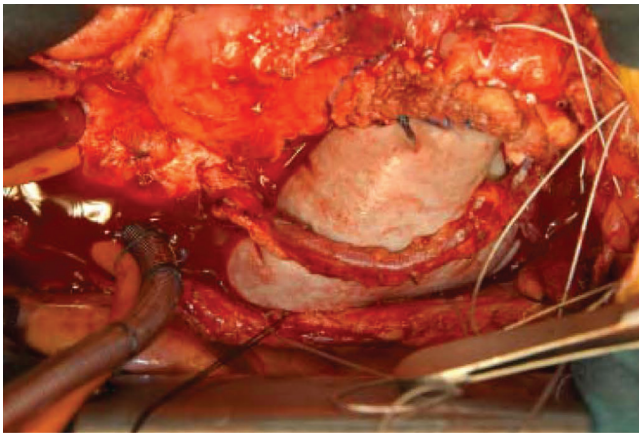


FIGURE 103-9 ■ Right atrial sarcoma resection and reconstruction.

Heart Transplantation

Malignant primary cardiac sarcomas often grow to a larger size until clinical detection. Extensive involvement may therefore make complete resection and reconstruction impossible. Because complete resection is necessary for improved results, cardiac transplantation has been considered in some cases.^{74,79} Twenty-eight patients were reported to have undergone transplantation as of 2000, with 21 of the tumors being malignant. The mean survival was 12 months.⁸¹ Transplantation has been used for sarcoma,⁸²⁻⁸⁴ pheochromocytoma,⁸⁵ lymphoma,⁸⁶ fibroma,⁸⁷ and myxoma.⁸⁸ Although often technically resectable by orthotopic transplantation, most benign tumors can be removed completely by experienced teams without the need for a new heart, but malignant tumors offer several other problems. Most cardiac sarcomas involve the right or left atrium and are often in areas not routinely resected for orthotopic transplantation. This may still pose an issue with getting negative margins. Many sarcomas have metastatic disease at presentation, and using a scarce donor organ in the setting of active malignancy is generally not reasonable. There is also the mortality and morbidity inherent in transplantation. With a mean survival after transplantation for malignant primary tumors of 12 months, transplantation must be considered on a case-by-case basis by a multidisciplinary team in a center of excellence.⁸¹

Nonsarcomatous Primary Malignant Cardiac Tumors: Lymphomas

Lymphomas can arise from the heart, although it is rare.⁸⁹ Most of these tumors respond to radiation and chemotherapy, and we recommend biopsy of all right atrial tumors before treatment decisions if the patient's clinical condition will allow for it. Even when complete resection is not possible, and incomplete resection is performed to relieve acute obstructive systems, radiation and chemotherapy have allowed for up to 3-year survival in some patients.

SECONDARY METASTATIC TUMORS

Approximately 10% of metastatic tumors eventually reach the heart or pericardium, and almost every type of malignant tumor has been known to do so.^{20,90} Secondary neoplasms are twenty to forty times more common than primary cardiac malignancies.⁹¹ Up to 50% of patients with leukemia develop cardiac lesions. Other cancers that commonly involve the heart include breast, lung, lymphoma, melanoma, and various sarcomas.^{91,92} Metastasis involving the pericardium, epicardium, myocardium, and endocardium roughly follows that order of frequency.^{20,90}

The most common means of spread, particularly for melanoma, sarcoma, and bronchogenic carcinoma, is hematogenous, and ultimately via coronary arteries. In addition, metastasis can reach the heart through lymphatic channels; through direct extension from adjacent lung, breast, esophageal, and thymic tumors; and from the subdiaphragmatic vena cava. The pericardium most often is involved by direct extension of thoracic cancer; the heart is the target of hematogenous or retrograde lymphatic metastasis, or both. Cardiac metastases rarely are solitary and nearly always produce multiple microscopic nests and discrete nodules of tumor cells.^{20,90} Cardiac metastases produce clinical symptoms in only about 10% of afflicted patients.⁹⁰ The most common symptom is pericardial effusion or cardiac tamponade. Occasionally, patients develop refractory arrhythmias or congestive heart failure. Chest radiographs and electrocardiograms tend to show nonspecific changes, but echocardiography is particularly useful for diagnosis of pericardial effusion, irregular pericardial thickening, or intracavity masses interfering with blood flow.

Surgical therapy is generally limited to relief of recurrent pericardial effusions or, occasionally, cardiac tamponade. In most instances, these patients have wide-spread disease with limited life expectancies. Surgical therapy is directed at providing symptomatic palliation with minimal patient discomfort and hospital stay. This is most readily accomplished via subxiphoid pericardiectomy, which can be accomplished using local anesthesia if necessary with reliable relief of symptoms, a recurrence rate of approximately 3%, and low mortality.⁹² Alternatively, a large pericardial window in the left pleural space can be created using thoracoscopy, but we would recommend this only under unusual circumstances. This can be accomplished with minimal patient discomfort, but it

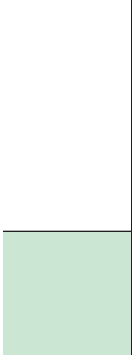
does require general anesthesia with single-lung ventilation and may be poorly tolerated by patients with hemodynamic deterioration secondary to large effusions. There are rare cases of metastatic disease isolated to the heart in which resection can be considered, but this should be done only in the context of a center of excellence with the decision made by an experienced multidisciplinary team.³

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SECTION 3

CONGENITAL HEART SURGERY

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CARDIAC EMBRYOLOGY AND GENETICS

Amy L. Juraszek

CHAPTER OUTLINE

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CONCLUSION

Development of the functioning heart is a complex process that is essential for survival of the embryo. The mechanisms responsible for cardiovascular morphogenesis have been studied for centuries by classical embryologists and more recently by molecular developmental biologists. Major progress in the understanding of cardiac specification and morphogenesis has been made from the study of cardiovascular development in a number of invertebrate and vertebrate model systems, from *Drosophila* to mouse. The conservation of many aspects of heart development across phylogeny has provided the basis for our increased understanding of the underlying principles of cardiac development and how congenital defects of the heart arise when development goes awry. Congenital heart malformations have long been recognized to be the result of developmental abnormalities affecting cardiac morphogenesis. Developmental defects can occur at any stage of heart development, resulting in phenotypes that vary widely, from severe morphologic abnormalities resulting in early embryonic lethality to mild defects having little physiologic impact. Because of the rapid rate of information entering the field of cardiac embryology and the scope of this chapter, detailed genetic descriptions of specific morphogenetic events are not discussed. Instead, examples are given to illustrate the current paradigms in the field. For the purposes of this book, greater detail is paid to developmental

abnormalities of the heart that result in congenital heart defects in humans.

CARDIAC SPECIFICATION

Early in embryonic development, after gastrulation at approximately day 17 to day 19 in human development, cells in the lateral mesoderm adopt a cardiogenic fate. The commitment of progenitor cells in the anterior left and right lateral plate mesoderm to the cardiogenic fate relies on inductive signals from the adjacent endoderm.¹⁻⁴ Specifically, the bone morphogenetic proteins (BMPs) expressed in the endoderm adjacent to the cardiogenic precursors play a role in cardiac induction and act with other signaling factors, including those from the fibroblast growth factor (FGF) family, hedgehog, Wnt ligands, and members of the transforming growth factor (TGF) superfamily.^{3,5-10} In vertebrates, the heart-forming region is bounded by repressive signals in addition to inductive signals. Repressive signals include members of the Wnt family of secreted molecules. In the cardiogenic region, Wnt antagonists oppose the repressive signals, allowing cells to commit to a cardiogenic fate.¹¹⁻¹³

Several lines of evidence suggest that cardiogenic precursors in the lateral plate mesoderm contain prepatterned information regarding their ultimate positional

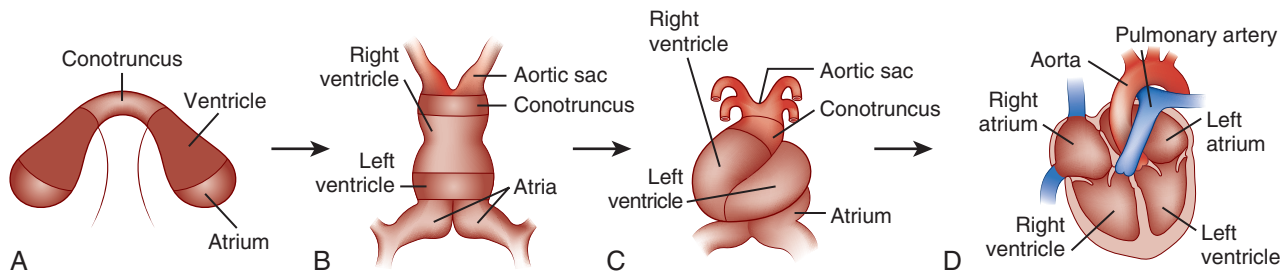


FIGURE 104-1 ■ Model of cardiogenesis. Cardiogenic precursors bilaterally positioned in the lateral plate mesoderm contain prepatterned information regarding their ultimate positional identity and cell fate, as modeled by color code (A). The convergence and fusion of the cardiac primordia form a linear heart tube (B), which undergoes rightward or D looping (C). Rightward looping appropriately aligns the cardiac chambers for morphogenesis into the mature four-chambered structure (D). (Adapted from Allen HD, Gutgesell HP, Clark EB, et al, editors: *Moss and Adams' heart disease in infants, children, and adolescents: including the fetus and young adult*, ed 6, Philadelphia, 2001, Lippincott Williams & Wilkins, p 4, Figure 1.1.)

identity and cell fate (Fig. 104-1A). Lineage analysis has demonstrated that cells in the caudal cardiogenic mesoderm contribute to the atria, whereas cells in the rostral cardiogenic mesoderm contribute to the ventricles.¹⁴ Explant experiments also demonstrate phenotypic differences between rostral and caudal precardiac mesoderm.^{15,16} However, cell transplant experiments also demonstrate that rostral-caudal fates of cardiogenic precursors remain plastic and require instructive cues from outside the cardiogenic region.¹⁷ Taken together, these results suggest that regional positional information is prepatterned in cardiogenic precursors before the development of the linear heart tube but that these positional identities appear not to be fixed until later. Several recent studies suggest that cell-type specification information, in addition to positional information, already resides in the field of cardiac progenitors. For example, precursors of both myocardial and endocardial cells can be found in the cardiogenic mesoderm, but no bipotential precursor has been identified.^{18,19}

The definitive heart and associated vascular structures receive contributions not only from the precardiac mesoderm that forms the cardiac crescent but also from two additional populations of cells. An anterior heart-forming field has been identified that lies adjacent to the crescent on its medial aspect, and that contributes to anterior structures of the outflow tract as well as to the myocardial mass of the ventricles.²⁰⁻²² In addition, the neural crest, a population of multipotential migratory cells, contributes to the outflow tract of the heart and is specifically required for outflow tract septation.

Bilaterally symmetrical cardiogenic primordia are formed from the lateral fields of mesoderm in the early embryo. The convergence and fusion of the bilateral cardiac primordia form the primitive cardiac tube in the ventral midline (see Fig. 104-1B). The anterior margins of the cardiogenic mesoderm fuse first to form the cardiac crescent at approximately day 23 of human development.¹⁵

Fusion of the bilateral cardiac primordia then occurs in a rostral to caudal direction, with sequential addition of precardiac mesoderm at the caudal end of the developing heart tube.²³⁻²⁵ The result is the formation of the primitive linear heart tube. The linear heart tube, already containing distinct myocardial and endocardial layers,

initiates contractions at approximately 4 weeks of fetal development in humans. Morphologic and molecular polarity along the heart tube (the anteroposterior axis) exists, with distinct regions from anterior to posterior of the aortic sac, conotruncus, right ventricle, left ventricle, and atria (see Fig. 104-1B).²⁶⁻²⁸

BODY-PLAN LATERALITY AND CARDIAC LOOPING

The tubular heart undergoes a morphogenetic process of rightward looping in all vertebrates. During this process, the linear heart tube is converted into an S-shaped heart with a complex, three-dimensional structure and asymmetry about the anterior-posterior, left-right, and dorsal-ventral axes (see Fig. 104-1C). Rightward looping is the visible start to the morphogenetic process that results in an asymmetrical, multichambered heart. The specificity of rightward looping is essential for the appropriate orientation of the developing cardiac chambers with one another, with the endocardial cushions that will contribute to chamber septation, and with inflow and outflow vascular connections.

Rightward looping of the heart is the first visible indication of left-right asymmetry in the developing vertebrate body plan. The consistent directionality of this process suggests a highly conserved molecular control mechanism of left-right patterning in the vertebrate embryo. This work demonstrates that significant molecular left-right differences are present in the embryo long before the visible morphogenetic event of rightward heart looping.

Early in embryonic development, during establishment of the lateral plate mesoderm, the Hensen node appears to control the genesis of left-right differences in gene expression despite its midline position. Beating cilia that project from the node undergo a counterclockwise vortex-like movement that creates a leftward flow of fluid across the Hensen node. The unidirectional ciliary movement appears to be established by the inherent molecular chirality of the ciliary protein machinery and its molecular motor on the node.²⁹⁻³¹ The flow across the node may mediate the movement of secreted molecules across the node in a leftward direction. Such molecules could then

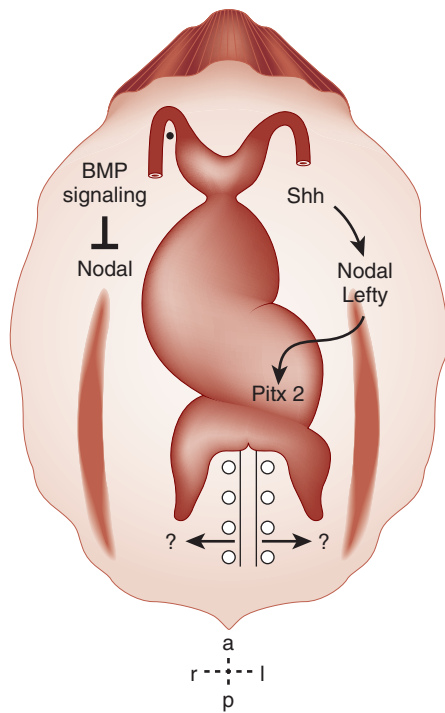


FIGURE 104-2 ■ Molecular determination of the direction of cardiac looping. Summary of the molecular signaling pathways implicated in visceral left-right axis determination and right-handed cardiac looping. *BMP*, Bone morphogenetic protein; *Shh*, sonic hedgehog. (Adapted from Allen HD, Gutgesell HP, Clark EB, et al, editors: *Moss and Adams' heart disease in infants, children, and adolescents: including the fetus and young adult*, ed 6, Philadelphia, 2001, Lippincott Williams & Wilkins, p 9, Figure 1.5.)

function as left-sided determinants on the left side of the node. Alternatively, evenly distributed mechanosensory cilia may be specifically activated on the left side of the node by the fluid flow across the node.³² The resultant signal transduction downstream of the activated mechanosensory cilia in left-sided cells could then initiate a left-sided molecular cascade.

A molecular cascade for left-right determination has been identified, beginning with asymmetrical expression of the morphogen sonic hedgehog (*Shh*) on the left side of the node (Fig. 104-2). Sonic hedgehog is able to induce left-sided perinodal expression of the left-sided determinant *Nodal*, a member of the transforming growth factor- β (TGF- β) signaling family.^{33,34} The molecular ground state of laterality in fact appears to be right-sidedness, with the expression of the *Nodal* normally repressed by BMP signaling. *Shh* induces the left-sided expression of *Caronte*, a secreted molecule, which overcomes BMP-mediated repression of *Nodal* in the lateral plate mesoderm.³⁵⁻³⁷ Thus, left-sided *Shh* results in the expression of *Nodal* locally and at a distance, and left-sided positional information is transferred to the left lateral plate mesoderm. One result of left-sided *Nodal* expression is the left-sided induction of *Pitx2*, a homeodomain-containing protein, throughout the left lateral plate mesoderm (see Fig. 104-2). *Pitx2* expression is maintained during subsequent organogenesis on the left side of the developing heart tube, gut, and lungs.³⁸⁻⁴⁶

This cascade thereby transmits left-sided positional information from the Hensen node to the visceral organs.

Clinical Correlate of Abnormal Laterality: Heterotaxy Syndrome

The molecular hierarchy of left-right positional information establishes global left-right differences in the vertebrate body plan. Defects in the proper establishment of left-right differences of the visceral organs are generally known as heterotaxy syndrome (derived from the Greek meaning “other arrangement”) or atrial isomerism. Often, the clinical phenotype reveals a predominance of one type of sidedness. In simple terms, asplenia syndrome can be thought of as demonstrating a bilateral right-sidedness and polysplenia syndrome can be thought of as demonstrating bilateral left-sidedness. The term *situs ambiguus* is used if the sidedness cannot be determined. Not surprisingly, mutations in the genes known to have a function in the normal establishment of left-right difference can result in the heterotaxy syndromes, both in animal models and in human patients.⁴⁷

Establishment of left-right asymmetry about the Hensen node has been demonstrated to require the *inversus viscerum* (*iv*) gene, encoding left-right dynein, the force-generating component in the cilia responsible for the vortical flow across the node. Mutation in *iv*, or in other genes that contribute components to the functional ciliary motor, causes immotile cilia syndrome and a failure to generate the initial left-right asymmetry in the Hensen node.^{48,49} Absence of asymmetry about the node results in randomized expression of left-sided determinants *Nodal* and *Pitx2* in the lateral plate mesoderm.^{39,40,42,48} The phenotypic result of the failure to generate the appropriate vector for laterality information is randomization of left- and right-sidedness in the visceral organs.

Mutations in single genes can therefore result in both polysplenia and asplenia syndromes, previously thought to be distinct entities, and therefore have distinct causes. The finding that expression of left-sided determinants *Nodal* and *Pitx2* are randomized in these cases helps to explain the variability of defects seen in the heterotaxy syndromes. For example, *Pitx2* expression can be normal, presumably resulting in *situs solitus*, or reversed, presumably resulting in *situs inversus* (the left-right mirror image specification of the visceral organs).^{43,44,50} However, it can also be bilateral, absent, or a range of relative left-right levels in between.⁵⁰ This range is similar to the wide range of *situs* abnormalities of the visceral organs observed in this model and in human patients with *situs ambiguus*. It also may help explain why previous efforts to categorize the specific morphology of heart defects in cases with asplenia and polysplenia have proved so difficult.⁵¹

The importance of ciliary function in sidedness determination has led to investigations of a mouse model with primary ciliary dyskinesia via a mutated dynein gene (*Dnabc5*), which showed a 40% incidence of heterotaxy in the homozygous mutant embryos.⁵² Translational research subsequently confirmed ciliary dysfunction in 42% of congenital heart disease (CHD) patients with heterotaxy syndrome, which may contribute to respiratory problems in addition to their heart disease.⁵³

CHAMBER SPECIFICATION AND THE CARDIOGENIC TRANSCRIPTIONAL PROGRAM

There is remarkable conservation, between animal models as disparate as *Drosophila* and vertebrates, of the early transcriptional hierarchy that specifies cardiogenic fate. The *tinman* gene, encoding a homeodomain-containing transcription factor, is required for formation of the *Drosophila* dorsal vessel (the dorsal vessel in the fly is analogous to the heart in vertebrates). *Tinman* directly activates transcription of several genes, including *pannier*, a GATA transcription factor, and myocyte enhancer factor-2 (MEF-2), a MAD-box-containing transcription factor. MEF-2 and *pannier* then contribute to the downstream transcriptional activation of cardiomyocyte structural genes.⁵⁴⁻⁵⁷

Nkx2.5 is the vertebrate ortholog of the *Drosophila tinman* gene. *Nkx2.5* is expressed early in the cardiogenic mesoderm, in part a response to induction of the heart-forming region by BMPs from the endoderm.⁵⁸⁻⁶⁰ Like *tinman* in *Drosophila*, the *Nkx2.5* transcription factor plays a role in cardiogenic differentiation in vertebrates. *Nkx2.5* physically interacts with vertebrate GATA factors, and these transcription factors mutually activate one another's promoters. This establishes a positive molecular feedback loop that appears to strengthen the choice of cardiomyocyte fate. As in *Drosophila*, the GATA and MEF-2 gene families have been demonstrated to play a role in the activation of a cardiomyocyte differentiation program throughout the myocardium. In vertebrates, three GATA family members, GATA-4, -5, and -6, demonstrate expression in cardiac lineages.⁶¹ GATA factors are required for transcriptional control of several cardiac muscle structural genes. GATA family members act in cooperation with transcription factors from other families, including *Nkx2.5* and MEF-2, to regulate the expression of target genes.⁶²⁻⁶⁴ There are four MEF-2 family members in vertebrates. As in *Drosophila*, these genes appear to directly activate structural genes of myocyte differentiation. For example, mice lacking the gene for one family member, *mef2a*, die with cardiovascular abnormalities at the looping stage and fail to express a group of muscle-specific structural genes.^{65,66}

Nkx2.5 has roles in cardiogenic differentiation and in pattern formation of the vertebrate heart. The multifaceted nature of its action perhaps results from its promiscuous interactions with transcription factors of other classes. Aside from the GATA class of transcription factors, *Nkx2.5* is able to physically interact with the T-box transcription factor *Tbx5*. The *Tbx5* gene is responsible for the human autosomal dominant disorder Holt-Oram syndrome. Cardiac manifestations of the loss of one copy of *Tbx5* or *Nkx2.5* overlap and include atrial septal defects and conduction system abnormalities. *Nkx2.5* and *Tbx5* have been shown to act synergistically on the promoters of genes with high levels of expression in the atria and the conduction system, including atrial natriuretic factor and connexin 40.^{67,68}

Concomitant with the activation of a cardiomyocyte differentiation program is the development of regional

differences between the chambers of the heart. As early as the tubular heart stage, the cardiac primordia demonstrate a segmental appearance. Morphologically, five primordial segments can be identified from posterior to anterior: sinus venosus or atrium, atrioventricular canal, left ventricle, right ventricle, and outflow tract (see Fig. 104-1B). These morphologically distinct regions must be indicative of distinct transcriptional domains in the developing heart primordia. In fact, a growing number of transcription factors have been identified that demonstrate chamber-specific patterns of transcription.

The chamber-specific expression patterns of the Iroquois family member *Irx4*, a homeobox-encoding gene, suggest a role in ventricular versus atrial chamber specification. *Irx4* is expressed specifically in the developing ventricular chambers of the heart and is excluded from the developing atria.⁶⁹ *Irx4* has been demonstrated to play an important transcriptional role in the selection of ventricular fate. Loss of *Irx4* function in the ventricles results in aberrant activation of atrial gene expression, whereas ectopic expression of *Irx4* in atrial chambers results in the aberrant activation of ventricular gene expression. Further evidence for the separate genetic control of atrial and ventricular fate is demonstrated by the zebrafish mutants *lonely atrium* and *pandora*, in which the ventricular chamber fails to form but the atrial chamber appears morphologically intact.^{70,71}

The beta helix-loop-helix factors HAND1 (eHAND) and HAND2 (dHAND) have been demonstrated to play a role in determining molecular differences between the ventricles. The chamber-specific expression of *HAND1* and *HAND2* suggested that these genes may play a role in right-versus-left ventricular chamber specification. Although both *HAND1* and *HAND2* are initially coexpressed throughout the precardiac mesoderm, *HAND2* expression becomes restricted to the right ventricular precursors during cardiac looping, whereas *HAND1* becomes restricted to left ventricular and conotruncal precursors.^{72,73} Functional analysis of *hand2* has demonstrated a role in chamber formation and may provide a molecular candidate for a severe form of human coronary heart disease. Mice homozygous for a null *hand2* allele appear to lack a morphologic right ventricle.⁷³ The phenotype of the heart in this animal model is similar to human right ventricular hypoplasia, establishing *hand2* as a candidate gene for this type of human CHD.

Irx4 and the *hand* genes suggest that the specification of chamber-specific modularity lies at least in part in the transcriptional localization of single genes. However, the notion that chamber identity as a whole is specified as a result of a small number of chamber-specific modules of gene expression is simplistic. The degree to which regulation of cardiac gene expression is a highly modular process has only begun to be understood. The analysis of the promoters of single cardiac-specific genes has demonstrated that a very large number of small promoter elements are required to recapitulate normal expression patterns.⁶¹ The degree of modularity is so high that some elements drive expression in regions not previously thought to be molecularly distinct from their neighbors.⁶¹ These findings suggest that complex combinatorial networks of

transcription factors are required for the molecular regionalization of information in the developing heart.

CARDIAC SEPTATION OF THE ATRIA, VENTRICLES, ATRIOVENTRICULAR JUNCTION, AND OUTFLOW TRACT

Cardiac septation is a complex process that begins after looping morphogenesis has realigned the cardiac segments so that the right ventricle and left ventricle are located beside one another. Complete septation of the heart is not necessary for survival of the embryo, which may in part explain the high incidence of septation defects seen in clinical cardiology practice. Four major components must develop to divide the heart into separate systemic and pulmonary circulations: (1) the atrial septum that separates the right and left atria, (2) the atrioventricular junction that contributes to atrial and ventricular septation as well as to atrioventricular valve formation, (3) the ventricular septum that separates the right and left ventricles, and (4) outflow tract or infundibular septum that separates the pulmonary from the aortic outflow tract.

Recent studies have resulted in a newer paradigm of atrial septal development than that presented by classical embryology studies.⁷⁴⁻⁷⁶ The atrial septum includes septum secundum (secondary atrial septum), septum primum (primary atrial septum), and contributions from the atrioventricular cushions (Fig. 104-3). Septum secundum is an infolding in the roof of the common primitive atrium. Septum primum develops from the dorsal wall of the atrium at 5 weeks' gestation, grows toward the atrioventricular cushions as a crescentic muscular septum, and closes off the ostium primum (primary atrial communication) when it fuses with the atrioventricular cushions during the sixth week of fetal development. Septum primum carries a "cap" of distinct mesenchymal tissue along its leading edge that is critical for fusion of the primary atrial septum with the atrioventricular cushions.⁷⁴ As septum primum grows toward the atrioventricular cushions and divides the atria, it develops fenestrations that coalesce into the ostium secundum (secondary foramen) and allow continued mixing of blood at the atrial level in the fetus.

Like the atrial septum, the ventricular septum is a complex structure that includes components derived from the atrioventricular cushions, the muscular ventricular septum, and the conal (infundibular) septum. In the early stages just after looping (31 to 35 days in the human), the muscular ventricular septum is a ridge of myocardium corresponding to the furrow of the primary fold on the outer curvature of the heart and separating the primitive left ventricle and primitive right ventricle.⁷⁷ In mammals, the muscular septum develops from a ridge of infolded compact myocardium.⁷⁸ As the heart grows markedly in size along the outer curvature, the muscular septum grows concordantly with the ventricles.²⁶ The muscular septum fuses with the endocardial cushions of the atrioventricular junction and with the outflow tract to completely separate the right and left ventricles.

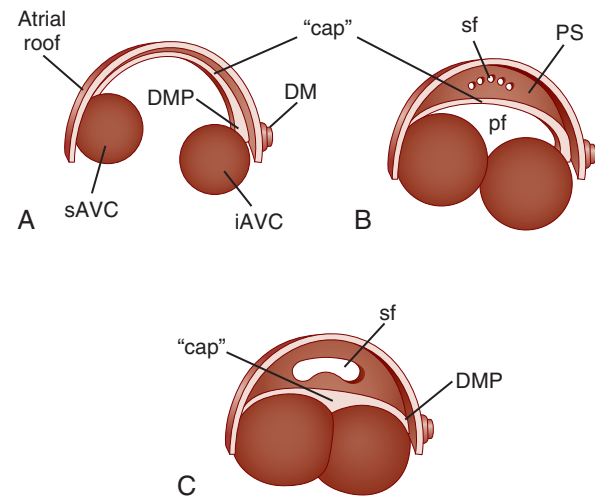


FIGURE 104-3 ■ Atrial septal development. The developing atrial septum has contributions from the septum secundum, the septum primum, and the atrioventricular (AV) cushions. **A**, Septum secundum ("atrial roof") is an infolding in the roof of the primitive common atrium. **B**, Septum primum (PS) grows from septum secundum toward the AV cushions (sAVC and iAVC), carrying with it a "cap" of mesenchymal tissue that is critical for the fusion of PS with the cushions. **C**, As PS closes off the primary interatrial communication (pf in **B**), fenestrations develop (sf in **B**) and coalesce into the foramen ovale (sf in **C**), which allows the shunting of blood at the atrial level that is necessary in the fetal circulation. DM, Dorsal mesocardium; DMP, dorsal mesenchymal protrusion. (From Wessels A, Anderson RH, Markwald RR, et al: Atrial development in the human heart: an immunohistochemical study with emphasis on the role of mesenchymal tissues. *Anat Rec* 259[3]:288-300, 2000.)

The atrioventricular junction (canal) segment of the developing heart initially connects the primitive atrium exclusively to the left ventricle (see Fig. 104-1C). Complex remodeling must occur to allow inflow from the atrium directly into both right and left ventricles (see Fig. 104-1D). In addition to establishing continuity between the right atrium and the right ventricle, the atrioventricular junction gives rise to the endocardial cushions that will form the atrioventricular valves. (Endocardial cushions also form in the outflow tract and contribute to the semilunar valves and septation of the outflow tract.) The superior and inferior atrioventricular cushions fuse in the midline to form the atrioventricular septum, with resultant separation of the inflow into mitral (left-side) and tricuspid (right-side) components. The mesenchyme of the atrioventricular junction contributes to the portion of the atrial septum just proximal to the atrioventricular valves by fusing with the primary atrial septum. In addition, the atrioventricular septum mesenchyme forms the inlet portion of the ventricular septum (between the atrioventricular valves).

The growth and maturation of the endocardial cushions has been studied at the molecular level. Cardiac cushions begin as localized thickenings of the extracellular matrix between the endocardial and myocardial layers of the primitive heart tube, termed the *cardiac jelly* (Fig. 104-4).⁷³ The cushions begin as acellular structures that become populated by cells that have undergone a transformation from endothelium to mesenchyme. JB3 is

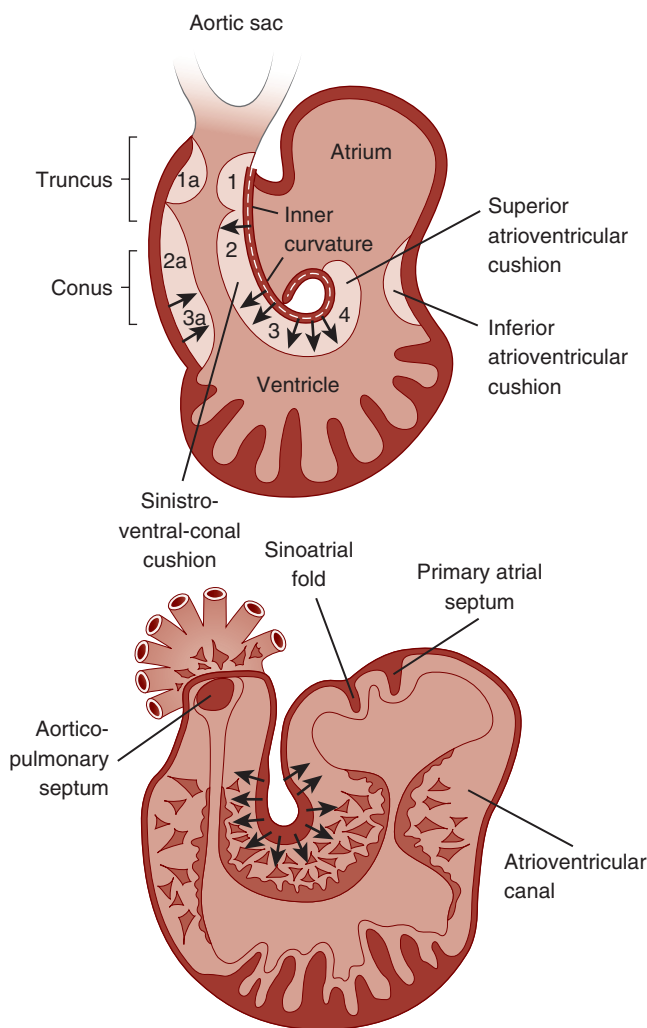


FIGURE 104-4 ■ Cushion development. The endocardial cushions appear in the atrioventricular (AV) junction (AV canal) and in the outflow tract (conus and truncus) after looping of the heart tube. The superior AV cushion (4) is contiguous with the cushions of the outflow tract (3, 3a, 2, 2a, 1, 1a) along the inner curvature of the heart. Cushion tissue contributes to the formation of the valves and also to septation of the heart. The inner curvature undergoes significant remodeling and participates in myocardialization of the cushions (arrows). (From Harvey RP, Rosenthal N, editors: *Heart development*, San Diego, 1999, Academic Press, p 171.)

an antibody that recognizes fibrillin-2,⁷⁹ and, in the heart, it recognizes only the subset of cells (JB3+) that have the potential to undergo the endothelium-to-mesenchyme transformation in the cushions.⁸⁰ The mesenchymal transformation is mediated by the myocardium of the atrioventricular junction via a number of molecules including BMP-2, BMP-4, and neuregulin, an epidermal growth factor-like molecule, as well as the homeobox-containing transcription factor *Msx-2*.⁸¹⁻⁸³ ES proteins that form complexes with fibronectin are also present in the developing cushions and appear important for the regulation of the mesenchymal transformation.^{80,81}

Contributions from the endocardial cushions and the cardiac neural crest are required for outflow tract septation (Fig. 104-5). The endocardial cushions of the

atrioventricular junction and the outflow tract are in physical continuity through the superior atrioventricular cushion, which extends along the inner curvature of the heart.⁸⁰ Extensive remodeling of the inner curvature occurs so as to connect the right atrium to the right ventricle and the left ventricle to the aorta.⁸⁴ Septation of the outflow tract results from the development of two structures. Below the level of the semilunar valves, the conal septum (infundibular septum or muscular outflow tract septum) develops from myocardialization of the outflow tract cushions, a process that also involves contributions from the cardiac neural crest and the epicardium.⁸⁴ Above the level of the semilunar valves, the aorticopulmonary septum grows from the aortic sac toward the heart to separate the pulmonary from the aortic outflow tracts.

The three components of the ventricular septum (the inlet and the muscular and conal septa) must join together to completely separate the ventricles. The region of the membranous ventricular septum in the adult heart is the approximate location where these three components join. This finding suggests that a defect in the development of either the inlet or the muscular or conal septa can result in a ventricular septal defect, suggesting a mechanistic rationale for the high frequency of defects at this anatomic location.

Clinical Correlates of Abnormal Chamber Septation

The term *common atrioventricular canal* (also called endocardial cushion defect or atrioventricular septal defect) refers to a spectrum of lesions that have improper development of the atrioventricular junction as the underlying developmental abnormality. In such cases, the atrioventricular junction has failed to undergo its normal septation and formation of separate atrioventricular valves, leaving a common atrioventricular valve providing inflow to both ventricles. The atrioventricular cushion contributions to atrial and ventricular septation are also abnormal, resulting in atrial septal defect of the ostium primum type and ventricular septal defect of the inlet (atrioventricular canal) type. This defect is reminiscent of the structure of the developing heart prior to atrioventricular junction septation by the developing endocardial cushions. Genes required for normal development of the atrioventricular endocardial cushions can result in common atrioventricular canal when mutated in a mouse model, as demonstrated by the *ALK3* conditional receptor knockout.⁸⁵ Common atrioventricular canal can therefore be conceptualized as a developmental arrest, in which chamber septation fails to progress past the common atrioventricular junction.

Although complete common atrioventricular canal accounts for only 7.3% of all congenital malformations,⁸⁶ it is observed in approximately 40% of patients with trisomy 21 (Down syndrome).⁸⁷ The epidemiologic data suggest that a gene important for the development of the atrioventricular junction resides on chromosome 21. To date, no single gene on chromosome 21 has been implicated in the genesis of common atrioventricular canal.⁸⁸

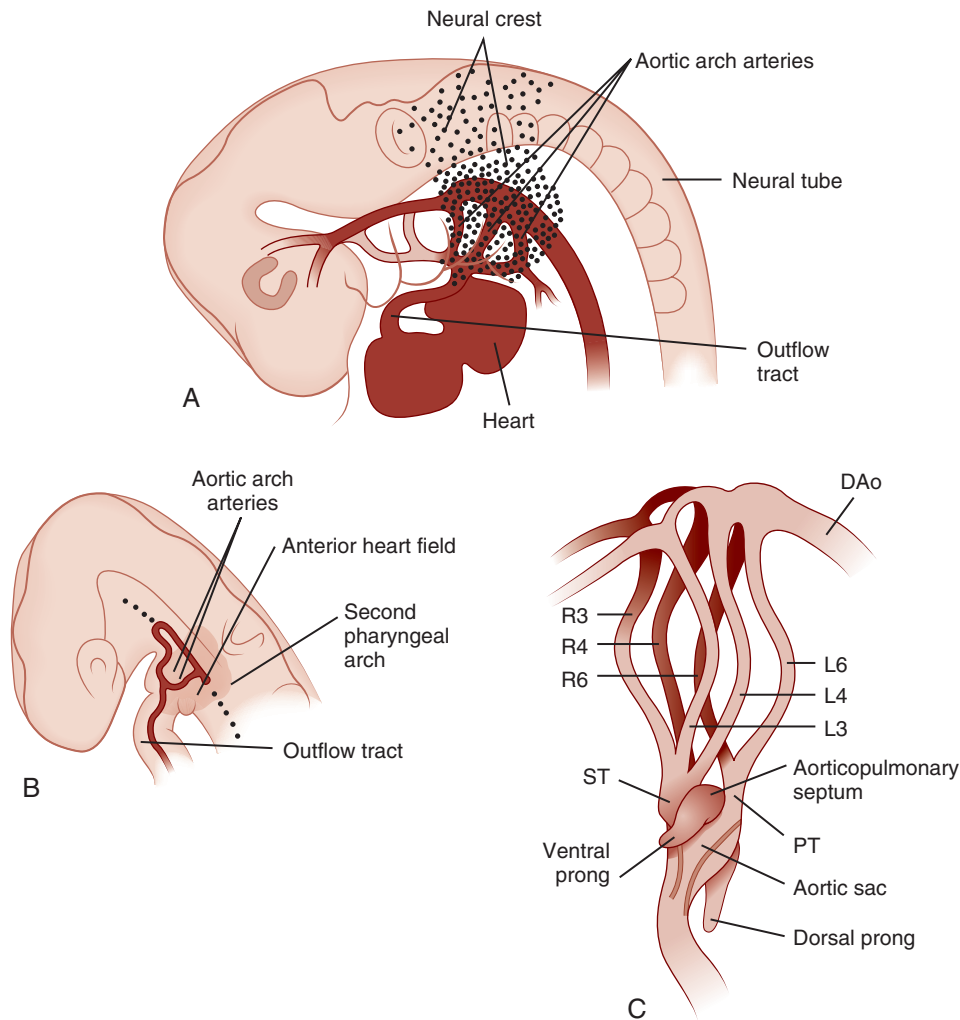


FIGURE 104-5 ■ Development of neural crest, anterior heart field, and outflow tract. **A**, The cardiac neural crest migrates into pharyngeal arches 3, 4, and 6, where it plays a crucial role in the patterning of the paired aortic arch arteries by preventing the regression of aortic arch arteries 3, 4, and 6, the precursors of the definitive great arteries. **B**, The anterior heart field is a recently described and separate migratory population of cells that originate near the second pharyngeal arch and contribute to cardiac outflow tract development. **C**, The neural crest cells condense into two prongs that insert into the endocardial cushions of the developing outflow tract. The third aortic arch arteries (L3 and R3) give rise to the right and left carotid arteries. The left fourth arch artery (L4) becomes part of the definitive aortic arch, and the right fourth arch artery (R4) contributes to the proximal right subclavian artery. The left sixth aortic arch artery (L6) forms the ductus arteriosus. DAo, Descending aorta; PT, pulmonary trunk; ST, systemic trunk. (**A** and **C** from Harvey RP, Rosenthal N, editors: *Heart development*, San Diego, 1999, Academic Press, pp 180, 182; **B** modified from Waldo KL, Kumiski DH, Wallis KT, et al: Conotruncal myocardium arises from a secondary heart field. *Development* 128:3179–3188, 2001.)

Isolated atrial septal defects are one of the most common congenital defects of the heart in humans. Secundum atrial septal defects result from a deficiency of septum primum in closing off the ostium secundum. Atrial septal defects are also frequently found in association with clinical syndromes. Secundum atrial septal defects are the most common structural defect resulting from the loss of one copy of the *Tbx5* gene in Holt-Oram syndrome, an autosomal dominant disorder.^{89,90} Mutations in the *Nkx2.5* gene have been linked to autosomal dominant secundum atrial septal defects,^{91,92} and more recently, mutations in the *GATA-4* gene have also been linked to secundum atrial septal defects.⁹³ The finding that *Tbx5*, *Nkx2.5*, and *GATA-4* all interact to regulate the expression of genes necessary for atrial septal development suggests that candidate genes for secundum atrial

septal defects may lie downstream of these important transcription factors.

OUTFLOW TRACT DEVELOPMENT: ANTERIOR HEART FIELD AND CARDIAC NEURAL CREST

Although the vertebrate heart develops primarily from the precardiac mesoderm (the cardiac crescent), two other cell populations, the anterior heart field and the cardiac neural crest, are critical for normal outflow tract development.^{20-22,94}

The existence of the anterior heart field was suspected 30 years ago, when Viragh and Challice⁹⁵ observed the

transformation of epithelial cells to myocardial cells at the arterial pole of the developing mouse heart. De la Cruz and colleagues⁹⁶ used marking studies in living chick embryos to demonstrate that the distal outflow tract was a late addition to the developing heart. A series of recent studies show that a population of cells in the anterior mesoderm adjacent to the aortic sac (see Fig. 104-5B), distinct from both the lateral cardiogenic mesoderm and the cardiac neural crest, contribute to the myocardium of the outflow tract in both avian^{21,22} and murine²⁰ models. In the murine model, the anterior heart field contributions extend past the outflow tract and also contribute to the developing right ventricle to the level of the interventricular septum.^{28,97} This finding may ultimately help explain observed gene expression differences between the right and left ventricles.

The cardiac outflow tract is initially a tubular structure connecting the primitive right ventricle to the aortic sac, and it must undergo septation to form the pulmonary artery and the aorta. In addition, the outflow tract must gain continuity with the primitive left ventricle. This occurs by a process termed *wedging*, in which the subaortic conus is remodeled to allow the aortic valve to reach its normal adult position between the tricuspid and mitral valves. This process establishes fibrous continuity of the mitral and aortic valves.⁹⁸ The aorticopulmonary septum develops from the aortic sac mesenchyme and grows into the outflow tract, where it interacts with neural crest-derived cells in the endocardial cushions, ultimately dividing the outflow tract into the aorta and the pulmonary artery.⁹³

The cardiac outflow tract receives a large contribution of cells from the neural crest, a population of migratory pluripotent cells that arise adjacent to the developing neural tube. The cardiac neural crest is a subpopulation of the neural crest that originates from between the midotic placode to the third somite (see Fig. 104-5A).⁹⁹ These cells migrate into the developing third, fourth, and sixth pharyngeal arches, where they interact with the third, fourth, and sixth aortic arch vessels, the progenitors of the definitive great arteries (aorta, carotid, and subclavian arteries, main pulmonary artery, and ductus arteriosus). The aortic arch vessels develop as symmetrically paired structures, but they undergo a highly specific and asymmetrical program of resorption, retaining the normal left aortic arch. The cardiac neural crest does not play a role in the formation of the aortic arch vessels but rather stabilizes the arch vessels and prevents their regression (see Fig. 104-5C).¹⁰⁰ A subpopulation of the cardiac neural crest migrates farther from the pharyngeal arches to the heart, where it forms the cardiac ganglia, participates in the septation of the outflow tract, and contributes to the formation of the semilunar valves.¹⁰¹ Neural crest also interacts with the pharyngeal arch mesenchyme to form the thymus, thyroid, and parathyroid glands.

Animal models of neural crest defects have been useful in determining the cause of some congenital heart malformations. Experimental ablation of the neural crest in avian embryos¹⁰² demonstrated abnormal development of the heart and great arteries, as well as abnormalities of the glandular derivatives of the pharyngeal arches and pouches (i.e., the thymus, thyroid, and parathyroid

glands).⁹⁴ Specifically, defects of the embryonic outflow tract were observed in embryos after neural crest ablation, including persistent truncus arteriosus, double-outlet right ventricle, and tetralogy of Fallot. Ventricular septal defects of the infundibular septum were also common.¹⁰³ Interestingly, defects of the inflow portion of the heart were occasionally described as well, including double-inlet left ventricle, straddling tricuspid valve, and tricuspid atresia, and they occurred in association with outflow defects.¹⁰³ Furthermore, abnormal aortic arch patterning occurred in virtually all embryos after neural crest ablation.¹⁰³⁻¹⁰⁵ The arch abnormalities demonstrated great variability and included various types of interrupted aortic arch.

Murine models with cardiac phenotypes reminiscent of neural crest ablation include the *Splotch* mouse, bearing a mutation in the *Pax3* homeobox gene. *Splotch* homozygotes demonstrate persistent truncus arteriosus and aortic arch anomalies as well as anomalies of the thymus, thyroid, and parathyroid glands. The homozygous mutation is lethal at embryonic day 14.¹⁰⁶ The *Patch* mutant mouse, bearing a deletion of a portion of chromosome 5, also demonstrates craniofacial, thymic, and outflow tract abnormalities, including arch patterning anomalies.¹⁰⁷ Initial efforts to understand this phenotype focused on the deletion of the gene for platelet-derived growth factor receptor (PDGFR). However, mice homozygous for a PDGFR-targeted null mutation do not consistently demonstrate cardiac anomalies, suggesting that other genes deleted in the *Patch* mutant must contribute to the cardiac phenotype.^{107a}

Retinoic acid, the active derivative of vitamin A, has been shown to play an important role in outflow tract development. Knockouts of the retinoic acid receptor in mice produce phenotypes reminiscent of neural crest ablation. There are two families of receptors, RAR and RXR, and each family contains three isoforms. Single-isoform knockouts produce no morphologic defects; however, double mutants of RAR and RXR produce outflow tract defects (persistent truncus arteriosus, double-outlet right ventricle, and arch anomalies), as well as craniofacial, thymic, thyroid, and parathyroid anomalies.^{88,107} If vitamin A is administered, the cardiac phenotype may be rescued.¹⁰⁸ This suggests a role for retinoic acid signaling in neural crest migration and cardiac development.

Clinical Correlates of Abnormal Outflow Tract Development: DiGeorge Syndrome and 22q11 Deletion

DiGeorge syndrome is an autosomal dominant disorder whose phenotype includes cardiac defects of the outflow tract—in particular, interrupted aortic arch, persistent truncus arteriosus, tetralogy of Fallot, and aortic arch anomalies. The syndrome also includes parathyroid hypoplasia with resultant hypocalcemia, thymic hypoplasia with resultant T cell deficit, and cleft palate and other craniofacial abnormalities. There are phenotypic similarities between DiGeorge, Takao (conotruncal anomaly face syndrome), and Shprintzen (velocardiofacial) syndromes, and, in fact, the same molecular lesion is present

in all three syndromes: deletion of 22q11. *CATCH* has been proposed as an acronym for the phenotype associated with these syndromes (cardiac defects, abnormal facies, T cell deficit, cleft palate, hypocalcemia).^{109,110} The phenotype demonstrates considerable variability between patients. The 22q11 deletion is the most common deletion in humans, occurring in 1 of 4000 live births¹¹¹ with an average of 30 genes removed, although smaller and larger deletions are not infrequent.⁹⁷

A vigorous search for candidate genes residing in the commonly deleted portion of human chromosome 22 has recently yielded some success in elucidating the molecular underpinnings of the cardiac defects. Mouse models with deletions of the region of chromosome 16 syntenic to human chromosomal region 22q11 have been used to identify and test candidate genes.¹⁰⁷ Three independent groups have reported that haploinsufficiency of the T-box transcription factor gene *Tbx1* results in cardiac phenotypes consistent with DiGeorge syndrome.¹¹²⁻¹¹⁴ However, not a single point mutation has been identified in any patient with DiGeorge syndrome; the phenotype in humans may require larger genetic alterations. The clinical variability seen among patients with DiGeorge syndrome has several possible sources, including variability in the size of the deletion, sensitivity to gene dosage from modifying genes (genetic background), and epigenetic factors. One study demonstrated that a targeted deletion of *Tbx1* in mice caused abnormal aortic arch patterning in 50% of embryos, implicating sensitivity to gene dosage in the variability of the DiGeorge phenotype.¹¹⁴ When a larger deletion containing additional genes was studied, the mice showed parathyroid hypoplasia, thymic insufficiency, and a higher perinatal lethality, implicating deletion size. Another group demonstrated abnormal development of the fourth aortic arch in mice heterozygous for a *Tbx1* deletion.¹¹³ Homozygous mutants were embryonic lethal with obliteration of the third, fourth and sixth arches.¹¹³ In this model, *Tbx1* haploinsufficient animals did not display thymic, parathyroid, or facial anomalies, again suggesting that a multiple gene deletion is required for the full clinical features of DiGeorge syndrome.¹¹³

THE CAUSES OF CONGENITAL HEART DISEASE: ADDITIONAL FACTORS

The genetic programs underlying heart development are beginning to be elucidated, but the complexity of the developmental process has made progress painstaking. Although these genetic abnormalities in animal models do correlate to certain forms of heart disease, other experimental models use variations in blood flow to produce structural heart abnormalities. An intriguing series of experiments in chick embryos used ligation of the left atrial appendage to produce a hypoplastic left heart syndrome phenotype.¹¹⁵ Subsequent work sequentially ligating the left atrial appendage and then the right atrial appendage demonstrated rescue of the hypoplastic left heart phenotype during embryonic development.¹¹⁵ These studies are suggestive that fetal interventional strategies¹¹⁶ and early surgical repair may positively impact heart development and chamber growth.

The interaction between genetic factors and environmental factors contributing to CHD is not yet fully understood. Observations of teratogen exposure such as thalidomide or retinoids producing congenital heart defects have been described for years.¹¹⁷ Hypoplastic left heart syndrome has been demonstrated to have a genetic component,¹¹⁸ but a geographic spatial analysis of cases of hypoplastic left heart cases in Baltimore, MD, demonstrated a cluster of cases near a region of industrial land with environmental exposures to solvents.¹¹⁹ Complex interactions between genetic predisposition and environmental insult may contribute to the phenotypic variability of congenital heart malformations.

GENETIC ABNORMALITIES ASSOCIATED WITH CONGENITAL HEART DISEASE

In the first portion of this chapter, developmental mechanisms critical for normal heart development were reviewed. The complexity of these processes has resulted in slow painstaking progress in the understanding of specific genetic abnormalities that are associated with CHD. Table 104-1 provides a list of single gene and chromosomal region abnormalities that have a strong association with congenital heart malformations. Aneuploidy syndromes are also known to be associated with CHD. Specifically, trisomy 21 (Down syndrome) has a 40% to 50% chance of associated CHD, most commonly atrioventricular canal defects; atrial septal defect, ventricular septal defect, patent ductus arteriosus, and tetralogy of Fallot may also be seen. Turner syndrome (monosomy, 45X0) has an association of left heart obstructive lesions including coarctation, bicuspid aortic valve, and hypoplastic left heart syndrome. Trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) are associated with atrial septal defect, ventricular septal defect, patent ductus arteriosus, and polyvalvular disease in 80% to 100% of patients.¹²⁰

CONCLUSION

This chapter demonstrates some of the progress that has been made in the molecular understanding of embryonic heart development and how specific structural defects of the heart arise when the activity of single genes is interrupted. Hemodynamic and environmental factors may also contribute to malformations of the heart, and the broad range of phenotypes may be a result of complex interactions between genes, blood flow, and exposures. Details of cardiac specification and development continue to be elucidated, and it is the hope that a better understanding of the genetic mechanisms involved in heart formation will improve the care of patients with CHD.

Acknowledgment

The author would like to recognize Ivan Moskowitz, MD, PhD, for contributions to an earlier version of this chapter.

TABLE 104-1 Genetic Abnormalities with Prominent CHD Phenotypes

Syndrome	Locus	Gene(s)	Inheritance	Clinical Features	Most Common CHD	Percentage with CHD	OMIM
Single Gene Mutation Syndromes							
Alagille	20p12; 1p12	JAG1; NOTCH2	AD	Paucity of hepatic bile ducts, CHD, skeletal abnormalities, skeletal abnormalities, distinctive facies	Pulmonary artery stenosis, pulmonary valve stenosis, TOF	>90%	118450
Noonan	12q24; 12p1.21; 2p21; 3p25.2; 7q34; 15q22.31; 11p15.5; 1p13.2; 10q25.2; 11q23.3; 17q11.2	PTPN11; KRAS; SOS1; RAF1; BRAF; MEK1; HRAS; NRAS; SHOC2; CBL; NF1	AD, AR	Distinctive facies, short stature, webbed neck, pectus deformity, cubitus valgus, CHD	PS, ASD, VSD, PDA	80%	163950
Holt-Oram Char	12q24 6p12	TBX5 TFAP2B	AD AD	Upper limb deformities, CHD Distinctive facies, PDA, limb deformities	ASD, VSD, PDA	85% 100% (CHD required to make diagnosis)	142900 169100
Ellis-van Creveld	4p16	EVC; EVC2	AR	Skeletal dysplasia (short limbs, short ribs, polydactyly, dysplastic teeth and nails), CHD	ASD	60%	225500
Costello	11p15.5	HRAS	De novo, AD	Distinctive facies, short stature, failure to thrive, heart defects, developmental delay	PS, hypertrophy, arrhythmias, other structural heart disease	63%	218040
Cardiofaciocutaneous (CFC)	12p12.1; 7q34; 15q22.31; 19p13.3	KRAS; BRAF; MAP2K1; MAP2K2	De novo, AD	Distinctive facies, mental retardation, heart defects	PS, ASD, hypertrophy	71%	115150
CHARGE	8p12; 7q21.11	CHD7; SEMA3E	AD	Choanal atresia, heart disease, eye coloboma, mental retardation, genitourinary abnormalities, ear abnormalities and deafness	TOF, ASD, VSD	85%	214800
Kabuki	12q13.12	MLL2	De novo, AD	Mental retardation, dwarfism, distinctive facies, spine deformities, cleft palate	VSD, ASD, TOF, COA, SV, PDA	31%-55%	147920
Abnormal Chromosomal Structural Syndromes							
22q11 Deletion (DiGeorge)	22q11.2 deletion	TBX1	De novo, AD	Thymus hypoplasia/aplasia, parathyroid hypoplasia/aplasia, distinctive facies, CHD (particularly outflow tract abnormalities)	TOF, IAA type B, aortic arch anomalies, truncus, VSD	80%-100%	188400
Williams-Beuren	7q11.23 deletion	ELN	De novo, AD	Arterial stenoses, mental retardation, distinctive facies, hypercalcemia	SVAS, multiple arterial stenoses	80%-100%	194050
Cri-du-chat	5p15.2 deletion	CTNND2	De novo	Microcephaly, mental retardation, distinctive facies, high-pitched cry	VSD, PDA, ASD, TOF	10%-55%	123450
1p36 Deletion	1p36 deletion	DVL1	De novo	Microcephaly, mental retardation, distinctive facies, CHD, hearing loss, hypotonia	ASD, VSD, PDA, dilated cardiomyopathy, LV noncompaction	43%-70%	607872

AD, Autosomal dominant; AR, autosomal recessive; ASD, atrial septal defect; CHD, congenital heart disease; COA, coarctation of the aorta; IAA, interrupted aortic arch; LV, left ventricular; OMIM, Online Mendelian Inheritance in Man; PDA, patent ductus arteriosus; PS, pulmonary stenosis; SV, single ventricle; SVAS, supraaortic stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

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SEGMENTAL ANATOMY

Stephen P. Sanders

CHAPTER OUTLINE

VISCERAL SITUS

LOCATION OF THE HEART

SEGMENTAL ANALYSIS

Segmental Situs

Segmental Alignments

Segmental Connections

Disharmony between Situs and Alignment

Examples of Segmental Analysis

SUMMARY

The heart is a complex organ. It is difficult to understand the anatomy of the heart, particularly when abnormal, and it is even more difficult to describe it clearly and succinctly. Yet this is the goal of the diagnostician cardiologist: to understand and describe the anatomy of a defective heart in a way that colleagues will comprehend sufficiently to be able to contribute meaningfully to the care of the patient. Another objective is to learn about the behavior of the various defects: occurrence rate, natural history, response to treatment, and long-term prospects. Finally, discovery of the causes and developmental mechanisms of heart defects is of great interest. These objectives require a system of analysis and naming that facilitates data gathering and communication of information.

The system of nomenclature should have certain characteristics if it is to be useful. First, the name should be descriptive and convey a picture of the defect. Who can remember the meaning of type 1B? On the other hand, tricuspid atresia with normally related great arteries and pulmonary stenosis is clear. Second, names should be unambiguous. Each name should refer to only one defect. It is less of a problem for a defect to have more than one name, as long as they map only to the same defect. For example, it makes little difference whether one uses the terms *membranous*, *perimembranous*, or *paramembranous ventricular septal defect*. They all refer to, and can be mapped to, the same type of ventricular septal defect. A problem arises if one calls a membranous defect *muscular* or *subpulmonary*, because these names refer to other types of defects as well. This would be hopelessly confusing because one name could refer to multiple types of defects. Third, the system of names should be inclusive. There should be a name for all defects, even rare ones. A large “other” category makes it hard to find rare defects, which can be highly informative regarding cause or developmental mechanism. Finally, the system must be capable of evolution and growth while remaining consistent.

The language used to describe the heart is an integral part of the analysis process. An effective way to discuss

the language of the heart is to describe a process for analyzing the heart. This process is called the “segmental approach to cardiac analysis and diagnosis.”¹⁻³ Why a segmental approach? The task of elucidating cardiac anatomy is made simpler by analyzing the cardiac segments separately and then constructing a synthesis or comprehensive diagnosis.

The heart is one of many organs in the abdomen and thorax. Analysis of the organization of these other organs provides a context for understanding and describing heart defects.

VISCERAL SITUS

The external bilateral symmetry of the human body hides the asymmetry of most internal organs. In the usual arrangement, called *situs solitus*, the left lung is bilobed and somewhat smaller than the trilobed right lung; this is apparent from the branching pattern of the bronchi. The abdomen contains several unpaired and lateralized organs, including the right-sided liver and gall bladder and the left-sided spleen and stomach. The normal rotation of the intestine places the caecum and appendix in the right lower quadrant and the sigmoid colon on the left. Rare individuals have inverted or mirror-image organization of the thoracic and abdominal viscera called *situs inversus*, which is inversion of the usual arrangement or *situs solitus*. In anatomy, inversion means left-right mirror imagery with no superior-inferior (cranial-caudal) or anterior-posterior (ventral-dorsal) change.

Laterality information is transmitted to the lateral plate mesoderm, the source of the viscera including the heart, around the time of gastrulation by the action of cilia in the node at the cranial end of the primitive streak.⁴ A cascade of transcription factors culminating in expression of *Pitx2* induces left-sided features in derivatives of the left lateral plate. Apparently, the absence of these factors leads to right-sided features in right lateral plate derivatives. The atria are lateralized structures whose

development is strongly influenced by the left-right gene regulatory networks (the left atrium, pulmonary vein, and atrial septal structures express *Pitx2c*, but right atrial structures do not⁵). Consequently, visceral and atrial situs are closely linked. In fact, the linkage is so tight that the term *visceroatrial situs* is often used to describe both at once.

The relationship between visceral situs and ventricular and outflow development is a little less strong. It is unknown how gene regulatory networks influence ventricular looping and development of the outflow and aortic sac derivatives.

Heterotaxy syndromes, abnormal symmetry and placement of usually asymmetrical and lateralized organs, result from defective or failed establishment of the left-right body axis. Abnormal atrial development is almost uniform in these conditions, whereas defective ventricular and outflow development is frequent but more variable. Heterotaxy syndromes are characterized by variability and unpredictability, although patterns of visceral and cardiac anatomy can be recognized. The concepts of “bilateral left sidedness” and “bilateral right sidedness” are useful mnemonic devices to help recall associations, but they should not be taken too seriously. These concepts probably apply best to the airways and lungs; symmetrical bronchi and lung lobation are

frequently encountered (Fig. 105-1). The liver lobation is often symmetrical, but duplication of the gall bladder rarely occurs. The spleen might be absent or multiple, but never duplicated on opposite sides of the abdomen. Similarly, the asplenia and polysplenia syndromes are often associated with particular combinations of findings, but the watchword is variability.

LOCATION OF THE HEART

The heart can be in the left chest with the apex to the left (levocardia), in the right chest with the apex to the right (dextrocardia), or in the midline with the apex down (mesocardia; Fig. 105-2). In some cases, the heart is partially or completely outside the chest (partial or complete ectopia cordis). It can be located partially or completely outside the body through a cleft in the sternum, predominantly in the abdomen, or even the neck. If the right lung is hypoplastic, or if there is a space occupying lesion in the left chest, the heart is often positioned in the right chest, but the apex points to the left or inferiorly (Fig. 105-3). This has been called *dextroposition* or *secondary dextrocardia*, as opposed to primary dextrocardia with a rightward apex. The implications of dextroposition differ from those of dextrocardia both for imaging the

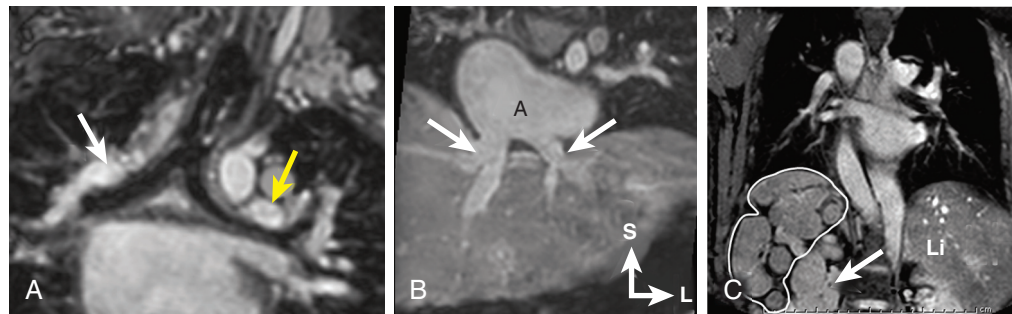


FIGURE 105-1 ■ Coronal magnetic resonance images in patients with heterotaxy syndrome. **A**, Symmetrical hyparterial bronchi, both of left-sided morphology (long bronchi with the first branch some distance from the carina), in a patient with polysplenia syndrome. The right (white arrow) and left (yellow arrow) pulmonary arteries are above the ipsilateral bronchus. **B**, Symmetrical hepatic veins (arrows) draining separately into the common atrium (A) in the same patient with polysplenia. (Directional marker applies to all three images.) **C**, Multiple spleens (white outline) on the right side of the abdomen in a patient with right-sided polysplenia. In our autopsy series, right polysplenia is slightly more frequent than left polysplenia. The right kidney (white arrow) is seen medial and inferior to the spleens. The liver (Li) is left-sided. L, Left; S, superior.

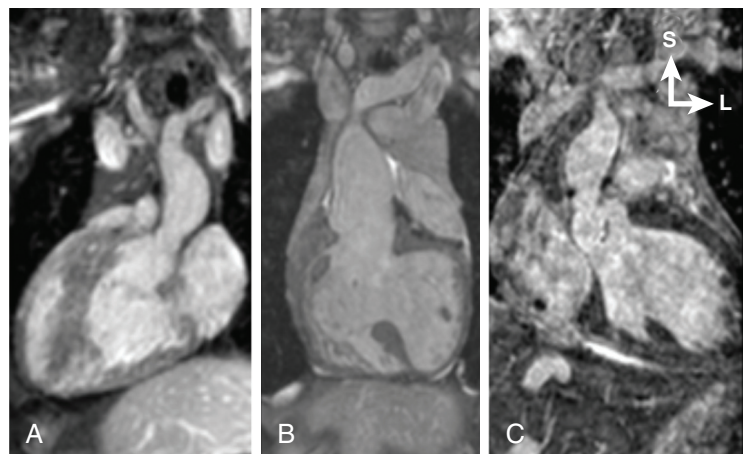


FIGURE 105-2 ■ Magnetic resonance images obtained using a steady-state free precession sequence reformatted in coronal plane showing: **A**, Dextrocardia with the apex of the heart to the right. **B**, Mesocardia with the apices of the ventricles directed inferiorly. **C**, Levocardia with the apex of the heart to the left. Directional marker applies to all three images. L, Left; S, superior.



FIGURE 105-3 ■ A frontal view of a three-dimensional volumetric reconstruction of a magnetic resonance angiogram in a patient with scimitar syndrome. A portion of the hypoplastic right lung is seen below the heart, which is displaced into the right chest exposing virtually all the left lung. The apices of the right (white arrowhead) and left (yellow arrowhead) ventricles point left and inferior, indicating a nearly normal orientation of the heart. A sequestration artery (arrows) originates from the descending aorta and enters the base of the right lung. L, Left; S, superior.

heart and for associated diagnoses. Dextroposition or secondary dextrocardia is associated with scimitar syndrome, right lung hypoplasia, and noncardiac diagnoses such as diaphragmatic hernia. The orientation of the heart is often similar to normal, simply moved into the right chest. Consequently, imaging planes are similar to those used in levocardia but centered over the right chest. Dextrocardia and mesocardia are associated with heterotaxy syndrome and congenitally corrected transposition. The defects tend to be more complex and very different imaging planes are usually required to display the anatomy.

SEGMENTAL ANALYSIS

Once the general location of the heart is determined, one can proceed with the segmental analysis.^{1,3} The heart is composed of three main segments: the atria, the ventricles, and the great arteries (Fig. 105-4). These main segments are joined—like bricks with mortar—by two connecting segments: the atrioventricular canal between

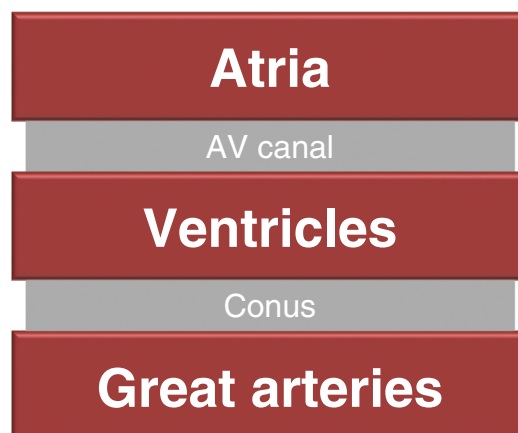


FIGURE 105-4 ■ The heart is composed of three main segments (the atria, ventricles, and great arteries) joined by two connecting segments (the atrioventricular [AV] canal and conus or infundibulum). The three main segments are not directly connected to each other. If they were, the spectrum of congenital heart defects might be more limited. The atria and ventricles are joined by the AV canal, which provides the AV valves, the membranous septum, and much of the fibrous insulating material that separates atrial and ventricular muscle (except at the AV penetrating bundle). The ventricles are joined to the great arteries by the conus or infundibulum. This connecting segment, derived from the primitive outflow, undergoes initial elongation, rotation, and subsequent shortening that usually results in normally related great arteries. If abnormal, it can be associated with one of the various anomalies of ventriculoarterial alignment and connection.

the atria and ventricles, and the conus or infundibulum between the ventricles and great arteries. The three main segments, although independent and relatively autonomous, develop harmoniously the great majority of the time. The location or situs and the internal organization of the segments are strongly correlated, but each segment can vary independently of the others.

Segmental Situs

First, the situs (location) and organization of each main segment is determined.⁶ The atrial situs is either solitus or usual, inversus or the mirror image of usual, or ambiguous where the identities of the atria are unclear or ill defined. The right atrium is right-sided and the left atrium left-sided in situs solitus. In situs inversus the right atrium is left-sided and the left atrium is right-sided with opposite right-left organization (Fig. 105-5). However, the anterior-posterior and superior-inferior organization is unchanged. Consequently, the superior vena cava arises from the superior aspect of the right atrium posterior to the atrial appendage and the inferior vena cava from the inferior aspect in both cases. *Situs ambiguus* is used to describe the heterotaxy syndromes (e.g., asplenia, polysplenia syndromes), which are also called *atrial appendage isomerism syndromes*. (It should be noted that these are not identical populations or concepts.)

Criteria for identifying the right atrium (Fig. 105-6), in an approximate order of reliability, include: (1) receives the coronary sinus, (2) has pectinate muscles extending to the vestibule of the atrioventricular valve, (3) receives

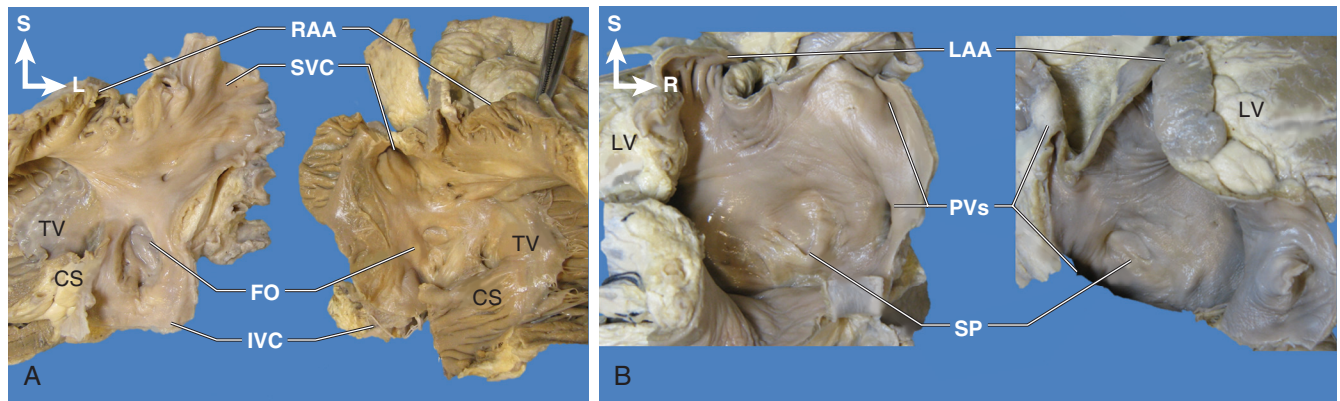


FIGURE 105-5 ■ **A**, The opened right atria of two hearts, one in situs solitus (*right*) and one in situs inversus (*left*). The atria are mirror images: there is left-right inversion but no superior-inferior or anterior-posterior change. Using the fossa ovalis (FO) as a reference point, the superior vena cava (SVC) is directed superior and rightward in situs solitus but superior and leftward in situs inversus. The coronary sinus (CS) is leftward and inferior in situs solitus but rightward and inferior in situs inversus, and the tricuspid valve (TV) is to the left in situs solitus but to the right in situs inversus. In both cases the inferior vena cava (IVC) is inferior to the fossa, and the right atrial appendage (RAA) is anterior to the superior vena cava (imagine closing the atrium by folding the right atrial appendage in front of the plane of the image). **B**, The opened left atria of the same two hearts placed back-to-back but with the situs solitus heart to the left and the situs inversus heart to the right (opposite placement to panel **A**) for clarity of labeling. Note the mirror image organization of the atria. The pulmonary veins (PVs) adjacent to the atrial septum are posterior to septum primum (SP) in both cases, but rightward in situs solitus (*left*) and leftward in situs inversus (*right*). The left atrial appendage (LAA) is superior to septum primum, but it points anterior and leftward in the situs solitus heart (*left*) but anterior and rightward in the situs inversus heart (*right*). L, Left; LV, left ventricle; R, right; S, superior.

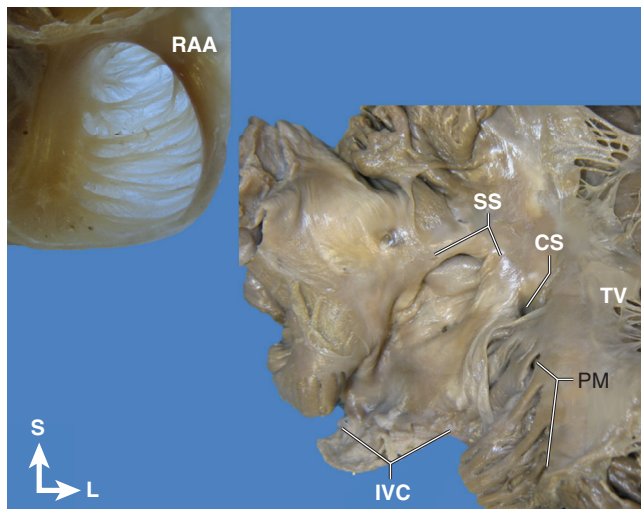


FIGURE 105-6 ■ The opened right atrium (*lower right*) and a section from a waxed, distended heart specimen (*upper left*) illustrate the characteristic right atrial features: coronary sinus (CS), pectinate muscles (PM) extending around the vestibule of the tricuspid valve (TV), inferior vena cava (IVC), septum secundum (SS) or superior limbic band on the septal surface, and large triangular appendage (RAA) with broad communication with the body of the atrium. L, Left; S, superior.

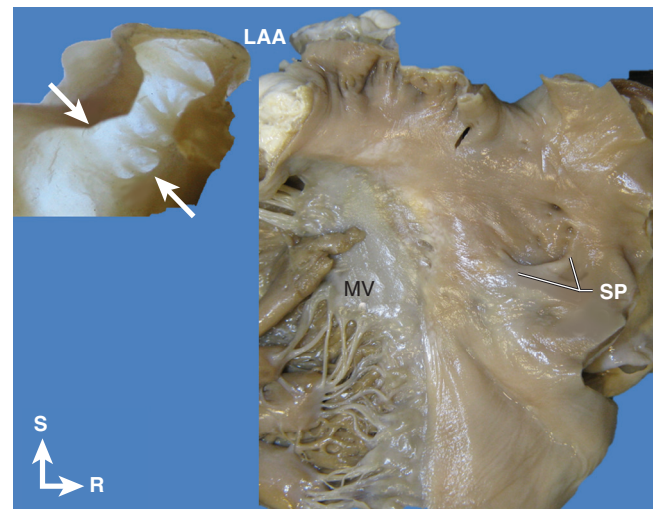


FIGURE 105-7 ■ The opened left atrium (*lower right*) and a section from a waxed, distended heart (*upper left*) illustrate the characteristic left atrial features: smooth walls with the pectinate muscles confined to the left atrial appendage (LAA), septum primum (SP) or primary atrial septum on the septal surface, and a small, finger-like appendage with a narrow junction (*arrows*) with the body of the atrium. MV, Mitral valve; R, right; S, superior.

the inferior vena cava, (4) has septum secundum on the septal surface, and (5) has a large, triangular appendage with a broad orifice communicating with the atrium. If the coronary sinus is present, it is an extremely reliable marker because it develops from the sinus horn contralateral to the one that forms part of the right atrium. Unfortunately, it is often absent (or unroofed) in heterotaxy syndromes, where most help is needed to identify the atria. The pectinate muscle morphology appears to be reliable as well but can be difficult to detect with

current imaging technology. The inferior vena cava is a useful practical marker for the right atrium but it can also drain to the coronary sinus and is often interrupted in heterotaxy syndromes.

Criteria for the left atrium (Fig. 105-7) include (1) smooth walls with pectinate muscles confined to the atrial appendage, (2) septum primum on the septal surface, and (3) small, finger-like appendage. Practically, if one can identify the right atrium, the other atrial chamber is the left atrium. If one cannot clearly identify the right atrium, the

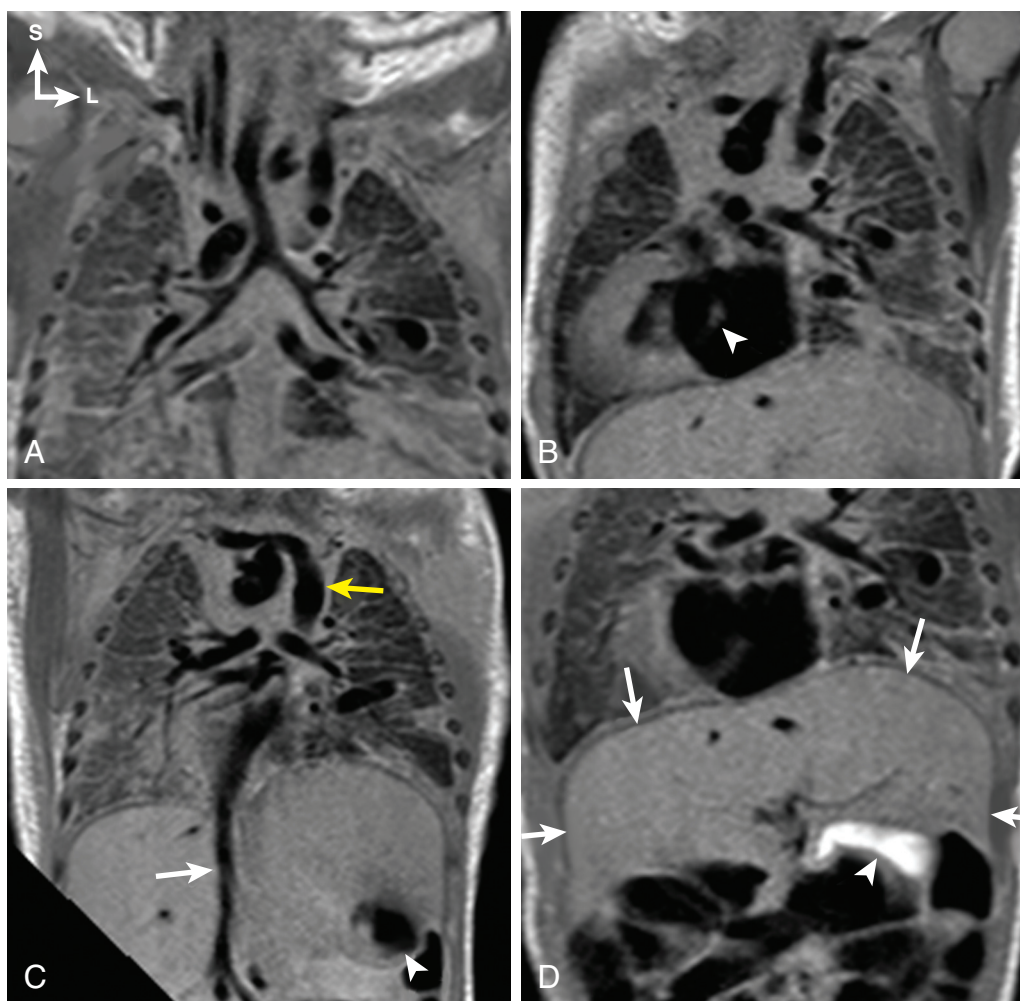


FIGURE 105-8 ■ A series of coronal sections of a black blood magnetic resonance sequence in an infant with a heterotaxy syndrome to illustrate the variability of organ symmetry and placement often seen in these syndromes. The directional indicator at the upper left applies to all images. **A**, Symmetrical bronchi of right-sided morphology (compare with Fig. 105-1A). The upper lobe bronchi arise a short distance after the carina on both sides in contrast to the long, unbranched bronchi seen in Figure 105-1A. **B**, Dextrocardia with near absence of atrial septum. Only a small strand of the atrial septum (arrowhead) remains. **C**, The inferior vena cava (white arrow) is right-sided, whereas the superior vena cava (yellow arrow) is left-sided. The stomach (arrowhead) is left-sided. **D**, Large, symmetrical liver (arrows) spans the upper abdomen. The gall bladder (arrowhead) is left-sided. L, Left; S, superior.

situs is likely ambiguous. The superior vena cava and pulmonary veins are not reliable markers of atrial identity.

In some hearts the atrial anatomy is difficult to discern. These are generally hearts with heterotaxy syndrome (see Figs. 105-1 and 105-8). The coronary sinus is usually absent or unroofed. The inferior vena cava often changes sides in the liver and hepatic veins enter the atrial floor separately. The atrial septum is poorly represented, with only a muscular strand of tissue remaining. The atria can exhibit similar pectinate muscle morphology, but the appendages are rarely similar in size and shape. In such cases, it is best to indicate that the atrial morphology is ambiguous and to describe the anatomy in detail.

The ventricular situs or loop is either solitus or d-loop, or inversus or l-loop. Rarely (most often in double-inlet right ventricle), it is impossible to determine the ventricular loop, which is then listed as unknown (X).

The definition of the ventricular loop or situs is based on internal organization or chirality of the ventricles and not on their locations. *Left* and *right* should be considered

as the names of the ventricles rather than an indication of location. Consequently, constructions such as *morphologically left ventricle* are superfluous. The analysis of chirality is most conveniently performed on the right ventricle because the inflow and outflow are separated by an angle of nearly 90 degrees, but it can be done on either ventricle. A d-loop or solitus right ventricle is organized with the inflow from the right and the outflow to the left as viewed from the free wall; an l-loop or inverted right ventricle is organized oppositely. A simple way to understand the organization of the ventricle is to imagine which hand can be used to describe the ventricle if the thumb represents the tricuspid valve, the fingers the outflow tract, and the palm is against the septal surface (Fig. 105-9A). Only the right hand works for a solitus or d-loop right ventricle. Only a left hand works for an inverted or l-loop right ventricle.

The left ventricle is organized oppositely (see Fig. 105-9B). The left hand describes a d-loop or solitus left ventricle and the right hand an inverted or l-loop left

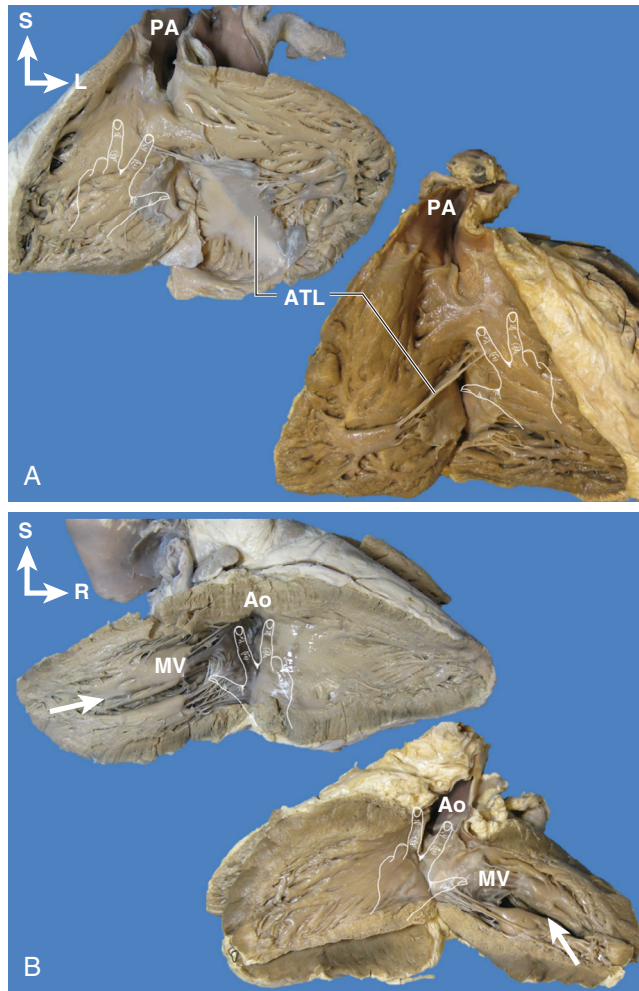


FIGURE 105-9 ■ **A**, The opened right ventricles of two hearts, one with solitus or d-loop ventricles (*lower right*) and one with inverted or l-loop ventricles (*left upper*). The chirality or handedness of the two right ventricles is opposite, as illustrated by the hand required to describe the ventricle. A right hand describes the d-loop ventricle on the right, with the thumb in the tricuspid valve, the fingers in the outflow and the palm against the septum. The l-loop right ventricle is organized oppositely and requires a left hand to describe it. **B**, The opened left ventricles of two hearts, one with solitus or d-loop ventricles (*lower right*) and one with inverted or l-loop ventricles (*left upper*). As for the right ventricles in the previous figure, the chirality or handedness of these left ventricles is opposite. A left hand, with the thumb in the mitral valve, the fingers in the outflow, and the palm against the septum, describes the d-loop left ventricle (*right*), whereas a right hand is needed for the l-loop left ventricle (*left*). Comparing this figure with the previous one shows that in both d-loop and l-loop ventricles, the left and right ventricles are organized oppositely: the d-loop right ventricle is right-handed while the d-loop left ventricle is left-handed; in l-loop ventricles the organization is opposite, the right ventricle is left-handed and the left ventricle is right-handed. *White arrow*, Papillary muscles on left ventricular free wall. *Ao*, Aorta; *ATL*, anterior tricuspid leaflet; *L*, left; *MV*, mitral valve; *PA*, pulmonary artery; *R*, right; *S*, superior.

ventricle. The septal wall of the left ventricle is present and identifiable even when there is only an outflow chamber or infundibulum, and no right ventricle, present on the other side. Consequently, one can use the hand rule even in cases of double-inlet left ventricle and

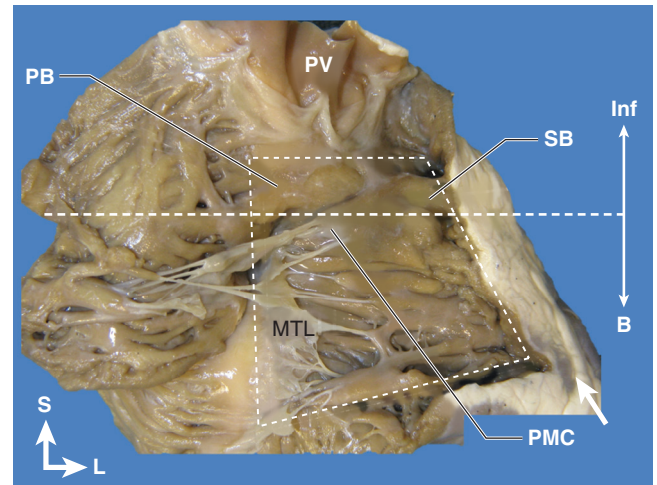


FIGURE 105-10 ■ Characteristic features of the right ventricle are illustrated in this opened specimen of a d-loop right ventricle: (1) trapezoidal shape bounded by the tricuspid annulus to the right, the diaphragmatic wall inferiorly, the apex and anterior wall to the left, and the pulmonary valve superiorly; (2) coarse trabeculations; (3) multiple attachments of the medial or septal tricuspid leaflet (MTL) to the septum; (4) division into an inflow or body (B) portion below the papillary muscle of the conus (PMC) and an outflow or infundibulum (Inf) above (the muscular crest marking the division between the two is composed of the septal band [SB], parietal band [PB], and moderator band [divided in this specimen]); and (5) discontinuity between the pulmonary valve (PV) and tricuspid valve because of intervening conal muscle (parietal band). *L*, Left; *S*, superior.

tricuspid atresia where there is generally only one ventricle. Conversely, in cases of double-inlet right ventricle where no left ventricle is found, it may be impossible to identify the septum.⁷ In such cases, the hand rule cannot be applied and the ventricular loop cannot be determined.

The morphologic features of the normal right ventricle include (Fig. 105-10) (1) trapezoidal shape; (2) coarse trabeculations; (3) a body or sinus portion and an outflow or infundibulum demarcated by a muscular crest composed of the parietal band, septal band, and moderator band; (4) a tricuspid valve with chordal insertions on the ventricular septum; and (5) tricuspid valve–pulmonary valve discontinuity owing to intervening infundibular muscle. The characteristic features of the left ventricle include (Fig. 105-11) (1) ellipsoidal or bullet shape; (2) fine trabeculations on the free wall and apical septum, with a smooth mid and basal septum; (3) adjacent inflow and outflow tracts; (4) two well defined papillary muscle groups originating from the free wall; (5) absence of septal insertions of the mitral valve; (6) an outflow tract between the medial leaflet of the mitral valve and the ventricular septum; and (7) fibrous continuity between the mitral and aortic valves.

The great artery position or situs is a little more complicated because there are more possibilities. First, consider situations in which the great arteries are normally related—to each other and to the ventricles. This can occur in situs solitus or the usual position of the great arteries (solitus normally related great arteries), where the aorta is posterior and rightward of the pulmonary

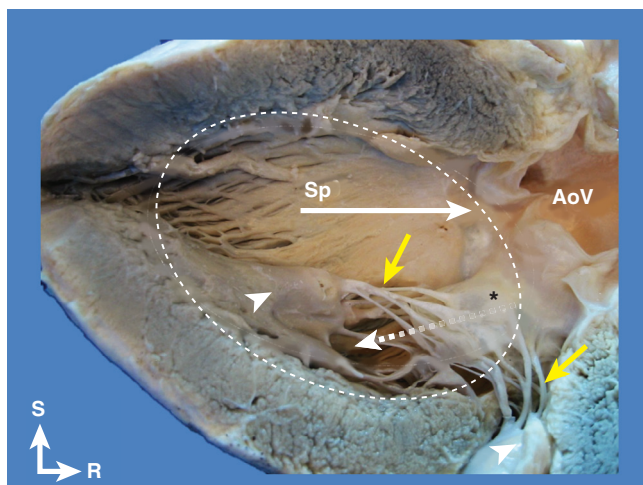


FIGURE 105-11 ■ Characteristic features of the left ventricle are shown in this specimen: ellipsoidal shape, smooth basal septal surface (Sp) with fine apical and free wall trabeculations, adjacent and nearly parallel inflow (dashed white arrow) and outflow (solid white arrow), two free-wall papillary muscle groups (white arrowheads) receiving chordal insertions of the mitral valve (yellow arrows), absence of septal insertions of the mitral valve, the outflow tract lying between the septum and the medial leaflet of the mitral valve (between yellow arrows), and fibrous continuity (asterisk) between the mitral and aortic (AoV) valves. R, Right; S, superior.

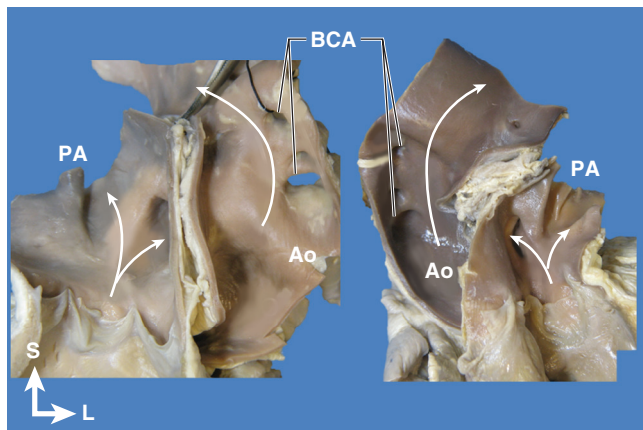


FIGURE 105-12 ■ The proximal aorta (Ao) and pulmonary artery (PA) from two hearts, one with solitus normally related great arteries (right) and one with inversus normally related great arteries (left). In the solitus great arteries (right), the aorta is rightward and posterior to the pulmonary artery and forms an arch (curved arrow), whereas the pulmonary artery is anterior and leftward with the bifurcation (bifurcating arrows) to the left. Conversely, in inversus normally related great arteries (left) the aorta is posterior and leftward, whereas the pulmonary artery is anterior and rightward with the bifurcation (bifurcating arrows) to the right. The pulmonary branch that passes posterior to the ascending aorta is the right pulmonary artery in situs solitus but the left pulmonary artery in situs inversus. BCA, Brachiocephalic arteries; L, left; S, superior.

artery and aligned with the left ventricle, or in situs inversus or the mirror image of usual (inversus normally related great arteries), where the aorta is posterior and leftward of the pulmonary artery and aligned with the left ventricle (Fig. 105-12). In both cases, the pulmonary

artery is aligned with the right ventricle. In situs solitus, the pulmonary artery bifurcation is to the left of the ascending aorta, whereas in situs inversus it is to the right.

Now consider situations in which the great arteries are abnormally related to each other or the ventricles. These malpositions of the great arteries are named according to the position of the aorta. If the aorta is to the right of the pulmonary artery, it is called *d-malposition* (*d* = dextro), to the left of the pulmonary artery is called *l-malposition* (*l* = levo), and directly anterior is called *a-malposition* (*a* = anterior). The term *p-malposition* has been used to describe cases in which the aorta is posterior to the pulmonary artery, mostly in rare cases of transposition of the great arteries. Malposition is a general and nonspecific term that includes all great artery arrangements, except solitus or inversus normally related great arteries.

Some hearts have only a single arterial trunk. In such cases, it makes no sense to describe its position because there is no other arterial root as a reference. An example is truncus arteriosus in which there is only the truncal root. The arterial arrangement in these hearts can be considered a form of normally related great arteries ($\{L,D,S\}$ or $\{L,L,I\}$). The same approach can be used for tetralogy of Fallot with aortopulmonary collaterals and no pulmonary trunk. The truncal root or aorta overrides the septum and is in fibrous continuity with the mitral valve (and often the tricuspid valve); this is much like the aorta in tetralogy of Fallot. Consequently, it seems reasonable to consider the arterial arrangement in these hearts a form of normally related great arteries.

There are other hearts with a single arterial trunk in which this is not the case. In rare cases of truncus arteriosus, the truncal root is completely related to the right ventricle and there is a complete subtruncal conus. Clearly, this is not a variation of normally related great arteries. Similarly, some hearts have a right ventricular aorta with subaortic conus and long-segment pulmonary atresia. This is surely not normally related great arteries, but what is it? One could assign it as transposition or double-outlet right ventricle with pulmonary atresia, but this seems arbitrary because there is no pulmonary trunk. The most accurate description is a single right ventricular arterial root—either truncus or aorta. An arterial position is not assigned because there is no other root for comparison, so that the third member of the segmental set is either left blank or assigned an X for unknown.

Practical criteria for identifying the great arteries include: (1) the aorta forms an arch and gives rise to at least some of the brachiocephalic arteries and (2) the pulmonary artery bifurcates into right and left branches (see Fig. 105-12); however, there are significant exceptions. The aortic arch can be interrupted; one or even both branch pulmonary arteries can arise from the ascending aorta; a branch pulmonary artery can be absent; the left pulmonary artery can arise distally from the right pulmonary artery in left pulmonary artery sling syndrome.

Set notation is used to summarize the situs of the three main segments (Fig. 105-13). The first element of the set is the atrial situs: *S* for solitus, *I* for inversus, or *A* for ambiguous. The second element is the ventricular situs or

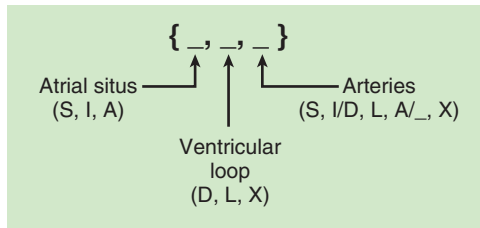


FIGURE 105-13 ■ Segmental set notation used to describe the segmental situs of the main cardiac segments. The first member of the set is the atrial situs: solitus (S), inversus (I), or ambiguus (A). The second member is the ventricular loop or situs: dextro (D), levo (L), or unknown (X). Finally, the situs of the great arteries is the third member: S and I are used only for normally related great arteries; D, L, and A are used for malpositions of the great arteries, where the letter refers to the location of the aorta, right, left, or anterior, respectively. In cases with a right ventricular single arterial root, the third element of the set is either blank or an X, indicating that it is not possible to assign arterial position.

loop: *D* for solitus or d-loop, *L* for inversus or l-loop, or, rarely, *X* for unknown loop. The third element is the great artery position: *S* or *I* for solitus or inversus normally related great arteries, respectively; *D*, *L*, or *A* (some include *P*) for the various malpositions; or blank or *X* for hearts with a right ventricular single arterial root.

Segmental Alignments

Next, the alignments of the segments are defined based on what is aligned with or drains into what. Chambers are aligned if blood flows from one to the other (e.g., from right atrium to right ventricle in the normal heart). Alignment is concordant if the aligned segments are appropriate (e.g., right atrium aligned with right ventricle, or left ventricle aligned with aorta), or discordant if inappropriate (e.g., left atrium with right ventricle, or left ventricle with pulmonary artery). The concept of concordant and discordant alignment is useful when it works, but it is not universally applicable.⁸ Is the ventriculoarterial alignment in double-outlet right ventricle concordant or discordant? It is concordant for the pulmonary artery but discordant for the aorta. What about the left ventricle? What is the atrioventricular alignment in straddling atrioventricular valve?

In fact, alignment is more complicated than simply concordance or discordance, because the blood must pass through the connecting segments before reaching the distal chamber or vessel; this adds a layer of variability and complexity. There are five basic types of atrioventricular alignment, determined by the situs of the atria and ventricles and the anatomy of the atrioventricular canal (Fig. 105-14):

1. Concordant—the atria are aligned with the appropriate ventricle through separate or a common atrioventricular (AV) valve ({S,D,_} or {I,L,_})
2. Discordant—the atria are aligned with the inappropriate ventricle through separate or a common AV valve ({S,L,_} or {I,D,_})
3. Straddling AV valve (including double-outlet atrium)—one atrium is aligned with one ventricle and the other with both ventricles

4. Double-inlet ventricle—both atria are aligned with one ventricle through two AV valves or a common AV valve, and
5. AV valve atresia—only one atrium is aligned with a ventricle and the other atrium drains across the atrial septum (Note that straddling of the remaining AV valve is possible in the context of AV valve atresia.)

There are five basic types of ventriculoarterial alignment (Fig. 105-15):

1. Concordant—both great arteries are aligned with the appropriate ventricle
2. Transposition (discordant)—the great arteries are on the opposite side of the septum from normal (i.e., aorta from right ventricle or infundibulum and pulmonary artery from left ventricle)
3. Double-outlet ventricle—both great arteries arise completely or nearly completely from one ventricle
4. Straddling single arterial trunk (sometimes considered a form of normally related great arteries and, therefore, concordant)—both ventricles are aligned with (eject into) a single arterial root, and
5. Right ventricular single arterial trunk—only the right ventricle is aligned with an arterial root and the left ventricle ejects across the ventricular septal defect

Concordant ventriculoarterial alignment includes normally related great arteries (in situs solitus and inversus), anatomically corrected malposition, isolated ventricular discordance, and isolated infundibuloarterial discordance (see Fig. 105-15A). In these, the sequence of blood flow is normal—from the left ventricle to the aorta and from the right ventricle to the pulmonary artery. However, the connection of the left ventricle to the aorta is abnormal in anatomically corrected malposition (see below, Segmental Connections).⁹

Transposition indicates that the great arteries arise on the opposite side of the ventricular septum from normal—the pulmonary artery from the left ventricle and the aorta from the right ventricle or outlet chamber.^{10,11} Although there is a strong association between transposition and anterior placement of the aorta, this is not the meaning of the term. It is possible to have transposition with side-by-side vessels or even a posterior aorta.^{12,13}

Double-outlet ventricle indicates just what the name says—both great arteries arise completely or nearly completely above one or the other ventricle. Although the “50% rule” is often used to define double-outlet ventricle,¹⁴ its only attractive feature is that it simplifies cardiac bookkeeping. It has little or no clinical significance and is of no help in clinical decision making. Because it seems important for names of defects to be clinically meaningful, we do not use the 50% rule.

Single arterial trunk includes hearts with truncus arteriosus and pulmonary atresia. The aorta (or truncus) can be aligned with both ventricles (e.g., tetralogy of Fallot with pulmonary atresia or usual truncus) or only with the right ventricle (e.g., truncus with complete conus, pulmonary atresia with right ventricular aorta). Note that in aortic atresia, there is virtually always a hypoplastic ascending aorta and aortic root that sits above an atretic ventricular outflow tract and supplies the coronary

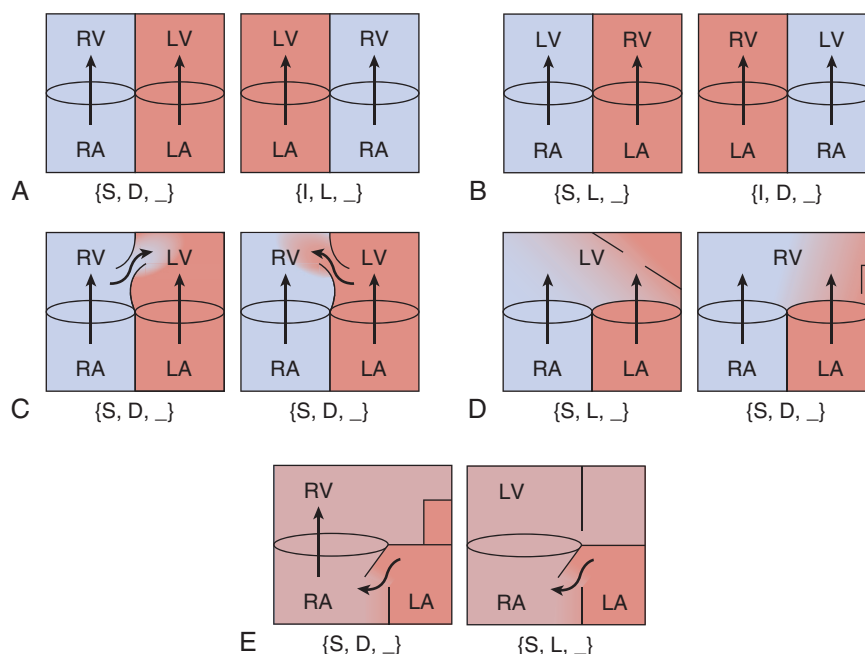


FIGURE 105-14 ■ Examples of the five types of atrioventricular alignments.* **A**, Concordant. The left figure is the usual alignment in situs solitus (right-sided right atrium [RA] aligned with right-sided right ventricle [RV] and left-sided left atrium [LA] aligned with left-sided left ventricle [LV]), but atrioventricular alignment is concordant as well if both atria and ventricles are inverted (*right panel*). **B**, Discordant. In the *left panel*, atrioventricular alignment discordance is due to ventricular inversion in situs solitus (right-sided right atrium aligned with a right-sided [inverted] left ventricle and a left-sided [inverted] right ventricle), which can be associated with isolated ventricular inversion {S,L,S}, an anatomically corrected malposition {S,L,D}, congenitally corrected transposition {S,L,L}, superior-inferior ventricles with double-outlet right ventricle {S,L,D}, and others. Note that the mirror images of these arrangements in situs inversus also produce atrioventricular alignment discordance (e.g., isolated ventricular noninversion {I,D,I}, anatomically corrected malposition {I,D,L}, congenitally corrected transposition {I,D,D}). Isolated atrial inversion (*right panel*), such as normally related great arteries {I,D,S}, also results in atrioventricular alignment discordance. **C**, Straddling atrioventricular valve. The example shows straddling tricuspid valve (*left panel*) and straddling mitral valve (*right panel*) in atrioventricular situs concordance (as in **A**) but could be situs discordance (as in **B**) as well. Although concordance–discordance works for situs, it does not work for alignment. What is the alignment of the right atrium in the left figure or the left atrium in the right figure? It is both concordant and discordant, because the atrium with the straddling valve is aligned with both ventricles through the normal and straddling orifices of the valve. **D**, Double-inlet ventricle. In the *left panel*, there is double-inlet left ventricle with atrioventricular situs discordance {S,L,_} (solitus atria with a right-sided right atrium and left-sided left atrium, but l-loop or inverted left ventricle with the outlet chamber to the left and the left ventricle to the right). Situs concordance is possible as well (e.g., double-inlet left ventricle with normally related great arteries {S,D,S}, also known as Holmes heart, which is not shown). The *right panel* illustrates double-inlet right ventricle with atrioventricular situs concordance {S,D,_} (the right atrium is right-sided and the left atrium left sided, the ventricles are solitus or d-loop with a right-sided right ventricle and a left-sided hypoplastic left ventricle). Concordance–discordance does not work for atrioventricular alignment in this case because both atria are aligned with the same ventricle so that the alignment of one atrium is concordant and the other discordant. **E**, Atrioventricular valve atresia. The *left panel* illustrates mitral atresia in atrioventricular situs concordance {S,D,_} (solitus atria with the right atrium to the right and the left atrium to the left and d-loop or solitus ventricles with the right ventricle to the right and the hypoplastic left ventricle to the left). This could also occur in situs inversus (the mirror image of the example shown) or in atrioventricular situs discordance, such as {S,L,_} with right-sided mitral atresia. The *right panel* shows tricuspid atresia in atrioventricular situs discordance {S,L,_} (solitus atria with a right-sided right atrium and left-sided left atrium and a right-sided inverted [l-loop] left ventricle and left-sided outlet chamber). Here the right atrial alignment is discordant, but the left atrial alignment is neither concordant nor discordant because it does not drain directly into either ventricle. It drains across the atrial septum into the right atrium. This could occur in atrioventricular situs concordance as well, such as tricuspid atresia with transposition {S,D,D}. Note that it is also possible for the remaining atrioventricular valve to straddle the septum. *Although we have stressed in the text that the ventricular loop or situs is based on the chirality or handedness of the chamber and not its position in space, we have used position as a surrogate for ventricular loop or situs in this and the next figure to facilitate creating the illustrations.

arteries. Consequently, the single arterial root is essentially never a pulmonary trunk.

Segmental Connections

Finally, the connections of the segments are described. Alignment and connection are different and both are important. As noted above, the three main segments

are not connected directly to each other. Rather, they are joined by the two connecting segments. Atrioventricular connections are (1) two valves into separate ventricles, (2) common valve into two ventricles, (3) straddling AV valve, (4) two valves into one ventricle, (5) common valve into one ventricle, (6) absent AV connection, and (7) imperforate AV valve. Atrioventricular alignments and connections are closely related. For example,

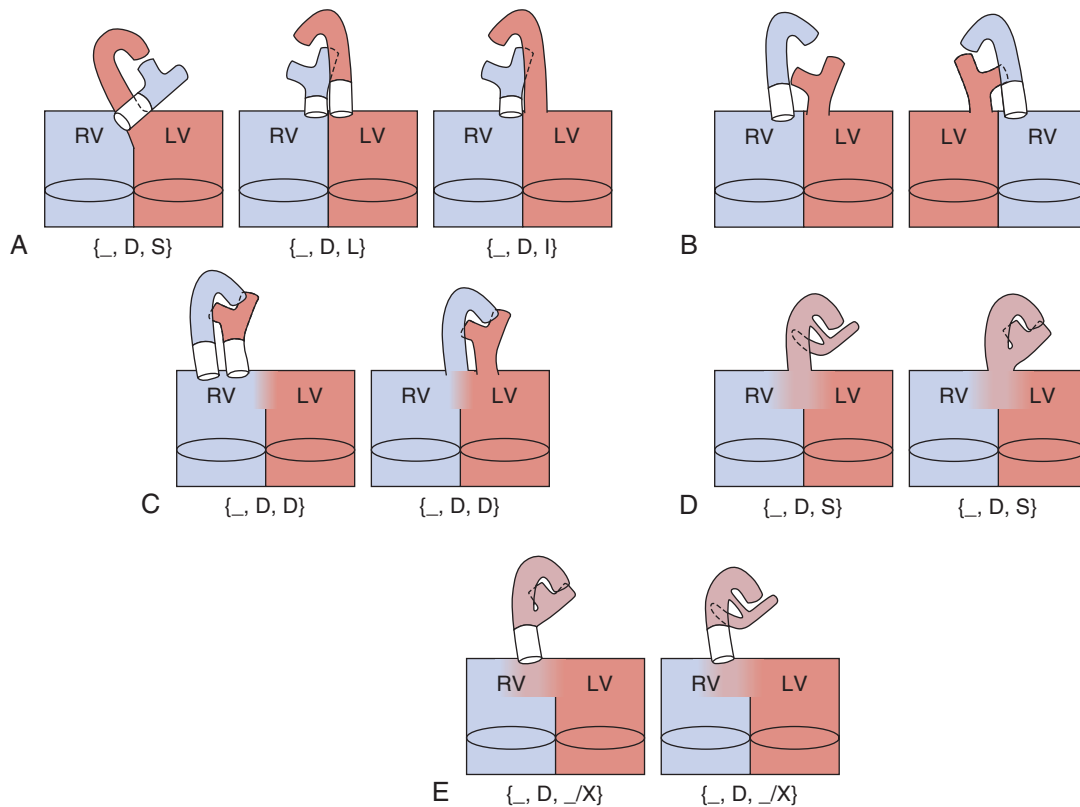


FIGURE 105-15 ■ Examples of the five types of ventriculoarterial alignment.* **A**, Concordant. The *left panel* shows normally related great arteries in situs solitus {_, D, S} (rightward and posterior aorta aligned with the left ventricle [LV] and connected by mitral-aortic fibrous continuity and the leftward, anterior pulmonary artery aligned with the right ventricle [RV] and connected by a subpulmonary conus). Ventriculoarterial alignment is also concordant in normally related great arteries in situs inversus {_, L, I} (the mirror image of the *left panel*, not shown), anatomically corrected malposition {_, D, L} (*middle panel*, left-sided d-loop left ventricle aligned with a left-sided aorta and connected by a subaortic conus, right-sided d-loop right ventricle aligned with the right-sided pulmonary artery and connected by a [often deficient] subpulmonary conus) or {_, L, D} (the mirror image of {_, D, L}, not shown), isolated infundibuloarterial discordance {S, D, I} (*right panel*, right-sided d-loop right ventricle aligned with a right-sided and anterior pulmonary artery and connected by subpulmonary conus, and a left-sided d-loop left ventricle aligned with a leftward and posterior aorta and connected by aortic-mitral fibrous continuity) or {I, L, S}, its mirror image, and others. **B**, Discordant. The *left panel* shows common transposition of the great arteries {S, D, D} (right-sided d-loop right ventricle aligned with the right-sided aorta and connected by subaortic conus and the left-sided d-loop left ventricle aligned with the leftward pulmonary artery and connected by pulmonary-mitral fibrous continuity). The *right panel* shows congenitally corrected transposition {S, L, L} (right-sided inverted or I-loop left ventricle aligned with the right-sided pulmonary artery and connected by pulmonary-mitral fibrous continuity and the left-sided inverted or I-loop right ventricle aligned with the left-sided aorta and connected by subaortic conus). **C**, Double-outlet ventricle. The *left panel* shows double-outlet right ventricle {S, D, D} (a right-sided d-loop right ventricle is aligned with both great arteries [the right-sided aorta and left-sided pulmonary artery], whereas the left-sided d-loop left ventricle is aligned with neither). The *right panel* shows double-outlet left ventricle {S, D, D} where both great arteries are aligned with the left ventricle and neither with the right ventricle. Concordance–discordance does not make sense in this context because one ventricle is aligned with both great arteries and the other with neither. In the illustration, the great arteries are connected to the right ventricle, in the case of double-outlet right ventricle, by bilateral subarterial conus and to the left ventricle, in the case of double-outlet left ventricle, by fibrous continuity between the mitral valve and both semilunar valves. Keep in mind, however, that more than one type of ventriculoarterial connection can occur with either type of double-outlet ventricle. **D**, Overriding single arterial trunk. The *left panel* shows tetralogy of Fallot with pulmonary atresia and no pulmonary trunk, considered to be a type of normally related great arteries. However, both ventricles are aligned with the overriding single aortic root, so that concordance–discordance does not really apply. The alignment is the same in typical truncus arteriosus with an overriding truncal root (*right panel*). In the great majority of such cases, there is semilunar-mitral fibrous continuity as shown in the illustration. **E**, Right ventricular single arterial trunk. In truncus arteriosus with complete subtruncal conus (*left panel*) the truncal root is completely above and aligned with the right ventricle. The left ventricle is not aligned with a great artery and ejects through the ventricular septal defect. The *right panel* demonstrates a right ventricular aorta with pulmonary atresia. The aorta is aligned with the right ventricle, but the left ventricle is not aligned with a great artery. Concordance–discordance is not useful for describing this arrangement. *Although we have stressed in the text that the ventricular loop or situs is based on the chirality or handedness of the chamber and not its position in space, we have used position as a surrogate for ventricular loop or situs in this and the previous figure to facilitate creating the illustrations. The cylinder indicates subarterial conus or infundibulum.

double-inlet alignment can only be associated with two valves or a common valve into one ventricle. The term *AV valve atresia* has been used both for conditions with absent connection (usual tricuspid atresia) and for conditions in which valve components are present but there is

no orifice (many cases of mitral atresia). This is unlikely to change, nor is such a change being proposed. However, distinguishing between these types of atrioventricular connection is likely to be informative regarding developmental mechanism and possibly outcome.

Ventriculoarterial connection and alignment are less closely related. The aorta might be connected normally to the left ventricle with fibrous continuity between the mitral and aortic valves (normally related great arteries) or abnormally by a muscular conus between the left ventricle and the aorta (anatomically corrected malposition). In both cases, the ventriculoarterial alignment is concordant; the aorta receives blood from the left ventricle and the pulmonary artery from the right ventricle. However, the ways in which the great arteries are connected to the ventricles differ. A given ventriculoarterial alignment can be associated with multiple types of connection. This has implications for associated abnormalities (e.g., the subaortic conus in anatomically corrected malposition can become obstructed) and surely for the developmental mechanisms that produce the defect.

There are four ventriculoarterial connections: subpulmonary conus only, subaortic conus only, bilateral subarterial conus, and bilaterally absent subarterial conus. A subpulmonary conus is typical of normally related great arteries, but it can occur with a rare form of transposition with a posterior aorta, with double-outlet right ventricle with mitral atresia, and with isolated infundibuloarterial discordance.¹⁵ Subaortic conus is typical of common and congenitally corrected transposition, but it occurs in some forms of double-outlet left ventricle.¹⁶ Bilateral conus is most often associated with double-outlet right ventricle, but it can occur with transposition¹³ and anatomically corrected malposition. Bilaterally absent subarterial conus is seen in double-outlet left ventricle,¹⁶ but it can also occur in transposition.¹³ As already noted, the ventriculoarterial connection has implications for outflow obstruction, great artery size, and arterial obstruction.

Disharmony between Situs and Alignment

There is typically concordance or harmony among the atrial situs, the loop or situs of the ventricles, and the situs or position of the great arteries. When the atrial situs is solitus, there are usually d-loop ventricles and the aorta is usually to the right—either solitus normally related great arteries or some type of d-malposition of the great arteries—and conversely in situs inversus.

Situs discordance between segments is a feature of a number of heart defects. For example, in congenitally corrected transposition {S,L,L}, there is atrioventricular situs discordance (solitus atria but inverted ventricles) and alignment discordance (right atrium aligned with right-sided left ventricle and left atrium aligned with a left-sided right ventricle). The situs correctly predicts the atrioventricular alignments; this is the case in the vast majority of hearts.

However, some hearts are characterized by discrepancy or disharmony between segmental situs and segmental alignments.^{4,17,18} In the vast majority of hearts, when there is situs solitus of the atria and d-loop ventricles, or situs inversus and l-loop ventricles, the right atrium is aligned with (drains into) the right ventricle and the left atrium is aligned with the left ventricle. The situs of the segments correctly predicts the alignments. There is said to be concordance or harmony between situs and

alignments. It is mostly in hearts with superoinferior ventricles and crisscross hearts where one sees discordance or disharmony between situs and atrioventricular alignment: a solitus right atrium aligned with a d-loop left ventricle and a solitus left atrium aligned with a d-loop right ventricle (and the converse). Especially in these hearts, one cannot assume that situs correctly predicts atrioventricular alignments. Virtually all the hearts with situs-alignment discordance that have been reported also have right juxtaposition of the atrial appendages.¹⁸ In other types of hearts, it seems a practical assumption that situs correctly predicts atrioventricular alignment.

Situs and ventriculoarterial alignment are less tightly linked. Often one cannot deduce the ventriculoarterial alignment from the situs of the ventricles and great arteries. For example, a heart with the cardiotype {S,D,D} could be transposition (discordant) or double-outlet ventricle (right or left). Or the cardiotype {S,D,L} could be associated with transposition (discordant), anatomically corrected malposition (concordant) or double-outlet ventricle. Sometimes this is because the concept of concordance and discordance does not apply, as in double-outlet ventricle. Other times it simply reflects the variability of arterial position. Consequently, the ventriculoarterial alignment is typically stated in the diagnosis along with the cardiotype (e.g., anatomically corrected malposition {S,D,L}).

Examples of Segmental Analysis

The following examples illustrate the use of segmental analysis.

1. Normal heart in situs solitus
 - a. Segmental situs: atrial situs solitus {S,_,_}; ventricular d-loop or situs solitus {_,D,_}; solitus normally positioned and related great arteries {_,_,S}. The cardiotype, using set notation, is {S,D,S}.
 - b. Segmental alignments: the atrioventricular alignment is concordant; the ventriculoarterial alignment is concordant (see [Figs. 105-14A](#) and [105-15A](#)).
 - c. Segmental connections: the atrioventricular connection is two valves into separate ventricles; the ventriculoarterial connection is subpulmonary conus only with mitral-aortic fibrous continuity.

The normal heart in situs inversus has the cardiotype {I,L,I} (situs inversus [I]; ventricular l-loop or situs inversus [L]; inversus normally related great arteries [I]), but the alignments and connections are the same as noted previously.

In these hearts, the location, alignments, and connections of the heart segments are all appropriate so that any hemodynamic abnormality is due to one or more of the myriad possible other defects such as a venous drainage anomaly, abnormal intracardiac communication, outflow obstruction, and so on.

2. Common transposition of the great arteries
 - a. Segmental situs: atrial situs solitus {S,_,_}; ventricular d-loop or situs solitus {_,D,_};

transposition of the great arteries with the aorta anterior and rightward {_,_,D}. The cardiotype is {S,D,D}.

- b. Segmental alignments: the atrioventricular alignment is concordant; the ventriculoarterial alignment is transposition (discordant; see Figs. 105-14A and 105-15B).
 - c. Segmental connections: the atrioventricular connection is two valves into separate ventricles; the ventriculoarterial connection is usually subaortic conus with pulmonary-mitral fibrous continuity, but, as noted, can be variable.
- Here there is a single segmental alignment discordance between the ventricles and great arteries. The patient is blue because systemic venous blood from the right atrium is recycled back to the aorta through the right ventricle. Creating ventriculoarterial alignment concordance by performing an arterial switch operation corrects the abnormal blood flow pattern and places the left ventricle in the systemic circulation.

3. Double-outlet right ventricle with straddling mitral valve

- a. Segmental situs: atrial situs solitus {S,_,_}; ventricular d-loop or situs solitus {_,D,_}; double-outlet ventricle with aorta rightward {_,_,D}. The cardiotype is {S,D,D}.
- b. Segmental alignments: the atrioventricular alignment is mitral straddling. The right atrium is normally aligned with the right ventricle; the left atrium is aligned partially with both ventricles. The ventriculoarterial alignment is double-outlet ventricle (right; see Figs. 105-14C and 105-15C).
- c. Segmental connections: the atrioventricular connection is two valves into separate ventricles with straddling of the mitral valve; the ventriculoarterial connection could be subaortic conus with fibrous continuity between the pulmonary valve and the straddling part of the mitral valve or bilateral subarterial conus.

The information conveyed by the situs, alignments, and connections is essential, but other important information must be supplied before a treatment plan can be formulated, including relation of the arterial roots to the ventricular septal defect (if one is present); presence, severity, and mechanism of outflow obstruction; and ventricular hypoplasia that might preclude a biventricular repair. Details of the mitral straddling are also important for surgical planning.

4. Anatomically corrected malposition of the great arteries

- a. Segmental situs: atrial situs solitus {S,_,_}; ventricular d-loop or situs solitus {_,D,_}; anatomically corrected malposition with the aorta to the left {_,_,L}. The cardiotype is {S,D,L}.
- b. Segmental alignments: the atrioventricular alignment is concordant. The right atrium is normally aligned with the right ventricle; the left atrium is normally aligned with the left ventricle. The ventriculoarterial alignment is concordant.

The left-sided aorta is aligned with the left-sided left ventricle, and the right-sided pulmonary artery is aligned with the right-sided right ventricle (see Figs. 105-14A and 105-15A).

- c. Segmental connections: the atrioventricular connection is two valves into separate ventricles; the ventriculoarterial connection is bilateral conus, although the subpulmonary conus is often deficient.

Anatomically corrected malposition {S,D,L} is the most frequent type. There is no alignment discordance here; therefore, ventricular septal defect closure might be all that is needed. This defect illustrates the difference between alignment and connection. Although the ventriculoarterial alignments are concordant (right ventricle–pulmonary artery and left ventricle–aorta), the connections are abnormal. There is typically a long subaortic conus or infundibulum connecting the aorta with the left ventricle and a deficient subpulmonary conus connecting the pulmonary artery with the right ventricle. Outflow obstruction can occur on either or both sides because of the abnormal conus or infundibulum.

There are types of anatomically corrected malposition with atrioventricular discordance (e.g., {S,L,D}). There is ventriculoarterial alignment concordance, because the right-sided left ventricle is aligned with the right-sided aorta and the left-sided right ventricle is aligned with the left-sided pulmonary artery, but the ventriculoarterial connections are abnormal as described previously. Here an atrial switch operation might be indicated to correct the segmental (atrioventricular) alignment discordance, but an arterial switch operation would not be so because there is already ventriculoarterial alignment concordance.

5. Isolated infundibuloarterial inversion

- a. Segmental situs: atrial situs solitus {S,_,_}; ventricular d-loop or situs solitus {_,D,_}; inverted normally related great arteries {_,_,I}. The cardiotype is {S,D,I}.
- b. Segmental alignment: the atrioventricular alignment is concordant; the ventriculoarterial alignment is concordant (see Figs. 105-14A and 105-15A). The posterior and leftward aorta is aligned with the left-sided left ventricle, and the anterior rightward pulmonary artery is aligned with the right-sided right ventricle.
- c. Segmental connections: the atrioventricular connection is two valves into separate ventricles; the ventriculoarterial connection is subpulmonary conus with aortic-mitral fibrous continuity.

This is an example of segmental situs discordance ({_,D,I}) with segmental alignment concordance. Although this anomaly can occur with an otherwise essentially normal heart, it is usually associated with subvalvar and valvar pulmonary stenosis. The conotruncus is similar to inverted tetralogy of Fallot.¹⁵ The patient is blue because of pulmonary outflow obstruction with

a right-to-left shunt through the ventricular septal defect rather than to an alignment discordance. The right coronary artery arises from the left-sided aorta and passes to the right AV groove in front of the obstructed pulmonary outflow, which can complicate treating this anomaly as one might treat tetralogy of Fallot.

SUMMARY

The segmental analysis provides a comprehensive understanding of the organization of the heart and the principal diagnoses. This type of analysis indicates whether cyanosis is due to alignment discordance or some other local problem (e.g., pulmonary atresia with atrial right-to-left shunt). If alignment discordance is part of the problem, segmental analysis also indicates the type of operation needed (e.g., atrial switch for isolated atrioventricular alignment discordance, arterial switch for isolated ventriculoarterial alignment discordance, double switch for both atrioventricular and ventriculoarterial [double] alignment discordance). Specific local diagnoses (e.g., additional muscular ventricular septal defect, subaortic stenosis, persistent ductus arteriosus) are then added to the context of the segmental analysis. It is useful to think of the heart segment by segment when establishing the comprehensive diagnosis—from veins, to atria, to atrioventricular valves, to ventricles, to outflow tracts, to great arteries—to avoid missing any component. Organizing the information segmentally in the diagnostic report not only helps to avoid oversight, it also lets the reader know where to find information about any specific part of the heart.

Acknowledgment

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DIAGNOSTIC IMAGING: ECHOCARDIOGRAPHY AND MAGNETIC RESONANCE IMAGING

Tal Geva

CHAPTER OUTLINE

ECHOCARDIOGRAPHY AND DOPPLER ULTRASOUND

Description of Technique

- M-Mode Echocardiography
- Two-Dimensional Echocardiography
- Three-Dimensional Echocardiography
- Doppler Echocardiography
- Speckle-Tracking Echocardiography
- Contrast Echocardiography

Objectives of the Echocardiographic Examination

- Examination Technique
- Anatomic Analysis

SPECIAL ECHOCARDIOGRAPHIC PROCEDURES

Transesophageal Echocardiography

- Indications and Objectives
- Safety and Complications

Fetal Echocardiography

- Indications and Objectives
- Description of Technique
- Clinical Implications
- Fetal Arrhythmia

QUANTITATIVE ANALYSIS

- Adjustment of Measurements to Body Size
- Ventricular Function
- Doppler Evaluation of Pressure Gradients
- Calculation of Pressure Gradients
- Safety and Complications

MAGNETIC RESONANCE IMAGING

- Magnetic Resonance Imaging Techniques
and Their Clinical Applications
- Cardiac and Respiratory Gating
- Anatomic Imaging and Tissue Characteristics
- Cine Magnetic Resonance Imaging
- Magnetic Resonance Imaging Assessment of
Ventricular Function
- Blood Flow Analysis
- Contrast-Enhanced Magnetic Resonance
Angiography
- Myocardial Ischemia and Viability
- Indications for Cardiovascular Magnetic
Resonance Imaging
- General Considerations
- Safety and Complications

SUMMARY

Before the advent of cardiopulmonary bypass in the mid-1950s, little attention was given to the diagnosis of congenital heart disease (CHD) because no effective treatment was available. Physical examination, auscultation, electrocardiography, and radiography were the main diagnostic tools. Progress in open-heart techniques for repair of CHD required accurate and comprehensive delineation of cardiovascular anatomy and function. During the 1960s and 1970s, cardiac catheterization and angiography were the principal tools used to diagnose CHD. Echocardiography entered the arena in the late 1970s. The diagnostic capability of M-mode echocardiography proved insufficient in patients with CHD, but the rapid evolution of two-dimensional

echocardiography during the following decade transformed the field. The technologic advances in transducer design, image processing, and image display—together with development and refinement of new imaging planes and examination techniques—allowed high-quality tomographic visualization of most cardiac defects.¹ The application of Doppler ultrasound to investigate blood flow allowed comprehensive hemodynamic assessment. By the mid-1980s, much of the necessary anatomic and hemodynamic information required for patient management could be obtained noninvasively, obviating the need for a diagnostic catheterization in many patients. During the late 1990s and into the 2000s, the field of pediatric cardiac imaging experienced accelerated progress in areas

such as three-dimensional echocardiography, sophisticated techniques for assessment of myocardial function, and the application of magnetic resonance imaging (MRI) to CHD. At the same time, the proportion of cardiac catheterization procedures performed solely for diagnostic purposes has drastically declined. More recently, the role of multimodality cardiac imaging for preintervention planning and for guidance of cardiovascular procedures has expanded dramatically.²

This chapter discusses the clinical application of the two main noninvasive diagnostic imaging modalities used for anatomic and physiologic evaluation of preoperative and postoperative CHD: echocardiography and cardiovascular MRI.

ECHOCARDIOGRAPHY AND DOPPLER ULTRASOUND

Echocardiography is an ideal diagnostic tool in pediatric cardiology because of its noninvasive nature, relatively low cost, superb spatial and temporal resolutions, and ability to image cardiovascular anatomy and to evaluate physiology in real time. In addition, modern cardiac ultrasound equipment is portable and adaptable to different environments, such as the operating room, intensive care unit, at the bedside, and in an outpatient office setting. In today's pediatric cardiology practice, echocardiography is the primary diagnostic modality used to evaluate anatomy and physiology preoperatively, intraoperatively, postoperatively, during follow-up of CHD, and prenatally.¹⁻³

Description of Technique

To obtain an echocardiographic image, a burst of ultrasound energy is generated by a piezoelectric crystal and travels through the soft tissue at an average speed of approximately 1540 m/sec. When the propagating ultrasound wave encounters an interface between tissues with different acoustic properties, some of the energy is reflected back toward the transducer and some of the energy is refracted and continues to travel in the medium until it encounters the next interface. The returning ultrasound energy is captured by the piezoelectric crystal and converted into an electrical energy that goes through a series of electronic processes, including amplification, filtering, postprocessing, and display.

M-Mode Echocardiography

A narrow beam of ultrasound energy is emitted toward the heart, and structures along the beam path reflect echoes back toward the transducer. A dot is displayed on the screen in a position corresponding to its distance from the transducer. This process is repeated rapidly to create an image. The distance from the transducer is displayed on the y-axis and time is displayed on the x-axis (Fig. 106-1). This provides an anatomic one-dimensional image of the heart that is characterized by excellent temporal and axial resolutions. In today's clinical pediatric echocardiography, two-dimensional imaging

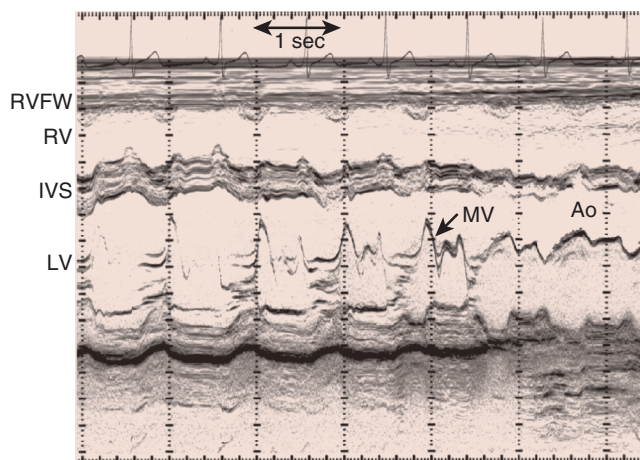


FIGURE 106-1 ■ M-mode tracing of the left ventricle and the aortic root. Ao, Aortic root; IVS, interventricular septum; LV, left ventricle; MV, mitral valve; RV, right ventricle; RVFW, right ventricular free wall.

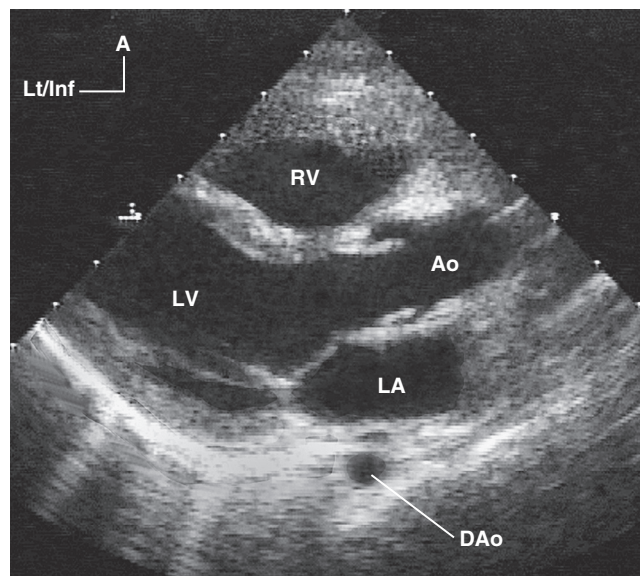


FIGURE 106-2 ■ Two-dimensional image from the parasternal long-axis view showing the left atrium (LA), left ventricle (LV), aortic root (Ao), descending aorta (DAo), and right ventricle (RV).

has replaced M-mode for anatomic imaging of the heart and for assessment of ventricular size and function.⁴ In selected circumstances, when superior temporal resolution is required, two-dimensional directed M-mode is used to assess motion of specific structures such as native and prosthetic valve leaflets.

Two-Dimensional Echocardiography

By rapidly sweeping an ultrasound beam through an arc, multiple “M-mode lines” are placed next to each other to construct a cross-sectional two-dimensional image of the heart (Fig. 106-2). This can be accomplished by electronically sweeping the sound beam through multiple

piezoelectric crystals (transducer elements), as in phased array transducers. Recent advances in transducer technology and image processing permit very high frame rates (>200 Hz), a feature that greatly enhances temporal resolution.⁵

Three-Dimensional Echocardiography

Accurate spatial perception of an object depends on recognition of its three dimensions: length, width, and depth. Although an experienced examiner can mentally construct a three-dimensional image of the heart from serial two-dimensional tomographic images obtained by sweeping the transducer across the heart, three-dimensional echocardiography offers enhanced perspective of cardiovascular structures and their interrelations. Previous approaches to obtaining three-dimensional echocardiographic images of the heart were based on computer reconstruction of contiguous two-dimensional cross-sectional images. These efforts were hampered by difficulties in accurately registering the ultrasound image data in time and space and by long processing times. Currently, three-dimensional images are generated by real-time three-dimensional echocardiography. This technology, which is based on a new generation of matrix array transducers with several thousands of simultaneously transmitting and receiving piezoelectric elements and sophisticated parallel data processing, provides real-time three-dimensional images with sufficient temporal resolution to display in cine-loop format (Fig. 106-3).⁶⁻⁸ More recently, miniaturization of matrix array transducer technology has allowed development of a real-time three-dimensional transesophageal echocardiographic probe.⁹ Further refinements of this technology will result in continued improvement of spatial and temporal resolutions as well as better, more intuitive, user interface. Such

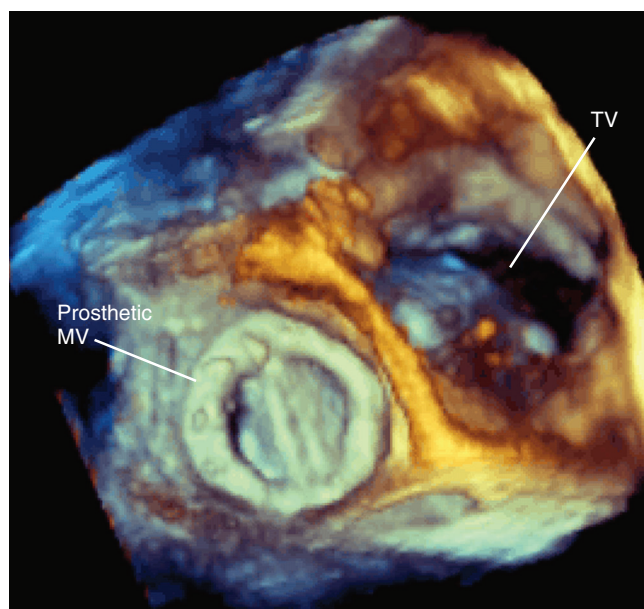


FIGURE 106-3 ■ Three-dimensional echocardiographic imaging of a prosthetic mitral valve (MV) seen from the atria. TV, Tricuspid valve.

advances will likely contribute to the ongoing acceptance of this technology in routine practice.

Doppler Echocardiography

The use of Doppler ultrasound to assess normal and abnormal hemodynamics has become an integral part of the echocardiographic examination.^{4,10} The advent of two-dimensional directed Doppler interrogation has greatly enhanced the clinical application of this technique by allowing evaluation of flow characteristics in specific regions within the heart and great vessels. In today's echocardiography, spectral and color-coded Doppler flow mapping are used extensively to measure velocity and direction of blood flow (Fig. 106-4). Calculations based on Doppler-derived measurements allow quantitative estimation of flow volume (such as cardiac output), pressure gradient across a stenotic region, cross-sectional flow area, and prediction of intracardiac pressures. Doppler echocardiography also provides qualitative and semiquantitative assessment of valve regurgitation, intra- and extracardiac shunts, as well as myocardial motion (tissue Doppler imaging). Detailed discussion of Doppler physics is beyond the scope of this text and can be found elsewhere.¹¹

Speckle-Tracking Echocardiography

Speckle-tracking echocardiography (STE) is an echocardiographic technique that allows depiction and measurements of myocardial motion and function. The technique is based on frame-to-frame analysis of changes in the unique ultrasonic backscatter features (speckles) of sequential two-dimensional images while filtering out noise. STE displays local displacement of the myocardium that can be then analyzed for indices of myocardial deformation such as strain and strain rate, in any direction within the two-dimensional image (Fig. 106-5).¹² The technique, which was introduced in 2004,¹³ has been validated in an animal model against sonomicrometry and in vivo against cardiac MRI tagging.^{14,15} Advantages of STE over Doppler-based techniques for assessment of tissue motion include independence of angle of interrogation and insensitivity to tethering of the myocardium. More recently, three-dimensional STE has been developed and validated.¹⁶ A review of the use of STE in CHD can be found elsewhere.¹⁷

Contrast Echocardiography

As early as the late 1960s, Gramiak and colleagues¹⁸ noted that intravascular injection of almost any solution resulted in a contrast effect detectable by echocardiography. Initially, this technique was used to identify structures seen by M-mode echocardiography. Contrast echocardiography has been used to detect systemic¹⁹ and pulmonary venous anomalies,²⁰ and for the detection of intracardiac and great artery level shunts.²¹ In today's pediatric echocardiography, contrast studies are infrequently performed and are usually limited to detection of intracardiac shunts in patients with limited echocardiographic windows, patch or baffle leak after cardiac surgery, and in pulmonary arteriovenous malformations.³

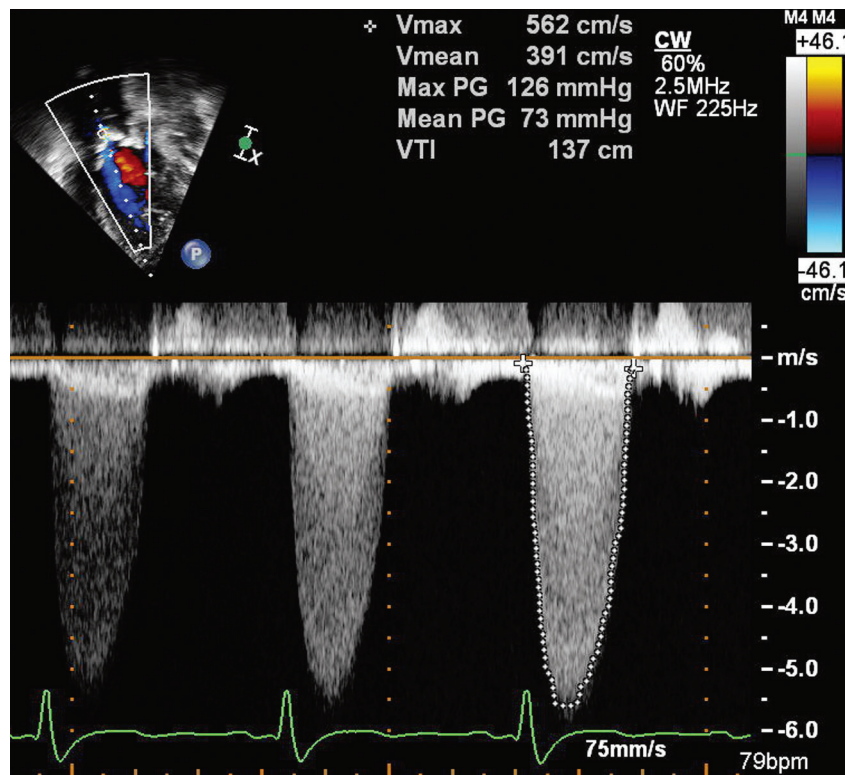


FIGURE 106-4 ■ Doppler echocardiography. Visualization of a high-velocity jet by color Doppler aids in aligning the continuous wave Doppler cursor in a patient with severe aortic valve stenosis (maximal instantaneous and mean gradients $\approx$ 126 and 73 mm Hg, respectively).

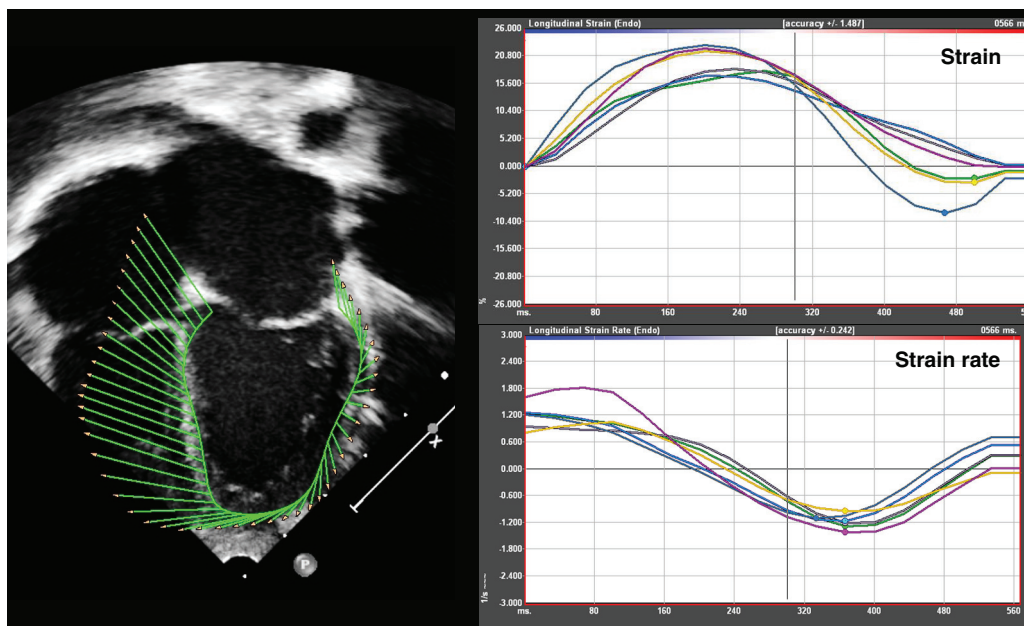


FIGURE 106-5 ■ Speckle-tracking echocardiography. Left panel: Apical four-chamber view with velocity vector mapping of the left ventricle. Right upper panel: Longitudinal strain versus time curves in six segments of the left ventricular wall. Right lower panel: Longitudinal strain rate versus time curves in the same segments.

Objectives of the Echocardiographic Examination

The objectives of the echocardiographic examination must be tailored to the individual patient. The initial

evaluation should include a comprehensive survey of all anatomic elements of the central cardiovascular system.¹⁰ Subsequent examinations are often targeted to answer specific clinical questions. It is important, however, to repeat complete echocardiograms during follow-up, even

in patients who underwent a comprehensive initial examination, because of the dynamic nature of CHD. Examples include the late onset of discrete subaortic stenosis in patients with ventricular septal defect and/or coarctation of the aorta,²² double-chambered right ventricle,²³ and supramitral stenosing ring.²⁴

Examination Technique

Proper planning of the echocardiographic examination is important to ensure that all diagnostic information is obtained most efficiently. This is particularly relevant in sedated patients in whom the time available for data acquisition is limited. Ideally, a complete segmental examination of cardiovascular anatomy and function should be performed in every new patient. This includes determination of visceral situs, heart position, atrial situs, systemic and pulmonary venous connections, ventricular situs, atrioventricular and ventriculoarterial alignments and connections, and coronary and great arterial anatomy. Assessment of ventricular function, intracardiac and vessel dimensions, and flow analysis across all valves, septa, chambers, and vessels are integral parts of the examination. Echocardiographic techniques include two-dimensional and three-dimensional imaging, blood flow imaging by color Doppler, measurements of flow velocities by pulsed and continuous wave Doppler, and assessment of myocardial function by tissue Doppler or STE. In young children with suspected heart disease, the examination begins from the subxiphoid approach by determining the abdominal situs and then proceeding by scanning the heart and great vessels, using a step-by-step segmental analysis (Fig. 106-6*A* and *B*).^{10,25,26} This approach is advantageous because it provides a wide-angle view of heart position and cardiovascular anatomy and function at an early stage in the examination. Subsequent two-dimensional and Doppler analyses from the apical, parasternal, and suprasternal notch views supplement and confirm findings from the subxiphoid window (see Fig. 106-6*C-G*). The examination strategy should be tailored to the individual patient and modified according to the clinical situation as necessary. Although the standard views just described should be obtained in almost every patient and represent the minimum acceptable examination, flexibility and improvisation are important to optimally use the full potential of echocardiography.

Anatomic Analysis

When performing and reviewing an echocardiographic examination in a patient suspected of having CHD, a stepwise segmental approach to analysis of cardiac anatomy is taken. Each component of the heart is analyzed separately according to its unique morphologic features.^{25,26} The heart is composed of five segments—three main segments and two connecting segments. The three main segments are the atria, the ventricles, and the great arteries. The atrioventricular canal, which includes the mitral and tricuspid valves and the atrioventricular septum, connects the atria with the ventricles. The infundibulum (or conus) connects the ventricles with the great arteries. When analyzing cardiac anatomy, each cardiac

chamber must be identified individually according to its unique anatomic-morphologic features and not according to its spatial position (right-sided or left-sided), valve of entry, or artery of exit. Throughout a systematic echocardiographic study, the examiner must go over a mental checklist of segments, their anatomic organization and position (situs), their connections and alignments with adjacent segments, and associated malformations. Using the aforementioned principles, any potential CHD can be accurately described in specific and precise terms. A detailed review of echocardiographic analysis of each cardiac segment can be found elsewhere.^{10,25}

SPECIAL ECHOCARDIOGRAPHIC PROCEDURES

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) was first introduced in 1976 and appeared in pediatric use in 1989. The miniaturization of probes and development of multiplanar imaging have greatly increased its role as an adjunct to transthoracic imaging, during surgical repair of CHD (intraoperative TEE), and to guide interventional catheterization procedures. Advances in transducer technology and image processing now allow real-time three-dimensional TEE.⁹

Indications and Objectives

A TEE examination is usually performed to answer specific clinical questions. It is advisable, however, to perform a comprehensive examination of the heart and blood vessels for additional unsuspected anatomic and/or hemodynamic anomalies (Fig. 106-7).²⁷ Miniaturization of TEE probes designed for use in young infants weighing 3 to 3.5 kg or less has greatly enhanced the scope of TEE in the pediatric age group.²⁸⁻³¹ Successful TEE examinations have been reported in patients weighing as little as 2.3 kg.^{32,33} The role of TEE in pediatric cardiology is continuously evolving. Although the transthoracic window is adequate in most situations, TEE provides distinct advantages during cardiovascular surgery,^{28,30,33} during video-assisted thoracoscopic procedures,³⁴ for guidance of interventional catheter procedures,^{35,36} in the intensive care unit,^{28,37} for detection of intracardiac thrombi and vegetations,³⁸ in the assessment of prosthetic valves,³⁹ in selected patients on mechanical assist device and extracorporeal membrane oxygenator,⁴⁰ and in selected patients with poor transthoracic windows, such as adults with CHD.⁴¹ The usefulness of selective versus routine use of intraoperative TEE in patients with CHD deserves further study.^{27,42}

Safety and Complications

Although in expert hands TEE is quite safe, complications have been reported, including oropharyngeal trauma and compression of airways and vascular structures.^{43,44} TEE is contraindicated in patients with an unrepaired tracheoesophageal fistula, esophageal

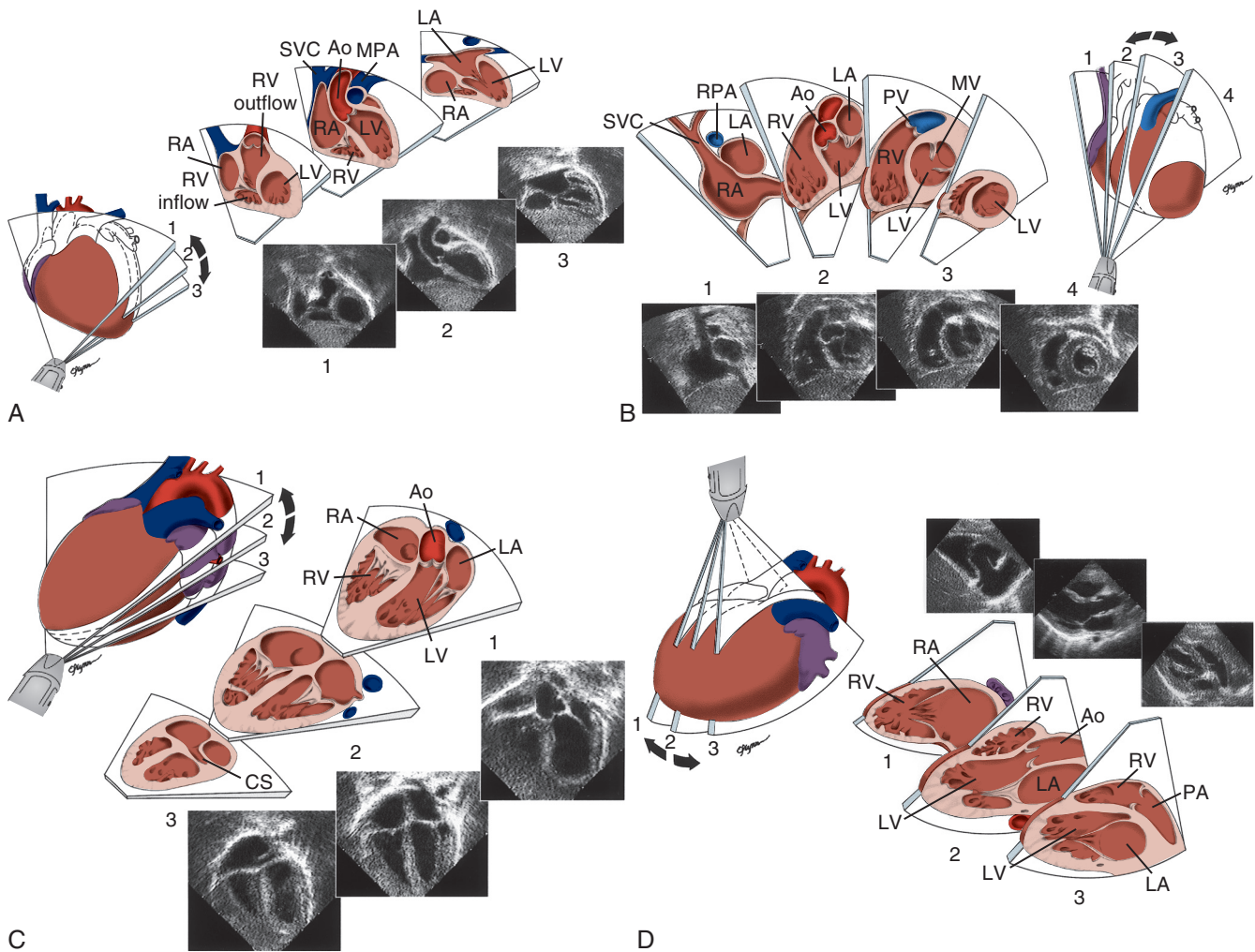


FIGURE 106-6 ■ Standard two-dimensional transthoracic imaging sweeps. **A**, Subxiphoid long-axis sweep. Slow gradual sweep starting at the level of the upper abdomen will show the connection of the inferior vena cava to the right atrium (RA). The left atrium (LA) is seen next. The connection of the pulmonary veins and the atrial septum can be demonstrated from this view. The left ventricle (LV) is seen along its long axis. Further superior angulation of the transducer depicts the left ventricular outflow tract, aortic valve, and ascending aorta (Ao). The superior vena cava (SVC) is seen to the right of the Ao and the main pulmonary artery (MPA) is seen to the left of the aorta. Further superior tilt of the transducer shows the inflow and outflow of the right ventricle (RV) and the pulmonary valve. The sweep ends with anterior free wall of the right ventricle. **B**, Subxiphoid short-axis sweep. From the subxiphoid long-axis view, the transducer is rotated clockwise approximately 90 degrees. The sweep begins at the rightward-most aspect of the heart and progresses from right to left through the cardiac apex. The superior vena cava (SVC) and inferior vena cava are seen entering the right atrium (RA). The right pulmonary artery (RPA) is seen in cross-section behind the SVC and above the left atrium (LA). The atrial septum is well seen in this plane. Sweeping the transducer leftward will show the base of the left ventricle (LV) and right ventricle (RV) and the atrioventricular valves. The aortic valve is seen in cross-section at this level. Further leftward tilt of the transducer depicts a cross-sectional view of the LV and mitral valve (MV) as well as the right ventricular outflow tract and pulmonary valve (PV). The sweep ends with imaging of the mid-muscular septum, the papillary muscles, and the apical portions of both ventricles. **C**, Apical four-chamber sweep. The transducer is positioned over the apex and angled to obtain a cross-sectional view of the atria and ventricles as shown in level 2. The transducer is then angled posteriorly to image the posterior aspect of the heart (level 3). In this plane, the coronary sinus (CS) can be viewed along the posterior left atrioventricular groove. Antero-superior tilt of the transducer will show the left ventricular outflow tract and proximal ascending aorta (Ao). **D**, Parasternal long-axis sweep. The transducer is placed over the left precordium to the left of the sternum with the index mark toward the patient's right shoulder. A rightward and inferior tilt of the transducer toward the right hip shows the right atrium (RA), tricuspid valve, and right ventricular inflow (RV) (level 1). The coronary sinus can be followed into the right atrium in this view. A leftward and superior tilt of the transducer toward the left shoulder depicts the right ventricular outflow tract (RV), pulmonary valve, and main pulmonary artery (PA) (level 3).

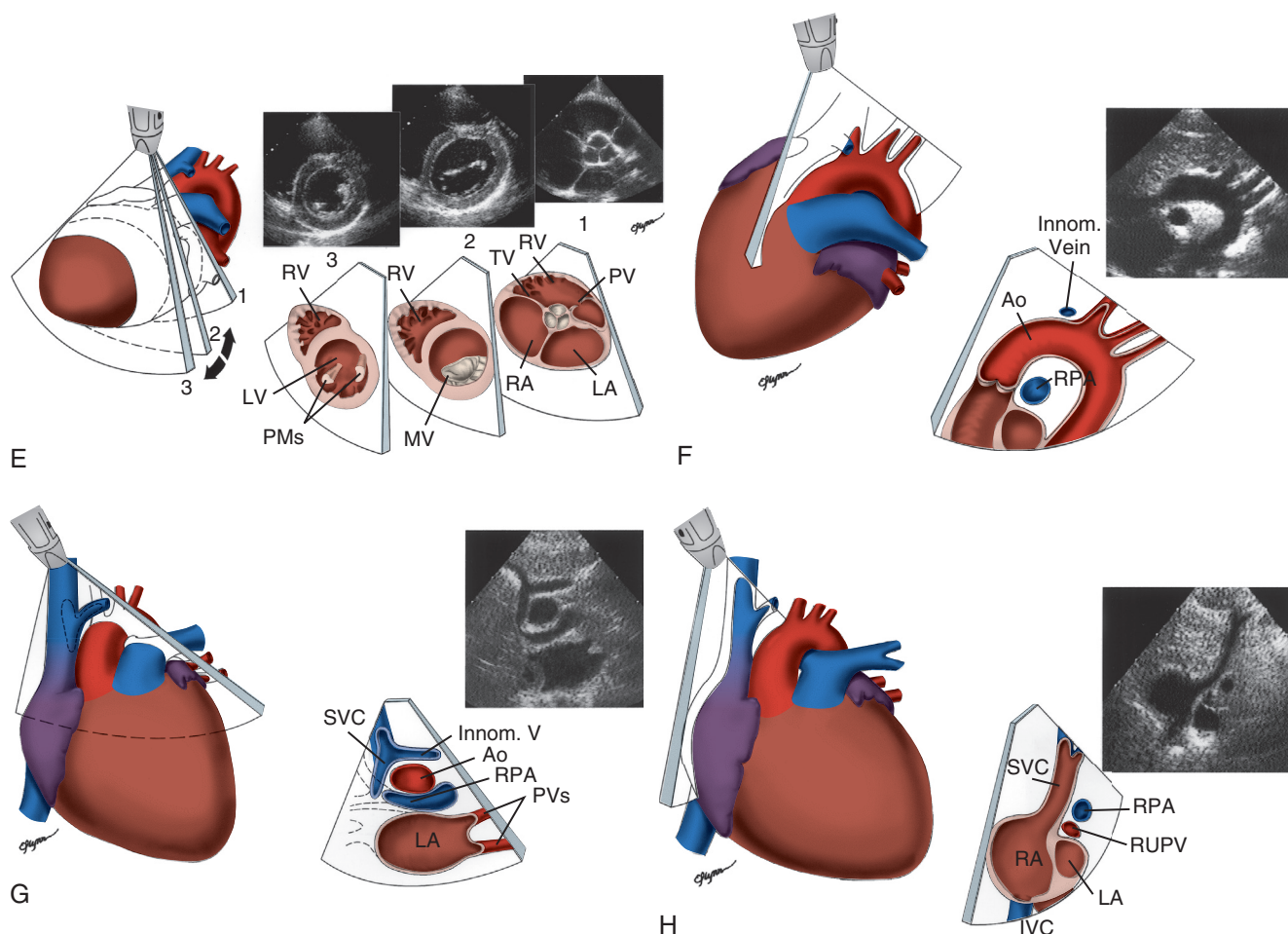


FIGURE 106-6, cont'd ■ **E**, Parasternal short-axis sweep. From the parasternal long-axis view, the transducer is rotated clockwise approximately 90 degrees. The sweep progresses from a plane that shows the right and left atria (RA and LA), atrial septum, tricuspid valve (TV), right ventricle (RV), pulmonary valve (PV), and main pulmonary artery (level 1) toward the apex. Cross-sectional views of the right ventricle (RV), left ventricle (LV), ventricular septum, mitral valve (MV), and papillary muscles (PMs) are obtained. **F**, Aortic arch view from the suprasternal notch window. The innominate vein (Innom. Vein) is seen anterior to the innominate artery. The right pulmonary artery (RPA) is seen in cross-section behind the ascending aorta. **G**, Suprasternal notch view in the transverse plane. The left innominate vein (Innom. V) is seen draining into the superior vena cava (SVC). The distal ascending aorta (Ao) is seen superior to the right pulmonary artery (RPA), which is seen along its length above the left atrium (LA). Note the pulmonary veins entering the left atrium. **H**, High right parasternal view in the sagittal plane view showing the superior vena cava (SVC) entering the right atrium (RA). This view allows demonstration of the sinus venosus septum. IVC, Inferior vena cava; RUPV, right upper pulmonary vein.

obstruction or stricture, perforated viscus, or active gastrointestinal bleeding; in an unwilling or uncooperative patient who is inadequately sedated; or with an uncontrolled airway in a patient with respiratory or cardiac decompensation. Relative contraindications include cervical spine injury, immobility, or deformity; history of esophageal surgery; known esophageal varices or diverticulum; oropharyngeal deformities; and severe coagulopathy.^{27,45,46}

Fetal Echocardiography

Examination of the human fetal cardiovascular system dates back to the late 1960s when continuous wave Doppler was used to record fetal heart rate. Although Kleinman and coworkers⁴⁷ in the late 1970s had some success in detecting CHD in the fetus by M-mode echocardiography, it was not until high-resolution two-dimensional imaging became available in the mid-1980s

that accurate delineation of cardiovascular anatomy became clinically routine. Today, prenatal detection of CHD can be reliably diagnosed by 17 to 20 weeks of gestation by transabdominal imaging. Using the transvaginal window, the heart and great vessels can be imaged as early as late first trimester.⁴⁸

Indications and Objectives

Although several studies have demonstrated a low detection rate of CHD by routine level I obstetric ultrasound,⁴⁹ cost-benefit considerations preclude universal fetal echocardiographic screening by expert pediatric echocardiographers. Alternatively, an approach based on targeting pregnancies that are at high risk for CHD is taken. Such an approach increases the yield of fetal echocardiography to approximately 30% when extracardiac anomalies are detected, to approximately 60% when level I scan detects possible CHD, and to almost 100% when a second

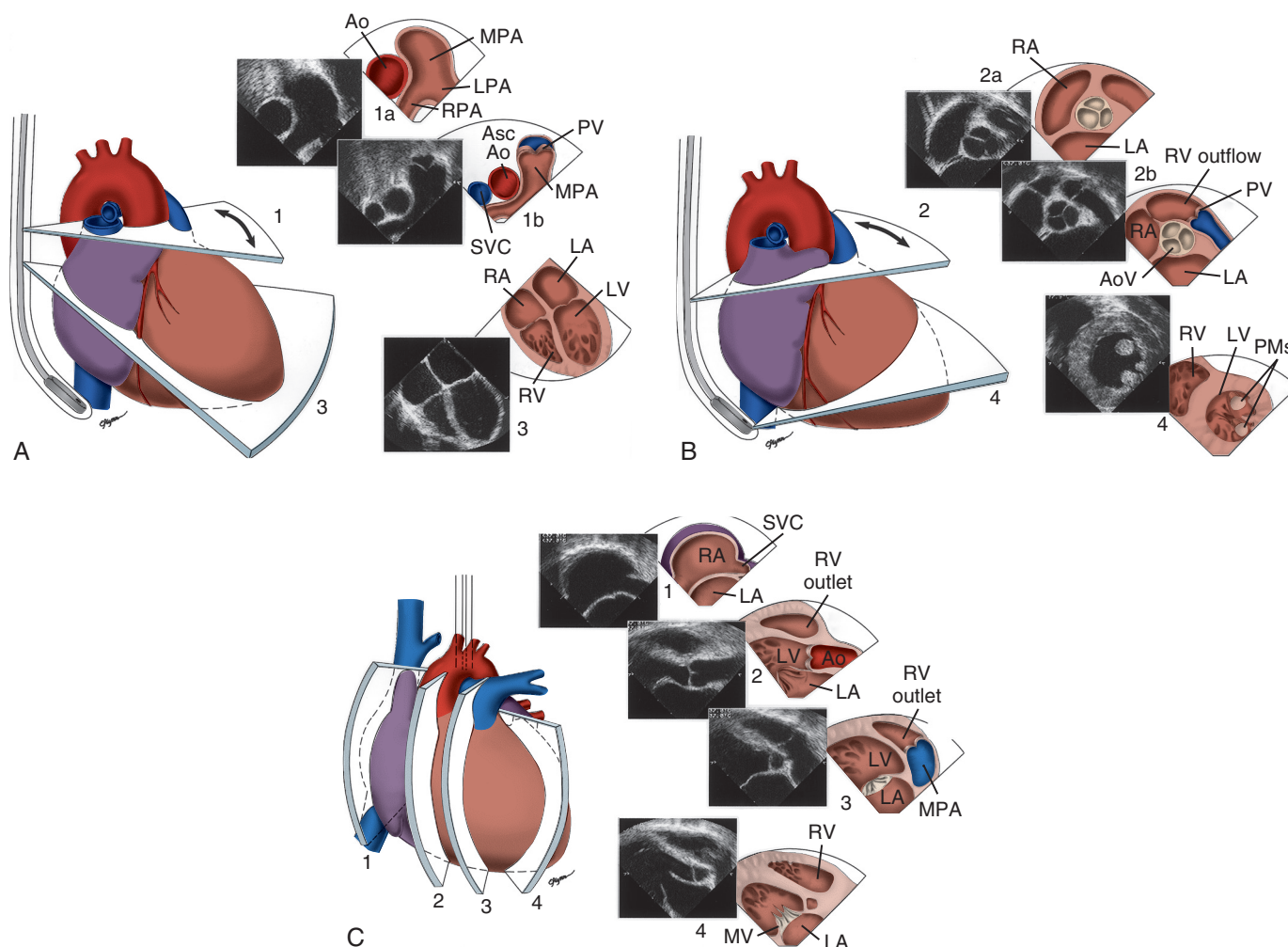


FIGURE 106-7 ■ Transesophageal imaging. **A**, Transverse plane: cross-sectional view at level 1a depicts the proximal ascending aorta (Ao), main pulmonary artery (MPA), and left and right pulmonary arteries (LPA and RPA, respectively). A rightward tilt of the transducer shows the RPA as it passes behind the superior vena cava (SVC) and ascending aorta (Asc Ao). To obtain a four-chamber view (level 3), the transducer is advanced in the esophagus with slight retroflexion of the scope. **B**, Level 2 is parallel to the transthoracic parasternal short-axis view. In level 2a, the atrial septum is imaged by a slight rightward tilt of the transducer. In level 2b, the aortic valve (AoV) is seen in cross-section in the center of the image, and the left atrium (LA), right atrium (RA), tricuspid valve, right ventricular outflow (RV outflow), pulmonary valve (PV), and the proximal main pulmonary artery are seen. By advancing the transducer into the lower esophagus and antelexing the scope, a cross-sectional view of the left ventricle (LV), mitral valve, and papillary muscles (PMs) is obtained (level 4). Note that image orientation is the same as in transthoracic echocardiography. **C**, Vertical (longitudinal) plane: the sweep begins at a plane that crosses the superior vena cava (SVC), left atrium (LA), right atrium (RA), and atrial septum (level 1). Next, a leftward tilt of the transducer shows an image parallel to the transthoracic parasternal long-axis view of the left atrium (LA), mitral valve, left ventricle (LV), left ventricular outflow tract, and proximal aorta (Ao) (level 2). Further leftward tilt of the transducer (level 3) shows the right ventricular outflow tract (RV outlet), pulmonary valve, and main pulmonary artery (MPA). The sweep continues leftward to show the leftward aspects of the left atrium, mitral valve, and left ventricle (level 4). Further leftward tilt depicts the left atrial appendage and the left pulmonary veins (not shown). Note that image orientation is the same as in transthoracic echocardiography. *MV*, Mitral valve.

opinion is requested.^{50,51} The indications for fetal echocardiography are summarized in [Box 106-1](#).

Description of Technique

Echocardiographic examination of the cardiovascular system in the fetus is based on the same principles of the segmental approach to diagnosis of CHD that is applied after birth. The main difference between examination of the fetus and the newborn is that the operator has no control over fetal position and, consequently, over the views obtained. Once fetal position is ascertained and the

spatial coordinates are determined, the examination then continues according to the principles outlined in the previous sections. Given optimal acoustic windows and favorable fetal position, even the most complex cardiovascular anomalies can be detected ([Fig. 106-8](#)).⁵² Defects that remain difficult to diagnose in utero include secundum atrial septal defect, patent ductus arteriosus, small or moderate ventricular septal defect, coarctation of the aorta, and some valve and great vessel abnormalities.⁵³ Distinguishing between normal patency of the foramen ovale and an atrial septal defect is usually not possible in the fetus. Similarly, it is not possible to predict whether

BOX 106-1 Indications for Fetal Echocardiography

FETAL RISK FACTORS

- Extracardiac structural anomalies
- Chromosomal abnormalities
- Fetal dysrhythmias
- Intrauterine growth retardation
- Nonimmune hydrops fetalis
- Multiple gestation and suspicion of twin-twin transfusion syndrome
- Suspected cardiac anomaly on level I scan
- Abnormal visceral situs

MATERNAL RISK FACTORS

- Congenital heart disease
- Exposure to teratogen (sample list only)
 - Lithium carbonate
 - Amphetamines
 - Alcohol
 - Anticonvulsants
 - Phenytoin
 - Trimethadione
 - Isotretinoin
- Exposure to prostaglandin synthetase inhibitors (e.g., ibuprofen, salicylic acid, indomethacin)
- Maternal autoimmune disease
- Maternal diabetes
- Phenylketonuria
- Maternal infection
 - Rubella
 - Toxoplasmosis
 - Coxsackie virus
 - Cytomegalovirus
 - Mumps virus
- In vitro fertilization

FAMILIAL RISK FACTORS

- Congenital heart disease
- Syndromes
 - Down
 - Marfan
 - Noonan
 - Tuberous sclerosis
 - Velocardiofacial
- Familial inherited disorders (e.g., Ellis van Creveld, Marfan, Noonan, etc.)

Modified from Kleinman C: *Fetal echocardiography: diagnosing congenital heart disease in the human fetus. ACC Educational Highlights Summer:10–14, 1996; and Rychik J, Ayres N, Cuneo B, et al: American Society of Echocardiography guidelines and standards for performance of the fetal echocardiogram. J Am Soc Echocardiogr 17:803–810, 2004.*

the normally patent ductus arteriosus will close after birth. In utero diagnosis of aortic coarctation may be difficult because the typical isthmic narrowing may not become apparent until after ductal closure.⁵³ However, the diagnosis may be suspected based on abnormal morphology of the transverse aortic arch (elongation and hypoplasia), size discrepancy between the diameters of the aortic isthmus and patent ductus arteriosus, continuous flow profile in the aortic isthmus, and size discrepancy between the ventricles (right ventricle is larger than left ventricle).^{54,55}

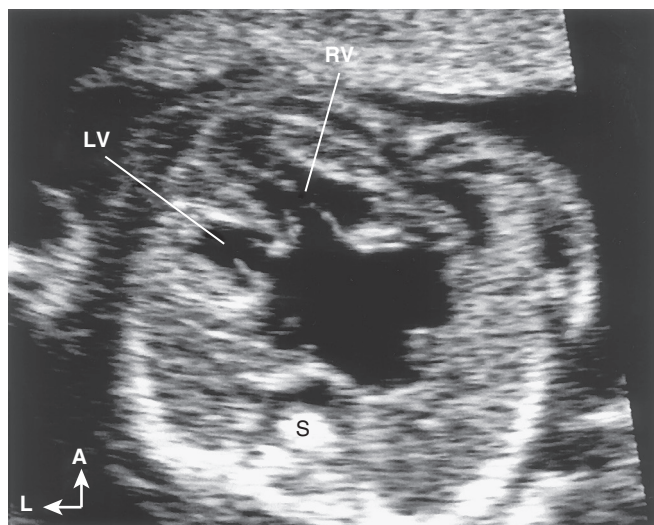


FIGURE 106-8 ■ Fetal echocardiogram in a 24-week-old fetus with a partial common atrioventricular (AV) canal as seen from a four-chamber view. The large deficiency of the atrial septum and apical displacement of the AV valve are clearly seen. A, Anterior; L, left; LV, left ventricle; RV, right ventricle; S, spine.

Clinical Implications

Early prenatal diagnosis of major CHD allows parents to consider the option of terminating the pregnancy. It is also common to recommend amniocentesis to detect associated genetic abnormalities. When pregnancy continues, prenatal diagnosis of CHD allows proper planning for postnatal cardiac care. When intervention is anticipated immediately or shortly after birth (e.g., ductal-dependent anomalies or balloon atrial septostomy in transposition of the great arteries), delivery in a pediatric cardiac center is arranged. The currently available literature provides conflicting views on whether prenatal diagnosis of CHD leads to a significant reduction in mortality.^{56,57} However, there is evidence it can reduce morbidity in certain lesions.⁵⁶ Other advantages, such as psychologic benefits to the parents are also valuable.⁵⁸

Fetal Arrhythmia

One of the major reasons for referral to fetal echocardiography is arrhythmia. Most commonly, irregular fetal heart rate is caused by either conducted or blocked premature atrial contractions. These are usually benign and require follow-up only if they are frequent or associated with supraventricular tachycardia. Among the serious arrhythmias encountered in the fetus, supraventricular tachycardia and atrial flutter are the most common.⁵⁰ Premature ventricular contractions and ventricular tachycardia are rare in the fetus but both have been reported.⁵⁰ Transplacental pharmacologic therapy is indicated in fetuses with incessant tachyarrhythmia, especially if signs of heart failure (e.g., enlargement of cardiac chambers, pericardial effusion and hydrops fetalis) are present. Complete heart block is the most common cause of prolonged bradycardia in the fetus.⁵⁹ The distinction between complete heart block and sinus bradycardia is important because the latter might indicate fetal distress. In fetuses with a structurally

normal heart, maternal lupus erythematosus should be suspected. The most common structural CHD associated with complete heart block are L-loop physiologically “corrected” transposition of the great arteries and heterotaxy syndrome with polysplenia.

Fetal arrhythmias have been traditionally diagnosed by Doppler and M-mode echocardiography.⁵⁰ Both methods rely on simultaneous recording of signals from the atria and ventricles. Fetal position, however, may not always allow optimal alignment of the M-mode cursor or the Doppler beam. Newer methods, tissue Doppler imaging and STE, provide a promising alternative to standard M-mode and Doppler echocardiography.⁶⁰

QUANTITATIVE ANALYSIS

Modern echocardiography allows accurate measurements of cardiovascular structures.⁴ These measurements are helpful in deciding whether the size of a certain structure is within normal limits and in quantifying the degree of deviation from the expected norm.

Adjustment of Measurements to Body Size

Measurements of linear dimensions (such as vessel diameter), cross-sectional areas (such as valve area), or volumetric dimensions (such as ventricular volume or mass) provide important quantitative information that can be used to assess the severity of disease process and to predict its course and prognosis. Because the pediatric age group encompasses a wide range of body sizes and because the heart and great vessels grow considerably from birth to adulthood, measured dimensions must be adjusted to allow meaningful comparisons between patients of different age and body size.⁶¹ For example, the mean value of the aortic valve annulus diameter is 0.74 cm in a 3.6-kg newborn (body surface area 0.24 m²) and 1.95 cm in a 60-kg adolescent (body surface area 1.66 m²). Indexing the aortic annulus diameter to body weight yields vastly different values (0.21 cm/kg in the newborn versus 0.032 cm/kg in the adolescent). Indexing the aortic valve diameter to the body surface area yields similarly unsatisfactory results (3.1 cm/m² in the newborn versus 1.17 cm/m² in the adolescent). Tanner⁶² in 1949 and, more recently, Gutgesell and Rembold⁶³ and Sluysmans and Colan⁶¹ noted that the growth of cardiac structures is not necessarily a linear function of the body surface area, the weight, the height, or the age. These findings are to be expected because the heart and great vessels grow much faster during the first 2 to 4 years of life compared with later childhood and adolescence. It was found that linear dimensions (such as diameters of valves and great vessels) should be indexed to the square root of the body surface area.⁶¹⁻⁶³ Returning to the preceding example of the aortic valve diameter, indexing the valve diameter to the square root of the body surface area yields 0.74/0.49 = 1.51 cm/m^{0.5} in the 3.6-kg newborn and 1.95/1.29 = 1.51 cm/m^{0.5} in the 60-kg adolescent (Fig. 106-9). Cross-sectional measurements (such as valve area) should be indexed to the body surface area.⁶³ Left ventricular volume should be indexed to the body surface

area raised to the power 1.28, and left ventricular mass should be indexed to the body surface area raised to the power 1.23.⁶¹

An alternative approach to comparing measurements between individuals is the use of z-scores.¹ The z-score is a statistical expression of the position of a data point relative to the regression line of a data set. The z-score is expressed as the number of standard deviations from the expected mean of a normal population. It is calculated as follows:

$$z\text{-score} = \frac{\text{measured value} - \text{mean value of normal population}}{\text{standard deviation of normal population}}$$

Returning to the preceding example of aortic valve diameter, the z-value of a 0.74-cm aortic valve diameter in a newborn with a body surface area of 0.24 m² is 0. That means that 0.74 cm is the mean value of aortic valve diameter in infants with that body size. In the adolescent with a body surface area of 1.66 m², the z-value of an aortic valve diameter of 1.95 cm is also 0. In other words, the same z-scores in the newborn and the adolescent indicate that both values are in the same position relative to the regression line of normal values and are comparable. An aortic valve diameter of 0.53 cm in the newborn would have a z-score of -2.0, which indicates that this value is 2 standard deviations below the expected mean. An aortic valve diameter of 0.96 cm in the same newborn would have a z-score of +2.0, which indicates that this value is 2 standard deviations above the mean. Thus, expression of measurements as z-values allows comparison between patients, regardless of differences in body size.

Estimation of left ventricular volume is an important factor in determining the adequacy of chamber size in patients with left ventricular hypoplasia and in the evaluation of patients with volume overload. Numerous algorithms based on several geometric models have been developed for calculation of left ventricular volume. These have been reviewed in detail elsewhere.^{1,3} The biplane Simpson rule is a popular method for estimation of left ventricular volume because of its simplicity. This method requires imaging of the left ventricle from two orthogonal views that share a common long axis: for example, the apical four- and two-chamber views (Fig. 106-10A). Left ventricular volume is calculated according to the following equation:

$$V = \frac{\pi}{4} \times \sum_{i=1}^N a_i \times b_i \times \frac{L}{N},$$

where a_i is the slice radius in the apical two-chamber view, b_i is the slice radius in the apical four-chamber view, L is the left ventricular length, N is the number of slices, and V is the volume.

Another method for estimation of left ventricular volume is the biplane area-length method, where $V = 5/6 \times \text{area} \times \text{length}$ (see Fig. 106-10B). Experience with assessment of left and right ventricular volumes by three-dimensional echocardiography suggests that this technique is more accurate and reproducible than

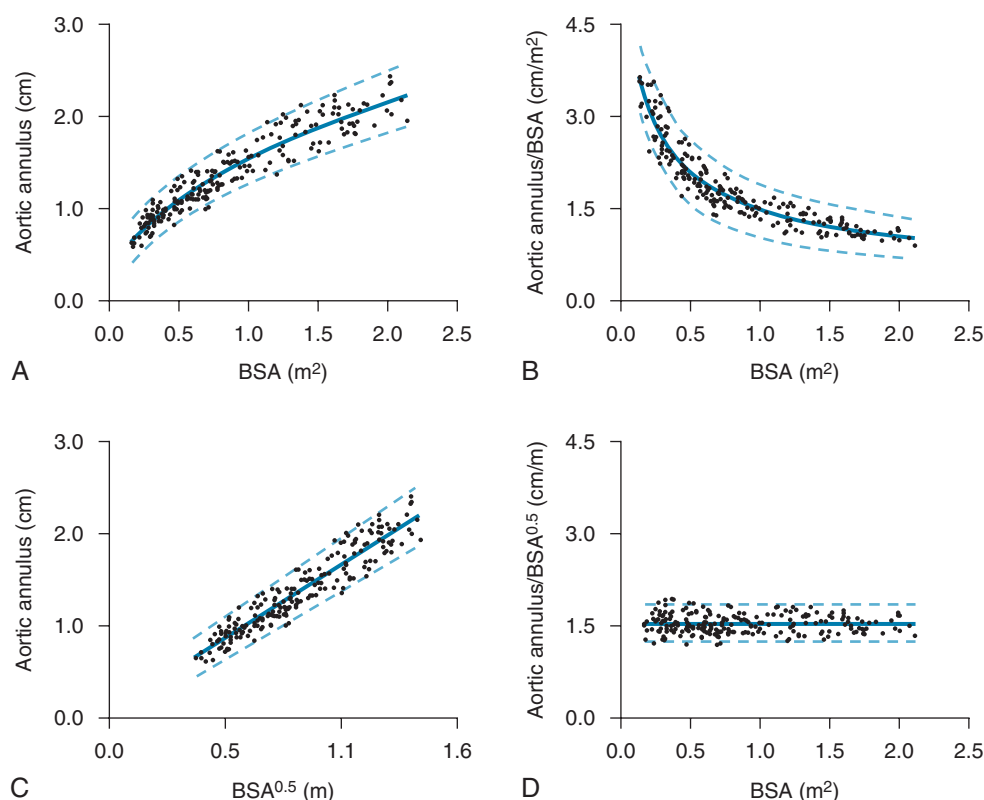


FIGURE 106-9 ■ Rationale for indexing linear measurements to the square root of body surface area (BSA). **A**, Plot of aortic valve annulus diameter against BSA showing a nonlinear curve. **B**, Plot of aortic valve annulus diameter indexed to BSA against BSA shows that the indexed diameter decreases exponentially as BSA increases. **C**, Aortic valve annulus diameter plotted against the square root of BSA showing a linear relationship. **D**, Plot of aortic valve diameter indexed to the square root of BSA against BSA showing that the indexed aortic valve diameter is the same in children and adults with widely varying body size.

two-dimensional techniques.^{8,64-68} Therefore, it is reasonable to expect that within several years three-dimensional echocardiography will replace two-dimensional methods for measurements of left and right ventricular volumes. Left ventricular myocardial volume can be measured from the two-dimensional echocardiogram by subtracting the endocardial volume from the epicardial volume. Left ventricular mass is calculated by multiplying the resultant myocardial volume by the density of muscle (1.055 g/mL). Because it is not influenced by acoustic windows and is independent of chamber geometry, MRI provides an excellent alternative to echocardiography in measuring chamber volume and mass and is considered the reference standard to which other techniques are compared (see Magnetic Resonance Imaging section, later).

Ventricular Function

Left ventricular function can be assessed at several levels. The heart may be viewed as a pump designed to maintain adequate flow to vital organs.⁶⁹ This approach focuses on the external work performed by the heart, but it ignores the internal work and the functional state of the myocardium. Measuring cardiac output and systemic and pulmonary venous blood pressures can assess the pump function of the heart. It is known, however, that cardiac output and blood pressure can remain within the normal limits despite significant myocardial dysfunction.⁶⁹

Ejection-phase indices of ventricular function, including shortening fraction, fractional area change, ejection fraction, velocity of circumferential fiber shortening (VCF), peak dP/dt, and systolic time intervals, measure global pump function.^{1,4,69} Common to these indices is their dependence on loading conditions. These indices are unable to distinguish between the effect(s) of altered loading conditions and abnormalities in myocardial contractility. Hence, abnormalities in preload and afterload can result in depressed shortening or ejection fractions leading to the erroneous interpretation that myocardial contractility is depressed. Conversely, left ventricular myocardial contractility may be depressed even in the presence of normal shortening or ejection fractions. The advantage of most of these indices is their relative simplicity and ease of acquisition. Load-independent assessment of left ventricular systolic function requires a more sophisticated analysis. The interested reader is referred to the relevant chapters in this book and to other reviews of this topic.⁶⁹

The previously described methods of ventricular function assessment rely in part on measurements of ventricular dimensions. An alternative approach is to evaluate myocardial motion and deformation.⁷⁰ Several methods have been developed to measure myocardial velocities, strain, strain rate, displacement, and torsion (twist). One method uses Doppler to measure myocardial velocities (Doppler tissue imaging [DTI]) and to calculate strain, strain rate, and other variables of tissue deformation

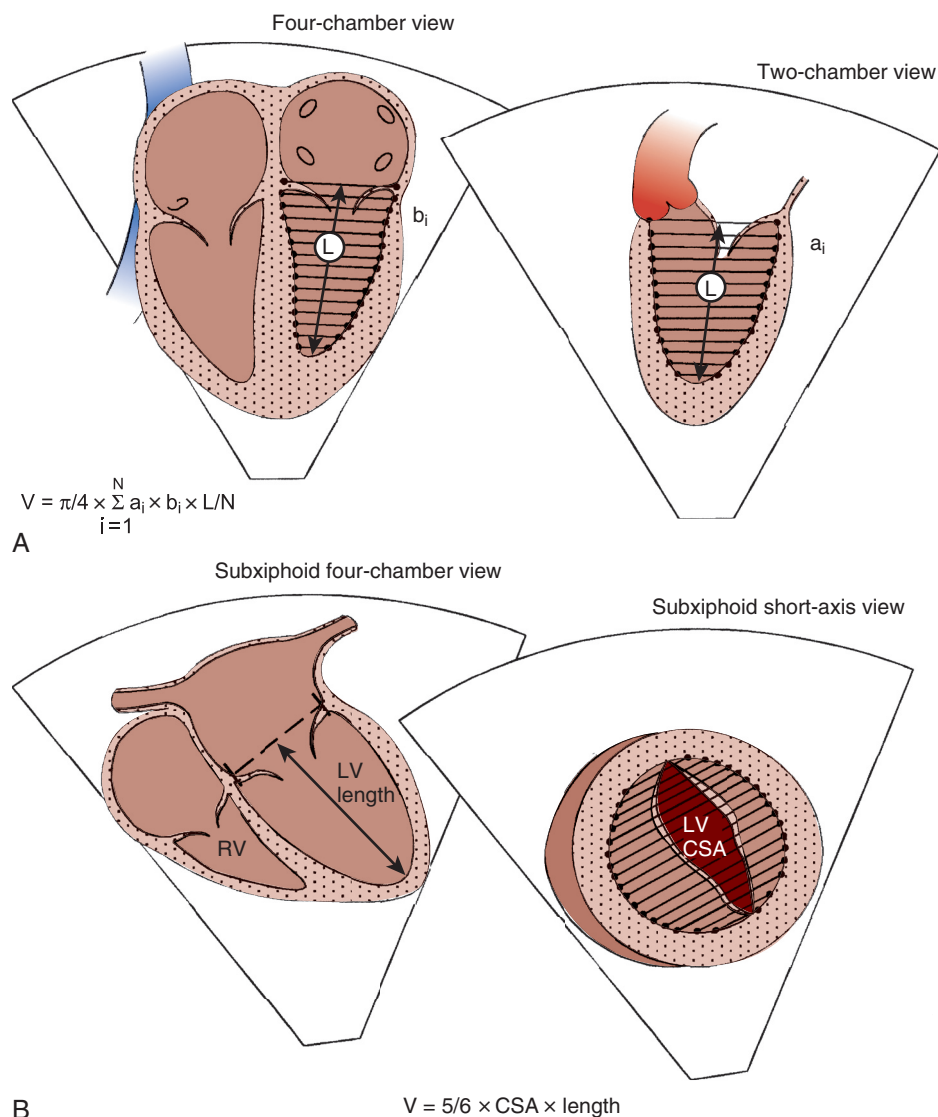


FIGURE 106-10 ■ Methods for assessment of left ventricular volume by two-dimensional echocardiography. **A**, Biplane Simpson rule for calculating left ventricular volume (see text for details). **B**, Area-length method for calculating left ventricular volume. a_i , Slice radius in the apical two-chamber view; b_i , slice radius in the apical four-chamber view; CSA, cross-sectional area; L, left ventricular length; N, number of slices; V, volume.

(Fig. 106-11A).⁷¹⁻⁷³ The other method, STE, analyzes the frame-to-frame changes in ultrasonic signal characteristics and uses that information to track the myocardium throughout the cardiac cycle (see Fig. 106-11B).^{12,74} These methods are independent of ventricular geometry and provide information on systolic and diastolic function.⁷⁵⁻⁷⁷ The reproducibility and the prognostic role of these techniques in patients with CHD are the subject of ongoing investigations.¹⁷

Doppler Evaluation of Pressure Gradients

Estimation of the pressure difference between adjacent compartments has been widely applied in clinical pediatric echocardiography (see Fig. 106-4).^{1,4,10} Among the most common uses is estimation of pressure drop across stenotic areas and prediction of pressure in cardiac

chambers. For example, the systolic pressure in the right ventricle can be predicted from the peak pressure difference between it and the right atrium derived from the peak velocity of the tricuspid regurgitation jet. Right ventricular systolic pressure can also be assessed from knowledge of left ventricular pressure (by measurement of systemic blood pressure by sphygmomanometry) and the pressure drop across a ventricular septal defect. In principle, the pressure gradient across any two compartments connected by flow can be estimated by Doppler, provided that the limitations of the technique are taken into consideration and the sources of error in the application and interpretation of the technique are eliminated.

Calculation of Pressure Gradients

The Bernoulli equation relates pressure difference (ΔP) between two points separated by a distance (s) to the

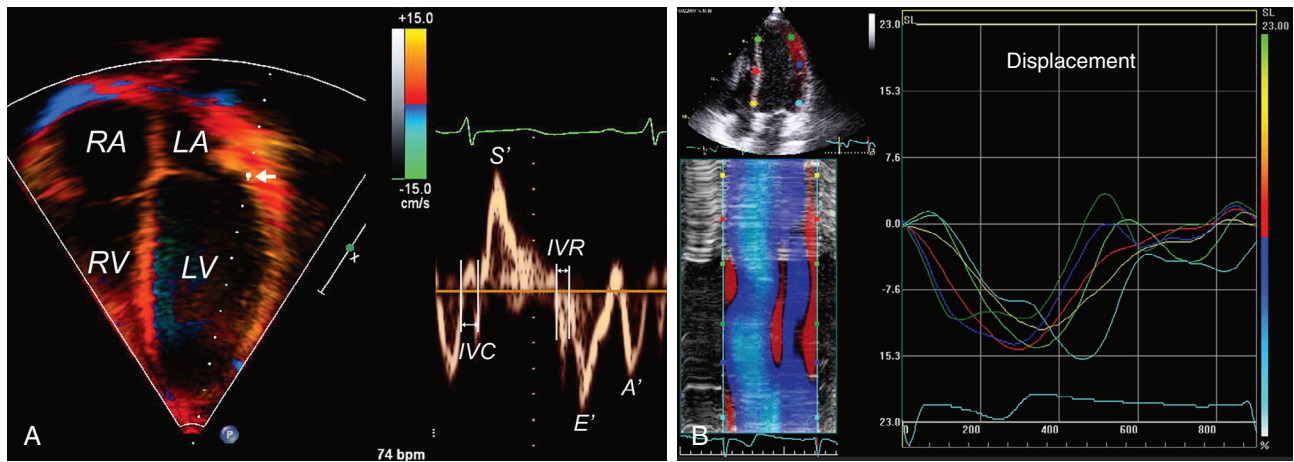


FIGURE 106-11 ■ Evaluation of myocardial motion by echocardiography. **A**, Tissue Doppler imaging. Left ventricular myocardial velocity is sampled at the level of the mitral valve annulus (arrow). The velocity-time curve shown on the right panel demonstrates myocardial velocities relative to the apex. **B**, Speckle-tracking evaluation of left ventricular wall motion evaluated from the apical four-chamber view. Displacement of the left ventricular free wall and septum is simultaneously tracked in multiple points. A' , Late (atrial) diastolic velocity; *bpm*, beats per minute; E' , early diastolic velocity; *IVC*, isovolumic contraction period; *IVR*, isovolumic relaxation period; *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle; S' , systolic velocity.

velocities at the two points (V_1 and V_2 , respectively), the fluid density (for blood, $\rho = 1060$ kg/liter), and the velocity-dependent viscous friction according to the following equation:

$$\Delta P = \underbrace{\frac{1}{2}\rho(V_2^2 - V_1^2)}_{\text{convective acceleration}} + \underbrace{\rho \int_1^2 \frac{d\vec{V}}{dt} d\vec{s}}_{\text{flow acceleration}} + \underbrace{R(\vec{V})}_{\text{viscous friction}}$$

For most clinical applications of the Bernoulli equation, the convective acceleration component of the formula is considered the most significant. After combining ρ for blood with conversion factors to mm Hg and velocity to m/sec, the coefficient calculates out to 3.98. In most clinical applications this factor is rounded to 4.0. The second term of the equation, flow acceleration, represents the pressure drop generated by flow acceleration. This phenomenon, however, is important only during a very brief period at the rapid acceleration phase when there is a lag between the velocity and the pressure curves. During that time period, the pressure gradient is not considered clinically important. The third term represents the force necessary to overcome viscous friction. When considering pressure drops across a discrete orifice, viscous friction becomes negligible. Hence, for most clinical applications the formula is simplified based on the following assumptions: (1) the velocity proximal to the obstruction (V_1) is assumed to be negligible compared with the velocity just distal to the obstruction (V_2); (2) in most clinical situations, peak flow acceleration occurs in early systole when the pressure gradient is irrelevant and can be ignored; and (3) viscous friction is assumed to be trivial. The Bernoulli equation can therefore be simplified: $\Delta P = 4(V_2)^2$. This formula has been shown to be valid in in vitro flow models⁷⁸ and in various clinical settings.⁷⁹ However, the assumptions that govern the use of the simplified Bernoulli equation may not always be correct. For example, in long-segment narrowing such as a

Blalock-Taussig shunt, ignoring the viscous friction term of the Bernoulli equation may lead to significant underestimation of the pressure drop. The limitations and pitfalls that can potentially lead to errors in estimation of pressure gradients have been reviewed elsewhere.^{1,11}

Safety and Complications

Because of the widespread use of echocardiography in the diagnosis and monitoring of children with suspected heart disease, safety of the technique is of prime importance. This is particularly relevant in fetal echocardiography where fetuses may be exposed to ultrasound energy early in gestation. To date, no reports on adverse effects from diagnostic ultrasound have been reported. Physicians involved with diagnostic ultrasound must be aware that ultrasound is a form of mechanical energy that under certain conditions can cause biological damage to exposed tissue. This damage can result from conversion of mechanical energy to heat or from creation of gaseous microcavitations. Thus far, it appears that biological damage has been observed only in nonclinical laboratory conditions. The American Institute of Ultrasound in Medicine stated that “no confirmed biologic effects on patients or instrument operator caused by exposure at intensities typical of present diagnostic ultrasound instruments have ever been reported. Although the possibility exists that such biologic effects may be identified in the future, current data indicate that the benefits to patients of the prudent use of diagnostic ultrasound outweigh the risks, if any, that may be present.”⁸⁰

MAGNETIC RESONANCE IMAGING

Cardiovascular MRI is a sophisticated noninvasive imaging modality that overcomes many of the limitations of echocardiography and cardiac catheterization. High-resolution static and dynamic images of the heart,

blood vessels, and other thoracic structures are obtained regardless of body size and acoustic barriers. Moreover, cardiovascular MRI provides additional unique information that is not made available by other imaging techniques. As a result of the rapid technologic evolution in computer sciences, electronics, and engineering over the past decade, cardiovascular MRI has evolved from a technique that produced several static images in an hour-long examination to a modality capable of real-time imaging,^{81,82} succinct dynamic three-dimensional visualization of cardiovascular anatomy,⁸³ imaging of the fetus,⁸⁴ and accurate quantification of blood flow⁸⁵ and myocardial function.⁸⁶ These capabilities have greatly expanded the role of cardiovascular MRI in preoperative and postoperative evaluation of infants, children, and adults with CHD.

Magnetic Resonance Imaging Techniques and Their Clinical Applications

In MRI, magnetic fields and radiofrequency energy are used to stimulate hydrogen nuclei in selected regions of the body to emit radiofrequency waves that are then used to construct images. As with other cardiovascular imaging modalities, a thorough understanding of the underlying imaging physics enhances the quality and interpretation of the diagnostic data. This section provides a practical introduction to cardiovascular MRI; a more detailed discussion can be found in other sources.^{87,88}

To produce an image, the patient is first placed inside the scanner, which applies a static high-strength magnetic field. Most clinical scanners use static magnetic field strengths ranging from 0.5 tesla (T) to 3 T (1 tesla = 10,000 gauss [G]; the strength of earth's magnetic field at its surface is approximately 0.5 G). Higher magnetic field strengths are used mostly in research scanners. Once positioned within the scanner, a section of the patient's body is then excited using a radiofrequency pulse, and an echo is formed by means of a second radiofrequency pulse (spin echo) and/or gradient pulses (gradient echo). The signal from the echo is then processed by Fourier transformation and the data are used to fill a line of matrix from which the image is generated.

Cardiac and Respiratory Gating

The heart, blood, and blood vessels are in relatively rapid motion compared with other body structures. Although the speed of MRI continues to improve, standard techniques are too slow to image the heart in real time with adequate spatial and temporal resolution for most applications. Rather, an image at a particular point during the cardiac cycle is built up from data acquired over multiple cardiac cycles. Consequently, synchronization with the cardiac cycle is required to "return" to the same point in the cycle and effectively freeze cardiac motion. Imaging may be synchronized or "gated" with a pulse oxymetry trace (so-called peripheral gating) or, more optimally, with a high-quality electrocardiogram signal. Because images are constructed over multiple cardiac

cycles, respiratory motion can degrade image quality. One approach to minimizing respiratory artifacts is to have the patient hold his or her breath during image acquisition. Although this solution is often effective, it cannot be used in patients who are too young or ill to cooperate. In such cases, respiratory motion compensation can be achieved by synchronizing image data acquisition to the respiratory as well as the cardiac cycle. Respiratory motion can be tracked either by a bellows device placed around the body or by MRI navigator echoes that concurrently image the position of the diaphragm or heart. The principal limitation of respiratory gating is that it substantially prolongs scan times because image data are accepted during only a portion of the respiratory cycle. A final strategy to minimize respiratory motion artifacts is to acquire multiple images at the same location and average them, thereby minimizing variations due to respiration. As expected, the disadvantage of this approach is again increased scan time.

This discussion highlights the need for more rapid high-quality MRI techniques that will obviate the need for cardiac gating and respiratory motion compensation. Recent advances in gradient coil performance and parallel acquisition methods have achieved this goal and have become widely available in the clinical arena.⁸⁹⁻⁹³

Cardiovascular MRI examination is performed by repeatedly selecting a pulse sequence, prescribing an imaging location, and acquiring the image data to address specific clinical questions.⁹⁴ The pulse sequence specifies how the magnetic field gradients and radiofrequency pulses are applied and read during image acquisition. [Table 106-1](#) summarizes the features of some of the common cardiovascular MRI sequences used in clinical practice. In general, there are two major categories of pulse sequences—spin echo and gradient echo (see [Table 106-1](#)). Spin echo sequences are characterized by applying a radiofrequency pulse that tips hydrogen protons by 90 degrees, followed by a second, 180-degree pulse, and they are usually used to generate images in which flowing blood appears black. Gradient echo sequences apply radiofrequency pulses that are less than 90 degrees (usually 15 to 60 degrees), are faster than spin echo sequences, and are usually used to generate images in which flowing blood appears white. Adding preparatory pulses that alter tissue contrast can often modify a particular pulse sequence. In addition, there are numerous user-selectable imaging parameters that affect tissue contrast, image quality, and temporal and spatial resolution. The numerous imaging techniques and parameters to choose from allow the operator to adjust image contrast for optimal anatomic definition and detection of abnormal tissue. They also provide the capability for sophisticated functional assessment. The following section reviews the more common cardiovascular MRI techniques with a focus on their clinical usefulness.

Anatomic Imaging and Tissue Characteristics

Spin echo pulse sequences are usually used to produce images in which flowing blood has low signal intensity and appears dark ("black blood" imaging). Other tissues

TABLE 106-1 Summary of MRI Techniques

Technique	ECG Triggering	Appearance of Blood Flow	Dynamic (Cine*) vs. Static†	Clinical Application
I. Spin Echo				
Standard spin echo	Yes	Dark	Static	Anatomy, tissue characterization
Fast spin echo with double-inversion recovery	Yes	Dark	Static	Anatomy, tissue characterization, faster image acquisition relative to standard spin echo
II. Gradient Echo				
Segmented k-space fast gradient echo or steady-state free precession	Yes	Bright	Dynamic	Anatomy, ventricular function, blood flow imaging
Phase contrast	Yes	Bright	Dynamic	Flow quantification and characterization
Tagging	Yes	Bright	Dynamic	Analysis of myocardial mechanics and flow
Gadolinium-enhanced three-dimensional MRA	No	Bright	Static	Three-dimensional anatomic data set
MR fluoroscopy	No	Bright	Dynamic	Anatomy, function, guidance of interventional procedures
Delayed enhancement	Yes	Intermediate	Static	Myocardial viability

*Cine: Multiple images are obtained throughout the cardiac cycle in each anatomic location. The stacked images are then displayed on a computer screen in a cine-loop format.

†Static: A single image is obtained in each anatomic location.

ECG, Electrocardiography; MR, magnetic resonance; MRA, magnetic resonance angiography.

appear as varying shades of gray. Although cardiac-gated spin echo sequences produce only one image per location and thus provide only static anatomic information, their advantages include high spatial resolution, excellent blood-myocardium contrast, and decreased artifact from metallic biomedical implants (e.g., sternal wires, stents, prosthetic valves). Spin echo sequences are also easily modified to alter tissue contrast and characterize abnormal structures. Their clinical uses include evaluation for arrhythmogenic right ventricular cardiomyopathy,⁹⁵ cardiac tumors,⁹⁶⁻⁹⁸ constrictive pericardial disease,⁹⁹ vessel wall abnormalities,¹⁰⁰ trachea and mainstem bronchi,¹⁰¹ and thoracic masses (Fig. 106-12).¹⁰² Fast (turbo) spin echo sequences allow one location to be imaged rapidly enough for the patient to breath-hold (10 to 15 seconds). A double-inversion preparatory pulse is usually applied to suppress the blood signal,¹⁰³ and an additional inversion pulse may be applied to suppress fat signal.

Cine Magnetic Resonance Imaging

Cardiac-gated gradient echo sequences can be used to produce multiple images over the cardiac cycle in each anatomic location. These images can then be displayed in a cine-loop format to demonstrate the motion of the heart and vasculature over the cardiac cycle. On such cine MR images, flowing blood produces a bright signal, and the myocardium and vessel wall are relatively dark ("bright-blood" imaging) (Fig. 106-13). The most commonly used cine MR technique is steady-state free precession cine MR sequences.^{104,105} This technique relies on the ratio of T2-to-T1 relaxation, which results in high contrast between the blood pool ($T2/T1 = 360/1200 =$

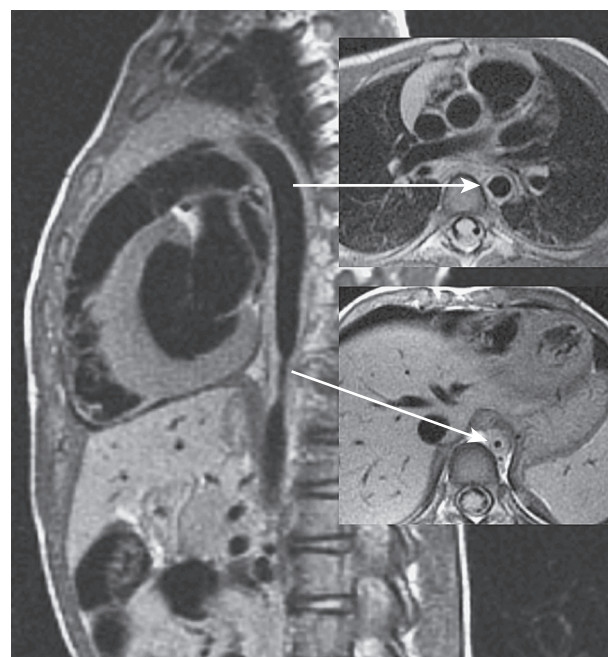


FIGURE 106-12 ■ Electrocardiographically triggered, breath-hold, proton density-weighted, fast spin echo with double-inversion recovery images showing severe coarctation of the descending aorta at the level of the diaphragm in a 5-year-old patient with Takayasu aortitis. Note the markedly thickened aortic wall with severe luminal narrowing on the axial plane image (arrows).

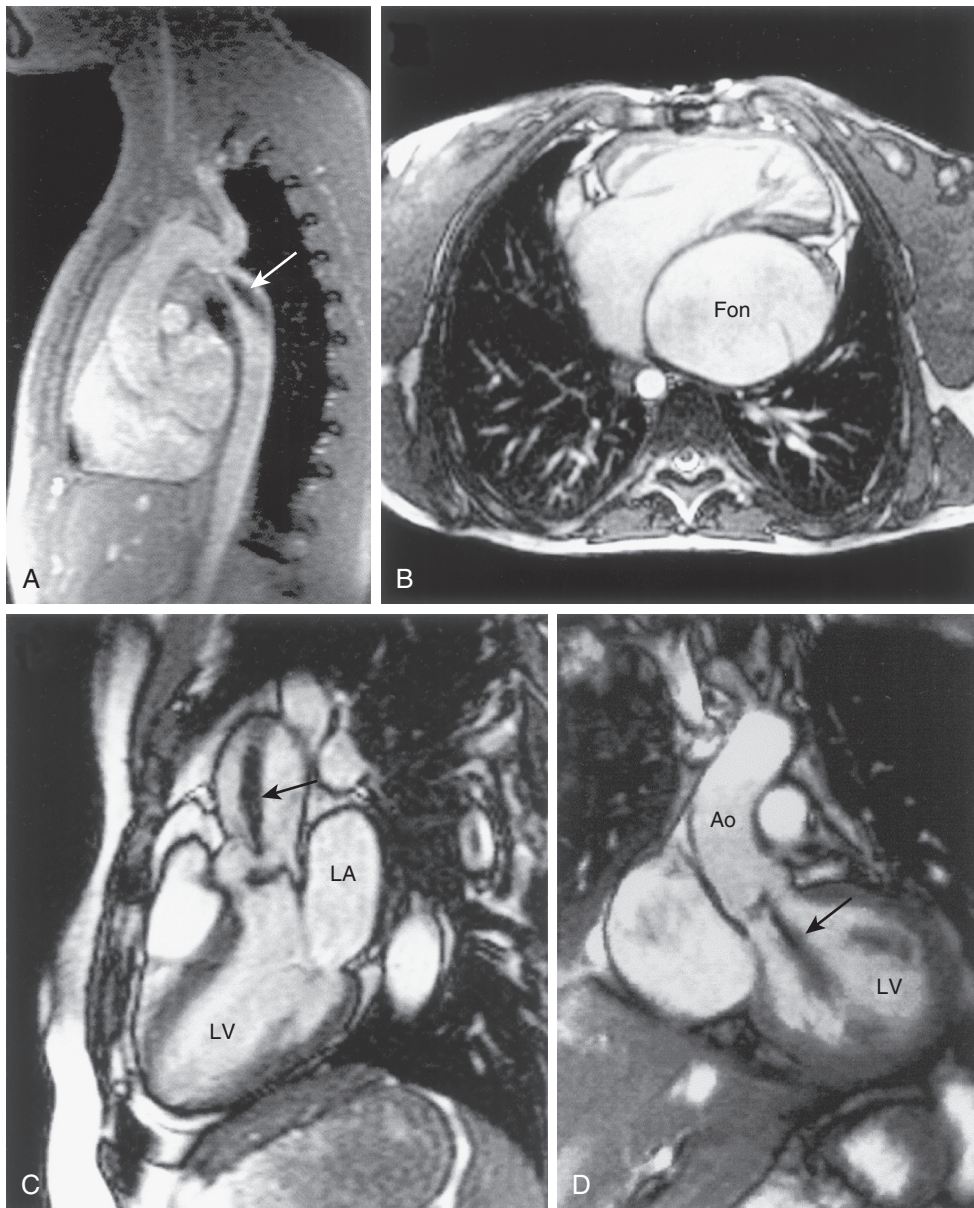


FIGURE 106-13 ■ Clinical applications of gradient echo cine magnetic resonance imaging. **A**, Electrocardiographically triggered breath-hold segmented k-space fast spoiled gradient echo multiphase sequence in a patient with severe coarctation of the aorta. The relatively long echo time allows for clear depiction of the dephasing jet in systole (*arrow*) indicating high-velocity turbulent flow. **B**, Axial plane electrocardiographically triggered steady-state free precession multiphase sequence in a patient with heterotaxy syndrome and single ventricle after a Fontan operation. Note the left-sided Fontan pathway (Fon) as well as the clear depiction of intracardiac anatomy. **C**, Systolic turbulent jet (*arrow*) in a patient with aortic valve stenosis. **D**, Diastolic turbulent jet (*arrow*) in a patient with aortic valve regurgitation. Ao, Aorta; LA, left atrium; LV, left ventricle.

0.3) and the myocardium ($T2/T1 = 57/880 = 0.085$), providing clear definition of cardiovascular structures. Image acquisition is short (4 to 10 seconds depending on heart rate) and is further shortened by parallel processing, permitting real-time magnetic resonance fluoroscopy.^{84,106-108}

Cine MRI is used to delineate cardiovascular anatomy and assess ventricular function. It is helpful for evaluating the systemic and pulmonary veins,¹⁰⁹ atrial and ventricular septa,¹¹⁰⁻¹¹² intracardiac baffles and pathways (e.g., after Fontan, Mustard, Senning, and Rastelli procedures),¹¹³ ventricular outflow tracts, ventricular-arterial conduits,¹¹⁴ pulmonary arteries, and the aorta. It is also

useful in identifying stenotic and regurgitant jets, which appear as dark signal voids (see Fig. 106-13). Myocardial tagging is a modification of cine MRI that allows for a sophisticated analysis of regional myocardial function (see Ventricular Function section, earlier).^{86,115}

Magnetic Resonance Imaging Assessment of Ventricular Function

The principal MRI sequence used for evaluation of ventricular function is gradient echo cine MRI. An electrocardiographically triggered segmented k-space fast (also termed *turbo*) gradient recall echo sequence was used

extensively during the 1990s, and its accuracy and reproducibility in measuring left and right ventricular volumes, mass, and ejection fraction have been extensively validated.¹¹⁶⁻¹¹⁸ Since the early 2000s, steady-state free precession cine MR has replaced other gradient echo techniques. This sequence has been shown to provide a sharper contrast between the blood pool and the myocardium and to reduce motion-induced blurring during systole.^{89,119,120}

Quantitative evaluation of ventricular function is achieved by obtaining a series of contiguous cine MRI slabs that cover the ventricles in short-axis view (Fig. 106-14).^{82,86,121,122} By tracing the blood-endocardium boundary, the slab's volume is calculated as the product of its cross-sectional area and thickness (which is prescribed by the operator). Ventricular volume is then determined by summation of the volumes of all slabs. The process can be repeated for each frame in the cardiac cycle to obtain a continuous time-volume loop, or it can be performed only on a diastolic and a systolic frame to calculate diastolic and systolic volumes. From these data, left and right ventricular ejection fractions and stroke volumes can be calculated. Because the patient's heart rate at the time of image acquisition is known, left and right ventricular output can be calculated. Ventricular mass is calculated by tracing the epicardial borders, subtracting the endocardial volumes, and multiplying the resultant muscle volume by the specific gravity of the

myocardium (1.05 g/mm^3). Most manufacturers of MRI scanners and some third-party companies offer software packages that automatically perform these calculations. Development of algorithms for automatic border detection has facilitated the application of these techniques, but further refinements are required to improve its accuracy.¹²³ Because of the accurate spatial and temporal registration of data, MRI measurements of chamber dimensions have become the accepted reference standard to which other methods are compared.^{124,125} For example, Bellenger and colleagues measured left ventricular volumes in 64 patients with dilated cardiomyopathy.¹²⁶ They reported an intraobserver variability of $2.4\% \pm 2.5\%$, interobserver variability of $5.1\% \pm 3.7\%$, and interstudy variability (repeat MRI examinations) of $2.9\% \pm 1.2\%$. In patients with normal and dilated right ventricles, Mooij and coworkers reported interobserver intraclass correlation coefficients of 0.977 for right ventricular end-diastolic volume, 0.989 for left ventricular end-diastolic volume, 0.947 for right ventricular stroke volume, 0.973 for left ventricular stroke volume, and 0.789 and 0.81 for right and left ventricular ejection fraction, respectively.¹²⁷

Steady-state free precession cine MRI is also used to evaluate regional wall motion abnormalities and segmental wall thickening.¹²⁸ Dobutamine stress MRI has been reported to be a useful test in adults with coronary artery disease,¹²⁹⁻¹³¹ and initial experience in pediatric patients is

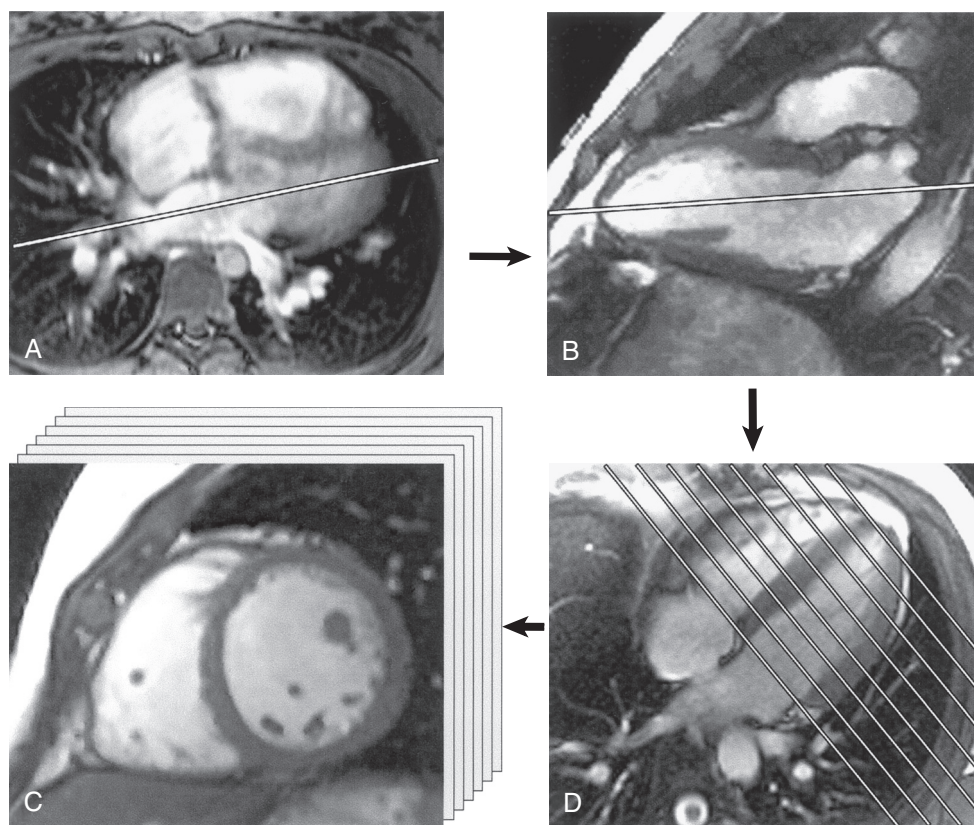


FIGURE 106-14 ■ Cine magnetic resonance imaging technique for assessment of ventricular dimensions and function. **A**, Using a localizing image in the axial plane, an imaging plane is placed parallel to the left ventricular septal surface. **B**, Two-chamber plane. **C**, Four-chamber plane. **D**, Short-axis plane. To obtain complete coverage of the ventricles, 12 contiguous imaging slabs are placed from the plane of the atrioventricular valves through the cardiac apex.

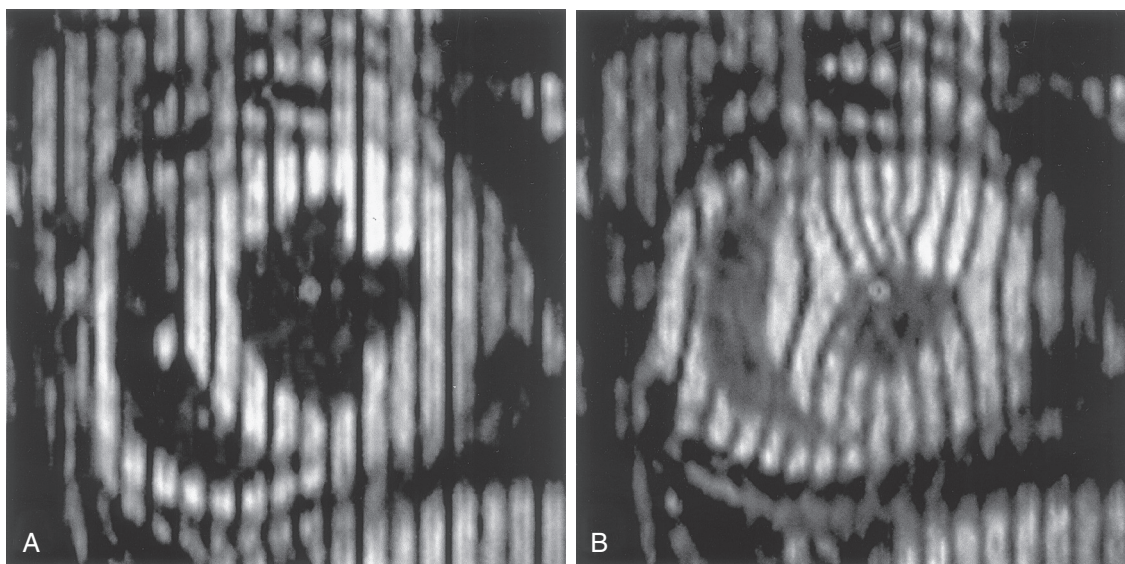


FIGURE 106-15 ■ Myocardial tagging. **A**, Diastolic frame shows the undistorted tags before the onset of systole. **B**, Systolic frame shows distortion of the myocardial tags caused by cardiac motion. Notice the undistorted tags on the chest wall and liver.

encouraging.¹³² More recently, the use of an MRI-compatible supine cycle ergometer has been reported to allow assessment of ventricular function and valve regurgitation response to exercise.^{133,134}

Another approach to MRI evaluation of ventricular function and myocardial mechanics is to visualize and measure myocardial motion. This can be done by myocardial tagging,¹³⁵ velocity-encoded cine MRI, or feature-tracking cardiac MRI.¹³⁶ In myocardial tagging, with the use of a preparatory radiofrequency gradient echo pulse sequence such as spatial modulation of magnetization (SPAMM), the spin of the protons in selected parts of the image volume are flipped in such a way as to render them incapable of producing a signal. This results in stripes of signal void (dark stripes) across the image (Fig. 106-15). The grid or stripes are placed at the onset of the R wave and is followed by a gradient echo cine MRI sequence. As the myocardium moves during the cardiac cycle, the tags follow it and their rotation, translation, and deformation can be tracked, allowing for calculation of myocardial strain and strain rate.¹³⁷⁻¹⁴⁰ A recently described technique for the analysis of myocardial tagging data, harmonic phase imaging, shortens the analysis time because it does not require manual tracing of the tags.¹⁴¹ Despite extensive research on myocardial tagging, the technique has not gained general acceptance in routine clinical practice. More recently, use of feature tracking MRI has been reported in CHD patients with promising early results (Fig. 106-16).^{142,143} An advantage of feature tracking over myocardial tagging is that it can be performed on routinely acquired cine SSFP images, as opposed to the special image acquisitions required for tagging analysis.

Blood Flow Analysis

An ECG-gated velocity-encoded cine MRI (VEC MRI) sequence, a type of gradient echo sequence, can be used to measure blood flow velocity and quantify blood flow

rate.^{85,144} The VEC MRI technique is based on the principle that the signal from hydrogen nuclei (such as those in blood) flowing through specially designed magnetic field gradients accumulates a predictable phase shift that is proportional to its velocity. Multiple phase images are constructed across the cardiac cycle in which the voxel intensity or brightness is proportional to blood velocity within that voxel. Flow quantification is performed by placing an imaging slab across a blood vessel or through the area at question within the heart (Fig. 106-17A). The operator then determines whether flow velocity encoding is performed only perpendicular to the imaging plane (z-axis) or in other directions as well (x-axis and y-axis). The data are then analyzed off-line using specialized software. A region of interest (ROI) is defined by the operator around the lumen of the relevant vessel and the instantaneous mean velocity of each voxel is calculated (see Fig. 106-17B and C). Flow rate is calculated as the product of the mean velocities within the ROI and its cross-sectional area. Integration of the instantaneous flow rates over the cardiac cycle yields the stroke volume (see Fig. 106-17D). This technique has been shown by in vitro and in vivo studies to be accurate and reproducible.^{144,145} Cine phase contrast has been widely applied to measure systemic and pulmonary blood flow and their ratio, as well as flow in individual pulmonary arteries, across the mitral and tricuspid valves, across an atrial septal defect, in systemic and pulmonary veins and in other individual blood vessels. This technique also allows accurate quantification of regurgitation volume and fraction across any cardiac valve.¹⁴⁶ An example of an important application of this technique in CHD is the quantification of pulmonary regurgitation in patients who have undergone tetralogy of Fallot repair.¹⁴⁷ When flow encoding is performed in three spatial directions, multidimensional flow imaging and analysis can be accomplished by resolving the flow velocities and directions into flow vectors that can be viewed in cine-loop format (Fig. 106-18). This technique allows unique

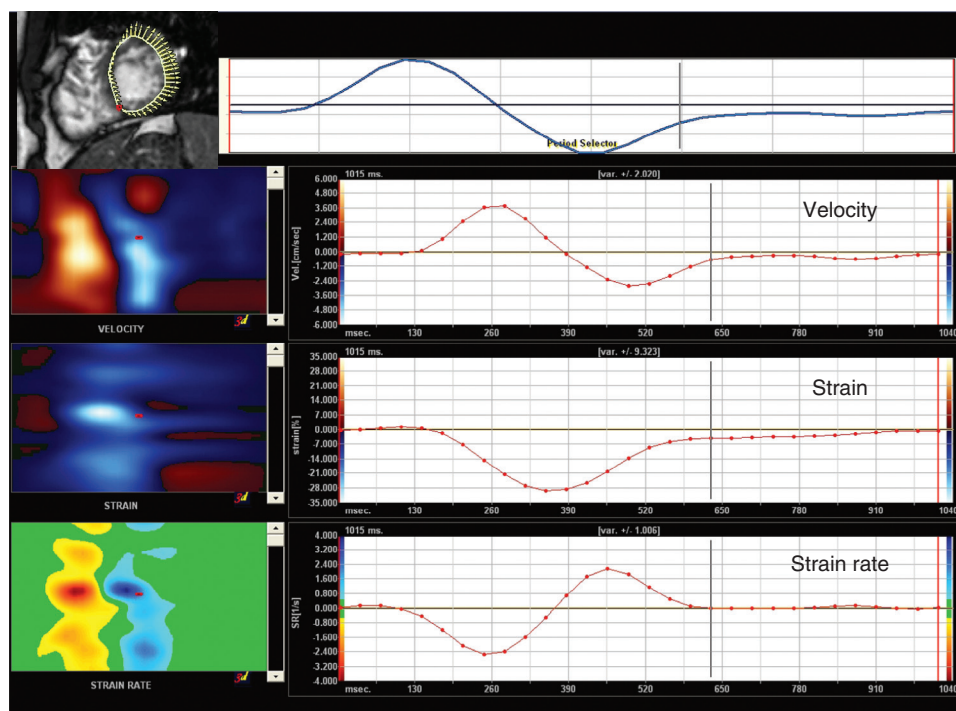


FIGURE 106-16 ■ Magnetic resonance imaging evaluation of myocardial deformation using speckle-tracking analysis. Circumferential left ventricular myocardial velocity, strain, and strain rates are shown.

imaging of blood flow in five dimensions (x , y , and z spatial dimensions, velocity, and time).¹⁴⁸ It also allows quantitative analysis of flow dynamics, including the ability to calculate the shear stress exerted by the flowing blood on the vessel wall.¹⁴⁹

Contrast-Enhanced Magnetic Resonance Angiography

Another approach for improving the contrast between vascular and nonvascular structures is to administer an exogenous intravenous contrast agent, typically a gadolinium chelate, which dramatically shortens the T1 relaxation of blood, resulting in a bright signal on T1-weighted sequences. This method of angiography is less prone to flow-related artifacts than other MR techniques and has a short acquisition time. Contrast-enhanced magnetic resonance angiography (MRA) is usually performed without cardiac gating using a three-dimensional fast gradient echo acquisition lasting 15 to 30 seconds while the patient holds his or her breath.¹⁵⁰ The time delay between contrast administration and image acquisition determines the vascular territory illustrated, and several acquisitions can be performed. The entire procedure takes only a few minutes to perform and yields a high-contrast and high-resolution three-dimensional data set depicting all or part of the thorax. The three-dimensional data set can be navigated on dedicated workstations using various image display techniques, including rapid construction of intuitive three-dimensional models (Fig. 106-19). Unlike cine MRI, conventional contrast-enhanced MRA is not time resolved. However, with continued improvements in imaging speed, time-resolved MRA is now possible.¹⁵¹

MRA is ideally suited to elucidate the anatomy of the aorta and its branches, pulmonary arteries, pulmonary veins, and systemic veins.^{152,153} Although this technique is mostly used for imaging of extracardiac anatomy, we have found it useful in the evaluation of intra-atrial systemic and pulmonary baffles (such as in Mustard and Senning operations and after Fontan procedures), as well as for imaging of the outflow tracts (such as in repaired tetralogy of Fallot and the arterial switch operation). In addition, MRA clearly delineates the spatial relationships between vascular structures, the tracheobronchial tree, chest wall, spine, and other landmarks that may be useful for planning of interventional catheterization or surgical procedures.

Myocardial Ischemia and Viability

Although traditionally the diagnosis of myocardial ischemia has not been a focus of imaging in CHD, it clearly has relevance in patients who have congenital and acquired coronary abnormalities (e.g., anomalous origin of the left coronary artery, pulmonary atresia with intact ventricular septum, and Kawasaki disease). Moreover, myocardial ischemia is an important diagnostic challenge in patients postoperatively and in adults with CHD. Several MRI techniques for imaging the coronary arteries with sufficient resolution to detect stenotic lesions are now available.¹⁵⁴ However, the optimal approach and clinical usefulness will likely remain in evolution for the next several years. MRI techniques are also available for assessment of regional left ventricular myocardial perfusion.^{155,156} Typically, after a rapid intravenous gadolinium contrast injection, ultrafast, multislice imaging with an

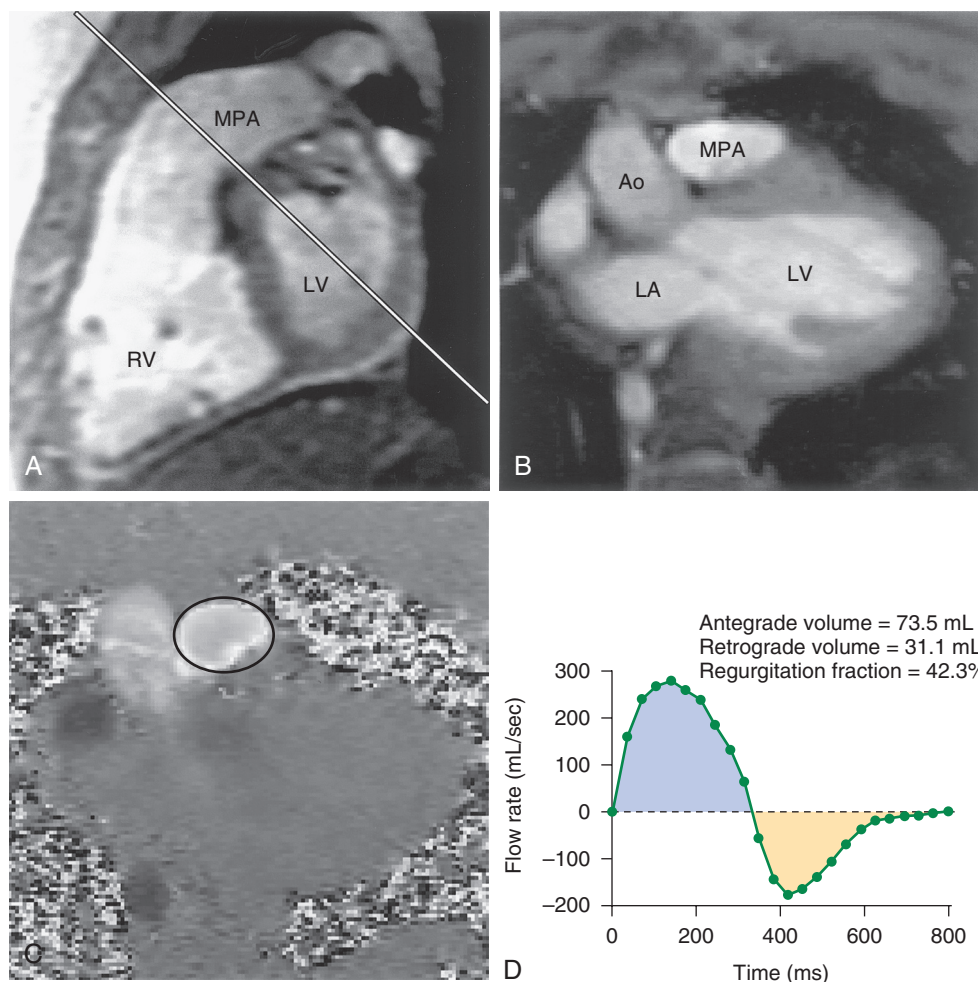


FIGURE 106-17 ■ Quantitative assessment of pulmonary regurgitation by velocity-encoded cine magnetic resonance imaging (MRI) in a 26-year-old patient with repaired tetralogy of Fallot. **A**, An imaging plane is placed across the main pulmonary artery (MPA) (multiphase gradient echo cine MR). **B**, Magnitude image showing bright signal in the proximal MPA. **C**, The corresponding phase image contains the velocity and directional data. Using a computer workstation, a region of interest (*oval*) is placed around the MPA. **D**, The systolic flow-time integral (area under the curve above the baseline) yields the antegrade flow volume, and the diastolic flow-time integral (below the baseline) corresponds to the regurgitant flow volume. Regurgitation fraction is calculated as the ratio of retrograde (regurgitant volume) to antegrade volume. Ao, Aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

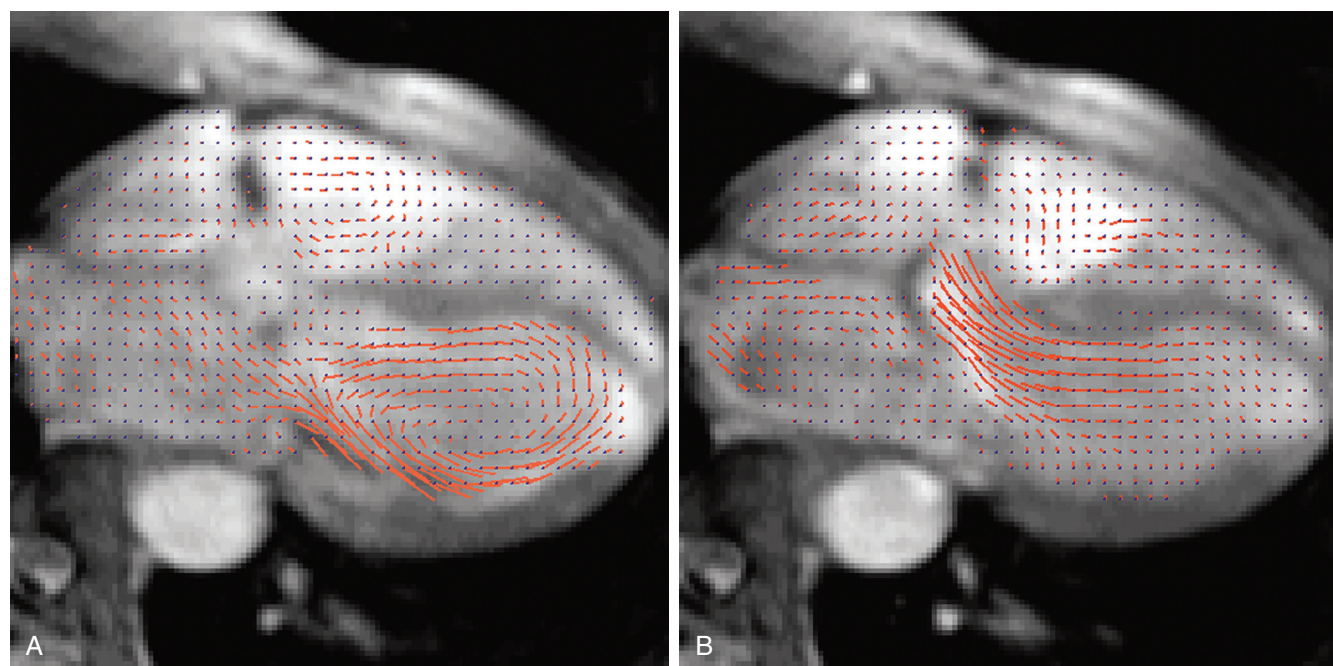


FIGURE 106-18 ■ Three-dimensional flow vector map showing intracardiac diastolic (**A**) and systolic (**B**) flow pattern. The orientation of the vector corresponds to the instantaneous in-plane direction of blood flow whereas the vector's length is proportional to instantaneous velocity.



FIGURE 106-19 ■ Gadolinium-enhanced three-dimensional magnetic resonance angiography in a patient with D-loop transposition of the great arteries after an arterial switch operation. **A**, Subvolume maximum intensity projection (MIP) image in an oblique sagittal plane showing the main (MPA) and right (RPA) pulmonary arteries. **B**, Leftward angulation of the imaging plane shows the left pulmonary artery. **C**, Axial plane MIP image demonstrates the left (LPA) and right (RPA) pulmonary arteries wrapped around the ascending aorta (Ao) (Lecompte maneuver). **D**, Three-dimensional volume reconstruction provides enhanced perception of the relationships between the great vessels. DAo, Descending aorta; LV, left ventricle; RV, right ventricle.

echo-planar pulse sequence is performed during a 20- to 25-second breath-hold to image the first pass of contrast through the myocardium (Fig. 106-20). The procedure can be repeated after administering a coronary vasodilator (e.g., adenosine or dipyridamole). Although MR perfusion imaging offers superior spatial resolution compared with nuclear cardiology techniques without the use of ionizing radiation, its widespread application has been limited by the need for time-intensive analysis and

insufficient clinical validation. Alternatively, cine MRI can be used to detect focal wall motion abnormalities with pharmacologic stress-induced ischemia. Several studies have demonstrated that for dobutamine stress studies, MRI compares favorably with transthoracic echocardiography, primarily as a result of its superior image quality.¹⁵⁷⁻¹⁵⁹ Finally, various MRI techniques have been used to assess myocardial viability. In particular, hyperenhanced myocardial regions observed 10 to 15

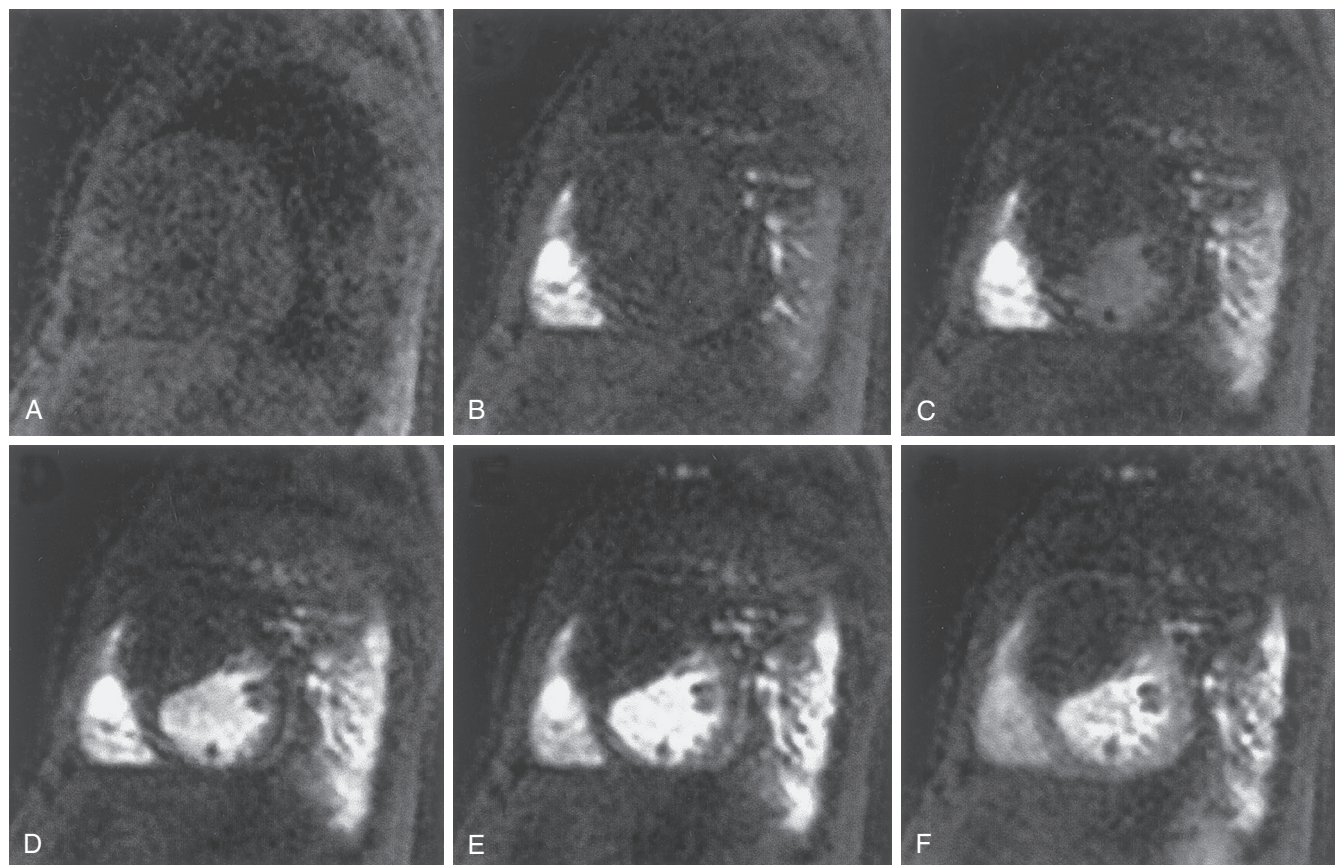


FIGURE 106-20 ■ First-pass myocardial perfusion scan in a patient with left ventricular fibroma. **A**, At onset of scan there is no contrast in the heart. **B**, Arrival of contrast in the right ventricle. **C**, Arrival of contrast in the pulmonary veins and early enhancement of left ventricular cavity. **D**, Arrival of contrast in the left ventricular cavity (notice the unenhanced left ventricular myocardium). **E**, Arrival of contrast in the left ventricular myocardium (notice the hypoperfused tumor in the anterolateral aspect of the septum). **F**, Late myocardial enhancement with hypoperfused tumor.

minutes after the administration of gadolinium contrast agents (termed *delayed myocardial enhancement*) are indicative of irreversible myocardial injury (Fig. 106-21).¹⁶⁰⁻¹⁶² Human studies assessing the usefulness of this technique have demonstrated its ability to detect scar tissue and other myocardial abnormalities in various types of acquired heart disease in adults.^{159,163-167} Although experience in patients with CHD is limited, several studies have demonstrated the ability of this technique to detect scar tissue in patients with tetralogy of Fallot, systemic right ventricle, endocardial fibroelastosis, and other conditions.^{156,168-171}

Indications for Cardiovascular Magnetic Resonance Imaging

The indications for cardiac MRI in patients with congenital and acquired pediatric heart disease are rapidly expanding. In general, the clinical reasons for a cardiac MRI examination may fall into one or more of the following three categories: (1) when transthoracic echocardiography is incapable of providing the required diagnostic information; (2) as an alternative to diagnostic cardiac catheterization with its associated discomfort, ionizing radiation exposure, contrast agent load, risks of morbidity and mortality, and high cost; and (3) for MRI's

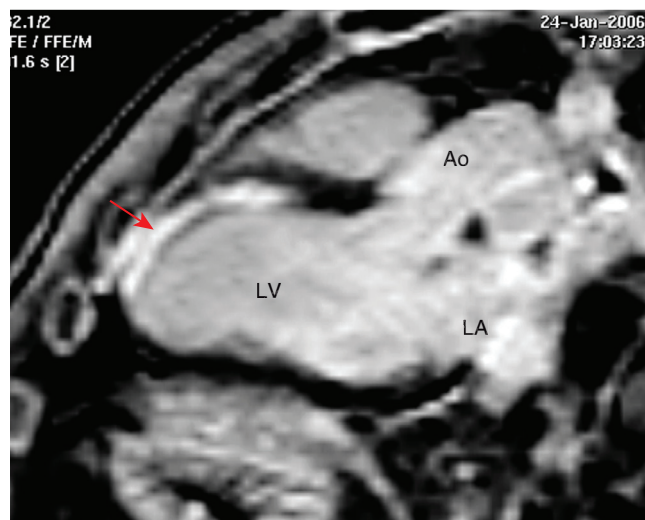


FIGURE 106-21 ■ Assessment of myocardial viability in a patient with Kawasaki disease, giant coronary artery aneurysm, and large anterior myocardial infarction extending to the apex. Nonviable myocardium produced bright signal (arrow) on an electrocardiographically triggered post-gadolinium, delayed-enhancement, inversion-recovery T1-weighted gradient echo sequence. Notice the dark signal from the viable left ventricular myocardium. Ao, Aorta; LA, left atrium; LV, left ventricle.

unique capabilities such as tissue imaging, myocardial tagging, and vessel-specific flow quantification.

General Considerations

Detailed preexamination planning is crucial given the wide array of imaging sequences available and the often complex nature of the clinical, anatomic, and functional issues in patients with CHD.⁹⁴ The importance of a careful review of the patient's medical history—including details of all cardiovascular surgical procedures, interventional catheterizations, findings of previous diagnostic tests, and current clinical status—cannot be overemphasized. As is the case with echocardiography and cardiac catheterization, cardiovascular MRI examination of CHD is an interactive diagnostic procedure that requires on-line review and interpretation of the data by the supervising physician. The unpredictable nature of the anatomy and hemodynamics often requires adjustment of the examination protocol; modification of imaging planes; adding, deleting, or changing sequences; and adjustment of imaging parameters. Reliance on standardized protocols and post hoc reading alone in these patients might result in incomplete or even erroneous interpretation.

Sedation is often required in young patients who cannot cooperate with a cardiac MRI examination. Most patients younger than 5 or 6 years require sedation, some patients between age 6 and 10 years are capable of cooperation, and most children older than 10 years can undergo a cardiac MRI study without sedation provided their mental development is age appropriate and they are not claustrophobic. Anxiolysis with oral midazolam or other medications is helpful in patients with mild or moderate claustrophobia or other forms of anxiety.¹⁷² Screening for sedation need is part of the scheduling process for cardiac MRI, and consultation with the referring cardiologist and parents is advised. Both conscious sedation and general anesthesia have been successfully used in cardiac MRI. In our experience, advantages of general anesthesia include a better safety profile (secured airways and close monitoring by a pediatric anesthesiologist); ability to suspend respiration, leading to improved image quality and a shorter examination time; and control over duration of sedation.^{173,174} Disadvantages of this approach include a higher cost and disability of skilled anesthesia personnel. Other centers have successfully used different methods of sedation.¹⁷⁵⁻¹⁷⁷

Safety and Complications

Standard clinical imaging scanners present no known hazards to biological materials. Three different magnetic fields are used by such magnets: the relatively large static magnetic field, smaller but rapidly varying magnetic fields secondary to the magnetic field gradients, and radio-frequency pulses. Guidelines set by the U.S. Food and Drug Administration keep the strength of these fields well below levels that could cause significant biological effects. Animal studies evaluating the influence of static magnetic fields have not demonstrated significant biological effects for fields of up to 2 T.¹⁷⁸ Millions of patients have undergone MRI studies without any noticeable immediate or

long-term sequelae. Pregnancy is presently a relative contraindication to MRI studies, although the magnetic field levels used in clinical imagers have no known effects on the embryo. Many women have undergone MRI during all trimesters of pregnancy without reported ill effect on the mother, fetus, or resultant infant. When maternal and fetal health considerations require diagnostic studies, MRI is preferable to methods that use x-rays, such as computed tomography (CT) or angiography.

Implanted metallic objects are of particular concern, because they could potentially undergo undesirable torquing movements if the magnetic field were sufficiently strong and if they contained sufficient ferromagnetic material. Fortunately, surgical clips and sternotomy wires implanted in the chest and abdomen are typically only weakly ferromagnetic. Furthermore, these devices quickly become immobilized by surrounding fibrous tissue, so MRI can be safely performed in patients with these implants.¹⁷⁹ The wires and clips, however, may cause image artifact. Similarly, patients with implanted intravascular coils, stents, and occluding devices can be imaged by MRI once the implants are believed to be immobile. Many centers choose to avoid exposing these patients to MRI for an arbitrarily chosen period of time after implantation (usually for several weeks), but such practice is not supported by conclusive published data. A decision to perform MRI examination shortly after cardiac surgery or implantation of a biomedical device must weigh the risk-to-benefit ratio for the individual patient.^{179,180}

A number of devices are considered either relative or absolute contraindications to MRI.^{179,180} Presence of an intracranial, intraocular, or intracochlear metallic object is considered a contraindication to MRI. The presence of a cardiac pacemaker is also considered a strong relative contraindication to MRI,¹⁸¹ although some reports have suggested that scanning patients who have modern pacemakers may be possible.¹⁸²⁻¹⁸⁵

Because MRI scanners attract ferromagnetic objects, extreme caution should be used in approaching magnets with objects containing iron or other ferromagnetic materials. Only specially designed MRI-compatible physiologic monitoring equipment should be used in conjunction with MRI studies. There have been several reported cases of patient burns resulting from the use of MRI-incompatible pulse oximeters and electrocardiographic monitoring devices.

SUMMARY

Accurate diagnosis of CHD can be accomplished by the judicious use of a variety of modalities. Echocardiography has assumed a leading role as the primary diagnostic tool in pediatric cardiology because of its noninvasive nature and its ability to provide comprehensive accurate diagnostic information in real time, in various clinical settings, and at a reasonable cost. Cardiovascular MRI is rapidly becoming an important diagnostic tool in pediatric cardiology because of its ability to provide anatomic and functional information that cannot be obtained by echocardiography or, in some cases, by catheterization.

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CARDIAC CATHETERIZATION AND FETAL INTERVENTION

Audrey C. Marshall

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INTRODUCTION AND OVERVIEW

Catheterization in the field of congenital cardiology continues to improve understanding of disease and expand options for therapy. Diagnostic information previously obtained exclusively through catheterization is now routinely acquired through use of a host of diverse and highly sophisticated, noninvasive diagnostic imaging modalities. Invasive hemodynamic measurement and angiographic assessment, however, remain a mainstay in the comprehensive evaluation of the patient with complex heart disease. Furthermore, the interventional role of cardiac catheterization in the management of congenital heart disease continues to evolve, and in conjunction with surgical improvements, presents expanding opportunities for therapeutic intervention. Thus, the catheterization laboratory is increasingly like an operative suite, and in many cases of “hybrid” suites, it incorporates functions of a more traditional cardiac operating room.

Ongoing advances in transcatheter technology ensure that the historical border zone between transcatheter and

open therapies will continue to shift and likely broaden. Thus, the team of cardiac surgeons and cardiologists who deal with congenital heart disease will benefit from a contemporary awareness of the capabilities and limitations of their partners' work. What follows is a brief summary of the basic hemodynamic and angiographic information acquired through cardiac catheterization and a rough sketch of the currently practiced procedures. The remainder of the chapter provides a survey of the current state of transcatheter therapies, from valvuloplasty to valve replacement, including angioplasty and defect closure using implantable devices. It also provides an overview of the experience to date with fetal cardiac intervention.

ROLE OF DIAGNOSTIC CATHETERIZATION

A primary role of the catheterizer, since the earliest days of invasive physiologic assessment of congenital heart disease, has been to safely obtain the data necessary to

formulate a complete and accurate anatomic and hemodynamic understanding of the patient. This role as an investigator of physiology remains a defining role of the best invasive cardiologists; a thorough diagnostic catheterization constitutes a valuable part of almost all studies performed, even in the current era of intervention. An equally important role is to assist in planning management and to perform necessary transcatheter interventions as indicated, part of the integrated care of the patient with congenital disease. The ideal care of the most anatomically complex patients will likely require an orchestrated series of both open surgical and catheter-based procedures to achieve good, long-term, functional outcomes. A third, and more recent, role of the interventional cardiologist is to provide definitive therapy via a minimally invasive route, for some highly selected cardiac defects, as an alternative to surgery.

For decades, traditional biplane angiographic imaging constituted an important component of anatomic assessment of congenital heart disease. Expertise in acquisition and interpretation of these images secured the role of angiography in the preoperative investigation of patients with most major anatomic defects. The enormous volume of information provided by this modality has, fortunately, been exhaustively catalogued by Freedom and colleagues.¹ Preoperative anatomic information is now routinely and comprehensively acquired by noninvasive imaging modalities, primarily echocardiography, and increasingly, magnetic resonance imaging (MRI) or computed tomography (CT), as discussed in [Chapter 106](#). Valvar anatomy is beautifully displayed using transesophageal or three-dimensional echocardiography; ventricular volumes and function are quantified using MRI. Vascular abnormalities, such as aortic arch anomalies, or the complex venous patterns in heterotaxy syndrome, can similarly be well rendered through CT or MRI reconstruction.² These modalities will no doubt continue to undergo improvements in ease of acquisition, image resolution, and post-processing capabilities, likely avoiding the need for diagnostic angiography in all but rare cases. With currently available technology, vascular beds in which angiography remains the gold standard include pulmonary vessels beyond the hilum, and the coronary arterial bed, particularly in younger and smaller patients with highly atypical variants ([Fig. 107-1](#)).³

With the changing, and increasingly interventional, role of catheterization, the need for integration of three-dimensional anatomic information into the procedure has driven the development of “overlay” technologies and transfer/display of non-angiographic imaging data into the catheterization laboratory. As a natural evolution, the techniques and technology to acquire three-dimensional angiographic data sets have developed and matured to the point of incorporation into clinical practice in many centers. For patients who may also have indications for direct hemodynamic measurement and are candidates for intervention, this alternative provides the advantage of giving the interventionalist highly directed, immediate, as-needed, anatomic information at the time of catheterization. This advantage obviously needs to be considered in the context of the associated radiation exposure but will certainly warrant the angiographic information in

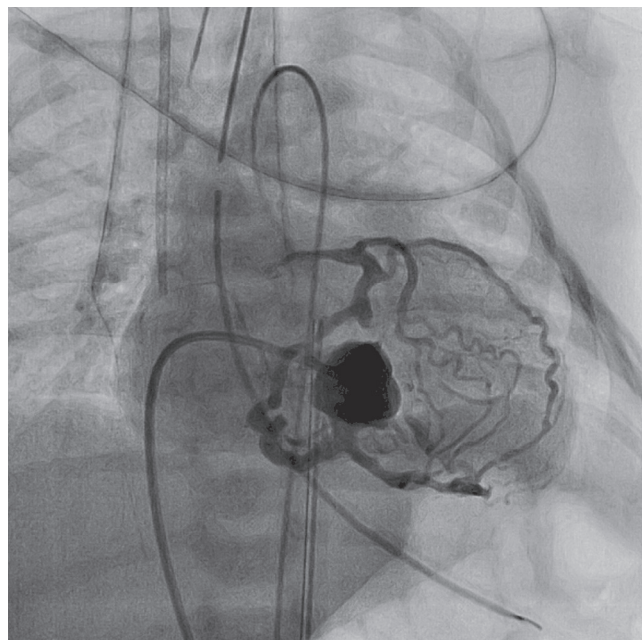


FIGURE 107-1 ■ Right ventricular angiography in a neonate with pulmonary atresia and intact ventricular septum. Injection in the right ventricle opacifies the entire coronary artery system and documents right coronary ostial atresia.

some cases. The feasibility of MRI-guided cardiac catheterization has been shown, and MRI-guided interventions have been performed in experimental settings.^{4,5} To date, limitations have been posed by the availability of adequate MRI-compatible intravascular tools and by the processing speed of MRI systems, which lack the real-time feedback of fluoroscopy.

Much hemodynamic information can also be derived from echocardiography and MRI, as is discussed in great depth in [Chapter 106](#). In some cases, there is no substitute for directly measured pressures that must be obtained invasively. When the best possible estimate of pulmonary vascular resistance is critical—as in the case of (1) pulmonary hypertension, (2) pretransplant evaluation, or (3) preoperative risk assessment for single ventricle palliation—cardiac catheterization is performed despite the availability of other methods. Similarly, even with a myriad of noninvasive indicators of diastolic function, direct measurement of the end-diastolic pressure is not infrequently an indication for catheterization. In the case of both pulmonary vascular assessment and measurement of filling pressures, the catheterization procedure also provides the opportunity to perform maneuvers to understand physiologic responses to intervention, such as administration of nitric oxide, expansion of intravascular volume, infusion of inotropes, or manipulation of pacing parameters. Fortunately for the invasive cardiologist, cardiac catheterization is a highly interactive process, and so as observations are made, hypotheses can be tested, disruptions such as test occlusions can be imposed, or interventions can be undertaken.

For surgical patients, the operating surgeon ultimately decides whether the accuracy and completeness of preoperative diagnostics is sufficient to plan and proceed

with the operation with the best possible outcome expected. For patients with complex disease or those with atypical management, early and steady involvement of the surgeon in the preoperative evaluation, including the conduct of the catheterization, is invaluable. A firm grasp of the advantages and limitations of data gained through all available techniques is critical, as is the ability to resolve apparently conflicting findings and place the appropriate weight on specific measurements or interpretations.

Although a series of preoperative hemodynamic catheterizations have been a staple of management for single ventricle disease, it is increasingly argued that many of these studies may be of marginal benefit and may not warrant the risk of an invasive procedure and radiation exposure. Most clinically well patients with favorable findings of noninvasive evaluation are likely to undergo successful bidirectional Glenn operation, or even Fontan, without excess of morbidity and without the benefit of a preoperative catheterization.^{6,7} The role of hemodynamic catheterization in this setting is ultimately determined by the reliability of noninvasive imaging modalities, primarily echocardiography, to screen for and accurately identify potential problems, such as pulmonary arterial distortion or arch obstruction, which should be addressed either in the catheterization laboratory or at the time of operation. Also, it is incumbent on the catheterizer to demonstrate the usefulness of some interventions that might occur at preoperative catheterization. The routine scheduling of catheterization before a Glenn or Fontan procedure is likely to receive increasing scrutiny in the future, and the added value of these studies will need to be defended.

HEMODYNAMIC ASSESSMENT

A full hemodynamic data set allows estimation of systemic and pulmonary blood flow, measurement of intracardiac and intravascular pressures with evaluation of pathologic gradients, and calculation of systemic and pulmonary vascular resistances. Two important vulnerabilities of traditional hemodynamic assessment in the catheterization laboratory are the designation of oxygen consumption, which is most often assumed, and the assumption of a steady state. Both of these limitations are more pronounced when dealing with more extreme or labile circulations. Ideally, the primary hemodynamic data can be obtained during catheterization under conditions that approximate each patient's baseline condition. The routine use of general anesthetic may pose some difficulty in this regard.

Flows

Systemic blood flow, or cardiac index, is commonly estimated either by a thermodilution technique or by using the Fick method. Calculation of flow using the Fick method is based on the principle that the total uptake (or release) of a substance by an organ is the product of blood flow to that organ and the difference between the concentrations of an indicator substance in the arteries and

veins leading into and out of that organ. When calculating the systemic blood flow, the whole of the systemic tissues are considered the organ, and oxygen is considered the indicator. By measuring the hemoglobin concentration, the percent oxygen saturation of hemoglobin, and the partial pressure of oxygen in a given sample of blood, the oxygen content can be calculated. The oxygen contents of aortic and mixed systemic venous blood samples serve as the necessary concentrations of indicator, and the patient's oxygen consumption represents the total uptake of indicator in a given unit of time (1 minute). The systemic blood flow, or cardiac index (Qs), can be calculated according to the following equation:

$$Q_s \text{ (L/min/m}^2\text{)} = \frac{\text{O}_2 \text{ consumption (mL O}_2\text{/min/m}^2\text{)}}{\text{systemic arterial - systemic venous O}_2 \text{ content (mL O}_2\text{/dL)} \times 10}$$

Although methods exist for measuring oxygen consumption during catheterization, most catheterization laboratories assume a level of oxygen consumption based on the patient's age, sex, and heart rate.

Pulmonary blood flow can be similarly calculated by calculating the oxygen content of pulmonary arterial and venous blood. With the systemic and pulmonary blood flow rates in hand, various shunts can be calculated, and the ratio of pulmonary to systemic blood flow, or Qp:Qs, can be determined. A rapid bedside calculation of Qp:Qs can be obtained by simply using the following equation:

$$Q_p : Q_s = \frac{\text{aortic saturation - mixed venous saturation}}{\text{pulmonary venous - pulmonary arterial saturation}}$$

Pressures

At catheterization, pressure measurements are obtained through fluid-filled catheters, which are vulnerable to various errors, ranging from an inappropriate zero level, to catheter entrapment with waveform distortion. Ideal catheters for pressure transduction provide free communication between the environment external to the catheter tip and the lumen of the catheter. Thus, larger-bore catheters, or catheters with multiple end or side holes, yield the most accurate depiction of the intracardiac waveform. A complete set of pressure measurements includes pressure waveforms recorded in all cardiac chambers and great vessels. When the left atrium is not entered directly, a pulmonary capillary wedge tracing is recorded in lieu of a left atrial trace. Systolic and diastolic pressures are noted in arterial vessels, whereas mean pressures are commonly noted in atrial or venous tracings. In the ventricle, the systolic and end-diastolic pressures are specified. Gradients can be documented by single catheter pullback or by simultaneous recordings in adjacent chambers or vessels using multilumen catheters or multiple catheters. When interpreting pressure gradients to determine the severity of obstructive lesions, the general principle of Ohm's law as it applies to hemodynamic variables must be considered, and the gradient should be considered in the context of the flow across the lesion.

Resistances

Having measured pressures and calculated flows, the resistance across a vascular bed can be calculated by relating the mean pressure change (ΔP) across that vascular bed to its flow. In the following equation,

$$R = \frac{\Delta P}{Q}$$

will thus be applied as

$$PVR = \frac{TPG}{Q_p},$$

where TPG is the transpulmonary gradient, which is equal to the mean pulmonary artery pressure minus mean pulmonary venous pressure, and PVR is pulmonary vascular resistance. The pressures are measured in millimeters of mercury (mm Hg), and flows are typically indexed and expressed in liter/min/m². Thus resistance is commonly expressed as mm Hg/liter/min/m², or indexed Wood units.

SEDATION AND ANESTHESIA

There is wide institutional variability in approaches to sedation for catheterization.⁸ Stimuli associated with catheterization include local pain related to percutaneous placement of access sheaths and more visceral pain related to intracardiac or intravascular manipulation and interventions. Provoked ectopy or arrhythmia, even if hemodynamically stable, may be disturbing to awake patients. Older, cooperative children without major hemodynamic compromise can, for the most part, undergo a routine catheterization safely and comfortably with conscious sedation and a spontaneous airway. In preparation for the procedure, oral benzodiazepines can be administered as anxiolytics before placing an intravenous line. Once intravenous access is established, a combination of benzodiazepines and opioids works well for most children who undergo catheterization without general anesthesia. Bolus doses of these drugs may be administered over the course of the procedure, or a continuous infusion may be preferable, depending on the nature and duration of the case. Alternative agents that have been used successfully with appropriate oversight are ketamine in conjunction with midazolam, and propofol infusion.

In the current era, general inhalational anesthetic is administered for most pediatric cases, to minimize the potential for patient discomfort. Some interventional cases warrant general anesthetic almost regardless of the tolerance or cooperativity of the patient, because of the anticipated duration of the procedure, high-risk nature of the intervention, necessity of patient immobility, and/or the need for both airway and hemodynamic control. Most infants and young children who are likely to be undergoing interventional procedures are most safely catheterized under general anesthesia. In addition, individuals who require uncomfortable additional impositions, such as placement of a transesophageal

echocardiographic probe for monitoring device closure of atrial septal defects (ASDs), or placement of internal jugular or subclavian catheters, are less likely to be distressed if under a general anesthetic.

Very rarely, the induction of general anesthesia or use of inhalational anesthetic may, in and of itself, be destabilizing, as can be the case in children with left ventricular (LV) outflow obstruction and/or coronary compromise, or those with severe restrictive physiology. Patients with severe heart failure who rely on endogenous catecholamine levels for maintenance of circulation can also be at risk with typical anesthetic induction techniques. Consultation with, and anticipatory inclusion of, members of a dedicated cardiac anesthesia team before catheterization serves the best interests of the patients and their caregivers and contributes to successful completion of the procedure.

VASCULAR ACCESS

Standard Arterial and Venous Access

For most catheterization procedures, intravascular access is established and maintained in both an artery and a vein. Even when a single venous catheter may provide access for a full hemodynamic data set, an arterial catheter is often placed for continuous intraprocedural monitoring. Placement of an arterial line in these cases should be weighed against the risk of compromised postprocedural perfusion of the extremity. Highly focused cases in stable, healthy subjects (e.g., ASD closure, pulmonary valvuloplasty) are usually performed with only a venous line, as are many pulmonary hypertension studies and routine cardiac biopsies. In some emergent clinical situations, when there is a premium on speed of intervention, the case should not be delayed while placing “elective” access, but rather the catheterizer should be creative about the most expedient access possible to complete the procedure.

Vascular access is typically established in the femoral vessels, as the consistent anatomy, superficial course, and relative sizes of these vessels allow straightforward percutaneous entry. The side-by-side placement of femoral venous and arterial lines allows the operator to stand over a well-circumscribed field that can easily be kept sterile and allows the patient to be continuously audited for catheter displacement or bleeding. Given the placement of standard anteroposterior and lateral cameras in a biplane lab, the femoral sites are also the most ergonomically favorable. Approach to the heart via the femoral vein and the inferior vena cava allows entry to almost all necessary catheter sites, including complex transseptal courses that can be difficult from a superior approach. At the conclusion of the procedure, catheter removal and control of the vessels in the groin with manual compression is relatively easy, and the procedure is well tolerated by individuals of all ages. In pediatric catheterization, manual compression is most often applied to achieve hemostasis. In larger patients, especially those who have had large caliber sheaths in the femoral vessels, the use of percutaneous site closure systems can

significantly reduce the time to hemostasis and the risk of late rebleeding.

Alternate Routes of Access

For some catheterizations, alternative sites of access are electively chosen. In newborns, part or all of the study can often be carried out from the umbilical vessels. The umbilical vein approach is ideal for balloon atrial septostomy in infants with transposition of the great arteries, and the use of this access site spares the femoral vein from potential injury by the relatively large sheath. Compared with standard femoral access, umbilical access makes complex venous catheter manipulation more difficult, and greater attention must be paid to maintaining sheath positioning. Only simple manipulation of the arterial catheter is possible, and catheter exchange should be limited, as the tortuous abdominal course from the umbilical artery to the aorta can predispose the patient to arterial trauma.

Access from the jugular or subclavian vein may be planned in some cases because of anatomic factors, such as the presence of a Glenn anastomosis, when there is typically no other navigable pathway to the pulmonary arteries. Non-femoral sites may also be electively chosen in smaller patients who require larger access sheaths, for example, for device delivery. The jugular or subclavian vein is typically larger than the femoral vein, and if both communicate in a usual way with the right atrium, these brachiocephalic vessels may be an alternative, or even preferred, route. In rare cases, transhepatic access is electively chosen to provide a short, direct course to the atrial septum or pulmonary veins for defect closure or creation, or for pulmonary venous sampling or interventions.

Increasingly, alternative (to the femoral vessels) access is used out of necessity, because the femoral vein or artery is occluded. Brachiocephalic veins may be used primarily when prior procedures or indwelling catheters have caused vascular compromise and loss of the femoral venous access. Similarly, a percutaneous transhepatic route can be used safely, even in infants.⁹ Importantly, we and others have found that in many cases of suspected or known loss of femoral vessels, taking a more aggressive approach with the use of specialized guidewires, catheters, and fluoroscopic guidance will often allow reestablishment or enlargement of femoral vascular continuity with the central circulation.¹⁰ This enables not only cardiac catheterization from these routes but placement of long-term indwelling lines. Long-term patency remains an issue and may be improved with placement of intravascular stents or antithrombotic therapy.

The cardiac surgeon may be asked to assist in a number of ways to facilitate the access for a catheterization procedure. In a backup capacity, surgical cutdown may be necessary when attempts at necessary percutaneous access fail. Most interventionalists have limited experience with these procedures and will require the assistance of a surgeon. This may involve cutdown on extremity vessels (femoral, radial, axillary) or on neck vessels. Surgical cutdown on the carotid artery can greatly facilitate aortic valve dilation in small infants, allowing for larger-caliber dilating balloons to be easily introduced and often for

easier retrograde passage through a highly obstructed valve.

Beyond extremity or neck cutdowns, the surgeon and interventionalist can work together to conduct procedures with a variety of alternative surgical exposures. A limited thoracotomy can enable a better angle of approach to the right atrium for device closure of large ASD, or a more controlled site of direct LV access for aortic valve delivery, or external control/reduction and visualization of the right ventricular (RV) outflow tract during placement of a transcatheter pulmonary valve. The hybrid stage I procedure is performed with open chest access to deliver the ductal stent directly from the main pulmonary artery and perform pulmonary arterial bands simultaneously. With the increasing use of catheter-based devices, many of which require relatively large delivery systems, surgical access to large intrathoracic vessels or even direct cardiac access, will likely become a more frequent opportunity for creative interaction between interventionalist and surgeon.

INTERVENTIONS

Balloon Atrial Septostomy

Rashkind and Miller reported the first balloon atrial septostomy in 1966, describing a new means of palliating the cyanotic child with transposition of the great arteries and launching the field of interventional congenital catheterization.¹¹ In the era of neonatal arterial switch operation, early postnatal septostomy allows preoperative stabilization, reduces the need for prostaglandin infusion (with its attendant morbidities), and can be lifesaving in neonates who lack favorable mixing. The potential for a causal relationship between preoperative septostomy and brain injury in neonates with transposition remains a matter of open debate.^{12,13}

There has been remarkably little change in the technique or equipment used since the first description of septostomy. A balloon-tipped catheter, introduced via the umbilical or femoral vein, is positioned in the left atrium through the patent foramen ovale and is rapidly accelerated across the septum into the right atrium (Fig. 107-2). Although traditionally performed under fluoroscopic guidance, results are equally satisfactory with echocardiographic guidance at the bedside in the intensive care unit, with only rare complications.¹⁴ Once access is established, the procedure takes only a few minutes, and immediate improvement in systemic saturations can be expected. Newborns now rarely need to be transported to and from the catheterization laboratory for the procedure.

Emergent septostomy can be lifesaving in the neonate with hypoplastic left heart syndrome (HLHS) and restrictive atrial septum, one of the few truly emergent call cases for the interventionalist. These patients are often deeply cyanotic and require ongoing hemodynamic support when they arrive in the catheterization laboratory, despite prostaglandin infusion. Cardiologists and surgeons who care for these infants increasingly recognize the benefit of immediate postnatal left atrial decompression to improve survival.¹⁵ When a small preexisting defect can

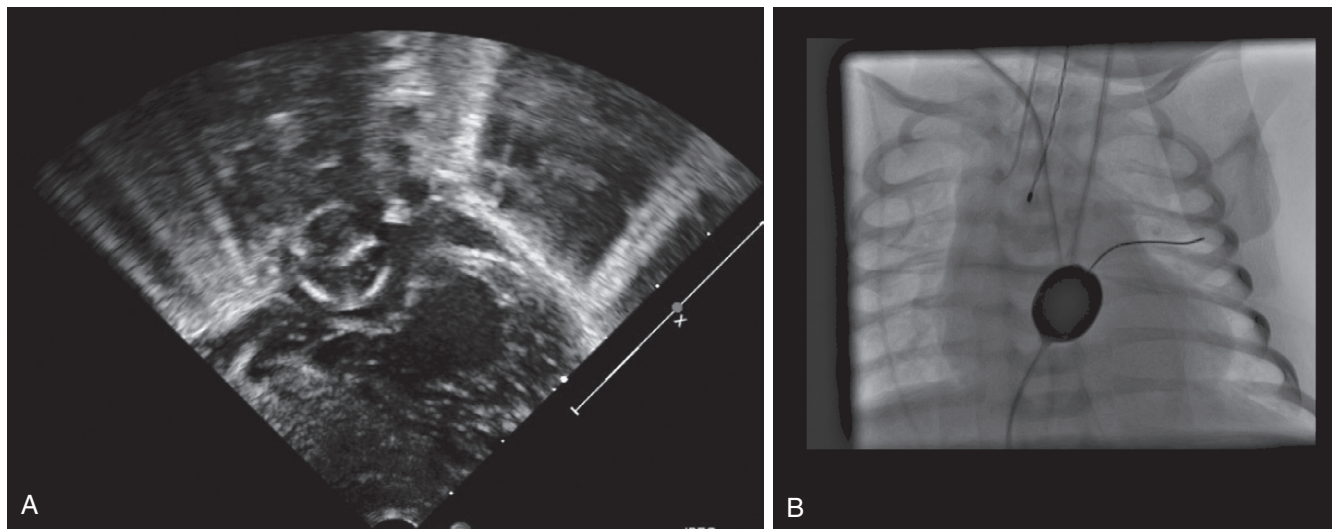


FIGURE 107-2 ■ The mode of imaging during balloon atrial septostomy depends largely on the location of the procedure. **A**, Echocardiographic image of the saline-filled septostomy balloon in the left atrium. **B**, Fluoroscopic visualization of the contrast-filled septostomy balloon in the left atrium over a wire course into a left pulmonary vein.

be crossed, a standard pull-through septostomy can be effective acutely, but restenosis occurs almost universally.¹⁶ Creation of an iatrogenic atrial defect by transseptal puncture, followed by static balloon dilation or stent placement (or both), may be more effective and durable but is associated with a known incidence of inadvertent cardiac perforation.^{17,18} This aggressive catheter-based approach may improve survival among patients with this disease, and fetal intervention may, in some cases, avoid catastrophic neonatal presentation altogether.¹⁹

Valve Interventions

The anatomic substrate of valvar obstruction in semilunar valve disease is most commonly commissural fusion, which lends itself to relief by “splitting” of the commissure, which can be accomplished effectively, perhaps not elegantly, by balloon valvotomy. Transcatheter balloon valvotomy is now primary therapy, in many centers, for pediatric valvar pulmonary and aortic stenosis, with good results. With regard to semilunar valves, most patients respond favorably to this simple mechanical enlargement of the effective orifice. In contrast, mechanisms of obstruction in congenital atrioventricular valve disease are less well understood and likely much more complex anatomically. Thus, mitral and tricuspid valve dilations are practiced relatively infrequently and with mixed results, highly dependent on the underlying valve morphology. In fact, there is no published experience with a significant series of patients who have undergone tricuspid valve dilation in the catheterization laboratory.

Pulmonary Valvuloplasty

Since Kan and colleagues reported the first static balloon dilation of the pulmonary valve in 1982, this procedure has become a universally practiced treatment of isolated valvar pulmonary stenosis.²⁰ The typical indication for

intervention is RV hypertension at or near systemic levels. A number of dilating techniques have been applied with good results, and long-term follow-up information is available. The Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry investigators reported excellent results in a large group of pediatric patients with pulmonary stenosis, with 89% of patients achieving gradients of less than 35 mm Hg after the procedure.^{21,22} The use of markedly oversized balloons in an attempt to maximize gradient reduction risks significant pulmonary insufficiency, generally believed to be of little clinical consequence in the short term but increasingly recognized as a long-term morbidity.^{23,24} Experimental induction of RV outflow tract damage, and the clinical observation of increased pulmonary insufficiency after oversized balloon dilation, support the current practice of moderately oversizing the balloons, with balloon-to-annulus ratio limited to 1.4:1.^{21,25,26}

When the mechanism of obstruction is a highly dysplastic valve, such as that seen in patients with Noonan syndrome, results of balloon valvuloplasty are less predictable; these patients may require surgery for adequate gradient relief.²² Other types of arteriopathy, such as that seen in association with Williams syndrome, may similarly exhibit limited response to balloon valvuloplasty; it is often the case that contribution of supravulvar pulmonary stenosis to RV outflow obstruction is underestimated prior to direct measurement and attempted dilation.

Pulmonary valvuloplasty techniques developed in older children have been successfully applied to the neonate with critical pulmonary stenosis, and balloon dilation is now essentially standard for primary treatment in this population as well.^{27,28} The valve is crossed antegrade from the RV outflow tract with a floppy-tipped wire. In the presence of a patent ductus arteriosus, an antegrade wire course into the descending aorta facilitates balloon passage across even very highly obstructed valves, and valve dilation will typically allow

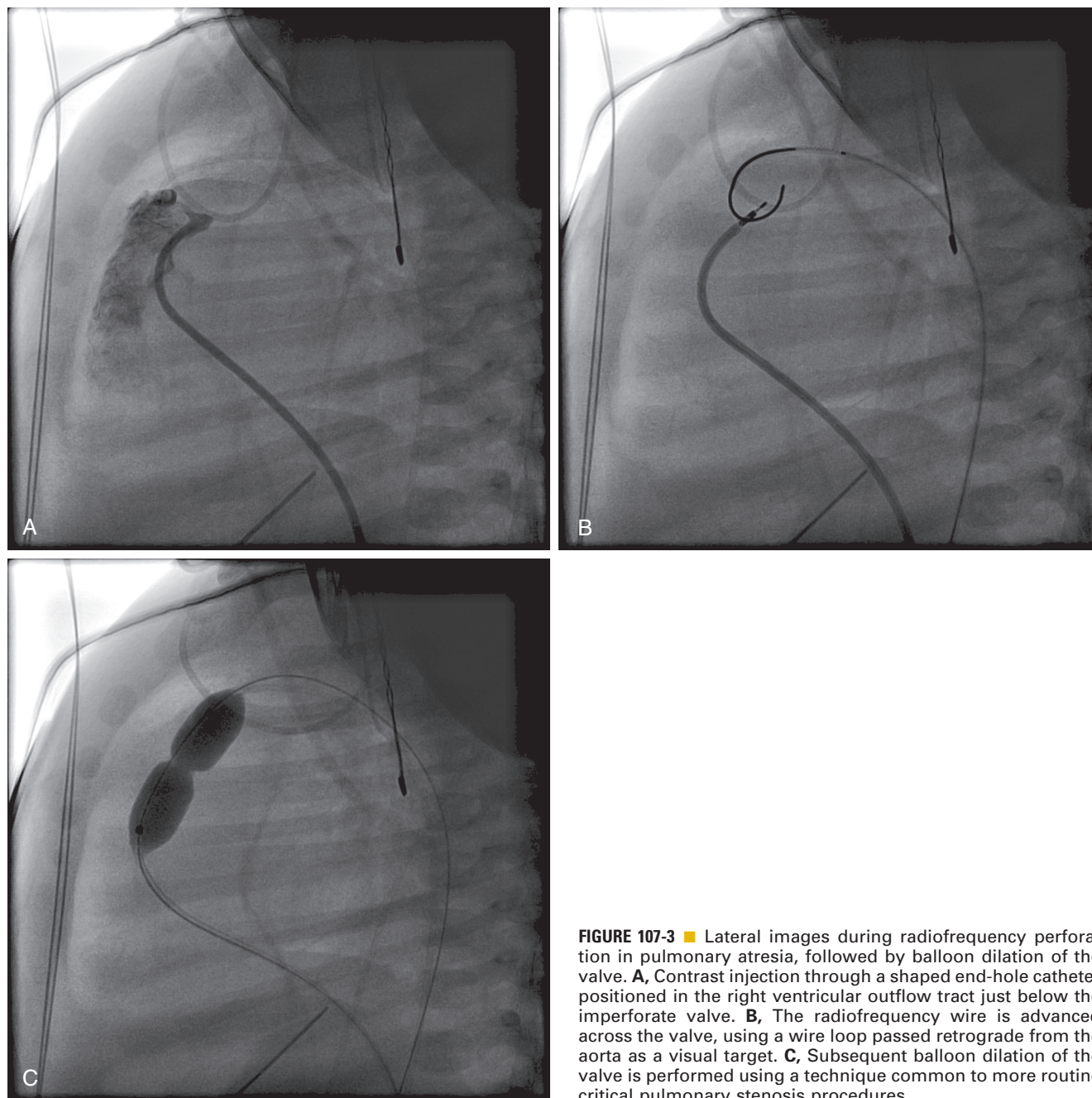


FIGURE 107-3 ■ Lateral images during radiofrequency perforation in pulmonary atresia, followed by balloon dilation of the valve. **A**, Contrast injection through a shaped end-hole catheter positioned in the right ventricular outflow tract just below the imperforate valve. **B**, The radiofrequency wire is advanced across the valve, using a wire loop passed retrograde from the aorta as a visual target. **C**, Subsequent balloon dilation of the valve is performed using a technique common to more routine critical pulmonary stenosis procedures.

discontinuation of the prostaglandins and result in definitive, nonsurgical therapy.

In some neonates with membranous pulmonary atresia and intact ventricular septum who are candidates for biventricular outcome, neonatal RV decompression can be accomplished percutaneously as a first step in management. An apparently atretic valve can be probed with a floppy-tipped wire, and, if truly imperforate, the valve can then be passed using a radiofrequency wire (Fig. 107-3).^{29,30} After the valve is crossed, serial balloon dilations can eliminate the valvar contribution to RV outflow obstruction, potentially with less resultant pulmonary regurgitation than would be acquired surgically, and allow some period of neonatal palliation prior to more definitive surgery. Establishment of sufficient pulmonary

blood flow through a Blalock-Taussig shunt or through maintenance of ductal patency is often still necessary, because of a prohibitively restrictive RV or persistent subvalvar obstruction.³¹

Aortic Valvuloplasty

When expanding the application of percutaneous valvuloplasty to aortic valve dilation, interventional cardiologists were presented with a number of new concerns. Intrinsic differences in the compliance characteristics of the stenotic aortic valve relative to that of the pulmonary valve required a unique determination of optimal balloon size. Identification of the ideal balloon-to-annulus ratio at the aortic valve took on heightened importance because

of the clinical implications of significant aortic regurgitation. Additionally, retrograde catheter courses from the femoral artery (e.g., advancing the dilating catheter from the ascending aorta into the left ventricle) increased the risk of vascular entry site injury and consequently imposed greater demand for low-profile equipment.

The first report of successful balloon dilation of an aortic valve appeared in 1984.³² The procedure is now routinely performed with good results in newborns, infants, and older children. Indications include moderate to severe aortic stenosis in the absence of more than moderate aortic regurgitation. Rarely in the older infant or child is there coexisting LV dysfunction, although LV hypertrophy is usually apparent, and with progressive degrees of obstruction and age, arrhythmia may become a more prominent clinical feature. In a large series of 192 procedures, percutaneous aortic valvuloplasty resulted in effective relief of severe aortic stenosis (reduction in peak gradient from 77 to 30 mm Hg).³³ Experience has shown that dilation using a balloon inflated to 80% to 100% of the annular dimension of the valve is effective.³⁴ Most procedures can be performed from the femoral artery, even in neonates. Techniques for antegrade, transvenous aortic valve dilation have been described, although this approach is used infrequently in current practice.^{33,35} Freedom from reintervention has been reported in both surgical and nonsurgical series and is estimated at 50% at 8 years after intervention.^{36,37} Repeated dilation of the aortic valve in the case of predominantly obstructive disease is possible, and gradient reduction of 50% at the second procedure can be expected.^{38,39}

Two large single-center experiences with neonatal aortic valvuloplasty have reviewed this procedure comprehensively, describing acute effects as well as observations of ongoing development of the valve. Infants were referred for the procedure based on prostaglandin dependence and/or LV dysfunction. The procedure was highly effective, with relative reductions in gradient of 54% and 69% as measured during the procedure.^{40,41} In the past, this procedure had a significant rate of associated mortality, but this rate has decreased over the almost 2 decades since the first procedure and is now approximately 4%.⁴¹ After retrograde aortic valvuloplasty, femoral pulse loss is common but can be treated with heparin infusion or thrombolytic therapy with some recovery.

New aortic regurgitation occurs in approximately 15% to 30% of infants after neonatal valvuloplasty.^{34,41} Among infants treated primarily with valvuloplasty, a steady increase in the frequency of significant aortic insufficiency has been noted. In a review of 113 young infants, freedom from moderate or severe aortic regurgitation was 65% at 5 years. In this group, survival free of reintervention was 48% at 5 years, a rate similar to that noted in earlier and more heterogeneous series, with many patients presenting for redilation and 16% proceeding to aortic valve replacement within 5 years. Independent predictors of shorter reintervention-free survival included younger age, higher gradient, and larger balloon-to-annulus ratio.

Often, in the setting of multiple left-sided obstructions, a hypoplastic aortic annulus contributes to obstruction that is not acutely relieved by commissural

modification. Of interest, among infants having catheter aortic valvuloplasty, hypoplastic aortic annuli have been observed to demonstrate catch-up growth of sorts, with normalization of hypoplastic left heart structures, including the aortic annulus and the left ventricle, observed within the first year of life. Whether this is directly related to anatomic effects of balloon stretch on the annulus, or secondary to changes in left heart flow following valve leaflet modification, is unknown.

Mitral Valvuloplasty

Whereas the aim of pulmonary and aortic valvuloplasty is to create tears along fused commissures to effect gradient relief, mitral valve dilation appears to create a tear, typically of the anterior leaflet itself or submitral apparatus, that may allow for increase in overall inflow orifice. The technique, applied to patients with rheumatic mitral valve disease, was first reported by Lock and associates in 1985.⁴² Pressed by poor surgical outcomes in young patients with congenital mitral stenosis, Spevak and colleagues attempted balloon mitral valvuloplasty in nine patients, predominantly infants and toddlers.⁴³ The procedure was successful in seven of nine patients with heterogeneous valve morphologies. Further exploration of this innovative intervention confirmed the feasibility of achieving short-term hemodynamic benefit and symptomatic improvement.⁴⁴ Follow-up over a 2-year period showed only 70% survival at 2 years despite dilation, whereas 55% survival was predicted among similar patients undergoing surgery. Indications for mitral valve dilation typically include left atrial and right ventricular hypertension; growth failure is commonly seen in these patients. Attempts to manage congenital mitral stenosis via balloon dilation can be expected to reduce the gradient by 30% using contemporary techniques, with the induction of significant mitral regurgitation in 28% of patients.⁴⁵ Survival at 5 years after surgery has improved from 69% in the early experience to 87% more recently. Even as surgical approaches to valve repair and even pediatric replacement continue to improve, mitral valve dilation will likely continue to play a role in the management of these difficult patients, many of whom will undergo multiple operations over a lifetime.

Pulmonary Valve Replacement

Management of valvular disease in the catheterization lab has been defined for more than 30 years by balloon dilation to relieve obstruction; transcatheter interventions to manage valvar regurgitation did not exist. Only within the past 5 years has the potential to restore valve competency percutaneously become a clinical reality. Among the growing population of older pediatric and adult patients with prior RV outflow tract reconstruction, chronic pulmonary insufficiency is associated with deleterious effects on clinical status and cardiac function.^{46,47} Increased attention to this phenomenon over the past decade spurred changes in clinical practice, favoring semi-elective pulmonary valve replacement in older pediatric patients with RV dilation or dysfunction. This trend in clinical practice coincided with the development of a

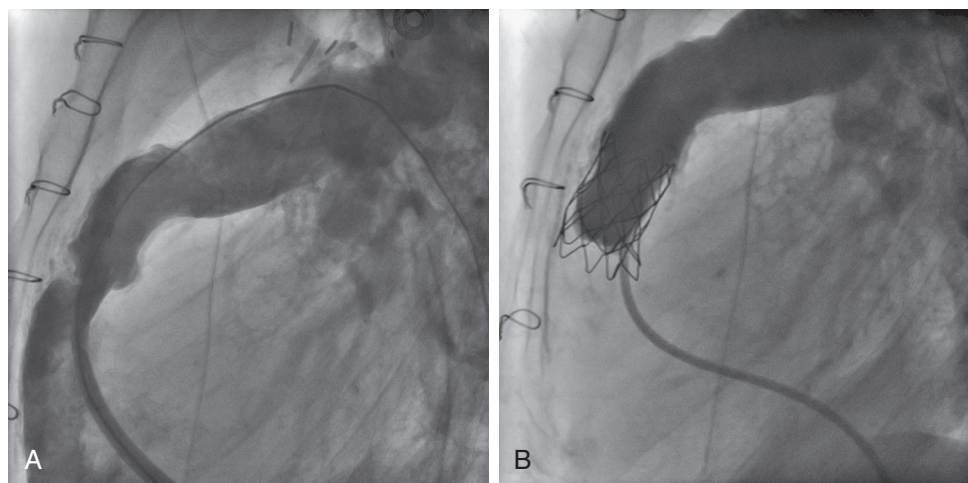


FIGURE 107-4 ■ Right ventricular outflow tract angiography in a lateral projection. The highly obstructed and calcified conduit is seen in an immediate retrosternal position. **A**, Contrast injection in the distal conduit demonstrates antegrade flow along the wire course into the right pulmonary artery, as well as severe pulmonary regurgitation opacifying the right ventricle. **B**, After placement of a stent-mounted bovine jugular valve, the pulmonary regurgitation is abolished.

stent-based valve and percutaneous delivery system and provided a candidate population in which to advance the concept of percutaneous valve replacement. A unique convergence of conditions—(1) driving clinical interest, (2) broad interventional experience with stent delivery in RV to pulmonary artery conduits, (3) surgical experience with bioprosthetic valve materials, and (4) multiple precedents for industry collaboration in device development—allowed the process to move rapidly.

The approval of the Melody stent-based, bovine jugular vein valve in 2010 marked a major milestone in interventional catheterization, with subsequent widespread use of this device and dissemination of the procedure.⁴⁸ Although the device was approved for use in patients with dysfunctional RV to pulmonary artery conduits, patients with native outflow tracts and sufficient narrowing to seat the device have now also been treated.⁴⁹ These patients are the target population of newer devices currently under study, tailored to the highly variable anatomy of the postoperative native outflow tract. The original device, used when indicated for conduit failure, effectively relieves obstruction and decreases pulmonary regurgitation as observed angiographically, echocardiographically, and by MRI-derived pulmonary regurgitant fraction (Fig. 107-4).⁵⁰⁻⁵² These improvements are sustained in medium-term follow-up. Perhaps of greatest significance is a demonstrable improvement in New York Heart Association class and measured exercise parameters.⁵³ Early concerns about valve failure related to stent fracture have been addressed in part by changes in delivery technique (pre-stenting), although debate continues regarding the possibility of predisposition of the device to infection.^{54,55} The concept of repeated re-replacement with serial, nested, stent-based devices offers, in theory, the potential for lifetime avoidance of reoperation. It seems likely that many patients will be managed with initial placement of a surgical bioprosthetic valve with subsequent catheter-based interventions. The off-label use of the Melody for valve replacement in other positions, including aortic and mitral, has been described.⁵⁶

Vascular Interventions

All manner of congenital and postoperative vascular obstructions, both venous and arterial, are responsive to balloon angioplasty. Although indications and results vary, the principles of effective angioplasty are common, regardless of the target site. Effective angioplasty is achieved by creating a controlled tear in the vessel wall—ideally, a partial-thickness medial tear. The conditions under which this tear can be produced depend on the intrinsic compliance of the vessel wall and the severity of the obstruction. Mild stenoses and highly compliant lesions are particularly difficult to dilate effectively but may respond to endovascular stent placement. In contrast, severe noncompliant obstructions present significant risk for an uncontrolled transmural tear. To perform angioplasty safely, empiric guidelines around technical variables have been established based on the nature of the vessel being intervened on. Common indications for balloon angioplasty in the treatment of congenital heart disease are coarctation of the aorta and pulmonary arterial stenosis.

Coarctation of the Aorta

Restenosis occurs after surgical repair of coarctation of the aorta, and its incidence has been estimated at 10% to 20%, related to age at repair, and the degree of associated arch hypoplasia.⁵⁷ After pioneering work by Sos and colleagues⁵⁸ and Lock and coworkers⁵⁹ to test the feasibility of balloon dilation on postmortem or surgically excised specimens, Singer and colleagues⁶⁰ reported the first successful balloon dilation of recoarctation in a patient in 1982. Kan and coworkers⁶¹ described the first seven patients in 1983, and, in 1990, the VACA Registry results showed gradient reduction to less than 20 mm Hg in 78% of patients treated.⁶² In 1991, Hijazi and coworkers argued that balloon dilation should be the treatment of choice for recurrent coarctation, based on an 88% success rate and a low rate of complications.⁶³ The field has

generally concurred, and recurrent coarctation is now largely managed in the catheterization laboratory.⁶⁴

Native coarctation of the aorta was one early target for catheter intervention, although the observation of aneurysm formation tempered initial enthusiasm. Through the current era, the reported efficacy of balloon dilation for native coarctation has failed to support primary, non-surgical intervention. Among infants younger than 3 months, authors have described favorable results of balloon dilation of native coarctation³² but with restenosis occurring in more than 50% of patients.^{65,66} Concern over these high restenosis rates and a 5% to 15% rate of late aneurysms has precluded widespread acceptance of angioplasty as primary therapy in unoperated infants.⁶⁷ Therefore, in these younger patients, balloon dilation is pursued primarily as a palliative procedure. Rates of iliofemoral arterial complications, which were high during the early experience with this infant population, have become lower as low-profile dilating balloon catheters have evolved.⁶⁸ In rarer, late-presenting older children and adults with unoperated coarctation, primary catheter intervention can be effective and may be considered an alternative to surgery, although there are few data to support this as a superior approach.⁶⁹ Patients with mild obstruction and potentially poorly developed collaterals may be good candidates for therapy without aortic cross-clamping.

Although the earliest discussion of stent implantation in coarctation described the treatment of severe aortic obstruction, the procedure has proven uniquely effective in treating disease at the other end of the spectrum—mild native or recurrent obstruction.⁷⁰ In this setting (peak gradient < 20 mm Hg), standard balloon angioplasty may be ineffective in the setting of a highly compliant lesion or segmental obstruction. Stent placement can allow a controlled enlargement of a mildly narrowed aorta over the length of the stent.⁷¹ Reduction of even relatively low gradients has been associated with improvement in LV end-diastolic pressure.⁷² Freedom from reintervention after stent placement for coarctation is 50% at 5 years, notably higher than in surgical series, reflecting a deliberate staged approach to transcatheter relief of some obstructions. This high rate of reintervention also reflects aggressive treatment of even mild obstruction, with 40% of reinterventions performed in patients with a gradient of 10 mm Hg or less. Overall, pathologic aortic mural injuries such as aneurysm, dissection, or rupture occurred at the time of dilation or stenting in 3 of 153 patients (2%).⁷³ These potentially catastrophic situations can be managed with placement of a covered stent, and this device is now available in trial. Whether covered stents will prove to be safe as a primary therapy for coarctation or should only be reserved for higher risk situations or as rescue therapy remains to be seen.

Pulmonary Artery Stenosis

As with coarctation, proximal pulmonary arterial obstructions confined to the prehilum area can often be relieved surgically, and balloon angioplasty provides an alternative to an open approach. In contrast, more distal obstructions, often inaccessible to the surgeons, are quite amenable to transcatheter therapy. These obstructions can

occur in association with congenital heart disease, most commonly tetralogy of Fallot variants, or in association with arteriopathies such as Williams syndrome.⁷⁴ Although a poorly studied population before now, older patients with chronic thromboembolic disease may also benefit from transcatheter therapy for relief of distal obstructions.^{75,76}

Tools for pulmonary artery dilations have improved considerably over the recent decade. Initial reports used compliant, low-pressure balloons, with perhaps predictably poor results. Since that time, high-pressure balloons, cutting balloons, and now ultra high-pressure balloons have become staples in labs treating these lesions.

Indications for balloon dilation or stenting of pulmonary arteries include elevated RV pressure, diminished distal flow, or hypertension in unaffected segments as a result of flow maldistribution. Postoperative anastomotic lesions, typically of the proximal branch pulmonary arteries, generally respond well to standard balloon dilation, as do some congenital stenoses and hypoplasia. In contrast, pulmonary arterial obstruction resulting from vessel kinking or compression often requires stent placement to achieve relief.

Using low-pressure balloons, with highly variable relative dilating diameters, the earliest pulmonary artery dilations achieved success in only 38% to 59% of cases.^{58-60,77-79} Results improved as high-pressure balloons came into use; these provided relief of obstruction in up to 72% of vessels.⁸⁰ Despite the use of high-pressure balloons, a significant proportion of pulmonary arterial obstructions remained resistant to balloon angioplasty. Newer strategies to treat these lesions involve cutting balloons that are used to initiate controlled vascular injury at the site of resistant lesions.⁸¹ By using coronary cutting balloons on small-vessel pulmonary arterial lesions resistant to high-pressure angioplasty, operators have substantially increased lumen diameter in 92% of previously refractory vessels.⁸² After the introduction of larger, peripheral cutting balloons, this technology has been applied to larger-caliber vessels with good effect, although the percentage increase in lumen diameter was less dramatic in these larger vessels.⁸³ The most recent addition to the treatment of pulmonary artery stenosis is the ultra high-pressure balloon, developed to treat peripheral vessels or grafts in adults. These balloons, capable of achieving inflation pressure of 30 atm (relative to 4 to 8 atm of a conventional balloon) can be applied to treat highly resistant lesions, whether native vascular obstruction or previously placed stents in noncompliant segments.⁸⁴

Balloon angioplasty of pulmonary vessels is associated with an appreciable rate of complications, some of which can be life-threatening. When obstruction to highly stenotic vessels is relieved, distal vessels may be exposed acutely to higher pressure, resulting in pulmonary edema.⁸⁵ This consequence can usually be averted by limiting relief of obstruction to create mean distal pressures not in excess of 25 mm Hg. Direct trauma to the dilation site can create obstructive intimal flaps, contained tears, and vascular rupture.⁸⁶ Strategies to manage these complications should be directed at reestablishing an unobstructed lumen (in the case of a flap), maintaining

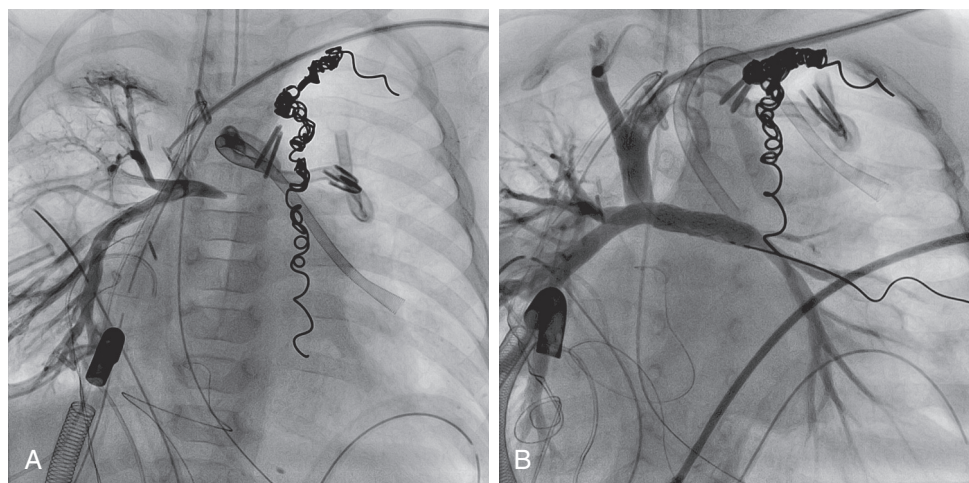


FIGURE 107-5 ■ Early postoperative pulmonary angiography in an infant after a bidirectional Glenn operation. Flow from the superior vena cava travels exclusively into the right pulmonary artery. **A**, A “beak” is evident at the site of acquired left pulmonary artery atresia. **B**, After wire recanalization and stent placement, bilateral pulmonary flow is reestablished.

distal flow, and controlling any hemorrhage. In some cases, uncontrolled tears may be managed by temporary occlusion of upstream vessels, when this maneuver can be hemodynamically tolerated. Occasionally, feeding vessel occlusion, using a coil or other occlusion device, may be necessary.

Balloon-expandable stents have been used successfully to relieve pulmonary arterial obstruction since the early 1980s. Stents were first applied predominantly in proximal branch pulmonary artery stenoses in larger children, simply because of the size of the available stents, the size of the stent or balloon delivery system, and the risk of iatrogenic “restenosis” caused by the stent after somatic growth. After experimental evidence that endovascular stents could be safely and effectively redilated, McMahon and associates reported on mechanisms of successful redilation in a large group of patients.⁸⁷ The introduction of more flexible, smaller, and lower-profile stenting systems in the early 2000s resulted in stents being placed more frequently in distal vessels and in infants and smaller children.^{88,89} Using tools such as ultra high-pressure balloons, the potential for some degree of further stent expansion at a later date can be presumed. In the case of early postoperative anastomotic obstruction, stent placement may be preferable to simple angioplasty, because vessel occlusions or stenoses can be opened without using oversize balloons and risking vessel or suture line rupture (Fig. 107-5).⁹⁰

Conduits, Systemic and Pulmonary Veins

Transcatheter angioplasty techniques have also proved valuable in extending the life of allograft or prosthetic shunts in palliated postoperative patients, such as those with RV to pulmonary artery conduits after stage I for HLHS or those with conduits used in RV outflow tract reconstruction as in tetralogy of Fallot with pulmonary atresia. These grafts can become obstructive and require replacement because of contraction, kinking, neointimal “peel” accumulation, external compression, or simply patient growth. Standard balloon angioplasty

rarely provides definitive relief, although ultra high-pressure balloons have been used with greater success.⁹¹ Predictably, balloon expandable stent placement can effectively delay the need for surgical reintervention although at the expense of loss of competency of any existent valve.^{92,93} In a single-center review of 221 patients with stents implanted in RV to pulmonary artery conduits, acute hemodynamic changes after stenting included significantly decreased RV systolic pressure and peak RV to pulmonary artery gradient. Stents could be redilated, and at subsequent catheterization, additional stents could be placed. By Kaplan-Meier analysis, median freedom from conduit surgery after stenting was almost 3 years. Younger age, smaller conduit diameter, and higher ratio of RV to aortic pressure predicted shorter freedom from surgery.⁹⁴

Systemic venous obstruction occurs in a number of postoperative congenital cardiac settings, most notably in patients after atrial switch procedures. In both cardiac and noncardiac patient populations, systemic venous obstruction occurs with increasing frequency as a result of chronic indwelling catheters and, in some cases, cannulation for extracorporeal membrane oxygenation. Both angioplasty and stent placement have been applied successfully in the setting of superior vena cava obstruction.^{95,96} Patients with extensive venous obstruction have been treated for the classical symptoms of superior vena caval syndrome but also for some less well understood indications, including respiratory insufficiency.⁹⁷ In these cases, elevated superior caval pressure is thought to contribute to impairments of pulmonary lymphatic drainage and thus lung function. The superiority of stent placement over simple balloon angioplasty with regard to gradient relief and durability of result is suspected but has not been firmly established, although stent placement should be carefully considered in the young infant with anticipation of significant superior vena cava growth over a lifetime.

Pulmonary vein stenosis that occurs either as “isolated” disease or in the context of congenital heart disease, particularly in young infants, remains one of the most challenging lesions to treat, either by surgery or with

transcatheter techniques. On the basis of favorable results after balloon dilation angioplasty of congenital lesions, Driscoll and colleagues attempted pulmonary vein dilation in the early 1980s, and they observed early restenosis associated with clinical decline.⁹⁸ Endovascular stents applied to pulmonary venous obstruction almost a decade later failed to alter the course of the progressive and intractable reobstruction, which rapidly redeveloped within months of intervention.^{99,100} All manner of therapies have been attempted in limited settings, including mass removal/endovascular biopsy, covered stents, drug-eluting stents, and rotational atherectomy. None of these have provided any measurable advantage in the treatment of pulmonary vein stenosis. Currently, we use standard high-pressure and cutting balloons rather than more elaborate tools, reserving stenting for multiply reobstructed vessels or those with clear kinking at the left atrial junction.^{101,102} None of these therapies has consistently provided lasting relief of obstruction/favorable remodeling; thus, frequent reintervention is often necessary, sometimes as often as every 8 to 10 weeks.

Defect Occlusion

To date, transcatheter relief of obstructions, whether valvar or vascular, has been accomplished largely by applying relatively simple devices, such as angioplasty balloons or balloon-expandable stents. In contrast, the field of defect closure has been defined by the variety of devices developed. In 1987, after almost 20 years of development, Rashkind and colleagues described the use of an occluding device to treat patent ductus arteriosus (PDA).¹⁰³ Since that time, numerous catheter-based devices have been used to close defects without surgery. These devices have encompassed a range of sizes, configurations, materials, delivery systems, and release mechanisms. They not only have been implanted in patients with PDA, ASD, and ventricular septal defect (VSD) but also have been used for innovative indications, including such lesions as perivalvular leak, coronary artery fistula, and pulmonary arteriovenous malformation.^{104,105}

Despite the broad range of devices produced and evaluated, only a few have been fully approved and marketed for use in patients with congenital heart disease. Perhaps the greatest evolution in the fields of pediatric interventional cardiology and device closure has been the engagement of the regulatory process by the interventional community. Only by carefully designing and carrying out intelligent, nonrandomized, multicenter trials has there been sufficient enrollment of patients and data collection to support device approval applications. Even so, the number of patients enrolled and devices implanted is typically in the range of a few hundred, and follow-up periods are relatively short. Ongoing evaluation of each approved device is the responsibility of the implanting interventional cardiology community.

Patent Ductus Arteriosus, Collaterals, and Shunts

The development and ultimate U.S. Food and Drug Administration (FDA) approval of the Amplatzer duct

occluder device changed the entire approach to PDA. The history of attempts at device closure of PDA provides a useful introduction to general principles of transcatheter defect closure. In 1967, Porstmann and colleagues reported the use of foam plugs to occlude PDA via a transcatheter approach.¹⁰⁶ After this isolated experience, a full decade elapsed before the Rashkind PDA occluder was developed to close moderate-size PDAs. Although more effective than the previous device, a high incidence of incomplete closure made it a poor alternative to surgical closure, and it never came to market.^{103,107} Ultimately, PDAs were effectively closed by catheter delivery of the Gianturco vascular occlusion coil used in an off-label fashion. This conceptually simple, inexpensive, versatile, and easy-to-use device rapidly came into widespread use. Coil occlusion of small PDAs (<3 mm) became a routine catheter procedure. Most small PDAs could be safely and effectively closed using a single coil,^{108,109} and closure rates when multiple coils were available were 93%.^{110,111}

Closure of larger PDAs continued to prove a challenge, often requiring multiple coils or advanced coil delivery techniques, with attendant increase in rates of embolization and residual flow. One device, essentially a sac designed to retain a large coil cluster, was approved for vascular occlusion, but the combination of a large delivery system, expense, and a complex delivery mechanism were unacceptable to most implanters.¹¹² The unsatisfactory results of coil-based approaches to large PDAs spurred a search for a different type of device, and the plugging concept was reexplored. In 1998, the Amplatzer duct occluder device received approval after a multicenter trial demonstrated successful closure of larger PDAs (>3.5 mm), with closure rates of 100% at the 1-year follow-up. The advantages over the existing products included ease of use, low-profile delivery, and retrievability.¹¹³ The recently approved Nit-Occlud device, resurrecting the coil concept, further increases the likelihood that the isolated PDA in an older infant or child will rarely be encountered by the cardiac surgeon.¹¹⁴ Although the hemodynamically important PDA in the premature infant has also been treated using these devices, in this population, surgical intervention remains the standard.¹¹⁵

In the setting of more complex heart disease, devices such as embolization coils and vascular occluders can be used to advantage in management of unwanted extracardiac shunts, whether biologic or prosthetic, as well as in the management of intracardiac defects. Aortopulmonary collateral vessels, commonly seen in patients with palliated single ventricle disease, may impair postoperative recovery by imposing a disadvantageous volume load on the single ventricle. Furthermore, they can inhibit efficient oxygenation by competing with caval flow for entry to the peripheral pulmonary vasculature, and they may contribute to persistent pleural effusions postoperatively.¹¹⁶ Closure of these vessels to decrease unwanted return into the field at the time of operation remains controversial, as flow studies have questioned the extent of their contribution to pulmonary venous return. Recent MRI data suggest that prior reports may have underestimated the flow capacity and clinical consequences of these vessels. Using embolization coils or particles,

flow may be eliminated in up to 75% of treated aortopulmonary collaterals in patients with congenital heart disease.^{117,118}

Occlusion devices may also be used in occlusion of iatrogenic shunts, such as a supplementary Blalock-Taussig shunt or a stented PDA in a patient with pulmonary atresia with an intact ventricular septum (PA/IVS). In patients with pulmonary atresia who undergo RV decompression, the shunt may become superfluous as RV compliance improves. At subsequent hemodynamic assessment, if shunt occlusion is indicated, it can be performed with high rates of total occlusion and minimal risk for adverse events, sparing the patient reoperation.¹¹⁷

Atrial Septal Defect Closure

Since the first clinical report of percutaneous, device-based ASD closure by King and Mills in 1974, transcatheter closure has repeatedly been shown to be feasible, safe, and effective in both standard-risk and high-risk surgical patients.¹¹⁹ This procedure is now available in most centers as an alternative to surgical closure for typical ASDs, although surgical closure may still yield the best outcome in specific cases. All catheter-based procedures for ASD closure rely on the implantation of a device that has some overlap onto surrounding septal tissue to permit device stabilization. These devices are appropriate only in secundum defects and have never been credibly applied to sinus venosus or primum-type ASDs. Furthermore, not all secundum ASDs are candidates for device closure, depending on their size and proximity to other cardiac structures (e.g., the aortic root, superior vena cava, or atrioventricular valves). Variability in septal defect size, shape, and position has thwarted efforts to design a single device that could be uniformly successful in closing ASDs (Fig. 107-6). As a result, a myriad of devices have been used, but results are difficult to compare because of inherent differences in mechanisms and timing of closure. Each device also results in unique unintended outcomes, including failure to implant, device fracture, erosion, malposition, and late embolization.

Early devices were based on the double umbrella concept, and in 1989, the clamshell device was the first to be implanted under protocol of a prospective multicenter investigational device exemption (IDE) trial. Although results were promising, difficulties with the device and the process of approval resulted in the abandonment of this device in favor of a second generation of umbrella devices. An alternative approach was pursued with the Amplatzer atrial septal occluder, which incorporated self-centering capability and retrievability into a remarkably simple and effective design. In 2002, the Amplatzer atrial septal occluder became the first device to receive FDA approval based on reports of a 100% successful implantation rate, a complete closure rate of 98%, and a low rate (2%) of complications.¹²⁰ This device was designed to close secundum ASDs up to 38 mm in diameter. Comparison with surgical closure showed comparable rates of defect closure (99%) and adverse events (8%). However, device closure offered the benefit of

shorter length of stay and lower rate of major adverse events. Subsequently, a second device was approved for closure of smaller ASDs. In a multicenter trial, the Helex device (Gore and Associates, Flagstaff, AZ) was implanted in 143 patients who had an ASD less than 22 mm in diameter, with good results.¹²¹ Closure rates using this device were comparable to surgery, although the size of the candidate defect was a limitation, and a 25% incidence of small residual leak was recognized. This device received approval in 2006, at which time development of an alternatively configured device with a somewhat simplified delivery system was already under way. The Gore Septal Occluder, marketed overseas, has yet to receive approval and is still in trial in the United States.

Ongoing evaluations of these devices have revealed late device-related complications, including malposition/embolization, thrombus formation, and erosion.^{122,123} When embolization occurs, devices can often be retrieved using tools such as intravascular snares. The potential for entrapment of the device, or valvar damage, should be considered and may dictate that surgical removal is a safer solution. The incidence of thrombus formation appears to be related to device type, although whether delivery, materials, or device configuration plays a causative role remains unknown.¹²⁴ Erosion has been reported immediately after implantation, as well as several years later, and can be catastrophic. Its occurrence remains rare but disturbingly poorly predicted. It is believed to result from ongoing radial and possibly rotational forces exerted by the edge of the device on cardiac tissues.¹²⁵ Biodegradable closure devices have historically been a topic of great interest, based on the potential superiority with regard to profile and thrombogenicity. These devices have thus far failed to equal the performance of the currently available, more traditional occluders.

Although most small or moderate-sized secundum ASDs can be closed using intracardiac devices, surgery remains the primary approach for most types of VSDs requiring closure. Some exceptions exist, as in the case of very apical or anterior muscular defects, postoperative intramural defects, or extensive multiple muscular defects (i.e., the “Swiss cheese” septum).^{126,127} These VSDs pose significant surgical challenges and may ultimately be most effectively managed through a combination of surgical and catheter intervention, or hybrid approach.

Ventricular Septal Defect Closure

The earliest attempts at transcatheter closure of VSDs, using a double umbrella device, were described by Lock and colleagues in 1988.¹²⁸ These authors described technical aspects and feasibility of the procedure for six patients who were not considered candidates for operative closure. Bridges and coworkers¹²⁹ added to the experience with a review of highly selected patients with muscular VSD occurring in association with complex heart lesions who underwent device closure. It was suggested that preoperative transcatheter closure could simplify subsequent surgical repair of relatively inaccessible lesions.¹²⁹ In the first large reported experience with transcatheter VSD closure, patients considered high risk for surgical VSD closure were treated with transcatheter

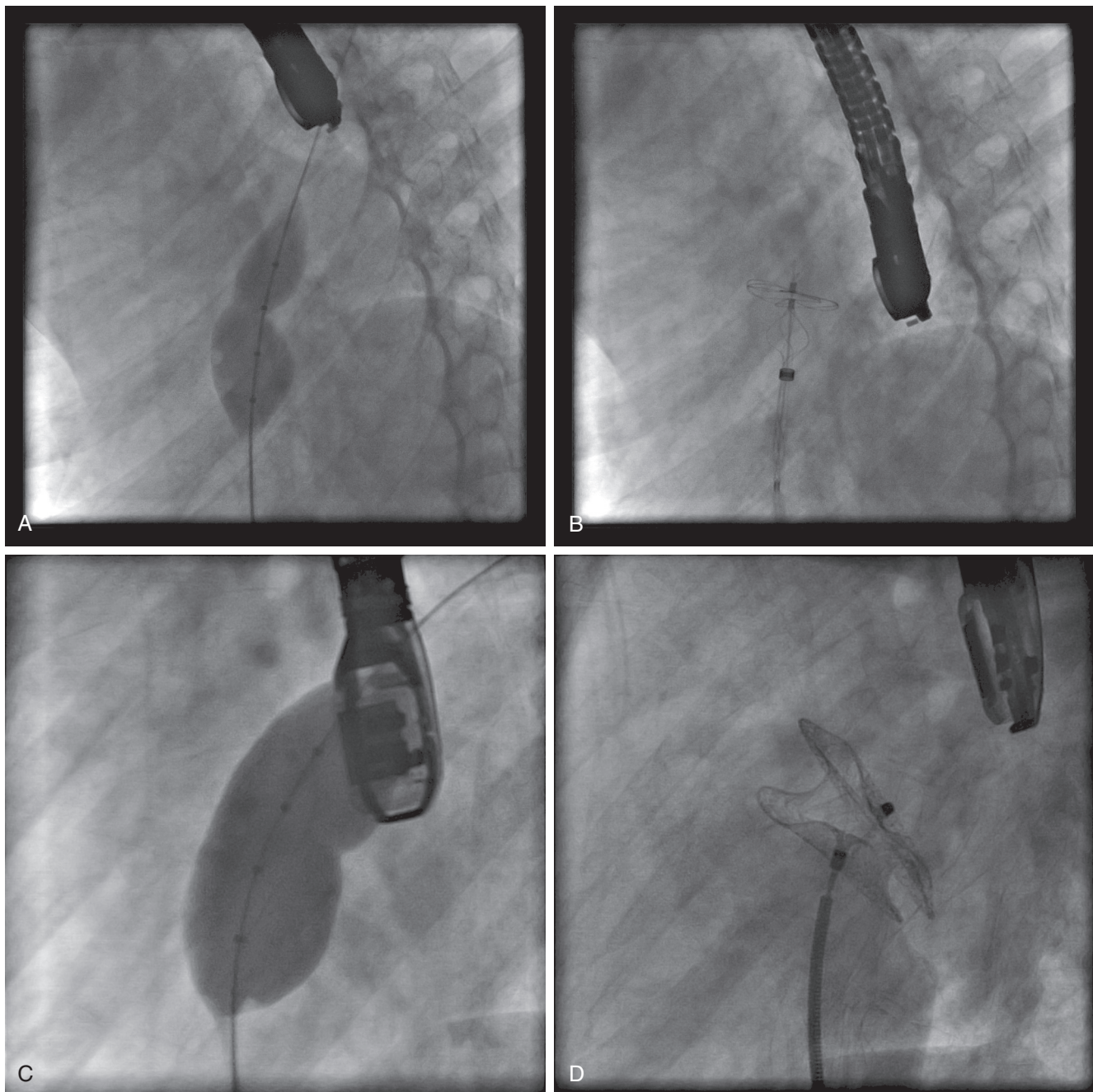


FIGURE 107-6 ■ Lateral projection images during transcatheter atrial septal defect closure with fluoroscopic and transesophageal echocardiographic imaging. **A**, Balloon sizing of a small defect. **B**, Imaging during partial deployment of the right atrial disc after complete formation of the left atrial disc, using a Helex device. **C**, Balloon sizing of a larger defect with minimal waist apparent on anterior aspect of balloon. **D**, Following left and right atrial disc deployment of an Amplatzer septal occluder, right atrial angiography aids in confirming appropriate position, particularly inferiorly.

device and showed improvement on a composite VSD size and severity scale.¹²⁷ However, the complex catheter courses, the size of the delivery system, and the vulnerable hemodynamic situation of patients resulted in a high rate of major adverse events, perhaps 45%.

Results of muscular VSD closure using the Amplatzer muscular VSD device were reported in 2004.¹³⁰ This device, similar in concept to the Amplatzer duct occluder and the Amplatzer septal occluder devices, offered the advantage of a smaller delivery system and a significantly

lower adverse event rate (11%) when compared with results for prior VSD devices. The procedural success rate of only 86% reflects the fact that despite significant improvements in deliverability of devices, transcatheter VSD closure remains a technically challenging intervention. Among 75 patients treated with the Amplatzer muscular VSD device, late complete closure was achieved by echocardiographic criteria in 92%, although follow-up was incomplete. This device received FDA approval for marketing in 2004. Periventricular delivery, or even

intraoperative delivery under direct visualization, has been described and should be considered as part of a surgical strategy for closure of complex, multiple muscular defects.

At this time, the feasibility of device closure of perimembranous VSD using an asymmetric device has been demonstrated and there is growing clinical experience overseas.¹³¹ However, no membranous VSD device has yet received domestic approval. The risks of percutaneous device delivery include interference with aortic and atrioventricular valves, leading to regurgitation, and device-related conduction abnormalities, including heart block. In the context of widely available surgical therapies with excellent results, outcomes of transcatheter closure will likely have to be improved over those seen thus far to justify a primarily device-based treatment.

COMPLICATIONS

In large centers, between 55% and 75% of all catheterizations now involve intervention.¹³² As with all minimally invasive techniques, effective transcatheter interventions for congenital heart disease offer the potential for treatment with lower morbidity and cost. However, the indirect nature of these catheter procedures also creates a unique set of potential complications. The overall rate of serious complications from interventional catheterization, investigated repeatedly, ranges from 3% to 7%.¹³³⁻¹³⁵ Although relatively few of these complications (approximately 2%) require emergent surgery, interventional procedures should not be undertaken unless surgical backup is available. Complications requiring surgical intervention include access vessel injury, valvar disruption, cardiac perforation, and device malposition or embolization.¹³⁶ A collaborative relationship between the interventional cardiologist and the pediatric cardiac surgeon allows each to better understand the benefits and risks of the two different therapeutic modalities.

SURGICAL COLLABORATION

Although hybrid procedures, using combined surgical and catheter collaboration, have been performed for decades, the publication of results of the hybrid stage I procedure for HLHS launched an era of enthusiastic expansion of this type of approach.^{137,138} The hybrid stage I was initially described as open chest placement of pulmonary artery bands, with direct main pulmonary artery access for placement of a catheter-delivered stent in the PDA and, often at a later procedure, the creation of an unrestricted ASD. Results at selected centers that gained routine experience with this approach were as good as standard surgical stage I, and because the patients were spared cardiopulmonary bypass and circulatory arrest, postprocedural recovery was remarkably rapid. At this time, most large centers continue to routinely perform surgical stage I.

The rewards of more extensive interventionalist-surgeon collaboration and promotion of the broader hybrid concept remain compelling. These approaches

will no doubt be applied more widely as devices for management of ASD, VSD, and valve failure become more sophisticated and widely available. Surgical control will allow the delivery of intravascular devices to be independent of access vessel patency or size and will also allow for stabilization of nonsecured devices. Balloons and stents, developed for percutaneous use, will increasingly become part of the surgeon's toolbox with procedures such as intraoperative stent placement or combined valve commissurotomy with annular balloon expansion. As experience with these collaborations accrues, the cross-disciplinary knowledge gained will benefit the field.

Surgeons and interventional cardiologists will also collaborate in the management of the postoperative patient. As patients with increasingly complex anatomy present for repair and can be supported with ever-improving intensive care, the opportunity to perform postoperative invasive assessment will present more frequently. Early intervention on residual postoperative lesions can be carried out safely and may shorten stays or reduce residual hemodynamic burden prolonging hospitalization.^{139,140} A generally held belief that angioplasty is safer after approximately 6 weeks following surgery will likely never be proven, and, to the contrary, increasing experience with intervention on postoperative obstruction will likely prove useful in postoperative management.

As extracorporeal support and circulatory assist devices are applied to greater numbers of patients with congenital heart disease, new situations will present themselves to the interventionalist. In cases of extracorporeal membrane oxygenation support, left atrial decompression may be necessary to protect from excessive pulmonary venous hypertension and pulmonary hemorrhage. This procedure can be performed safely and can be associated with near immediate improvement in pulmonary conditions of the circulation at various levels of device support.¹⁴¹

FETAL INTERVENTION

Background

The rationale for fetal cardiac intervention, as for all fetal invasive procedures, is based on the premise that intervention in the rapidly changing and potentially highly responsive fetal environment may alter the natural history of a developmental error and possibly avert serious, even lethal, postnatal disease. For intervention to be considered, the diagnosis must be certain, the procedure must be feasible, and the risk of fetal or neonatal morbidity without intervention must be sufficient to justify the risk posed to both fetus and mother. Given the rapid sequencing of serial heart development, once developmental derangement is diagnosed, early intervention likely yields the greatest potential for significant clinical benefit.

Fetal Cardiac Interventions

Conditions for which prenatal cardiac interventions may be considered include those in which (1) the fetus is at risk for demise as a result of the condition, (2) the

TABLE 107-1 Congenital Cardiovascular Anomalies Potentially Amenable to Prenatal Intervention

Indication for Intervention	Condition	Intervention
Risk of fetal death	Congenital heart block	Pacemaker
	Severe congenital MR with AS and intact atrial septum	Maternal pharmacotherapy Balloon aortic valvuloplasty
Risk of acute neonatal instability or death	HLHS with intact atrial septum	Creation of ASD
	Obstructed, totally anomalous pulmonary venous return	Creation of ASD Stenting of obstructed vertical vein or ductus venosus
Risk of primary anomaly evolving into more severe condition	Fetal AS with evolving HLHS	Balloon aortic valvuloplasty
	Pulmonary atresia with evolving HRHS	Pulmonary valve perforation and dilation
	Premature closure of ductus arteriosus	Ductal stenting
	Absent pulmonary valve syndrome	Closure of pulmonary valve

AS, Aortic stenosis; ASD, atrial septal defect; HLHS, hypoplastic left heart syndrome; HRHS, hypoplastic right heart syndrome; MR, mitral regurgitation.

disorder is likely to result in acute neonatal instability or death, or (3) intervention may alter the evolution of the disease so that the postnatal morbidity is substantially reduced. Potential examples of these classes of indication are listed in Table 107-1. Of course, the ability to carry out an appropriate intervention must be taken into consideration. To illustrate this point, although fetal Ebstein anomaly and severe fetal mitral regurgitation pose risks of hydropic demise, fetal interventions to address atrioventricular disease do not exist. In contrast, fetuses with HLHS face a significant risk of neonatal mortality and lifelong morbidity, and in the cases related to aortic stenosis, a procedure can be performed to dilate the aortic valve. The clinical benefit of the procedure depends on the probability that the anatomic change imposed by the successful intervention in utero will alter the subsequent course of cardiac growth and development sufficiently to have a major impact on survival or postnatal outcome.

The mechanism through which anatomic modification of the fetal heart alters subsequent development is postulated to be through alteration in loading conditions. Although there is no conclusive evidence that abnormalities or alterations of flow or loading contribute to the development of cardiovascular malformations in the human fetus, data from various experimental animal systems support this contention. Fetal lambs exposed to chronically decreased LV preload by late partial occlusion of the left atrial cavity exhibit significant decrease in combined ventricular output and placental blood flow and a significant decrease in LV mass and volume.¹⁴² These changes appear to be time dependent, with more marked alterations in fetuses with longer exposure to decreased LV inflow. In another model, in fetal lambs exposed to increased LV afterload by banding of the ascending aorta, there is a decrease in combined ventricular output, in conjunction with a significant decrease in LV chamber volume and an increase in LV wall thickness.¹⁴² Initially, LV weight increases relative to the weight of the RV, but with a prolonged duration of aortic banding, the ratio of LV to RV weight decreases significantly. These studies and others demonstrate that alterations in ventricular loading or embryonic blood flow patterns in normal fetuses and embryos can be associated with cardiovascular development and function.

The potential for prenatal cardiac intervention has been realized for nearly three decades; as early as 1986 there was a reported attempt at in utero pacing for fetal complete heart block.¹⁴³ By 1991, there were reports of prenatal aortic valve dilation and prenatal pericardiocentesis in human fetuses.^{144,145} Through the 1990s, there were several additional reports of human fetal cardiac intervention, mostly sporadic, primarily for aortic stenosis.¹⁴⁶ Also during this period, a number of animal studies were performed to investigate the pathophysiology of cardiac bypass and cardioprotection in the fetus, anticipating fetal cardiac surgery, as well as alternative approaches to transvascular fetal cardiac intervention.¹⁴⁷⁻¹⁵⁰

In 2000, we at Boston Children's Hospital initiated a program for fetal cardiac intervention, focusing on treatment of fetal aortic stenosis with evolving HLHS. Later, the program expanded to include procedures for established HLHS with an intact or highly restrictive atrial septum, pulmonary atresia with evolving hypoplastic right heart syndrome, and structural anomalies causing fetal hydrops.¹⁵¹⁻¹⁵⁶ At this time, more than 160 procedures have been carried out, numerous publications have described our experience, and the outcomes of the first 100 procedures for fetal aortic stenosis have recently been reported.¹⁵⁷

General Approach to Fetal Cardiac Intervention

Common to all of the procedures that we perform is a percutaneous ultrasound-guided approach with maternal and fetal anesthesia. In an operating room environment, with the mother supine with left lateral tilt for uterine displacement, the location of the placenta and the fetal orientation are determined using conventional ultrasonographic techniques. A combination of spontaneous fetal movements and external version maneuvers are used to accomplish fetal positioning, and once an approach vector for percutaneous cardiac puncture is identified, fetal intramuscular anesthetic is administered intramuscularly. In the early experience, a limited laparotomy without externalization of the uterus was used to enable direct, manual, transuterine fetal positioning. This incision has been largely obviated by the application of more refined

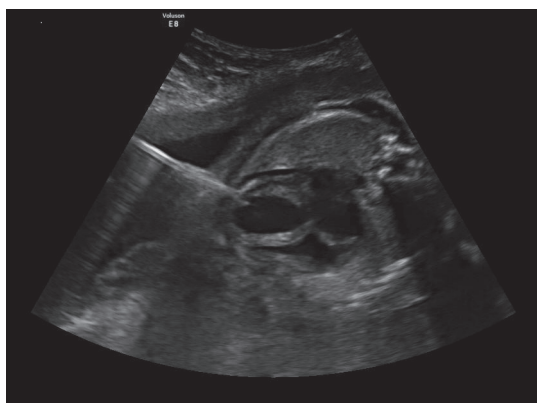


FIGURE 107-7 ■ Fetal echocardiography during prenatal intervention for critical stenosis of the fetus with evolving hypoplastic left heart syndrome. The left ventricle is dilated and dysfunctional, appearing globular, and the stainless steel needle is positioned to enter the ventricle from the apex.

maternal/fetal selection criteria and improvements in the techniques of cannula manipulation. Access to the target is achieved by direct puncture of the maternal abdomen, uterus, fetal chest wall, and the target cardiac chamber. The most commonly used cannula is a 19-gauge, 11-cm-long biopsy needle with a sharp, solid stylet and a non-beveled, dull edge, because this instrument is commercially available (Fig. 107-7). The length enables percutaneous access in most mothers between 20 and 30 weeks gestation and with a body mass index of less than 40. The inner and outer diameters of this thin-walled cannula allow for passage of most coronary artery angioplasty balloons while minimizing the potential for uterine/placental trauma and pericardial effusion.

Aortic Stenosis with Evolving HLHS

A subset of patients born with HLHS are diagnosed during the mid-second trimester with valvar aortic stenosis and a left ventricle that is normal in size or dilated but has severe dysfunction. When the left ventricle is normal in size or dilated, abnormal physiologic features associated with progression to a diagnosis of HLHS at birth include retrograde flow in the transverse aortic arch, truncated, monophasic mitral valve inflow, and left-to-right flow across the foramen ovale.¹⁵⁸ We refer to such mid-gestation fetuses as having severe aortic stenosis with evolving HLHS. The goal of fetal aortic valve dilation is to avert HLHS in favor of a biventricular postnatal circulation.

Predicting the evolution from aortic stenosis with a normal-size or dilated left ventricle in mid gestation to HLHS at term is complicated, and although several predictive models have attempted to predict left heart adequacy among neonates with aortic stenosis,¹⁵⁹⁻¹⁶¹ choosing the optimal approach in a given patient remains a challenge. Furthermore, few prenatal studies report serial data, and most include only a small number of fetuses.^{162,163} Nonetheless, mid-gestation fetal aortic stenosis that does not progress to HLHS is rare, and it can be distinguished from aortic stenosis with evolving HLHS on the basis of the previously described physiologic features.¹⁵⁸

Decreasing LV afterload and promoting flow through the left side of the heart by relieving aortic obstruction may help prevent progressive left heart dysfunction and growth failure over the subsequent course of gestation. Candidates with the diagnosis of aortic stenosis with evolving HLHS should be considered in light of (1) the likelihood that a technically successful procedure can be performed, and (2) the potential for salvage of the left heart—that is, the potential for LV functional recovery and growth enabling a biventricular circulation postnatally.

Fetal aortic valvuloplasty is performed according to the general practices outlined earlier. The goal is to enter the left ventricle apically but away from the interventricular septum, with a trajectory that is in line with the outflow tract. The dilating balloon size, a function of nominal balloon size and inflation pressure, is targeted to a balloon-to-annulus diameter ratio of 1.0 to 1.2. Once the cannula has been advanced to the LV cavity and the stylet removed, the coaxial guidewire and dilating balloon are introduced down its lumen, and the wire is used to probe for the orifice of the aortic valve. Once the wire is clearly visualized in the ascending aorta, the balloon is advanced across the valve and serial inflations are performed with an inflation gauge after systematic adjustment of balloon depth. When it is clear that the valve has been dilated, the entire cannula-balloon system is removed from the fetus and mother without resheathing the balloon into the cannula, and ultrasound imaging is continued. Treatment for fetal hemodynamic instability or hemopericardium is administered as necessary.¹⁶⁴

We reported our initial experience with aortic valvuloplasty for fetal aortic stenosis in 2004.¹⁵³ In 2007, we reviewed outcomes of 56 fetuses with similar echocardiographic features at diagnosis, 28 of whom underwent technically successful aortic valve dilation, in an attempt to characterize a number of potentially important physiologic changes that occur after successful fetal aortic valvuloplasty.¹⁶⁵ On follow-up echocardiography at 32.8 ± 2.8 weeks, all control (unintervened) patients continued to have retrograde flow in the transverse aortic arch and exclusively left-to-right flow across the foramen ovale; notably, left heart structures seemed to become frozen in their anatomic size once we made the diagnosis of critical aortic stenosis with impending HLHS, and thus they became progressively more abnormal as the fetus grew.

Refinement of selection criteria has increased the percentage of infants achieving biventricular outcome after fetal aortic valve dilation, and at this time, almost 50% will not require a stage I procedure. Pediatric follow-up of these infants born after fetal aortic valvuloplasty reveals that many have significant, persistent, and sometimes refractory dysfunction of both left heart valves and myocardium. Many have significant medical and surgical burden through early childhood. With the oldest survivor just now reaching teen years, we look forward to continuing to learn what the longer-term natural history of “averted” HLHS will be. We continue to work to improve our understanding of how best to select fetuses with aortic stenosis and evolving HLHS for prenatal aortic valvuloplasty and when to intervene for optimal benefit.¹⁵⁷

HLHS with Intact or Restrictive Atrial Septum

HLHS with an intact or highly restrictive atrial septum can be diagnosed on the basis of fetal imaging of the septum in conjunction with demonstration of markedly abnormal pulmonary venous flow patterns in dilated-appearing pulmonary veins.¹⁶⁶ Although limited pulmonary venous egress may be well tolerated in utero, neonates with major septal restriction are at substantially higher risk of death than are those without such restriction.^{15,18,167} They present with profound hypoxemia after birth and often shock. Chronic pulmonary venous hypertension in utero also appears to cause pulmonary venous changes, contributing to neonatal and perioperative morbidity and mortality over the course of single ventricle palliation.

Prenatal intervention may be of benefit in fetuses with HLHS and an intact atrial septum with respect to both of the major problems posed by the restriction of pulmonary venous outflow. If the left atrium can be decompressed before birth, the profound hypoxemia and acidosis that can occur shortly after birth may be prevented and the morbidity of these metabolic insults and the risks of emergency neonatal intervention can be avoided. Also, if pulmonary venous decompression can be achieved sufficiently early in gestation, the pulmonary venous remodeling that occurs may be prevented or given an opportunity to subside or reverse. We first reported atrial septoplasty for fetuses with HLHS and intact atrial septum in 2004, and cases of prenatal atrial septoplasty for this condition have been reported by investigators from other centers as well, using various monitoring and interventional approaches.^{152,168}

In theory, immediate treatment of left atrial hypertension on diagnosis would maximize the potential benefits. However, technical difficulties encountered in performing the procedure on very young fetuses have led to a shift in focus. Rather than risk fatal events in very young fetuses for the advantage of long-term preservation of pulmonary vasculature, we have prioritized early neonatal stabilization, which is dependent on a maximal ASD at the time of delivery, therefore favoring intervention later in gestation (i.e., early to mid third trimester).

The atrial septum is typically approached from the right atrial aspect. The atrial septum is perforated with a sharp instrument, either the access cannula or a smaller-gauge ultra-sharp biopsy needle, after which a dilating balloon is used to enlarge the newly created atrial defect. The largest effective balloon that can be introduced through equipment currently in use is less than 4 mm. The size of the resultant defect, as measured by intraprocedural ultrasound, is invariably smaller than the size of the dilating balloon, ranging from 1 to 3 mm. When the atrial septum appears very thick and there is an expectation that simple balloon dilation will result in septal recoil and only a very small communication, septal stent placement is feasible but exceedingly challenging.¹⁵⁶

We recently reported our experience with prenatal intervention for 21 fetuses with HLHS and an intact or highly restrictive atrial septum.¹⁶⁹ Fetal demise occurred in two cases after the intervention, and complications,

including bradycardia and pericardial or pleural effusion, occurred in eight procedures. Among neonates delivered after fetal intervention for HLHS with highly restrictive or intact atrial septum, surgical survival remains poor (58%), although in utero creation of an ASD did appear to have some benefit in terms of pre-stage I management.

Pulmonary Atresia with Intact Septum

Isolated cases of fetal pulmonary valvuloplasty in the third trimester have been reported by several groups.¹⁷⁰⁻¹⁷² It is impossible to determine from isolated cases whether prenatal intervention has the intended benefit. Since 2002, we have offered prenatal pulmonary valvuloplasty for selected mid-gestation fetuses with pulmonary atresia and evolving hypoplastic right heart, with the intent of promoting right heart growth and functional development and increasing the likelihood of a biventricular circulation after birth. Identification of potential candidates for prenatal treatment of PA/IVS has been a challenge, given the rarity of the disease, the wide spectrum of severity, and the paucity of insight about prenatal predictors of biventricular circulation.¹⁷³ Technically, the procedure presents a unique challenge because the RV (as opposed to the left ventricle in fetal aortic stenosis) is usually hypoplastic (rather than dilated) and the angle of the pulmonary valve arising off the conus can be very difficult to achieve. The effects of this strategy on right heart growth and functional development, and, ultimately, on postnatal outcome, remain to be determined.

Much remains to be learned about the benefits and potential adverse effects of prenatal cardiac intervention. Since our first procedure in 2000, referrals have grown steadily, with more than 90% of prospective and actual patients coming from outside our usual geographic catchment area. Ultimately, the value of prenatal cardiac intervention will depend on a variety of clinical and technological factors, including more frequent, earlier diagnosis of congenital heart disease in utero, characterization of prognostic features in fetuses with congenital heart disease, better understanding of the optimal gestational windows and their capacity for cardiovascular remodeling after fetal intervention, and improved and focused technology. Advances in imaging technologies and specially developed instrumentation should facilitate greater precision and effectiveness of intervention and may open the door to procedures for other, more complex indications.

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SURGICAL APPROACHES AND CARDIOPULMONARY BYPASS IN PEDIATRIC CARDIAC SURGERY

Luis Quinonez • Pedro J. del Nido

CHAPTER OUTLINE

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Midsternal Mini-Sternotomy
Anterior or Anterolateral Thoracotomy

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Thoracic incisions traditionally used in adult cardiac and thoracic surgery have been used in children with varying success with respect to exposure, pain, and cosmetic result. Special considerations relevant to pediatric surgery are related to the lack of development and growth of soft tissue structures such as breast tissue and bony structures such as ribs and vertebra. Thus, incisions that fix growing bony structures, such as ribs in a posterior or lateral thoracotomy, may lead to scoliosis.¹ Anterior thoracic incisions may also injure underdeveloped breast tissue and pectoral muscles, resulting in chest wall deformities and sensory loss. Then again, the flexibility of the chest cage and ribs in young children permit the use of limited incisions with adequate exposure of relevant structures, whereas in adults this may not be possible without the

risk of rib or sternal fracture or instability of the chest cage. Therefore, these factors should be considered when selecting the optimal approach to intrathoracic structures in children, to optimize exposure and for the safe conduct of the procedure, and to minimize pain and achieve a cosmetically acceptable result.

The child should be positioned so that the surgeon and assistant have a direct view of the relevant anatomic structures and so that the anesthesiologist has access to the airway and major access lines. Because the head size of newborns and infants is significantly larger in proportion to the chest than it is in older children and adults, a shoulder roll should be used when children are placed supine on the table, to elevate the shoulders and relieve some of the pressure from the occiput. Soft padding, such

as gel-filled plastic bags, should be placed under all pressure areas. Cooling or heating blankets are used routinely in pediatric cardiac surgery, but these require relatively direct patient contact to optimize heat transfer. Perforated blankets, filled with cold or heated air that is blown through, have improved heat-transfer properties compared with water-filled blankets. Direct skin contact should be avoided, however, with either method, because injury to the skin can result in full-thickness skin loss, particularly in infants. For a lateral thoracotomy, an axillary roll is used to elevate the thorax and relieve pressure on the shoulder and potentially the brachial plexus. As with any thoracotomy incision, care must be taken not to extend the arm and shoulder under tension, even in infants, because this may cause injury to the brachial plexus.

For cosmetic purposes, the skin incision can be placed below the actual entry site into the thorax, whether the incision is a sternotomy or a lateral intercostal approach. Care must be taken, however, to minimize creation of flaps, particularly in infants, because this often leads to breakdown of subcutaneous tissue with fat necrosis, resulting in wound separation. Excessive use of cautery, particularly in the subcutaneous fat in infants, is another cause of fat necrosis and wound separation, often prolonging hospital stay and resulting in a poor cosmetic result.

APPROACHES TO CARDIAC STRUCTURES AND GREAT VESSELS FOR TRANSTHORACIC CANNULATION FOR BYPASS

Full Sternotomy

The most commonly used incision for access to the heart and anterior mediastinal structures is a sternotomy. A vertical skin incision over the sternum, staying below the manubrium, permits full division of the sternum and provides an unobstructed view of all anterior mediastinal structures and direct access from branches of the aortic arch down to the inferior vena cava (IVC) at the level of the diaphragm. This approach is necessary when the surgical procedure requires access to upper and lower mediastinal structures, such as the aortic arch and right atrium, branch pulmonary arteries, and right ventricle. Examples include a first-stage procedure for hypoplastic left heart syndrome, repair of truncus arteriosus, and pulmonary atresia with ventricular septal defect.

The incision in the pericardium is also vertical. If it is placed directly over the cardiac structures to be accessed, it can facilitate exposure, particularly when transatrial procedures to access the ventricles are being performed. By opening the pericardium to the right of midline and retracting the right side of the pericardium to the sternum, the ventricles fall away leftward, aiding exposure. Sutures to suspend the pericardium to the sternum are critical in children, and they should also be used to rotate the heart to facilitate exposure to the chamber or vessels required. When the right atrium and cavae need

exposure, suspension of the right-sided pericardial edge to the periosteum of the sternum is often required to visualize the lateral wall of the right atrium and inferior cava. If the left side of the pericardium is left unsuspended and is incised along the edge of the diaphragm to the apex, the entire ventricular mass will rotate away from the surgeon, facilitating exposure of the atrioventricular valves and interventricular septum to the level of the apex. A similar approach can be used to optimize exposure of the right ventricular outflow tract for surgery to correct tetralogy of Fallot. Here, the pericardium at the level of the great vessels is suspended to the periosteum, leaving the pericardial edge at the diaphragm unsuspended, facilitating the view of the ventricular septal defect through the ventriculotomy.

Limited Sternotomy Incisions

For many procedures, a full sternotomy is not necessary to provide adequate access to all the relevant structures of the heart. This is particularly true in infants and young children because their sternum and rib cage are pliable, which permits retraction with minimal force. Preoperative planning of the procedure includes determining which mediastinal structures will need exposure for the surgical procedure and for cannulation for cardiopulmonary bypass (CPB). With the availability of thin-walled, wire-reinforced, small-diameter cannulas for use in children, cannulation for CPB can often be achieved with minimal extension of the thoracic incision beyond that needed for the repair itself. These approaches usually provide exposure sufficient to use standard techniques for myocardial protection, such as cardioplegia and left ventricular venting. A full sternotomy is unnecessary when, for example, the intracardiac repair is accomplished via a right atriotomy, such as for repair of atrial septal defect, ventricular septal defect, or complete atrioventricular canal defect, and in transatrial repair of tetralogy of Fallot and mitral valve repair.²⁻⁴

Trans-Xyphoid Mini-Sternotomy

With the trans-xyphoid mini-sternotomy approach, the skin incision extends from the level of the areola (mid thorax) down to the tip of the xyphoid process (Fig. 108-1). By detaching anterior diaphragm attachments to the cartilaginous segment of the rib cage anteriorly, access is gained to the anterior mediastinum. Before

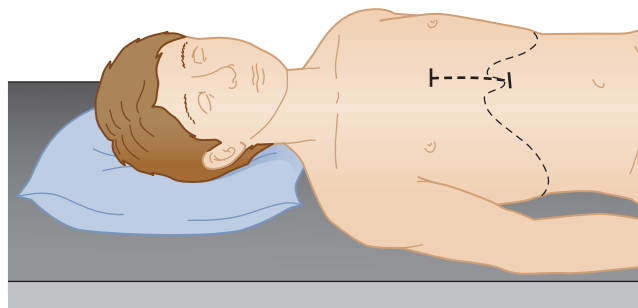


FIGURE 108-1 ■ A partial or limited sternotomy incision.

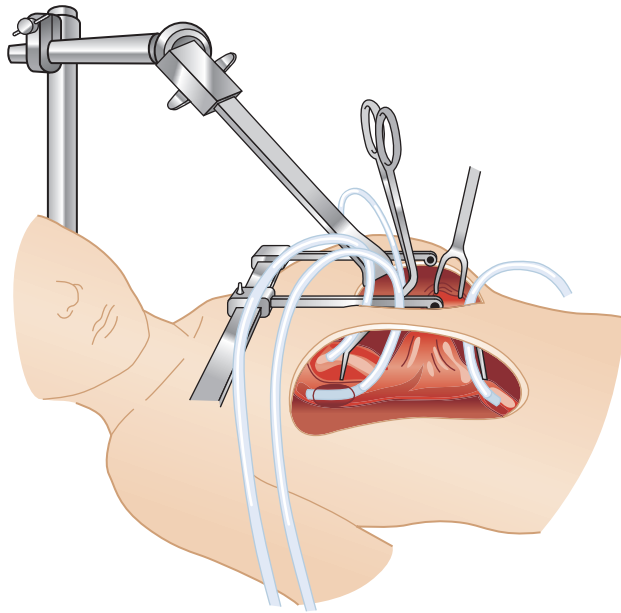


FIGURE 108-2 ■ The limited sternotomy allows cannulation of the ascending aorta and both cavae. Insertion of the inferior caval cannula through a separate skin incision keeps the cannula out of the way, and the incision can later be used for tube thoracostomy.

performing the partial sternotomy, blunt dissection is required to detach the pericardium and thymus from the sternum. A partial sternotomy can be performed with a saw, but in infants, heavy bandage scissors are sufficient for dividing the lower sternum. Once the partial sternotomy is completed, a narrow-blade retractor such as an army-navy retractor is used to lift the sternum anteriorly and cephalad to provide exposure to the ascending aorta for cannulation. The retractor should not be placed on the skin and subcutaneous tissue, because adequate exposure of the upper mediastinum will not be achieved and necrosis of the skin could occur from prolonged retraction. To expose the aorta, however, caudal and anterior traction must be placed on the pericardium. This maneuver requires that thymus attachments to the pericardium be divided, or mobility of the pericardium and aorta will be inadequate. The pericardial incision must be made to the right of midline, and the pericardium should be pinned to the right edge of the divided sternum to expose the right atrium and cavae. In most cases, cannulation of the ascending aorta and both cavae can be easily achieved with this approach. Insertion of the inferior caval cannula through a separate skin incision keeps the cannula out of the way, and the incision can later be used for tube thoracostomy (Fig. 108-2).

Midsternal Mini-Sternotomy

When the right ventricular outflow tract or aortic root must be accessed, the partial sternotomy approach may still be used, but usually the skin and sternal incisions need to be extended superiorly 1 or 2 cm above the level of the areola. In this case, traction sutures on the pericardium at the level of the pulmonary and aortic roots suspend these structures into view, permitting adequate

exposure. To assist with caval cannulation, traction sutures should be placed only on the right side of the pericardium, lifting both cavae toward the right side of the sternotomy. The cardiac structures are allowed to rotate and shift leftward, enhancing exposure to the right atrium, the left atrium via the right upper pulmonary veins, and the aortic root.

Anterior or Anterolateral Thoracotomy

An anterior thoracotomy has been advocated for surgical repair of atrial septal defect and occasionally ventricular septal defects.^{5,6} A meta-analysis of six case control trials found that intubation time and hospital length of stay were shorter using an anterolateral mini-thoracotomy over a median sternotomy, whereas cardiopulmonary and cross-clamp times were longer.⁷ Axillary incision have also been advocated for simple heart lesions using CPB.^{8,9}

For the anterolateral thoracotomy, the incision is made in the anterior fourth intercostal space (ICS), and in females great care must be taken to incise well below breast tissue. Dissection of the pericardial attachments to the sternum and thymus greatly facilitates exposure by permitting retraction of the pericardium down toward the diaphragm and bringing the ascending aorta closer into view. Direct cannulation of the ascending aorta is preferable to peripheral cannulation via the femoral or axillary artery because these vessels are small in children and stenosis at the cannulation site can result in claudication with exercise. Recently, more flexible cannulas, available in all sizes for pediatric use, have facilitated aortic cannulation. Some arterial cannulas can be introduced over a guidewire, which makes insertion easier and safer. The cavae can be cannulated directly, although the superior cava cannula is often best introduced via the right atrial appendage and directed retrograde into the superior vena cava (SVC). Aortic clamping to achieve cardiac arrest can be difficult with conventional arterial clamps, which were designed for application via a sternotomy. In small children, a bulldog clamp is sufficient for aortic occlusion, and for larger children and teenagers, flexible clamps are available. Cardioplegia can be delivered via a small flexible cannula inserted into the aortic root; some have advocated transthoracic insertion of a needle into the aortic root.

APPROACHES TO EXTRACARDIAC STRUCTURES IN INFANTS AND CHILDREN

Noncardiac thoracic surgery for the treatment of congenital cardiac defects or complications of cardiac surgery most often requires exposure to the posterior mediastinum. Exceptions include procedures to plicate the diaphragm, or for unifocalization of aortopulmonary collaterals, which requires dissection of the hilum of the lung. A posterolateral incision extending from just anterior to the tip of the scapula to the mid-posterior scapula provides access, through the fourth, fifth, or sixth ICS, to posterior mediastinal structures as well as the hilum of

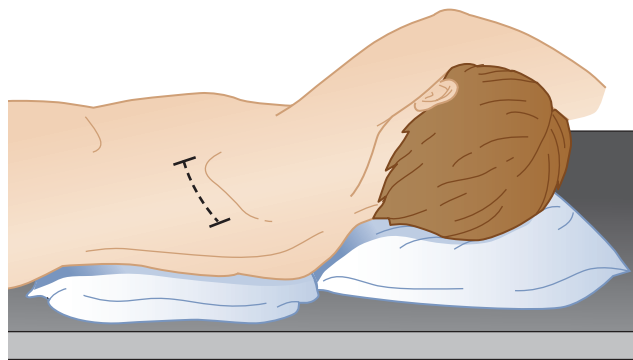


FIGURE 108-3 ■ A left posterolateral incision extending from just anterior to the tip of the scapula to the mid-posterior scapula provides access, through the fourth, fifth, or sixth intercostal spaces, to posterior mediastinal structures, as well as to the hilum of the lung, pericardium, and diaphragm.

the lung, the pericardium, and the diaphragm (Fig. 108-3). If the upper half of the mediastinum needs exposure, an incision through the fourth ICS is optimal. For access to the hilum of the lung, the fifth ICS is optimal, and, for access to the thoracic duct at the level of the diaphragm, or to the central tendon of the diaphragm, a sixth ICS incision is optimal. The most common procedures in which a thoracotomy is performed routinely are operations on the thoracic aorta or branches, such as surgery for repair of coarctation of the aorta or for ligation of the patent ductus. Care should be taken to ensure that the appropriate interspace is entered, because exposure to the upper thorax can be very difficult in small children if the fifth interspace, or lower, is entered. Although counting ribs starting at the second rib, which has attachments of the anterior scalene muscle, can be done, external landmarks can also be used. A useful landmark is the position of the areola when the arm is extended over the head. With the arm extended, the interspace below the areola is usually the fourth ICS, and this landmark can confirm a particular interspace identified by other techniques. This method for identification of interspace is particularly useful in neonates and premature infants. Extensive division of the intercostal muscle is usually unnecessary in infants and small children. Adequate exposure can be obtained by separating the ribs, which are more flexible in this age group and entail less risk for fracture.

This same approach can be used for exposure of intra-pericardial structures such as the pulmonary trunk for pulmonary artery banding and even for intracardiac procedures. Exposure to the IVC for cannulation through a posterolateral thoracotomy can be difficult, however, and may require division of one rib posteriorly. Closure of the thoracotomy incision, as in adults, should be done in layers, approximating the serratus muscle and fascia separate from the latissimus dorsi muscle and subcutaneous tissue. This approach minimizes distortion of the chest wall muscles and provides the best cosmetic results as well.

A transaxillary approach has been described for ligation of the patent ductus, access to the transverse aortic arch and descending aorta, and, from the right axilla, closure of atrial septal defects. Either a transverse incision

is made over the third interspace between the fold of the pectoralis muscle and scapula or, as some have described, a vertical incision is made from the axilla down to the fourth ICS. The third interspace is then entered, which provides direct access to the distal aortic arch and arterial duct. However, exposure is limited and extension of the incision, if more exposure is required, is difficult. In experienced hands, however, this approach is adequate for ductus ligation, even in small infants, with a less visible incision.

Thoracoscopic Approach in Children

Because most cardiac procedures in children require CPB and intracardiac repair, port access for reconstruction has been applied almost exclusively to adult patients or, rarely, adult-size teenagers. Thoracoscopic procedures in children have been, for the most part, confined to approaches to noncardiac structures or to the pericardium. Examples include ligation of the patent ductus, division of vascular rings, creation of a pericardial window, and, more recently, insertion of pacer leads.^{10,11} More recently, total thoracoscopic approaches for repair of atrial and ventricular septal defects have been described.^{12,13} Much of the instrumentation has been adapted from other surgical applications, and the thoracoscopic procedures have involved primarily dissection and ligation or division with little reconstruction or suturing. Using induced electromyography to establish the location and local course of the recurrent laryngeal nerve may be of some benefit in infants and small children undergoing patent ductus arteriosus ligation or vascular ring procedures.¹⁴

Positioning and location of port incisions follow the principles of thoracoscopy or thoracotomy in adults. For access to the distal transverse aortic arch and descending aorta, the patient should be in a full lateral decubitus position. For access to anterior mediastinal structures, such as the anterior pericardium or thymus, a partial decubitus position with the thorax tilted toward a supine position is optimal. Usually, four incisions are required, two for the surgeon's instruments for the dissection, one for the scope and camera, and the fourth for the assistant to introduce lung retractors or occasionally a grasper or suction. As with any thoracoscopic procedure, the central port is used for the camera and the instrument ports are to each side of the camera port, separated by sufficient distance to prevent the scope from interfering with instrument movement. When a surgical robot is used to assist, the same port position is used, but the port for the lung retractor and suction is placed at the midaxillary line at the sixth or seventh ICS (Fig. 108-4).

For the approach to anterior mediastinal structures, the same arrangement is used with respect to the camera and instrument ports. In cases such as dissection of the right lobe of the thymus for thoracoscopic innominate artery suspension to relieve tracheal compression, the central port for the scope is placed at the anterior axillary line in the fourth ICS, and the two instrument ports are placed two or three interspaces to each side and 2 to 3 cm more anterior. A fourth port can be used for lung retraction and should be placed one or two ICSs lower toward

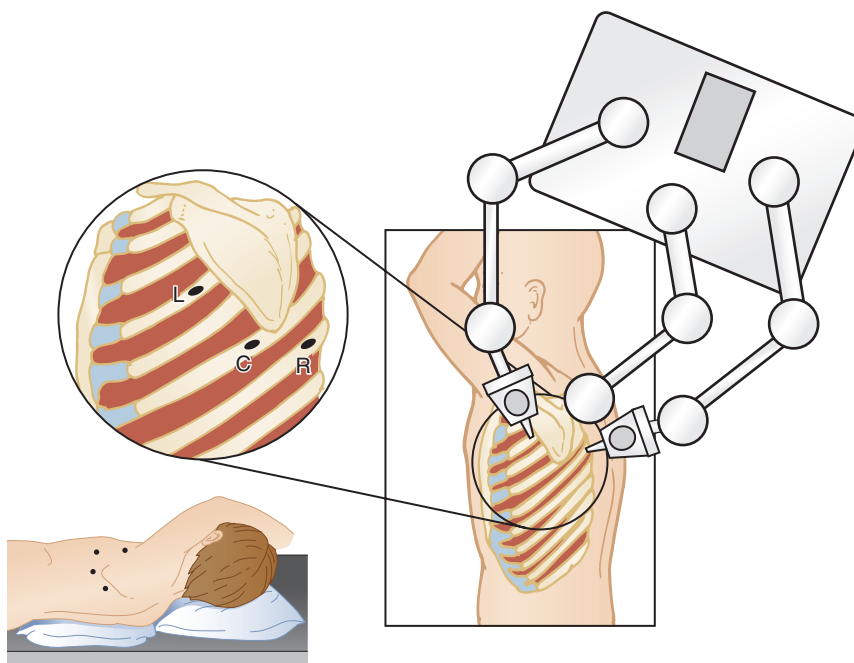


FIGURE 108-4 ■ Port position for robot-assisted thoracoscopic division of vascular ring. The scope and camera are introduced through the central port (C), and instruments are introduced through the other two ports for the robot's left arm (L) and right arm (R). (From Mihaljevic T, Cannon JW, del Nido PJ: Robotically assisted division of a vascular ring in children. *J Thorac Cardiovasc Surg* 125:1163–1164, 2003.)

the diaphragm so as not to interfere with instrument motion. For the anterior pericardium, the three ports are placed more inferiorly on the chest using the fourth or fifth ICS for the scope and camera, and the instrument ports one or two interspaces on either side.

CARDIOPULMONARY BYPASS IN CHILDREN

History

The use of extracorporeal circulatory techniques in the repair of congenital cardiac defects began in the 1950s, shortly after the concept of CPB appeared and a heart-lung machine was constructed. Gibbon repaired an atrial septal defect using the first heart-lung machine, which required 12 to 14 units of blood prime, in 1953.¹⁵ At approximately the same time, Lillihei and colleagues began using cross-circulation to repair a variety of defects in relatively young infants and children, including ventricular septal defects, atrioventricular canal defects, and tetralogy of Fallot, achieving a remarkable overall survival of greater than 60%.¹⁶ Shortly thereafter, Kirklin developed a pump oxygenator derived from Gibbon's earlier efforts.¹⁷ This device required approximately half of the original amount of fresh blood prime but also extreme care to prevent severe foaming of blood, which was lethal; nonetheless, the survival rate was 50%. These early reports prompted many subsequent investigations aimed at developing the scientific and technologic knowledge needed to successfully

undertake extracorporeal circulation in infants and children. In spite of these efforts, the morbidity and mortality associated with the use of CPB remained high throughout the 1960s.

The next major advance occurred in the early 1970s, when Castaneda and colleagues¹⁸ and Barratt-Boyes¹⁹ described the use of deep hypothermic circulatory arrest (DHCA) in infants. These techniques relied primarily on surface cooling, with exposure to the CPB circuit limited to a brief period of core cooling and rewarming, so that total CPB time was typically kept under 20 to 30 minutes. Progressive advances in the design of circuit components and perfusion techniques for infants and small children occurred throughout the 1980s and into the early 1990s. As a result, the "toxicity" associated with the use of CPB in infants declined significantly. Currently, lengthy and complex repairs, such as the arterial switch procedure for transposition of the great arteries and primary repair of tetralogy of Fallot, can be undertaken using CPB in neonates and very young infants and result in an overall mortality rate of less than 5%. Nonetheless, the morbidity associated with the use of CPB in infants and children is still widely held to be a major limitation to completely successful outcomes.

Differences between Pediatric and Adult Cardiopulmonary Bypass

There are many significant differences in circuit technology and the physiologic effects of CPB in neonates, infants, and small children compared with adults. The surface area and volume of the CPB circuit relative to

TABLE 108-1 Sample Scheme for Infant and Pediatric Oxygenators*

Oxygenator	Optimal Body Surface Area (m ²) [†]	Estimated Total Prime Volume [‡] (mL)	Membrane Surface Area (m ²)	Heat Exchange Surface Area (m ²)	Manufactured Recommendation Maximal Flow Rate (mL/min)
Dideco Kids D100	<0.23	240-265	0.22	0.03	700
Terumo Baby RX	0.3-0.4	290-320	0.5	0.035	1500
Terumo RX15-30	0.5-0.7	590-655	1.5	0.14	4000
Terumo RX15-30 Small Adult/KVAD	1.0-1.3	990-1075	1.5	0.14	5000
Terumo RX25 Adult/KVAD	>1.34	1200-1275	2.5	0.2	7000

*Used under standard configuration.

[†]Assuming maximum 3 liter/min/m² flow rate.

[‡]Assuming use of standard configuration and usual tubing size and length for weight. KVAD, Kinetic-assisted venous drainage.

patient size and blood volume is much greater for neonates and infants. Arterial and venous cannulas are smaller but more likely to deform or obstruct the aorta or venae cavae. The placement of these cannulas can be different and more variable than in adults—for example, separate superior and inferior vena caval cannulas or initial placement of the aortic cannula in the pulmonary artery (with retrograde systemic perfusion via the ductus arteriosus) during stage I repair of hypoplastic left heart syndrome. To minimize hemodilution, the sizes of various circuit components and tubing diameters are kept as small as possible. Nonetheless, hemodilution that is equivalent to one to two blood volumes from the circuit prime and cardioplegia is fairly common in neonates and small infants (see Table 108-1).

DHCA, although used much less frequently than even a few years ago, is still used occasionally. Overall, pump flow rates can range from no flow (i.e., circulatory arrest) to more than 200 mL/min; mean arterial pressures can vary from 10 to 20 mm Hg during low-flow CPB to more than 50 mm Hg at full or high flow. Temperatures are typically lower in CPB for infants (core temperatures of 15° to 18° C for deep hypothermia; 22° to 25° C is used by some for many other complex repairs), and different blood pH management strategies may be used (i.e., alpha-stat versus pH-stat). In part because of these differences, the magnitude of neuroendocrine stress responses and systemic inflammatory responses to CPB, as well as their consequences, are generally believed to be more profound in neonates and infants than in adults.

Patient Factors

Patient-specific variables and the diverse pathophysiology associated with specific congenital cardiac defects further complicate CPB in neonates, infants, and small children. It is likely that neonates, in general, and particularly those who are premature or weigh less than 1.8 to 2.0 kg, comprise a high-risk group because of immature organ function and coexisting diseases such as sepsis, respiratory distress syndrome, and other congenital anomalies.²⁰ The immature myocardium may be similarly prone to CPB-related dysfunction for several reasons, including its relatively deficient (compared with in adults) contractile protein mass and organization of contractile

proteins, the presence of fetal contractile protein isoforms, immature calcium cycling (which occurs primarily via the sarcolemmal membrane as opposed to the sarcoplasmic reticulum, which is less abundant and less well organized), and fewer mitochondria.

Various aspects of congenital heart disease can mean additional complicating features. Hypertrophic and cyanotic myocardium is more likely to be injured by ischemia-reperfusion and other consequences of CPB.²¹⁻²⁴ Aortopulmonary collaterals, which can be particularly significant in various cyanotic lesions, may promote pulmonary dysfunction as a result of high flow on CPB, whereas steal from systemic perfusion can compromise the function of other organs, and collaterals to the coronary circulation can wash out cardioplegia and thereby hinder effective myocardial preservation. Pulmonary dysfunction after CPB may be more prevalent in infants with other routes of high pulmonary blood flow (e.g., truncus arteriosus, hypoplastic left heart syndrome, transposition of the great arteries) and in cyanotic infants.^{20,25} Diffuse organ dysfunction is likely to be more common in patients who were severely cyanotic and hypoperfused at the time of delivery or who required complex surgery in the early neonatal period. In the neonate who was compromised at the time of delivery or thereafter, most centers have found it beneficial to allow a period of stabilization of the circulation and recovery of organ function prior to undertaking CPB and cardiac surgery, using lesion-appropriate interventions such as prostaglandin E1, inotropic support, ventilatory strategies to balance systemic and pulmonary blood flow, and even extracorporeal circulatory support (see later). Post-CPB organ dysfunction (e.g., kidney, liver) can also be a source of morbidity in older (i.e., adult-age) patients with various forms of congenital heart disease complicated by long-standing cyanosis, low cardiac output, or high systemic venous pressures.

Differences in the Cardiopulmonary Bypass Circuit

A summary of the components of different-sized CPB circuits is shown in Table 108-1.

Oxygenators. Oxygenator systems for infants and children must function over a wide range of pump flow rates

(maximal flow rates range between 800 and 4000 mL/min, and they must be efficient over a range of flows equivalent to 0 to 250 mL/kg), temperatures (10° to 38° C), hematocrits (15% to 40%), and line pressures (because of different sizes of cannulas and tubing).

Virtually all current pediatric CPB applications use membrane-type oxygenators. The two main types are microporous (hollow-fiber or folded-membrane) and nonporous membrane oxygenators. The major advantage of microporous-type membranes is their ability to effect gas exchange with a relatively modest membrane surface area, typically in the range of 0.2 to 1.5 m², depending on the specific oxygenator and configuration. Major disadvantages include some blood-gas contact at the start of CPB (until protein accumulation blocks the 0.05- to 0.25-μm pores) and protein leakage across the membrane, along with the potential for gas embolization if negative pressure develops on the blood side of the artificial membrane. Nonporous oxygenator membranes, typically of the folded-sheet silicone-membrane variety, require a larger surface area to achieve gas exchange but do not accumulate or leak protein as readily and are therefore more often selected for longer-term circulatory support applications (e.g., extracorporeal membrane oxygenation).

There is a real need to minimize circuit priming volume to minimize hemodilution, blood product exposure, and the potential for fluid overload and edema.²⁶ Priming volume is usually defined as the volume of the membrane compartment plus the minimal amount required for the venous reservoir. Typical priming volumes of commercial membrane oxygenators range from approximately 225 to 375 mL when used in the open configuration. The Dideco Lilliput hollow-fiber membrane oxygenator (Dideco, Mirandola, Italy) is an example of one with a smaller prime volume (≈70 mL), but it is not available in an open-system configuration. More recently, oxygenators and arterial filters have been combined into one unit, further reducing priming volume (e.g., Quadrox-I Neonatal and Pediatric with integrated arterial filter, Maquet, Rastatt, Germany; or Capiiox FX05, Terumo Corporation, Tokyo, Japan). Various schema for achieving low priming volume and thereby reducing or avoiding the need for blood products as a component of the priming solution have been described.²⁷⁻³³

Pumps. Most pediatric circuits use roller pumps. Pump flow rate is governed by the revolutions per minute (rpm) of the pump head, the degree of occlusion produced by the rollers, and the internal diameter of the tubing. A significant advantage is that pump flow is relatively independent of resistive and hydrostatic forces in the circuit. However, adequate flow is highly dependent on proper setting of roller head occlusion (which also affects the degree of blood trauma and hemolysis), along with accurate knowledge of pump head speed (rpm) and tubing size. Failure to accurately account for any of these variables can lead to excessive or inadequate pump flow.

Tubing. Competing considerations govern selection of tubing size for infant and pediatric CPB (Table 108-2). The internal diameter needs to be large enough to permit

TABLE 108-2 Infant and Pediatric Cardiopulmonary Bypass Tubing

Tubing Diameter (inch)	Tubing Volume (mL/ft)	Flow Rate (mL/revolution)
3/16	5.0	7.4
1/4	9.7	13
3/8	21.7	27
1/2	38.6	45

the required full flow rate (see later) without inordinately increasing circuit line pressures. On the other hand, the tubing should be as narrow and as short as practical, to minimize priming volume. Some neonatal circuits use 1/4-inch tubing on both arterial and venous limbs, and most centers have further decreased the diameter of the arterial tubing to 3/16 inch; some use 3/16-inch tubing for both arterial and venous limbs (although vacuum-assisted venous drainage may be required in this case).²⁰ The pump is usually situated as close to the surgical field as possible to reduce tubing length, which is a major contributor to overall circuit volume.

Venous Drainage. As in adult circuits, venous blood usually flows from the patient to the venous reservoir of the CPB circuit by gravity. The level of blood in the venous reservoir serves as an important safety mechanism: it is a source of volume to increase arterial inflow and to assess the adequacy of venous return. If venous return and the level in the venous reservoir decline, the cause (e.g., unrecovered or lost blood in the surgical field, malpositioned venous cannulas, excessive capillary leak) can be identified, and interventions (e.g., decreasing pump flow rate, adding volume, adjusting operating table height, repositioning venous cannulas) can be performed.

Many venous reservoirs are rigid and used in a configuration that is open to the atmosphere. Advantages include ease of removing entrained venous air, free flow of venous drainage (i.e., no air lockage or buildup of pressure in the reservoir), integration of the cardiectomy reservoir (as opposed to having a separate reservoir for cardiectomy suction), and the ability to accurately measure reservoir volume via calibration lines on the side of the chamber. This last feature is a useful aid to assess the patient's intravascular volume and may therefore facilitate weaning from CPB. Major disadvantages of open, rigid venous reservoirs include the presence of a blood-air interface, which may promote blood trauma and activation of the coagulation, fibrinolytic, and inflammatory cascades (see later), and the need for a larger priming volume.

A soft, collapsible venous reservoir bag that expands and contracts in relationship to overall blood volume, venous return, and arterial inflow rate is used with increasing frequency in infant CPB. Advantages include the absence of direct blood-air contact and the fact that air is not entrained if the venous reservoir becomes empty, which collapses the bag. A major disadvantage can be the inability to accurately measure venous reservoir

volume or to recognize subtle but important changes in venous return. Other relative disadvantages compared with rigid reservoirs include the need for a removal mechanism if air is entrained, the need for a separate cardiectomy suction reservoir, and the fact that venous drainage will be significantly reduced if pressure builds up as a result of overfilling of the reservoir with blood volume or air.

Vacuum-assisted venous drainage has been used for pediatric patients.^{20,28,34-36} Although this has not been well studied in a controlled or prospective fashion, advantages may include the ability to reduce total circuit volume by using lower venous reservoir volume and $\frac{3}{16}$ -inch venous tubing, improving operating conditions to some extent by allowing use of smaller venous cannulas, and improving venous drainage through the small cannulas and tubing. Theoretically, the improvement of venous drainage could lead to reduced tissue and organ edema and congestion, improved organ function, and reduced inflammatory activation (e.g., via endotoxin release from congested, hypoperfused intestine). A major potential complication of vacuum-assisted venous drainage is venoarterial air embolism.³⁷⁻⁴¹

Arterial Cannulas. Issues regarding cannula size are much more significant in infants and small children than in adults. Arterial cannulas for neonates and small infants must be of sufficient size to permit appropriate arterial inflow rates at reasonable line pressures, with minimal shearing or jetting of blood flow (which can damage the vessel intima, aortic valve, or blood elements), yet small enough to fit in small aortas without obstructing aortic flow (Table 108-3). Small cannulas (i.e., 8 Fr) with a thin-walled, reinforced design that prevents cannula kinking and allows a larger luminal diameter for a given external diameter have become popular choices for infant bypass (Biomedicus, Medtronic, Minneapolis, MN). Care also needs to be taken not to kink or compress the infant's pliable aorta by the location and orientation of the aortic cannula and its tubing. As noted, the cannula itself can significantly obstruct flow in the vessel around the cannula. Location of the tip can direct blood flow toward or away from specific vessels; for example, locating and directing the tip more distally toward the transverse arch may reduce flow through the right carotid artery or favor lower body perfusion at the expense of cerebral perfusion and optimal brain cooling.⁴²

Certain congenital cardiac lesions require unique aortic cannulation sites. For example, the aortic cannula

is typically placed more distally in the aorta for repairs that involve extensive proximal aortic surgery, such as the arterial switch procedure for transposition of the great vessels; this distal location may alter distribution of blood flow to the carotid vessels. Repair of interrupted aortic arch requires two arterial cannulas, one in each segment of the aorta (perfusing the head and lower body, respectively). The aortic cannula is placed in the pulmonary artery at the beginning of CPB for stage I repair of hypoplastic left heart syndrome because of the typically diminutive size of the ascending aorta in this lesion. The distal pulmonary arteries are occluded with tourniquets and the aorta is perfused via the ductus arteriosus until the aortic reconstruction is completed, at which time the cannula is repositioned in the neo-aorta. The aortic cannula can also be placed into a side graft, which is anastomosed to the innominate artery, for arch reconstruction using antegrade cerebral perfusion.

Unlike in adults, femoral arterial cannulation for CPB is not usually a viable option in infants and small children (weighing less than ≈ 10 to 15 kg), because small vessel size precludes inserting an arterial cannula that is large enough to allow arterial inflow rates that are sufficient to completely meet metabolic needs (see later). In small infants (without recent sternotomy), the neck vessels are the preferred extrathoracic cannulation sites (see later). However, as a resuscitative measure in emergent situations (e.g., cardiopulmonary arrest in the cardiac catheterization laboratory, particularly when femoral vascular access is already in place), insertion of smaller perfusion cannulas in the femoral artery has often been life-saving in terms of facilitating rapid establishment of extracorporeal support. Femoral access is performed occasionally for older children, either electively, when there is concern that a cardiac chamber or vascular conduit lies immediately beneath the sternum, or emergently, when one of these structures is entered inadvertently during the dissection.

Venous Cannulas. Choice and location of venous cannulas can also be more complex and variable than is typically the case in adults, and variations in venous anatomy and drainage as well as the operative approach must be taken into account. Venous cannulas are available in a variety of sizes and with design features for particular indications (Table 108-4). For example, thin-walled cannulas with multiple side holes enhance venous drainage; right-angled tips are frequently used in the SVC to improve alignment (and therefore drainage) and minimize impact on the surgical field; metal-tipped, to prevent kinking; straight, short-tipped in the IVC, to limit hepatic venous obstruction.

Overall, most repairs use separate SVC and IVC cannulas to achieve maximal collection of venous return and to minimize interference with the operative field. Common variations in venous anatomy that can complicate venous cannulation and must be taken into account include left or bilateral SVCs, azygous or hemiazygous continuation of the IVC, and direct drainage of the hepatic veins into the atrium. A single atrial cannula is frequently used when DHCA is planned; in this case, the venous cannula is removed after the patient is adequately cooled, to provide a clear operative field.

TABLE 108-3 Representative Pediatric Arterial Cannulas

Weight (kg)	Standard Arterial Size (Fr)	Biomedicus Pediatric Arterial Size (Fr)
<5	10	8
5-10	12	10
10-14	14	12
14-28	16	14
28-40	18	15
40-55	20	17

TABLE 108-4 Representative Venous Cannulas for Pediatric Cardiopulmonary Bypass

Weight (kg)	Single Venous (Fr)	
<3.5	14	
3.5-5	14	
5-8	16	
8-12	16	
12-18	18	
18-26	20	
26-55	22	
>55	24	

Metal-Tip, Right-Angle Venous* (Fr)		
Weight (kg)	SVC	IVC
<3	12	12
3-6	12	14
6-8	12	16
8-12	14	16
12-16	14	18
16-22	16	18
22-30	16	20
30-34	18	20
34-46	18	20-22
46-58	20	22

Weight (kg)	Dual-Stage† (Fr)	
<12	18/24	
12-30	20/28	
30-65	29/29	
>65	29/37*	

Weight (kg)	Dual-Stage with Venous Assist (Fr)	
<20	18/24	
20-45	20/28	
45-85	29/29	
>85	29/37	

*For example, the Medtronic DLP (Minneapolis, MN).

†For example, Edwards Lifesciences (Irvine, CA).

IVC, Inferior vena cava; SVC, superior vena cava.

Regardless of location, it is important that the cannula be appropriately sited and that it cause as little obstruction to venous drainage as possible. Poor venous drainage may be difficult to detect and is more likely to occur in patients with complicated venous anatomy. The consequences of impaired venous drainage and increased venous pressures are likely to be magnified during CPB because arterial perfusion pressure is frequently reduced. Obstruction of the SVC may promote cerebral edema and otherwise increase the risk of brain injury by decreasing cerebral blood flow (CBF) and hindering effective brain cooling. Many physicians find monitoring of SVC pressure by a catheter placed in the internal jugular vein useful to detect possible SVC obstruction in this setting. In addition, the patient's head and face should also be inspected at regular intervals during CPB for the appearance of congestion or swelling. It is likely that monitoring CBF velocity using transcranial Doppler methodology might be useful in this regard. A drop in cerebral near-infrared spectroscopy (NIRS) saturation may herald poor

SVC drainage and need for cannula adjustment. IVC obstruction will increase lower body venous pressures and potentially decrease hepatic, renal, or mesenteric perfusion; isolated hepatic vein obstruction can also occur. Consequences can include hepatic dysfunction, renal dysfunction, ascites, and perhaps increased inflammatory consequences of mesenteric congestion.^{43,44} IVC obstruction during CPB can be difficult to detect and should be suspected whenever there is development of ascites, decreased urine output, or impaired venous return.

Filters. Almost all applications use 0.2- μ m filters in the gas inflow lines to prevent bacterial or particulate contamination. Similarly, all crystalloid prime and cardioplegia solutions are passed through 0.2- μ m filters prior to final addition to the CPB circuit. A 20- or 40- μ m filter is used on the cardiotomy suction return line to remove macro- and microaggregates and other debris from the blood returning from the surgical field. Exogenous blood is also filtered (typically through a 40- μ m blood filter) before it is added to either the pump circuit or to cardioplegia. Specific removal of blood polymorphonuclear leukocytes using leukocyte-depleting filters placed in-line on the CPB circuit (which typically reduces circulating leukocyte counts in the patient by $\approx 75\%$) is advocated by some centers as a significant means to reduce reperfusion injury.^{25,45}

Use of an arterial filter (40 μ m) is somewhat more controversial. Many consider arterial filtering essential to limit the microemboli and amount of other debris from platelet and leukocyte microaggregates, traumatized blood elements, fat, and other sources, particularly because these might contribute to post-CPB neurologic injury and damage to other organ systems. Some physicians do not feel strongly about these issues and omit arterial line filters, at least in part to reduce priming volume and hemodilution.²⁰ As mentioned previously, there are now oxygenators with integrated arterial filters.⁴⁶

Cardiopulmonary Bypass Prime. The priming volume of even the smallest neonatal and infant CPB circuits is usually equivalent to approximately 1.5 to 3 times the patient's blood volume. Thus, dilution of red cells, clotting factors, and other plasma constituents is potentially of far greater magnitude than in adults. Physiologic crystalloid solutions (e.g., Normosol-R, Hospira, Lake Forest, IL) are the major component of CPB priming solutions in infants and children; colloidal primes are used infrequently. Significant additions to the infant CPB prime include packed red blood cells (or occasionally whole blood), as well as fresh-frozen plasma or other colloids such as albumin.

Other agents that may be included in the pump prime include mannitol, steroids, heparin, and buffers (e.g., sodium bicarbonate or tris[hydroxymethyl]aminomethane [THAM]). Mannitol is used primarily for its osmotic properties and is intended to reduce organ and cellular edema as well as to promote diuresis and thereby contribute to renal protection. The osmotic diuresis may be particularly beneficial in some congenital cardiac

operations in which a substantial amount of hemolysis from blood trauma caused by cardiomy suction and high pump flow rates can occur. Stabilization of cellular membranes and various antioxidant properties, including radical scavenging, have also been attributed to mannitol. The significance of any of these effects has not been proven in pediatric CPB. Steroids are used to reduce inflammatory effects of CPB (see later).

The use of albumin or other colloid to prime CPB circuits is also controversial.⁴⁷⁻⁴⁹ There is evidence that reduced plasma protein concentrations and diminished plasma oncotic pressure can reduce lymphatic flow and increase capillary leak in the lung and other vascular beds.⁵⁰⁻⁵³ Although fluid balance and weight gain were favorably influenced, a recent study that randomized pediatric CPB patients to crystalloid or colloid prime did not demonstrate significant differences in mortality or in length of mechanical ventilation, intensive care unit stay, or hospital stay.⁵³ These results are similar to those obtained in adults, where albumin does prevent CPB-induced reductions in colloid oncotic pressure and lung water accumulation, but it appears to have little effect on overall outcome or measures of pulmonary, myocardial, or renal function. Synthetic colloids are available but have not demonstrated benefits in adults.

Hemodilution. As noted earlier, some centers have gone to substantial lengths to modify circuit design to reduce the degree of hemodilution associated with infant CPB and decrease the use of exogenous blood and other products. These modifications have included the use of the smallest possible tubing, cannulas, and oxygenators; altered orientation of the CPB circuit to decrease tubing length; vacuum-assisted venous drainage to improve return through the small cannulas and tubing; and omission of arterial filters. Resultant priming volumes in the range of 180 to 250 mL have been reported. Ultrafiltration techniques (see later) are also used to offset the hemodiluting effects of CPB and thereby reduce the requirement for donor blood and blood products. With the possible exception of ultrafiltration, there is no evidence that edema, the inflammatory response to CPB, or overall outcome is improved by these measures, and, at present, it remains difficult to avoid the use of exogenous blood or blood products in patients who weigh less than approximately 10 kg.

Both packed red cells and whole blood have been used to ensure age-, lesion-, and temperature-appropriate hematocrit during CPB. Packed red cells are readily available and are probably used by most centers to increase and maintain hematocrit during CPB. A major disadvantage of whole blood compared with packed red cells is the higher glucose load that accompanies whole blood; hyperglycemia may increase the risk of brain injury during cerebral ischemia. On the other hand, whole blood more effectively maintains plasma factor concentrations, which can be significantly reduced by CPB in these patients (see later). Questions about the actual oxygen carrying and delivery capacity of stored red blood cells have been raised.⁵⁴ Increased duration of blood cell storage has been related to postoperative morbidity.⁵⁵

The optimal hematocrit for neonatal and infant CPB remains controversial. Perhaps the most important consideration is the temperature and flow rate that are to be used (e.g., deep hypothermia, low flow, or circulatory arrest). More profound degrees of hypothermia are used in pediatric patients to suppress metabolic demands and increase tolerance to periods of low flow (25° to 18° C) or absent flow (15° to 18° C). Although the oxygen-carrying capacity of hemoglobin increases at lower temperatures, its ability to donate oxygen to the tissues is also reduced. Moreover, the increase in blood viscosity that accompanies hypothermia is a significant impediment to microcirculatory flow and can lead to sludging and regional ischemia. The nonpulsatile flow patterns typical of most CPB applications may also decrease microcirculatory flow, particularly in the setting of increased viscosity. It is also important to note that the oxygen-carrying capacity of the non-red cell fluid component of blood (i.e., plasma) increases at decreasing temperatures because of the increased solubility of gas in the liquid phase that occurs as temperature declines; as a result, the net effect of hemodilution during hypothermia is to improve microvascular flow and oxygen delivery.

Despite these theoretical considerations, the optimal and maximal tolerable levels of hemodilution for a given degree of hypothermia are not established. Normovolemic hemodilution with hematocrit levels down to 15% is believed to be well tolerated during normothermia in terms of cerebral and myocardial function as long as blood pressure, oxygenation, and cardiac output are maintained.^{56,57} Long-standing practice at many centers has been to aim for hematocrit levels in the 18% to 22% range during deep hypothermic CPB, and this is based on the aforementioned improvements in blood rheology and overall oxygen-carrying capacity that accompany the combination of hemodilution and hypothermia. Animal studies and reports of children of the Jehovah's Witnesses faith undergoing hypothermic CPB suggest no detectable effect on overall outcome or cerebral or cardiovascular morbidity at hematocrits in the range of 10% to 18% when a low temperature, perfusion pressure, and flow rate are maintained.⁵⁷⁻⁶⁰ Hematocrits of 10% or less in infants have been associated with acidosis and other evidence of inadequate oxygen delivery.

More recent evidence has cast doubt on the safety of very low hematocrits during hypothermic CPB in infant patients. In experimental infant CPB models, higher hematocrit (in the 25% to 30% range) has been associated with enhanced preservation of brain high-energy phosphates, intracellular pH, tissue oxygenation, maintained capillary density and microvascular flow, reduced leukocyte activation, and reduced neurologic injury.⁶¹⁻⁶³ A recent clinical study that randomized infants to either a low hematocrit (mean hematocrit, 22% $\pm$ 3%) or high hematocrit (28% $\pm$ 3%) strategy at the start of low-flow hypothermic CPB found lower postoperative cardiac index, higher serum lactate, and higher total body water in the low hematocrit group. At 1 year, overall neurologic evaluations and mental development index scores were similar in the two groups, but the low hematocrit group had significantly lower psychomotor development index scores.⁶⁴ Our current practice is to aim to keep the

hematocrit between approximately 25% and 30% during all types of CPB. A hematocrit level at the onset of low-flow CPB of approximately 25% was associated with higher psychomotor development index scores and reduced lactate levels.^{65,66} In addition to any direct effects, it is likely that the somewhat higher hematocrit provides some degree of safety margin against other problems with perfusion, collaterals, and alterations in cerebral autoregulation and CBF.^{59,65-70} However, similar variations in patient age, anatomy, collaterals, flow rate, pH strategy, and cooling, for example, make it impossible to pronounce a single optimal hematocrit for infants or children.

The optimal hematocrit for weaning from CPB is also controversial. The overall goal is adequate systemic oxygen delivery. Our current practice is to aim for hematocrits in the range of 25% to 30% during rewarming and at termination of CPB. These levels (and perhaps even somewhat lower) are likely to be well tolerated by patients who have good myocardial function, minimal or no hemodynamic lesions, and a physiologic repair with normal oxygen saturation at the conclusion of their surgery. Consideration should be given to increasing hematocrit to improve oxygen-carrying capacity and oxygen delivery in patients with reduced myocardial function or palliative or staged operations that result in cyanosis. In these cases, hematocrits of 40% or even slightly higher may be beneficial, but definitive data are lacking.

Pump Flow Rates during Pediatric Cardiopulmonary Bypass. Optimal pump flow rates for pediatric CPB are, as for adults, based on considerations of adequate systemic oxygenation, oxygen delivery, and organ perfusion at normothermia as assessed by oxygen consumption and metabolic rate, mixed venous oxygen saturation, acid-base balance, and lactate production.⁷¹ These are typically indexed to body weight. The higher metabolic rate of neonates and infants (≈ 1.5 - to 2.5 -fold greater than that of adults) mandates proportionately higher flow rates during normothermic CPB (Table 108-5).

Heparinization. The approach to anticoagulation during pediatric CPB is similar to that for adults. Heparin is administered in a dose of approximately 4 mg/kg (400 U/kg) prior to initiation of bypass, either directly into the right atrium or into a central venous catheter; teams at some centers include a portion of the total heparin dose in the CPB pump prime. Confirmation of heparin injection by blood aspiration, as well as the

adequacy of heparin effect, should be performed before beginning CPB. The activated clotting time (ACT) is the primary method of monitoring the efficacy of heparin anticoagulation (and reversal) in infants and children. Typical guidelines require an ACT of greater than 400 seconds before initiating CPB, and ACT should be maintained between 400 and 600 seconds during CPB to prevent activation of blood coagulation pathways and clot formation. Inadequate concentrations of heparin are believed to be a major contributor to excessive activation of the coagulation and fibrinolytic systems.⁷² Other methods of monitoring heparin effect, anticoagulation, and clotting parameters, such as blood heparin concentration and thromboelastography, are adjunctive at present and used mainly to assess residual heparin activity and diagnose and treat coagulopathies after termination of CPB.⁷³ Heparin brand and formulation will affect the level of anticoagulation and even the amount of postoperative bleeding.^{74,75}

Although substantive data are scant, there is some evidence that, generally, neonates and young infants are more sensitive to the effects of heparin administered for CPB and that the efficacy and duration of heparin-based anticoagulation is significantly more variable in neonates and young infants.^{72,76-78} Potential mechanisms include the variable and generally lower levels of both procoagulant and anticoagulant factors present during the first few months of life and in some patients with congenital heart disease.⁷⁹⁻⁸² The degree of hypothermia, amount of hemodilution, and relative immaturity of drug metabolism can also contribute to an increased and prolonged heparin effect in infants. Heparin resistance, on the other hand, is seen infrequently in infants, although sporadic examples resulting from recent heparin exposure or antithrombin III deficiency do occur. Heparin-induced thrombocytopenia and thrombosis appear to be less common in infants and children than in adult heart surgery patients, but the incidence may increase as the number of children who are repeatedly exposed in the operating room, catheterization laboratory, and other sites continues to increase.^{83,84} There is at present only limited and anecdotal experience with the use of heparin alternatives such as bivalirudin, hirudin, and argatroban, for anticoagulation during pediatric CPB.⁸⁵⁻⁸⁷

Heparin Reversal. Protamine sulfate is administered at the end of CPB to reverse the anticoagulant effects of heparin. As with heparin, there is little prospective, controlled information about the dosing of protamine in neonates and infants. Protamine dosing is usually based on body weight (3 to 4 mg/kg) or in a ratio to the heparin dose (milligrams-to-milligrams) of 1:1 or 1.3:1; in vitro titration to neutralize heparin in a patient sample is also used by some physicians. In general, the target ACT after protamine administration is within approximately 10% of the pre-CPB baseline. The first two empirical methods usually result in relative protamine excess, which is intentional because of greater heparin sensitivity and duration in infants and because of other factors that may potentiate heparinization, such as hemodilution, hypothermia, and delayed metabolic clearance. However, as with adults, there is evidence that empirical protamine dosing is

TABLE 108-5 Estimated Flow Rates for Normothermic Infant and Pediatric Cardiopulmonary Bypass

Body Weight (kg)	Flow Range (mL/kg/min)	Usual Full-Flow Rate (mL/kg/min)
<3	150-200	200
3-10	125-175	150
10-15	120-150	125
13-30	80-120	100

associated with excess protamine administration and perhaps greater blood loss and transfusion requirements as compared with doses that directly measure blood heparin using titration or other methods.^{77,78,88,89} Another argument against empiric dosing is that relatively small excesses of circulating protamine compared with heparin may have direct antiplatelet effects that can exacerbate bleeding after CPB.⁹⁰

Typically, the drug is administered slowly over approximately 10 minutes. For unclear reasons, severe hypotensive, pulmonary vasoconstrictive, or anaphylactic/anaphylactoid reactions to protamine are uncommon in infants and children.⁹¹ Of these, hypotension is most frequent, occurring in between approximately 1.5% and 3% of protamine administrations. It is dependent on dose and rate of administration, most likely resulting from histamine release, usually fairly mild and transient, and responsive to volume replacement or calcium administration. Severe pulmonary vasoconstriction appears to be much less common than in adults, maybe as a result of complement activation or pulmonary thromboxane release, and can be particularly troubling in patients with depressed contractile function.

Initiation of Pediatric Cardiopulmonary Bypass

CPB is initiated once the arterial and venous cannulas are correctly positioned and connected to the circuit, the absence of air in the arterial line (especially at the connection between cannula and circuit tubing) is confirmed, and adequate anticoagulation is established. Under most circumstances in neonates and infants, arterial inflow is begun slowly and then the venous line is unclamped. Rapid onset of bradycardia and loss of myocardial function can ensue when a cold prime is used. Therefore, when using either normothermic or cold pump primes, full flow is usually reached fairly rapidly in neonates and infants to ensure adequate systemic perfusion and oxygen delivery. When it is important to keep the heart beating and potentially ejecting, prime electrolyte concentrations—specifically calcium and potassium—are usually normalized, along with the temperature of the prime solution, so as to maintain myocardial function and prevent myocardial distention during the initiation of bypass. Compromised venous drainage can also distend the heart and promote myocardial damage.

Large collateral vessels arising from the arterial tree (as can be seen in many forms of cyanotic heart disease, including tetralogy of Fallot and pulmonary atresia), patent ductus arteriosus, and surgical aortopulmonary shunts can promote runoff from the systemic circulation during CPB and thereby reduce perfusion pressure, effective organ (i.e., brain, heart, kidneys) blood flow, and cooling despite seemingly adequate total pump flow. Surgical control and effective occlusion of large aortopulmonary collateral vessels, surgical shunts, and the patent ductus arteriosus is accomplished immediately before or shortly after commencing CPB. Significant aortopulmonary collateral vessels that are not important sources of pulmonary blood flow or contributors to arterial oxygenation can be coil-occluded in the cardiac catheterization

laboratory before surgery, which will also decrease the volume load on the systemic ventricle.

Monitoring during Pediatric Cardiopulmonary Bypass

Circuit Monitoring

Important CPB circuit variables include arterial line pressure, pump flow rate, oxygenator gases, and temperature. Arterial line pressure is measured via a pressure transducer placed in the arterial inflow limb. Line pressure can be substantially higher than patient arterial pressure because of the driving pressure required to achieve adequate flow through small-diameter infant arterial cannulas and tubing, and it is typically in the range of 225 to 260 mm Hg at mean arterial pressures of 40 to 60 mm Hg. Excessively high arterial line pressures (>300 to 400 mm Hg) can result from tubing or cannula obstruction or cannula malposition and can result in circuit rupture. Many circuits include a sensor on the oxygenator reservoir to detect critically low volume levels and a sensor on the arterial line to detect air.

The flow output of roller pumps is governed by roller head rpm, occlusion pressure, and the internal tubing diameter. Pump flow rate on roller pumps is not measured directly but rather *calculated* by the perfusionist (or electronics on the pump) based on these variables. Because the flow output of the pump is not measured directly, incorrectly measuring or inputting rpm, tubing size, or occlusion, as well as possible shunts in the circuit, can lead to potentially harmful perfusion errors (either increased or decreased). Unexpectedly low or high mean arterial pressure for the calculated flow rate may be the first clue to these possibilities. In the case of low flow in particular, abnormal biochemical variables result if the condition is of sufficient magnitude and duration (see later).

Oxygenator gases can include oxygen, air, and carbon dioxide. Continuous in-line monitors of pH, PO₂, and PCO₂ are used frequently. The gas “sweep speed” (flow rate) and oxygen concentration delivered to the oxygenator are controlled with a flowmeter or blender and measured with appropriate electrodes. Starting sweep speeds are usually at a ratio to pump flow rate of 1:1 for membrane oxygenators. However, the variability in pump flow rates, temperatures, and blood gas management strategies leads to wide variations in gas flow and composition in pediatric patients. pH-stat management can require altered gas sweep rates and the ability to add and precisely control carbon dioxide in the sweep gas.

Thermistors measure temperatures of the water bath and heat exchanger, along with arterial and venous blood temperatures. The temperature gradient between the patient and perfusate should not exceed 10° C. This can be especially important during rewarming to prevent formation of gaseous bubbles and emboli that result from decreased gas solubility as fluid temperature increases.

Patient Monitoring

Monitoring of mean arterial pressure is required during CPB and is most often accomplished via catheters in

either the radial or the femoral arteries. Arterial catheter location can occasionally be governed by considerations such as prior surgical or shunt (e.g., Blalock-Taussig) sites and the current lesion and planned operation. Femoral arterial pressure monitoring (with or without concomitant radial arterial monitoring) is preferred by some for aortic reconstructions and for increased reliability when deep hypothermia is planned, particularly in small infants. Left atrial and SVC or right atrial filling pressures are also measured routinely, depending on the surgery.

Nasopharyngeal, esophageal, and rectal temperatures are measured with appropriate thermistors. Nasopharyngeal or tympanic membrane temperatures are most often used and are probably the most accurate in terms of tracking brain temperature, although no extracranial site is truly reliable in this regard.⁵⁷ Rectal (or occasionally bladder) temperature is used to monitor core temperature. Esophageal temperature reflects aortic temperature and does not correlate well with core or brain temperatures.

Arterial and venous blood gases should be measured within 5 to 10 minutes after commencing and then at 15- to 30-minute intervals for the remainder of CPB but more frequently if there is evidence of compromised perfusion. In addition to pH, PO₂, and PCO₂, most analyzers can use the same samples to simultaneously measure hematocrit and serum electrolyte levels, including levels of sodium, potassium, and ionized calcium. Many centers favor allowing or even promoting (e.g., via the chelating effects of citrate in added blood products) reduced ionized calcium during CPB in an attempt to reduce the contribution of that cation to reperfusion injury. Ionized hypomagnesaemia, another potential contributor to ischemia-reperfusion damage and dysrhythmias, has been found after pediatric CPB, although its clinical significance is unclear.^{92,93} Increasing blood lactate concentrations before and shortly after pediatric CPB have been suggested to correlate postoperative morbidity and mortality.⁹⁴

The oxygen saturation of venous blood (SVO₂) is an important index of tissue perfusion, and it should be measured from venous blood samples at intervals as discussed in the previous paragraph and also continuously via a calibrated in-line monitor on the venous line. Optimal and minimal acceptable values for SVO₂ during CPB, particularly as temperature and flow rate decrease, are not well defined. At normothermic or near normothermic temperatures, SVO₂ can be interpreted as is done in non-CPB situations, and hence low values (less than ~60% to 70%) should raise concern about inadequate tissue oxygen delivery (e.g., inadequate flow, low hemoglobin). The development of shunting around major vascular beds that may occur as a consequence of CPB, in addition to any preexisting collateral vessels, may increase SVO₂ in an artifactual way; in other words, some degree of organ hypoperfusion may exist despite what appear to be acceptable SVO₂ values. At deeper levels of hypothermia, dissolved oxygen contributes an increasing proportion of total oxygen delivery, and the increased affinity of hemoglobin for oxygen impairs transfer from hemoglobin to tissue.⁹⁵ As a result, the interpretation of SVO₂ during deep hypothermia becomes more problematic,

and it may be prudent to require substantially higher levels of SVO₂ (>90%) when this measure is used to infer the adequacy of perfusion during deep hypothermic CPB.

Cerebral saturation measured by NIRS has been used as a surrogate for SVO₂ and, therefore, tissue perfusion. Cerebral NIRS correlates with SVC saturation.⁹⁶ Decrease in cerebral NIRS can be a warning of decreased cerebral perfusion. Periods of diminished intraoperative and perioperative cerebral saturation, as measured by NIRS, has been related to compromised neurodevelopmental outcome and abnormalities in cerebral magnetic resonance imaging.⁹⁷ Flank saturation measured with NIRS can also be used to alert to decreased tissue perfusion to the lower body during bypass.

Frequent monitoring of blood glucose and efforts to maintain it in the normoglycemic range are important during CPB in neonates, infants, and children. The major cause of hypoglycemia appears to be limited hepatic glycogen stores and gluconeogenic capability, especially in neonates, and perhaps also in cyanotic and malnourished (e.g., because of congestive heart failure) infants and young children. Failure to provide exogenous glucose can result in severe hypoglycemia and neurologic injury. The potential neurologic consequences of hypoglycemia may be exacerbated by hypocarbia, which seems to lower the threshold for hypoglycemic neuronal damage, and by patient lesions (e.g., aortopulmonary collaterals) and bypass strategies that independently reduce cerebral autoregulation or CBF (or both).⁹⁸⁻¹⁰⁰

Hyperglycemia can also be a frequent occurrence during pediatric CPB. Blood glucose may increase because of an increased supply from exogenous sources such as intravenous fluids and cardioplegia, or because of reduced glucose uptake, which is primarily caused by increases in stress hormones such as cortisol, growth hormone, and catecholamines that counter the effects of insulin.¹⁰¹ Additionally, deep hypothermia can also suppress glucose-stimulated insulin secretion during hypothermic CPB and for at least a few hours thereafter. Hyperglycemia can potentiate cerebral ischemia-reperfusion injury under a variety of circumstances in infants and children¹⁰²⁻¹⁰⁴ and a trend is seen toward similar results in pediatric CPB patients, although these data are largely retrospective and uncontrolled.^{98,105} Proposed mechanisms of hyperglycemic-ischemic brain injury include hyperosmolar cellular swelling from glucose loading and promotion of lactic acidosis or increased intracellular acidosis caused by increased anaerobic glycolytic flux.

However, this issue remains controversial. Increased blood glucose concentration may be important for adequate brain glucose delivery when CBF and autoregulation are impaired. There was only a weak correlation between blood glucose with brain creatine kinase (CK-BB) levels and no correlation with neurodevelopmental outcome in the Boston Circulatory Arrest study, and there was some evidence that post-CPB hyperglycemia was in fact protective, particularly against seizures, which are associated with worse neurodevelopmental outcomes.^{106,107} There are also substantial data in a variety of non-CPB animal models that pre-ischemic

hyperglycemia may protect immature brain from hypoxia, asphyxia, or hypoxia-ischemia.¹⁰⁸⁻¹¹¹ One important caveat is that these studies were conducted almost exclusively in immature rat models where circulation and ventilation were unsupported, and some of the protective effect of hyperglycemia may have resulted from better maintenance of the circulation or ventilation in hyperglycemic animals (an effect that would be largely irrelevant during CPB).

Further complicating this issue are reports suggesting that relatively modest degrees of hyperglycemia were associated with worse overall outcome in a variety of circumstances, including adult cardiac surgery and in at least some adult and pediatric patients under intensive care, and that tight glucose control could be beneficial.¹¹²⁻¹²⁰ Particularly in the case of adult cardiac surgery patients, at least some of the benefit appeared to be obtained in diabetic (and perhaps prediabetic) patients and to involve risks and complications not typically associated with infant congenital heart surgery.¹²¹⁻¹²³ However, additional and more recent analyses have called this conclusion into question, with a number of studies suggesting that moderate degrees of hyperglycemia are not associated with worse outcome and that tight control may in fact be detrimental.^{114,117,124-126}

In 2012 the *New England Journal of Medicine* published the results of a randomized controlled trial of tight glycemic control compared with standard care after pediatric cardiac surgery. Investigators found low hypoglycemia rates but were not able to demonstrate changes in mortality, infection, or organ failure between the two groups.¹²⁷

Hypothermia

Hypothermia continues to be the mainstay for protection of the brain and other organs during CPB. Its major and most pervasive effect is to decrease metabolic rate and consequently decrease metabolic demand for oxygen and other substrates. During ischemia, hypothermia slows consumption of high-energy phosphate compounds and also maintains them intracellularly, thereby facilitating recovery of adenosine triphosphate (ATP) and phosphocreatine during reperfusion. Hypothermia delays loss of ionic homeostasis during ischemia, particularly entry of sodium and calcium and resultant cellular edema, by energy-dependent, energy-independent, and membrane-stabilizing mechanisms.¹²⁸ Reduced amounts of free-radical generation, inflammatory cytokine production, white cell activation, and leukocyte adhesion molecule synthesis have all been associated with hypothermia or hypothermic CPB. Hypothermia suppresses release of excitatory amino acid neurotransmitters during ischemia and reperfusion, which is likely to be an important cerebral protective mechanism, especially in neonatal and immature brains.^{107,128}

Low-Flow Hypothermic Cardiopulmonary Bypass

The reductions in metabolic rate produced by hypothermia allow CPB flow rates to be reduced, thereby reducing the amount of blood returning to the heart and

improving surgical conditions. Most centers use values of approximately 50 mL/kg/min or 0.70 liter/min/m² for low-flow CPB. Studies in adults and children have suggested the relative safety, particularly in terms of cerebral protection compared with DHCA, of this range of low-flow CPB in combination with hypothermia.^{57,71,129-131}

Further reductions in pump flow to one quarter or less of normal may be used at deep levels of hypothermia (<18° C). However, there is no agreement on what a safe degree of flow reduction might be for a given temperature in infants and children. Kern and colleagues⁷⁰ have suggested that the critical pump flow rate in terms of the crucial juncture at which cerebral metabolism becomes flow dependent is between approximately 30 and 35 mL/kg/min at moderate hypothermia (26° to 29° C) and between 5 and 30 mL/kg/min during deep hypothermia (18° to 22° C). The bulk of evidence suggests that cerebral autoregulation is markedly diminished or absent at temperatures below 20° C, and hence CBF becomes pressure-passive at very low temperatures during CPB in infants.^{57,67,70} Burrows and Bissonnette showed that a significant percentage of neonates and infants who undergo low-flow CPB (<22% of normal pump flow) have no detectable CBF as measured by transcranial Doppler and require higher perfusion pressures to reestablish CBF.¹³² Similar results have been found by others at flow rates typical during profound (14° to 20° C, nasopharyngeal temperature) hypothermic CPB, where some infants lost CBF at flow rates as high as 25% to 35% of normal.¹³³ Thus, it is possible that the result of low-flow CPB in at least some infants is the opposite of what is intended in terms of using low-flow to avoid DHCA—that is, low-flow hypothermic CPB may result in, rather than prevent, cerebral ischemia. The development of critical closing and opening pressures during CPB may contribute to a no-reflow phenomenon and uneven brain cooling during low-flow CPB.⁵⁷ The notion of critical closing and opening pressures in the cerebral vascular bed (and other vascular beds as well) also suggests that blood flow may be more dependent on arterial pressure than pump flow rate in these circumstances and that a minimum mean arterial pressure is necessary to maintain adequate flow to the brain and other organs.

Hypothermic protection of the brain during periods of low or absent flow depends on homogeneous cooling of all brain regions. There is evidence that this may not occur, based on the temperature or oxygen saturation of jugular bulb venous blood, which indicates the likelihood of ongoing cerebral metabolic activity despite low tympanic or nasopharyngeal temperatures.^{42,57} These data indicate that tympanic or nasopharyngeal temperatures may not identify subsets of patients with inadequately cooled brains. Risk factors for nonhomogeneous and delayed brain cooling may include the position of the aortic cannula, vascular anomalies, and aortopulmonary and other collaterals, as well as blood gas or pH management strategy (see later), and the duration of cooling. For example, using alpha-stat pH management, the duration of core cooling prior to a period of DHCA was the intraoperative variable most closely associated with postoperative cognitive outcome. Over cooling times between 11 and 18 minutes, increasing cooling time by 5 minutes

increased the development score by 26 points. It was speculated that shorter cooling times (less than ≈ 15 minutes) permitted ongoing metabolism in nonhomogeneously cooled regions of the brain, making them susceptible to injury during the period of DHCA.¹³⁴ Also of interest, there was a trend for worse neurodevelopmental outcome (that did not reach statistical significance) with cooling times longer than 20 minutes, perhaps because of the effects of prolonging exposure to the deleterious consequences of CPB, including microembolic events.

Deep Hypothermic Circulatory Arrest

DHCA has been used since the 1970s for the repair of congenital heart defects, primarily in neonates and small infants, and occasionally in older children. Use of DHCA can decrease the length of time the patient is on CPB. This was an important advantage during the early congenital cardiac surgical experience, when limitations in CPB equipment and techniques put the neonate and small infant at increased risk. The impetus to minimize exposure to CPB has diminished as CPB methods for infants have improved. Continuous refinement of perfusion methods for neonates and infants has led to a reduction in DHCA use in many centers. Nonetheless, DHCA offers optimal surgical exposure in a small heart and chest by allowing removal of the perfusion cannulas, and its use (or similar alternatives, such as DHCA alternated with periods of intermittent perfusion) is unavoidable for some lesions.

Both surface and core cooling are used prior to DHCA. Surface cooling is facilitated during the induction of anesthesia and surgical exposure and cannulation for CPB by lowering the room temperature as low as possible (to $<20^{\circ}\text{C}$), placing ice-filled bags around the head and neck, and positioning the patient on a cooling/warming blanket set to approximately 10°C . Using these methods, the usual rectal temperature at the time of initiating CPB is approximately 33°C (temperature-related dysrhythmias and ventricular fibrillation are rare in neonates and small infants at core temperatures of greater than 28° to 30°C). For most cases of DHCA, an ascending aortic arterial cannula (the pulmonary artery is cannulated initially for hypoplastic left heart syndrome) and a single right atrial venous cannula are inserted. As noted, extremely rapid cooling (core temperature decreasing to 15° to 18°C in less than ≈ 15 minutes) is usually avoided. The efficiency of different heat exchangers can vary widely, in part because of their surface areas relative to membrane surface area and flow rates (see Table 108-1). Cooling is continued until both rectal and tympanic membrane temperatures are less than 18°C . Cardioplegia is administered, and CPB is then discontinued. Several pharmacologic adjuncts are usually given as part of DHCA. Many include an alpha blocker (such as phentolamine or phenoxybenzamine) in the pump prime to reduce vascular resistance, improve regional blood flow, and aid in homogeneous and effective cooling. High-dose methylprednisolone (30 mg/kg) is given for the reasons already discussed. Some administer sodium pentothal (5 to 10 mg/kg) just prior to the start of DHCA to reduce cerebral electrical activity and metabolism; this is based

in part on experience showing that up to 20% to 30% of neonatal brains will not be electrically silent despite tympanic and core temperatures of less than 18°C . As discussed previously, a higher hematocrit than used previously ($\approx 25\%$ to 28% instead of 15% to 20%) is now favored by many, on the basis of evidence that it does not impair the hypothermic cerebral circulation and may be associated with improved myocardial function, less total body water accumulation, and perhaps improved performance on some neurodevelopmental tests at 1 year of age.^{61,63} Finally, drainage of blood from the patient is promoted by several inflations of the lungs and manual compression of the abdomen. The venous cannula is then usually clamped and removed.

Before rewarming, initial steps are taken to remove air from the left ventricle, left atrium, and pulmonary veins. Cannulas are reinserted, and CPB is slowly resumed at 18°C .

There are different approaches to rewarming. In the oldest approach, rewarming begins immediately, maintaining a temperature differential between the warming circuit and patient's venous blood of less than 10°C and a maximum water temperature of 42°C . Because concerns about cerebral injury after DHCA and information about the potential protective effects of hypothermia and harmful effects of even mild hyperthermia after a cerebral injury have increased, many centers currently undertake a period (≈ 10 to 15 minutes) of 18°C perfusion on resumption of CPB after DHCA and try to limit both hyperthermic reperfusion (by keeping aortic perfusate temperatures lower) and post-CPB hyperthermia.^{20,57,135,136} Prior to aortic cross-clamp removal, mannitol (0.25 to 0.5 g/kg) is frequently given. Ionized calcium, which had been allowed to decrease to approximately 0.4 to 0.8 mmol/L during cooling and early rewarming, is normalized once the heart has had a period of reperfusion and the core temperature has increased to approximately 30° to 32°C . It is probably important to keep both flow rate and mean arterial pressure at age-appropriate normal values because of the loss of cerebral autoregulation and consequent pressure-flow dependence of CBF after DHCA. Once calcium is normalized and the patient is rewarmed to approximately 34°C , pulsatile ejection is stimulated by restricting venous return, and ventilation is begun; this is another opportunity to remove any residual intracardiac air. Observations of the heart, intracardiac filling pressures, arterial blood pressure, and other available information (e.g., contractility and filling on transesophageal echocardiography) are useful at this point to estimate the degree of inotropic support required when weaning from CPB. Typically, low doses of dopamine (≈ 5 to $7.5\text{ }\mu\text{g/kg/min}$) are all that is required.

Management of Arterial Blood Gases during Pediatric Cardiopulmonary Bypass

Most centers adjust oxygen delivery to the CPB circuit so that arterial PO_2 values are in the range of approximately 400 to 600 mm Hg. This hyperoxic approach is based on evidence that brain injury is greater during

normoxic CPB than with hyperoxic CPB.¹³⁷ Potential explanations for this effect include that the brain mainly uses dissolved oxygen during deep hypothermic CPB, the amount of gas microemboli is decreased when nitrogen is omitted from the sweep gas, and oxygen microemboli are resorbed much faster than those containing nitrogen.^{95,135} On the other hand, some centers favor significantly reducing PO₂ during CPB, to reduce oxygen radical production.^{25,137} This mechanism may be especially important in cyanotic infants, in whom antioxidant reserves and scavenging enzyme systems may be down-regulated.^{25,137,138} The issue remains unresolved, and it is likely that the relative benefits of the two oxygenation strategies depend in part on the organ system in question. For example, reperfusing myocardium (especially cyanotic myocardium) at lower PO₂ may be quite beneficial for recovery of cardiac function, whereas it has recently been stated that the significance of hyperoxia-induced oxygen radical injury to the brain is far less important than the deleterious effects of low perfusate PO₂, especially when CBF and cerebral autoregulation are impaired, as is the case with low-flow deep hypothermic (or circulatory arrest) CPB.¹³⁵

The optimal management strategy for pH and CO₂ during profound hypothermia, with or without DHCA, remains controversial. Both alpha-stat and pH-stat management strategies are used during pediatric CPB, and both have potential advantages and disadvantages. During hypothermia, the efficacy of the body's primary buffering systems (e.g., bicarbonate, phosphate) is markedly reduced, and amino acids become the most important intracellular buffers as temperature falls; of these, the α -imidazole ring of histidine is the most effective proton acceptor (i.e., buffer). Water is less ionized (into H⁺ and OH⁻) as temperature falls, and thus the pH of water (the major fluid in the body) increases with falling temperature. The neutral point of water (i.e., the pH at which [H⁺] = [OH⁻]) also rises as temperature falls. This state (the pH at which water is electrochemically neutral) is approximately pH 7.4 at 37° C and approximately pH 7.7 to 7.8 at profound hypothermic temperatures. Alpha-stat management is based on preserving electrical neutrality at reduced temperatures and therefore the buffering capability of the α -imidazole ring of the amino acid histidine. Most enzyme, receptor, and metabolic systems function best at pH 7.4; several have been shown to function more efficiently at 20° C and at a pH of approximately 7.7.^{139,140} Blood from a normal patient cooled under alpha-stat methods will have a pH of approximately 7.4 and a CO₂ concentration of approximately 40 mm Hg when the sample is warmed to 37° C in the blood-gas analyzer. The alleged biochemical advantages of preserving electrochemical neutrality and intracellular buffering via alpha-stat management include better preservation of metabolism and protein and enzyme function (by preserving intracellular pH [pH_i] and preventing abnormal charge accumulation on proteins) and slowing the diffusion of key charged intermediates such as ADP and adenosine monophosphate (AMP) out of the cell, thereby promoting faster recovery of oxidative metabolism and high-energy phosphates when oxygen and substrate supply are restored.¹⁴⁰ Alpha-stat management is

likely to be associated with better preservation of cerebral autoregulation at mild to moderate hypothermic temperatures, lower CBF, and less brain swelling. These features may have a net beneficial effect in adults, where microemboli and cerebral edema appear to be major components of the insult, as compared with the higher brain blood flow and greater microemboli load associated with pH-stat.^{107,141} On the other hand, the alpha-stat strategy causes a leftward shift in the oxyhemoglobin dissociation curve. In the setting of low flow, low perfusion pressures, and low temperatures, overall oxygen delivery under alpha-stat management may be marginal to meet metabolic needs, and CBF may be inadequate to evenly and effectively cool the brain.^{107,142,143}

In contrast, pH-stat uses a mathematical correction for the effects of temperature on pH and then adds CO₂ to the circuit to correct pH for the fall in temperature. pH-stat therefore attempts to normalize the patient's pH (i.e., make it ≈ 7.4) and PCO₂ at the hypothermic temperature. When this sample is analyzed at 37° C, it will be relatively acidotic (pH of ≈ 7.1 to 7.2) and hypercarbic (PCO₂ ≈ 60 to 70 mm Hg). The addition of CO₂ will theoretically lower pH_i and disrupt electrical neutrality. However, evidence suggests that pH-stat may only minimally reduce pH_i.^{144,145} The increase in CBF associated with pH-stat, along with the rightward shift in the oxyhemoglobin dissociation curve, may favor even and effective brain cooling and oxygen delivery as long as perfusion pressure and flow are maintained. Hypercapnia decreases cerebral metabolic rate, energy use, glycolytic flux, and lactate production.^{107,146-148} Hypercapnia and acidosis may also decrease excitatory amino acid neurotoxicity by inhibiting N-methyl-D-aspartate (NMDA) receptor function, glutamate release, and neuronal calcium fluxes.^{107,148,149}

Based on the work of Aoki and Swain showing that cerebral pH_i becomes alkalotic during deep hypothermia even with pH-stat management, it may be that the biochemical advantages of alpha-stat are largely present during pH-stat management and are supplemented by the effects of pH-stat to increase CBF and oxygen availability as a result of its effect to shift rightward the oxyhemoglobin dissociation.^{130,145,150} These effects are likely to be paramount in the neonate and infant exposed to low flow or no flow, because hypoxic and ischemic injury probably pose the greatest risk to the infant, in contrast to the adult with significant atherosclerosis and vascular disease managed at mild or moderate hypothermia, in whom minimizing microemboli and preserving autoregulation (and therefore favoring alpha-stat management) may be the primary pathophysiologic considerations.

A small retrospective study using relatively brief cooling times (<15 minutes on average) suggested that pH-stat might be preferable to alpha-stat in terms of neurodevelopmental outcome when DHCA is used for Senning correction of arterial transposition.¹⁵¹ In a larger, prospective, randomized, single-center study, no consistent improvement or impairment could be related to pH management strategy during deep hypothermic CPB.¹⁵² Overall, DHCA has been found to result in greater short-term (1 year) and long-term (8 years of age) functional neurologic and neurodevelopmental deficits compared

with low-flow CPB; interestingly, both strategies were associated with increased neurodevelopmental risk.¹⁵³ By contrast, in another study of patients with hypoplastic left heart after Norwood procedure, impaired neurodevelopmental outcome was not associated with the use of DHCA and also not associated with pH strategy or hematocrit.¹⁵⁴

On the basis of this information, many centers have begun to favor pH-stat management for infant and pediatric CPB when deep hypothermia, low flow, or circulatory arrest is going to be used.* Patient factors can also influence this choice. The presence of cyanosis and aortopulmonary collaterals are considered by many to be indications for pH-stat management; CO₂ increases pulmonary vascular resistance, leading to improved systemic blood flow in these patients; cerebral perfusion is directly increased by CO₂ and also by the reduction in flow through the collaterals.^{128,135,155}

Bleeding after Pediatric Cardiopulmonary Bypass

Bleeding is a significant problem after many cardiac surgical procedures in neonates, infants, and children. The cause in most cases is likely to be multifactorial. In addition to the difficulties surrounding heparinization and its antagonism by protamine (see Heparin Reversal, earlier), numerous factors (related to the patient, pathophysiology of the lesion, technical aspects of the operation, and the effects of CPB) can promote blood loss. Most of the procoagulant and anticoagulant blood factors are present in reduced concentration in neonates and infants; these concentrations approach adult values at varying rates over the first 6 to 12 months of life.^{79,80,82,157} Infants therefore appear to be functionally balanced albeit at a lower set-point, which enhances the effects of hemodilution by CPB. Reduced levels of both procoagulant and anticoagulant factors compared with age-matched controls have been found in many infants and children with congenital heart disease, particularly those with various forms of single-ventricle physiology.^{79,80,158} The cause is unclear at present, as is whether these abnormalities are linked to any functional disturbances (either increased or decreased) in ability to clot.

Increased bleeding can occur in association with lesions that increase systemic venous pressures (e.g., Fontan physiology, Mustard or Senning atrial baffles, right ventricular dysfunction) resulting from hepatic dysfunction, development of large venous collateral vessels, and high venous pressures. Hepatic dysfunction can also occur in lesions with significant systemic hypoperfusion (large left-to-right shunt, left-sided obstructive lesion such as critical coarctation). Cardiac lesions that generate large shear forces such as aortic stenosis and ventricular septal defects can promote the degradation of active von Willebrand factor multimers to less active and inactive monomers, leading to an acquired form of von Willebrand disease. Prostaglandin E1, used to maintain ductal patency preoperatively, can impair platelet function.

Changes attributed to cyanosis that increase the risk of bleeding may include reduced platelet function, increased fibrinolysis, decreased total body amount of clotting factors (resulting from polycythemia and hence decreased plasma volume), and the development of collateral vessels. Unlike most adult cardiac surgery, many congenital cardiac operations require extensive suture lines and reconstructions using tissue or prosthetic graft materials, often on high-pressure vessels (e.g., stage I operation for hypoplastic left heart syndrome, the arterial switch procedure). Reoperations also make up a substantial part of pediatric cardiac surgery.

The effects of CPB on blood activation, coagulation, and fibrinolysis are arguably greater in neonates and infants because of the greater degree of hemodilution, deeper degrees of hypothermia, higher shear forces resulting from higher flow rates, more blood trauma and greater blood-air contact (higher flows, small tubing and cannulas, more cardiomyotomy suction), and proportionately greater degree of blood contact with the foreign surface. CPB reduces platelet number and causes platelet dysfunction by several mechanisms, including hypothermia, contact activation from the CPB circuit, activation via coagulation mechanisms, and cleavage of platelet adhesive receptors by fibrinolytic proteases that are also activated by CPB. Platelet number in neonates and small infants is approximately halved at the end of bypass following protamine reversal, and platelet function is believed to be markedly impaired for the reasons outlined. Ongoing consumption of platelets and clotting factors resulting from bleeding at complex and pressurized anastomotic sites can add to the problem.

Neonates presenting for CPB are likely to have normal platelet counts but reduced (compared with age-matched subjects, who, as already noted, have lower clotting factor levels compared with adult values) concentrations of factors II, VII, VIII, IX, and X. A subset of neonates may also have significantly lower fibrinogen at the outset, which can then be critically low at the end of bypass and be a major contributor to post-bypass bleeding.¹⁵⁷ Other significant abnormalities at the end of CPB after protamine administration include further reductions and functionally low concentrations of factors V, VII, and VIII. Low post-protamine platelet counts and fibrinogen concentrations correlate with bleeding in neonates and small infants.¹⁵⁹

Treatment of Bleeding after Cardiopulmonary Bypass

The treatment approach to post-CPB bleeding in pediatric patients is based on the preceding considerations, driven by both the expected coagulation abnormalities and the presence of complex reconstructions and extensive vascular suture lines. Platelets are the initial therapy after adequate heparin reversal because of the documented deficiencies in platelet count and function. One to two units of platelets are typically administered to neonates and small infants to start, and up to six to eight units are administered in larger children. One rule of thumb has it that each unit per 10 kg body weight will increase platelet count by approximately 50,000/mm³;

*References 20, 61, 143, 151, 155, and 156.

the actual result in this setting is less, at least in part because administration is done during ongoing bleeding and consumption. Also, platelets are supplied in fluid that is essentially plasma, so a fair amount of clotting factors is supplied simultaneously. Cryoprecipitate is usually the next blood component administered after platelets, and it is chosen in part because it is a good source of fibrinogen in a relatively small volume. This sequence of platelets followed by cryoprecipitate has been shown to restore hemostasis in most pediatric patients after CPB.¹⁵⁹ Fresh-frozen plasma is usually reserved to replete measured factor deficiencies not amenable to cryoprecipitate, particularly because there is some evidence that it has little effect or may even be detrimental to most post-CPB infants.¹⁵⁹ Some pediatric cardiac centers prefer to use fresh whole blood as the primary therapy after protamine reversal. When used within 24 to 48 hours of collection, fresh whole blood contains active platelets and significant amounts of clotting factors, and it has been shown to reduce bleeding, transfusion requirements, and the use of other components in both neonates and adults.^{160,161} One major limitation is the difficulty in obtaining reliable quantities within the 48-hour time frame, in part because of required blood banking procedures and testing for infectious agents. Thromboelastography may help identify coagulopathy and may help direct the treatment of bleeding after CPB, thereby reducing blood product utilization.^{162,163}

Although truly accelerated fibrinolysis is probably uncommon during pediatric CPB (and largely resolves after protamine administration),^{73,159} it is likely that the activation of the fibrinolytic system that accompanies surgical trauma and bleeding, and particularly in association with CPB-induced activation of coagulation and inflammatory cascades, has a significant role in consumption of clotting factors, generation of anticoagulant degradation products, and loss of adhesive receptors on platelets. For these reasons, antifibrinolytic agents such as ϵ -aminocaproic acid and tranexamic acid have become increasingly popular. Until recently, in many pediatric centers, aprotinin was also used frequently for neonates and for complex repairs. It is not available for clinical use at present because of reports of increased complications in adult cardiac surgery patients; these include stroke, renal failure, graft occlusion, and perhaps death. Interestingly, meta-analyses of adult aprotinin studies indicate a protective effect against neurologic injury, particularly stroke, that appeared to be at least in part the result of reduced patient reinfusion of shed blood.^{164,165} Of course, the applicability of the adverse events and likely underlying mechanisms in adult patients to the pediatric population is highly questionable.^{166,167} At present, there is little controlled evidence that antifibrinolytic agents are beneficial in terms of, for example, blood loss, transfusion requirement, and platelet dysfunction, in primary operations, although many centers use them for procedures such as arterial switch operations and stage I hypoplastic left heart reconstruction. A meta-analysis of randomized trials using tranexamic acid concluded that the evidence in support of its use is weak.¹⁶⁸ There is evidence in favor of their use for reoperations, particularly of the complex variety.¹⁶⁹⁻¹⁷³ Theoretical concerns remain about potential

deleterious prothrombotic consequences during low flow or DHCA and in tenuous anatomic or circulatory situations postoperatively (e.g., Fontan fenestration, coronary anastomoses, surgical shunts), although there are no direct reports of such and one retrospective study was unable to identify any role for these agents in similar problems.^{169,174}

For problematic and excessive bleeding resistant to blood product treatment, administration of activated recombinant factor VII has been described as being effective.¹⁷⁵⁻¹⁷⁷ There are concerns of the potential risk of thrombotic complications associated with factor VIIa administration. This has not been demonstrated in accumulated series.¹⁷⁷

Organ Injury during Pediatric Cardiopulmonary Bypass

The damaging mechanisms of CPB include global (i.e., low-flow or DHCA) and regional (e.g., heart, lung, gastrointestinal tract) periods of ischemia and reperfusion, activation of multiple limbs of the systemic inflammatory response, and intramyocardial and systemic air and particulate microemboli. During hypothermic CPB at full flow rates, the skeletal muscle functions as a large-capacitance reservoir, and blood flow is to some extent shunted away from the vital organs. During low-flow hypothermic CPB, skeletal muscle vasculature constricts and the flow to vital organs is preserved, so oxygen delivery is able to maintain oxygen consumption despite approximately a 50% reduction in flow rate.¹⁷⁸ The presence of large collateral vessels, arterial obstructive lesions, cannula position, and other shunts from the systemic circulation may further compromise vital organ blood flow, as previously discussed.

Pulmonary Effects

The lungs are at significant risk for injury from CPB. This is likely to be caused by hemodilution, inflammation, and ischemia-reperfusion effects.^{179,180} Infants with current (e.g., infection, congestive heart failure, pulmonary overcirculation) or prior (e.g., respiratory distress syndrome, bronchopulmonary dysplasia) disorders may be at greater risk. Manifestations of CPB-induced lung injury include loss of endothelium-dependent dilation and increased pulmonary vascular resistance, decreased compliance, decreased functional residual capacity, increased alveolar-arterial oxygen difference, leakage of fluid into the interstitial space, and reduced surfactant activity.¹⁸⁰⁻¹⁸⁶ Hemodilution promotes fluid extravasation by reducing oncotic pressure. Activated complement, leukocytes, cytokines, and leukotrienes induce alveolar and capillary membrane damage; augment capillary leak; increase platelet and white blood cell plugging; and induce the release of additional mediators that further increase pulmonary vascular resistance and pulmonary parenchymal and vascular damage. Facilitating lung cooling by allowing a period of pulmonary blood flow on CPB during core cooling has been suggested as one means to reduce ischemic lung injury and its consequences.¹⁸⁷

Renal Effects

As many as 3% to 7% of children have evidence of renal dysfunction after CPB.¹⁸⁸ However, estimates vary depending on the criteria used: 11% using AKIN (Acute Kidney Injury Network) criteria or 51% when using RIFLE (*risk, injury, failure, loss, and end-stage kidney disease*) criteria.^{189,190} Most of the acute kidney injury defined this way will resolve in 48 to 72 hours, and mild renal dysfunction may not have any bearing on postoperative outcomes.^{189,190} The risk of acute kidney injury in neonates may be as high as 64%.¹⁹¹ Preoperative renal dysfunction or injury and low cardiac output after CPB may be the best predictors of post-CPB renal dysfunction. Glomerular filtration rate and renal diluting and concentrating abilities are immature in neonates and very young infants. Preoperative renal injury appears to be more likely in neonates, who may in fact have multiorgan dysfunction after delivery and initial stabilization (e.g., hypoplastic left heart syndrome, arterial transposition), as well as in older patients with long-standing systemic ventricular dysfunction, chronically elevated systemic venous pressures, or cyanosis (e.g., “failing” Fontan circulations, tetralogy of Fallot with severe right or biventricular dysfunction).¹⁹² Low flow and reduced mean arterial pressure, nonpulsatile perfusion, and hypothermia lead to the production and release of hormones such as endothelin, catecholamines, antidiuretic hormone, atrial natriuretic factor, and renin/angiotensin.^{101,180,188,193} In addition to renal dysfunction, these factors may contribute to increased total body water, delayed fluid clearance after CPB, and related complications such as myocardial and pulmonary interstitial edema, delayed chest closure, and prolonged ventilatory support. Few studies have been specifically devoted to infant and pediatric heart disease patients in terms of renal protection or preventive therapies. In larger patients, vacuum-assisted venous drainage has some theoretical advantages. Several recent adult cardiac surgery studies (where, of course, much of the underlying pathophysiology may be different) suggest that relatively low doses of fenoldopam or nesiritide can reduce renal-related morbidity in at-risk patients.¹⁹⁴⁻¹⁹⁸

Brain Injury

Neurologic injury continues to be one of the most problematic aspects of surgery for congenital heart disease. As overall operative mortality has declined in association with improved cardiac outcomes and life expectancy, quality-of-life issues have assumed greater importance. Prevention of neurologic injury has therefore become increasingly important. Earlier retrospective series estimated the incidence of major neurologic injuries after pediatric heart surgery to be between approximately 2% and 30%.^{57,199,200} Although there appears to have been a progressive decline in major complications such as seizures, persistent choreoathetosis, and severe developmental delay (for reasons that are largely unknown), more subtle but significant cognitive and neurodevelopmental delays in IQ, language and motor skills, attention, learning skills, visual and spatial skills, and working memory have recently been found in children who underwent

neonatal repair of arterial transposition, as well as in some single-ventricle patients and those who underwent complicated biventricular repairs; outcomes were generally worse in those who underwent DHCA.^{153,201-203} Cognitive development also appears to be lower in school-age survivors of hypoplastic left heart syndrome and patients with Fontan physiology.^{204,205} Risks for lower achievement included hypoplastic left heart syndrome, use of DHCA, and reoperation within 30 days; brain magnetic resonance imaging (MRI) has been used with increasing frequency to detect abnormalities before and after infant cardiac surgery and other procedures.²⁰⁶⁻²¹² Interestingly, it appears that a substantial number of infants with congenital heart disease can manifest a variety of brain MRI abnormalities before surgery as well as after interventional cardiac procedures (e.g., balloon atrial septostomy). New MRI abnormalities have been observed at equal rates in children undergoing cardiac surgery with and without CPB, although, when CPB was used, the duration of bypass was associated with increased severity of the new abnormalities; DHCA was associated with the severity of new MRI findings in infants undergoing arch surgery; and the severity of new postoperative MRI abnormalities was associated with brain maturity score and their presence before surgery.²¹³

It has become apparent that preoperative, intraoperative, and postoperative factors are involved.²¹⁴ The developing infant brain may be particularly susceptible to injury by hypoxia, ischemia-reperfusion, and the systemic inflammatory response because of its relatively fragile vasculature, high metabolic activity, and the fact that it is undergoing an intensive period of neuronal migration, axonal outgrowth, target finding and arborization, synaptogenesis, myelination, astroglial development, and selective neuronal reduction (largely via apoptosis).¹⁰⁷ Most if not all of these processes are under the control of biochemical factors, neurotransmitters, and gene expression pathways that are likely to be affected by CPB and its consequences (e.g., cytokine and growth factor production, generation of oxygen radical and nitroxyl radical species, and altered release and reuptake of excitotoxic amino acid neurotransmitters caused by ischemia).

A substantial number of children with congenital heart disease have genetic syndromes associated with developmental delay of various sorts, including Down syndrome and the CATCH-22 syndrome.²¹⁵ The latter is linked to microdeletions in the 22q11 region of chromosome 22, DiGeorge and velocardiofacial syndromes, developmental delays in language and speech, and mild hypotonia, and it is present in 2% to 10% of children with congenital heart disease. It seems likely that other genetic abnormalities as yet undefined result in both neurologic problems and congenital heart disease. Indeed, a sizable number of children with heart disease may have congenital brain malformations; more than 30% of infants with hypoplastic left heart syndrome have evidence of brain dysgenesis or other anomalies before surgery.^{98,216,217} Low cardiac output, high venous pressures, thromboemboli, and chronic cyanosis are all likely to contribute to both gross and subtle neurocognitive lesions.^{135,216,218}

Intraoperative causes of brain injury include abnormalities of cerebral autoregulation and cerebral perfusion,

ischemia-reperfusion mechanisms, and emboli. Many of these factors were discussed previously. The “safe” period of DHCA remains controversial, and in part it depends on how it is defined and under what conditions of flow, pH, temperature, cooling strategy, and patient population it is assessed. Using experimental energetic depletion or the cerebral metabolic rate for oxygen as the endpoint led to estimates of 20 to 30 minutes or 40 to 65 minutes, respectively.^{69,130} Clinical experience and some evidence suggest periods of DHCA as short as 20 minutes or as long as 45 minutes before major complications such as seizures or choreoathetosis begin to increase in frequency.¹⁰⁷ Overall, the consensus has become that the risk of neurologic injury and developmental abnormalities increase and IQ decreases in direct proportion to the duration of DHCA.^{143,153,202,203,219-222}

This realization has led to evaluation of methods to avoid DHCA or reduce its duration, with the understanding that in some anatomic circumstances it cannot be avoided. The problems and potential for neurologic dysfunction with low-flow hypothermic bypass were discussed previously, and recent clinical outcome evidence supports the notion that this strategy is far from a perfect solution, although it is better than DHCA.^{57,132,133,153,201} Use of selective cerebral perfusion to avoid or reduce the use of DHCA appears to be an attractive and increasingly popular option. In many centers, the flow rates and perfusion pressures used during selective cerebral or arch perfusion are guided by continuous measurement of CBF velocity or NIRS.²²³⁻²²⁹ It is important to note, however, that these techniques have yet to be subjected to widespread and thorough appraisals or to controlled comparisons with DHCA or other low-flow techniques.⁶¹

The post-bypass period is also receiving increased attention as a vulnerable period for neurologic injury. As discussed, both low-flow deep hypothermic CPB and DHCA techniques can lead to compromises in CBF, autoregulation, and metabolism. Therefore, ensuring appropriate cardiac output, cerebral perfusion pressure, and oxygen delivery (i.e., appropriate hematocrit for the level of oxygen saturation and cardiac output) in the post-operative period are probably quite important. In addition to standard volume replacement and inotropic maneuvers, more novel strategies to support cardiac output in this setting include delayed sternal closure and ready use of extracorporeal membrane oxygenation.^{20,230,231} Maintaining normothermic or even mildly hypothermic body temperatures in the first 24 to 48 hours postoperatively may also be beneficial.¹³⁶

Clearly, the ability to sensitively and accurately assess and follow the status of the brain, as well as to guide and evaluate therapeutic interventions, would be advantageous. Although various forms of perioperative neurologic monitoring (e.g., electroencephalography, NIRS, cerebral Doppler blood flow velocity) are used and advocated with increasing frequency, no one technique or combination of techniques has emerged to fill this need.^{229,232-236} Most centers currently use some form of NIRS monitoring of cerebral (and often somatic as well) oxygen saturation. The NIRS value reflects tissue (arterioles, venules, capillaries) oxygen saturation, and is (in a somewhat oversimplified fashion) algorithmically

weighted to represent approximately 85% venous blood and 15% arterial blood. When used in the cerebral position, the NIRS value reflects frontal cortex oxygen content; the measured values most closely correlate with, in most patients, jugular bulb/jugular venous or SVC oxygen saturation; thus, in some ways, it can function as a noninvasive monitor of “mixed” venous O₂ saturations. There is some experimental data indicating that both the degree and the duration of cerebral “desaturation” may predict neurologic injury.²³⁷⁻²³⁹ However, human clinical data demonstrating a correlation between NIRS and neurologic injury or outcome are minimal, and data defining when intervention based on NIRS (i.e., level of desaturation) might be indicated. How to best intervene and whether NIRS-driven interventions alter outcome remain to be generated.²³⁹⁻²⁴¹ There may also be a role for improved techniques to detect microemboli during CPB.²⁴²⁻²⁴⁴

Stress Response to Cardiopulmonary Bypass

The stress response to CPB is characterized by the release of a large number and diverse group of neurohumoral substances, including catecholamines, endothelin, various prostaglandins, cortisol, and growth hormone. The concentrations that have been measured in neonates and infants during or soon after CPB are some of the highest measured in humans, and they generally exceed those measured in adult CPB patients by 5-fold to 10-fold.^{101,245} Stimuli include extensive and prolonged foreign surface contact, profound hypothermia, low flow, low perfusion pressure, and nonpulsatile perfusion. Clearance of many of these compounds by the liver, kidney, or lungs may also be delayed. Possible deleterious consequences include vasoconstriction and reduced organ perfusion, direct tissue injury, pulmonary hypertension, endothelial damage, and increased pulmonary vasoreactivity.

On the other hand, the release of many of these compounds and the response overall clearly has adaptive benefits. However, it is unclear what level, circumstances, or substances cause a net harmful response, to what extent acutely ill infants with congenital heart disease require some degree of stress response for hemodynamic stability, wound repair, and overall homeostasis, and to what degree the seemingly exaggerated response seen particularly in neonates and infants exposed to CPB is pathologic and should be attenuated. Decreased stress response hormones and possibly improved morbidity and mortality have been associated with high-dose synthetic opioid administration to infants undergoing CPB and other stressful procedures.^{245,246}

Systemic Inflammatory Response to Cardiopulmonary Bypass

CPB causes a systemic inflammatory response via multiple mechanisms. These mechanisms include surgical trauma, blood contact with the CPB circuit, ischemia-reperfusion injury, and protamine administration.^{179,247-254} These initiating events stimulate complex and interconnected cell- and humoral-based systems that include activation of the complement, coagulation, and fibrinolytic pathways, endotoxin release, cytokine production,

endothelial activation and expression of leukocyte adhesion molecules, leukocyte and platelet activation, and production and release of oxygen radicals, nitric oxide, prostanoids, eicosanoids, and proteolytic enzymes (e.g., myeloperoxidase and superoxide from activated neutrophils). The resultant tissue and organ injury, capillary leak, increased need for inotropic and ventilatory support, and perhaps effects on infection risk are widely believed to have a major impact on duration of hospitalization and overall outcome.²⁵⁵

Complement activation occurs via both alternate (stimulated by foreign surface contact, endotoxin, and kallikrein) and classical (protamine) pathways. Significant increases in activated complement fragments occur with initiation of bypass, and further still during rewarming, and these levels have correlated with post-CPB renal, cardiac, and pulmonary dysfunction.^{179,180,247,249,256} Various complement fragments cause white cell and platelet activation, white cell free-radical production and degranulation, smooth muscle constriction, and capillary leak. Terminal complement fragments and the membrane attack complex can cause direct cell lysis.

Blood concentrations of bacterial endotoxin can increase because of its almost ubiquitous presence in sterile fluids and equipment and also perhaps because of decreased intestinal perfusion, which can augment reperfusion injury independent of endotoxin.^{257,258} Endotoxin can directly injure endothelial cells and cause capillary leak, and it can stimulate the production of proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, and IL-8. Cytokine production can also be stimulated by foreign surface contact, complement fragments, and other cytokines. Mechanisms of cytokine-induced tissue injury are multiple.

Cytokines such as IL-1 and TNF are directly toxic to endothelial and other cells, cause wasting and edema, cause myocardial contractile dysfunction, and stimulate a number of cytotoxic and cytoprotective signaling mechanisms such as inducible (high-output and potentially cytotoxic) nitric oxide production, various proapoptotic and antiapoptotic pathways and proteins, enhanced oxygen radical injury, and induction of cellular antioxidant enzymes. Levels of TNF and IL-1 are inconsistently increased by CPB in neonates and infants. Cytokine-induced nitric oxide production can result in profound hypotension (it is the major mechanism of vascular depression in septic shock), myocardial depression, and inhibition of cellular respiration and metabolism. IL-6 has been demonstrated in some studies to be a good predictor of clinical outcome and may be related to the extent of tissue injury.¹⁸⁰ IL-8 is a potent neutrophil chemoattractant and also causes leukocytosis and activation of neutrophil proteases and free radical enzymes. Increased IL-8 has been found in pediatric CPB in proportion to ischemic and total bypass times.^{180,183,248,259} Some children have increased levels of some cytokines preoperatively; the causes and significance of this finding are unclear, but there is some evidence that neonates with a preoperative biochemical profile consistent with inflammation (e.g., increased plasma elastase and complement fragments) are more likely to manifest a capillary leak syndrome postoperatively.^{248,255}

Neutrophil activation is believed to be an important mechanism of cellular injury during and after CPB. It is produced by a wide variety of stimuli, including foreign surface contact, endotoxin, cytokines, complement, platelet-activating factor, and ischemia-reperfusion. Activated neutrophils express proadhesive molecules on their cell surface (that are complementary to ones induced on endothelial and other cell membranes), marginate into the tissue, and have increased lipoxygenase and myeloperoxidase activities (the source of superoxide and hypochlorous acid, respectively) and release neutrophil elastase. These products cause damage to lipids, proteins, and DNA. Elastase also causes endothelial damage, inactivates serine proteases in the coagulation pathway, and cleaves adhesive receptors from the platelet membrane.^{107,260-262} Both myeloperoxidase and elastase, as well as evidence of neutrophil-mediated oxidant injury, have been detected after pediatric CPB.^{25,180,263}

It has recently become apparent that CPB also induces a corresponding increase in anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (IL-1ra). C-reactive protein (CRP), an acute phase protein that is a marker of inflammation and has anti-inflammatory effects by decreasing neutrophil chemotaxis, also increases during and after pediatric CPB.[†] Transient immunosuppression mediated by these events and others such as loss of activated neutrophils and inhibition of cellular immune responses have also been found after pediatric CPB.²⁶⁴

Overall, there is substantial variability in the release pattern and plasma concentrations of cytokines in infants and children undergoing cardiac surgery compared with adults.^{183,248,254,265-267} Although increased elements of the systemic inflammatory response are generally associated with increased risk of postoperative organ dysfunction and morbidity and mortality, better-designed studies with direct assays and endpoints are necessary to truly define any cause-effect relationship between systemic inflammatory response mediators and organ damage. It is also likely that the *balance* between proinflammatory and anti-inflammatory stimuli and their diverse effects on a wide range of cellular types and functions must be taken into account.^{254,268} Finally, the possibility that at least some of these substances are required to regulate the overall response and in fact potentially contribute to eventual repair and resolution should not be forgotten. For example, although the deleterious effects of substances such as TNF- α and cyclooxygenase pathway derivatives have been demonstrated in numerous cellular and animal models, genetic or pharmacologic abrogation of these pathways can also lead to increased cell death and organ dysfunction under clinically relevant circumstances (e.g., ischemia-reperfusion).

Other Current Approaches to Limiting the Negative Consequences of Pediatric Cardiopulmonary Bypass

Efforts and potential targets to decrease the negative impact of CPB in infants and children that have been

[†]References 179, 180, 248, 252, 254, and 264.

discussed include modifications to reduce circuit area and volume, improve venous drainage, and define the optimal pH, hematocrit, temperature,²⁶⁹ flow rate, arterial pressure, and duration of CPB and DHCA. Additional targets of intervention have included oxygen, anesthetic technique, remote ischemic preconditioning, and peritoneal dialysis.²⁷⁰⁻²⁷³

Steroids

Administration of relatively high doses of steroids prior to pediatric CPB (either dexamethasone or methylprednisolone) may suppress the production of proinflammatory cytokines and improve organ function.^{223,274-276} Because a major effect of steroid treatment is to alter gene expression and cellular activation, maximal effect may require administration some time before bypass (up to 8 hours) and repeated dosing.²⁰ Improvements in body water accumulation, alveolar-arterial oxygen gradients, pulmonary artery pressure, duration of mechanical ventilation, and length of intensive care unit stay have been observed.^{20,274,275} Results from more extensive investigations in adults confirm beneficial alterations in the balance of proinflammatory to anti-inflammatory mediators.²⁷⁷ However, there were no significant effects on fluid balance, and there were possibly detrimental effects on pulmonary function and glucose homeostasis (hyperglycemia). Furthermore, as with the stress response, it remains unclear whether broad-spectrum suppression of the systemic inflammatory response is beneficial. These differences may be partly because steroids may be more likely to show a positive effect in neonates and infants in whom the magnitude and consequences appear to be greater. However, there is some evidence that at least more prolonged periods of corticosteroid administration may be detrimental to the developing brain. Steroids are being used not only preoperatively and intraoperatively but also postoperatively for the treatment of hemodynamic instability and around the time to extubation. Prolonged steroid exposure may suppress the adrenal gland and use may also predispose to infection. In retrospective studies, data are conflicting as to the benefit of steroids.²⁷⁸⁻²⁸¹ Thus, it would seem that caution is warranted until large randomized, prospective, placebo-controlled studies with tightly regulated perioperative management are performed in pediatric patients.

Ultrafiltration

Conventional and modified ultrafiltration techniques are being used with increasing frequency during pediatric cardiac surgery. Potential beneficial mechanisms include hemoconcentration, removal of various inflammatory mediators and vasoactive compounds in the ultrafiltrate, and decreased total body water and tissue edema. Significant clinical improvements in tissue edema, post-CPB weight gain, hematocrit, blood pressure, global left ventricular function, lung compliance, oxygenation, and duration of mechanical ventilation have been reported, along with decreased postoperative bleeding, decreased postoperative transfusion and blood product requirements, and decreased pulmonary vascular resistance; one

or more of these benefits have been observed in many, but not all, studies.^{252,259,282-289} Less clear are the mechanisms responsible for these effects, because significant reductions in blood concentrations of inflammatory cytokines, complement fragments, and prostanooids have not been universally identified.^{252,282,290} Although ultrafiltration techniques appear to be safe for infants and children, there is theoretically valid concern about removal of protective mediators and deleterious increases in viscosity and clotting factors (i.e., hypercoagulability). A recent meta-analysis of randomized trials found that modified ultrafiltration led to higher hematocrit and higher mean arterial pressure compared with conventional ultrafiltration.²⁹¹ Future studies are needed to define the mechanisms of the ultrafiltration effect and identify patients who are most likely to benefit.

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SURGICAL APPROACHES, CARDIOPULMONARY BYPASS, AND MECHANICAL CIRCULATORY SUPPORT IN CHILDREN

Francis Fynn-Thompson • Ravi R. Thiagarajan • Luis Quinonez

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LONGER-TERM OUTCOMES FROM MECHANICAL SUPPORT IN CHILDREN

For infants and children, mechanical support of the circulation has important roles in providing short-term circulatory support for reversible myocardial failure, in providing cardiopulmonary support before and after cardiac surgery, and in providing longer-term support as a potential bridge to cardiac transplantation. Mechanical circulatory support (MCS) modalities commonly available include extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP) counterpulsation, and ventricular assist devices (VADs). Although a variety of assist devices are available for adult-size patients, the need for miniaturization has delayed their application in children. ECMO therefore remains the most common form of MCS for pediatric patients. ECMO was first introduced to provide respiratory support in pediatric patients with severe lung

disease failing mechanical ventilator support. Some institutions with an established ECMO program have been able to transition this methodology to provide biventricular support and oxygenation in pediatric patients with a failing circulation.¹⁻³ There are no established guidelines for the indications or management of cardiac ECMO support, and there is considerable inter-institutional variability with respect to use and outcomes, based on local experience and philosophy. VADs offer the potential for both short- and long-term support of circulation in patients who do not have concurrent pulmonary parenchymal or vascular disease, and there is increasing experience in developing this form of support as an effective longer-term bridge to transplantation in the pediatric patients with heart disease.

EXTRACORPOREAL MEMBRANE OXYGENATION

Overview of Uses

The use of ECMO to support children with impaired gas exchange failing to respond to mechanical ventilation as a result of acute respiratory disease is now an accepted and successful therapy. This is particularly true in neonates with a variety of parenchymal and vascular lung diseases (e.g., meconium aspiration, respiratory distress syndrome, diaphragmatic hernia, persistent hypertension of the newborn) survival outcomes are excellent with the use of ECMO.^{3,4} Good ECMO outcomes in these patients depends on the early diagnosis of severe pulmonary failure, the prompt institution of ECMO, and the reversible nature of the pulmonary dysfunction.⁴ However, the advent of other therapies, such as high-frequency oscillatory ventilation, surfactant therapy, permissive hypercapnia, and inhaled nitric oxide, has led to a reduction in the need for ECMO in neonates.⁵⁻⁷ According to the cumulative data on 55,658 patients reported by the Extracorporeal Life Support Organization (ELSO) Registry, 75% of all neonates who have been placed on ECMO for respiratory support have survived to discharge from hospital (Table 109-1).⁵ The outcome for older patients with

respiratory failure is considerably lower, with the reported cumulative survival for pediatric and adult patients placed on ECMO for respiratory support being approximately 57% and 56%, respectively.

The past decade has seen a steady increase in the number of patients and institutions using ECMO to support a failing circulation, both after congenital cardiac surgery or as a bridge to transplantation.^{5,8-19} Another growing indication for ECMO is its use during resuscitation from cardiac arrest. ECMO can be deployed rapidly during cardiac arrest in patients failing to respond to conventional cardiopulmonary resuscitation; however, ECMO use and efficacy in promoting survival when used for this indication is controversial.^{8,10,11,20-22}

Despite the increased enthusiasm for ECMO support of the circulation, the survival to discharge as reported by the ELSO registry (40% for neonates and 49% for pediatric patients) has not changed much over the past decade (Fig. 109-1) and has lagged considerably when compared with the experience with respiratory ECMO (Table 109-2).⁵ The majority of cardiac patients are given ECMO after cardiac surgery. Adverse outcomes after cardiac ECMO are primarily related to irreversible underlying cardiac disease and to the presence of significant end-organ injury before ECMO deployment. Recovery from severe myocardial dysfunction while on mechanical support can occur, provided the myocardium has only sustained a transient and reversible injury. ECMO facilitates ventricular recovery by reducing myocardial wall tension, increasing coronary perfusion

TABLE 109-1 Survival after ECMO Support

Age Group and Indication	No. of Patients	No. That Survived to Discharge
Neonates		
Respiratory	26,583	19,818 (75%)
Cardiac	5,159	2,078 (40%)
ECPR	914	358 (39%)
Pediatric Age Group		
Respiratory	5,923	3,359 (57%)
Cardiac	6,459	3,197 (49%)
ECPR	1,878	770 (41%)
Adults		
Respiratory	4,382	2,439 (56%)
Cardiac	3,401	1,349 (40%)
ECPR	969	267 (28%)
Total	55,668	33,635 (60%)

ECMO, Extracorporeal membrane oxygenation; ECPR, ECMO for cardiopulmonary resuscitation.

From Extracorporeal Life Support Organization: International Summary, July 2013.

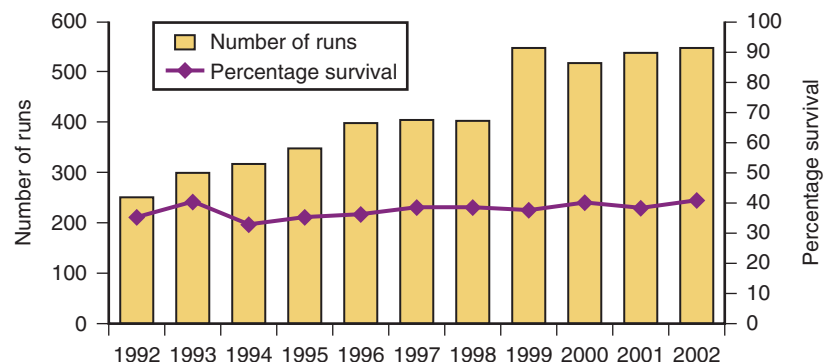
TABLE 109-2 Neonatal Respiratory and Cardiac ECMO: Differences in Survival Reported by the ELSO Registry for Specific Diagnostic Groups

Diagnosis	Survival (%)
Meconium aspiration syndrome	94
Primary pulmonary hypertension	77
Sepsis	73
Air leak syndrome	73
Congenital diaphragmatic hernia	51
Cardiac disease	40

ECMO, Extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization.

From Extracorporeal Life Support Organization: International Summary, July 2013.

FIGURE 109-1 ■ Number of cardiac extracorporeal membrane oxygenation (ECMO) runs and survival rates for all patients receiving cardiac ECMO support reported to the Extracorporeal Life Support Organization Registry over a 10-year period.



pressure, and maintaining systemic perfusion with oxygenated blood.

In infants, in whom myocardial failure is frequently biventricular and associated with respiratory insufficiency or pulmonary hypertension, ECMO is the preferred means of mechanical support. Although there has been some support for the concept of “resting the lungs” for patients who are given ECMO for respiratory failure and lung injury,⁴ in cardiac patients in who ejection is present, coronary blood flow is often from left ventricular ejection. Mechanical ventilation with increased fraction of inspired oxygen concentration in inspired air can increase oxygen content of blood returned to the left heart and thus can improve myocardial oxygen delivery and may promote recovery. The heart must regain contractile function and conduction as soon as possible to maintain a workload and to avoid involution of the myocardial mass. This requires frequent evaluation, often with echocardiography, and it is critical that overdistention of the heart be avoided.

It also is important to appreciate the differences between the ECMO circuit and management, and the routine cardiopulmonary bypass (CPB) used during cardiac surgery. The ECMO circuit is a closed circuit. It has limited ability to handle any air in the venous limb of the circuit, and careful de-airing of both the arterial and venous cannulas is essential when connecting to the ECMO circuit. The average duration for cardiac ECMO runs reported to ELSO over the past 15 years has increased slightly from approximately 4 to 5 days to about 5 to 7 days; the longest reported run is 62 days.⁵ These data emphasize that ECMO should be viewed only as a relatively short-term support of the circulation; beyond 7 days of ECMO support, the chances of successful decannulation and survival decrease substantially. These data also support the need to develop longer-term mechanical support devices, particularly as a bridge to transplantation for patients on ECMO who remain suitable candidates for cardiac transplantation.

The significant time limitation associated with cardiac ECMO use indicates that, ideally, only patients with known reversible cardiac disease should be considered candidates for cardiac ECMO. However, this is often not possible when a quick decision needs to be made to place a patient on ECMO because of cardiac arrest or a severe low cardiac output state. In general, institutions with an efficient and well-established ECMO service are more likely to use this form of support for the failing circulation. However, differences in decision making regarding ECMO candidacy and timing of ECMO deployment, case type and surgical complexity, surgical technique and CPB management used, and many other confounding factors make comparison of efficacy of ECMO among institutions difficult.²³ However, one can make a case that ECMO should be readily available in any center undertaking complex congenital cardiac surgery, as it can provide effective short-term cardiac support while awaiting myocardial recovery in some patients improving their probability of survival. Establishing a structured and coordinated team approach to cannulation is a key step for any successful ECMO service.¹¹ In our experience at Boston Children’s Hospital, the introduction

of a dedicated cardiac ECMO program and development of a rapid response system for its use during active resuscitation has contributed to an increase in the survival-to-discharge rate for ECMO circulatory support, from 45% in 1995 to 59% in 2002, regardless of the diagnosis or indication for cardiac support.²¹

Indications

There is no specific cardiac procedure or diagnostic group for which ECMO is a proven therapy. Rather than trying to determine indications for cardiac ECMO according to specific diagnoses or procedures, the indications can be examined in five broad categories: preoperative resuscitation; inability to wean from cardiopulmonary bypass; postcardiotomy; cardiomyopathy, myocarditis, and bridge to transplantation; and after in-hospital cardiac arrest and cardiopulmonary resuscitation (CPR). According to the ELSO Registry report of outcomes based on broad diagnostic categories, patients given ECMO because of complications related to fulminant myocarditis have the highest survival rate (Table 109-3), although it lags behind the successful outcomes achieved with ECMO for respiratory support in neonates. The survival from cardiac ECMO to hospital discharge according to selected congenital defects is shown in Table 109-4.

TABLE 109-3 Survival for Cardiac ECMO Runs Based on Broad Diagnostic Categories

Diagnosis	Survival (%)
Congenital cardiac defect	39
Cardiac arrest	28
Cardiogenic shock	38
Cardiomyopathy	60
Myocarditis	50

ECMO, Extracorporeal membrane oxygenation.

From Extracorporeal Life Support Organization: International Summary, July 2013.

TABLE 109-4 Survival for Selected Congenital Cardiac Defects by Age and Diagnosis

Diagnosis	Neonates (%)	Infants (%)
Left-right shunt	37	43
Left obstruction	33	40
Hypoplastic left heart syndrome	32	40
Right obstruction	43	49
Cyanosis (with increased pulmonary blood flow)	34	42
Total anomalous pulmonary venous return	43	42
Cyanosis (with decreased pulmonary blood flow)	40	41
Other	45	51

From Extracorporeal Life Support Organization: International Summary, July 2013.

Preoperative Resuscitation

ECMO can be beneficial for critically ill patients awaiting cardiac surgery, enabling preoperative stabilization and optimization or prevention of end-organ dysfunction before repair. These patients represent a small group (usually newborns), and indications include severely low cardiac output states (e.g., critical aortic stenosis), pulmonary hypertension (e.g., obstructed total anomalous pulmonary venous drainage), and severe hypoxemia (e.g., transposition of the great arteries and pulmonary hypertension).²³⁻²⁵

Inability to Wean from Cardiopulmonary Bypass

The reported survival is poor for patients who are given ECMO because they were unable to wean directly from CPB in the operating room (i.e., without any period of stability off CPB).^{8,9,16,23} Issues such as primary myocardial dysfunction, pulmonary hypertension, severe hypoxemia, and refractory dysrhythmias are recognized as major factors in determining successful outcome, but unrecognized residual or irreparable defects are also important.⁹ Residual cardiac defects must be investigated in the operating room, using a combination of echocardiography and the careful measurement of oxygen saturations and intracardiac pressures. Ideally, only children with potentially reversible myocardial injury who cannot be weaned from CPB should be considered candidates for ECMO; however, this can be extremely difficult to determine in the operating room immediately after cardiac surgery. Additional considerations for use of ECMO in patients failing to wean from cardiopulmonary bypass after cardiac surgery include preoperative condition, intraoperative course, and the likelihood of being a transplant candidate. Severe hemorrhage is a major problem in the transition from the CPB circuit to the ECMO circuit. Although a lower activated clotting time (ACT; 160 to 180 seconds) can be used, small doses of protamine are often necessary to assist with the initial control of bleeding. We usually administer protamine in 1-mg/kg increments until a target ACT of 180 seconds is achieved. Infusions of antifibrinolytic drugs such as tranexamic acid (bolus of 100 mg/kg, followed by infusion at 10 mg/kg/hr), or ε-aminocaproic acid (bolus of 100 mg/kg, followed by infusion at 30 mg/kg/hr) should be considered. Exploration of the chest may be necessary, particularly if the bleeding persists at a rate greater than 10 mL/kg/hr and if problems with ECMO flow are encountered because of decreased venous cannula drainage from a tamponade-like effect. The large transfusion requirement can place a considerable burden on the supply of donor blood products. As an alternative, it is possible to connect a chest tube to cell-saver tubing to enable blood to be collected in the cell-saver reservoir and subsequently spun for retransfusion.

When a patient requires ECMO in the operating room, discussions with the patient's family must be clear and direct. Recovery of myocardial function should be expected within 2 to 3 days,²⁶ and if this is not evident, either listing for cardiac transplantation, if appropriate, or withdrawal from support must be considered.

After Cardiotomy

ECMO is an effective therapeutic option for infants and children who have had a period of relative stability after successful termination of CPB and exclusion of significant residual cardiac defects. Myocardial or respiratory failure causing a low cardiac output state, hypoxemia, or pulmonary hypertension and cardiac arrest are the major indications in this group. This group of patients is large, with reported good survival rates (60% to 70%), provided ECMO is instituted rapidly and effectively.^{8-10,16,23,27}

Cardiomyopathy, Myocarditis, and Bridge to Transplantation

Patients with acute fulminant myocarditis can be managed successfully with ECMO.^{5,28} Patients with fulminant myocarditis may arrive at the hospital undergoing full cardiac arrest, but more commonly they are in cardiogenic shock from an extremely low cardiac output state or they have hemodynamically significant dysrhythmias, including ventricular tachycardia or heart block. The heart is usually distended and is contracting poorly. Prompt institution of ECMO may allow sufficient resuscitation and stabilization to prevent end-organ injury and to enable the myocardium to rest while awaiting potential recovery. After ECMO is instituted, the heart must be fully decompressed, and urgent atrial septostomy or left atrial vent placement may be necessary.^{4,29} The heart might not begin to eject for the first 24 to 36 hours after ECMO is started, although recovery of electrical activity within the first few hours should be expected. If recovery of ventricular ejection is not evident within 2 to 3 days, ECMO can be continued either as a bridge to heart transplantation or as a bridge to alternative longer-term support with a VAD, if feasible.^{14,26,30-37} ECMO should be viewed as a short-term bridge to transplantation because of the limited donor availability and the time-related risks for complications, such as infection, bleeding, end-organ impairment, problems resulting from immobilization, and difficulties in maintaining adequate nutrition.^{32,38} In our experience at Boston Children's Hospital, the median time spent on ECMO awaiting heart transplantation is currently 140 hours (range, 26 to 556 hours), and only 50% of our listed patients have been effectively bridged. In a small number of older and larger children, ECMO has been used to initially resuscitate the circulation and end-organs, and if a donor heart has not become available by day 6 or 7 of ECMO, we have successfully transitioned from ECMO to longer-term VAD. Survival for patients with acute myocarditis supported with ECMO was recently reported to be 61% using data reported to the ECMO registry of ELSO. Because ECMO can provide good survival in any patients with acute fulminant myocarditis these patients should be cared for in facilities that have an ECMO or other MCS options.

ECMO also has been used to support the failing heart after transplantation. This may be necessary immediately after transplantation because of graft failure, usually in the setting of pulmonary hypertension and acute right ventricle failure of the donor heart. ECMO also is

effective in supporting the heart during periods of acute rejection.³⁴ The inflammation and myocardial edema are similar to that seen with fulminant myocarditis, and they lead to a similar spectrum of clinical features. ECMO allows the transplanted heart to decompress with decreased wall tension while antirejection therapy is increased. In our experience, survival to discharge for this indication is currently 64%, and the median duration of ECMO support is 4 days.

After In-Hospital Cardiac Arrest and CPR

Survival and outcome after in-hospital resuscitation of pediatric patients after a cardiac arrest continues to be extremely poor.³⁹⁻⁴⁴ Even in a highly monitored and resource-intensive area such as a pediatric intensive care unit (ICU), the survival rate after cardiac arrest has been reported to be only 9% to 31%. The duration of cardiac arrest and resuscitation is also an important determinant of subsequent outcome, and a number of reports have noted a critical threshold of approximately 15 minutes.^{39,40} ECMO has been successfully used to support children after prolonged periods of cardiac arrest that have been unresponsive to closed or open cardiac massage and all other usual interventions.^{4,8,20,21} Again, it is important to emphasize that the underlying lesion, in conjunction with the effectiveness of CPR while instituting ECMO, is a major determinant of outcome when mechanical support is used in this setting. Although the exact place of ECMO in the CPR algorithm remains ill defined, patients with a witnessed arrest and rapid institution of effective CPR, and who have no apparent recovery of cardiac function within 5 to 10 minutes of initiating resuscitation and no contraindications, may be suitable candidates for ECMO.

Determining the relative contraindications to ECMO support during active resuscitation attempts can be difficult (Table 109-5). Although not always possible, discussions regarding the use of ECMO in certain patients should be undertaken before an event occurs. We have been able to successfully use our rapid-response ECMO system during CPR in patients with acquired and structural heart disease, and in patients with double- or single-ventricle defects. In the latter group are neonates who have had a sudden, reversible event, such as acute thrombosis and obstruction to a systemic-to-pulmonary artery shunt after a Norwood procedure, and they have been readily resuscitated with ECMO. On the other hand, patients with cavopulmonary corrections (i.e., Fontan or bidirectional Glenn anastomosis) have been difficult to resuscitate using ECMO, in part because of limitations with cannulation, and an inability to maintain adequate systemic oxygen delivery and avoid cerebral venous hypertension during CPR with chest compressions. Although we have used ECMO in the resuscitation of patients with pulmonary hypertension and patients with systemic outflow obstruction, the severe limitation to cardiac output and oxygenations during CPR in these patients has meant that their overall outcomes on ECMO have been poor because of the development of severe end-organ injury.

Historically, successes using ECMO during active resuscitation and chest compressions (E-CPR) have been

TABLE 109-5 ECMO Support during Active Cardiopulmonary Resuscitation

Resuscitation Event	Considerations
Indications	
Event witnessed and monitored (e.g., tamponade, arrhythmia, systemic to pulmonary artery shunt, obstruction)	In-hospital event: ICU, OR, catheterization laboratory
Immediate and effective basic life support and CPR	Effective ECMO system and resources
No response to advanced life support in 10 min	Primed circuit (vacuumed or crystalloid)
Acceptable cardiac transplant candidate (e.g., fulminant myocarditis)	Equipment and personnel immediately available
Absolute Contraindications	
Event not witnessed or monitored	Out-of-hospital arrest
Known comorbidities that preclude listing for transplantation	Other congenital or chromosomal abnormalities
	Sepsis
	Central nervous system injury
	Renal failure
Relative Contraindications	
Effective ECMO support system not established	Circuit not immediately available
Known comorbidities that preclude effective resuscitation (e.g., pulmonary hypertension, systemic in-house outflow tract obstruction, semilunar or AV valve insufficiency, hypertrophic cardiomyopathy, cavopulmonary connection)	Equipment and personnel not trained for CPR

AV, Atrioventricular; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; OR, operating room.

reported for a small number of series.^{8,20-22,45} A recent subanalysis of the ELSO Registry E-CPR data reports a 37% overall survival to discharge for patients placed on ECMO in this circumstance.^{4,5} To avoid significant delays, a rapid response ECMO system has been established at some institutions.^{4,21,22} The success of a rapid response system depends on a multidisciplinary approach, with equipment being immediately available, and the personnel with assigned roles being in-house, including cardiac surgery and intensive care fellows, respiratory and ECMO specialists, and trained nursing staff. At Boston Children's Hospital, a vacuum and CO₂-primed circuit using a roller pump and a 0.8- to 1.5-m² membrane oxygenator is available at all times and is suitable for children weighing up to approximately 15 kg. Even in older children, this circuit initially provides sufficient flow for resuscitation, stabilization, and hopefully prevention of end-organ damage, until a larger oxygenator can be spliced into the circuit. Generally, however, for older children and adults, a new circuit with a hollow-fiber membrane is used, which takes little time to de-air and

can be established within 15 minutes. Once the patient is in stable condition with ECMO, the hollow-fiber membrane can be exchanged for a conventional membrane for longer-term support as necessary. An alternative rapid response system has been described, which uses a heparin-coated circuit, centrifugal pump, and a hollow-fiber membrane with a priming volume of only 250 mL and a priming time of only 5 minutes.

In postoperative cardiac patients, atrial and aortic cannulation via a reopened sternotomy is usually the access mode of choice. In other patients, experienced practitioners can rapidly gain access via the neck vessels. During resuscitation, the circuit is primed with crystalloid supplemented with 5% albumin. We do not wait for donor blood to be crossmatched to complete a blood prime of the circuit because of the inevitable delay. We prefer to reestablish organ perfusion as soon as possible, and once ECMO is satisfactorily established, blood products can be added or the priming crystalloid can be removed via hemofiltration. To assist with neurologic protection, where possible we maintain mild hypothermia (34° to 35° C) for the first 12 hours after administering ECMO during active resuscitation. Using the rapid response system, we can be ready to place a patient on ECMO within 15 minutes, and the main limitation is then the problems associated with cannulation. We have deployed the rapid response system during active resuscitation in more than 170 children since 1996, and we have been able to achieve a survival-to-discharge rate of 51% in this group of patients.⁴

TECHNICAL ASPECTS OF ECMO CANNULATION

Cannulation for ECMO begins with preemptive maneuvers that will ensure expedient delivery of this lifesaving measure. Prior planning is key and can ensure smooth cannulation in a situation that may be chaotic. The first step is identifying patients in unstable condition and who may require institution of ECMO. If during the evaluation of the patient by the treating team in the ICU, a patient is believed to be at risk of hemodynamic or respiratory deterioration enough to require AV or VV ECMO, then it is important to communicate with the ECMO team. This communication includes the surgeon who will be performing the procedure and the ECMO specialists who will be priming and running the circuit. This will give them time to know patient details that will help to develop a cannulation and support strategy. Heparin can be drawn up and prepared. A range of cannulas can be preselected. An appropriately sized circuit can be prepared. The blood bank can be alerted. Identifying potential ECMO patients early can also allow for calm and sober discussion about the appropriateness of the intervention.

For the cannulating surgeon, intimate knowledge of the systemic venous and arterial anatomy, especially the patency of the peripheral vessels that may be considered for access, is vital. If peripheral cannulation is to be performed, it is appropriate to have confirmatory imaging obtained beforehand. In our cardiac ICU, we maintain a

sheet of paper by the bedside detailing which peripheral arterial and venous access points are patent. This sheet can prevent unnecessary delays from cutting down on a vessel that is stenosed, scarred, or not patent. For patients with congenital cardiac anomalies, it is important to know in detail the topography of the heart, the intracardiac anatomy, and systemic venous arrangement. These details can have bearing on the cannulation strategy. For example, if a patient has a single left superior vena cava (SVC), venous access should be ideally obtained in the left neck. A patient with unoperated hypoplastic left heart syndrome may occasionally need to be cannulated centrally in the duct or main pulmonary artery for arterial inflow.

Access

Cannulation access can be central or peripheral. By central cannulation, we mean access to the intrathoracic structure to cannulate. This access can be gained through a sternotomy or, less commonly, a thoracotomy. The indications for central cannulation include postcardiotomy, open chest, small neonate or infant, need for supraphysiologic flows, when peripheral access cannot sustain adequate ECMO flow, and when no other access is available. Venous drainage can be obtained via the right atrium, superior vena cava, inferior vena cava (IVC), or even the pulmonary artery. Rarely, the only access for return to the pump is from the pulmonary venous atrium. Arterial perfusion is most commonly performed into the aorta, although arch vessels can be accessed. Direct cannulation of the artery is usually performed, although if time allows, placing a graft on an arch vessel is feasible and has the advantage of minimizing the risk of occluding that vessel.

The advantages of central cannulation are that it is the easiest access after sternotomy, it provides the most reliable cannula position, it gives the best venous drainage and therefore most optimal flows, it is easy to vent the left side, and it can be easily converted to cardiopulmonary bypass. The disadvantages of central cannulation are that it is labor intensive, it is better done in the operating room, it is not ideal if the chest is closed in an emergency, there may be more bleeding, and there is the risk of mediastinal infection. Central cannulation can be very difficult if a previous sternotomy was performed greater than 2 weeks prior. In this circumstance we may elect to cannulate peripherally, even in the context of recent cardiac surgery.

Peripheral cannulation is cannulation of the extra thoracic vessels. This can be performed in the neck for neonates, infants, children (including teenagers), and young adults. The subclavian and axillary vessels can be used occasionally in older patients. The other common point of access is the femoral artery and vein. Rarely, the iliac vessels, abdominal aorta, or abdominal cava may be used. The indications for peripheral cannulation include an arrest situation, a contraindication to central cannulation, and in some circumstances after cardiotomy. Contraindications to peripheral cannulation include a known small vessel and vessel stenosis or occlusion. Previous cannulation of a peripheral vessel is not an absolute

contraindication to repeat access, as long as the vessels are known to be adequate in size and patent.

Access to the peripheral vasculature can be open or closed. Open technique involves a surgical cutdown to visualize the vessel directly. Indications for vessel cutdown include surgeon preference, an arrest situation, uncertainty about vessel patency, or failure of percutaneous access. The advantages of open technique include certain identification of vessels, the ability to assess the vessels, less risk of injury to the vessels and adjacent structures, and the ability to insert larger cannulas. We believe that in the context of cardiopulmonary resuscitation with ongoing cardiac massage, cutdown is the most reliable way to differentiate an artery from a vein. Both vessels may have pulsatile deoxygenated blood during cardiac massage, making needle identification unreliable. Disadvantages of the cutdown technique include the time to perform the procedure, the need for available equipment and expertise, bleeding, infection, and the potential need for secondary intervention to decannulate. Once the vessels are identified by cutdown, the cannulas can be introduced using arteriotomy and venotomy or direct Seldinger technique.

Closed access to the peripheral vessels is also referred to as *percutaneous access*. This is commonly done with the Seldinger technique. It is best performed in a patient in stable condition or during an arrest situation when the vessels have already been identified by previous vascular access. Contraindications to percutaneous access are known obstruction of the vessel, percutaneous cannulas not being available, and a small patient (neonate, infant, small child weighing < 15 kg). The advantages of closed access is that it is less technically demanding, less personnel and equipment are required, it can be faster, it is more hemostatic, and it is usually a single procedure. Disadvantages are that it is a blind technique (unless ultrasound is available); it is unreliable for distinguishing an artery from a vein with cardiac massage; it is associated with the use of smaller cannulas, which can compromise flow; it is difficult to perform in a small patient; and it makes the open technique more difficult if there is a technical failure.

Special Circumstances

Single Ventricle

Patients with single-ventricle physiology can be cannulated centrally or peripherally, depending on the circumstances. When performing the first stage of palliation, we use antegrade cerebral perfusion through a graft anastomosed end-to-side onto the innominate artery. At the end of the procedure, the graft is clipped at the base and left long. If ECMO support is needed, the graft can be cannulated for arterial inflow. It is extremely important to flush the graft to remove any debris or thrombus before placing a cannula.

Patients with a modified BT shunt may require the shunt to be clipped partially to maintain adequate perfusion pressure, while receiving ECMO. Clipping the shunt completely risks thrombosis of pulmonary arteries and lung ischemia because of unreliable bronchial

circulation. Despite narrowing of the BT shunt, ECMO flows may need to be supraphysiologic to maintain adequate perfusion.

Patients with a superior cavopulmonary connection present a challenge when cannulated through the neck. Care must be taken to avoid perforating the pulmonary arteries by advancing the venous cannula too far. Obtaining sufficient venous drainage for adequate support is difficult and, therefore, additional sites for drainage may be necessary. Femoral cannulation is usually not an option when the child is small. Central cannulation may be necessary to get adequate flows.

Patients with a Fontan circulation needing ECMO may present at a wide range of ages. It is ideal to place the venous drainage cannula in the Fontan pathway. However, whether doing cervical or femoral cannulation, it may be difficult to negotiate the cannula into the pathway. Occasionally, image guidance may be necessary. The presence of aortopulmonary collaterals may require supraphysiologic flows to maintain adequate perfusion.

Femoral Cannulation

Cannulation of the femoral artery and ipsilateral vein risks ischemia of the lower extremity. One option is to cannulate the contralateral vein. If the artery and vein are cannulated on the same side, we routinely place a small distal perfusion catheter on the distal femoral artery. It may be advanced into the superficial femoral vein or the profunda femoris. An additional maneuver is to place a distal drainage cannula in the femoral vein, to avoid suffusion of the leg.

Neck Cannulation

Internal jugular venous drainage can be optimized by placement of a small catheter up toward the head for cephalic drainage. It can contribute a significant amount of venous return obviating the need for an additional cannula elsewhere. Cephalic drainage is especially important to avoid cerebral edema, if the contralateral internal jugular vein is obstructed.

Venting

It is paramount to have an adequately decompressed ventricle while receiving ECMO to maximize the chances of ventricular recovery and to avoid lung injury from left atrial hypertension. The ventricle must be able to handle the pulmonary venous return. One must always be aware that significant left atrial hypertension can occur, even in the presence of apparent ventricular contractility. However, if there is any ventricular distention by echocardiography, this should be dealt with urgently. In a child, often all that is necessary is to create or enlarge an interatrial communication, to allow left to right shunting. This can be done in the catheterization laboratory. Alternatively, a vent can be placed into the left atrium; into the ventricle across the mitral valve, or into the ventricle itself. Any of these can be done surgically during central cannulation. A vent can also be placed across an interatrial communication in the catheterization laboratory. In

TABLE 109-6 ECMO Circuit Guidelines: Boston Children's Hospital

	Weight (kg)					
	2-15	16-20	21-35	36-60	>60	Stat (>15 kg)
Circuit	Neonatal	Pediatric	Pediatric	Adult	Adult	Stat
Membrane (m ²)	0.8-1.5	2.5	3.5	4.5	4.5	Optima*
Prime						
5% albumin (mL)	50	100	100	100	100	100
Packed red blood cells (mL)	500	1000	1000	1500	1500	1000
Fresh-frozen plasma (mL)	200	400	400	500	500	400
Cryoprecipitate (U)	2	3	3	4	4	3
Platelets (U)	2	4	4	6	6	6
Medications						
Heparin (U)	500	500	500	800	800	500
THAM (mL)	100	200	300	300	300	200
Calcium gluconate (mg)	1500	3000	3000	4000	4000	3000
Flows						
Minimum (mL/min)	100	200	250	300	600	0.5
Maximum (L/min)	1.8	4.5	5.5	6.5	6.5 (ea)	8.0
Sweep gas range (L/min)	1-4.5	2-8	2-11	2-13	2-13	0.5-20
Membrane volume (mL)	174	455	575	665	1330	260
Circuit volume (mL)	580	1500	1600	2500	3200	1000

*Cobe Cardiovascular, Inc., Amada, CO.

ECMO, Extracorporeal membrane oxygenation.

children, vents are prone to thrombosis because of their small size, long length, and limited flows.

Conduct of Cannulation

ECMO cannulation is often done under emergent circumstances during a resuscitation in an ICU. It is important for the cannulating surgeon to remain calm in the face of chaos. Communication with the entire team during the procedure is key. If CPR is ongoing, it must be stopped at the request of the surgeon. Timing of heparin delivery must be communicated clearly to the ICU team by the surgeon. The surgeon communicates with the ECMO specialists regarding cannula choice and required pump flows.

The importance of adequately positioning the patient for access to the neck, chest, or groin, as necessary, cannot be overstated. Necessary equipment for the procedure must be immediately available, ideally in the ICU. A head light is invaluable, as well as operating loupes for small children. Sometimes, the surgeon will have to begin the procedure with an inexperienced assistant and without an operating room team. The surgeon must be able to direct their assistant precisely, and be very familiar with the organization of the available surgical instruments. To mitigate the stress of cannulation, simulation team training with "cannulatable" models may be helpful.

Circuit and Cannula Management

The ECMO system circuit includes a reservoir, membrane oxygenator, and heat exchanger. The ECMO and cannula guidelines used at Boston Children's Hospital are shown in Tables 109-6 and 109-7. The circuit volume can range from approximately 350 mL (in neonates) to 2 to 3 L (in adults). Before cannulation, heparin is administered and the ACT is usually maintained between 180 and 200 by continuous heparin infusion. Occasionally,

TABLE 109-7 ECMO Cannula Size According to Patient Weight

Weight (kg)	Venous (Fr)	Arterial (Fr)
2-4	8-14	8-10
5-15	15-19	12-15
16-20	19-21	15-17
21-35	21-23	17-19
35-60	23	19-21
60+	23	21

ECMO, Extracorporeal membrane oxygenation.

the ACT is maintained at a somewhat lower level in the presence of significant bleeding. At times, large doses of drugs such as heparin, fentanyl, or midazolam may be necessary because of binding to the circuit and oxygenator, or because of dilution by bleeding. Perfusion flow rates in infants and small children typically range from 100 to 150 mL/kg/min during full circulatory support. Blood products are administered to keep the hematocrit level between 35% and 45%, typically, and the platelet count greater than 100,000/mm³.

Arteriovenous cannulation is usually used for cardiac ECMO, although venovenous bypass can be used in patients who require ventilatory support only. In the immediate postoperative period, mediastinal cannulation, using single right atrial and ascending aortic cannulas, is often preferable because cannulation can be rapidly achieved, along with left atrial decompression if necessary. For the risk of infection to be reduced further, if possible, the skin is closed over the cannulas and the chest, or a surgical Silastic membrane is used instead. Alternatively, the internal jugular vein and carotid artery can be used, with the potential advantage of less bleeding, a more stable cannula position, and, by avoiding an open sternum, a possible reduction in the risk for infection. If neck cannulation is used, the carotid artery can be either

ligated or repaired. Despite concerns about uneven cerebral blood flow, ligation seems to be surprisingly well tolerated clinically, but reconstruction requires long-term follow-up because of the increased risk of stenosis at the anastomotic site.^{46,47} The femoral vessels in infants and young children might not accommodate cannulas of sufficient size to permit complete circulatory support. However, these sites have been used occasionally to provide resuscitation and stabilization in acute emergency situations (e.g., in the cardiac catheterization laboratory) or when femoral access has already been established.

Children with complex structural cardiac defects may have associated abnormalities with systemic venous damage (e.g., heterotaxy syndromes), or they may have undergone previous cardiac catheterization or interventions that have caused occlusion of femoral vessels. Therefore, their venous and arterial anatomy must be well known and well documented to prevent inappropriate cannulation attempts.

The daily management of a patient on ECMO or other forms of extracorporeal life support requires a meticulous assessment of cardiorespiratory function, end-organ perfusion and injury, evolving complications such as bleeding or sepsis, and the mechanics of the ECMO circuit.⁴⁸ If a patient fails to wean from ECMO or there is a delay in anticipated recovery of myocardial function, the possibility of a residual surgical problem must always be considered. This is usually difficult to diagnose by echocardiography alone, and cardiac catheterization (diagnostic or interventional) should be considered.

Assessing the adequacy of flow and systemic perfusion soon after initiation of ECMO is of paramount importance. Inadequate flow states or persistent hypotension despite perceived adequate flow requires immediate analysis and intervention (Table 109-8). Venous cannula malposition or inadequate size limits venous drainage if a roller pump is used, thereby contributing to circuit chatter and bladder collapse. This should be addressed immediately, and the venous cannula should be repositioned, an additional venous cannula placed, or the existing cannula upsized. When ECMO flow appears inadequate to meet the needs of the patient and limited venous drainage restricts additional flow, interpretation of arterial and atrial pressures may aid the formulation of a differential diagnosis. For example, a low atrial pressure and inadequate venous drainage may represent hypovolemia from ongoing or unrecognized bleeding. On the

other hand, high atrial pressures with inadequate venous drainage may represent tamponade physiology that requires surgical exploration in a postoperative patient, or it may reflect left ventricle overdistention from inadequate decompression or aortic valve regurgitation. Elevated postmembrane pressures may reflect malposition of the arterial cannula or a cannula that is too small and needs to be revised. Elevated premembrane pressure (e.g., >350 mm Hg) at normal flows without change in postmembrane pressure, or evidence of a blood-gas leak, constitutes membrane oxygenator dysfunction and may dictate oxygenator replacement. Extensive thrombus and consumptive coagulopathy with hypofibrinogenemia and thrombocytopenia are other indications for circuit replacement.

Echocardiography, especially transesophageal (and occasionally cardiac catheterization), is used to assess cardiac structure and contractile function and to detect residual lesions and the need for left atrial decompression.^{29,49} Venting the left atrium may be necessary to lower the left atrial pressure and decrease left ventricular wall stress, thereby minimizing ongoing myocardial injury. Adequate decompression can be assessed early by echocardiography and signs of pulmonary edema. Strategies to assist with decompressing the ventricle include placing a vent in the left atrium by direct placement through an open chest, a transcatheter approach in the catheterization laboratory,²⁹ or by creating an unrestricted atrial septal defect via septostomy and then augmenting ventricular ejection with inotropic agents.

Once ECMO is successfully established, inotropic support is usually reduced, and vasodilators may be required to improve systemic perfusion and enable appropriate flow rates. The fraction of inspired oxygen (FiO₂) and ventilatory support also are decreased to a low respiratory rate (5 to 10 breaths/min), low peak inspiratory pressures (20 to 25 cm H₂O), and low levels of positive end-expiratory pressure to preserve lung volume and to limit inactivation of alveolar surfactant.

Considerations regarding cannulation and flow rates once the patient is receiving ECMO may be specific to the underlying cardiac defect or surgical repair. For example, the management of an aortopulmonary shunt is critical in patients with single-ventricle physiology. Systemic and pulmonary flow should be balanced by either partially clipping the shunt or using high ECMO flows. With ECMO, circuit flows up to 200 mL/kg/min (or even greater) are usually necessary to maintain adequate systemic perfusion while accounting for runoff into the

TABLE 109-8 Causes of Inadequate ECMO Flow and Perfusion

	Cannula	Anatomic	Physiologic
Inadequate venous drainage	Too small Malpositioned Air occlusion	Heterotaxy syndromes Vessel occlusion or stenosis	Hypovolemia Tamponade
Inadequate systemic perfusion	Too small (high postmembrane pressure) Malpositioned Occlusion	Aortic valve regurgitation Vessel stenosis	Nonvented, distended ventricle Systemic vasoconstriction or vasodilation

ECMO, Extracorporeal membrane oxygenation.

pulmonary circulation through the shunt. Although partial temporary narrowing of the shunt may be advisable in some circumstances, it is unwise to completely occlude the only source of pulmonary blood flow to the pulmonary endothelium. It is possible to bypass the membrane oxygenator in patients after the Norwood procedure with a modified Blalock-Taussig shunt in patients without lung disease if higher flows are maintained and the shunt is patent.⁵⁰ This maneuver simplifies the circuit and can permit the use of less of heparin. ECMO thus effectively becomes a VAD.

Problems related to cannula placement and adequacy of venous drainage may be particularly evident in patients with complex venous anatomy, such as heterotaxy syndrome, and in patients with a cavopulmonary connection. The site of cannulation is affected by vessel patency, and the underlying physiology might influence the number of venous cannulas used. For example, patients with a superior cavopulmonary anastomosis (bidirectional Glenn shunt) as the primary source of pulmonary blood flow frequently require separate venous drainage of the SVC and IVC, unless there is congenital interruption of the infrahepatic IVC with drainage of lower body blood to the azygos vein. In the latter case, a single venous cannula in the SVC might be sufficient. On the other hand, placement of a cannula in the SVC may be detrimental in patients with bidirectional Glenn shunt physiology because of the potential for reduced cerebral venous drainage and therefore decreased cerebral perfusion. This is also a concern for patients with Fontan physiology; although it may be possible to achieve adequate drainage with a venous cannula placed in the Fontan baffle, an additional SVC catheter is often necessary to achieve the desired or necessary flow rates on ECMO.⁵¹

Weaning from Extracorporeal Membrane Oxygenation

The strategies for weaning from cardiac ECMO are often quite different from those used to wean patients who are receiving ECMO for respiratory support. For patients with structurally normal hearts who require ECMO support for respiratory illness, the ability to wean depends on resolution of the primary pulmonary process, often with little need for support of the myocardium beyond moderate inotropic support, fluid and electrolyte management, and nutritional support. Once lung compliance and gas exchange are normalized, improvement of the lungs on the chest radiograph is apparent, and a stable circulation with sufficient negative fluid balance has been achieved, the patient is sedated, paralyzed, and fully ventilated, and the ECMO circuit is clamped.

Before weaning a patient from ECMO used for circulatory support, an understanding of the underlying cardiac physiology and cardiorespiratory interactions and an appreciation for the expected range of oxygen saturation levels are important. Because of the increased risk of complications and mortality in patients with cardiac disease when the duration of MCS extends beyond 7 days, consideration as to when and how to wean cardiac patients from ECMO should begin once circulatory

stability has been established. The disease process and circumstances resulting in hemodynamic failure or cardiac arrest can influence the expected duration of mechanical support. For example, patients who fail to separate from CPB after cardiac surgery as a result of severe pulmonary hypertension usually respond to a period of 24 to 48 hours on ECMO with inhaled nitric oxide (NO) therapy and inotropic support of the right side of the heart. Similarly, patients who have a low cardiac output state or suffer cardiac arrest after cardiac surgery may have residual defects that allow rapid weaning and decannulation soon after reoperation. The likelihood of recovery of ventricular function should be decided within the first 48 to 72 hours so that cardiac transplantation status can be ascertained. ECMO instituted for catheter intervention or arrhythmia ablation procedures may be discontinued within hours of patient cannulation.⁵² In contrast, patients with severe cardiomyopathies or those awaiting heart transplantation may require mechanical assistance for a much longer period. Patients with severe bronchiolitis because of respiratory syncytial virus complicating repair of congenital heart disease on CPB typically require 2 to 3 weeks of ECMO support for respiratory failure.

Patients requiring cardiovascular support with ECMO are partially weaned within the first 48 hours for assessment of myocardial function by echocardiography and hemodynamic evaluation. An acceptable PaO₂ obtained while the ECMO circuit is clamped varies substantially according to the underlying anatomy and pathophysiology. If transthoracic cannulation was used and problems with bleeding were encountered during the ECMO run, the mediastinum may require exploration before or during the weaning process. If only a short period of reconditioning of the myocardium is anticipated, the patient is frequently sedated and paralyzed, dopamine infusion is increased to 5 to 10 mg/kg/min, intravascular volume status is optimized, and ventilator settings are adjusted according to lung compliance and expected arterial O₂ saturation. ECMO flow is decreased by 25% to 50% over a period of time until the circuit is clamped. Volume is infused to achieve appropriate preload. Echocardiographic assessment of ventricular systolic function, valvular function, systemic and pulmonary outflow obstruction, and location and direction of intracardiac shunts is useful before weaning, as well as if there is a change in hemodynamics after the circuit has been clamped. Arterial blood gases, serum lactate levels, and systemic and mixed venous oxygen saturation levels are important guides to the stability of the circulation, ventilation, and adequacy of perfusion after the circuit has been clamped. Decannulation from ECMO is undertaken once the patient has maintained a stable circulation and acceptable gas exchange for a period of up to 4 hours.

INTRA-AORTIC BALLOON COUNTERPULSATION

Intra-aortic balloon pump (IABP) counterpulsation is commonly used for the treatment of myocardial failure in adults, especially in the postoperative period. When

used in infants and children, however, results have been disappointing, with survival rates of less than 50%.⁵³⁻⁵⁵ Many factors contribute to the reduced efficacy in children. Heart failure in pediatric patients is often caused by either right ventricular or biventricular dysfunction, conditions in which the IABP is not effective. Placement of an IABP in the pulmonary artery has been reported but is usually challenging, in part because of the small balloon size required and the increased compliance of the pulmonary artery.^{56,57} The relatively rapid heart rate of infants and small children and the variable delay between aortic valve closure and the appearance of the arterial tracing on the oscilloscope make effective timing of inflation and deflation more difficult. At heart rates greater than 160 beats/min, the IABP is often reduced to a 1:2 or even 1:4 pumping frequency to facilitate cycle timing, at the same time decreasing the effectiveness to 50% to 80%.^{58,59} The aorta is typically more distensible in both infants and children; therefore, both coronary flow augmentation during diastole (balloon inflation) and afterload reduction during systole (balloon deflation) are likely to be less. In addition, the effect of diastolic augmentation on normal coronaries, prevailing in the pediatric population, has been questioned.^{60,61} Severe cyanotic heart disease in children can be accompanied by extensive aortopulmonary collateral vessels, which permit shunting of blood into the pulmonary circulation during balloon inflation, thus reducing augmentation of coronary blood flow.

The smallest balloon system available for children is 2.5 mL, which can be used for neonates as small as 2 kg. In general, for children weighing less than 30 kg, a balloon volume of 0.5 mL/kg is recommended. For balloon inflation, helium is preferred over CO₂, as it allows a faster pneumatic response because of its low density. Interestingly, the incidence of vascular complications, such as bleeding, emboli, or limb ischemia, correlates well with the adult population, where it is reported in 10% to 20% of cases. Other potential complications are infection, renal dysfunction, mesenteric occlusion or embolism, and cerebrovascular accidents.^{62,63}

Numerous technical improvements have been made to enhance efficacy in the pediatric population. These improvements include modified pumping consoles and small-sized catheters, improved tracking at higher heart rates, more rapid inflation and deflation, and the use of M-mode echocardiography for cycle timing.⁶⁴ Further study is necessary to evaluate the importance and continued role of IABP support for pediatric patients, particularly in the face of growing availability of other modes of circulatory support.

VENTRICULAR ASSIST DEVICES

The experience with VADs in infants and children remains relatively small when compared with that in adults, but it has been growing steadily over the last 5 years. As with adult patients, VAD support is useful as a bridge to transplantation, and it allows recovery of end-organ function, elimination of edema, and improvement in nutrition, and it provides rehabilitation of critically ill

patients. An important component of these benefits is the ability of the device to allow extubation and ambulation, which cannot be accomplished currently with ECMO and centrifugal VADs.

The main problem in adapting the VADs used for adult patients had been size limitations and flow requirements; the risk for thromboembolic complications increases with lower flow. In pediatric patients, the selection of pump sizes carries particular importance. A pump that is too small can result in less than adequate cardiac output, and when run at higher rates, it risks inducing significant hemolysis. However, if the pump is too large and is then run at rates too slow, it can result in increased risk of thrombus formation and can be associated with persistent systemic hypertension.

In addition to the obvious variability in size, there are other factors that provide distinct differences between adult and pediatric recipients. These factors include the anatomic variations that are encountered in complex congenital heart disease, the potential of growth, and the unique susceptibility to anticoagulation that children can exhibit. Because of these differences, VAD therapy in children imposes unique challenges that must be anticipated with its application.⁶⁵

As with ECMO, the selection of appropriate candidates for VAD therapy is crucial, and surgical problems or residual defects should be excluded where possible. Whereas ECMO can be instituted by peripheral cannulation of neck or femoral vessels, the currently available VADs require direct cannulation of the heart through a sternotomy. The reported survival rates with VADs are similar to those achieved with cardiac ECMO,^{12,26,66,67} and left VADs (LVADs), right VADs (RVADs), or dual-support VADs (biVADs) can successfully support the circulation, depending on the circumstances. The majority of reported pediatric patients have received LVADs, which have been particularly beneficial in patients with decompensated cardiomyopathy, an ischemic myocardium secondary to an anomalous origin of left coronary artery from the pulmonary artery, and for "retraining" of the poorly prepared left ventricle after an arterial switch procedure.⁶⁸⁻⁷⁰ There are also increasing numbers of case reports describing the use of VAD support in patients with complex congenital heart disease such as single ventricles, including the Fontan circulation (Fig. 109-2).^{71,72}

The advantages of the VAD circuit over ECMO are that the former is relatively simple in design, takes less time to prime, and requires little technical assistance once established. Bleeding complications and requirements for blood products and platelet transfusions are generally less in patients on VADs compared with those on ECMO.^{12,47} Requirement for heparinization and maintaining a prolonged ACT is proportionately less. Because of the lower complication rate, a VAD is more suitable for long-term support as a bridge to transplantation.^{11,12,73}

Another possible advantage of VADs is superior left ventricular drainage and unloading, a prerequisite for myocardial rest and potential recovery.^{11,47,74} While adequate ventilation of the left atrium on ECMO is possible, it does not provide equivalent ventricular decompression when compared with a VAD. Whenever a patient is connected to a VAD, the response of the

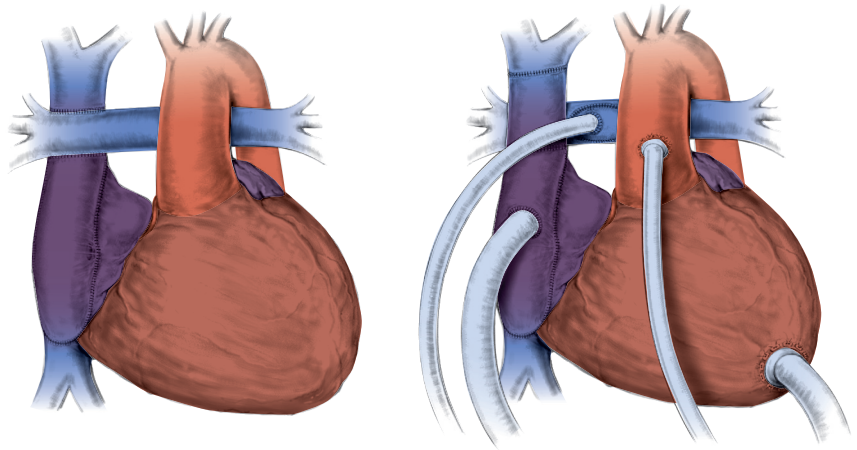


FIGURE 109-2 ■ Use of a ventricular assist device after a Fontan operation.

unsupported ventricle must be closely monitored. Ideally, the reduction in left atrial pressure during LVAD support, associated with adequate decompression of the left ventricle, reduces pulmonary venous and arterial pressures and improves right ventricular function. Unfortunately, based on adult data, right ventricular failure can still develop in up to 25% of patients, especially in LVAD-supported patients with ischemic myocardium, with pre-existing anatomic defects, or after prolonged bypass procedures.⁷⁵⁻⁷⁷

Nonpulsatile Devices

Early in the pediatric VAD experience, most VADs for small children were nonpulsatile systems, either roller pumps or a centrifugal pump such as the Bio-Medicus circuit (Medtronic; Bio-Medicus, Minneapolis, MN). Although these pumps are now mostly of historical value, excellent results were reported using them to support infants and children (<6 kg).⁴² The centrifugal pump, in which blood is entrained by creating a vortex using spinning cones, is highly sensitive to changes in preload and systemic resistance. This is useful when adapting inotropic support or afterload reduction in preparation for weaning. Furthermore, the pump is designed to create constant flow rather than pressure, so the risk of accidental line disruption is reduced. The Bio-Medicus centrifugal pump can be used in infants and older children, and because gravity is not needed to achieve venous drainage, the pump housing can be placed close to the patient and is readily portable.

In 2004, the DeBakey VAD Child (Micromed Technology, Houston, TX) became the first VAD to receive U.S. Food and Drug Administration (FDA) humanitarian device exemption approval for use in children (with a body surface area [BSA] of 0.7 to 1.5 m²). It is a fully implantable axial flow pump that is electromechanically coupled to its power source. The inlet flow is achieved by apical ventricular cannulation with outlet cannulation of the ascending or descending aorta. Early results for the device had been mixed and the experience is still limited. Hemolysis is a concern with axial flow and roller pumps, and this possible complication needs to be monitored closely.^{78,79} Other devices, such as the PediVas

(Levitronix Centrimag and Maquet Rotaflow), and more minimally invasive devices (e.g., the Tandem Heart) and impeller-type pumps (e.g., the Impella VAD) are currently under evaluation in pediatric patients, mostly as temporary devices as a bridge to decision or bridge to recovery.

Pulsatile Devices

Several pulsatile devices (both paracorporeal and implantable) used in adult patients have been adapted for use in older children (BSA > 1.2 m²) to achieve a flow rate of at least 2 L/min. Successful use of the HeartMate LVAD (Thermocardiosystems, Woburn, MA) has been reported in adolescents with a BSA ranging from 1.4 to 2.2 m².⁸⁰ The implantation of the paracorporeal Thoratec VAD (Thoratec Laboratories, Berkeley, CA) has been used extensively in teenagers and has been reported in children as young as 11 years.⁸¹ Other such paracorporeal devices include the Abiomed AB 5000. In our experience at Boston Children's Hospital, the smallest patient to undergo implantation of this device had a BSA of 1.3 m². The reported incidence of thromboembolic events with the adult devices is higher in the pediatric population than in the adult population.

The Berlin Heart VAD (Berlin Heart AG, Berlin, Germany) and the Medos HIA-VAD (Medos Medizintechnik AG, Stolberg, Germany) are paracorporeal pneumatic devices for longer-term support in infants and small children.^{73,82-85} Both are produced in various sizes. Both are pneumatically driven pumps that can deliver varying stroke volumes that can be matched to even the smallest pediatric patients. A measured amount of compressed air is delivered through a pneumatic line that then compresses the ventricular chamber or bladder, thereby enforcing ejection of blood. Diastolic pump filling is achieved with gravity or gentle suction. Because of the high resistance of the small-bore cannulas, positive systolic pressures of up to 350 mm Hg and negative suction of 100 mm Hg at pumping rates of up to 140 beats/min may be necessary, increasing the power requirements for the driving unit considerably, compared with adult devices. Polyurethane trileaflet valves with low transvalvular pressure gradients and rapid closure, as well

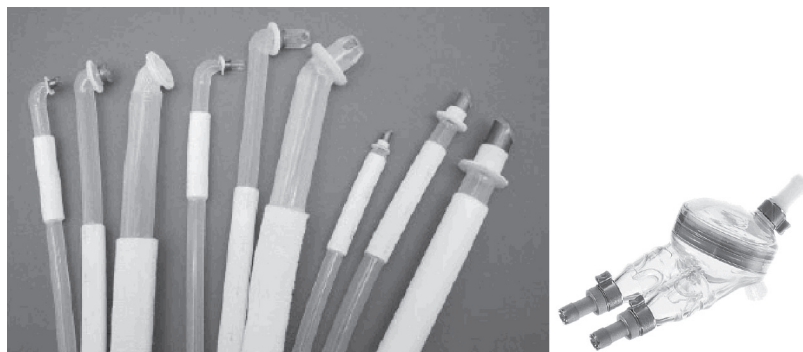


FIGURE 109-3 ■ The Berlin Heart Excor ventricular assist device.

as the use of heparin-coated (Carmeda) systems, reduce the thromboembolic risk, one of the major problems associated with VADs in children.⁸⁶

Berlin Heart

The Berlin Heart Excor VAD (Berlin Heart AG) was the first commercially available ventricular assist system designed specifically for pediatric patients. First developed in Germany, it has been the paracorporeal device most frequently implanted in children in the United States. The Excor pediatric VAD is an extracorporeal, pneumatically driven, pulsatile VAD designed to support the right or left ventricle (or both) synchronously or asynchronously. Cannulas connect the blood pumps to the atrium or ventricle and to the great arteries, and an electropneumatic driving unit provides alternating air pressure to the blood pumps through drive lines (Fig. 109-3). The blood pump is divided into an air chamber and a blood chamber by a polyurethane membrane, and pulses of air pressure move the membrane, allowing both filling and emptying of the blood chamber. Polyurethane valves are located at the inlet and outlet positions of the blood pump, thus ensuring unidirectional blood flow. The blood pumps are available in six different sizes, with stroke volumes of 10, 25, 30, 50, and 60 mL that can be matched for all patient ages and sizes (Fig. 109-4).

Being a pulsatile and mobile support system, the Berlin Heart enables patients to be extubated from mechanical ventilation, to discontinue sedative and paralytic drugs, and to transition to enteral nutrition. A major benefit is the improvement in end-organ function, particularly renal and gut function and, in many cases, patients can be ambulatory. This benefit is particularly important because patients are able to undergo cardiac transplantation in a much better overall condition, which hastens their subsequent recovery after heart transplantation.⁸⁷

The device was first approved in Europe in the 1990s, and experience suggests that the Berlin Heart can provide effective ventricular support for a number of months in children as small as 3 kg. The North American experience dates back to 2000, when the first implantation was performed at the University of Arizona. In early 2007, a multicenter North American trial evaluating the Berlin Heart Excor Pediatric VAD was initiated. The 12-center study, which included two Canadian centers, was designed to provide basic safety information needed to support FDA approval of the device under a formal

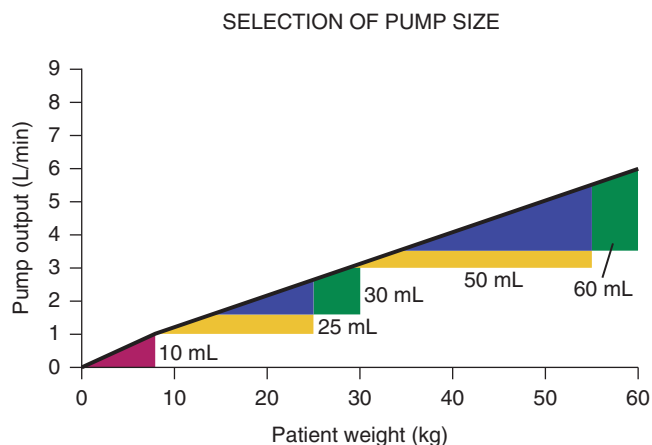


FIGURE 109-4 ■ Selection of pump size matched to patient weight for the Berlin Heart.

investigational device exemption status. This clinical trial was a prospective, multicenter, single-group cohort study comparing children who had implantation of the Excor Pediatric VAD (Berlin Heart) as a bridge to transplantation, with a historical control group of children who received circulatory support with ECMO. Forty-eight Berlin Heart patients were matched with 48 patients from the ELSO Registry. The Berlin Heart patients were divided equally into two cohorts: cohort 1 with BSA < 0.7 m² and cohort 2 with BSA of 0.7 to 1.5 m². For cohort 1, the median time to death or weaning from the device with unacceptable neurologic outcome had not been reached at 174 days. By contrast, the matched ECMO group median time to death was 13 days. For cohort 2, the median time was 144 days, and the matched ECMO group was 10 days. For cohort 1, at 174 days, 88% had undergone transplantation and 12% had died or had an unacceptable neurologic outcome after device wean. In the matched ECMO group for cohort 1, 35% had died at 21 days and none were alive receiving support. For cohort 2, at 192 days, 92% had undergone transplantation or weaning from device, while 8% had died. In the matched ECMO group for cohort 2, 33% had died at 30 days and none were alive on support. Serious adverse events included major bleeding (cohort 1, 42% and cohort 2, 50%); infection (63% and 50%, respectively); and stroke (29%, in each). Although not a randomized trial, this study demonstrated that survival to transplant

or recovery was better with a VAD compared with ECMO. Nevertheless, the rate of complications with the Berlin Heart was significant. Most concerning was the 29% stroke rate. The device received humanitarian device exemption approval in December 2011.

Although the Berlin Heart is currently the most widely used pediatric VAD available for longer-term support of the circulation in children, a number of alternative devices now under investigation will increase the treatment options and, it is hoped, improve outcomes for children with acute and chronic heart failure. There are also a multitude of other MCS devices that are being used in children with increasing frequency through other regulatory pathways. The FDA permits VAD implantation in children under the following pathways: (1) off-label use of an otherwise FDA-approved adult device, (2) compassionate use of investigational adult devices, (3) emergency use of investigational device on a case-by-case basis, and (4) use of a device fabricated from FDA-approved components (e.g., ECMO circuits). Once medical devices are approved for use in adults, they can then be used in children depending on how the device is labeled (i.e., whether there is a specific weight, size or age restriction listed for the device). Currently approved VADs in adults have no restriction specifically outlined for age or size; therefore, they can be used in children. Off-label use of medical devices is a common occurrence in the field of pediatric MCS. It entails the use of a device outside the population or purpose for which the device's safety and efficacy profile was originally evaluated. For short-term support (temporary MCS), the following devices have been used in children: the TandemHeart (Cardiac Assist, Inc., Pittsburgh, PA) percutaneous VAD, the Rotaflow (Maquet Medical Systems, Wayne, NJ), the Centrimag (Thoratec Corporation, Pleasanton, MA), and the Abiomed Impella 2.5/5.0 (Abiomed, Inc., Danvers, MA). For long-term support (durable MCS), the following devices have been used primarily in larger children and adolescents: the HeartMate II (Thoratec Corporation), the HeartWare HVAD (HeartWare, Inc., Framingham, MA), and the Syncardia Total Artificial Heart (TAH; Syncardia Systems, Inc., Tucson, AZ).

Recognizing that pediatric mechanical support represents an unmet need in the United States, the National Heart Lung and Blood Institute (NHLBI) under its Pediatric Circulatory Support initiative, awarded five contracts in 2004, exceeding \$20 million, to support the preclinical development of innovative circulatory support devices designed specifically for infants and smaller children.⁸⁸ As a follow-up to its Pediatric Circulatory Support Program initiative, the NHLBI awarded four contracts totaling \$23.6 million in January 2010 to begin preclinical testing of devices to help children with congenital heart defects or those who develop heart failure. The 4-year program is called *Pumps for Kids, Infants, and Neonates (PumpKIN)*. It includes three of the original five contractors from the previous 2004 NHLBI Pediatric Circulatory Support Program and another. As such, the PumpKIN program is the next phase of NHLBI support for the development and clinical realization of novel pediatric circulatory support devices. The program's goal is to complete the needed investigational device

exemption clinical studies for some of the new investigational pediatric circulatory support devices.

EXPANDING VAD SUPPORT TO CHALLENGING PEDIATRIC POPULATIONS

Single-Ventricle Anatomy and Ventricular Assist Device Support

Improvement in preoperative, perioperative, and postoperative management of patients with congenital heart disease (CHD) has resulted in dramatic increase in long-term survival. Life expectancy for children with most types of congenital heart lesions is comparable to the general population; however, there is a subset of CHD—namely single ventricle anatomy—in which long-term mortality and morbidity into adulthood remains unacceptably high. This growing population of failed single ventricle palliations will benefit from effective mechanical support as a bridge to transplantation or even destination therapy; however, to date this endeavor has been disappointing, with higher mortality and morbidity reported in a variety of single-center experiences. The unnatural history of Fontan (total cavopulmonary connection) circulation is that of progressive systemic venous congestion with the sequelae of protein-losing enteropathy, renal, hepatic and intestinal congestion. The pathways of deterioration can vary and include systemic systolic ventricular dysfunction with low cardiac output and elevated left atrial pressures or diastolic ventricular dysfunction with elevated ventricular end-diastolic pressures resulting in elevated Fontan pressures. Pure systolic ventricular dysfunction can be managed successfully with implantation of a VAD. In situation of diastolic dysfunction or restrictive physiology in addition to decreased systolic function, a continuous-flow pump may be superior by providing continuous unloading of the pulmonary venous system.

Options to unload the systemic venous system in failed Fontan circulation include (1) revision of the Fontan pathway with creation of a larger systemic venous capacitance chamber and insertion of cannula to an extracorporeal device (Berlin Heart EXCOR or centrifugal pump), or (2) takedown of the Fontan back to Glenn (bidirectional cavopulmonary anastomosis) and implantation of systemic VAD. This last option provides better unloading of the infradiaphragmatic circulation, at the cost of lower oxygen saturations and risk of paradoxical emboli. There is also the possibility that a systemic VAD in patients with preserved systolic function but elevated end-diastolic pressures and consequently pulmonary venous congestion may be beneficial in lowering left atrial pressures and alleviating symptoms of Fontan failure. Even a marginal decrease in left atrial pressures may be sufficient to decrease Fontan pressures and improve systemic venous congestion. As device technology improves—with lower adverse event profile and better compatibility with activities of daily living—VADs may soon prove to be adjunctive therapy in

protein-losing enteropathy refractory to maximal medical therapy.

Posttransplant Graft Failure and Ventricular Assist Device Support

Cardiac graft failure can manifest either early (<30 days) or late after transplantation because of variable causes. Current strategies to increase the donor pool—including the use of marginal donors²⁸ and desensitization with human leukocyte antigen-incompatible donor²⁸—may be increasing the risk of posttransplant graft failure.

ECMO has been the mainstay of MCS strategies for graft dysfunction, providing complete respiratory and cardiac support, allowing for recovery or preservation of end-organ function. However, ECMO is limited in its duration of support to weeks and fraught with bleeding, thrombotic, and infectious complications that increase exponentially over time. As such, intermediate to long-term MCS strategies have been attempted with guarded success. The challenges of MCS in graft failure are multifaceted and include redo sternotomy, increased risk of infection and poor wound healing in the setting of continued immunosuppression, progressive biventricular dysfunction with polyvalvar involvement, and arrhythmia. Thus, standard LVAD support is generally not successful, with most patients requiring biventricular support. As such, many believe that total extraction of the graft with implantation of a total artificial heart, the Syncardia TAH (Syncardia Systems, Inc., Tucson, AZ), may be an advantageous support strategy, as it obviates the need for continued immunosuppression. Currently, the TAH is not applicable for use in most children, as the two 70-cc pneumatically driven pumps for right and left heart support require a minimum anterior-posterior chest diameter of 10 cm at the level of thoracic vertebra 10 (T10) to fit. However, a 50-cc Syncardia TAH pump has been developed with a lower size range of 1 m² BSA which may have a wider applicability to the pediatric population.

Destination Ventricular Assist Device Therapy in Children

Destination therapy (DT) is the use of a VAD as a primary therapeutic option when heart transplantation is contraindicated or not desired. The landmark Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure (REMATCH) trial in adults demonstrated that the implantation of LVADs for DT was superior to standard medical therapy in patients with end-stage heart failure who were not eligible for transplantation.³² Now, more than a decade after this trial, the use of VADs as DT in adults is an accepted therapy to improve quality of life.^{33,34}

Based on the success of DT in adults, it is not surprising that this indication is now being more widely considered for children. However, the ability to offer DT remains restricted to children who are large enough to use the currently available intracorporeal devices suitable for outpatient care. Patient selection for this type of therapy will be of paramount importance, and likely an

evolving process. Children who may benefit from DT include those with Duchenne muscular dystrophy with cardiomyopathy, chemotoxicity induced cardiomyopathy with ongoing malignancy or unlikely long-term remission, complex palliated CHD with multiple comorbidities, retransplant graft dysfunction in the setting of noncompliance, and cardiac dysfunction in the setting of neurological impairment or uncertain neurodevelopmental outcomes. There have been reported cases of LVAD implantation for Duchenne Muscular Dystrophy (MD),³⁵ and it is expected that this will continue to grow because of strong advocacy by the patients and their families.

Pediatric DT programs are now emerging in North America. DT VAD programs mandate the integrated services of an extensive and dedicated multidisciplinary team, with heavy involvement of psychology, social work, occupational and physiotherapy, in addition to nursing and medical support. Perhaps the most important aspect of DT is outlining the expectations of what VAD therapy may offer the patients and their families prior to device implantation. Ultimately, the goal of DT is not only to prolong life, but to improve the quality of life for the patient and family. The use of VADs for DT in children will continue to evolve as device technology improves, narrowing the gap between quality of life and survival outcomes for VADs and heart transplantation. Commensurate with the advancement in device technology, we, as a field in pediatric advanced cardiac support, will need to keep pace with the ethical implications and clinical challenges of altering the natural history of life limiting conditions by acknowledging the benefits and critically evaluating the consequences.

LONGER-TERM OUTCOMES FROM MECHANICAL SUPPORT IN CHILDREN

Formal, prospective evaluation of the longer-term outcomes for children receiving mechanical support of the circulation has not been undertaken. Despite the successful deployment of mechanical support to enable cardiac recovery and discharge from hospital, longer-term cardiac function and the functional status of patients should be determined. In addition to cardiac status, end-organ injury and residual deficits need to be evaluated, particularly neurologic outcomes.⁴⁵ The ELSO Registry data indicate a combined neurologic complication rate of 26% in all patients receiving cardiac ECMO, with seizures being the most common neurologic event (9.5%). In a recent retrospective report of outcomes for infants supported with ECMO after cardiectomy (median follow-up, 55 months), only 50% of survivors were determined to have no motor or cognitive deficit of any sort.⁸⁹ As waiting times for cardiac transplantation increase as a result of the increasing number of potential recipients, the need for device options that can provide extended durations of support is more pressing than ever. Longer-term VAD support often allows patients to be bridged more effectively to transplantation than on continuous inotropic support. A multi-institutional retrospective analysis from the Pediatric Heart Transplant Study examined the outcomes in nearly 100 children supported with a variety of

VADs while awaiting transplantation from 1993 to 2003.⁹⁰ In the study, overall, three quarters of the children survived to transplantation—a figure that improved to 85% in the more recent era and is comparable to outcomes reported in adults. Notably, the wait-list survival with mechanical support exceeded that of patients who were supported on maximal medical therapy.

Concurrently with the Pediatric Circulatory Support initiative from the NHLBI in 2004, the National Institutes of Health also sponsored the creation of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). This registry is being designed to have a dedicated pediatric arm that will collect both retrospective and prospective data and will hopefully facilitate the eventual approval of pediatric devices in the United States.

As the technology and indications for mechanical support of the circulation in children continue to evolve and advance, simultaneous outcome studies will be essential to allow us to make better decisions about available mechanical support options for children.

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PEDIATRIC ANESTHESIA AND CRITICAL CARE

Kirsten C. Odegard • James A. DiNardo

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The management of congenital heart disease (CHD) has progressed significantly over the past three decades. Most congenital heart lesions are now amenable to anatomic or physiologic repair early in infancy. Advances in diagnostic and interventional cardiology, the evolution of surgical techniques and conduct of cardiopulmonary bypass, and refinements in postoperative management have all contributed to a substantial decrease in morbidity and mortality associated with CHD. The approach to repairing CHD as early as possible, preferably in the neonatal period, has had significant implications for the anesthetic care of these critically ill infants during cardiac surgery. To meet this challenge, a clear understanding of neonatal respiratory and cardiac physiology, neonatal responses to anesthesia and surgery, and the pathophysiology of complex congenital heart defects is necessary.

PATHOPHYSIOLOGY

Care of the critically ill neonate requires an appreciation of the special structural and functional features of immature organs. The neonate appears to respond more quickly and extremely to physiologically stressful

circumstances; this can be expressed in terms of rapid changes in, for example, pH, lactic acid, glucose, and temperature.¹

The physiology of the preterm and full-term neonate is characterized by a high metabolic rate and O₂ demand (a twofold to threefold increase compared with adults), which may be compromised at times of stress because of limited cardiac and respiratory reserve. The myocardium in the neonate is immature, with only 30% of the myocardial mass being composed of contractile tissue, compared with 60% in mature myocardium. In addition, neonates have a lower velocity of shortening, a diminished length-tension relationship, and a reduced ability to respond to afterload stress.^{2,3} Because the compliance of the myocardium is reduced, the stroke volume is relatively fixed and cardiac output is heart rate dependent; therefore, the Frank-Starling relationship is functional only within a narrow range of left ventricular end-diastolic pressure. The cytoplasmic reticulum and T-tubular system are underdeveloped, and the neonatal heart is dependent on the trans-sarcolemmal flux of extracellular calcium both to initiate and sustain contraction.

Cardiorespiratory interactions are important in neonates and infants. In simple terms, *ventricular*

interdependence refers to a relative increase in ventricular end-diastolic volume and pressure, causing a shift of the ventricular septum and diminished diastolic compliance of the opposing ventricle.⁴ This effect is particularly prominent in the immature myocardium. Therefore, a volume load from an intracardiac shunt or valve regurgitation, and a pressure load from ventricular outflow obstruction or increased vascular resistance, could lead to biventricular dysfunction. For example, in neonates with tetralogy of Fallot and severe outflow obstruction, hypertrophy of the ventricular septum can contribute to diastolic dysfunction of the left ventricle and an increase in end-diastolic pressure. This does not improve immediately after repair in the neonate, as it takes some weeks or months for the myocardium to remodel; therefore, an elevated left atrial pressure is not an unexpected finding after neonatal tetralogy repair. This circumstance can be exacerbated further if there is a persistent volume load to the left ventricle after surgery, such as from residual ventricle septal defects (VSDs).

The mechanical disadvantage of an increased chest wall compliance and reliance on the diaphragm as the main muscle of respiration limits ventilatory capacity in the neonate. The diaphragm and intercostal muscles have fewer type I muscle fibers (i.e., slow-contracting, high oxidative fibers for sustained activity), and this contributes to early fatigue when the work of breathing is increased. In the newborn, only 25% of fibers in the diaphragm are type I, reaching a mature proportion of 55% by 8 to 9 months of age.^{5,6} Diaphragmatic function can be compromised significantly by raised intra-abdominal pressure, such as from gastric distention, hepatic congestion, or ascites.

The tidal volume of full-term neonates is 6 to 8 mL/kg and, because of the mechanical limitations just mentioned, minute ventilation is respiratory-rate dependent. The resting respiratory rate of the newborn infant is between 30 and 40 breaths per minute, which provides the optimal alveolar ventilation to overcome the work of breathing and match the compliance and resistance of the respiratory system. When the work of breathing increases, such as with parenchymal lung disease, airway obstruction, cardiac failure, or increased pulmonary blood flow, a larger proportion of total energy expenditure is required to maintain adequate ventilation. Infants therefore fatigue readily and fail to thrive.

The neonate has a reduced functional residual capacity (FRC) secondary to an increased chest wall compliance (FRC being determined by the balance between chest wall and lung compliance). Closing capacity is also increased in newborns, with airway closure occurring during normal tidal ventilation.⁷ Oxygen reserve is therefore reduced, and in conjunction with an increased basal metabolic rate and oxygen consumption two to three times adult levels, neonates and infants are at risk for hypoxemia. However, atelectasis and hypoxemia do not occur in the normal neonate because FRC is maintained by dynamic factors, including tachypnea, breath stacking (early inspiration), expiratory breaking (expiratory flow interrupted before zero flow occurs), and laryngeal breaking (auto-positive end-expiratory pressure [PEEP]).

Organ immaturity of the liver and kidney may be associated with reduced protein synthesis and glomerular filtration, such that drug metabolism is altered and synthetic function is reduced. These problems can be compounded by the normally increased total body water of the neonate compared with the older patient, along with the propensity of the neonatal capillary system to leak fluid out of the intravascular space.⁸ This is especially pronounced in the neonatal lung, in which the pulmonary vascular bed is almost fully recruited at rest and the lymphatic recruitment required to handle increased mean capillary pressures associated with increases in pulmonary blood flow may be unavailable.⁹

The caloric requirement for neonates, especially preterm neonates, is high (100 to 150 kcal/kg per 24 hr) because of metabolic demand. The task of supplying nutrition for growth becomes even more difficult when necessary limits are placed on the total amount of fluid that may be administered parentally or by the enteral route. Hyperosmolar feedings have been associated with an increased risk for necrotizing enterocolitis in the preterm neonate, or to the neonate born at term who has decreased splanchnic blood flow of any cause (e.g., left-sided obstructive lesions).^{10,11}

PHYSIOLOGIC APPROACH TO CONGENITAL HEART DISEASE

Specific classification of congenital heart defects is difficult because of the complex nature of many lesions. Basing identification and classification on physiology brings an organized framework to the intraoperative anesthetic management and postoperative care of children with complex CHD.

Single Ventricle Physiology

Single ventricle physiology is used to describe the situation wherein complete mixing of pulmonary venous and systemic venous blood occurs at the atrial or ventricular level and the ventricles then distribute output to both the systemic and pulmonary beds. Because of this physiology:

- Ventricular output is the sum of pulmonary blood flow (Qp) and systemic blood flow (Qs).
- Distribution of systemic and pulmonary blood flow is dependent on the relative resistances to flow (both intra- and extra-cardiac) into the two parallel circuits.
- Oxygen saturations are the same in the aorta and the pulmonary artery.

This physiology can exist in patients with one well-developed ventricle and one hypoplastic ventricle and in patients with two well-formed ventricles.

In the case of a single anatomic ventricle, there is always obstruction to either pulmonary or systemic blood flow because of complete or near complete obstruction to inflow and/or outflow from the hypoplastic ventricle. In this circumstance, there must be a source of both systemic and pulmonary blood flow to assure postnatal survival. In some instances of a single anatomic ventricle,

a direct connection between the aorta and the pulmonary artery via a patent ductus arteriosus (PDA) is the sole source of systemic blood flow (hypoplastic left heart syndrome) or of pulmonary blood flow (pulmonary atresia with intact ventricular septum); this is known as *ductal dependent circulation*. In other instances of a single anatomic ventricle, intracardiac pathways provide both systemic and pulmonary blood flow without the necessity of a PDA. This is the case in tricuspid atresia with normally related great vessels, a nonrestrictive VSD, and minimal or absent pulmonary stenosis.

Single ventricle physiology can exist in the presence of two well-formed anatomic ventricles when there is complete or near complete obstruction to outflow from one on the ventricles:

- Tetralogy of Fallot (TOF) with pulmonary atresia (PA) where pulmonary blood flow is supplied via a PDA or multiple aortopulmonary collateral arteries (MAPCA)
- Truncus arteriosus
- Severe neonatal aortic stenosis and interrupted aortic arch (in both lesions a substantial portion of systemic blood flow is supplied via a PDA)
- Heterotaxy syndrome, in which there are components of systemic venous (superior vena cava, inferior vena cava, hepatic veins, azygous veins) and pulmonary venous return to both right and left sided atria, and in which atrial morphology is ambiguous

With single ventricle physiology, the arterial saturation (SaO_2) will be determined by the relative volumes and saturations of pulmonary venous and systemic venous blood flows that have mixed and reach the aorta. This is summarized in the following equation:

$$\text{Aortic saturation} = \frac{[(\text{Systemic venous saturation}) \times (\text{Total systemic venous blood flow}) + (\text{Pulmonary venous saturation}) \times (\text{Total pulmonary venous blood flow})]}{(\text{Total systemic venous blood flow} + \text{Total pulmonary venous blood flow})}$$

A typical example is as follows:

$$\text{SaO}_2 = [(65)(3.3) + (98)(2.8)] / (3.3 + 2.8) = 80\%$$

Intercirculatory Mixing

Intercirculatory mixing is the unique situation that exists in transposition of the great vessels, in which two parallel circulations exist because of the existence of atrioventricular concordance (RA-RV, LA-LV) and ventriculoarterial discordance (RV-Ao, LV-PA). This produces a parallel rather than a normal series circulation. In this arrangement, blood flow will consist of parallel recirculation of pulmonary venous blood in the pulmonary circuit and systemic venous blood in the systemic circuit. Therefore, the physiologic shunt or the percentage of venous blood from one system that recirculates in the arterial outflow of the same system is 100% for both circuits. Unless there are one or more communications (atrial septal defect [ASD], PFO, VSD, PDA) between the

parallel circuits to allow intercirculatory mixing, this lesion is incompatible with life.

An anatomic right-to-left (R-L) shunt is necessary to provide effective pulmonary blood flow, whereas an anatomic left-to-right (L-R) shunt is necessary to provide effective systemic blood flow. Effective pulmonary blood flow, effective systemic blood flow, and the volume of intercirculatory mixing must always be equal. Total systemic blood flow is the sum of recirculated systemic venous blood plus effective systemic blood flow. Likewise, total pulmonary blood flow is the sum of recirculated pulmonary venous blood plus effective pulmonary blood flow. Recirculated blood composes the largest portion of total pulmonary and total systemic blood flow, with effective blood flows contributing only a small portion of the total flows. This is particularly true in the pulmonary circuit in which the total pulmonary blood flow (Q_p) and the volume of the pulmonary circuit (LA-LV-PA) is twofold to threefold greater than the total systemic blood flow (Q_s) and the volume of the systemic circuit (RA-RV-Ao). The net result is transposition physiology, wherein the pulmonary artery oxygen saturation is greater than the aortic oxygen saturation.

Arterial saturation (SaO_2) will be determined by the relative volumes and saturations of the recirculated systemic and effective systemic venous blood flows reaching the aorta. This is summarized in the following equation:

$$\text{Aortic saturation} = \frac{[(\text{Systemic venous saturation}) \times (\text{Recirculated systemic venous blood flow}) + (\text{Pulmonary venous saturation}) \times (\text{Effective systemic venous blood flow})]}{(\text{Total systemic venous blood flow})}$$

A typical example is as follows:

$$\text{SaO}_2 = [(50)(1.2) + (99)(1.1)] / 2.3 = 73\%$$

Simple Shunts

Shunting is the process whereby venous return into one circulatory system is recirculated through the arterial outflow of the same circulatory system. Flow of blood from the systemic venous atrium or right atrium to the aorta produces recirculation of systemic venous blood. Flow of blood from the pulmonary venous atrium or left atrium to the pulmonary artery produces recirculation of pulmonary venous blood. Recirculation of blood produces a physiologic shunt. Recirculation of pulmonary venous blood produces a physiologic L-R, whereas recirculation of systemic venous blood produces a physiologic R-L shunt. A physiologic R-L or L-R shunt commonly is the result of an anatomic R-L or L-R shunt. In an anatomic shunt, blood moves from one circulatory system to the other via a communication at the level of the cardiac chambers or great vessels. Physiologic shunts can exist in the absence of an anatomic shunt. Transposition physiology is the primary example of this process.

Effective blood flow is the quantity of venous blood from one circulatory system reaching the arterial system of the other circulatory system. Effective pulmonary

blood flow is the volume of systemic venous blood reaching the pulmonary circulation, whereas effective systemic blood flow is the volume of pulmonary venous blood reaching the systemic circulation. Effective pulmonary blood flow and effective systemic blood flows are the flows necessary to maintain life. Effective pulmonary blood flow and effective systemic blood flow are always equal, no matter how complex the lesions. Effective blood flow usually is the result of a normal pathway through the heart, but it can occur as the result of an anatomic R-L or L-R shunt.

Total pulmonary blood flow (Qp) is the sum of effective pulmonary blood flow and recirculated pulmonary blood flow. Total systemic blood flow (Qs) is the sum of effective systemic blood flow and recirculated systemic blood flow. Total pulmonary blood flow and total systemic blood flow do not have to be equal. Therefore, it is best to think of recirculated flow (physiologic shunt flow) as the extra, non-effective flow superimposed on the nutritive effective blood flow.

Shunts causing an increase in pulmonary blood flow may be simple or complex, occurring among the ventricles, atria, or great arteries, and they are described by the ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs), or Qp/Qs. Patients may be acyanotic or cyanotic, have one or two ventricles, or have a single outflow trunk, yet have a significant increase in Qp/Qs and be at risk for congestive heart failure (CHF) and pulmonary hypertension (Table 110-1).

In patients with large L-R shunts and low pulmonary vascular resistance, a substantial increase in pulmonary blood flow can occur. If the increase in pulmonary blood flow and pressure continues, structural changes occur in the pulmonary vasculature until eventually pulmonary

vascular resistance (PVR) becomes persistently elevated.^{12,13} The time course for developing pulmonary vascular obstructive disease depends on the amount of shunting, but changes with some lesions may be evident by 4 to 6 months of age. The progression is more rapid when both the volume and pressure load to the pulmonary circulation is increased, such as with a large VSD. As PVR decreases in the first few months after birth and the hematocrit falls to its lowest physiologic value, the increased L-R shunt, and therefore volume load on the systemic ventricle, can lead to congestive cardiac failure and failure to thrive.

The end-diastolic volume is increased in patients with an increased Qp/Qs ratio, but the time course over which irreversible ventricular dysfunction develops is variable. Generally, if surgical intervention to correct the volume overload is undertaken within the first 2 years of life, residual dysfunction is uncommon.¹⁴

The volume load on the systemic ventricle and increased end-diastolic pressure contribute to increased lung water and pulmonary edema by increasing pulmonary venous and lymphatic pressures. Compliance of the lung is therefore decreased, and airway resistance increased secondary to small airway compression by distended vessels.¹⁵⁻¹⁷ Lungs may feel stiff on hand ventilation and deflate slowly. Besides cardiomegaly on the chest radiograph, the lung fields are usually hyperinflated. Ventilation-perfusion mismatch contributes to an increased alveolar-arterial oxygen gradient, and dead-space ventilation.¹⁸ Minute ventilation is therefore increased, primarily by an increase in respiratory rate. Pulmonary artery and left atrial enlargement may compress main-stem bronchi, causing lobar collapse. Symptoms and signs of CHF to note in neonates and infants are shown in Box 110-1.

Manipulating PVR is an important means of limiting pulmonary blood flow and pressure. During anesthesia, PVR can be maintained or increased by using a low fraction of inspired oxygen (FiO₂) and altering ventilation to achieve a normal pH and PaCO₂.¹⁹ Care must be taken at induction of anesthesia, because patients may have a

TABLE 110-1 Simple Shunts: Defects and Surgical Procedures Contributing to an Increased Ratio of Pulmonary Blood Flow (Qp) to Systemic Blood Flow (Qs)

Type of Shunt	Acyanotic	Cyanotic
Two ventricles	ASD VSD CAVC DORV	D-TGA/VSD PA/VSD
Single ventricle	—	TA ± TGA HLHS DORV/MA Norwood/Sano procedure BT shunt PA/MAPCA
Aortopulmonary (AP) connection	PDA Truncus arteriosus AP window	

AP, Aortopulmonary; ASD, atrial septal defect; BT, Blalock-Taussig; CAVC, complete atrioventricular canal; DORV, double-outlet right ventricle; D-TGA, dextro-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; MA, mitral atresia; MAPCA, multiple aortopulmonary collateral arteries; PA, pulmonary atresia; PDA, patent ductus arteriosus; TA, tricuspid atresia; TGA, transposition of the great arteries; VSD, ventral septal defect.

BOX 110-1 Symptoms and Signs of Cardiac Failure in a Neonate or Infant

POOR GROWTH

- Poor feeding
- Diaphoresis

INCREASED WORK OF BREATHING

- Tachypnea
- Grunting
- Flaring of ala nasi
- Chest wall retraction

DECREASED CARDIAC OUTPUT

- Tachycardia
- Gallop rhythm
- Cardiomegaly
- Poor extremity perfusion
- Hepatomegaly

diminished contractile reserve. Preload, contractility, and heart rate must be maintained; afterload reduction is often well tolerated and will reduce pulmonary flow and myocardial work.

Complex Shunts

In complex shunts, there is additional pulmonary or systemic outflow obstruction, and the Qp/Qs ratio is determined by the size of the orifice, the outflow gradient, and the resistance across the pulmonary or systemic vascular bed. The obstruction may be fixed as with valvular stenosis, or dynamic as in forms of TOF.

Outflow Obstruction

Severe outflow obstruction in the newborn may be associated with ventricular hypertrophy and vessel hypoplasia distal to the level of obstruction. The increased pressure load can cause ventricular failure, with mixing or shunting at the atrial or ventricular level (or both) necessary to maintain cardiac output if there is complete outflow obstruction. Maintenance of preload, afterload, and normal sinus rhythm is important to prevent a fall in cardiac output or coronary hypoperfusion. As the time to develop significant ventricular dysfunction is longer in patients with a chronic pressure load than in those with a chronic volume load, symptoms of CHF are uncommon unless the obstruction is severe and prolonged.

Pulmonary Hypertension

Pulmonary hypertension may be idiopathic. Patients with CHD typically have pulmonary hypertension secondary to increased pulmonary artery flow and pressure, pulmonary venous obstruction, or left atrial hypertension from systemic ventricular atrioventricular valve dysfunction or ventricular systolic or diastolic dysfunction. Factors that increase PVR and pulmonary pressures include light anesthesia with a poorly attenuated stress response, hypoxemia, hypoventilation with a fall in FRC and respiratory acidosis, metabolic acidosis, hypothermia, prolonged bypass with associated inflammatory response and capillary leak, and administration of protamine or blood products (e.g., platelets; [Box 110-2](#)).

After repair of defects with large L-R shunts, pulmonary artery pressures may remain elevated immediately after bypass, as the pulmonary arteries initially remain reactive to factors that increase PVR. While the patient is on bypass, factors contributing to this elevated pressure include compression and atelectasis of the lung, and pulmonary edema from inadequate venting of the left atrium or from the humoral and cellular response to bypass. Attenuation of the stress response with deep anesthesia using high-dose narcotics will prevent increases in PVR.²⁰ A high FiO₂ and hyperventilation to induce a respiratory alkalosis will reduce PVR, and boluses of bicarbonate may be necessary to maintain metabolic alkalosis.²¹⁻²³ Ideally, the pH should be approximately 7.45 to 7.50 and the arterial CO₂ should be 30 to 35 mm Hg. A strategy of hyperventilation to induce a respiratory alkalosis and lower PVR may have an adverse effect on central nervous

BOX 110-2 Causes of Abnormally Elevated Pulmonary Artery Pressure

- Left-to-right shunt lesion (e.g., large ventricular septal defect or patent ductus arteriosus)
- Pulmonary arteriolar smooth muscle hypertrophy (e.g., pulmonary vascular obstructive disease)
- Increased pulmonary venous pressure
- Mechanical obstruction of the pulmonary circulation
- Anatomic defects (e.g., pulmonary vein or branch pulmonary artery stenosis)
- Pulmonary embolus
- Raised intrathoracic pressure
- Lung hyperinflation
- Lung hypoinflation and hypoplasia
- Decreased alveolar oxygen tension
- Acidemia (respiratory or metabolic)
- Inflammatory response to cardiopulmonary bypass
- Drugs: protamine
- Hyperviscosity (from polycythemia)
- Blood product administration (platelets)
- Artifactual (e.g., monitoring problems, catheter malposition)

system recovery by lowering cerebral blood flow. The pattern of ventilation and maintenance of lung volumes is important: atelectasis and decreases in lung compliance can cause a significant rise in PVR and pulmonary pressures. Changes in ventilation must be made cautiously and reassessed frequently.

Several intravenous vasodilators, including the nitric oxide (NO) donors nitroprusside and glycerol trinitrate, the phosphodiesterase inhibitor milrinone, the eicosanoids prostaglandin E₁ and prostaglandin I₂,²⁴ tolazoline, and isoproterenol have been used to treat postoperative patients with elevated PVR.²⁵⁻²⁷ The chief limitation of these pharmacologic agents is that their vasodilatory effects are not specific to the pulmonary vasculature; therefore, vasodilation of the systemic vasculature and systemic hypotension may accompany reduction of pulmonary hypertension.

Inhaled NO selectively dilates smooth muscle cells in small pulmonary vessels and lowers PVR.²⁸ The selective effect of inhaled NO on the pulmonary vasculature is a result of the rapid uptake and inactivation by hemoglobin as NO diffuses from alveoli to the lumen of lung capillaries. The usefulness of inhaled NO for patients with congenital heart disease and pulmonary hypertension has been documented in several populations.^{29,30} After surgery, NO has been shown to reduce pulmonary artery pressure and PVR in patients with pulmonary venous obstruction, such as total anomalous pulmonary venous connection and mitral stenosis, to a lesser extent in patients with a large preexisting L-R shunt, and in those with cavopulmonary connections (Fontan physiology)³¹ or pulmonary hypertensive crises related to cardiopulmonary bypass (CPB). NO has also improved both pulmonary hypertension and impaired gas exchange in patients who have undergone lung transplantation. Patients with a variety of other pulmonary vascular or parenchymal diseases, including persistent pulmonary hypertension of the newborn,³²⁻³⁴ primary pulmonary hypertension, acute

respiratory distress syndrome,³⁵ and acute chest syndrome in sickle cell disease³⁶ have also shown significant improvements in oxygenation from treatment with inhaled NO.

Recent therapeutic advances have significantly improved the prognosis for patients with pulmonary arterial hypertension.^{24,37,38} The role of newer pulmonary vasodilating drugs such as the phosphodiesterase type V inhibitor sildenafil, and endothelin I blocking drugs, such as bosentan, have shown encouraging results.³⁹⁻⁴² The value of these drugs in children with CHD is yet to be established.

PREOPERATIVE EVALUATION

Patients with complex defects require frequent evaluation and often repeated cardiac operations as a staged approach to surgical repair. Previous anesthetic, bypass, or surgical problems should be noted. In general, providing continuity of care in these patients, such as by a dedicated cardiac anesthesia service, is useful to ensure consistent management practices, and it enhances the long-term relationship with patients and families.

Failure to thrive is an important indicator of cardiopulmonary compromise. Symptoms as described in [Box 110-1](#) should be noted. Murmurs and extra heart sounds may be difficult to interpret if tachycardic, but a palpable thrill usually indicates a significant murmur. Failure to thrive, lethargy, and poor exercise tolerance are significant symptoms in older children. Orthopnea, syncope, and palpitations may also be described. Recurrent respiratory infections and wheezing are common in patients with L-R shunts. Four-limb blood pressures should be compared, and room air baseline peripheral arterial saturations should be noted along with potential airway problems. The chest radiograph should be analyzed for cardiomegaly, pulmonary congestion, airway compression, and atelectasis. Echocardiographic assessment and cardiac catheterization results provide valuable information about anatomic structure, myocardial function, intracardiac pressures, shunting, and gradients across obstructions. They should be interpreted in conjunction with the cardiologist and surgeon. Patients with cardiac failure are often stabilized on digoxin, diuretics, and oral vasodilators such as captopril. Preoperative digoxin levels and hypokalemia must be checked.

The consequences of chronic hypoxemia also need special consideration. Polycythemia increases oxygen-carrying capacity, but when the hematocrit rises to greater than 65%, the increased blood viscosity causes stasis and potential thrombosis, and it exacerbates tissue hypoxia. Dehydration must be avoided, and intravenous (IV) maintenance fluids should be begun while the patient is fasting preoperatively. Bleeding disturbances, common in cyanotic patients,⁴³ can result from thrombocytopenia, defective platelet aggregation, or clotting factor abnormalities.

MONITORING

The monitoring technique used for a patient should depend on the child's condition and the magnitude of the

planned procedure. For elective patients, noninvasive monitoring (electrocardiography, pulse oximetry, capnography, and a noninvasive blood pressure cuff) is placed before induction of anesthesia.

Monitoring by electrocardiogram (ECG) is essential, because significant rhythm disturbances can occur before and after bypass, particularly with VSD and outflow tract surgery. Myocardial ischemia occurs in pediatric patients mostly because of anatomic and shunt-related problems rather than coronary occlusive disease. Anomalous coronary arteries are associated with a number of complex defects, such as transposition of the great vessels and pulmonary atresia. Ischemia also occurs when coronary perfusion pressure falls, such as in hypoplastic left heart syndrome, truncus arteriosus, and critical aortic stenosis. Ventricular fibrillation can occur in these settings,⁴⁴ particularly on induction of anesthesia. Ischemia after bypass can result from air embolism or complications related to surgery, such as coronary reimplantation or coronary compression from conduits.

Pulse oximetry is an important monitor before and after bypass, as peripheral arterial saturation levels provide an indicator of pulmonary blood flow. The anesthesiologist needs to know the patient's baseline, prebypass peripheral O₂ saturation (SpO₂), and the anticipated level after surgery. Causes for lower than expected SpO₂, in patients with single-ventricle physiology, include pulmonary venous desaturation and intrapulmonary shunt, reduced pulmonary blood flow, and low cardiac output. For patients who have undergone a two-ventricle repair, a lower than expected SpO₂ is usually secondary to intrapulmonary shunting, because of parenchymal lung disease (e.g., atelectasis, edema) or restrictive pulmonary defects (e.g., pleural effusion, pneumothorax). After repair of a neonatal right ventricular outflow tract, such as TOF or truncus arteriosus, a small atrial communication is an advantage as it provides a R-L atrial shunt. Although these patients may be cyanotic immediately after surgery, the R-L shunt will decrease and the SpO₂ will rise as the compliance of the right ventricle improves.

Once the patient is anesthetized, a direct arterial line is placed percutaneously or through a cutdown. The site of the arterial line placement needs careful consideration. For example, patients undergoing placement of a modified Blalock-Taussig shunt from the subclavian or innominate artery should have the radial arterial line placed in the opposite extremity. Similarly, a right radial arterial line is necessary when repair of coarctation of the aorta is planned. The arch anatomy and possible aberrant arterial vessels are additional considerations when planning arterial access. Aortic root pressure monitoring may be necessary immediately after bypass if the peripheral arterial pressure is damped from hypothermia or low output state. Alternatively, a femoral artery catheter may provide a more reliable arterial waveform after CPB, particularly in newborns and infants, and it is often preferable to a peripheral arterial catheter. Care must be taken to prevent thrombus and distal limb ischemia, and femoral lines are best removed early once the patient is in stable condition. Caution is necessary when flushing arterial catheters in neonates and infants, because retrograde flow into the carotid arteries is possible.⁴⁵

Some centers routinely use central venous pressure monitoring for all cardiovascular surgery. Percutaneous central venous access enables titration of volume replacement and administration of vasoactive infusions before CPB, and during CPB it may provide a measure of the adequacy of cerebral venous drainage. Insertion of central venous catheters can be particularly difficult in pediatric patients, and central venous lines should be used with caution in neonates and infants because of the risk for infection and superior vena cava thrombosis, which can have significant sequelae if collateral veins are poorly developed. Transthoracic right and left atrial lines can be inserted by the surgeon for hemodynamic pressure monitoring and drug infusions after bypass.⁴⁶ They have a low complication rate. In addition, they can be left in situ for longer during postoperative recovery and then easily removed in the intensive care unit (ICU). Swan-Ganz catheters are rarely used in pediatric cardiac surgery because of anatomic limitations. Direct pulmonary artery catheters can be inserted by the surgeon to measure pulmonary saturations, to detect residual outflow tract gradients, and for thermodilution measurement of cardiac output. Oximetric catheters can be placed percutaneously for continuous measurement of mixed venous oxygen saturation (SvO₂) in the superior vena cava.⁴⁷

Ultrasound-guided technique has been shown to increase the overall success rate and reduce the incidence of traumatic complications associated with central venous cannulation.^{48,49} The anatomy of the central venous drainage should be known before attempting percutaneous cannulation. Heterotaxy syndrome and possible vein occlusions after previous catheterization are considerations, and if in doubt, ultrasound evaluation of the position and size of a central vein before cannulation is useful.

Neurologic Monitoring

Long-term neurodevelopmental impairment is common in newborns and infants undergoing repair for complex CHD. The etiologies of adverse neurologic sequelae in these patients are multifactorial and include prenatal, preoperative, intraoperative, and postoperative factors. Cerebral protection is a concern during bypass for congenital heart surgery, particularly if deep hypothermic arrest or low-flow bypass is used, and the importance of routine perioperative monitoring of the brain is increasingly recognized. Tympanic or nasopharyngeal temperature monitoring is used to assess the adequacy of cerebral cooling and rewarming. Continuous electroencephalographic monitoring,⁵⁰ transcranial Doppler,⁵¹ and frontal lobe near-infrared spectroscopy⁵²⁻⁵⁵ or cerebral oximetry can be used to evaluate cerebral blood flow velocity and perfusion, and O₂ delivery and extraction.

Intraoperative Echocardiography

Intraoperative transesophageal echocardiography (TEE) has achieved a role in intraoperative monitoring of patients undergoing repair of CHD.⁵⁶⁻⁵⁸ The development of smaller probes has allowed transesophageal monitoring to replace epicardial echocardiographic imaging in many cases, and it is performed routinely. Placement of a

transesophageal probe after the induction of anesthesia in the operating room enables reevaluation of the anatomy before surgical intervention, but, more importantly, the adequacy of surgical repair can be evaluated as soon as the patient is weaned from CPB. Interference of the probe with the airway and the effect on unstable hemodynamics before and after CPB must be evaluated carefully to avoid the complications of this monitoring.

ANESTHESIA

Risks of Anesthesia for Children with Congenital Heart Disease

The frequency of anesthesia-related cardiac arrests during general pediatric procedures has been reported to be between 1.4 and 4.6 per 10,000 anesthesia events, which is higher than that reported in adults. An American Society of Anesthesiologists (ASA) Physical Status of greater than 3 and younger age are risk factors for cardiac arrest during pediatric anesthesia, and a recent study demonstrated that patients with CHD are also at increased risk for cardiac arrest during cardiac surgery.⁵⁹ The incidence of anesthesia-related and procedure-related cardiac arrests was highest in neonates, and although it can be difficult to distinguish contributing factors in patients with underlying cardiac disease, there is a possible association between altered coronary perfusion and myocardial ischemia and cardiac arrest. Coronary perfusion can be reduced in patients who have uncontrolled or continuous runoff of blood flow from the systemic to pulmonary circulation, and therefore low aortic root diastolic pressure (e.g., patients with a diagnosis of truncus arteriosus, and patients with a ductus-dependent systemic circulation such as hypoplastic left heart syndrome and interruption of the aortic arch or coarctation with VSD). Patients with altered coronary blood flow, such as those with pulmonary atresia, an intact ventricular septum, and a right ventricle-dependent coronary circulation from fistulas, are also at increased risk for ischemia. These patients also have a limited ability to increase coronary blood flow when myocardial oxygen demand is increased, such as occurs secondary to tachycardia, increased contractility, or wall stress in response to a surgical stimulus if there is an inadequate depth of anesthesia to blunt a stress response.^{20,44,60} The importance of maintaining diastolic pressure and coronary perfusion is also important in the setting of severe left ventricle hypertrophy (e.g., Williams syndrome, hypertrophic cardiomyopathy).⁶¹

Induction of Anesthesia

Because of the potential for rapid and dramatic hemodynamic changes in young patients with CHD, especially infants, the complete preparation of anesthetic and monitoring equipment and required drugs is essential. Adequate assistance should be immediately available during the induction of anesthesia in case problems develop.

The choice of induction technique is influenced by the response to premedications, the parent-child-anesthesiologist relationship, and the anesthetic management

plan. In older patients who have minimal compromise of their cardiac reserve, the choice of induction techniques is large. Inhalation, intravenous, or intramuscular induction of anesthesia can be accomplished provided individual pathophysiologic limitations are understood. Cooperative children with an adequate cardiac reserve and difficult intravenous (IV) access or a morbid fear of needles can have anesthesia induced cautiously with inhaled anesthetics, even if the patients are cyanotic. An inhalation induction with sevoflurane is suitable for most infants and children, provided they have stable ventricular function and adequate hemodynamic reserve. This emphasizes the importance of preoperative evaluation when planning the induction technique. Inhalational induction can be used safely in patients with cyanotic heart disease, although uptake may be slower because of the R-L shunt.⁶² Saturations will generally increase, provided cardiac output is maintained and airway obstruction is avoided.

An IV induction should be used for all patients with severely limited hemodynamic reserve, particularly those with severe ventricular failure or pulmonary hypertension. When hemodynamic instability during induction is likely, starting an inotropic agent such as dobutamine or dopamine before induction should be considered. Although the stress of placing an IV line may be considerable for some patients, particularly those with difficult IV access after previous procedures, the IV line is preferable to the potential myocardial depression during an inhalation induction.

A combination of fentanyl (15 to 25 µg/kg) and rocuronium (1.0 mg/kg) provides hemodynamic stability and prompt airway control, and it attenuates the stress-induced increase in PVR associated with intubation. IV ketamine (1 to 3 mg/kg) is safe and reliable, providing hemodynamic stability and minimal increases in PVR. It is particularly useful in patients with severe CHF and ventricular outflow tract obstructions. Atropine (20 µg/kg) or glycopyrrolate (10 µg/kg) is traditionally given concurrently because of increased secretions. If IV access is difficult and stressful in infants, a combination 4 mg/kg of ketamine, 10 µg/kg of glycopyrrolate, and 2 mg/kg of suxamethonium intramuscularly allows prompt induction and airway control.

Etomidate is an anesthetic induction agent with minimal cardiovascular and respiratory depression,⁶³ and it is frequently used to induce anesthesia in patients with limited hemodynamic reserve. An IV dosage of 0.1 to 0.3 mg/kg induces rapid loss of consciousness with a duration of action of 3 to 5 minutes. Etomidate can be used as an alternative to the synthetic opioids for induction of anesthesia in patients with limited myocardial reserve.

Barbiturates and propofol can be used in patients with normal ventricular function. The principal hemodynamic effect of propofol in children with CHD is a decrease in systemic vascular resistance (SVR) and direct myocardial depression. In children with an intracardiac L-R shunt, this can result in changes in the Qp/Qs ratio, and it can lead to a low cardiac output state.⁶⁴ Patients with a R-L intracardiac shunt may experience a faster induction and loss of consciousness, and the dosage must be carefully

titrated to effect in these circumstances. Titrated dosages are suitable for short procedures, such as cardioversion or TEE. Midazolam (0.1 to 0.2 mg/kg) is also a useful adjunct during a narcotic induction, but it can cause hypotension in patients dependent on a high sympathetic drive.

Maintenance of Anesthesia

Anesthesia maintenance techniques depend on the patient's preoperative cardiorespiratory status, the pathophysiology of the underlying cardiac defect, the surgical procedure, the conduct of CPB, potential postoperative surgical problems, and the anticipated postoperative management. Once induction of anesthesia and control of the airway are accomplished and monitoring is adequate, anesthesia can be maintained with inhaled anesthetics or additional IV drugs as dictated by the response of each patient, intraoperative events, and postoperative plans.

Stress responses to pain and other noxious stimuli are profound in even the youngest neonates, regardless of postconception age.^{1,65} These hormonal and metabolic stress responses can be deleterious,⁶⁶ particularly in patients with marginal hemodynamic reserve. High-dose narcotic techniques provide hemodynamic stability and are commonly used to maintain anesthesia, with the choice of agent and dosage dependent on the planned procedure, the duration of bypass, and the anticipated postoperative management. Patients with good cardiac function undergoing relatively short bypass procedures, such as ASD closure, can be extubated in the operating room or soon after surgery. Fentanyl (10 to 20 µg/kg) in combination with isoflurane or sevoflurane is suitable before bypass. During CPB, awareness is a potential problem. Methods to prevent this vary, but isoflurane (1%) can be continued on the bypass machine or doses of midazolam might be given intermittently. After bypass, inhalational agents are titrated as required according to hemodynamic responses.

Stress Response

In general terms, the stress response is a systemic reaction to injury, with hemodynamic, endocrinologic, and immunologic effects (Box 110-3). Stress and adverse postoperative outcome have been closely linked in critically ill newborns and infants, which is not surprising because of the precarious balance of limited metabolic reserve and increased resting metabolic rate. Metabolic derangements, such as altered glucose homeostasis, metabolic acidosis, salt and water retention, and a catabolic state contributing to protein breakdown and lipolysis, are commonly seen in sick neonates and infants after major stress.⁶⁷ This complex of maladaptive processes may be associated with prolonged mechanical ventilation and ICU stay, as well as increased morbidity and mortality.

The neuroendocrine stress response is activated by afferent neuronal impulses from the site of injury, traveling via sensory nerves through the dorsal root of the spinal cord to the medulla and hypothalamus. Anesthesia can therefore have a substantial modulating effect on the

BOX 110-3 Systemic Response to Injury**AUTONOMIC NERVOUS SYSTEM ACTIVATION**

- Catechol release
- Hypertension, tachycardia, vasoconstriction

ENDOCRINE RESPONSE

- Anterior pituitary: ↑ ACTH, growth hormone
- Posterior pituitary: ↑ Vasopressin
- Adrenal cortex: ↑ Cortisol, aldosterone
- Pancreas: ↑ Glucagon, insulin resistance
- Thyroid: ↓/→ T_4/T_3

METABOLIC RESPONSE

- Protein catabolism
- Lipolysis
- Glycogenolysis/gluconeogenesis
- Hyperglycemia
- Salt and water retention

IMMUNOLOGIC RESPONSES

- Cytokine production
- Acute phase reaction
- Granulocytosis

ACTH, Adrenocorticotrophic hormone.

neuroendocrine pathways of the stress response by virtue of providing analgesia and loss of consciousness.

It is important to distinguish between suppression of the endocrine response and attenuation of hemodynamic responses to stress. Because of their direct effects on the myocardium and vascular tone, anesthetic agents can readily suppress the hemodynamic side effects of the endocrine stress response. The same is true when inotropic and vasoactive agents are administered during anesthesia. However, the postoperative consequences of the endocrine stress response—in particular, fluid retention and increased catabolism—remain unabated. Relying on hemodynamic variables to assess the level of stress is therefore often inaccurate. Metabolic indices such as hyperglycemia and hyperlactatemia are also indirect markers of stress, particularly as they are influenced by other factors such as fluid administration and cardiac output.

The effect of surgical stress has been particularly evaluated in neonates and infants undergoing cardiac surgery.^{66,68,69} A conclusion from these studies supported the notion that reducing the stress response with large-dose opioid anesthesia, and extending this into the immediate postoperative period, was important to reduce the morbidity and mortality associated with congenital heart surgery in neonates.

However, these studies were performed over a decade ago, and during the intervening period, there have been substantial changes in the perioperative management of children with heart disease as well as the management of cardiopulmonary bypass in general. With these changes, outcomes have improved considerably. In the early experience of bypass in neonates and infants, the use of high-dose opioid anesthesia to modulate the stress response was perceived to be one of the few clinical strategies available that was associated with demonstrable

improvement in morbidity and mortality.⁶⁸ More recently, it has been demonstrated that opioids do not in fact modify the endocrine or metabolic stress response initiated by CPB; despite this, mortality and morbidity continue to remain low.

Although the neonate may be more labile to changes in intravascular pressures, PVR, and cardiac output than older children, in fact the neonate is highly capable of coping with the acute phase of surgical stress. It is less common nowadays to see neonates in the immediate post-bypass period with extensive peripheral edema or anasarca and, along with that, impaired ventricular function, reactive pulmonary hypertension, and substantial alterations in lung compliance and airway resistance. One example is the incidence of postoperative pulmonary hypertensive events. Pulmonary hypertensive crisis was more common a decade or more ago in infants who had been exposed to weeks or months of high pulmonary pressure and flow, such as truncus arteriosus, complete atrioventricular canal defects, and transposition of the great arteries with ventricular septal defects. High-dose opioids were an important component of management for patients at risk for pulmonary hypertensive crises, but this occurs much less frequently nowadays when patients undergo an operation at an earlier age and are therefore less likely to have significant or irreversible changes in the pulmonary vascular bed. Therefore, changes in surgical practice, and in particular the timing of surgery, have meant that the longer-term pathophysiologic consequences of various defects are less apparent than they were 10 to 20 years ago. A strategy of high-dose opioid anesthesia to blunt the stress response may therefore be a less critical determinant of outcome.

This is not to say, however, that high-dose synthetic opioids are not necessary for neonatal cardiac surgery. Synthetic opioids are potent analgesics and provide hemodynamic stability because of their lack of negative inotropic or vasoactive properties. Because of the limited physiologic reserve, the pathophysiology of underlying cardiac defects, and the clinical consequences of the systemic inflammatory response to bypass in the neonates, using an anesthetic technique that has minimal hemodynamic side effects is clearly desirable.

The main aim is to provide an anesthetic that maintains hemodynamic stability and allows the anesthesia team to concentrate on all other aspects of the surgery, bypass, and post-CPB care. Sudden changes in hemodynamics before and after bypass may develop secondary to myocardial dysfunction, residual anatomic lesions, loss of sinus rhythm, changes in preload state, variable pulmonary vascular resistance, and alterations in mechanical ventilation, to mention a few. Using a high-dose opioid anesthesia technique allows the anesthesiologist to focus on an evolving hemodynamic picture without the distraction of side effects from anesthetic drugs.

DISCONTINUATION OF CARDIOPULMONARY BYPASS

The effects of prolonged CPB are in part related to the interactions of blood components with the extracorporeal

circuit, which cause a systemic inflammatory response. This is magnified in children because of the large bypass circuit surface area and priming volume relative to patient blood volume. The clinical consequences include increased interstitial fluid and generalized capillary leak, and potential multiorgan dysfunction. Total lung water is increased with an associated decrease in lung compliance and increase in the alveolar–arterial oxygen gradient. Myocardial edema results in impaired ventricular systolic and diastolic function. A secondary fall in cardiac output by 20% to 30% is common in neonates in the first 6 to 12 hours after surgery, contributing to decreased renal function and oliguria.⁷⁰ Sternal closure may need to be delayed because of mediastinal edema and associated cardiorespiratory compromise when closure is attempted. Ascites, hepatic congestion, and bowel edema may affect mechanical ventilation, cause a prolonged ileus, and delay feeding. A coagulopathy after CPB can contribute to delayed hemostasis.

An organized approach must be taken to weaning a patient from CPB so that a smooth transition is ensured. There should be communication between the surgeon and the anesthesiologist regarding anticipated difficulties. Blood volume is assessed by direct visualization of the heart and by monitoring right or left atrial filling pressures. When filling pressures are adequate, the patient is fully warmed, acid–base status is normalized, heart rate is adequate, adequate minute ventilation is established, and sinus rhythm is achieved, the drainage from the venous cannula is retarded, flow is reduced gradually, and the patient is weaned from CPB. The need for vasopressor and inotropic support during weaning from bypass is determined by close observation of the heart during the rewarming phase.

Optimal ventricular filling pressures are estimated by referring to filling pressures from preoperative catheterization data, the appearance of the heart, and infusion of small increments of volume while watching filling and systemic arterial pressures. The direct measurement of oxygen saturations from chambers of the heart enables calculations of a residual intracardiac shunt immediately after surgery, and direct pressure measurements across systemic and pulmonary outflow tracts enables detection of significant residual obstruction. TEE can be used to evaluate ventricular function and to assess surgical repair.

After discontinuing bypass, and despite full rewarming on bypass, rebound mild hypothermia often develops in neonates and infants. Active measures to decrease radiant and evaporative losses are necessary because of the increased metabolic stress, pulmonary vasoreactivity, coagulopathy, and potential for dysrhythmias associated with hypothermia. However, hyperthermia must also be actively avoided because of the associated increase in metabolic rate and the potential for ongoing neurologic injury, particularly when myocardial function may be depressed and cerebral autoregulation impaired.⁷¹

Hemostasis may be difficult to obtain if bypass has been prolonged and if there are extensive, high-pressure (often concealed) suture lines. Prompt management and meticulous control of surgical bleeding is essential to prevent the complications associated with a massive

transfusion. Besides hemodilution of coagulation factors and platelets, complex surgery with long bypass times increases endothelial injury and exposure to the non-endothelialized surface of the pump circuit, thereby stimulating the intrinsic pathway, and thus platelet activation and aggregation. Early transfusion of platelets and clotting factors, either as cryoprecipitate or fresh-frozen plasma, is recommended. Pharmacologic approaches to reduce bleeding and transfusion in cardiac surgical patients include the use of lysine analogue antifibrinolytics, which have been demonstrated to reduce blood loss and transfusion requirements after cardiac surgery.⁷² The optimal doses and target plasma level of these agents have not been established, but typically aminocaproic acid is administered as a 75-mg/kg bolus to the patient, a 75-mg/kg bolus to the CPB pump prime, and a continuous infusion of 75 mg/kg/hr. Recently it was suggested that low plasma levels (20 µg/mL) of tranexamic acid would be obtained for children between 5 and 40 kg with a 6.4-mg/kg bolus followed by a continuous infusion of 2.0 to 3.1 mg/kg/hr (larger infusion rate in smaller patients).⁷³ At Boston Children's Hospital, we typically administer a 100-mg/kg bolus to the patient, a 100-mg/kg bolus to the CPB pump prime, and a continuous infusion of 10 mg/kg/hr in neonates, infants, and children weighing less than 20 kg.

The serine protease inhibitor aprotinin was effective⁷⁴ but it has been withdrawn from clinical use because of concerns for possible increase in mortality and end-organ damage after cardiac surgery in the adult.^{75–78} Recombinant factor VIIa seems to effectively and immediately reduce excessive or life-threatening nonsurgical bleeding that is unresponsive to standard hemostatic therapy, but caution is required because of an increased risk for thromboembolic complications, such as graft occlusion, stroke, and myocardial infarction.^{79–81} In addition, administration of rFVIIa should not halt efforts to find and remedy all sources of medical and surgical bleeding.

POSTOPERATIVE MANAGEMENT

The optimal postoperative management of patients with CHD requires a multidisciplinary approach, with a thorough understanding of the precise anatomic diagnosis, pathophysiology, and details of the surgical and CPB technique. For most patients, postoperative recovery is uncomplicated, and, in general, when the patient's clinical progress or postoperative cardiorespiratory function does not follow the expected course, myocardial function must be evaluated and possible residual defects must be investigated with echocardiography, cardiac catheterization, or both.

Analgesia

The assessment of adequate analgesia in children can be difficult, particularly when they are paralyzed and ventilated. Primarily, autonomic signs such as hypertension, tachycardia, pupillary size, and diaphoresis are used. If not paralyzed, children will grimace and withdraw from a painful stimulus, and if they are breathing

spontaneously, changes in respiratory pattern may be evident, such as tachypnea, grunting, and splinting of the chest wall.

However, changes in autonomic signs reflect not only pain. Other causes include awareness as patients emerge from anesthesia and sedation, fever, hypoxemia, hypercapnia, changes in vasoactive drug infusions, and seizures. If not diagnosed correctly, patients may receive additional opioid or benzodiazepine doses when hypertensive and tachycardic, which will only contribute to tolerance and possible withdrawal symptoms later.

Sedatives

Chloral hydrate is commonly used to sedate children before medical procedures and imaging studies.⁸² It can be administered orally or rectally in a dose ranging from 25 to 50 mg/kg (maximum dosage, 1 g), with an onset of action within 15 to 30 minutes and a duration of action 2 to 4 hours. Chloral hydrate should be used to promote intermittent sedation in the ICU and not be prescribed as a repetitive scheduled medication.⁸³ Administered intermittently, it can be used to supplement benzodiazepines and opioids, it can assist sedation during drug withdrawal, and it is useful as a nocturnal hypnotic when trying to establish normal sleep cycles.

Benzodiazepines are the most commonly used sedatives in the ICU because of their anxiolytic, hypnotic, and amnesic properties. Although they provide excellent conscious sedation, they can cause dose-dependent respiratory depression and result in significant hypotension in patients with limited hemodynamic reserve. After long-term administration, tolerance and withdrawal symptoms are common.

Opioid analgesics are the mainstay of pain management in the ICU. They can also provide sedation for patients who require mechanical ventilation and for blunt hemodynamic responses to procedures such as endotracheal tube suctioning. Intermittent dosing of opioids can provide effective analgesia and sedation after surgery, although periods of oversedation and undermedication can occur because of peaks and troughs in drug levels. A continuous infusion is therefore advantageous.

Morphine, in intermittent IV doses of 0.05 to 0.1 mg/kg or as a continuous infusion at 50 to 100 µg/kg/hr, provides excellent postoperative analgesia for most patients. The sedative property of morphine is an advantage over the synthetic opioids; however, histamine release can cause systemic vasodilation and an increase in pulmonary artery pressure.

The synthetic opioids fentanyl, sufentanil, and alfentanil have a shorter duration of action than morphine and do not cause histamine release; therefore, they produce less vasodilation and hypotension. Fentanyl is commonly prescribed after cardiac surgery. It blocks the stress response in a dose-related fashion while maintaining both systemic and pulmonary hemodynamic stability.^{20,84} Chest wall rigidity is an idiosyncratic and dosage-related reaction that can occur with a rapid bolus in newborns and older children. A continuous infusion of fentanyl (5 to 10 µg/kg/hr) provides analgesia after surgery, although it often needs to be combined with a benzodiazepine to

maintain sedation. High variability between children exists in fentanyl clearance, making titration of an infusion difficult. The experience with extracorporeal membrane oxygenation indicates that tolerance to and dependence on a fentanyl infusion develops rapidly, and significant increases in infusion rate may be required.

The development of tolerance is dose and time related, and it is a particular problem after cardiac surgery in patients who received a high-dose opioid technique to maintain anesthesia. Physical dependence with withdrawal symptoms (e.g., dysphoria, fussiness, crying, agitation, tachypnea, tachycardia, diaphoresis, feeding intolerance) may be seen in children and can be managed by gradually tapering the opioid dosage or administering a longer-acting opioid, such as methadone. Methadone has a potency similar to that of morphine, with the advantage of a prolonged elimination half-life of 18 to 24 hours. It can be administered IV and is absorbed well orally.

Alternative methods of opioid delivery that are often effective after cardiac surgery include patient-controlled analgesia and epidural opioids, as a bolus or by continuous infusion. Patients receiving epidural opioids must be monitored closely for potential respiratory depression, and side effects include pruritus, nausea, vomiting, and urinary retention.

Newer agents such as dexmedetomidine (an α_2 -adrenergic agonist) are being used increasingly for sedation and analgesia in pediatric patients because of their favorable sedative and anxiolytic properties combined with their limited effect on respiratory function. Dexmedetomidine is used during general anesthesia or for conscious sedation, and for sedation in the critical care unit, and it also has a potential role in preventing emergence delirium and helping with narcotic withdrawal.⁸⁵ Because of its adverse cardiovascular effects, including hypotension and bradycardia, it should be used with caution in children with CHD.⁸⁶

In children who are difficult to sedate, and in those who have often received significant doses of opioids or benzodiazepines for sedation, a low-dose infusion of propofol (30 to 100 µg/mg/min) can be used. It is not approved for sedation in children in the intensive care setting, but it can be highly effective for a short period (up to 6 to 8 hours) to assist with weaning from mechanical ventilation and, in effect, with detoxification from previous sedatives to which they have become tolerant. Because of potential hemodynamic complications, propofol must be used with caution in patients with limited hemodynamic reserve, and the dosage and duration of use must be strictly limited because of the potential yet rare complication of propofol infusion syndrome.⁸⁷

Assessment of Cardiac Output

A complete evaluation of cardiac output (CO) should be the initial focus of management in the ICU after cardiac surgery. Low CO is associated with longer duration of mechanical ventilatory support, ICU stay, and hospital stay, all of which can increase the risk for morbidity or mortality. Data from physical examination, routine laboratory testing, and bedside hemodynamic monitoring are all considered during the initial assessment.

Postoperative patients with low CO can exhibit a variety of abnormalities on physical examination or on bedside monitoring and laboratory values (Table 110-2). The mechanisms underlying low CO in a specific patient can be related to a number of factors, including residual or unrecognized anatomic cardiovascular defects, type of surgical procedure (e.g., right ventricular [RV] dysfunction after right ventriculotomy), surgical complications (e.g., compromised coronary artery perfusion), dysrhythmia (supraventricular or ventricular) or loss of atrioventricular conduction, low preload (ongoing bleeding), high afterload (e.g., systemic vasoconstriction related to CPB), metabolic derangement (e.g., hypocalcemia, hypomagnesemia), and pulmonary hypertension (primarily affecting RV function).

In neonates and infants, a fall in CO of approximately 30% within 9 to 12 hours after surgery can be anticipated even when the surgical repair is excellent. This pattern is best documented for neonates with d-transposition of the great arteries,⁷⁰ but it also occurs in neonates undergoing complete repair of TOF or truncus arteriosus. Pharmacologic support of the myocardium may be necessary and anticipated to mitigate the effects of decreased cardiac

index in these patients, including an increase in inotropic support with dopamine or the use of drugs such as milrinone to lower afterload.

Strategies for treating the patient with a low CO state should focus on optimizing the balance between oxygen delivery and demand. In a low CO state, oxygen and metabolic demand should be minimized by maintaining an adequate depth of analgesia and sedation, including chemical paralysis to avoid movement and reduce muscle tone and oxygen debt. Strict avoidance of hyperthermia from any cause is essential, and in some circumstances mild hypothermia may be preferable, although the effect of peripheral vasoconstriction and increase in SVR could have an adverse effect on myocardial wall stress and oxygen requirement.

Oxygen delivery can be increased by optimizing O₂ content (hemoglobin and FiO₂) and by a combination of the factors contributing to CO (i.e., contractility, preload, afterload, and heart rate). Because decreased myocardial contractility occurs frequently after reparative or palliative surgery with CPB, pharmacologic enhancement of contractility is used commonly in the ICU. Before initiating treatment with an inotrope, the volume status, serum ionized Ca²⁺ level, and cardiac rhythm should be evaluated. Dopamine is often the initial treatment for hypotension; it increases contractility by elevating intracellular Ca²⁺, from direct binding to myocyte β_1 -adrenoceptors, and by increasing norepinephrine levels. At a dose of greater than 5 $\mu\text{g/kg/min}$, dopamine should be infused through a central venous catheter to avoid superficial tissue damage should extravasation occur. The dose is titrated to achieve the desired systemic blood pressure, although some patients, especially older children and adults, may develop an undesirable dose-dependent tachycardia. Dobutamine may be less effective than dopamine as a single agent in the treatment of moderate hypotension because it reduces SVR.⁸⁸

If a patient does not respond adequately to dopamine (up to 10 $\mu\text{g/kg/min}$) and has persistent signs of a low CO state, including poor extremity perfusion, hypotension (>30% decrease in mean arterial blood pressure for age), tachycardia, elevated atrial filling pressure, oliguria, and lactic acidemia, treatment with epinephrine should be considered. Epinephrine can be added to dopamine at a starting dose of 0.05 to 0.1 $\mu\text{g/kg/min}$, with subsequent titration of the infusion to achieve the target systemic blood pressure. At high doses (i.e., $\geq 0.5 \mu\text{g/kg/min}$), epinephrine can produce significant renal and peripheral vasoconstriction plus significant tachycardia, and those who require persistent doses of epinephrine greater than 0.3 to 0.5 $\mu\text{g/kg/min}$ should be evaluated for the possibility of mechanical circulatory support. Norepinephrine at doses of 0.01 to 0.2 $\mu\text{g/kg/min}$ can also be considered in patients with severe hypotension and low SVR (e.g., “warm” or “distributive” shock), inadequate coronary artery perfusion, or inadequate pulmonary blood flow with a systemic-to-pulmonary artery shunt. A combination of low-dose epinephrine (e.g., <0.1 $\mu\text{g/kg/min}$) or dopamine with an IV afterload-reducing agent such as milrinone is frequently beneficial to support patients with significant ventricular dysfunction accompanied by elevated afterload. There can be a decrease in

TABLE 110-2 Manifestations of Low Cardiac Output after Cardiac Surgery

By Examination

Core hyperthermia
Tachycardia or bradycardia
Hypotension (for age and weight)
Narrow pulse pressure
Decreased peripheral perfusion
Hepatomegaly
Ascites
Oliguria

By Monitoring

Arterial waveform Blunted or dampened upstroke
Narrow pulse pressure
RAp or CVP, LAP Low intravascular fluid status
(decreased) Inadequate preload
RAp or CVP, LAP Poor ventricular function
(increased) Residual volume load
Residual outflow tract obstruction
Ischemia
Loss of normal sinus rhythm
Atrioventricular valve regurgitation/
stenosis
Tamponade

By Laboratory and Radiographic Results

SVO₂ Decreased with an increased
arteriovenous O₂ difference
(>25%-30%)
Acid-base balance Metabolic acidosis with increased
anion gap
Increased arterial lactate
Elevated blood urea nitrogen and
creatinine
Increased liver transaminases
Chest radiography Cardiac enlargement
Pulmonary edema
Pleural effusion

CVP, Central venous pressure; LAP, left atrial pressure;
RAp, right atrial pressure.

responsiveness to increasing dosages of catecholamines over time, and vasopressin, at a dose of 10 to 120 mU/kg/hr, is a potent vasopressor, which could help to improve the hemodynamics in advanced shock without compromising cardiac function.⁸⁹

Patients with the clinical features of relative adrenal insufficiency can benefit from stress steroid therapy. This insufficiency is primarily a clinical finding of poor vascular tone with persistent hypotension and volume requirement, refractory to increasing inotrope and vasopressor support. The serum cortisol level may be low or show a limited response to adrenocorticotrophic hormone stimulation testing, but the ranges of normal have not been established for pediatric patients, in particular for newborns and infants after cardiac surgery, and there is no consistent correlation between serum cortisol level and low cardiac output state. Nevertheless, stress doses of hydrocortisone (50 mg/m²/day) have been demonstrated to increase systemic blood pressure and lower inotrope scores, although they have not been definitively demonstrated to improve eventual survival.⁹⁰⁻⁹² The increased risk for infection and poor wound healing dictates that stress dosing of steroids should be for a brief period (3 to 5 days) rather than continuing with a long taper.

Hypothyroidism is another cause for persistent low cardiac output state after cardiac surgery. Triiodothyronine (T₃) levels have been demonstrated to be low after CPB, and they may remain low for up to 48 hours after surgery, particularly if a sick euthyroid state develops and there is decreased conversion of thyroxine to the active T₃ in peripheral tissues. An infusion of T₃ at a dose of 0.05 µg/kg/hr has been shown to improve blood pressure and a composite score of recovery after cardiac surgery in newborns and infants.^{93,94}

If the rhythm cannot be determined with certainty from a surface 12- or 15-lead ECG, then temporary epicardial atrial pacing wires, if present, can be used with the limb leads to generate an atrial ECG.⁹⁵ Temporary epicardial atrial or ventricular pacing wires (or both) are routinely placed in most patients to allow mechanical pacing should sinus node dysfunction or heart block occur in the early postoperative period. Because atrial wires are applied directly to the atrial epicardium, the electrical signal generated by atrial depolarization is significantly larger and thus easier to distinguish than the P wave on a surface ECG. Sinus tachycardia, which is common and often secondary to medications (e.g., sympathomimetics), pain and anxiety, or diminished ventricular function, must be distinguished from a supraventricular, ventricular, or junctional tachycardia. Heart block can diminish cardiac output by producing either bradycardia or loss of atrioventricular synchrony, or both. Complete heart block may be transient in approximately a third of cases, but if it persists beyond postoperative day 9 or 10, it is unlikely to resolve, and a permanent pacemaker is indicated.⁹⁶

Elevated afterload in both the pulmonary and systemic circulations frequently follows surgery with CPB.⁹⁷ An increase in systemic afterload from elevated SVR may significantly increase myocardial work and reduce end-organ perfusion. Treatment of elevated SVR includes recognizing and improving conditions that exacerbate

vasoconstriction (e.g., pain and hypothermia) and administering a vasodilating agent such as a phosphodiesterase inhibitor milrinone or a NO donor (e.g., nitroprusside).⁹⁸⁻¹⁰²

Fluid Management

Fluid management in the immediate postoperative period is critical because of the inflammatory response to CPB and significant increase in total body water that often occurs. Capillary leak and interstitial fluid accumulation continue after surgery in neonates and infants, often necessitating ongoing volume replacement. A fall in cardiac output and increased antidiuretic hormone secretion contribute to delayed water clearance and potential pre-renal dysfunction. An elevated CVP will result in elevated renal venous pressure, further compromising renal perfusion particularly in the setting of diminished arterial blood pressure. During bypass, optimizing the circuit prime hematocrit and oncotic pressure, attenuating the inflammatory response with steroids, and using modified ultrafiltration techniques may help to limit interstitial fluid accumulation.¹⁰³⁻¹⁰⁵ During the first 24 hours after surgery, maintenance fluids should be restricted to 50% of full maintenance, and volume replacement should be titrated to appropriate filling pressures and hemodynamic response.

Oliguria in the first 24 hours after complex surgery and CPB is common. Cardiac output should be enhanced, with volume replacement and vasoactive drug infusions if necessary, before diuretics can be effective. In addition, low-dose dopamine (3 µg/kg/min) has the advantage of redistributing renal blood flow to promote diuresis. Fenoldopam mesylate, a selective dopamine (DA₁) receptor agonist that causes smooth muscle relaxation, leading to both renal and splanchnic vasodilation, has been used to provide renal protection during periods of ischemia and hypoxia such as during hypothermic CPB.¹⁰⁶ At a dose of 0.1 to 0.5 µg/kg/min, it may also have a role in postoperative ICU management to enhance renal perfusion by decreasing renal vascular resistance.¹⁰⁷ It should be recognized that fenoldopam has a hemodynamic profile similar to sodium nitroprusside and as such the advantages of selective renal vasodilation may be offset by systemic hypotension.

Furosemide (1 to 2 mg/kg IV every 8 hours) is a commonly prescribed loop diuretic that is excreted into the renal tubular system before producing diuresis; therefore, low cardiac output reduces its efficacy. Bolus dosing may result in a significant diuresis over a short period, thereby causing changes in intravascular volume and possibly hypotension. A continuous infusion of 0.2 to 0.3 mg/kg/hr after an initial IV bolus of 1 mg/kg often provides a consistent and sustained diuresis without sudden fluid shifts. Chlorothiazide (10 mg/kg IV or orally every 12 hours) is also an effective diuretic, particularly when used in conjunction with loop diuretics.

Peritoneal dialysis, hemodialysis, and continuous venovenous hemofiltration provide alternative renal replacement therapy in patients with persistent oliguria and renal failure.^{108,109} In addition to enabling water and solute clearance, nutritional support can be increased. A

peritoneal dialysis catheter can be placed into the peritoneal cavity at the completion of surgery or later in the ICU. This can be done in the ICU because of the need for renal support, to reduce intra-abdominal pressure from ascites that may be compromising mechanical ventilation, and to improve fluid management to allow administration of parenteral nutrition. Drainage may be significant in the immediate postoperative period as third-space fluid losses continue, and replacement with albumin or fresh-frozen plasma (or both) may be necessary to treat hypovolemia and hypoproteinemia. To enhance fluid excretion if oliguria persists, low-volume peritoneal dialysis may be effective, although a persistent communication between the peritoneum, mediastinum, and pleural cavities after surgery will limit the effectiveness of peritoneal dialysis and is a relative contraindication.

Pulmonary Function and Mechanical Ventilation

Altered respiratory mechanics and positive-pressure ventilation may have a significant influence on hemodynamics after congenital heart surgery. Although changes in alveolar O_2 (PAO_2), $PaCO_2$, and pH significantly affect PVR, the mean airway pressure and changes in lung volume during positive-pressure ventilation also affect PVR, preload, and ventricular afterload. Therefore, the approach to mechanical ventilation should be directed not only at achieving a desired gas exchange but also at addressing the potential cardiorespiratory interactions of positive-pressure ventilation. This is particularly critical during weaning.

Altered lung mechanics and ventilation-perfusion abnormalities are common problems in the immediate postoperative period.^{110,111} Besides preoperative problems resulting from increased Q_p/Q_s , additional considerations include the surgical incision and lung retraction, increased lung water after CPB, possible pulmonary reperfusion injury, surfactant depletion, and restrictive defects from atelectasis and pleural effusions. In general, neonates and infants, with their limited physiologic reserve, should not be weaned from mechanical ventilation until hemodynamically stable, and until factors contributing to an increase in intrapulmonary shunt and altered respiratory mechanics have improved.

An increase in mean intrathoracic pressure during positive-pressure ventilation decreases preload to both pulmonary and systemic ventricles, but it has opposing effects on afterload to the ventricles^{112,113} (i.e., it decreases afterload to the systemic ventricle but increases afterload on the pulmonary ventricle). Changes in lung volume have a major effect on PVR, which is lowest at FRC, whereas hypoinflation or hyperinflation can result in a significant increase in PVR.¹¹⁴ An increase in PVR increases the afterload or wall stress on the right ventricle, compromising RV function and contributing to decreased LV compliance secondary to interventricular septal shift. In addition to low cardiac output, signs of RV dysfunction (e.g., tricuspid regurgitation, hepatomegaly, ascites, pleural effusions) may be observed. An increase in mean intrathoracic pressure increases the afterload on

the RV from direct compression of extra-alveolar and alveolar pulmonary vessels. Patients with normal RV compliance, and without residual volume load or pressure load on the ventricle after surgery, usually show little change in RV function from the alteration in preload and afterload that occurs with positive-pressure ventilation. However, these effects can be magnified in patients with restrictive RV physiology or poor diastolic function after congenital heart surgery, especially in neonates who have required a right ventriculotomy for repair of TOF, pulmonary atresia, or truncus arteriosus, and in patients with concentric RV hypertrophy.

The systemic arteries are under higher pressure and not exposed to radial traction effects during inflation or deflation of the lungs. Therefore, changes in lung volume will affect LV preload, but the effect on afterload depends on changes in intrathoracic pressure alone rather than changes in lung volume. Wall stress is directly proportional to the transmural LV pressure—that is, to the difference between the intracavity LV pressure and surrounding intrathoracic pressure. An increase in intrathoracic pressure, as occurs during positive-pressure ventilation, therefore reduces the transmural gradient and wall stress on the left ventricle. This is one explanation for the beneficial effect of positive-pressure ventilation and PEEP in patients with LV failure.¹¹⁵ In addition, patients with LV dysfunction may have impaired pulmonary mechanics secondary to increased lung water, decreased lung compliance, and increased airway resistance. The work of breathing is increased and neonates and infants in particular can fatigue early because of limited respiratory reserve. A significant proportion of total body oxygen consumption is directed at the increased work of breathing in neonates and infants with LV dysfunction, contributing to poor feeding and failure to thrive. Therefore, positive-pressure ventilation has an additional benefit in patients with significant volume overload and systemic ventricular dysfunction by reducing the work of breathing and oxygen demand.

Weaning from positive-pressure ventilation can be difficult in patients with persistent systemic ventricular dysfunction. During spontaneous respiration, the transmural pressure across the systemic ventricle is increased, and this sudden increase in wall stress can contribute to pulmonary edema and low cardiac output state. It is therefore often beneficial to continue vasoactive support during weaning and extubation if there is concern for ventricular dysfunction.

Weaning from Mechanical Ventilation

After congenital cardiac surgery, most patients wean without difficulty if they have had no complications with repair or CPB, but some patients with borderline cardiac function and residual volume overload may require prolonged mechanical ventilation and a slower weaning process. Weaning is a dynamic process, and continued reevaluation is necessary.

The method of weaning varies among patients. Most patients can be weaned using either a volume- or pressure-limited mode by simply decreasing the intermittent mandatory ventilation rate. Guided by physical examination,

BOX 110-4 Factors Contributing to the Inability to Wean from Mechanical Ventilation after Congenital Heart Surgery

RESIDUAL CARDIAC DEFECTS

- Volume load
- Pressure load
- Ventricular dysfunction
- Dysrhythmias

PULMONARY RESTRICTIVE DEFECTS

- Pulmonary edema
- Pleural effusion
- Atelectasis
- Ascites
- Chest wall edema
- Phrenic nerve injury

AIRWAY

- Edema or subglottic stenosis
- Retained secretions
- Vocal cord injury
- Extrinsic compression
- Bronchomalacia

METABOLIC

- Inadequate nutrition
- Diuretic therapy (contraction alkalosis)
- Sepsis

hemodynamic criteria, respiratory pattern, and arterial blood gas measurements, the mechanical ventilator rate is gradually reduced. Patients with limited hemodynamic and respiratory reserve may demonstrate tachypnea, diaphoresis, and shallow tidal volumes as they struggle to breathe spontaneously against the resistance of the endotracheal tube. The addition of pressure- or flow-triggered pressure support of 10 to 15 cm H₂O above PEEP is often beneficial in reducing the work of breathing.

Numerous factors contribute to the inability to wean from mechanical ventilation after congenital heart surgery (Box 110-4). In general, however, residual cardiac defects after surgery causing either a volume or pressure load must be excluded by echocardiography or cardiac catheterization if a patient fails to wean from ventilation as expected.

Indications for Early Tracheal Extubation

The heterogeneous nature of congenital cardiac defects and wide age range make it difficult to establish rigid protocols for cardiovascular and respiratory management after surgery. Each patient must be viewed individually and managed according to preoperative condition and stability, surgeon preference, any surgical or CPB-related complications, and postoperative cardiorespiratory status (Box 110-5). In keeping with the strategy of early surgical intervention and repair to promote improved longer-term growth and development, and with less emphasis on

BOX 110-5 Considerations for Planned Early Extubation after Congenital Heart Surgery

PATIENT FACTORS

- Limited cardiorespiratory reserve
- Pathophysiology of specific congenital heart defects
- Timing of surgery and preoperative management

ANESTHETIC FACTORS

- Premedication
- Drug distribution and maintenance of anesthesia on cardiopulmonary bypass
- Postoperative analgesia requirements

SURGICAL FACTORS

- Extent and complexity of surgery
- Residual defects
- Risks for bleeding and protection of suture lines

CONDUCT OF CARDIOPULMONARY BYPASS

- Degree of hypothermia
- Level of hemodilution
- Myocardial protection
- Modulation of the inflammatory response and reperfusion injury

POSTOPERATIVE MANAGEMENT

- Myocardial reserve
- Cardiorespiratory interactions
- Neurologic recovery
- Analgesia management

complete suppression of the stress response in the immediate postoperative period, it is possible to move patients expeditiously through the ICU in a safe yet efficient fashion.

Patients undergoing selected non-CPB or closed cardiac surgery and thoracic procedures are usually suitable for early tracheal extubation. This includes infants and older children undergoing procedures such as patent ductus arteriosus and vascular ring ligation. Infants and older children undergoing repair of coarctation of the aorta may benefit from early extubation to avoid the hypertension and tachycardia that often accompanies a slow wean from mechanical ventilation in the ICU after surgery. The risk for rebound hypertension and need to protect high-pressure surgical suture lines often dictates early blood pressure control with vasodilating and β -blocking drugs. In addition, mild-to-moderate hypothermia is often deliberately induced during surgery in an effort to optimize spinal cord protection while the aorta is cross-clamped, and tracheal extubation should be delayed until patients are normothermic.

In our experience, neonates and infants who require surgical modification of pulmonary blood flow, either by placement of a pulmonary artery band or creation of a systemic-to-pulmonary artery shunt, are not suitable for early extubation management protocols. We routinely continue mechanical ventilation and deep sedation for at least the first postoperative night until cardiorespiratory stability is attained.

Children undergoing relatively short bypass procedures using mild-to-moderate hypothermia, such as ASD repair, small VSD closure, and right ventricle-to-pulmonary artery conduit replacement, are often suitable for weaning and extubation in the operating room or early after ICU admission. These patients generally have a stable preoperative clinical status, demonstrate few complications related to CPB, and have an uncomplicated postoperative course.¹¹⁶

Infants who are in stable clinical condition before surgery and who are undergoing a complete repair using moderate-to-deep hypothermia on CPB, such as those undergoing closure of a large VSD, complete atrioventricular canal defect, or TOF, are often suitable for early extubation in the first 6 to 12 hours after surgery, provided they have stable cardiac output, stable gas exchange, and no surgical complications such as bleeding. Nevertheless, if there has been a large volume load on the ventricle before surgery or a labile pulmonary vascular resistance secondary to increased pulmonary blood flow, cautious management should be guided by hemodynamic and respiratory function as patients begin to emerge from sedation.

Infants and older children undergoing some types of LV outflow tract repair, including subaortic stenosis repair with the Konno operation or subaortic membrane resection, and aortic valvuloplasty or replacement, usually have well-preserved and often hyperdynamic ventricular systolic function. Hypertension and tachycardia are frequently a management concern in these patients in the immediate postoperative period. Not only will these factors increase the risk for disruption of suture lines, but the increased myocardial work can contribute to ischemia and increase the likelihood for ventricular tachyarrhythmias. This is especially a concern during emergence from anesthesia and sedation. Provided ventricular function is stable, hemostasis has been secured, and there are no concerns for ventricular tachyarrhythmias, it is often preferable for these patients to be extubated early after surgery (6 to 12 hours), rather than undergoing a more prolonged weaning process. The combination of esmolol and sodium nitroprusside is useful for controlling blood and reflex increases in contractility in patients with increased LV mass following procedures to relieve LVOTO. This combination prevents the development of tachycardia and diastolic hypotension that potentially compromises subendocardial perfusion in patients with LVH.

After creation of a cavopulmonary connection, such as a bidirectional Glenn shunt or a modified Fontan procedure, patients usually benefit from early tracheal extubation. Effective pulmonary blood flow is enhanced during spontaneous ventilation because of the lower mean intrathoracic pressure, but despite this goal, these patients should be weaned only after hemodynamic stability is achieved. After a bidirectional Glenn procedure, it is usually possible to extubate the trachea within 12 hours after surgery.

After the modified Fontan procedure, patients can also typically be weaned and extubated within 12 hours of surgery. In the current surgical era of almost routine fenestration of the right atrial baffle, the arterial oxygen saturation should be in the range of 80% to 90% after

surgery. Provided the patient is well perfused, has a transpulmonary gradient of 5 to 10 mm Hg, does not have an acidosis or persistent large volume requirement, transfer from the ICU within 2 to 3 days of surgery can be accomplished.

The response to surgery and bypass can vary considerably between neonates and is often unpredictable. At Boston Children's Hospital, neonates undergoing two-ventricle repairs are usually managed with sedation or paralysis, or both, in the immediate postoperative period until hemodynamic and respiratory stability has been attained, although there are clear differences depending on diagnosis and procedure. For example, after procedures such as an uncomplicated arterial switch operation for d-transposition of the great arteries, or repair of an interrupted aortic arch with VSD closure, many neonates are sufficiently stable to start to wean from mechanical ventilation and be extubated by the first or second postoperative day.

On the other hand, neonates who have undergone a right ventriculotomy, such as after neonatal repair of TOF or truncus arteriosus, commonly demonstrate restrictive RV physiology in the immediate postoperative period. A low cardiac output state with increased right-sided filling pressure may be evident, and continuing sedation and paralysis is often necessary for the first 48 to 72 hours until diastolic function improves.

Neonates undergoing a Norwood-type or a Sano procedure for hypoplastic left heart syndrome or other forms of single ventricle with aortic arch obstruction, can pose considerable management problems in the immediate postoperative period. This is one group of patients in whom sedation and paralysis should be continued initially after surgery to minimize the stress response and any imbalance between oxygen supply and demand until a stable circulation and gas exchange has been achieved. Inotrope and vasoactive support is usually required, often combined with afterload reduction to reduce myocardial work and improve systemic perfusion. Volume replacement to maintain preload is essential, and monitoring mixed venous O₂ saturation as an indicator of cardiac output is beneficial.

Discharge

The cost of intensive care medicine is high. As the mortality and morbidity associated with congenital cardiac surgery have declined, length of ICU stay, total hospital stay, and cost effectiveness have become important outcome variables. The timing of discharge from the ICU is therefore an important management decision. For the majority of patients who have a stable hemodynamic and respiratory status, the decision to transfer out of the ICU is not difficult. The function of all organ systems should be assessed and considered in this decision, although the focus will be on cardiovascular and respiratory function. In addition to poor cardiac output and residual anatomic lesions, a variety of noncardiac problems can complicate recovery and prolong ICU stay (Box 110-6). This decision should be multidisciplinary, with particular attention paid to nursing availability and experience, and the availability of adequate monitoring.

BOX 110-6 Criteria for Intensive Care Unit Discharge

CARDIOVASCULAR

- Stable blood pressure and systemic perfusion without requiring intravenous vasoactive support
- Invasive intravascular monitoring not indicated
- Stable cardiac rhythm (usually sinus) and no need for external pacing using temporary wires

RESPIRATORY

- Adequate ventilation rate and pattern, no signs of airway obstruction, and effective cough
- Appropriate oxygenation (according to physiology after surgery)
- No restrictive pulmonary defects that would limit ventilation or oxygenation, including atelectasis, pneumothorax (after chest tube removal), or pleural effusion
- Neurologic status adequate to protect airway

FLUID AND METABOLISM

- Afebrile
- Advancing on caloric requirements with stable glucose levels
- Even fluid balance with stable diuretic management
- Stable electrolyte balance with appropriate supplementation

APPROPRIATE NURSING INTENSITY

- Minimal chest physical therapy or bronchodilator treatments required
- Established nutrition plan (enteral or parenteral)
- Controlled analgesic or sedation requirements
- Appropriate nursing staff numbers according to the intensity of care

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NEUROMONITORING AND NEURODEVELOPMENTAL OUTCOMES IN CONGENITAL HEART SURGERY

Christopher E. Mascio • J. William Gaynor

CHAPTER OUTLINE

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HISTORY OF INTRAOPERATIVE NEUROMONITORING

Brain injury is the most common and potentially disabling complication following congenital heart surgery. With improved survival, the focus has shifted to optimizing functional outcomes. An important goal of therapy for every congenital heart surgical patient is to reduce the risk of brain injury as much as possible. Along with updated perfusion, anesthetic, and surgical strategies, techniques for neuromonitoring have been refined and adopted by many centers performing pediatric cardiothoracic surgery.

Penfield and Boldrey first reported intraoperative neurophysiologic monitoring in 1937.¹ They used direct cortical stimulation during operations for epilepsy. Recording an electroencephalogram directly from the cerebral cortex, also for epilepsy surgery, was first done in 1949 by Jasper and Marshall and Walker.¹ Routine scalp electroencephalography (EEG), used first during carotid endarterectomy, was introduced in the late 1960s.¹ Doppler ultrasound evaluation of the extracranial cerebral arteries was first reported in 1965 by Miyazaki and Kato.² Transcranial Doppler (TCD) was reported by

Aaslid in 1982 after measuring the flow of the middle cerebral artery with a probe placed on the scalp over the temporal bone.³ Near-infrared spectroscopy (NIRS) was introduced clinically in 1985 for monitoring cerebral oxygenation in preterm infants.⁴ Spinal intraoperative monitoring, specifically somatosensory evoked potentials, was developed in the 1970s.¹ The first intraoperative neuromonitoring clinical service was established at the University of California at Los Angeles in 1979,¹ and commercial neurophysiologic monitoring equipment became available in the early 1980s.

NEURODEVELOPMENTAL OUTCOMES

Introduction

Survival after congenital heart surgery has improved, and the focus has shifted to optimizing neurodevelopmental outcomes. Survivors of repair of congenital heart disease in the neonatal period demonstrate cognitive, motor, speech, visual, and learning abnormalities.⁵

Determining causation in abnormal neurodevelopment and the occurrence of neurodevelopmental disability is a challenging endeavor. Genetic predisposition and

many other nonmodifiable patient factors, including prematurity, socioeconomic status, and maternal education, have been shown to be risk factors for worse neurodevelopmental outcomes. In addition, there is increasing evidence that congenital heart disease alters fetal brain growth and development.

In addition to nonmodifiable factors, operative management factors have been implicated in altering neurodevelopmental outcome. This includes preoperative/postoperative hypoxemia and arrest, cardiopulmonary bypass and circulatory arrest strategies, hematocrit levels during cardiopulmonary bypass, and blood gas management during bypass.

Nonmodifiable Factors Associated with Adverse Neurodevelopmental Outcomes

Fetal Brain Development and Preoperative Brain Abnormalities

Beginning in the third trimester of fetal life, patients with congenital heart disease are known to have smaller gestational age- and weight-adjusted brain volumes and impaired neuroaxonal development and metabolism.⁶ These abnormalities are most pronounced in patients with complex types of heart defects such as hypoplastic left heart syndrome and transposition of the great arteries.⁶ Structural malformations of the brain occur at a much higher rate in patients with congenital heart disease than in the general population.⁷ Microcephaly, microencephaly, and other malformations, including absence of the corpus callosum, have been documented in necropsy series of patients with hypoplastic left heart syndrome.⁸ Neonates with congenital heart disease have altered cerebral hemodynamics often with lower than normal cerebral blood flow and/or oxygen delivery. There is evidence of delayed white matter development, which can lead to an increased risk of white matter injury (periventricular leukomalacia [PVL]) and microcephaly. One study of neonates with complex congenital heart disease used preoperative pulsed arterial spin-label perfusion magnetic resonance imaging (MRI) to quantify cerebral blood flow.⁹ More than half of the cohort had developmental or acquired lesions, and the cerebral blood flow was less than half of that reported in normal, term neonates.¹⁰ The same study also examined cerebrovascular responsiveness to CO₂, and found that PVL was associated with decreased CO₂ responsiveness. Abnormal cerebrovascular reactivity to CO₂ has been associated with increased mortality and worse neurodevelopmental outcomes.^{11,12} White matter injury characterized by PVL is the most common pattern of injury.¹³ The mechanism of this injury is thought to be the result of effects of hypoxia and/or ischemia on pre-myelinating oligodendrocyte precursors during their most vulnerable time of 24 to 34 weeks gestation.¹⁴ Up to 40% of neonates with congenital heart disease have PVL on preoperative MRI, and PVL has been shown to be associated with poor neurodevelopmental outcomes.^{9,15,17} The incidence of PVL is highest in neonates undergoing cardiopulmonary bypass. A study by Galli and colleagues revealed a 54% incidence of PVL in neonates compared

to 4% in infants.¹⁸ PVL is the neurologic lesion associated with cerebral palsy in infants born prematurely.¹⁹ This pattern of brain injury is seen not only in preterm newborns but also in term neonates with congenital heart disease.²⁰ A comparison of newborns with congenital heart disease and a control cohort without heart defects revealed that almost one third of those with congenital heart disease had white matter injury.²¹ The injury pattern was not seen in those without heart defects.

Prematurity

Preterm birth, even in infants without congenital heart disease, is a powerful predictor of worse neurodevelopmental outcome. Along with low birth weight, preterm birth has been associated with long-term behavioral and learning issues. In a study of 125 very low-birth-weight preterm infants who were evaluated with the Bayley Scales of Infant and Toddler Development III at 24 months, later gestational age was associated with better neurodevelopmental outcome.²²

Socioeconomic Factors

Other nonmodifiable patient factors that adversely affect neurodevelopmental outcomes are socioeconomic status and maternal education. In a study of neurodevelopmental outcomes after repair of total anomalous pulmonary venous connection, lower socioeconomic status was predictive of lower scores on the Mental Developmental Index (MDI) of the Bayley Scales of Infant Development II.²³ The Single Ventricle Reconstruction trial is the randomized, prospective trial comparing shunt types in the Norwood procedure. Evaluation of this cohort at 14 months demonstrated that lower maternal education was associated with lower MDI scores.²⁴

Genetic Polymorphisms

Many genetic syndromes are associated with congenital heart disease, including Down syndrome,²⁵ Noonan syndrome,²⁶ Williams syndrome,²⁷ and DiGeorge syndrome (22q11.2 microdeletion).²⁸ These syndromes are associated with developmental delay, and assigning causation of neurodevelopmental delay can be challenging. For example, individuals with DiGeorge syndrome have a mean IQ in the 70s,²⁹ a predisposition to psychiatric disorders,³⁰ and an increased incidence of white matter abnormalities.³¹

There is also evidence that genetic variants that modify the brain's response to injury and subsequent recovery may also be important determinants of neurodevelopmental outcomes. The first genetic polymorphism studied in relation to congenital heart disease and operations was apolipoprotein E (APOE).⁵ APOE regulates cholesterol metabolism and is the primary lipid transport vehicle in the central nervous system; there also is evidence that APOE is important for neuronal repair.⁵ There are three APOE alleles (e2, e3, e4) on chromosome 19 that vary by a single amino acid. The Children's Hospital of Philadelphia evaluated the association of APOE genotype and

postoperative neurodevelopmental outcome at age 1 year.⁵ Neurodevelopmental outcomes were evaluated using the Bayley Scales of Infant Development II. The APOE e2 allele was associated with a significantly lower Psychomotor Developmental Index (PDI) score after adjustment for perioperative covariates, including gestational age, age at operation, sex, race, socioeconomic status, cardiac defect, and the use of circulatory arrest. Further analysis of this group revealed patient-specific factors that significantly predicted neurodevelopmental outcomes at age 1 year, including presence of genetic syndrome, low birth weight, and presence of APOE e2 allele.³³ Neurobehavioral outcomes were then evaluated in the cohort between ages 4 and 5.³⁴ Those with the APOE e2 allele had increased behavior problems, restricted behavior patterns, and impaired social skills. The entire cohort had a significantly higher proportion of patients considered either at risk for, or in the clinically significant range for, neurodevelopmental problems. The cohort was further evaluated for other genetic causes of poor neurodevelopmental outcomes beyond APOE genetic polymorphisms. A genome-wide association study identified single nucleotide polymorphisms (SNPs) associated with neurobehavioral abnormalities.³⁵ Ten SNPs reached a threshold for suggested significant associations with neurobehavioral phenotypes. These results identify additional genes—after adjusting for the effects of APOE and other genetic syndromes—that may contribute to adverse neurodevelopmental outcomes.

A study comparing the relative contribution of patient factors (gestational age, genetic syndrome, birth weight, etc.) to management factors on neurodevelopmental outcomes at 1 year of age after neonatal and infant cardiac surgery showed that patient factors explained more of the variability in the PDI (21% vs. 8%) and MDI (13% vs. 5%) than did management factors.³⁶ Factors such as gender, birth weight, and presence of genetic syndrome had a more significant impact on neurodevelopmental outcomes than did cardiopulmonary bypass time, circulatory arrest time, and hematocrit. Not all patients with congenital heart disease enter the operating room with the same neurodevelopmental prognosis. Interindividual variation of many nonmodifiable patient factors significantly contributes to widely disparate neurodevelopmental outcomes of different patients with the same cardiac diagnosis.

Management Factors Associated with Adverse Neurodevelopmental Outcomes

Many studies have examined the impact of different management strategies before and during congenital heart operations on neurodevelopmental outcomes. Operative management strategies and type of support (circulatory arrest versus low-flow cardiopulmonary bypass), pH strategy, target hematocrit value, and others have all been evaluated in relation to postoperative neurodevelopmental outcomes. Preoperative management can have a profound impact on neurodevelopmental outcomes. Acidosis, hypoxemia, hypotension, and cardiac arrest are all examples of preoperative management factors that contribute to neurodevelopmental outcomes.

Hypoxemia, Cardiac Arrest

Ductal-dependent cardiac lesions put patients at risk of acidosis, hypoxemia, and cardiovascular collapse if the diagnosis is not known and ductal closure occurs.^{8,37} The number of prenatal diagnoses of congenital heart lesions has increased in recent years. This often results in delivery in centers equipped to care for severe forms of congenital heart disease and has permitted immediate or early infusion of prostaglandin to maintain ductal patency and avoid profound acidosis and subsequent neurologic issues.³⁸⁻⁴⁰ Preoperative hypoxemia has been shown to be associated with abnormal neurodevelopmental outcomes. Neurodevelopmental testing done on a cohort of patients 5 to 10 years after repair for both cyanotic and acyanotic heart defects demonstrated more speech and language dysfunction in the group with preoperative cyanosis.⁴¹ Cardiac arrest puts all organs at risk until circulation (spontaneous or mechanical) is restored. A recent review of extracorporeal cardiopulmonary resuscitation (ECPR) survivors identified 10 studies that examined neurologic outcomes after ECPR.⁴² Overall survival of ECPR was 79%, and nine of the reports described Pediatric Cerebral Performance Category (PCPC) scores, an early test of neurologic function. Seventy-nine percent of survivors had a PCPC score of 2 or less, indicating normal or mild impairment. There are no data describing long-term neurodevelopmental outcomes after cardiac arrest and ECPR.

Many intraoperative aspects of pediatric cardiac operations have been thought to put the patient at risk for acute neurologic injury and subsequent suboptimal neurodevelopmental outcomes. As mentioned earlier, type of support (circulatory arrest versus low-flow cardiopulmonary bypass), pH strategy, and target hematocrit value have all been evaluated in relation to postoperative neurodevelopmental outcomes.

A prospective, randomized study from Boston Children's Hospital in 1988 assigned patients with transposition of the great arteries undergoing the arterial switch operation to receive either hypothermic circulatory arrest or low-flow cardiopulmonary bypass.⁴³ Neurodevelopmental outcomes (formal neurodevelopmental evaluation and MRI) for this cohort were reported at age 1 year. Patients randomized to circulatory arrest had a significantly lower mean score on the PDI of the Bayley Scales of Infant Development, and the score was inversely related to the duration of circulatory arrest. A longer duration of circulatory arrest was associated with an increased risk of neurologic abnormalities. The authors were unable to determine a safe threshold for circulatory arrest but noted that a period shorter than 35 minutes had minimal effect on the PDI score and that significant deficits were more prevalent in the group of children that had a circulatory arrest period greater than 45 minutes. At 4- and 8-year follow-up, the Boston study revealed worse motor and speech function in the circulatory arrest group.^{44,45} However, measures of behavior were worse in subjects randomized to continuous cardiopulmonary bypass. At the 16-year evaluations, most differences between the treatment groups had disappeared, but the circulatory arrest cohort scored lower on tests of executive function and visual spatial skills.⁴⁶ Both treatment groups fared worse on tests of neurodevelopment

than did population controls. Socioeconomic status explained more test variation than did treatment group assignment.

Cerebral Perfusion

A study of 57 neonates examined pre- and postoperative MRI and 1-year neurodevelopmental outcomes after receiving regional cerebral perfusion (RCP) during aortic arch reconstruction.⁴⁷ The mean RCP time was 71 minutes and the mean RCP flow was 57 mL/kg/min. New postoperative brain injury on MRI was seen in 40% of patients, which is comparable to other studies examining new postoperative MRI brain injury. The 1-year cognitive testing was at reference population norms, whereas language and motor outcomes were lower than reference population norms.

There has been increasing interest in RCP to avoid use of circulatory arrest. A study from the University of Michigan randomized 77 patients to receive either circulatory arrest or RCP during the Norwood operation.⁴⁸ They then performed neurodevelopmental testing on each cohort before the second stage operation and at age 1. The entire cohort demonstrated delayed neurodevelopment with the PDI scores being lower than the MDI scores. No statistically significant difference in MDI or PDI scores was found between the two groups, although the RCP group had lower average point estimates for both the MDI and the PDI compared with the circulatory arrest cohort.

pH strategy is an important part of the operative management of patients requiring hypothermic cardiopulmonary bypass. A recent study from the Netherlands randomized neonates to either deep hypothermic circulatory arrest or antegrade cerebral perfusion.⁴⁹ MRI was done preoperatively and 1 week postoperatively. The authors found no difference between the circulatory arrest and antegrade perfusion cohorts in terms of new cerebral injury (78% vs. 72%, respectively; $P=0.66$). The most common type of injury was white matter injury, but infarctions of the thalamus and/or basal ganglia were seen only after antegrade cerebral perfusion. Motor and cognitive testing done at 24 months showed no difference between the two groups.

Neurodevelopmental outcomes were evaluated at 4 years of age in an observational study of the impact of *APOE* genotype for an association with the use of deep hypothermic circulatory arrest.⁵⁰ No differences in unadjusted outcomes were found between those that received circulatory arrest and those that did not. However, consistent with previously published data, nonmodifiable patient factors were significantly associated with neurodevelopmental outcomes. Presence of a genetic anomaly, lower socioeconomic status and maternal education, and younger gestational age were all associated with worse outcomes.

Blood Gas Management

Two methods of blood gas management during cardiopulmonary bypass are commonly used: alpha stat and pH stat. A prospective, randomized study comparing these two strategies demonstrated an early return of

electroencephalographic activity in patients randomized to pH-stat management.⁵¹ However, neurodevelopmental testing at 1 year of age showed no benefit or detriment associated with either strategy.^{51,52}

Hematocrit

Hematocrit is a modifiable, operative management variable. It is vitally important for oxygen delivery and has been shown to affect neurodevelopmental outcomes. A prospective, randomized study done at Boston Children's Hospital assigned patients to a hypothermic bypass hematocrit of either 20% or 30%.⁵³ At 1 year, the lower hematocrit group had lower PDI scores. A second prospective, randomized study by the same group compared bypass hematocrits of 25% and 35%.⁵⁴ There were no differences between the groups on tests of neurodevelopment at 1 year of age. Based largely on these studies, most centers have chosen 25% as the lowest acceptable hematocrit while on cardiopulmonary bypass.

Glucose Management

Adult cardiac surgery literature has recently touted the benefits of tight glycemic control.⁵⁵ One study of glycemic control in a mixed (medical and surgical patients) pediatric intensive care unit compared tight glycemic control with standard management.⁵⁶ The cohort receiving tight glycemic control had a lower mortality rate but experienced high rates of hypoglycemia. Hypoglycemia is potentially dangerous to the developing brain. A more recent randomized, prospective trial enrolled 980 patients after cardiopulmonary bypass to receive either tight glycemic control or standard glucose management. No differences were found in infection rate, mortality, length of stay, or measures of organ failure. This trial had a low rate of hypoglycemia; but, with no obvious benefits, it seems unnecessary to institute tight glycemic control and risk deleterious effects on the developing brain with episodes of hypoglycemia.

INTRAOPERATIVE NEUROMONITORING

Introduction

Many institutions have adopted intraoperative neuromonitoring as a potential mechanism to minimize brain injury resulting from congenital heart surgery. It can be as simple as having the anesthesiologist monitor NIRS or as complex as using four modalities with a certified neuromonitoring professional in the operating room providing feedback during each case. The most common modalities used are NIRS, EEG, and TCD. Intraoperative NIRS is used at most congenital heart centers for all cardiopulmonary bypass cases. Somatosensory evoked potentials (SSEPs or SEPs) are used very little in congenital heart surgery and will not be discussed. [Figure 111-1](#) demonstrates the appearance of a patient after placement of multimodality neuromonitoring devices. It should be noted, however, that there is a lack of prospective, randomized data showing any benefit to intraoperative neuromonitoring.

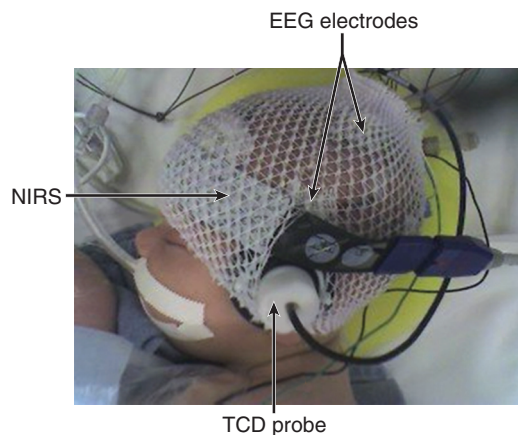


FIGURE 111-1 ■ Intraoperative photograph demonstrating the proper placement of multimodality neuromonitoring probes. EEG, Electroencephalography; NIRS, near-infrared spectroscopy; TCD, transcranial Doppler. (Photo used with permission and courtesy of Harvey L. Edmonds, Jr., PhD.)

Near-infrared Spectroscopy

NIRS noninvasively provides an estimate of cerebral oxygen saturation because of the different absorption spectra between oxygenated and total hemoglobin. The translucency of the skull of the pediatric patient allows probes placed on the forehead to monitor the cerebral cortex. The value obtained is predominately from blood in tissue that is mostly venous blood (75% venous blood). NIRS is the only modality capable of monitoring the brain during circulatory arrest as EEG is flat and TCD will indicate no flow. Cooling and increasing levels of anesthetics will decrease metabolism and increase an individual patient's NIRS value. It is unknown what thresholds are important in the pediatric cardiac surgery patient. Some centers use parameters derived from adult studies (a decrease in NIRS below 50% and/or a drop greater than 20% from baseline) because there are no established guidelines in pediatric patients. Many centers follow trends rather than absolute numbers because there is significant interindividual variation.

Electroencephalography

Intraoperative electroencephalography is used to detect ischemia during congenital heart surgery. In normothermic patients under anesthesia, electroencephalographic slowing indicates inadequate cerebral perfusion and/or oxygenation. To monitor the EEG, cup electrodes are placed on the scalp and shaving hair is not required. Four-channel EEG (four electrodes over each hemisphere and a ground in the middle) will measure the anterior and posterior circulations of both hemispheres. Electroencephalographic recordings demonstrate significant variability between individuals, and proper analysis requires experience and skill at pattern recognition.⁵⁷ In general, patients with adequate cerebral oxygen delivery will demonstrate low-amplitude, high-frequency EEG. Ischemia is represented by high-amplitude, low-frequency waveforms.

Increasing amounts of anesthetics reliably cause diffuse slowing.⁵⁷ Slowing is usually not focal or asymmetric unless there is previous cortical injury, cortical abnormality, or new, acute injury. Fast-frequency activities are seen with lower levels of anesthetics.⁵⁷ They can be difficult to distinguish from epileptiform waves. As with slowing, focal disparities are a sign of previous injury or new, acute ischemia or injury. New epileptiform or epileptic activity indicates cortical dysfunction usually caused by ischemia. Distinguishing concerning changes from artifact can be a challenge and requires significant experience. Artifact can be caused by pulsation (near a pulsatile vessel), electrocardiogram (ECG) interference, electrical interference (such as a headlight, operating room bed, or lower extremity compression devices), or a loose electrode.⁵⁸ Comparing the EEG abnormalities to the QRS complexes on the ECG often helps resolve cases of suspected pulsation and ECG artifact.⁵⁸ Temporarily interrupting other electrical sources in the operating room can help determine if electrical interference is present.⁵⁸ Securing electrodes and checking them will help prevent artifact caused by loose electrodes.⁵⁸

There are times during a congenital heart operation with cardiopulmonary bypass that changes in the EEG can be expected.⁵⁹ Slowing in the EEG is often seen during cannulation of smaller patients. It is thought that the larger cannula-to-vessel ratio in small patients may cause obstruction to flow. In addition, a moderate amount of blood loss has a larger negative impact on circulating blood volume than in an adult. There is a transient depression in the EEG at the onset of cardiopulmonary bypass, likely caused by the relatively oxygen-deficient pump prime. Finally, hypotension after the release of the aortic crossclamp will cause EEG slowing. Deep hypothermic circulatory arrest causes slowing, and eventually flattening, of the EEG. One limitation of EEG monitoring is that the slowing seen with ischemia and/or hypoxia cannot be differentiated from that caused by anesthetics and/or cooling. The most important neuromonitoring change associated with cerebral ischemia is EEG slowing.⁵⁹ It provides continuous feedback on the function of the cerebral cortex. Combined with the other modalities, it can be used to help decide if a response to worsening neuromonitoring parameters is indicated.

Bispectral Index Scale (BIS) is another neuromonitoring tool that is used for intraoperative monitoring. The Food and Drug Administration approved it in 1996 as an EEG-based monitor of anesthetic effect.⁶⁰ BIS describes the continuous, varying signal of EEG as a number ranging from 100 (awake) to 0 (complete cortical suppression).⁶¹ It is an easy-to-use, quickly applied, one-channel processed EEG.⁶¹ In congenital heart surgery, it can be used as a marker of cortical silence when deep hypothermic circulatory arrest is used. It has also been used in conjunction with other neuromonitoring modalities to assess adequacy of cerebral perfusion.⁶²

Transcranial Doppler

TCD measures the velocity of red blood cells.⁵⁹ TCD can determine both the presence and direction of blood flow. The probe is positioned over the temporal bone and

monitors flow in the middle cerebral artery. Peak systolic velocity is a marker of cerebral inflow, and end-diastolic velocity is inversely related to cerebrovascular resistance. Inflow obstruction will result in a decrease in the peak systolic velocity. If accompanied by EEG slowing, an ischemic process is likely evolving.⁵⁹ Outflow obstruction (venous cannula malposition, for example) will increase the cerebrovascular resistance and decrease the end-diastolic velocity. High-intensity transient signals (HITSs) represent the presence of gaseous or particulate emboli within the blood vessel. Data from adult studies indicate that an increasing number of HITSs may predict postoperative neurobehavioral, pulmonary, and renal complications.⁶³ TCD is unable to differentiate between types of emboli.

Biomarkers

Various serum biomarkers have been found to be associated with neurodevelopmental outcome. In a study of infants undergoing congenital heart surgery aged 6 weeks and younger, postoperative lactic acid level correlated with survival and neurodevelopmental outcome. Adverse survivors, or those survivors with suboptimal neurodevelopmental outcomes, had a higher peak lactate concentration (7.9 vs. 6.5 mmol/liter) and a longer time to plasma lactate normalization (16 vs. 11 hours) when compared with those survivors with normal or intact neurodevelopmental outcomes.⁶⁴

Brain type natriuretic peptide (BNP) is a serum marker of heart failure that is elevated when right and/or left heart pressures are increased. A study of single ventricle patients in the enalapril trial examined the association of BNP and height with neurodevelopmental outcomes.⁶⁵ The investigators discovered that patients with high BNP values and poor growth had worse MDI (Bayley Scales of Infant Development II) scores at 14 months.

CURRENT DATA

Optimizing long-term functional outcome for every patient is a major focus of congenital heart surgery as survival has improved. As mentioned earlier, many institutions now use one or more modalities of intraoperative neuromonitoring. However, there is a paucity of randomized, prospective trials and there remains considerable debate about the benefit, if any, that intraoperative neuromonitoring provides. Many single-institution case-control, observational, and retrospective studies have been conducted.

Surgeons at one institution discussed their approach to multimodality monitoring and reviewed available evidence.⁶⁶ Clark and colleagues use NIRS, TCD, EEG, and SEP and intervene when NIRS decreases more than 20% from baseline. However, they admit that this threshold is derived from adult studies and that a pediatric threshold has not been defined. Their use of TCD is no different than what has been reported previously; that is, they use TCD for detecting alterations in

cerebral blood flow and emboli. The surgeons also describe their preference for four-channel EEG in patients younger than 2 years (eight-channel EEG for patients older than 2 years) and their routine use of SEP in patients older than 2 years. Clark and colleagues then provide a review of the available data for NIRS, TCD, EEG, SEP, and multimodality monitoring and conclude there are no data that support the routine use of these modalities in the operating room.

Another report describes an institution's attempts to decrease the risk of neurologic injury to neonates undergoing cardiac surgery through the use of intraoperative neuromonitoring.⁶⁷ Khan and Fraser review their protocol for neonatal cardiopulmonary bypass and discuss their use of bilateral NIRS and TCD to guide antegrade cerebral perfusion to minimize time of deep hypothermic circulatory arrest. They review the literature on intraoperative NIRS and TCD and describe their plans for future neuroprotection studies. The authors conclude that their cardiopulmonary bypass strategy is based on the data currently available but that further studies of long-term neurologic outcomes are warranted.

A systematic review done by a group that included pediatric cardiac surgeons, a pediatric neurologist, and a pediatric anesthesiologist concluded that data supporting the use of current neuromonitoring and neuroprotective techniques are limited.⁶⁸ The literature review encompasses 20 years (1990 to 2010) and initially identified 527 manuscripts. Review of this group of abstracts resulted in 187 potential manuscripts based on inclusion and exclusion criteria. Another review generated the final list of 162 manuscripts. The primary outcome was evidence of structural brain injury or functional disability and was demonstrated in only 43% of the manuscripts analyzed. Only 13% of the studies were randomized prospective trials. Manuscript categories analyzed included blood gas management, hematocrit, EEG, cooling, glycemic control, S-100 β , TCD, NIRS, and deep hypothermic circulatory arrest/low-flow cardiopulmonary bypass/RCP. The largest groups were those of deep hypothermic circulatory arrest/low-flow cardiopulmonary bypass/RCP ($n = 44$ manuscripts) followed by NIRS ($n = 35$). Only two studies (1.3%) were graded as procedures or treatments that are recommended because the benefits clearly outweigh the risks (American College of Cardiology/American Heart Association level of evidence grade class I, level B).⁶⁸ These two studies examined the effect of hemodilution on neurodevelopmental outcomes; results suggest that severe hemodilution (probably 24% or less) is associated with adverse neurodevelopmental outcomes.⁶⁸ No category reached class I, level A—demonstration of a clear benefit and recommended as effective.⁶⁸ Since this systematic review was done, few manuscripts have been added to the literature on the subject of intraoperative neuromonitoring.

Neuroprotection

The aforementioned study that reviewed 20 years of literature on neuroprotection included examination of many aspects of neuroprotection done during the

perioperative period, including some of the following: blood gas management, hematocrit, EEG, cooling, glyce-mic control, S-100 β , TCD, NIRS, and deep hypo-thermic circulatory arrest/low-flow cardiopulmonary bypass/RCP. As mentioned, of the 162 manuscripts that met inclusion criteria, only two were recommended as having benefits that outweighed the risks. Both involved hemodilution and advised that the hematocrit stay at or above 24% during cardiopulmonary bypass cases. The study also reviewed the use of perioperative medications, including phenobarbital, erythropoietin, allopurinol, aprotinin, tranexamic acid, steroids, methylprednisolone, and dexamethasone. There are no studies that report a benefit to using any of these medi-cations. Most centers have adopted protocols for neu-roprotection and neuromonitoring that they feel are safe and work best at their institution. At the Children's Hospital of Philadelphia, the neuromonitoring and neu-roprotection strategy currently includes the following: The cardiopulmonary bypass pump setup contains a bubble detector and continuous arterial blood gas and venous saturation monitors. The priming protocol con-tains Solu-Medrol. The goal hematocrit for patients younger than 1 year of age is higher than 30%. For patients older than 1 year, the goal hematocrit is higher than 25%. While on cardiopulmonary bypass, the goal mean arterial pressure is 25 to 55 mm Hg for neonates weighing 5 kg or less. This increases to 60 to 80 mm Hg for patients aged 11 years and older and weighing more than 40 kg. Alpha stat is used at normothermia and when warming. pH stat is used when cooling and when maintaining hypothermia. The arterial-to-patient temperature gradient is maintained between 8° C and 10° C when cooling. Cooling is performed for at least 15 minutes prior to circulatory arrest, and the arterial temperature is maintained higher than 15° C. Warming is also done with the arterial-to-patient temperature gradient maintained at 8° C to 10° C.

Many questions about neurodevelopmental outcomes, neuromonitoring, and neuroprotection remain unan-swered. It is clear now that many patients have preopera-tive cerebral abnormalities. Some patients with a structurally and functionally normal brain are at higher risk of brain injury during congenital heart surgery because of a genetic predisposition. Longer-term follow-up will continue to help plan future strategies to optimize neurodevelopmental outcomes. Available modalities of intraoperative neuromonitoring include EEG, TCD, NIRS, and SSEP. Whether these techniques prevent brain injury remains to be seen. A prospective, randomized study with longer-term neurodevelopmental outcomes has not been accomplished. This study may never be accomplished because many centers have already adopted these technologies as standard without proof of benefit. The hardware used in the cardiopulmonary bypass circuit continues to evolve. However, there is still no consensus on what type of cerebral perfusion, if any, is best during deep hypothermic circulatory arrest. The best outcomes in such a heterogeneous field of congenital heart surgery are often achieved by doing what is com-fortable and safe for an individual surgeon, team, and institution.

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CONGENITAL TRACHEAL DISEASE

Emile A. Bacha

CHAPTER OUTLINE

HISTORY OF PEDIATRIC TRACHEAL SURGERY

CLINICAL PRESENTATION AND DIAGNOSTIC TECHNIQUES

SURGICAL TECHNIQUES

General Principles
Tracheal Resection
Slide Tracheoplasty
Cartilage Tracheoplasty
Pericardial Tracheoplasty

Tracheal Autograft Technique
Homograft Tracheoplasty

PEDIATRIC TRACHEAL ANOMALIES

Pulmonary Artery Sling
Tracheomalacia
Postintubation Stenosis
Tracheal Web

SUMMARY

HISTORY OF PEDIATRIC TRACHEAL SURGERY

In 2000, the Congenital Heart Surgery Nomenclature and Database Project classified congenital tracheal stenosis as congenital–complete tracheal rings, postintubation, traumatic, or congenital web.¹ Localized stenosis was defined as less than 50% of the tracheal length, and long-segment stenosis as greater than 50% of the tracheal length.¹ The initial classification of tracheal stenosis had been proposed by Drs. Cantrell and Guild from the University of Washington, Seattle, in 1964.² They classified these patients into three morphologic types: (1) generalized hypoplasia, (2) funnel-like stenosis, and (3) segmental stenosis. They also noted the frequent association of a tracheal right upper lobe bronchus that is present in 20% of these patients (Fig. 112-1). Dr. Hermes Grillo from Massachusetts General Hospital is considered to be the father of tracheal surgery. In a series of landmark publications in the 1960s, he defined the blood supply of the trachea, the surgical approach to the trachea, and tracheal release procedures for resection.^{3,4} The first successful operation for congenital stenosis of the trachea was reported by Dr. Ken Kimura from Kobe Children's Hospital in Kobe, Japan, in 1982.⁵ He used a costal cartilage graft to augment the tracheal lumen of a 12-month-old infant with tracheal stenosis secondary to complete tracheal rings (cartilage tracheoplasty). The use of pericardium to augment the tracheal lumen was first performed by Dr. Farouk Idriss from Children's Memorial Hospital, Chicago, in 1982.⁶ The operation was facilitated by the use of cardiopulmonary bypass for respiratory support during the procedure. Slide tracheoplasty was first reported by Drs. Victor Tsang and Peter

Goldstraw from Brompton Hospital in London, England, in 1989.⁷ Its use in children was popularized by Dr. Grillo and his associates.⁸ Drs. Claus Herberhold and Martin Elliott from Great Ormond Street Hospital, London, performed the first successful tracheal homograft to augment the lumen of a patient with a failed prior intervention for tracheal stenosis from congenital tracheal rings in 1994.⁹ Drs. Carl Backer and Constantine Mavroudis reported the use of a free tracheal autograft for infants with congenital tracheal stenosis in 1998, 2 years after they performed the first operation.¹⁰ Pulmonary artery sling repair was first performed by Dr. Willis J. Potts at Children's Memorial Hospital in 1953.¹¹ The left pulmonary artery was divided at its origin from the right pulmonary artery and reanastomosed anterior to the trachea.

CLINICAL PRESENTATION AND DIAGNOSTIC TECHNIQUES

The two most common congenital tracheal anomalies in infants and children are tracheomalacia and tracheal stenosis. Congenital tracheal stenosis is most commonly caused by complete cartilage tracheal rings, and it is the most common indication for surgical intervention.¹² The normal trachea has an anterior arch-shaped cartilage and a posterior membranous trachea. In children with complete tracheal rings, the cartilage ring is circumferential and the membranous trachea is absent (Fig. 112-2). In contrast, tracheomalacia is associated with a normal or sometimes broad membranous trachea. Failure of the C-shaped cartilaginous portion to maintain a minimum of rigidity to the trachea results in “floppiness,” which results in functional tracheal narrowing, particularly

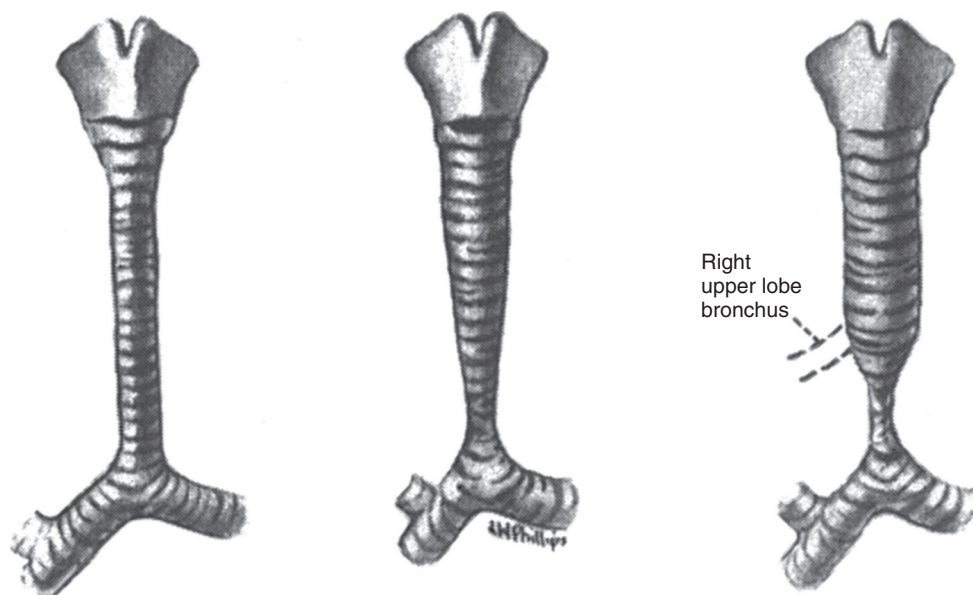


FIGURE 112-1 ■ The three morphologic variants of congenital stenosis of the trachea. *Left*, Generalized hypoplasia; *center*, funnel-like stenosis; *right*, segmental stenosis. The occurrence of an anomalous right upper lobe bronchus (or tracheal right upper lobe) (*right*) is most common in the segmental form. (From Cantrell JR, Guild HG: Congenital stenosis of the trachea. *Am J Surg* 108:297, 1964.)

during expiration. The circumference of the trachea is typically normal during inspiration, or when a patient is intubated (e.g., for a computed tomography [CT] study). Tracheomalacia is a chronic condition that infrequently requires surgical intervention. It often improves with time and growth of the child. Patients with tracheal stenosis often have associated anomalies, most commonly pulmonary artery sling and congenital cardiac anomalies.¹³ Pulmonary artery sling is present in a third of patients with congenital tracheal stenosis. Major intracardiac anomalies are present in 25% of the patients with congenital tracheal stenosis.

The diagnosis of congenital tracheal stenosis should be suspected in any infant who has stridor (noisy breathing), respiratory distress, apnea, cyanosis, wheezing, retractions, or respiratory failure requiring intubation. Tracheal stenosis can result in a difficult intubation (e.g., the endotracheal tube selected for the patient's size fails to pass into a normal location in the trachea), and this traumatization of the trachea can cause future tracheal stenosis.

Patients with known or suspected tracheal problems should be evaluated with a chest radiograph, CT or magnetic resonance imaging (MRI) (or both), bronchoscopy, and echocardiography (Box 112-1). The chest radiograph often demonstrates the diminutive nature of the tracheal lumen. It reveals lung agenesis or hypoplasia. A CT scan or MRI shows the tracheal lumen in cross section and provides a measurement of the tracheal stenosis. A tracheal right upper lobe can be identified if present. Three-dimensional reconstruction can generate a very good representation of the tracheal pathology (Fig. 112-3).¹⁴

In our experience, CT has been more helpful than MRI because it is usually quicker (i.e., requires less sedation, or obviates the need for intubation), and there is less movement artifact. It can be performed as a dynamic expiratory CT scan—that is, in synchrony with the child's

BOX 112-1 Diagnostic Techniques for Infants with Complete Tracheal Rings

- Chest radiography
- Computed tomography (CT) with contrast, including three-dimensional reconstruction or dynamic CT
- Rigid bronchoscopy
- Echocardiography (to rule out pulmonary artery sling, congenital cardiac anomalies)

inspiration and expiration. End-inspiratory and dynamic expiratory volumetric imaging can be obtained. This type of dynamic study is helpful when evaluating children who might have tracheomalacia but do not fit a typical symptomatic pattern.¹⁵ However, CT results in a much higher radiation burden, which should be taken into consideration if the child is likely to require repeated imaging studies. Contrast tracheobronchography, which generates high-quality images, is still used sometimes. However, CT generates such excellent images that the risks of contrast tracheograms mostly outweigh the benefits, so this technique is usually used only in conjunction with a catheterization. A pulmonary artery sling can be demonstrated by CT if the CT is performed with contrast, or by MRI. For the sick neonate who is transferred with a critically positioned endotracheal tube and congenital tracheal stenosis, transthoracic echocardiography is the diagnostic procedure of choice to demonstrate a pulmonary artery sling.¹⁶ Echocardiography should be performed on all of these infants because of the 25% incidence of congenital heart disease found in patients with congenital tracheal stenosis.¹³

The most important diagnostic procedure in all patients is a rigid bronchoscopy. This can be performed as a separate procedure before the planned tracheal operation, or it can be done at the time of the tracheal

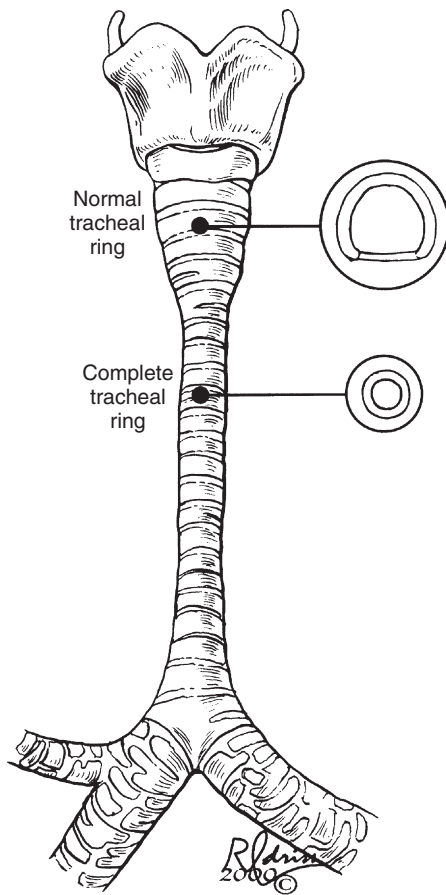


FIGURE 112-2 ■ The trachea of an infant with long-segment tracheal stenosis secondary to complete tracheal rings. There are three normal tracheal rings immediately below the cricoid. The upper cutaway shows a normal tracheal ring with the anterior cartilage and flat posterior membranous trachea. This is followed by 18 complete tracheal rings that progress almost to the carina, one of which, shown in the lower cutaway, is a complete cartilage ring with a substantially reduced tracheal lumen. The tracheal lumen in some of these infants is as small as 1.5 to 2 mm.

procedure. In some severe cases, distal visualization of the trachea cannot be obtained by bronchoscopy because of the risk of occluding the tracheal lumen. The child can then be placed on cardiopulmonary bypass, and bronchoscopy can be performed safely.¹⁷

SURGICAL TECHNIQUES

General Principles

In general, the incidence of airway complications, including anastomotic dehiscence, rises with the length or amount of trachea that is resected. Younger patients and reoperative tracheal procedures also have significantly higher complication rates.¹⁸ Tracheal anatomy, including blood supply, should be well understood. Grillo expressed concern about devascularization in adults,³ but this appears to be less important in children, who have an excellent mediastinal blood supply. Right and left recurrent laryngeal nerves should be protected at all cost. A

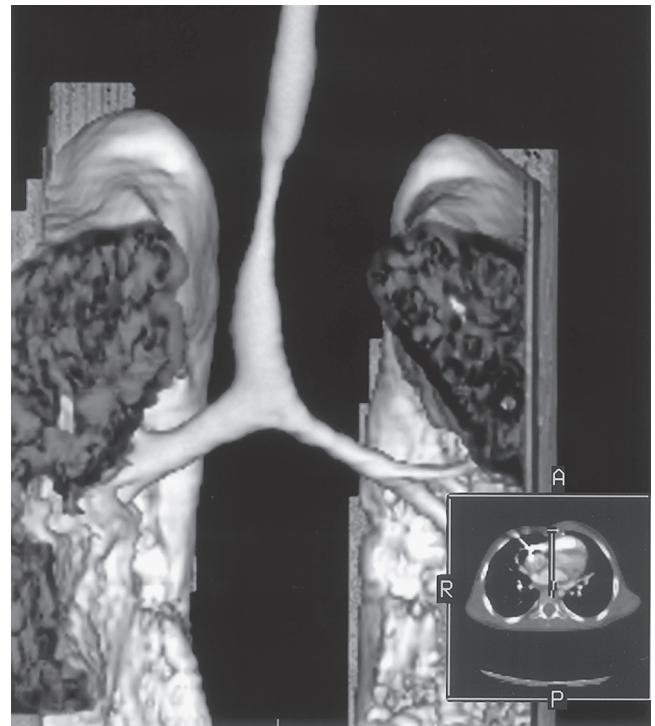


FIGURE 112-3 ■ Computed tomography (CT) (inset) with three-dimensional reconstruction reveals a significant tracheal stenosis in the midportion of this child's trachea. The pathology at the time of surgery was essentially identical to the pathology indicated by the CT scan. A, Anterior; P, posterior; R, right.

good relationship with pediatric otorhinolaryngologists with special expertise in endoscopic and surgical airway management is essential.

Postoperative management differs with the age of the child. For older children, adult principles can be applied, and a "chin stitch" can be used to prevent neck extension. In all cases, a flexible bronchoscopy is performed at 5 to 7 postoperative days. Younger children can be fitted with a neck prosthesis to prevent important neck excursions, but this is rarely used. It may be best to leave neonates and young infants sedated and intubated for 5 to 7 days, and to perform flexible bronchoscopic examination before extubation.

Tracheal Resection

Cantrell and Guild published an early report of a successful tracheal resection in a child in 1964, and they also reported the three morphologic varieties of congenital tracheal stenosis.² The 7-year-old patient had a tracheal right upper lobe and a bridging bronchus to the carina. The bridging bronchus, which was stenotic, was excised, and the carina was brought up to the main trachea. An anastomosis was performed with interrupted sutures of braided stainless steel. The child survived the operation and was asymptomatic on follow-up.

Tracheal stenosis amenable to tracheal resection with end-to-end anastomosis was originally thought to be feasible for stenosis involving up to 50% of the total tracheal length. However, a report from Massachusetts General

Hospital has indicated that resections of more than 30% of the trachea have a substantial failure rate.¹⁹ We believe that tracheal resection is the preferred technique if the stenosis is less than a third of the total tracheal length. This is usually six to eight complete tracheal rings.

We use the technique developed by Grillo for tracheal resection and reanastomosis (TRR).²⁰ In adults, most TRRs are performed via a transverse cervical (“collar”) incision. The airway can be safely managed intraoperatively with careful endotracheal tube positioning. In children, especially small children and infants, control of the airway is much more precarious. As in most experienced pediatric centers, we believe that most if not all tracheal resections in younger children should be performed through a median sternotomy approach with cardiopulmonary bypass. If the tracheal stenosis extends up to the cricoid, a collar incision is made in the neck, forming a “T” with the median sternotomy incision. This incision tends to heal better than a midline extension of the median sternotomy onto the neck. The strap muscles are divided in the midline. The thymus is partially or entirely excised. The innominate artery and vein are dissected free and encircled with vessel loops. These may then be retracted superiorly or inferiorly to address the various components of the trachea. The aorta is mobilized from its pericardial attachments and retracted with a small pledgeted suture to the left. Care is taken to avoid injury to the right or left recurrent laryngeal nerves. The anterior surface of the trachea is freed from pericardial attachments so that it may be completely visualized from cricoid to carina if necessary.

The site of the stenosis is identified externally. At the site of the stenosis and up to one ring above and below the stenotic segment (at most, two rings above or below), dissection must be performed circumferentially and posteriorly to facilitate the removal of the stenotic portion of the trachea. Attention must be paid to the lateral blood supply of the tracheal wall and a decision made regarding which vessels can be preserved for an adequate blood supply to the eventual anastomosis. In most cases, the carinal attachments are freed, as are the pericardial attachments of the right and left mainstem bronchi. Cardiopulmonary bypass is initiated with a single right atrial and aortic cannula, and the aorta is retracted to the left. Cooling is not necessary, and we aim for a temperature of 32° to 34°C. The trachea is opened in the midline through the extent of the tracheal stenosis. If the stenotic portion can be identified from the outside, bronchoscopic guidance is not needed. Three-dimensional CT scan reconstruction has been used to identify the area of stenosis with enough accuracy to allow opening at the correct site. If the focal area of stenosis cannot be identified externally, intraoperative bronchoscopy, using the illuminated tip of the bronchoscope for guidance, can demonstrate the area of stenosis.

The technique of passing a 25-gauge needle through the lightest portion of the stenosis also is useful for some patients. The anterior tracheal incision is extended proximally and distally until the extent of the complete tracheal rings or stenosis has been encompassed. If this length is less than 30% of the trachea (six to eight complete tracheal rings), the segment is then simply excised.

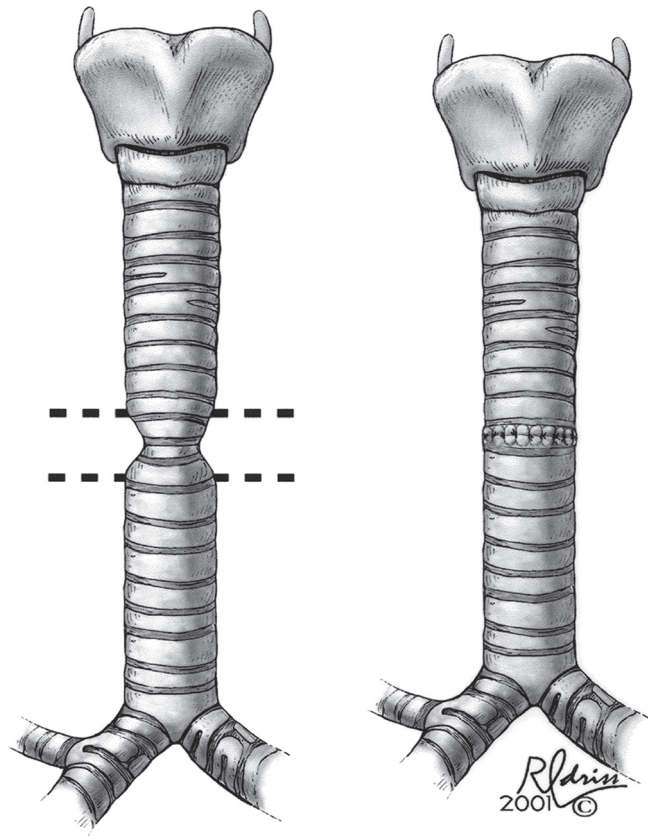


FIGURE 112-4 ■ Tracheal resection. The localized segment of tracheal stenosis is excised. The trachea is extensively mobilized, specifically in the right and left mainstem bronchi and carina. This allows the trachea to be brought together without tension for an end-to-end anastomosis using interrupted polydioxanone sutures. (From Backer CL, Mavroudis C, Holinger LD: Repair of congenital tracheal stenosis. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 5:173–186, 2002.)

The two ends are brought together, and the anastomosis is performed with interrupted polydioxanone (PDS) sutures (Fig. 112-4), with the knots tied outside. If there is little tension, it is acceptable to run the posterior wall. Before the anterior sutures are tied, the trachea is suctioned free of secretions and blood with a fine plastic suction catheter. At completion, flexible bronchoscopy is always performed before leaving the operating room. A tension-free anastomosis is the key, and we liberally use the Grillo-derived lateral stay sutures, placed one ring above and one below the anastomosis, to bring the two edges together and take some of the tension away from the suture line itself.

It is important to determine before the resection of tracheal tissue (including the stenotic portion) whether a TRR or a slide tracheoplasty will be performed. In the slide tracheoplasty, the extent of tracheal resection should be minimized to use the tracheal wall as a flap. If the length of the stenosis is too long for a successful end-to-end anastomosis, the operation can be converted to the tracheal autograft technique. Results of tracheal resection in infants and children are shown in Table 112-1.^{19,21-23} Complications include anastomotic leak, restenosis, and tracheomalacia.

Slide Tracheoplasty

Slide tracheoplasty is our preferred technique for long-segment narrowing, typically seen in complete tracheal rings. It was first reported by Tsang and colleagues from Brompton Hospital, London, England, in 1989.⁷ The slide tracheoplasty can be performed through a cervical collar incision or through a median sternotomy approach. The procedure has been performed with and without cardiopulmonary bypass. Only the midportion of the tracheal stenosis is transected (Fig. 112-5). The two tracheal halves are then opened longitudinally, one anteriorly and the other posteriorly. The corners of the transecting tracheal incision are trimmed. Figure 112-6 shows an anterior tracheotomy inferiorly and a posterior tracheotomy superiorly. The two openings are then “slid” together and approximated with interrupted absorbable sutures (Fig. 112-7) or with a continuous absorbable suture. It is

TABLE 112-1 Results of Tracheal Resection in Infants and Children

Surgeon	Year	Patients (N)	Mortality
Ziemer ²³	1998	8	1 (12%)
Jones ²²	1999	6	1 (16%)
Grillo ¹⁹	2002	46	2 (4%)
Backer ²¹	2002	12	1 (8%)
Totals		72	5 (7%)



FIGURE 112-5 ■ Slide tracheoplasty. The trachea is transected at the midpoint of the long-segment congenital tracheal stenosis. The superior position of the trachea is incised posteriorly, and the inferior aspect of the trachea is incised anteriorly. (From Dayan SH, Dunham ME, Backer CL, et al: Slide tracheoplasty in the management of congenital tracheal stenosis. *Ann Otol Rhinol Laryngol* 106:914–919, 1997.)

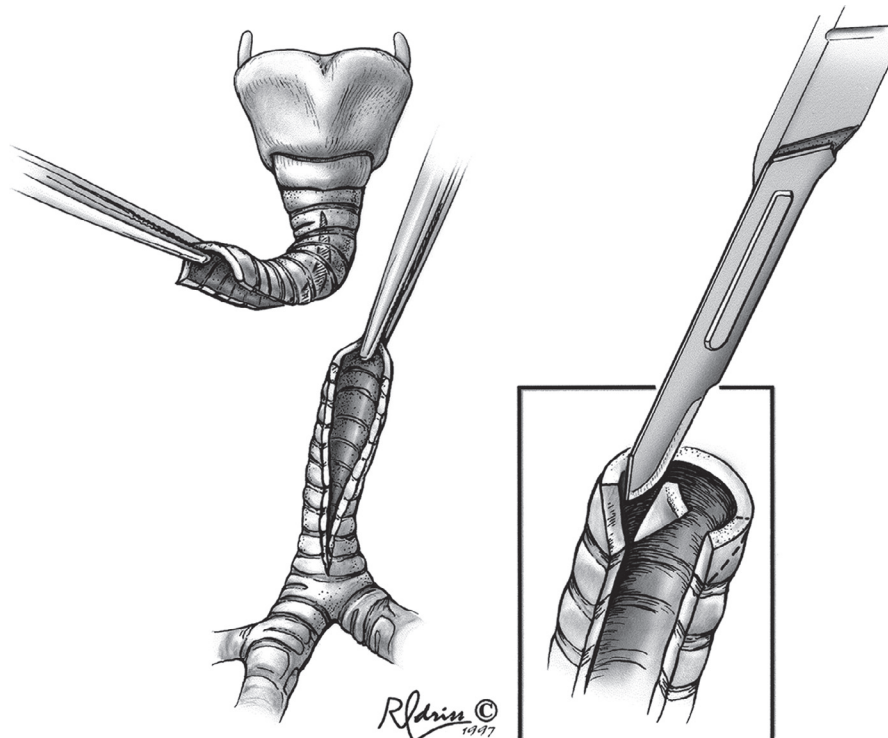


FIGURE 112-6 ■ Slide tracheoplasty. The upper trachea has been opened posteriorly, and the lower trachea has been opened anteriorly. The corners of the transected trachea are trimmed so that the leading edge will fit into the V-portion of the other component. (From Dayan SH, Dunham ME, Backer CL, et al: Slide tracheoplasty in the management of congenital tracheal stenosis. *Ann Otol Rhinol Laryngol* 106:914–919, 1997.)

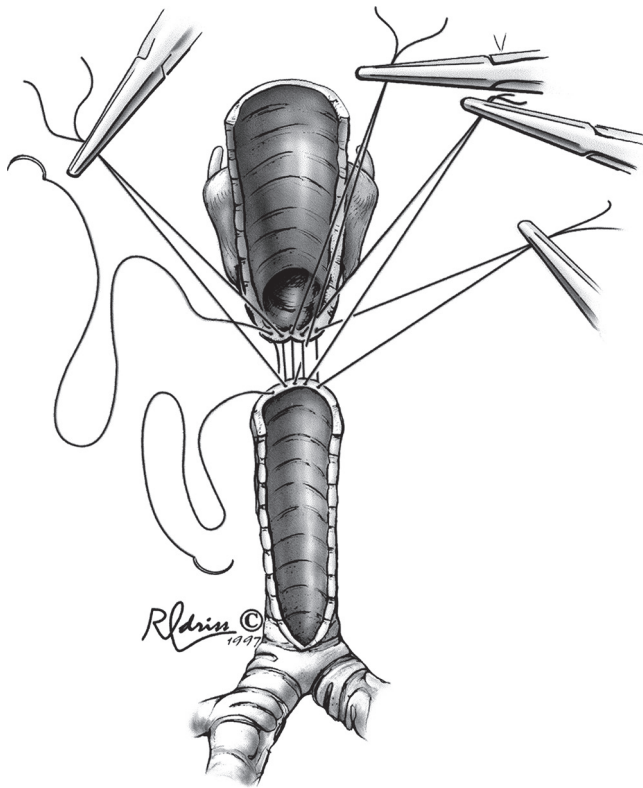


FIGURE 112-7 ■ Slide tracheoplasty. The beginning of the long anastomotic suture line is performed with an interrupted 6-0 polydioxanone suture while the patient is on cardiopulmonary bypass. (From Dayan SH, Dunham ME, Backer CL, et al: Slide tracheoplasty in the management of congenital tracheal stenosis. *Ann Otol Rhinol Laryngol* 106:914–919, 1997.)

important to carry the suture as an everting suture line; otherwise, a ledge of cartilage will protrude into the tracheal lumen. Correctly done, the result is a trachea that is half the original length with four times the internal luminal diameter, as seen in [Figure 112-8](#), where the configuration of the anastomosis is shown in the small inset. If the tracheal stenosis extends into one of the right or left mainstem bronchi, the slide incisions can be performed laterally, so that the inferior incision extends onto the superior surface of the narrow bronchus.

The results of slide tracheoplasty are reported in [Table 112-2](#).^{7,8,11,21,24–26} The overall mortality was 12% in 33 patients. Complications include granulation tissue, a figure-eight configuration of the trachea, and recurrent stenosis.^{8,11,27}

Cartilage Tracheoplasty

The first report of a successful surgical procedure for long-segment congenital tracheal stenosis described a cartilage tracheoplasty performed by Kimura and associates⁵ in 1982, at Kobe Children's Hospital in Japan. They operated on a 12-month-old female infant who had had recurrent respiratory distress since birth. The entire trachea was stenotic, as seen by bronchoscopy. The left bronchus was of normal caliber, and the right lung was completely aplastic. Through a median sternotomy incision, the left bronchus was incised and cannulated for ventilation. A longitudinal incision was made through the entire length of the anterior wall of the trachea. Two separate pieces of costal cartilage were used to fill the defect in the anterior wall of the trachea. The grafts were

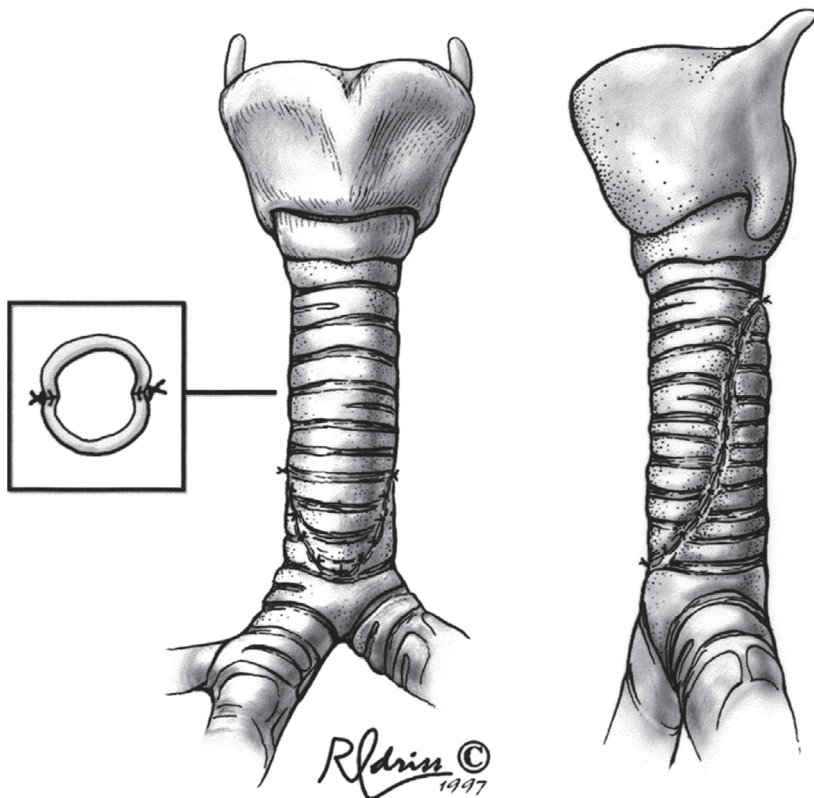


FIGURE 112-8 ■ Slide tracheoplasty. Anterior (left) and lateral (right) views of the anastomosed trachea. The tracheal length has been reduced by almost half, and the internal luminal diameter has been increased by four times. The cross-sectional appearance of the trachea is shown in the inset. (From Dayan SH, Dunham ME, Backer CL, et al: Slide tracheoplasty in the management of congenital tracheal stenosis. *Ann Otol Rhinol Laryngol* 106:914–919, 1997.)

TABLE 112-2 Results of Slide Tracheoplasty

Surgeon	Year	Patients (N)	Mortality
Tsang ⁷	1989	2	1 (50%)
Lang ²⁵	1999	2	0
Harrison ²⁴	2000	3	0
Matute ²⁶	2001	4	0
Backer ²¹	2002	3	1 (33%)
Grillo ⁸	2002	8	0
Manning ¹¹	2003	11	2 (18%)
Totals		33	4 (12%)

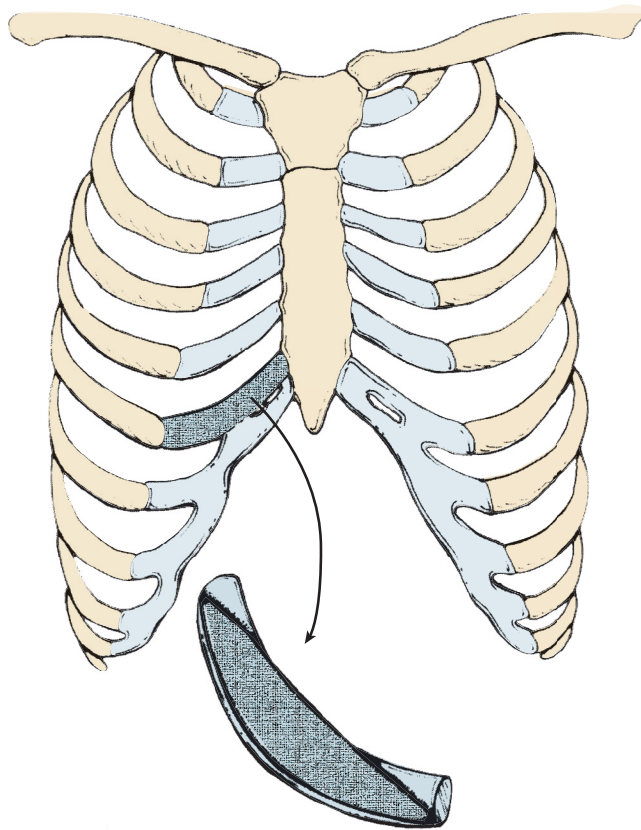


FIGURE 112-9 ■ Cartilage tracheoplasty. Before the median sternotomy, a segment of cartilage is harvested from the sixth or seventh rib. The cartilage is then tailored to correspond to the subsequent tracheal opening. (From Jaquiss RD, Lusk RP, Spray TL, et al: Repair of long-segment tracheal stenosis in infancy. *J Thorac Cardiovasc Surg* 110:1504–1512, 1995.)

attached to the tracheal edges with interrupted 5-0 Dexon sutures. This patient required prolonged intubation and ventilation but was successfully extubated 2 months postoperatively.

For airway control in the infant, cartilage tracheoplasty for long-segment congenital tracheal stenosis is best performed via a median sternotomy with cardiopulmonary bypass. The midline incision is extended onto the neck, or (preferably) a collar incision is used for further exposure of the trachea in the neck. The cartilage graft can be harvested via the median sternotomy incision (Fig. 112-9). Median sternotomy is performed while preliminary preparation of the cartilage graft takes place. The trachea is dissected and exposed on its anterior surface.

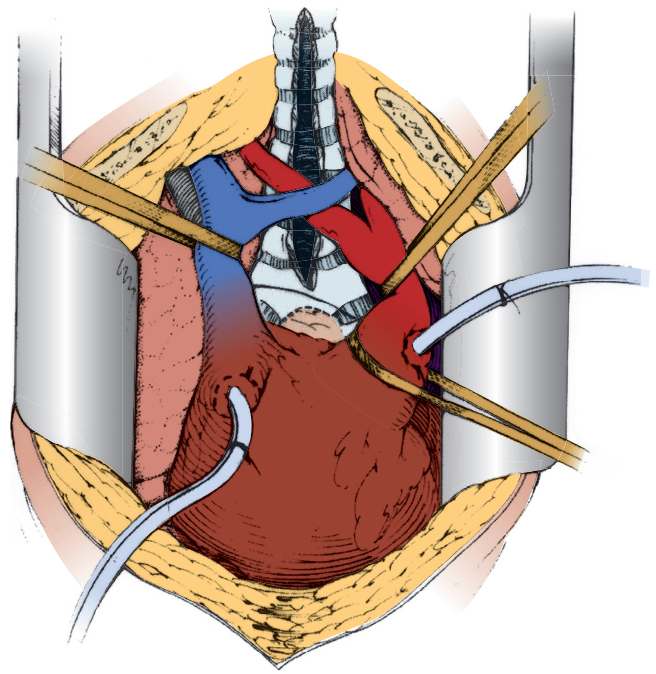


FIGURE 112-10 ■ Cartilage tracheoplasty. Exposure of the trachea through a sternotomy is demonstrated, including the relative positions of bypass cannulas and retraction of the great vessels for optimal exposure. Tracheal incision has been performed to the carina. (From Jaquiss RD, Lusk RP, Spray TL, et al: Repair of long-segment tracheal stenosis in infancy. *J Thorac Cardiovasc Surg* 110:1504–1512, 1995.)

The patient is heparinized and cannulated for cardiopulmonary bypass via the right atrium and ascending aorta. Extracorporeal circulation is initiated, with cooling to 32°C, so the heart remains beating in normal sinus rhythm. Ventilation is stopped. The anterior wall of the stenotic trachea is opened through the extent of the stenosis (Fig. 112-10). Bronchoscopic guidance is often helpful to assess the degree of stenosis. The segment of costal cartilage is then tailored to a size and shape suitable for the anterior opening of the trachea. Care is taken to preserve the perichondrium, which is placed on the luminal surface, and the graft is secured with interrupted absorbable monofilament suture (Fig. 112-11). Intraluminal suture exposure is avoided, and the graft is seated on the tracheotomy rather than being allowed to prolapse into the lumen.

After completion of the graft suture line, the anesthesiologist inflates the lungs with air, and the suture line is confirmed to be airtight, with additional sutures placed as necessary. Bronchoscopy is performed to confirm the tracheal lumen adequacy and to clear retained secretions. The endotracheal tube is repositioned in the midportion of the cartilage graft. The patient is ventilated and weaned from cardiopulmonary bypass. The tracheal suture line can be sealed with biological glue. Hemoclips are placed in the soft tissue adjacent to the trachea to mark the location of the cartilage graft. Sternotomy is closed in the standard fashion. Patients are maintained on heavy sedation and with muscle relaxant to minimize motion of the endotracheal tube in the airway.

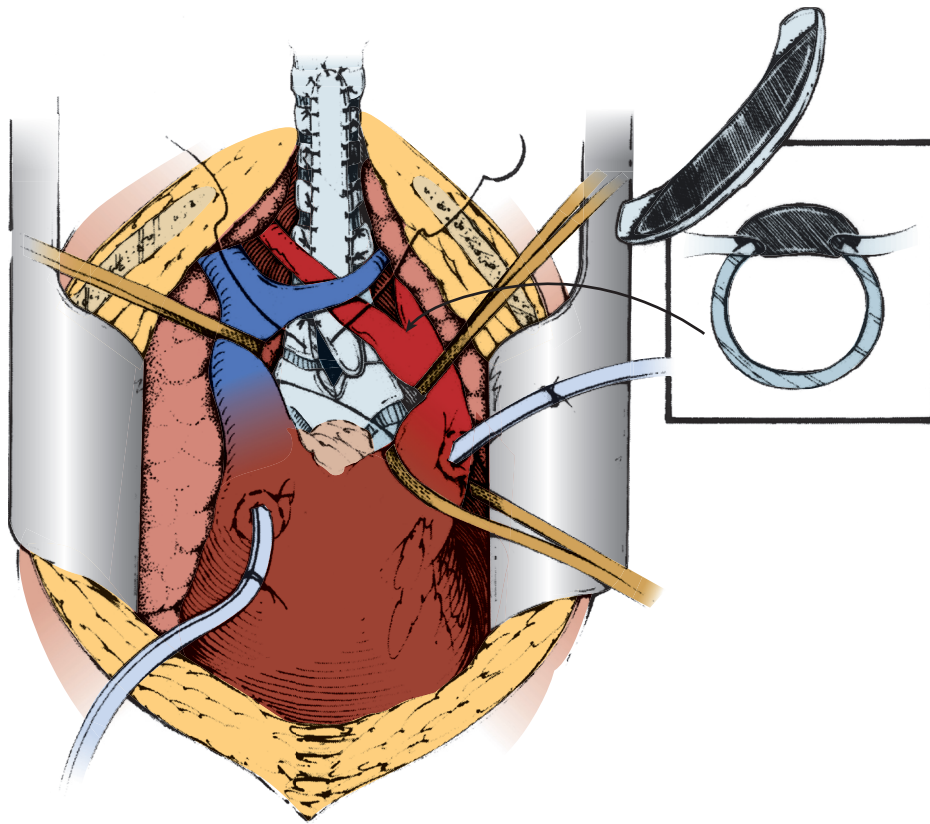


FIGURE 112-11 ■ Cartilage tracheoplasty. Placement of the cartilage graft is indicated. The graft is oriented with preserved perichondrium placed on the luminal side and secured with interrupted sutures. Intraluminal suture exposure is avoided, and the graft is seated on the tracheal opening, rather than being allowed to prolapse into the lumen. (From Jaquiss RD, Lusk RP, Spray TL, et al: Repair of long-segment tracheal stenosis in infancy. *J Thorac Cardiovasc Surg* 110:1504–1512, 1995.)

One week after the procedure, the patient is reexamined with bronchoscopy. If necessary, granulation tissue is removed and secretions are suctioned. If the airway appears to be stable and adequately healed, the patient is weaned from the ventilator over the next several days and extubated. Follow-up bronchoscopies are performed as necessary until the trachea is cleared of granulation tissue.

Long-term follow-up of these infants has shown that the graft becomes incorporated into the tracheal structure and grows with the patient. In addition, reepithelialization of the graft site with ciliated columnar epithelium occurs.²⁸ The most common indication for this surgery is a prior failed pericardial or slide tracheoplasty.²⁹

Pericardial Tracheoplasty

Pericardial tracheoplasty was first performed by Idriss in 1984 at Children's Memorial Hospital.⁶ This procedure also marked the first use of cardiopulmonary bypass for a patient undergoing an operation for complete tracheal rings. Idriss reported on five infants with long-segment tracheal stenosis, all operated on through a median sternotomy with extracorporeal circulation, and all had a pericardial patch inserted to augment the tracheal lumen. There were no deaths or infections. This technique was the procedure of choice at Children's Memorial Hospital for the next 15 years. However, it was not used often in other centers because of problems related to granulation

tissue formation, the need for repeated bronchoscopies for airway clearance, and the need for repeat operations for restenosis.²⁹ The typical approach was through a median sternotomy, with cardiopulmonary bypass for respiratory support.

The approach is similar to that used for TRR. Once the full extent of the tracheal stenosis has been opened, a suitably shaped pericardial patch is fashioned. The patch should be oversized in both width and length, because some shrinking will occur over time. The patch is made of autologous pericardium and is not treated with glutaraldehyde but simply kept in a saline-soaked sponge during the dissection and opening of the trachea. The patch is anchored in place using interrupted or running Vicryl (Polyglactin 910; Ethicon, Somerville, NJ) or PDS sutures (Fig. 112-12).

The suturing begins in the area of the carina, which is the most critical location. This area is chosen because it is the most inferior point of the dissection, and once the lower portion of the patch is in place, less blood and fluid tend to accumulate in the tracheal lumen. A completion bronchoscopy is performed, and the endotracheal tube is replaced and repositioned under direct vision. The patient is ventilated, and the anesthesiologist inflates the lungs to a pressure of 35 or 40 cm H₂O to test the patch for air leaks, which are controlled with additional sutures. The patient is then ventilated and weaned from cardiopulmonary bypass. The heparin is reversed with

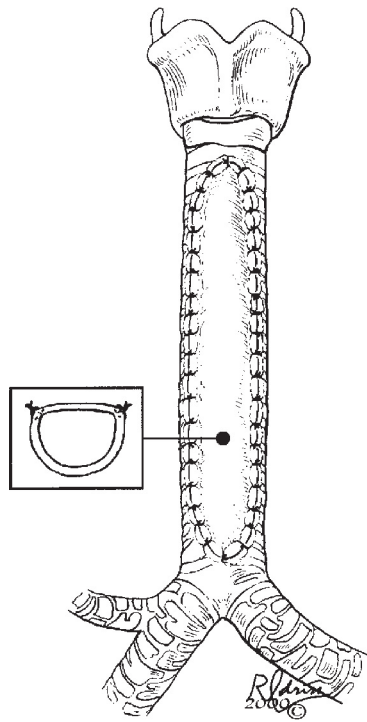


FIGURE 112-12 ■ A completed pericardial patch tracheoplasty. The pericardium is anchored with interrupted Vicryl sutures. In cross section (*inset*), the tracheal lumen is now normal in size. (From Backer CL, Mavroudis C, Gerber ME, et al: Tracheal surgery in children: an 18-year review of four techniques. *Eur J Cardiothorac Surg* 19:777–784, 2001.)

protamine. The edges of the patch are sealed with a very fine spray of biological glue. The extent of the pericardial patch is marked with small hemoclips placed in the soft tissues of the adjacent mediastinum at the superior and inferior portions of the patch. For prevention of patch tracheomalacia, fine monofilament Prolene sutures are used to take partial-thickness bites of the pericardium and fix it to the posterior wall of the ascending aorta and the innominate artery. This acts as a suspending device, holding the patch open. The patient is kept on muscle relaxants and heavily sedated for 1 week. Repeat bronchoscopy is performed.

If the repair is adequate, with a good tracheal lumen and minimal granulation tissue, the patient is then weaned from the ventilator and extubated in 5 to 7 days. Many of these patients, however, have patch tracheomalacia, necessitating a prolonged period of intubation for 1 or 2 more weeks after the first successful bronchoscopy. Repeat bronchoscopies are performed as needed to clear granulation tissue and retained secretions. Over several months, the patch becomes reepithelialized with pseudostratified columnar epithelium.³⁰

As mentioned, the pericardial tracheoplasty has a low operative mortality rate, but it requires a prolonged hospitalization because patients must be kept intubated for a prolonged time. In addition, these patients require frequent bronchoscopic examinations for resection of granulation tissue, which tends to occur chiefly at the carinal area, where there is a critical junction of the pericardial patch, the carina, and the irritation from the distal end

of the endotracheal tube. In addition, a significant percentage of these patients have required a repeat procedure—a tracheotomy to stent the patch, an intraluminal stenting, or other tracheal reoperations.²⁹ Because of all these chronic problems, we consider this procedure to be essentially obsolete. A small pericardial patch can be helpful, however, as an adjunct when tracheal tissue is lacking, for example, to complete a slide tracheoplasty.

Tracheal Autograft Technique

The principle of the tracheal autograft technique is to shorten the trachea and use the excised piece of trachea as an anterior patch (i.e., as an autograft).¹⁰ Patients are operated on through a median sternotomy, with cardiopulmonary bypass. The trachea is incised anteriorly through the area of stenosis, and the midportion of the stenotic trachea is excised. The posterior trachea is brought together with interrupted 6-0 PDS sutures (Fig. 112-13). This leaves an anterior opening that is then augmented with the autograft.²¹ The corners of the autograft are trimmed so that the autograft fits into the anastomosis. The autograft does not shrink like pericardium and therefore does not need to be oversized. The autograft is sutured in place with multiple interrupted 6-0 PDS sutures (Fig. 112-14). If the autograft is not long enough to completely augment the anterior tracheal lumen, the superior portion of the tracheal opening that remains after autograft insertion can be patched with pericardium or cartilage (Fig. 112-15). Placement of the endotracheal tube depends on the anatomy. If the autograft is low enough, we prefer to keep the tube above the anastomosis to avoid irritation of the suture line from tube friction. Alternatively, the tube can be positioned through the area of the autograft if it is in a superior location. After the patients have been ventilated and assessed for air leaks, they are weaned from cardiopulmonary bypass. The autograft is sealed with glue. If the autograft suture line ends up being compressed by the innominate artery, a cervical strap muscle can be mobilized and brought in as an interposition between the innominate artery and the tracheal autograft. The largest published series using this technique is from Children's Memorial Hospital of Chicago.^{10,13,21} We have used this technique occasionally, but we prefer the slide tracheoplasty when feasible.

Homograft Tracheoplasty

The homograft tracheoplasty technique was first performed in adults by Claus Herberhold of Germany. Herberhold and Elliott first applied the technique to a child in 1994.⁹ Jacobs and colleagues reported the largest series of patients undergoing this procedure.³¹ Most of these patients were infants who had a prior failed operation for complete tracheal rings. Cadaveric trachea is harvested, fixed in formalin, washed in thimerosal, and stored in acetone. The operation is performed through a median sternotomy with the patient on cardiopulmonary bypass. The stenosed tracheal segment is opened to widely patent segments proximally and distally. The anterior cartilage is partially excised, and the posterior tracheal muscle or

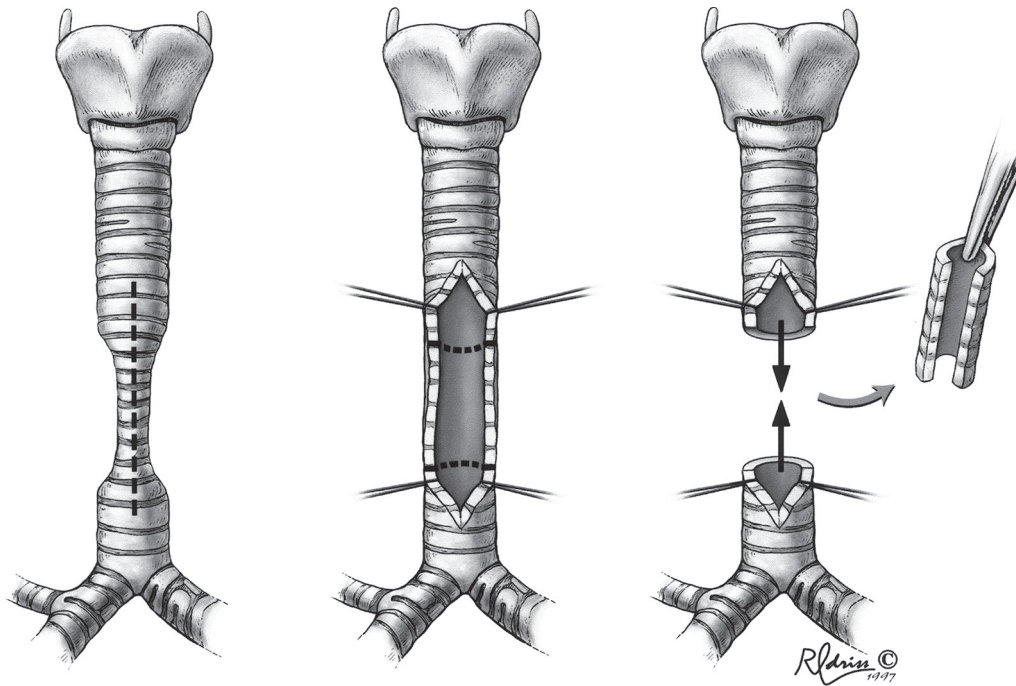


FIGURE 112-13 ■ Tracheal autograft. An anterior longitudinal incision is made through the complete extent of the tracheal rings (*left*). The midportion of the trachea is excised (*center*) to be used as the tracheal autograft. The two remaining orifices of the trachea are reapproximated posteriorly (*right*). (From Backer CL, Mavroudis C, Dunham ME, et al: Repair of congenital tracheal stenosis with a free tracheal autograft. *J Thorac Cardiovasc Surg* 113:869–874, 1998.)

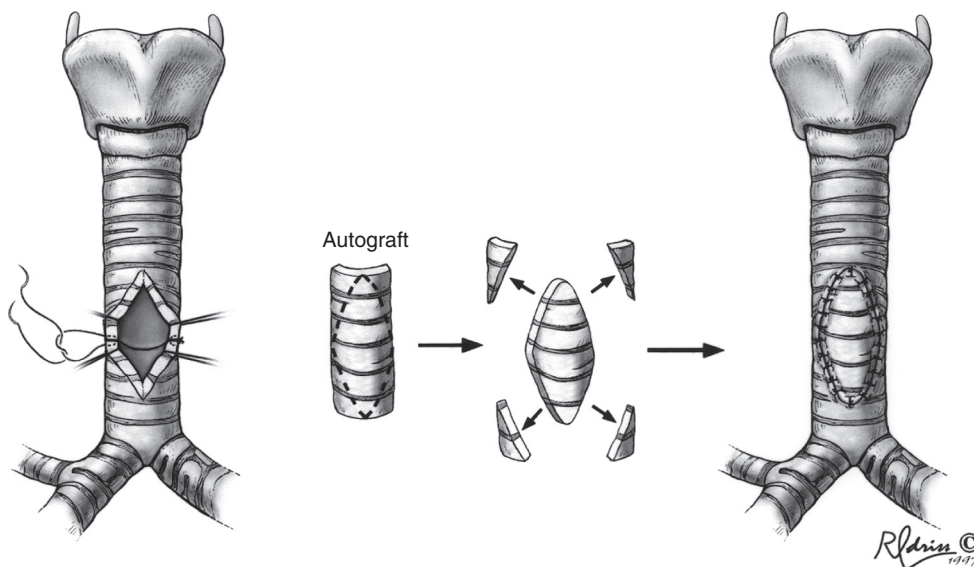


FIGURE 112-14 ■ Tracheal autograft. The posterior tracheal anastomosis is performed with interrupted 6-0 polydioxanone sutures (*left*). The corners of the autograft are trimmed (*center*). The autograft is sutured in place to cover the remaining opening in the anterior trachea (*right*). (From Backer CL, Mavroudis C, Dunham ME, et al: Repair of congenital tracheal stenosis with a free tracheal autograft. *J Thorac Cardiovasc Surg* 113:869–874, 1998.)

tracheal wall remains. A temporary silicone rubber intraluminal stent is placed, and absorbable sutures secure the homograft (trimmed appropriately) in position. Regular postoperative bronchoscopic treatments are needed to clear granulation tissue. The stent is removed endoscopically after endothelialization occurs over the homograft. In Jacobs and colleagues' initial report there were 24

patients, most of whom were reoperations.³¹ Four deaths occurred, for an overall mortality rate of 17%. In Jacobs and associates' more recent report of their North American experience with the homograft, there was one early death among six patients.³² The procedure is used only as an alternative for the patient who had a failed previous primary procedure.

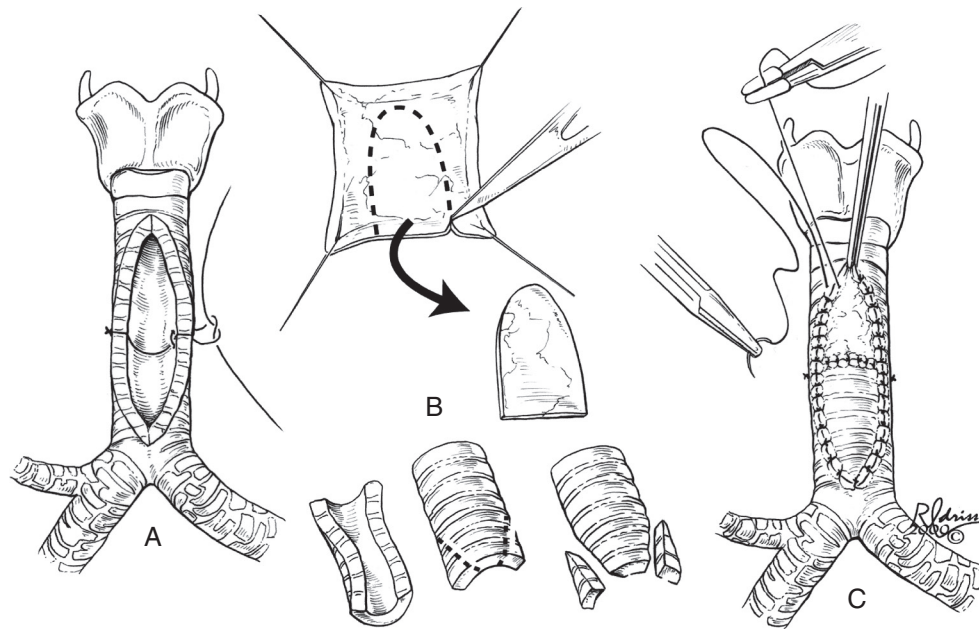


FIGURE 112-15 ■ Composite tracheal autograft. **A**, The posterior anastomosis is performed. **B**, The autograft is trimmed, cutting only the inferior corners of the autograft. A portion of pericardium is harvested and tailored. **C**, The autograft is sutured in place anteriorly, adjacent to the carina. The pericardial patch is inserted superiorly to complete the repair. (From Backer CL, Mavroudis C, Gerber ME, et al: Tracheal surgery in children: an 18-year review of four techniques. *Eur J Cardiothorac Surg* 19:777–784, 2001.)

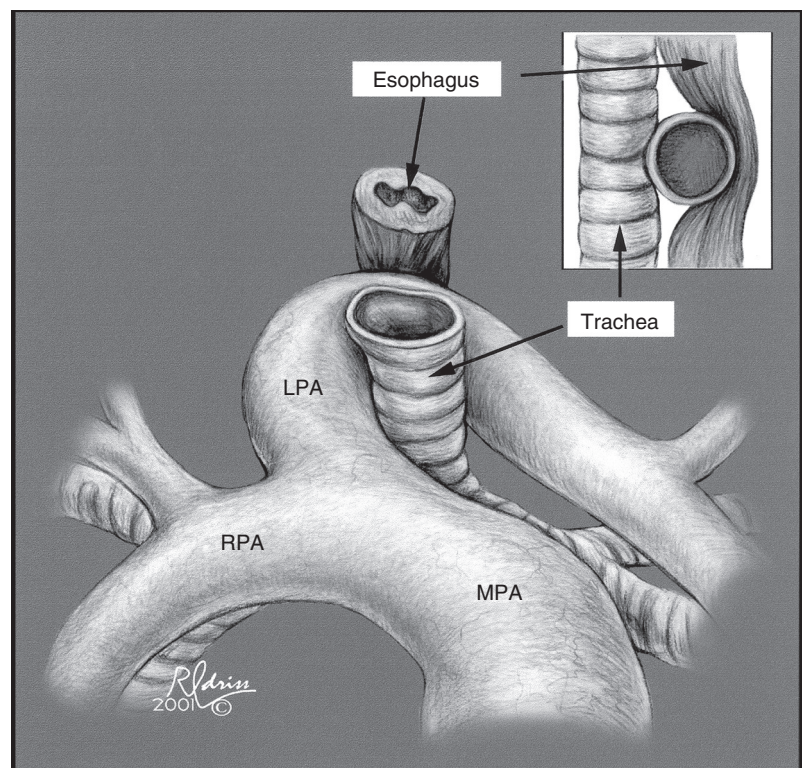


FIGURE 112-16 ■ Pulmonary artery sling. The left pulmonary artery (LPA) originates from the right pulmonary artery (RPA) and acts as a sling, pulling on and compressing the distal trachea and right main bronchus. The *inset* shows anterior compression of the esophagus by the anomalous LPA on the lateral view. *MPA*, Main pulmonary artery. (From Mavroudis C, Backer CL: Vascular rings and pulmonary artery sling. In Mavroudis C, Backer CL, editors: *Pediatric cardiac surgery*, ed 3, Philadelphia, 2003, Mosby, pp 234–250.)

PEDIATRIC TRACHEAL ANOMALIES

Pulmonary Artery Sling

A pulmonary artery sling is found in one third of patients who have tracheal stenosis.¹³ The left pulmonary artery originates anomalously from the right pulmonary artery and courses cranial to the right mainstem bronchus and

posteriorly to the trachea on the way to the left lung. This compresses the right main bronchus and distal trachea (Fig. 112-16). The first pulmonary artery sling repair was reported by Potts from Children's Memorial Hospital.³³ Potts operated on a 5-month-old child who had severe right bronchial compression without a known diagnosis. Potts approached the sling through a right thoracotomy. He made the intraoperative diagnosis of a pulmonary

artery sling with origin of the left pulmonary artery from the right pulmonary artery. After considering several surgical alternatives, including a pneumonectomy, Potts clamped and divided the left pulmonary artery and transposed it anterior to the tracheobronchial tree. He then reanastomosed the site of origin into the right pulmonary artery. The patient survived the operation but was found, almost 25 years later, to have an occluded left pulmonary artery.³⁴

Historically the next series of patients who underwent pulmonary artery sling repair were operated on through a left thoracotomy.³⁵ This allowed better exposure for the anastomosis. However, many of these patients continued to have significant problems with tracheal stenosis and left pulmonary artery stenosis or occlusion. This is because none of the techniques described up to that time had dealt directly with the associated tracheal stenosis that is present in roughly two thirds of patients with pulmonary artery sling. Thus, once the diagnosis of pulmonary artery sling is made, a workup of the airway must be performed in all cases. The current approach is via a median sternotomy with cardiopulmonary bypass, which allows the surgeon to approach both pathologies if necessary.³⁶ Mild hypothermia is used, and the heart remains beating throughout the procedure. The right, left, and main pulmonary arteries are widely mobilized to minimize the tension of the anastomosis. As it passes behind the posterior trachea, the left pulmonary artery may be closely adherent to it and must be dissected off with caution. The left pulmonary artery is divided and transposed anterior to the trachea. It is then reanastomosed to the distal main pulmonary artery, at a site selected to approximate the normal origin of the left pulmonary artery (Fig. 112-17). The anastomosis is performed with running polypropylene suture that is locked at every three to four bites. The tracheal repair is also performed while the patient is on cardiopulmonary bypass. Depend-

ing on the length of the stenosis, TRR or slide tracheoplasty is performed.

Tracheomalacia

Tracheomalacia can be a difficult entity to deal with in the infant and young child. It can be classified as primary or secondary. Causes of secondary tracheomalacia include tracheoesophageal fistula and external compression from vascular structures (i.e., the innominate artery, vascular rings), cardiac structures, congenital cysts, and neoplasms. Tracheomalacia accounts for almost half of all congenital tracheal anomalies that are seen with stridor.³⁷ Symptoms depend on the location, length, and severity of the pathology. Intrathoracic tracheomalacia typically produces expiratory stridor or wheezing, which mimics asthma. Symptoms also may include a harsh barking cough, hyperextension of the neck, recurrent respiratory infections, and, when associated with compression by an anomalous innominate artery, reflex apnea.

Lateral chest radiograph shows narrowing of the trachea during expiration. The diagnosis is confirmed at bronchoscopy if spontaneous respiration is maintained during bronchoscopy—the wide posterior membranous trachea is observed to collapse anteriorly during expiration. These dynamics are not observed when the child is paralyzed and ventilated with positive pressure. Dynamic CT with contrast medium is performed after bronchoscopy to define the nature of underlying suspected extrinsic compression.

Most patients with mild to moderate tracheomalacia eventually grow to the point where the tracheomalacia does not require surgical intervention. However, a small number of patients who have severe tracheomalacia require intubation, ventilation, and usually very high positive end-expiratory pressure (PEEP) to keep the airway open and allow adequate ventilation of the patient.

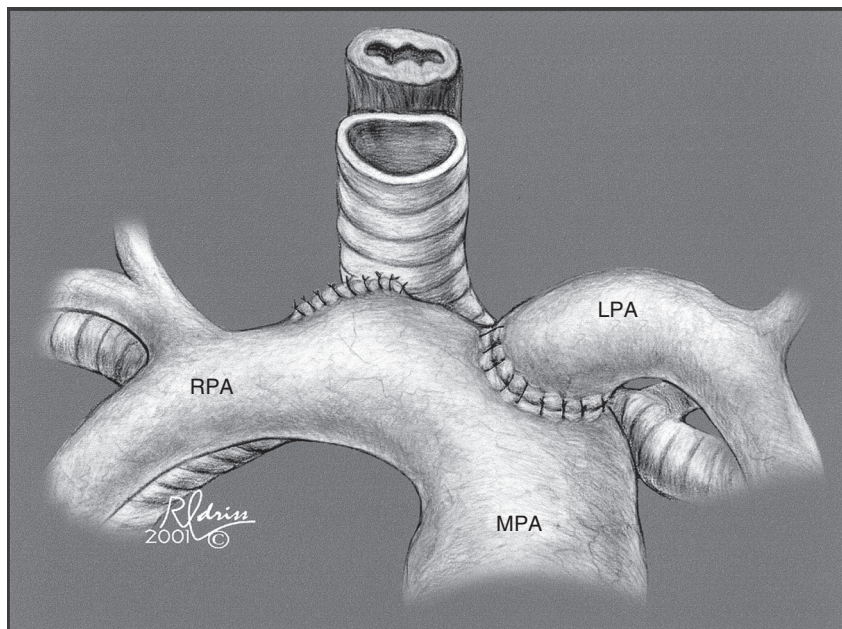


FIGURE 112-17 ■ Pulmonary artery sling repair. The right pulmonary artery (RPA) origin of the left pulmonary artery (LPA) has been oversewn with interrupted sutures (to prevent RPA stenosis). The LPA has been anastomosed to an opening created in the main pulmonary artery (MPA), again with interrupted sutures. The LPA is now anterior to the trachea.

For these severe cases of tracheomalacia, there are several surgical alternatives.

Secondary tracheomalacia is always treated by treating the offending compressing structure first—for example, by repair of a vascular ring or by fixation of an innominate artery. The trachea itself is typically left alone with the anticipation that decompression in conjunction with the growth of the child will result in a more stable airway.

For primary tracheomalacia, one option is tracheostomy. This may obviate the need for positive pressure ventilation because the tracheostomy tube holds open the trachea. With associated bronchomalacia, PEEP may be necessary. Increasingly, these patients are discharged home on ventilation. Many children's hospitals have a separate service for those who become chronically ventilator dependent for a variety of reasons. As the trachea matures and the cartilage gains more strength, these patients can eventually be weaned from their ventilators.

A second alternative is to bronchoscopically place a balloon-expandable wire stent (Fig. 112-18). Stents are usually a procedure of last resort in pediatric airway surgery. However, for severe primary tracheomalacia in patients who are usually ventilator dependent, this can be a life-saving procedure. The largest experience in infants is with the Palmaz stent (Johnson & Johnson International Systems, Warren, NJ).^{38,39} The most common indications in the series from Children's Memorial in Chicago occurred after pericardial tracheoplasty or in patients with tetralogy of Fallot and absent pulmonary valve who had severe compression of the tracheobronchial tree

from enlarged pulmonary arteries. These stents were effective in selected patients, but several patients had complications from significant granulation tissue formation. Again, stents are usually used as a measure of last resort in infants who have not responded to tracheostomy and positive pressure ventilation.

A surgical procedure for infants with tracheomalacia was reported by Hagl and associates from Heidelberg, Germany.⁴⁰ This operation was performed either through a thoracotomy or via a median sternotomy approach. External stabilization of the severely dysplastic distal trachea (six patients) or left main bronchus (two patients) was achieved by suspending the malacic segment in an oversized and longitudinally opened, ring-reinforced polytetrafluoroethylene prosthesis. Multiple pledgeted sutures were placed extramucosally to the dysplastic tracheal wall and the dyskinetic pars membranacea, as well as to the polytetrafluoroethylene prosthesis in a radial orientation. Guided by simultaneous video-assisted bronchoscopy, reexpansion of the collapsed segments was achieved by gentle traction on the sutures while tying (Fig. 112-19). Hagl and associates reported excellent results in six of seven patients. Long-term results are unknown.

Postintubation Stenosis

The largest series of pediatric patients undergoing tracheal surgery for a postintubation stenosis was reported from Massachusetts General Hospital.¹⁹ Wright and colleagues reported 72 patients evaluated for postintubation

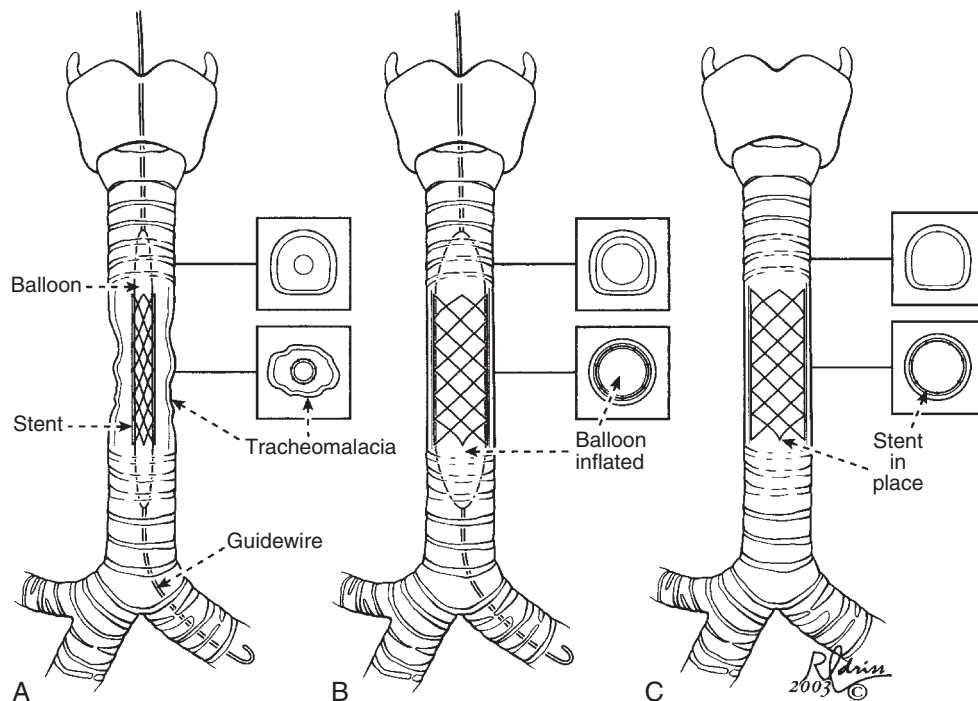


FIGURE 112-18 ■ Palmaz stent insertion in a child with severe tracheomalacia. **A**, The Palmaz stent (mounted on a balloon-tipped catheter) has been positioned in the mid trachea. Positioning of the stent is with both fluoroscopy and bronchoscopy. **B**, The balloon is inflated, compressing the stent against the tracheal wall. **C**, The balloon catheter has been removed, and the stent is now in place. The tracheal lumen is held open by the stent.

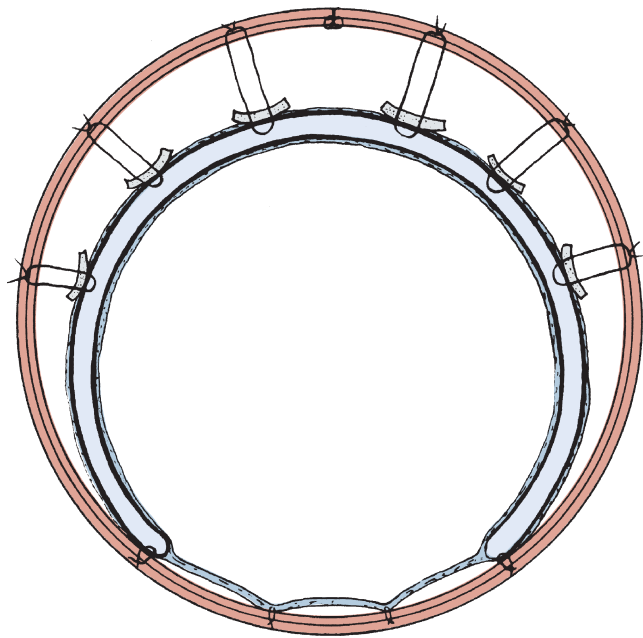


FIGURE 112-19 ■ Cross-sectional view of tracheal external stabilization with “onlay” fixation of the flaccid pars membranacea and free suspension of the malacic cartilaginous portions within an oversized polytetrafluoroethylene prosthesis. (From Hagl S, Jakob H, Sebening C, et al: External stabilization of long-segment tracheobronchomalacia guided by intraoperative bronchoscopy. *Ann Thorac Surg* 64:1412–1421, 1997.)

stenosis during an almost 25-year period. Of these patients, 31 were treated with tracheal resection and 17 were treated with laryngotracheal resection. Postintubation tracheal stenosis typically occurs from a stricture caused by scarring at the site of compression of the tracheal mucosa by the balloon from the endotracheal tube. Historically, balloons were used with low volume and high pressure. Since converting to high-volume, low-pressure balloons, the incidence of postintubation stenosis has diminished significantly. Evaluation of postintubation stenosis is chiefly with bronchoscopy. The larynx should undergo a detailed examination to identify commonly associated supraglottic (arytenoid scarring and fixation), glottic (vocal cord paralysis or granulomas), or proximal subglottic pathology. Here again, the connection with a pediatric otolaryngologist is paramount. These commonly associated problems may require attention before the tracheal stenosis is repaired. The technical details of the tracheal resection for these patients are similar to those of resection for patients with congenital stenosis secondary to complete tracheal rings.

Tracheal Web

Web-like diaphragms most often occur at the subcricoid level. These webs typically do not involve a significant length of the trachea. Tracheal webs are evaluated in a fashion similar to that used for other patients with tracheal stenosis, and bronchoscopy continues to be the primary diagnostic tool. Tracheal webs have been removed or excised bronchoscopically with biopsy forceps and occasionally with the use of an insulating cauterizing

electrode. Laser therapy or balloon dilation also may be successful. If this should fail, a tracheostomy done below the web may be a temporary solution, allowing the patient to grow and have a definitive resection later in life. In most cases, these webs are cared for by the pediatric otolaryngologist, with only occasional need for tracheal resection by the thoracic surgeon.

SUMMARY

The most common indication for a surgical procedure on the trachea of an infant or small child is tracheal stenosis secondary to complete tracheal rings. Close cooperation between the pediatric cardiothoracic surgeons and the otolaryngologists is essential. We approach all cases via a median sternotomy and perform the repair on beating-heart cardiopulmonary bypass. We prefer TRR for short segments (six to eight tracheal rings, one third of the trachea), and slide tracheoplasty for long-segment stenosis. If the patient has an associated pulmonary artery sling or intracardiac anomaly, that lesion should be repaired simultaneously. Bronchoscopic expertise is essential to make the diagnosis, for intraoperative management, and for postoperative airway management and clearance. The outlook for these patients has evolved significantly from the mid 1970s, when most of these patients died, to the current era—the mortality rate for complete tracheal rings is now less than 15%. The postoperative management of these patients is complex, often because of comorbid conditions, and requires extreme attention to detail and vigilance.

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PATENT DUCTUS ARTERIOSUS, COARCTATION OF THE AORTA, AND VASCULAR RINGS

Sitaram M. Emani

CHAPTER OUTLINE

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Included under the rubric of congenital heart defects are abnormalities involving the distal transverse arch and proximal descending aorta. Clinical manifestations range widely, from severe congestive heart failure or debilitating stridor to mere incidental finding on routine evaluation. The treatment of these conditions represents the first procedures performed for congenital cardiovascular malformations. The first surgical closure of a patent ductus arteriosus (PDA), performed by Dr. Robert Gross in 1938, opened the era of pediatric cardiac surgery.

PATENT DUCTUS ARTERIOSUS

Introduction

The prevalence of PDA at several days of age varies from 20% to 80% and varies inversely with gestational age and birth weight.¹ Between 1998 and 2008, the Nationwide Inpatient Sample database demonstrated increase in the prevalence of PDA in the United States from 1.9 to 2.8 per 1000 live births, likely because of increased detection and improvements in prenatal and neonatal care.² It is

frequently associated with other heart defects ranging in severity from patent foramen ovale to complex congenital malformations. Several genetic defects have been implicated in the development of PDA, including genes that encode prostaglandin receptors and regulators of smooth muscle cell contraction.³⁻⁵

Pathophysiology and Natural History

Although the ductus arteriosus shunts mostly right to left in utero, expansion of the lungs shortly after birth results in a decline in the pulmonary vascular resistance and increased pulmonary blood flow and arterial oxygen tension. Ductal closure usually occurs within the first several hours after birth, and is thought to be mediated by loss of the placental source of prostaglandins, increased degradation of prostaglandins within the lungs, and increased arterial oxygen tension, which stimulate constriction of smooth muscle cells within the wall of the ductus. The prostaglandin-mediated mechanism is most active in the ductus of premature infants, whereas oxygen tension primarily promotes ductal closure in the term infant, likely because of differences in cyclooxygenase (COX) isoforms present in the ductal tissue at various stages of gestation.⁶ Thus, the PDA of a term infant is generally unresponsive to COX inhibition, whereas the PDA of a premature infant frequently responds.

Spontaneous closure of the ductus within 4 days occurs in 90% to 95% of full-term infants and in 80% to 90% of premature infants at 30 to 37 weeks' gestation.⁷ The rate of spontaneous closure is inversely proportional to birthweight, with only 50% spontaneous closure in extremely low-birthweight infants (500-999 g).⁸ In premature infants, PDA increases the risk of prolonged ventilation and oxygen requirements, pulmonary hemorrhage, and bronchopulmonary dysplasia.⁹⁻¹¹ The diastolic steal is associated with renal hypoperfusion, intestinal ischemia, necrotizing enterocolitis (NEC), reduced middle cerebral artery blood flow velocity, and increased risk of intraventricular hemorrhage.¹²⁻¹⁸ The long-term persistence of PDA is associated with development of endocarditis, congestive heart failure, and eventual development of irreversible pulmonary vascular obstructive disease. Estimated mortality without intervention is 60% by 60 years of age.¹⁹

Clinical Presentation

Presentation ranges from asymptomatic murmur on examination to symptoms of congestive heart failure caused by large left-to-right shunting. Manifestations of pulmonary overcirculation include hypotension, pulmonary edema, and failure to thrive in infants and children. Neonates, particularly premature neonates, may demonstrate intestinal malperfusion and renal insufficiency in addition to respiratory compromise. Cyanosis is occasionally the presenting symptom in older patients with pulmonary hypertension.

Diagnosis

Physical examination reveals the presence of a "to and fro" murmur heard best from the left upper sternal

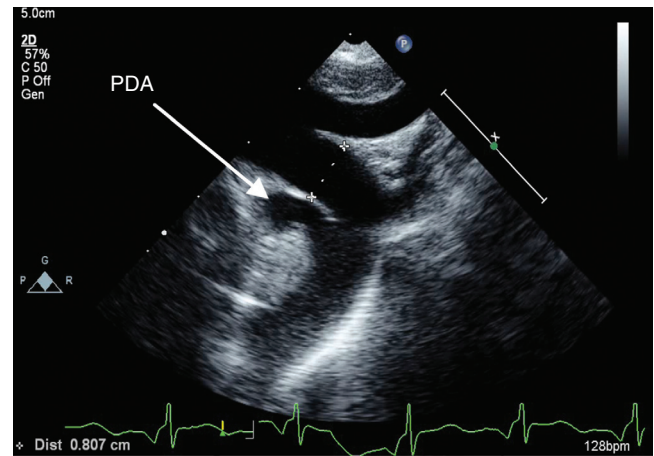


FIGURE 113-1 ■ Echocardiographic appearance of the patent ductus arteriosus (PDA). Note the insertion just distal to the takeoff of the left subclavian artery.

border, and leads to suspicion of PDA. Chest radiography may show cardiomegaly, signs of pulmonary congestion, and pulmonary edema. Transthoracic echocardiography is used to make the diagnosis (Fig. 113-1). Retrograde flow in the descending aorta indicates significant left-to-right shunting. The presence of a left-sided aortic arch must be confirmed if surgical therapy is contemplated, as this influences the choice of incision. Continuous left-to-right shunting through the ductus is expected, and the presence of right-to-left shunting or bidirectional shunting should raise suspicion for pulmonary hypertension. In adults, echocardiographic windows may be suboptimal, and computed tomography (CT) or magnetic resonance angiography may be necessary to establish the diagnosis. Diagnostic cardiac catheterization is only necessary if pulmonary hypertension is suspected.

Treatment

Medical

Medical treatment of PDA can be separated into (1) management of heart failure and (2) pharmacologic closure in premature neonates. Management of heart failure focuses on reducing the clinical impact of left to right shunting. Diuretics are the mainstay of therapy in patients with pulmonary congestion, but afterload reduction with angiotensin-converting enzyme inhibitor may be a useful adjunct. In hospitalized patients, strategies to avoid reduction of pulmonary vascular resistance limit the degree of left-to-right shunting, and include maintenance of spontaneous ventilation and avoidance of supplemental oxygen when possible. In intubated patients, an increase in the peak end expiratory pressure can reduce left-to-right shunting.²⁰

Pharmacologic closure of PDA with a COX inhibitor (COXi) in premature neonates, even if asymptomatic, improves the rate of eventual ductal closure and incidence of intraventricular hemorrhage, decreases the need for surgical closure, but does not improve mortality or incidence of NEC. Early treatment of a symptomatic

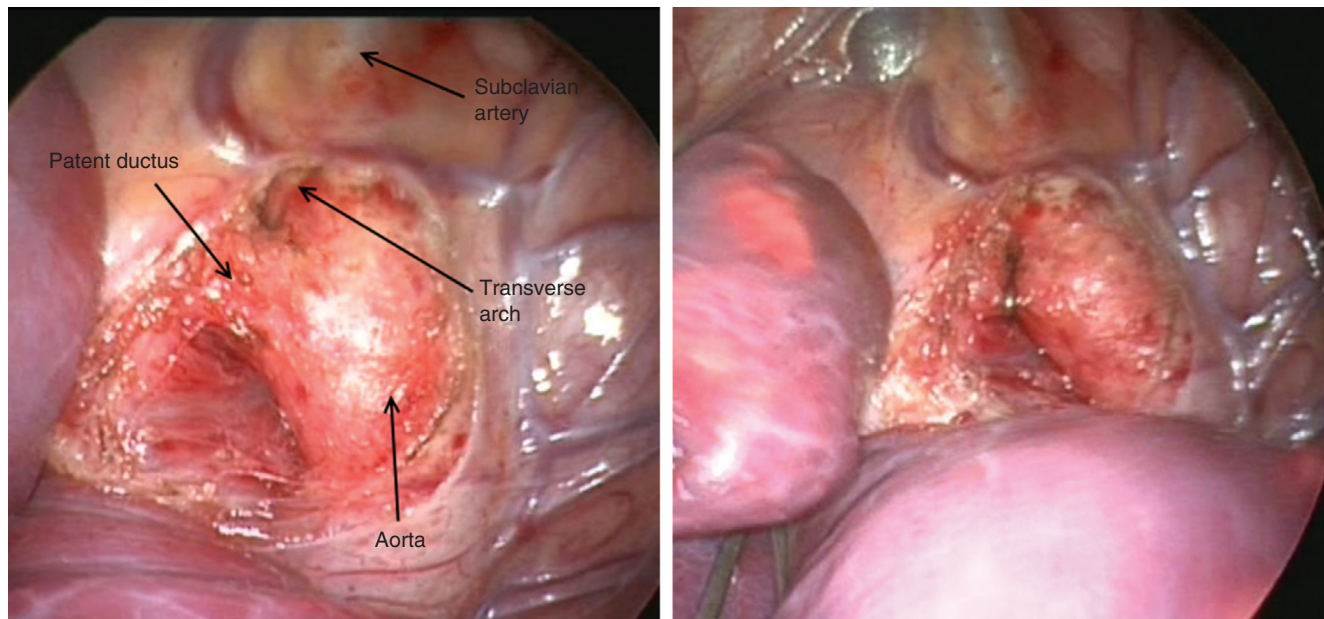


FIGURE 113-2 ■ Intraoperative view of patent ductus arteriosus before (*left*) and after (*right*) clip placement.

PDA (i.e., when clinical signs first appear) has been shown to decrease the incidence of chronic lung disease, duration of mechanical ventilation, and NEC when compared with late symptomatic treatment (i.e., after signs of congestive cardiac failure).²¹ The COXi indomethacin and ibuprofen are equally effective at producing ductal closure. Closure rate between 60% and 80% is achieved with one course of indomethacin, but the success rate of each subsequent course is 40%.^{22,23} A COXi is ineffective at producing ductal closure in term infants because of the lack of prostaglandin-responsive contractile smooth muscle in the ductal tissue. Complications owing to COXi include renal impairment, intestinal perforation, and NEC.²⁴ A randomized clinical study compared oral paracetamol with ibuprofen in preterm infants and demonstrated that paracetamol may be a medical alternative in the management of PDA.²⁵

Surgical

Premature Infants. In premature infants, surgical therapy is generally reserved for failure of COXi therapy in symptomatic patients or for those who develop contraindications to COXi therapy: NEC, renal dysfunction, and intraventricular hemorrhage. This strategy of reserving surgery for failure of medical therapy can lead to a higher incidence of NEC when compared with early surgery, although no difference in mortality has been demonstrated.²⁶⁻²⁹ Early surgical duct closure allows early institution of full oral feeding, but this does not necessarily translate into shorter hospital stay.³⁰ Yet controversy regarding the indications and timing for surgical therapy remains, and variability in practice patterns have been observed.³¹

Preoperative evaluation focuses on medical stabilization, including detection and appropriate treatment of pre-existing infections prior to surgery. Surgery for premature infants can be performed either in the intensive

care unit or in the operating theater. Surgical ductal ligation is generally performed via left thoracotomy, although video-assisted thoracoscopic surgery (VATS) approach has been described, and the PDA is occluded by placement of an external clip (*Fig. 113-2*). Preoperative imaging must exclude the presence of ductal or pulmonary artery aneurysms, which may necessitate extensive resection and vascular reconstruction rather than simple ductal ligation.³²

Full-Term Infants, Children, and Adults. Pharmacologic closure is ineffective in full-term infants, children, and adults, leaving surgical or transcatheter closure as the only options. Ductal closure is indicated in both symptomatic and asymptomatic patients to reduce the risks of endocarditis and pulmonary hypertension. Asymptomatic infants may undergo elective closure between 1 and 2 years of age to facilitate VATS or transcatheter closure, whereas symptomatic infants should undergo prompt evaluation and closure. The presence of cyanosis and bidirectional shunting through the PDA on echocardiography should prompt preoperative cardiac catheterization to measure pulmonary vascular resistance. If elevated pulmonary vascular resistance is unresponsive to oxygen or nitric oxide, closure is contraindicated.

Options for surgical closure in infants include thoracotomy or VATS (see *Surgical Approaches*). Children and adults are candidates for closure via the transcatheter, thoracotomy, VATS, or sternotomy approaches, depending on the morphology of the PDA. Short length and large diameter of the PDA increase the risk of device embolization during transcatheter closure and bleeding during VATS closure.³³ A severe adverse event rate of approximately 2% is seen with transcatheter closure, with younger age being a significant risk factor.^{34,35} To avoid the risk of recanalization, some advocate ductal division in addition to ligation in children and adults.³⁶ Extensive ductal calcification increases the risk of bleeding during

external ligation by VATS or thoracotomy. In these patients, median sternotomy, cardiopulmonary bypass, and closure through a pulmonary arteriotomy may be the safer alternative.

Prognosis

Operative mortality related to PDA ligation in full-term infants and children is less than 1%.³⁶ Premature infants with multiple comorbidities may have hospital mortality as high as 20%. Complications of surgical ligation include left recurrent laryngeal nerve injury, bleeding, postoperative chylothorax, and development of coarctation. Asymptomatic recurrent laryngeal nerve injury can be detected in up to 7% of patients by systematic endoscopy, and the major risk factor for this injury is birth weight less than 1 kg.³⁷ Symptomatic nerve injury manifested by aspiration of feeds is rare.

COARCTATION OF THE AORTA

Introduction

Narrowing of the thoracic aorta beyond the level of the innominate artery (discrete coarctation of the aorta or transverse arch hypoplasia) represents 4% to 8% of cases of congenital heart disease, with an incidence in the general population estimated at 0.2 per 1000 live births.² Bicuspid aortic valve is an associated finding in up to 50% of patients, and hypoplasia of left heart structures is relatively common. A ventricular septal defect (VSD) may be seen in 30 to 60% of patients, and it may be associated with posterior malalignment of the conal septum leading to left ventricular outflow tract obstruction. Complex congenital heart disease and associated with hypoplasia of the systemic ventricle (hypoplastic left heart syndrome, right dominant atrioventricular canal, transposition of the great arteries with hypoplastic right ventricle) may have associated coarctation that affects management. The incidence of coarctation in patients with right aortic arch is unknown, but it has been estimated to be approximately 4%.³⁸

Anatomy and Pathophysiology

The location and extent of aortic obstruction can vary from patient to patient. Discrete coarctation typically occurs just below the origin of the left subclavian artery at the insertion of the ductus arteriosus (juxtaductal coarctation). More diffuse hypoplasia of the distal arch between the left carotid artery and left subclavian artery occurs more commonly in patients with bovine arterial trunk, in which the innominate artery and the right carotid artery arise within close proximity from the proximal transverse arch. An aberrant right subclavian artery arising distal to the coarctation occurs in approximately 3% of patients.

The etiology of coarctation with hypoplasia of the distal transverse arch is not well defined, but its association with hypoplasia of left heart structures suggests common genetic, hemodynamic, or environmental

mechanisms.³⁹ Discrete coarctation of the aorta at the isthmus likely results from abnormal infiltration of ductal tissue onto the juxtaductal aorta.⁴⁰ Synchronous with ductal closure, the contractile ductal tissue within the aorta constricts, resulting in luminal narrowing of the aorta and development of a posterior shelf. It is not uncommon for the aorta to appear of adequate size in the presence of a patent ductus arteriosus, yet manifest coarctation following ductal closure.

Natural History

If the coarctation is left untreated, the prognosis varies from severe heart failure in infancy to asymptomatic hypertension in older children and adults. Collateral vessels become prominent because of increased flow within the intercostal, internal mammary, and scapular blood vessels. The increased flow within these vessels can be sufficient to reduce the blood pressure gradient between the upper and lower extremities at rest. With exercise, however, the gradient may rise significantly because of the elevated vascular impedance. Upregulation of circulating catecholamines and the renin-angiotensin system leads to systemic hypertension. Left ventricular hypertrophy is a result of elevated systemic vascular resistance. Untreated coarctation is associated with a substantially diminished long-term survival, with 75% mortality by 50 years of age.⁴¹ Death in these patients is usually due to systemic effects of hypertension, including heart failure, intracranial hemorrhage, coronary artery disease, or aortic rupture or dissection.

Clinical Presentation

The clinical presentation varies depending on the age at presentation. Almost half of patients with coarctation will develop symptoms within the first month of life and will often have the preductal subtype of coarctation with hypoplasia of the arch. Neonates with unsuspected critical coarctation usually have systemic hypoperfusion, metabolic acidosis, and congestive heart failure manifested as tachypnea and difficulty feeding. The timing of the onset of symptoms generally correlates with constriction of the PDA, which provides systemic circulatory support for a period of time after birth. As the ductus closes, perfusion to the lower extremities and abdominal viscera becomes compromised, and end-organ failure manifests with renal dysfunction, hepatic failure, intestinal ischemia, and profound metabolic acidosis. On physical examination, prominent upper extremity and weak lower extremity pulses may be found. Neonates presenting in this manner have a high mortality without urgent intervention. With less severe degrees of coarctation, or in the presence of sufficient collateral development, symptoms may not develop until infancy or adolescence. Asymptomatic patients have a murmur or hypertension. Young adults usually demonstrate hypertension refractory to pharmacotherapy, exercise intolerance, headaches, or angina.

The classic physical findings include the presence of brachiofemoral pulse delay, diminished or absent femoral pulses, and a blood pressure gradient between the upper

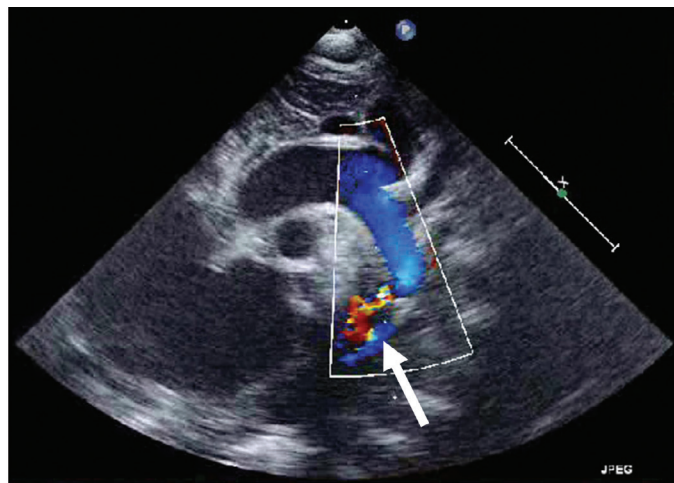
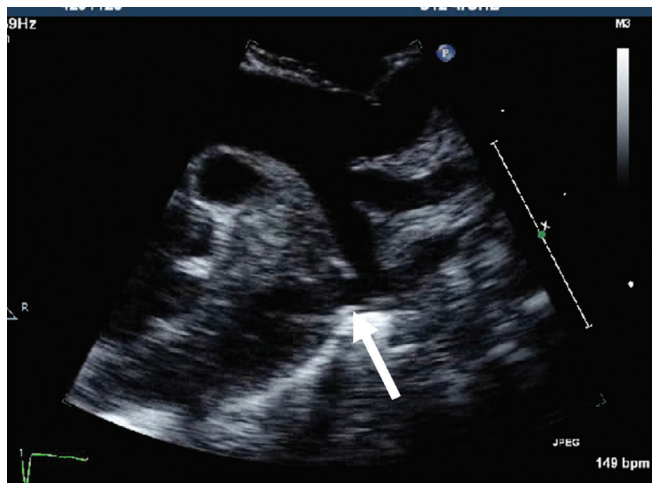


FIGURE 113-3 ■ Discrete coarctation of the aorta on two-dimensional echocardiography and color Doppler imaging. Although there appears to be mild hypoplasia of the transverse arch, color Doppler does not reveal flow acceleration across this segment.

and lower extremities. In the presence of well-developed collaterals, there might not be a significant gradient between upper and lower extremity blood pressures. A systolic ejection murmur is audible over the base of the heart and left interscapular region. The electrocardiogram may reveal evidence of left ventricular hypertrophy in older patients.

Diagnosis

Infants with severe coarctation may demonstrate radiographic signs of cardiac enlargement and pulmonary congestion. During adolescence or adulthood, the findings can include a “figure-three” configuration resulting from proximal and post-stenotic dilation of the aorta. Notching of the inferior border of the ribs from the development of intercostal collateral vessels is common by adolescence.

The segment of coarctation can usually be visualized easily in neonates and children with two-dimensional echocardiography (Fig. 113-3). Normalized measurements of the transverse aorta, aortic isthmus, and descending aorta must be obtained. In neonates, a z-score less than -2 indicates significant narrowing. In older children and adults, a greater than 50% decrease in diameter at the aortic isthmus should be considered severe coarctation. As mentioned previously, associated VSD, aortic and mitral valvular abnormalities, and ventricular hypoplasia must be ruled out. Pulsed- and continuous-wave Doppler estimates the pressure gradient directly at the area of coarctation. In the neonate, the pressure gradient measured by echocardiography may be confounded by presence of a PDA or severe ventricular dysfunction. Similarly, in the older child or adult, the pressure gradient may underestimate the severity of the narrowing because of the presence of significant collaterals. A peak gradient greater than 20 mm Hg, especially if accompanied by continuous forward flow during diastole in the descending or abdominal aorta, suggests significant aortic coarctation.

It is important to define the anatomy of the aortic arch in patients with coarctation, because hypoplasia of the

transverse arch can alter surgical management. A transverse arch z-score of less than -2 often requires surgical management at the time of coarctation repair. The presence of a “bovine trunk,” in which the innominate artery and left common carotid artery arise as a single trunk, should raise concerns of hypoplasia of the transverse arch between the common trunk and the left subclavian artery.

In older children and adults, the anatomy may be difficult to define with echocardiography because of poor sonographic windows. CT, CT angiography, and magnetic resonance imaging (MRI) have become valuable diagnostic tools in these patients, because they provide superior imaging of the transverse and descending aorta, as well as important information regarding the extent of collateral development. Catheterization with angiography is used to determine the diagnosis and severity of coarctation in patients with disparate clinical and echocardiographic findings. It is also used to determine the degree of coronary artery stenosis in adult patients requiring surgical repair. Transcatheter intervention is preferred for treatment of recoarctation, but its application for native coarctation remains controversial.

Treatment

Patients with significant coarctation or recoarctation are candidates for surgical or transcatheter intervention to reduce the risk of long-term complications. This includes patients with arm-to-leg systolic blood pressure difference greater than or equal to 20 mm Hg, brachiofemoral pulse delay, peak transcoarctation gradient greater than 20 mm Hg at angiography, and those with long-standing hypertension or left ventricular hypertrophy. Elective repair in asymptomatic patients should be performed before 2 years of age, because persistent hypertension following repair has been documented in patients undergoing delayed repair.

Medical Management

Severe neonatal coarctation manifests with profound acidosis from lower extremity hypoperfusion caused by

ductal closure, and it can be associated with moderate to severe ventricular dysfunction. Medical stabilization before operating in these patients improves outcomes compared with emergent operation. Ventilatory and inotropic support and intravenous administration of bicarbonate are used to control the metabolic acidosis and ventricular dysfunction. Prostaglandin E₁ (0.01–0.1 µg/kg/min) is given to reestablish ductal patency, and its efficacy is monitored with serial echocardiograms. Cardiovascular collapse can be difficult to resuscitate medically, and may require extracorporeal membrane oxygenation support (ECMO). A major pitfall of preoperative ECMO support in a patient with coarctation is the inadequacy of lower-body perfusion. Neonatal ECMO cannulation is often performed through the carotid artery and jugular vein. With this approach, however, perfusion distal to the coarctation segment remains compromised, and measures to improve distal perfusion must be pursued immediately. These measures include prostaglandin E₁ infusion, transcatheter intervention (balloon angioplasty), or traditional surgical resection and reanastomosis.

Surgical Repair

Surgical repair may entail anatomic repair versus extra-anatomic bypass. Anatomic repair involves reconstruction with native aortic tissue, patch augmentation, or interposition grafting, and it is the preferred strategy for primary repair and reoperative repair in children. Extra-anatomic ascending aorta to descending aortic bypass is reserved for adults with complex coarctation undergoing concomitant cardiac surgical procedures (valve replacement or coronary artery bypass grafting).

Anatomic repair in children entails resection of the coarctation segment with end-to-end anastomosis of the distal transverse arch to the descending aorta. Primary treatment for neonates and infants is extended end-to-end anastomosis in which (following coarctation resection) the descending aorta is mobilized, advanced, and anastomosed onto the undersurface of the transverse arch at the level of the left carotid artery (Fig. 113-4). Patch angioplasty or interposition grafts are typically necessary for adults and adolescents, in whom limited aortic mobility prevents a tension-free aortic anastomosis. Subclavian flap angioplasty involves division of the left subclavian artery and use of the proximal portion for aortic reconstruction. The flap is placed on the aorta distal to the subclavian artery for traditional coarctation repair, whereas a reverse flap is used to augment the transverse arch when hypoplasia between the left carotid and subclavian artery is encountered. Coarctation in patients with right aortic arch is approached with a right thoracotomy and treated by patch angioplasty rather than extended end-to-end anastomosis.³⁸

Recurrent aortic arch obstruction following previous coarctation repair can be treated surgically with native arch reconstruction, patch aortoplasty, or placement of an interposition graft.⁴² In rare circumstances, ascending-to-descending aortic grafts are used for repair of native or recurrent coarctation associated with significant cardiac disease that requires concomitant surgical

management (coronary artery bypass grafting, aortic valve replacement).⁴³ Access to the descending aorta can be obtained by incising the posterior pericardium and dissecting the supradiaphragmatic aorta. Ascending to abdominal aorta bypass avoids the risk of paraplegia associated with left thoracotomy repair of recoarctation in adults.^{43,44}

During thoracotomy in an older child or adult, large collateral vessels may be encountered and require meticulous hemostasis. To minimize the risk of spinal cord injury, hyperthermia should be treated aggressively, and mild hypothermia (33–35° C) is preferred. Although repair of coarctation through a left thoracotomy does not require circulatory support, partial bypass may be helpful in adolescents and adults in whom collateral vessels are underdeveloped or have been surgically interrupted. Partial left heart bypass is instituted by providing venous drainage (left atrial appendage or pulmonary vein) and arterial cannulation (femoral artery or descending aorta). Native heart ejections are maintained to provide antegrade blood flow to the upper body during the cross-clamp period.

Coarctation and Ventricular Septal Defect

The presence of a VSD can alter the management of coarctation. Elevated resistance to systemic outflow from coarctation or associated left ventricular outflow tract obstruction can drive increased pulmonary blood flow and result in profound heart failure. Factors that influence therapeutic strategy include the size and likelihood of closure of the VSD and the degree of proximal transverse arch hypoplasia. The location of the VSD is an important determinant of the probability of eventual closure, with the highest closure rates seen with muscular VSDs. Surgical options for patients with unrestrictive VSD and coarctation include single-stage and staged repair of both lesions. Single-stage repair of both coarctation and VSD through a midline sternotomy requires cardiopulmonary bypass but is preferred if transverse arch hypoplasia (z-score < -3.0) is present.⁴⁵ Staged repair of the coarctation through a left thoracotomy with or without placement of a pulmonary artery band to control left-to-right shunting avoids the use of cardiopulmonary bypass. This approach is preferable if spontaneous closure of the VSD is likely or if cardiopulmonary bypass is contraindicated.⁴⁶

Transcatheter Intervention

Balloon angioplasty with stenting is an effective treatment for recurrent coarctation of the aorta and is the treatment of choice.⁴⁷ For native coarctation, percutaneous balloon angioplasty with or without stenting is an evolving modality of treatment.⁴⁸ Compared with surgical repair, balloon angioplasty is associated with a higher incidence of restenosis.^{49,50} Acute outcomes of stenting for native coarctation are favorable, but long-term follow-up is lacking.^{51,52} The use of a covered stent instead of a bare metal stent may be associated with decreased recoarctation rate, but it does not prevent aneurysm formation.⁵³

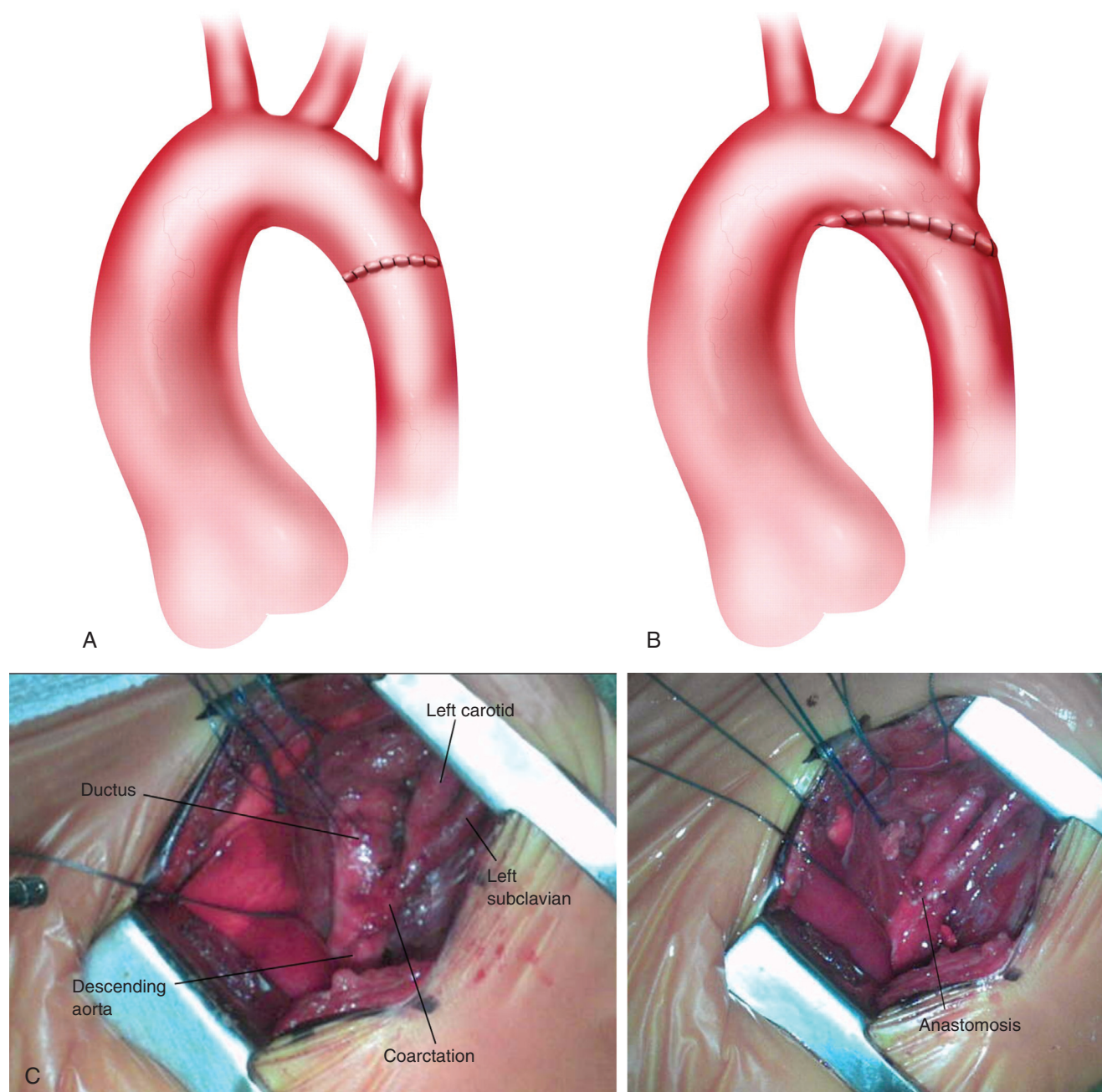


FIGURE 113-4 ■ Techniques for surgical repair of coarctation include (A) end-to-end anastomosis or (B) extended end-to-end anastomosis. C, Intraoperative appearance of coarctation segment (*left*) and extended end-to-end anastomosis (*right*).

Angioplasty and stenting are alternatives to surgery in high-risk patients in whom temporary relief of discrete coarctation is desired. In adults, balloon dilation and stenting of native coarctation has resulted in aneurysm formation, rupture, and aortic dissection, and recoarctation.⁵⁴⁻⁵⁶

Postoperative Complications

Complications specific to coarctation repair include persistent hypertension, mesenteric arteritis, spinal cord ischemia, aneurysm formation, and recurrent coarctation. Significant hypertension can persist in the postop-

erative period despite a successful operation, and intravenous esmolol is effective at controlling this in the acute postoperative period.^{57,58} Acute abdominal pain, thought to be secondary to mesenteric arteritis, was once a common occurrence following coarctation repair. In recent years, the reported incidence of this complication has been low, likely because of improvements in early diagnosis and intervention. Complications related to the thoracotomy and aortic dissection include pneumothorax, chylothorax, and recurrent laryngeal nerve injury. The major risk factor for persistent late hypertension is older age at time of repair, such that 70% of adult patients require ongoing long-term antihypertensive therapy.⁵⁹⁻⁶¹

Prognosis

Operative mortality for neonates and infants with isolated coarctation or coarctation with VSD ranges from 1% to 5%.⁶²⁻⁶⁴ Survival rates at 10 and 30 years following repair are approximately 90% and 70%, which is slightly less than the age-matched general population.⁶⁵ The incidence of recoarctation ranges from 10% to 30% in infants, with younger age being a significant risk factor for recurrence and shorter duration to reintervention.⁶⁶⁻⁷⁰ The presence of a small transverse arch is also a risk factor for reintervention.⁶⁷

In infants, the surgical techniques of extended end-to-end anastomosis and subclavian flap arterioplasty have been associated with the lowest risk of recoarctation in most series.^{71,72} Subclavian artery ligation affects limb development, but it does not result in limitation of life-style.⁶³ In children, adolescents, and adults, patch repair of coarctation with or without luminal ridge resection has been associated with a higher incidence of late aneurysm formation when compared with end-to-end anastomosis or interposition grafting.^{73,74} Extra-anatomic bypass is associated with a low rate of paraplegia and stroke in adults with complex coarctation.⁷⁵ Although low rates of recoarctation have been demonstrated following balloon angioplasty of native coarctation, these results have not been reproduced consistently.^{76,77}

VASCULAR RINGS

Introduction

The term *vascular ring* refers to a vascular anomaly that leads to encirclement of the trachea and esophagus. Included in this discussion are vascular compression syndromes, in which the trachea and esophagus are compressed by vascular structures that do not form a complete ring. Symptomatic vascular rings constitute approximately 1% of all cardiovascular anomalies; however, the prevalence of asymptomatic vascular rings, which are more common than symptomatic rings, is unknown. Associated intracardiac pathology may be present in 10% to 30% of patients and includes VSDs, tetralogy of Fallot, patent ductus arteriosus, and congenitally corrected transposition of the great arteries.

Classification

The Congenital Heart Surgery Nomenclature and Database Project classifies vascular rings and compression syndromes as double aortic arch, right arch/left ligamentum, pulmonary artery sling, and innominate compression.⁷⁸ Double aortic arch and right aortic arch with left-sided ductus are examples of complete rings. Innominate artery compression and pulmonary artery sling, which do not form complete rings, lead to specific compression syndromes.

Anatomy and Pathophysiology

During normal embryologic development of the thoracic great vessels, regression of specific segments of the

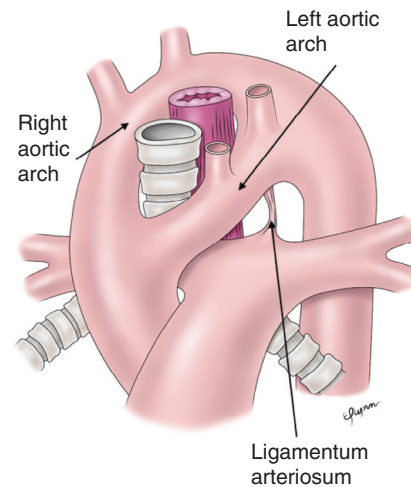


FIGURE 113-5 ■ Double aortic arch creating complete ring around aorta and esophagus. (Compliments of Andrew Powell, MD, and Emily Flynn-Thompson, Children's Hospital Boston.)

embryologic aortic arch results in normal development of a left-sided aorta with the typical branching pattern and a normal pulmonary artery. Both a right and left dorsal aorta are present in the embryo during the first 3 weeks of development. Dissolution of the right dorsal aorta leads to persistence of a dominant left dorsal aorta. Abnormal regression of the dorsal aortic segments leads to abnormalities of the aortic arch.

Double Aortic Arch

Failure of the regression of the right fourth arch and persistence of the left fourth arch results in development of a double aortic arch. In this abnormality, two separate arches from the distal ascending aorta travel on opposite sides of the trachea and esophagus and join the descending aorta (Fig. 113-5). The trachea and esophagus are compressed by the two arches, which are connected proximally and distally, thus forming a complete ring. In many cases, one of the arches, typically the left, is either hypoplastic or atretic. The right-sided arch is dominant in 70% to 75% of patients, the left arch is dominant in approximately 20%, and codominance is seen in the remainder. Because the complete ring is created by proximal and distal continuity of the right and left aortic arches, interruption of the ring requires division of one of the arches.

Right Aortic Arch with Left Ligamentum

Right aortic arch results from regression of the left fourth arch and persistence of the right fourth arch, with an incidence that ranges between 0.05% and 0.2% in adult patients with congenital heart disease. A complete vascular ring is formed if there is a left-sided ductus or ligamentum arteriosum. The boundaries of the complete ring are the right aortic arch posteriorly and rightward, the pulmonary artery anteriorly, and the ligamentum arteriosum or ductus arteriosus to the left (Fig. 113-6). The ligamentum arteriosum usually arises from the base of the left subclavian artery and connects to the pulmonary artery. Thus, if there is an aberrant left

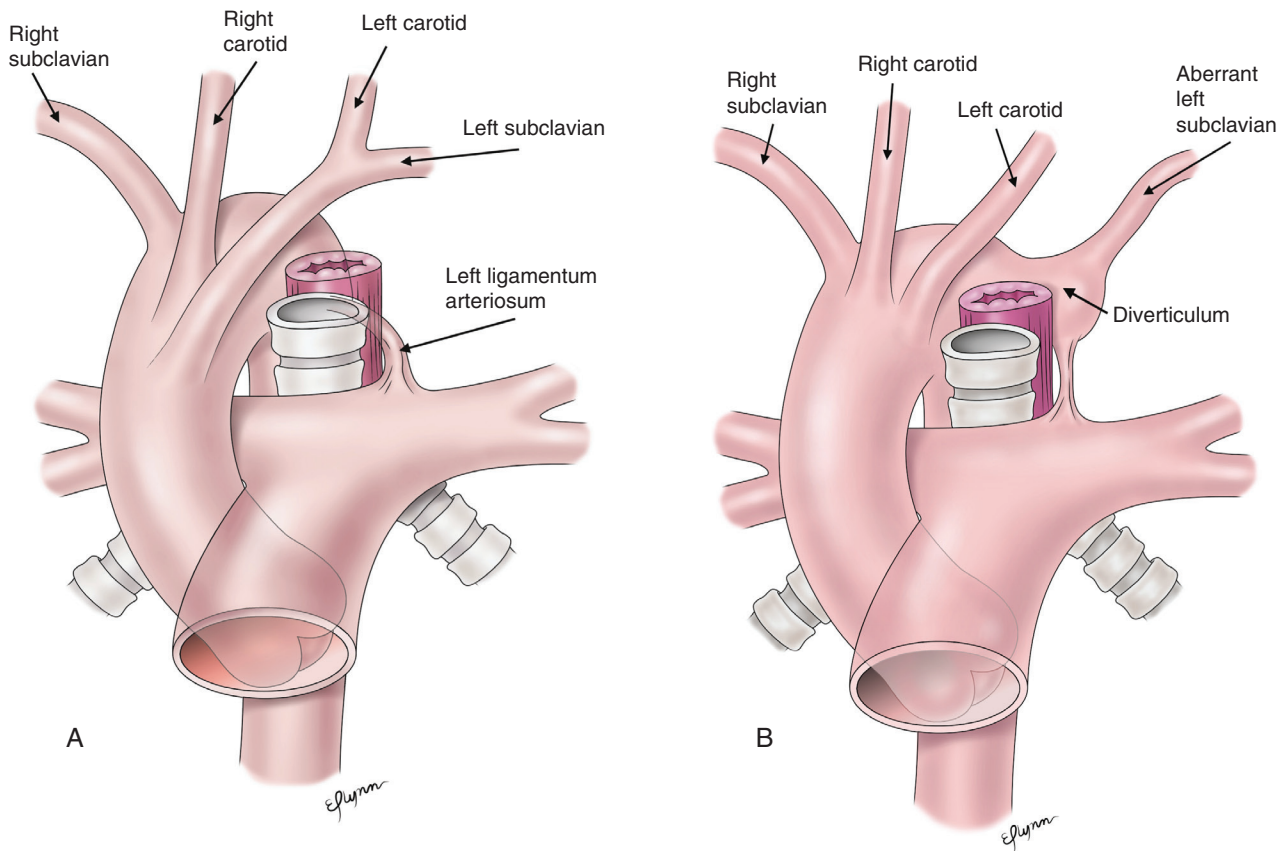


FIGURE 113-6 ■ Right aortic arch with left ligamentum arteriosum. **A**, Mirror-image branching. **B**, Aberrant right subclavian artery. (Compliments of Andrew Powell, MD, and Emily Flynn-Thompson, Children's Hospital Boston.)

subclavian artery that arises from the descending aorta, a left ligament is almost always present. Similarly, in patients with mirror-image branching (MIB), the left subclavian artery arises from the proximal ascending aorta. Because the ligament courses anterior to the airway, most patients with MIB do not experience airway compression. Occasionally, however, in a patient with MIB, the ligamentum may connect to the descending aorta (left ligamentum) and create a complete vascular ring (see Fig. 113-6). This arrangement, although uncommon, must be suspected in a patient with MIB and airway compression. In patients with right aortic arch and left ligamentum, the ligamentum may attach to a diverticular remnant of the left fourth arch, referred to as the *diverticulum of Kommerell*. Associated aneurysm of the diverticulum has been described and may contribute to symptoms by direct compression of the trachea and esophagus.⁷⁹ Interruption of the ring is most easily performed by dividing the ligamentum arteriosum or ductus arteriosus, whereas management of the diverticulum is controversial.

Circumflex Retroesophageal Aorta

A rare form of complete vascular ring is the circumflex retroesophageal aortic arch. In this anomaly, the distal transverse arch crosses the midline, posterior to the esophagus, to descend on the contralateral side, thus placing the aortic arch and the descending aorta on the opposite sides of the spine. A complete ring is formed if the ligamentum arteriosum or ductus arteriosus is present

on the side contralateral to the aortic arch. Even if a complete vascular ring is not formed (in the presence of an ipsilateral ligamentum), posterior compression of the esophagus can still occur.⁸⁰ Embryologically, this malformation is a consequence of preservation of the proximal ipsilateral fourth arch (right or left aortic arch), and persistence of the contralateral sixth segment (ligamentum or ductus) and distal portion of the contralateral fourth arch (descending aorta). The two forms of this anomaly are left aortic arch (LAA) with right descending aorta (Fig. 113-7) and right aortic arch with left descending aorta. Circumflex left aortic arch is frequently associated with aberrant origin of the right subclavian artery (RSCA) from the descending aorta. Right aortic arch can be associated with either MIB or aberrant left subclavian artery (LSCA) patterns, but a complete ring only occurs in the presence of a left ligamentum. Cervical aortic arch is an associated finding in some patients consisting of superior extension of the aortic arch into the cervical region. This results from persistence of the right or left third branchial arch and regression of the fourth branchial arches.

Left Aortic Arch and Anomalous (Retroesophageal) Right Subclavian Artery

The most common arch anomaly, present in approximately 0.5% of the population, is the LAA with aberrant RSCA and left-sided ligamentum arteriosum (Fig. 113-8). Embryologically, this anomaly results from normal involution of the right fourth arch and dorsal

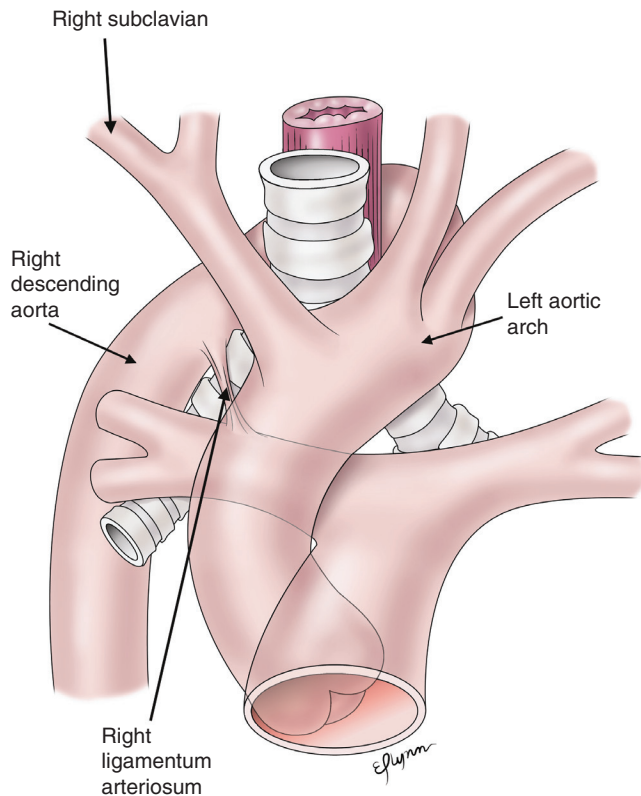


FIGURE 113-7 ■ Circumflex left aortic arch with right descending aorta and right ligamentum, creating a complete vascular ring. (Compliments of Andrew Powell, MD, and Emily Flynn-Thompson, Children's Hospital Boston.)

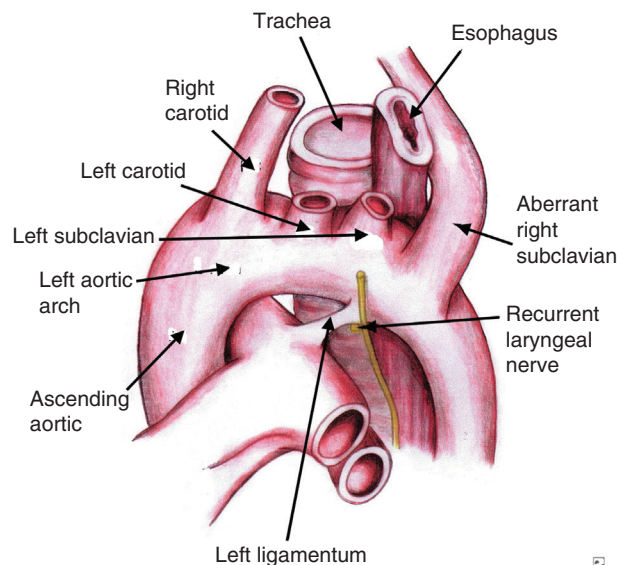


FIGURE 113-8 ■ Aberrant right subclavian artery coursing posterior to esophagus.

aorta, but persistent attachment of the right seventh intersegmental segment to the descending aorta. Most individuals with this anomaly are asymptomatic, but symptoms of dysphagia can occur if this vessel compresses the esophagus as it courses posteriorly. The presence of an aneurysm of the artery or Kommerell diverticulum at its aortic origin is more likely to produce

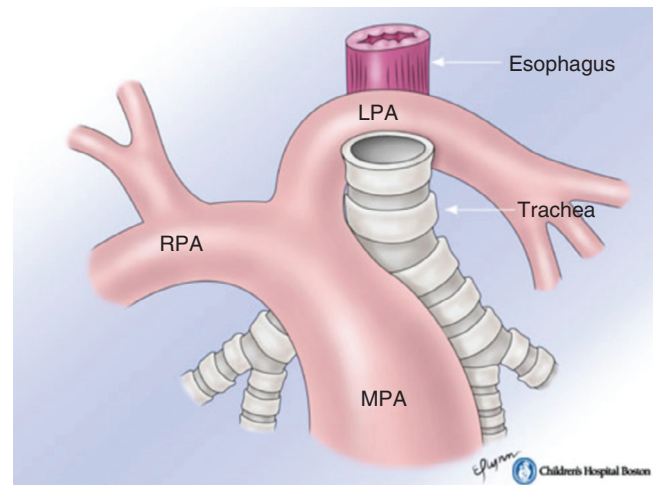


FIGURE 113-9 ■ Left pulmonary artery (LPA) sling originating from the right pulmonary artery (RPA) and coursing posterior to the trachea. MPA, Main pulmonary artery. (Compliments of Andrew Powell, MD, and Emily Flynn-Thompson, Children's Hospital Boston.)

symptoms from esophageal compression, but it can also result in hematemesis from arterial-esophageal fistula.⁸¹ There have been case reports of LAA, aberrant RSCA, and right ligamentum attaching to the right subclavian artery, which creates a complete vascular ring and tracheal compression.⁸²

Pulmonary Artery Sling

This vascular malformation is formed when the left pulmonary artery (LPA) arises from the right pulmonary artery (RPA), and it courses around the right mainstem bronchus toward the left lung between the airway and the esophagus (Fig. 113-9). In the developing embryo, the pulmonary artery is formed by amalgamation of the sixth branchial arch with postbranchial vessels that arise from the primitive lung bud. If the left postbranchial vessel connects to the right instead of left sixth branchial arch, then a pulmonary artery sling develops. This results in compression of the tracheobronchial tree, most commonly at the distal trachea or the right mainstem bronchus. It is associated with complete tracheal rings in approximately 50% of patients, and has been associated with agenesis of the right lung.⁸³

Innominate Artery Compression Syndrome

Anterior compression of the airway can occur because of an unusual (leftward and posterior) takeoff of the innominate artery from the aorta. The presence of a prominent thymus gland and pectus deformity of the chest wall exacerbate the anterior tracheal compression. Innominate artery compression of the trachea in infants can cause severe biphasic stridor, cyanosis, and respiratory arrest, sometimes referred to as *dying spells*.

Clinical Presentation

Most common forms of presentation include respiratory distress, stridor, dysphagia or a combination of these

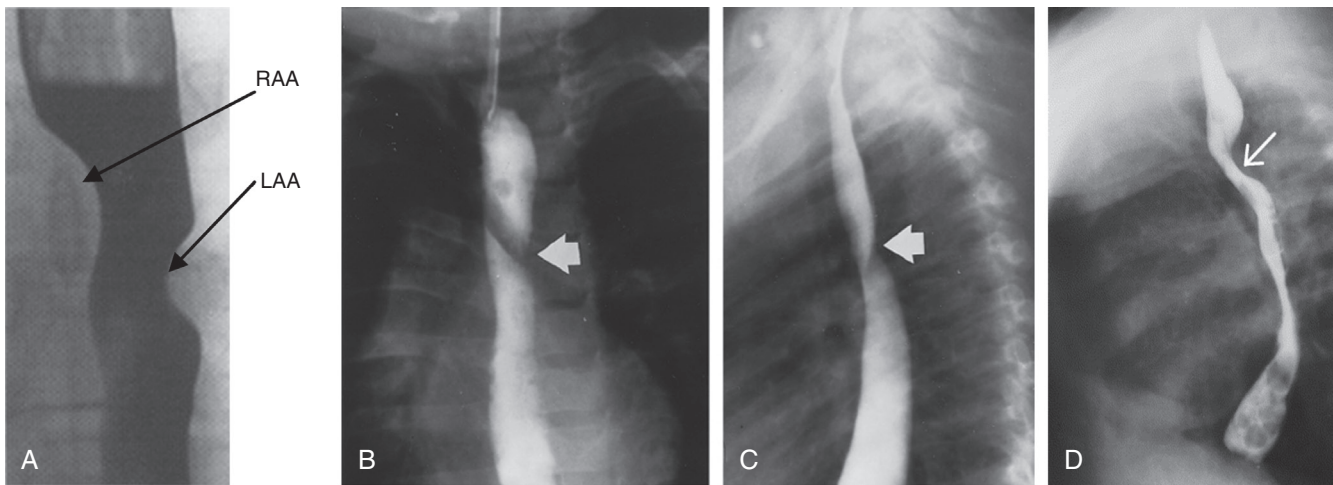


FIGURE 113-10 ■ Barium esophagograms demonstrating bilateral compression of the esophagus by a double aortic arch (A) and posterior compression of the esophagus by an aberrant right subclavian artery (B, C) and circumflex aorta (D). Arrow in B-D demonstrates area of compression. LAA, Left aortic arch; RAA, right aortic arch.

symptoms, depending on the underlying lesion. Compression of the esophagus by an aberrant right subclavian artery can produce dysphagia, previously called *dysphagia lusoria* (or “dysphagia by freak of nature”). Patients with pulmonary artery sling can be in severe respiratory compromise, occasionally severe enough to require salvage by preoperative ECMO.⁸⁴ Coarctation of the aorta or hypoplasia of aortic segments can accompany arch abnormalities and manifest as a murmur, hypertension, or blood pressure gradient between extremities. On physical examination, the child may have stridulous breathing that must be differentiated from wheezing or asymmetric breath sounds from unilateral airway compression. Many patients are referred after being treated with bronchodilators for presumed asthma. A pulsatile mass in the neck suggests the presence of a cervical aorta.

Diagnosis

A diagnostic workup for vascular ring should be initiated in a child or adolescent with airway or esophageal symptoms if symptoms are not relieved by medical management. History of recurrent pneumonia, bronchoconstriction that is unresponsive to bronchodilators, and dysphagia to solid foods should raise suspicion and further workup. On chest radiography, the findings include tracheal narrowing at the level of the aortic arch and unclear delineation of the aortic knob. Unilateral hyperinflation of one lung field may suggest obstruction at the mainstem bronchial level.

CT and MRI are the primary modalities to establish the diagnosis and plan an operative procedure.^{85,86} MRI with three-dimensional reconstruction is preferred in most centers to avoid exposure to ionizing radiation (Fig. 113-10).⁸⁷ Specific information that must be obtained includes the course and origin of arterial branches, arch dominance in patients with double aortic arch, location of the ligamentum arteriosum, and the degree of airway or esophageal compression. Airway compression might not be apparent in patients who are intubated and mechanically ventilated, and dynamic imaging during

inspiration and expiration increases the sensitivity of detecting airway compromise. Echocardiography is helpful for delineating the arch anatomy in neonates and infants, but it cannot definitely make the diagnosis of a vascular ring unless there is a double aortic arch and both arches are patent.

Barium esophagography is a reliable initial study for workup of the patient with dysphagia. The most common appearance on esophagogram includes the presence of posterior extrinsic compression in the presence of a right aortic arch, anterior esophageal compression in the presence of a pulmonary artery sling, and extrinsic compression on anteroposterior views of the esophagus in the setting of double aortic arch (Fig. 113-11).

Bronchoscopy is helpful in the assessment of patients with vascular rings and suspected airway compression. Although routine bronchoscopy is not necessary in the setting of a complete vascular ring with clinical or imaging evidence of airway obstruction, it may be useful in situations where the diagnosis or significance of vascular anomaly is unclear. Anterior compression of the trachea by the innominate artery visualized at bronchoscopy may establish the diagnosis and severity of innominate artery compression when noninvasive imaging is equivocal, and thus guide clinical management. Under certain circumstances, bronchoscopy can reveal several separate causes of airway compromise in a patient with a vascular ring, thus altering surgical management. For example, bronchoscopy can detect the presence of associated complete tracheal rings or tracheomalacia. Immediate postprocedure intraoperative bronchoscopy allows the surgeon to assess the efficacy of the intervention. Adjunctive aortopexy or anterior tracheal suspension can be performed during the same operative procedure if persistent airway compromise is encountered.⁸⁸ Preoperative or intraoperative bronchoscopy alters management in approximately 3% to 5% of patients.⁸⁹

Angiography is rarely indicated for patients with vascular rings, but it may be necessary if coexistent coarctation of the aorta is suggested. In patients with right or left aortic arch and contralateral ligamentum, the

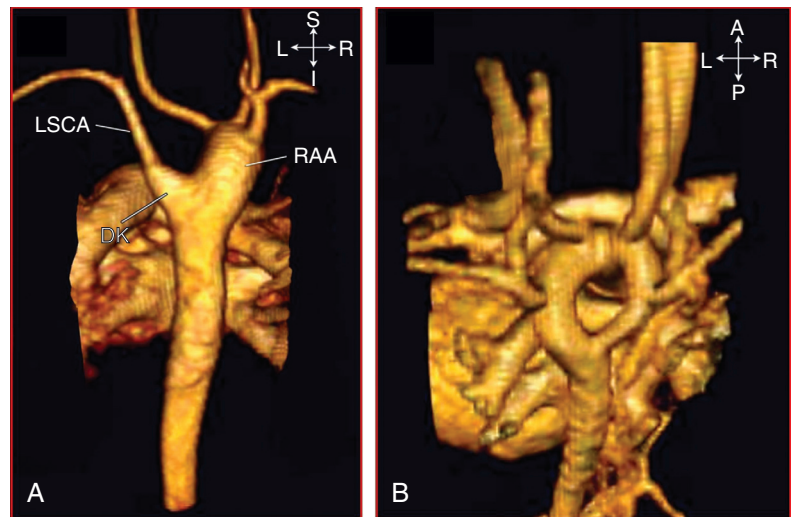


FIGURE 113-11 ■ Three-dimensional magnetic resonance imaging reconstructions demonstrating right aortic arch (RAA), aberrant left subclavian artery (LSCA) (A), and double aortic arch (B). DK, Diverticulum of Kommerell. (Compliments of Andrew Powell, MD, Children's Hospital Boston.)

presence of a ligamentum might not be demonstrated by noninvasive methods. In these cases, a rudimentary diverticulum at the insertion of the ligament into the aorta may be detected by angiography, suggesting the presence of the vascular ring.⁹⁰

Treatment

Controversy exists regarding indications for repair of the vascular ring. The presence of airway or esophageal symptoms corresponding with anatomic narrowing on imaging should prompt surgical treatment. In the asymptomatic patient, surgical treatment should be considered in patients with evidence of significant narrowing (>50%) by imaging, whereas patients with negligible anatomic narrowing can be managed safely by observation with serial imaging. Patients with pulmonary artery sling are likely to develop tracheal narrowing with time, and early operative intervention is recommended.

The options for surgical approach to a vascular ring include sternotomy, thoracotomy, or VATS. The optimal approach depends on the morphology of the arch anomaly and associated abnormalities (coarctation or complete tracheal rings) that require intervention. Regardless of the etiology of the vascular ring or the surgical approach, an important component of ring division is lysis of residual fibrotic tissue overlying the adventitia of the esophagus and trachea.

Double Aortic Arch

More than 85% of patients with double aortic arch display right dominance with atresia or hypoplasia of the left arch. Even when balanced arches or left dominance are present, division of the LAA is possible without development of significant obstruction to flow through the remaining right-sided arch. Measurement of upper and lower extremity blood pressures during test occlusion of the left arch can be used to predict adequacy of the right arch. If the right-sided arch is significantly hypoplastic or atretic, then division of the right aortic arch becomes necessary. Regardless of which arch requires division,

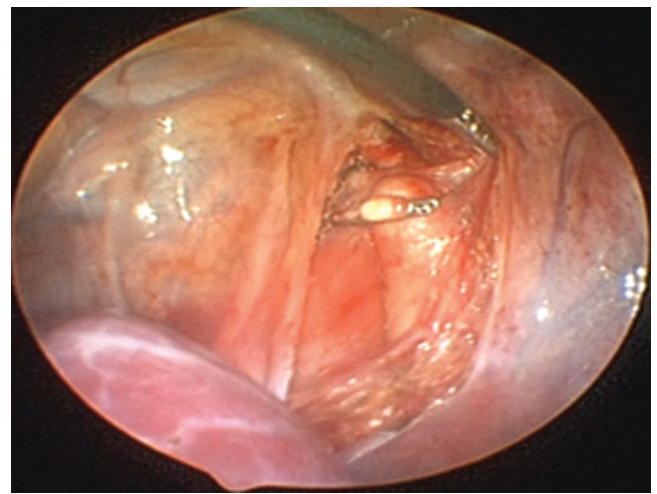


FIGURE 113-12 ■ Division of left ligamentum arteriosum in a patient with right aortic arch. Tethering attachments across the underlying esophagus must be divided to provide complete relief of obstruction in patients with double aortic arch or right aortic arch with left ligamentum.

surgery for double aortic arch can be performed through the left pleural space, using thoracotomy or VATS. The open approach is generally required for division of the right arch and may be preferable for division of a patent left arch. A ligamentum arteriosum or PDA is divided before further dissection. If this is not performed and only the left arch is divided, a vascular ring will persist. When atresia of the nondominant arch is present, division must be performed at the atretic segment to preserve blood flow to the branch vessels. Once the vascular ring has been divided, fibrous attachments tethering the trachea and the esophagus must be divided longitudinally to ensure relief of anatomic obstruction (Fig. 113-12).

Right Aortic Arch with Left Ligamentum Arteriosum

Division of the ligamentum arteriosum and underlying fibrous bands along the esophagus relieves tracheal and

esophageal compression (see [Figure 113-12](#)). Occasionally, the left ligamentum (and aberrant LSCA, if present) will arise from a diverticulum of Kommerell. Management of this diverticulum is controversial. Diverticular resection and repeated anastomosis of the aberrant LSCA to the left carotid artery avoids the risk of further dilation of the diverticulum and recurrent tracheoesophageal compression.⁹¹ Other options for management include plication and posterior diverticulopexy to the prevertebral fascia.

Circumflex Retroesophageal Aorta

The boundaries of the complete ring include the circumflex aorta, the pulmonary artery, and the ligamentum arteriosum or ductus arteriosus contralateral to the aortic arch, and division of the ring is simply performed by dividing the ligamentum. If the aberrant subclavian artery arises from a diverticulum, resection of the diverticulum and reimplantation of the subclavian artery is recommended. This is performed through a thoracotomy ipsilateral to the ligamentum. In some patients with circumflex aorta, simple division of the ligamentum and reimplantation of aberrant subclavian artery might not be sufficient to relieve the posterior esophageal compression. In these patients, aortic division and “uncrossing” by mobilization and rerouting of the descending aorta ipsilateral to the descending aorta relieves esophageal compression. Extra-anatomic reconstruction with division of the transverse aorta and ascending to descending prosthetic graft is another option.⁹² Coarctation and hypoplasia of the circumflex aorta (particularly right circumflex aorta) can occur, and they are treated with resection with reanastomosis or interposition graft.^{93,94}

Left Aortic Arch and Aberrant Right Subclavian Artery

Patients with a diagnosis of LAA and aberrant RSCA rarely experience airway compromise, and alternative causes of airway symptoms should be sought. In the rare patient with a right ligamentum, a complete vascular ring is formed, and division of the ligamentum provides relief of airway compression. For symptomatic esophageal compression, surgical treatment involves division of the subclavian artery at its origin from the aorta. This can be performed through a sternotomy or left thoracotomy approach. Reimplantation of the RSCA into the ascending aorta avoids the small risk of chronic upper extremity ischemia, but is controversial. If aneurysmal dilation of the aorta or proximal subclavian artery is encountered, one must be prepared to institute left heart or cardiopulmonary bypass and possibly hypothermic circulatory arrest during repair. Endovascular options for treatment have emerged, but the long-term results of this approach are still lacking.⁹⁵

Pulmonary Artery Sling

The repair of this anomaly is typically performed via median sternotomy, and consists of division of the LPA from the RPA and reimplantation into the main

pulmonary artery anterior to the trachea. Alternatively, the trachea can be divided and brought posterior to the pulmonary artery. The latter approach is useful if tracheal resection or reconstruction is necessary because of the presence of complete tracheal rings and tracheal stenosis. The decision to perform concomitant airway reconstruction depends on the degree of intrinsic airway abnormality, and it can be aided by performance of intraoperative bronchoscopy following release of the pulmonary artery sling. If concomitant airway surgery is required, the reconstruction with sliding tracheoplasty is the preferred procedure.⁹⁶ Cardiopulmonary bypass is essential if airway reconstruction is required. For LPA reimplantation alone, bypass is not essential but minimizes the hemodynamic burden on the right ventricle and allows unencumbered performance of the anastomosis. Immediate postoperative complications following repair of a pulmonary artery sling include persistent respiratory difficulties secondary to an abnormal airway, and long-term complications are seen in patients who require tracheal reconstruction during infancy.⁹⁷ Late stenosis of the LPA anastomosis occurs infrequently and is effectively treated with percutaneous balloon dilation.

Innominate Artery Compression

Children with suspected innominate artery compression syndrome should undergo thorough imaging and preoperative bronchoscopy to confirm anterior airway compression attributable to the innominate artery before proceeding with repair. Direct compression of the airway by the innominate artery or the aorta can be treated with thymectomy and innominate artery suspension through the right or left transpleural approach. Thymectomy is helpful when preoperative studies indicate the presence of a large thymus, which can exacerbate the posterior displacement of the innominate artery onto the anterior trachea. Innominate artery suspension can be performed through a right- or a left-sided approach, or through a partial sternotomy. The pericardial reflection at the base of the innominate artery is suspended to the posterior aspect of the sternum, thus lifting the innominate artery anteriorly. Improvements in symptoms and pulmonary function have been demonstrated following repair.^{98,99}

Prognosis

Low hospital mortality is expected following division of vascular ring. The proportion of patients experiencing improvement in respiratory symptoms following surgery ranges widely from 50% to 90%.¹⁰⁰⁻¹⁰² Recurrence of symptoms may be attributed to the presence of an enlarging Kommerell diverticulum, circumflex aorta, or underlying tracheobronchial malacia.¹⁰³ Management with resection of the diverticulum and primary reanastomosis of the LSCA into the left carotid artery, aortic “uncrossing” for circumflex aorta, or aortopexy and tracheopexy for trachea-broncho-malacia.^{103,104} Bronchoscopy at the time of vascular ring division or reoperation for residual compression provides feedback during surgical manipulation. The long-term results of vascular ring division are generally dependent on the degree of intrinsic airway

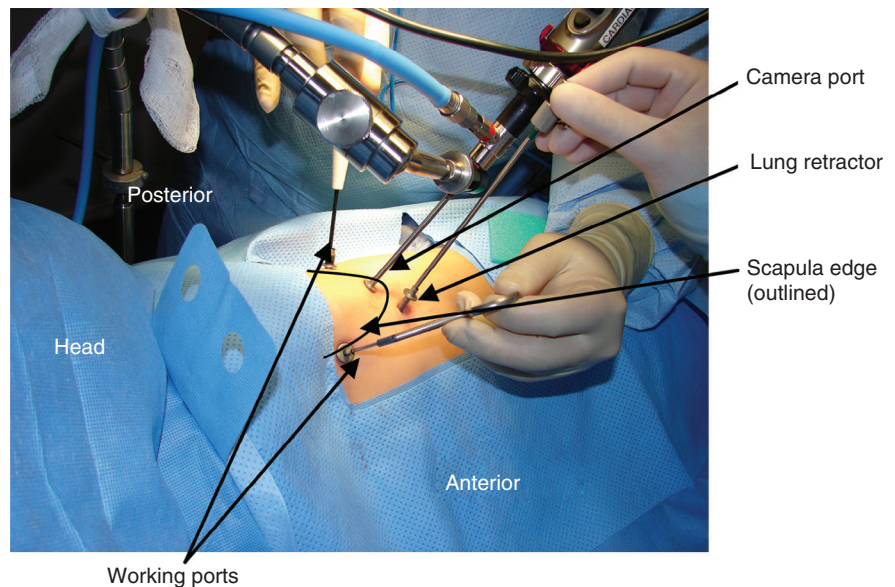


FIGURE 113-13 ■ Placement of ports in relationship to scapula during left video-assisted thoracoscopic surgery with the patient in the right decubitus position.

abnormality, such as tracheomalacia or complete tracheal rings. In one long-term analysis, follow-up surveys revealed that approximately half of the patients with preoperative breathing difficulties were symptom free at long-term follow-up, and the remaining patients described improvement in symptoms compared with preoperative status.¹⁰⁵ Younger age at operation and underlying genetic syndromes are risk factors for persistent symptoms. After repair of pulmonary artery sling, significant improvements in pulmonary function tests have been noted.¹⁰⁶

Complications

The most common cause of in-hospital morbidity relates to underlying airway abnormalities, and adequate pulmonary toilet must be maintained in the postoperative period. Patients undergoing pulmonary artery sling repair are at the highest risk for persistent airway instability and pulmonary insufficiency. Surgical complications related to the mediastinal dissection include recurrent laryngeal nerve injury, pneumothorax, chylothorax, and esophageal leak. Chylothorax is best managed by early reoperation for ligation of the injured lymphatic vessel, although percutaneous embolization of the thoracic duct is an effective alternative.¹⁰⁷

Surgical Approaches

The muscle-sparing thoracotomy, VATS, and sternotomy are the most commonly used approaches for repair of PDA, coarctation, and vascular rings. Sternotomy is the approach used if cardiopulmonary bypass is necessary (hypoplastic arch in addition to coarctation, calcified PDA in an adult). Sternotomy can provide security of cardiopulmonary bypass in case of unexpected vascular injury in a patient with unusual anatomy (PDA associated with ductal aneurysm). Although selective single-lung ventilation by means of a double-lumen endotracheal tube provides superior visualization in adults, a single-lumen endotracheal tube is sufficient to perform

procedures in most patients. For left-sided aortic arch, a left chest approach is preferred. The patient is placed in a right lateral decubitus position with a roll under the axilla to avoid nerve compression injury. A blood pressure cuff on the lower extremity allows intraoperative measurement of upper-lower extremity gradient, which is a crude but useful estimate of residual aortic obstruction. In the operating room, a pulse oximeter or blood pressure cuff should be placed on a lower extremity to confirm lower body perfusion after surgical manipulation of the descending aorta. Early identification and treatment of obstruction prevents subsequent morbidity and delay in treatment.

Thoracotomy

A posterolateral thoracotomy is performed by making an infrascapular incision parallel to the course of the underlying ribs. The latissimus muscle is divided, but the serratus anterior muscle is spared. For repair of coarctation or vascular ring, the fourth intercostal space is entered, and for PDA ligation the third interspace provides direct exposure. The pleura is opened for vascular ring and coarctation surgery, whereas an extrapleural or transpleural approach can be used for PDA ligation. With either approach, the pleura overlying the aorta is mobilized, and the recurrent laryngeal is identified and dissected away from the aorta. Complications related to the thoracotomy and dissection include recurrent laryngeal nerve injury, chylothorax, pneumothorax, and surgical site infections. Musculoskeletal deformities late after thoracotomy in children have become less frequent with the adoption of muscle-sparing techniques.¹⁰⁸

Video-Assisted Thoracoscopic Surgery

There are several different methods of VATS for division of vascular rings or patent ductus arteriosus. Our approach is to make four 3 mm incisions as shown in [Figure 113-13](#). Exposure of the aorta is provided by an

expandable lung retractor, and thoracoscopic instruments are used to perform the dissection, ligation, and division of atretic ligaments. Thoracoscopic division of a patent double aortic arch must be performed with a plan for vascular control (tourniquet, direct pressure, thoracotomy) should uncontrollable bleeding be encountered. Thoracoscopic division of vascular rings and PDA has not been shown to decrease operative times, postoperative pain, or hospital length of stay compared with the thoracotomy approach.¹⁰⁹

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ATRIAL SEPTAL DEFECT AND COR TRIATRIATUM

David P. Bichell • Thomas P. Doyle

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HISTORICAL CONSIDERATIONS

Ingenious and risky surgical corrections of atrial septal defect (ASD) predated cardiopulmonary bypass. The earliest closed approaches included a technique in which a straight needle with suture, guided by palpation, was passed blindly through the defect and both atria, and the free walls of the left and right atria were drawn together to obstruct the defect.¹ Bailey and colleagues described the “atrio-septo-pxy” consisting of a digital invagination of the atrial appendage through the defect with external suture attachment of the atrial tissue to the perimeter of the defect (Fig. 114-1A).² Tyge Sønnergaard devised a purse-string external suture closure of ASD by a near circumferential dissection around the defect in the plane

of the interatrial groove and a plication of its edges (see Fig. 114-1B).³

Semiopen techniques used before cardiopulmonary bypass became common practice included the “atrial well” technique, where a right atriotomy was formed, controlled by partial atrial clamping. A 15-cm tall, open-ended rubber cone was then attached to the atriotomy to produce an open column of blood in continuity with the beating heart. Working through the atrial well by palpation, the defect was closed by direct suture or patch. Regional intermittent heparinization prevented blood clotting within the well (see Fig. 114-1C).⁴

Lewis and Taufic reported the first successful open-heart ASD closure under direct visualization, using surface cooling and circulatory arrest by inflow occlusion in 1953.⁵

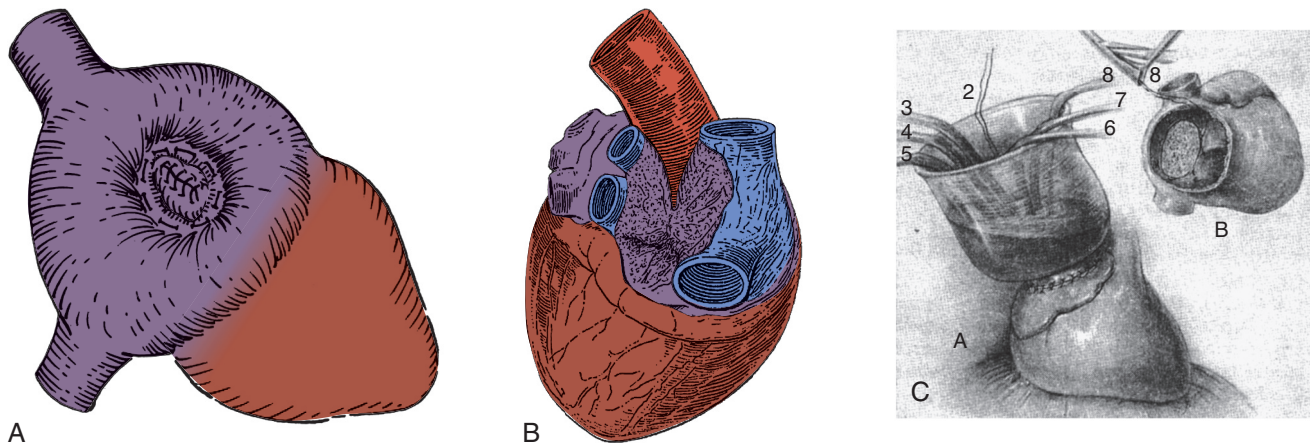


FIGURE 114-1 ■ Techniques for surgical atrial septal defect closure predating cardiopulmonary bypass. **A**, Atrio-septo-plexy. **B**, External purse-string suture closure. **C**, Atrial well technique. (**A**, From Bailey CP, Nichols HT, Bolton HE, et al: Surgical treatment of forty-six interatrial septal defects by atrio-septo-plexy. *Ann Surg* 140:805–820, 1954; **B**, from Sønndergaard T: Closure of atrial septal defects; report of three cases. *Acta Chir Scand* 107:492–498, 1954; **C**, from Barratt-Boyes BG, Ellis FH Jr, Kirklin JW: Technique for repair of atrial septal defect using the atrial well. *Surg Gynecol Obstet* 103:646–649, 1956.)

Further modification of this technique to include continuous coronary perfusion improved the safety of this and other early intracardiac procedures and represented a precursor to modern myocardial protection techniques.⁶

The modern era of cardiac surgery was heralded by the introduction of the pump oxygenator in 1953, and the earliest application of this technology was for ASD closure.⁷ Intracardiac repairs by inflow occlusion were not uniformly replaced by cardiopulmonary bypass techniques until 1960.

EMBRYOLOGY AND GENETICS

Formation of the Interatrial Septum

The embryonic common atrium undergoes partitioning by the formation of two parallel, overlapping septa, the septum primum and the septum secundum, starting in the fourth week of gestation.

The septum primum, emerging from the roof of the embryonic common atrium, begins the septation. The ostium primum, a gap between the septum primum and the atrial floor, almost closes by the completion of the septum primum. A de novo defect in the septum primum forms when a portion of its superior aspect resorbs, forming the ostium secundum.

The septum secundum, forming by the end of the sixth week of gestation, grows parallel to and immediately rightward of the septum primum, obliterating any remaining ostium primum, and circumscribing a central opening, the fossa ovalis.

In its final configuration, the atrial septum consists of the two layers, fused except for the overlapping, offset openings of the fossa ovalis and the ostium secundum. The free edge of the ostium secundum forms a flap valve covering the left side of the fossa ovalis, providing free right-to-left flow through the foramen ovale, until post-natal physiology closes the valve (Fig. 114-2). Conditions

impairing the competence of the valve, or abnormalities in the formation of its components, lead to a persistent interatrial communication.

Simultaneous with atrial septal formation, pulmonary vein connections with the primitive left atrium are forming. During the fourth week of gestation, the common pulmonary vein orifice forms from posterior invaginations of the sinus venosus segment into the mesenchyme of the primitive lung buds. The sinus venosus segment of the posterior common atrium forms where right and left omphalomesenteric and cardinal veins drain into the left and right sinus horns. An abnormal persistence of the right-sided anlage of the common pulmonary vein might be the embryologic basis for the development of abnormal connections of pulmonary veins to the right atrium, or partial anomalous pulmonary venous connection (PAPVC).⁸

Genetics

A familial predisposition to ASD is well documented. A study that included more than 18,000 subjects with congenital heart disease from a Danish population determined a recurrence risk for isolated secundum ASD of approximately 7%, a finding similar to prior studies.^{9–11}

Numerous genetic conditions and syndromes known for their extracardiac manifestations are also associated with ASD. Secundum ASD is the most common congenital cardiac defect associated with VACTERL (vertebral anomalies, anal atresia, cardiac defects, tracheal anomalies, esophageal atresia, renal anomalies, and limb anomalies). Genetic syndromes with associated ASD include Holt-Oram, Rubinstein-Taybi, Okimoto, and Townes-Brocks syndromes.¹² Trisomy 21 is associated with ASD either in isolation or as part of a constellation of endocardial cushion defects. Noonan syndrome is associated with ASD and pulmonary valve stenosis.¹³ DiGeorge syndrome (22q11.4 deletion) and Ellis-Van Creveld syndromes are associated with primum ASD. Additional

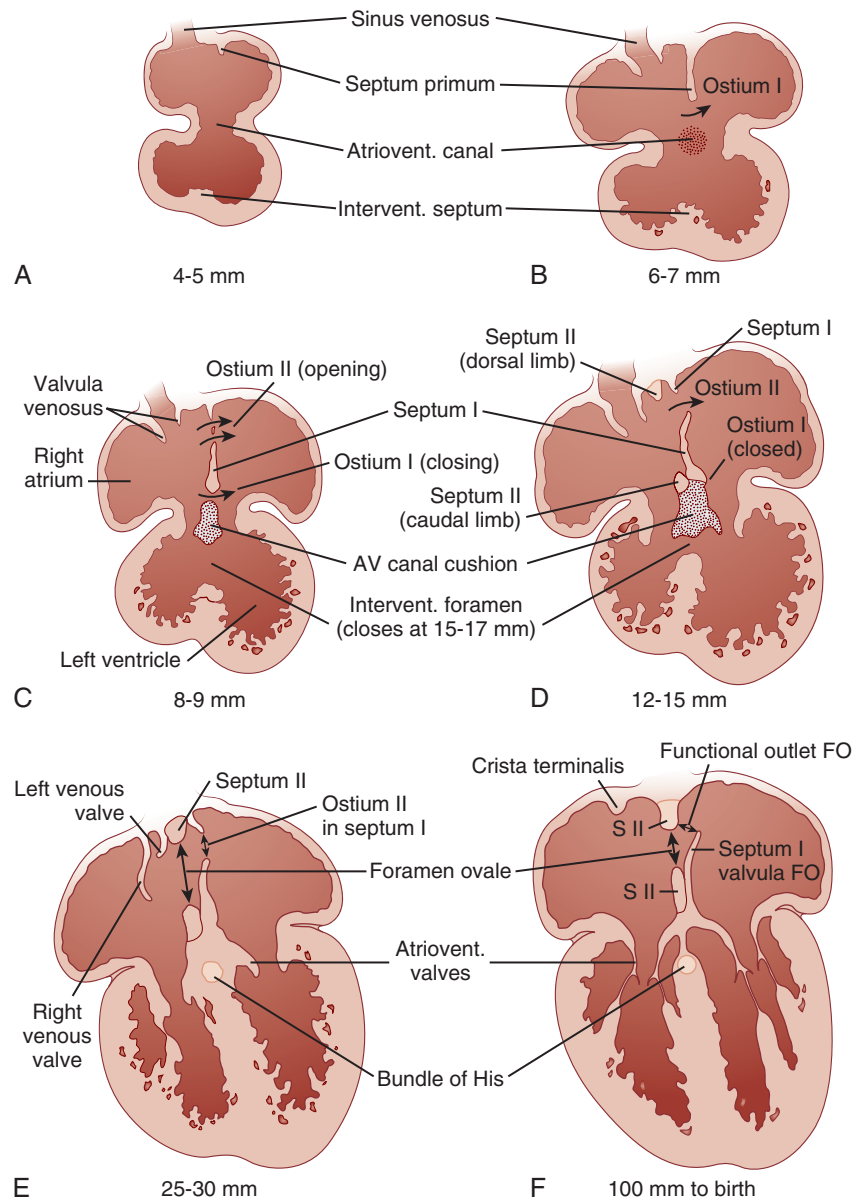


FIGURE 114-2 ■ Four-chamber sectional diagrams of the fetal heart with particular attention to the morphology of the forming interatrial septum and the foramen ovale. **A**, The early stages in the formation of the septum primum, from the superior aspect of the common atrium. **B**, As the septum primum grows toward the endocardial cushion, the ostium primum is defined. **C**, As the ostium primum closes, the ostium secundum forms by the resorption of the cephalad portions of the septum primum. **D**, The septum secundum begins to form rightward and parallel to the septum primum, obliterating the remaining ostium primum. **E** and **F**, The septum secundum circumscribes the foramen ovale, and the septum primum creates a flap valve permitting only right-to-left flow. AV, Atrioventricular; FO, foramen ovale. (Reproduced with permission from Patten BM: Developmental defects at the foramen ovale. *Am J Pathol* 14:135-161, 1938.)

specific genes implicated in familial forms of ASD include *GATA4*, *NKX2.5*,¹⁴ alpha-cardiac actin 1 (*ACTC*),¹⁵ alpha-myosin heavy chain (*MYH6*),¹⁶ and *MSX1*.¹⁷

The conduction system forms concurrently with atrial septation and PR prolongation can accompany ASD, in likely association with abnormalities of the *TBX5* transcription factor gene.¹⁸

Patent Foramen Ovale

The patent foramen ovale (PFO) denotes a failure of the septum primum and septum secundum to fuse. A failure of fusion results in either a valve-competent, “probe patent” PFO or valvular incompetence with or without an aneurysm of the septum primum component (Fig. 114-3A). Forces producing an enlarged foramen ovale or a deficient septum primum contribute to incompetence of the valve, a physiologically significant PFO, and transseptal shunting.

Secundum Atrial Septal Defect

The secundum defect lies within the bounds of the fossa ovalis, widely ranging in morphology from the slit-like PFO at the superior aspect of the fossa, to defects involving part or all of the remainder of the fossa, with a single or multiply fenestrated communication. Defects of various specific morphologies classified as secundum ASD can form as a result of underdevelopment of the septum secundum or a malformation of the septum primum resulting in incomplete coverage of the ostium secundum (see Fig. 114-3B).

Primum Atrial Septal Defect

The primum defect is a persistence of the ostium primum and is most commonly associated with an atrioventricular (AV) septal defect (see Fig. 114-3C). This lesion is discussed further in Chapter 116.

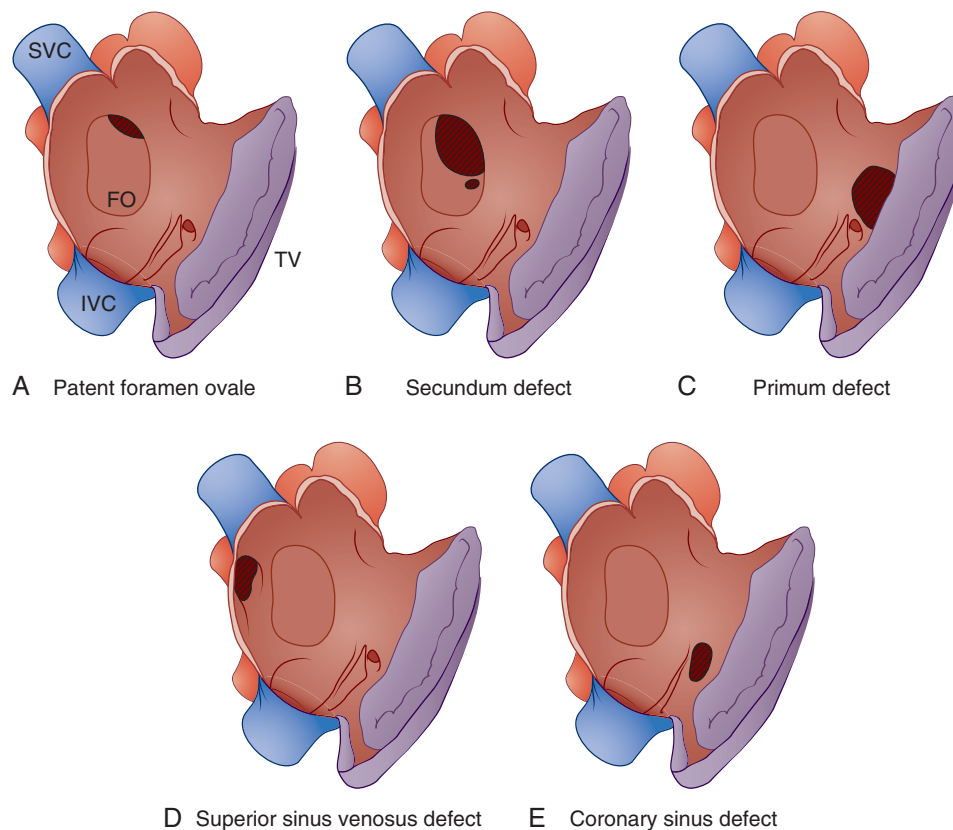


FIGURE 114-3 ■ The morphologic classification of atrial septal defects. **A**, Patent foramen ovale. **B**, Secundum atrial septal defect. **C**, Primum atrial septal defect. **D**, Superior sinus venosus defect. **E**, Coronary sinus interatrial defect. FO, Foramen ovale; IVC, inferior vena cava; SVC, superior vena cava; TV, tricuspid valve.

Sinus Venosus Defect

The sinus venosus interatrial defect is associated with a PAPVC. Ninety percent of PAPVCs are right-sided, 7% left-sided, and 2% bilateral. The most common subtype is right upper pulmonary vein-to-superior vena cava (SVC) connection, accounting for 74% of PAPVC cases, in usual association with sinus venosus ASD.¹⁹ The more common superior variant of sinus venosus defect is an interatrial communication lying posterior and superior to the true atrial septum, and the SVC overrides the defect. The right upper pulmonary veins, usually two or more, drain to the right atrium at the superior cavoatrial junction or enter the SVC directly (see Fig. 114-3D). In rare cases, they may enter the azygous vein as well. The SVC is commonly enlarged as it enters the right atrium.

The less common inferior sinus venosus defect is a communication inferior and posterior to the fossa ovalis with the right pulmonary veins entering the right atrium near the inferior cavoatrial junction. Although the sinus venosus ASD is remote from the fossa ovalis, a PFO or secundum ASD also may be present.

Atrial Septal Aneurysm

Redundant atrial septal tissue within the fossa ovalis with a respiratory excursion greater than 10 mm is termed an *atrial septal aneurysm* (ASA).²⁰ The ASA may occur with or without a PFO and has been implicated in the

formation of paradoxical embolus. ASA is present in 2% to 4% of the normal population, and 70% of cases are associated with a PFO.²¹

Coronary Sinus–Type Atrial Septal Defect

The uncommon coronary sinus–type ASD results from a complete or partial unroofing of the coronary sinus along its course through the floor of the left atrium. A communication of the coronary sinus with the left atrium results in an interatrial communication at the level of the coronary sinus ostium, the size of which is determined by the extent of unroofing and the size of the ostium (see Fig. 114-3E). Concomitant cardiac lesions occurring with coronary sinus ASD include ASDs within the fossa ovalis, persistent left-sided SVC, and pulmonary or tricuspid atresia. The rarity of coronary sinus defects, their tendency to elude echo diagnosis, and the finding that many elude even intraoperative recognition, underscore the importance of maintaining suspicion for this lesion when the degree of intracardiac shunt observed is inordinate for the known defect elsewhere.

Iatrogenic and Traumatic Atrial Septal Defect

Iatrogenic ASDs are found after 87% of catheter-based transseptal pulmonary vein isolation procedures. Most

are smaller than 1 mm in diameter and 96% resolve spontaneously, requiring no intervention.²² Rare cases of traumatic ASD after blunt or penetrating trauma have been described.²³

INCIDENCE AND NATURAL HISTORY

More than 60% of healthy full-term infants have a PFO identifiable on transthoracic echocardiogram.²⁴ With the postnatal fall in pulmonary resistance and rise in left ventricular end-diastolic pressure, the pressure in the left atrium exceeds that in the right atrium, and the flap valve consisting of septum primum closes the foramen ovale. Fibrous adhesions form in the first year of life to seal the interatrial communication in most cases. Spontaneous closure rates of PFO diagnosed in infancy are high—87% to 96% for those diagnosed in the first 12 months of life.²⁵ The overall incidence of persistent PFO in adulthood, deduced from autopsy specimens, is 27%. A PFO is present in one third of people younger than 29 years of age, one fourth of those 30 to 79 years, and one fifth of persons older than 80.²⁶

Secundum ASD occurs in 1.6 out of 1000 live births, second in prevalence only to ventricular septal defect (VSD). ASD accounts for 10% to 15% of congenital heart defects in children²⁷ and 20% to 40% of defects discovered in adults. Women are affected twice as often as men.²⁸ Maternal exposures associated with ASD in offspring include alcohol, hydantoin, valproic acid, and amphetamines. Infections and additional conditions associated with ASD include cytomegalovirus or rubella infection during pregnancy, diabetes, older maternal age, multigestational birth, and obesity. Low-birth-weight and premature infants have a higher prevalence of ASD than does the general population.²⁹⁻³¹

A significant number of ASDs close spontaneously within the first few years of life, but spontaneous closure after age 3 to 4 is rare.³² The likelihood of spontaneous closure is best predicted by the initial diameter of the secundum defect. Longitudinal data demonstrate that more than half of defects diagnosed in infancy and measuring 4 to 5 mm close spontaneously. Thirty percent regress in size to smaller than 3 mm. However, none close spontaneously when the defect measures larger than 10 mm at diagnosis.³³ Defects larger than 8 mm at diagnosis usually enlarge over time. If there is aneurysmal formation, sizes diminish regardless of whether they are larger than 8 mm.³⁴

In contrast to children with ASDs, most patients older than 40 years of age are symptomatic and have evidence of elevated pulmonary vascular resistance. If these patients are not treated, their average life expectancy is 40 to 50 years. Seventy-five percent die by age 50, and 90% die by 60 years of age.³⁵ Even the asymptomatic adult with ASD has a measurably diminished aerobic exercise capacity, which further declines with advancing age.³⁶ A 2008 European heart survey of 882 adults with isolated secundum ASD, including 505 unrepaired patients, demonstrated a precipitous rise in the prevalence of right ventricular dysfunction in unrepaired patients after 45 years of age. The degree of right ventricular volume

overload was the best predictor of reduced exercise capacity. A steady rise in the prevalence of pulmonary hypertension was observed in unrepaired patients after age 30. Findings support the suggestion that the magnitude of the intracardiac shunt may increase over time. Hemodynamically small defects tend more to remain stable and may not require closure.³⁷

Isolated ASD can predispose the patient to subacute bacterial endocarditis, although the actual incidence of endocarditis in this setting is rare. Scattered case reports describe atrial septal endocarditis in direct association with native ASD, ASD repaired by surgical or device closure, and by septal involvement of endocarditis that extends from other intracardiac structures. Risk of endocarditis from an unrepaired ASD is sufficiently low that antibiotic prophylaxis is not recommended, according to the latest American Heart Association guidelines. Incompletely repaired defects and those closed with prosthetic material or devices suspected of incomplete endothelialization are regarded as endocarditis risks, and do require antibiotic prophylaxis for dental or surgical procedures.³⁸

ASSOCIATED FEATURES

Isolated ASD in infancy and childhood is seldom symptomatic, even for large defects, and symptoms of congestive failure should prompt a careful effort to rule out additional associated abnormalities. Associated lesions found in the study of infants with ASD dying in the first year of life included left-to-right shunting lesions, such as VSD or patent ductus arteriosus (PDA); right-sided obstructive lesions, such as pulmonary stenosis; and left-sided obstructive lesions, such as aortic stenosis, mitral stenosis, or coarctation of the aorta. Necropsy data show that patients with VSD had an associated ASD in 18% of cases, those with left-sided obstruction had an associated ASD in 29% of cases, and those with right-sided obstructive lesions had ASD in 31% of cases.³⁹ These associations support the hypothesis that some secundum ASDs are acquired, driven by remote lesions that favor persistent atrial level shunting and atrial dilation, in turn leading to valvar incompetence at the fossa ovalis.

Mitral valve abnormalities have long been recognized as associated with ASD, although their associated incidence is uncommon. Mitral stenosis with pulmonary artery dilation in association with ASD, or Lutembacher syndrome, was perhaps a more frequent association found in the era when rheumatic heart disease was more prevalent, although nonrheumatic mitral stenosis is occasionally found in association with ASD.⁴⁰ A cleft anterior mitral leaflet, mitral prolapse, or regurgitation has also been reported in uncommon association with ASD. Mitral prolapse may be a result of septal distortion by right ventricular volume overload and a secondary effect on mitral valve geometry. As evidence in favor of this hypothesis, mitral prolapse has been shown to reverse after ASD closure.⁴¹

Tricuspid regurgitation in association with ASD is usually caused by annular dilation from the enlarged right ventricle, and it also reverses with ASD closure. The

most common additional cardiac anomalies associated with ASD include PAPVC, VSD, PDA, persistent left SVC, pulmonary valve stenosis, and branch pulmonary artery stenosis.⁴²

P wave prolongation associated with ASD may predispose the patient to the eventual development of atrial fibrillation. P wave duration may be shortened by ASD closure in younger adults, suggesting that the chronicity of atrial stretch is a contributing factor.⁴³ Closure of ASD in older adults does not affect this electrical pathophysiology and does not shorten preexistent P wave prolongation.⁴⁴ The presence of paroxysmal atrial fibrillation prior to ASD closure results in no shortening of P wave duration by closure.⁴⁵

HEMODYNAMICS AND PATHOPHYSIOLOGY

Left-to-Right Shunt

In early infancy, when pulmonary resistance is high, left and right ventricular compliances are similar, and net shunting through an ASD is typically slight. As the left ventricle matures, it becomes less compliant in diastole than the right, and left atrial pressure rises. This drives a left-to-right shunt at the atrial level in the presence of an ASD. With age, the disparity between systemic and pulmonary resistance, and in turn between left and right ventricular compliance, results in increased left-to-right shunting and advancing right ventricular volume loading. Over time, right ventricular volume load results in dilation and hypertrophy, eventually affecting the function of both ventricles. Atrial enlargement may contribute to the late incidence of atrial fibrillation. Right ventricular volume overload is noted to occur as a rule when ASDs are larger than 6 mm in diameter.⁴⁶

Volume-induced hypertrophy of the right ventricle produces a loss of coronary reserve and eventual impairment of right ventricular systolic and diastolic function. Left ventricular functional reserve is diminished by adulthood in most patients with ASD. Although left ventricular systolic function may be normal at rest, the left ventricle exhibits a subnormal diastolic dimension, and a loss of functional reserve at exercise. Mechanisms that account for left ventricular dysfunction include (1) septal displacement secondary to right ventricular dilation and hypertrophy and (2) systolic anterior movement of the mitral valve. In general, the functional loss in the left and right ventricles is normalized 6 months following ASD closure in children and young adults.⁴⁷

Pulmonary Vascular Disease

Pulmonary hypertension associated with an isolated ASD is rare in childhood, although 35% to 50% of patients with unrepaired ASD have elevated pulmonary resistance by age 40. The development of pulmonary vascular disease is not uniformly related to age or degree of shunting across the ASD. In contrast, patients with VSD predictably develop pulmonary hypertension earlier and more severely, subjected to similar left-to-right

shunting and elevated pulmonary blood flow. No explanation has been found for why shunts of similar volume from ASDs or VSDs, generating similar elevations in pulmonary blood flow, produce different patterns of pulmonary hypertension. In a study of 128 patients with ASD and pulmonary hypertension (all older than 18 years), one third demonstrated an elevation in pulmonary vascular resistance (PVR) before 20 years of age, one third between 20 and 40, and the remainder after 40 years of age.⁴⁸

Pulmonary hypertension can develop at an earlier age in premature infants and in children with Trisomy 21. Histopathologic evidence of increased preacinar and intra-acinar arterial muscularity in infants with ASD and pulmonary vascular disease suggests that the pulmonary vasculopathy is the primary disorder in the uncommon population with early pulmonary vascular disease. The ASD may be acquired as a consequence, or it may be incidentally associated.⁴⁹

Clinical Presentation

A great majority of ASDs are asymptomatic, and palpitations, atrial fibrillation, and congestive failure are late sequelae, uncommon in patients younger than 40 years of age. Occasional dyspnea on extreme exertion is observed even in children. Recurrent respiratory infection in the presence of a large ASD is not uncommon. Chylothorax has been reported as a presenting manifestation of ASD and is cured by ASD closure.⁵⁰

In rare cases, ASDs may be associated with cyanosis. Bidirectional shunting across the ASD without an elevation in the pulmonary resistance has been demonstrated as a source of cyanosis.⁵¹ An alternative anatomic source for cyanosis is a streaming of desaturated inferior vena cava (IVC) blood across the ASD, caused by a persistently enlarged eustachian valve or other venous drainage anomaly that directs blood flow into the left atrium.⁵² More ominously, cyanosis can develop in the setting of advanced irreversible pulmonary hypertension.

Additional clinical associations with PFO include stroke, migraine headache, high altitude pulmonary edema, and diver's decompression disease.⁵³

Diagnostics and Examination

Findings consistent with ASD at physical exam largely reflect the left-to-right shunting and elevated right ventricular volume and flow. A prominent right ventricle impulse is present, with a precordial right ventricular lift, leftward displacement of the apex, and possible left chest wall prominence.

Auscultatory findings include a systolic flow murmur heard over the left upper sternal border from elevated flow across the pulmonary valve, a split S2, fixed throughout the respiratory cycle, with a prominent pulmonary valve component. An apical mid-diastolic murmur, especially at inspiration, reflects increased flow across the tricuspid valve.

The chest X-ray demonstrates cardiomegaly with prominent pulmonary vascularity and a prominent pulmonary artery bulb.

The electrocardiogram in ASD shows right ventricular hypertrophy, lengthened PR interval, incomplete right bundle branch block, and an RSR pattern in V₁. Electrocardiographic criteria for right ventricular enlargement are found in more than 50% of young patients with a large ASD. A traditional teaching is that the secundum ASD is associated with right-axis deviation and incomplete right bundle branch block (rSR' pattern in right precordial leads), whereas the primum defect exhibits left-axis deviation with incomplete right bundle branch block. A normal preoperative electrocardiogram was found in only 6% of a study population of sinus venosus ASD.⁵⁴ Although some of these electrocardiographic findings are reported as useful in children, they are not sensitive diagnostic features in adults and are seldom referenced in an era when an echocardiographic diagnosis is sensitive, specific, and readily available.⁵⁵

Cardiac catheterization is similarly seldom used in the diagnosis of ASD, but, when performed, an SVC to right atrium O₂ saturation step-up is reflective of the left-to-right shunting at the atrial level. A pressure gradient, usually less than 25 mm Hg at peak, may be detected across the pulmonary valve that is physiologic, reflecting the elevated pulmonary blood flow. Echocardiography is the most common mode of diagnosis, capable of acquiring sufficient morphologic and physiologic data to obviate the need for catheterization in a great majority of cases.

Transthoracic echocardiography with color Doppler flow mapping is accepted as the most accurate modality of ASD diagnosis in children, capable of detecting smaller intracardiac shunts compared with two-dimensional echocardiography alone. Small defects and defects in obscure locations, such as coronary sinus defects and some sinus venosus defects, may remain difficult to image by echocardiogram. High-resolution computed tomography (CT) and cardiac magnetic resonance imaging (MRI) have been used to image some interatrial defects that have eluded adequate echocardiographic characterization. MRI is particularly useful in imaging partial anomalous pulmonary venous structures that may lie adjacent to the airways and lung, where air interface interferes with the echocardiographic image resolution (Fig. 114-4).⁵⁶

MANAGEMENT OF ATRIAL SEPTAL DEFECT AND PATENT FORAMEN OVALE

Indications and Contraindications for Atrial Septal Defect Closure

The patients benefiting most from ASD closure are those at risk for developing pulmonary hypertension, but once pulmonary hypertension is present, surgical risk increases. This principle is the basis for the recommendation to close all significant ASDs.⁵⁷ Elective closure of ASD is generally recommended when the ratio of pulmonary to systemic blood flow (Q_p:Q_s) is 1.5:1 or greater. Ideally, ASD closure should be performed at age 2 to 5 years, before exercise capacity changes, while chest wall compliance is optimal, and before school age. An echo diagnosis

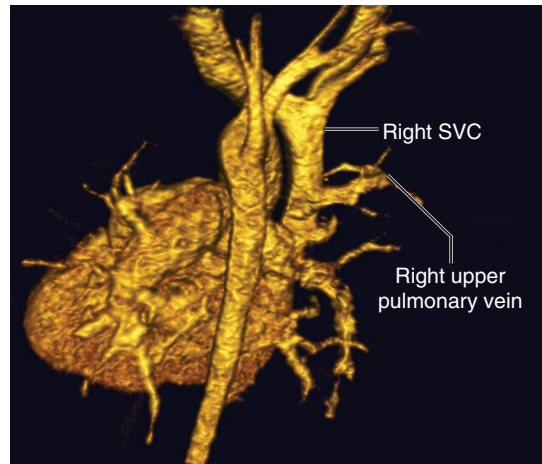


FIGURE 114-4 ■ Three-dimensional cardiac magnetic resonance image of a heart (posterior view), showing right upper pulmonary veins anomalously entering the superior vena cava (SVC), cephalad to the atriocaval junction in a patient with superior sinus venosus atrial septal defect. (Courtesy David Parra, MD, Vanderbilt Children's Heart Institute.)

of a significant defect with right ventricular volume overload is common and is a sufficient indication to close an ASD. Long-term follow-up data after surgical ASD closure show survival equal to the normal population when repair is performed early in life, with an age-related diminution in survival when closure is delayed. The 27-year survival for those repaired after 40 years of age is only 40%.⁵⁸

A small hemodynamically insignificant ASD, without cardiomegaly, does not warrant closure. Pregnancy is a relative contraindication to closure, with closure safely delayed until after delivery. Severe left ventricular failure is a contraindication to ASD closure.

Advanced pulmonary hypertension is a contraindication to ASD closure. It is important to consider that, in a high flow state, with a large Q_p:Q_s, high pulmonary artery pressure may not represent fixed pulmonary hypertension. As a general guideline, irreversible pulmonary hypertension is characterized by a PVR 8 to 12 Wood unit X m², with Q_p:Q_s less than 1.2:1, despite aggressive vasodilator challenge.

Moderate pulmonary hypertension with a reactive component is not a contraindication to ASD closure, although pulmonary hypertension may progress in these patients regardless of closure. In cases of severe pulmonary hypertension, a fenestrated ASD closure may be successfully performed, depending on the degree of reversibility and PVR. Guidelines for inoperability are largely based on VSD data. Generally, the PVR must fall below 7 Wood unit X m² with vasodilator therapy at cardiac catheterization for ASD closure risk to be less than prohibitive.⁵⁹ Vasodilators used at cardiac catheterization to determine the reversible component of pulmonary hypertension include hyperoxia, inhaled nitric oxide, and intravenous prostacycline (Flolan). Chronic preparatory vasodilator therapy with sildenafil has been successfully used to convert inoperable pulmonary hypertension to operable.⁶⁰

Patent Foramen Ovale Management

Indications for Patent Foramen Ovale Closure

The aggressive expansion of catheter-based therapies for PFO has resulted in a proliferation of clinical studies and case reports to reexamine indications for PFO closure. Although a subject of some continuing controversy, there are presently insufficient data to support the medical, surgical, or device treatment of the incidentally diagnosed, hemodynamically insignificant PFO. Adverse events attributed to the presence of a PFO or associated ASA include embolic stroke or peripheral embolus, brain abscess, gas embolization in diver's decompression illness, platypnea-orthodeoxia syndrome, migraine headache, and exacerbated hypoxia in settings of pulmonary embolus or elevated right heart pressures following a right ventricle infarct.⁶¹ Indications for PFO closure in these settings are also controversial and are discussed later.

Patent Foramen Ovale and Stroke

The associations of PFO with stroke are complicated, age dependent, and not fully resolved. When discussing the risk of stroke, it is important to distinguish first ischemic stroke from cryptogenic stroke (stroke with no known underlying causal condition) and from recurrent stroke.

An association between PFO and cryptogenic stroke is accepted in the younger population, an age group for whom stroke is rare in general. An association between cryptogenic stroke and the presence of PFO is strong for patients younger than 55 years of age, and the association is even stronger if ASA, with or without PFO, is present.⁶² Prospective studies corroborate this trend but with no statistical significance, leaving some room for controversy.⁵³

Causality after 55 years of age is less clear, complicated by various other sources for ischemic stroke that occur concurrently in the older population. Although the association is not as strong as that of the younger population, PFO independently remains associated with cryptogenic stroke in older patients.⁶³

There appears to be no relationship between size of interatrial shunt and risk of recurrent stroke.^{62,64}

Although there is a convincing association between cryptogenic stroke and PFO, the presence of PFO as predictor of first or recurrent stroke is less well established. Whereas the presence of untreated PFO predicts a 2.3% risk of recurrent cerebrovascular event by 4 years after the initial event, the presence of ASA with PFO predicts a 15.2% recurrence risk at 4 years.⁶⁵ Antiplatelet therapy following stroke mitigates the risk for recurrent stroke. For stroke victims with PFO and no ASA younger than 55 years of age, the annual risk of recurrent stroke while taking aspirin is only 1% to 2%.

Strategies for treatment of PFO after an ischemic event include PFO closure or medical management with aspirin or Coumadin. Various reports support the superiority of either anticoagulation therapy or mechanical closure of PFO for patients who have suffered cryptogenic stroke.

Obstacles remain to fully understanding the relationship of PFO to stroke and to determining the optimum treatment strategy. Antiplatelet therapy routinely applied after device closure further confuses the distinction between the effects of mechanical versus medical treatment. Systematic review fails to demonstrate advantages of closure versus anticoagulant therapy for the prevention of recurrent cryptogenic stroke in the presence of PFO, although there are data to suggest that the benefit of device closure may be device specific and that treatment may need to be individualized.⁶⁶⁻⁶⁸

Generally accepted practice guidelines suggest a treatment strategy as follows:

1. Aspirin alone for any asymptomatic patients with PFO or ASA. Risk of stroke in this population is 1%/yr or less.
2. Coumadin for patients with PFO and a hypercoagulable state, history of stroke, transient ischemic attack (TIA) or deep vein thrombosis (DVT) preceding stroke. Coumadin imposes a 2.2%/yr risk of bleeding complication, 0.2% fatal. PFO closure for this population may be indicated.
3. PFO closure for patients younger than 60 years old who have suffered cryptogenic stroke if the PFO is associated with ASA (4%/yr risk of stroke, even on aspirin), with DVT before stroke, or with TIA or stroke while on antithrombotic therapy.⁶⁹

Patent Foramen Ovale and Migraine

Although PFO may be present in more migraine sufferers than in the general population, especially for those with migraine accompanied by an aura, a clear association is not well established. Migraine cure or improvement has been reported in many patients undergoing closure of PFO, but the association of PFO closure and migraine improvement may be affected by placebo effect, periprocedural anticoagulation therapy, short follow-up, and device complications. The only randomized clinical trial of PFO closure for severe migraine has failed to demonstrate a positive effect.⁷⁰ Closure of PFO cannot firmly be recommended for the treatment of migraine at present, although additional randomized clinical trials are under way.^{53,71}

Patent Foramen Ovale and Diver's Decompression Illness

Bubbles in the left heart are documented by echocardiogram to demonstrate diver's decompression illness in association with PFO. Underwater pressure and its effects on ventilation elevate the pulmonary resistance, reducing left ventricular preload while increasing right-sided pressures, and favoring right-to-left shunting across the PFO. The overall risk of diver's decompression illness with PFO is low, with 5 events per 10,000 divers, but these odds are fivefold above the odds for those without PFO.

In a prospective, nonrandomized, controlled trial of PFO closure among divers with PFO, long-term follow-up demonstrated an apparent advantage to PFO closure in preventing symptomatic decompression injury and asymptomatic neurologic findings on MRI.⁷² These

findings suggest consideration of PFO closure for frequent divers, although firm evidence to support screening or prophylactic PFO closure is lacking.³⁵

Catheter-Based Treatment

King and Mills reported the first catheter-delivered ASD closure in 1976, using a double umbrella device and a 23 Fr delivery catheter. The large-delivery catheter and complex delivery method prevented widespread use.⁷³ In 1983, Rashkind introduced a self-expanding patch device that attached to the septum with small barbed hooks. The device was unfortunately hindered by the inability for repositioning and its risk of inadvertent attachment to other structures within the heart.⁷⁴ The concept of a self-expanding patch led to the development of the Lock Clamshell device—a double disc, self-expanding device that could be delivered through an 11 Fr delivery sheath. First reported in 1990, this was the first device to receive widespread use.⁷⁵ Device arm fracture resulted in its eventual redesign. In 1993, Das reported the use of the Angel Wings device—a self-expanding, double patch device with a conjoint central ring acting as a waist. Although its use was limited by its rigid frame, its sharp edges, and difficulty with its retrieval, its circular central waist demonstrated the benefit of a self-centering device.⁷⁶ Over the subsequent 20 years, numerous devices have been designed and investigated for the treatment of secundum ASDs. The two devices currently approved by the Food and Drug Administration (FDA) in the United States are the Amplatzer septal occluder (St. Jude Medical, St. Paul, MN)⁷⁷ and the Helex septal occluder (Gore & Associates, Flagstaff, AZ).⁷⁶ Devices currently available outside the United States include the Gore septal occluder (W.L. Gore & Associates, Flagstaff, AZ)⁷⁸; the Ultrasept ASD occluder, which is a modification of the Atriosept device (Cardia, Inc., Eagan, MN)⁷⁹; Occlutech Figulla ASD occluder (Occlutech, Jena, Germany)⁸⁰; the Cardio-Fix (CSO) ASD occluder (Starway Medical Technology, Inc., Beijing, China)⁸¹; and the Cera ASD occluder (Lifetech Scientific Co., Ltd., Shenzhen, China).⁸²

Most ASDs today are closed by catheter-based devices. The Amplatzer and Helex occluders are the most commonly used approved devices at this time. A national sampling of community hospital practices found a 58-fold increase in the annual number of devices placed from 2002 to 2004, whereas surgical closure rates remained constant.⁸³ The success rate and morbidity are almost equal when comparing device closure with surgical closure. Current published studies comparing the two approaches with anatomically similar defects show a device success rate of 80% to 95.7% and a surgical closure success rate of 95% to 100%, although the success of device closures continues to evolve. Complications requiring treatment (defined to include anemia, arrhythmia requiring minor treatment, post pericardotomy syndrome, pericardial or pleural effusion, transfusion, fever, wound complication) occur in up to 8% of device closures and 23% to 24% of surgical closures, and mean length of hospital stay is 1 day in the device group versus 3.4 days in the surgical group.^{84,85} Continual advances in the hardware and experience with device closures are

improving the success rate of these catheter-based approaches.

Anatomic determinants that prohibit device closure remain the major indications for surgical ASD closure in the current era. Defects unsuitable for device closure include those that have failed attempted device closure, common atria or those without sufficient septal rim to engage the device, and sinus venosus defects for which device closure would threaten obstruction of pulmonary veins, IVC, or SVC. Anterior-inferior septal deficiency can result in device interference with the tricuspid valve, mitral valve, or coronary sinus. Individual deficient septal rims, although originally constituting contraindication to device closure, no longer are absolute contraindications but may reduce success rates.⁸⁶ The largest Amplatzer septal occlusion device presently available in the United States is 38 mm, and defects exceeding this size require surgical closure. Multiple defects can be closed with multiple devices, although the cost of multiple device closures may exceed the cost of surgery. Determinants of the limitations to device closure are under evolution as devices and their delivery systems continue to undergo refinements.

Pooled data from multiple sources estimate that major complications of device closure of ASD and PFO occur in 1.4% of cases and minor complications in 1.4%.⁸⁷ Early major procedural complications of device closure include device embolization; cardiac tamponade; stroke or TIA; retroperitoneal hematoma; thrombosis; device erosion; obstruction of the IVC, coronary sinus, or pulmonary vein; and tricuspid or mitral insufficiency. Non-cardiac complications include iliac vein dissection, retroperitoneal or groin hematoma, and leg ischemia. Minor complications include minor vascular complications, arrhythmia, transient ST-segment elevation, percutaneously retrieved device embolization, pericardial effusion, device malposition not requiring surgery, and pulmonary edema. Late complications include device-related death, cerebrovascular events, device thrombosis or malposition, embolization, erosion, aortoatrial fistula, arrhythmia, device fracture, pericardial effusion, endocarditis, and nickel toxicity.⁸⁷

As experience with devices matures, their indications and limits are better defined. Evidence suggests that a higher incidence of complications is expected for patients who weigh less than 15 kg and that waiting for somatic growth may be preferable.⁸⁸ A fluoroscopically guided catheter-based approach raises concern for radiation exposure; this consideration is eliminated when echo-guided ASD closure is used.^{89,90} A large defect or a large device is a risk factor for AV block.⁹¹ Careful avoidance of device oversizing, especially in patients with a deficient aortic rim, may prevent erosion or perforation.^{92,93} Absent posterior-inferior rims may increase risk of dislodgement, and patients with this anatomy might more safely be served by surgery.⁹⁴

A recent 20-year outcome comparison of device versus surgical treatment of comparable ASDs shows no significant differences in survival, functional capacity, arrhythmia, or late embolic stroke between methods of closure, supporting a transcatheter approach for defects amenable to device closure.⁹⁵

Surgical Treatment

Secundum Atrial Septal Defect and Patent Foramen Ovale

The standard surgical incision for the repair of ASD is partial or complete median sternotomy. A portion of the anterior pericardium is preserved for use as a patch. Various other materials have been used as a patch, including bovine pericardium and polytetrafluoroethylene (PTFE), but autologous pericardium is a compliant, durable, and cost-efficacious choice. Bicaval venous cannulation, mild hypothermia, and antegrade cardioplegia are used to provide a still, blood-free field through which to expose the interatrial septum via right atriotomy. A careful examination of the interatrial septum ensures the correct identification of the margins of the defect. The SVC and IVC are identified, with special attention to any structures that might represent partial anomalous pulmonary venous return (PAPVR) to the right atrium or vena cavae. The eustachian valve is identified to avoid the error of baffling the IVC to the left atrium. The coronary sinus is identified and protected from inclusion in the suture line. A determination is made to close the defect primarily where there is sufficient septum primum tissue, or with a patch. Care is exercised to place sutures firmly into surrounding tissue but without interfering with the adjacent noncoronary sinus of the aorta superiorly, the tricuspid or mitral valves anteriorly, the coronary sinus and AV node inferoanteriorly, the IVC and right lower pulmonary vein orifice inferiorly and posteriorly, or the right upper pulmonary vein and SVC superoposteriorly (Fig. 114-5). When the defect is closed primarily, adequate redundant tissue must be present to ensure that no tension will be placed on the repair once the heart is filled and beating.

Sinus Venosus Atrial Septal Defect with Partial Anomalous Pulmonary Venous Return

The most common variant of sinus venosus ASD is the superior, when the right upper pulmonary vein drains anomalously to the right atrium or SVC. A single intra-atrial patch can be positioned to baffle the pulmonary vein through the septal defect into the left atrium in many cases. Care is exercised to place the SVC incision remote from the sinoatrial node. The single-patch technique may predispose to SVC narrowing, as the baffle occupies space within the SVC lumen.⁹⁶ A two-patch approach enlarges the SVC to accommodate the baffle.

When one or more pulmonary veins connect to the SVC too cephalad to permit simple baffling, an adjunctive patch plasty of the lateral SVC must be carried out. Anticipating such geometry, an atriotomy can be planned at the lateral base of the SVC, so that septal and caval patch plasties can be placed through a single atriotomy, extended as far as necessary onto the SVC (Fig. 114-6). ASD enlargement may also be needed to ensure an unobstructed baffle.

The Warden procedure, described in 1984,⁹⁷ consists of transection of the SVC cephalad to the connection of

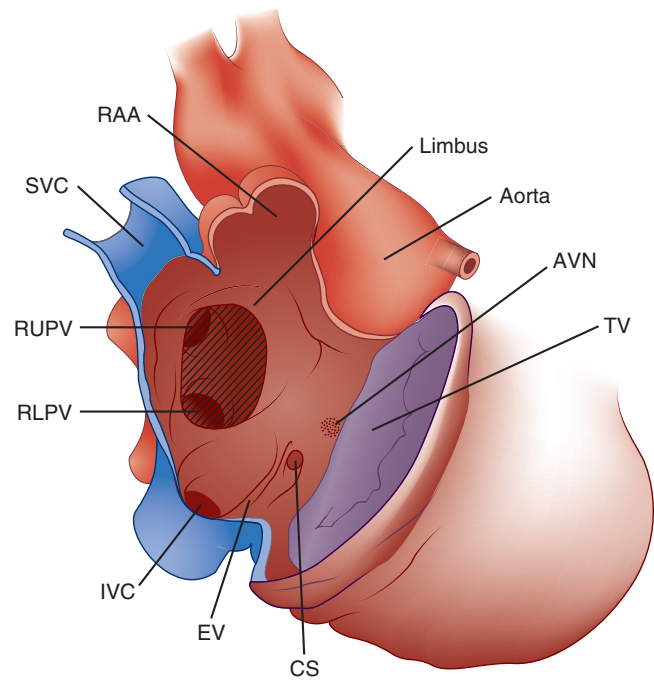


FIGURE 114-5 ■ Surgical anatomy of the interatrial septum with atrial septal defect. AVN, Atrioventricular node; CS, coronary sinus; EV, eustachian valve; IVC, inferior vena cava; RAA, right atrial appendage; RLPV, right lower pulmonary vein; RUPV, right upper pulmonary vein; SVC, superior vena cava; TV, tricuspid valve.

the anomalous pulmonary vein, thereby committing the atriocaval junction to pulmonary venous blood flow exclusively. An intra-atrial patch baffles the atriocaval junction to the left atrium, through a preexistent or created ASD. The transected SVC is then reimplanted into the right atrial appendage by direct anastomosis (Fig. 114-7). A tensionless SVC anastomosis is imperative to the success of the SVC reimplantation, and patch augmentation is sometimes necessary. Special care must be taken to resect all trabecular muscle in the atrial appendage that might impair SVC flow through the reimplantation site.

A retrospective examination of 54 patients with superior sinus venosus ASD and PAPVR treated at Children's Memorial Hospital showed a 55% incidence of the loss of sinus rhythm. These patients had a low atrial or junctional rhythm that did not increase normally with exercise. These data support consideration of the Warden procedure for the correction of all superior sinus venosus ASDs when the right upper pulmonary veins enter the SVC.⁹⁸

Primum Atrial Septal Defect

Characterized by the absence of any septal tissue between the AV valves, the primum ASD closure requires that the patch be sutured directly to mitral or tricuspid tissue, avoiding the subjacent ventricular septum and the His bundle, and sometimes leaving the coronary sinus on the left atrial side to avoid the AV node. An examination of the mitral valve and closure of the associated cleft is

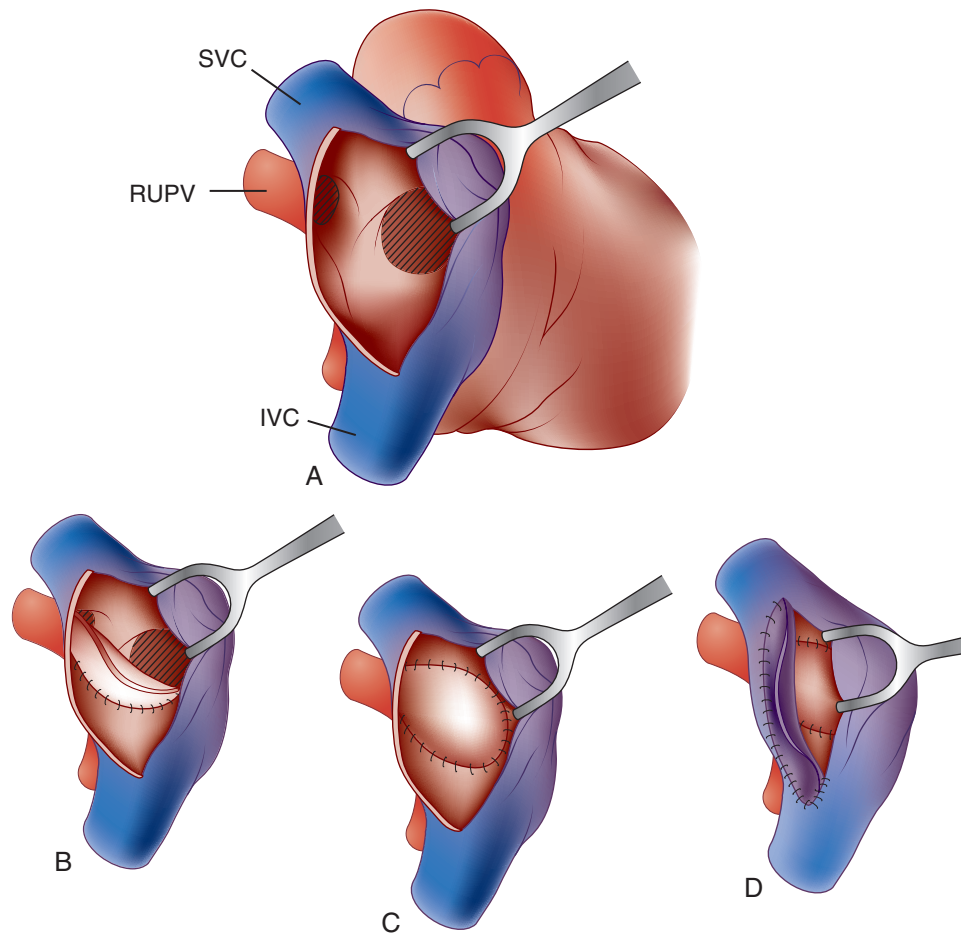


FIGURE 114-6 ■ Repair of superior sinus venosus atrial septal defect. **A**, A lateral atriotomy provides exposure to the anomalous right upper pulmonary vein. **B**, A pericardial baffle is constructed to direct right upper pulmonary vein flow to the left atrium, through a created or enlarged secundum defect. **C**, Completed intra-atrial baffle. **D**, A patch plasty of the atriotomy extends sufficiently cephalad on the superior vena cava to avert caval obstruction. IVC, Inferior vena cava; RUPV, right upper pulmonary vein(s); SVC, superior vena cava.

indicated, even in the absence of mitral regurgitation. Care is taken to avoid creating mitral stenosis. The primum defect is discussed fully with AV septal defects.

Minimally Invasive Approaches

Various alternatives to the median sternotomy have been described for the repair of ASD. An inframammary or axillary incision with thoracotomy provides exposure of the right atrium with a scar that is more easily concealed than the full median sternotomy. The subxiphoid “min-isternotomy” or partial lower sternotomy can be performed through small vertical or transverse inframammary incisions, and cannulation through the incision rather than peripherally.⁹⁹ Experience continues to expand with methods that use even smaller incisions, femoral cannulation, and video or robotic assistance.¹⁰⁰⁻¹⁰² These alternative approaches may confer a cosmetic advantage over the standard midline incision and median sternotomy, although to date it has been difficult to demonstrate objective advantages in cardiac physiology, pulmonary physiology, pain, length of anesthesia, length of hospital stay, or cost.¹⁰³

Complications of Surgery

Early complications following the surgical closure of ASD include patch dehiscence, thromboembolism, and arrhythmia such as heart block, sinus node dysfunction, and atrial fibrillation or flutter. Early postoperative arrhythmia following ASD repair may predict an eventual need for pacemaker.¹⁰⁴ The incidence of residual shunt after surgical closure is negligibly small.⁸⁴ Residual right-to-left shunting can occur with incomplete closure, with undiagnosed additional defects, and when ASD closure mistakenly engages the eustachian valve, baffling the IVC inadvertently to the left atrium and resulting in cyanosis. In the setting of pulmonary hypertension, ASD closure can result in systemic venous hypertension, right ventricular failure, or low cardiac output and can require a return to cardiopulmonary bypass to fenestrate the closure.

An examination of late outcome 27 to 32 years after surgical repair of ASD showed that age at the time of repair is an independent risk factor for late complications. Late cardiac failure, stroke, and atrial fibrillation are more frequent when the patient’s age at repair is older

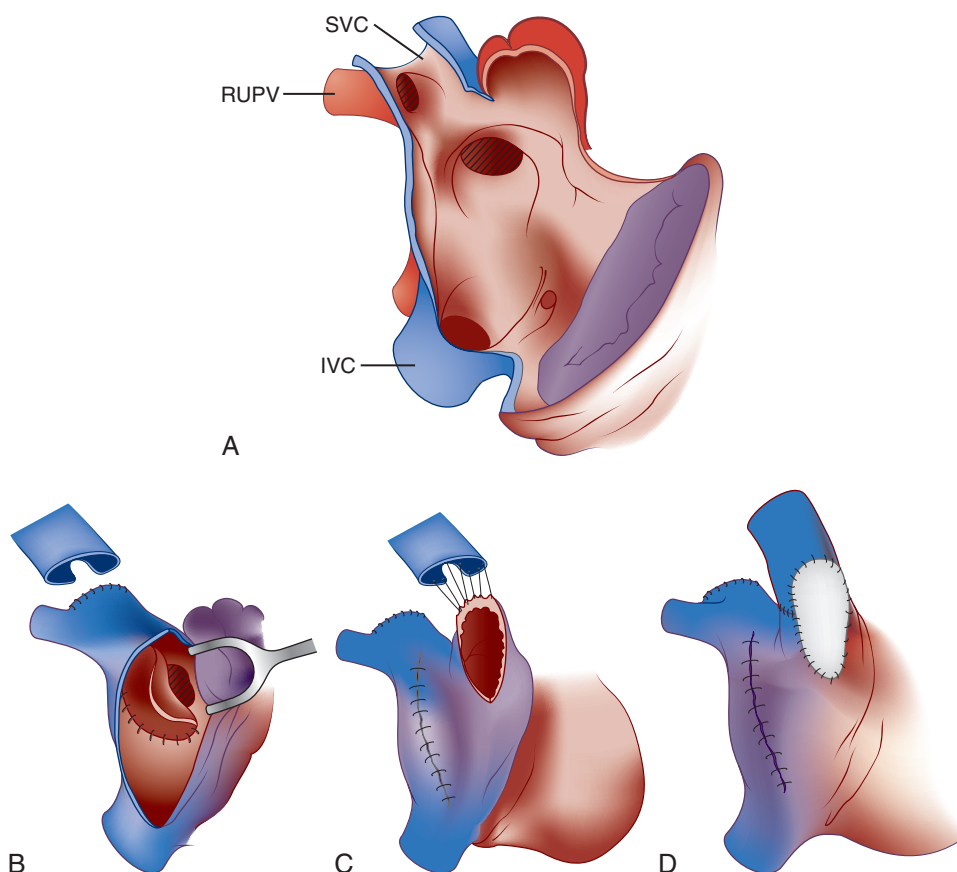


FIGURE 114-7 ■ The Warden procedure. **A**, Cutaway view of the right atrium, showing the relationship of the displaced right upper pulmonary vein (RUPV) and its distance from the atrial septal defect and left atrium. **B**, Superior vena cava (SVC) transected above the abnormal pulmonary vein. The RUPV with the SVC orifice is baffled to the left atrium. **C**, The transected SVC is anastomosed directly to the right atrial appendage. **D**, Patch augmentation of the anastomosis averts cavoatrial obstruction. IVC, Inferior vena cava.

than 25 years.⁵⁸ Independent risk factors for the development of atrial fibrillation with ASD, repaired or not, include age older than 25 years, left atrial enlargement, and mitral or tricuspid regurgitation.¹⁰⁵ Thirty to forty percent of patients older than 40 who exhibit atrial fibrillation after ASD repair may have an embolic event within 10 years of ASD repair, and systemic anticoagulation is a consideration in this group.¹⁰⁶

Reported complications of thoracotomy approaches include phrenic nerve palsy, lung herniation, cardiac herniation, scoliosis, and breast or chest muscle deformity.^{107,108}

OUTCOME

Physiology of Atrial Septal Defect Closure

Subtle changes in exercise performance in ASD patients can be measured even in childhood. An abnormal ventilatory threshold during submaximal exercise returns to normal by 6 months after repair of ASD in patients younger than 5 years of age but remains subnormal for patients repaired older than 5 years.¹⁰⁹ Most patients older than 5 years old at the time of repair have at least

some residual right ventricle dilation and abnormal septal wall motion after ASD closure, not predicted by preoperative shunt or ASD size.¹¹⁰ The clinical significance of this finding is unclear. These data may further support a strategy of ASD closure before school age.

Adults

Although the adult with ASD benefits by improvement in exercise physiology and reduction of right ventricle dilation after closure of ASD, the improvements are less pronounced with advancing age.^{57,111} There is a clear survival advantage and a reduction in the incidence of cardiovascular events for ASD closure in patients younger than 40, when compared with expectant management.¹¹² Some controversy remains as to the best treatment strategy in the older adult population.

Regardless of the presence of symptoms, the incidence of right heart enlargement in adults decreases after surgical or device closure of ASD, although right atrial enlargement may persist, proportional to the age at repair.¹¹³⁻¹¹⁵ Although younger adults demonstrate an improved $\text{VO}_{2\text{max}}$ within months of ASD closure, patients older than 40 years who undergo repair may take years to show improvement. A low preoperative peak oxygen uptake has been demonstrated in adults with ASD,

increasing by 4 months after repair, fully normalizing by 10 years after surgical ASD repair.^{113,116} Prior to ASD closure, more than 60% of patients older than 40 years of age are New York Heart Association (NYHA) class III to IV, whereas after ASD closure, more than 80% are NYHA class I to II.¹¹⁷ Patients older than 60 show functional class improvement, immediate and late reduction in pulmonary artery pressure, and improved 5- and 10-year survival after ASD closure in comparison with expectant management.^{118,119} These data support a strategy of ASD closure regardless of age for most patients. Independent risk factors for prolonged hospital stay in adults after ASD closure include preoperative atrial fibrillation, larger ASD, older age at operation, and longer cardiopulmonary bypass time.¹²⁰ A higher incidence of postclosure acute left ventricular failure and pulmonary congestion occurs with larger ASDs and with older age at repair.¹²¹

Arrhythmia

If ASD closure is performed in childhood, the incidence of early or late atrial tachyarrhythmia or sinus node dysfunction is rare.¹²² The prevalence of atrial flutter or fibrillation may already be rising in the unrepaired young teenager, and prevalence is clearly increased after age 40.^{14,44,58}

A significant incidence of postoperative atrial fibrillation in the adult has given consideration to performing a Cox-Maze arrhythmia ablation procedure concurrent with ASD closure for patients older than 40 years of age. No randomized data support performing a Cox-Maze procedure, but observational studies show benefit in adult patients undergoing ASD closure who have preoperative atrial fibrillation or flutter.¹²³ A right atrial Maze procedure alone may be ineffective in restoring and maintaining sinus rhythm after ASD closure, and higher success is achieved by performing a biatrial Maze procedure.¹²⁴

COR TRIATRIATUM

Cor triatriatum sinistrum, one of the rarest cardiac anomalies, comprises 0.1% of congenital heart defects. In the classic form, described by Church in 1868, cor triatriatum is a separation of the pulmonary veins from the left atrium by a fibromuscular membrane. The anatomic elements of the left atrium, including the atrial appendage, are all ventral to the membrane, and the communication between pulmonary veins and left atrium is restricted to an orifice in the membrane.¹²⁵ The membrane can contain single or multiple fenestrations and can also communicate with the right atrium directly through an ASD, or indirectly, through an ascending or descending vertical vein. A variety of classifications have been devised to characterize the various drainage patterns of the pulmonary venous chamber into the heart (Fig. 114-8).

A subdivided right atrium, sometimes referred to as cor triatriatum dexter, is a membranous division of the right atrium, unrelated to cor triatriatum sinistrum. Cor

triatriatum dexter forms from a persistence of the right sinus venosus valve, which normally regresses by 12 weeks of embryonic age.¹²⁶ The subdividing right atrial membrane can take on a variety of forms, ranging from a prominent Chiari network to a full septation that subdivides the right atrium or prolapses through the tricuspid valve, even to the extent that right ventricular outflow is obstructed.¹²⁷

Embryology

The cor triatriatum sinistrum membrane contains elements of the embryonic common pulmonary vein and the wall of the left atrium. Van Praagh suggests that the dorsal chamber is the embryonic common pulmonary vein and that entrapment of the left atrial ostium of the common pulmonary vein by sinus venosus tissue results in a failure of the normal course of incorporation into the ventral left atrial chamber during the fifth embryonic week.¹²⁸ Van Praagh's explanation is the most widely accepted. Other theories postulate a malformation of the septum primum or an incomplete incorporation of the common pulmonary vein into the left atrium.¹²⁹⁻¹³¹

The partially obstructed pulmonary venous chamber of cor triatriatum may form an ascending or descending vertical vein decompressing it into the systemic venous circulation at the IVC or SVC, similar to that of supracardiac or infracardiac total anomalous pulmonary venous connection. The degree of connectedness between the chambers determines the degree of obstruction.

Associated Abnormalities

Combinations of cor triatriatum and partial anomalous pulmonary venous drainage have been described, with normally draining left- or right-sided veins to the proper left atrium and contralateral veins connecting to a dorsal venous chamber. Associated partial anomalous pulmonary venous drainage to a vertical vein or to the coronary sinus has been described.¹³² Cor triatriatum has a high association with the presence of a left SVC, an association theorized to be involved in the pathogenesis of cor triatriatum.¹³¹

Other intracardiac anomalies associated with cor triatriatum sinistrum include pulmonary stenosis, Ebstein anomaly, tricuspid anomalies, VSD, tetralogy of Fallot, AV septal defect, and hypoplastic left heart.^{133,134}

Clinical Presentation

The clinical presentation of cor triatriatum is usually in infancy and is manifested by symptoms and signs of pulmonary venous congestion and pulmonary hypertension. Poor growth, episodic exacerbations of pulmonary edema, and frequent pulmonary infections are common. The severity of the presentation is dependent on the degree of pulmonary venous obstruction. Those patients with a communication to the right atrium generally have a milder progression of symptoms, as the pulmonary venous chamber decompresses into the right atrium. Patients presenting later in life may additionally have syncope, hemoptysis, atrial fibrillation, embolic

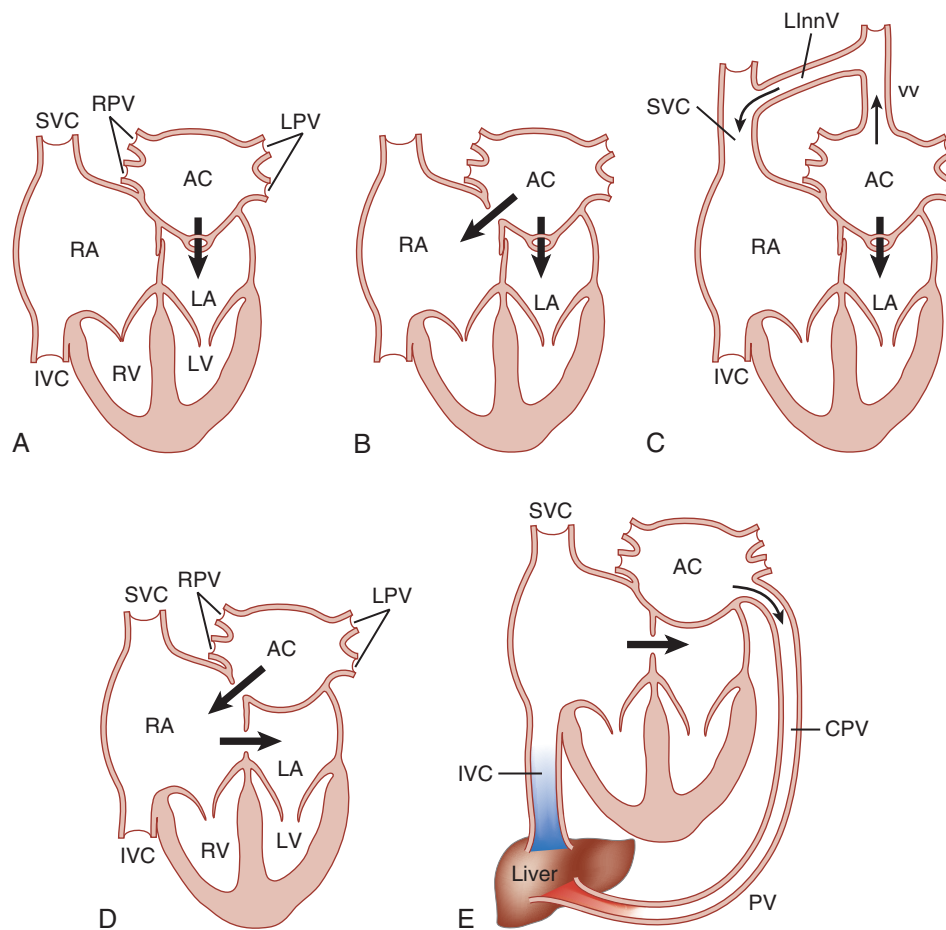


FIGURE 114-8 ■ The subtypes of cor triatriatum. **A**, The classic cor triatriatum, with the common pulmonary chamber draining through a restrictive membrane perforation, into the true left atrium. **B**, Communications between the common pulmonary venous chamber and both right and left atria. **C**, A vertical decompressing vein from the common pulmonary venous chamber to the innominate vein. **D**, Pulmonary venous effluent entering the right atrium through a direct communication, and the left atrium through a secundum atrial septal defect. **E**, An infracardiac vertical decompressing vein from the pulmonary venous chamber to the systemic venous system. AC, Accessory chamber; CPV, common pulmonary vein; IVC, inferior vena cava; LA, left atrium; LInnV, left innominate vein; LPV, left pulmonary vein; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RPV, right pulmonary vein; RV, right ventricle; SVC, superior vena cava; vv, vertical vein. (Reproduced with permission from Hammon JW, Bender HW: Major anomalies of pulmonary and thoracic systemic veins. In Sabiston DC, Spencer FC, editors: *Surgery of the chest*, ed 6, Philadelphia, 1995, WB Saunders, p 1422.)

complications, and right heart failure.¹³⁵ The progression of symptoms in the adult with cor triatriatum may be the result of the development of mitral regurgitation. Calcification of the membrane is found in adults and can account for a narrowing of the perforation in the membrane, with a resultant exacerbation of symptoms. In a study of 31 necropsy specimens from untreated patients prior to 1960, the mean age at death was 3.3 months if the ostial diameter was smaller than 3 mm and 16 years for an ostial diameter larger than 3 mm.¹³⁶ Patients presenting as adults may exhibit progressive dyspnea and palpitations as presenting symptoms.

The physical exam is remarkable for congested lungs and a prominent second pulmonary sound on auscultation. Findings in patients presenting late with longstanding pulmonary hypertension and right heart failure include liver enlargement and jugular venous distention with a V wave. A systolic murmur at the left sternal border may be present.

The electrocardiogram demonstrates peaked P waves, suggesting right atrial enlargement. Right-axis

deviation and voltage are consistent with right ventricular enlargement.

The chest radiograph shows cardiomegaly consistent with right ventricular enlargement, prominent pulmonary artery, and vascular markings.

The diagnosis of cor triatriatum is typically made by echocardiogram, and cardiac catheterization is seldom necessary. Findings at cardiac catheterization include a gradient from pulmonary capillary wedge pressure to left atrium, pulmonary hypertension, venous phase angiographic imaging of an upper chamber, prolonged pulmonary transit time, differential opacification of upper chamber and left atrium, and an occasional linear definition of the membrane. In rare cases, thrombus may occur proximal to the membrane and present as a left atrial mass.

Pathophysiology

In the anatomic subtype in which the orifice of the membrane communicates exclusively with the left atrium, the

physiology of cor triatriatum is similar to that of mitral stenosis, with pulmonary congestion and/or edema depending on the degree of restriction at the membrane. For the subtypes with communication to the right atrium, a convoluted pathway of pulmonary venous flow delivers pulmonary venous effluent to the right atrium and then back to the left atrium through an interatrial communication below the membrane. Restricted filling of the left heart, low cardiac output, and pulmonary edema result, dependent on the degree of restriction along the pathway to the left atrium.

Pulmonary vein obstruction from cor triatriatum has been demonstrated to produce progressive medial thickening and intimal fibrosis in pulmonary veins and arteries, and lymphangiectasia, although neither as early nor as severe as is the progression of pulmonary vascular disease in VSD. The cellular intimal proliferation and advanced irreversible vascular changes characteristic of VSD or other left-to-right shunting lesions are not seen with pulmonary venous obstruction, and reversibility is the rule.¹³⁷

When an interatrial communication exists between the proximal chamber and the right atrium, a left-to-right shunt exists. When a communication exists between the right atrium and the underfilled left atrial chamber, a right-to-left shunt can occur.

Treatment and Outcome

The surgical repair of cor triatriatum is performed with bicaval venous cannulation, moderate hypothermia, and cardioplegic arrest. An examination of the surface anatomy of the heart often confirms the presence of a dilated pulmonary venous chamber behind the heart. The repair is typically performed through a right atriotomy and a subsequent incision into the left atrium across the interatrial septum. Caution is exercised to identify the mitral valve and protect it from injury during the resection of the membrane. Time taken to fully define the membrane prevents injury to adjacent structures, notably the mitral valve. The membrane is widely excised, so as to leave no flow gradient from the pulmonary vein orifices to the mitral inflow region of the left atrium. A careful external examination of the heart exposes any ascending or descending venous structures for ligation.

Cor triatriatum repair has excellent outcomes, with expected mortality of less than 2% of cases. Reintervention for recurrent obstruction is rare.¹³³

A concomitant Maze procedure has been described for the treatment of adults with cor triatriatum and atrial fibrillation.¹³⁸

Although the standard approach includes a complete surgical resection of the obstructing membrane, a percutaneous balloon dilation of cor triatriatum membranes by a transseptal approach has been reported.¹³⁹

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SURGICAL CONSIDERATIONS IN PULMONARY VEIN ANOMALIES

Mauro Lo Rito • Osami Honjo • Christopher A. Caldarone

CHAPTER OUTLINE

ETIOLOGY

PARTIAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Anatomy
Presentation
Pathophysiology
Surgical Repair
Planning the Superior Vena Caval Cannulation
Results

SCIMITAR SYNDROME

Surgical Management
Results and Complications

TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Anatomy
Supracardiac Anatomy
Cardiac Anatomy
Infracardiac Anatomy
Mixed Anatomy

Presentation

Pathophysiology

Diagnostic Techniques

Chest Radiography
Echocardiography
Cardiac Catheterization
Magnetic Resonance Imaging
Computed Tomography Angiography

Surgical Repair

Results

SPECIAL CONSIDERATIONS

Total Anomalous Pulmonary Venous Drainage in Heterotaxy
Pulmonary Vein Stenosis After Repair
Surgical Techniques for Pulmonary Vein Stenosis After Repair of Total Anomalous Pulmonary Venous Return
Congenital (Primary) Pulmonary Vein Stenosis

ETIOLOGY

Normal embryologic development of the pulmonary venous system involves creation of a connection between the left atrium and the pulmonary venous plexus, and subsequent regression of systemic-to-pulmonary venous connections. Inappropriate connection of the pulmonary venous system to the systemic venous system is termed *anomalous pulmonary venous drainage*.

As part of normal embryologic development, the lungs are derived from buds arising from the primitive foregut. During the initial stages of pulmonary development (25 to 27 days' gestation), the pulmonary venous drainage is through the cardinal and umbilical-vitelline venous system (systemic veins). During the later stages of development (27 to 29 days' gestation), an outpouching of the common atrium forms to the leftward of the developing septal primum.¹ The structure, termed the common pulmonary vein, primordial pulmonary vein, or pulmonary pit, extends and bifurcates into the pulmonary venous

plexus and establishes venous drainage of the developing lung buds at 28 to 30 days' gestation (Fig. 115-1). Thereafter, the connection between the lung buds and the systemic venous system regresses, leaving the developing lungs with direct drainage to the left atrium.

Human genetic studies of kindreds with total anomalous pulmonary venous drainage showed an autosomal-dominant inheritance with incomplete penetrance and variable expression with involvement of genetic loci located in the human chromosome 4q12.² During heart morphogenesis, an avascular zone forms between the caudal primitive vascular structures (that will become part of the systemic vein circulation) and the pulmonary vein plexus, which arises from the lung.³ Disruption of this avascular zone and of the patterning of the pulmonary vein may be the primary developmental anomaly in the genesis of total anomalous pulmonary connection. In mice, a secreted repellent guidance molecule, semaphorin 3d, is located in the avascular zone and plays a key role in the correct patterning of the pulmonary vein connection to the left atrium (Fig. 115-2). Deficiency of

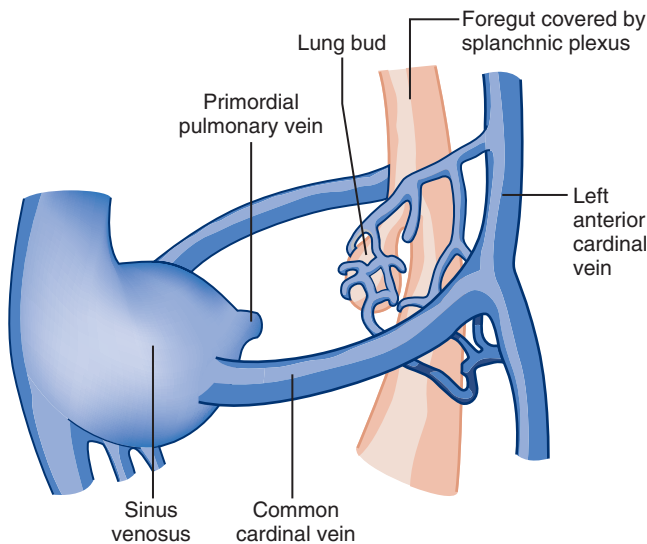


FIGURE 115-1 ■ Lung buds arise from the primitive foregut with systemic venous drainage during early embryologic development. At later stages, an outpouching from the common atrium extends and bifurcates into the pulmonary venous plexus to establish drainage to the atrium, followed by regression of the systemic venous drainage. (Modified from Jonas RA, Smolinsky A, Mayer JE, et al: Obstructed pulmonary venous drainage with total anomalous pulmonary venous connection to the coronary sinus. *Am J Cardiol* 59:431–435, 1987.)

semaphorin 3d is associated with anomalous connection of pulmonary veins with both atria or the coronary sinus. The mechanism suggested is based on the lack of repulsion guidance that leads to a broad domain of abnormal endothelial sprouts from the lung buds which may persist when blood flow through the connection begins (Fig. 115-3). In preliminary studies in humans with anomalous pulmonary venous connection, specific mutations in the gene sequence for semaphorin 3d have been identified.⁴

Anomalous pulmonary venous drainage can result from failure of fusion between the left atrial outpouching and the pulmonary venous plexus, or from malposition of the relationship between the atrial outpouching and the development of the atrial septum. If all the pulmonary veins maintain an anomalous connection to a single systemic venous site, the lesion is termed *total anomalous pulmonary venous drainage*. If all the pulmonary veins drain anomalously to multiple discrete systemic veins, the lesion is called *mixed total anomalous pulmonary venous drainage*. If one to three pulmonary veins drain via an anomalous pathway and at least one pulmonary vein drains to the left atrium, the lesion is termed *partial anomalous pulmonary venous drainage*.

PARTIAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Anatomy

Partial anomalous pulmonary venous drainage is characterized by a failure of one to three of the pulmonary veins

to connect with the left atrium during fetal development. Typically, the pulmonary vein has an abnormal connection to the superior vena cava near the cavoatrial junction. More than 80% of patients have associated congenital heart defects, the most common of which is an atrial septal defect. A minority of patients (18%) have an intact atrial septum.⁵ Most commonly, a combination of right upper and middle lobe pulmonary veins drain to the superior vena caval–right atrial junction (Fig. 115-4). Less commonly, isolated anomalous right upper lobe venous drainage is present. Least commonly, the entire right lung drains via an anomalous vein into the right atrium.⁵ Other less common sites of anomalous venous drainage include the inferior vena cava (e.g., as part of the scimitar syndrome), the left-sided superior vena cava, and the innominate vein. The left pulmonary veins rarely can also have an anomalous drainage to the systemic venous circulation as isolated disease.⁶

Presentation

Patients are often asymptomatic and display a murmur noted on routine examination that is caused by increased flow across the pulmonary valve. A split and prominent second heart sound is also present. Symptomatic patients display the sequelae of a left-to-right shunt, including decreased exercise tolerance and poor growth. Patients are not cyanotic unless they have developed pulmonary hypertension as a late manifestation of a large left-to-right shunt. In such patients, Eisenmenger syndrome is characterized by the reversal of the shunt from right to left in association with an atrial septal defect.

Pathophysiology

The dominant hemodynamic abnormality is related to the left-to-right shunt imposed by pulmonary venous drainage into the right atrium. In the absence of an atrial septal defect, the left-to-right shunt is limited by the amount of flow in the anomalous pulmonary vein. In contrast, an associated atrial septal defect adds potential for increased left-to-right shunting at the atrial level. Increased right-sided flow can lead to right ventricular dilation, tricuspid insufficiency, and supraventricular arrhythmias.

Surgical Repair

The goal of surgical therapy is to divert the anomalous pulmonary venous effluent to the left atrium in an unobstructed fashion. In the presence of a sinus venosus atrial septal defect and anomalous right upper pulmonary veins, the flow is diverted with a baffle constructed along the edge of the sinus venosus atrial septal defect. The defect may have to be enlarged to create an unobstructed pathway to the left atrium. In the absence of an atrial septal defect (i.e., the atrial septum is intact), an atrial septal defect must be created in the region of the fossa ovalis with extension in the region of the limbus and a similar baffle constructed to divert flow from the anomalous pulmonary vein to the newly created atrial septal defect.

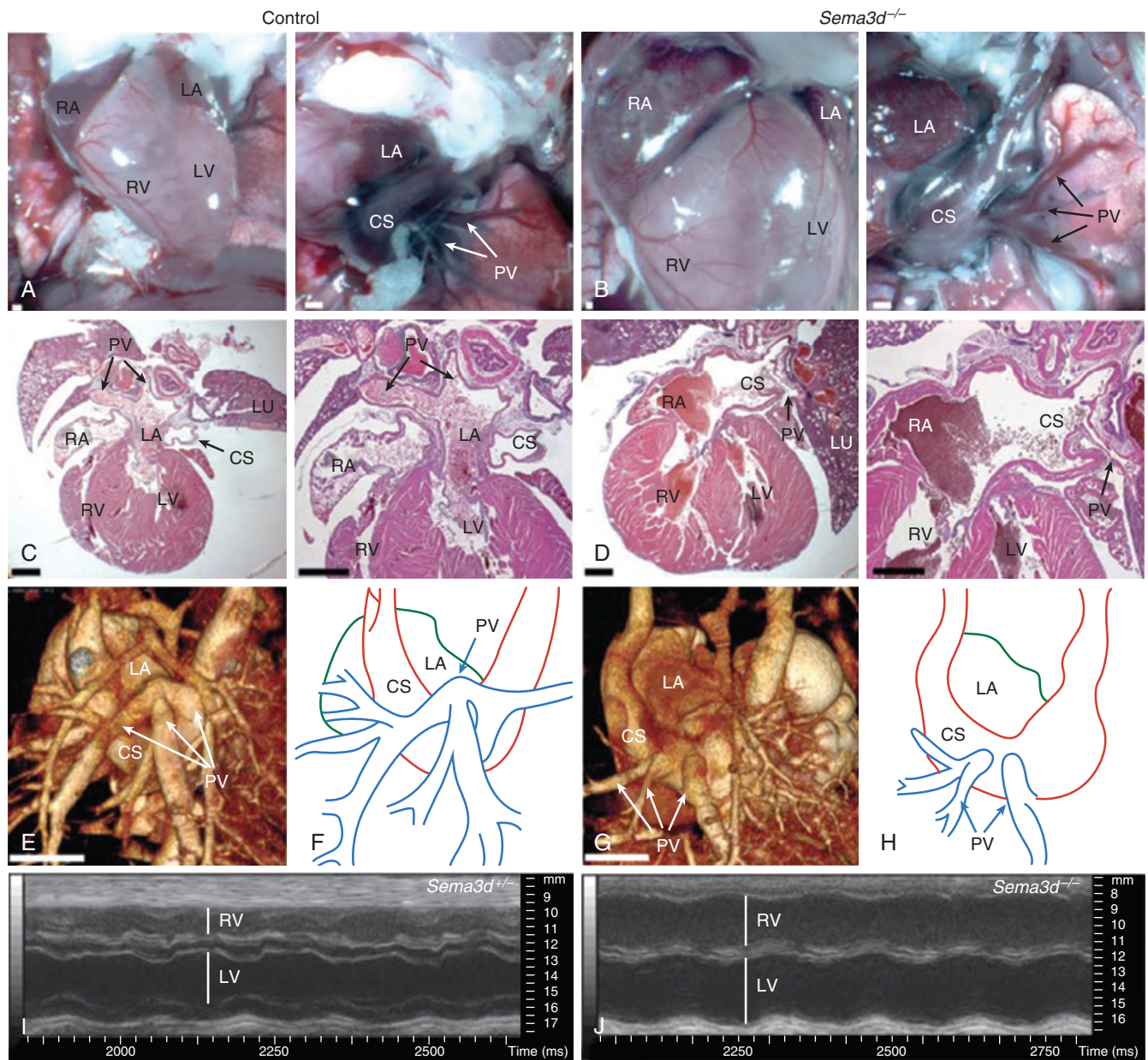


FIGURE 115-2 ■ Mice heart comparison between Semaphorin3d^{-/-} type and control. Anterior views of (A) adult control and (B) Semaphorin3d^{-/-} hearts. Severe cardiomegaly is shown in the mutants (B) because of right atrial (RA) and right ventricular (RV) dilation. In mutant mouse pulmonary veins (PV) enter the coronary sinus (CS; in B, left image). In control mice (A), pulmonary veins (PV) enter the left atrium (LA) as normal. C and D, Photomicrographs of hematoxylin and eosin-stained sections showing a normal connection of the pulmonary veins to the left atrium in Semaphorin3d^{+/+} mice (C) and anomalous pulmonary venous connections to the coronary sinus in Semaphorin3d^{-/-} mice (D). E–H, Volume-rendered micro-computed tomography images (dorsal view) showing the pulmonary veins entering the posterior left atrium in a newborn wild type mouse (E) and entering the coronary sinus in a newborn mutant mouse (G). F and H, The diagrams of the microCT images in E and G, respectively. I and J, M-mode echocardiograms through the ventricles of a Semaphorin3d^{+/+} (I) and a Semaphorin3d^{-/-} (J) heart showing the relative dilation of the right ventricle in an adult Semaphorin3d^{-/-} mouse and paradoxical septal wall motion indicative of right-sided volume overload. Scale bars (in panels A–E and G) = 1 mm. LU, Lung; LV, left ventricle. (Modified from Degenhardt K, Singh MK, Aghajanian H, et al: Semaphorin 3d signaling defects are associated with anomalous pulmonary venous connections. *Nat Med* 19:760–765, 2013.)

Planning the Superior Vena Caval Cannulation

Careful review of the anatomy by preoperative echocardiography, computed tomography, or magnetic resonance imaging⁷ is the single most important component

in developing an operative plan. Definition of the pulmonary venous anatomy and associated defects allows assessment of options for cannulation techniques and surgical approaches. This is especially important in preparation for partial anomalous pulmonary venous drainage, because the location of the anomalous pulmonary venous

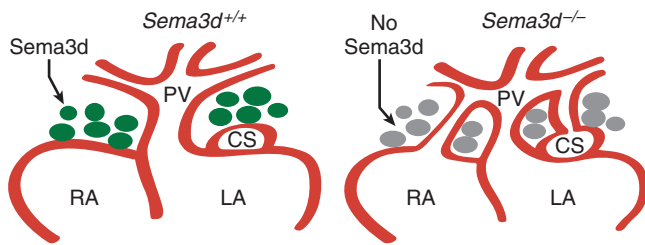


FIGURE 115-3 ■ Model showing the role of Sema3d in pulmonary vein patterning. Normally (*left*) Sema3d is expressed between the heart and the developing pulmonary vasculature where it repels endothelial cells to prevent the formation of anomalous connections. Deficiency of Sema3d (*right*) allows endothelial cells to enter this region and form anomalous vascular connections. CS, Coronary sinus; LA, left atrium; PV, pulmonary veins; RA, right atrium. (Modified from Degenhardt K, Singh MK, Aghajanian H, et al: Semaphorin 3d signaling defects are associated with anomalous pulmonary venous connections. *Nat Med* 19:760–765, 2013.)

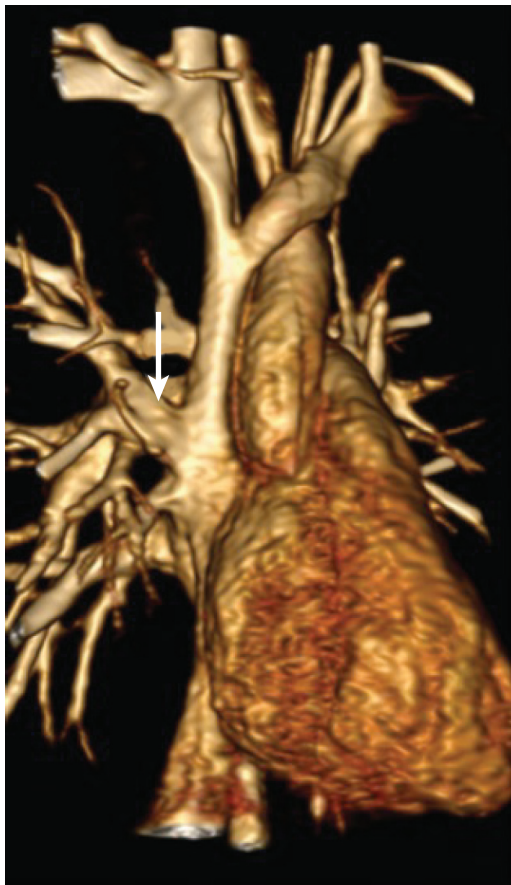


FIGURE 115-4 ■ A contrast-enhanced magnetic resonance three-dimensional angiogram seen from right anterior projection shows an anomalous connection of the right upper and middle pulmonary vein draining into the superior vena cava (arrow). The right lower pulmonary vein normally drains into the left atrium. (Modified from Vyas HV, Greenberg SB, Krishnamurthy R: MR imaging and CT evaluation of congenital pulmonary vein abnormalities in neonates and infants. *Radiographics* 32:87–98, 2012.)

drainage determines the feasibility of a minimally invasive approach and placement of venous cannulas. A common clinical scenario involves an anomalous right upper pulmonary vein inserting high into the superior vena cava, at or above the level of the pulmonary artery. Options for control of the superior vena cava include a high cannulation of the superior vena cava, cannulation of the innominate vein, or percutaneous cannulation via the internal jugular vein with vacuum-assisted venous drainage. A minimally invasive approach through a lower midline partial sternal split can be difficult when a high insertion of an anomalous pulmonary vein is present. In this case a right posterior lateral minithoracotomy can be used as a minimally invasive approach to achieve better access to the high pulmonary veins. The cannulation strategy for this approach includes percutaneous cannulation of the internal jugular vein and direct surgical cannulation of the right femoral vein and artery. The use of peripheral cannulation augmented with vacuum assisted venous drainage is helpful.⁸ Limitations to the use of this approach are: patient's weight less than 20 kg and femoral vein or artery anomalies. During cardiopulmonary bypass, monitoring of right leg near-infrared spectroscopy is suggested. Near-infrared spectroscopy saturations less than 30% suggest that distal leg perfusion is insufficient. In patients with small femoral arteries, the use of a graft sewn to the femoral artery in end-to-side fashion can be helpful to avoid problems with distal leg perfusion.⁹

A final technique to consider is the use of a straight venous cannula in the right atrial appendage, which can be directed into the superior vena cava. After snaring the cava around the cannula (cephalad to the anomalous pulmonary vein insertion), an atrial incision allows access to the origin of the anomalous pulmonary vein from within the atrium. Although this technique is easily accomplished with a minimally invasive lower midline partial sternal split, working around the cannula through the right atrial–superior vena caval junction can be challenging.

Before initiation of cardiopulmonary bypass (CPB), the location of the pulmonary veins is confirmed. Drainage to the superior vena cava requires dissection of the lateral margin of the superior vena cava to identify all pulmonary vein branches. During dissection of the superior vena cava and right pulmonary veins particular attention is needed to avoid injury to the right phrenic nerve. Frequently, multiple branches drain into the vena cava through a large confluence. The source of the veins is not always clear, and any systemic veins draining into the region must be identified. When the source of the pulmonary venous drainage is not clearly defined, needle aspiration can be used to determine the oxygen saturation of the effluent, and then the systemic veins can be distinguished from the pulmonary veins.

After heparinization, cannulation, and initiation of normothermic CPB, the aorta is clamped and blood cardioplegic arrest is obtained. It is often helpful to place a vent into the left atrium for later de-airing. A lateral right atriotomy is made and the atrium is explored to identify any additional anomalies (Fig. 115-5). If the atrial septum is intact, an atrial septal defect is created by incising the region of the foramen ovale and extending the incision

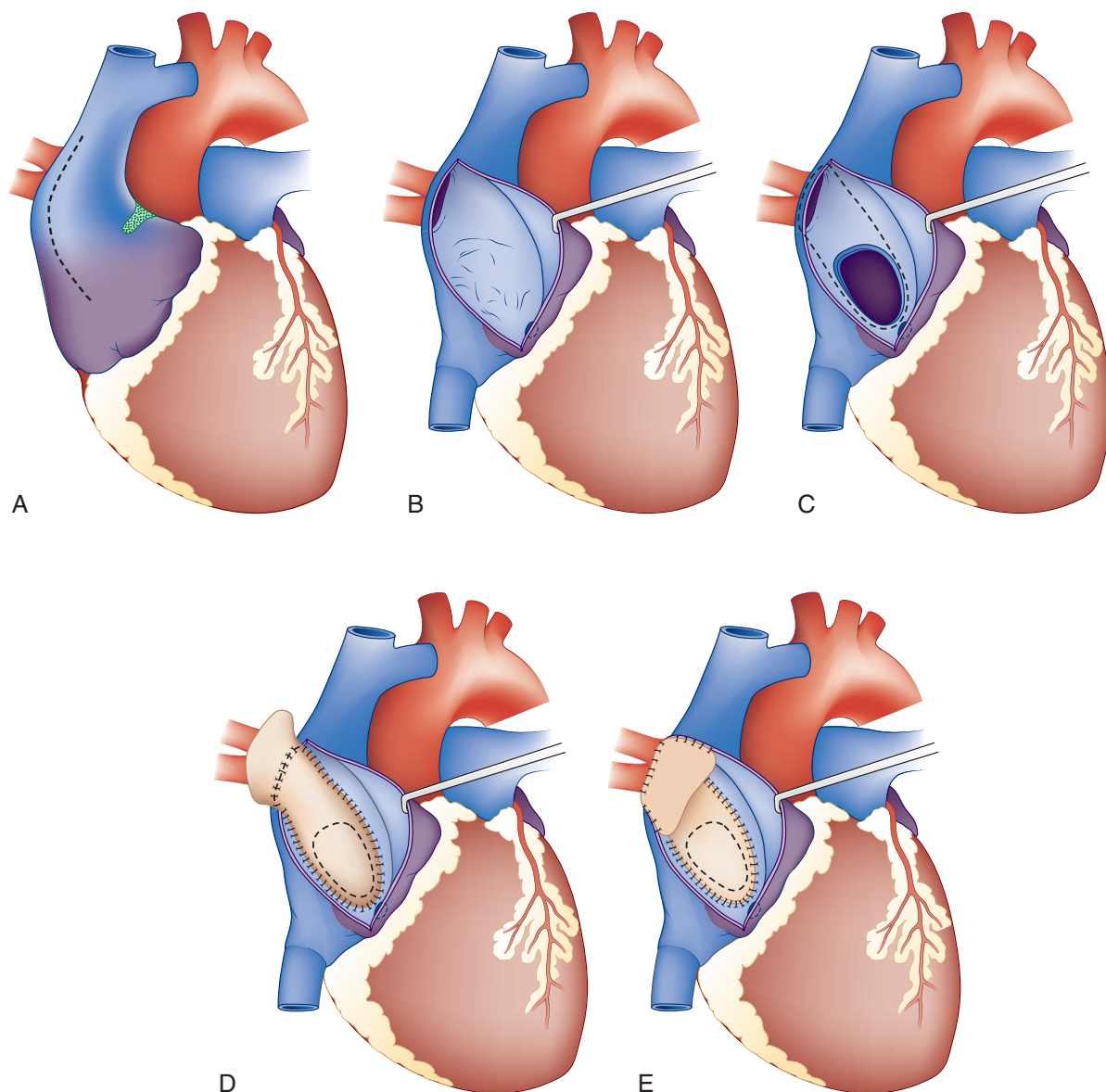


FIGURE 115-5 ■ **A**, After initiation of cardiopulmonary bypass and cardioplegic arrest, a lateral right atrial incision is made (*dashed line*). The *stippled area* represents the approximate location of the sinoatrial node. **B**, The orifice of the anomalous pulmonary veins and the intact atrial septum are exposed. A secundum atrial septal defect is created by excising the septum primum in the region of the limbus, with care taken to avoid potential injury to the conduction system by keeping clear of the triangle of Koch. **C**, The limbus can be resected cephalad to increase the diameter of the atrial septal orifice. **D**, A glutaraldehyde-treated autologous pericardial patch is sutured in place along the rim of the newly created defect, thereby creating a tunnel from the pulmonary vein orifice to the left atrium. **E**, The patch is deliberately longer than necessary to reach the pulmonary vein orifice, and the redundant portion is left unattached as the suture line is extended across the edge of the divided pulmonary vein–atrial edge. The redundant portion of the patch is then folded anteriorly to augment the diameter of the superior cavoatrial junction, thereby preventing obstruction of the superior vena cava.

across the limbus in the direction of the anomalous pulmonary vein. Resection in the region of the limbus allows enlargement of the newly created atrial septal defect. Injury to the sinus node artery can occur when creating the atrial septal defect in patients whose artery courses through the superior portion of the intra-atrial septum. Enlargement of the sinus venosus defect might be necessary if it is too small to divert the anomalous pulmonary veins to the left atrium. Typically, a glutaraldehyde-treated pericardial patch can be used to create a baffle, so that pulmonary venous blood flows beneath the baffle and through the atrial septal defect into the left atrium.

Systemic venous blood from the superior vena cava must pass to the right atrium over the pulmonary vein–to–left atrial baffle without obstruction. If the origin of the pulmonary vein was high in the superior vena cava, the baffle must be constructed carefully to avoid obstruction to flow on either side of the baffle. A longitudinal incision in the lateral aspect of the superior vena cava allows the baffle construction to be better visualized. Placement of the incision on the lateral aspect of the superior vena cava is important to diminish the risk of injury to the sinus node. Closure of the superior vena cava incision with a generous patch to augment the

superior vena cava diameter can be used to prevent stenosis of the superior cavoatrial junction.

Alternatively, a new anastomosis between the superior vena cava and the right atrial appendage is established by dividing the superior vena cava cephalad to the anomalous pulmonary venous entry and translocating the cephalad end of the superior vena cava to the right atrial appendage (Warden technique). The divided cardiac end of the superior vena cava (bearing the anomalous pulmonary venous connection) is closed, and a baffle is created from the orifice of the superior vena cava to the newly created atrial septal defect.^{5,10} By creating a new superior vena caval–right atrial junction, this procedure eliminates the need to partition the superior vena cava with a baffle dividing the systemic and pulmonary venous flow paths. This approach can be particularly helpful in infants and small children with a high insertion of an anomalous pulmonary vein into the superior vena cava.

Results

Early and long-term outcomes for patients after repair are excellent. In children, closure of an associated atrial septal defect almost eliminates the risk of late development of atrial arrhythmias. However, in adults, closure of the atrial septal defect is associated with persistent risk of development of atrial arrhythmias.¹¹ Although extrapolation of these data for atrial septal defect closure to patients with partial anomalous pulmonary venous drainage and intact atrial septum has not been specifically validated, it seems reasonable to conclude that early removal of a left-to-right shunt associated with right ventricular overload is appropriate. In fact, surgical closure of the sinus venosus atrial septal defect at an older age is associated with increased risk of mortality, adverse events, and poor functional outcomes.¹²

Pertinent complications after repair of partial anomalous pulmonary venous drainage include stenosis of the superior vena cava or the anomalous pulmonary vein,¹³ residual atrial septal defects, and atrial arrhythmias or sinus node dysfunction (or both).¹⁴ Failure to include all pulmonary veins in the newly constructed baffle to the left atrium can result in a residual left-to-right shunt. However, incorporation of a systemic vein into the newly constructed baffle results in a residual right-to-left shunt. Finally, injury to the sinus node or sinus node artery can lead to the requirement for pacemaker insertion in patients with severe sinus node dysfunction.¹⁴

SCIMITAR SYNDROME

Scimitar syndrome is an unusual congenital anomaly that is manifested by partial anomalous pulmonary venous drainage of the right lung to the inferior vena cava; it is often associated with hypoplasia of the right lung, dextrocardia, systemic pulmonary arterial supply from the abdominal aorta to the lower lobe of the right lung, and bronchial abnormalities. Other commonly associated anomalies include atrial septal defect, aortic coarctation, and a left-sided superior vena cava.^{15,16} The morphology of the anomalous pulmonary venous drainage to the right



FIGURE 115-6 ■ Contrast-enhanced magnetic resonance angiogram shows the scimitar vein draining most of the right pulmonary venous blood flow into the inferior vena cava (arrow). The scimitar vein has severe stenosis at its junction with the inferior vena cava.

lower lobe creates a characteristic appearance to the right-sided heart border suggestive of a Turkish sword, hence the term *scimitar syndrome* (Fig. 115-6). The right-sided pulmonary veins drain to the inferior portions of the right atrium, the inferior vena caval–right atrial junction, or, more commonly, the inferior vena cava below the diaphragm. Stenosis can occur in 10% to 20% of scimitar veins at their junction to the inferior vena cava.^{16,17}

The presentation of patients with scimitar syndrome can be variable and depends on the severity of the associated lesions. There are generally two forms of clinical presentation in scimitar syndrome: (1) an infantile form with significant symptoms, morbidity, and mortality and (2) a form with mild symptoms seen in children or adults. At the most benign end of the spectrum, patients can display an asymptomatic flow murmur on physical examination as a result of increased pulmonary blood flow secondary to the left-to-right shunt caused by the anomalous pulmonary venous drainage to the inferior vena cava. At the most severe end of the spectrum, infants can exhibit symptoms of severe congestive heart failure, failure to thrive, tachypnea, and occasionally cyanosis. Infantile pulmonary artery pressures are often elevated (e.g., >40% of the systemic pressure), with a ratio of pulmonary blood flow (Qp) to systemic blood flow (Qs), or Qp/Qs, of up to 2:1.¹⁵

Surgical Management

The management strategy for patients with scimitar syndrome is determined by the degree of right lung hypoplasia, the presence of aortopulmonary sources of blood

flow to the right lung, and the location and pattern of the right-sided pulmonary venous drainage. The degree of right lung hypoplasia is an important determinant of the likelihood of salvaging a functional right lung, and in cases of severe hypoplasia, a right pneumonectomy has been advocated.¹⁸ In cases with less severe hypoplasia, attention is turned to correction of the pulmonary venous drainage patterns, control of aortopulmonary sources of blood flow, and correction of associated anomalies. Control of the aortopulmonary sources of blood flow can be achieved with coil embolization in the catheterization laboratory or with ligation in the operating room.¹⁹

Surgical repair of the pulmonary venous drainage is designed to create unobstructed flow from the anomalous pulmonary vein to the left atrium. To accomplish this repair, a direct surgical approach is to place a long baffle in the lumen of the inferior vena cava to channel the anomalous pulmonary vein effluent to the right atrium, and then through an atrial septal defect to the left atrium (originally described by Zubiate and Kay in 1962).²⁰ It can be challenging to create an unobstructed baffle when the anomalous pulmonary venous connection is relatively caudad in the inferior vena cava. To construct a partitioning baffle, a period of circulatory arrest is typically necessary to secure a baffle between the pulmonary vein orifice and left atrium that allows unobstructed pulmonary vein flow without restricting flow in the inferior vena cava or in nearby hepatic veins.

When partitioning the inferior vena cava between the systemic and pulmonary venous flow paths, a right atrial incision can be carried down to the level of the anomalous pulmonary vein orifice, and the orifice is augmented with a patch of autologous pericardium if stenosis is present. The baffle is then constructed in the lumen of the inferior vena cava, and, if necessary, the inferior vena cava diameter can be augmented with a patch to ensure that there is no residual obstruction in the vena cava. This technique has a relatively high incidence of late stenosis, presumably because of the length of the intracaval baffle and because the blood must pass through a nearly 180-degree turn as it travels caudad toward the inferior vena cava and then cephalad up through the baffle to the atrial septal defect.^{16,18}

A second approach is to divide the anomalous pulmonary vein and reimplant it at a convenient location in the right atrium and then create a baffle to divert flow to the left atrium through an atrial septal incision or atrial septal defect if present.^{16,21} This approach provides a shorter, more direct pathway for the pulmonary venous effluent. It is difficult to use this approach, however, when the anomalous pulmonary vein courses in the posterior portion of the lung and necessitates a great deal of augmentation to create an anastomosis with the atrium. When the pulmonary vein passes through the posterior mediastinum and the right lung is relatively hypoplastic, Huddleston and associates¹⁸ recommend pneumonectomy because of the high incidence of late stenosis with reimplantation techniques. As further justification of pneumonectomy in this setting, Huddleston and colleagues point out that the left lung has typically undergone some compensatory growth. Furthermore, perfusion scans typically demonstrate diminished pulmonary blood

flow to the right lung in patients with scimitar syndrome.¹⁵ Calhoun and Mee²² described an alternative surgical approach for this entity, in which the inferior vena cava is transected under deep hypothermic circulatory arrest and divided into posterior (the anomalous pulmonary vein channel) and anterior (inferior vena cava and hepatic vein) compartments with a pericardial patch. An incision is made on the inferior aspect of the left atrium and carried to the atrial septum. The posterior compartment of the inferior vena cava is sutured to the left atriotomy, and the pericardial patch is used to close the atrial septal defect. The anterior compartment of the inferior vena cava is anastomosed to the right atrium. This approach connects the anomalous pulmonary vein to the left atrium at a relatively gentle angle. Brown and coworkers¹⁷ reported favorable results with direct anastomosis of the anomalous pulmonary vein to the left atrium via right thoracotomy without the use of CPB.

Results and Complications

Survival after complete repair (embolization or ligation of anomalous pulmonary arterial flow with correction of the anomalous pulmonary venous return) is anticipated in older children and adults. In recent series, 5-year survival rates have reached 100%, although a significant incidence of late pulmonary vein obstruction remains. In the infantile form of the lesion, however, hospital mortality is higher and depends on the degree of lung hypoplasia and the presence of pulmonary hypertension.¹⁵ Even with a technically perfect repair, blood flow to the right lung often remains diminished. The left-to-right shunt, however, is eliminated. Pulmonary venous obstruction is a prevalent late finding in many series and may be related to the surgical techniques used. Long pulmonary venous pathways through the inferior vena cava with acute angulation may predispose to stenosis. Recent reports using direct reimplantation techniques have demonstrated minimal rates of postoperative stenosis in small series of patients.¹⁷ Pneumonectomy remains an option in patients with persistently compromised pulmonary blood flow resulting from pulmonary hypertension or pulmonary venous obstruction.¹⁸

TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

Total anomalous pulmonary venous drainage is a condition in which all the pulmonary venous effluent from the lungs drains to the systemic venous system, creating a large left-to-right shunt. This entity accounts for 1% to 3% of all congenital heart malformations, with an incidence of 7.1 per 100,000 live births.²³ A right-to-left shunt must be present to allow blood to reach the left ventricle and thereby contribute to systemic cardiac output. Commonly, this shunt is at the atrial level as an atrial septal defect or patent foramen ovale. Less commonly, the shunt may be present as a ventricular septal defect. The absence of a shunt is incompatible with survival, and the magnitude of the shunt determines the systemic cardiac output.

Anatomy

Although well palliated in utero, infants with total anomalous pulmonary venous drainage have abnormalities in the pulmonary vascular system. There is often hypertrophy of the media of the pulmonary veins and arteries, intimal fibrous thickening of the pulmonary veins, and lymphangiectasia. These findings are accentuated in patients with pulmonary hypertension and evidence of pulmonary venous obstruction.²⁴ The various types of total anomalous pulmonary venous drainage are classified by the site of connection to the systemic venous system.

Supracardiac Anatomy

Supracardiac drainage is the most common anatomic variant, occurring in 45% to 55% of patients with total anomalous pulmonary venous drainage.^{23,25} The venous connection is typically through a pulmonary venous confluence behind the left atrium to a connecting vein (often termed a vertical vein) to the innominate vein. Other sites of pulmonary–systemic connection can be to a left- or right-sided superior vena cava.²³

Cardiac Anatomy

The pulmonary–systemic venous connection can be present at the cardiac level in 15% to 20% of patients.^{23,25} In this setting, the pulmonary veins typically drain to a pulmonary venous confluence behind the left atrium. The confluence then drains into the coronary sinus or, less commonly, to the right atrium. In some patients, the right- and left-sided pulmonary veins converge into a short vertical vein before draining into the coronary sinus. The latter variant may be more susceptible to late obstruction.^{25,26}

Infracardiac Anatomy

The systemic–pulmonary venous connection is present at the infracardiac level in 15% to 26% of patients.^{23,25} In this setting, the pulmonary veins drain to a confluence behind the left atrium, which drains via a descending vertical vein to the portal vein, to the ductus venosus (Fig. 115-7) or directly to the inferior vena cava. This subset displays obstruction in the pulmonary venous circuit in the majority of patients.

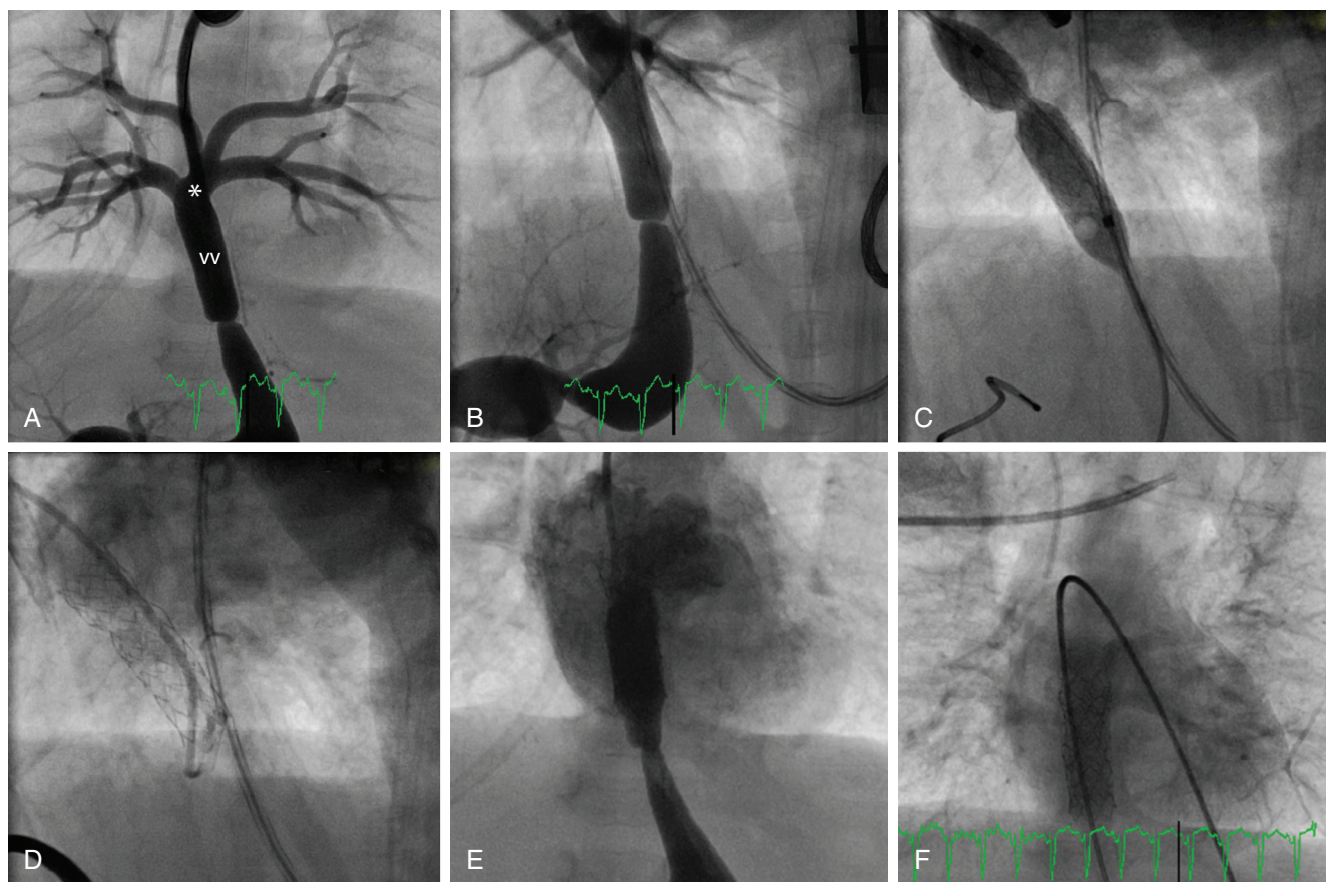


FIGURE 115-7 ■ **A** and **B**, Angiogram shows the infracardiac total anomalous pulmonary venous drainage (*asterisk*) draining in a stenotic vertical vein (VV). **C**, Stent deployment in the stenotic vertical vein during balloon inflation. **D** and **E**, Different projection of the stent implanted. **F**, Final result shows no obstructed flow returning from the pulmonary veins to the vertical vein. (Modified from Chaturvedi RR, Van Arsdell GS, Jacques F, et al: Delayed repair of right atrial isomerism with obstructed total anomalous pulmonary venous drainage by hybrid stent insertion between the left-sided atrium and pulmonary venous confluence. *J Thorac Cardiovasc Surg* 144:271–273, 2012.)

Mixed Anatomy

Mixed-type total anomalous pulmonary venous drainage accounts for 5% to 10% of patients.^{23,25} The most common mode (46%) of mixed-type total anomalous pulmonary venous drainage consists of bilateral and asymmetrical connections, with three pulmonary veins typically draining to a common site and one pulmonary vein to a remote site.²⁷ The second most common mode (29%) is bilateral and symmetrical connections, with separate anomalous connections of all veins from each lung forming confluences and then connecting to the systemic veins at separate sites. The third group, which accounts for 18%, has a common confluence to which all pulmonary veins drain, and then the confluence itself drains to the systemic veins at separate sites. Sites of connection can be at the supracardiac, cardiac, and infracardiac levels.

Presentation

Patients without significant pulmonary venous obstruction present in infancy or early childhood with signs and symptoms related to the presence of a large left-to-right shunt. These patients have dyspnea, poor feeding, and poor growth. They may have cyanosis on examination, but this manifestation is usually mild. Other findings include a second heart sound that is split and a systolic flow murmur caused by increased flow across the pulmonary valve.

Patients with high-grade pulmonary venous obstruction present in the neonatal period with cyanosis, respiratory distress, and poor growth. On examination, the infant is tachypneic and cyanotic and has poor systemic perfusion. The second heart sound is prominent and split as a result of pulmonary arterial hypertension. Obstruction in the pulmonary venous pathway in patients with total anomalous pulmonary venous drainage constitutes a surgical emergency. Medical measures to stabilize and resuscitate the patient include intubation, ventilation with 100% oxygen, hyperventilation, correction of pH, and inotropic support. These medical measures are minimally effective. Administration of prostaglandin E₁ has been reported to open the ductus venosus in an attempt to decompress the pulmonary veins in patients with infracardiac total anomalous pulmonary venous drainage and obstruction.²⁸ Catheter-based techniques to place a stent in the obstructed pulmonary venous confluence have been reported to relieve obstruction and to allow resuscitation of the patient in preparation for surgical repair.²⁹

Pathophysiology

The hemodynamic abnormality, in patients with total anomalous pulmonary venous drainage, is related to the complete diversion of pulmonary venous blood away from the left atrium to a systemic vein. Consequently, the most important anatomic factors in determining the clinical status of the patient include the presence and location of a right-to-left shunt, and the presence or absence of obstruction in the pulmonary venous circuit.

Because pulmonary venous blood is diverted from the left atrium, blood cannot reach the left ventricle in the absence of a right-to-left shunt. Therefore, to sustain life, a right-to-left shunt must be present. Most commonly, a patent foramen ovale or atrial septal defect is present to allow entry of blood into the left atrium and then to the left ventricle for systemic output. The cardiac output of the patient is therefore limited by the amount of blood that can cross the atrial septum. Thus, the characteristics of the obligatory right-to-left shunt determine the systemic cardiac output.

A second important anatomic factor determining the clinical status of the patient is the presence or absence of obstruction in the pulmonary venous pathway. When obstruction is present, egress of blood from the lungs is limited, resulting in pulmonary venous congestion and impairment of oxygenation. This can lead to life-threatening cyanosis in neonates. In addition to deficits in oxygenation and pulmonary blood flow, restriction at the level of the atrial septal defect reduces systemic cardiac output and further exacerbates the patient's precarious clinical status.

In patients with supracardiac anomalous pulmonary venous drainage, obstruction can occur in the ascending vertical vein connecting the pulmonary venous confluence to the innominate vein. In this situation, the passage of the vertical vein between the left pulmonary artery and the left bronchus can cause compression in the vertical vein. As the egress of blood from the lungs is restricted, the pulmonary artery pressure rises, causing further distention of the pulmonary artery and further compression of the vertical vein. This can create a repeating cycle of progressive pulmonary venous obstruction. Obstruction also can occur at the site of the connection between the pulmonary venous confluence and the systemic vein. This is a common feature of infracardiac total anomalous pulmonary venous drainage.

Diagnostic Techniques

Arterial blood gas sampling is useful in resuscitation of a neonate with obstruction and total anomalous pulmonary venous drainage. Often, severe metabolic acidosis and mild hypoxemia are seen.

Chest Radiography

The appearance of the lung fields on chest radiographs is determined by the presence or absence of obstruction to pulmonary venous drainage. In patients without obstruction, pulmonary vascularity is increased because of the large left-to-right shunt created by drainage of pulmonary venous return into the right side of the heart. In patients with obstruction, the lung fields may be extremely congested because of the obstruction of blood egress from the pulmonary veins and the left-to-right shunt. A prominence of the pulmonary artery shadow and the right atrium silhouette often exists. In supracardiac drainage, the prominence of the upper mediastinal silhouette can create the classic "snowman" or figure-eight appearance.

Echocardiography

Echocardiography is the study of choice in diagnosing total anomalous pulmonary venous drainage. The pulmonary venous confluence, pulmonary veins, and connection to the systemic venous system can typically be defined, allowing an expeditious and noninvasive diagnosis in critically ill infants, as well as in asymptomatic children. Consequently, echocardiography has largely replaced angiography as the principal diagnostic study in patients with total anomalous pulmonary venous drainage. Echocardiography also can offer important prognostic data. Jenkins and colleagues³⁰ correlated operative survival to the size of the pulmonary venous confluence and the sum of the pulmonary venous diameters (Fig. 115-8).

Fetal echocardiography can diagnose total anomalous pulmonary venous drainage and potential obstruction of the pulmonary venous pathways.³¹ Fetal diagnosis of total anomalous pulmonary venous drainage is of particular importance if the patient has prominent obstruction in the pulmonary venous pathway, because the patient requires immediate medical and surgical intervention after birth. The sensitivity of fetal echocardiography, however, is uncertain, and the impact of fetal diagnosis of total anomalous pulmonary venous drainage on clinical outcomes is yet to be fully clarified.

Echocardiography is also helpful in monitoring pulmonary veins for obstruction during preoperative and long-term postoperative follow-up. The demonstration of turbulence in the pulmonary veins can be used as a sensitive marker for the presence of obstruction in the pulmonary venous circuit. Because obstruction in the pulmonary veins late after surgical repair can progress in a clinically silent fashion, the sensitivity of the

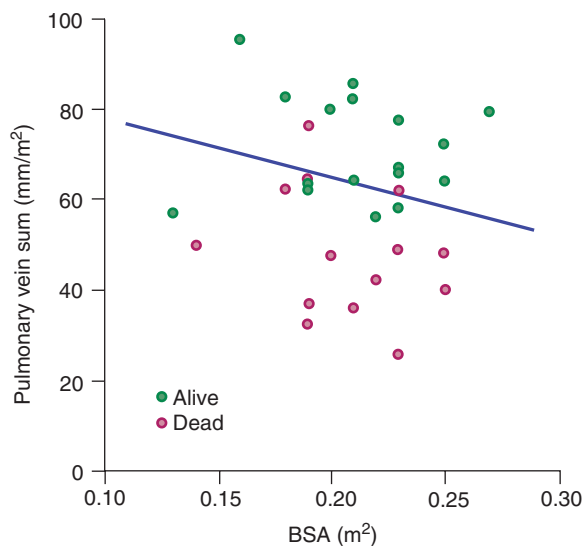


FIGURE 115-8 ■ Graph showing the distribution between operative survival and the pulmonary veins diameters sum at the confluence indexed to body surface area (BSA). The straight line is the regression line for indexed pulmonary vein sum and BSA derived from normal data. (From Jenkins KJ, Sanders SP, Orav EJ, et al: Individual pulmonary vein size and survival in infants with totally anomalous pulmonary venous connection. *J Am Coll Cardiol* 22:201–206, 1993.)

echocardiogram to detect the presence of turbulence in the pulmonary vein may allow early detection and correction of pulmonary vein stenosis after repair.

Cardiac Catheterization

Cardiac catheterization is used infrequently for diagnosis of routine total or partial anomalous pulmonary venous drainage. Cardiac catheterization is helpful when echocardiographic findings are ambiguous or when the patient has other complex defects. A classic finding at catheterization associated with total anomalous pulmonary venous drainage is identical oxygen saturations in all chambers of the heart. This occurs because of upstream mixing of oxygenated pulmonary venous effluent and deoxygenated systemic venous blood, and subsequent delivery of partially saturated blood to the right side of the heart, as well as to the left side of the heart through the atrial septal defect. Catheterization is also helpful in defining the anatomy of pulmonary vein stenosis, which can develop after repair of total anomalous pulmonary venous drainage.

Catheterization is helpful when the patient needs catheter-based intervention to stabilize the clinical status. Balloon atrial septostomy may be helpful in hemodynamic stabilization before surgical repair in patients with obstruction of pulmonary venous return at the level of a restrictive atrial septal defect. In this situation, the relief of an obstruction at the atrial septal defect allows increased right-to-left shunting and improved systemic cardiac output. Stent placement in the obstructed vertical vein in a patient with infracardiac total anomalous pulmonary venous drainage has been reported (see Fig. 115-7).^{29,32} These procedures may temporarily stabilize critically ill patients with obstructive anomalous pulmonary venous drainage, allowing time to recover from multiorgan dysfunction before definitive surgical repair.

Magnetic Resonance Imaging

Recently, magnetic resonance imaging has emerged as an important diagnostic tool in evaluating total anomalous pulmonary venous drainage. It offers complete visualization of all pulmonary veins, with precise delineation of stenotic segments. In addition, it offers hemodynamic evaluation, including measurement of segmental blood flow and blood flow velocity of the pulmonary veins, calculation of the pulmonary-to-systemic blood flow ratio (Q_p/Q_s) and the possibility of three-dimensional reconstruction.⁷

Computed Tomography Angiography

Computed tomography angiography can be used to define the anatomy of the total anomalous pulmonary venous return because of its superior spatial definition and its shorter examination duration compared with magnetic resonance imaging. Computed tomography also allows the creation of three-dimensional reconstruction of the cardiac structures. The disadvantages are related mainly to exposure to ionizing radiation, more nephrotoxic contrast used and due to the fact that

computed tomography does not provide any hemodynamic measurement. Computed tomography can be used in cases in which magnetic resonance imaging cannot be performed or is contraindicated.³³

Surgical Repair

The goal of surgical intervention is to create unobstructed egress of blood from the pulmonary veins into the left atrium. Aorto-bicaval cannulation offers the flexibility to repair all forms of total anomalous pulmonary venous drainage. In some centers, deep hypothermic circulatory arrest is preferred to allow improved visualization of the pulmonary veins in a bloodless field. Continuous perfusion techniques require the use of cardiotomy suction devices in the pulmonary veins to allow visualization during the repair. For this reason, systemic hypothermia is used to allow the safe decrease of perfusion flow rates during the critical portions of the anastomosis.

After initiation of CPB, ductus arteriosus ligation, and systemic cooling to 18° to 20° C, the aorta is cross-clamped, and cold antegrade blood cardioplegia is administered. The vertical vein is ligated. The pulmonary venous confluence is seen in the posterior pericardium by retracting the heart anteriorly and to the right. Because of the lack of pulmonary vein attachments to the left atrium, the heart is usually mobile, and retraction of the heart out of the mediastinum offers excellent exposure of the pulmonary venous confluence. A longitudinal incision is created in the pulmonary venous confluence to match a corresponding incision in the posterior left atrium, extended out towards the left atrial appendage. With care to avoid distortion, a left-atrial-to-pulmonary-confluence anastomosis is made using fine sutures. Controversy exists regarding the use of absorbable versus nonabsorbable sutures, as well as interrupted versus

continuous techniques.^{34,35} With all techniques, the primary goal is to create a large, unobstructed anastomosis, and the superiority of any one of these techniques has not been convincingly demonstrated. A short period of low-flow CPB may be needed to improve visualization during construction of a meticulous anastomosis.

The use of the approach described in the preceding paragraph is applicable to all types of total anomalous pulmonary venous drainage. It can be challenging, however, to orient the left atrial and pulmonary vein confluence incisions while simultaneously retracting the heart. Furthermore, the retraction required to visualize the anastomosis can place tension on the developing suture line during construction of the anastomosis. Finally, the left atrium tends to be small in patients with total anomalous pulmonary venous drainage and, consequently, the limitation to rightward extension of the anastomosis by the atrial septum can limit the size of the anastomosis. The limitation imposed by the location of the atrial septum is a greater issue in patients in whom the pulmonary venous confluence is oriented rightward with respect to the left atrium.

An alternative approach is to create the anastomosis through a generous atriotomy extended transversely across the right atrium and then across the atrial septum (Fig. 115-9). This approach allows visualization of the posterior wall of the left atrium, which allows the surgeon to place the left atrial incision precisely over the area corresponding to the incision in the pulmonary venous confluence. Furthermore, in patients with a small left atrium and rightward displacement of the pulmonary vein confluence, the approach allows patch augmentation of the left atrium when reconstructing the atrial septum and right atrial incision.

A third operative approach to construction of a pulmonary-vein-to-left-atrial anastomosis is between the

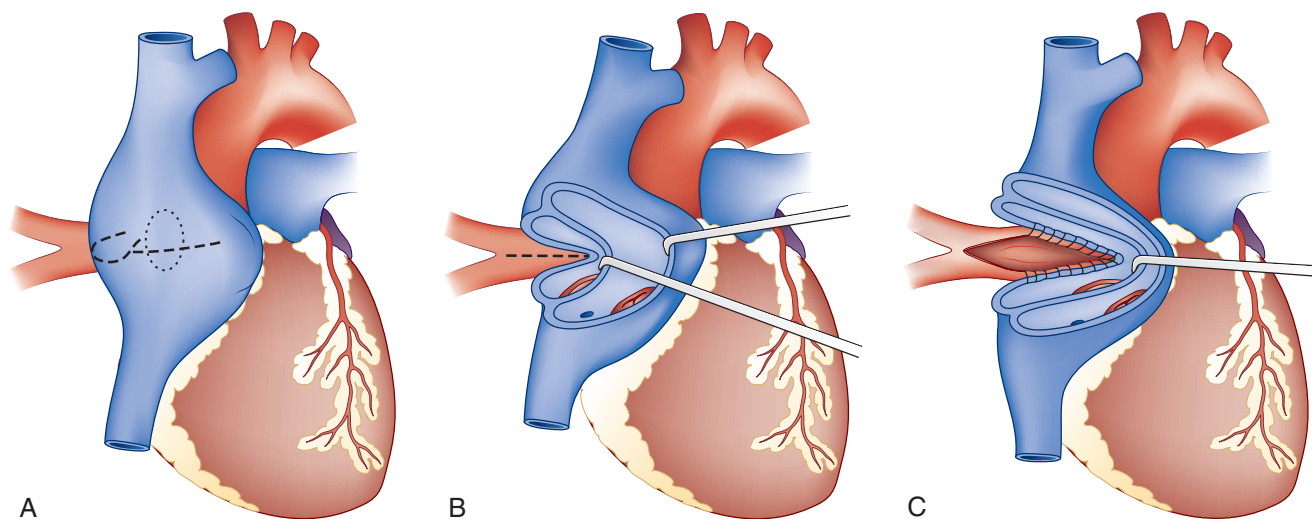


FIGURE 115-9 ■ Repair of total anomalous pulmonary venous drainage under hypothermic cardiopulmonary bypass and cardioplegic cardiac arrest. **A**, A right atrial incision is made from the midportion of the right atrium and extends posteriorly to the pulmonary venous confluence (*dashed line*). The incision is carried leftward across the atrial septum to the secundum atrial septal defect (*dotted line*) and posterior across the back of the left atrial wall in the direction of the left atrial appendage. **B**, Retraction of the atrium to the left exposes the pulmonary venous confluence, which is incised as widely as possible (*dashed line*). **C**, A direct anastomosis is constructed between the divided pulmonary veins and the left atrial wall. If the left atrium is small, or if the pulmonary venous confluence is rightward, the left atrial size can be augmented with a patch along the rightward edge of the anastomosis.

aorta and the superior vena cava. Using this technique, the aorta and the superior vena cava are retracted laterally, exposing the dome of the left atrium and the pulmonary vein confluence. This approach is especially helpful in patients with supracardiac variants of total anomalous pulmonary venous drainage. Further exposure can be obtained easily by dividing the aorta.³⁶

Repair of the intracardiac type of total anomalous pulmonary venous drainage is performed using moderate hypothermia and standard cannulation techniques. If obstruction in the individual pulmonary veins is suggested, deep hypothermic CPB is considered for possible circulatory arrest. A transverse right atriotomy is made, and the atrial septum is exposed. If the pulmonary vein confluence enters the coronary sinus, the atrial septum between the patent foramen ovale and the coronary sinus is incised (Fig. 115-10A). The superior aspect of the coronary sinus is unroofed until the left atrial wall and coronary sinus becomes a common chamber without any separating ridge (see Fig. 115-10B). Care must be taken that the incision and resection are not too close to the mitral valve or to individual pulmonary veins. Any connecting vein between the pulmonary venous confluence and the coronary sinus must be completely incised so that there is no residual circumferential connecting vein. If completely unroofed, the pulmonary vein ostia should be easily visualized through the unroofed coronary sinus. A glutaraldehyde-treated or fresh autologous pericardial patch is used to reconstruct the atrial septum, leaving the pulmonary venous drainage to flow through the unroofed coronary sinus into the left atrium (see Fig. 115-10C). Concern has been expressed that this unroofing technique may have a higher risk of late stenosis in patients who have a short segment of venous confluence interposed between the pulmonary venous confluence and the coronary sinus.²⁶ As an alternative, direct anastomosis of the pulmonary veins to the left atrial wall can be performed.

In patients with infracardiac pulmonary venous connections, the pulmonary venous confluence tends to be oriented more vertically, creating a Y-shaped confluence that drains through a vertical vein to the portal system. Consequently, the incision into the left atrium is more vertical or Y-shaped to maximize the size of the newly created left atrium. Some surgeons leave the vertical vein intact to provide a pressure relief “pop-off” if left atrial pressure is high in the early postoperative period because of small left atrial size or poor ventricular compliance.^{37,38}

Poor hemodynamics in the early postoperative period should raise concerns for potential obstruction at the site of the venous anastomosis and for pulmonary hypertensive crisis. Any suspicion of residual postoperative pulmonary venous obstruction should prompt echocardiographic examination to interrogate the pulmonary venous anastomosis. In patients with preoperative pulmonary venous obstruction, chest radiographic findings of pulmonary vascular obstruction persist for several days despite normal hemodynamics. Therefore, the presence of congestion on a chest radiograph is not sufficient to make the diagnosis of postoperative pulmonary venous obstruction. Pulmonary hypertensive crises are a common

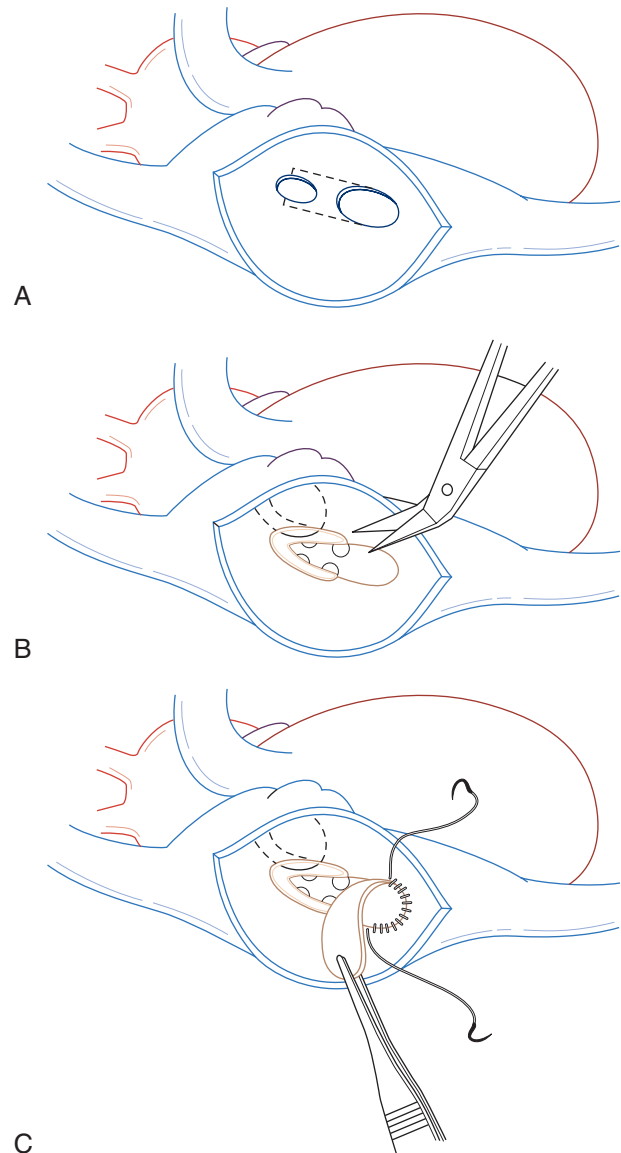


FIGURE 115-10 ■ Repair of intracardiac-type total anomalous pulmonary venous drainage. **A**, The atrial septum between the patent foramen ovale and coronary sinus is incised, and the septal tissue surrounded by the dotted lines is resected. **B**, The superior aspect of the coronary sinus is incised until close to the mitral valve, creating a common chamber including the left atrium and the dilated coronary sinus. The surgeon must identify all four pulmonary vein orifices. **C**, A large defect created by resection of the tissue between the foramen ovale and the coronary sinus is patched with a glutaraldehyde-treated or fresh autologous pericardial patch, redirecting the coronary sinus drainage to the left atrium.

feature in the postoperative management of infants after repair of total anomalous pulmonary venous drainage. In many centers, routine postoperative pulmonary artery or right ventricular pressure monitoring allows early detection and treatment of pulmonary hypertensive crises with deep sedation, controlled ventilation, and inotropic support for right-sided heart failure. Inhaled nitric oxide also can be used for postoperative pulmonary arterial hypertension, although it can create paradoxical pulmonary venous hypertension by rapidly increasing the

left ventricular preload in patients with noncompliant or small left ventricles.³⁹

In patients with a small pulmonary venous confluence and small pulmonary veins, direct anastomosis of the divided edge of the pulmonary veins to the left atrial wall can lead to geometric distortion of the pulmonary vein anastomosis, local trauma from handling the delicate pulmonary vein, and local reaction from suture-related ischemia. In patients with small pulmonary vein confluences, the preferred anastomotic technique at the Hospital for Sick Children in Toronto has evolved into a “sutureless” anastomosis.^{40,41} This technique includes a longitudinal incision in the posterior pericardium and the underlying pulmonary venous confluence. A corresponding incision is made in the overlying portion of the left atrium (Fig. 115-11A). In contrast to direct suture techniques, however, the left atrium is not sutured directly to the divided edge of the pulmonary veins. Instead, the left

atrial edge is sutured to the pericardium circumferentially around the pericardial incision, avoiding direct suturing to the pulmonary veins (see Fig. 115-11B). A “neo-atrium” is thereby created, into which the pulmonary veins bleed in a controlled fashion into the remainder of the left atrium and the left ventricle.

Results

Operative survival for patients with total anomalous pulmonary venous drainage has markedly improved in the most recent decade, with survival rates of more than 90% reported in the current era.^{23,25} Long-term prognosis for patients after repair of total anomalous pulmonary venous drainage is also favorable, with relatively few late deaths.^{23,25} Approximately 10% to 17% of patients have some evidence of late pulmonary vein obstruction; therefore, long-term surveillance is important.⁴² Recent studies raise concerns about neurologic development after repair of total anomalous pulmonary venous drainage—concerns associated with the use of deep hypothermic circulatory arrest and metabolic instability at the early postoperative period.⁴³

SPECIAL CONSIDERATIONS

Total Anomalous Pulmonary Venous Drainage in Heterotaxy

Visceral heterotaxy is characterized by abnormalities of multiple organ systems, including the heart, lungs, liver, spleen, and systemic veins. In the subset of patients with asplenia, or right atrial isomerism, cardiac anomalies include a common atrium, common atrioventricular valves, pulmonary outflow tract obstruction, and hypoplastic left or right ventricles resulting in functional single ventricles. Total anomalous pulmonary venous drainage is present in approximately 90% of patients.⁴⁴

Patients with the common combination of total anomalous pulmonary venous drainage and functional single ventricles typically present within the first month of life for palliation.⁴⁴ The type of palliation required is determined by the presence of uncontrolled pulmonary blood flow (e.g., a functional single ventricle with unrestrictive pulmonary valve) or restricted pulmonary blood flow (e.g., pulmonary stenosis or atresia). Superimposed on the alterations of pulmonary arterial flow is the frequent presence of pulmonary venous obstruction, which may be present in up to 30% of patients.⁴⁴ The presence of obstruction, however, may not be readily apparent until after augmentation of pulmonary blood flow (e.g., systemic-to-pulmonary shunt) in patients initially displaying pulmonary stenosis or atresia.⁴⁵ The majority of these patients have increased muscularity of the pulmonary arteries and “arterialization” of the pulmonary veins.

Patients requiring palliation in the neonatal period often have a complex combination of physiologic problems because pulmonary venous obstruction may coexist with either an unrestricted source of pulmonary blood flow or a restricted source of pulmonary blood flow. Thus, the patient might require repair of obstructed total

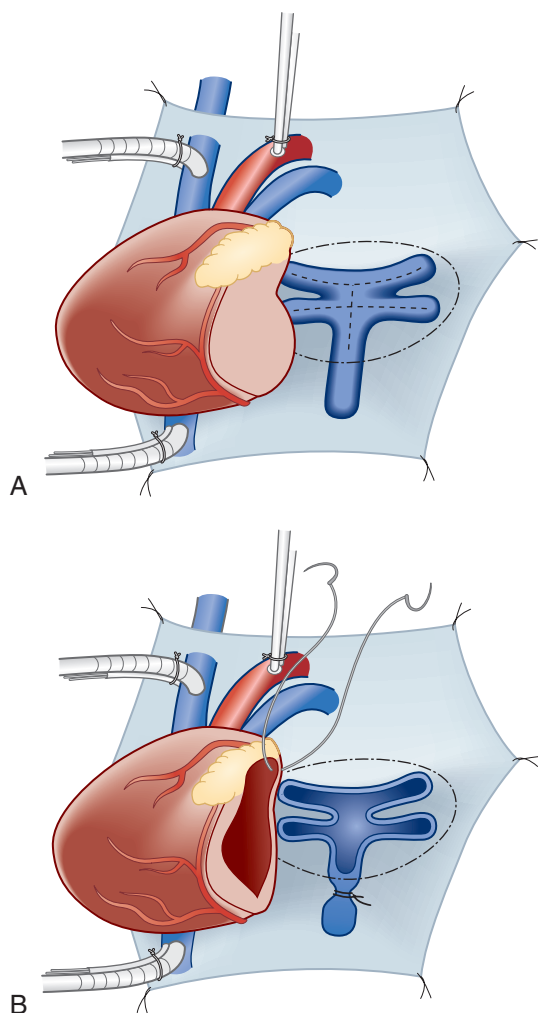


FIGURE 115-11 ■ Primary repair of infracardiac total anomalous pulmonary venous drainage using a “sutureless” technique. **A**, The heart is retracted anteriorly and rightward, exposing the pulmonary venous confluence. **B**, The vertical vein is ligated, and the divided edges of the left atrial wall are sutured to the posterior pericardium using a suture line that is remote from the incised pulmonary venous confluence.

anomalous pulmonary venous drainage in combination with pulmonary artery banding or a systemic to pulmonary artery shunt—with a poor prognosis.^{44,45} Recent reports suggest that aggressive repair of total anomalous pulmonary venous drainage repair for right atrial isomerism is associated with improved survival in the more recent era. The sutureless repair is associated with a trend for improved survival but so far has not shown statistical significance for this patient subset.⁴⁶

Pulmonary Vein Stenosis After Repair

Development of stenosis after repair of total anomalous pulmonary venous drainage occurs in 5% to 17.5% of patients after initial repair,^{23,42,47,48} and the patients typically present within the first year after initial repair. The obstruction can occur in one of three general patterns. The simplest form involves a ring of fibrosis limited to the site of the anastomotic suture line. The second form is more complex, involving the distal pulmonary veins in a localized region of intimal proliferation. The most complex form involves diffuse retrograde pulmonary vein stenosis extending far into the distal pulmonary veins. These types of obstruction can occur in a unilateral fashion, progressing to complete occlusion of the pulmonary venous drainage of the involved lung.⁴⁷ Patients with unilateral pulmonary vein stenosis have better survival than patients with bilateral stenosis.^{47,48} Diffuse pulmonary vein stenosis after repair is associated with a high mortality rate.

Pulmonary vein obstruction after repair is associated with pulmonary vascular congestion on chest radiographs. On echocardiogram, the principal diagnostic criterion is the presence of turbulence at the pulmonary venous anastomosis.⁴⁹ Angiography can add information to the echocardiographic findings. Because the echocardiographic window can be limited in postoperative patients, angiography can be helpful in defining the status of the pulmonary veins further upstream in the lung—outside the echocardiographic window. Angiography, however, is an invasive procedure and requires the use of ionizing radiation. Contrast-enhanced magnetic resonance angiography is an extremely useful diagnostic modality for pulmonary vein stenosis.⁷ Contrast-enhanced magnetic resonance angiography provides anatomically detailed analysis of the stenotic pulmonary veins at the site of anastomosis and, importantly, in the lung.⁷ The presence or absence of a distal dilated portion of pulmonary vein is a crucial determination in evaluating a patient with pulmonary vein stenosis after repair. Absence of dilation in the intrapulmonary portion of the pulmonary vein precludes the rationale for surgical attempts to decompress the pulmonary veins.

The presence of turbulence at the site of the anastomosis has been postulated to create a cycle of local injury leading to hyperplasia and increasing turbulence, thereby perpetuating a process of diffuse pulmonary vein stenosis. The progression of pulmonary vein stenosis retrograde (upstream) into the lung parenchyma is associated with a poor prognosis. In an animal model, upstream pulmonary vein stenosis is associated with transforming growth factor β 1 expression and progressive obstruction of the

pulmonary veins through a process consistent with endothelial to mesenchymal transition.⁵⁰ Identification of the mediators of progressive upstream pulmonary venous obstruction can lead to pharmacologic therapies as adjuncts to surgical or stent-based decompression at the left atrial-pulmonary venous junction.

Surgical revision of the pulmonary venous anastomosis, lung transplantation⁵¹ and pulmonary vein stenting⁵² are the most commonly prescribed therapies for pulmonary vein stenosis after repair. Pulmonary vein stenting represents a useful approach on acute relief of stenosis, but it is still associated with high reintervention rate and in stent stenosis.⁵² The diameter of the stent correlates with the risk of re-stenosis, and stent diameters larger than 6 mm are associated with more prolonged patency rates.⁵² Drug-eluting stents and stents delivering local doses of radiation or chemotherapy may offer benefit in the future but have not yet been demonstrated to be efficacious.

Surgical Techniques for Pulmonary Vein Stenosis After Repair of Total Anomalous Pulmonary Venous Return

Some surgeons emphasize the importance of prevention of pulmonary vein stenosis after repair by reducing surgical trauma on the endocardium of the pulmonary vein at the time of the initial repair, thereby minimizing the stimulus for ingrowth of the intimal tissue.⁵³ Nevertheless, approximately 10% to 17% of patients develop pulmonary vein stenosis after repair.

If the obstruction is exclusively at the anastomotic site, the surgical revision can be accomplished by resection of the ingrowth tissue obstructing the anastomotic site or by patch enlargement of the left atrial anastomosis. A polytetrafluoroethylene or pericardial patch is commonly used for enlargement. Other conventional approaches for individual pulmonary vein stenosis include endarterectomy and patch venoplasty. These approaches are associated with a high risk of recurrence ranging from 60% to 90%.^{47,48}

Recent reports have described the use of sutureless techniques to treat pulmonary vein stenosis after repair.⁵³ Cardiopulmonary bypass is established with ascending aortic and bicaval cannulation. Patients are cooled for possible low-flow bypass or circulatory arrest to attain a bloodless field. The heart is retracted cephalad, and the posterior aspect of the left atrium is incised in the region of the previous anastomosis. The stenotic pulmonary vein tissue is incised longitudinally leftward and rightward to the level of the pericardial reflection until non-stenotic segments of pulmonary vein are reached, possibly requiring the incision of veins into secondary or tertiary branches in the pulmonary hilum or parenchyma. Stenotic areas in the mediastinum can be resected circumferentially. The left atrial incision is extended to the left atrial appendage, creating a widely open incision. The left atrial edge is then sutured to the pericardium using 6-0 or 7-0 nonabsorbable polypropylene suture extending around the site of pulmonary vein resection or incision. Midterm outcomes with sutureless techniques have

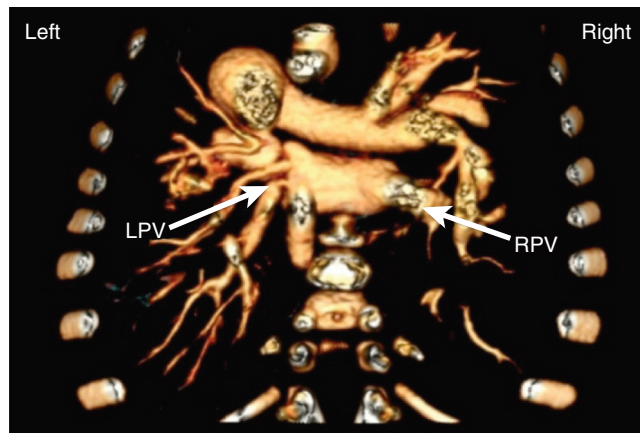


FIGURE 115-12 ■ CT reconstruction of congenital pulmonary vein stenosis: from a posterior view of the chest the reconstruction shows diffuse stenosis of the left pulmonary veins (LPV; arrow) upper compared to unobstructed right lower pulmonary vein (RPV; arrow). Right upper pulmonary severe stenosis is not visualized in this projection.

been reported to be superior to conventional surgical techniques.^{40,41,47,54}

Congenital (Primary) Pulmonary Vein Stenosis

Congenital pulmonary vein stenosis is the syndrome of primary endoluminal stenosis of one or multiple individual pulmonary veins (Fig. 115-12), which is not associated with previous surgery or catheter intervention. Pathogenesis of this entity has been postulated as being an abnormal incorporation of the common pulmonary vein into the left atrium in the later stage of cardiac development.⁵⁵ This anomaly is frequently associated with other congenital heart malformation, ranging from 30% to 80%.^{56,57} Congenital pulmonary stenosis can be discrete stenosis caused by the intimal shelf or diffuse hypoplasia of the pulmonary veins. Pathologic studies have demonstrated the presence of proliferative myofibroblastic cells in the fibrotic tissue.⁵⁰

Clinical presentation of children with congenital pulmonary vein stenosis depends on the number of pulmonary veins involved and on the severity of stenosis in the individual pulmonary veins. Most patients present in the first months to years of life with respiratory symptoms, including tachypnea, and recurrent respiratory infection. Patients with severe pulmonary venous obstruction have signs of pulmonary hypertension.

Prognosis of progressive congenital pulmonary vein stenosis is extremely poor, and it is strongly related to the number of pulmonary veins involved. Breinholt and colleagues⁵⁸ reported 13 patients with congenital pulmonary vein stenosis; 83% of the patients with three or four pulmonary vein stenosis died, whereas all patients with stenosis limited to one or two pulmonary veins survived. Conventional scar excision techniques appear to be associated with less favorable outcomes than sutureless techniques. Survival rates after sutureless repair for pulmonary vein stenosis, as reported by Viola and colleagues,⁵⁹ were 64%, 47%, and 31% at 1, 5, and 10 years, respectively,

and are directly related to the preoperative severity of the stenosis. Sutureless technique reduces in the postoperative period the grade of stenosis and provides a lower incidence of reoperation in the long term but does not prevent intraparenchymal lung disease progression.

In conclusion, the prognosis for these patients is poor with either technique.^{54,59} Pneumonectomy may be necessary for refractory hemoptysis. Lung transplant can be considered as a viable treatment for patients with recurrent stenosis after primary repair or diffuse disease.⁵¹ Encouraging results with bilateral sequential lung transplantation for this entity have been reported by Bharat and colleagues.⁵¹ Catheter intervention for congenital pulmonary vein stenosis had negligible benefits.⁶⁰ The efficacy of new therapies such as sonotherapy or chemotherapy remains uncertain.

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ATRIOVENTRICULAR CANAL DEFECTS

Aditya K. Kaza • Pedro J. del Nido

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SUMMARY

Atrioventricular (AV) canal defects include a spectrum of lesions in which the common etiology appears to be abnormal development of the endocardial cushions, resulting in a defect in the AV septum and AV valves. This group of lesions forms approximately 3% of all major congenital cardiac defects, and approximately half of the patients have Down syndrome.¹ In children with Down syndrome, AV canal defects are seen in 20% to 25%—a 1000-fold increased risk when compared with the incidence in the general population.²

Although AV canal defects constitute a continuum of related anatomic lesions, it is useful to divide them into two main groups³—partial and complete AV canal defects—on the basis of the extent of the interventricular communication.

Partial AV canal defects consist of a large ostium primum atrial septal defect (ASD) and a cleft between the left superior and inferior bridging leaflets. In most cases, there is no interventricular communication. However, when the cleft extends to the crest of the interventricular septum, a small shunt can occur at this location between the two ventricles. There are generally two distinct AV valve orifices, corresponding to the mitral and tricuspid valves. Leaflet tissue joins the left superior and inferior

leaflets together at the crest of the interventricular septum, eliminating the interventricular communication. In general, partial AV canal defects constitute approximately 5% to 10% of all ASDs.

Complete AV canal defects constitute the other end of the spectrum and are the most common form of AV canal defects. There is generally an ostium primum ASD and a nonrestrictive ventricular septal defect (VSD) in the inlet portion of the interventricular septum. One common AV valve orifice is present, with left and right components. An inlet-septal VSD alone does not fall under the heading of AV canal defects, because the AV septum is intact in these malformations and the AV valves usually form normally. On the other hand, some patients have an inlet-septal VSD and a cleft mitral valve with a restrictive or absent interatrial communication; these should be considered to be in the spectrum of AV canal defects.

In this chapter, we describe the principal anatomic features relevant to the preoperative evaluation and surgical management of defects amenable to a two-ventricle repair, and we briefly discuss the features that may preclude such an approach. Surgical techniques with early and late results are described. Various associated cardiac lesions are discussed, in addition to the management of

recurrent mitral regurgitation. We will not discuss the management of AV canal defects associated with heterotaxy syndrome, because the AV canal defect is not the primary pathophysiologic abnormality, and because the anatomy of the AV valve and leaflet configuration are quite different from those of AV canal defects.

ANATOMY

The anatomic malformation that is common to all forms of AV canal defects is a deficiency in the AV septum caused by incomplete embryonic development of superior and inferior endocardial cushion tissue. The common AV canal is normally present during the early tubular stage of fetal life and constitutes the sole connection between the primitive common atrium and the primitive common ventricle. After cardiac looping, the valves of the heart develop in the embryo from precursor structures, called *endocardial cushions*. These endocardial swellings become populated by valve precursor cells formed by a transformation from endothelial to mesenchymal tissue, and they undergo directed growth and remodeling to form the valvular structures and the membranous septa of the mature heart (Fig. 116-1). Abnormal differentiation and remodeling of the cushion mesenchyme into valvuloseptal tissue is thought to be a mechanism for the development of AV canal defects.⁴ The resultant anatomic defect involves the abnormal development of AV valves and the persistence of interatrial and interventricular communications.⁵

The wide variability in the degree of development of the endocardial cushions explains the variability in size and extent of the septal defects and the degree of involvement of the AV valves. Nevertheless, several anatomic features are shared between all types of AV canal defects. These include the following:

- Shortened dimension of the inlet septum-to-ventricular apex, giving the interventricular septum a “scooped-out” appearance. This deficiency in the inlet septum is typically deeper in complete AV canal defects than in partial AV canal defects.
- Lengthened dimension of the outlet septum-to-ventricular apex, resulting in a goose-neck appearance and anterior displacement of the left ventricular (LV) outflow tract. Although the LV outflow tract appears narrow, true LV outflow tract obstruction (LVOTO) is rare in the absence of accessory chordal attachments of the AV valve leaflets to the outflow tract. In the normal heart, the inlet-septum-to-ventricular-apex length and the outlet-septum-to-ventricular-apex length are equal.
- Absence of the usual wedged position of the aortic valve between the AV valves, caused by maldevelopment of the endocardial cushions. This results in elevation and anterior deviation of the aortic valve.
- Decreased contribution of the left lateral leaflet to AV valve circumference. In the normal situation, the posterior mitral leaflet forms two thirds of the mitral valve circumference. In AV canal defects, the left lateral leaflet, which corresponds to the posterior mitral leaflet in the normal heart, forms only a third or less of the circumference of the AV valve.
- Inferior displacement of the AV node and coronary sinus. The bundle of His is also displaced inferiorly, coursing at the inferior rim of the scooped-out basal portion of the interventricular septum.

In addition to these fundamental concepts, anatomic features of significance to the surgeon include the following:

- Size and extent of the interventricular and interatrial communications
- Valve leaflet morphology, including papillary muscle anatomy, valve regurgitation, and presence of chordal attachments to the septum
- Relative balance of the common AV valve orifice over the two ventricles
- Other major associated cardiac and noncardiac defects

The AV valve in a canal defect has an area of apposition of leaflets that, unlike a normal commissure, is not supported by a papillary muscle. This area of apposition is called a *cleft*, and it is the apposition of the superior and inferior bridging leaflets. This cleft is not a commissure,⁶ as was once thought,⁷⁻⁹ for two reasons. First, a commissure is generally supported by chordae on either side of the defect, whereas a cleft is unsupported, with paucity of chordae at the edges. Second, the chordae that arise from the two adjacent leaflets in a commissure usually attach to a single papillary muscle, which promotes coaptation and prevents regurgitation. The chordae that arise from the left superior and inferior leaflets attach to two different papillary muscles; this increases the distracting force during ventricular systole and predisposes to regurgitation through the cleft. The extent of regurgitation is generally mild to moderate, although severe regurgitation can be present.

In 1966, Rastelli and colleagues¹⁰ described a classification of complete AV canal defect based on the extent

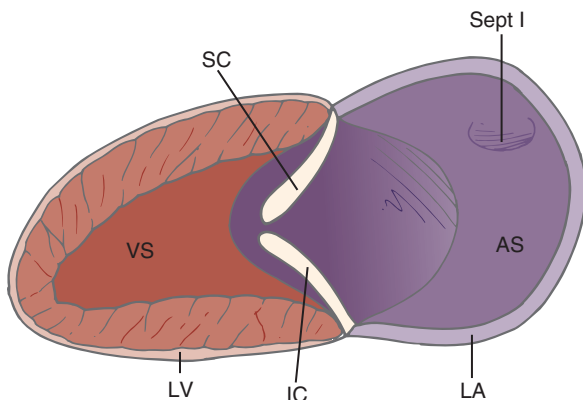


FIGURE 116-1 ■ Schematic of complete atrioventricular (AV) canal defect during morphogenesis, with the AV canal region shown in dark gray. Projections from the superior and inferior endocardial cushions normally differentiate into the AV valves and AV septum. AS, Atrial septum; IC, inferior endocardial cushion; LA, left atrium; LV, left ventricle; SC, superior endocardial cushion; Sept 1, septum primum; VS, ventricular septum. (Modified from Van Praagh R, Litovsky S: Pathology and embryology of common atrioventricular canal. *Prog Pediatr Cardiol* 10:115–127, 1999.)

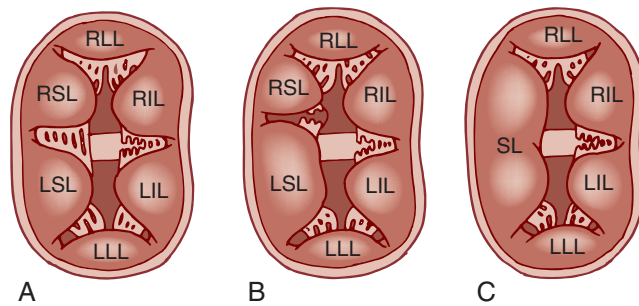


FIGURE 116-2 ■ The Rastelli classification for complete atrioventricular canal defects. **A**, In the Rastelli type A defect, the superior bridging leaflet is divided into two leaflets at the crest of the interventricular septum, corresponding to the right superior leaflet (RSL) and the left superior leaflet (LSL). **B**, In the Rastelli type B defect, the LSL bridges across the septum and attaches to a papillary muscle in the right ventricle. **C**, In the Rastelli type C defect, there is marked bridging of the superior bridging leaflet (SL), making it free floating and unattached to the underlying interventricular septum. LIL, Left inferior leaflet; LLL, left lateral leaflet; RIL, right inferior leaflet; RLL, right lateral leaflet. (Modified from Jacobs JP, Burke RP, Quintessenza JA, et al: Congenital Heart Surgery Nomenclature and Database Project: atrioventricular canal defect. *Ann Thorac Surg* 69:S36–S43, 2000.)

of bridging of the left superior leaflet (LSL) across the interventricular septum (Fig. 116-2). In complete AV canal defects, the left inferior leaflet (LIL) is not well developed; it is usually short and immobile, with rolled edges. The Rastelli classification does not take into consideration the LIL, which displays greater anatomic variation. No clear morphologic relationship exists between the LSL and the LIL.

The most common Rastelli type, present in approximately 55% of patients, is the Rastelli A defect. There is no bridging of the LSL; instead, its chordae attach to the crest of the interventricular septum. The superior bridging leaflet can be divided into left and right components over the crest of the interventricular septum. The inferior bridging leaflet is rarely divided and is often attached by short, dense chordae to the crest of the interventricular septum.

In the rare Rastelli B defect, the superior bridging leaflet is often partially divided into right and left components, with associated mild to moderate bridging of the LSL. Its chordae attach either to the right of the crest of the interventricular septum or to a prominent papillary muscle in the right ventricle, depending on the extent of bridging. The moderator band is often short. The Rastelli B subtype is often associated with unbalanced AV canal defect.

In the Rastelli C defect, there is extensive bridging of the LSL. Its chordae are free floating and are not attached to the underlying crest of the interventricular septum but rather to the anterolateral papillary muscle of the right ventricle. The Rastelli C type of complete AV canal defect can be seen in association with other complex heart lesions such as tetralogy of Fallot (TOF), transposition of the great arteries (TGA), and double-outlet right ventricle (DORV).

The development of the Rastelli classification facilitated the widespread application of corrective surgery for this defect. Although it is an oversimplification and

represents categorization of a continuum of leaflet abnormalities, it may still have a limited role in the repair of complete AV canal defects using the classic single-patch technique. In that setting, recognition of whether the bridging leaflets are undivided over the crest of the interventricular septum is important because undivided leaflets need to be surgically incised into right and left components to allow placement of a patch to close the interventricular and interatrial communications. Even in those settings, however, the Rastelli classification may have limited applications because neither the extent nor the location of naturally occurring divisions in the bridging leaflets is taken into account. The Rastelli classification is of less importance in the double-patch or modified single-patch techniques that are described later in the chapter.

Lev's¹¹ description of the location of the conduction tissue was another important contribution in the field, because it facilitated the development of surgical techniques that avoided injury to the His bundle and the AV node. The coronary sinus ostium and the AV node are displaced inferiorly in AV canal defects. The AV node lies at the junction of the interatrial septum and the hinge point of the AV valve. This places the AV node between the coronary sinus ostium and the crest of the interventricular septum, in the so-called nodal triangle, which is not at the tip of Koch's triangle. The nodal triangle is bound by the inferior extent of the right AV valve annulus, the coronary sinus orifice, and the inferior edge of the interatrial septum (Fig. 116-3). The bundle of His then passes superiorly and anteriorly from the AV node to the crest of the interventricular septum, reaching it where the crest is fused posteriorly with the AV valve annulus. The bundle then travels along the crest of the interventricular septum, in an inferior-to-superior direction, giving rise to the left bundle branches. Before reaching the midpoint of the interventricular crest, it becomes the right bundle branch and heads toward the moderator band and the muscle of Lancisi.¹² The superior aspect of the interventricular septum is devoid of conduction fibers. The only exception is that, in patients with complete AV canal defects and heterotaxy syndrome, two AV nodes may be found.¹³

The relationship between the common AV valve and the ventricles varies. If the AV valve is situated primarily over one ventricle, associated hypoplasia of the contralateral ventricle frequently occurs, which in extreme cases precludes a two-ventricle repair. Abnormal papillary muscle development, such as two closely spaced papillary muscles or a single papillary muscle, is seen in right ventricle–dominant forms of complete AV canal defect. In left-dominant forms, often the papillary muscles are closely spaced and fused to the septum, giving the appearance of chordal attachments to the septum. In fact, the papillary attachments to the septum can usually be divided to achieve a two-ventricle repair in many of these patients.

Approximately 50% to 75% of patients with complete AV canal have Down syndrome, whereas Down syndrome is rare in patients with partial AV canal defects,¹ occurring in less than 10% of these patients. AV canal defects represent approximately 3% of all major congenital cardiac defects and are seen in approximately 25% to

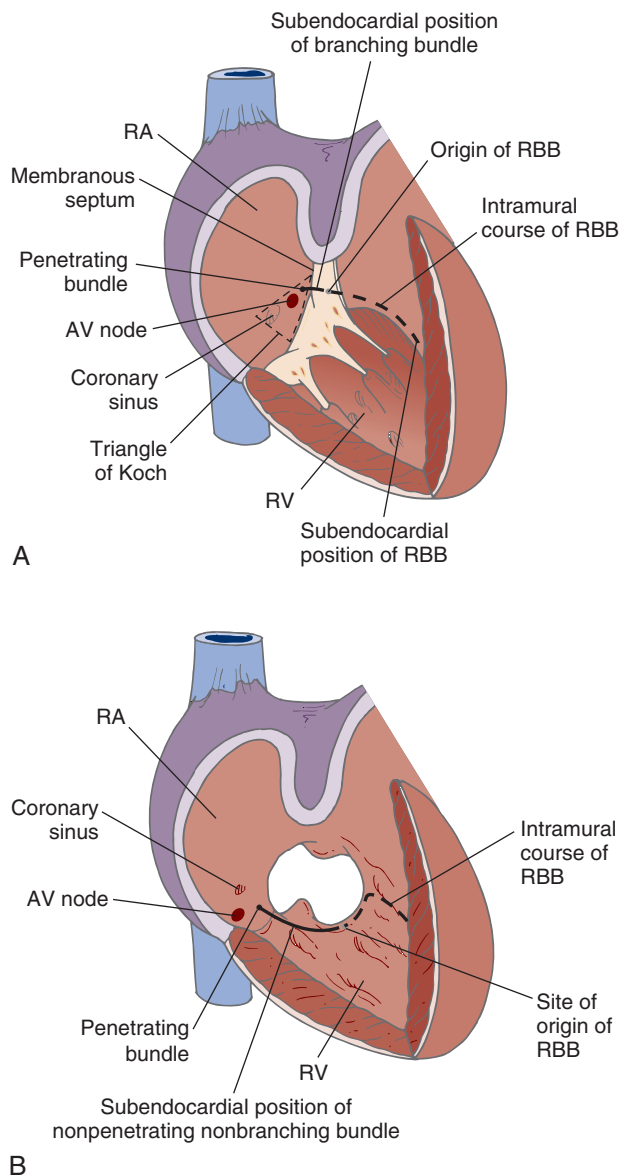


FIGURE 116-3 ■ The location of the atrioventricular (AV) node and the conduction tissue. **A**, Normal heart. Note the location of the AV node at the tip of the triangle of Koch. **B**, AV canal heart. The AV node is now located in the nodal triangle, not at the tip of the triangle of Koch. The coronary sinus, AV node, and bundle of His are displaced inferiorly compared with the normal heart. RA, Right atrium; RBB, right bundle branch; RV, right ventricle. (Modified from Kertesz NJ: The conduction system and arrhythmias in common atrioventricular canal. *Prog Pediatr Cardiol* 10:153–159, 1999.)

30% of patients with Down syndrome. This represents a 1000-fold higher rate than in the general population.² AV canal defects are the most common congenital heart anomaly in patients with Down syndrome. The presence of Down syndrome is thought to accelerate the development of pulmonary vascular obstructive disease (PVOD), especially in the setting of complete AV canal. An additional 15% to 20% of fetuses with AV canal syndrome have heterotaxy syndrome. AV canal defects are present in almost all patients with asplenia and in a high number of patients with polysplenia. Although an underlying

genetic mechanism has not been identified, some intriguing evidence exists in that regard. First, there is a strong association between AV canal defects and Down syndrome. High levels of endostatin, which is known to regulate endocardial cushion development, have been found in patients with Down syndrome. Second, a weaker association exists with heterotaxy syndrome. Third, familial clustering of AV canal defects has been reported.¹⁴ Fourth, the incidence of recurrent congenital heart disease in offspring of patients with AV canal defects is approximately 10%.¹⁵ In another study, approximately 14% of offspring of mothers with isolated AV canal defects had congenital heart disease, usually either TOF or AV canal defects.¹⁶ This contrasts with the 2% to 4% probability of congenital heart disease in children of parents with other congenital cardiac lesions.

PATHOPHYSIOLOGY

A left-to-right shunt is present in patients with AV canal defects, unless PVOD or coexistent right ventricular (RV) outflow tract obstruction is present. Patient presentation depends on the extent of left-to-right shunting, which in turn depends on pulmonary vascular resistance. The amount of left-to-right shunting increases in the first few weeks of life, paralleling the fall in pulmonary vascular resistance. At this stage, symptoms of congestive heart failure, such as poor weight gain, tachypnea, and sweating, begin to appear.

In partial AV canal defects, where an interventricular communication is absent, the shunt is located only at the atrial level. Patients with partial AV canal defects with little or no regurgitation through the AV valves have a clinical presentation similar to that of patients with secundum ASDs. The degree of shunting depends on the size of the ostium primum ASD defect and the relative diastolic compliance of the two ventricles. RV stroke volume is increased, whereas RV systolic pressure may be normal or only slightly increased. Patients may remain asymptomatic for years. An exception is the presence of significant left AV valve regurgitation in the setting of an ostium primum ASD, which is the case in 10% to 15% of patients. The regurgitation increases left-to-right shunting considerably; a left-ventricle-to-right-atrium shunt may also be present. This results in increased RV and LV stroke volume, cardiomegaly, tachypnea, tachycardia, poor feeding, and failure to thrive, leading to progressive heart failure in infancy. Without treatment, patients with partial AV canal defects and large interatrial communications rarely survive beyond 40 years of age, although older patients have been reported.¹⁷ Atrial arrhythmias are common, increase in frequency with advancing age, and are a poor prognostic sign.

Patients with complete AV canal defects exhibit left-to-right shunting because the VSD is large and nonrestrictive. The extent of the shunt at the ventricular level depends primarily on pulmonary vascular resistance. The pathophysiology in complete AV canal defects is similar to that of a large nonrestrictive VSD with two additional features. First, an atrial level shunt is present, with the potential for a left-ventricle-to-right-atrium shunt and

increased volume loading of the ventricle. Second, AV valve regurgitation may be present, further increasing the volume load. These factors accelerate the development of heart failure symptoms in early infancy.

In many patients, particularly those with Down syndrome, pulmonary vascular resistance remains elevated after birth, which decreases the magnitude of left-to-right shunting. In other infants, pulmonary vascular resistance drops in the first few weeks of life, resulting in a large left-to-right shunt. Patients typically display tachypnea, failure to thrive, cardiomegaly, and diminished distal perfusion in the first few months of life. If AV valve regurgitation is coexistent, the extent of left-to-right shunting is increased because of shunting at both atrial and ventricular levels, resulting in biventricular volume overload. This accelerates the development of heart failure. In one study, moderate AV valve regurgitation was present in approximately 20% of complete AV canal defects, whereas severe regurgitation was present in 15% of such lesions.¹⁸ In our experience,¹⁹ mild AV valve regurgitation is common, occurring in approximately 35% of patients in the first year of life, although the incidence of severe AV valve regurgitation is less frequent, occurring in approximately 4% of patients.

Irreversible changes in the pulmonary vasculature are seen as early as 6 months in patients with unrepaired complete AV canal defects.²⁰ The presence of Down syndrome accelerates the development of PVOD.²¹ This can result partly from an underlying pulmonary vascular defect predisposing to PVOD and partly from increased bronchial secretions, decreased number of distal bronchi, inherent abnormalities of the lung parenchyma, and the thick tongue that predisposes to oropharyngeal airway obstruction, hypoventilation, sleep apnea, tracheobronchomalacia, and CO₂ retention. These factors accelerate the development of respiratory infections and PVOD. If PVOD progresses, eventually the shunt reverses to a right-to-left shunt and the Eisenmenger complex develops, with progressive cyanosis in later stages.

Without surgery, patients with complete AV canal defects and Down syndrome have an 80% survival rate at 10 and 15 years.²² The primary causes of death within the first several years of life are heart failure and recurrent pulmonary infections. Subsequently, PVOD becomes an increasingly prevalent cause of death. Toward the end of the second decade of life, exercise tolerance begins to decrease progressively, leading to premature death from PVOD by the third to fourth decades of life. One of the more dramatic causes of death in patients with PVOD is massive hemoptysis, which can occur as early as the third decade of life.

TIMING OF SURGERY

The development of surgical techniques to treat AV canal defects parallels the evolution of cardiac surgery for congenital heart defects. Initial attempts at repair were complicated by limited knowledge of the anatomic features, particularly regarding the conduction tissue.

The first cardiac operation using a pump oxygenator was attempted by Dennis and Varco in 1952 in a patient

with a preoperative diagnosis of an ASD. The patient did not survive surgery. Postmortem examination revealed a partial AV canal defect. In 1955, Lillehei and colleagues²³ were the first to report repair of complete AV canal using cross-circulation. Successful repair of an ostium primum defect using cardiopulmonary bypass was first reported by Kirklin and colleagues in 1955.²⁴

Complete Atrioventricular Canal

Two techniques have been proposed for repair of complete AV canal defects. A single patch covering atrial and ventricular defects with partition of the superior bridging leaflet was originally developed by Rastelli and Kirklin at the Mayo Clinic.^{25,26} Separate atrial and ventricular patches were proposed by Carpenter⁸ and advocated by others.^{27,28} A recent modification of the single-patch technique has been introduced.^{29,30}

Management of the cleft has evolved over the years. Carpentier,⁸ Anderson and associates,⁷ and others⁹ recommended that the cleft be viewed as a commissure. They advocated leaving the cleft open to result in a "trifoliate" left AV valve and prevent the development of stenosis. However, the left-sided cleft is not a normal commissure, as discussed earlier. Left AV valve regurgitation frequently originates at the cleft; in later stages, as the regurgitation progresses, a central regurgitant jet may also be seen. Many surgeons in the 1980s left the cleft open only to have a sizable number of patients return with significant mitral regurgitation (MR) primarily through the cleft. For this reason, most surgeons close the cleft completely. However, the cleft should be left open or only partially closed in patients with a single papillary muscle in the left ventricle, the so-called parachute mitral valve, because mitral stenosis can result when complete cleft closure is undertaken in this setting.

Many surgeons during the 1970s and early 1980s advocated palliation with pulmonary artery banding to delay surgical repair beyond infancy. However, as surgical techniques improved and cardiopulmonary bypass in infants became safer and more widely applied, most centers abandoned this practice and opted for elective repair before 6 months of age. One exception is children with partial and transitional AV canal defects, who are frequently asymptomatic; repair can generally be deferred until the first few years of life unless AV valve regurgitation is severe. Although we advocate primary repair of complete AV canal in early infancy, there may be a limited role for the use of a palliative pulmonary artery band in patients with highly complex anatomy, such as unbalanced complete AV canal defects in which single-ventricle management is planned. Palliation by construction of a modified Blalock-Taussig shunt has been proposed in patients with complete AV canal defects and TOF to avoid early repair; although we do not advocate this approach, it will be discussed later.

We advocate repair in symptomatic infants regardless of age, and elective repair within the first 2 to 4 months of age in asymptomatic infants with complete AV canal defects. Delay beyond this age is unnecessary and is potentially hazardous. Repair of AV canal defects beyond 6 months of age has recently been shown to be

an incremental risk factor for death.³¹ Freedom from reoperation for left AV valve regurgitation is higher when patients are repaired at a younger age.³¹ Prematurity and severe AV valve regurgitation should not be contraindications for corrective surgery, because the results with palliation in these groups are particularly poor.

Another sequela of delaying surgery is the development of pulmonary hypertension with elevated pulmonary vascular resistance, predisposing to postoperative pulmonary hypertensive crises, which are serious and life-threatening postoperative complications. Although pulmonary hypertension can, in most cases, be treated with sedation, hyperventilation, and inhaled nitric oxide, prevention by timely elective repair is far safer and avoids the risk of development of irreversible PVOD, which can occur within the first year of life, especially in the presence of Down syndrome.

Transitional Atrioventricular Canal

Patients with transitional AV canal defects fall in a category between partial and complete AV canal because of the restrictive nature of the VSD, which protects against the harmful sequelae of torrential pulmonary blood flow. Usually, the restrictive VSD is small, which allows transitional AV canal defects to be repaired in the first 1 to 2 years of life. If the restrictive VSD is moderate in size, then repair should proceed earlier to prevent the complications of PVOD.

Partial Atrioventricular Canal or Ostium Primum Defects

Asymptomatic patients with partial AV canal defects should be repaired by 1 to 3 years of age in the majority of patients. This is similar to the recommendation for closure of isolated secundum ASDs. If significant left AV valve regurgitation is present, then earlier repair is recommended.

Sommerville³² reviewed the outcome of 122 unoperated patients with ostium primum ASDs between 1958 and 1964. Increasing morbidity and mortality occurred with increasing age. The presence of significant MR correlated with increasing symptoms. Of 96 patients younger than 30 years of age, 14% died ($n = 5$) or had significant disabling symptoms ($n = 8$).

A subgroup of patients with partial AV canal defects display heart failure symptoms that are unresponsive to medical management in the first year of life.³³ They require early surgical correction. Frequent associated findings include the presence of several left-sided obstructive lesions such as hypoplasia of the left AV valve, the left ventricle, the aortic valve, and the aortic arch, in addition to aortic coarctation. Complex mitral valve anomalies have also been documented in this subset of patients.³⁴

PREOPERATIVE EVALUATION

Because of the nearly continuous spectrum of lesions involving the atrial, ventricular, and valvular portions of

the AV canal defects, preoperative definition of the anatomic features in each case is helpful. Information regarding the mechanism of valve regurgitation and LVOTO are especially valuable in planning operative intervention. Intraoperative confirmation of the anatomic features is imperative to guide decisions regarding patch size, position of valve leaflets, and extent of cleft closure.

Physical examination correlates with the type of AV canal defect. In patients with partial AV canal defects, a systolic pulmonary flow murmur is heard, along with fixed wide splitting of the second heart sound, as in a secundum ASD. An apical blowing systolic murmur of MR may be present. If a VSD is present, as in transitional or complete AV canal defects, then a harsh holosystolic murmur is present, best heard at the left lower sternal border or the ventricular apex. A hyperactive precordium may be present. P2 is often loud, with fixed splitting of the second heart sound. Often a mid-diastolic low-pitched rumble is present. A pulmonary flow murmur may also be present.

The electrocardiogram reveals marked RV hypertrophy and sometimes may reveal LV hypertrophy and biatrial enlargement. The PR interval is often prolonged. The chest radiograph shows evidence of increased pulmonary blood flow, along with cardiomegaly. The presence of left AV valve regurgitation accentuates these findings; the left atrium may be severely dilated, with resultant elevation of the left main-stem bronchus.

In nearly all cases, the anatomic features, associated defects, and mechanism of valve dysfunction can be obtained from two-dimensional echocardiography, along with Doppler evaluation of blood flow direction and velocity.³⁵ The four-chamber view shows the left and right AV valves at the same horizontal level, which is in contradistinction to the normal situation, in which the tricuspid valve is attached to the AV septum more toward the apex of the heart than the mitral valve. Other features on echocardiography include the elongated LV outflow tract and the unwedged aortic valve. It is important to assess the presence of chordal attachments to the LV outflow tract, because this is a substrate for the development of LVOTO. The AV valve leaflets should be examined, and the mechanism of AV valve regurgitation should be assessed carefully. The availability of real-time three-dimensional echocardiography (RT-3DE) has been helpful in the assessment of the defect and to determine the mechanism of regurgitation. We use either epicardial or transesophageal RT-3DE in the assessment and management of AV valve repair, especially in reoperations for AV valve regurgitation. Studies have shown that RT-3DE can be used successfully in the repair of AV canal defects, with a short learning curve.³⁶ Echocardiography can be used to determine whether the common AV valve is balanced or not.³⁷ Using a subcostal view and planimetry technique, the area of the AV valve positioned over the left ventricle is divided with the area of the AV valve positioned over the right ventricle to derive the AV valve index. The valve index can be used to determine how balanced or unbalanced the AV valve complex is and to guide the treatment process.

For the majority of patients, cardiac catheterization and angiography rarely add information not obtained by

echocardiography. One notable exception is the unoperated patient older than 1 year in whom measurement of pulmonary vascular resistance is needed to determine operative risk. Another exception is the postoperative patient in whom quantification of residual postoperative lesions, such as residual VSDs and LVOTO, are required to assess the need for reoperation.

SURGICAL TECHNIQUE

Median sternotomy, either partial or complete, has been the standard technique for exposing the heart and great vessels. Some have advocated a right anterior thoracotomy for partial AV canal defects in older female children to improve cosmesis. More recently, however, techniques to minimize surgical trauma by limiting the extent of the sternotomy have been used, such as a lower mini-sternotomy (Fig. 116-4).³⁸ This approach can be applied to infants and children of all ages and may be helpful in decreasing postoperative pain and development of chest wall deformities, such as pectus carinatum. We are now using this mini-sternotomy approach for nearly all AV canal defects, except when there are major associated cardiac lesions such as aortic coarctation, TOF, or TGA, where a full sternotomy is required for optimal exposure.

Cardiopulmonary bypass with moderate hypothermia and bicaval cannulation is used in nearly all cases; deep hypothermic circulatory arrest is rarely required. Aortic cross-clamping and cardioplegia are used in all cases to facilitate repair, particularly during the attachment of the septal patches near the AV node and coronary sinus.

In the setting of a large ostium primum ASD, both AV valves and intraventricular anatomy can be readily visualized. If a small or absent interatrial communication is present, then an incision in the septum primum provides access to the left AV valve for valve testing and cleft closure. This also aids in securing the VSD patch to the crest of the interventricular septum.

Complete Atrioventricular Canal

In complete AV canal defects, there is usually a large ostium primum defect and a moderate to large nonrestrictive VSD under the superior and inferior bridging leaflets (Fig. 116-5). There may be chordal attachments of either bridging leaflet, or both, to the crest of the septum, and these leaflets may be partitioned into right and left components or may form a single bridging leaflet over the crest of the septum. Two surgical approaches have been developed and are commonly used in this setting. A double-patch technique involves the placement of two separate patches, one to close the VSD and the other to close the ASD. Alternatively, a single-patch technique with autologous pericardium is used to close the VSD and ASD components, often with division of the superior bridging leaflet. More recently, a modified single-patch technique has been introduced, where the VSD is obliterated by suturing the bridging leaflets to the crest of the interventricular septum; a single pericardial patch is then used to close the ASD. Although there are

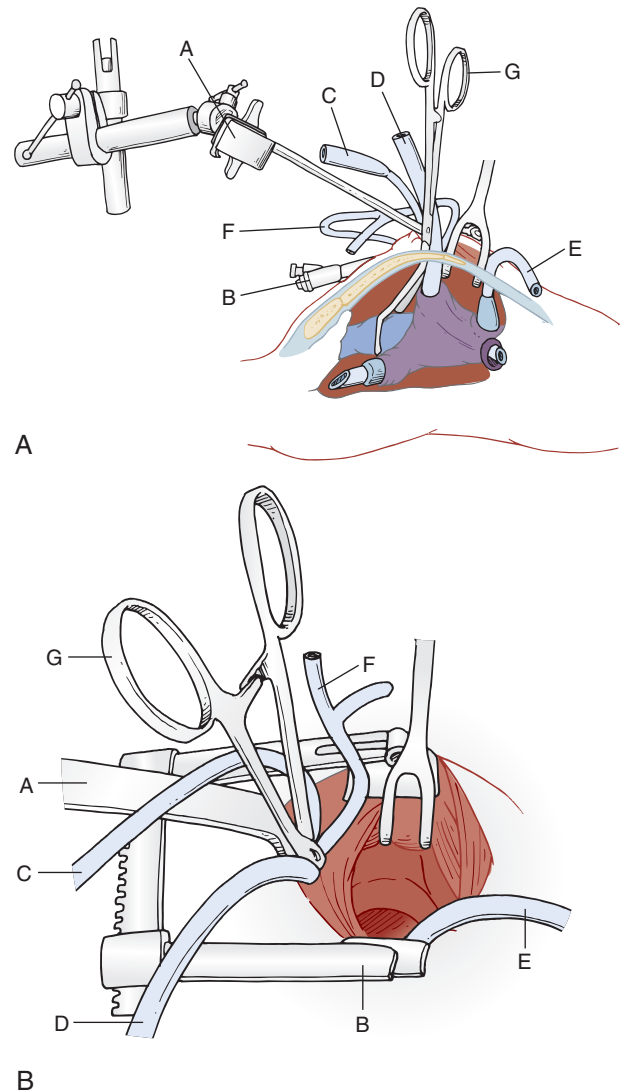


FIGURE 116-4 ■ Mini-sternotomy setup for repair of atrioventricular (AV) canal defects. **A**, Representative parasagittal cross-section with bicaval cannulation and aortic cross-clamping. **B**, Surgeon's view of the operative field. The inside of the atrium is well visualized for AV canal repair. **A**, Bookwalter retractor arm connected to an army-navy retractor; **B**, pediatric sternal retractor; **C**, aortic cannula; **D**, superior vena cava cannula via the right atrium, although direct cannulation is preferred for complete AV canal repair; **E**, inferior vena cava cannula; **F**, cardioplegia cannula; **G**, aortic cross-clamp. (Modified from del Nido PJ, Bichell DP: Minimal-access surgery for congenital heart defects. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 1:75–80, 1998.)

advantages and disadvantages to each technique, excellent results have been reported with all three methods.

Double-Patch Technique

In the double-patch technique, separate patches are used for closure of the ventricular and atrial septal defects. The ventricular patch is made of synthetic material, such as Dacron, or glutaraldehyde-treated pericardium. The atrial patch is usually autologous pericardium, either untreated or treated with glutaraldehyde. The use of a

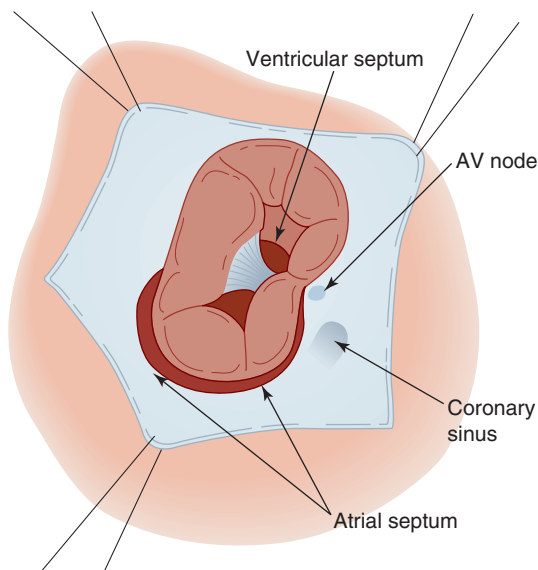


FIGURE 116-5 ■ Surgeon's view of complete atrioventricular (AV) canal defect. The superior bridging leaflet (*left*) is undivided and unattached to the underlying crest of the interventricular septum, as in a Rastelli type C defect. The AV node and coronary sinus ostium are displaced inferiorly. There is a cleft between the left superior and inferior leaflets. A large ostium primum defect is present, allowing good visualization into the left atrium.

synthetic atrial patch should be avoided, because hemolysis can result when a left AV valve regurgitant jet strikes the patch.

Initial inspection of the AV valve and filling of the left ventricle with cold saline facilitates the delineation of the point of coaptation of the left superior and inferior bridging leaflets. This permits measurement of the base-to-apex dimension of the VSD at the point of leaflet coaptation, corresponding to the height of the VSD patch. The distance between the two junction points of the interventricular septum and the AV valve annulus, at the aortic valve cephalad and the AV node caudad, should also be determined. This is helpful in determining the width of the VSD patch.

The patch shape is that of a crescent rather than a half circle because of the apical displacement of the point of coaptation of the superior and inferior bridging leaflets (*Fig. 116-6A*). The VSD patch is attached to the right of the crest of the interventricular septum using running or horizontal mattress interrupted pledgeted sutures. Care should be taken to avoid distortion of valve chordae that attach to the septum. As the suture line approaches the AV node area, the patch is attached more to the right of the septum, fixed 3 to 4 mm away from the junction of the interventricular septum and the AV valve.

The superior and inferior leaflets are then draped over the edge of the VSD patch. The pericardial patch is cut to an appropriate width, made narrower than the true distance between the aortic valve and the AV node to perform an annuloplasty of the AV valve, thereby decreasing the incidence of MR. A running horizontal suture line is performed to sandwich the AV valve leaflets between the VSD and ASD patches. These sutures pass through the pericardial patch, the left AV valve leaflets, the VSD

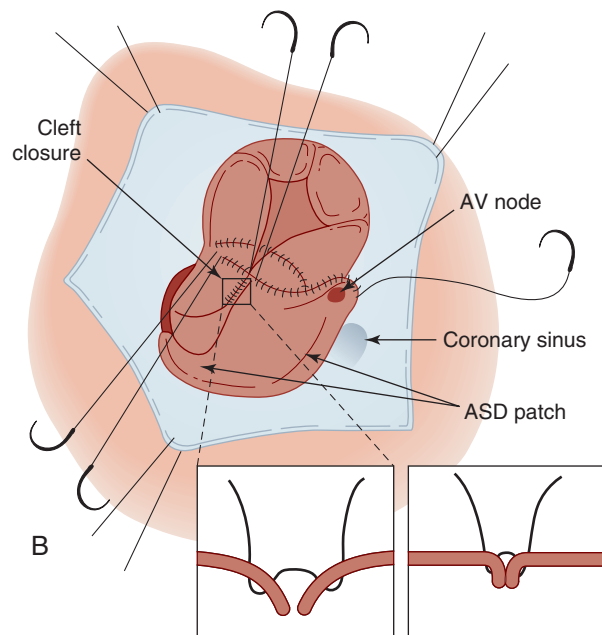
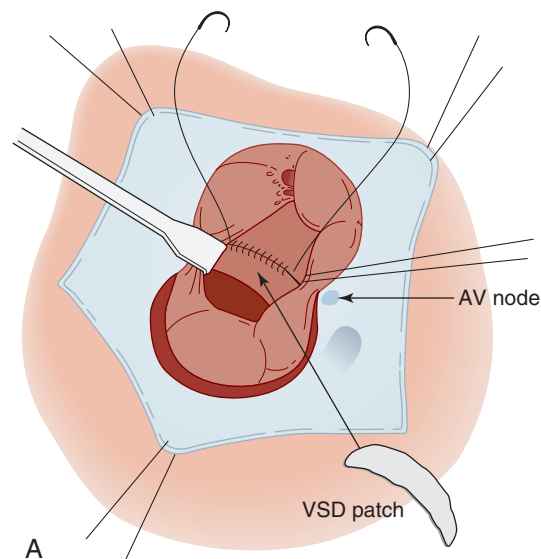


FIGURE 116-6 ■ The double-patch technique for repair of complete atrioventricular (AV) canal defects. **A**, Placement of the crescent-shaped ventricular septal defect (VSD) patch, showing suturing to the crest of the interventricular septum. The superior leaflet is retracted cephalad to allow accurate suturing without entrapment of chordae. Similar retraction is used at the inferior leaflet, where the patch is sewn to the right of the crest of the interventricular septum to avoid iatrogenic injury to the AV node. **B**, Completion of the double-patch repair is achieved by inserting the atrial septal defect (ASD) patch. Sutures are passed through the VSD patch, valve leaflets, and ASD patch, thereby sandwiching the valve between the two patches. In this example, the ASD patch is sewn to the right of the AV node and to the left of the coronary sinus. If a secundum defect or patent foramen is present, the ASD patch can be extended to cover both defects. Cleft closure is usually completed once the valve leaflets are attached to the ASD and VSD patches. *Inset*, Apposition of the cleft edges during systole.

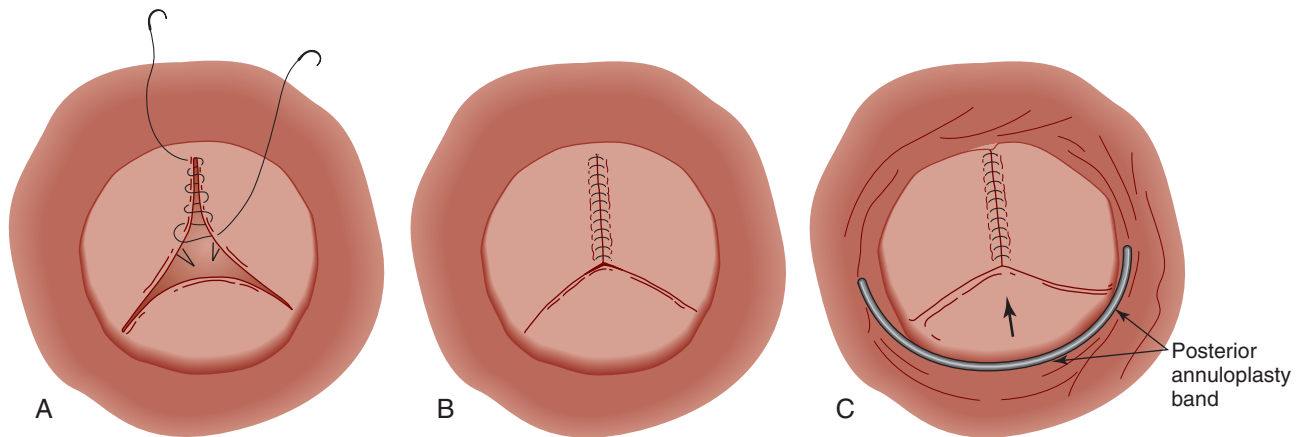


FIGURE 116-7 ■ Closure of the left atrioventricular (AV) valve cleft. Once the leaflets are attached to the ventricular septal defect and atrial septal defect patches, the zone of apposition of the superior and inferior bridging leaflets is usually well aligned. The cleft is then closed in two layers. **A**, The first layer is a running mattress suture, apposing the edges of the leaflets. **B**, The second running simple suture line ensures apposition of the leaflet edges. **C**, When there is significant annular dilation, a posterior annuloplasty is performed by inserting a flexible partial ring from the anterior fibrous continuity with the aortic valve to just posterior to the interatrial septum. The latter should remain 3 to 4 mm posterior to the junction between atrial septum and AV valve annulus to avoid injury to conduction tissue.

Dacron patch, and the right AV valve leaflets (see Fig. 116-6B).

The mitral valve cleft, created by coaptation of the superior and inferior bridging leaflets, is then closed, using either running or interrupted horizontal mattress sutures (Fig. 116-7A, B). Our preferred technique is the double-layer cleft closure. The first layer is a horizontal mattress layer, and the second layer is a simple running over-and-over suture, which is not tightened but left loose enough to help the pliability of the unified leaflet. The extent of cleft closure is determined in great part by the position of the papillary muscles and the size of the left lateral leaflet. Because closure of the cleft limits mobility of the superior and inferior leaflets, the greater the valve orifice area that is covered by these two leaflets, the greater the chance for creating valve stenosis. When the papillary muscles are close together or a single papillary muscle is present, closure of the cleft creates a slit-like orifice of the mitral valve, resulting in significant stenosis. In these cases, the cleft must be left at least partially open to facilitate leaflet mobility. Frequently, the edges of the leaflets creating the cleft are rolled and coapt over a small surface area. Care must be taken to preserve this degree of coaptation in closing the cleft and not to unroll the leaflet edges, because leaflet coaptation adds strength to the cleft closure, particularly during systole, thereby minimizing MR (see Fig. 116-6B).

The degree of MR is determined by injecting cold normal saline into the LV cavity. If significant regurgitation is present after cleft closure, then central regurgitation from poor leaflet coaptation is the usual culprit. This is managed by narrowing the commissure between the LSL and the left lateral leaflet and the LIL and lateral leaflet with placcation sutures. When there is annular dilation, placing a posterior intra-annular absorbable suture from LIL to LSL suspends the entire lateral leaflet. This brings the left lateral leaflet closer to the interventricular septum and improves central leaflet coaptation. An

additional maneuver that we have used when the left lateral leaflet does not coapt well with the sutured anterior leaflet is a posterior suture annuloplasty. We perform this maneuver using an absorbable monofilament suture, placing the suture in the annulus and then tying the suture over an appropriate sound to avoid valve stenosis. Commercially available posterior annuloplasty bands made of absorbable material can also be useful in cases of recurrent AV valve regurgitation (see Fig. 116-7C).

The ASD patch is then sutured to the remnants of the interatrial septum. The two surgical options available for avoiding injury to the AV node are attachment of the patch to the right or to the left of the AV node. Attaching the ASD patch to the right of the AV node involves suturing to the *right* inferior leaflet, where superficial bites are taken. The suturing continues to the right of the coronary sinus orifice, leaving the coronary sinus draining into the left atrium (Fig. 116-8A). Alternatively, the suturing can be extended to the edge of the coronary sinus orifice, leaving the orifice on the right atrial side (see Fig. 116-8B). The advantage of placing the patch to the right of the coronary sinus ostium is that the suture line remains far from conduction tissue. The disadvantage is that the coronary sinus is left draining to the left atrium. This can cause variable degrees of obstruction to coronary sinus drainage unless the coronary sinus is surgically unroofed. The arterial saturation is typically minimally affected. In a variant of this latter technique, the ASD patch can be attached to the *left* inferior leaflet, gradually returning to the edge of the interatrial septum, as initially advocated by McGoon and colleagues.²⁵ This leaves the coronary sinus draining into the right atrium. The disadvantage of this technique is that sutures must be placed through the LIL; in small infants, these sutures can tear through the delicate leaflet tissue or distort the leaflet enough to cause significant MR. In patients with complete AV canal and a left superior vena cava draining to the coronary sinus, the patch should be to the right of

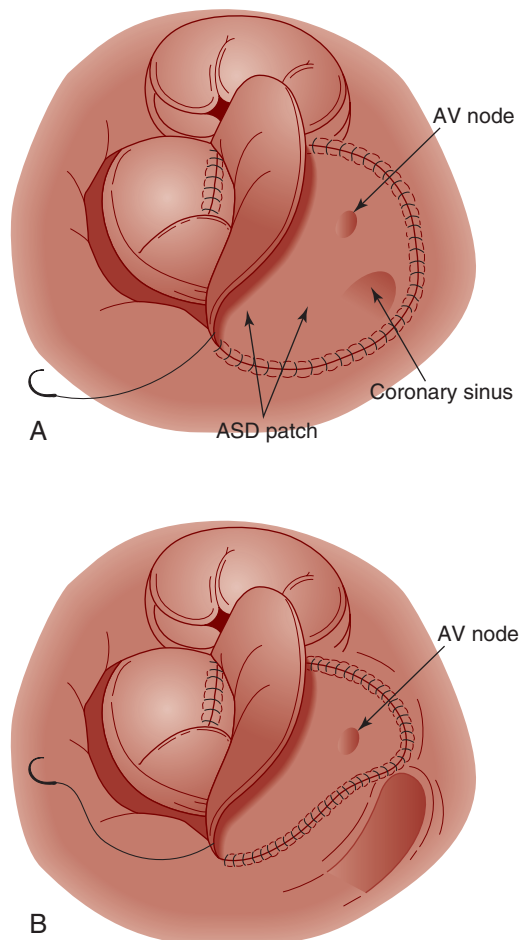


FIGURE 116-8 ■ Placement of the atrial septal defect (ASD) patch. **A**, The ASD patch can be placed entirely to the right of the atrioventricular (AV) node and coronary sinus, leaving the coronary sinus on the left atrial side of the newly constructed septum. **B**, Alternatively, the patch can be placed to the right of the AV node, but by turning the suture line back to the left of the coronary sinus, the sinus is left on the right atrial side.

the AV node and sutured to the edge of the coronary sinus ostium, leaving the ostium draining into the right atrium (see Fig. 116-8B).

Classic Single-Patch Technique

In the classic single-patch technique, the same patch of autologous pericardium, usually treated with glutaraldehyde, is used to cover both ventricular and atrial septal defects (Fig. 116-9).³⁹ It is critically important to determine the position of the mitral cleft and superior bridging leaflet with respect to the crest of the interventricular septum. When the right and left components of the AV valve are already partitioned with chordal attachments to the crest of the septum, only the position of the mitral valve cleft needs to be determined. Often, incisions must be made in the superior and inferior bridging leaflets parallel to and to the right of the interventricular septum to permit proper positioning of the single patch. The extent of leaflet division depends on the extent of the

underlying VSD. Because the VSD under the superior bridging leaflet often extends to the AV valve annulus, the leaflet incision has to extend to the AV annulus as well. This is often not the case for the inferior bridging leaflet, especially in the Rastelli A subtype, where the underlying VSD may not extend to the AV valve annulus because of variable fibrous fusion between the LIL and the crest of the interventricular septum. The leaflet incision in that case is only partial, without extension to the AV valve annulus. This protects the conduction tissue and AV node from iatrogenic injury. When the VSD under the inferior bridging leaflet extends to the AV valve annulus, the division of the leaflet should be to the right of the crest of the interventricular septum. This allows placement of the patch toward the right, thereby avoiding injury to the underlying conduction tissue at the crest of the interventricular septum.

As with the double-patch technique, precise measurement of the width of the patch with respect to the width of the AV canal defect is necessary to prevent MR caused by distortion of valve leaflets. If the patch is too wide, then the AV valve annulus size will increase, particularly over the interventricular septum; the superior and inferior bridging leaflet tissue available might not be sufficient to cover the orifice, resulting in MR.

Once the AV valve is partitioned into the right and left components, the VSD patch is attached to the right of the crest of the interventricular septum using running or interrupted pledgeted sutures. As with the double-patch technique, the suture line is placed to the right of the crest of the interventricular septum to avoid injury to the bundle of His. Once the patch is attached to the ventricular septum, the AV valve leaflets must be reattached to the patch. This maneuver is greatly facilitated by prior placement of a suture marking the coaptation point of the LSL and LIL at the base of the cleft at the crest of the interventricular septum. The valve leaflets should not be reattached too far to the atrial side of the patch, because this would tether the leaflets and limit coaptation, resulting in MR. Attachment of valve leaflets to the patch is done with pledgeted sutures because these valve leaflets are thin and friable, particularly in infants, predisposing to tearing if attached with nonpledgeted sutures.

The mitral cleft is closed next. The same considerations regarding cleft closure as described for the double-patch technique are applicable here. Similarly, individual commissuroplasty sutures can be placed for the treatment of central left AV valve regurgitation. The patch is then sutured to close the interatrial communication. As discussed earlier for double-patch repair, the coronary sinus may be left draining into the right or left atrium.

Modified Single-Patch Technique

The original description of complete AV canal repair by Dr. Lillehei involved attaching the AV valve leaflets to the crest of the interventricular septum primarily, because patch material was not readily available at the time; the ASD was also closed primarily.²³ Wilcox and colleagues³⁰ reintroduced this method of repair for patients with small VSDs. Nicholson and colleagues²⁹ broadened

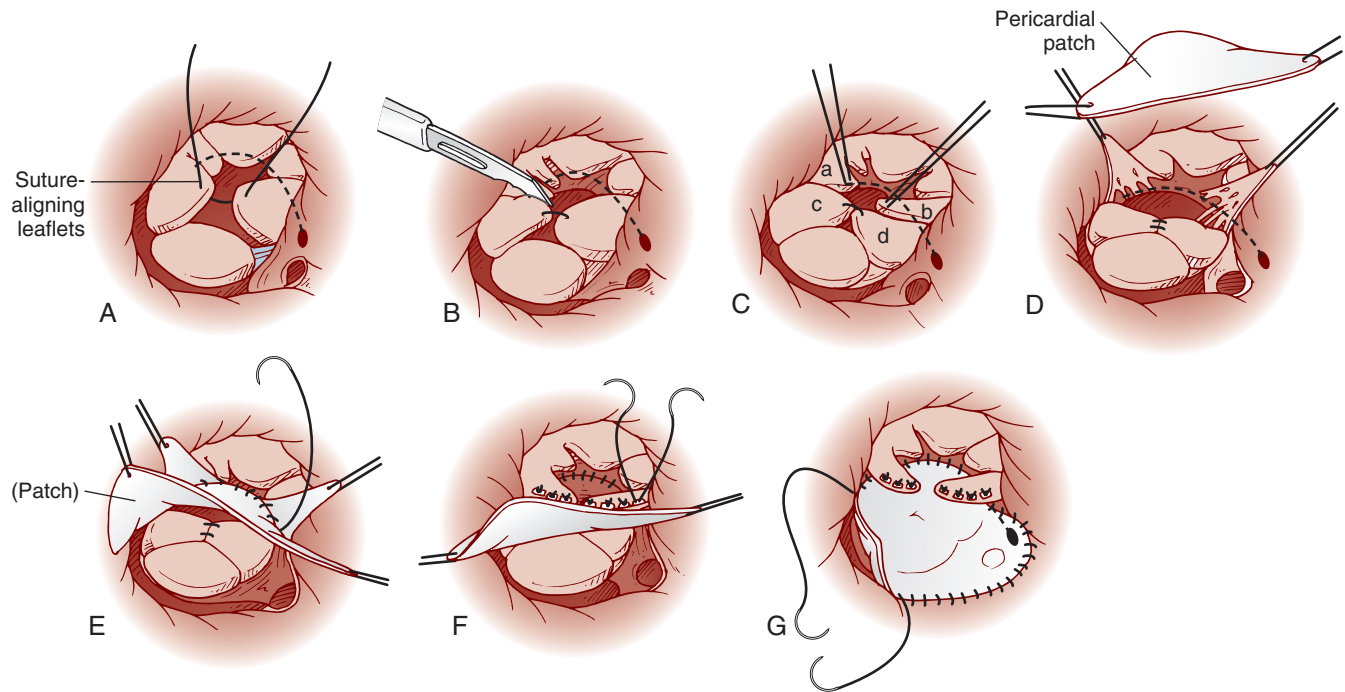


FIGURE 116-9 ■ Classic single-patch technique for repair of complete atrioventricular (AV) canal defects. **A**, Alignment sutures placed through the left superior leaflet and left inferior leaflet at the crest of the interventricular septum. **B**, The superior bridging leaflet is incised. **C**, Two portions of the superior bridging leaflet (*a* and *c*) and two portions of the inferior bridging leaflet (*b* and *d*) are shown after division of the corresponding leaflets. The division of the inferior bridging leaflet need not extend beyond the underlying interventricular communication. **D**, The left-sided cleft is closed. **E**, The pericardial patch is sewn to the crest of the interventricular septum. **F**, The right and left AV valve leaflets are suspended onto the pericardial patch. **G**, Completion of the repair by closure of the atrial septal defect. The AV node and coronary sinus ostium are shown draining on the left atrial side. (Modified from Castaneda AR, Jonas RA, Meyer JE Jr, et al: Atrioventricular canal defect. In Castaneda AR, Jonas RA, Meyer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, p 179.)

the indications to patients with moderate and large VSDs. Other reports have confirmed their findings.^{40,41}

In this technique, several pledgeted horizontal mattress sutures are brought through the crest of the interventricular septum, the AV valve leaflets, the autologous pericardial patch, and a narrow strip of Dacron, in that order (Fig. 116-10). Care should be taken to avoid damage to the bundle of His by keeping the sutures to the right of the crest of the interventricular septum, especially inferiorly. Suturing through the AV valve leaflets effectively partitions the bridging superior and inferior leaflets into right and left components. The strip of Dacron acts as an annuloplasty because its superior-inferior dimension is approximately 80% of the superior-inferior dimension of the AV canal defect, thereby bringing the left-sided AV valve leaflets into closer apposition and minimizing MR. Some have advocated avoiding the use of a strip of Dacron because of concerns about the effect of fixation of the mitral annulus on its long-term growth potential. One potential disadvantage of this technique is the development of LVOTO because the interventricular communication is closed primarily, without patch material. So far, although follow-up is limited, this has not been seen. The amount of MR appears similar to that seen with the classic single-patch and double-patch methods, although long-term follow-up is not yet available.

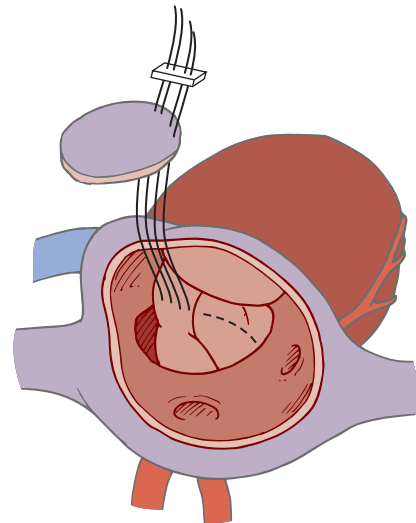


FIGURE 116-10 ■ Modified single-patch technique for repair of complete atrioventricular (AV) canal defects. Horizontal mattress pledgeted sutures are passed through the crest of the interventricular septum, the AV valve leaflets, and the pericardial patch, and then through a Dacron strip annuloplasty. (Modified from Nicholson IA, Nunn GR, Sholler GF, et al: Simplified single patch technique for the repair of atrioventricular septal defect. *J Thorac Cardiovasc Surg* 118:642–646, 1999.)

Transitional Atrioventricular Canal

In this form of AV canal defect, the VSD is restrictive and usually centrally located, formed by incomplete fusion of the point of coaptation between the LSL and LIL over the crest of the septum. There is usually a large ostium primum defect and a cleft mitral valve. The bridging leaflets are fused to the crest of the septum except for the central portion, and small VSDs may be found under the superior or inferior leaflets when the leaflets have not completely fused to the crest of the interventricular septum. When the VSDs are small, they can be difficult to identify intraoperatively. Retraction of the right superior leaflet can provide adequate access to these small defects, and a small (1- to 2-mm) probe can be used to identify residual interventricular communications.

These small VSDs can usually be closed primarily with sutures. Closure of the central VSD is usually done with the same suture that is used to close the cleft, but starting at the crest of the interventricular septum. Closure of the interatrial communication is done in a manner similar to ostium primum defects (Fig. 116-11).

Partial Atrioventricular Canal or Ostium Primum Defects

As with repair of complete AV canal, initial inspection and testing of the mitral valve is done. The presence of a partial or complete cleft is noted; in the majority of cases, the cleft extends to the interventricular septum. The technique for cleft closure is the same as that described earlier, with emphasis on maintaining leaflet coaptation. The ostium primum ASD is closed using autologous pericardium, because this tissue is more pliable than synthetic material and is less likely to distort valve leaflets. A secundum ASD or patent foramen ovale, if present, is closed either separately or with the same patch (see Fig. 116-11).

ASSOCIATED CARDIAC LESIONS

Associated cardiovascular lesions are not uncommon, particularly with complete AV canal defects. Extracardiac defects such as patent ductus arteriosus and aortic coarctation are usually treated during the operative procedure for repair of the AV canal defect. The surgical techniques for repair of associated defects are usually not different in the presence of an AV canal defect from when the lesions are isolated defects. Exceptions to this include the presence of secundum ASDs or additional muscular VSDs that are close to the AV canal defect; these can be repaired by extension of the septal patch to cover both lesions. Lesions that include conotruncal abnormalities such as TOF require significant modifications to the surgical approach and are discussed separately.

Tetralogy of Fallot

Tetralogy of Fallot is a complication in approximately 5% of patients with complete AV canal defects. The LSL is typically free floating over the interventricular crest of

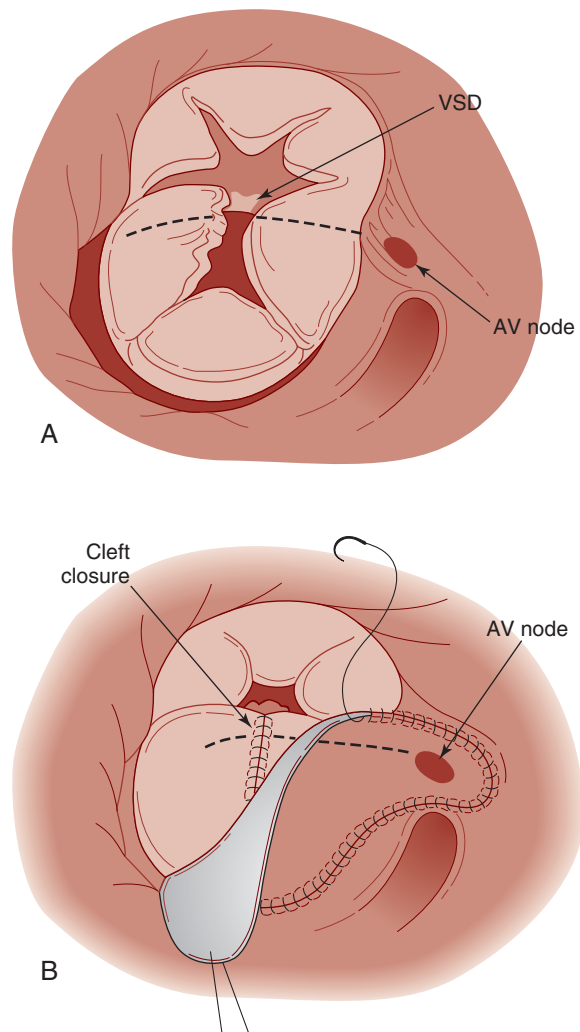


FIGURE 116-11 ■ Repair of transitional atrioventricular (AV) canal defect. **A**, The bridging leaflets are usually attached to the crest of the septum (*dashed line*) except for the central area of coaptation where there is a small ventricular septal defect (VSD). **B**, Closure of the VSD is accomplished using the same suture line as was used for cleft closure. Closure of the mitral cleft in this case is done first, then pericardial patch closure of the ostium primum defect is done. The patch is sutured to the right inferior leaflet tissue and then heads down toward the coronary sinus. An alternative technique (not shown) is suturing to the left inferior leaflet tissue, at the rim of the ostium primum defect.

the septum, as in a Rastelli type C defect, resulting in a large VSD with outlet extension. In contrast to the heart failure symptoms seen in the majority of patients with isolated complete AV canal defects, the main symptom in the combined lesion is cyanosis. This occurs because of right-to-left intracardiac shunting, which depends primarily on the degree of RV outflow tract obstruction. In a minority of patients, the degree of RV outflow tract obstruction is minimal; these patients display heart failure symptoms in early infancy that are similar to the symptoms in patients with isolated complete AV canal defects.

The operative management of complete AV canal defects associated with TOF requires modification of the VSD patch, because it has to extend to cover the conoventricular, anteriorly malaligned VSD. As with most forms of TOF, there is frequently infundibular

obstruction, along with pulmonary valvar hypoplasia and stenosis requiring augmentation of the entire RV outflow tract. Because of the anterior position of the aortic valve annulus in this defect, visualization of the anterosuperior edge of the VSD is best accomplished through a right infundibulotomy. As with cases of uncomplicated AV canal defects, the width of the VSD patch at the AV valve annulus level must be chosen carefully to prevent enlarging the AV valve annulus and resulting in MR.

When the single-patch technique is used to repair complete AV canal in association with TOF, an incision in the superior bridging leaflet is usually needed and is particularly critical. This incision should be farther toward the right of the crest of the interventricular septum, toward the right AV valve, to accommodate the underlying anterior deviation of the conal septum. This prevents the development of subaortic obstruction and LVOTO, seen when the patch is placed too far to the left of the interventricular septum. This is less an issue with the double-patch method of repair, although correct positioning of the VSD patch under the superior leaflet is still required. The shape of the VSD patch for the combined lesion resembles a teardrop rather than the typical crescent shape in isolated complete AV canal defect. The modified single-patch technique as originally described is not applicable to canal defects with TOF, because the large malalignment defect precludes direct suturing of the LSL to the crest of the interventricular septum.

Repair of the RV outflow tract obstruction is managed in a manner similar to that of isolated TOF, often with an incision in the RV outflow tract. The major difference in the combined lesion is that MR can result in left atrial hypertension with subsequent pulmonary arterial hypertension. If a transannular patch is used, the regurgitant fraction across the enlarged RV outflow tract is increased, leading to RV distention and dysfunction. The right ventriculotomy combined with division of RV muscle bundles in the outflow tract further exacerbates RV dysfunction. In such cases, consideration should be given to the creation of a temporary single-leaflet valve made from autologous pericardium. Careful testing of the tricuspid valve should be undertaken to rule out the presence of significant tricuspid regurgitation. If present, this can often be repaired by closure of the cleft between the right superior and inferior leaflets while avoiding the underlying conduction tissue.

Some have advocated the placement of a systemic-to-pulmonary shunt (e.g., a right modified Blalock-Taussig shunt) in the neonatal period in patients with severe cyanosis, with subsequent repair at 1 to 3 years of age, which potentially decreases the need for a transannular patch.⁴² We have usually undertaken complete repair in infants to avoid the episodes of hypercyanosis seen in tetralogy physiology. As with management of tetralogy, a small atrial septal communication is left to permit some right-to-left shunting because of RV diastolic dysfunction early after surgery.

Double-Outlet Right Ventricle

An anatomic scenario that can be similar to TOF is DORV, which is differentiated from TOF by the degree

of aortic override. When more than 50% of the aortic valve is located over the right ventricle, the lesion is defined as DORV rather than TOF. DORV is present in approximately 1% to 2% of patients with complete AV canal defects.⁴³ Typically, DORV in this setting is associated with heterotaxy syndrome and unbalanced AV canal defects, increasing the likelihood of univentricular palliation.

Two-ventricle repair of DORV and complete AV canal defects parallels the repair of the two separate lesions. If the VSD is in the subaortic position, the repair is similar to TOF with complete AV canal defect. The patch is more complex, because the left ventricle has to be baffled through the VSD to the aortic valve.

Coarctation of the Aorta

If aortic coarctation is present, the left-sided cardiac structures need to be studied carefully to ensure that they are of adequate size and to rule out unbalanced AV canal with RV dominance. Aortic coarctation has been associated with a mild degree of LV outflow obstruction for valvar or subvalvar stenosis. Often, these patients have closely spaced papillary muscles in the left ventricle or, in extreme cases, a parachute mitral valve with a single papillary muscle.

If significant MR is present after repair of complete AV canal defects, an exhaustive search should be performed to rule out the presence of residual LVOTO or aortic coarctation. If present, this increases LV afterload, which increases the distracting pressure on the thin and friable mitral leaflets and worsens the degree of MR. Repair of aortic coarctation in this setting often decreases the degree of MR.

Left Ventricular Outflow Tract Obstruction

Hemodynamically significant LVOTO is relatively rare in the setting of AV canal defects. Interestingly, LVOTO is rare in the presence of Down syndrome.⁴⁴ It is more common in partial AV canal defects than in complete AV canal defects,⁴⁵ unless ventricular imbalance is present. This may be due to the modification of the LV outflow tract in complete AV canal repair through the insertion of a VSD patch, whereas no such patch is needed during partial AV canal repair because no VSD is present. LVOTO results in an increased left-to-right shunt with accelerated development of heart failure symptoms. LVOTO appears to be more commonly associated with the Rastelli A subtype of complete AV canal.⁴⁶ The development of LVOTO can be acquired, progressive, or recurrent.⁴⁷

The normal LV outflow tract has an angle of almost 90 degrees between the plane of the crest of the interventricular septum and the plane of the outlet septum. This angle is significantly decreased in AV canal defects, measuring 22 degrees in one study.⁴⁶ In the Rastelli C subtype, the angle is nearly normal after repair of complete AV canal, accounting for the decreased incidence of LVOTO in this setting.

The mechanism and severity of LVOTO usually can be delineated with two-dimensional echocardiography.

Cardiac catheterization is reserved to confirm the degree of obstruction, particularly in patients presenting late after AV canal repair.

The surgical treatment is usually determined by the mechanism of obstruction. Obstructing primary AV valve chordal attachments can be divided off the crest of the septum if they are secondary chordae. If the cleft is directed to the LV outflow, division of the chords and closure of the cleft usually treats the outflow obstruction. In tunnel-like LVOTO, more extensive enlargement of the LV outflow tract is required, such as a modified Konno procedure. Unlike the more common forms of tunnel-like LVOTO, in AV canal defects the conduction tissue is farther away from the area of enlargement, and injury to the AV node is rare. Subaortic obstruction may be recurrent. In one study of 19 patients with subaortic stenosis associated with AV canal defects,¹⁶ operations for LVOTO were performed.⁴⁶ The most common procedure was fibrous resection of a subaortic membrane with myectomy. Mean time to reoperation for recurrent LVOTO was 4.9 years, with a median follow-up period of 5.6 years. This resulted in a 6-year actuarial freedom from reoperation of 66%. To decrease the incidence of reoperation, leaflet augmentation with pericardium and fibromyotomy have been suggested.

Transposition of the Great Arteries

Management of TGA associated with complete AV canal defect is similar to the surgical treatment of each isolated defect. The AV canal defect is repaired, and an arterial switch procedure is performed. The AV canal repair is more challenging because valve leaflets are very friable in the first week of life compared with the first few months of life. All heart structures are smaller as well, which increases the technical complexity of the procedure. We recommend reinforcement of all sutures through AV valve leaflets with autologous pericardial pledgets, especially those placed for cleft closure. If the superior bridging leaflet is undivided, we recommend avoiding the classic single-patch technique because leaflet division is necessary. Resuspension of the leaflets onto the single patch may gather too much precious leaflet tissue, predisposing to the development of MR.

Double-Orifice Mitral Valve

Another unusual abnormality of the left-sided AV valve is double-orifice mitral valve, present in approximately 5% of cases. A second accessory orifice is present, usually on the inferior aspect of the left lateral leaflet, which can vary substantially in size. If the second orifice is small, it may be left open without consequence.

If large, the papillary muscles need to be examined because one papillary muscle may be related to each orifice, resulting in a parachute mitral valve of the major orifice. In these situations the cleft should be closed only partially, because postoperative mitral stenosis results with complete cleft closure. Splitting the bridging leaflet tissue between the two orifices is not advised; this can result in significant MR because the leaflet tissue becomes unsupported. In some cases, when regurgitation is present

at the accessory orifice, addition of a triangular patch made from glutaraldehyde-treated autologous pericardium has been advocated in an attempt to extend the width of the leaflets and improve coaptation.

Parachute Mitral Valve

A single papillary muscle is present in 5% of cases of complete AV canal defect. The presence of two closely spaced papillary muscles or a single papillary muscle can result in all chordal structures attaching to a single point, referred to as *parachute mitral valve*. Closure of the cleft between the LSL and LIL frequently results in postoperative mitral stenosis in this setting. We elect to leave the cleft either partially or fully open, depending on the degree of separation of the papillary muscles, the thickness of the chordae, and the width of the interchordal spaces. Rarely, this still results in significant regurgitation at initial operation. Techniques to split the papillary muscle improve leaflet mobility by separating the chordae. Similarly, when there are two separate but closely spaced papillary muscles, mobilizing the papillary muscles away from one another may be effective in improving the effective orifice of the mitral valve.

Unbalanced Atrioventricular Canal

Bharati and colleagues⁴⁸ pointed out that the AV junction may be committed primarily to one ventricle in some cases of complete AV canal defects, resulting in associated hypoplasia of the contralateral ventricular cavity and outflow structures. This occurs in approximately 5% to 7% of patients with complete AV canal defects. In the more common right ventricle–dominant form, there is significant hypoplasia of the left ventricle, aortic valve, ascending aorta, and aortic arch. Conversely, in the left ventricle–dominant type, hypoplasia of the right ventricle is seen.

Management decisions regarding the potential use of the hypoplastic chamber as part of a two-ventricle repair should be based on objective criteria quantifying absolute ventricular volumes indexed to body surface area. Measurement of relative ventricular cavity volume to compare RV and LV volumes is frequently unreliable. Absolute ventricular volumes with values of 15 mL/m² or greater are felt to be sufficient criteria for successful two-ventricle repair. Three-dimensional echocardiography has significantly improved ventricular volume measurements.

If the canal is only mildly unbalanced, then a two-ventricle repair can often be performed. If the canal is grossly unbalanced with severe hypoplasia of one ventricular cavity, then a single-ventricle approach may be followed. However, there is a growing experience with two-stage repair of unbalanced defects, with partial closure of the interatrial communication performed in the first stage to encourage ventricular growth. At the second stage, VSD closure is performed. Traditionally, criteria have been developed to decide between two-ventricle and single-ventricle management. They involve a determination of relative ventricular size, AV valve architecture and function, outflow tract size and position, and the presence of associated cardiac lesions:

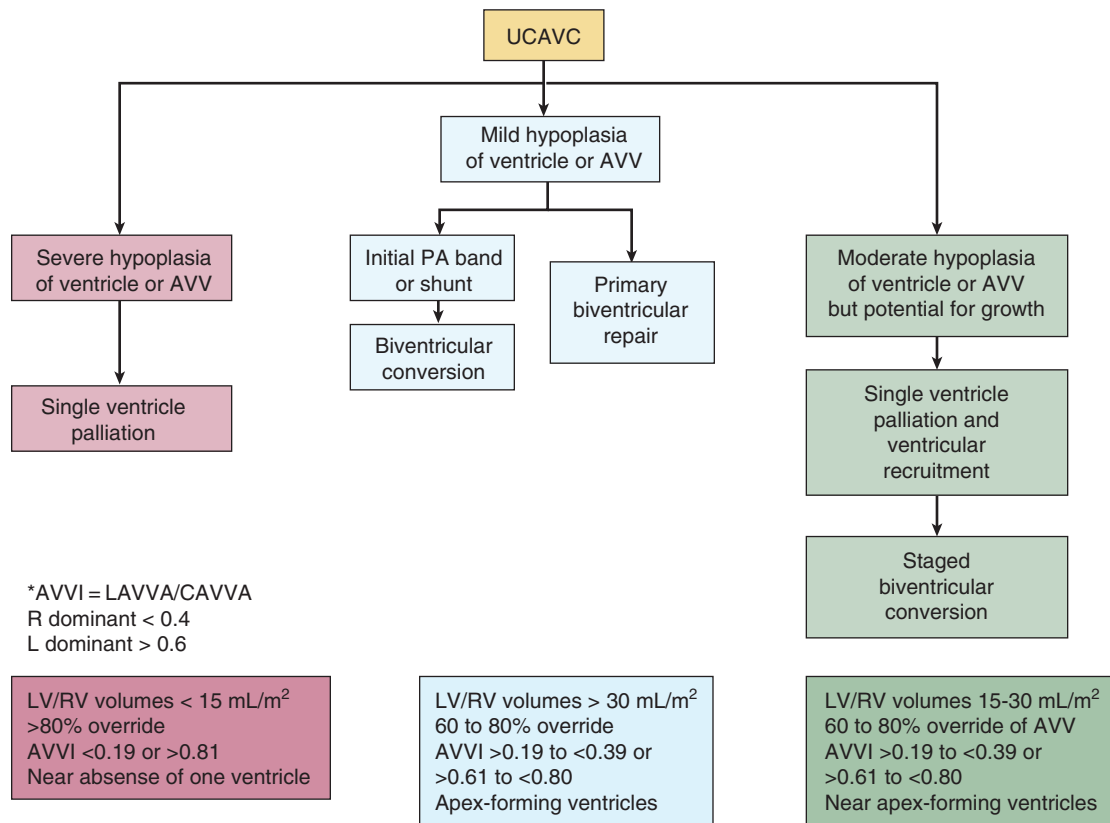


FIGURE 116-12 ■ Proposed algorithm for management of unbalanced complete atrioventricular canal defects. AVV, Atrioventricular valve; AVVI, atrioventricular valve index; CAVVA, common atrioventricular valve area; L, left; LAVVA, left atrioventricular valve area; LV, left ventricle, PA, pulmonary artery; R, right; RV, right ventricle; UCAVC, unbalanced complete atrioventricular canal. (Adapted from Nathan M, Liu H, Pigula FA, et al: Biventricular conversion after single-ventricle palliation in unbalanced atrioventricular canal defects. *Ann Thorac Surg* 95:2086–2096, 2013.)

- The left ventricle reaches the apex or near the apex.
- The calculated postoperative LV volume is 15 mL/m² or greater.
- The calculated postoperative mitral valve annulus z-score is –2 or greater.
- Two papillary muscles are present, although a single papillary muscle is not an absolute contraindication for two-ventricle repair.
- AV valve chordae attaching to the conal septum, which is a substrate for LVOTO, are absent. Associated aortic coarctation is often present.
- Heterotaxy syndrome is absent, although rarely a patient with polysplenia has two well-balanced ventricles that are amenable to two-ventricle repair.

These criteria, however, do not account for the growth potential that exists, particularly in very young infants. Recent reports have described growth of the LV cavity after closure of interatrial communications by forcing blood flow across the left AV valve.⁴⁹ A study from Boston analyzed biventricular conversions after initial single ventricle palliation in 16 patients with unbalanced complete AV canal defects.⁵⁰ All patients had either unequal distribution of the common AV valve or hypoplastic ventricle. Eight patients were right dominant with median LV end-diastolic volume of 32 mL/m², and eight were left dominant with RV end-diastolic volume of 42 mL/m². Biventricular conversion was achieved in these patients

with two patient deaths and eight patient reinterventions in the study follow-up period. The algorithm proposed by these authors for management of unbalanced complete AV canal defect patients is shown in [Figure 116-12](#).

Heterotaxy Syndrome

There is a distinct group of patients with heterotaxy and AV canal defects. These patients are challenging to manage. The criteria for biventricular repair outlined here still apply to these patients. However, consideration needs to be given to septation of systemic and pulmonary venous return as well as repair of the common AV valve. Patients with complex anatomy may benefit from early single ventricle palliation and conversion to biventricular repair at older age.

Single Ventricle

When more complex malformations are present, such as severely unbalanced AV canal defects, consideration should be given to managing these patients along a single-ventricle pathway. In patients with complete AV canal defects and heterotaxy syndrome, associated conotruncal anomalies such as transposition and pulmonary stenosis or atresia are often treated with single-ventricle management.⁵¹

Recurrent Mitral Regurgitation

Significant postoperative MR requiring reoperation is present in 4% to 15% of patients after repair of AV canal defects.^{52,53} In our experience, those at highest risk had at least moderate MR early postoperatively.¹⁹ Other factors associated with progressive late postoperative MR include parachute mitral valve,⁵⁴ double-orifice mitral valve,^{19,55,56} absence of Down syndrome,²⁸ no closure of the cleft at primary repair,^{28,56,57} and preoperative MR.^{53,55} Although mild deterioration is fairly common after complete AV canal repair, serious deterioration is rare, especially after the first 30 postoperative months, as reported in one study of 39 patients.⁵⁸ Another study followed two groups of patients, one in whom the cleft was closed at the time of initial AV canal surgery, and the other in whom the cleft was deliberately left open as part of a trifoliate repair.⁵⁷ Overall survival and freedom from reoperation for MR were significantly better when the mitral valve cleft was closed at the time of initial AV canal surgery. One confounding variable was the earlier date of surgery in the group in whom the cleft was left open; improvements in myocardial preservation and postoperative care could have contributed to the improved results seen in the more recent group of patients in whom the cleft was closed.

The mechanism of late MR in the majority of cases has been regurgitation through the cleft, because it was either left open initially or reopened after complete or partial closure. Annular dilation with central regurgitation is frequently an associated finding. Worsening MR leads to worsening LV volume overload and eccentric LV hypertrophy, ultimately leading to LV dysfunction and failure. One study looked at the echocardiographic changes associated with left AV valve after complete AV canal repair, this study showed that a potential mechanism for recurrent MR could be due to annular dilation which occurs posteriorly toward the free wall.⁵⁹ This mechanism points to the beneficial effect of posterior annuloplasty performed at the time of original repair to lift the left lateral leaflet toward the septum and potentially to prevent development of MR.

Preoperative echocardiographic studies should delineate the mechanism of regurgitation and the location of the regurgitant jet (either centrally or through the cleft or both). A direct measurement of the diameter of the mitral annulus should be performed and compared with the expected annular diameter for the patient's age, corresponding to a z-score of 0.

Reoperative mitral valve repair depends on the underlying anatomic abnormality. If the regurgitation is through a cleft, then closure of the cleft, along with reduction of the mitral annular diameter to an appropriate size (z-score between -2 and +2), is often effective. More complex mechanisms such as immobile, thickened, or retracted mitral leaflets are more difficult to repair and frequently require leaflet augmentation with autologous pericardium, along with reduction of the annular diameter. The presence of MR thickens the leaflets, allowing closure of the tear either primarily or with a small pericardial patch. In the older child, a flexible partial annuloplasty ring should be implanted to provide support for the repaired valve, especially during ventricular systole.

In rare cases, mitral repair is not possible, and mitral valve replacement becomes necessary, typically using a mechanical prosthesis. Because the native left AV valve encroaches on the LV outflow tract, valve replacement can result in significant LVOTO. This can be avoided by first suturing a rectangular Dacron patch to the left AV valve annulus in the subaortic region. The mitral prosthesis can then be attached to the Dacron patch superiorly.⁶⁰ The conduction tissue is located at the anteroinferior aspect of the left AV valve annulus. The native AV valve leaflet tissue should be preserved in that location and not excised. Sutures can be passed through these native leaflets rather than through the mitral annulus in that location to minimize the incidence of heart block. Care should also be taken to avoid injury to the left circumflex coronary artery, which can be surprisingly close in small patients.

Outcomes after surgical management of recurrent MR are inferior to those reported after initial AV canal defects. In a study from our institution representing the largest series to date, 46 patients underwent reoperation between 1988 and 1998 for recurrent hemodynamically significant MR.⁴⁹ Survival at 10 years was 86.6%. Three of nine patients undergoing mitral valve replacement developed complete heart block. Significant improvements in clinical status were present after mitral valve surgery. Overall freedom from reoperation at 5 years was 78.5% for mitral valve repair and 85.7% for mitral valve replacement.

POSTOPERATIVE CARE

Postoperative management of patients after repair of complete AV canal defects is similar to the management of other patients after complex cardiac surgery. Intraoperative confirmation of complete closure of the VSD and ASD should be obtained. Our preference is to use measurements of right atrial and pulmonary artery oxygen saturations to detect residual left-to-right shunts. An increase in oxygen saturation greater than 10 mm Hg or an absolute pulmonary artery oxygen saturation greater than 80% while on 50% inspired oxygen suggests the presence of a hemodynamically significant residual VSD (i.e., ratio of pulmonary blood flow [Qp] to systemic blood flow [Qs], or Qp/Qs > 1.5). This should prompt intraoperative confirmation by echocardiography before a return to cardiopulmonary bypass and closure of the residual VSD.

Intraoperative transesophageal echocardiogram (TEE) is highly recommended for patients weighing more than 5 kg. TEE can be performed in patients as small as 2.5 kg, albeit with a higher risk of esophageal trauma and perforation coupled with a higher probability of left atrial compression by the posteriorly positioned TEE probe, which raises left atrial pressure. TEE is especially useful in evaluating AV valve function, particularly if significant MR is suspected. Monitoring left atrial and pulmonary artery pressures aids in the postoperative care of these patients, especially when preoperative pulmonary hypertension is present.

Low cardiac output state should be judiciously managed by aggressive use of inotropic support rather

than volume resuscitation, because excessive volume infusion can lead to ventricular distention and valvar dilation, resulting in worsening MR. The atrial filling pressures should be kept low, not significantly higher than 10 mm Hg, especially in the first 24 hours postoperatively. Use of afterload reduction, particularly with phosphodiesterase inhibitors such as milrinone, is particularly valuable in the early postoperative period. An aggressive search should be undertaken to exclude anatomic causes of low cardiac output syndrome.

Early postoperative pulmonary hypertension can be seen in patients with complete AV canal defects, and it is more prevalent with increasing age at the time of definitive repair and correlates with surgical mortality. Patients with Down syndrome usually have increased pulmonary artery pressure and increased pulmonary vascular resistance in the perioperative period.⁶¹ The insertion of a pulmonary artery line at the time of surgery aids in making the diagnosis. Anatomic causes that mimic pulmonary hypertension need to be excluded, such as severe MR, severe mitral stenosis, and residual VSD. Echocardiography is helpful in differentiating anatomic from nonanatomic causes of postoperative pulmonary hypertension.

OUTCOMES

Between January 1990 and December 1998, 365 patients with various forms of AV canal defects underwent two-ventricle repair at Children's Hospital Boston.⁶² Of these, 191 had a complete AV canal defect in which the VSD was deemed at least moderate in size and required patch closure. Among these 365 patients, 19 had associated TOF (5%) and 140 had either an ostium primum ASD alone or a transitional AV canal defect. Five patients had associated coarctation of the aorta, and seven had preoperative LVOTO. Trivial to mild AV valve regurgitation was present preoperatively in 159 patients (83%), and 26 (13%) had moderate to severe AV valve regurgitation. Of the patients with complete AV canal defects, 11% had at least moderate hypoplasia of one ventricle, 4% had a dominant left ventricle, and 7% had a dominant right ventricle.

The classic one-patch technique was used in 83% of the children with complete AV canal defects; the remaining 16% were repaired using the two-patch technique, depending on surgeon preference. The median age at repair was 4.6 months, and median weight was 4.5 kg.

In the 191 patients with complete AV canal defects undergoing biventricular repair, there were three early deaths, for an operative mortality of 1.5%. Three patients had complete heart block postoperatively, which required pacemaker insertion during the initial hospitalization. Trivial to mild MR was present on postoperative echocardiographic follow-up in 66% of the patients, whereas 10% had at least moderate MR at the time of discharge. There was no correlation between the presence of MR preoperatively and its presence postoperatively.

A review of 215 patients from the Pediatric Heart Network study examined outcomes and risk factors for development of MR across the various types of AV canal

repairs.⁶³ This study included 60 patients with partial AV canal, 27 with transitional AV canal, 120 with complete AV canal, and 8 with canal-type VSD. Independent risk factors for moderate to severe MR at 6 months after surgery included older age at repair and presence of moderate or greater MR on the immediate postoperative echo. This study did not show any significant benefits of annuloplasty performed at time of original repair.

Complete Atrioventricular Canal Defect

Several factors have contributed to decreasing mortality for repair of complete AV canal defects over the past two decades. Mortality ranges between 0.5% and 13% in various studies.^{27,64,65} Risk factors that affect overall survival and the need for reoperation include the following:

- *Earlier era of operation:* This has been a consistent risk factor for both early death and late reoperation in a variety of studies.^{19,65-67} Improvements in myocardial preservation, intraoperative anesthetic management, perfusion methods, intraoperative TEE, postoperative care, and better understanding of lesion anatomy, along with better surgical techniques, have contributed to decreasing mortality over time.
- *Older age at surgery:* Repair beyond age 3 to 4 months has been correlated with increased perioperative mortality.^{31,55} This may be related to the higher incidence of pulmonary hypertensive crises seen with increasing patient age at the time of definitive surgery.⁶⁸ Postoperative pulmonary hypertensive crises have been correlated with increased operative mortality and need for reoperation.^{27,66} Increasing age as a risk factor for mortality has not been shown to be the case in all studies.^{67,69} In fact, in one study of 274 patients, repair at less than 6 months of age was an incremental risk factor for perioperative mortality.⁶⁷
- *Postoperative left AV valve regurgitation:* This has been identified in most series to be a key risk factor for the subsequent need for reoperation^{56,66,70,71} and death.^{19,66} The overall incidence of significant postoperative MR has slowly decreased over the years as surgical techniques have improved and a better understanding of the underlying anatomy has evolved. A review from our institution revealed a reoperation rate of 7% in recent years.¹⁹ Other contemporary series have noted an incidence of 16% for at least moderate postoperative MR.⁷²
- *Preoperative AV valve regurgitation:* A higher incidence of postoperative MR is seen in patients with higher degrees of preoperative AV valve regurgitation.⁷² Leaflet division may exacerbate this association.⁷² This has not been a consistent finding, with one recent study of 115 patients reporting that moderate to severe preoperative left AV valve regurgitation, present in 21 patients, was not a risk factor for operative mortality.⁶⁵ In the same study, moderate or severe late MR was present in 17% of patients with mild or less preoperative left AV valve regurgitation compared with 33% of patients with

moderate or severe preoperative left AV valve regurgitation, although this difference was not statistically significant. An earlier study of 62 infants operated on before 1987 also failed to show the correlation between preoperative and postoperative MR.²⁸

- *Double-orifice mitral valve:* This adversely affects both survival and freedom from reoperation. It may be associated with unbalanced AV canal with RV dominance, a single papillary muscle, LVOTO, and aortic coarctation. If the cleft is closed completely, postoperative mitral stenosis can result. Some have recommended leaving a fenestration in the interatrial septum to allow decompression of the left atrium as needed.⁵⁶

Partial Atrioventricular Canal Defect

The operative mortality for partial AV canal defects is low—less than 1% in most series. A small subset of patients display heart failure symptoms and several left-sided obstructive lesions within the first year of life.³³ These patients represent a higher-risk subgroup. In a study of 180 patients repaired between 1982 and 1996,⁵³ early mortality was 1.6%. The mean age at repair was 4.6 years; repair at less than 1 year of age was a significant risk factor for mortality. With a mean follow-up period of 6 years, 10-year actuarial survival was 98%. Important long-term sequelae were the development of late MR and subaortic obstruction.

Similar findings were reported in 2000 in the largest series to date of patients with ostium primum ASD.⁷³ A total of 334 patients who underwent repair over a 40-year period between 1955 and 1995 were studied, with a median follow-up period of 19 years. The 30-day perioperative mortality was 2%, whereas 20- and 40-year survival rates were 87% and 76%, respectively. Although this long-term survival was good, it was lower than that for the general population. Reoperation occurred in 11% of patients, most commonly for mitral stenosis or MR. LVOTO occurred in 11% of patients ($n = 36$), although only seven patients required reoperation. Postoperative supraventricular arrhythmias were common, especially in older patients. Although the study was descriptive, with important limitations with respect to data collection and analysis, it does provide long-term insight regarding outcomes in these patients.

Late MR, although rare, correlates with late morbidity, similar to the situation for complete AV canal defects. In partial AV canal defects, the incidence of significant MR requiring reoperation ranges between 7% and 10%, depending on the study and the length of follow-up.⁷⁴ This may be correlated with a more frequent need for valve replacement than in complete AV canal defects,^{74,75} possibly related to the fixation of the superior leaflet to the crest of the interventricular septum and the association of subvalvar abnormalities.

SUMMARY

Atrioventricular canal defects represent a continuum of lesions with varying degrees of AV valvar abnormalities

and interatrial and interventricular communications. In complete AV canal defects, complete elective repair should be performed early in infancy, preferably between 2 and 4 months of age. Equivalent results have been obtained with the three standard techniques of repair. Surgical intervention results in low mortality and morbidity, in both the short and the long term. When congestive heart failure or moderate to severe MR is present, complete repair should be undertaken at the time of presentation, because further delay or use of palliative procedures only increases the risks of subsequent definitive surgical therapy.

Surgical management of transitional and partial AV canal defects should include elective repair in early childhood. When left AV valve regurgitation is significant, repair should be undertaken earlier to prevent further deterioration of valve function and LV dilation and dysfunction.

Associated cardiac surgical lesions should be repaired at the time of complete AV canal repair. A remaining management dilemma is the patient with unbalanced AV canal defect, where surgical options include biventricular correction versus univentricular palliation.

Outcomes of patients with complete AV canal defects have improved steadily over the years. This reflects not only better intraoperative management, but also improved preoperative and postoperative care and follow-up in these patients.

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VENTRICULAR SEPTAL DEFECT AND DOUBLE-OUTLET RIGHT VENTRICLE

Emile A. Bacha

CHAPTER OUTLINE

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VENTRICULAR SEPTAL DEFECT

A ventricular septal defect (VSD) is a hole between the left and right ventricles. A VSD may occur as an isolated anomaly or with a wide variety of intracardiac anomalies, such as tetralogy of Fallot or transposition of the great arteries. This chapter discusses isolated VSD.

Banding of the pulmonary artery as a palliative maneuver was first described in 1952.¹ This decreased left-to-right shunting and as a consequence prevented the development of pulmonary vascular obstructive disease and left-sided volume overload. Until the mid-1960s when primary VSD closure became safer, pulmonary artery banding was the procedure of choice in managing VSDs. The first VSD closure was performed in 1955 by Lillehei and associates² at the University of Minnesota, using

controlled cross-circulation between the child and parent. Nineteen of the 27 patients who underwent this procedure survived. In 1957, Kirklin and associates³ at the Mayo Clinic closed a VSD using a heart-lung machine. In 1957, transatrial VSD closure was performed,⁴ followed in 1971 by the popularization of primary repair in symptomatic infants by Barratt-Boyes and associates⁵ using cardiopulmonary bypass, deep hypothermia, and circulatory arrest.

Anatomy

Anatomy of the Tricuspid Valve, Right Ventricular Septum, and Conduction System

Surgeons planning VSD surgery must have intimate knowledge of the tricuspid valve, the right ventricular septal anatomy, and the conduction system.

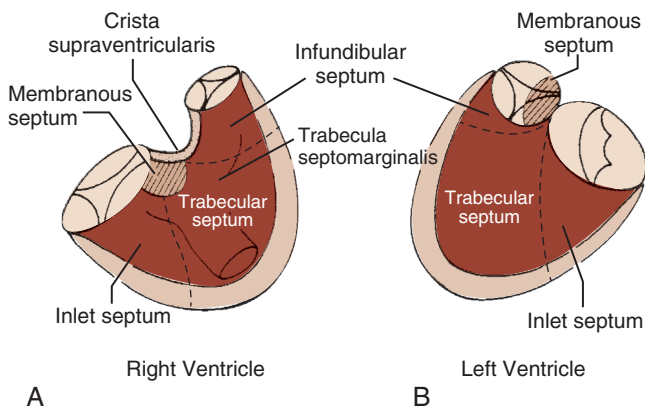


FIGURE 117-1 ■ The components of the ventricular septum as seen from the right ventricle (A) and the left ventricle (B). (Modified from Soto B, Becker AE, Moulart AJ, et al: Classification of ventricular septal defects. *Br Heart J* 43:332–343, 1980.)

The tricuspid valve has three leaflets: anterior, septal, and posterior. The anterior leaflet is connected via the chordae tendineae cordis to the anterior papillary muscle (located on the anterior right ventricular free wall) and to the septal papillary muscle (sometimes called muscle of Lancisi). The septal papillary muscle is itself part of the septal band of the septomarginal trabecula. The posterior leaflet is attached to the anterior and posterior papillary muscles, and the septal leaflet attaches to the posterior and septal papillary muscles.

The right ventricular septum has five components (Fig. 117-1):

1. The membranous septum
2. The atrioventricular (AV) canal or inlet septum
3. The muscular septum (apical trabecular septum or sinus septum)
4. The trabecula septomarginalis (septal band and moderator band)
5. The conal septum (infundibular septum and parietal band)

Unlike the left ventricular septum, which is free of any papillary muscle attachment (the mitral valve can be called “septophobic,” whereas the tricuspid valve can be called “septophilic”), the right ventricular septum is where the septal (sometimes called medial) papillary muscle and part of the posterior papillary muscle originate. The septal papillary muscle is a portion of the septal band, which runs along the septum (hence its name). The septal band is a portion of the septomarginal trabecula, which also includes the moderator band. The moderator band links the septum to the anterior papillary muscle (called moderator band because it was erroneously thought to “moderate” the right ventricular free wall—that is, keep in sync with the rest of the ventricle). The membranous septum is the only fibrous component of the septum. It is wedged between the aortic valve, the tricuspid valve, and the mitral valve. Because the tricuspid valve is normally apically displaced vis-à-vis the mitral valve, a portion of membranous septum ends up between the right atrium and the left ventricle, called the AV part of the membranous septum. The portion of membranous septum located between both ventricles is called the interventricular part.

Knowledge of the conduction system of the heart also is critical when approaching VSDs so as to avoid damaging it (Fig. 117-2). The various atrial conduction tracts all converge toward the AV node of Aschoff-Tawara. The AV node is located in the inferior-posterior portion of the membranous septum, just inferior to the antero-septal commissure of the tricuspid valve. A different description of its location is that it occupies the apex of the triangle of Koch, which is limited by the ligament of Todaro posteriorly, the orifice of the coronary sinus inferiorly, and the tricuspid valve annulus superiorly (see Fig. 117-2). From the AV node, the common AV bundle of His descends within the interventricular part of the membranous septum (or, in the case of a membranous VSD, the posteroinferior rim of the VSD), traverses the septum, and then courses along the left ventricular aspect of the septum. It then separates into a right bundle branch, which travels back to the right ventricular surface, as well as a left bundle branch. At the anteroinferior border at the level of the muscle of Lancisi, the right bundle branch descends toward the right ventricular apex.

Anatomic Classification of Ventricular Septal Defects

A useful surgical classification of VSDs was initially developed in 1980 by Soto and associates⁶ (Fig. 117-3) and then further modified by Van Praagh and associates (Fig. 117-4).⁷ Variations of this classification are used in most pediatric cardiac centers. VSDs can be classified as follows:

- Conoventricular (or membranous) defects
- Conal (or outlet) VSDs
- Inlet (or AV canal type) VSDs
- Muscular VSDs (single or multiple)

Conoventricular (or Membranous) Defects. Conoventricular defects are located between the conal septum and the ventricular septum. They are centered around the membranous septum and comprise 80% of all VSDs. They may be located exclusively in the membranous septum, or they can extend beyond the boundaries of the membranous septum in the inferior, posterior, or anterior direction and are then sometimes called perimembranous or paramembranous VSDs. The prefix *peri-*, appearing in loan words from the Greek, means “surrounding” (e.g., perimeter). Thus, a truly perimembranous VSD would surround the membranous septum. In contrast, the prefix *para-*, also from the Greek, means “adjacent to” or “beside” and more accurately reflects the notion of a defect adjacent to the membranous septum. Neither *perimembranous* nor *paramembranous* correctly describes the typical defect involving the membranous septum and extending into the adjacent septum. The current recommendation is to call these defects either membranous VSDs or conoventricular defects. Malalignment of the conal septal plane vis-à-vis the ventricular septal plane results in the typical conoventricular defect. The malalignment can be anterior, as seen in tetralogy of Fallot, for example, or posterior, as seen in interrupted aortic arch. In addition to resulting in a VSD, anterior conal septal malalignment also results in right

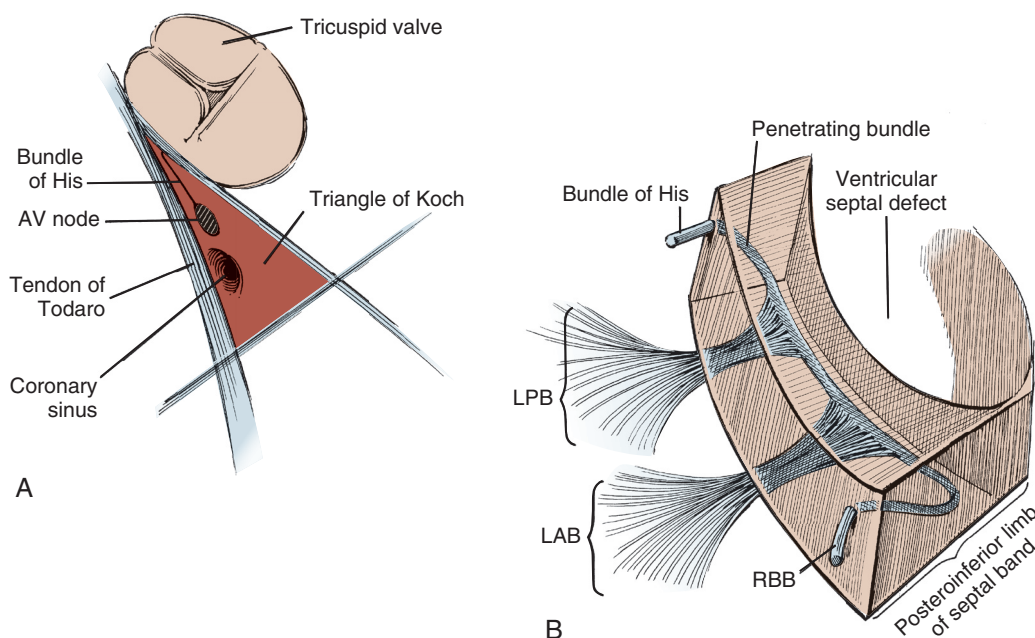


FIGURE 117-2 ■ Schematic representation of the conduction system. **A**, The atrioventricular (AV) node lies embedded within the triangle of Koch, close to the orifice of the coronary sinus and between the annulus of the tricuspid valve and the tendon of Todaro. The bundle of His originates from the AV node, extends toward the commissure between the septal and anterior leaflets of the tricuspid valve, and penetrates along the posteroinferior margin of the membranous septum and across the muscular ventricular septum. **B**, The bundle of His gives rise to the left posterior branch (LPB) and the left anterior branch (LAB). The right bundle branch (RBB) then travels back along the ventricular septum toward the right ventricular septal surface. At the level of the muscle of Lancisi, the right bundle branch descends toward the right ventricular apex. (Modified from Castaneda AR, Jonas RA, Mayer JE Jr, et al: Double outlet right ventricle. In Castaneda AR, Jonas RA, Mayer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, pp 445–449.)

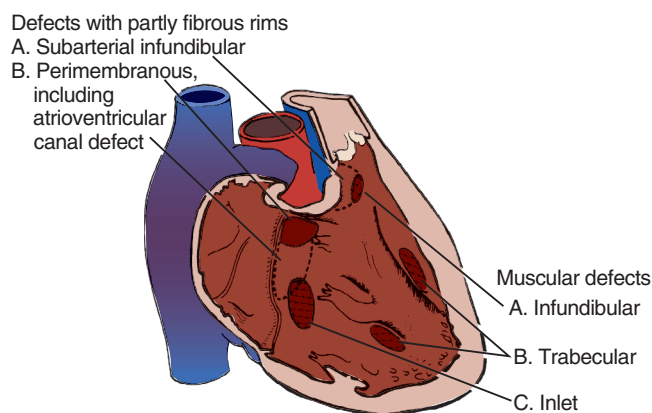


FIGURE 117-3 ■ Classification of ventricular septal defects according to their location in the septum. (Modified from Soto B, Becker AE, Moulart AJ, et al: Classification of ventricular septal defects. *Br Heart J* 43:332–343, 1980.)

ventricular outflow tract obstruction, whereas posterior malalignment of the conal septum results in left ventricular outflow tract obstruction. Important landmarks in conoventricular septal defects are the anterosseptal commissure of the tricuspid valve inferiorly and the noncoronary cusp of the aortic valve. When the ventricular portion of the membranous septum is entirely absent, the VSD extends to the base of the aortic valve (sometimes called subaortic VSD). The medial papillary muscle (muscle of Lancisi) located at the inferoposterior border

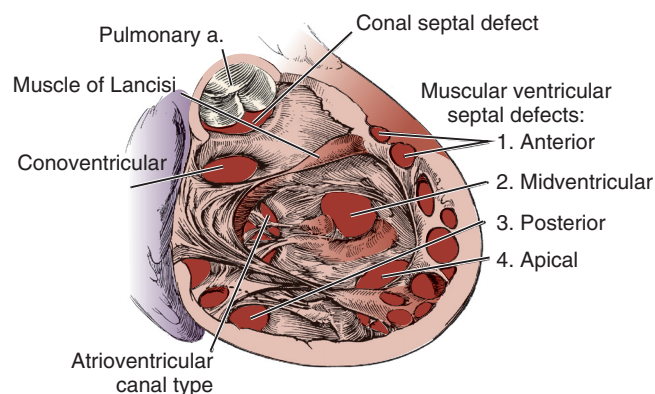


FIGURE 117-4 ■ Classification of ventricular septal defects (VSDs): atrioventricular canal type; muscular VSDs (anterior [1], midventricular [2], posterior [3], and apical [4]); conoventricular septal defect, which includes paramembranous and malalignment conoventricular septal defects; and conal septal defects. (Modified from Castaneda AR, Jonas RA, Mayer JE Jr, et al: Double outlet right ventricle. In Castaneda AR, Jonas RA, Mayer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, pp 445–449.)

of the defect is also an important landmark. Both the septal and the anterior tricuspid valve leaflets are attached to it.

Conal Ventricular Septal Defects. Approximately 8% of VSDs are located in the conal (infundibulum or outlet)

septum. They also are called supracristal VSDs. They are either entirely surrounded by muscle (muscular conal VSDs) or limited upstream by the aortic or pulmonary annuli (sometimes called subarterial VSDs).

Inlet (or Atrioventricular Canal Type) Ventricular Septal Defects. Inlet VSDs are characterized by the absence of part or all of the AV canal (inlet) septum. These VSDs are located immediately underneath the septal leaflet of the tricuspid valve, with no tissue in between. Approximately 6% of all VSDs are inlet-type VSDs.

Muscular Ventricular Septal Defects. Muscular VSDs (10% of all VSDs) are entirely surrounded by muscle. They can occur anywhere in the trabecular portion of the septum and can be isolated or multiple. They are described by their location—that is, anterior, midventricular (between the muscular septum and the septal band), posterior, or apical. When inspected through the left side of the septum, what appeared to be multiple muscular defects often converge into either a single hole or two separate holes.

Commonly Associated Defects

VSDs are an intrinsic portion of many, if not most, complex cardiac malformations. These VSDs are discussed separately with their respective entities (see other chapters). Almost half of patients who undergo surgical treatment of primary VSD have an associated lesion.

A large patent ductus arteriosus (PDA) is present in approximately 25% of symptomatic neonates and infants with VSDs.⁵ This is important to know because preoperative echocardiography may fail to show a PDA in the presence of a large amount of left-to-right shunting. Furthermore, intraoperative transesophageal echocardiography (TEE) is notoriously unreliable in excluding PDAs. Therefore the possibility of a PDA should be kept in mind when approaching a VSD, and if there is any doubt, or if there is a large amount of backflow through the pulmonary arteries on cardiopulmonary bypass, the PDA should be ligated or clipped.

A hemodynamically significant aortic coarctation is present in approximately 10% of cases. Because of the unique pathophysiology of aortic coarctation (more left-to-right shunting across the VSD because of increased afterload caused by the coarctation), these patients usually have presenting symptoms before 3 months of age.⁸

Congenital valvar or subvalvar aortic stenosis, resulting in left ventricular outflow tract obstruction, is seen in approximately 4% of patients requiring an operation for a VSD.⁹ The most common type of subaortic stenosis associated with VSDs involves the discrete fibromuscular membrane of the VSD that is located inferior or upstream to it. Congenital mitral valve stenosis is rare and occurs in approximately 2% of patients.

Other significant anomalies include large atrial septal defects (ASDs), right ventricular outflow tract obstruction, vascular ring, and persistent left superior vena cava.

Pathophysiology

Shunt Direction and Magnitude

The magnitude and direction of the shunt across a VSD depend on the size of the defect and the pressure gradient across it during the various phases of the cardiac cycle. Large VSDs offer little or no resistance to blood flow and are therefore called nonrestrictive. The right ventricular pressure equals the left ventricular pressure, and the ratio of pulmonary to systemic flow (Q_p/Q_s) (or shunt) is dependent on the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR). On the other hand, small VSDs offer resistance to flow across the defect and are therefore termed restrictive VSDs. The Q_p/Q_s rarely exceeds 1.5. Moderate-sized VSDs fall between these two categories and the Q_p/Q_s usually ranges between 2.5 and 3. To a lesser degree, further determinants of shunt magnitude also include the relative compliance of both ventricles and the pressure relationships during the various phases of the cardiac cycle. The size of the VSD—in particular, of muscular VSDs—also may vary during various phases of the cardiac cycle. Because the PVR is elevated during the first few weeks of life, it is unusual to have to close an isolated VSD. As the PVR falls with increasing age, left-to-right shunting increases, necessitating treatment.

Sequelae of Left-to-Right Shunting

Left-to-right shunting at the ventricular level implies increased pulmonary blood flow. Therefore, left ventricular preload is similarly increased, resulting in increased workload for both left and right ventricles. The left atrium is enlarged, and the left atrial pressure is elevated. The left ventricle dilates. The raised left atrial pressure causes many infants with VSD to have an increased accumulation of interstitial fluid in the lungs, resulting sometimes in repeated pulmonary infections. The work of breathing is increased as the lung compliance is decreased. This increases energy expenditure, which, along with the relatively low systemic blood flow, causes these infants to have striking failure to thrive. When pulmonary resistance rises as a result of the development of pulmonary vascular disease, pulmonary blood flow is reduced and the child appears to improve. Unfortunately, further increases in PVR occur, and the classic Eisenmenger complex results. These patients are characterized by fixed pulmonary hypertension, bidirectional shunting, right ventricular hypertrophy, and a normal-sized left ventricle. They are often inoperable and require heart-lung transplantation for further survival.

Pulmonary Vascular Disease

The classic description of the pathology of hypertensive pulmonary vascular disease is that of Heath and Edwards.¹⁰ They correlated the PVR of patients with large VSDs with the histologic severity of pulmonary vascular changes. Grade 1 changes were defined as medial hypertrophy without intimal proliferation; grade 2 as medial hypertrophy with cellular intimal reaction; grade 3 as

intimal fibrosis and medial hypertrophy; grade 4 as generalized vascular dilation, an area of vascular occlusion by intimal fibrosis, and plexiform lesions; grade 5 as other "dilation lesions" such as cavernous and angiomatoid lesions; and grade 6 as necrotizing arteritis. It is assumed that Heath-Edwards grade 3 or greater is not reversible. The importance of lung biopsies has decreased over the years, with catheterization-based data increasing in importance in terms of suitability for repair.

Natural History and Indications for Surgery

Approximately 30% of infants with severe symptoms such as intractable congestive heart failure or failure to thrive require surgery within the first year of life.¹¹ The remainder can usually be managed medically, because the natural history of VSDs is well known.¹² Aggressive medical management is indicated because most membranous and muscular VSDs tend to close spontaneously.¹² Malalignment conoventricular VSDs or inlet-type VSDs are unlikely to close spontaneously, and therefore closure at the time of diagnosis is recommended, regardless of age or weight. Asymptomatic children with isolated small restrictive VSDs can be followed safely with serial echocardiograms.

The development of pulmonary vascular disease is a tragedy that can be prevented with virtually no mortality by VSD closure. If in doubt, cardiac catheterization and measurement of PVR-to-SVR ratio should help with decision making. In addition, pulmonary artery (PA) pressures greater than one half the systemic pressure in a child older than 1 year indicate the need for surgery. If PA pressures are greater than one half the systemic, the response of the pulmonary vasculature to inhaled nitric oxide and 100% inspired oxygen should be studied during catheterization. Even children who have significant pulmonary hypertension with a reversible component to it can become operative candidates.

During the first decade of life, a small proportion (5%) of patients with membranous or outlet VSDs develop prolapse of an aortic cusp into the VSD. This usually results in a gradual decrease of the effective orifice and shunt flow and also in increasing aortic regurgitation. Increasing aortic cusp prolapse and regurgitation are an indication to operate.

Diagnosis and Workup

Results of the physical examination, chest radiograph, and electrocardiogram (ECG) depend on the underlying pathophysiology. Patients with large VSDs and increased pulmonary blood flow usually have symptoms such as tachypnea, growth failure, profuse sweating during feeding, a bulging precordium, a pansystolic murmur, an enlarged liver, and thready pulses. The chest film shows a large central and peripheral PA and enlarged left atrium and ventricles (Fig. 117-5). ECG shows signs of biventricular enlargement. In contrast, patients with small VSDs and small left-to-right shunts have only a systolic murmur. The chest radiograph and ECG may be entirely normal (Fig. 117-6). Two-dimensional echocardiography

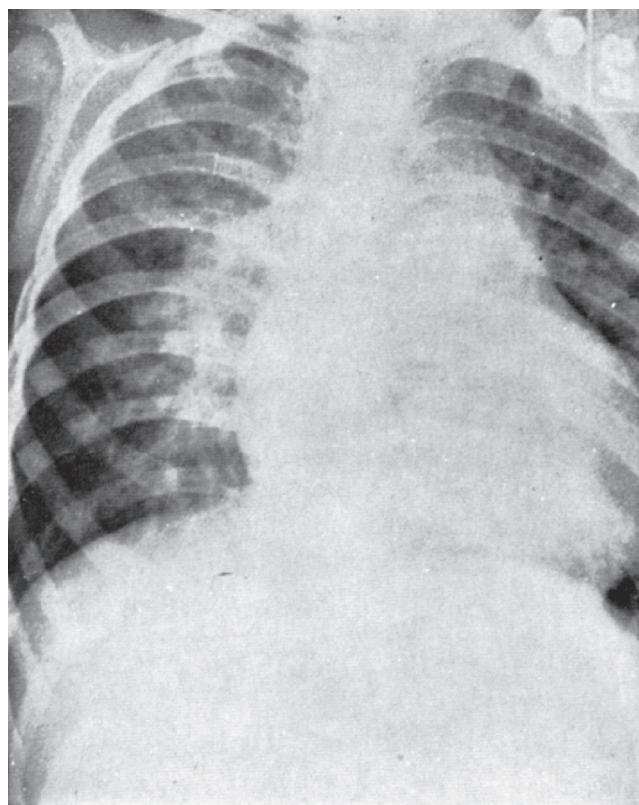


FIGURE 117-5 ■ Chest radiograph of a child with a large ventricular septal defect, large pulmonary blood flow, and pulmonary hypertension, but only mildly elevated pulmonary vascular resistance, as indicated by left and right ventricular enlargement, enlargement of the main pulmonary artery, and a sharp increase in pulmonary vascular pattern.

and color flow Doppler studies have essentially replaced cardiac catheterization in most patients with isolated VSDs. Cardiac catheterization is needed only when PVR and PA pressure need to be measured.

Surgical Technique

For closure of conoventricular septal defects, the PDA is routinely dissected and ligated as soon as cardiopulmonary bypass is instituted. The left branch PA and distal aortic arch should be positively identified before ligation. Moderate hypothermia (rectal temperature, 28° C to 32° C) is usually sufficient. Small infants weighing less than 2.5 kg may require lower temperatures (18° C to 25° C) to safely institute low-flow bypass. Deep hypothermic circulatory arrest is rarely used for closure of VSDs. After cross-clamping the aorta and delivering the cardioplegia solution, the caval tapes are tightened. A right atriotomy approach is preferred for most VSDs. The atrium is opened obliquely (Fig. 117-7) to avoid the area of the sinus node. The atrial septum is inspected first, and if a patent foramen ovale (PFO) is present, a left atrial sucker can be placed. Retraction of the septal and anterior leaflets of the tricuspid valve usually provides adequate exposure. The area located behind the antero-septal commissure of the tricuspid valve often is the most difficult to expose. If the tricuspid valve attachments are in

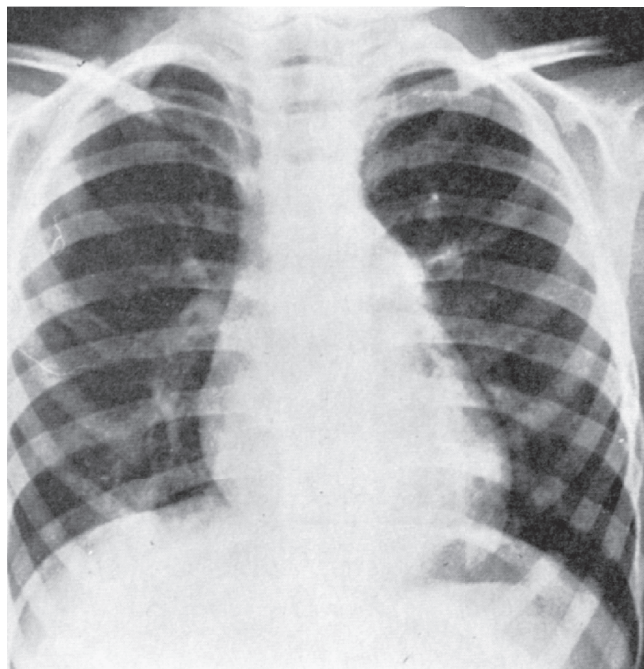


FIGURE 117-6 ■ In contrast to the heart shown in Figure 117-5, the heart in this chest radiograph is not enlarged overall. The main pulmonary artery is enlarged, but there is no evidence of increased pulmonary blood flow. This patient has a large ventricular septal defect, pulmonary hypertension, severe elevation of pulmonary vascular resistance, and pulmonary blood flow that is less than systemic blood flow. The condition is inoperable and usually requires a heart-lung transplant or a lung transplantation with concomitant intracardiac repair. (Modified from Dushane JW, Kirklin JW: Selection for surgery of patients with ventricular septal defects and pulmonary hypertension. *Circulation* 21:13, 1960; with permission of the American Heart Association, Inc.)

the way, the surgeon can detach the septal or anterior leaflet by making an incision that parallels the tricuspid annulus (see Fig. 117-7). Some surgeons perform this maneuver routinely. If VSD exposure remains poor despite rearranging the field, an infundibular incision is the usual fallback option for exposure. Interrupted mattress or running nonabsorbable sutures are used. Teflon pledgets are very useful in neonates and infants, in whom the myocardium is friable. The first suture is usually placed into the midportion of the defect, approximately 3 mm from the rim of the defect. When the inferior margin is reached (at approximately the level of the muscle of Lancisi), sutures should be placed farther away from the edge and become more superficial. At the tricuspid annulus, sutures are passed through its fibrous tissue. Because conduction tissue is composed of specialized muscle cells, fibrous tissue offers a safe area to place sutures. There is usually very little tissue separating the aortic valve from the posterosuperior margin of the defect. Therefore, several sutures are usually placed from the right atrial side through the tricuspid valve annulus to avoid damage to the aortic valve cusp. Infusion of cardioplegic solution fills the aortic root and allows accurate delineation of the insertion of the aortic valve cusps. All sutures are then passed through an appropriately tailored patch (Dacron, Gore-Tex, or pericardium) and tied in place. The tricuspid valve should be routinely inspected

and passively inflated with saline to ensure that no significant tricuspid valve regurgitation has been inadvertently created.

For closure of an AV canal type of VSD (Fig. 117-8), exposure is usually straightforward. A continuous suture technique is often preferred, because it allows weaving in and out between the various chordae and papillary muscles that usually crowd the edge of these defects. To avoid damage to the bundle of His and the right bundle branch that course along the posteroinferior edge, stitches in that area are placed farther away from the edge of the VSD.

For closure of conal VSDs (Fig. 117-9), exposure is obtained through the infundibulum, the pulmonary artery, or the aorta. Often no muscle lies between the superior edge of the defect and the pulmonary valve. Again, it can be useful to fill the aortic root with cardioplegic solution to determine the exact position of the cusps. The initial sutures are placed either within the fibrous rim separating the two semilunar valves or within the left and right pulmonary sinuses of Valsalva. The remaining sutures can be placed with no fear of injury to the conduction tissue as it travels farther caudally between the infundibular and trabecular ventricular septum.

The approach used in closure of muscular VSDs depends on their location. Mid-muscular defects are preferably closed through a right atriotomy. A single patch can cover several separate defects. Posterior muscular defects are hidden behind the posterior leaflet of the tricuspid valve. Anterior muscular defects are often difficult to find, because they are hidden behind the septal band and hypertrophied trabeculae of the right ventricular free wall. It is important to divide the muscle bundles that bind the septal band to the septum to adequately expose the true margins of the VSD. A patch is used, and the surgeon must pay close attention to avoid distortion of the left anterior descending coronary artery. Apical defects can also be difficult to expose. The coarse trabeculations located in the right ventricular apex make the exact determination of the true margins difficult. An apical right ventriculotomy is extremely helpful and virtually always allows good exposure of the apical muscular septum. Left ventricular apical incisions are essentially obsolete because of the high prevalence of left ventricular dyskinesia and apical aneurysms after this incision. Percutaneous transcatheter closure of muscular VSDs with occluding devices is another approach for patients with apical VSDs or multiple muscular VSDs. When the percutaneous approach is not possible, intraoperative deployment of a device on the beating heart via a right ventricular puncture can be used.¹³

Surgical Management of Ventricular Septal Defect with Associated Anomalies

The vast majority of patients who have VSD with coarctation of the aorta are young infants. The traditional approach has been to simultaneously repair the coarctation and band the pulmonary artery. This evolved into aortic coarctation repair followed by VSD repair during the same hospitalization, if symptoms of heart failure persisted, in the form of failure to extubate, for example.

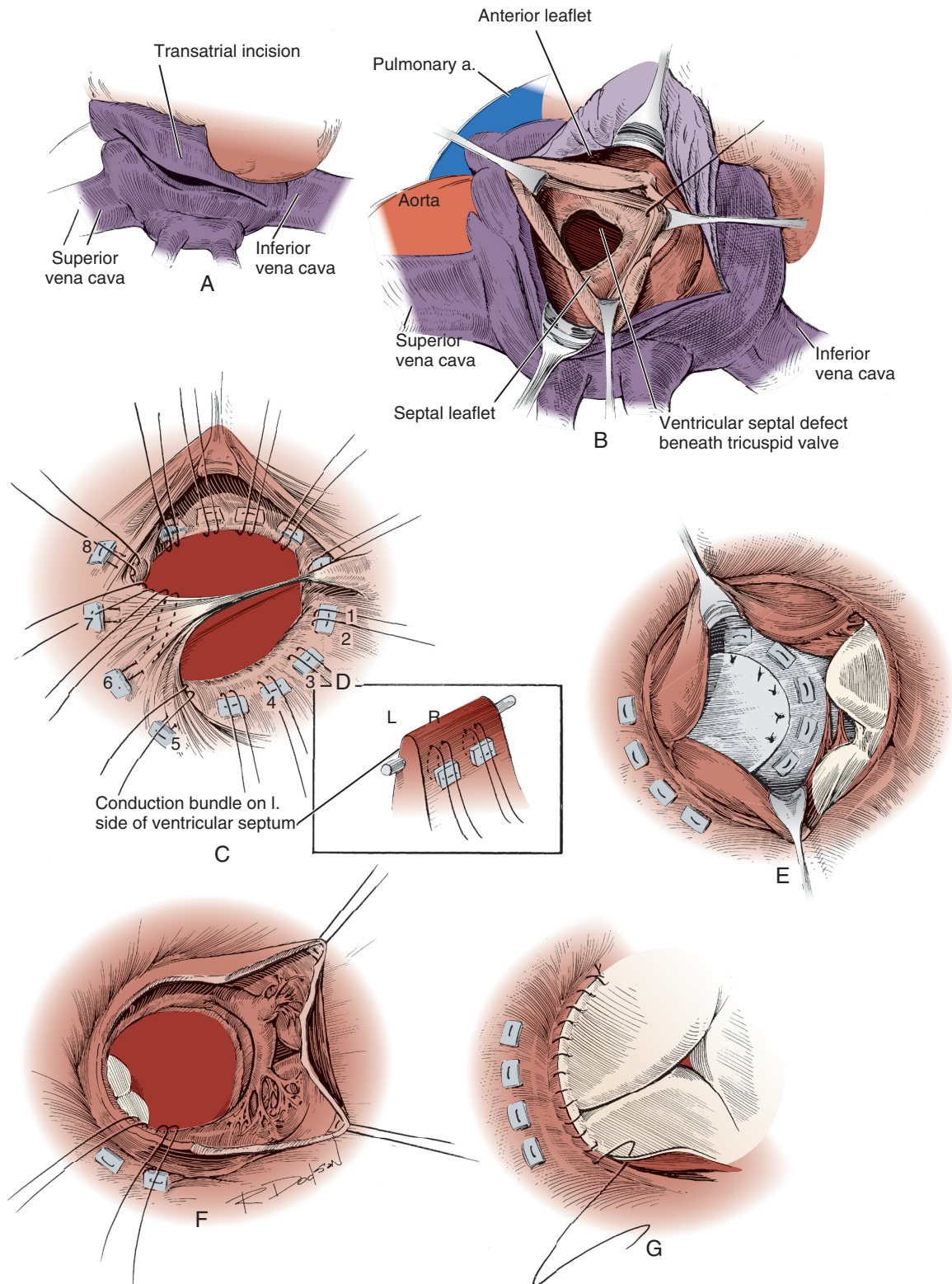


FIGURE 117-7 ■ Trans-right atrial exposure of conoventricular ventricular septal defect (VSD). **A**, Incision in the right atrium. **B**, Exposure of conoventricular VSD with retraction of the anterior and septal leaflets of the tricuspid valve. **C**, Sutures 1, 2, 3, and 4 are placed in the ventricular septal wall, approximately 3 mm from the rim of the defect. **D**, Suture 5 is placed where the leaflet fuses with the crest of the VSD, and sutures 6, 7, and 8 are passed from the right atrial side through the tricuspid annulus; the rest of the sutures are placed in the anterosuperior rim of the VSD. **E**, Completed closure of the VSD with a Dacron patch and pledgeted sutures. **F**, If chordae and papillary muscles obliterate the view of the VSD, the septal and anterior leaflets of the tricuspid valve are incised along the base, permitting complete exposure of the VSD. **G**, Septal and anterior leaflets of the tricuspid valve are resutured after closure of the VSD with a patch. (Modified from Castaneda AR, Jonas RA, Mayer JE Jr, et al: Double outlet right ventricle. In Castaneda AR, Jonas RA, Mayer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, pp 445–449.)

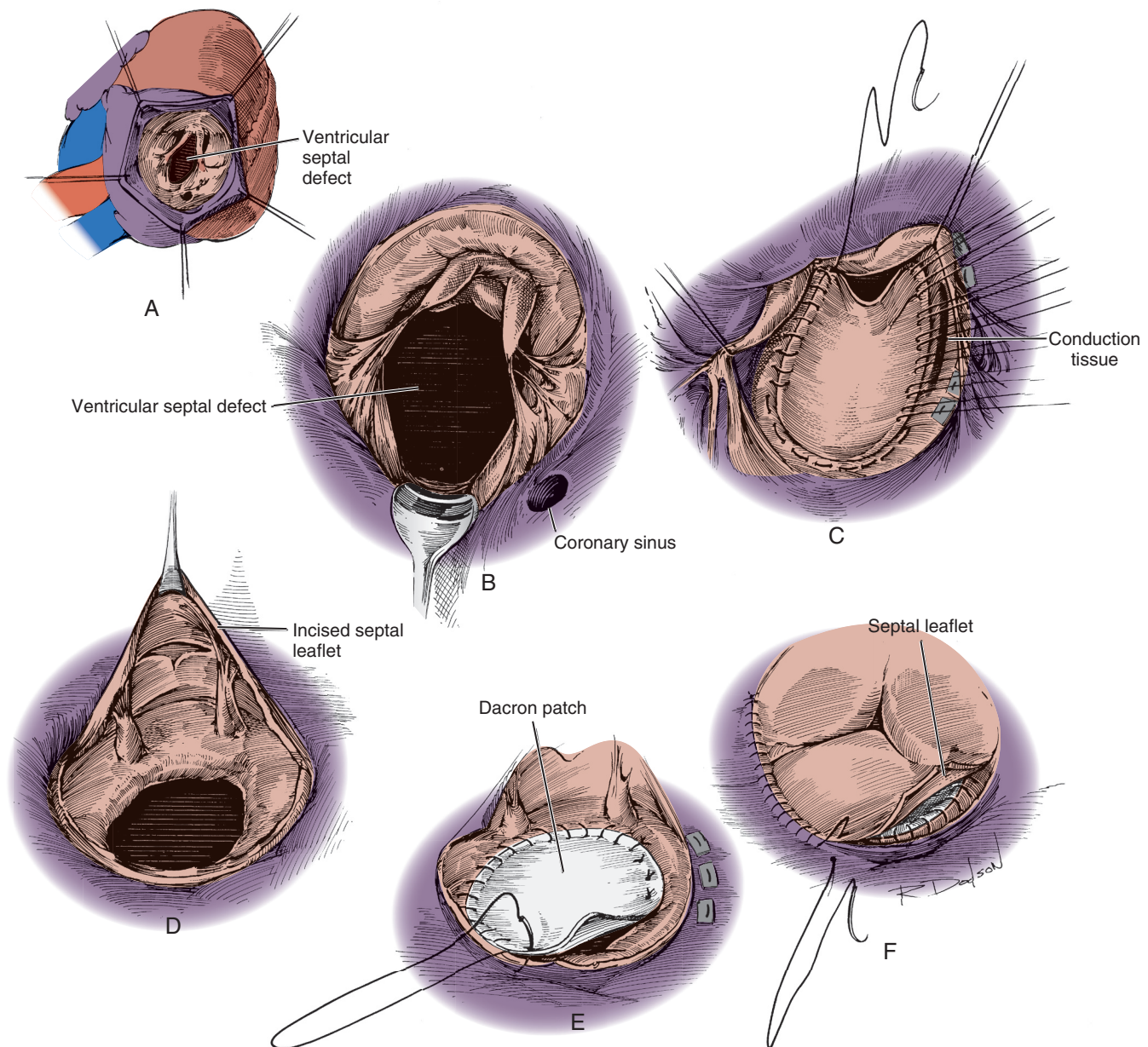


FIGURE 117-8 ■ Closure of atrioventricular (AV) canal type of ventricular septal defect (VSD). **A**, Transatrial view of AV canal type of VSD. **B**, Retraction of the septal leaflet of the tricuspid valve exposes the defect to the tricuspid valve annulus. **C**, Closure of AV canal defect with the continuous suture technique. (Note the continuous horizontal mattress suture with the septal leaflet tissue and also the interrupted horizontal mattress sutures along the posteroinferior portion of the VSD, placed approximately 4 mm from the VSD to avoid damage of the conduction bundle.) **D**, If dense chordae obstruct the view of the defect, the septal leaflet of the tricuspid valve is incised along its base, providing exposure of the entire circumference of the AV canal type of VSD. **E**, Patch closure of the AV canal type of VSD. **F**, The incised leaflet is reattached with continuous suture. (Modified from Castaneda AR, Jonas RA, Mayer JE Jr, et al: Double outlet right ventricle. In Castaneda AR, Jonas RA, Mayer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, pp 445–449.)

As techniques for complex neonatal repairs matured and results improved, many centers have come to favor a single-stage method of simultaneously repairing the coarctation and the VSD via a midline approach.⁸ Of course, this is done only if the VSD is judged not likely to close spontaneously, whether by size or location.

Patients who have VSD with aortic insufficiency are usually older children. The right or noncoronary cusp is prolapsing into the VSD secondary to the Bernoulli effect. When there is mild to mild-moderate aortic

regurgitation with little scarring or fibrosis of the cusps, VSD closure alone is required. Patients with more than moderate aortic incompetence and cusp retraction usually require commissural resuspension of the affected cusp via an aortotomy (see [Chapter 123](#)).

Patients with VSD with prior banding are most often those with multiple muscular VSDs. The resulting right ventricular hypertrophy makes the intraoperative identification of these VSDs even more difficult. Intraoperative device closure via right ventricular puncture has been

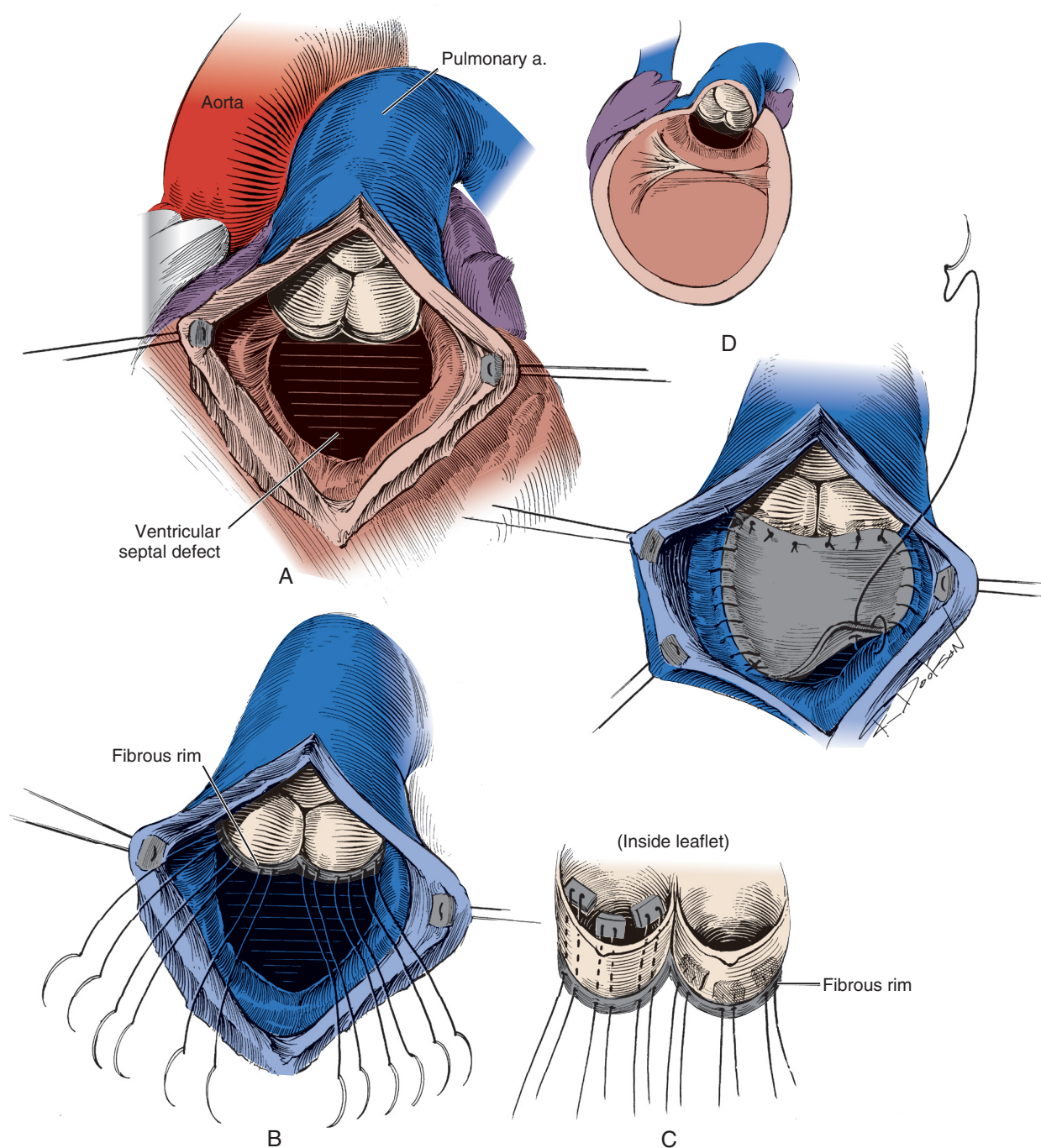


FIGURE 117-9 ■ Transventricular approach to closure of conal ventricular septal defect. **A**, Commonly there is no intervening muscle between the superior edge of the defect and the pulmonary valve. **B**, Initial sutures placed in the fibrous rim separating the two semilunar valves. **C**, If the area between the aorta and the pulmonary cusps is tenuous, interrupted pledgeted mattress sutures are passed within the right and left pulmonary sinuses. **D**, The Dacron patch is anchored to the remainder of the ventricular septal defect with a continuous suture. (Modified from Castaneda AR, Jonas RA, Mayer JE Jr, et al: Double outlet right ventricle. In Castaneda AR, Jonas RA, Mayer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, pp 445–449.)

used successfully, along with removal of the PA band and PA plasty in one setting.¹³

Postoperative Care

Most infants convalesce normally after VSD repair, and special treatment is usually not required. Patients are generally extubated within 24 hours of surgery and

recover rapidly. In the unusual case of low cardiac output after surgery despite the usual supportive treatment, it is the surgeon's responsibility to prove that there are no technical issues causing the unusual postoperative course. Problems could include a large residual VSD, injury to the aortic cusp that occurred during suture placement, or tricuspid regurgitation. Bedside echocardiography usually quickly diagnoses these problems. If

complete AV dissociation occurs after cardiopulmonary bypass, temporary pacing wires are used until sinus rhythm reappears. AV block can last up to 10 to 14 days, beyond which time it is usually permanent and a permanent pacemaker should be placed.

Pulmonary hypertensive crisis is a severe postoperative complication that can occur in older patients with a reactive pulmonary vasculature. If the patient is at risk, then, in the operating room, a pulmonary arterial line should be placed, introduced either via an infundibular puncture or under direct vision via the right atrium. A pulmonary hypertensive crisis can occur without a precipitating factor; however, tracheal suctioning, respiratory or metabolic acidosis, hypoxemia, and high-dose inotropes can be precipitating factors. Patients benefit from increased sedation, muscular paralysis, and hyperventilation with a high level of inspired oxygen. Inhaled nitric oxide, at dosages ranging from 5 to 40 ppm, is the preferred agent in managing pulmonary hypertension. Ideally, it is started prophylactically in the operating room as soon as ventilation resumes, while the patient is still on cardiopulmonary bypass.¹⁴

Results of Surgical Treatment

Early Results. Because of improvements in intraoperative and postoperative management and minimization of human error, the hospital mortality rate for repair of isolated VSD now approaches 0% in most experienced pediatric cardiac centers. Since the late 1980s, along with marked improvement in survival after complex neonatal cardiac surgery, very low-weight or very young infants with isolated VSDs also have a mortality rate of less than 5%.¹⁵ Prematurity, significant preexisting respiratory problems such as bronchopulmonary dysplasia, or unrecognized respiratory syncytial virus infection increases morbidity and mortality slightly but not significantly. In an operable patient, elevated PVR is a risk factor for complications or prolonged hospital stay, but it is not a determinant of hospital mortality. Unrecognized additional cardiac lesions can lead to significant problems if reoperation is required. Although complete AV dissociation is uncommon after isolated VSD repair, it remains a complication that occurs in 0.5% to 3% of patients after VSD closure. Right bundle branch block occurs in most patients after VSD closure and is usually very well tolerated. Its implications in the long term are unclear. Significant residual postoperative left-to-right shunting is uncommon when proper techniques are used. Most frequently it results from suture dehiscence, seen most often in small infants with friable myocardium. When it is hemodynamically significant, reoperation should be performed expeditiously. When the patient is asymptomatic and progressing well during the postoperative course, the leak is usually smaller, and the surgeon may elect to observe the patient with serial echocardiograms for a period of several weeks. Most small residual VSDs (<3 mm) close spontaneously over a period of months because of scar formation at the edge of the patch.

Late Results. Repair of VSD in the first year or two of life cures most patients and results in full functional

activity and normal or almost normal life expectancy. Normal or near-normal long-term growth and cardiac function are expected in most patients.¹⁶ Late deaths virtually never occur in patients with normal or near-normal PVR. Detailed studies of PA pressure and PVR were performed in infants undergoing VSD closure at the Boston Children's Hospital, where 96% of infants had a mean PA pressure of greater than 40 mm Hg, and 51% continued to have elevated PA pressures at 24 hours postoperatively. Postoperative catheterization studies done 1 year later showed that PA pressure in this group had decreased to a mean of 14 mm Hg.^{17,18} Severe pulmonary hypertension postoperatively can increase with time and cause premature death, usually within 3 to 10 years after the operation. Other patients with pulmonary hypertension have a stabilization of their pulmonary vascular process, with neither increase nor decrease of the PVR. They usually have limitations in their exercise tolerance. In a study of 296 surviving patients after VSD closure followed for 30 to 35 years postoperatively, higher mortality was observed in those who underwent surgery after the age of 5 years, in those with PVR greater than 7 U/m², and in those with transient or permanent complete heart block.¹⁹

DOUBLE-OUTLET RIGHT VENTRICLE WITH NORMALLY RELATED GREAT ARTERIES

Simply defined, double-outlet right ventricle (DORV) refers to a heterogeneous group of cardiac malformations in which both great arteries arise from the right ventricle.^{4,7} Although the term DORV can be correctly applied to single-ventricle hearts or hearts with AV discordance (e.g., congenitally corrected transposition of the great arteries), for simplicity of discussion, only hearts with AV concordance and two adequate ventricles are discussed in this chapter. Furthermore, the management of DORV with transposition of the great arteries is discussed in greater detail in [Chapter 126](#). Two definitions, not mutually exclusive and best used concurrently, are as follows^{17,20}: The 50% rule states that a heart is termed DORV if, in addition to the PA, more than 50% of the aorta (or the PA, in DORV with transposition) arises from the right ventricle. The other definition is that a double conus (subaortic and subpulmonary conal tube, also called infundibulum) is present. This means that there should be no aorta-to-mitral valve continuity.

Classification of DORV by VSD Location and Other Anatomic Determinants of Physiology

DORV is virtually always associated with a VSD. The physiology of DORV encompasses a spectrum that extends from a tetralogy type of DORV to a transposition type of DORV ([Fig. 117-10](#)). The classic pathologic classification of DORV centers on the location of the VSD²⁰ ([Fig. 117-11](#)) and differentiates between subaortic,

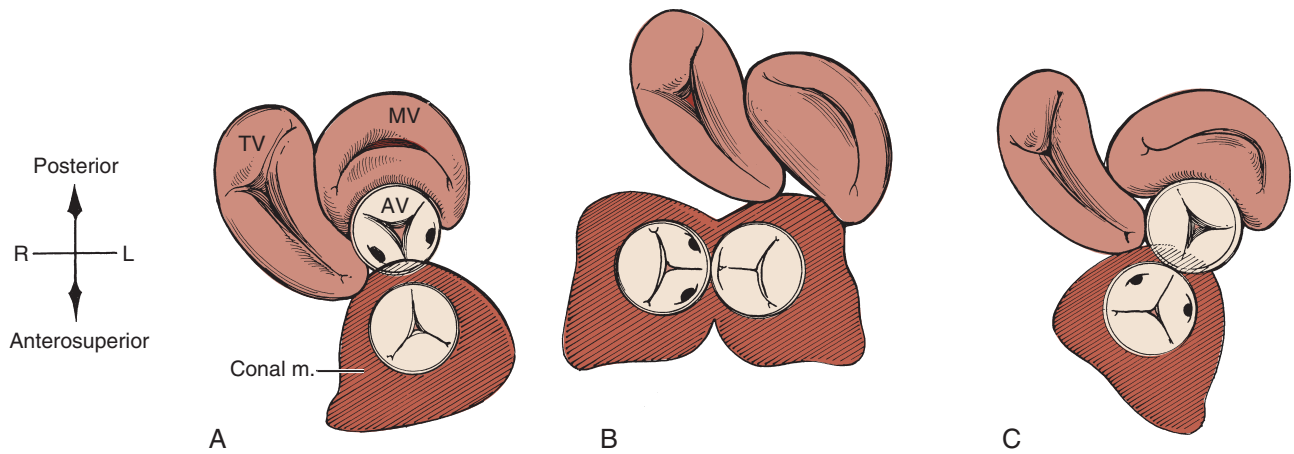


FIGURE 117-10 ■ The spectrum of conus development between the tetralogy and transposition ends of the double-outlet right ventricle (DORV). **A**, Tetralogy of Fallot. There is a subpulmonary conus with fibrous continuity between the aortic and mitral valve. **B**, The middle of the DORV spectrum. There are both subpulmonary and subaortic conus. **C**, Transposition of the great arteries. There is a subaortic conus with fibrous continuity between the pulmonary and mitral valves. In all diaphragms, the aortic valve is indicated by the coronary ostia, the tricuspid valve by three leaflets, and the mitral valve by two leaflets; *hatching* indicates conal myocardium. AV, Aortic valve; MV, mitral valve; TV, tricuspid valve. (Modified from Castaneda AR, Jonas RA, Mayer JE Jr, et al: Double outlet right ventricle. In Castaneda AR, Jonas RA, Mayer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, pp 445–449.)

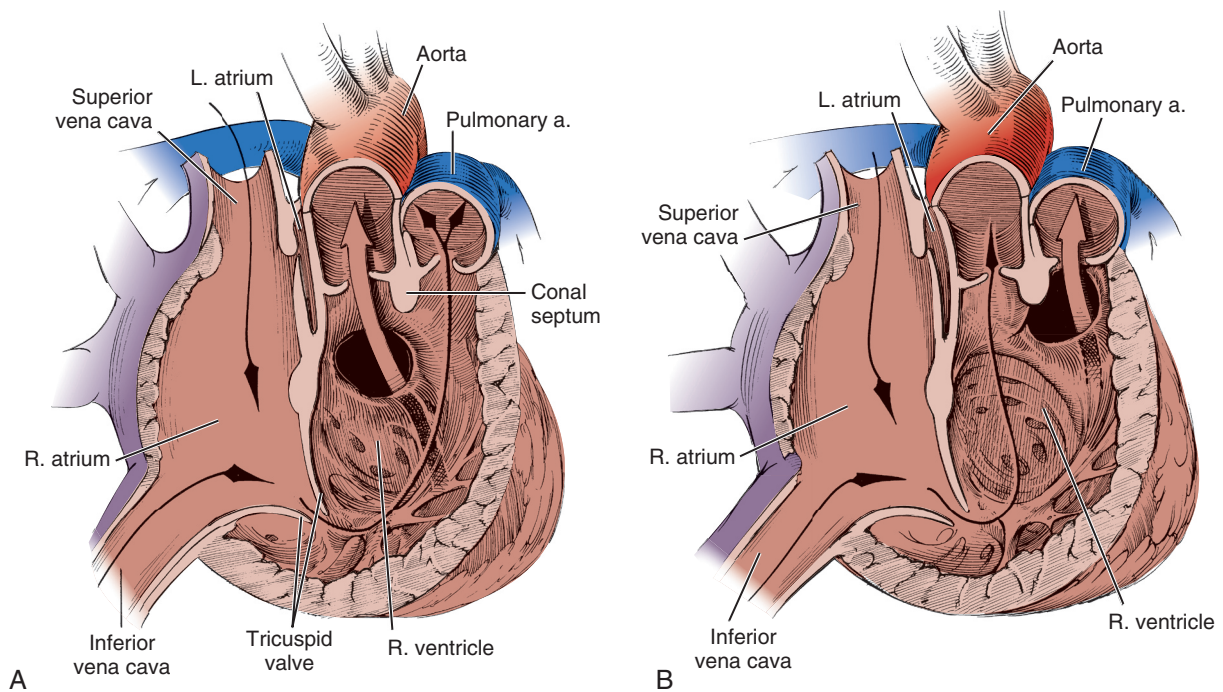


FIGURE 117-11 ■ **A**, Double-outlet right ventricle (DORV) with a subaortic ventricular septal defect (VSD). Flow from the left ventricle preferentially enters the aorta. This is similar to what occurs in tetralogy of Fallot. **B**, DORV with a subpulmonary VSD. Left ventricular blood preferentially enters the pulmonary artery, resulting in physiology similar to that seen in transposition of the great arteries. (Modified from Castaneda AR, Jonas RA, Mayer JE Jr, et al: Double outlet right ventricle. In Castaneda AR, Jonas RA, Mayer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, pp 445–449.)

subpulmonic, doubly committed, and noncommitted types of VSD. VSD location alone, although important, neither defines the physiology nor is enough information on which to base a decision of the optimal method of repair. The presence or absence of right ventricular outflow tract obstruction is critical to the physiology and clinical presentation (Table 117-1). Furthermore, the great artery relationship, the distance between the pulmonary and tricuspid valves, the prominence of the conal

septum, and the coronary artery anatomy are all important factors that help determine what type of repair should be performed.²¹

DORV with subaortic VSD (see Fig. 117-11) is the most common type of DORV, comprising approximately 50% of all patients with DORV.²¹ With right ventricular outflow tract obstruction, the presentation is similar to tetralogy of Fallot, where a subaortic anterior malalignment VSD is also present. However, tetralogy of Fallot

TABLE 117-1 Pathophysiology of Double-Outlet Right Ventricle

Location of VSD	Right Ventricular Outflow Tract Obstruction	Clinical Presentation
Subaortic	Absent	VSD
Subaortic	Present	TOF
Subpulmonary	Absent	TGA/VSD
Subpulmonary/ TGA	Present (subaortic stenosis)	Ductal-dependent lesion
Doubly or noncommitted	Absent	VSD
Doubly or noncommitted	Present	TOF

TGA, Transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

patients will not have a subaortic conus. The presentation and physiology without pulmonary stenosis is similar to that of a child with a large VSD.

DORV with subpulmonary VSD (see Fig. 117-11) is the second most common type of DORV, occurring in 30% of patients.²¹ Because of the location of the VSD, oxygenated left ventricular blood preferentially streams through the VSD into the pulmonary artery while desaturated right ventricular blood streams into the aorta, thereby resulting in a transposition type of physiology. Association with subaortic stenosis, aortic coarctation, or interrupted aortic arch is common. The term *Taussig-Bing heart* is usually applied for hearts with subaortic and subpulmonary coni, side-by-side great arteries, and a subpulmonary VSD.²¹

The doubly committed VSD is immediately beneath both the PA and the aorta. The conal septum is absent or hypoplastic. Clinical presentation is usually similar to that of a subaortic VSD with or without pulmonary stenosis.

The noncommitted VSD type includes any VSD that is located below the conal septum or the junction of conal and muscular interventricular septa. These VSDs are likely to be so remote from the semilunar valves that it is very difficult to create a baffle that directs left ventricular blood flow into the aortic valve. These VSDs are frequently located in the inlet septum (AV canal type), or they can be mid-muscular or apical. Clinical presentation is similar to that of DORV with subaortic VSD and depends on the presence or absence of pulmonary stenosis.²²

Other Important Anatomic Features and Impact on the Type of Repair

Distance between Tricuspid and Pulmonary Valve

The judgment as to which type of repair is best in a specific anatomic situation constitutes the fundamental complexity of the surgical management of DORV. An

intraventricular repair denotes a baffle that is entirely in the right ventricle. The baffle is constructed around the VSD and creates a pathway from the left ventricle to the aorta. The right ventricular outflow thus curves around the left ventricular baffle. When the aorta is pushed away from the left ventricle by a very prominent subaortic conus or if the VSD is remote, a longer tunnel must be created. This often results in D-malposition of the aorta, where the aortic valve moves superior and anterior to the tricuspid valve, allowing the pulmonary valve to move closer to the tricuspid valve. Because the baffle must pass between the tricuspid and pulmonary valves, there is a point when this is no longer possible without either creating baffle obstruction (subaortic stenosis) or occluding the pulmonary valve, thus creating the need for a right ventricle-to-PA conduit. Thus, when planning an intraventricular repair, the distance between the tricuspid valve and the pulmonary valve must be carefully studied on multiple views obtained with echocardiography and angiography (ventriculogram).

Conal Septum

A prominent conal septum also may be in the way of a successful intraventricular baffle. The length of the conal septum is determined by the development of the subaortic and subpulmonary coni. The conal septum may be resected if there are no important AV valve chordae attached to it (Fig. 117-12). A long conal septum may be associated with a closer proximity between the tricuspid valve and the pulmonary valve. It also may be a substrate for the development of future subaortic stenosis, which in turn can be associated with aortic arch hypoplasia.²³

Pulmonary Outflow Tract Obstruction

The presence of pulmonary outflow tract obstruction also needs to be carefully managed during surgery. Intraventricular repair must include relief of any subpulmonary stenosis, usually by means of division of hypertrophied muscle bands and placement of an infundibular outflow patch. Even in mild forms of subpulmonary stenosis, an infundibular patch may be needed because, by definition, an intraventricular baffle protrudes to some extent into the right ventricular outflow tract, thus crowding the right ventricular outflow. An infundibular patch thus prevents the creation of iatrogenic subpulmonary stenosis. Pulmonary stenosis is dealt with as it is during tetralogy surgery, by transannular patch or by valvuloplasty. A Rastelli type of repair is sometimes required when the space between the tricuspid valve and the pulmonary annulus is not sufficient and there is significant pulmonary annular hypoplasia. It is best to then incorporate the entire pulmonary annulus into the baffle, thus creating a generous subaortic passage; divide the main PA; and place a conduit (usually a homograft) between the right ventricle and distal main PA. If the pulmonary annulus is of normal size but an intraventricular baffle is not possible for the reasons cited previously, an arterial switch operation with baffling of the VSD to the pulmonary valve should be performed.²⁴

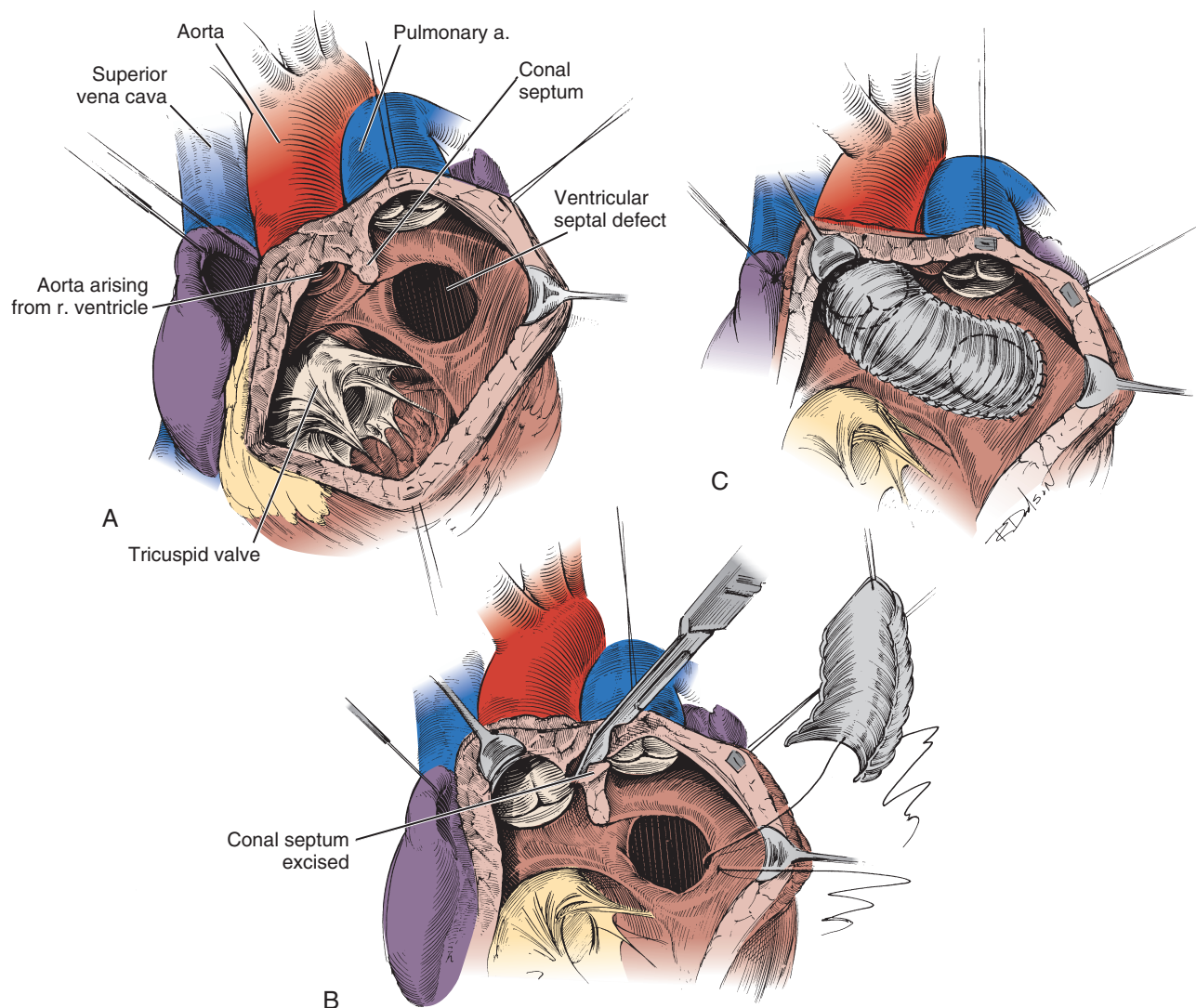


FIGURE 117-12 ■ **A**, Prominent conal septum can project into the intraventricular baffle pathway. **B**, Resection of the conal septum may be necessary to prevent subaortic stenosis. **C**, Completion of intraventricular repair with a baffle. (Modified from Castaneda AR, Jonas RA, Mayer JE Jr, et al: Double outlet right ventricle. In Castaneda AR, Jonas RA, Mayer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, pp 445–449.)

Coronary Artery Anatomy

Knowledge of the coronary artery anatomy is also critical to successful management of DORV, because a left anterior descending coronary artery passing anterior to the right ventricular outflow in the tetralogy end of the spectrum excludes an intraventricular repair and requires a conduit. Complex coronary artery anatomy, frequently seen in Taussig-Bing hearts, renders an arterial switch operation more challenging.

Great Artery Relationship

Most hearts with DORV have normally related great arteries spiraling around each other, with the aorta posterior and to the right of the pulmonary artery. The VSD is usually subaortic. When the great arteries are parallel to each other without a spiral, the aorta can be found side by side with and rightward of the pulmonary artery (D-malposition), anterior to the PA, or side by side and

leftward (L-malposition). The VSD is usually subpulmonary, but it can also be noncommitted.²⁵ Great artery relationship gives an indication of VSD location, but the two can also be independent of one another.²¹

Preoperative Evaluation

The age of the patient and the patient's symptoms are mostly determined by the degree of pulmonary stenosis. Most cases are diagnosed during the neonatal period. Echocardiography is the test of choice for neonates and young infants and is usually sufficient. At the transposition end of the spectrum, a balloon atrial septostomy may be needed to improve mixing. Catheterization also may be necessary in older children to exclude pulmonary vascular disease. To plan (or exclude) a potential intraventricular baffle, a left ventricular injection is helpful so that the dye can be followed as it is ejected by the left ventricle (preferentially into the aorta or pulmonary artery). Important echocardiographic details include the annular sizes of all

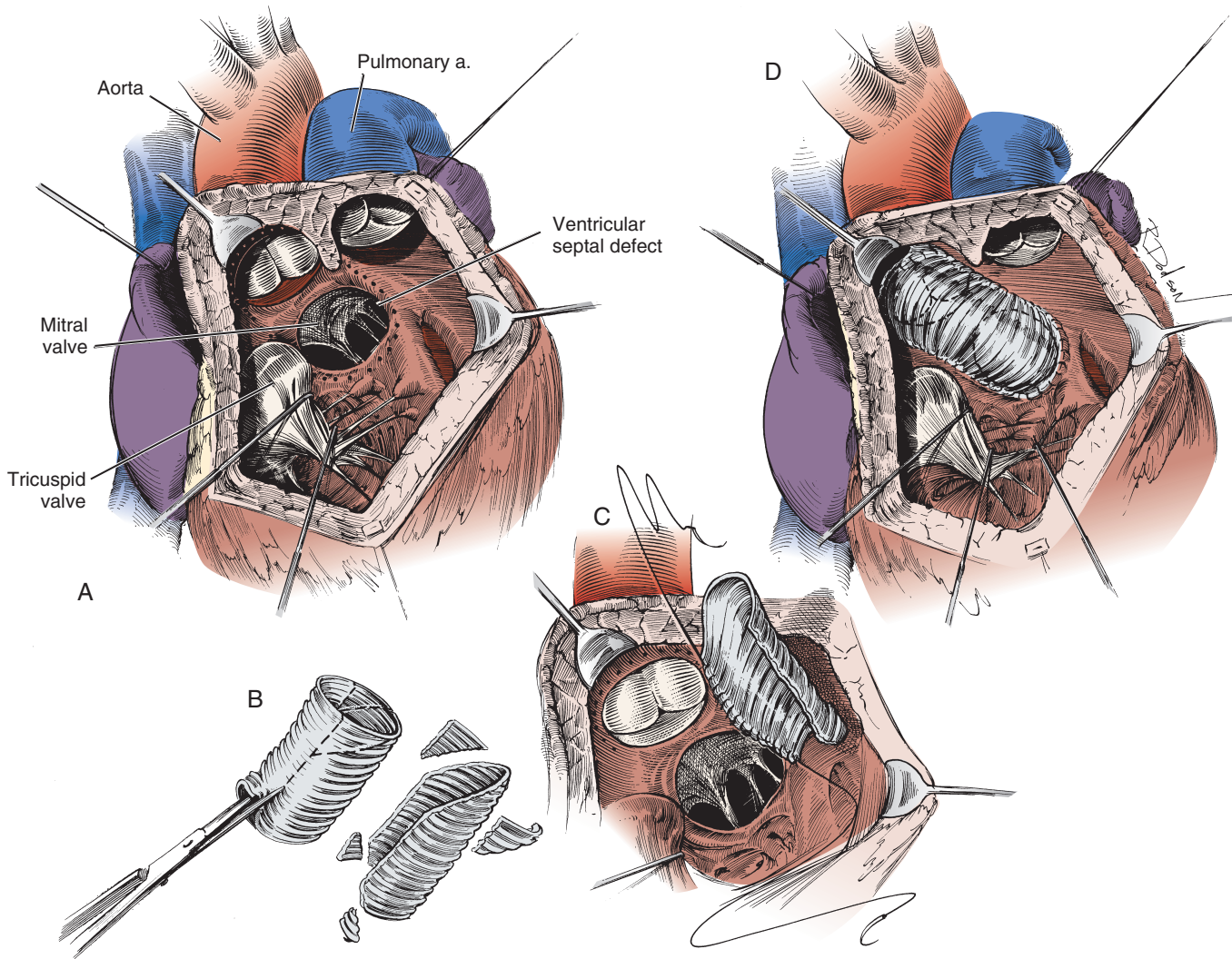


FIGURE 117-13 ■ The long synthetic baffle used to direct left ventricular blood to the aorta is best constructed from a partial tube graft. **A**, The suture line is indicated by a dotted line. **B**, Tailoring of the baffle from a tube graft. **C**, A continuous suture technique may be necessary for a very long baffle. **D**, Completion of intraventricular baffle repair of tetralogy of Fallot type of double-outlet right ventricle. (Modified from Castaneda AR, Jonas RA, Mayer JE Jr, et al: Double outlet right ventricle. In Castaneda AR, Jonas RA, Mayer JE Jr, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, pp 445–449.)

valves; the size of the left and right ventricles; the relative positions of the great arteries to one another; the degree of development of the conal septum; the chordal attachment to the conal septum; the level and degree of subpulmonary or pulmonary stenosis; the position of the VSD; and the status of the remainder of the septum, the coronary artery anatomy, and the aortic arch anatomy.

Surgical Management

Management of DORV is always surgical. Medical management may be indicated in relatively asymptomatic neonates with tetralogy-type physiology until they are a few months old. Because of markedly improved results with neonatal repairs, surgical palliation in the form of pulmonary artery banding in VSD-type physiology or aortopulmonary shunting in tetralogy-type physiology is

rarely performed. Routine cardiopulmonary bypass with bicaval cannulation is usually used.

Intraventricular Repair of DORV with Subaortic VSD or Doubly Committed VSD without Pulmonary Stenosis

Patients without pulmonary stenosis can generally be managed by placement of a patch baffle around the VSD, thus connecting the left ventricle to the aorta. The relationship of the aortic valve annulus to the VSD rims and to the conal septum must be carefully studied. If there appears to be a need for a larger subaortic circumference, a portion of a synthetic tube graft can be used rather than a flat patch, thus giving the baffle more of a tunnel appearance (Fig. 117-13).¹⁷ If the VSD appears restrictive, it should be enlarged by making an incision

anterosuperiorly, by resecting a wedge of the conal septum, or by doing both.

Intraventricular Repair of DORV with Subaortic VSD or Doubly Committed VSD with Pulmonary Stenosis

Techniques of repair are generally similar to those described for repair of tetralogy of Fallot. However, the VSD is closed by creation of a tunnel rather than a straight patch. Performing an infundibulotomy is generally recommended because subpulmonary stenosis is almost always present. The site of the infundibulotomy has to be carefully planned, staying away from any major coronary arteries. In case of an anomalous coronary artery crossing the right ventricular outflow tract, a conduit is sometimes necessary. Division of parietal and septal bands is always performed, along with placement of an infundibular outflow patch. Stenoses at the level of the pulmonary annulus, pulmonary valve, or branch pulmonary arteries can be handled as in tetralogy of Fallot (see [Chapter 119](#)).

Repair of DORV with Noncommitted VSD

The VSD is generally of the inlet type. Intraventricular (and thus biventricular) repair is difficult, but it can sometimes be accomplished by creating a tunnel from the left ventricle to the aorta. Anatomic variations generally considered to contraindicate a biventricular repair are multiple muscular VSDs, straddling AV valve tissue, or an inability to reliably channel the remote VSD to the aorta. If it is easier to baffle left ventricular blood to the pulmonary valve, or if the pulmonary valve is in the pathway of the baffle and there is no pulmonary stenosis, consideration should be given to performing an arterial switch procedure along with the intraventricular repair.²⁴ It is virtually always necessary to enlarge the VSD superoanteriorly. If the tunnel obstructs the right ventricular outflow tract, an infundibular patch or transannular patch should be placed. If there are significant tricuspid valve attachments to the anterior and superior edge of the VSD, or if a straddling tricuspid or mitral valve is present, attempting an intraventricular repair is generally contraindicated. However, there have been reports of successful division and reimplantation of the tricuspid chordae on the patch.

In the long term, the problem of subaortic stenosis with these complex baffles is real. A double-patch technique has been described that may mitigate this problem.²⁶ A noncommitted muscular trabecular defect can also sometimes be enlarged anteriorly and inferiorly, because the conduction system courses on the superior-posterior aspect of the defect. However, these baffles are often bulky, do not grow with the child, and are generally not very satisfactory. With the improving medium-term outcome for the single-ventricle approach in recent years, it is generally preferable to perform a straightforward single-ventricle repair with preservation of excellent ventricular function rather than a less-than-satisfactory higher-risk biventricular repair, after which multiple and usually complex reoperations will be necessary.²¹ This

approach might also be extended to patients who are at increased operative risk with a conventional biventricular repair.

Repair of DORV with Subpulmonary VSD

At the transposition end of the DORV spectrum, an arterial switch operation is usually preferred. A Taussig-Bing type of DORV can be repaired by an arterial switch operation (the most commonly used type of repair), a Rastelli procedure with Damus-Kaye-Stansel anastomosis, a Nikaidoh procedure, or a REV (réparation à l'étage ventriculaire) procedure. Surgical management of DORV transposition of the great arteries is discussed in [Chapter 126](#).

Results of Surgical Treatment

The early mortality rate is low among patients with non-complex forms of DORV, but it is higher in patients with complicating anatomic features.²⁷ Most complications are mechanical and should be routinely sought with the use of TEE before the patient leaves the operating room. As with VSD surgery, complete heart block and residual VSDs can occur. Inadequate enlargement of VSD or poor baffle configuration can result in subaortic obstruction. Direct measurements in the operating room can help elucidate cases in which TEE is not definitive. Residual muscular obstruction can often be resected through the aortic valve, and an aortotomy is generally a good first approach when approaching this problem. A separate patch also can be placed inside the original patch if it is too narrowing or if there is a waist created by a tortuous course. In cases of DORV with noncommitted VSD, it sometimes may be necessary to convert an acutely failed biventricular repair to a single-ventricle strategy. Significant right ventricular outflow tract obstruction can occur and should be managed as for tetralogy of Fallot. Patients with preoperative pulmonary hypertension are usually better served with implantation of a pulmonary valve. Because of the prolonged myocardial ischemic times needed for these complex repairs, myocardial protection should be carefully attended to; myocardial dysfunction can be a significant problem. Delayed sternal closure and mechanical assistance are important fallback measures that can be lifesaving.

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PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

Erle H. Austin, III • Deborah J. Kozik

CHAPTER OUTLINE

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PATHOPHYSIOLOGY

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SURGICAL MANAGEMENT

Initial Palliation

Definitive Procedures

Two-Ventricle Repair

One-and-One-Half Ventricle Repair

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RESULTS

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TRENDS AND CONTROVERSIES

Transcatheter Pulmonary Valvotomy

Hybrid Procedures

Decompression of the Right Ventricle in the Presence of Right Ventricle to Coronary Connections

Indications for Transplantation

Pulmonary atresia with intact ventricular septum (PA/IVS) is a rare congenital heart defect occurring at a rate of 4 to 10 per 100,000 live births.^{1,2} This malformation is characterized by a variably sized right ventricle that has no exit, failing to provide pulmonary blood flow and unable to decompress itself through the interventricular septum. Blood flow through the ductus arteriosus permits survival at birth, but within hours hypoxemia progresses to death as the ductus closes. Thus, without early diagnosis and treatment, PA/IVS is uniformly fatal. Before 1970, reported survival to 3 years of age was less than 3%.³ By the early 1990s, improvements in diagnosis and management resulted in a 3-year survival rate greater than 60%.⁴ More recent reports indicate that careful initial evaluation and selective management of these patients can achieve survival rates in excess of 90%.⁵

Because this anomaly is rare and its morphology is heterogeneous, most reports and recommendations have been derived from small series with variable morphologic compositions. Although a great deal has been learned from the experiences of individual centers,⁶⁻⁹ much more has been learned from a prospective multi-institutional study initiated by the Congenital Heart Surgeons Society in 1987^{4,10,11} and from more recent, population-based studies from the United Kingdom and Ireland^{1,12} and from Sweden.² Data acquired from these studies have provided important new insights into the spectrum of morphology and about outcomes of surgical treatment of this malformation.

PA/IVS has been described by other monikers in the past, including pulmonary atresia with normal aortic root

and hypoplasia of the right heart. The first description of pulmonary atresia with an intact ventricular septum was in 1784 by Hunter.¹³ Connections between the right ventricle and the coronary arteries were described by Grant in 1926 after examining the heart of a 14-month-old girl.¹⁴ Lauer and colleagues in 1964 were the first to angiographically demonstrate intramyocardial sinuoids.¹⁵ Freedom and colleagues postulated in 1974 that the connections between the right ventricle and the coronary arteries could possibly be related to myocardial ischemia.¹³ The first successful surgical repair of a patient with PA/IVS involved a transventricular valvotomy and was reported by Weinberg and associates in 1962.¹⁵

ANATOMY

Characteristically, PA/IVS occurs in hearts with situs solitus and atrioventricular and ventriculoarterial concordance. The aortic arch is usually left-sided, and a left-sided ductus arteriosus is typical. The essential feature of this lesion is an absent communication between the right ventricle and the pulmonary trunk (Fig. 118-1). The character of the atretic segment ranges from a thin imperforate membrane to a long section of infundibular muscle without a definable lumen. In contrast to pulmonary atresia with ventricular septal defect, in PA/IVS the pulmonary trunk and branch pulmonary arteries are usually near normal in size and configuration. The size and morphology of the right ventricle varies significantly in this condition, and in most patients, the right

ventricular cavity is reduced in size. There is a continuum from tiny “unipartite” chambers that have only an inlet component to larger-than-normal “tripartite” ventricles that have well-defined inlet, trabecular, and infundibular portions. The rare patients with enlarged right ventricular cavities also may have Ebstein anomaly with severe tricuspid regurgitation. More typically, the cavity is small, and marked hypertrophy of the right ventricular wall is present, often contributing to obliteration of the outflow (infundibular) portion of the cavity. The tricuspid valve is usually small with thickened leaflets and abnormal chordae. The diameter of the tricuspid valve correlates

with the size of the right ventricular cavity and provides a useful index of right ventricular size. The right atrium is enlarged, and an interatrial communication, usually a patent foramen ovale, is present. At birth, the ductus arteriosus is patent, providing the only blood flow to the lungs. Significant aortopulmonary collateral arteries are uncommon.

An important anatomic feature of PA/IVS is the presence in some patients of connections between the right ventricle and the coronary circulation (Figs. 118-2 and 118-3). Sinusoids or “intermuscular spaces” in the right ventricular myocardium occur in approximately 50% of patients.⁴ In 90% of these patients, the sinusoids communicate with the coronary arteries. The smaller the tricuspid valve (and thus the right ventricular cavity) is, the more likely it is that right ventricle–coronary arterial fistulas are present. In 15% of patients with these fistulas, significant proximal coronary artery stenoses exist, making myocardial blood flow dependent on blood from the right ventricle (see Table 118-2).¹⁰ Knowledge of the presence of right ventricle–dependent coronary circulation (RVDCC) is important in deciding on surgical therapy, because in these cases, decompression of the right ventricle may cause myocardial ischemia or infarction.¹⁶

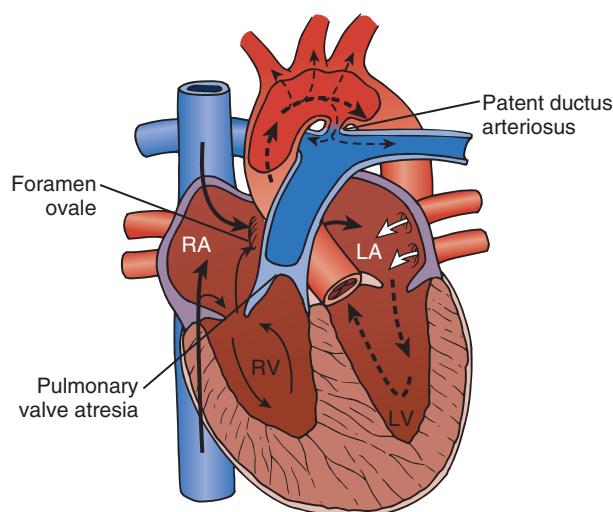


FIGURE 118-1 ■ Schematic representation of blood flow in patients with pulmonary atresia with intact ventricular septum. An obligatory right-to-left shunt occurs at the atrial level. Peripheral oxygenation depends on flow through the ductus arteriosus. (Black arrows, deoxygenated blood; white arrows, oxygenated blood; dashed arrows, mixed blood; larger arrows, larger amount of blood flow.) LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

PATHOPHYSIOLOGY

In PA/IVS, desaturated systemic venous blood is obliged to cross the interatrial septum to mix with saturated pulmonary venous blood in the left atrium (see Fig. 118-1). The resultant admixture is ejected into the systemic arterial circulation, and the systemic arterial saturation depends on adequate pulmonary blood flow. Closure of the ductus arteriosus soon after birth markedly reduces pulmonary blood flow, and progressive hypoxemia and tissue acidosis leads to death. Expedient administration of prostaglandin E₁ can temporarily reverse ductal closure

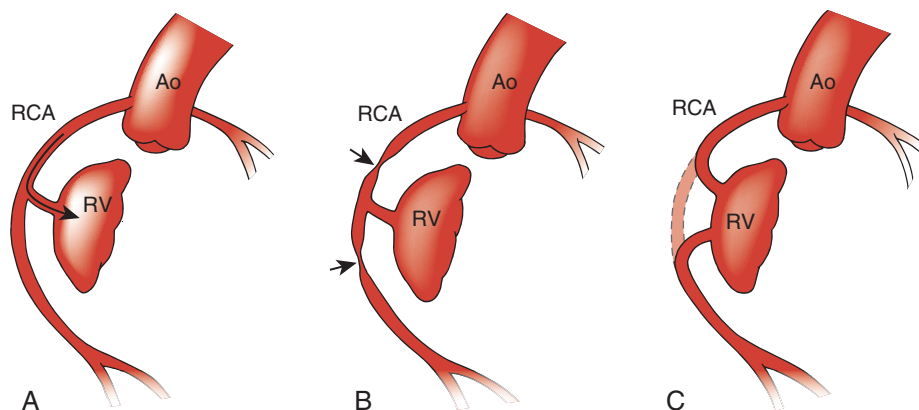


FIGURE 118-2 ■ Right ventricle-to-coronary artery fistulas in pulmonary atresia with intact ventricular septum. **A**, Without coronary stenosis: potential right ventricular steal phenomenon. **B**, With proximal or distal coronary stenosis: potential steal or ischemia. **C**, With coronary occlusion or atresia: potential isolation and myocardial infarction. (Modified from Giglia TM, Mandell VS, Connor AR, et al: Diagnosis and management of right ventricle-dependent coronary circulation in pulmonary atresia with intact ventricular septum. *Circulation* 86:1516–1528, 1992.)

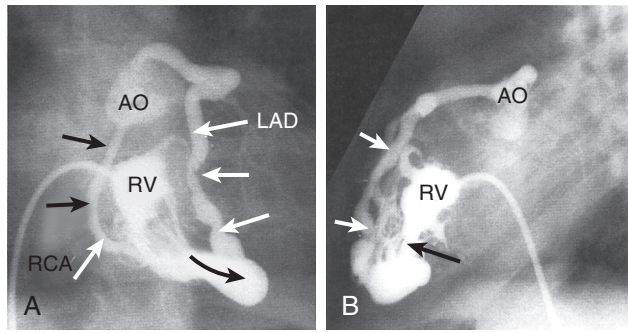


FIGURE 118-3 ■ Right ventriculogram in patient with pulmonary atresia and intact ventricular septum and ventriculocoronary connections. **A**, Frontal right ventriculogram showing severe hypoplasia of the right ventricular cavity. The right ventricle (RV) connects to the left anterior descending artery (LAD) through a ventriculocoronary connection (curved arrow). **B**, Lateral right ventriculogram showing ectasia and narrowing of the LAD (white arrows), and the connection between the RV and the coronary circulation (black arrows). AO, Aorta; RCA, right coronary artery. (Modified from Freedom RM, Anderson RH, Perrin D: The significance of ventriculo-coronary arterial connections in the setting of pulmonary atresia with an intact ventricular septum. *Cardiol Young* 15[5]:447–468, 2005.)

until a surgical procedure to increase pulmonary blood flow can be performed.

INITIAL CLINICAL PRESENTATION AND MANAGEMENT

Infants with PA/IVS are typically full-term, well-developed infants without other anomalies. Delivery is usually uncomplicated, but cyanosis develops on the first day of life and rapidly progresses to respiratory distress and metabolic acidosis. A murmur is unusual unless significant tricuspid regurgitation exists. There is no splitting of the second heart sound. Chest radiography demonstrates clear lung fields with decreased vascular markings. The electrocardiogram is often normal, although the typical neonatal pattern of right ventricular hypertrophy may be absent. Definitive diagnosis is made using two-dimensional echocardiography, which reveals the right ventricular outflow obstruction and the size of the right ventricle and tricuspid valve and, combined with color flow Doppler techniques, can identify right ventricle–coronary artery fistulas.^{17,18}

As soon as the diagnosis of PA/IVS is suspected, an infusion of prostaglandin E₁ is begun. Elective intubation and controlled ventilation may be advisable, especially if the infant is to be transported to a tertiary treatment center, because apnea is a common complication of prostaglandin E₁ infusion. Cardiac catheterization and cine-angiography are recommended for most of these patients, especially for those with moderate or severe right ventricular hypoplasia. Right ventriculography, aortography, and, when indicated, selective coronary angiography are performed to determine the presence and extent of right ventricle–to–coronary artery fistulas and the presence of coronary artery obstructions (see Figs. 118-2 and

118-3).^{16,19} At catheterization, an adequate atrial communication must be ensured. If echocardiography and catheterization indicate that right ventricle–to–pulmonary artery decompression cannot be performed and a flow gradient exists between the right and left atrium, a balloon atrial septostomy is performed at this catheterization.

SURGICAL MANAGEMENT

The ideal long-term outcome for all infants with PA/IVS would be to achieve a two-ventricle circulation with the right ventricle providing all blood flow to the lungs at a low filling pressure without residual right-to-left shunt. The anatomic heterogeneity of this group of patients, however, prevents the achievement of this goal in all patients. In fact, this ideal is achieved in only one third of patients surviving infancy (see Fig. 118-10).¹⁰ A more realistic outcome for the remaining patients is the elimination of cyanosis by separating the systemic and pulmonary circulations without limiting cardiac output or inducing excessively elevated systemic venous pressures. Such an outcome can be achieved with a one-ventricle repair (the Fontan operation) for hearts whose right ventricle cannot contribute to pulmonary blood flow, or with a one-and-one-half-ventricle repair for hearts whose right ventricle can provide a portion of pulmonary blood flow. Careful assessment of right ventricular size and coronary artery anatomy is crucial to selecting the appropriate strategy for each patient.

In neonates, it is useful to classify right ventricular hypoplasia into mild, moderate, and severe degrees (Table 118-1). Echocardiographic measurement of the diameter of the tricuspid valve with conversion to a z-value provides a quantitative measurement to facilitate classification.²⁰ A website (www.parameterz.com) is available for rapid and easy determination of z-scores. Patients with mild right ventricular hypoplasia have tricuspid valve z-values of –2 or greater. Tricuspid z-values between –4 and –2 indicate moderate right ventricular hypoplasia, and z-values of –4 or less are seen in patients with severe right ventricular hypoplasia. Tripartite right ventricles with a well-developed right ventricular outflow tract fall into the mild group, whereas unipartite right ventricles without a definable infundibular or trabecular portion are classified as severe.²¹ Patients with mild right ventricular hypoplasia have definite potential for conversion to a two-ventricle system at the time of definitive repair, whereas those with severe right ventricular hypoplasia can achieve only separation of systemic and pulmonary circulations with a one-ventricle repair (a Fontan operation). Patients with moderate right ventricular hypoplasia are also potential candidates for two-ventricle or one-and-one-half-ventricle repair, provided they do not have RVDCC.

Initial Palliation

The surgical management of PA/IVS is typically undertaken in two or more stages, the first for palliation and subsequent procedures directed at definitive repair. To

TABLE 118-1 Effect of Degree of Right Ventricular Hypoplasia on Management of Pulmonary Atresia with Intact Ventricular Septum

Parameter/ Management	Degree of Right Ventricular Hypoplasia		
	Mild	Moderate	Severe
Tricuspid z-value	>−2	−2 to −4	<−4
Right ventricular morphology	Tripartite	Bipartite	Unipartite
Infundibular cavity	Present	Intermediate	Absent
Right ventricle–dependent coronary circulation	Rare	Possible	Common
Initial palliation	Transannular patch ± shunt. Consider transcatheter valvotomy or hybrid procedure	Transannular patch + shunt. Consider hybrid procedure (no right ventricular decompression if right ventricle–dependent coronary circulation)	Shunt only
Definitive operation	Two-ventricle repair	Two-ventricle repair; one-and-one-half-ventricle repair; Fontan if right ventricle–dependent coronary circulation	Fontan

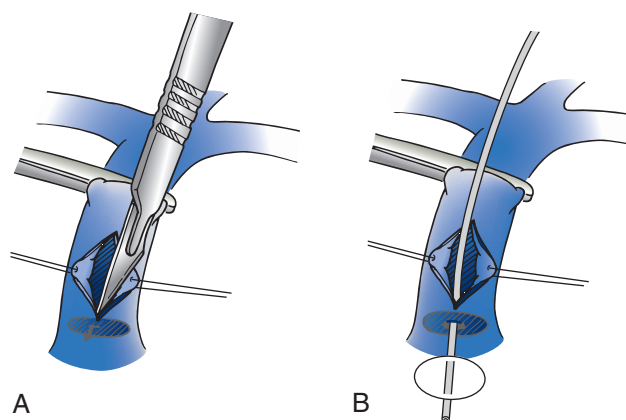


FIGURE 118-4 ■ Open pulmonary valvotomy without cardiopulmonary bypass can be performed via a median sternotomy or a left thoracotomy. **A**, After clamping the pulmonary trunk just proximal to the bifurcation, the pulmonary artery is opened and the atretic pulmonary valve is opened sharply. **B**, A Fogarty catheter positioned in the infundibulum provides hemostasis as the atretic valve is excised. (Modified from Kanter KR, Pennington DG, Nouri S, et al: Concomitant valvotomy and subclavian-main pulmonary artery shunt in neonates with pulmonary atresia and intact ventricular septum. *Ann Thorac Surg* 43:490–494, 1987.)

ensure early survival, pulmonary blood flow must be maintained after ductal closure. Although the creation of a systemic-to-pulmonary shunt can ensure continued pulmonary blood flow, the right ventricle must be assessed for its potential recruitment into the circulation. When possible, decompressing the right ventricle into the pulmonary artery permits right ventricular growth such that a two-ventricle repair may become feasible. Failure to decompress the right ventricle at initial palliation essentially eliminates the possibility of ever achieving a definitive two-ventricle repair.²²

Thus, neonates with mild to moderate right ventricular hypoplasia are best served by relieving the right ventricle-to-pulmonary artery obstruction. This may be accomplished with or without cardiopulmonary bypass. Without bypass, a pulmonary valvotomy can be performed blindly, with a transventricular dilator,²³ or under direct vision through the main pulmonary artery (Fig.

118-4).²⁴ Interventional catheter and hybrid techniques are now being applied at some centers for this purpose (see [Trends and Controversies](#), later). The use of cardiopulmonary bypass allows more controlled access into the right ventricular outflow tract so that obstructing infundibular muscle can be excised under direct vision and a transannular outflow patch can be placed (Fig. 118-5). By maximizing unobstructed forward flow, transannular patching provides the greatest possibility for right ventricular growth.^{4,25} Because early postoperative right ventricular failure may cause increased right-to-left shunting across the patent foramen ovale, and antegrade flow from the right ventricle may be limited, a systemic-to-pulmonary artery shunt (a 3- or 3.5-mm polytetrafluoroethylene [PTFE] tube graft) also should be placed to prevent life-threatening hypoxia. Initial results from the Congenital Heart Surgeons Society's study suggest that concomitant insertion of a transannular patch and placement of a systemic-to-pulmonary artery shunt is the optimal initial treatment for neonates with tricuspid valve z-values between −1.5 and −4 (Fig. 118-6).⁴ In that study, when a valvotomy or transannular patch was performed without a concomitant systemic-to-pulmonary artery shunt, approximately 50% of the patients required shunt placement within the first 4 weeks after the initial procedure. In addition, approximately 40% of patients treated initially with pulmonary valvotomy required a transannular patch at a subsequent operation.⁴ On the other hand, any form of right ventricular decompression is contraindicated if RVDCC exists.

Neonates with severe right ventricular hypoplasia or RVDCC (or both) are best placed on a definitive one-ventricle (Fontan) pathway. Thus, initial surgical therapy should be limited to a systemic-to-pulmonary artery shunt (see Fig. 118-6).⁴ A 3.5-mm PTFE tube graft placed via a median sternotomy or a right thoracotomy from the innominate or right subclavian artery to the right pulmonary artery provides adequate pulmonary blood flow and facilitates shunt access at the time of definitive one-ventricle repair. Shunts greater than 4 mm should be avoided because they may result in excessive pulmonary blood flow and low diastolic arterial blood pressure, causing life-threatening myocardial ischemia.

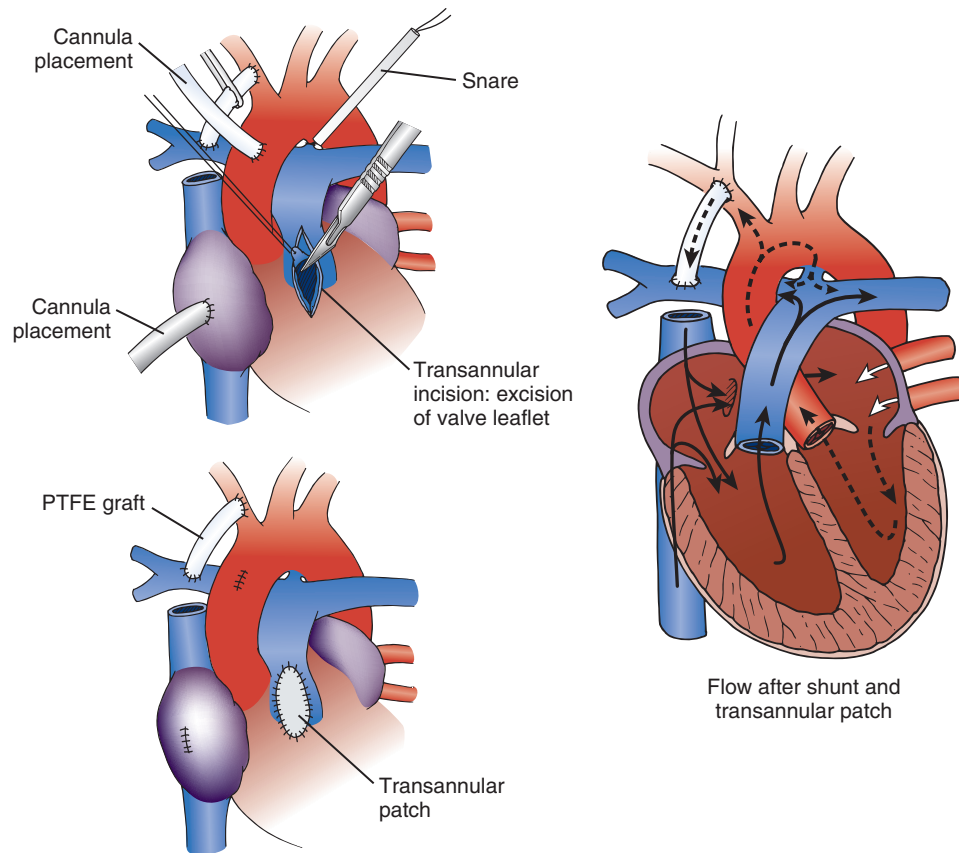


FIGURE 118-5 ■ Placement of a transannular patch and a systemic-to-pulmonary artery shunt. A 3- or 3.5-mm polytetrafluoroethylene (PTFE) tube graft is placed from the innominate artery to the right pulmonary artery. Cardiopulmonary bypass is established and the shunt and ductus are temporarily occluded. A pulmonary artery incision is extended into the right ventricular outflow tract. Obstructing tissue is excised, and a pericardial patch is sewn in place. Separation from bypass is done with the shunt open and the ductus occluded. If peripheral oxygen saturations exceed 80%, the ductus is ligated. If peripheral oxygen saturations are less than 80%, the ductus is unsnared as demonstrated at right. (Black arrows, deoxygenated blood; white arrows, oxygenated blood; dashed arrows, mixed blood).

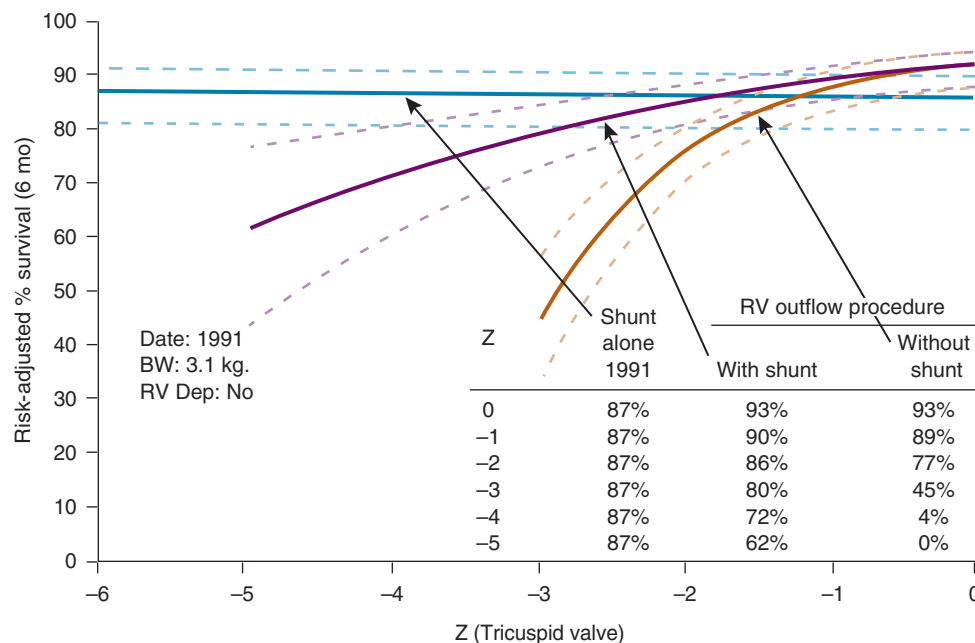


FIGURE 118-6 ■ The effect of tricuspid valve diameter (z-value) and type of initial procedure on 6-month survival in neonates with pulmonary atresia and intact septum. This nomogram was derived after analyzing 171 neonates and solving a multivariable equation setting birth weight (BW) at "3.1 kg," right ventricle (RV)-dependent circulation at "no," and date of shunt operation at "1991." RV outflow procedure includes valvotomy and transannular patch. (Modified from Hanley FL, Sade RM, Blackstone EH, et al: Outcomes in neonatal pulmonary atresia with intact ventricular septum. A multiinstitutional study. *J Thorac Cardiovasc Surg* 105:406-423, 1993.)

Definitive Procedures

Two-Ventricle Repair

Patients selected at initial palliation for a two-ventricle strategy should have echocardiographic evidence of satisfactory right ventricular decompression with estimated right ventricular pressure less than or equal to one half of systemic arterial pressure. Those infants treated originally with valvotomy rather than transannular patching are especially vulnerable to residual or recurrent right ventricular outflow tract obstruction,^{4,22} which should be relieved by a second right ventricular outflow tract procedure (a transannular patch) before considering conversion to a two-ventricle circulation. Follow-up cardiac catheterization should be performed between 6 and 12 months of age. At catheterization, the systemic-to-pulmonary artery shunt is temporarily occluded. If arterial saturations remain high, the atrial septal defect (patent foramen ovale) is occluded as well. If right atrial pressure remains below 15 mm Hg and cardiac output is adequate, the shunt and atrial communication can be closed permanently and a two-ventricle circulation achieved. At some centers, the shunt and atrial defect can be closed during the catheterization using percutaneous techniques.^{26,27}

One-and-One-Half Ventricle Repair

Patients studied at 6 to 12 months who do not tolerate temporary occlusion of the systemic-to-pulmonary artery shunt are receiving too little pulmonary blood flow from the right ventricle to achieve success from a two-ventricle repair. Assuming there is no significant residual right ventricular outflow obstruction, these patients should be considered candidates for a one-and-one-half-ventricle repair. This repair involves takedown of the arterial systemic-to-pulmonary shunt and the creation of a bidirectional superior cavopulmonary anastomosis (a bidirectional Glenn procedure), which relieves the right ventricle of the superior vena caval blood flow. Ideally, the atrial septal communication is closed at the same operation. However, if the right atrial pressure exceeds 15 mm Hg, a small (4-mm) fenestration can be left. Catheter closure of the fenestration can usually be performed within months of the surgical procedure.²⁷

Alternatively, a purse-string suture and an adjustable snare can permit incremental closure of the atrial septal defect in the postoperative period (Fig. 118-7).²⁸ Patients with tricuspid z-values as small as -6 may be definitively managed with the one-and-one-half-ventricle strategy.²⁹

One-Ventricle Repair

Infants with severe right ventricular hypoplasia or RVDCC (or both) are typically designated for a one-ventricle strategy at initial palliation. At 4 to 6 months of age, these patients undergo takedown of the systemic-to-pulmonary shunt and the creation of a bidirectional cavopulmonary anastomosis. At 2 to 4 years of age, they are considered candidates for the Fontan operation. Before the Fontan operation, cardiac catheterization is essential to ensure adequate left ventricular function and low pulmonary vascular resistance. Poor left ventricular function would leave cardiac transplantation as the only alternative therapy. Heart-lung transplantation is the only alternative if pulmonary vascular resistance is elevated. Fortunately, the early creation of a bidirectional cavopulmonary anastomosis appears to help preserve ventricular function and prevent the development of pulmonary vascular disease so that those drastic measures are rarely necessary. When performing the bidirectional Glenn procedure on cardiopulmonary bypass in patients with RVDCC, the surgeon must avoid low right ventricular preload to avoid poor coronary perfusion. The right ventricle should remain filled and ejecting, because myocardial perfusion occurs only during systole. Patients with RVDCC who sustain cardiac arrest may not respond well to resuscitation with extracorporeal membrane oxygenation (ECMO). ECMO will empty the right heart and significantly hinder coronary perfusion.³⁰ After the superior cavopulmonary anastomosis, the saturations in the right ventricular cavity are significantly increased, and this is likely beneficial for patients with RVDCC.³¹

When the Fontan procedure is performed, inferior vena caval blood flow is directed to the pulmonary arteries. This can be performed with a lateral atrial tunnel technique, wherein a baffle of PTFE is placed inside the right atrium (Fig. 118-8),³² or with an extracardiac conduit.³³ Many surgeons prefer to place a small fenestration in the baffle to permit some right-to-left shunting

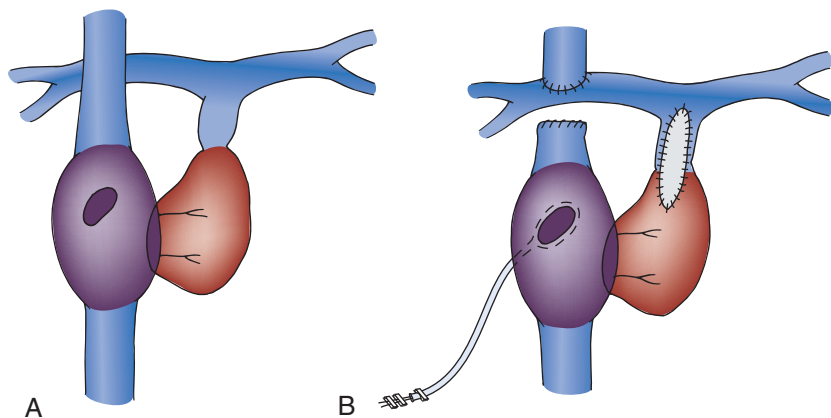


FIGURE 118-7 ■ Creation of a one-and-one-half-ventricle circulation. **A**, Small right ventricle unable to support two-ventricle repair. **B**, Superior vena caval flow is directed to the right pulmonary artery with a bidirectional cavopulmonary anastomosis. Residual right ventricular outflow tract stenosis is relieved with a transannular patch. Placement of an adjustable snare around the atrial septal defect permits incremental closure in the postoperative period. (Modified from Billingsley AM, Laks H, Boyce SW, et al: Definitive repair in patients with pulmonary atresia and intact ventricular septum. *J Thorac Cardiovasc Surg* 97:746-754, 1989.)

to maintain cardiac output in the perioperative period, when pulmonary vascular resistance may be elevated.³⁴ Routine fenestration, however, may not be necessary when an extracardiac conduit is used.³⁵ It also may be preferable to avoid fenestration when RVDCC is present. Enlarging the atrial septal defect and unroofing the coronary sinus to ensure that the blood entering the right ventricle is well oxygenated has also been recommended for RVDCC (see Fig. 118-8).

RESULTS

Early and Midterm Outcomes

The reports from the Congenital Heart Surgeons Society (CHSS) continue to provide the best overall perspective of outcomes in neonates with PA/IVS.^{4,10,11} This prospective multi-institutional study involves 31 institutions and enrolled 408 unselected neonates with this diagnosis within a 10-year period (1987-1997). The initial right ventricular morphology and tricuspid valve size (z-value) were known for all patients, and follow-up through 2002 was 91% complete. Techniques for surgical management were not randomized but left to the discretion of each institution. The overall survival was 60% at 5 years and 58% at 15 years (Fig. 118-9). At 15 years, 33% had undergone a two-ventricle repair, 20% a Fontan repair, and 5% a one-and-one-half-ventricle repair, and 38% died before reaching definitive repair (Fig. 118-10). In this unselected group, 49% of patients were found to have severe right ventricular hypoplasia (z-score ≤ -4), and 36% had moderate right ventricular hypoplasia (z-score -2 or -3) (Table 118-2). Additionally, 6% of the cohort had RVDCC (none with a z-score ≥ -2), and 38% had right ventricle–coronary artery fistulas. Increasing tricuspid valve z-score, larger right ventricle size, higher

birth weight, and a lesser degree of right ventricle–to–coronary artery fistulas were all found to be significant determinants of achieving a two-ventricle repair. Also, tricuspid valve morphology was found to be an important determinant of successful two-ventricle repair, as Ebstein malformation was associated with an increased risk of death. The 2004 CHSS report highlighted the importance of morphology-specific repair.¹⁰ The most favorable outcomes were achieved by institutions that applied the Fontan operation for patients with severe morphology, and a two-ventricle repair for patients with favorable morphology (Fig. 118-11).

The 2005 report from the United Kingdom and Ireland Collaborative Study of Pulmonary Atresia with Intact Ventricular Septum identified three variables as independent predictors of death—these variables are birth weight, right ventricular dilation, and the partite status of the right ventricle.³⁶ Only one third of patients born at less than 2 kg survived, and each additional kilogram of weight was associated with a 44% reduction in the risk of death. Eighty percent of those undergoing operation with a significantly dilated right ventricle died. The 1- and 5-year survival rates for those with a tripartite right ventricle were 78% and 74%, respectively (Fig. 118-12). This is significantly better than the 44% and 22% seen for those with unipartite right ventricle anatomy. At this 9-year follow-up report, 29% had achieved a biventricular repair, 3% a one-and-a-half-ventricle repair, and 10.5% a univentricular repair, and 41% had died.

Using information derived from the CHSS study, Boston Children's Hospital applied a policy of routine coronary angiography, right ventricular decompression with transannular patching for patients without RVDCC, and a systemic-to-pulmonary shunt in virtually all patients. In a consecutive group of 47 patients from 1991 to 1998, this institution achieved an actuarial survival rate

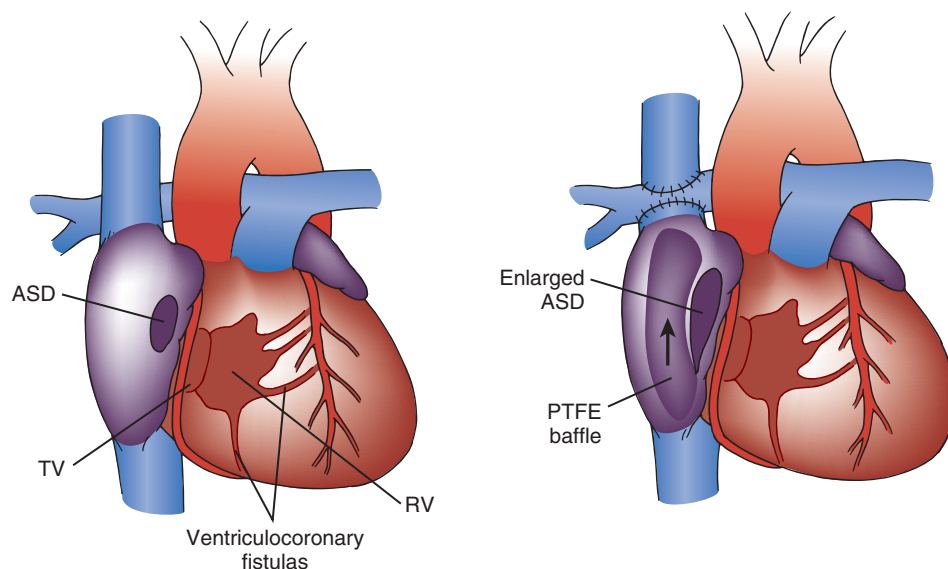


FIGURE 118-8 ■ Lateral-tunnel Fontan procedure in a patient with right ventricle–dependent coronary circulation. Inferior vena caval flow is directed to superior vena cava by polytetrafluoroethylene (PTFE) baffle. Atrial septal defect (ASD) is enlarged, allowing fully saturated pulmonary venous blood to enter the right ventricle (RV). TV, Tricuspid valve. (Modified from Pearl JM, Laks H, Stein DG, et al: Total cavopulmonary anastomosis versus conventional modified Fontan procedure. *Ann Thorac Surg* 52:189–196, 1991.)

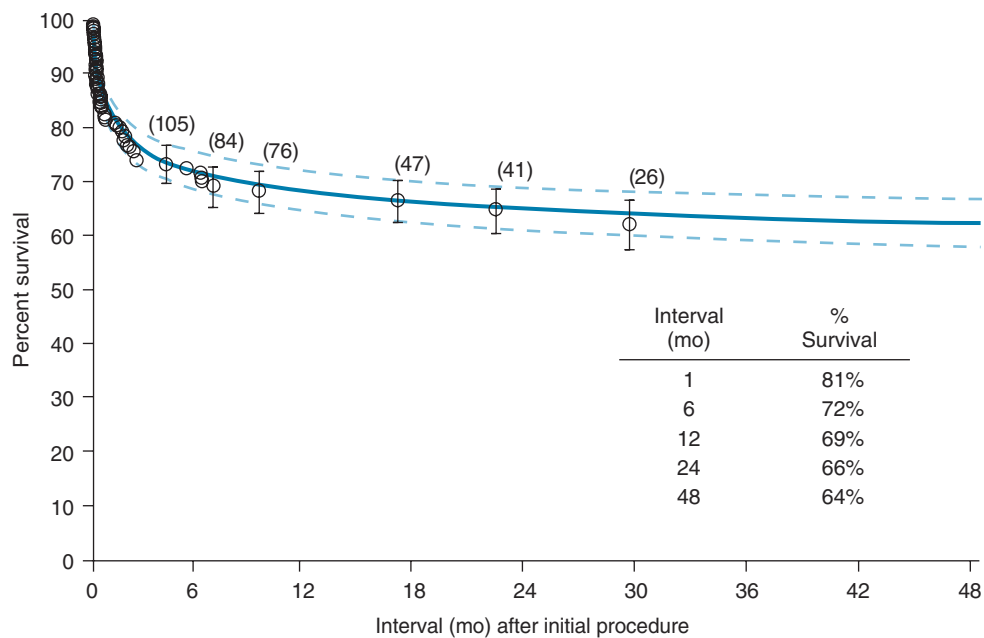


FIGURE 118-9 ■ Survival (derived from life-table and parametric methods) after the initial procedure performed on neonates with pulmonary atresia and intact ventricular septum. Circles represent individual deaths. Vertical bars and dashed lines represent 70% confidence intervals. (Modified from Hanley FL, Sade RM, Blackstone EH, et al: Outcomes in neonatal pulmonary atresia with intact ventricular septum. A multiinstitutional study. *J Thorac Cardiovasc Surg* 105:406–423, 1993.)

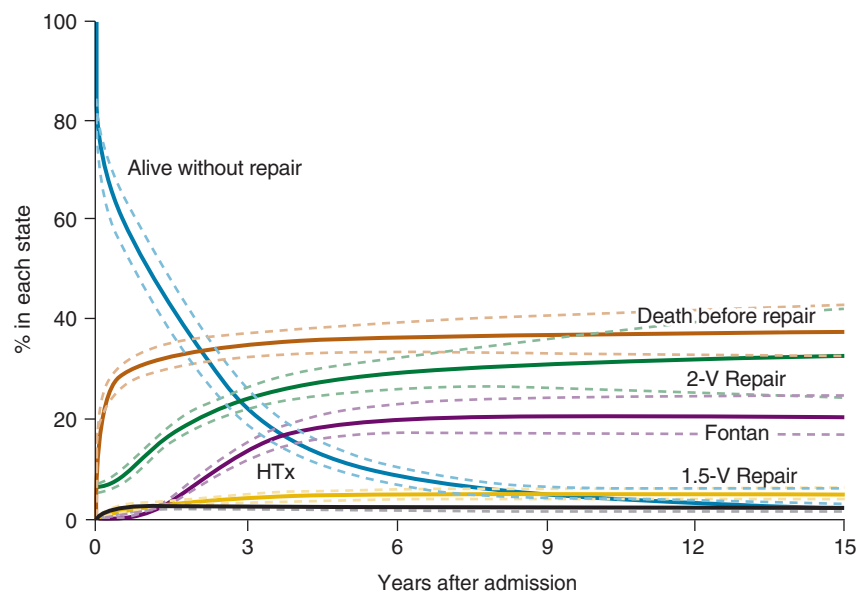


FIGURE 118-10 ■ Proportion of children reaching each end state over time after initial hospital admission. All patients begin alive at the time of initial admission (time = 0) and thereafter migrate to an end state at a time-dependent rate defined by the hazard functions. At any point in time, the sum of the proportion of children in each state is 100%. HTx, Heart transplantation; V, ventricle. (Modified from Ashburn DA, Blackstone EH, Wells WJ, et al; Congenital Heart Surgeons Study members: Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum. *J Thorac Cardiovasc Surg* 127[4]:1000–1007, 2004; discussion 1007–1008.)

of 98% at 1 year, 5 years, and 7.5 years.⁵ To achieve this excellent survival rate, a one-ventricle or a one-and-one-half-ventricle repair was required in most patients. On the other hand, in patients with RVDCC, survival is not nearly as good. In another report from the same institution, patients with RVDCC had an overall mortality of almost 19%. Also, patients with aortocoronary atresia had 100% mortality.³⁰ Green Lane Hospital in New

Zealand also had an extremely high mortality rate (91%) among patients with aortocoronary atresia.³⁷

Late Follow-up

The Congenital Heart Surgeons Society recently evaluated surviving patients from its original multi-institutional study to determine if biventricular repair was associated

TABLE 118-2 Morphologic Characteristics in 334 Neonates for Whom an RV Size Score Was Assigned

RV Size	Patients (n)	% of 334	Tricuspid Value Z-Score			RV-CA Fistulas	RVDCC
			Median	Range*	25th Percentile		
-5 (severe hypoplasia)	62	19	-2.3	-5.4 to 4.8	-3.3	35 (56%)	5 (8%)
-4	100	30	-2.3	-5.3 to 0.6	-3.1	55 (55%)	10 (10%)
-3	79	24	-1.1	-5.2 to 5.0	-1.9	28 (35%)	4 (14%)
-2	40	12	-0.3	-3.1 to 3.2	-1.0	5 (13%)	0
-1	22	7	0.4	-2.9 to 2.9	-1.2	3 (14%)	0
0 (normal for age)	16	5	1.5	-1.6 to 5.0	0.6	0	0
≥1 (enlarged)	15	4	2.4	-1.0 to 6.0	0.4	0	0

*High upper limits of tricuspid valve z-score in neonates with a diminutive right ventricle are attributable to associated Ebstein malformation.

CA, Coronary artery; RV, right ventricle; RVDCC, right ventricle-dependent coronary circulation.

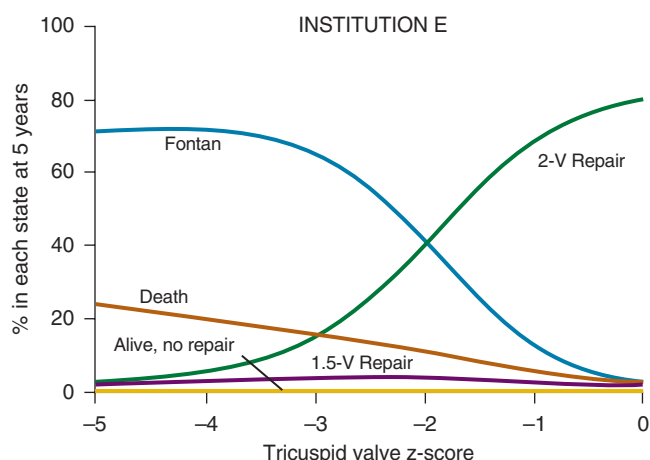
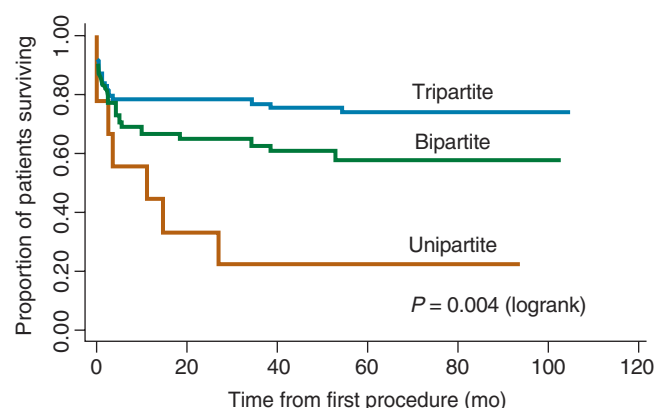


FIGURE 118-11 ■ Results at an institution favoring both two-ventricle (2-V) and Fontan pathways. Patients with severe morphologies undergo the Fontan operation, and patients with favorable morphologies undergo two-ventricle repair. The mortality rate is low, and most children have had a definitive repair by 5 years. (Modified from Ashburn DA, Blackstone EH, Wells WJ, et al; Congenital Heart Surgeons Study members: Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum. *J Thorac Cardiovasc Surg* 127[4]:1000–1007, 2004; discussion 1007–1008.)

with late (≥ 10 years) benefit in terms of functional health status and exercise capacity relative to a univentricular or one-and-one-half-ventricle repair.¹¹ Of 271 current survivors of the original cohort, 106 participated in the cross-sectional study. In this report, patient-perceived physical functional health status and measured exercise capacity were reduced, regardless of repair pathway. Peak oxygen consumption was low across all groups and was positively correlated with larger initial tricuspid valve z-score. The peak VO_2 in the biventricular repair group with low tricuspid valve z-scores tended to be lower than peak VO_2 in the one-and-one-half-ventricle group with comparable tricuspid valve z-scores. These findings suggest that patients with more severe degrees of right heart hypoplasia who are forced down a biventricular pathway may be at greater risk of late deficits in aerobic capacity.

Another study, from the Mayo Clinic, looked at clinical outcomes in adult survivors with PA/IVS.³⁸ Of 20



Survival	1 Year (CI)	5 Year (CI)
Tripartite	78% (69%-87%)	74% (64%-84%)
Bipartite	67% (53%-80%)	57% (43%-72%)
Unipartite	44% (12%-77%)	22% (0%-49%)

FIGURE 118-12 ■ Survival curve for all patients undergoing operative procedures, grouped by so-called partite status of the right ventricle ($N = 168$). CI, 95% confidence interval. (Modified from Daubeney PE, Wang D, Delany DJ, et al; UK and Ireland Collaborative Study of Pulmonary Atresia with Intact Ventricular Septum: Pulmonary atresia with intact ventricular septum: predictors of early and medium-term outcome in a population-based study. *J Thorac Cardiovasc Surg* 130[4]:1071, 2005.)

patients, 5 died during the 10-year study period at a median age of 32 years. All patients in this cohort required surgical or catheter reinterventions in adulthood, regardless of type of repair, and 80% developed atrial arrhythmias. Thus, despite survival into adulthood, the risk of morbidity and mortality continues for these patients.

TRENDS AND CONTROVERSIES

Transcatheter Pulmonary Valvotomy

Advances in interventional techniques now make it possible for some infants with PA/IVS to undergo antegrade decompression of the right ventricle without surgery, while still in the catheterization laboratory. Using mechanical, laser, or radiofrequency energy at the tip of

a catheter, the membranous atresia can be perforated and the resulting communication dilated with percutaneous balloon technique.³⁹⁻⁴¹ As experience with this procedure increases, it is being considered as first-line treatment in place of surgical intervention at some centers.⁴² Right ventricular growth and a definitive two-ventricle circulation have been achieved with this technique in some patients.^{41,43} Use of this approach, however, requires careful selection of patients and is essentially limited to infants with a patent infundibulum and a right ventricle large enough to support the pulmonary circulation without a systemic-to-pulmonary shunt. This approach may not adequately address the small pulmonary annulus or significant subpulmonary obstruction. Accordingly, after catheter valvotomy, some patients have required prolonged hospitalization for continued administration of prostaglandin E₁ or surgery (or both) to place a systemic-to-pulmonary shunt.⁴⁰

In one recent series, 88% of those undergoing transcatheter pulmonary valvotomy required surgical intervention within 2 weeks of the initial interventional procedure.⁴⁴ In that series, most operations (87%) involved a procedure directed at the right ventricular outflow tract in addition to shunt placement. In another single-institution review, 64% of those initially receiving catheter-based therapy required surgical intervention before discharge.⁴⁵ A more recent report from Boston Children's Hospital confirms a similar rate (62%) of surgery prior to discharge.⁴⁶ In this study all but one patient required a systemic to pulmonary shunt to augment pulmonary blood flow.

Stenting of the arterial duct has become an alternative technique for ensuring adequate pulmonary blood flow in selected patients while right ventricular function is being established. Ductal stenting can be performed within days after catheter-based valvotomy if the infant cannot be weaned from prostaglandin⁴⁷ or concomitantly with the valvotomy.⁴⁸ The risk factors determining the need for an additional source of pulmonary blood flow (shunt or ductal stent) continue to be defined for these patients. As expected, smaller tricuspid valve z-scores correlate with a greater need for adding pulmonary blood flow.^{46,49} In one study 80% of patients with a bipartite right ventricle required an additional source of pulmonary blood flow.⁴⁷ Another case series looked at 143 patients with PA/IVS, 37 of whom had a bipartite right ventricle.⁴⁸ All 37 patients underwent radiofrequency valvotomy and stenting of the ductus as the initial procedure. Forty-eight percent of these patients went on to

achieve a biventricular circulation, and 26% underwent one-and-one-half-ventricle repair. A large multicenter study that examined ductal stenting over an 18-year period reported a 94% success rate in patients with PA/IVS.⁵⁰ The long-term impact of ductal stenting on future operations and pulmonary artery anatomy is not clear. In one study, major late complications of patent ductus arteriosus stenting were not encountered, and the stented patent ductus arteriosus did not pose a major surgical challenge at the time of bidirectional Glenn surgery.⁴⁸

Catheter-based therapy for PA/IVS patients is becoming the preferred approach at most centers when the anatomy is favorable. Moller's analysis of more than 1000 PA/IVS patients from the multi-institutional Pediatric Cardiac Care Consortium from 1982 to 2006 revealed a steady increase in the frequency of balloon pulmonary valvotomy along with a corresponding decrease in surgical pulmonary valvotomy (Table 118-3).⁵¹

Hybrid Procedures

Despite the increasing preference for catheter-based therapy in select neonates with PA/IVS, the percutaneous approach is associated with significant rates of procedural failure and serious complications. Many neonates have required surgical intervention in the neonatal period, either to augment pulmonary blood flow or to repair a complication associated with the percutaneous approach. An alternative hybrid approach integrating a sternotomy with transventricular perforation of the atretic pulmonary membrane and balloon pulmonary valvotomy was first described in 2007.⁵² This approach also allows for radiofrequency perforation of the valve membrane.⁵³ Potential advantages of the hybrid approach include avoidance of neonatal cardiopulmonary bypass, mitigation of the technical failure rate of the percutaneous approach (due to direct access to the right ventricular outflow tract), and a lower complication rate.

A recent study prospectively enrolled 10 neonates with PA/IVS to undergo a hybrid procedure.⁵⁴ All patients had a successful balloon valvotomy, one patient required reopening of the patent ductus arteriosus, and one required a concomitant Blalock-Taussig (BT) shunt. Of note, all patients had a tricuspid valve z-score of -2 to 2, suggesting mild right ventricular hypoplasia. The investigators also reported mild complications in three patients and no mortality. Another single-center report compared patients who underwent surgical right ventricular decompression with a hybrid cohort.⁵⁵ The researchers found

TABLE 118-3 Frequency of Procedures in Neonates with PA/IVS by Time Periods

Time Period	1982-1989	1990-1995	1996-2001	2002-2006
Number of neonates	199	287	298	255
Systemic-pulmonary shunt	170 (85%)	243 (85%)	255 (86%)	206 (81%)
Pulmonary valvotomy	81 (41%)	71 (25%)	57 (19%)	22 (10%)
Balloon pulmonary valvuloplasty	0	15 (5%)	46 (15%)	81 (32%)

PA/IVS, Pulmonary atresia with intact ventricular septum.

Modified from Moller JH: Operative and interventional procedures in 1039 neonates with pulmonary valve atresia and intact ventricular septum. A multi-institutional study. *Prog Pediatr Cardiol* 29:15-18, 2010.

no difference between the surgical and hybrid cohorts in terms of maximum vasoactive-inotropic score, duration of mechanical ventilation, intensive care unit length of stay, or overall hospital length of stay. Overall complication rates were also similar. All surgical patients received a BT shunt, whereas only 71% of the hybrid patients received a BT shunt.

Decompression of the Right Ventricle in the Presence of Right Ventricle to Coronary Connections

Antegrade right ventricular decompression is required to recruit the right ventricle for an ultimate two-ventricle or one-and-one-half-ventricle circulation. When significant communications (fistulas) between the right ventricle and the coronary circulation are present, controversy exists regarding the advisability and technique of right ventricular decompression. Virtually all authors agree that when proximal coronary obstructions are also present that make the coronary circulation dependent on the right ventricle, decompression of the right ventricle is contraindicated. Consensus is not uniform, however, when significant right ventricle-to-coronary circulation connections are present without proximal coronary artery obstructions. Some authors advise against decompression in these cases for fear that decreasing right ventricular pressure will result in a steal phenomenon, with compromised blood flow to portions of myocardium (see Fig. 118-2A).⁵⁶⁻⁵⁸ Other authors express concern that failure to decompress the right ventricle will allow these fistulas to persist, resulting in ischemia and progressive myocardial fibrosis.^{23,59} To encourage regression of these connections, these authors recommend antegrade decompression if an infundibular cavity is present, or retrograde decompression by tricuspid valve excision if there is no infundibulum.²³ Other authors recommend tricuspid valve closure⁶⁰ or right ventricular thromboexclusion⁵⁹ to prevent deoxygenated blood from entering the coronary circulation. It was recently reported that thromboexclusion may increase the left ventricular shortening fraction.⁶¹

In a study of patients with PA/IVS who have right ventricle-to-coronary artery connections and a spectrum of coronary artery abnormalities, Giglia and associates¹⁶ found that antegrade right ventricular decompression could be performed without jeopardizing left ventricular function when coronary stenoses were absent or when stenosis involved only a single coronary artery. At present, therefore, most centers attempt right ventricular decompression in the presence of right ventricle-to-coronary artery connections when RVDCC has been ruled out and antegrade decompression is possible.⁵ When antegrade decompression is not possible, the approach to right ventricular decompression remains controversial and continues to be institution specific.^{5,23,59,60,62}

Indications for Transplantation

Because early mortality continues to occur despite appropriate surgical management,^{1,2} cardiac transplantation has

been considered a suitable therapy for a small subset of patients with PA/IVS.⁶² In the 2004 CHSS report (408 patients), only 2% of patients underwent cardiac transplantation.¹⁰ Among patients with PA/IVS who should be considered for heart transplantation are those with RVDCC and aortocoronary atresia. The few reports of this subset indicate that other methods of treatment have resulted in almost uniform mortality.^{30,37} Also, patients with PA/IVS who have severe tricuspid regurgitation and a massively dilated right ventricle ("wall-to-wall" heart) have an extremely poor prognosis and should be considered for primary heart transplantation.⁶³ The presence of RVDCC alone is not an absolute indication for cardiac transplantation unless there is poor left ventricular function. Some centers, however, have recommended that infants with RVDCC and satisfactory left ventricular function be considered appropriate candidates because of the high early mortality in this group, even when right ventricular decompression is avoided.^{56,64} Such a policy remains controversial, however, because other centers have had satisfactory results using a single-ventricle approach with these patients,^{5,59} including Powell and associates,⁶⁵ who reported a 5-year survival of 83% in these patients. Such survival exceeds the 65% to 70% that is currently being achieved for infant heart transplantation.⁶⁶ Nevertheless, for a specific infant with signs of ischemia or left ventricular dysfunction (or both), transplantation may be the best strategy.

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TETRALOGY OF FALLOT WITH PULMONARY STENOSIS

Giovanni Stellin • Vladimiro Vida • Massimo Padalino

CHAPTER OUTLINE

HISTORY

PREVALENCE

ANATOMY AND PHYSIOLOGY

Pulmonary Valve and Pulmonary Valve Annulus

Ventricular Septal Defect

Main Pulmonary Artery and Branch Pulmonary Arteries

Coronary Arteries

PHYSICAL EXAMINATION

MEDICAL MANAGEMENT

DIAGNOSTIC STUDIES

SURGICAL TREATMENT

Palliations

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SPECIAL TOPICS IN SURGICAL MANAGEMENT

Anomalous Coronary Patterns

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CONTROVERSIES IN SURGICAL MANAGEMENT

Ventriculotomy versus Transatrial-Transpulmonary Approach

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LONG-TERM FOLLOW-UP

Right Ventricular Performance and Functional Status

Arrhythmias and Sudden Death

Late Pulmonary Valve Implantation

ATRIOVENTRICULAR CANAL AND TETRALOGY OF FALLOT

TETRALOGY OF FALLOT WITH ABSENT PULMONARY VALVE

HISTORY

Stensen, in 1672, described for the first time the anatomic features of what is now termed *tetralogy of Fallot* (TOF).¹ In 1888, Etienne-Louis Arthur Fallot published his findings describing the four features of the congenital cardiac anomaly that bears his name²: infundibular pulmonic stenosis, ventricular septal defect (VSD), dextroposition of the aorta, and right ventricular (RV) hypertrophy.

More than 50 years later, the first successful palliative surgical therapy for TOF was performed by Alfred Blalock and Helen Taussig in 1944 at the Johns Hopkins University, following the experience of Vivien Thomas, who in Blalock's laboratory was producing an animal model of pulmonary hypertension by anastomosing end-to-side the subclavian artery to the pulmonary artery in dogs.³ Other operative operations to augment the pulmonary blood flow were soon developed by Potts, Waterston, and others.⁴⁻⁷ The first successful repair of this condition was performed by Lillehei and Varco at the

University of Minnesota in 1954 using "controlled cross circulation," with either father or mother serving as the oxygenator and blood reservoir.^{8,9} Kirklin reported the first repair of TOF using a pump oxygenator at the Mayo Clinic in 1955.^{10,11} Barrett-Boyes and Neutze¹² and Castaneda¹³ opened the avenue of the new era of TOF repair by demonstrating the feasibility and the advantages of one-stage repair compared with a two-stage approach. The literature reveals excellent operative results and a low mortality rate. Nevertheless, the results of repair over decades have shown that chronic pulmonary valve (PV) regurgitation, together with a RV geometries distortion secondary to ventricular patching, leads to chronic RV failure.¹⁴⁻¹⁵ Therefore, one is now focusing on techniques aimed to preserve the long-term RV function.

PREVALENCE

Tetralogy of Fallot is the most common cyanotic congenital heart defect in all age groups, constituting

approximately 8% of all congenital heart defects. It occurs in nearly 0.19 to 0.26 in 1000 live births, with a prevalence of about 3.9 per 10,000 live births in the United States.¹⁶⁻²⁰ Furthermore, TOF is one of the most common congenital heart lesions requiring intervention in the first year of life and occurs equally in males and females.¹⁶⁻¹⁸ Mutations in several human genes have thus far been identified in TOF. The deletion of human *TBX1* appears to be the basis for the 15% of TOF attributable to chromosome 22q11.2 microdeletion, although *TBX1* mutations in nondeleted TOF patients remain to be identified.²¹⁻²³ Other identified mutations included the *NKX2.5*, which accounts for 4% of TOF²⁴ and the mutation *JAG1* in Alagille syndrome in which the incidence of TOF is high.^{25,26} The gene or genes causing TOF in trisomy 21, 18, and 13, which together account for 10% of TOF cases,²⁷ are as yet unidentified. Thus, in approximately 70% of TOF patients, a genetic etiology remains to be determined.

ANATOMY AND PHYSIOLOGY

The original concept of four coexisting defects described by Fallot in 1888, was revisited by Richard Van Praagh in 1970,²⁸ who introduced the concept that TOF is actually a “monology” resulting essentially from the underdevelopment and malalignment of the RV infundibulum or conus. According to Anderson and colleagues,²⁹ however, the right ventricular outflow tract (RVOT) in TOF results from the deviation of the infundibular septum cephalad and anterior. This anomaly of the infundibular septum narrows the RVOT, leading to a subpulmonary obstruction of variable degree, the more severe creating an atretic infundibulum and/or valve. Prominent muscle bands originating from the septal region of the infundibular septum to extend the RV free wall contribute to the RVOT obstruction. Displacement of the infundibular septum away from the anterior and posterior limbs of the trabecula septomarginalis (septomarginalis trabeculation, septal band) results in a typical anterior malalignment VSD. The aortic valve is located directly behind the infundibular septum because of the anterior displacement of this structure; therefore, the aortic valve overrides the ventricular septum by various degrees. In those cases in which the aortic valve remains aligned predominantly to the RV, particularly when a mitral-aortic valve discontinuity (subaortic conus) is present, such a malformation is termed *double outlet right ventricle*, TOF-type.³⁰

The foramen ovale is mostly open in young infants. If left open during correction, it allows decompression of the right ventricle, when failing during the early postoperative period.

Pulmonary Valve and Pulmonary Valve Annulus

The pulmonary valve is stenotic in 75% of cases because of a hypoplasia of the annulus and fusion of leaflets, supravalar tethering, or a combination of these factors.^{29,31,32} Tethering of the leaflets often distorts the

main pulmonary artery at the sinotubular junction, forming a ridge that can be obstructive, producing supravalar stenosis. The leaflets themselves are often thickened and dysplastic with fusion at their commissural attachment, further reducing the effective annulus size. The pulmonary valve annulus is invariably smaller than the aorta (the opposite of normal); however, it is not necessarily significantly obstructive.

A recent unpublished combined study of the University of Padua, Italy, and the Cardiac Registry at the Children’s Hospital, Boston, have analyzed 101 heart specimens (67 belonging to Children’s Hospital in Boston and 34 to the University of Padua) with TOF, focusing specially on the PV anatomic features. The PV proved to be predominantly bicuspid in 65 specimens (65%), less frequently tricuspid ($n = 23$ [23%]) and rarely unicuspid ($n = 12$ [12%]) and quadricuspid in 1 case (1%). In 53 specimens (53%) of all cases, the PV cusps were normal. This is an important finding, in view of recent new surgical techniques aimed at preserving the native PV during repair (Figs. 119-1 and 119-2).

Ventricular Septal Defect

The VSD is typically large and subaortic, and it reflects in its very nature the deviation of the infundibular septum.²⁹ The VSD is located between the deviated infundibular septum (conus) and the two limbs of the trabecula septomarginalis (septal band). Its posterosuperior margin is limited by the ventriculo-infundibular fold and the aortic valve (which is visible by the surgeon during repair), superiorly by the infundibular septum, anteriorly by the anterosuperior limb, and inferiorly by the posteroinferior limb of the septal band and the muscular septum (Figs. 119-3 through 119-6). In 20% of cases, there is a well-developed posterior limb, essentially forming a continuous muscular border, where the His bundle penetrates and crosses the ventricular septum deeply embedded within this muscle. In the majority of anatomic variants, however, the posteroinferior rim of the VSD is wrapped by a rim formed by the confluence

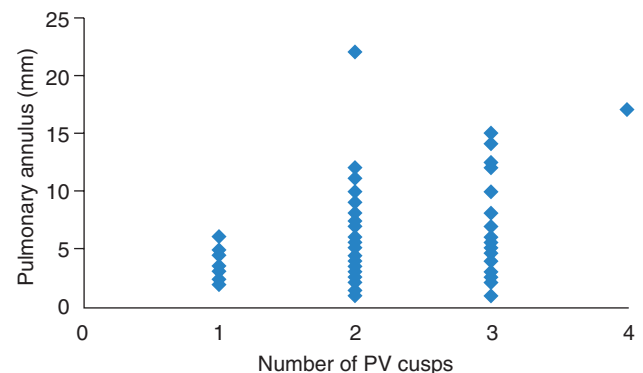


FIGURE 119-1 ■ Graph showing unpublished data on pulmonary valve (PV) anatomy of 101 heart specimens with tetralogy of Fallot (67 belonging to Children’s Hospital in Boston and 34 to the University of Padua). The PV was bicuspid in 65 specimens (65%), tricuspid in 23 (23%), unicuspid in 12 (12%), and quadricuspid in 1 (1%).

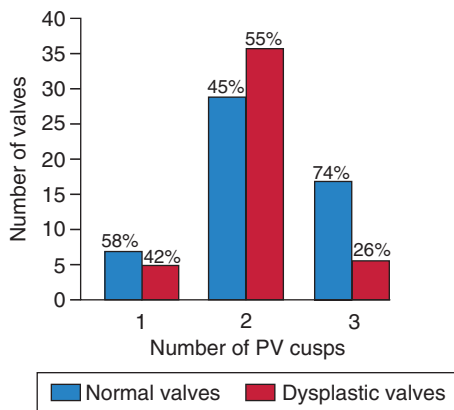


FIGURE 119-2 ■ Graph showing unpublished data on pulmonary valve (PV) anatomy of 101 heart specimens with tetralogy of Fallot (67 belonging to Children's Hospital in Boston, and 34 to the University of Padua). The PV cusps were normal in 53 specimens (53% of all cases).

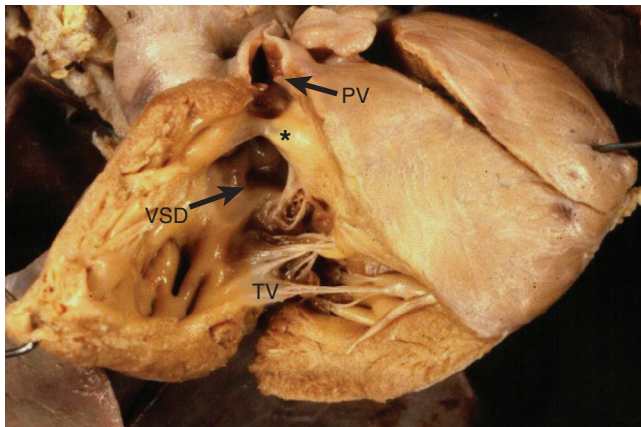


FIGURE 119-3 ■ Anatomic image of a specimen with tetralogy of Fallot showing the inflow and the outflow tracts of the right ventricle, including the infundibular septum (*asterisk*), malalignment ventricular septal defect (VSD), pulmonary valve (PV), and tricuspid valve (TV). (Courtesy Professor Gaetano Thiene.)

of the membranous septum, attachment of the tricuspid valve, and the aortic valve annulus (perimembranous malalignment VSD).^{29,33-35} The posteroinferior limb of the septal band is hypoplastic and therefore does not extend to the posteroinferior border. In this case, the His bundle penetrates and traverses the septum near the fibrous posteroinferior rim of the VSD, being at risk of injury during VSD closure, particularly when the anterior and septal TV leaflets are scarcely developed.

In a small subset of patients, the infundibular septum is extremely hypoplastic or even macroscopically absent. Consequently, the aortic and pulmonary valves are in anatomic fibrous continuity, and the VSD is positioned mostly within the subpulmonary area.

Up to 15% of patients have additional VSDs, which are usually single and muscular, residing mostly within the anterior portion of the ventricular septum.³⁶⁻³⁷ In rare cases, an additional VSD exists in the inlet portion of the septum. Since the His bundle is within the bridge of muscular tissue separating the two VSDs, closure of such defects can be at risk for conduction disturbances.

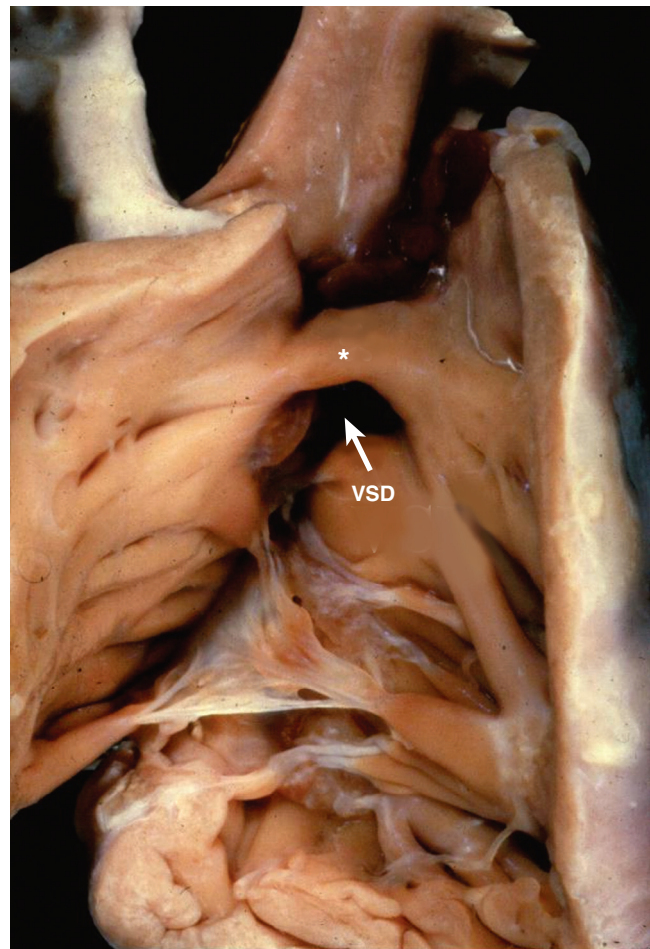


FIGURE 119-4 ■ Anatomic image of a specimen with tetralogy of Fallot showing in detail the anterior deviation of the infundibular septum (*asterisk*) and the malalignment ventricular septal defect (VSD). (Courtesy Professor Gaetano Thiene.)

Main Pulmonary Artery and Branch Pulmonary Arteries

The main pulmonary artery (MPA) and its right and left branches are smaller caliber than normal; localized stenosis is most often confined to the origin of the left branch, believed to be due to ductal tissue constriction or iatrogenic located at the level of previous systemic/pulmonary arteries shunts anastomosis.^{34,36} In TOF and pulmonary stenosis, the pulmonary trunk and branches are rarely in discontinuity and arborization abnormalities of either left or right pulmonary artery branches are equally rare. It must be emphasized that, in the absence of major aortopulmonary collateral arteries, the pulmonary artery (PA) branches in TOF are almost never prohibitively hypoplastic, even in the presence of severe narrowing of the RVOT, and therefore remain candidates for complete repair.

Coronary Arteries

Coronary arteries anomalies are present in 5% to 12% of patients with TOF.³⁷⁻⁴¹ Most frequently, the left

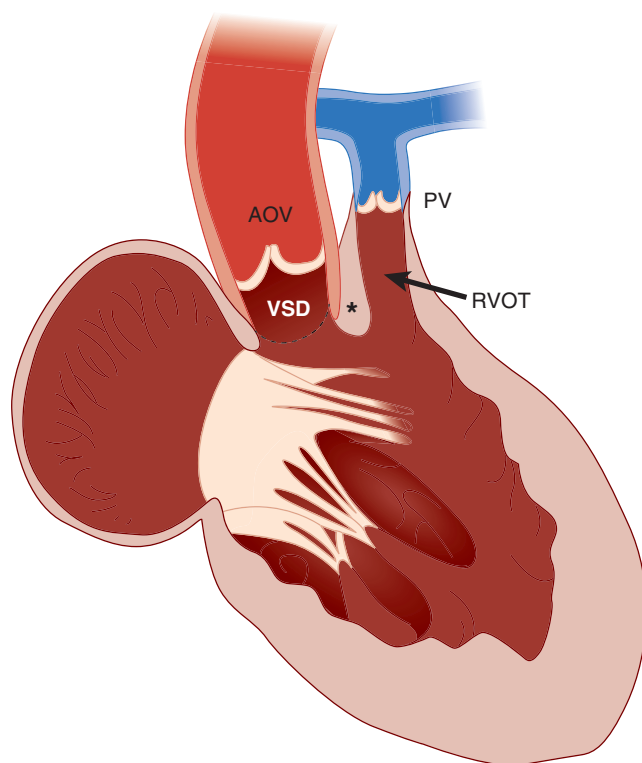


FIGURE 119-5 ■ The deviated infundibular septum (*asterisk*) and the narrow right ventricular outflow tract (RVOT). AOV, Aortic valve; PV, pulmonary valve; VSD, ventricular septal defect.

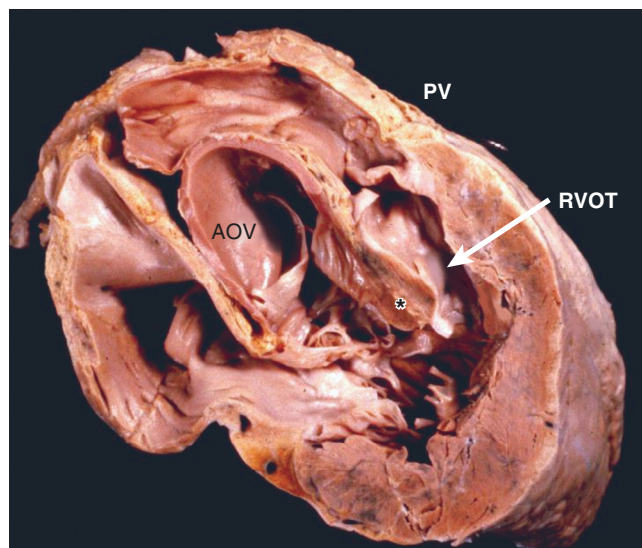


FIGURE 119-6 ■ Anatomic image of a specimen with tetralogy of Fallot showing the deviated infundibular septum (*asterisk*) and the narrow right ventricular outflow tract (RVOT). AOV, Aortic valve; PV, pulmonary valve. (Courtesy Professor Gaetano Thiene.)

anterior descending coronary artery (LAD) arises from the right coronary artery (RCA) and traverses the RVOT at various distances from the PV annulus. This anomaly is of great importance for the surgeon to avoid transection or distortion during repair. A transannular incision is at risk under this circumstance. Other coronary artery

anomalies encountered in TOF include: origin of RCA from the left coronary artery; left coronary artery from the MPA; a single coronary artery originating from the left coronary sinus; and an accessory LAD from the RCA.³⁷ Rarely, significant LAD coronary artery branches from the RCA cross the RVOT within the infundibular muscle and are therefore not visible on the epicardial surface, making injury of these arteries possible at the time of repair.

These coronary artery anomalies are more likely to occur in severe forms of TOF, such as coexisting with severe MPA hypoplasia and anterior and lateral rotation of the aorta.⁴¹

Significant coronaries abnormalities can be frequently detected preoperatively with two-dimensional echocardiography, and surgical management can be modified during repair to avoid injuring these vessels.³⁷

PHYSICAL EXAMINATION

When children are admitted electively, during early infancy, they usually exhibit a good clinical state, with no or mild cyanosis (transcutaneous oxygen saturation is often greater than 80%). Cyanosis can be more than mild in the very severe forms or in older children who are presenting late with a progressive myocardial compensatory hypertrophy and significant arterial collateral vessels.

On examination of the heart, the second heart sound is often single and accentuated because of anteriorization of the aortic root. A moderate intensity midsystolic ejection murmur is heard loudest in the second and third intercostal space. Rarely in the less severe forms, TOF can present with signs of increased pulmonary blood flow.

Blood sampling to determine the presence of deletion on the long arm of chromosome 22q11 is part of the routine workup to provide the opportunity for genetic counseling and to identify other organ systems that are frequently involved, as summarized by the acronym CATCH-22 (cardiac disease, abnormal face, thymic hypoplasia, cleft palate, and hypocalcemia).

MEDICAL MANAGEMENT

Since the introduction of early repair of TOF, the preoperative medical management has lost its important role in treating cyanotic children with TOF. Children are usually asymptomatic for the first 2 to 3 months after birth. Cyanosis usually progresses with spells in older children. A cornerstone of the preoperative management is maintaining these infants in well-hydrated state and to avoid contacts to protect them from viral infections. Beta blockers can be used to treat or prevent cyanotic spells. Nevertheless, early repair can avoid most of these complications by restoring a “normal” circulation. Balloon angioplasty and stenting of the RVOT has been recently developed as a palliative procedure for insuring adequate pulmonary blood flow, particularly in those centers where surgical correction in neonates and young infants is postponed (see [Palliations](#)).

DIAGNOSTIC STUDIES

Cardiac catheterization is seldom necessary for assessing the surgical anatomy, except to rule out the presence of major aortopulmonary collateral vessels, often suspected in children who are relatively pink, despite a severe obstruction of the RVOT⁴² or to confirm the echocardiographic diagnosis of coronary artery anomalies (Figs. 119-7 and 119-8).

Two-dimensional echocardiography has become the gold standard to define most details required for surgical correction. A prenatal echo diagnosis is nowadays often

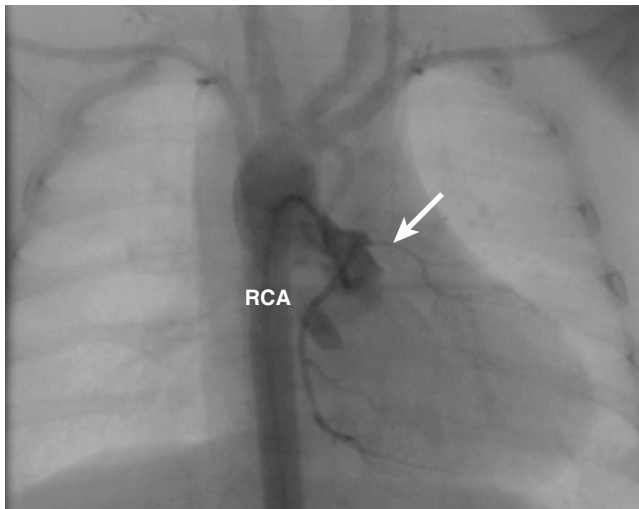


FIGURE 119-7 ■ Preoperative angiographic image showing a large conal coronary artery branch (arrow) originating from the right coronary artery (RCA) and crossing the right ventricular infundibulum. (Courtesy Professor Ornella Milanese.)

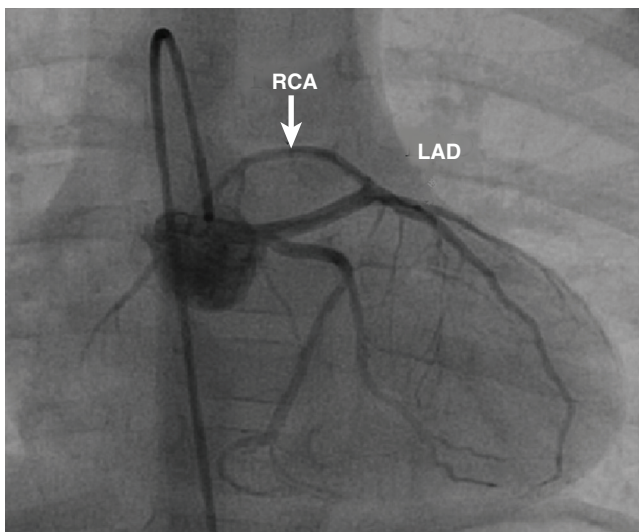


FIGURE 119-8 ■ Preoperative angiographic image showing the left coronary artery selective injection. The arrow indicates the anomalous origin of the right coronary artery (RCA) from the left anterior descending coronary artery (LAD) crossing the right ventricular infundibulum.

available and it is usually reconfirmed, soon after birth.⁴³⁻⁵¹ Two-dimensional echocardiography and Doppler in TOF is routinely used for delineating the important features of the malformation and for supplying the surgeons all relevant information essential for achieving a proper repair.

In the long-axis view, the degree of overriding of the aortic valve across the VSD is assessed (Fig. 119-9). The anterior muscular septum is also interrogated to rule out any additional muscular anterior VSDs.

In the parasternal short-axis view, the degree of displacement and length of the infundibular septum is well seen together with all the pertinent anatomy related to the RVOT obstruction, including level of obstruction, type, and severity (Figs. 119-10 and 119-11). In this projection, the PV annulus, MPA, and branches are visualized and measured (see Figs. 119-10 and 119-11). Pulmonary arteries discontinuity or stenosis (particularly at the LPA origin) are usually well identified in this projection. In the absence of localized stenosis, hypoplastic pulmonary arteries very rarely contraindicate total repair (see *Anatomy and Physiology*).

Excellent anatomic images are also obtained from a right or oblique subcostal view. This projection is important for gathering additional information concerning the anatomy and degree and level of RVOT obstruction. Pulmonary valve anatomy, MPA and its branches are also clearly visible and measurable using this projection (Fig. 119-12).

In an apical four-chamber view, the VSD is also well visualized and sized. The muscular septum is screened to rule out any additional VSD. Through a short parasternal axis view, at the base of the heart, both coronary arteries are visualized to exclude any anomaly in origin of the LAD and of major branches of the RCA, including crossing of the RV infundibulum.

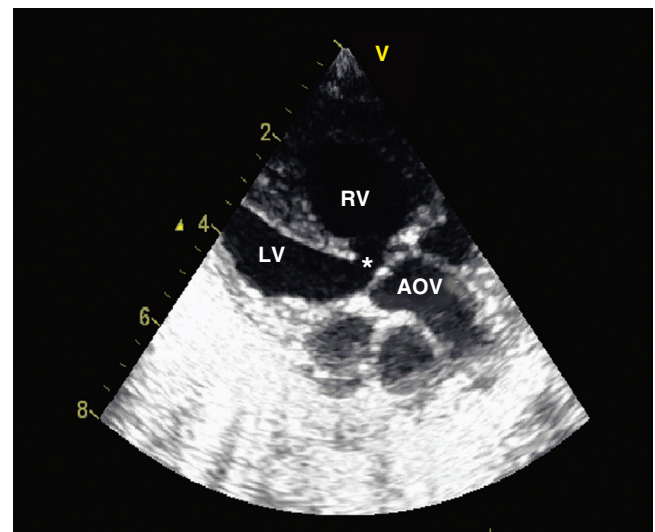


FIGURE 119-9 ■ Preoperative two-dimensional echocardiographic image, long-axis view, showing the degree of overriding of the aortic valve across the ventricular septal defect (asterisk). AOV, Aortic valve; LV, left ventricle; RV, right ventricle. (Courtesy Professor Ornella Milanese.)

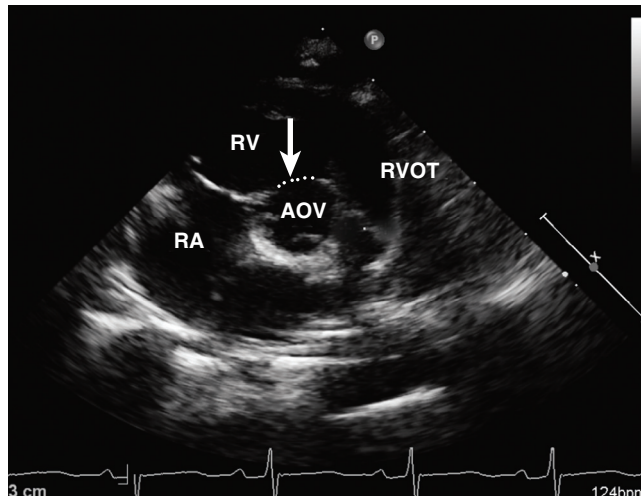


FIGURE 119-10 ■ Preoperative two-dimensional echocardiographic image, short-axis view, showing the deviation of the infundibular septum creating the interventricular communication (white dots) and the obstruction at the right ventricular outflow tract (RVOT). AOV, Aortic valve; RA, right atrium; RV, right ventricle. (Courtesy Professor Ornella Milanese.)

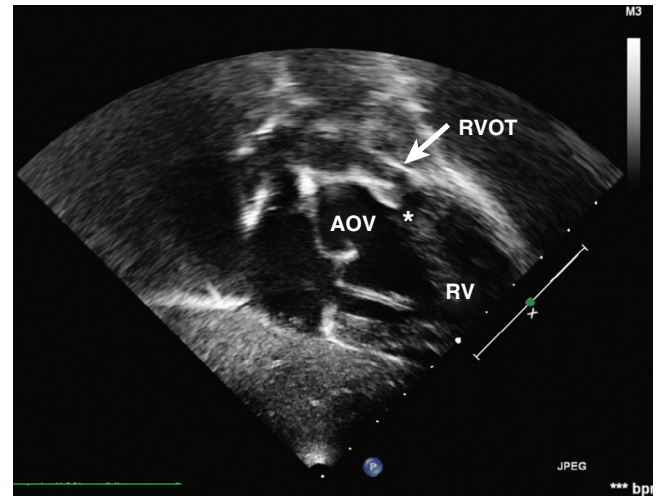


FIGURE 119-12 ■ Preoperative two-dimensional echocardiographic image, oblique subcostal view, showing the right ventricular outflow tract (RVOT) and the deviated infundibular septum (asterisk). AOV, Aortic valve; RV, right ventricle. (Courtesy Professor Ornella Milanese.)

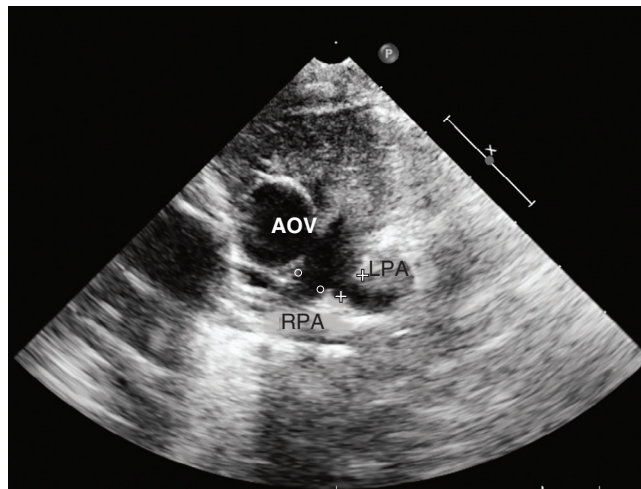


FIGURE 119-11 ■ Preoperative two-dimensional echocardiographic image, short-axis view, showing the origin of the right pulmonary artery (RPA; empty dots) and left pulmonary artery (LPA; asterisks) branches. AOV, Aortic valve. (Courtesy Professor Ornella Milanese.)

The presence of abnormal coronary origin or course (see anatomy) is detected with two-dimensional echocardiography and Doppler, particularly for young infants and neonates, when coronary arteries are readily visible.⁵²

SURGICAL TREATMENT

Palliations

A modified Blalock-Taussig (B-T) shunt is still the preferred palliation, in many centers, in the presence of contraindications for primary repair, which are usually dictated by local preferences and experiences. The approach is through a right or left thoracotomy, for

interposing a tubular graft between the right subclavian artery (or innominate artery) or left subclavian artery, and the ipsilateral PA branch. There is a recent trend in approaching these structures through a midline sternotomy, with cardiopulmonary bypass (CPB) on standby (for achieving a total exposure of both PA branches and for better controlling episodes of hemodynamic instability).

Another palliative shunt can also be achieved by interposing a short segment of a tubular graft connecting the ascending aorta and the main pulmonary artery, with the aim of avoiding any distortion to the small and fragile PA branches.

Other palliative alternatives have been introduced by interventional cardiologists, such as stenting of the RVOT.^{53,54} This procedure can be effective for delaying complete repair and for limiting increasing cyanosis and spells. Stenting of the RVOT, however, will inevitably trigger the formation of scar tissue and possibly distortion of PV, rendering the RVOT anatomy more difficult at the time of definite repair.⁵⁵

A patent ductus arteriosus is rarely present in the absence of PV atresia. However its patency can also be maintained with transcatheter stenting when repair is to be delayed.

Repair

The timing of complete repair is still controversial and varies from center to center. Nevertheless the worldwide trend favors early repair, just as for many other complex congenital heart lesions.⁵⁶⁻⁶¹

Complete early repair has been advocated to avoid:

1. Chronic cyanosis and spells
2. Systemic-to-pulmonary artery shunts and their consequences
3. Chronic RV pressure overload and myocardial compensatory hypertrophy (which requires a more extensive resection, at the time of the repair)

4. Hospital costs and offering patients one instead of two operations

Early repair will also establish a permanent physiological circulation, including a normal O₂ saturation, which will avoid the negative effects of cyanosis (and possible cyanotic spells) upon the cerebral nervous system and other developing organs.¹³

Techniques of Complete Repair

Anesthetic Management

Anesthetic management is critical for avoiding cyanotic spells during preparation and induction. A transesophageal or epicardial two- or three-dimensional echocardiogram and Doppler can be used to recall the preoperative images to the surgeon,⁵⁸ and for monitoring the heart performance before and after repair. At the end of CPB, detection of possible residual lesions and then immediate repair are of paramount importance, before transferring patients to the intensive care unit.

Surgical Access

Repair is performed via a median sternotomy. A partial division of the sternum can also be used, particularly in the less severe forms or for bigger children, according to the surgeon's preference. A large segment of anterior pericardium is harvested and treated with the glutaraldehyde used for VSD patch closure, RVOT reconstruction, MPA or branch enlargement, or PV leaflets extension. Total CPB is established by aorta and double caval cannulation. A left ventricular vent is usually placed through the interatrial sulcus, guided into the LV, placed on suction to achieve a bloodless field. Moderate hypothermia is usually induced, according to center or surgeon preference. During the cooling phase, the MPA is dissected from the aorta and its branches are explored. Right pulmonary artery and left pulmonary artery branches are then occluded distally with a Silastic double loop, to avoid blood return from the bronchial arteries which can be disturbing, particularly in very cyanotic children. On a beating heart, the MPA is incised longitudinally. The PA branches are explored and sized. The PV is inspected and sized to assess the effective PV orifice diameter. The heart is then stopped by aorta cross-clamping and by injecting cardioplegia into the aortic root. The right atrium (RA) is incised above the tenia sagittalis, parallel to the atrioventricular groove, and the whole anatomy of the RA cavity is visualized. The fossa ovalis is inspected and the presence of a foramen ovale (or an atrial septal defect) is assessed. The tricuspid valve (TV) is then retracted and the whole RV anatomy is carefully inspected, with particular attention to the size and type of the VSD (malalignment muscular, malalignment perimembranous) and the whole RVOT up to the PV annulus. The subpulmonary fibromuscular obstructions are then resected through the TV. Particular care is taken to remove any subpulmonary muscular obstruction up to the subannular level.

Further resection of the distal part of the RVOT can be achieved through the PV annulus, aiming to enlarge

the whole RV outlet, up to the PV hinges. The VSD is then patch closed with continuous suture or interrupted stitches, according to the surgeon's preference. Particular care must be taken not to damage the aortic valve (the aortic valve can be better visualized through the VSD and protected by delivering short injections of cardioplegia). To facilitate the VSD closure, significant TV chordae crossing the VSD can be detached at their base, and then reattached in the same position, at the end of the VSD patch closure. The TV is then hydrodynamically tested by gentle injection of cold saline solution into the RV cavity. Any possible TV distortion must be repaired, with the aim of preserving long-term TV performance and RV functional integrity.

The foramen ovale, when present, can be left open to reduce the RV preload by allowing right-to-left shunting during the early postoperative period, when the RA pressure is not uncommonly higher than the left atrial (LA) pressure. Before RA closure, cold saline solution is injected through the foramen ovale into the LA and left ventricle (LV), for clearing the LV of air through the cardioplegia needle in the ascending aorta. During the re-warming phase, the PV valve is again inspected. This maneuver can be achieved on a beating heart during re-warming. When a transannular patch is needed, PV competence can be obtained by adding a "new cusp" of biological or prosthetic material. We have used in small children a RVOT patch bearing a valve cusp that is obtained by a divided adult size pulmonary homograft. An LA line is preferably inserted via the previous LA vent purse string. Temporary ventricular and atrial pacing wires are placed on the epicardium, and the patient is weaned from CBPB transesophageal (or epicardial) echocardiography monitoring before decannulation is routinely performed for detecting any possible residual lesions and for assessing the RV and LV performance. Right ventricular pressure can be directly measured by RV puncture, and compared with the LV pressure. Residual dynamic mild obstruction can be predicted to decrease within the 24 to 48 hours following repair.

SPECIAL TOPICS IN SURGICAL MANAGEMENT

Anomalous Coronary Patterns

Conventional repair is complicated by the occurrence of the LAD coronary artery originating totally or in part (dual LAD coronary pattern) from the RCA with the arterial supply from the right coronary artery crossing the RVOT.⁶²⁻⁶⁸ Achieving adequate relief of the RVOT obstruction while maintaining the integrity of the coronary supply requires an understanding of different surgical options and flexibility in their application. Conduit reconstruction of the RVOT with origin from a ventriculotomy placed below the anomalous coronary has given reliable results but ultimately necessitates reoperation for conduit replacement. Translocation of the pulmonary artery to a distal ventriculotomy and use of the native pulmonary artery as a composite conduit to create a double outflow from the right ventricle have also been

used successfully.⁶⁴⁻⁶⁷ The transatrial transpulmonary approach has been especially successful in dealing with this difficult anatomy.^{65,66} Brizard and coworkers⁶⁵ reported on Duncan's approach in 36 patients, which allowed a conduit to be avoided in all but two cases. Twenty-five patients required a limited transannular patch that was slightly deviated, when necessary, to avoid injuring the anomalous coronary artery. There were no perioperative or long-term deaths, and postoperative right ventricular pressures were low and equivalent to those obtained in contemporaneous patients undergoing TOF repair without coronary anomalies. There was also no difference in reoperation rates for patients with or without anomalous coronaries.⁶⁵ A more recent report provided evidence that adequate relief of RVOT obstruction can usually be performed with a relatively straightforward approach to patch reconstruction without the need for conduits or translocation of the coronary artery.⁶⁸

Use of a Monocusp Valve in Reconstruction of the Right Ventricular Outflow Tract

Monocusp reconstruction of the RVOT (Fig. 119-13) can be achieved by sawing a triangular shape of tissue from the distal part of the ventriculotomy, up to the margin of the natural PV leaflets, using either autologous pericardium or heterologous tissue or prosthetic material (polytetrafluoroethylene [PTFE]). Reports vary regarding the usefulness of monocusp valve reconstruction for the RVOT.⁶⁹⁻⁷⁴ Augmentation plasty of the PV leaflets, by adding an additional cusp can avoid PV regurgitation, early postoperatively, improving the short-term clinical

outcome. Nonetheless, when a cusp needs to be added, leaflet function often deteriorates over time, resulting in a progressive PV regurgitation. When pericardium or PTFE are used to create a monocusp, the valve function is probably limited to the first weeks to months after repair, but the mode of valve failure (adherence of the monocusp to the RVOT patch) is never obstructive.^{69,71} Our unpublished experience with adding a prosthetic cusp material shows that a better short and mid-term performance is achieved with a "built-in" cusp obtained from an adult size pulmonary homograft when compared with other biological added material.

Preservation of the Pulmonary Valve

The use of a transannular patch, necessary in some cases, often results in pulmonary insufficiency with chronic RV volume overload, leading inevitably to progressive RV dilation and dysfunction which is associated with impaired functional capacity. The interest in preserving PV function has stimulated surgeons to devise valve-sparing techniques for TOF repair. During the last few years, some centers have combined the routine correction of TOF with intraoperative balloon dilation of the hypoplastic pulmonary annulus⁷⁵⁻⁷⁹ in selected cases. At the time of repair, the PV is usually inspected and sized to assess the effective PV orifice diameter. In the presence of a stenotic PV, a valvar commissurotomy is performed at each commissure, down to the sinotubular junction. After this maneuver, the valve is again sized to measure the true annular diameter.

Particular care is taken to remove any possible RVOT obstruction up to the subannular level by combining transatrial, transtricuspid muscle band resection and a further transpulmonary residual muscle band excision through the PV annulus, before and after balloon dilation.

Only after a satisfactory muscle bundle resection is achieved, a high pressure, appropriate size, valvuloplasty balloon catheter is introduced through the TV across the PV orifice and inflated under direct vision,^{77,78} while securing its tip, until the inner pressure reaches 10 atm (Fig. 119-14). We use short (2 cm), high-pressure (>10 atm), noncompliant balloons sized according to the calculated size of the PV orifice relative to the body surface area of the patient. When the PV effective orifice is particularly narrow (z-score < -3), we use an "in-series

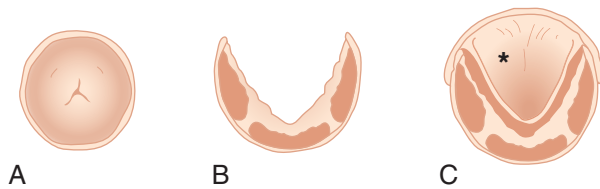


FIGURE 119-13 ■ **A**, The native hypoplastic pulmonary valve in a patient with tetralogy of Fallot. **B**, The native pulmonary valve after transannular incision. **C**, The monocusp-patch augmentation (asterisk) of the right ventricular outflow tract.

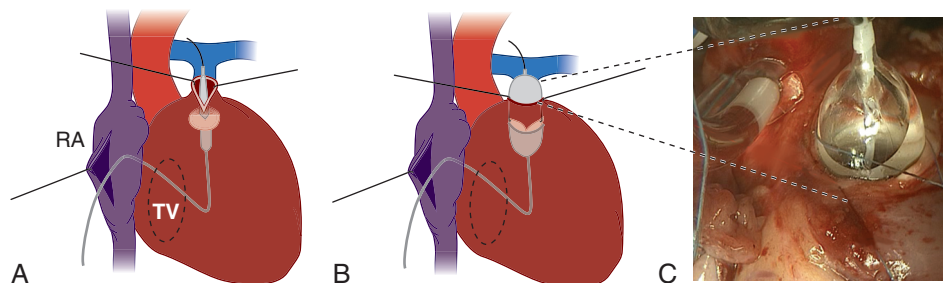


FIGURE 119-14 ■ **A** and **B**, Cartoon showing the intraoperative balloon dilation of the pulmonary valve. It is notable that, because of the transatrial approach, the balloon catheter is inserted through the right atrium (RA) and tricuspid valve (TV) into the pulmonary valve annulus. **C**, Intraoperative details of the balloon catheter through the pulmonary valve.

balloon dilation strategy” by using increasing diameters of balloons for allowing a progressive stretching and dilation of the PV annulus up to the ideal size according to body surface area. While dealing with a highly hypoplastic PV annulus (z-score range, -3 to -4), the PV leaflets, which are often separated by the balloon dilation at the commissure level, are then reconstructed by carefully delaminating them with a fine scalpel at the PV hinge point and down to the RV epicardium, thus extending the leaflets coaptation area (Figs. 119-15 through 119-17). Subsequently, the extended leaflets are “re-suspended” either directly or after further augmentation with small prosthetic (biologic) patch material. An appropriate Hegar dilator for PV size (PV z-score = 0) is passed through the new PV annulus. The MPA is eventually patch enlarged, when needed, with an autologous pericardial patch that is anchored proximally below the PV annulus, onto the RVOT epicardium, with the aim of avoiding any potential early or late constriction over the reconstructed PV apparatus (Fig. 119-18). In case the PV anatomic integrity cannot be preserved, a transannular incision is performed into the distal part of the RVOT.

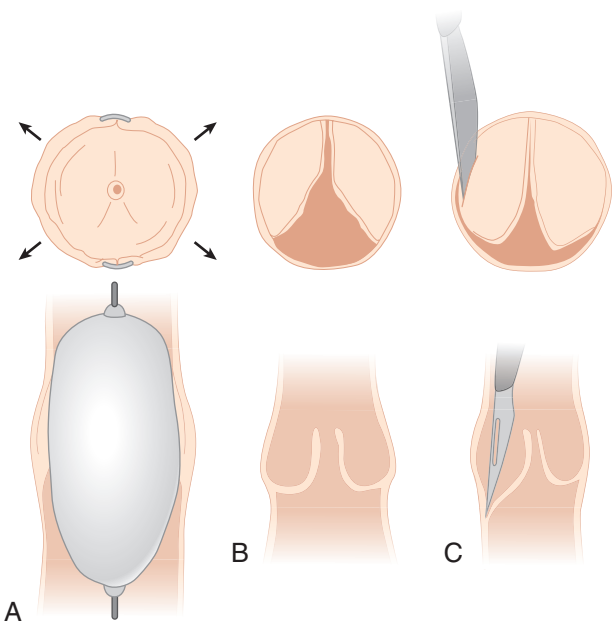


FIGURE 119-15 ■ The intraoperative delamination of the pulmonary valve leaflets to increase its coaptation area (B and C) after balloon dilation (A).

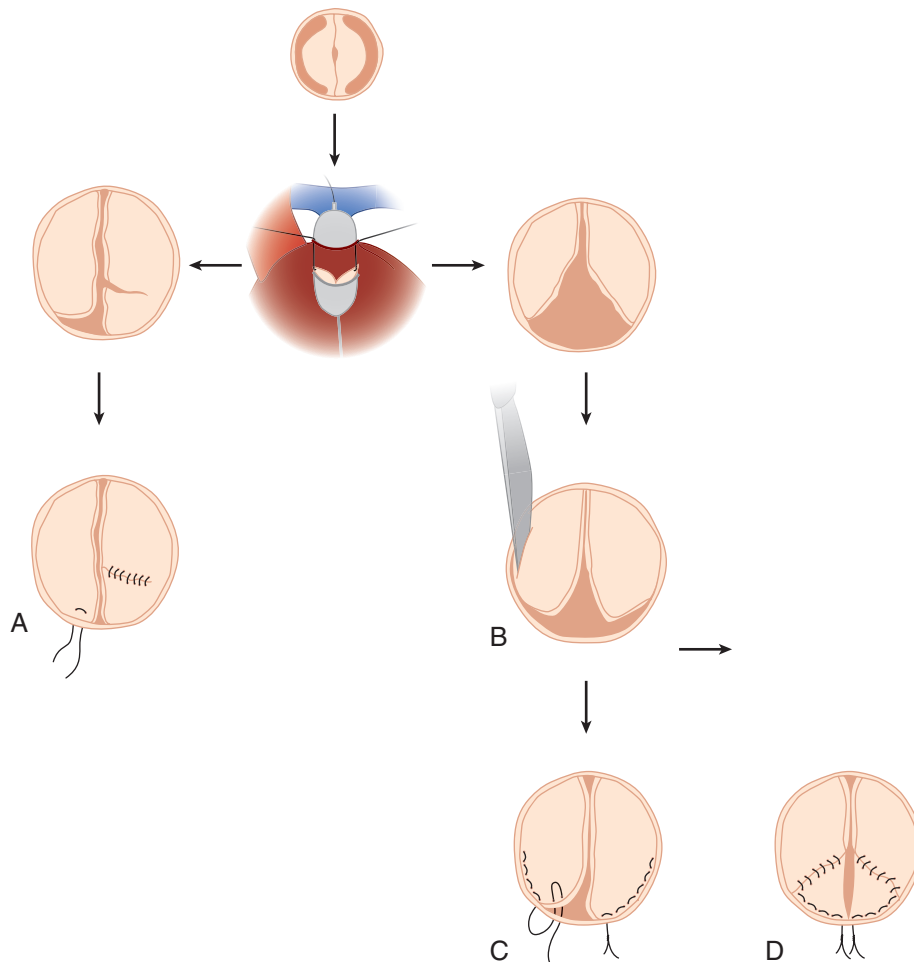


FIGURE 119-16 ■ Cartoon showing the different additional surgical maneuvers on the pulmonary valve after balloon dilation. A, Leaflet repair. B, Leaflet delamination. C, Leaflet resuspension. D, Leaflet patch augmentation and resuspension.

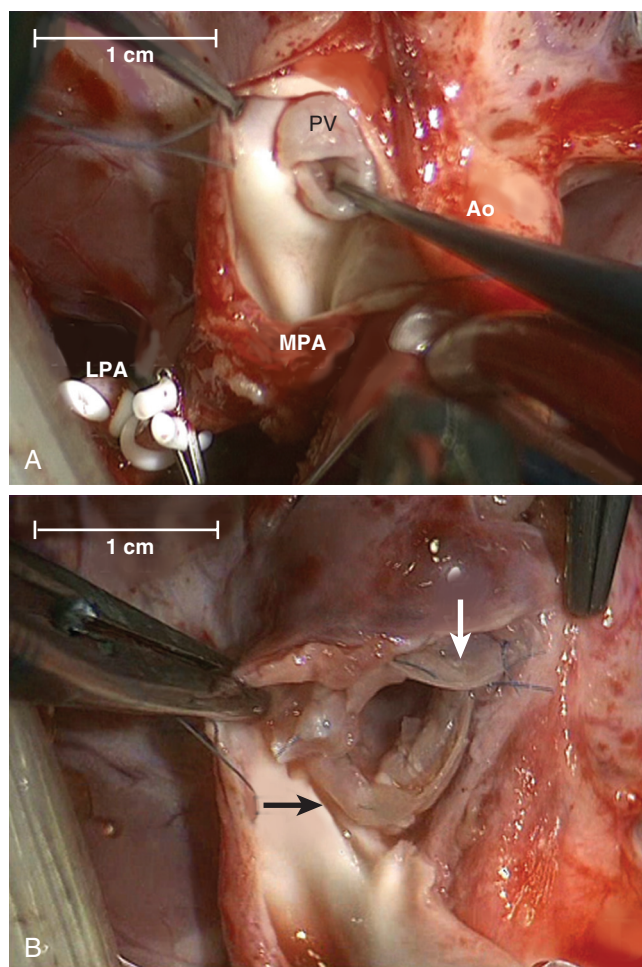


FIGURE 119-17 ■ Intraoperative images of a 3.5-month-old boy with tetralogy of Fallot showing the (A) initial (4 mm) and (B) final (10 mm) diameters of the pulmonary valve after pulmonary valve preservation technique. Arrows indicate the pulmonary valve leaflets. Ao, Ascending aorta; LPA, left pulmonary artery; MPA, main pulmonary artery; PV, pulmonary valve.

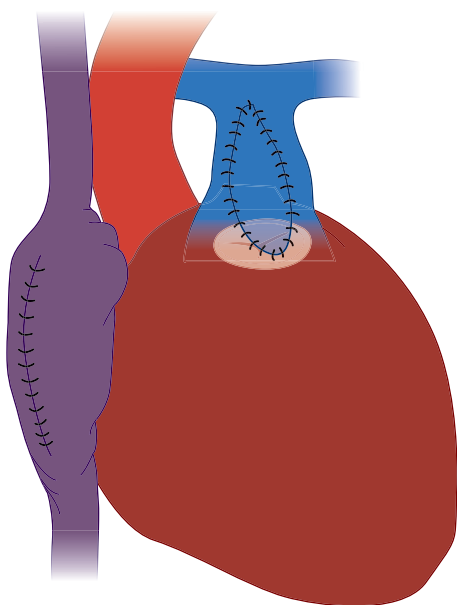


FIGURE 119-18 ■ Patch augmentation of the main pulmonary artery after pulmonary valve preservation.

CONTROVERSIES IN SURGICAL MANAGEMENT

Ventriculotomy versus Transatrial-Transpulmonary Approach

Excellent exposure of the VSD and obstructive muscle bundles in the RVOT can be achieved through either a right ventriculotomy or through an incision in the right atrium.^{11,13} An approach through a right ventriculotomy (Fig. 119-19) is still preferred, in many centers.⁸⁰⁻⁸⁶ Access to the VSD, and to obstructing muscle bundles of the RVOT is more easily achieved by incising longitudinally the RV infundibulum. After muscle bundle resection, the VSD is patch closed either with interrupted stitches or continuous suture. In light of the long-term results that reveal a chronic RV dysfunction after “pioneeristic” TOF repair, which was routinely achieved by means of a “generous” ventriculotomy, there is now a common trend in limiting the right ventriculotomy for, as much as possible, limiting in this way the RV geometry distortion. In addition, some groups have reported a lower incidence of recurrent RVOT obstruction in lesions corrected through the RV ventriculotomy.⁸⁷⁻⁸⁹

Approach through a RA incision (Fig. 119-20) and, when necessary, a combined incision in the pulmonary artery avoids a ventriculotomy and may help to avoid RV dysfunction after repair, especially in the immediate post-operative period and in the very young heart.⁹⁰⁻¹⁰⁰ Miura and coauthors⁹² demonstrated better preservation of right ventricular function at baseline and in response to catecholamine infusion in patients who had undergone a transatrial transpulmonary approach than in those with a right ventriculotomy. In 1995 Stellin and colleagues⁵⁸ demonstrated a trend toward a reduced RV volume and a better ejection fraction in the long term after transatrial repair, when compared with a classic transventricular repair. If a transannular patch is required, a limited right ventriculotomy extending only a few millimeters below the pulmonary annulus is possible.^{58,101} Minimizing or eliminating a right ventriculotomy altogether by using a transatrial or combined transatrial transpulmonary approach may also reduce the substrate for ventricular arrhythmias arising from incisions in the right ventricle.

Timing of Operation

The predominant trend in the timing of surgical intervention has been toward earlier intervention with elective repair in the first 4 to 6 months of life.^{56-60,102-115} There is less consensus regarding the best treatment for patients who become symptomatic early in infancy or in the neonatal age. Some advocate primary repair in symptomatic infants regardless of age.^{114,115} Whereas some centers have adopted a policy of elective repair for all infants at the time of presentation, even for neonates.^{96,104,107,116,117} Advocates of early primary repair note that this approach limits the duration of exposure of these children to cyanosis and its attendant cumulative complications. In addition, initial complete repair avoids the attrition that can

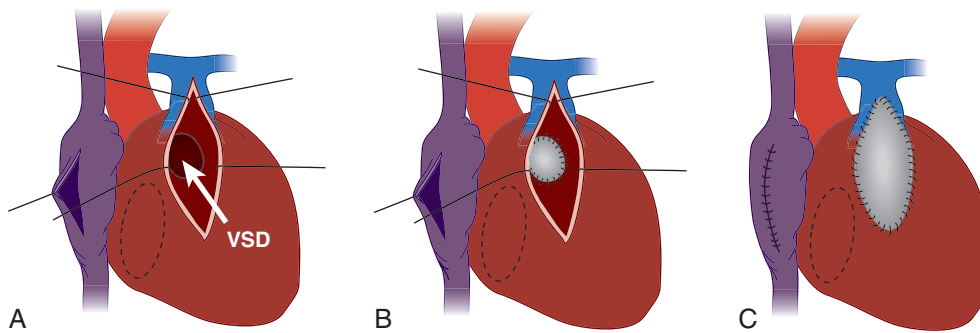


FIGURE 119-19 ■ The intraoperative phases of the transventricular tetralogy of Fallot repair. **A** and **B**, The ventricular septal defect (VSD) is visualized and closed through the right ventriculotomy. **C**, The right ventricular outflow tract and the main pulmonary artery are eventually patch augmented.

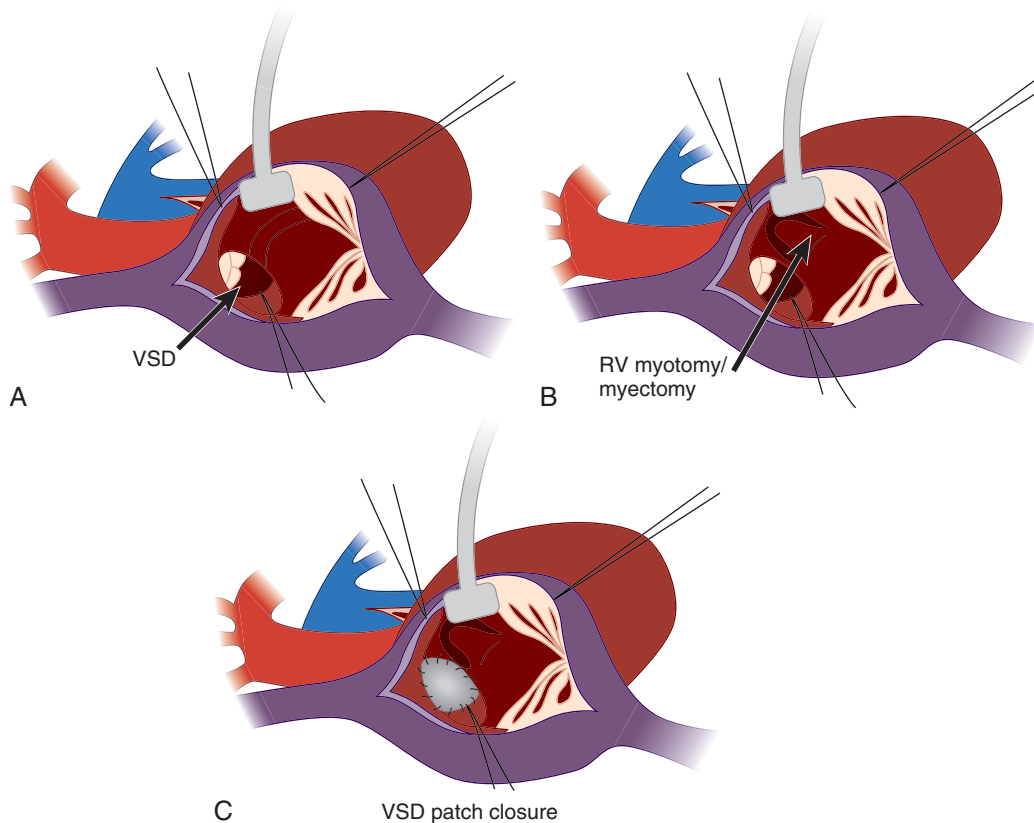


FIGURE 119-20 ■ The intraoperative phases of the transatrial tetralogy of Fallot repair. **A–C**, The ventricular septal defect (VSD) is visualized and closed through the right atrium after **(B)** a combined transatrial/transpulmonary myotomy and myectomy of the right ventricular (RV) outflow tract.

occur during the time between initial placement of a systemic-to-pulmonary arterial shunt and full repair in patients who undergo a staged approach. Furthermore, it has been postulated that ongoing pressure loading of the RV, in combination with chronic hypoxia, creates a substrate in the RV myocardium that predisposes to arrhythmia and diastolic dysfunction in patients who undergo later complete repair.¹⁰⁸ Some authors have reported primary repair of TOF in early infancy with mortality rates as low as 3%.⁸⁰ Nevertheless, primary repair in early infancy has been shown to require transannular patch placement as part of the repair in a higher percentage of

patients and to require longer stays in the intensive care unit.^{113–115} Excellent results have also been achieved with approaches that selectively use systemic-to-pulmonary arterial shunting as initial palliation for symptomatic neonates and young infants.^{1,90,94} Proponents of this approach cite that mortality and morbidity are higher in the youngest infants in many series that report success with early primary repair. The neonatal myocardium may be less capable of handling the RV volume overload that follows VSD closure in a cyanotic patient, and this can be exacerbated by the additional RV volume loading from pulmonary incompetence and possible tricuspid valve

(TV) incompetence in a heart that has undergone the ischemic period required for surgical repair. Well-executed shunting in early infancy for TOF carries a very low risk of pulmonary artery distortion or early or interval mortality.^{94,96,118} Fraser and colleagues⁹⁶ reported on selective application of primary repair for patients larger than 4 kg, with initial shunting of smaller patients who required earlier attention because of symptoms or anatomy. Although the majority of patients had TOF with pulmonic stenosis, this series also included patients with TOF and pulmonary atresia and patients with TOF and an AV septal defect. A single-shunted patient with TOF and a complete AV septal defect died in the interval before primary repair, but there were no perioperative deaths at the time of complete repair. Patch reconstruction of the RVOT either with a fenestrated VSD patch or without any attempt to close the VSD can be performed as an alternative to systemic-to-pulmonary arterial shunting in symptomatic patients with TOF and diminutive pulmonary arteries.^{119,120}

POSTOPERATIVE MANAGEMENT

The majority of patients have a relatively uncomplicated postoperative course. Inotropic support is usually provided with low doses of dopamine, and extubation is generally possible during the first 12 to 48 hours after surgery. Right ventricular dysfunction as a cause of low cardiac output in the immediate postoperative period is rarely seen, especially when the PV integrity is preserved.¹²¹ Significant diastolic dysfunction of the RV after TOF repair can produce a “restrictive physiology” in which the stiff RV demonstrates inadequate filling and can behave almost like a passive conduit for pulmonary blood flow.^{108,122,123} The causes of RV dysfunction include PV, the presence of a right ventriculotomy, and residual lesions such as a hemodynamically significant VSD or RVOT obstruction. Right ventricular dysfunction is apparent by elevation in the RA pressure along with the accompanying clinical manifestations of liver enlargement, edema, and effusions in a patient with evidence of low cardiac output (decreased cutaneous temperature, elevated lactate levels, decreased urine output). Right ventricular dysfunction after TOF repair is usually transient and responds to increased inotropic support and diuretics. A patent foramen ovale (or a calibrated atrial septal defect) allows right-to-left shunting at the atrial level with decompression of the right heart chambers at the expense of a slight arterial oxygen desaturation. A progressive increase in the oxygen arterial saturation can be interpreted as an improvement in the RV performance in the early postoperative period. Junctional ectopic tachycardia (JET) can occur after TOF repair, especially in the first few hours after surgery.^{58,78,86} When it does occur, postoperative JET is characterized by atrioventricular dissociation with rapid junctional rates of up to 230 beats per minute. In a recent report, JET occurred in 22% of patients who had undergone TOF repair,^{124,125} with resection rather than simple transection of muscle bundles within the RVOT, a higher bypass temperature, and a transatrial approach to VSD closure were all

associated with a higher incidence of postoperative JET. The authors concluded that avoidance of excessive muscle resection in the RVOT and traction during VSD exposure should reduce the incidence of postoperative JET. Treatment of JET includes core cooling (34–35° C), reduction in inotrope dosages, atrial pacing above the junctional rate, and the administration of antiarrhythmic agents.^{126,128} Also loading with amiodarone over 2 to 4 hours, followed by continuous infusion, is a useful pharmacologic approach to JET after TOF repair.^{126,128} We have found that an induced surface hypothermia (rectal temperature of 34–35° C) is a useful tool for treating a low output syndrome, particularly when in combination with arrhythmias.

Residual lesions after TOF repair include residual VSDs and significant RVOT obstruction. Even small residual VSDs (3–4 mm) that would be well tolerated in patients with repaired large left-to-right shunts (VSD, truncus arteriosus) may be poorly tolerated after TOF repair. Poor tolerance of residual left-to-right shunts after TOF repair can result from a combination of factors including coexisting pulmonic regurgitation, noncompliant ventricles, and sudden volume loading of the left ventricle, particularly in neonates and young infants.^{121–123,129} The presence of a residual VSD should be ruled out using intraoperative transesophageal or epicardial echocardiography. Patients with significant VSDs will demonstrate a higher than expected LA pressure. If a pulmonary artery catheter is in place, an oxygen saturation of greater than 80% in pulmonary arterial blood is predictive of a hemodynamically significant residual VSD.^{121,129} Significant residual RVOT obstruction is usually tolerated in the immediate postoperative period, but late problems including ventricular tachyarrhythmias and the need for late reoperation occur more commonly.¹³⁰ Hemodynamic instability arising from residual VSDs or RVOT obstruction may also be attributed to postoperative RV dysfunction alone, therefore residual lesions should be aggressively ruled out in patients with poor postoperative hemodynamics. An accurate intraoperative echocardiographic assessment is essential for ruling out any important residual lesion, before transferring the patient to the intensive care unit.

LONG-TERM FOLLOW-UP

Currently, surgery for TOF repair has reached excellent early and late outcomes in either neonates or children.¹³⁰ Decisions made at the time of surgery have a definite effect on the performance of TOF repair in the long-term follow-up. Despite institutional differences in surgical approach, timing of surgery, and many other aspects of management, long-term outcomes in survivors of TOF repair are uniformly favorable. Alexiou and colleagues¹⁰³ reported a 20-year survival of 98% after TOF repair, with 99% of survivors in New York Heart Association (NYHA) functional class I. Knott-Craig and coworkers¹³¹ reported a 20-year survival of 98% with 86% freedom from reintervention on the RVOT after 20 years of follow-up. Katz and coauthors¹³² demonstrated an 8-year actuarial survival of 96% after TOF repair, with

98% freedom from reoperation. In this study, older age at surgery, an increased ratio of RV to LV pressure, and the use of a preceding Potts shunt were all risk factors for late events. The use of a transannular patch during repair or a Blalock-Taussig shunt before repair were not associated with adverse late events. Murphy and associates¹³³ found a 32-year actuarial survival of 86%, which was less than the expected rate of 96% in age-matched controls. In this report, the authors also found that age at operation beyond 12 years and an elevated ratio of RV/LV pressure is associated with late mortality, whereas the presence of a transannular patch or a Blalock-Taussig shunt was not a significant risk factor for late mortality. Mimic and associates¹³⁴ from Great Ormond Street, have recently reported their experience with TOF repair, confirming that age at repair was not linked to early clinical outcome or reoperation/reintervention rate, and that palliative procedures postponed the timing of complete repair, but did not increase the reintervention rate. Kobayashi and coworkers¹³⁵ reported that 85% of patients had no more than mild TV regurgitation during a mean follow-up of 7 years after repair and that the development of moderate to severe TV regurgitation was independent of the operative approach used (transatrial versus transventricular) but was associated with significant pulmonary regurgitation and elevated right ventricular pressure. As a result of these improved results, currently there are an increasing number of patients with repaired TOF who reach adult age.^{133,136} Thus, new problems have recently arisen other than survival to surgery: RV dysfunction and exercise intolerance, arrhythmias and sudden death, and importantly, pulmonary valve regurgitation requiring replacement.

Right Ventricular Performance and Functional Status

Right ventricular dysfunction can occur in the long term as a result of pulmonary regurgitation, a large right ventriculotomy, and eventual residual lesions.¹³⁷ In the hope of decreasing long-term complications of conventional transventricular repair, a transatrial/transpulmonary approach with limited (<1 cm) transannular right ventriculotomy has been adopted by many centers.^{58,60,138} Nevertheless, benefits of this technique on RV performance in the long term are still not clearly demonstrated. Van den Berg and colleagues⁹⁸ have studied using magnetic resonance imaging (MRI), electrocardiography, and stress test in a cohort of 59 patients treated for TOF with a transatrial transpulmonary approach. At a mean follow-up time of 14 years, when compared with current data on healthy controls, TOF patients had significantly larger RV end-diastolic and end-systolic volumes and smaller RV and LV ejection fraction. In addition, maximum oxygen consumption was $97\% \pm 17\%$ and maximum workload $89\% \pm 13\%$ of predicted. Despite well-preserved clinical conditions, these patients exhibited RV dilation and dysfunction associated with impaired functional capacity. Sfyrdis and colleagues¹³⁸ analyzed early and late results of transatrial/transpulmonary TOF repair over almost 14 years, with the aim of assessing the long-term RV function. Among 245 consecutive patients

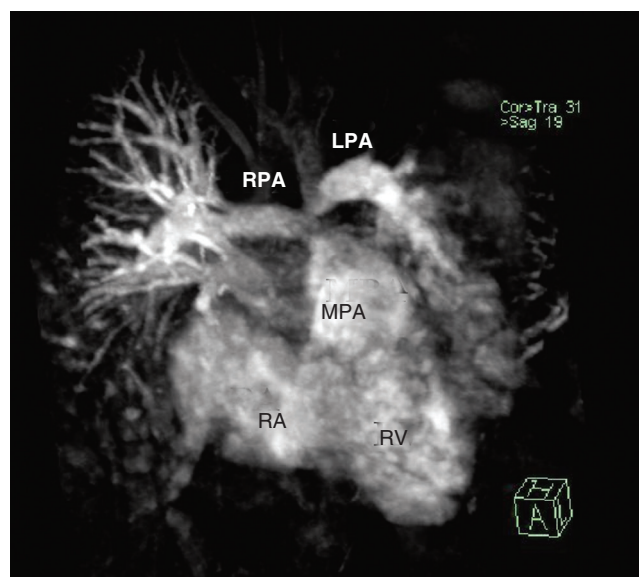


FIGURE 119-21 ■ Magnetic resonance imaging at follow-up. Three-dimensional reconstruction shows the dilated right ventricle (RV) and main pulmonary artery (MPA). Note the proximal stenosis at the left pulmonary artery branch (LPA) origin. RA, Right atrium; RPA, right pulmonary artery. (Courtesy Dr. Martina Perazzolo Marra.)

with repaired TOF (median age, 1.6 years), at a median follow-up of 8.5 years, there were no operative deaths, and only three early reoperations. Actuarial survival at 14 years was 98.8%, but 25 patients required late reoperation (mostly for pulmonary valve implantation). All survivors were asymptomatic at follow-up, and right ventricular function was reported within normal limits in most patients. Cheul and associates¹³⁹ have recently reported results from MRI (Fig. 119-21) comparing patients after a transatrial versus a transventricular TOF repair, with the aim of demonstrating whether a transatrial approach would result in less RV dilation and dysfunction, in the long term. Although the two groups differed significantly in follow-up time (12.7 ± 3.8 years vs. 17.2 ± 4.7 years; $P < 0.001$), pulmonary regurgitation fraction, indexed RV volumes and RV ejection fraction were not significantly different.

The importance of preserving the pulmonary valve function to permit a better RV late outcome has been investigated by different authors.^{75-78,140,141} Recently, our institution has reported⁷⁷⁻⁷⁸ the midterm results of 39 patients after early transatrial repair and an attempt of pulmonary valve preservation by intra-operative balloon dilation of the pulmonary valve annulus. Of these, 34 underwent a successful preservation of the pulmonary valve, at a median age of 3.8 months. Pulmonary regurgitation was absent or mild in 88% at discharge. At a median follow-up time of 1.2 years (range, 0.5-5.3 years) the integrity of the PV seemed to achieve improved RV function in comparison to patients who underwent a classical transannular patch.⁷⁸

The performance of TOF repaired patients during exercise testing is also well maintained as reported by several authors.¹⁴¹ Mahle and colleagues¹⁴² reported that

the mean maximal VO_2 of patients after conventional TOF repair was 95% of the predicted mean value for a control population, and the mean maximal work rate was 98% of predicted. In this study, the age of repair (<1 year of age versus >1 year of age) showed no effect on exercise performance, which is an important finding for decisions regarding timing of repair. Kondo and colleagues¹⁴³ found that cardiac output was normal at rest and during exercise in patients after repair, but that the incremental increase in left ventricular ejection fraction during exercise was reduced. The authors hypothesized that RV enlargement with pathologic changes in the septum (e.g., fibrosis) causes latent left ventricular dysfunction during exercise in these patients. Mueller and associates¹⁴⁴ investigated health-related quality of life (QOL) in children after TOF repair, and they compared the self-reported physical ability with objective exercise performance. This study included 168 patients, aged 8 to 16 years. Health-related QOL and cardiopulmonary exercise capacity were compared with those of an age-matched standard population, and correlations of health-related QOL with self-estimated physical rating and cardiopulmonary exercise capacity were analyzed. Despite health-related QOL in children and adolescents after TOF repair, results indicated no limitations; objective exercise capacity was actually impaired when compared with the standard population. Thus, the self-estimated physical functioning result was significantly overestimated compared with actual exercise capacity.

Arrhythmias and Sudden Death

Supraventricular and ventricular arrhythmias are not uncommon late after TOF repair; however, they can occur with increasing frequency as the duration of follow-up increases.¹⁴⁵⁻¹⁵⁵ Various studies have reported that in patients followed for more than 20 years after TOF repair incidence of arrhythmias requiring treatment was 2% to 4% for atrial fibrillation or flutter, 3% to 4% for sustained ventricular tachycardia, and 2% to 4% for sudden cardiac death.^{148,152,153,155} Holter monitoring detected a higher percentage of arrhythmias, with one report demonstrating that 19% of patients had sustained ventricular tachycardia and 23% of patients had atrial fibrillation or flutter on 24-hour Holter monitoring.¹⁴⁹ After TOF repair, the occurrence of arrhythmias is associated with elevated RV volumes and pressure, decreased right and left ventricular ejection fractions, pulmonic regurgitation, and other pathology of the RVOT such as aneurysm or significant stenosis.^{127,150-154,156} Gatzoulis and associates found that PV regurgitation was associated with ventricular tachycardia and sudden death, whereas TV regurgitation was associated with atrial fibrillation or flutter.¹⁴⁸ In addition, they demonstrated that a substantially widened QRS complex on ECG is a prognostic marker of ventricular tachycardia and sudden cardiac death, with a QRS duration greater than 180 msec sensitively predicting the occurrence of life-threatening ventricular ectopy.^{148,155} Dietl and coauthors¹²⁷ found that the type of operative approach for TOF repair was associated with significant ventricular ectopy after surgery. In fact, they reported that 39% of

patients had significant ventricular ectopy after a ventricular approach to TOF repair, whereas only 2.8% had significant ventricular ectopy after a transatrial approach. In this report, the incidence of moderate to severe pulmonary regurgitation was nearly twice as high in the ventricular repair group (25.9%) as in the transatrial repair group (12.5%). Therrien and colleagues¹⁵³ found that PV replacement, when performed in the presence of important regurgitation and RV enlargement, was associated with a substantial decrease in arrhythmias and stabilization of the QRS duration. These authors used intraoperative electrophysiologic mapping and cryoablation in addition to pulmonary valve replacement in selected cases. In this series, atrial arrhythmias decreased from 17% to 12% postoperatively, and ventricular tachyarrhythmias decreased from 22% to 9%. In the 15 patients who underwent intraoperative cryoablation, there were no postoperative recurrences of significant arrhythmia.

All these studies emphasize that residual hemodynamic abnormalities drive postoperative arrhythmias after TOF repair and that all efforts should be made at the time of repair to provide the anatomic substrate to minimize long-term hemodynamic problems.

In a recent report,¹⁵⁶ atrial reentrant tachycardia is reported to be expected in more than 30% of patients, and high-grade ventricular arrhythmias in about 10%. The overall incidence of sudden cardiac death is estimated at 0.2% per year. Placement of an implantable cardioverter-defibrillator, despite high complications and inappropriate discharges, is often recommended for patients at higher risk. The Mayo clinic group reports that patients with TOF represent up to 40% of candidates for implantable cardioverter-defibrillator therapy.¹⁵⁷ Ongoing surveillance of RV function is a critical component of clinical assessment. Once RV dysfunction occurs, there are no medical therapies that have been shown to be effective, except for resynchronization with biventricular pacing in selected cases.

Late Pulmonary Valve Implantation

Currently, PV implantation is a common procedure during follow-up of patients after TOF repair, that can be done either surgically or percutaneously.¹⁵⁸⁻¹⁶⁰ Timing and indicators for late PV implantation for PV regurgitation after TOF repair are not yet clearly defined and universally accepted.^{36,161-164} MRI has been used increasingly to evaluate RV volumes and function. In most cases, PV implantation can be expected to reduce RV volumes; however, there is a point of RV enlargement beyond which normalization of RV size is unlikely to occur. Several reports support this concept of RV size reduction without normalization when pulmonary valve implantation is performed when RV end-diastolic volume is above 160 to 170 mL/m²¹⁶³⁻¹⁶⁴ or even less.¹⁶⁵ Beyond its impact on RV dimensions, PV implantation reduces tricuspid regurgitation and clinical symptoms, and it often results in improved RV function.^{145,166} The effects of pulmonary valve implantation on QRS duration and the incidence of RV arrhythmia are less well established.^{146,166,167} Based on existing literature, an argument can be made to consider

PV implantation when there is documentation of progressive RV enlargement ($>150 \text{ mL/m}^2$) and RV dysfunction, particularly in the presence of progressive TV regurgitation or decreased exercise tolerance.^{168,169} A number of reports have detailed various clinical aspects of PV implantation in patients after TOF repair.^{145,146,161-164,166-179}

In addition to the standard surgical approach, percutaneous valve implantation has been used increasingly.¹⁵⁸⁻¹⁶⁰ Discigil and coauthors¹⁷² reported on 42 patients who underwent surgical pulmonary valve implantation approximately 11 years after TOF repair. Decreased exercise tolerance (58%), right heart failure (21%), arrhythmias (14%), syncope (10%), and RV dilation (7%) were the main indications for PV implantation. Ninety-eight percent of patients were hospital survivors with 5- and 10-year survival rates of 95% and 76%, respectively. Before surgery, 27% of patients were in NYHA class I or II, and after PV implantation, 97% were in NYHA class I or II. Significant atrial arrhythmias were present in 14% preoperatively and 2% postoperatively. Freedom from repeat PV implantation was 93% at 5 years and 70% at 10 years. Vliegen and coworkers¹⁷⁶ used MRI to evaluate patients before and after PV implantation and found that RV end-diastolic volume and RV end-systolic volume decreased, and RV ejection fraction increased, after PV implantation. As a functional correlate, NYHA class was also found to improve substantially after PV implantation. Despite improvement in RV volumes and functional status after PV implantation, a number of studies demonstrated improvement only if valve implantation was performed appropriately early.^{173,174,177} De Ruijter reported an incidence of severe PV regurgitation of 31% at an average of nearly 10 years after TOF repair, with significant RV dilation in 38%.¹⁷⁴ For patients treated with pulmonary valve implantation, only 44% had normalization of RV size and symptomatic relief. Therrien and coworkers¹⁷³ reported no improvement in RV volumes after PV implantation. In addition, RV ejection fraction remained depressed (<0.4) in 87% of patients in whom preimplantation RV ejection was less than 0.4, whereas 50% of patients with preimplantation RV ejection fraction greater than 0.4 maintained postimplantation RV ejection fractions greater than 0.4. In light of these results, they concluded that late PV implantation failed to normalize RV volumes, and that the best chance of restoring a normal RV function was to perform PV implantation before significant RV dysfunction had occurred. Controversial results were reported by Quail and associates,¹⁴ who studied TOF repaired patients with PV regurgitation. They compared the group of patients treated with PV implantation with matched untreated patients who were eligible for PV implantation based on hemodynamic status. Among 87 patients recruited, 51 underwent surgery while 36 were managed conservatively. Comparing 25 patients from each group using propensity score matching, they found that at 1.8 years of follow-up in patients with intermediate RV dilation, there was a very low risk of significant deterioration in RV or LV volumes and function. They concluded that slow deterioration can guide the interval for repeat imaging studies and determine the appropriate timing for PV implantation. Finally, a recent meta-analysis¹⁸⁰ has

concluded that after PV implantation, there is an improvement of RV volumes and function and of LV function, a reduction of QRS duration, and improvement of symptoms. However, the preoperative RV geometry was capable of modulating the effect of PV implantation. In conclusion, despite important heterogeneity of the effects among the different studies, PV implantation is currently recommended as a reasonable approach to the problem even if surgical timing remains to be further defined and controversies still remain.

Finally, homografts or bioprosthetic valves are usually preferred in the PV position in patients with congenital heart disease.¹⁶¹⁻¹⁶⁵ However, unsatisfactory long-term results have reawakened interest in the use of mechanical valves in the pulmonary position. Waterbolk and associates¹⁸¹ report excellent early and late outcomes of mechanical valve implantation in the pulmonary position in 27 of 79 patients indicated for PV replacement. Tetralogy of Fallot was the most common basic lesion. Thirty-day hospital mortality was 1 of 28 (3.6%), because of a cerebrovascular accident. One patient died late (2.8 years postoperatively). Median age was 33 years, and the median interval between primary repair and insertion of the prosthesis was 26 years. Freedom from reoperation at 1 year was 100%. No thromboembolic events were observed. Recently, Shin and colleagues¹⁸² have investigated the long-term outcomes of mechanical valves implanted in the pulmonic position in 37 patients (median age, 13.5 years; range, 7 months to 23 years) who had undergone 38 mechanical pulmonary valve implantations. Most patients ($n = 23$) had TOF, and the median valve size was 23 mm (range, 17–27 mm). At a median follow-up of 24.6 months (range, 1.3 months to 22.5 years), survival rates were 97%, 97%, and 97%, at 1, 5, and 10 years, respectively. Freedom from thromboembolism or bleeding events was 92%, 92%, and 78.8%, at 1, 5 and 10 years, respectively. Freedom from reoperation was 100%, 100%, and 85.7%, at 1, 5, and 10 years, respectively. Thus they conclude that in growing patients who have undergone prior sternotomies requiring a pulmonary valve replacement, a mechanical valve could be an attractive option. Although life-long anticoagulation therapy is indicated for mechanical prostheses, the chance of subsequent reoperations can be expected to be low.

Further study is necessary for developing an ideal long-standing biological valve in the pulmonary position. Preliminary studies with decellularized pulmonary homograft are promising.¹⁸³⁻¹⁸⁴ A European multicenter ongoing trial will soon report on the use of such a prosthesis, on a larger scale.

Such a new type of tissue engineered valve will certainly show, in the near future, the advantage of treating chronic PV regurgitation in an increasing population after TOF repair in comparison to conventional valve substitutes that are implanted surgically or transcatheterally.

ATRIOVENTRICULAR CANAL AND TETRALOGY OF FALLOT

A common AV valve, an ostium primum atrial septal defect, and a nonrestrictive inlet ventricular septal defect

occur in combination with an anterior malalignment VSD and RVOT obstruction typical of TOF in approximately 2% of all cases of TOF.^{36,185} Repair can be accomplished with a single- or double-patch technique, depending on institutional habits. In addition, transventricular or transatrial transpulmonary approaches can be used successfully.¹⁸⁵⁻¹⁹³ Usually, most or all VSDs can be closed through the right atrium, as is standard for repair of an AV septal defect, but the VSD patch must be shaped appropriately for the peculiarity of this defect; in fact, it has to be elongated and wide enough anteriorly so as to close the anterior extension of the VSD without causing subaortic obstruction. Closure of the cleft in the left-sided AV valve and closure of the ostium primum ASD is performed in a standard fashion, and relief of the RV outflow tract obstruction is performed as would normally be done for TOF. In a recent retrospective analysis from Kotani and colleagues from Sick Children's Hospital in Toronto,¹⁹⁴ of 41 patients who underwent repair for TOF with AV septal defect, only 3 died early. The RV outflow tract was reconstructed, with pulmonary valve sparing in 56%. There was no late death, and survival was 92.1% at 15 years. During a median follow-up period of 5.9 years, freedom from all reinterventions at 15 years was 52.8%; approximately half of those procedures were related to the RV outflow tract revision, whereas only a minority had AV valve dysfunction. Freedom from RV outflow tract-related reintervention and atrioventricular valve/LV outflow tract-related reintervention were comparable between the TOF with atrioventricular septal defect and matched control groups (TOF with atrioventricular septal defect, 95.2% and 88.6% versus atrioventricular septal defect alone, 86.0% and 83.9% at 5 years, respectively; *P* value not significant). Thus, in the current era, the surgically modified history of TOF with atrioventricular septal defect is not significantly different from that of isolated TOF.^{185,187-189,191}

TETRALOGY OF FALLOT WITH ABSENT PULMONARY VALVE

The anatomic features of TOF with absent pulmonary valve include massively enlarged pulmonary arteries, anterior malalignment VSD, absent (aplasia) or rudimentary development of the PV, a relatively small PV annulus, and usually absence of the ductus arteriosus. The etiology of the aneurysmal enlargement of the pulmonary arteries may be related to the effects of regurgitation throughout fetal development, or to abnormalities in the vessel wall. Massive enlargement of the pulmonary arteries frequently causes obstruction of the central bronchi and also alveoli. The degree of airway obstruction dictates the clinical course observed in affected patients. Presentation varies from no clinically significant airway obstruction in asymptomatic patients, to severe bronchioalveolar obstruction requiring mechanical ventilation and surgical repair in the newborn period. Operative repair requires intracardiac correction typical of simple TOF on cardiopulmonary bypass, with surgical reduction in the size of the dilated main and branch pulmonary arteries, that can be

performed by different techniques.¹⁹⁵⁻²¹⁰ In most cases, both the MPA and branches are massively enlarged and must be reduced surgically. Stellin and colleagues²⁰³ advocated surgical intervention to relieve the bronchial obstruction by plicating the pulmonary artery and its branches under deep hypothermia and circulatory arrest. Alternatively, it can be transected with a portion excised posteriorly, which effectively pulls the pulmonary arteries anteriorly away from the tracheobronchial tree. The branch pulmonary arteries are reduced in diameter by resecting portions of the anterior wall, often with plication of the posterior wall.^{197,198,201,202} In most cases, a transannular incision is necessary; reconstruction of the RV outflow tract can then be performed with a homograft valve insertion.^{201,204,206,209} However, RV outflow tract reconstruction can also be performed with a monocusp or, often, without any valve implantation.^{197,198,202,208} McDonnell and coworkers reported an experience with surgical management for 28 patients with TOF and absent pulmonary valve,¹⁹⁷ in which 13 patients (46%) required preoperative intubation and mechanical ventilation. There was a 21% in-hospital mortality, and rates of freedom from death or reintervention at 1 and 10 years were 68% and 52%, respectively. The requirement for preoperative mechanical ventilation was the only risk factor for mortality in this series. Hraska and associates^{196,210} have reported a novel approach to this problem that includes transection and removal of a wedge-shaped portion of the ascending aorta so as to bring the aorta caudally and to the left. A LeCompte maneuver bringing the pulmonary arteries anterior to the aorta is then performed with or without concomitant plication of the branch pulmonary arteries. This approach pulls the pulmonary arteries off the tracheobronchial tree without requiring extensive suture lines, and the method of resection of the aorta creates a space for the new location of the pulmonary arteries while minimizing the risk of compression of the RCA. In a retrospective review of 62 consecutive patients following repair of TOF and absent pulmonary valve, Alsoufi and coworkers²⁰⁶ reported three perioperative deaths in neonates and five late deaths. Five- and ten-year survival was 93% $\pm$ 4% and 87% $\pm$ 5%. On multivariable analysis, significant factors associated with prolonged ventilation were neonatal age (*P* < 0.0001) and preoperative mechanical ventilation (*P* = 0.088). Eight airway reinterventions were needed in seven infants with persistent postoperative airway compromise, pulmonary artery suspension (*n* = 4), innominate artery suspension (*n* = 2), and lobectomy (*n* = 2). Freedom from RV outflow tract reoperation was 89% $\pm$ 5% and 59% $\pm$ 9% at 5 and 10 years, respectively. In conclusion, TOF with absent pulmonary valve remains a complex congenital heart defect, with a perioperative mortality mainly related to a preoperatively compromised bronchial tree, and a higher rate of reintervention in follow-up when compared with classic TOF.

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PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT AND RIGHT VENTRICLE-TO-PULMONARY ARTERY CONDUITS

Sitaram M. Emani

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PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT

Pulmonary atresia with ventricular septal defect (PA/VSD) is a congenital cardiac malformation characterized by discontinuity of blood flow from the right ventricle to the pulmonary arteries, a ventricular septal defect (VSD) resulting from anterior deviation of the infundibular (conal) septum, and an overriding aorta. Because it shares many attributes of tetralogy of Fallot, it is also referred

to as tetralogy of Fallot with pulmonary atresia. Incidence of PA/VSD is estimated to be 1 in 10,000 live births.¹ A right aortic arch may be seen in up to 45% of patients.² PA/VSD is also associated with major aortopulmonary collateral arteries (MAPCAs) that, in some cases, are the sole supply of pulmonary blood flow. The morphology of the pulmonary circulation, which varies significantly among patients, determines the management and prognosis of this malformation. PA/VSD may also be associated with other intracardiac defects, such as tricuspid atresia or stenosis, complete atrioventricular canal,

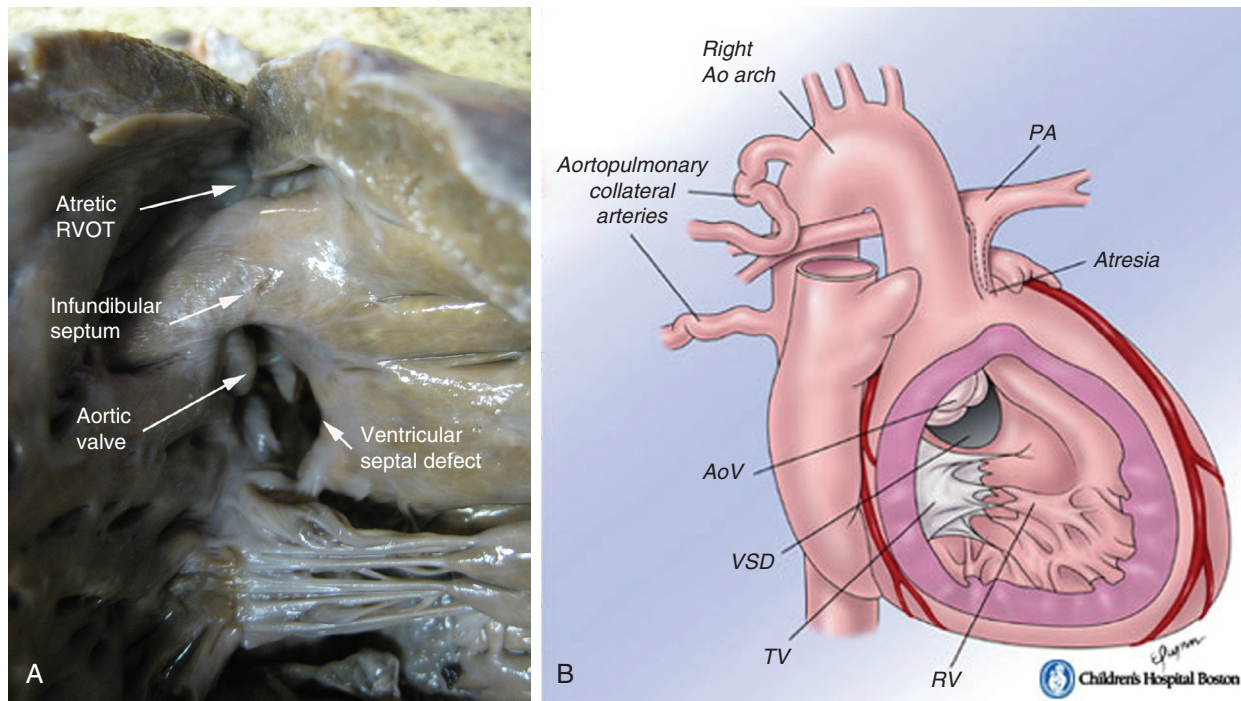


FIGURE 120-1 ■ Anatomic specimen and schematic demonstrating the features of pulmonary atresia with ventricular septal defect. Ao, Aortic; AoV, aortic valve; PA, pulmonary artery; RV, right ventricle; RVOT, right ventricular outflow tract; TV, tricuspid valve; VSD, ventricular septal defect. (Courtesy Children's Hospital Boston.)

complete or corrected transposition of the great arteries, left superior vena cava, anomalies of the coronary sinus, dextrocardia, and asplenia or polysplenia syndrome. These more complex forms of PA/VSD are not discussed in this chapter. The most common associated genetic defect is 22Q11 microdeletion, which is found in up to 34% of patients, and up to 65% of patients with MAPCAs are found to have this abnormality.³ Other phenotypic abnormalities with the 22Q11 microdeletion include submucosal cleft palate, abnormal facies, delayed development, and mental retardation. Neonates with trisomy 13 or 18 may have PA/VSD as well, and the prognosis is extremely poor for these children.

Anatomy and Pathophysiology

As in tetralogy of Fallot, PA/VSD is associated with anterior deviation of the infundibular septum, a conoventricular VSD, and the resulting aortic override (Fig. 120-1). The spectrum of pulmonary atresia varies from purely valvular or subvalvular atresia (with intact main and branch pulmonary arteries) to complete absence of central pulmonary arteries. Pulmonary blood flow is dependent on the presence of an aortopulmonary communication, which may exist in the form of a patent ductus arteriosus (PDA), other major nonductal collaterals arising from the descending aorta that connect to the central native pulmonary arteries, or MAPCAs that directly enter the hilum and join the segmental pulmonary arteries. In utero, the pulmonary parenchyma is perfused by branches from the dorsal aorta as well as by the sixth aortic arch, which forms the basis for the central pulmonary arteries. Abnormal development of the central

pulmonary arteries leads to persistence of the dorsal aortic branches, which ultimately develop into MAPCAs.

The lungs may be supplied by the native pulmonary arteries, by MAPCAs, or by both. If confluent central pulmonary arteries are present, the blood supply to the lung may arise from a PDA, a central “ductlike” collateral, or a MAPCA. The behaviors of these three sources of pulmonary blood flow differ in their predisposition to constrict over time, which has implications for the stability of pulmonary blood flow. Whereas MAPCAs or ductlike collaterals might remain patent beyond the neonatal period, the PDA is likely to constrict postnatally because of the presence of prostaglandin-responsive ductal tissue. Although the distinction may be difficult to establish by preoperative imaging studies, the location on the aorta from which the collateral originates is suggestive. A solitary collateral that arises just distal to the left subclavian artery (if left aortic arch) and travels to a central pulmonary confluence is likely to be a PDA, whereas a collateral that arises from any other location off the aorta and supplies a central confluence is termed a ductlike collateral. A vessel that exits the descending aorta and travels directly to the pulmonary parenchyma is likely a MAPCA. There may be heterogeneity in the sources of pulmonary blood flow within any given patient, such that one segment of lung may be supplied by the native pulmonary artery whereas another segment may be supplied by a MAPCA. Some segments may have a dual supply (Fig. 120-2). Patients with confluent central pulmonary arteries that are supplied by a PDA are less likely to have significant MAPCAs, and those with nonconfluent central pulmonary arteries depend on MAPCAs for pulmonary blood flow.

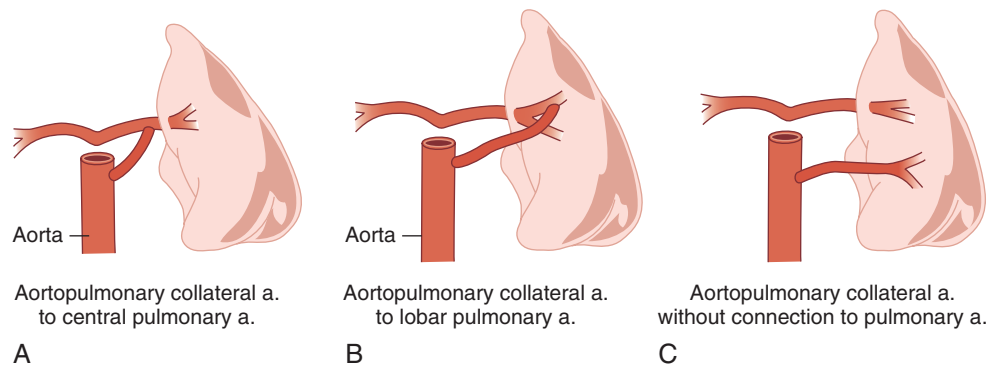


FIGURE 120-2 ■ Variations in aortopulmonary collateral morphology in pulmonary atresia with ventricular septal defect.

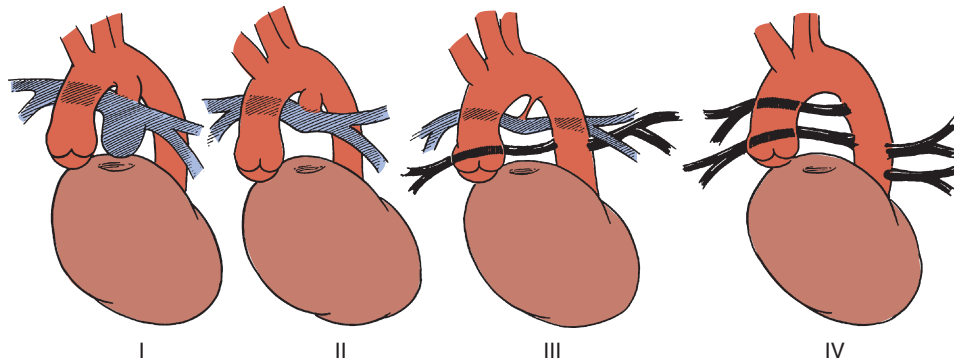


FIGURE 120-3 ■ Variations in pulmonary supply from native pulmonary arteries (*hatched gray*) and major aortopulmonary collateral arteries (*solid black*) encountered in patients with pulmonary atresia with ventricular septal defect.

Classification

There is no standard classification system for PA/VSD; however, several have been purported. Most classification schemes focus on the patterns of pulmonary blood flow. The classification system adopted by the Congenital Heart Surgery Nomenclature Project broadly divides pulmonary artery anatomy according to the following: central pulmonary arteries without MAPCAs, confluent central pulmonary arteries and dual supply with MAPCA, nonconfluent or absent central pulmonary arteries with MAPCA.⁴

Another classification scheme divides patients further according to specific patterns of pulmonary artery anatomy that are most commonly encountered (Fig. 120-3):

- I. Valvar pulmonary atresia with a decent-sized main pulmonary artery and confluent central pulmonary arteries. This variant is associated with a PDA and therefore not associated with MAPCAs.
- II. Absent main pulmonary artery with confluent, decent-sized or mildly hypoplastic central pulmonary arteries supplied by a PDA, without MAPCAs.
- III. Confluent central pulmonary arteries with MAPCAs but no PDA.
 - a. Central pulmonary artery z-score > -2.5
 - b. Central pulmonary artery z-score < -2.5

- IV. Nonconfluent or absent central pulmonary arteries with MAPCAs.
- V. Nonconfluent central pulmonary artery with PDA and MAPCAs.

Natural History

The natural history of PA/VSD varies significantly depending on the pulmonary artery morphology. Patients presenting with PA/VSD that has ductal dependent pulmonary blood flow will experience profound fatal cyanosis in the neonatal period as the ductus begins to close. On the other hand, patients with MAPCAs with mild stenosis of collateral vessels and balanced pulmonary blood flow exhibit mild cyanosis and may survive into adolescence or adulthood without repair. Progressive development of ostial stenosis within the collateral leads to progressive cyanosis. Alternatively, excessive pulmonary blood flow from an unrestrictive collateral results in congestive heart failure. The presence of long-standing unrestrictive blood flow within a MAPCA may result in irreversible elevation of pulmonary vascular resistance within that segment. Pulmonary hypertension within a segment of the lung is seen commonly in patients who present at later age. Heterogeneity in pulmonary vascular resistance within a lung segment results in $\dot{V}/\dot{Q}$ mismatch. Without timely intervention, the overall mortality rate is approximately 60% by 30 years of age, with most of the mortality occurring within the first year of life.^{1,5}

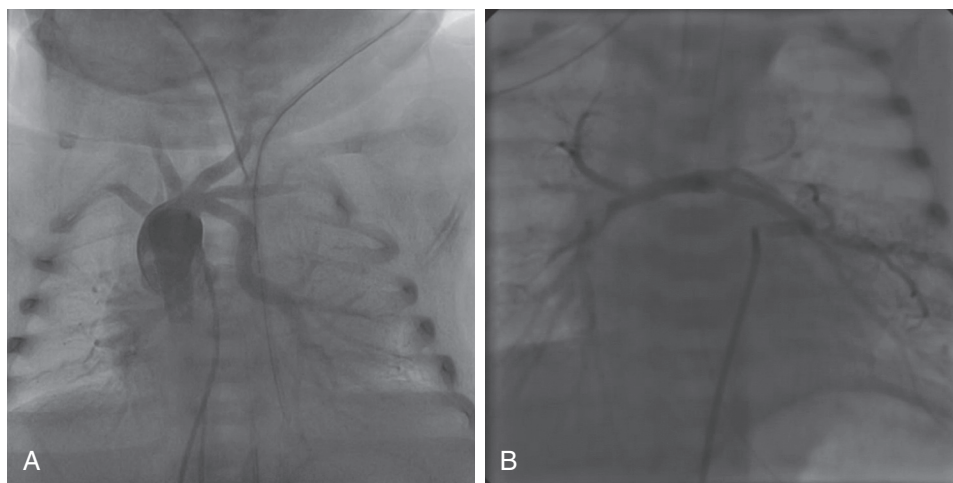


FIGURE 120-4 ■ Angiograms demonstrating major aortopulmonary collateral artery to left lung (A) and redundant collateral to left lung also supplied by hypoplastic native pulmonary arteries (B).

Clinical Presentation

The clinical presentation varies according to pulmonary artery morphology. Patients with ductal-dependent pulmonary circulation present with profound cyanosis during the first several weeks of life as the ductus begins to close. Children with progressively restrictive aortopulmonary collaterals may present in childhood with cyanosis, whereas patients with large, unrestrictive collaterals may present with heart failure symptoms such as failure to thrive, tachypnea, or feeding intolerance. Among infants presenting during infancy, 50% present with cyanosis and 25% present with heart failure symptoms.⁵ Rarely, in a child with balanced pulmonary blood flow, symptoms may not manifest until adolescence or adulthood.

Diagnostic Studies

Initial Studies

In the current era, prenatal diagnosis is frequently established by fetal ultrasound and echocardiography by the demonstration of absence of antegrade pulmonary artery blood flow. A neonate presenting with cyanosis following ductal closure may demonstrate hypovascular lung fields by chest radiography, whereas an infant presenting with excessive pulmonary blood flow and congestive heart failure may demonstrate interstitial edema and prominent hilar vessels. A right-sided aortic arch may be demonstrated by the position of the aortic knob by chest x-ray, and the diminutive main pulmonary artery results in an exaggerated sabot shape of the cardiac silhouette. By electrocardiography, rightward deviated QRS axis and evidence of right atrial and ventricular hypertrophy are frequently seen.

Echocardiography is the primary modality for diagnosis of this defect, and it provides a significant portion of the anatomic information needed for initial decision making in neonates and infants. The data to be obtained by echocardiography include location, size, and direction of flow in the ventricular and atrial septal defects; size and confluence of the central pulmonary vessels; and

presence of a PDA or other collaterals. Color flow Doppler may suggest the presence of a collateral arising from the descending aorta, but it is not reliable at delineating the entire course. Retrograde flow in the descending aorta suggests significant pulmonary flow through the collateral or PDA. Coronary artery anatomy should be delineated, particularly to exclude the presence of a left anterior descending coronary artery arising from the right coronary artery, because this impacts surgical management.

Cardiac Catheterization

Cardiac catheterization is indicated in patients with PA/VSD who have nonconfluent or hypoplastic central pulmonary arteries in whom MAPCAs are suspected (Fig. 120-4). The goal of catheterization in these patients is surgical planning by evaluating the anatomy, size, degree of stenosis, and the presence of dual supply from native pulmonary arteries or collaterals. Vascular supply to all segments must be clearly determined. Native pulmonary arteries may require visualization by pulmonary venous wedge injection if no antegrade flow to the native pulmonary arteries can be identified. Relationship of collaterals to the airway (seen best on the lateral view) is important in guiding surgical approach (sternotomy vs. thoracotomy). In older children and adults, measurements of individual pulmonary artery pressures are obtained to determine the risk of development of pulmonary hypertension in high-pressure collaterals. The pulmonary-to-systemic blood flow ratio (Q_p/Q_s) can be estimated by the Fick method if all pulmonary flow arises from collaterals (i.e., if there is no previous right ventricle-to-pulmonary artery [RV-to-PA] conduit). Interventions that may be performed at catheterization include balloon dilation of native pulmonary vessels, stenting of highly restrictive MAPCAs, or coiling of redundant dual-supply collaterals.

Cardiac catheterization is rarely indicated for types I or II PA/VSD with normal-sized central confluent pulmonary arteries demonstrated by echocardiogram, because the risk of collaterals is low and surgical

management is complete repair. Exceptions include patients at high risk for surgical management, in whom catheter-based intervention (stenting of PDA or right ventricular outflow tract [RVOT]) is contemplated.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a useful adjunct to cardiac catheterization in patients with MAPCAs. The advantage of MRI is its ability to image native pulmonary arteries that may not be accessible by cardiac catheterization. It is superior to other imaging modalities at delineating the relationship of MAPCAs to other mediastinal structures (airway, esophagus).⁶ MRI is used to estimate right ventricular volumes and conduit regurgitation fraction in completely repaired patients and guides decision making regarding conduit replacement.

Radionuclide Lung Perfusion Scanning

In patients with stenosis of pulmonary arteries (within collaterals or following unifocalization), decreased blood flow to specific segments of lung may portend irreversible vascular occlusion. Segmental malperfusion detected by lung perfusion scanning can be used to screen patients for the presence of significant stenoses of the native pulmonary arteries or MAPCAs.⁷ A heterogeneous perfusion pattern may indicate that certain segments are under high pressure and others are underperfused. Progressive reduction in segmental lung perfusion prompts cardiac catheterization and intervention to prevent irreversible vascular occlusion.

Medical Treatment

In a neonate with PDA-dependent pulmonary blood flow, prostaglandins are infused at 0.01 to 0.1 $\mu\text{g/kg/min}$ to maintain ductal patency and preserve pulmonary blood flow. Preoperative mechanical ventilation is not necessary and may even be detrimental if it lowers the PVR and increases the left-to-right shunt. Diuretics may be used for patients with heart failure symptoms.

Surgical Treatment

The ultimate goal of the surgical repair strategy is creation of biventricular circulation with unobstructed RV-to-PA continuity and elimination of intracardiac or extracardiac shunts with low resultant right ventricular pressure. To attain this goal, the VSD must be closed and branch and segmental vasculature must be recruited, and vascular caliber must be maximized to minimize pulmonary resistance. Generally, the repair strategy centers on optimizing pulmonary artery recruitment and thus varies depending on native pulmonary artery morphology and collateral supply.

Confluent Central Pulmonary Arteries without Major Aortopulmonary Collateral Arteries

If the central pulmonary arteries are confluent and normal in caliber, a PDA is usually present. Complete repair in

the neonatal period consists of reconstituting RV-to-PA continuity, ligation of the PDA, and VSD closure. In most patients, RV-to-PA continuity is established with a valved conduit (see [Right Ventricle-to-Pulmonary Artery Conduit](#) section). In patients with purely valvular atresia who have a patent main pulmonary artery segment, a transannular patch may be associated with longer freedom from reintervention compared to an RV-to-PA conduit.⁸ However, this approach may be associated with longer postoperative recovery and cyanosis related to a noncompliant right ventricle. Conversion to RV-to-PA conduit may become necessary in a subset of these patients.

Some centers prefer to perform a palliative systemic artery-to-pulmonary artery or RV-to-PA shunt in neonates, followed by complete repair later in infancy.⁹ This strategy minimizes the potential morbidity of neonatal repair and promotes growth of the central pulmonary arteries but places the patient at risk for shunt thrombosis, which can be fatal if the ductus is closed.¹⁰ Shunting as the initial procedure has been identified as a risk factor for early mortality in several retrospective series.^{11,12}

Transcatheter procedures such as radiofrequency perforation or ductal stenting are palliative alternatives to complete repair. Radiofrequency perforation of membrane-like atresia of the pulmonary valve combined with balloon dilation or stenting of the outflow tract can delay complete repair for 2 to 4 months.¹³ Stenting of PDA maintains stable blood flow in a neonate with confluent central pulmonary arteries following discontinuation of prostaglandins and promotes vascular growth.¹⁴ Stent implantation is hampered by tortuosity of the PDA. Stent migration, embolization, and restenosis have been reported.^{12,15} Given the low mortality of neonatal complete repair, palliation may be most appropriate for high-risk patients (genetic abnormalities, intracranial hemorrhage, pulmonary disease).

Hypoplastic Central Pulmonary Arteries with Major Aortopulmonary Collateral Arteries

In patients with diminutive central pulmonary arteries, simple VSD closure and RV-to-PA conduit would lead to elevated right ventricular pressure because of small vascular caliber, segmental vascular discontinuity, and accessory collateral supply. Delineation of branch pulmonary artery anatomy and collateral supply by cardiac catheterization is imperative in guiding the reconstructive strategy. If native central and branch pulmonary arteries are simply diminutive yet demonstrate continuity with all lung segments, initial intervention to promote growth of the central native pulmonary artery can be followed by eventual complete repair. Central pulmonary artery growth in this setting is stimulated by providing antegrade blood flow via either an aortopulmonary shunt or a restrictive RV-to-PA conduit and elimination of redundant collateral supply. There are several advantages of an RV-to-PA conduit over aortopulmonary shunt for this indication. Transcatheter access to the branch pulmonary arteries for sequential dilation is much easier through an RV-to-PA conduit than through an aortopulmonary shunt. Particularly in older infants, the use of an RV-to-PA

conduit may be superior to an aortopulmonary shunt in promoting growth of native pulmonary arteries.¹⁶

Aortopulmonary collaterals that are discontinuous with central pulmonary arteries may provide the sole supply to significant segments of lung. Recruitment of these collaterals into the central pulmonary artery segment is essential to ensure low right ventricular pressures and optimize V/Q matching. Unifocalization refers to the technique by which collaterals are disconnected from the aorta and anastomosed to a common confluence that can receive blood supply from a stable source—usually an RV-to-PA conduit or aortopulmonary shunt. If the collaterals are accessible from an anterior approach, unifocalization at the time of shunting or RV-to-PA conduit placement is performed by end-to-side anastomosis.

Anastomotic stenosis at the site of unifocalization requires transcatheter intervention to avoid loss of segmental blood flow in approximately 50% of patients at 5 years.¹⁷ High rate of collateral occlusion or stenosis has prompted some groups to pursue rehabilitation of hypoplastic native pulmonary arteries by a neonatal shunting regimen alone, without collateral unifocalization in select patients with diminutive central pulmonary arteries and MAPCAs.^{18,19}

Once growth of the central and branch pulmonary arteries is achieved, closure of the VSD with an unrestricted RV-to-PA conduit can be performed. Nuances regarding the timing and technical aspects of VSD closure are discussed later in this chapter (see [Closure of Ventricular Septal Defect](#) section).

Absent Central Pulmonary Arteries with Major Aortopulmonary Collateral Arteries

If central pulmonary arteries are absent, or if significant segments of pulmonary blood flow are supplied solely by MAPCAs, the repair strategy mandates unifocalization of branch pulmonary arteries and reconstruction of central pulmonary arteries prior to consideration of complete repair. Many of these patients demonstrate stable balanced pulmonary blood flow for a period of time as the collaterals are restrictive enough to limit pulmonary blood flow. Thus, the initial intervention may be delayed for several months. With time, however, segmental pulmonary hypoperfusion or hyperperfusion may lead to cyanosis or segmental pulmonary vascular disease, respectively. Close observation is imperative, and repair is recommended if significant imbalance of circulation develops.

Cardiac catheterization is essential to delineate anatomy as well as perform initial palliative interventions. Collaterals can be coil occluded if they provide redundant blood flow to segments also supplied by native pulmonary arteries. This reduces competitive flow and prevents overcirculation. Highly restrictive collaterals that are essential to maintaining pulmonary blood flow are stented at their proximal portions (the segment most likely to develop stenosis) until unifocalization can be performed.

Although most patients with PA/VSD and MAPCAs undergo initial surgical intervention between 3 and 6 months of age, earlier surgery may be necessary in certain

patients with (1) heart failure related to unrestrictive collaterals, (2) a ductal-dependent collateral that is prone to early occlusion, and (3) hemitruncus to one lung and contralateral MAPCAs.²⁰

The operative approach to and timing of unifocalization of collaterals, RV-to-PA conduit, and VSD closure hinge on the morphology of collaterals. Unifocalization involves identification and recruitment of branch pulmonary arteries into a centrally located confluence to which a conduit may eventually be sewn. Successful unifocalization requires careful review of preoperative studies (catheterization and MRI) to delineate the size, course, and location of stenoses within each collateral. Important considerations related to the unifocalization procedure include approach (sternotomy vs. thoracotomy), timing (single operation or multiple-stage procedures), and the source of blood flow to the unifocalized vessels (aortopulmonary shunt vs. RV-to-PA conduit).

Decision regarding timing of closure of the VSD depends on the anticipated or measured resistance of unifocalized vessels. If all segments of pulmonary vasculature are satisfactorily unifocalized and resistance is low, then VSD closure may be performed at the time of unifocalization (one-stage complete repair). If high resistance is anticipated or encountered, then unifocalization with a shunt or RV-to-PA conduit to promote growth of the vasculature followed by subsequent VSD closure is preferable.

Single-Stage Unifocalization and Complete Repair

A patient with MAPCAs that are large in caliber and easily accessible from a sternotomy approach (course anterior to the bronchus) may be a candidate for *single-stage unifocalization*, during which all significant collaterals are detached from the aorta and implanted into a central confluence during a single operation ([Fig. 120-5](#)). Following single-stage unifocalization, if the vascular bed is deemed suitable to handle a full cardiac output, then *single-stage complete repair* (VSD closure with an unrestrictive valved RV-to-PA conduit) is feasible. However, if high vascular resistance is anticipated or encountered following unifocalization, options include (1) fenestrated VSD closure with an RV-to-PA conduit or (2) restrictive source of pulmonary blood flow (aortopulmonary shunt or RV-to-PA conduit), leaving the VSD open. These two options promote growth of unifocalized vessels and allow access for subsequent catheter-based interventions. Complete repair with an RV-to-PA conduit and VSD closure is performed once satisfactory pulmonary vascular bed is achieved.

Because single-stage complete repair depends on morphology of the pulmonary vascular bed, several scoring systems based on preoperative imaging (MRI, CT scan, or angiography) have been developed to predict likelihood of successful VSD closure at the time of single-stage unifocalization. The number of pulmonary vascular segments to be recruited has been used to predict low right ventricular pressures following VSD closure.²¹ The total neopulmonary arterial index is the sum of the cross-sectional areas of the right and left pulmonary arteries as

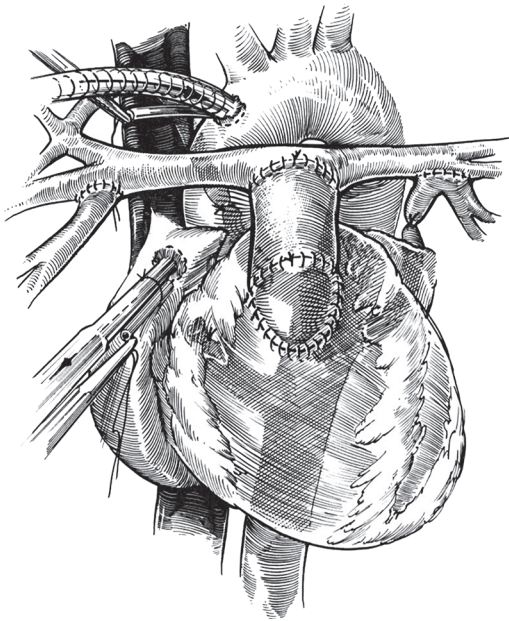


FIGURE 120-5 ■ Single-stage reconstruction of pulmonary atresia with ventricular septal defect with unifocalization, ventricular septal defect closure, and right ventricle-to-pulmonary artery conduit.

well as all collateral vessels, normalized to body surface area, and an index greater than $150 \text{ mm}^2/\text{m}^2$ has been associated with successful VSD closure at the time of unifocalization.²² Functional assessment of vascular resistance following single-stage unifocalization may also be used to guide intraoperative decisions regarding VSD closure.²³ Intraoperative determination of vascular resistance by measuring the pressure generated on perfusing the unifocalized pulmonary arteries with constant flow perfusate has been shown to predict postoperative right ventricular pressures.²⁴

The advantages of the single-stage unifocalization or complete repair include avoidance of bilateral thoracotomies, avoidance of multiple operations, and immediate antegrade access for transcatheter intervention on the unifocalized pulmonary vasculature. The major disadvantage of this approach is the risk of progressive stenosis of the unifocalized collateral. A typical MAPCA consists of a proximal muscular segment that resembles a systemic arterial vessel and a distal thin-walled segment that resembles a pulmonary artery. The proximal muscular segment is susceptible to progressive stenosis. Although it is preferable to perform unifocalization anastomoses to the distal pulmonary artery-like segment to reduce the risk of restenosis, this is not always feasible through a sternotomy approach. Additional disadvantages include the long duration of cardiopulmonary bypass and difficult access to the posteriorly located collaterals.

Multiple-Stage Repair Strategy

A patient with long-segment stenoses of collateral vessels or patency of only hilar vessels requires a thoracotomy approach to provide adequate visualization of the hilar

pulmonary vessels, which are not accessible through a sternotomy approach. Generally, staged bilateral thoracotomies are performed with eventual complete repair once adequate recruitment of branch pulmonary arteries and caliber of central pulmonary arteries has been achieved. At each thoracotomy procedure, segmental pulmonary vessels are brought into continuity with a conduit (typically a homograft) and provided a source of blood flow, generally via a polytetrafluoroethylene (PTFE) shunt from the ipsilateral subclavian artery.

Catheterization within several months of each thoracotomy allows delineation of resultant pulmonary artery morphology and dilation of stenoses. MRI provides not only anatomic but also functional information to aid surgical decision making in patients with multiple sources of pulmonary blood flow.²⁵ Once vascular segments to both lungs have been satisfactorily recruited and rehabilitated, complete repair via sternotomy is performed for placement of an RV-to-PA conduit (connecting to the conduits placed at previous thoracotomy) and closure of the VSD (+/- fenestration).

Under rare circumstances, transverse thoracosternotomy or bilateral thoracotomies for unifocalization followed by sternotomy for an RV-to-PA conduit and VSD closure at a single procedure (modified single-stage unifocalization and complete repair) may be performed.²⁶ The disadvantage of this approach includes longer operative time and increased risk of bleeding at the distal pulmonary anastomoses.

Transplantation

Lung or heart-lung transplantation has been applied selectively for certain patients, generally adolescents or adults, with irreversible pulmonary hypertension. For patients with normal ventricular function, lung transplantation, with or without cardiac repair (VSD closure or conduit change), may be performed. Heart-lung transplantation must be considered for patients with myocardial dysfunction or complex intracardiac defects.²⁷

Technical Considerations

Cardiopulmonary Bypass Strategy

Cardiopulmonary bypass is required for procedures involving VSD closure or RV-to-PA conduit placement. Thus, single-stage unifocalization with an RV-to-PA conduit via a sternotomy approach requires cardiopulmonary bypass, whereas unifocalization to a systemic shunt through a thoracotomy does not. The bypass strategy must be tailored to patients with MAPCAs because runoff into the pulmonary circulation can result in systemic hypoperfusion as well as poor visualization during intracardiac repair or pulmonary artery reconstruction as a result of flooding of the field with collateral blood flow. Control of all accessible collaterals following initiation of bypass is recommended, and higher flows (cardiac index of up to $4.0 \text{ liter}/\text{min}/\text{m}^2$ if necessary) are used to maintain systemic perfusion. Hypothermia reduces metabolic demand and provides protection of end organs in situations of reduced systemic perfusion. It allows the surgeon

to reduce or briefly interrupt bypass flow to improve visualization of the surgical field during critical portions of the operation. When appropriate, maintenance of cardiac contractions and pulsatile flow (by not completely emptying the heart) during bypass may provide superior systemic perfusion in the presence of collateral runoff. Cardioplegic arrest is required for repair of VSD but can also be used during placement of the RV-to-PA conduit.

Closure of Ventricular Septal Defect

The VSD may be closed with Dacron, PTFE, or pericardial patch material. The decision to close the VSD depends on the preoperative and intraoperative assessment of the pulmonary runoff. Failure to close the VSD in the setting of unobstructed right ventricular outflow leads to significant left-to-right shunting and congestive heart failure. In contrast, closure of the VSD in the presence of inadequate pulmonary artery bed results in right ventricular hypertension and low cardiac output. Fenestrated VSD closure is performed in equivocal or borderline cases. Use of PTFE or tissue material for patch closure (in contrast to Dacron) facilitates catheter-based enlargement of fenestration should elevated right ventricular pressures be encountered postoperatively. Fenestration within the VSD patch may spontaneously close over time or may be closed in the catheterization laboratory.

The conduction system is generally remote from the edges of the VSD in a typical patient with PA/VSD. However, extension of the VSD into the membranous septum may place the conduction system at risk for injury at its posterior and inferior margin. Acute angulation of the VSD contour at the ventricular-infundibular fold (rightward margin just beneath the conal septum) may lead to residual patch margin VSD following closure, and special care must be taken when placing sutures at this location.

Right Ventricle-to-Pulmonary Artery Conduit

An RV-to-PA conduit can be sewn either to confluent central native pulmonary arteries or to unifocalized pulmonary vascular segments. The type of conduit chosen depends on the size of the child, caliber of the distal pulmonary vascular bed, and status of the VSD. If the VSD is left unrestrictive and the purpose of the RV-to-PA conduit is to promote vascular growth, then a nonvalved PTFE graft or restrictive homograft is selected. Following complete repair, an unrestrictive, valved conduit (homograft, xenograft) is preferred to minimize right ventricular pressure and volume load.

Details regarding coronary artery anatomy should be obtained prior to incising the infundibulum. The course of the left anterior descending coronary artery may be marked prior to cardioplegic arrest so that the location of ventriculotomy can be performed a sufficient distance from this structure. Presence of the left anterior descending artery arising from the right coronary artery (either as dual or sole supply) must be excluded, as this vessel frequently crosses the infundibulum. If anomalous origin

is identified, the location of the right ventriculotomy must be modified to avoid injury to this vessel.

Transannular Patch

In patients with pulmonary valvular atresia, the presence of an imperforate membrane at the valve level is the primary abnormality. Infundibular muscular stenosis may also be present, and the main pulmonary artery is variably hypoplastic. This anatomy is amenable to augmentation of the RVOT with a transannular patch that extends from the infundibulum to the bifurcation of main pulmonary artery. This approach reduces the need for RVOT reoperation but creates pulmonary regurgitation. Use of a monocusp transannular patch may prevent early pulmonary regurgitation with this approach.^{28,29}

Complete division of the parietal muscle bands at the time of transannular patching reduces the risk of recurrent RVOT obstruction. Presence of anomalous left anterior descending artery crossing the RVOT is not an absolute contraindication to transannular patching but may limit the extent of the ventriculotomy. An alternative approach with an RV-to-PA conduit should be considered in these patients.

Maintenance of Patent Foramen Ovale

Following complete repair of PA/VSD, low right ventricular compliance related to the ventriculotomy and hypertrophic ventricle leads to elevated right atrial pressures and low cardiac output, which manifests as hepatic congestion, anasarca, and renal insufficiency. A small atrial septal defect between 3 and 4 mm (in an infant) prevents right atrial hypertension and preserves cardiac output by allowing right-to-left shunting at the atrial level. Closure of the patent foramen ovale (PFO) at the time of complete repair has been associated with increased length of stay and hospital death.³⁰ Right-to-left shunting results in systemic oxygen desaturation, which is well tolerated in neonates and infants and improves as right ventricular compliance normalizes. Balloon dilation of the PFO may be performed in the catheterization laboratory if elevated atrial pressures are encountered postoperatively. Closure of residual intracardiac shunts may be performed at the time of conduit replacement or cardiac catheterization.

Aortopulmonary Shunting

Aortopulmonary shunts can be used after unifocalization of MAPCAs or as initial palliation in patients with diminutive but confluent central pulmonary arteries. The PDA or other major collateral supplying the pulmonary artery is generally ligated at the time of shunting, although several centers have advocated for maintaining PDA patency.³¹ These shunts are constructed with PTFE tube grafts or direct anastomosis and promote growth of pulmonary artery segments prior to eventual complete repair. The most common form of aortopulmonary shunt is the modified Blalock-Taussig shunt (subclavian artery-to-pulmonary artery PTFE graft), but other forms include the central PTFE shunt, Waterston shunt

(ascending aorta-to-pulmonary artery graft) and Mel-bourne shunt (direct end-to-side anastomosis of pulmonary artery to ascending aorta).³²

The modified Blalock-Taussig shunt may be performed through a sternotomy or thoracotomy incision. The size of shunt used depends on the size of the child and morphology of the pulmonary artery. A 3.5-mm shunt supplies adequate flow to both lungs in a neonate, whereas 3.5- to 4-mm shunt is used to provide flow to each vascular bed for an infant undergoing thoracotomy for staged unifocalization. Thrombosis prophylaxis with the platelet inhibitor aspirin is the standard of care; the addition of clopidogrel may or may not provide further advantage.^{33,34} The shunt is divided once continuity is established between the right ventricle and the unifocalized confluence.

Single-Stage Unifocalization

Through a sternotomy incision, MAPCAs, as they arise from the descending aorta, are identified in the posterior mediastinum by dissecting the infracarinal and paratracheal space. On institution of cardiopulmonary bypass, all MAPCAs must be controlled to avoid significant runoff into the pulmonary vasculature. MAPCAs are identified, divided, and incorporated into a central confluence. Functional assessment of pulmonary resistance may be performed at this time to guide the decision regarding VSD closure. One-stage complete repair entails VSD closure and an RV-to-PA conduit at the time of unifocalization. After cardioplegic arrest, an infundibular right ventriculotomy is performed, through which the VSD is closed with or without a fenestration. If adequacy of the pulmonary vasculature is questionable, it is safe to leave a fenestration because suprasystemic right ventricular pressures are not as well tolerated as a small residual left-to-right shunt. The unifocalized confluence is sewn to the distal end of the conduit. The proximal portion of the conduit is anastomosed to the right ventriculotomy incision, generally with a hood of pericardium to avoid distortion and tension at the proximal anastomosis.

Multiple-Stage Unifocalization

The decision regarding order of MAPCA unifocalization (right vs. left vessels) depends on the degree of compromise of vascular supply. The side with the most severe MAPCA restrictions is generally unifocalized first because these are at highest risk for progressive occlusion, and ligation of these collaterals at the time of the procedure is less likely to result in significant systemic desaturation. Through a thoracotomy, all MAPCAs are identified and ligated proximally. The distal pulmonary vessels are exposed and correlated with preoperative images to ensure that all essential vessels are unifocalized. Hilar dissection may be necessary to expose segmental vessels. A vascular graft (homograft, pericardial tube, or prosthetic) is anastomosed to all essential branch vessels. The proximal end of this vascular graft is placed anteriorly in the pleural space to facilitate eventual access through sternotomy at the time of complete repair. A shunt is

placed between the subclavian artery and the conduit to provide antegrade pulmonary blood flow. This process is repeated in the contralateral thoracic cavity during a separate operation, although staged unifocalization at a single procedure has been performed.

Postoperative Assessment and Management

The success of repair for PA/VSD depends primarily on the anatomic result of pulmonary artery unifocalization or reconstruction. If a low-impedance pulmonary vascular system is achieved, closure of VSD may be performed with low right ventricular pressures. Right ventricular pressures of less than two-thirds systemic are generally felt to be well tolerated long term, whereas suprasystemic pressures are poorly tolerated in the short or long term.

Right ventricular pressure can be assessed following closure of the VSD in the operating room by direct measurement after separation from bypass. Right ventricular pressures greater than 80% of systemic arterial pressures often indicate inadequate pulmonary vascular bed. Because elevated right ventricular pressures are poorly tolerated long term, fenestration of the VSD patch must be performed if suprasystemic right ventricular pressures are encountered.

Postoperative echocardiography and lung perfusion scanning are noninvasive modalities used to follow up on the results of repair and guide further management. Lung perfusion scanning detects perfusion defects within various pulmonary segments and indicates pulmonary artery or MAPCA occlusion. Echocardiography is used to assess right ventricular pressures, intracardiac shunts, RVOT obstruction, and conduit regurgitation. The direction of flow across any residual VSD helps determine the degree of RVOT obstruction in patients undergoing staged palliation. The presence of primarily right-to-left shunting indicates inadequate pulmonary bed and warrants further pulmonary vascular rehabilitation or recruitment prior to VSD closure.

If progressive vascular disease is suspected by echocardiogram or perfusion scanning, cardiac catheterization is indicated. If multistage repair strategy has been undertaken, catheterization is performed before each stage. At cardiac catheterization, pulmonary artery pressures and Qp/Qs are measured. The Qp/Qs measurement by the Fick method may be inaccurate if dual sources of blood supply (MAPCA and right ventricle) are present. Cardiac catheterization also reveals pulmonary artery arborization pattern and size and allows intervention for pulmonary vascular rehabilitation. Transcatheter closure of fenestration in the VSD patch or PFO is possible if favorable conditions are present.

Results

Hospital survival for the initial procedures is greater than 90% in most series. Risk factors for poor outcome (mortality, reoperation, or failure of repair) following complete repair of PA/VSD and MAPCAs that have been identified include pulmonary artery morphology, 22Q11 microdeletion, and older age at palliation.^{3,35,36}

Long-term results of repair for patients with hypoplastic or absent central pulmonary artery with MAPCAs are highly variable.^{17,18,20,21,37-40} Approximately 80% of infants presenting with this anatomy may be amenable to single-stage unifocalization, and up to 50% of these patients are candidates for simultaneous complete repair. The operative mortality rate for single-stage unifocalization ranges from 2% to 15%. Survival rate at 5 years with either single- or multiple-stage unifocalization is 85% with eventual complete repair achieved in 70% to 90% of patients. In patients who undergo complete repair, elevated right ventricular pressures may be encountered in up to 50% of patients. Mean right ventricular to left ventricular pressure ratio reported in the literature at mid-term follow-up ranges from 0.4 to 0.6.^{35,39} More than half of septated patients will require catheter intervention within 10 years following complete repair.⁴¹ Reoperation following complete repair for conduit replacement is inevitable when complete repair is performed in neonates and infants.

Conclusion

PA/VSD encompasses a wide spectrum of lesions that are distinguished primarily by the pulmonary vascular morphology. The preoperative evaluation must delineate the source, size, and adequacy of pulmonary blood flow. Therapeutic strategy and timing are tailored according to the pulmonary vascular morphology, with the ultimate goal being establishment of a low-resistance pulmonary vascular bed, RV-to-PA continuity, elimination of intracardiac and extracardiac shunts, and resultant low right ventricular pressure. Surgical options include single-stage complete repair or staged palliation followed by complete repair, depending on the pulmonary artery morphology. Following complete repair, reintervention for pulmonary artery balloon dilation or conduit replacement is common. Long-term outcomes are dependent on the morphology of the pulmonary vasculature and the surgeon's ability to recruit a low-resistance vascular bed.

RIGHT VENTRICLE-TO-PULMONARY ARTERY CONDUITS

Introduction

Prosthetic valves and conduits are used to establish continuity between the pulmonary ventricle (morphologic right ventricle or left ventricle) and the pulmonary arteries as a part of complete repair or palliative reconstruction. Examples of defects with pulmonary obstruction that may require conduit placement include tetralogy of Fallot, pulmonary atresia (with intact ventricular septum or VSD), truncus arteriosus, D-transposition of the great arteries (TGA)/VSD or double-outlet right ventricle with pulmonary stenosis (as a part of Rastelli or Nikaidoh operations), and L-TGA/VSD with pulmonary stenosis. Conduits are also used concomitantly during procedures for left ventricular outflow tract (LVOT) obstruction that

use the normal native pulmonary valve for the LVOT reconstruction. The Ross procedure, in which the pulmonary autograft is harvested and placed into the LVOT position, uses a conduit to reestablish RV-to-PA continuity. Similarly, the operation described by Yasui and colleagues^{41a} for repair of interrupted aortic arch/VSD/severe LVOT obstruction uses the normal pulmonary valve for LVOT reconstruction and requires placement of an RV-to-PA conduit.

Choice of Conduit

Options for ventricle-to-pulmonary artery continuity include synthetic, allograft, xenograft, and autologous tissue conduits. Unfortunately, none of the currently available conduits is ideal, and each is associated with specific advantages and disadvantages. None of the currently available conduits demonstrates growth potential, and conduit stenosis develops as the child grows. Factors to consider in the choice of a conduit include the pulmonary vascular resistance, age and size of the patient, and nature of the concomitant operation (complete repair versus palliation). For example, in the presence of elevated pulmonary vascular resistance, placement of a valved conduit (as opposed to nonvalved conduit) may be preferred to mitigate the effects of pulmonary regurgitation. Age and size of the patient are important because each type of conduit has a specific size limitation (Table 120-1). The type of operation influences the type and size of conduit to be implanted. Thus, if a conduit is required as a part of a palliative operation in which the VSD is left open, a restrictive conduit may be desirable to prevent excessive pulmonary blood flow. If reoperation is planned within a short time interval as a part of staged repair strategy, implantation of a low-cost but less durable conduit may be acceptable.

Allograft

Cryopreserved aortic and pulmonary allografts (or homografts) may be used for ventricle-to-pulmonary artery reconstruction. Advantages of allografts include availability in a wide range of sizes and favorable handling characteristics during implantation. Bifurcating pulmonary grafts or aortic branch vessels can be directly anastomosed to branch pulmonary arteries in the absence of adequate central pulmonary arteries. Major disadvantages include limited supply of the smaller sizes necessary for neonatal repair, the limited shelf life of each allograft (approximately 2 years), and high cost.

Choice of allograft characteristics and size depend on the age of patient and operative indication. For infants and small children who undergo conduit placement, use of conduit other than pulmonary allograft (synthetic, porcine xenografts, aortic homograft) has been shown to be a predictor of early reintervention, suggesting superiority of the pulmonary allograft for RVOT reconstruction.⁴²⁻⁴⁶ Several studies have demonstrated superior longevity of pulmonary allografts compared with aortic allografts, partly because of the accelerated calcification seen in the latter.^{42,45,47,48} However, aortic

TABLE 120-1 Conduit Choices for Patients Based on Age

Conduit Type	Sizes Available	Typical Patient Age Range	Commercial Name (U.S. Manufacturers)
Allograft			
Aortic	6-25 mm	All ages	CryoLife, LifeNet
Pulmonary	8-29 mm	All ages	CryoLife, LifeNet
Xenograft			
Bovine jugular vein	12-22 mm	<5 yr	Contegra (Medtronic)
Bovine jugular vein (stent-mounted)	18 mm	6 mo to 5 yr	Melody (Medtronic)
Porcine aortic root	19-29 mm	>5 yr	Freestyle (Medtronic) Prima Plus (Edwards)
Synthetic			
Composite porcine aortic valve within fabric conduit	12-30 mm	All ages	Hancock valved conduit (Medtronic) Carpentier-Edwards bioprosthetic valved conduit (Edwards)
Polyester Tube Graft			
Nonvalved + implanted	>4 mm	<12 mo	Hemashield (Atrium)
bioprosthetic valve (>19 mm)	20-30 mm	>5 yr	Gelweave (Vascutek) Ultramax (Atrium)
PTFE Tube Graft			
Nonvalved + implanted	>3 mm	<12 mo	Gore-Tex (Gore)
bioprosthetic valve	20-24 mm	>5 yr	Impra (Bard) Advanta (Atrium)

PTFE, Polytetrafluoroethylene.

homograft is chosen if elevated pulmonary artery pressures are anticipated (palliative conduit following unifocalization), as pulmonary allografts are associated with an increased risk of pseudoaneurysm formation in this setting.^{49,50} The choice of size for a neonate may be influenced by limited availability of small-sized conduits. Modification of an allograft by excision of one leaflet and creation of a smaller “bicuspid” allograft allows use of larger-sized allografts in smaller patients when the appropriate-sized smaller allografts are unavailable.⁵¹ The practice of implanting an oversized allograft into neonates and small children to improve conduit longevity may be associated with early development of conduit regurgitation in children.^{52,53}

Whereas short-term competence of the homograft valve is acceptable, long-term freedom from regurgitation and stenosis is highly variable. Freedom from reintervention rates reported in the literature range widely from 30% to over 80% at 10 years.^{8,44,48,54,55}

Smaller conduit size, or younger age at operation, has been consistently shown in multiple series to be a risk factor for allograft conduit failure with freedom from reoperation at 10 years being less than 50% for homografts less than 19 mm in diameter.⁵⁴ In adolescents, freedom from valvar dysfunction and conduit reintervention at 10 years is approximately 50% and 70%, respectively.⁵⁶ Other risk factors include use of aortic homografts, residual branch pulmonary artery stenosis, ABO or HLA mismatch, and non-Ross operation (particularly operation for truncus arteriosus).^{48,52,57,58} The reason for the discrepancy in durability between Ross and non-Ross patients is unclear but may be related to orthotopic position of the conduit in the former; it is placed more

anteriorly in Rastelli, Yasui, and truncus repairs, which may predispose to compression from the sternum.

Xenograft

Currently available xenograft conduits include bovine jugular vein and porcine aortic root. Advantages of xenograft conduits include abundant supply, low cost, wide range of sizes, and favorable suturing characteristics. The list of commercially available xenograft conduits and size ranges are listed in Table 120-1. Choice of xenograft conduit depends primarily on size and age of patient.

An alternative to allograft in a neonate or infant is the Medtronic Contegra graft, obtained from bovine jugular vein with similar short-term durability between Contegra and pulmonary allografts.^{46,55,57,59} Although short-term durability is acceptable, long-term data are highly variable. Freedom from reintervention ranges from 66% at 3 years to 90% at 7 years.^{57,59-61} Young age at implantation is a risk factor for reintervention and distal conduit stenosis.⁶² In patients with elevated right ventricular pressure or pulmonary hypertension, the Contegra has been associated with graft dilation and decreased durability, raising concern for its use in these patients.^{60,62,63} Surgical implantation of the externally stented bovine jugular vein graft (Melody valve) may limit graft dilation and improve long-term durability.

The porcine aortic root has been used for RVOT reconstruction in older children and adults and is available in sizes ranging from 19 to 29 mm.⁶⁴ These grafts appear to have excellent durability at short-term follow-up, but long-term data are still lacking.^{65,66} This is

an alternative to allograft or synthetic conduit in adolescents and adults.

Autologous Tissue

Autologous pericardium can be fashioned into a valved or valveless conduit and used for RV-to-PA reconstruction.⁶⁷ Monocusp and bicuspid valved conduits have been constructed by sewing autologous pericardial leaflets within a tubular pericardial conduit. Although there have been a few reports describing acceptable durability and even increase in the size of some conduits over time in certain cases, experience with this technique is limited.⁶⁸ Smaller conduit size is associated with increased risk of failure and limits its use in neonatal applications. Lack of access to commercially available conduits (in developing countries) may be an indication for its use.

Synthetic Conduits

Nonvalved. Valveless conduits are used in several settings. A palliative synthetic tube graft from an RV-to-PA conduit may be used in patients with PA/VSD and confluent but hypoplastic central pulmonary arteries in whom pulmonary artery growth is desired. In these patients, the VSD is left open and exposes the pulmonary arteries to elevated pressure. Nonvalved PTFE tube grafts are also used for the RV-to-PA conduit in the stage 1 reconstruction of hypoplastic left heart syndrome. Transmural insertion of a ring-reinforced RV-to-PA PTFE conduit reduces the risk of proximal obstruction compared with epicardial suture technique.⁶⁹ In patients undergoing complete repair with VSD closure, selective use of nonvalved conduits is acceptable but should be avoided in patients with elevated pulmonary vascular resistance, unrepaired tricuspid valve regurgitation, or right ventricular failure.^{70,71}

Valved. Composite conduits made of polyester or PTFE tube grafts with bioprosthetic or mechanical valves are available commercially or can be assembled at the time of the operation (see Table 120-1). Manually constructed composite conduits use a low profile valve secured within the synthetic conduit. Bioprosthetic valves are almost exclusively used because anticoagulation is necessary for mechanical valves, and transcatheter valve replacement is feasible only for the bioprosthetic valves.⁷² Advantages of the synthetic valved conduits include excellent longevity and virtually unlimited shelf life, which makes them readily available. The enclosed bioprosthetic valves have a rigid annulus that is resistant to distortion or compression by external structures (sternum).

A major disadvantage of composite polyester conduits less than 19 mm is accelerated stenosis compared with homografts, which has limited their application in neonates and infants.^{61,73,74} Manually constructed conduits are limited by size availability (the smallest bioprosthetic valve is 19 mm) and are commonly used for replacement of obstructed conduits in older children and young adults. Unlike tissue conduits, these conduits are not amenable to catheter-based enlargement if a child were to outgrow the conduit; thus, implantation of a graft between 24 and

28 mm is optimal. Previous studies suggested inferior durability of these conduits compared with allografts, but recent studies have demonstrated freedom from reintervention of greater than 90% at 5 years.⁷⁵⁻⁷⁸ For larger-sized conduits (>19 mm), durability of porcine-valved polyester or PTFE conduit appears to be equivalent, and perhaps superior, to that of allografts.^{56,71,79,80}

Results

Short- and long-term mortality rates following implantation of an RV-to-PA conduit depend primarily on the underlying cardiac diagnosis and hemodynamic result of the operation. In most recent series, the hospital mortality rate among patients who underwent RV-to-PA conduit implantation has ranged from 1% to 10%, depending on the complexity of the underlying cardiac disease.⁷¹ Risk factors for late mortality have included older age at primary operation and elevated right ventricular to left ventricular pressure ratio.⁶⁰ Conduit freedom from reintervention (surgical or catheter-based) varies significantly depending on conduit or patient type. The strongest risk factor for early reintervention in most of these series has been younger age at operation or use of smaller-sized conduits.⁸¹

Conduit Replacement or Reconstruction

Conduit failure may present in the form of either obstruction or valvular incompetence. The decision to intervene on a conduit hinges on the deleterious effects of conduit failure on right ventricular function. Intervention on the conduit may come in the form of catheter-based balloon dilation and stenting for conduit stenosis or endovascular implantation of pulmonary valve for conduit regurgitation. Surgical reconstruction includes patch augmentation of stenotic conduit and implantation of a prosthetic valve within the in situ conduit. Conduit replacement refers to removal of the conduit and the insertion of a new conduit.

Although there are no established guidelines for conduit replacement, common indications for conduit reintervention include symptoms of right heart failure as well as evidence of right ventricular deterioration in an asymptomatic patient. In the presence of conduit stenosis, the development of right ventricular hypertension (>3/4 systemic) or right ventricular dysfunction should prompt consideration of intervention. Isolated conduit regurgitation, even if severe, can be well tolerated for many years. Data regarding indications for PVR following transannular patch repair of tetralogy of Fallot have been extrapolated to guide management of conduit dysfunction.⁸² Symptoms of exercise intolerance, peripheral edema, and arrhythmias are considered indications for surgery. In an asymptomatic patient, right ventricular dilation (>150 mL/m²), progressive tricuspid regurgitation, QRS prolongation, and ventricular dysfunction are relative indications.⁸²⁻⁸⁵

Frequently, catheter-based intervention is successful at relieving conduit obstruction. Greater than 90% of patients presenting with conduit stenosis are amenable to such intervention, and an immediate reduction in right

ventricular pressures by approximately 20% can be expected.^{86,87} Although conduit stenting has been shown to delay the need for surgical intervention, smaller conduit sizes (less than 10 mm), use of a homograft conduit, and younger age are associated with shorter freedom from surgery.⁸⁷ Experience with percutaneous transcatheter implantation of Melody valve within previous RVOT conduit is encouraging. Freedom from valvular dysfunction of 93% at 1 year and greater than 70% at 5 years has been demonstrated.^{88,89} Use of this transcatheter valve has increased dramatically over the past 5 years but is limited to patients in whom conduit internal diameter can be expanded to 22 mm, which is the optimal external diameter of the Melody valve. Patients with conduit internal diameter greater than 24 mm are not candidates, because the valve cannot be sealed within the RVOT.

Options for surgical intervention on dysfunctional conduit include replacement and reconstruction. Conduit reconstruction is performed by incising the anterior portion of the conduit, implantation of a prosthetic valve, and placement of a prosthetic roof over the remaining fibrous bed of the explanted conduit. This type of reconstruction is a durable alternative to conduit replacement, with 90% freedom from reoperation at 10 years.⁹⁰ Alternatively, conduit replacement may be performed with an appropriately sized graft.

Increasing experience with transcatheter valves has prompted interest in hybrid techniques for valve insertion in patients with high surgical risk but enlarged RVOT (hence not candidates for transcatheter replacement). Techniques include transapical or transfemoral delivery with fixation in the pulmonary artery without the use of cardiopulmonary bypass.

Technical Considerations

It is important to evaluate the position of the conduit relative to the sternum on the available preoperative imaging (lateral chest x-ray, catheterization, MRI, or CT scan).⁹¹ Fusion of calcified conduit to the posterior table of the sternum may warrant cannulation of the femoral vessels and institution of cardiopulmonary bypass prior to sternal entry.^{91,92} The presence of residual intracardiac shunts (PFO or VSD) should be determined preoperatively because the decision to close any residual defects guides the intraoperative cannulation and bypass strategy. Air entrainment during cardiopulmonary bypass can be associated with stroke, and the use of cardioplegic arrest or fibrillation with left ventricular venting is preferable to empty, beating heart.

If atrial or ventricular arrhythmias are present, preoperative evaluation by electrophysiologic mapping and ablation are appropriate. Surgical cryoablation is recommended for patients with atrial or monomorphic ventricular arrhythmias in whom preoperative ablation is not performed or is unsuccessful.⁹³

Results

The operative mortality rate of conduit replacement or reconstruction is 5% to 10%, and long-term results

(mortality, freedom from reoperation) after reoperation for conduit replacement or reconstruction are equivalent to those of primary conduit placement.^{58,94}

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TRUNCUS ARTERIOSUS AND AORTOPULMONARY WINDOW

Jennifer C. Hirsch-Romano • Richard G. Ohye • Ming-Sing Si • Edward L. Bove

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TRUNCUS ARTERIOSUS

Truncus arteriosus is a relatively rare congenital heart defect with a single vascular trunk arising from the heart, giving origin to the true pulmonary arteries, aorta, coronary arteries, and brachiocephalic vessels. The lesion accounts for approximately 0.4% to 4.0% of all congenital heart lesions.¹⁻³ Truncus arteriosus was first described by Wilson⁴ in 1798. In 1942, Lev and Saphir⁵ defined the anatomy currently associated with truncus arteriosus.

Embryology

During the fifth week of gestation, paired lateral ridges appear in the cephalic portion of the truncus. These truncal swellings ultimately form the aortopulmonary septum. The right superior truncus swelling, located on the right superior wall of the truncus, grows distally and leftward, whereas the left inferior truncus swelling, located on the left inferior wall, moves distally and rightward. The opposing movements of the swellings as they grow toward the aortic sac result in the spiraling of the aortopulmonary septum. The most proximal portions

of the swellings form parts of the infundibular or conal septum. Hence, variable deficiency of these truncal swellings results in the various forms of truncus arteriosus and the commonly present ventricular septal defect (VSD).

Pluripotent neural crest cells play an important role in the development of the conotruncus and aortic arch. Deletion of *Cdc42* (cell division cycle 42), a GTP-binding protein that regulates cytoskeleton remodeling and is essential for neural crest cell migration, results in persistent truncus arteriosus and interrupted aortic arches in murine models.⁶ Selective ablation of neural crest cells in chick embryos before migration results in a number of congenital heart defects.⁷ These anomalies include truncus arteriosus and interrupted aortic arch, explaining their coexistence in approximately 10% to 20% of patients with truncus arteriosus.^{8,9}

Animal models provide further insight into the genetic basis for truncus arteriosus. The mouse mutant *Spitch*, which has a mutation in the homeobox gene *Pax3*, has a phenotype with truncus arteriosus and aortic arch abnormalities.¹⁰ In humans, monoallelic microdeletion of chromosome 22q11 is associated with multiple defects of neural crest origin, including typical facies, cleft palate, thyroid and parathyroid gland aplasia, and conotruncal

and aortic arch abnormalities. The resulting phenotypic syndromes include DiGeorge, velocardiofacial, and Shprintzen syndromes, which are associated with truncus arteriosus. One candidate gene identified in the area of the microdeletion is *HIRA*. *HIRA* interacts with *Pax3*, and thus may be integral to *Pax3* regulation of neural crest cells.¹¹ Environmental risk factors for the development of truncus arteriosus include maternal diabetes and exposure to retinoic acid.

Anatomy

In truncus arteriosus, there is generally situs solitus and D-looping of the ventricles. A single great vessel arises from the base of the heart, giving origin to the pulmonary, systemic, and coronary arteries. Classifications of truncus arteriosus were proposed by Collett and Edwards¹² in 1949 and by Van Praagh and Van Praagh¹³ in 1965 (Fig. 121-1). The system described by Collett and Edwards (Table 121-1) is based on the site of origin of the pulmonary arteries, whereas the Van Praagh classification (Table 121-2) is based on the degree of septation of the trunk and the presence or absence of a VSD. The Van Praagh scheme also requires that at least one of the pulmonary arteries arise from the common trunk. This stipulation appropriately relegates Collett-Edwards type IV, or *pseudotruncus*, to the spectrum of pulmonary atresia with aortopulmonary collaterals. The Van Praagh classification also provides for the inclusion of the relatively common association of hypoplastic or interrupted aortic arch. The term *hemitruncus* is frequently encountered in the literature to describe the anomalous origin of the right pulmonary artery from the ascending aorta with a normal origin of the left pulmonary artery from the main

pulmonary artery, usually in the absence of a VSD. This lesion is distinct from Van Praagh type B3 and should not be considered a form of truncus arteriosus.

A VSD is nearly always present. It results from the deficiency of the infundibular septum and is generally

TABLE 121-1 Collett and Edwards Classification

Type	Description
I	Branch pulmonary arteries arise from a segment of the main pulmonary artery off the common trunk.
II	Branch pulmonary arteries arise in close proximity from the posterior aspect of the common trunk.
III	Branch pulmonary arteries arise from separate, widely spaced origins.
IV	Absent “true” branch pulmonary arteries with aortopulmonary collaterals

TABLE 121-2 Van Praagh and Van Praagh Classification

Classification	Description
Type A	Ventricular septal defect present
Type B	Ventricular septal defect absent
1	Partial development of the aorticopulmonary septum
2	Absence of the aorticopulmonary septum
3	Absence of one of the branch pulmonary arteries
4	Coarctation, hypoplasia, or interruption of the aortic arch with a patent ductus arteriosus

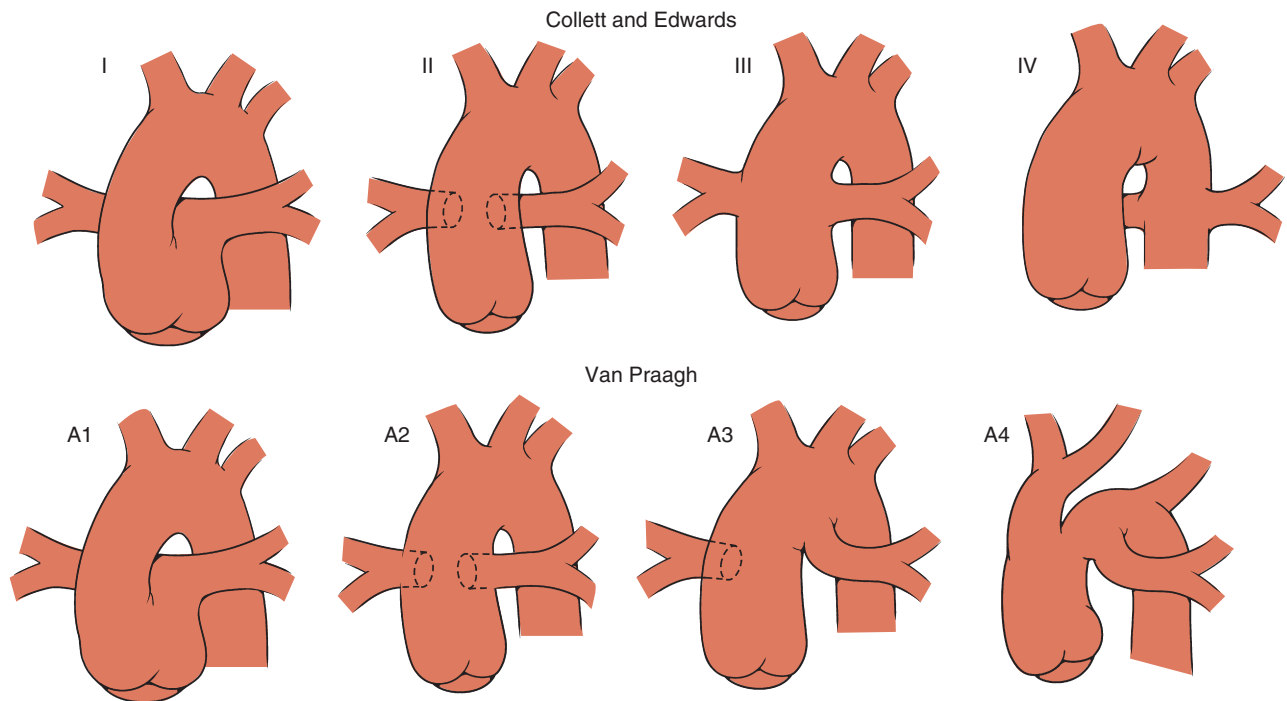


FIGURE 121-1 ■ Comparison of the Collett and Edwards and the Van Praagh and Van Praagh classifications of truncus arteriosus.

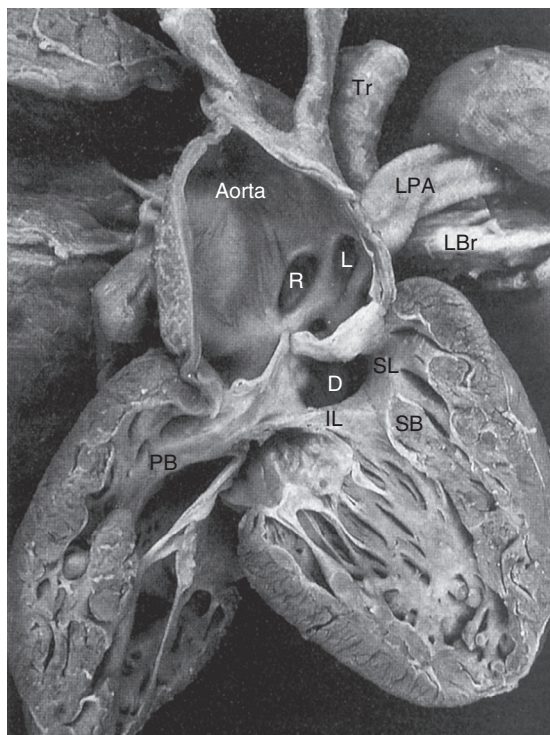


FIGURE 121-2 ■ Right ventricular view of the pathologic anatomy of truncus arteriosus. The truncal origins of the aorta and left (L) and right (R) pulmonary arteries are apparent. The ventricular septal defect (D) is cradled between the inferior (IL) and superior (SL) limbs of the septal band (SB). Insertion of the IL into the parietal band (PB) provides muscular discontinuity between the tricuspid and truncal valves. *LBr*, Left bronchus; *LPA*, left pulmonary artery; *Tr*, trachea. (Reprinted with permission from Mair DD, Edwards WD, Julsrud PR, et al: Truncus arteriosus. In Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, editors: *Moss and Adams' heart disease in infants, children and adolescents*, Philadelphia, 2001, Lippincott Williams & Wilkins, p 505.)

nonrestrictive. The VSD is cradled by the two limbs of the septal band and bounded superiorly by the truncal valve (Fig. 121-2). The posterior (inferior) limb of the septal band usually inserts into the parietal band, resulting in discontinuity of the tricuspid and truncal valves, maintaining a muscular rim between the conduction system and the VSD. When there is failure of insertion, the VSD extends into the membranous septum, with the conduction system running along the posterior-inferior rim of the defect.

The truncal valve can be tricuspid (69%), quadricuspid (22%), bicuspid (9%), or, rarely, unicuspid or pentacuspid.¹⁴ The valve is usually in continuity with the mitral valve and infrequently with the tricuspid valve. The truncus equally overrides both ventricles in 68% to 83% of cases, is deviated over the right ventricle in 11% to 29%, and is deviated to the left in 4% to 6%.^{7,15} The valve may be stenotic or regurgitant, which can complicate management of the patient with truncus arteriosus. A moderate or greater degree of truncal insufficiency is present in 20% to 26% of patients.^{16,17} Mild stenosis is generally detected on preoperative evaluation because of the increased flow across the truncal valve. Significant stenosis is present in only 4% to 7% of patients.^{16,17}

Gradients of greater than 30 mm Hg are concerning for residual stenosis after complete repair.¹⁸

The branch pulmonary arteries generally originate from the left posterolateral aspect of the truncus, just distal to the truncal valve. They are usually of good size without ostial or branch stenosis. Collett and Edwards type I is most frequently encountered, occurring in 48% to 68% of cases, followed by type II (29% to 48%) and type III (6% to 10%).^{7,15} In practice, most cases seem to fall into a category of "type 1½," with the branch pulmonary arteries arising not from a main pulmonary artery but in proximity from the posterior aspect of the truncus. Origin of one pulmonary artery from a systemic artery other than the truncus (Van Praagh type A3/B3) is relatively rare, with an incidence of 2% to 5%.^{16,19}

Associated Anomalies

An interrupted aortic arch, most commonly type B, is present in association with truncus arteriosus (Van Praagh type A4/B4) in approximately 10% to 20% of patients.^{8,9} The arch is rightward, generally with mirror image branching, in 21% to 36% of patients.^{8,20} Aberrant origins of the brachiocephalic vessels are reported, most commonly an aberrant right subclavian artery in 4% to 10%.^{15,20}

Coronary variations are common in truncus arteriosus and are of potential importance in the surgical repair of the lesion. The left anterior descending artery is often small, with prominent conal branches from the right coronary artery supplying the right ventricular infundibulum.²¹ The left anterior descending artery can originate from the right coronary artery, which has clear surgical ramifications for the right ventricular infundibulotomy. There is left coronary dominance in 27%, which is approximately threefold the incidence found in the general population.²² Coronary ostial abnormalities are of particular surgical significance and occur in 37% to 49% of cases.²² The usual arrangement, regardless of the number of cusps, is for the left coronary artery to arise from the left posterolateral cusp and for the right coronary artery to originate from the right anterolateral cusp. Coronaries can arise from a single orifice or from two ostia in a single cusp.⁸ There may be ostial stenosis, often described as a slitlike orifice, or obstruction from abnormal valve tissue. The left coronary artery is frequently noted to have a high origin, not uncommonly near the takeoff of the pulmonary arteries. Rarely, the left coronary artery can originate from the main pulmonary trunk or a branch pulmonary artery.¹⁵

Other cardiac anomalies are common, and a patent foramen ovale (PFO) is usually present. A true atrial septal defect is found in 9% to 20%, a persistent left superior vena cava in 4% to 9%, and mild tricuspid valve stenosis in 6%.^{15,20} Mitral valve abnormalities are reported in 5% to 10% of patients. Tricuspid atresia, complete atrioventricular septal defect, anomalies of pulmonary venous return, mitral atresia, hypoplastic left ventricle, ventricular inversion, and heterotaxy syndrome have all been reported in association with truncus arteriosus.

Extracardiac anomalies are reported in approximately 28% of patients with truncus arteriosus.¹⁷ Described

abnormalities include skeletal, genitourinary, and gastrointestinal deformities. As mentioned earlier, monoallelic microdeletion of chromosome 22q11 is common, and DiGeorge syndrome is diagnosed in at least 11%.¹⁷ These patients are at increased risk for more complicated operative courses, longer hospital stays, and greater resource utilization.²³

Pathophysiology

The pathophysiology of truncus arteriosus is one of a total admixture lesion, with mixing occurring at the level of the VSD and proximal truncus. Although there is cyanosis, systemic oxygen saturations are frequently 85% to 90% in the newborn period because of elevated pulmonary blood flow. In the absence of pulmonary artery stenosis or systemic outflow obstruction, the amount of pulmonary blood flow is mainly affected by the pulmonary vascular resistance (PVR). In the first few days of life, PVR remains relatively high, limiting pulmonary blood flow. As PVR decreases, the amount of pulmonary blood flow increases, leading to pulmonary overcirculation and signs and symptoms of congestive heart failure. The unrestricted left-to-right shunt results in both pressure and volume overload to the pulmonary circuit. In addition, truncus arteriosus is distinguished from other left-to-right shunt lesions by both systolic and diastolic shunting. These factors lead to the early development of irreversible pulmonary vascular occlusive disease in patients with truncus arteriosus.

Truncal valve regurgitation and, less frequently, stenosis can exacerbate the hemodynamic stresses placed on the heart in truncus arteriosus. Regurgitation adds an additional volume overload to the ventricles, worsening the signs and symptoms of congestive heart failure. The diastolic runoff, which occurs not only because of the insufficient valve but also as a result of the low-resistance pulmonary vascular bed, can lead to poor systemic perfusion, most notably to the coronary arteries. Stenosis increases the afterload on the ventricles and thereby increases myocardial oxygen demand. Significant truncal valve stenosis can limit systemic perfusion, again compounded by the runoff into the pulmonary circuit.

Diagnosis

Clinical Features

The diagnosis of truncus arteriosus is generally made in early infancy, often during the neonatal period. The lesion can also be recognized antenatally on fetal echocardiography. The degree of cyanosis or congestive heart failure depends on the PVR and the resultant volume of pulmonary blood flow. The clinical manifestations can be exacerbated by associated lesions, such as truncal valve insufficiency or interrupted aortic arch, or ameliorated by pulmonary artery stenosis.

Physical findings depend on the amount of pulmonary blood flow and the degree of truncal valve insufficiency. In general, the neonate with truncus arteriosus shows only mild cyanosis at the time of birth. As the PVR falls and pulmonary blood flow increases, signs of congestive

heart failure become manifest and cyanosis decreases. Truncal regurgitation accelerates the onset and increases the severity of congestive heart failure. The infant shows the typical findings of tachypnea, tachycardia, diaphoresis, and poor feeding. The precordium is hyperactive, and a thrill may be palpable over the left sternal border. There is a normal S1 and a single loud S2, which may be associated with an opening click. An S3 is not uncommon as the degree of failure progresses. A pansystolic murmur is common at the left sternal border. A low-pitched diastolic murmur at the apex, representing increased flow across the mitral valve, may be present. A high-pitched diastolic murmur along the left sternal border is indicative of truncal valve regurgitation. In the absence of the rarely encountered pulmonary artery stenosis, a continuous murmur is distinctly uncommon. The detection of a continuous murmur is consistent with other diagnoses, notably pulmonary atresia with a patent ductus or aortopulmonary collaterals. The peripheral pulse pressure is widened because of the diastolic runoff into the pulmonary bed and is further widened by truncal insufficiency.

Diagnostic Studies

The chest radiograph generally shows moderate cardiomegaly with increased pulmonary vascular markings. The arch is rightward in approximately one third of patients, and the thymus gland may be absent in those with 22q11 microdeletion. The combination of a right arch and increased pulmonary vascular markings is strongly suggestive of truncus arteriosus. The two-dimensional and Doppler echocardiography examinations are the diagnostic modalities of choice. The echocardiogram can define the anatomy of truncus arteriosus at birth or in utero. Prenatal echocardiography is increasingly identifying congenital heart anomalies; however, because of the challenges of imaging the branch pulmonary arteries, truncus arteriosus remains one of the more commonly misdiagnosed heart defects (78.6% accuracy).^{24,25} A parasternal long-axis view will demonstrate the large truncal valve overriding the VSD (Fig. 121-3A). The addition of Doppler interrogation will reveal truncal valve stenosis or regurgitation (see Fig. 121-3B). Suprasternal notch views can further define the anatomy of the pulmonary arteries and aortic arch (Fig. 121-4). Cardiac catheterization is generally reserved for the delineation of the anatomy in complex forms of truncus arteriosus, such as truncus arteriosus with a single pulmonary artery (Van Praagh type A3/B3). Cardiac catheterization is also indicated to assess PVR in the patient presenting late with truncus arteriosus. Magnetic resonance imaging (MRI) is a useful alternative or adjunct to cardiac catheterization for defining the anatomy of complex truncus arteriosus. MRI increasingly plays a role in the postoperative assessment of these patients in evaluating ventricular function as well as conduit and branch pulmonary artery anatomy.²⁶

Natural History

The typical natural history of truncus arteriosus is characterized by early demise because of congestive heart

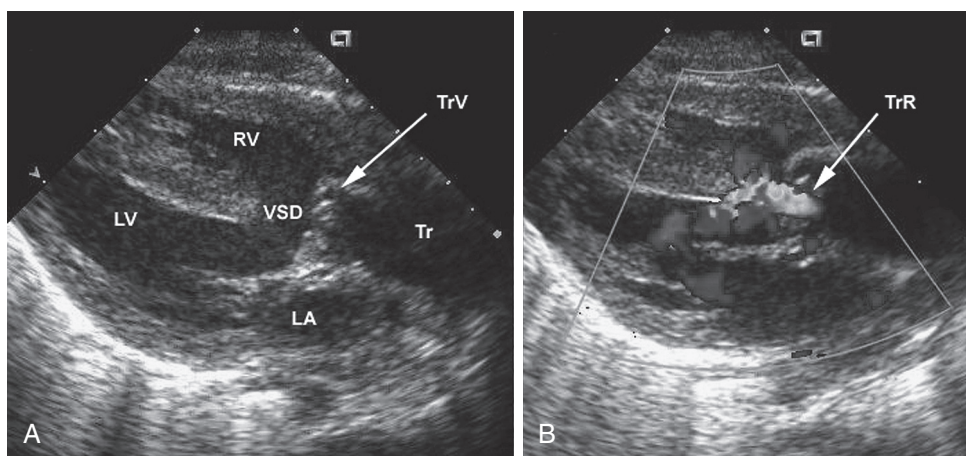


FIGURE 121-3 ■ Parasternal long-axis view of a patient with truncus arteriosus. **A**, The large truncus (Tr) overriding the ventricular septal defect (VSD) is demonstrated. **B**, The addition of Doppler reveals a jet of truncal regurgitation (TrR). LA, Left atrium; LV, left ventricle; RV, right ventricle; TrV, truncal valve.

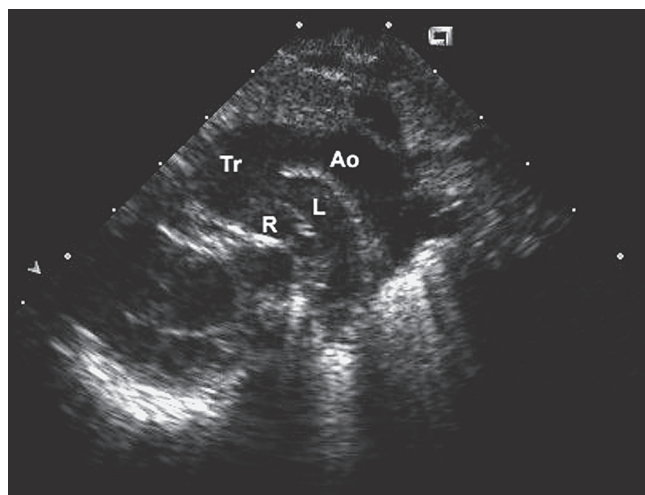


FIGURE 121-4 ■ Suprasternal notch view demonstrating close but separate origins of the right (R) and left (L) pulmonary arteries from the truncus (Tr) with continuation as the aorta (Ao).

failure. Death rates are approximately 40% at 1 month, 70% at 3 months, and 90% at 1 year.²⁷ Patients who survive infancy generally succumb by childhood or early adolescence because of congestive heart failure or, more commonly, pulmonary vascular obstructive disease. Rarely, patients survive infancy without developing pulmonary vascular obstructive disease, although those who do so are estimated to be less than 5% of all patients.²⁷

Treatment

Because of the inherent high early mortality, truncus arteriosus warrants early intervention. Initially, the surgical treatment of truncus arteriosus was limited to the banding of one or both of the branch pulmonary arteries. The first successful intracardiac repair was accomplished by Sloan's group at the University of Michigan in 1962 using an unvalved polytetrafluoroethylene (PTFE) conduit for the pulmonary reconstruction.²⁸ In 1967, McGoon and colleagues²⁹ performed the first valved

conduit repair, using an aortic allograft. During this period, complete repair was often undertaken as a staged procedure after initial pulmonary artery banding. However, complications of pulmonary artery banding, including pulmonary artery distortion, band migration, and failure to prevent the development of pulmonary vascular obstructive disease, resulted in a continued high mortality with this strategy. Ebert and coworkers³⁰ published the first series of patients undergoing repair of truncus arteriosus in infancy in 1984. With continued improvements in neonatal operative techniques, as well as perioperative care, management has evolved to earlier complete repair. After the early reports of neonatal repair from the University of Michigan¹⁸ and the Children's Hospital of Boston,³¹ neonatal repair has become the treatment of choice for truncus arteriosus.

Surgical Technique

The repair is performed using a standard median sternotomy. Although deep hypothermia with circulatory arrest or low-flow bypass has been advocated by some authors, the repair of simple forms of truncus arteriosus is performed easily on full-flow bypass with moderate hypothermia. More complex forms, such as Van Praagh type A3/B3 (one pulmonary artery absent) or A4/B4 (with interrupted aortic arch), may require periods of deep hypothermic circulatory arrest. The arterial cannula is placed distally in the ascending aorta at the base of the innominate artery. Bicaval cannulation is used for venous return, with an additional left ventricular vent placed through the right upper pulmonary vein. The pulmonary arteries are mobilized and snared to direct cardiopulmonary bypass flow to the systemic circulation.

The heart is arrested with antegrade cardioplegia, with the aortic crossclamp placed as distally as possible. Significant truncal valve regurgitation may necessitate the use of retrograde cardioplegia. Once the cardioplegia is delivered, the pulmonary arteries are removed. If the coronary arteries can be positively identified and the exposure is adequate, the pulmonary arteries can be removed directly from the posterior aspect of the truncus,

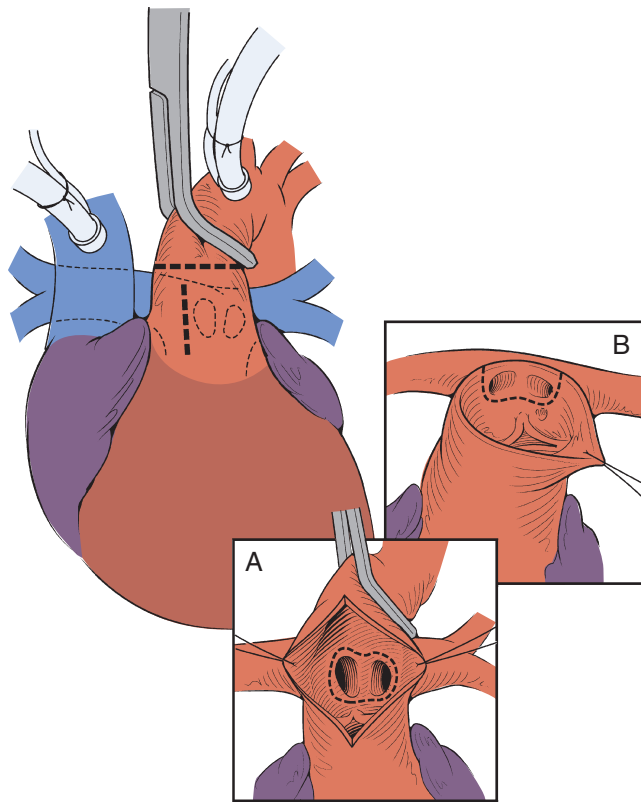


FIGURE 121-5 ■ Repair of truncus arteriosus. Removal of the pulmonary arteries from the truncus is facilitated by an anterior longitudinal aortotomy (A) or by transecting the aorta (B).

particularly for Collett and Edwards type I truncus arteriosus. The ostia of the coronary arteries can originate high in the sinuses or have an intramural course.³² Direct assessment of the coronary anatomy in the aortic root is crucial if there is any uncertainty. Often, it is helpful to open the aorta anteriorly to aid in the removal of the pulmonary arteries and to identify the origins of the coronary arteries (Fig. 121-5A). Transection of the aorta just distal to the origins of the branch pulmonary arteries is another useful technique to facilitate pulmonary artery and coronary exposure (see Fig. 121-5B). The pulmonary arteries are removed, together with a small rim of adjacent truncal wall. Care is taken to avoid injuring the left coronary artery or truncal valve, which are often in close proximity to the pulmonary arteries. The truncal defect is then repaired primarily or with a patch of PTFE. At this point, additional doses of cardioplegia can be given at intervals, depending on surgeon's preference.

The heart is inspected for the presence of any large conal branches, the location of the left anterior descending artery, and the possibility of aberrant coronary arteries. A right infundibulotomy is then made in an avascular area of the right ventricular outflow tract. The infundibulotomy is carried cranially toward the truncal valve and is limited to the size necessary to allow unobstructed output from the right ventricle through the anticipated conduit (Fig. 121-6A). Through the infundibulotomy, the VSD is closed with a patch of PTFE. We use a running suture technique, although an interrupted

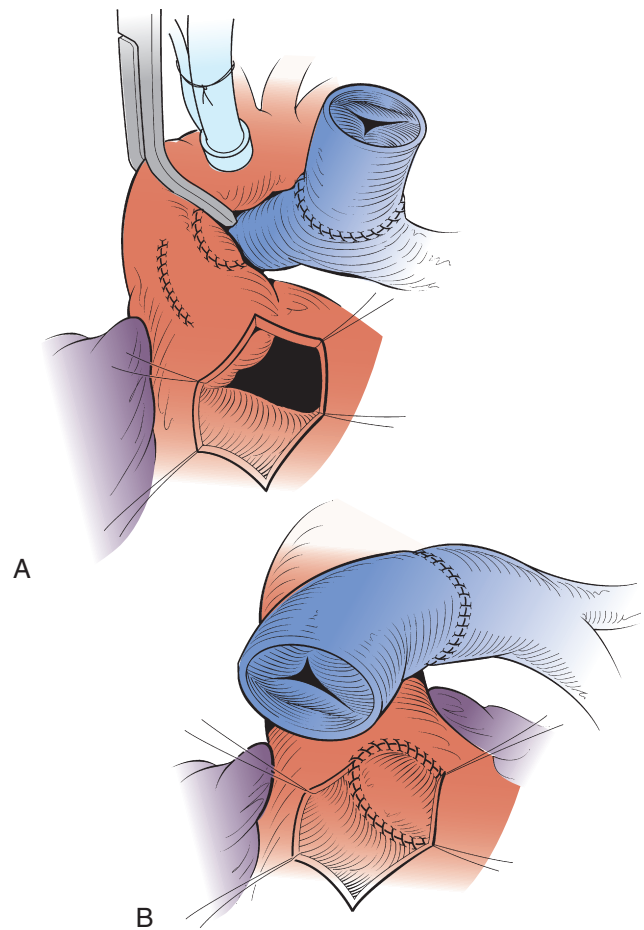


FIGURE 121-6 ■ Repair of truncus arteriosus. A, The ventricular septal defect (VSD) is exposed through a right infundibulotomy. B, The VSD patch is transitioned to the epicardium at the superior-most portion of the infundibulotomy. The posterior aspect of the pulmonary allograft is sewn directly to the superior portion of the infundibulotomy.

technique can be used as well. When there is membranous or inlet extension of the VSD, care is taken not to injure the conduction tissue in the posteroinferior aspect of the VSD. It is helpful to transition from the endocardium of the right ventricular outflow tract to the epicardium in the anterosuperior-most portion of the infundibulotomy, to avoid injuring the truncal valve and to ensure a widely patent left ventricular outflow tract (see Fig. 121-6B). If present, the atrial septal defect is then closed. A small PFO can be left as a “popoff valve” to aid in postoperative management.

Once the VSD is closed, the remainder of the procedure can be performed with the crossclamp removed and the heart beating. We prefer to use cryopreserved pulmonary or aortic allografts for reconstruction of the pulmonary outflow tract, although either bovine jugular vein grafts or heterograft valved conduit are viable alternatives. The distal anastomosis of the allograft is performed to the confluence of the native branch pulmonary arteries. The posterior aspect of the allograft is then approximated to the superior portion of the right infundibulotomy. Anteriorly, the conduit is augmented with a patch of PTFE or additional allograft material (Fig. 121-7). A

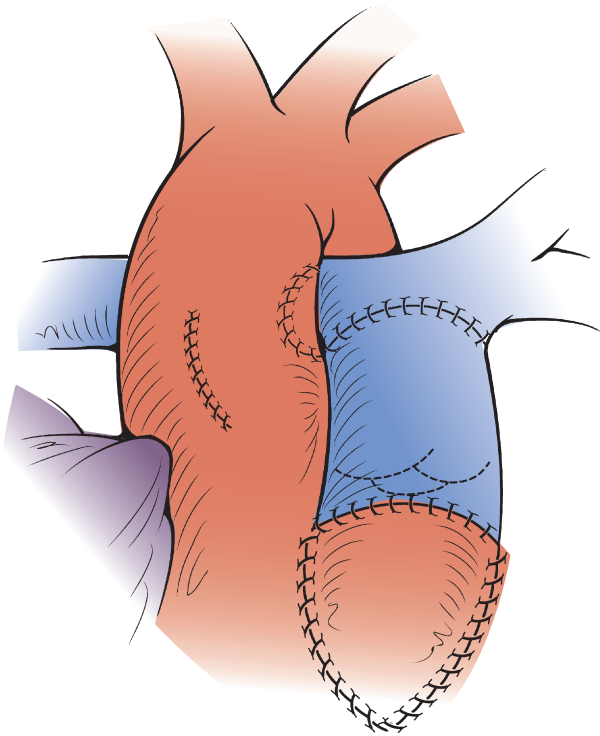


FIGURE 121-7 ■ Repair of truncus arteriosus. Right ventricle-to-pulmonary artery continuity is then completed with a hood of polytetrafluoroethylene.

benefit of the bovine jugular vein grafts is the proximal extension of tissue, which can be used to patch the right infundibulotomy without additional patch material.

Other Surgical Considerations

Interrupted Aortic Arch

The surgical repair of truncus arteriosus with interrupted aortic arch (Fig. 121-8) requires several modifications to the basic operative procedure. The aortic cannulation is performed proximally at the base of the innominate artery to perfuse all of the brachiocephalic vessels, and distally in the ductus arteriosus to perfuse the distal aorta. Bicaval cannulation is used for venous return, with a left ventricular vent placed through the right upper pulmonary vein. The patient is placed on cardiopulmonary bypass and cooled to 18° C for a minimum of 20 minutes. The pulmonary arteries are snared to prevent pulmonary overcirculation. During cooling, the ascending aorta, arch, proximal descending aorta, brachiocephalic vessels, and pulmonary arteries are mobilized. The arch repair can be performed under deep hypothermic circulatory arrest. Alternatively, regional cerebral perfusion, as described by Pigula and coworkers³³ and others, can be performed by anastomosing a PTFE tube graft to the innominate artery or by directly cannulating the aorta at the base of the innominate artery and advancing the cannula into the innominate. After adequate cooling, the head vessels are snared, bypass is discontinued, and regional cerebral perfusion is initiated, if desired. The

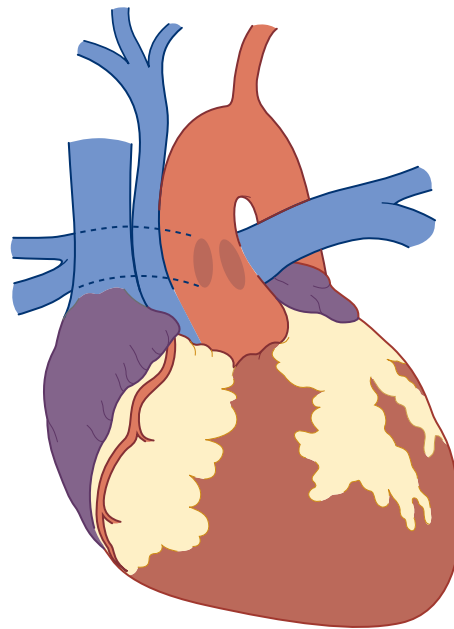


FIGURE 121-8 ■ Truncus arteriosus (Collett and Edwards type II) with a type B interrupted aortic arch.

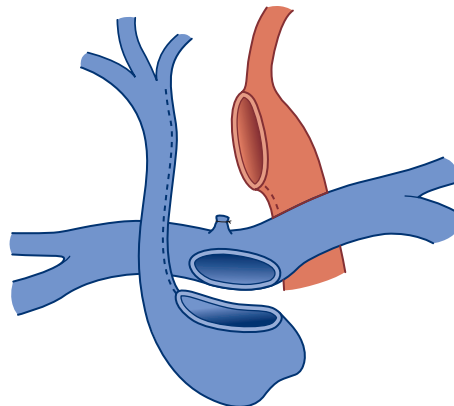


FIGURE 121-9 ■ Repair of truncus arteriosus with interrupted aortic arch. The ductus arteriosus has been ligated and divided, and the pulmonary arteries have been removed from the truncus. The areas for spatulation on the ascending aorta and proximal descending aorta are indicated (dashed lines).

ductus arteriosus is ligated just distal to the origin of the pulmonary arteries and divided. All residual ductal tissue is resected from the proximal descending aorta. The ascending aorta and proximal descending aorta are spatulated (Fig. 121-9). The back walls of the distal ascending aorta and proximal descending aorta are approximated, and the repair is augmented with a patch of cryopreserved pulmonary allograft (Fig. 121-10). Once the arch reconstruction is completed, the aorta can be recannulated and de-aired, an aortic crossclamp can be placed, and cardiopulmonary bypass can be resumed. Additional doses of cardioplegia can be administered and rewarming can begin. The remainder of the repair, including VSD closure and pulmonary outflow tract reconstruction, is similar to the simple truncus arteriosus surgical procedure.

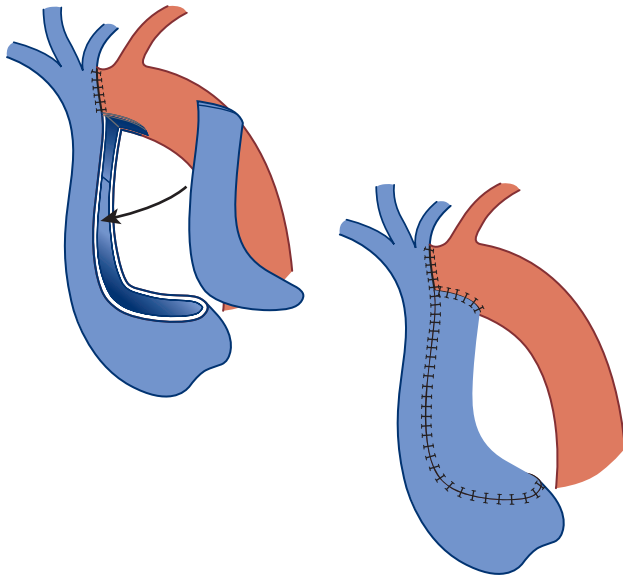


FIGURE 121-10 ■ Repair of truncus arteriosus with interrupted aortic arch. The distal ascending and proximal descending aorta are reapproximated and augmented with cryopreserved pulmonary allograft.

Truncal Valve Regurgitation or Stenosis

Significant truncal valve regurgitation, or, less frequently, stenosis, can complicate the operative management of truncus arteriosus in approximately a quarter of cases. A conservative approach is warranted, as frequently both regurgitation and stenosis improve after corrective surgery and relief of the volume overload. Gradients of less than 30 mm Hg generally do not require intervention.¹⁸ In addition, even moderate degrees of truncal regurgitation are well tolerated, and delay of valve repair or replacement can often be accomplished. A recent analysis of the Society of Thoracic Surgeons Congenital Heart Surgery database from 2000-2009 demonstrated that concomitant truncal valve surgery at the time of truncus arteriosus is associated with a significantly higher operative mortality compared with repair of the truncus arteriosus in isolation (30% vs. 10%; $P = 0.0002$). This mortality risk increases to 60% when the truncal valve surgery is combined with repair of an interrupted aortic arch—the caveat being that patients who did not have an initial truncal valve surgery, but subsequently required surgical intervention during their index hospital admission, had a 100% mortality.³⁴ Hence, appropriate patient selection is essential in terms of timing of truncal valve intervention. Many patients with severe truncal regurgitation do not survive to operation. For the patients who do survive, the presence of moderate to severe truncal regurgitation after the initial operation is a risk factor for late truncal valve reintervention but not early mortality.³⁵ At the time of truncal valve intervention, truncal valve repair is preferred if the valve is amenable with other options, including root replacement with cryopreserved aortic allograft or mechanical valve replacement. Truncal valve replacement can be facilitated by enlargement of the valve annulus by the VSD patch. For truncal valve repair, several techniques have been described in

small series of patients with reasonable survivals. These techniques include annuloplasty, resection of cusps, closure of commissures, resuspension of cusps, and cusp repair.^{36,37} Backer and Mavroudis^{38,39} have reported that truncal valve remodeling by leaflet excision or reduction annuloplasty is the most effective and durable method of truncal valve repair. In long-term follow-up, this group demonstrated that durable results can be achieved with valve morphology as the key determinant of success, with 75% of patients having a quadricuspid valve requiring leaflet excision and tricuspidization of the valve, with only two patients proceeding to valve replacement 9 and 10 years after repair.⁴⁰ Risk factors for reoperation following truncal valve repair include neonatal repair (hazard ratio 4.1; $P = 0.03$) and performance of leaflet thinning (hazard ratio 22.5; $P = 0.002$).⁴¹ Older children and adults have a greater number of options for valve replacement, including aortic allograft, stented or stentless tissue valves, and mechanical valves. Repair is also an option in this population if the anatomy is amenable to a durable repair.

Pulmonary Outflow Tract Reconstruction

Although the majority of surgeons use valved heterograft or allograft conduits, several other techniques have been described. These other techniques include the use of unvalved conduits, fresh autologous pericardial valved conduits, monocusps, and various methods for achieving native tissue apposition between the right ventricle and the pulmonary artery.

Unvalved tube grafts have been used in the past with good results, but they have been largely abandoned with the development of appropriately sized valved conduits.⁴² Advantages include availability and lower risk of stenosis related to valve dysfunction or calcification. The clear disadvantage is the lack of a valve in the immediate postoperative period, with free regurgitation into a right ventricle compromised by a ventriculotomy and periods of ischemia and cardiopulmonary bypass. In addition, a valve may be advantageous in neonates with labile PVR or in older patients with pulmonary vascular obstructive disease. One study analyzing neonatal repair with unvalved conduits found that patients with truncus arteriosus had the highest rate of reintervention for conduit failure compared with other diagnostic groups.^{43,44}

Options for valved conduits include composite heterografts, allografts, and bovine jugular vein grafts. Porcine heterografts in Dacron tube grafts are available in sizes as small as 12 mm. Advantages include ready availability. Disadvantages are primarily related to the stiff Dacron tube graft, which is less hemostatic and less forgiving, with a greater risk of distortion of the branch pulmonary arteries. Dacron also tends to form a neointimal peel, potentially leading to stenosis. In addition, the rigid metal ring of the heterograft valve can be compressed beneath the sternum, obstructing the left anterior descending artery. Bovine jugular vein grafts have increased in popularity. They are readily available in small sizes, down to 12 mm. These grafts have excellent handling characteristics, are hemostatic, and minimize branch pulmonary artery distortion. They are available with or without supporting rings to minimize distortion

from sternal compression. The bovine jugular vein grafts have similar durability to traditional allografts, however enthusiasm has been tempered by increased risk of distal stenosis especially in patients younger than 2 years.^{45,46,47} Another larger series has shown the Contegra conduit and size less than 20 mm to be independent risk factors for need for graft replacement when compared with allografts.⁴⁸

Cryopreserved pulmonary allografts have the advantages of excellent tissue handling characteristics and ease of implantation. Aortic allografts can also be used, although they appear to be less durable than their pulmonary counterparts.^{17,49} The disadvantage of these conduits is primarily related to the limited availability in the very small sizes, although allografts in the range of 12 to 16 mm can generally be placed in neonates without difficulty. A larger pulmonary allograft can be downsized by removal of one of the cusps, creating a bicuspid valve. Our group and others⁵⁰⁻⁵² have successfully used this technique when appropriately sized allografts are unavailable.

Whether heterografts or allografts have superior longevity remains controversial. Several published studies, including our own experience, have shown that pulmonary allografts are the optimal conduit in neonates and infants.^{17,53} Our results for the placement of a right ventricle-to-pulmonary artery conduit in a series of 155 infants demonstrated a significantly greater 5-year freedom from reoperation for cryopreserved pulmonary allograft (50%) compared with aortic allograft (24%; $P = 0.02$) and heterograft (26%; $P = 0.05$).³⁹ It has been shown that optimizing allograft size (z-score within +1 to +3) is important to conduit longevity, with no additional benefit from oversizing conduits.^{45,54} Others have found no significant difference in longevity between heterografts and allografts for the repair of truncus arteriosus.⁵⁵

In an effort to decrease the need for reoperation, several groups have suggested methods for achieving native tissue apposition in the right ventricular outflow tract to allow for growth. In 1990, Barbero-Marcial and associates⁵⁶ introduced a technique for anastomosing the pulmonary bifurcation directly to the superior margin of the infundibulotomy. The anterior aspect of the anastomosis is then augmented with a patch, which includes a monocusp. Late follow-up of 45 patients by Barbero-Marcial and Tanamati⁵⁷ demonstrated that this technique resulted in a reintervention rate of 12% over a mean follow-up of 47 months, with an 11.4-year actuarial survival rate of 67.5%. In addition, 44.4% had moderate to severe pulmonary regurgitation and 23.3% had pulmonary stenosis. Lacour-Gayet and colleagues¹⁶ reported their experience with 56 consecutive patients undergoing repair for truncus arteriosus using a number of different techniques for pulmonary outflow tract reconstruction. They found equivalent rates of reintervention for heterograft and direct anastomosis of approximately 80%. Danton and associates⁵⁸ published a series of 61 patients with truncus arteriosus, 38 repaired with a conduit and 23 with direct anastomosis. Although mortality was not influenced, 10-year actuarial freedom from reoperation was 89% in the direct anastomosis group, compared with 56% in the conduit group ($P = 0.023$).

Right ventricular outflow tract reconstruction using fresh autologous pericardial valved conduits has been described by Kreutzer and associates.⁵⁹ Their series of 86 patients undergoing this technique included 23 cases of truncus arteriosus. Operative mortality for the patients with truncus arteriosus was 26%. Among the entire group, moderate to severe conduit regurgitation was present immediately after surgery in 12.7%. By 6 months after surgery, no valve tissue could be identified in any patient, either by echocardiography or by visual inspection in those patients requiring reoperation. For the entire cohort, the need for conduit-related reintervention was 83% at 5 years and 60% at 10 years for conduits less than 16 mm at the time of implantation. By contrast, in the report by Lacour-Gayet and coworkers,¹⁶ freedom from reoperation or angioplasty at 7 years was 100% for patients receiving a pericardial conduit in the repair of truncus arteriosus. However, the authors also found the use of direct anastomosis or pericardial conduit to be a significant risk factor for operative mortality (43%), when compared with a heterograft or allograft (7.1%; $P = 0.015$).

Postoperative Management

Most patients require low doses of inotropic support with standard postoperative care techniques. The placement of a left atrial transthoracic monitoring line is helpful, as the central venous pressure may not accurately reflect left-sided filling pressures because of right ventricular dysfunction. Early operation has virtually eliminated the postoperative pulmonary hypertensive crises seen in earlier studies. For older patients in whom pulmonary vascular hypertensive crisis or pulmonary vascular obstructive disease can be anticipated, the placement of a transthoracic pulmonary artery line can aid in postoperative management. Avoiding acidosis, hypercarbia, and hypoxia can minimize PVR. Sedation and paralysis are also used to minimize fluctuations in PVR. The use of nitric oxide and sildenafil can induce pulmonary vascular smooth muscle relaxation and can be particularly useful in older patients with reversible pulmonary vascular obstructive disease.

Results

Since the first large series of truncus arteriosus repair in infants by Ebert and colleagues³⁰ in 1984, the management has evolved to earlier neonatal repair, with a continual improvement in survival. Hospital mortality for the neonatal repair of truncus arteriosus from the Society of Thoracic Surgeons Congenital database from 2005 to 2009 was 10.9% (range, 0%-100%).⁶⁰ The majority of deaths occur in patients with complex truncus arteriosus or truncus arteriosus associated severe truncal valve regurgitation.^{16-19,32,61} More complex forms of truncus arteriosus are also associated with increased hospital morbidity and prolonged length of stay.⁶² Risk factors for poor outcome identified in various studies include significant truncal regurgitation, need for truncal valve replacement, birth weight less than 2.5 kg, presence of interrupted aortic arch or coronary artery anomalies,

pulmonary reconstruction with a technique other than valved heterograft or allograft, and age greater than 100 days.^{16-19,31,55,61} Some single-center studies have demonstrated that interrupted aortic arch is not a risk factor.^{18,19} However, a recent Congenital Heart Surgeons' Society study and a single-center study have again shown a high early mortality rate of 42% to 56% for truncus arteriosus associated with interrupted aortic arch.^{63,64}

Long-term survival for patients with truncus arteriosus is also encouraging with actuarial survivals of 90% at 5 years, 85% at 10 years, and 83% at 15 years, with the majority of survivors (97%) in New York Heart Association class I or II.^{20,55} Examination of the Kaplan-Meier survival curves reveals that the majority of mortality is associated with the initial operation. Late follow-up has demonstrated that although the greatest need for intervention or hospitalization is in the first year of life, patients with truncus arteriosus have significantly impaired exercise capacity and diminished physical health status and health-related quality of life compared to normative standards.⁶⁵ An issue for patients with a variety of conotruncal abnormalities is the finding of a dilated ascending aorta in adolescents and adults and the question of whether this requires intervention. The majority of patients have been found to have an aorta z-score of ≥ 2 ; however, the risk of dissection is believed to be rare and therefore conservative management with close observation is the recommended approach at this time.^{66,67}

AORTOPULMONARY WINDOW

Aortopulmonary window is an uncommon malformation characterized by an anomalous communication between the adjacent portions of the ascending aorta and the main pulmonary artery. Distinctively, the aortic and pulmonary semilunar valves are both present, and the ventricular septum is typically intact. This lesion represents between 0.2% and 0.3% of all congenital heart lesions.^{68,69} Aortopulmonary window was first described by Eliotson in a clinicopathologic discussion given at St. Thomas' Hospital in London in 1830.⁷⁰

Embryology

Descriptions of cardiac embryology can be confusing because of varying terminology used by different authors. For the purpose of this discussion, the embryonic cardiac outflow tract can be considered as the portion of the primitive heart tube that connects the ventricles with the aortic arch vessels. This outflow tract comprises the conus, the truncus, and the aortic sac. Histologically, the conotruncus has an external muscle layer and internal cardiac jelly (which is cellular), whereas the aortic sac has a wall consisting of endothelium surrounded by loose mesenchyme. Septation of the outflow tract seems to occur in a craniocaudal direction by two mechanisms.⁷¹ Initial septation occurs by an ingrowth of mesenchyme (principally neural crest tissue), which separates the aortic sac into the definitive aorta and the pulmonary artery. This aorticopulmonary septum then extends caudally to divide the distal truncus. Meanwhile, in the proximal

conotruncus, paired ridges (consisting of both neural crest and non-neural crest tissue) bulge into the lumen and meet. The caudal portion of the aorticopulmonary septum ultimately fuses with the cranial extent of the conotruncal ridges to complete septation. This entire process occurs in human embryos beginning when the crown-rump length is 6 mm, and it is completed by the 9-mm stage over a period of approximately 5 days.⁷²

The embryologic defect in aortopulmonary window is presumed to be related to nonfusion of the aorticopulmonary septum with the conotruncal septum, malalignment of the two septa, or complete absence of the aorticopulmonary septum.⁶⁹ The defects leading to truncus arteriosus and aortopulmonary window are thought to be distinct. Although a number of gene mutations that lead to a phenotype of truncus arteriosus have been identified, none of these has resulted in isolated aortopulmonary window. In addition, isolated aortopulmonary window is generally not seen in the constellation of conotruncal abnormalities that occur in conjunction with DiGeorge syndrome.

Anatomy

The defect in aortopulmonary window is usually oval and solitary, although its precise location can vary. Many classification schemes have been proposed to describe the variation in morphology of this anomaly. One widely used classification, proposed by Richardson and colleagues, describes three variants.⁷³ Type I defects represent the classic proximal window involving the posteromedial wall of the ascending aorta just above the left sinus of Valsalva and the adjacent wall of the main pulmonary artery. The inferior extent of the proximal defect may be close to the origin of the left coronary artery. Type II defects are more distal communications occurring near the origin of the right pulmonary artery. Distal windows can be associated with a variable degree of "unroofing" of the right pulmonary artery, which can lead to the apparent origin of this vessel from the posterolateral aspect of the ascending aorta. Finally, type III defects describe anomalous origin of the right pulmonary artery from the posterolateral wall of the ascending aorta (without an associated window). The type III defect has also been called *hemitruncus*, although the use of this term has been discouraged in favor of the more descriptive "anomalous origin of the right pulmonary artery from the aorta."

A more useful scheme was advanced by Mori and associates.⁷⁴ In the Mori classification, type I and II defects are analogous to their counterparts in the Richardson classification, with type I (proximal) defects occurring between the adjacent portions of the proximal ascending aorta and main pulmonary artery, and type II (distal) defects located more distally near the origin of the right pulmonary artery. Mori type III (total) defects are large defects representing a combination of types I and II.

Recently, Jacobs and members of the Congenital Heart Surgery Nomenclature and Database Project proposed general use of the Mori classification (proximal, distal, and total), with the addition of a fourth type termed intermediate and representing a window similar to the total defect but slightly smaller, with well-defined

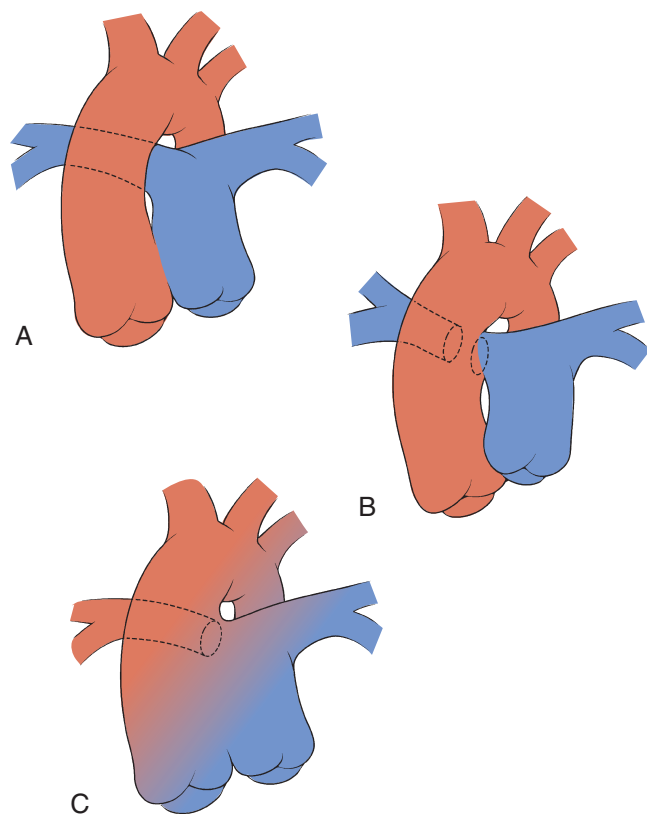


FIGURE 121-11 ■ Anatomy and classification of aortopulmonary window as recommended by the Congenital Heart Surgery Nomenclature and Database Project. **A**, Type I (proximal) defects occur between adjacent portions of the proximal ascending aorta and the main pulmonary artery. **B**, Type II (distal) defects are located more distally, near the origin of the right pulmonary artery. **C**, Type III (total) defects are large defects with poorly defined margins representing a combination of types I and II. Intermediate defects (not illustrated) are similar to total defects but are slightly smaller and have well-defined superior and inferior rims.

superior and inferior rims.⁷⁵ The remainder of this chapter will adhere to this terminology. [Figure 121-11](#) illustrates the anatomic subtypes of aortopulmonary window.

Associated Anomalies

Associated anomalies can occur in 25% to 65% of cases of aortopulmonary window.^{69,76-79} These associated defects may be considered minor or major.⁸⁰ Common minor defects include right aortic arch, patent ductus arteriosus, atrial septal defect, and PFO. Major defects commonly seen with aortopulmonary window include interrupted aortic arch (usually type A), tetralogy of Fallot, VSD, anomalous coronary artery, coarctation of the aorta, and univentricular heart lesions. Berry and colleagues⁸¹ described a syndrome characterized by a distal aortopulmonary window, aortic origin of the right pulmonary artery, intact ventricular septum, patent ductus arteriosus, and interruption or coarctation of the aortic isthmus. Braunlin and coworkers⁸² emphasized the frequency of arch obstruction in patients with an aortopulmonary window, reporting interrupted aortic arch in

43% and coarctation in 14%. The presence of an aortopulmonary window must always be excluded in infants with an interrupted aortic arch and an intact ventricular septum. A high index of suspicion for an aortopulmonary window is also warranted in cases of unexplained pulmonary artery hypertension or cardiac dilation.⁸³

Pathophysiology

An aortopulmonary window invariably leads to excessive pulmonary blood flow secondary to a large-volume left-to-right shunt that occurs during systole and diastole. The degree of shunting is, of course, determined by the size of the window and the ratio of systemic to pulmonary vascular resistance. The window is usually nonrestrictive in nature, thereby leading to equalization of pressures in the aorta and pulmonary arteries. As PVR decreases after birth, shunt volume increases. The result is left ventricular volume overload, as well as a pressure load on the right ventricle. Excessive pulmonary blood flow can lead acutely to the development of interstitial pulmonary edema. Over time, pulmonary overcirculation can lead to the development of pulmonary vascular obstructive disease.

The presence of associated defects can affect the physiology of this condition. Most importantly, the presence of aortic arch obstruction exacerbates left-to-right shunting across the aortopulmonary window. In cases of severe coarctation or arch interruption, in which systemic perfusion is ductal dependent, closure of the ductus will precipitate severe systemic malperfusion and divert even more blood flow to the lungs.

Diagnosis

Clinical Features

As with truncus arteriosus, the diagnosis of aortopulmonary window is generally made during infancy. A loud continuous murmur with systolic accentuation is heard best at the left upper sternal border and may be confused with the murmur associated with a patent ductus arteriosus. The second heart sound may be accentuated and narrowly split. The diastolic blood pressure is usually reduced, with a concomitant widened pulse pressure and, on occasion, a water-hammer pulse. Patients typically present with symptoms of congestive heart failure (tachypnea, diaphoresis, failure to thrive, or recurrent respiratory infections).

The differential diagnosis of aortopulmonary window includes patent ductus arteriosus, truncus arteriosus, VSD with aortic insufficiency, and ruptured sinus of Valsalva aneurysm.

Diagnostic Studies

A chest radiograph demonstrates moderate cardiomegaly and increased pulmonary vascular markings. A right aortic arch may be present.

Echocardiography is generally diagnostic and has replaced angiography as the gold standard.⁸⁴⁻⁸⁸ The margins of the window can be imaged with two-dimensional echocardiography, and Doppler color-flow

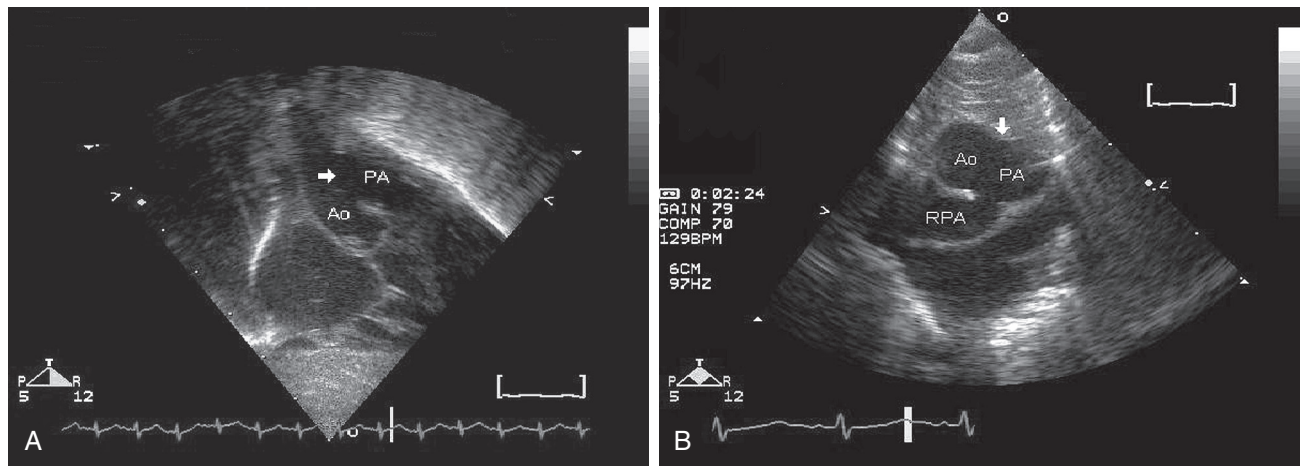


FIGURE 121-12 ■ Echocardiographic views in a patient with a large (total-type) aortopulmonary window (as well as a type A interrupted aortic arch). **A**, Subcostal coronal view shows the large communication (arrow) between the ascending aorta (Ao) and the main pulmonary artery (PA). **B**, Parasternal short-axis view demonstrates that the distal extent of the aortopulmonary window involves the origin of the right pulmonary artery (RPA). The anterior border of the window is identified by the arrow.

mapping can confirm flow across the communication. The most useful echocardiographic views to delineate the margins of the window include the suprasternal long axis, the subcostal coronal plane through the pulmonary trunk, and the high parasternal short plane cephalad to the aortic valve (Fig. 121-12). Additional echocardiographic findings include left atrial and left ventricular enlargement, which are usually in proportion to the degree of volume overload. Continuous forward flow in the distal main or branch pulmonary arteries is evident. When a jet of tricuspid or pulmonary insufficiency is present, pulmonary hypertension can be confirmed. The diagnosis of aortopulmonary window can also be made during fetal echocardiography.⁸⁹ MRI is an emerging technique that is capable of clarifying anatomy with great detail.^{90,91}

Cardiac catheterization is rarely necessary unless clarification of associated defects is needed or if the coronary anatomy cannot be imaged well by echocardiography. In patients who present beyond infancy, catheterization allows the calculation of PVR to determine surgical candidacy.

Natural History

Patients with large aortopulmonary windows generally do not survive beyond childhood. Of untreated patients, 40% die within the first year of life.⁹² Untreated patients generally develop pulmonary vascular obstructive disease. Because of the poor prognosis associated with this condition, it is recommended that all patients with aortopulmonary window undergo repair.

Treatment

The initial repair of aortopulmonary window involved, of necessity, closed techniques. Robert Gross performed the first surgical closure of an aortopulmonary window in 1948.⁹³ The patient was a 4-year-old girl who was explored via a left thoracotomy for a presumptive patent ductus arteriosus. The correct diagnosis was made at

operation. Gross successfully ligated the window but acknowledged the potential risks and limitations of this technique. Scott and Sabiston⁹⁴ developed an animal model for aortopulmonary window and then devised techniques for closed division and suture closure using partial occluding clamps; they subsequently applied these techniques clinically in 1951. These closed techniques, however, were associated with several major limitations. First, dissection of the window was fairly risky because of potential bleeding complications. Second, division and primary closure of the window could lead to significant narrowing of both the aorta and the pulmonary artery and potential distortion of the semilunar valves. Third, the closed approach did not allow visualization of the coronary ostia, so coronary perfusion might be compromised after repair.

The introduction of cardiopulmonary bypass brought a greater margin of safety to the closed approach, but, more importantly, cardiopulmonary bypass permitted the development of open techniques that could be applied to the repair of all types of aortopulmonary window defects and their associated defects. Cooley and colleagues were the first to use cardiopulmonary bypass to facilitate division and oversewing of an aortopulmonary window in 1956.⁹⁵ Since that time, most published reports have emphasized the adjunctive use of cardiopulmonary bypass. In 1966, Putnam and Gross suggested a transpulmonary approach to repair, whereby the defect could be sutured closed from within the lumen of the main pulmonary artery using a longitudinal arteriotomy.⁹⁶ Although most early repairs were performed in older children, Cordell and associates reported the first closure of an aortopulmonary window in an infant (6 months of age) in 1967.⁹⁷ Wright and coworkers⁹⁸ described suture closure of the defect via a transaortic approach. This approach provided excellent exposure of the margins of the defect and the origins of the left coronary artery and right pulmonary artery. In 1969, Deverall and colleagues⁹⁹ reported their experience using a transaortic approach with closure of the defect using a Dacron patch. The

advantages of patching the defect with a transaortic approach were emphasized in a report from Clarke and Richardson.¹⁰⁰ This became the early standard approach for most cases of aortopulmonary window. Operative mortality was significantly reduced with this change in operative strategy.⁷⁶ Studies in the early twenty-first century have demonstrated that early repair, preferably in infancy, along with concomitant repair of associated anomalies is imperative for optimal outcomes.¹⁰¹⁻¹⁰³

The preoperative care of patients with aortopulmonary window primarily involves the management of associated congestive heart failure using standard techniques. Patients with significant aortic arch obstruction require infusion of prostaglandin E₁.

All symptomatic patients should undergo prompt repair, once the diagnosis is confirmed. Asymptomatic patients should undergo repair by 3 to 4 months of age to avoid the development of pulmonary vascular obstructive disease, which can occur in some patients at as early as 6 months of age. Older patients should undergo preoperative catheterization to assess PVR and its response to oxygen and nitric oxide. A ratio of pulmonary vascular resistance (Rp) to systemic vascular resistance (Rs) of greater than 0.4 has been shown to be a risk factor for perioperative death.¹⁰⁴ A PVR greater than 8 to 10 and an Rp/Rs greater than 0.7 probably represent absolute contraindications for repair.

Surgical Technique

The repair is performed using standard median sternotomy. Bicaval venous and distal aortic cannulation is recommended. Snare is placed around both branch pulmonary arteries. Cardiopulmonary bypass with moderate hypothermia is initiated, and pulmonary arterial snares are tightened. After aortic cross-clamping, standard cardioplegia is delivered via the aortic root. Subsequent doses of cardioplegia (if necessary) are readily given by retrograde or direct antegrade approach.

Many centers continue to use the transaortic approach for the repair of aortopulmonary window. A longitudinal aortotomy is made in the ascending aorta. For simple proximal (type I) defects, closure is readily accomplished using a PTFE patch (Fig. 121-13). Care must be taken to identify and protect the left coronary orifice. For distal (type II) defects, a more extensive patch must be fashioned (Fig. 121-14). When there is considerable unroofing of the right pulmonary artery, the creation of an intra-aortic baffle can result in aortic obstruction; this can be alleviated by simply closing the aortotomy with an elliptical patch (Fig. 121-15). Total (type III) and intermediate-type defects are repaired using analogous techniques (Fig. 121-16).

Johansson and colleagues⁸⁵ described a transwindow approach (also called a *sandwich-type repair*), which has gained wide acceptance as the optimal approach for the repair of aortopulmonary window. In this technique (Fig. 121-17), an incision is made in the anterior wall of the communication between the aorta and the pulmonary trunk. A patch is then sutured to the posterior wall of the defect. The suture line is subsequently carried anteriorly to incorporate the patch in the closure of the arteriotomy.

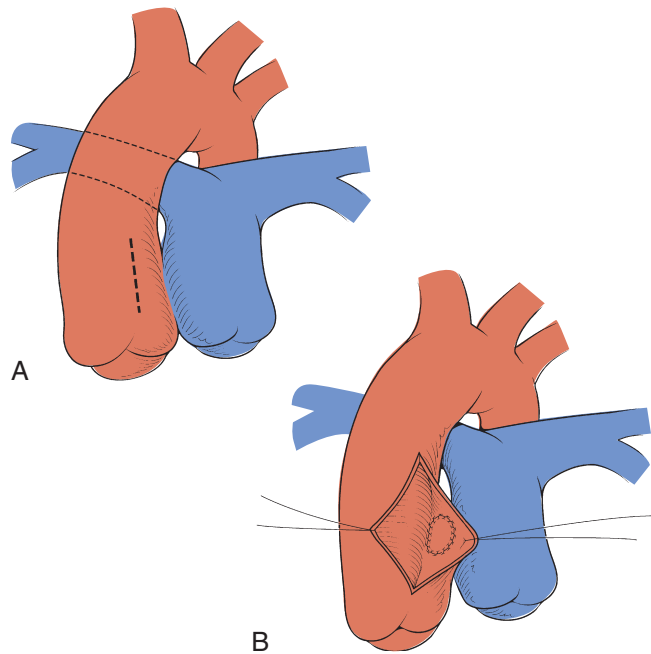


FIGURE 121-13 ■ Transaortic patch repair of a proximal aortopulmonary window. **A**, A vertical aortotomy in the proximal ascending aorta provides excellent exposure. **B**, Patch closure of the defect. Care must be taken to identify and protect the origin of the left coronary artery.

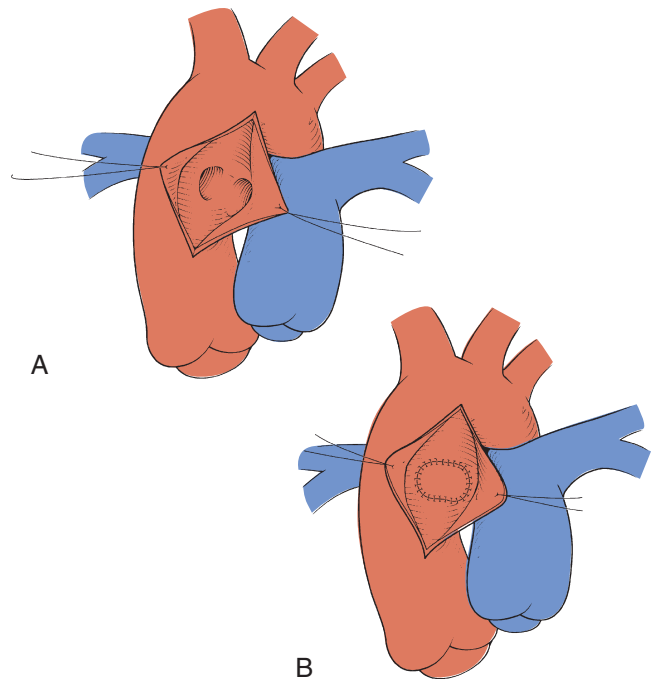


FIGURE 121-14 ■ Repair of a distal aortopulmonary window. **A**, A more distal aortotomy exposes the defect that is related to the origin of the right pulmonary artery. **B**, Use of a generous patch avoids stenosis of the origin of the right pulmonary artery.

This approach has the advantage of being slightly quicker to perform, as there is no need to close a separate aortotomy.

Several authors have used a pulmonary flap technique to avoid the use of prosthetic patch material to

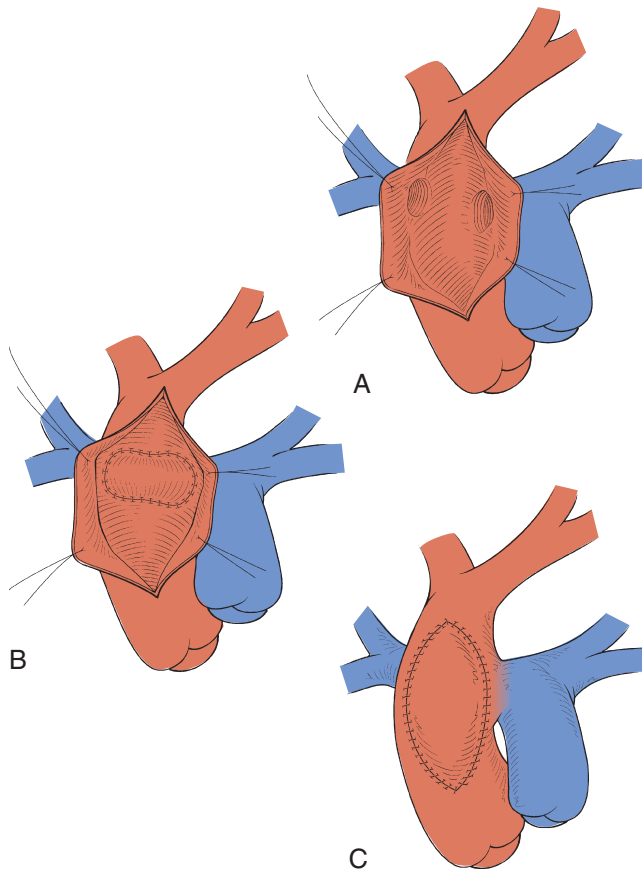


FIGURE 121-15 ■ Repair of a distal aortopulmonary window with extensive unroofing of the right pulmonary artery. **A**, Extensive unroofing leads to the appearance of anomalous origin of the right pulmonary artery from the ascending aorta. **B**, An extensive intra-aortic baffle created to join the window to the origin of the right pulmonary artery. **C**, Obstruction of the lumen of the ascending aorta can be obviated by closing the aortotomy with an elliptical patch.

reconstruct the ascending aorta.¹⁰⁵⁻¹⁰⁸ In this approach, an anterior flap of pulmonary artery is incised in continuity with the aorta along the anterior border of the window. The anterior flap is then sewn to the posterior margin of the aortopulmonary window, thereby closing the defect in the aorta. The resultant defect in the pulmonary artery is then closed with a patch (autologous or heterologous).

Kitagawa and associates¹⁰⁹ reported an alternative technique to repair a distal aortopulmonary window with extensive unroofing of the right pulmonary artery. In this approach, the ascending aorta is transected at the distal extent of the window, and the right pulmonary artery is excised along with a strip of posterior aorta in continuity with the window and pulmonary trunk. The defect in the pulmonary artery is then repaired either primarily or using a patch, and the aorta is reconnected primarily. This technique has the advantage of avoiding any potential problems resulting from an intra-aortic baffle.

Other Surgical Considerations

Associated defects are generally repaired concurrently. Special consideration should be given to the repair of

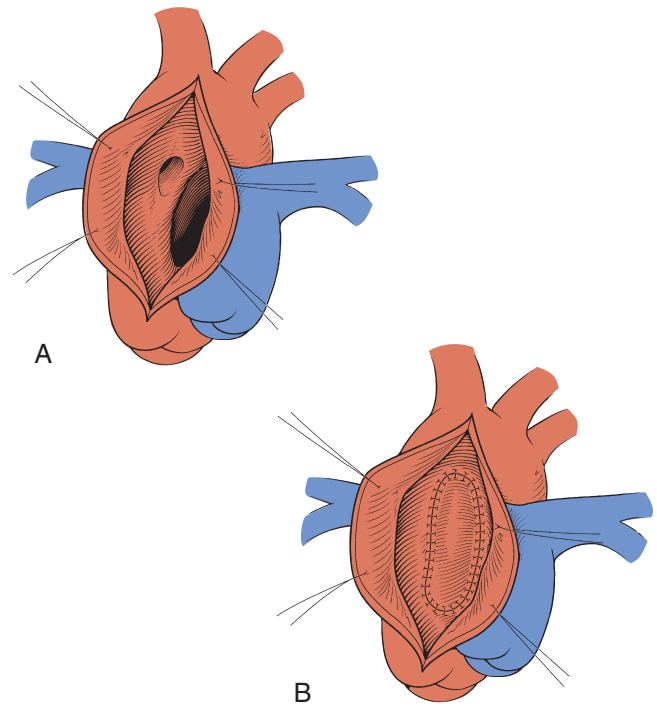


FIGURE 121-16 ■ Repair of a total-type (or intermediate-type) aortopulmonary window. **A**, Exposure is achieved with an extensive aortotomy. **B**, A large patch is used to close the defect.

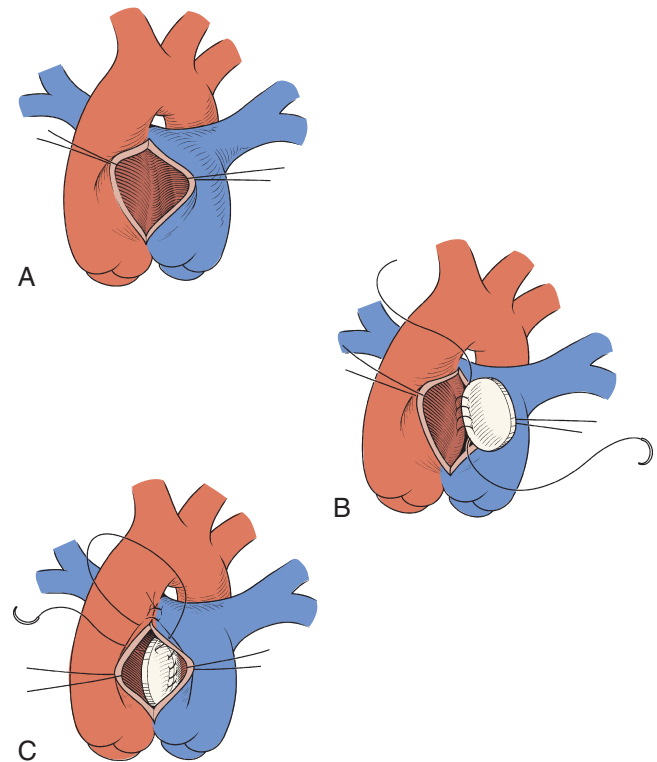


FIGURE 121-17 ■ Transwindow (sandwich) repair of aortopulmonary window. **A**, An incision is made in the anterior wall of the window. **B**, A patch is then sewn to the posterior border of the defect. **C**, Finally, the anterior portion of the defect is closed by incorporating the patch in the closure of the aortotomy.

defects associated with arch interruption, as this is associated with increased mortality and the need for late reoperation.^{110,111} Because of the presence of the window, single arterial cannulation of the ascending aorta is sufficient. Cardiopulmonary bypass with deep hypothermia is used (with occlusion of the branch pulmonary arteries). The repair is typically performed under circulatory arrest or with adjunctive regional cerebral perfusion. The ductus is ligated proximally, and ductal tissue is resected distally. Two operative strategies can then be considered. Using a conventional approach, the arch interruption can be repaired first (using standard techniques), followed by repair of the window (transaortic patch or sandwich-type repair). Alternatively, the ascending aorta can be separated from the pulmonary artery at the level of the window, leaving defects in both vessels. The aortic arch is then reconstructed with patching of the defect in the ascending aorta, if necessary. Finally, the defect in the pulmonary artery is repaired with a patch.

Interventional Techniques

On rare occasions, a native aortopulmonary window or residual aortopulmonary defect after surgical closure may be small enough to allow an interventional approach. Several groups have reported success using percutaneously placed devices to close such defects.¹¹²⁻¹¹⁶ With improved devices and experience, even large, nonrestrictive aortopulmonary windows in infants have been closed with a transcatheter approach when the anatomy is appropriate.^{117,118} Following device closure, patients need to be followed for the development of aortic regurgitation at the time of the procedure as well as long-term.¹¹⁹ For now, however, surgical closure remains the standard of care.

Postoperative Management

Currently, because the diagnosis and treatment of aortopulmonary window are accomplished in early infancy, pulmonary hypertensive crises are rare. However, in patients presenting later in life, management of pulmonary hypertension is the most critical aspect of postoperative care of patients undergoing repair of aortopulmonary window. A pulmonary arterial catheter can be placed with a pursestring in the right ventricular infundibulum in selected patients. Conventional methods for the control and prevention of pulmonary hypertension include the use of inhaled nitric oxide, administration of other pulmonary vasodilators, liberal use of fentanyl and muscle relaxants, and mild hyperventilation.

Results

Early mortality following the repair of simple aortopulmonary window should approach 0% in the contemporary era with excellent long-term outcomes. Even with associated arch obstruction, overall mortality has improved significantly over time. Tkebuchava and colleagues reported a 92% operative survival and an actuarial survival of 90% at the 10-year follow-up.⁹² In one of the largest series, Hew and colleagues⁷⁸ observed an

early survival of 92% and an actuarial survival of 88% at 10 years. Reviewing a series of 19 patients who underwent repair from 1953 to 1990, van Son and colleagues reported an overall early mortality of 21%.¹⁰⁴ The authors noted that all deaths occurred in patients who underwent repair before 1962. They also observed that the long-term outcome after repair depended on the PVR at the time of closure of the defect. Backer and Mavroudis reported a similar improvement in results.⁷⁷ They reported an operative mortality of 33% when the repair was performed using the technique of closed division of the window. Since changing the operative technique to the transaortic approach, they have seen no mortality. Patients need to be followed for the late development of pulmonary artery stenosis.

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INTERRUPTED AORTIC ARCH

Marshall L. Jacobs • Jeffrey P. Jacobs • Alvin J. Chin

CHAPTER OUTLINE

HISTORICAL NOTES

ANATOMY AND NOMENCLATURE

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SUMMARY

Interrupted aortic arch (IAA) is a rare genetic disorder of the cardiovascular system, present in approximately two cases per 100,000 live births and comprising 1.5% of all cases of congenital heart disease. Its hallmark feature is a lack of luminal continuity between the ascending aorta and the descending aorta. In the absence of surgical repair, mortality approaches 75% in the first month of life and 90% by 1 year. Despite tremendous recent progress in the management of complex congenital heart malformations in neonates and infants, the mortality and morbidity associated with surgical management of IAA and the spectrum of associated anomalies remain substantial. Areas of controversy include the choice of single-stage versus multistage repair, the assessment and management of associated obstruction or hypoplasia of the left ventricular outflow tract, and the intraoperative management of cardiopulmonary bypass with or without periods of hypothermic circulatory arrest. Important late-phase events after repair of IAA are related to the potential for development or recurrence of systemic ventricular outflow tract obstruction or aortic arch obstruction, and presurgical and postsurgical abnormalities of neurodevelopmental outcome and their impact on functional status.

HISTORICAL NOTES

The first description of an IAA is attributed to Steidele in 1778.¹ That case involved absence of the aortic isthmus. Absence of the aortic arch segment between the left common carotid artery and the left subclavian artery was described by Seidel in 1818.² Absence of the aortic segment between the innominate artery and the left

common carotid artery was described by Weisman and Kesten in 1948.³ In 1955, Samson and colleagues⁴ performed the first successful surgical repair of IAA in a 3-year-old child. The anatomy included absence of the aortic isthmus, the presence of a patent ductus arteriosus, and two ventricular septal defects (VSDs). In the initial operation, the ductus was divided, and then it was joined to the underside of the proximal left subclavian artery, creating luminal continuity between the ascending aorta and the descending aorta. The VSDs were closed 4 years later. Case reports in the 1960s described interposition of prosthetic grafts to bridge the gap between aortic segments. The first use of turned-down aortic arch branches (left subclavian or left common carotid artery) to achieve end-to-end anastomosis to the descending thoracic aorta was described by Sirak and coworkers in 1968.⁵ One of Sirak's three patients was the first neonate to survive operation. In 1970, Litwin and associates⁶ palliated a neonate with arch interruption and VSD by interposition of a prosthetic tube graft between the proximal main pulmonary artery and the descending thoracic aorta, with banding of the distal main pulmonary artery.

In 1970, Barratt-Boyes and colleagues⁷ described successful repair of IAA and simultaneous correction of intracardiac lesions (VSD and total anomalous pulmonary venous connection). Through a left thoracotomy incision, a 12-mm prosthetic tube graft was connected to the descending thoracic aorta. Next, through a median sternotomy, the proximal end of the conduit was connected to the ascending aorta. Hypothermic circulatory arrest facilitated this anastomosis and the repair of the intracardiac lesions. In 1975, Trusler and Izukawa⁸ were the first to accomplish direct anastomosis of the descending aorta to the ascending aorta and transverse arch (with

excision of all ductal tissue and with no interposition graft), together with VSD closure. The operation was accomplished through a median sternotomy approach, using cardiopulmonary bypass and deep hypothermic circulatory arrest. Primary repair via median sternotomy using continuous cardiopulmonary bypass (without a period of circulatory arrest) was reported by Asou and colleagues in 1996.⁹

In the mid-1960s, Angelo DiGeorge, a pediatric endocrinologist, described the association of hypoparathyroidism (with hypocalcemia), thymic aplasia, cleft lip and palate, and altered immunity (eventually recognized to be the consequence of a T cell abnormality). Several of the patients with this constellation had cardiac anomalies—the most prevalent among DiGeorge's patients was IAA. DiGeorge syndrome and the closely related velocardiofacial syndrome were subsequently found, in the majority of instances, to be related to a chromosomal deletion in the region of 22q11.2.¹⁰⁻¹³ In a prospective evaluation of 251 patients with conotruncal defects who were screened for the presence of a 22q11 deletion, 50% (12 of 24) of patients with IAA were found to have a 22q11 deletion at locus D22S75 (N25).¹⁰

ANATOMY AND NOMENCLATURE

The definition of *interrupted aortic arch* adopted in 2000 by the International Congenital Heart Surgery Nomenclature and Database Project is “loss of luminal continuity between the ascending and descending aorta.”¹⁴ *Absence* of luminal continuity would also be an acceptable description. As a congenital defect, IAA represents a developmental abnormality of the embryologic arch elements. In the instance of left-sided aortic arch, the proximal arch (between the normally positioned innominate artery and the left common carotid artery) is derived from the aortic sac. The distal arch (between the left common carotid artery and the left subclavian artery) is derived from the left fourth embryonic arch, and the isthmus (between the left subclavian artery and the descending thoracic aorta) from the junction of the left sixth embryonic arch (ductus arteriosus) with the left dorsal aorta and the left fourth embryonic arch. It is therefore not surprising that many anatomic variants of IAA are observed, with respect to the site of discontinuity and the sites of origin of the brachiocephalic vessels.

Aberrant origin of the right subclavian artery from the descending thoracic aorta is encountered frequently in some forms of IAA, and rarely in others.¹⁵ It is generally associated with hypoplasia or obstruction of the left ventricular outflow tract (LVOT), as there is less antegrade flow from the left ventricle. Rarely, the site of origin of the right subclavian artery is a persistent right-sided ductus. Interrupted arch can occur with a right aortic arch, with persistence of a right-sided ductus (or bilateral ducts).

In nearly 100% of cases, loss or absence of luminal continuity reflects complete absence of one element of the aortic arch. In rare instances, a fibrous strand connects the ascending aorta and associated arch elements

with the descending aorta. By convention, these rare cases can be referred to as *interrupted aortic arch*, although some would make a distinction and refer to such cases as *atresia* of a particular portion of the arch. Celoria and Patton originally described the most widely accepted classification for IAA in 1959.¹⁶ They divided interrupted arch anomalies into three varieties, based on the site of aortic arch interruption (Fig. 122-1). In the common circumstance of left-sided aortic arch, type A refers to interruption that is distal to the left subclavian artery. In type B, the interruption is between the left common carotid and the left subclavian artery. Finally, in type C, the interruption is between the innominate and left carotid arteries. In a multi-institutional outcome study of 472 patients with IAA by the Congenital Heart Surgeons' Society (CHSS), McCrindle and associates¹⁷ reported that type A was observed in 28% of patients, type B was by far the most common in 70%, and type C was the rarest, seen in only 1%. An aberrant right subclavian artery, originating from the descending aorta and taking a retroesophageal course, is frequently seen in patients with IAA, particularly type B.¹⁵ In other uncommon variations, the aberrant right subclavian artery can originate instead from the right pulmonary artery via a persistent right-sided patent ductus arteriosus (isolated subclavian artery), or the right pulmonary artery can be the vessel that is isolated. These variations have been reported and analyzed, and attempts have been made to expand on the classification system of Celoria to include a description of the origin of the right subclavian artery. The classification system reported by Dische and coworkers in 1975¹⁸ added the subscript 2 to the letter A, B, or C from the Celoria classification when the aberrant right subclavian artery originated from the descending aorta distal to the interruption. Thus, in the system described by Dische, in type A₂ the interruption is distal to the left subclavian artery, and the only major arch vessel taking origin from the aorta distal to the interruption is the aberrant right subclavian artery. Similarly, in type B₂, both carotid arteries arise from the aortic arch proximal to the interruption and both subclavian arteries arise from the aorta distal to the interruption. In 1982, the nomenclature system of Oppenheimer-Dekker and colleagues¹⁹ offered an alternative subclassification also based on the system of Celoria and Patton. This system also includes subdivisions based on the presence of an aberrant right subclavian artery, but here nine types of IAA are classified. Types A, B, and C are determined based on the system of Celoria. No subscript number is used if the right subclavian artery has a normal origin, a subscript 1 is used when the aberrant right subclavian artery originates from the descending aorta, and a subscript 2 is used when the aberrant right subclavian artery arises from the right pulmonary artery via ductal tissue. Most common usage involves the A-B-C system of Celoria together with a specific verbal description of abnormalities of the origin of brachiocephalic vessels, branch pulmonary arteries, or patent ductus arteriosus.

The following is the classification of IAA used in the Diagnostic Long List of the version of the International Paediatric and Congenital Cardiac Code derived from the nomenclature of the International Congenital Heart

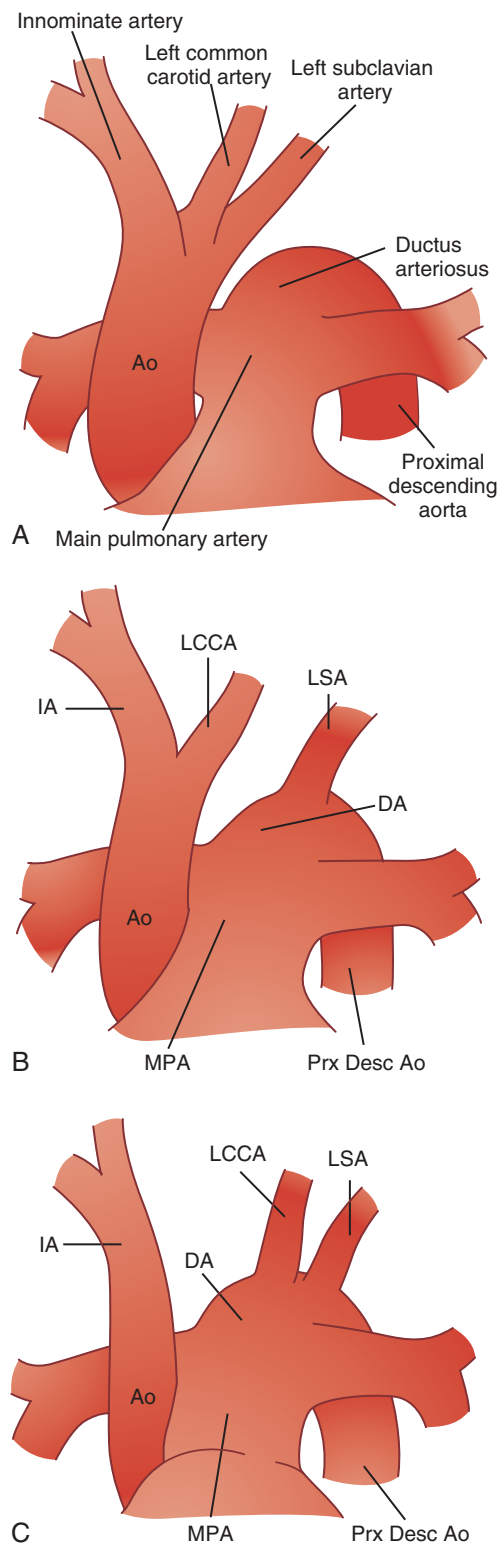


FIGURE 122-1 ■ Anatomic types of interrupted aortic arch. **A**, Type A, interruption distal to the left subclavian artery. **B**, Type B, interruption between the left subclavian and left carotid arteries. **C**, Type C, interruption between the left carotid and innominate arteries. Ao, Aorta; DA, ductus arteriosus; IA, innominate artery; LCCA, left common carotid artery; LSA, left subclavian artery; MPA, main pulmonary artery; Prx Desc Ao, proximal descending aorta. (From Jonas RA: Interrupted aortic arch. In Mavroudis C, Backer CL, editors: *Pediatric cardiac surgery*, ed 3, Philadelphia, 2003, Mosby.)

Surgery Nomenclature and Database Project of the European Association for Cardio-Thoracic Surgery and the Society of Thoracic Surgeons²⁰:

1. IAA
2. IAA, type A (interruption distal to the subclavian artery)
3. IAA, type A2 (interruption distal to one subclavian artery, with the only major arch vessel taking origin from the aorta distal to the interruption being an aberrant subclavian artery)
4. IAA, type B (interruption between the carotid and subclavian arteries)
5. IAA, type B2 (interruption between the carotid and subclavian arteries, with both subclavian arteries arising from the aorta distal to the interruption)
6. IAA, type C (interruption between the carotid arteries)
7. IAA, type C2 (interruption between the carotid arteries, with both subclavian arteries arising from the aorta distal to the interruption)

Interrupted aortic arch complexes nearly always have a large VSD (the exception being cases of IAA with aortopulmonary window, of which a majority have an intact ventricular septum). In the setting of IAA with VSD, the VSD can be of any type. Most commonly, it is of the malalignment type. In this circumstance, the conal (outlet) septum is malaligned posteriorly and leftward with respect to the true trabecular septum.^{21,22} The malalignment of the conal septum is associated with varying degrees of subaortic obstruction.²³⁻²⁵ When a malalignment-type VSD is present, the conal septum may be not only misplaced but also hypoplastic. In an echocardiographic study of 53 patients with IAA with VSD, Chin and Jacobs²⁶ found that 43 of 45 patients with type B IAA had VSDs involving maldevelopment of the outflow region. In type A IAA, only four of eight had this type of VSD.²⁶ In the complex of the left side of the heart and the aorta (the left heart–aorta complex), other levels of obstruction that are often associated with IAA include a prominent and obstructive anterolateral muscle of the left ventricle (muscle of Moutaert), aortic valvar stenosis with or without aortic annular hypoplasia, and fibrous or fibromuscular subaortic stenosis.²⁷ IAA can coexist with a wide variety of cardiac lesions, as evidenced by the first report from the CHSS in 1994. Jonas and associates¹⁵ reported that among 250 cases of IAA at participating centers, associated cardiac anomalies included VSD (183 [73%]), truncus arteriosus (25 [10%]), aortopulmonary window (10 [4%]), univentricular atrioventricular connection (9 [4%]), transposition of the great arteries with VSD (8 [3%]), double-outlet right ventricle (5 [2%]), Taussig-Bing anomaly (4 [2%]), complete atrioventricular canal defect (1 [0.4%]), and congenitally corrected transposition of the great arteries (1 [0.4%]). Isolated IAA (without VSD or associated anomalies) was present in only 4 of 250 patients [2%]. More unusual associations have been the subject of individual case reports, including several cases of aortic atresia with IAA and VSD, in which flow to the ascending aorta and thus the coronary arteries depended on flow either through the circle of Willis or through a patent right-sided ductus arteriosus.

PRESENTATION AND PREOPERATIVE MANAGEMENT

During fetal development, the left ventricular output supplies the arterial circulation proximal to the interruption, and right ventricular output supplies arterial circulation distal to the interruption via the left ductus arteriosus. Postnatally, this arrangement continues, with the addition of the pulmonary blood flow to the volume load of the left ventricle. The postnatal pathophysiology of virtually all IAA complexes is predicated on ductal dependency of a portion of the systemic circulation (distal to the interruption), and on a usually large but variable ratio of pulmonary to systemic blood flow (Q_p/Q_s). This ratio is influenced by the anatomic substrate for left-to-right shunting. That may be a VSD alone or a variety of other lesions such as common arterial trunk or aortopulmonary window. In addition, the physiology is influenced by the presence of other obstructive lesions in the left heart–aorta complex. Obstructive or hypoplastic elements of the left heart–aorta complex, alone or in combination with left ventricular dysfunction, may contribute to left-to-right shunting at the atrial level, through either an atrial septal defect or a stretched patent foramen ovale.

Despite the markedly abnormal circulatory arrangement, manifestations of the abnormal physiology may be subtle in the early neonatal period. If ductal patency persists, typical signs of congestive heart failure may emerge in the first few weeks of life, as the pulmonary vascular resistance begins to fall and pulmonary blood flow increases. More typically, and importantly, constriction of the ductus arteriosus can begin and progress any time in the first days or weeks of life. This may be manifest as a mottled or gray appearance of the lower body, and it is accompanied by signs of congestive heart failure (tachypnea, tachycardia, hepatomegaly, and poor feeding) and then of circulatory insufficiency (irritability progressing to lethargy, oliguria, and then metabolic acidosis and profound shock with multiple organ dysfunction and coagulopathy). Early visual evidence of the difference in oxygen saturation between the upper and lower body may be present. Neither this nor differential blood pressure between upper and lower extremities is a constant or particularly useful finding, as either may be influenced by the dynamic variability of the Q_p/Q_s , by diminished cardiac performance, and by abnormal anatomy, including aberrant origin of the right subclavian artery (which, in the setting of IAA type B or type C, results in all four extremities having postductal blood pressures). In the absence of a prenatal diagnosis, approximately half of patients present during the first day of life, and nearly all do within the first 2 weeks of life. In rare instances, persistent patency of the ductus arteriosus is associated with a later presentation.

Echocardiography with color flow mapping is the primary diagnostic study in virtually all cases. When the diagnosis is suspected or established, evaluation as an inpatient in an intensive care setting is advised. Intravenous prostaglandin E_1 should be administered promptly to maintain patency of the ductus arteriosus.²⁸

The need for an arterial line and assisted ventilation can be judged best from the initial arterial blood gas measurement. Unless a period of shock has accompanied ductal constriction, pharmacologic support with catecholamine infusions is rarely indicated. In recent years, the use of milrinone, a phosphodiesterase-3 inhibitor, as a continuous infusion has achieved wide acceptance. It probably contributes to the improvement of myocardial performance that generally occurs with correction of acidosis, and it has the added effect of reducing systemic vascular resistance. Assessment of the presence and degree of secondary organ dysfunction includes laboratory evaluation of metabolic status, serum indicators of renal and hepatic function, and a coagulation profile. Hypocalcemia, a frequent finding, may indicate the presence of DiGeorge syndrome, including the hypoparathyroidism phenotype. Fluorescent *in situ* hybridization can reveal the typical hemizygous 22q11.2 deletion seen in 85% to 95% of patients with DiGeorge syndrome.¹⁰

In most cases, the key features of the anatomy are revealed by a detailed echocardiographic evaluation. A complete study should clarify the site of aortic interruption and the sites of origin of the arch branches. Additional essential information includes the presence and nature of atrial and VSDs, and a detailed assessment of the LVOT. This includes measurement of the dimensions of the subaortic region (including a description of the outlet or conal septum, which may be either thickened or hypoplastic, and which may be posteriorly malaligned, thus narrowing the caliber of the subaortic LVOT), as well as the aortic valve annulus and orifice, and the sinotubular junction and ascending aorta.²⁹ The mitral valve is assessed, including the size of its orifice, its competence, and the nature of the subvalvar apparatus. The size of the left ventricle is measured, and a determination is made regarding whether it extends to the apex of the ventricular mass. Important associated diagnoses to consider include truncus arteriosus communis,³⁰ aortopulmonary window,^{31,32} transposition of the great arteries, and various forms of univentricular atrioventricular connection. A general visual or quantitative assessment of myocardial contractility is made. Although color flow mapping with Doppler studies can be helpful in evaluating some intracardiac obstructive lesions, the definitive echocardiographic assessment is most often made in the setting of a widely patent ductus (and, in most cases, a nonrestrictive interventricular communication). As a result, quantitation of the degree of LVOT obstruction by estimation of a gradient in that region can be misleading.

In some cases, cardiac catheterization with angiography provides important additional information. In particular, it may be helpful in clarifying instances of discontinuous branch pulmonary arteries, anomalous pulmonary venous connections, or transposition of the great arteries (in which case, balloon atrial septotomy may be beneficial). In cases with coexistent aortic atresia, it may help to define the source of coronary blood flow. Another indication for cardiac catheterization is the need to restore and/or maintain patency of the arterial duct. Until recently, maintenance of ductal patency by means

of deployment of an intravascular stent was reserved for unusual circumstances. An example would be the case of late presentation of an infant with IAA type A with VSD, who had a restrictive duct and respiratory syncytial virus pneumonia. Ductal dilation and stenting provided temporary palliation, making it possible to defer arch repair and VSD closure for several weeks to allow resolution of airway inflammation and improvement of pulmonary function. The recent emergence and increasingly widespread adoption of so-called hybrid strategies for initial management of numerous forms of critical heart disease in neonates that share the common feature of ductal dependency of the systemic circulation has added to the surgical armamentarium and increased the therapeutic options for patients with IAA. When such a strategy is applied to neonates with IAA, maintenance of ductal patency (either by stent deployment or by continuous administration of prostaglandin E1) is generally accompanied by bilateral application of pulmonary artery bands to the proximal branch pulmonary arteries to limit pulmonary blood flow.

Increasingly, both computed tomography (CT) and magnetic resonance imaging (MRI) are being used to further clarify the anatomy of complex cardiac anomalies in neonates and infants.³³ Each technology lends itself to three-dimensional reconstruction, which can be helpful in clarifying anatomic details, with particular attention to spatial relationships. CT has the advantage of rapid data acquisition, and in some instances it can be accomplished without general anesthesia. It has the disadvantage of radiation exposure. MRI does not involve radiation exposure, but it generally requires the patient to be anesthetized for the study.

SURGICAL MANAGEMENT

Indications and Timing of Surgery

Interrupted aortic arch is incompatible with life without patency of the ductus arteriosus or an alternative pathway for perfusion of the lower body. Before the availability of prostaglandins, the diagnosis of IAA was a surgical emergency. Most often, neonates were in poor condition, with a closing ductus, and resuscitative measures had little efficacy. Patients had to be taken to surgery in poor condition. Emergent palliative operations were performed under less than ideal conditions, and they often yielded less than optimal outcomes. In the current era, restoration of ductal patency after infusion of prostaglandin E₁ is generally accomplished, facilitating resuscitation in an intensive care unit.²⁸ Recovery of renal and hepatic function usually follows correction of acidosis and optimization of respiratory parameters and fluid and metabolic status. This then facilitates stabilization and assessment of neurologic status, and recovery or correction of coagulation disorders. Genetic evaluation can be initiated, and meaningful family education and counseling can occur before surgery is undertaken. An operation is usually indicated as soon as these preliminary objectives have been achieved, as there is no definitive medical therapy for IAA.

Operative Management

As noted, the history of surgery for IAA began during an era when the use of cardiopulmonary bypass to accomplish repair of intracardiac defects in infants and neonates was a theoretical goal for the future rather than a therapeutic reality. As a result, most early arch repairs were closed-heart (i.e., nonbypass) procedures.^{6,34} Arch repair was accomplished using an interposition graft or a brachiocephalic vessel turn-down, either in isolation or in combination with banding of the pulmonary artery. In most instances, repair of the VSD (with removal of the pulmonary artery band) would be undertaken some months later. Even after the introduction and successful achievement of one-stage repair of IAA and VSD closure, both via median sternotomy with cardiopulmonary bypass and hypothermic circulatory arrest, there persisted at many centers a bias favoring a staged approach to IAA with VSD or other more complex cardiac anatomy.³⁵ In 1997, Mainwaring and Lamberti reported on their 10-year experience with a two-stage approach to repair IAA type B with VSD.³⁶ Twenty-six of 27 patients survived stage 1 (arch repair with interposition graft). Twenty-two of 25 patients who underwent subsequent VSD closure were long-term survivors. Freedom from reoperation for arch graft enlargement was 86% at 3 years and 55% at 5 years.

In 1994, the CHSS published a report of their first multi-institutional outcome study of patients with IAA and VSD.¹⁵ Patients were enrolled as neonates between 1987 and 1992, and 173 patients underwent reparative surgery. The initial procedure consisted of arch repair and VSD closure (one stage) in 116 (67%), arch repair and banding of the pulmonary trunk in 40, and only repair of the arch interruption in 17. Thus, one-stage repair was chosen in 67% of cases, with intent to undertake two-stage repair in 33%. In the past two decades, single-stage repair of IAA and intracardiac defects has gained wide acceptance. At most centers, it is the usual or routine technique used, with a two-stage approach being reserved for specific uncommon circumstances.³⁷⁻⁴¹

Techniques of Arch Repair

An optimal method of arch repair would be one that could be performed safely and reproducibly in neonates, with minimal likelihood of stenosis in the short or long term. Thus, it would result in normal growth of all aortic segments including the anastomotic area. Ideally, it would not require use or division of any of the principal brachiocephalic vessels. In the traditional multistage approach, a synthetic tube graft was interposed between the proximal (ascending) and distal (descending) aortic elements. Although this can generally be accomplished without cardiopulmonary bypass support through either a lateral or an anterior approach, the certainty that the graft will not grow with the patient ensures an absolute requirement for arch reintervention in all survivors.⁴²⁻⁴⁴ That reintervention can consist of graft replacement in situ, augmentation in situ, or extra-anatomic placement of an additional graft. An alternative technique that has been used in both one-stage and two-stage strategies is

the use of a turned-down brachiocephalic artery (carotid or subclavian artery) that is anastomosed to the descending aorta. Monroe and colleagues⁴⁵ published a small series demonstrating satisfactory growth of the arch elements and anastomotic region in the majority of patients at follow-up of 8 to 19 years. More recently, John Brown and associates⁴⁶ reviewed their experience with 47 patients who underwent repair of IAA by means of left carotid artery turn-down. Approximately one third of patients underwent subsequent reinterventions on the arch. The authors claimed as advantages the reduced exposure to circulatory arrest and cardiopulmonary bypass in the newborn period and low incidence of bronchial compression by the reconstructed arch.

In the current era, the approach most often used is a one-stage approach entailing direct anastomosis between the ascending aorta and the descending aorta. This approach involves extensive mobilization of both proximal and distal elements. Several centers have reported excellent early outcomes with the technique of end-to-side anastomosis of the descending thoracic aorta either to the ascending aorta or to the ascending aorta and the underside of the proximal aortic arch.^{41,47-49} Patch augmentation of the anastomosis of the proximal and distal aortic segments was described by Norwood in 1990, and intermediate-term results were reported by Jacobs and Norwood in 1995.⁵⁰ This technique is intended to reduce tension on the anastomosis, to enlarge the connection between segments, and to address hypoplasia of the ascending aorta, which is particularly common in IAA types B and C.^{22,25} In addition, the use of patch augmentation generally obviates the need to divide either the left subclavian artery or an anomalous right subclavian artery to bring the elements of the arch together. It also lessens the likelihood of left bronchial compression, which can complicate some repairs of IAA.⁵¹ We have used cryopreserved pulmonary artery homograft tissue for the patch material. Successful use of other patch materials has been reported, including pulmonary artery autograft tissue.⁵²

The 1994 CHSS report of outcomes in patients with IAA and VSD included an important observation concerning the potential benefit of patch augmentation of the amalgamation of the ascending and descending aorta in patients with additional levels of obstruction or hypoplasia in the left heart-aorta complex.¹⁵ Multivariable analysis identified subaortic or annular narrowing as incremental risk factors for death after repair (Fig. 122-2). The report by Jonas and associates¹⁵ concluded, "In the 20% of patients in whom obstruction existed elsewhere in the left heart-aorta complex, the percent survival was highest among those undergoing ascending aorta/arch augmentation." More recently, in a CHSS analysis of intermediate- and long-term outcomes of an expanded cohort of 472 neonates with IAA, McCrindle and associates¹⁷ reported that reintervention was more likely for those who had IAA repair by a method other than direct anastomosis with patch augmentation. In a single institution study from Marie Lannelongue Hospital in 2002, Roussin and associates⁵³ described excellent results with the incorporation of a pulmonary artery autograft patch into the aortic arch reconstruction. Among 20 patients who underwent repair of IAA with

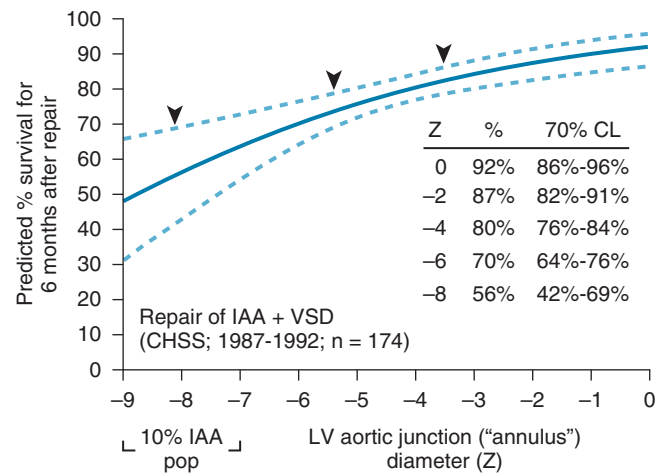


FIGURE 122-2 ■ Data from the Congenital Heart Surgeons' Society (CHSS) study of outcomes in neonates with interrupted aortic arch (IAA) and ventricular septal defect (VSD). Nomogram of a specific solution of a multivariable equation demonstrating the risk-adjusted effect of the measured diameter of the left ventricular (LV)-aortic junction. The value of 3.1 kg was entered for the birth weight, 7 days for age at repair, type B for IAA, and conoventricular for the VSD. Arrowheads indicate points of evident difference, from right to left. CL, Confidence limits. (From Jonas RA, Quaegebeur JM, Kirklin JW, et al: Outcomes in patients with interrupted aortic arch and ventricular septal defect. A multiinstitutional study. Congenital Heart Surgeons Society. *J Thorac Cardiovasc Surg* 107:1099-1109, 1994.)

pulmonary autograft patch aortoplasty, actuarial freedom from interventions for recurrent arch obstruction was 100% at median follow-up of 29 months.

Left Ventricular Outflow Tract Obstruction

Estimates of the incidence of occurrence of important LVOT obstruction in the setting of IAA vary considerably^{24,34,54-59} because of the inability to measure an outflow tract gradient accurately in the setting of a large VSD and a patent ductus, and also because there currently is no consensus on the morphologic criteria or threshold measurements that should be used to assign such a diagnosis. Narrowing of the subaortic region can be mild to severe as a consequence of deviation of the conal septum into the LVOT in the setting of IAA with malalignment-type VSD. In addition, as mentioned, posterior deviation of the conal septum can contribute to LVOT obstruction even when the conal septum is hypoplastic and entirely fibrous. In these cases, there is generally hypoplasia of the aortic annulus. As there is no option of resecting muscle to enlarge the subaortic region, the need to anchor the top of the VSD patch to this fibrous rim not only results in a narrow subaortic region; it can also result in fixation of a portion of the aortic annulus, preventing subsequent normal growth. In the 1994 report of the first multi-institutional study of IAA by the CHSS, subaortic or annular narrowing was predictive of mortality after repair.¹⁵ The techniques used by participating surgeons to address subaortic narrowing included partial resection of obstructing muscle in the LVOT (myotomy or myectomy) and techniques to bypass the narrowed systemic

ventricular outflow tract. In the analysis, these were combined together as Damus-Kaye-Stansel procedures. The analysis led to an interesting but unsatisfying conclusion. Investigators reported, "Procedural risk factors for death after repair were (1) repair without concomitant procedures in patients with other important levels of obstruction in the left heart-aorta complex, (2) a Damus-Kaye-Stansel anastomosis, and (3) subaortic myotomy or myectomy in the face of subaortic narrowing. One-stage repair plus ascending aorta/arch augmentation had the highest predicted time-related survival in the 20% of patients with IAA and one or more coexisting levels of obstruction in the left heart-aorta complex, as did initial repair without or with aorta/arch augmentation in the 80% without these." The troubling inference, of course, was that the presence of obstructing lesions in the left heart-aorta complex was associated with an increased likelihood of death after repair, but that specific procedures directed at these obstructions (other than patch augmentation of the arch repair) did not (in this study) reduce the risk of mortality.

It is important to recognize that not all procedures to bypass subaortic obstruction are the same. The first report of such a procedure was by Yasui and colleagues in 1987.⁶⁰ The operation consisted of ligation of the patent ductus arteriosus, restoration of aortic continuity with an 8-mm polytetrafluoroethylene graft, placement of an internal patch to tunnel all left ventricular blood from the left ventricle through the VSD into the pulmonary artery, transection of the main pulmonary artery, anastomosis between the proximal pulmonary artery and the ascending aorta, and interposition of a valved conduit between the right ventricle and the distal pulmonary artery. Others adapted the type of aortopulmonary amalgamation with arch augmentation developed by Norwood to cases of IAA with severe LVOT obstruction. Jacobs and Norwood⁵⁰ reported a series of nine patients treated with arch repair, aortopulmonary amalgamation, and homograft patch augmentation of the entire aortic reconstruction (Fig. 122-3). Seven patients received aortopulmonary shunts, and two patients underwent one-stage biventricular repair with tunneling of left ventricular outflow through the VSD to the pulmonary valve, and establishment of continuity between the right ventricle and the confluence of branch pulmonary arteries using a valved homograft. There was one hospital mortality.

As part of the aforementioned study by Jacobs and associates,⁵⁰ Chin undertook a detailed retrospective analysis of all of the preoperative echocardiography studies. One important observation was that when the dimensions of the subaortic region were measured in images obtained from four standard echocardiographic windows, the values for a given patient varied considerably from one view to another. In most instances, the smallest dimensions were measured using the subcostal left anterior oblique window. Another observation was that nearly half of the patients in this series with narrowing of the subaortic region also had a bicuspid aortic valve. Investigators from other centers have also reported encouraging surgical results using a technical approach that combines features of the Norwood procedure with the Rastelli operation. In 2001, Erez and associates⁶¹

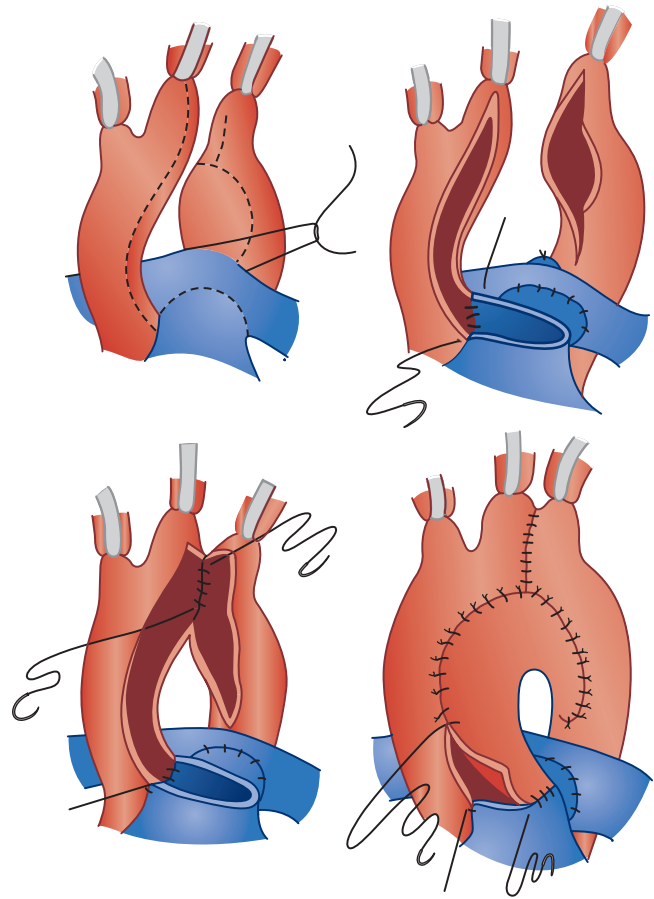


FIGURE 122-3 ■ A technique for repair of interrupted aortic arch with a severe degree of left ventricular outflow obstruction. The repair incorporates transection of the main pulmonary artery, proximal main pulmonary artery–ascending aortic amalgamation, anastomosis of proximal and distal aortic elements, and pulmonary homograft patch augmentation of the reconstructed arch. (From Jacobs ML, Chin AJ, Rychik J, et al: Interrupted aortic arch. Impact of subaortic stenosis on management and outcome. *Circulation* 92[9 suppl]:II128–II131, 1995.)

reported a series of 12 patients with IAA and LVOT obstruction treated initially with a Norwood procedure. The mean z-value for the subaortic diameter was -5 ± 1.7 . There were no hospital deaths. At the time of the report, six patients had gone on to successful biventricular repair. Therefore, Norwood's technique of aortopulmonary amalgamation, modified to include augmentation of the reconstructed aortic arch, can be applied to patients with IAA and LVOT obstruction to accomplish biventricular repair in one stage at the time of initial arch repair, or as part of a staged approach leading either to biventricular repair or to univentricular palliation.

Others have reported success with less radical procedures for management of IAA with LVOT obstruction. In 1993, Bove and associates⁵⁴ described an approach to LVOT enlargement in patients with IAA and LVOT obstruction. At operation, the posteriorly displaced infundibular septum was partially removed through a right atrial approach by resecting the superior margin of the VSD up to the aortic annulus. The resulting enlarged VSD was then closed with a patch to widen the subaortic

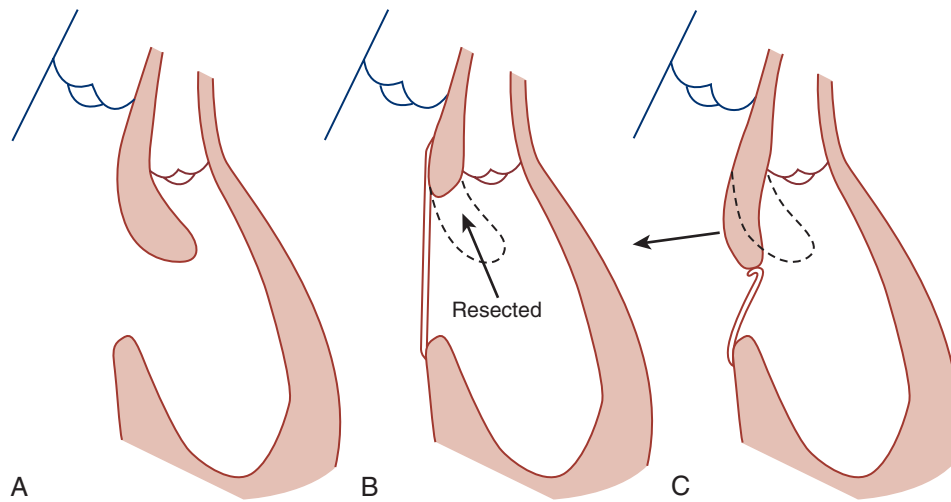


FIGURE 122-4 ■ Alternative techniques for closure of the ventricular septal defect (VSD) in the setting of interrupted aortic arch with malalignment type VSD. **A**, Preoperative anatomy, showing displacement of the malaligned conal septum into the left ventricular outflow tract. **B**, Patch closure of the VSD after partial resection of the conal septum. **C**, Patch closure of the VSD as advocated by Luciani and associates.⁶³ The upper end of the VSD patch is placed on the left side of the septum to deflect the conal septum anteriorly and away from the subaortic area. (From Tchervenkov CI, Jacobs JP, Sharma K, et al: Interrupted aortic arch: surgical decision making. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 92–102, 2005.)

area. In each patient, the aortic arch was repaired by direct anastomosis. All three patients survived operation. More recently, investigators from the same center analyzed a group of 27 patients with IAA and malalignment type VSD.⁶² Fifteen patients with the smallest subaortic areas underwent myectomy or myotomy of the infundibular septum concomitant with IAA and VSD repair. Two hospital deaths occurred in this group. No late deaths occurred. Six patients required nine reoperations for LVOT obstruction. Five patients underwent resection of a new subaortic membrane. Only one patient had recurrent muscular LVOT obstruction. Three patients required a second reoperation, primarily related to aortic valve stenosis. The authors concluded that this approach to subaortic narrowing was effective at preventing or prolonging the interval to reinterventions for recurrent LVOT obstruction.

In 1997, Luciani and associates⁶³ described a novel approach to one-stage repair of IAA, VSD, and subaortic obstruction. In nine neonates, the VSD was closed with either a transpulmonary (seven patients) or crossatrial (two patients) approach. Without resection of the conal septum, the upper end of the ventricular septal patch was placed on the left side of the septum to deflect the conal septum anteriorly and away from the subaortic area. The authors emphasized the importance of not oversizing the VSD patch, so as to keep it from bulging into the LVOT (Fig. 122-4). It is noteworthy that the degree of severity of subaortic stenosis according to preoperative echocardiography (mean ratio of subaortic to descending aortic diameter, 0.63 ± 0.08) was somewhat less in patients in this series than in those judged to have significant LVOT obstruction in some other series.

Schreiber and associates⁴⁰ recently reported a single institution's 20-year experience with 94 patients diagnosed with IAA. Thirteen patients were considered to have significant LVOT obstruction. Procedures directed at subaortic obstruction included myomectomy,

homograft aortic root replacement, and the Norwood procedure. A preoperative diagnosis of LVOT obstruction was found to be a significant predictor of early and late mortality. More recently, several groups have described success with Ross-Konno procedures for IAA with LVOT obstruction either as a primary repair or, more frequently, as a reintervention in the setting of recurrent LVOT obstruction.^{64–66}

Not all investigators agree that LVOT obstruction is a risk factor for mortality after repair or for the need for reoperation. In 1999, Fulton and associates reported outcomes of a series of 72 patients who underwent repair of IAA between 1985 and 1997.⁵⁵ Thirty-six patients (50%) had LVOT obstruction by one or more of the authors' multiple criteria: (1) dimensions of the LVOT smaller than the mean value minus 1 standard deviation (indexed to body surface area), (2) presence of a gradient of greater than 10 mm Hg across the LVOT, measured by Doppler echocardiography or at cardiac catheterization, (3) posterior deviation of the conal septum into the LVOT, and (4) presence of obstructing tissue in the subaortic area. Patients with LVOT obstruction had comparable survival rates to those without obstruction. At 10 years, the difference in freedom from reoperation did not significantly differ between groups. However, of 36 patients judged to have LVOT obstruction, only 15 (42%) were believed to have obstruction that was severe enough to require surgical treatment at the initial operation. This is an example of the difficulty encountered in interpreting various investigators' recommendations in regard to LVOT obstruction in the setting of IAA. There is no consensus definition, and the criteria vary from one study to another. Unlike Fulton and associates, authors of many outcome studies include in the LVOT obstruction group only those patients for whom the initial operative approach is altered to address the problem specifically.

Tchervenkov and associates⁶⁷ recently undertook a review of published experiences with management of

IAA with LVOT obstruction and offered the following guidelines:

- If the diameter of the LVOT is smaller in millimeters than the baby's weight in kilograms, then survival with a conservative approach is unlikely. For example, for a 3-kg baby, survival is unlikely if the LVOT is smaller than 3 mm and the LVOT is not addressed.
- If the LVOT diameter is greater than the baby's weight (in kilograms) plus 2 mm (e.g., if weight is 3 kg, then diameter greater than 5 mm), survival without significant LVOT obstruction is likely.
- Between these two numbers is a gray zone, where, although survival may be possible, it is likely that significant residual LVOT obstruction will exist.

These general guidelines were based on impressions drawn by Tchervenkov and his coauthors⁶⁷ from their review of other surgeons' series and from personal experience. It is important to recognize that they are not derived from a statistical analysis of any actual data set.

The foregoing discussion addresses the questions of the potential effects of LVOT obstruction on survival after repair, and the primary surgical approaches to the management of moderate to severe LVOT obstruction. Important information is also available regarding the effects of LVOT obstruction on the need for subsequent interventions and long-term survival after repair. Geva and associates⁶⁸ undertook a retrospective study of 37 patients who had undergone repair of IAA, and they investigated the relationship between preoperative morphology and postoperative development of LVOT obstruction. They found a correlation between a preoperative indexed LVOT cross-sectional area of less than 0.7 cm²/m² and subsequent development of LVOT obstruction. They used a threshold value of a gradient of 20 mm Hg to define the presence of LVOT obstruction. This value is lower than has been applied by some others. Apfel and associates⁶⁹ used a gradient of 40 mm Hg as their definition of postoperative LVOT obstruction. They reviewed the preoperative echocardiograms and the postoperative clinical course and echocardiograms of 23 consecutive patients who underwent primary repair of IAA without a surgical modification aimed at widening of the subaortic region. Nine patients (39%) went on to develop significant LVOT obstruction (seven of them by 1 month, eight by 2 months, and all nine by 1 year). On retrospective analysis of the preoperative echocardiograms, the indexed cross-sectional area of the LVOT, the subaortic diameter index, and the subaortic diameter z-score were all significantly smaller in those requiring re-intervention ($P < 0.04$, $P < 0.05$, $P < 0.05$, respectively). Indexed cross-sectional area had the least reproducibility, and subaortic diameter index had the most. The authors concluded that most patients who develop significant LVOT obstruction after repair of IAA do so early after operation. Although subaortic indexed cross-sectional area was the most sensitive predictor of LVOT obstruction after primary repair, other, simpler standardized measurements of the subaortic diameter were comparably predictive and had better reproducibility.

In 2010, Hirata and associates⁷⁰ reported an analysis of outcomes of 38 patients who underwent single-stage

complete repair at Morgan Stanley Children's Hospital of New York. Using a minor modification of the criteria described by Tchervenkov,⁶⁷ they classified patients into two groups. If the aortic annulus was greater than the patient's weight (in kilograms) plus 1.5 mm, the patient was included in group "large," and if the aortic annulus was equal to or smaller than the patient's weight plus 1.5 mm, the patient was included in group "small." The average follow-up was 7.9 ± 4.2 years. Among the patients with small aortic annulus ($n = 12$), there was one hospital death and six reoperations for LVOT obstruction, and one late death. There was only one reoperation for LVOT obstruction among the patients with larger aortic annulus ($n = 26$; $P < 0.001$).

In 2013, Chen and associates⁷¹ at Boston Children's Hospital reported their analysis of predictors of reintervention following neonatal repair of IAA with VSD. Retrospective data were collected on neonates with IAA with VSD who underwent single-stage repair from 1995 to 2009. Sixteen patients (23%) required surgical or percutaneous reintervention for clinically significant postoperative LVOT obstruction. By univariate analysis, LVOT cross-sectional area, LVOT diameter, and aortic root size (all from two-dimensional echocardiography before neonatal repair) were predictors of reintervention. On multivariable linear regression model, aortic root size (from the parasternal long-axis view in end systole) was identified as an independent predictor of reintervention. In identifying an aortic root size inflection point, patients with an aortic root size less than 6.5 mm were at greater risk for reintervention compared with patients with a root size greater than 6.5 mm (reintervention rate 44% and 12%, respectively).

The procedures used to address residual or recurrent LVOT obstruction after initial repair of IAA are numerous, and the choice depends on the specific morphology encountered. Fibrous or fibromembranous subaortic stenosis can generally be approached through the aortic valve. Enucleation of fibrous tissue from the LVOT may need to be preceded by aortic valvotomy (if valvar stenosis is present) and accompanied by myotomy and myectomy of obstructing muscle in the LVOT. Long-segment fibromuscular subaortic stenosis, if present, is best managed with extended ventricular septoplasty (the modified Konno procedure). Working through a right ventricular infundibular incision, an incision is made in the ventricular septum, generally through the area of the previously closed VSD. This incision is carefully monitored by periodic visualization through an aortotomy, looking down through the aortic valve. From the right ventricular approach, the septal incision is extended into the LVOT and is carried up to within a few millimeters of the aortic valve annulus. A patch is then placed on the right ventricular aspect of the surgically enlarged VSD. The infundibulotomy is closed either directly or with a patch. If significant aortic annular hypoplasia is an element of complex LVOT obstruction, then a conventional Konno procedure (with aortic valve prosthesis) or a Ross-Konno procedure is performed. The latter involves an anterior incision through the aortic annulus and into the ventricular septum, and pulmonary autograft replacement of the aortic valve, with the use of a patch or of

infundibular muscle attached to the autograft to enlarge the LVOT.⁶⁵ Finally, the placement of a valved conduit from the left ventricular apex to the descending thoracic aorta remains an option,⁴⁴ although it is rarely used.

Conduct of Surgery and Cardiopulmonary Bypass Support

The availability of prostaglandin and the resultant opportunity to stabilize the condition of most patients before surgery, together with refinements in the technology and conduct of cardiopulmonary bypass and the use of deep hypothermia with circulatory arrest, led to the widespread acceptance and performance of one-stage repair of IAA and associated intracardiac defects. Operative strategies based on preliminary surface cooling and core cooling on cardiopulmonary bypass, followed by a period of circulatory arrest and then reperfusion and rewarming on bypass, remain in widespread use today. Essential features include perfusion inflow through the main pulmonary trunk, with temporary tourniquet occlusion of the branch pulmonary arteries. Although adequate cooling of the brain (as reflected by appropriately falling nasopharyngeal and tympanic temperature) can generally be accomplished in this fashion, many surgeons routinely place an additional small (6- or 8-French) inflow cannula in the ascending aorta. The two perfusion cannulas are set up in advance, joined by a Y-connector. Cannulation of the ascending aorta must be undertaken with great care, as the vessel is particularly small in the setting of IAA type B or C (Fig. 122-5). The purse-string suture through which the aortic perfusion cannula will be inserted should be placed so that it will be just opposite the anastomosis that will be made; it is generally slightly more than half-way between the aortic valve and the origin of the first branch vessel (innominate or right common carotid artery) and toward the right side of the ascending aorta. Alternatively, the need for an aortic perfusion cannula can be assessed by addition of cerebral monitoring with near infrared spectroscopy to supplement temperature monitoring.

Regardless of perfusion technique, all repairs of IAA are facilitated by extensive mobilization of the ascending aorta and each of its branches, as well as the descending aorta and its branches. In general, this can be accomplished during the initial cooling phase of cardiopulmonary bypass. Extensive manipulation and dissection before the initiation of bypass can sometimes upset the already fragile hemodynamic state. If hypothermic circulatory arrest is anticipated, suture tourniquets are loosely placed around each of the aortic arch branches; they are not snugged down and occluded until immediately before circulatory arrest. Venous return to the pump oxygenator is either by single cannula in the right atrium (in which case, closure of a VSD is accomplished either during the period of circulatory arrest or by a transpulmonary approach while on cardiopulmonary bypass) or by means of bicaval cannulation (in which case, the intracardiac portion of the repair can be accomplished on bypass, either before or after the arch repair). If single cannulation of the right atrium with transpulmonary closure of the VSD is planned, intracardiac visualization can be

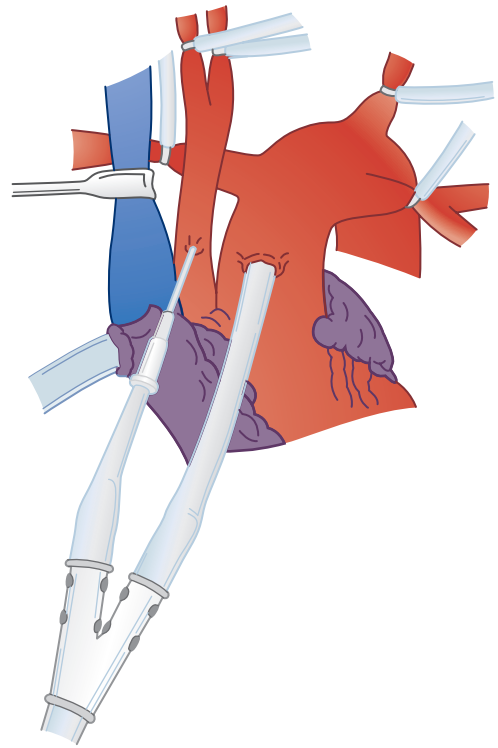


FIGURE 122-5 ■ Systemic perfusion via cannulation of both the main pulmonary trunk and the diminutive ascending aorta. Tourniquets are used to occlude the right and left branch pulmonary arteries during perfusion, and to occlude the aortic arch branches only during a period of hypothermic circulatory arrest. (From Luciani GB, Ackerman RJ, Chang AC, et al: One-stage repair of interrupted aortic arch, ventricular septal defect, and subaortic obstruction in the neonate: A novel approach. *J Thorac Cardiovasc Surg* 111:348–358, 1996.)

enhanced with the use of vacuum-assisted venous drainage. Although a single dose of antegrade cardioplegia suffices in most cases, this can be replaced or supplemented with single or multiple doses of retrograde cardioplegia via the coronary sinus. If the total duration of hypothermic circulatory arrest is anticipated to exceed 35 to 40 minutes, a brief period of hypothermic reperfusion can be accomplished immediately after completion of the arch reconstruction, with the remainder of the repair being accomplished during a second period of circulatory arrest.

Many surgeons have been pleased with the results of direct end-to-side anastomosis of the descending aorta to the left lateral aspect of the ascending aorta (Fig. 122-6), or to the left side of the distal ascending aorta and the underside of the proximal arch (in IAA type A). We and others⁷² have generally preferred to create an anastomosis that is augmented with a gusset of homograft vascular patch material (Fig. 122-7). To accomplish this, an incision is made in the left lateral aspect of the ascending aorta beginning a few millimeters above the sinotubular junction. The incision is carried onto the left side of the most distal arch branch associated with the ascending aorta. (To facilitate this, the occluding suture tourniquet must be placed as far distally as possible.) After ligation of the pulmonary artery end of the ductus, the ductus is divided, and all ductal tissue associated with the

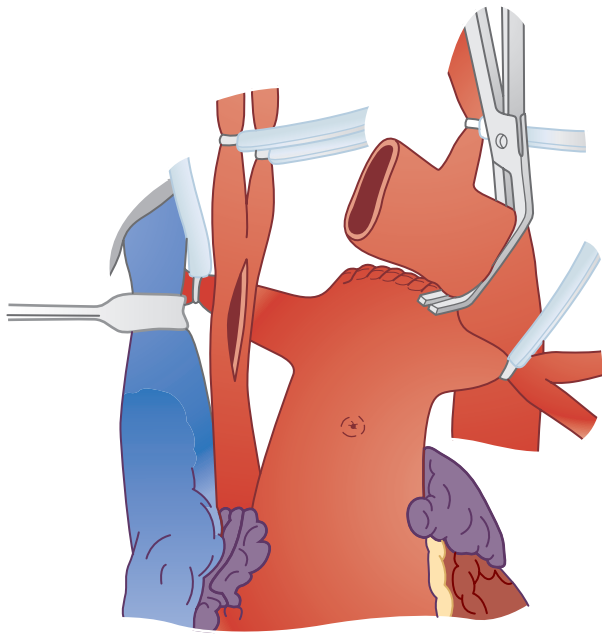


FIGURE 122-6 ■ Direct end-to-side anastomosis of the descending aorta to the left lateral aspect of the ascending aorta. A vascular clamp is applied across the descending thoracic aorta to facilitate positioning of this segment for the anastomosis. (From Luciani GB, Ackerman RJ, Chang AC, et al: One-stage repair of interrupted aortic arch, ventricular septal defect, and subaortic obstruction in the neonate: A novel approach. *J Thorac Cardiovasc Surg* 111:348–358, 1996.)

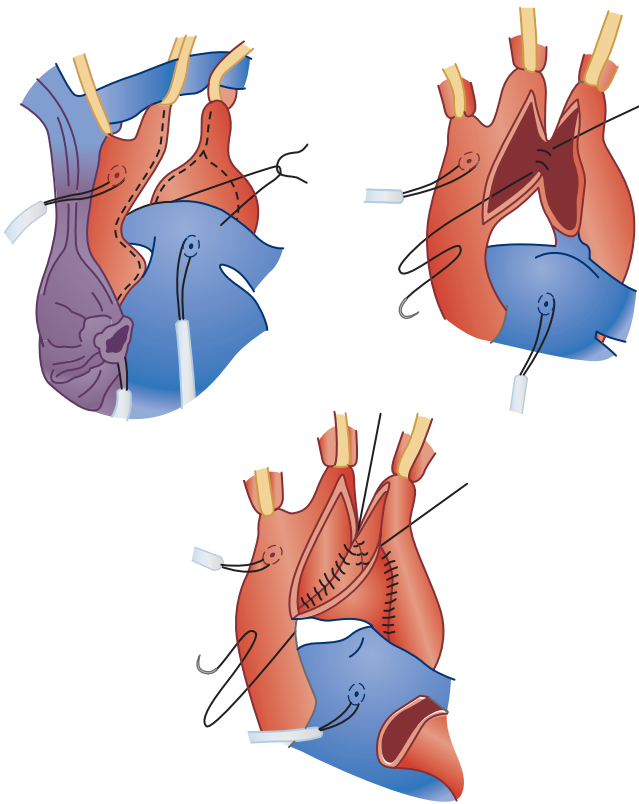


FIGURE 122-7 ■ Our preferred technique for interrupted aortic arch repair with homograft vascular patch augmentation of the aortic anastomosis. (From Jacobs ML, Chin AJ, Rychik J, et al: Interrupted aortic arch. Impact of subaortic stenosis on management and outcome. *Circulation* 92[9 suppl]:II128–II131, 1995.)

descending thoracic aorta is excised. The resulting opening into the descending aorta is extended a few millimeters along the right side of the first branch associated with the descending aorta (in IAA type B, this is the left subclavian artery). An incision is also carried down from the opening into the descending aorta, along the medial aspect of the aorta, to a point approximately 1 cm below the opening of the ductus into the aorta, as is done in a stage I Norwood procedure. Direct anastomosis of the proximal and distal aortic elements along their greater curvature is accomplished, including side-to-side amalgamation of the last aortic branch associated with the proximal segment and the first branch associated with the distal segment. The entire aortic arch is then augmented along its lesser curvature with a homograft vascular patch, beginning distally on the descending thoracic aorta. Once the arch reconstruction has been completed, the aorta is cannulated through a pursestring suture that, ideally, is situated on the right side of the augmented ascending aorta, several millimeters distal to the most proximal extent of the homograft patch. This minimizes the likelihood of aortic narrowing resulting when tying down the pursestring suture after decannulation. Perfusion can be resumed at this time, or alternatively the VSD can be closed before resumption of cardiopulmonary bypass. The technique of homograft patch augmentation of the aortic anastomosis has proved particularly useful in the setting of repair of truncus arteriosus with IAA.⁷³

These methods have yielded satisfactory outcomes, and they remain in use at many centers. Recently, however, techniques allowing continuous cerebral perfusion have gained favor, because they minimize the use or duration of hypothermic circulatory arrest.^{9,74,75} Clinical studies comparing neurodevelopmental outcomes in patients undergoing arch repair with continuous cerebral perfusion to those with hypothermic circulatory arrest have, for the most part, been in the setting of stage I Norwood procedures, and the results at 1 year are similar between groups. Issues pertaining to optimal temperature, rates of flow, and pH strategy remain to be resolved. Nonetheless, the idea of continuous cerebral perfusion is appealing to many surgeons, and its use is increasing steadily.

Continuous antegrade cerebral perfusion is accomplished either by advancing a small aortic perfusion cannula into the right common carotid artery⁷⁵ or by direct cannulation of the innominate artery (with a 6 or 8 Fr cannula),⁷⁴ or by anastomosis of a 4- or 5-mm polytetrafluoroethylene graft to the innominate artery, into which a perfusion cannula is placed with care to exclude air. A second perfusion cannula is placed in the main pulmonary artery (Fig. 122-8). After hypothermic bypass is established and the target core temperature is reached, the perfusion cannula in the pulmonary artery is clamped and removed. Flow is reduced and maintained at a level of 40 to 70 mL/kg/min. The ductus is suture-ligated at the pulmonary artery end. A small vascular clamp is placed on the descending aorta approximately 1 cm distal to the point of insertion of the ductus. The left subclavian artery (and an aberrant right subclavian artery if present) is occluded temporarily with a small removable neurovascular clip. The ductus is divided, and

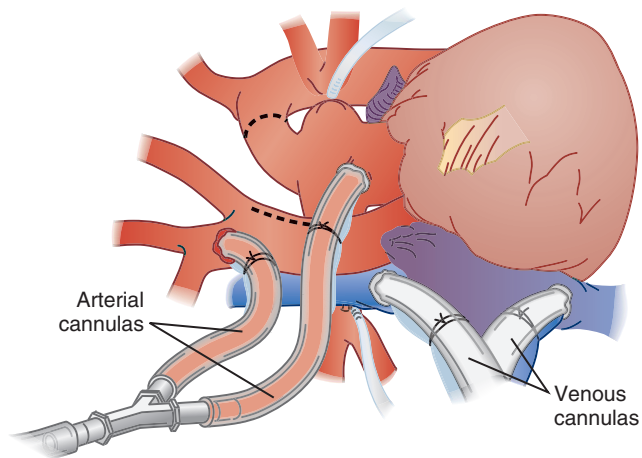


FIGURE 122-8 ■ A perfusion arrangement for interrupted aortic arch repair that facilitates arch anastomosis during a period of selective antegrade cerebral perfusion. This arrangement, used by Malhotra and Hanley⁷⁴ and others, includes direct cannulation of the innominate artery and the main pulmonary trunk. The dotted line indicates proposed sites for incision in the ascending aorta and for transection of the ductus arteriosus. (From Coarctation of the aorta and interrupted aortic arch. In Kouchoykos NT, Blackstone EH, Doty DB, Hanley FH, Karp RB, editors: *Kirklin and Barratt-Boyes' cardiac surgery*, ed 3, Philadelphia, 2003, Churchill Livingstone, pp 1315–1375.)

any ductal tissue associated with the descending thoracic aorta is excised. The vascular clamp on the descending aorta is required in this circumstance to prevent back-bleeding, but it is also useful under conditions of circulatory arrest to aid in manipulation of the distal aortic segment. If direct end-to-side anastomosis of the descending aorta to the ascending aorta is planned, a small straight vascular clamp is placed across the arch of the aorta at the base of the innominate artery and the left common carotid artery (Fig. 122-9), maintaining luminal continuity and facilitating perfusion of both branches.⁷⁴ The end-to-side anastomosis is accomplished proximal to this point (Fig. 122-10). Cardioplegia solution is administered in antegrade fashion into the ascending aorta. If patch augmentation of the anastomosis is planned, the straight vascular clamp is applied proximal to the perfusion cannula at the base of the innominate artery. The left common carotid (in addition to any more distal branches associated with the ascending aorta) is gently occluded somewhat distally, with either a suture tourniquet or a neurovascular clip. In this way, the anastomosis of the proximal and distal aortic segments can include side-to-side amalgamation of most proximal portions of the last aortic branch associated with the ascending aorta, and the first branch associated with the descending aorta. The anastomosis is augmented along its lesser curvature with a gusset of cryopreserved homograft vascular patch material. When this technique is used, it is rarely necessary to ligate and divide a left or an aberrant right subclavian artery. All tourniquets and other occluding devices are removed from the aorta and its branches. Full flow (or systemic perfusion at a level appropriate to the core temperature) is resumed. An additional dose of antegrade cardioplegia is given if so desired, and the intracardiac repair is undertaken. The VSD is closed using a

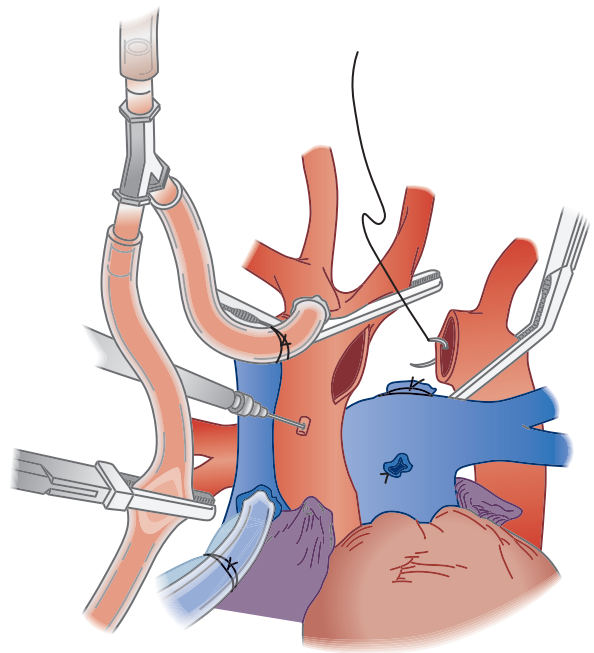


FIGURE 122-9 ■ The operation shown in Figure 122-8, here showing the placement of a small vascular clamp across the arch of the aorta at the base of the innominate artery and left common carotid artery, maintaining luminal continuity and facilitating continuous perfusion of both branches. (From Coarctation of the aorta and interrupted aortic arch. In Kouchoykos NT, Blackstone EH, Doty DB, Hanley FH, Karp RB, editors: *Kirklin and Barratt-Boyes' cardiac surgery*, ed 3, Philadelphia, 2003, Churchill Livingstone, pp 1315–1375.)

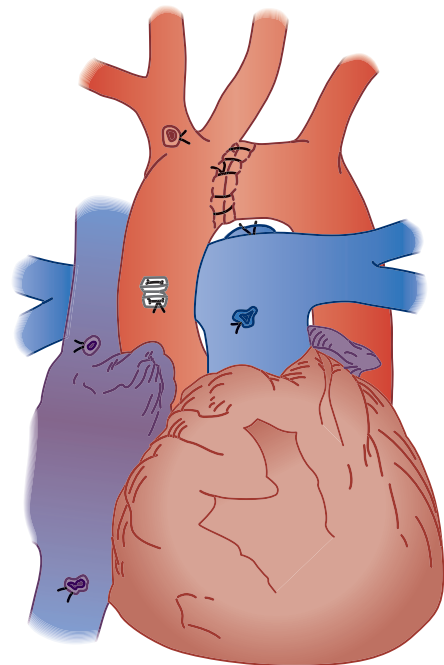


FIGURE 122-10 ■ The completion of the operation illustrated in Figures 122-8 and 122-9, here showing the end-to-side anastomosis of the descending aorta to the ascending aorta. Also shown are the oversewn cannulation sites for arterial perfusion, venous drainage, and cardioplegia administration. (From Coarctation of the aorta and interrupted aortic arch. In Kouchoykos NT, Blackstone EH, Doty DB, Hanley FH, Karp RB, editors: *Kirklin and Barratt-Boyes' cardiac surgery*, ed 3, Philadelphia, 2003, Churchill Livingstone, pp 1315–1375.)

transpulmonary or transatrial approach, and an atrial septal defect or stretched foramen is approached through the right atrium. After rewarming, separation from bypass is accomplished.

Hybrid Palliation

In selected cases, a decision may be made to delay definitive repair of the interrupted arch and associated intracardiac defects, in favor of a course of treatment based on initial stabilization of the circulation by a combination of maneuvers that restore and maintain patency of the arterial duct and that limit pulmonary blood flow. Based on the same principles as the so-called hybrid strategy for initial palliation of hypoplastic left heart syndrome, this generally involves a median sternotomy approach for bilateral application of bands to the right and left branch pulmonary arteries and either prolonged continuous infusion of prostaglandin E1 or transpulmonary artery deployment of an intravascular stent in the arterial duct.^{76,77} This alternative strategy is generally reserved for instances of rescue therapy for neonates with shock and secondary organ dysfunction in the setting of ductal constriction or with significant infection. It can also be used when temporary delay of definitive repair requiring cardiopulmonary bypass is judged to be advantageous, which might include instances of extreme prematurity or of neurologic complications such as intraventricular hemorrhage.

RESULTS: SURVIVAL, COMPLICATIONS, AND LATE EVENTS

In general, single-institution series describing results of surgical management of IAA reflect the challenge and complexity of this group of lesions, but they offer encouraging results that in the aggregate suggest that a good deal of progress has been made over the past 2 decades.^{41,42,46,55} Several institutions describe operative survival on the order of 90%. In individual series, the incidence of reintervention during follow-up varies from as little as 10% to greater than 50%.* In the Congenital Heart Surgery Database of the Society of Thoracic Surgeons,⁷⁹ the mortality at discharge from hospital after IAA repair in the 4-year interval from 2004 through 2007 is 8.9% (32/359).

Multi-institutional outcome studies provide a broader overview of experience and offer the opportunity to undertake risk analysis on a large set. The CHSS initiated its first prospective multi-institutional outcome study of patients with IAA in 1987, with patient enrollment at 30 participating institutions. In 1994, the first CHSS report, by Jonas and associates,¹⁵ analyzed the outcomes from management of 183 neonates with IAA and VSD entering the study between 1987 and 1992. Nine patients died without any surgery. Among the remaining 174, survival rates at 1 month and 1, 3, and 4 years after repair were 73%, 65%, 63%, and 63%, respectively. The risk factors

for death were low birth weight, younger age at repair, interrupted arch type B, outlet and trabecular VSDs, smaller size of the VSD, and subaortic narrowing.

Echocardiographically measured dimensions at all levels of the left heart–aorta complex were small. As previously noted, procedural risk factors for death after repair were (1) repair without concomitant procedures in patients with other important levels of obstruction in the left heart–aorta complex, (2) a Damus-Kaye-Stansel anastomosis, and (3) subaortic myotomy or myectomy in the face of subaortic narrowing. One-stage repair plus ascending aorta or arch augmentation had the highest predicted time-related survival in the 20% of patients with IAA and one or more coexisting levels of obstruction in the left heart–aorta complex, as did initial repair without or with aorta or arch augmentation in the 80% without these. Only 26% of patients in whom a lateral thoracotomy was used (as in most initial repairs in which the VSD was not closed) had a direct anastomosis, in contrast to 92% of those in whom a median sternotomy with a one-stage repair was performed. Among the 57 patients who did not have the VSD closed at the initial procedure, essentially all who survived had it closed within 36 months of the initial repair. The peak rate of VSD closure by a subsequent procedure was highest during the first month after the initial procedure, suggesting that the untreated VSD was not being well tolerated and that a one-stage repair at the initial procedure might have been preferable. By the time the analysis was undertaken, 20 patients had undergone reintervention for arch obstruction. In nine patients, the procedure was percutaneous balloon dilation. The peak of the hazard function for this reintervention was approximately 4 months after the initial repair. Fifteen of the 116 patients undergoing one-stage repair had a first reintervention for one or more coexisting obstructive lesions in the left heart–aorta complex (e.g., LVOT obstruction). Freedom from such reinterventions was only 77% at 3 years. This unique multi-institutional study revealed that optimal management of coexisting obstructive left heart lesions in association with IAA remained an unresolved challenge at the time. It also pointed out the ongoing risks of recurrent arch obstruction and LVOT obstruction in survivors of neonatal repair. These findings encouraged the CHSS to enlarge the patient cohort through further enrollment, and to continue the analysis of these late-phase events.

A more recent CHSS multi-institutional study on IAA reported in 2005 by McCrindle and associates¹⁷ evaluated an expanded cohort of 472 patients (including the patients previously reported by Jonas and associates). Additional insights concerning the significance and management of LVOT obstruction became apparent, at least in part because of the large size of the study population. Of the 472 patients with IAA, 143 underwent a variety of interventions to address LVOT obstruction, of which 52 took place some time after the initial IAA repair. Subaortic resection was performed in 75 of these patients, and 51 underwent LVOT bypass procedures (Norwood or Yasui). Two patients required cardiac transplantation. Competing risks analysis revealed that at 16 years after initial admission, 38% were alive without a LVOT procedure,

*References 15, 41-43, 55, 58, 59, 62, 73, and 78.

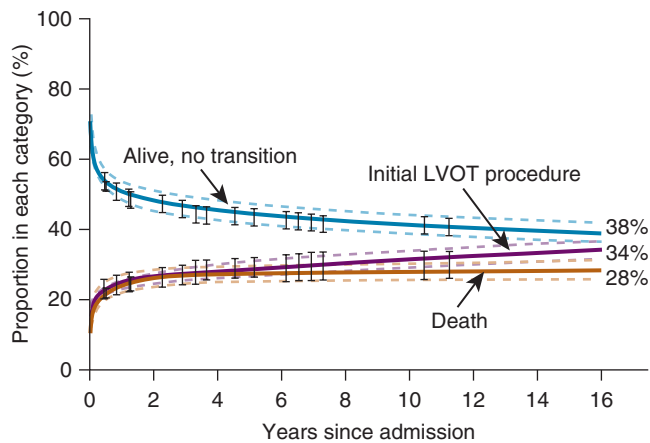


FIGURE 122-11 ■ Graphic representation from the 2005 Congenital Heart Surgeons' Society (CHSS) study of interrupted aortic arch (IAA) competing risks analysis for initial procedure aimed at addressing potential or actual left ventricular outflow tract (LVOT) obstruction. All patients began at the time of initial admission to a CHSS member institution ($N = 472$) and could transition to either death or initial procedure aimed at addressing potential or actual LVOT obstruction. *Solid lines*, parametric point estimates; *dashed lines*, limits of 70% confidence intervals; *circles with error bars*, nonparametric estimates; *y-axis*, proportion of patients (expressed as percentage of total) in each of three categories at any given time after IAA repair. (From McCrindle BW, Tchervenkov CI, Konstantinov IE, et al; Congenital Heart Surgeons Society: Risk factors associated with mortality and interventions in 472 neonates with interrupted aortic arch: a Congenital Heart Surgeons Society study. *J Thorac Cardiovasc Surg* 129:343–350, 2005.)

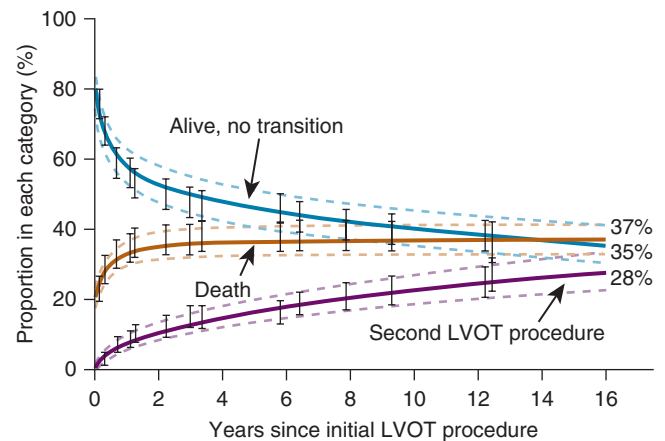


FIGURE 122-12 ■ Graphic representation from the 2005 Congenital Heart Surgeons' Society study of interrupted aortic arch (IAA) competing risks analysis for subsequent procedure aimed at addressing residual or recurrent left ventricular outflow tract (LVOT) obstruction. All patients began at the time of the initial procedure aimed at addressing potential or actual LVOT obstruction ($N = 143$) and could transition to either death or similar subsequent procedure. *Solid lines*, parametric point estimates; *dashed lines*, limits of 70% confidence intervals; *circles with error bars*, nonparametric estimates; *y-axis*, proportion of patients (expressed as percentage of total) in each of three categories at any given time after IAA repair. (From McCrindle BW, Tchervenkov CI, Konstantinov IE, et al; Congenital Heart Surgeons Society: Risk factors associated with mortality and interventions in 472 neonates with interrupted aortic arch: a Congenital Heart Surgeons Society study. *J Thorac Cardiovasc Surg* 129:343–350, 2005.)

whereas 34% had undergone an initial LVOT procedure (Fig. 122-11). For the 143 patients who had an initial LVOT procedure, there was a high risk of early death and a nearly constant risk of a second procedure. At 16 years after the initial LVOT procedure, 35% were alive without a second procedure, and 28% required a second LVOT procedure. Of the patients who had an initial LVOT procedure, 37% had died by 16 years (Fig. 122-12). Risk factors for a second LVOT procedure were absence of a large VSD and initial balloon dilation of the LVOT. These observations certainly emphasize the significance of the problem of LVOT obstruction in IAA and its negative effects on survival and reoperation-free survival. Regarding the fate of the initial arch repair, reintervention for arch obstruction occurred in 109 cases. Of these, 52 were by transcatheter balloon dilation and 57 were surgical. The time-related hazard function for survival to an arch repair intervention showed two phases: an early phase accounting for 89 events and a smaller constant hazard phase accounting for 20 events. The time-related hazard function for death without an IAA repair intervention was characterized by an early phase only. The competing risks for the two events showed that 16 years after IAA repair, 33% had died without an IAA repair intervention, 29% were surviving to an IAA repair intervention, and 38% remained alive without an IAA repair intervention (Fig. 122-13). Finally, with respect to overall mortality, improving outcomes were evident for patients born later in the study enrollment period (Fig. 122-14). This

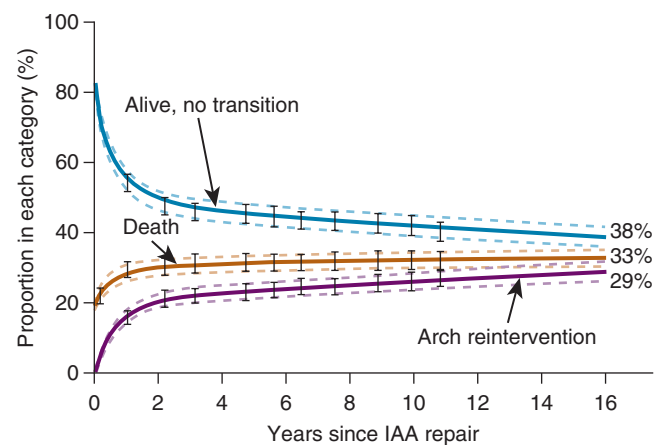


FIGURE 122-13 ■ Graphic representation from the 2005 Congenital Heart Surgeons' Society study of interrupted aortic arch (IAA) competing risks analysis for subsequent intervention for residual or recurrent obstruction at IAA repair site. All patients began at the time of repair of IAA ($N = 453$) and could transition to either death or subsequent intervention for residual or recurrent obstruction at the arch repair site. *Solid lines*, parametric point estimates; *dashed lines*, limits of 70% confidence intervals; *circles with error bars*, nonparametric estimates; *y-axis*, proportion of patients (expressed as percentage of total) in each of three categories at any given time after IAA repair. (From McCrindle BW, Tchervenkov CI, Konstantinov IE, et al; Congenital Heart Surgeons Society: Risk factors associated with mortality and interventions in 472 neonates with interrupted aortic arch: a Congenital Heart Surgeons Society study. *J Thorac Cardiovasc Surg* 129:343–350, 2005.)

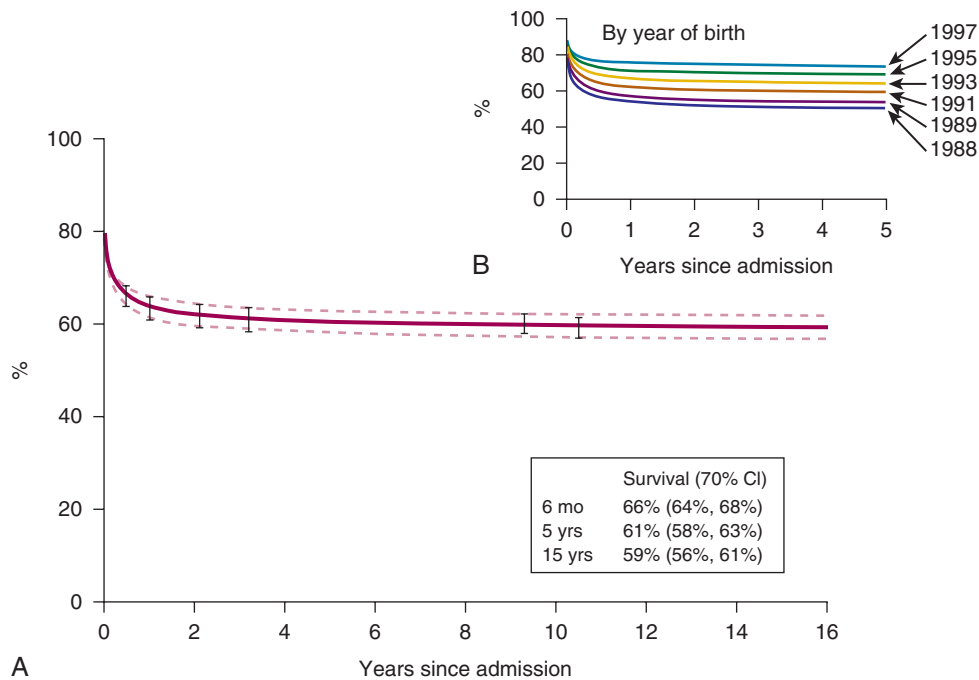


FIGURE 122-14 ■ Graphic representation from the 2005 Congenital Heart Surgeons' Society (CHSS) study of interrupted aortic arch (IAA) depicting overall time-related survival of 472 neonates with IAA. All patients began at the time of initial admission to a CHSS member institution. **A**, Overall survival. **B**, Predicted overall survival for first 5 years after admission, stratified by patient date of birth. *Solid lines*, Parametric point estimates; *dashed lines*, limits of 70% confidence intervals (CI). (From McCrindle BW, Tchervenkov CI, Konstantinov IE, et al; Congenital Heart Surgeons Society: Risk factors associated with mortality and interventions in 472 neonates with interrupted aortic arch: a Congenital Heart Surgeons Society study. *J Thorac Cardiovasc Surg* 129:343–350, 2005.)

positive message regarding steadily improving rates of overall survival over the period of patient enrollment (1987 to 1997) is tempered by the sobering data concerning the significant requirement for late re-interventions. It should also be noted that, while the initial CHSS report was restricted to patients with IAA and VSD, the 2005 report by McCrindle and associates also included patients with complex lesions, including IAA with truncus arteriosus, with an aortopulmonary window, and with a single ventricle.

The most recent report on the CHSS cohort by Jegatheeswaran and associates⁸⁰ clearly reinforced the impression that IAA is a chronic disease, with many repaired patients requiring multiple subsequent procedures. Among 447 patients with IAA enrolled from 1987 to 1997 at 33 institutions, there were 158 subsequent arch interventions and 100 left ventricular outflow tract procedures. Overall freedom from death at 21 years was 60%. The risk of additional subsequent arch procedures decreased after the first subsequent arch procedure in the acute phase, but did not significantly change in the chronic phase. The risk of additional subsequent left ventricular outflow tract procedures increased after the first subsequent left ventricular outflow tract procedure in the chronic phase. These results indicate the need for practitioners, patients, and their families to understand the concept that IAA is a chronic disorder and not a structural anomaly definitively treated in the newborn period.

This concept is further amplified by a recent single-center follow-up study undertaken at the Children's

Hospital of Philadelphia. Intermediate term status of children and adolescents who had undergone repair of IAA as neonates was evaluated by O'Byrne and associates.⁸¹ A cross-sectional study of patients age 8 to 18 years included genetic testing, cardiac magnetic resonance imaging, cardiopulmonary exercise testing, and assessment of health status and health-related quality of life. A concurrent retrospective study reviewed their postoperative use of medical care, including operative and transcatheter reinterventions, noncardiac surgeries, and hospitalizations. Twenty-one subjects with a median age of 9 years were studied. Reintervention rates were 38% for left-ventricular outflow tract, 33% for aortic arch, and 24% for both. Rates of reintervention were highest in the first year of life. Left-ventricular ejection fraction was preserved ($72\% \pm 6\%$). Maximal oxygen consumption, maximal work, and forced vital capacity were significantly decreased from age and sex norms ($P < 0.0001$). Health status and quality of life were both severely decreased.

An uncommon but important complication that can occur after IAA repair is compression of the left mainstem bronchus. This problem has been reported after repair of IAA with VSD and with truncus arteriosus. Signs of this complication may be present or appear early after initial repair; they can cause failure to liberate from mechanical ventilation. While the patient is receiving positive-pressure ventilation, the compression can manifest as air trapping and hyperinflation. Without mechanical support and positive pressure, it can give the opposite picture—that of total atelectasis of the left lung.

Alternatively, it can become evident at some later time after initial repair, with symptoms of wheezing or recurrent respiratory infection. Bronchoscopy reveals extrinsic compression with collapse of the airway. CT or MRI with three-dimensional reconstruction is helpful. The problem occurs when either an interposition graft or a primary anastomosis under tension compresses the left bronchus. Historically, this has been treated with division of the reconstructed aortic arch and placement of an extra-anatomic ascending-to-descending aortic conduit. Mitchell and associates⁸² reported a case of successful management of bronchial compression with severe bronchomalacia in a patient after IAA repair. They achieved transverse aortic arch extension with a pulmonary artery autograft and performed a left bronchial sleeve resection. Advocates of simple primary anastomosis believe that this rare complication can be avoided with full mobilization of all aortic elements at the time of repair. Some believe that dividing an aberrant right subclavian artery at its origin from the descending thoracic aorta contributes to minimization of tension at the anastomosis. Others recommend division of the left subclavian artery at its aortic origin if the anastomosis is under tension. We hold that routine augmentation of the aortic anastomosis with a homograft vascular patch at the time of IAA repair is the best way to minimize tension on the aortic elements and to avoid compression of the adjacent airway, without sacrificing major aortic branches.

Recent emphasis on understanding the neurodevelopmental effects of complex congenital heart disease and its treatment, as well as the influence of underlying genetic abnormalities, has prompted clinical investigators to realize that patients born with aortic arch anomalies are a heterogeneous group for whom risk of neurodevelopmental abnormalities is significant and multifactorial. The Western Canadian Complex Pediatric Therapies Follow-up Group evaluated 26 survivors of neonatal cardiac surgery for IAA at 6 weeks old or younger (1996 and 2006), with multidisciplinary neurodevelopmental assessment at 18 to 24 months of age.⁸³ Mental and psychomotor developmental indices were 75.8 ± 17.1 and 72.3 ± 16.9 , respectively, with significantly lower scores for children with chromosomal abnormalities, which accounted for 29% of the variance in developmental indices. For the remaining 17 children without chromosomal abnormalities, mental and psychomotor developmental indices were 82.7 ± 14.5 and 79.1 ± 14.3 , respectively.

In 2009, investigators in the Netherlands commenced a randomized controlled trial of deep hypothermic circulatory arrest (DHCA) versus antegrade cerebral perfusion (ACP) in neonates undergoing aortic arch reconstruction, with the primary outcome measure being incidence of new postoperative brain injury on MRI. As reported by Algra and associates in 2013,⁸⁴ the protocol included preoperative and 1 week postoperative MRI of the brain. Approximately half of the 36 patients had IAA, and the remainder had other anomalies treated by arch reconstruction with cardiopulmonary bypass in the newborn period. After the thirty-sixth patient, it was clear that there was no difference between DHCA and ACP in terms of new cerebral injury. Preoperatively, 50% of

patients had evidence of cerebral injury. Postoperatively, 14 of 18 (78%) DHCA patients had new injury, versus 13 of 18 (72%) ACP patients ($P = 0.66$). White matter injury was the most common type of injury in both groups, but central infarctions occurred exclusively after ACP (0 vs. 6 of 18; $P = 0.02$). Early motor and cognitive outcome at 24 months was assessed and was similar between groups ($P = 0.28$ and $P = 0.25$, respectively). Additional analysis revealed lower postoperative arterial $p\text{CO}_2$ as a risk factor for new white matter injury. Important conclusions were that perioperative cerebral injury is common in this population and that there was no demonstrable difference in the incidence of perioperative cerebral injury after ACP compared with DHCA. Both techniques resulted in a high incidence of new white matter injury, with central infarctions occurring exclusively following ACP.

SUMMARY

Advancements in surgical technique, and markedly improved survival following initial surgical repair of IAA and associated intracardiac anomalies, have led to the recognition that these patients face ongoing risks associated with residual or recurrent obstructions in both the left ventricular outflow tract and the aortic arch. In addition, many patients face important deficits in exercise performance, health status, and health-related quality of life. In essence, IAA and its associated morbidities should be viewed as a chronic disease. Future improvements in patient management are likely to be based on understanding and acceptance of this challenge.

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SURGERY FOR CONGENITAL ANOMALIES OF THE AORTIC VALVE AND AORTIC ROOT

Christopher W. Baird • Frank A. Pigula

CHAPTER OUTLINE

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PROSTHETIC MECHANICAL VALVES, ANTICOAGULATION, AND PREGNANCY

SUMMARY

Congenital aortic valve disease is one of the more commonly encountered congenital cardiac defects, occurring in 3% to 6% of children born with congenital heart disease. Congenital aortic valve disease primarily manifests as aortic stenosis and tends to be a progressive disease with morbidity and mortality resulting from the hemodynamic burden imposed on the left ventricle. Aortic stenosis is generally defined as a narrowing at the valvar, subvalvar, supravalvar, or multiple levels along the left ventricular outflow tract (LVOT). Although the same pathologic mechanisms are operational in both

congenital and acquired aortic valve disease, the context differs dramatically. Congenital aortic valve pathology often manifests alongside multiple associated cardiovascular lesions, and multiple levels of the LVOT can be involved. There are multiple considerations when caring for these children regarding the timing of intervention and approach (catheter-based intervention versus surgical). Because of growth, behavior, and anticoagulation further surgical considerations often include single versus biventricular repair, valve repair versus replacement, and type of valve replacement. Thus, the evaluation

and treatment of congenital aortic valve disease may present unique anatomic and physiologic considerations. Although aortic insufficiency can afflict congenitally abnormal valves later in life, it is an uncommon lesion during infancy and early childhood. When present in these age groups, it is usually an iatrogenic consequence of a procedure designed to relieve congenital aortic stenosis. This chapter will address these considerations and the related challenges encountered in the surgical treatment of congenital aortic valve disease.

SURGICAL ANATOMY OF THE AORTIC VALVE AND ROOT

The aortic valve and root span the transition from the left ventricular chamber and the systemic circulation, and they include the subaortic LVOT, the aortic valve, and the aortic wall up to the level of the sinotubular junction. Congenital heart disease can involve one or more levels of the aortoventricular complex. A thorough understanding and appreciation of these inconspicuous anatomic relationships form the basis of successful surgical treatment of congenital aortic valve disease, and these relationships will be referred to throughout this chapter.¹

The normal aortic valve sits wedged into the LVOT. In addition to supporting the coronary circulation, this central location places the aortic valve at the nexus of several critical intracardiac structures. Among these structures are the anterior leaflet of the mitral valve, the membranous interventricular septum, and the conduction apparatus. Because multiple levels of the aortoventricular complex can be involved in congenital heart disease, it is helpful to consider the normal anatomy to consist of subvalvular, valvular, and supravvalvular components.

The subvalvular anatomy is dominated by the anatomic relationships among the aortic valve, interventricular septum, membranous septum, mitral valve, and conduction apparatus (Fig. 123-1). Parts of the aortic

leaflets are in fibrous continuity with the anterior leaflet of the mitral valve as well as the tricuspid valve (via the membranous septum). These structures contribute to the central supporting structure of the heart, the fibrous skeleton. In addition to providing points of fixation for the atrioventricular valves, the fibrous skeleton also provides electrical insulation between the atria and the ventricles, restricting impulse conduction to the bundle of His. After arising from the atrioventricular node, the bundle of His penetrates the membranous septum, emerging on the surface of the left ventricular septum immediately below the aortic annulus. Looking through the aortic valve, the bundle will lie beneath the annulus, just below the commissure between the noncoronary and right coronary leaflet. From the surgeon's perspective, important radiations of the bundle reach to the nadir of the right coronary leaflet as they fall away, toward the apex of the heart.

Valvular anatomy is dominated by the semilunar leaflets, commissures, and sinuses of Valsalva. The leaflets and their sinuses are identified by the associated coronary artery. The right coronary artery ostium is found in the right coronary sinus, which is almost directly anterior as viewed by the surgeon. The left coronary artery emerges posteriorly from the left coronary sinus. The leaflets themselves are composed of a fibrous core lined by endothelium. The commissures, along with the free-edge coaptation provided by the leaflets themselves, provide the strength necessary to provide a competent valve.

The aortic sinuses are dilations of the aortic wall above distal to the insertion of the semilunar leaflets, and they are well suited to support the coronary ostia. While the leaflets retract during systole, eddy currents developing within the sinuses prevent occlusion of the coronary ostia by the retracted aortic leaflets. Their presence is probably important to the long-term function of the aortic valve leaflets.²⁻⁴

Finally, the supravvalvular area denotes the transition from the left ventricle–aorta complex to the aorta proper. For practical purposes, this area includes the sinotubular junction, the area just distal to the tips of the commissural posts, and the dilations of the aortic sinuses. Abnormalities at any level can be expected in congenital heart disease, and a discussion of the various forms of congenital aortic valve pathology will be categorized by its level: valvular, subvalvular, or supravvalvular.

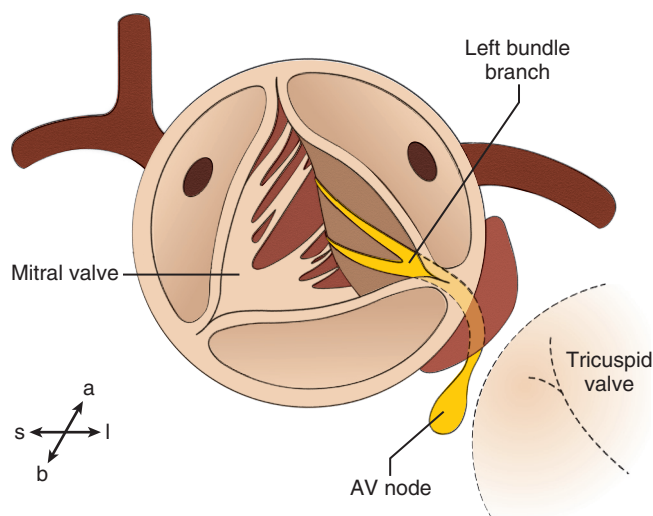


FIGURE 123-1 ■ Anatomic relationships within the aortic valve. AV, Atrioventricular.

AORTIC STENOSIS

Valvular Aortic Stenosis

Prevalence

Congenital aortic stenosis has been reported to be present in between 3% and 6% of children with congenital heart disease.⁵ Males are affected more commonly than females with an incidence of 3:1.⁶

Clinical Characteristics

The clinical presentation varies with the severity of the lesion and the age at presentation. In the neonate, critical aortic stenosis may present rapidly and dramatically, with

abrupt hemodynamic deterioration, cardiovascular collapse, and shock. The cardiogram may reveal left ventricular hypertrophy with S-T and T wave abnormalities. On chest radiography, there may be cardiomegaly and pulmonary edema. Transthoracic echocardiogram will rapidly establish the diagnosis, and it is useful to determine the presence of associated abnormalities of the left ventricle, mitral valve, or aortic arch. Aggressive resuscitation with inotropes and prostaglandin is required to support the circulation.

Older children may be asymptomatic, and aortic stenosis may be suggested by physical examination results. Chest pain and exercise intolerance is possible but uncommon. Like the neonate, the diagnosis can be confirmed with echocardiography.

Diagnosis

Physical examination results may be suggestive of the diagnosis of congenital aortic valve disease. There may be a harsh crescendo-decrescendo murmur heard best at the right second interspace, with transmission into the neck. A thrill will be present in the suprasternal notch, and over the right second intercostal spaces in severe aortic stenosis. Because ventricular systole is prolonged in the setting of aortic stenosis, the second heart sound may be prolonged, resulting in narrowly split second heart sound. An associated diastolic murmur would suggest an element of aortic insufficiency.

Electrocardiographic changes are consistent with ventricular hypertrophy, as evidenced by increased left-sided R wave voltage. Changes in S-T segment and T wave in the left precordial leads may denote LV strain. Except in the situation of obvious congestive heart failure, the chest radiograph is usually unremarkable.

Echocardiography. Echocardiography is the mainstay for contemporary diagnosis of congenital aortic valve disease. This noninvasive test provides important anatomic and physiologic information, such as the number and anatomy of the aortic leaflets, the size of the aortic annulus and ascending aorta, the location of the coronary arteries, the adequacy of the subaortic LVOT, and the site of the hemodynamic stenosis. The peak instantaneous gradient can be estimated by measuring the velocity of blood flow across the stenosis, and using a modification of the Bernoulli equation ($\text{velocity [m/sec]}^2 \times 4$).⁷

Recent developments in imaging include the availability of three-dimensional echocardiographic technology. Ventricular mass and volume measurements obtained with three-dimensional echocardiography compare well with those obtained with cardiac magnetic resonance imaging, and their utility in determining the etiology of congenital aortic valvular disease is currently under investigation.⁸

Stress Testing. Stress testing may be helpful in older patients with mild to moderate aortic stenosis in whom symptoms may be vague or suspicious and are not clearly related to the aortic valve disease. Stress-related changes in the S-T segment or T wave morphology would suggest important stenosis with myocardium at jeopardy. In these

instances, relief of the stenosis should be seriously considered, despite mild to moderate resting peak gradients.

Cardiac Catheterization. Currently, the major roles of cardiac catheterization include diagnostic and therapeutic options. Diagnostically, catheterization may be helpful to assess left ventricular diastolic function, pulmonary artery pressure, and associated vascular lesions. Therapeutically, balloon valvotomy can be used in patients with isolated aortic valvular stenosis or occasionally in patients with complex multilevel LVOT obstruction.

Natural History

Critical "valvular" aortic stenosis in the neonate often presents as an "emergent" situation, and without prompt treatment these children may succumb from cardiovascular collapse. By contrast, older children with aortic stenosis are often asymptomatic. Given the important considerations pertaining to pediatric aortic valve repair and replacement, the timing of the operation becomes an important consideration, and understanding the natural history and progression of asymptomatic children is useful.

Aortic valve disease in children tends to be a progressive disease. Valvar aortic stenosis can be classified as mild, moderate, or severe. Categorized by Hossack and colleagues,⁹ mild stenosis includes those patients with normal pulse volumes with a resting peak systolic gradient (measured at catheterization) between the left ventricle and aorta of less than 40 mm Hg. Patients are considered to have moderate aortic stenosis when they exhibit diminished pulse volumes by palpation and resting peak systolic gradients of 40 to 75 mm Hg at rest. Patients are considered to have severe stenosis when they present with abnormal pulse volumes and a resting peak systolic pressure gradient in excess of 75 mm Hg.

It should be noted that these gradient criteria were obtained at catheterization by direct pullback measurements. Currently, gradients across the LVOT are frequently obtained with echocardiography, and in most cases Doppler-derived peak instantaneous gradient correlates well with catheter-derived data; however, at lower gradients, Doppler echocardiography can result in an overestimation.^{10,11}

Because aortic valve disease in children is a progressive disease, the natural history of this progression is of some interest. Among children with nonobstructive aortic lesions, Mills and colleagues¹² reported that 7% progressed to mild obstruction after 7 to 15 years. When mild stenosis was present upon the initial evaluation, progression was rapid.¹² Twenty percent of patients developed moderate or severe stenosis within 10 years, with 45% progressing within 20 years. Finally, approximately 60% of patients presenting with moderate stenosis will progress to severe stenosis within 10 years.⁹

Treatment

Catheter versus Surgical Relief of Aortic Stenosis in the Neonate. Aortic stenosis presenting in the neonatal

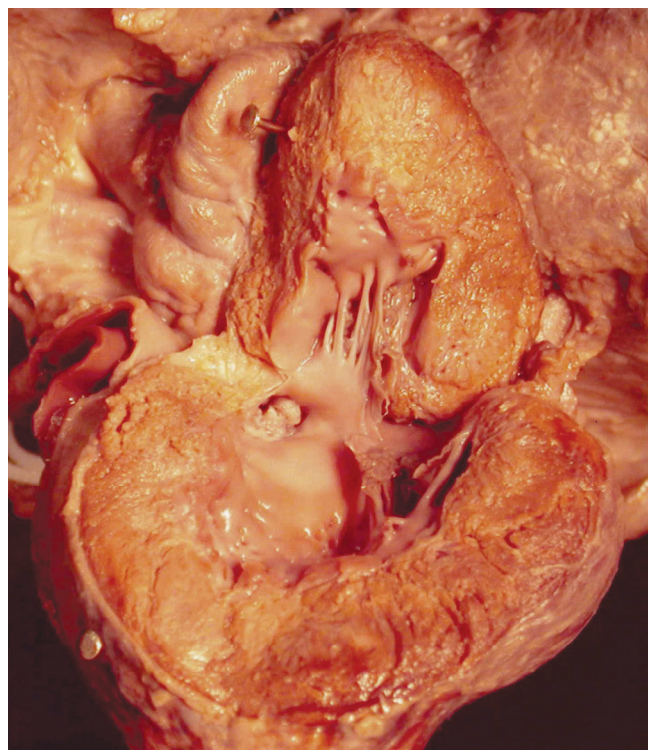


FIGURE 123-2 ■ Pathologic specimen showing aortic stenosis in the neonatal heart.

period can be a severe hemodynamic lesion that is life threatening (Fig. 123-2). These children often present in shock as a consequence of ductal closure in the setting of left heart structures that are inadequate to support the systemic circulation; their systemic circulation is “ductal dependent.” These children require urgent medical stabilization, including assisted ventilation and inotropic support. Prostaglandin E1 is administered to reopen the duct and to maintain ductal patency. Once stabilized, a thorough echocardiographic examination of the left-sided structures is required to determine their suitability to support the systemic circulation.

When approaching critical aortic stenosis in neonates, the single most important decision regarding treatment is to decide which patients will benefit from biventricular repair, and which are better suited to a single ventricle approach. The importance of proper treatment selection is reflected by the high mortality in older, unstratified series of neonates undergoing valvotomy for critical aortic stenosis.¹³ An accurate determination of which patients will benefit from a single ventricle treatment pathway (Stage I/Norwood operation) is critical, and it has been the impetus for the study sponsored by the Congenital Heart Surgeons Society (CHSS) and designed to accomplish this.¹⁴ An estimate of survival benefit for specific left heart morphology can be obtained at the CHSS website (www.chssdc.org). The management of these patients has been detailed elsewhere. This discussion will focus on patients with aortic stenosis as the dominant lesion in the setting of two adequate ventricles.

For patients with anatomy deemed suitable to support a two-ventricle circulation, aortic valvotomy provides

effective relief of aortic stenosis. Two techniques of aortic valvotomy have been developed: balloon dilation of the stenotic valve and surgical valvotomy (open and closed). While balloon valvotomy is the favored technique at many institutions, surgical valvotomy remains preferred by some. Proponents of balloon valvotomy cite avoidance of potential surgical morbidity, while advocates of surgical valvotomy maintain that a more accurate valvotomy is possible under direct vision.

Although there are no prospective randomized studies directly comparing these two techniques, some data are available. McCrindle and colleagues¹⁵ reported a CHSS-sponsored multi-institutional review of 110 neonates undergoing either surgical (28) or balloon (82) valvotomy for critical aortic valve stenosis in the neonatal period. Survival was similar between the two procedures (82% at 1 month, 72% at 5 years).¹⁵ Balloon valvotomy was more effective at relieving stenosis (mean residual gradient 20 vs. 36 mm Hg), but it was accomplished at the expense of a higher incidence of important aortic insufficiency (18% after balloon valvotomy versus 3% after surgical valvotomy). Despite these differences, the outcome data between the two techniques is comparable. Overall freedom from reintervention was similar for both groups (91% at 1 month, 48% at 5 years). The need for subsequent procedures, regardless of technique, emphasizes the palliative nature of valvotomy for critical aortic stenosis.

McElhinney and colleagues¹⁶ reported medium- and long-term follow-up of 113 patients (age ≤ 60 days) from Children’s Hospital Boston performed between 1985 and 2002. They reported a normalization of aortic annular and left ventricular end-diastolic dimensions within 1 to 2 years. Freedom from moderate or severe aortic regurgitation was 65%, with a reintervention free survival of 48% at 5 years. These data suggest that early relief of the LVOT obstruction allows for catch-up growth without neonatal surgery.

Although balloon valvotomy has assumed a prominent role in the treatment of congenital aortic stenosis in many institutions, its role vis-à-vis surgical valvotomy remains controversial. Hawkins and colleagues¹⁷ have estimated the incidence of aortic valve operation after balloon valvotomy to be 5% to 7% per year. Others have reported the risk of surgery to be lower, but the incidence of reintervention, including subsequent balloon dilation, remains high (60% at 8 years).¹⁸ It may be, however, that specific aortic valvular substrates lend themselves to one treatment or the other. In a group of 54 infants (57% neonates) undergoing surgical aortic valvotomy, Bhabra and colleagues¹⁹ reported significant differences in the long-term outcomes based on leaflet morphology. When valvotomy resulted in a trileaflet structure, patients did significantly better than when only a bileaflet valve was achieved. At 10 years, the actuarial freedom from reintervention was 92% among trileaflet valves, but only 33% among bileaflet valves ($P = 0.01$). Similar differences were reported for freedom from aortic valve reoperation ($P = 0.04$). Freedom from aortic valve replacement (AVR) was 100% in trileaflet valves and 57% in bileaflet valves. However, by echocardiogram, the authors were only able to retrospectively identify 14 of 28 bileaflet valves,

whereas 7 of 8 valves with trileaflet potential could be identified (88% sensitivity, 50% specificity). These results have yet to be confirmed, but closer examination of the anatomic subtypes of aortic valve stenosis may be justified before selecting the appropriate technique.

Currently there appears to be little if any role for surgical transventricular (closed) aortic valvotomy.

Catheter versus Surgical Relief of Aortic Stenosis in Infancy. A few studies have compared balloon aortic valvotomy to surgical valvotomy in older children. McCrindle and colleagues²⁰ reported their analysis of 630 balloon valvotomies on 606 patients from 23 institutions, with a median age of 6.8 years (range, 1 day to 18 years). The procedure was abandoned 4.1% of the time because of technical issues, and procedural mortality was 1.9%. A suboptimal result (including failure to complete procedure, residual gradient >60 mm Hg, left ventricle aortic pressure ≥ 1.6) or major morbidity or mortality were reported in 17% of patients. Independent risk factors for poor outcomes were age less than 3 months, earlier procedure date, higher preoperative gradient, unrepaired aortic coarctation, and the use of undersized balloons.

Other groups have reported similar results with balloon valvotomy in non-neonates. Moore and colleagues reported successful dilation in 87% of patients (129/148), with a very low procedural mortality (0.7%) and good long-term survival (95% at 8 years).¹⁸ Freedom from reintervention at 8 years was 50%, a figure that is consistent with other studies.²¹

In these patients, the risk of repeated intervention was related to the degree of regurgitation and to residual gradients after initial balloon valvotomy. Reminiscent of the report by Bhabra and colleagues,¹⁹ they reported differential results based on angiographic morphology of the stenotic aortic valve; however, as in neonates, it is difficult to demonstrate clearly the superiority of balloon or surgical aortic valvotomy. Chartrand and colleagues²² reported their experience with 67 children (age > 6 months) undergoing surgical valvotomy during 1960 to 1992. There was no operative mortality, and the 20-year freedom from death, reoperation, and AVR was 94%, 63%, and 73%, respectively. The authors concluded that surgical valvuloplasty is a safe and effective procedure with durable results.

In summary, as in neonates, aortic valve morphology appears to influence the response to intervention in infants, and further characterization may be justified. Currently there appear to be institutional preferences for balloon or surgical valvotomy that can be defended on the basis of experience.

Aortic Stenosis in the Older Child. In contrast to clinical presentation of the neonate with critical aortic stenosis, older children are commonly asymptomatic. For them, durable preservation of left ventricular function becomes the primary goal of treatment. The etiology of aortic stenosis in the older child (>1 year of age) is most commonly due to valvular aortic stenosis (79%), followed by subvalvular aortic stenosis (7%) and supra-aortic stenosis (6%) being much less common.⁶ Aortic regurgitation is often associated with congenital aortic stenosis and

may be the result of previous interventions for the relief of stenosis.

Older children with aortic stenosis generally enjoy normal growth and development. When present, symptoms such as chest pain, exercise intolerance, or syncope constitute clear surgical indications. For asymptomatic patients, the indications for intervention are subtler. For patients with severe stenosis in whom the left ventricle to aortic (LV-Ao) gradient is greater than 75 mm Hg, operation is recommended. For children thought to have moderate stenosis (40-75 mm Hg LV-Ao gradient), more information may be needed before a recommendation can be made. In this setting, electrocardiographic changes (ST-T wave changes consistent with left ventricular strain, left ventricular hypertrophy) or a positive stress test result would be indications for operation. For these asymptomatic patients, somatic growth, surgical options, and timing of intervention become important concerns.

Because of the progressive nature of the disease, older children thought to have mild aortic stenosis (gradient < 40 mm Hg) should be followed with periodic examinations and echocardiograms. It should be remembered that the gradient depends on the cardiac output and in a severely dysfunctional left ventricle the gradient may be unimpressive.

The management options for older children depend on the context of their disease. Older children newly diagnosed with important aortic stenosis with minimal insufficiency may be well served by balloon valvotomy. The more common scenario is several years of excellent palliation following an initial valvotomy, during which time the child grows and develops normally. However, with time or repeated interventions, or both, many patients will develop important aortic insufficiency (see Aortic Regurgitation section). Any residual valvular stenosis can be magnified by the resulting volume load, and the combinations of these lesions conspire to threaten left ventricular function. However, by virtue of their older age and larger size, these children are better candidates for durable surgical palliation, usually including valve replacement.

SUBVALVULAR AORTIC STENOSIS

Congenital subvalvular aortic stenosis is an obstruction below the aortic valve secondary to a discrete or short, localized fibrous or fibromuscular ridge or a longer diffuse fibromuscular tunnel (Fig. 123-3). It is important to note that there is a spectrum between discrete and tunnel-like subaortic stenosis, which has contributed the variable difference in the reported prevalence. In addition, it is often difficult to distinguish hypertrophic obstructive cardiomyopathy from tunnel-like subaortic stenosis (see [Hypertrophic Obstructive Cardiomyopathy](#)).

Subaortic Membrane

Subaortic membrane is found in association with other congenital lesions in 60% to 70% of cases, with ventral septal defect being the most common (35%).²³

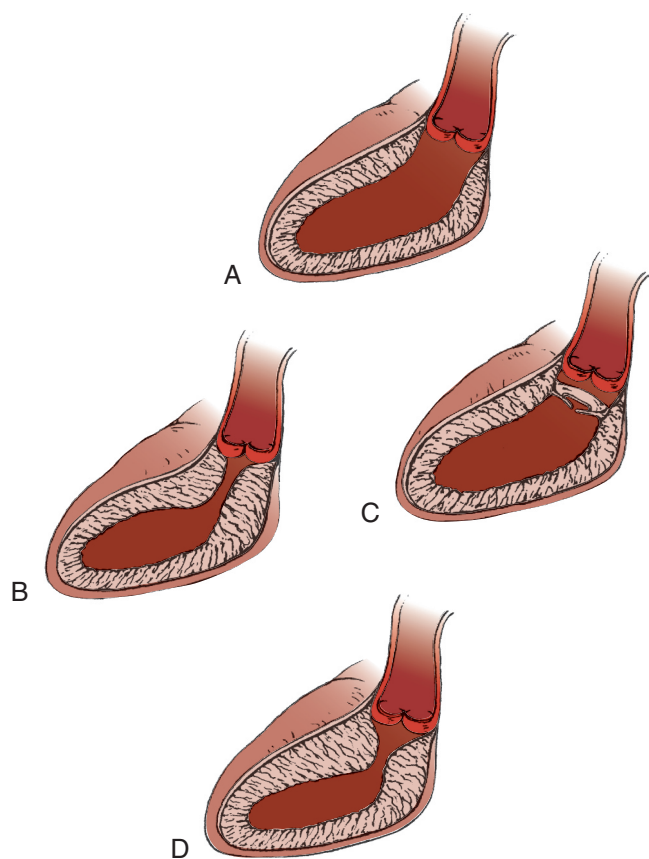


FIGURE 123-3 ■ Examples of forms of (A) fixed aortic stenosis, (B) discrete membrane, (C) tunnel-like stenosis, and (D) muscular obstruction.

Membranous subaortic stenosis results from the proliferation of fibrous tissue just beneath the leaflets of the aortic valve. This tissue may be very thin and tough, and is often circumferential, involving the underside of the anterior leaflet of the mitral valve. In fact, careful review of the echocardiogram may suggest a hinge point representing tethering on the leaflet by the membrane.^{24,25} Although the etiology of this form of aortic pathology is not known, studies have implicated shear stress, precipitated by abnormal angles between the ventricular septum and the aortic barrel, as playing an important role. The addition of a ventral septal defect adds to the generation of shear stress in this setting.²⁶

Natural History and Surgical Indications

In general, the surgical indications for membranous subaortic stenosis adhere to the general recommendations for aortic stenosis. However, citing a lower incidence of recurrence, some centers advocate earlier surgical resection for subaortic stenosis. Brauner and colleagues²⁷ reported that the recurrence rate of subaortic stenosis (predominately composed of membranous, but with a few tunnel-like stenoses) was related to a preoperative gradient of 40 mm Hg or greater and suggested that surgical resection at lower gradients was justified. Others have advocated repair at the time of diagnosis, irrespective of the gradient.^{28,29} However, the advantages

of early intervention have not been confirmed, as other investigators have reported no benefit of early surgery on recurrence.³⁰

Because the timing of surgery remains controversial, it is helpful to examine the natural history of membranous subaortic stenosis. There are data suggesting that some children with mild subaortic stenosis (peak systolic gradient < 40 mm Hg) might not require surgery for several years. A large representative study of the rate of progression of subvalvular aortic stenosis was reported by Rohlicek and colleagues³¹ studying children from several centers in Eastern Canada. To document the natural history and surgical outcomes, they followed 92 children from the time of diagnosis. There were slightly more males (1.6:1), and the mean age at diagnosis was 5.3 years. Thirteen patients had bicuspid aortic valves. At a mean follow-up of four years, 42 of these children ultimately came to surgery an average of 2.2 ± 0.4 years after diagnosis; 44 were followed medically and never came to operation. Children ultimately requiring surgery presented with higher initial gradients (40 ± 5 mm Hg vs. 21 ± 2 mm Hg) and were more likely to present with aortic insufficiency at diagnosis (35% vs. 13%). Analysis showed the echo gradient at diagnosis to be predictive of subsequent gradient progression as well as the appearance of aortic insufficiency. Eight children undergoing surgery required reoperation for recurrent subaortic stenosis at an average of 4.9 ± 0.9 years after initial resection. These patients initially presented with significantly higher gradients (66 ± 10 mm Hg).

In contrast to a more aggressive approach of aggressive surgical resection of membranous subaortic stenosis at time of diagnosis, these data suggest that a significant proportion of these patients will have stable or at least slowly progressive gradients. The management approach to patients remains variable, but it seems reasonable to pursue surgical resection for peak systolic gradients of 40 mm Hg or greater (obtained by echocardiography). The new onset of aortic insufficiency should be considered an important indication for surgery, regardless of the gradient. While these authors did not discern any improvement in aortic insufficiency following operation, it has been the experience of others that careful débridement of fibrous tissue encroaching on the aortic leaflets often results in significant improvement in aortic insufficiency.³²

Surgical Approach

The surgical approach to this lesion requires cardiopulmonary bypass. A single right atrial venous cannula is usually adequate. The aortic valve is exposed through a transverse aortotomy, which can be carried down into the noncoronary sinus if needed. Careful retraction of the aortic leaflets will reveal the subaortic membrane. The distance between the aortic valve and the membrane may vary slightly, but can usually be well visualized. The membrane is incised in the safe zone of the ventricular septum, just leftward of the nadir of the right coronary sinus. In many instances, the membrane can be peeled or endarterectomized from the endocardium anteriorly and rightward, and from the anterior leaflet of the mitral

valve posteriorly. In severe cases, this membrane may encroach upon and even involve the belly of the aortic valve leaflets. In this instance, the leaflets require careful débridement of the thick, fibrous tissue.

Surgical Results

Membranous subaortic stenosis has been the subject of intense scrutiny for its incidence and its propensity for recurrence after seemingly adequate surgical resection. The recurrence rate for membranous subaortic stenosis has been reported to be between 0% and 55%, with most reports documenting a recurrence rate of 15% to 21%.^{30,33-37}

Independent predictors of reoperation for recurrent subaortic stenosis include proximity of the membrane to the aortic valve (<6 mm), and a peak gradient greater than 60 mm Hg. Adherence of the membrane to the aortic or mitral valve identified at surgery was also a predictor for recurrence.³⁸ Septal myotomy, in addition to membrane resection, has been reported to reduce the incidence of recurrence. Lupinetti and colleagues³⁹ reported a recurrence rate of 4% when a septal myotomy was performed in addition to membrane resection; however, this finding has not been confirmed by others.^{27,40}

Other surgeons advocate an even more aggressive approach. Yacoub and colleagues³³ have suggested that an important pathologic feature of membranous subaortic stenosis is fibrous tissue ingrowth at the point of insertion of the anterior leaflet of the mitral valve into the left ventricular myocardium (Fig. 123-4). This ingrowth interferes with dynamic widening of the outflow tract, including posterior displacement of the mitral apparatus, during systole. Adding resection of the fibrous tissue from the mitral valve trigones to membrane resection and septal myotomy, Yacoub and colleagues³³ reported excellent relief of LVOT gradient (mean, 8 mm Hg) in 57 patients. Over an average follow-up of 15 years, seven patients had mild to moderate aortic regurgitation, but importantly, no patient required reoperation for recurrent stenosis.

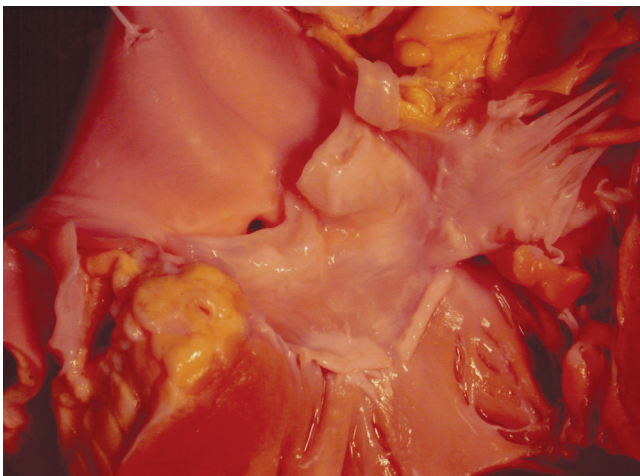


FIGURE 123-4 ■ Pathologic specimen showing fibrous tissue ingrowth at the insertion of the anterior leaflet of the mitral valve into the left ventricle.

While periodic attempts at balloon dilation in these patients have been performed, the resulting gradients are generally high (≈ 30 mm Hg), and subsequent surgery is required in a majority. Among 13 patients undergoing dilation, Moskowitz and colleagues⁴¹ reported that 9 required subsequent surgery. Suarez de Lezo and colleagues^{42,43} reported a 50% recurrence rate within 3 years. At this time, balloon dilation should not be considered a primary treatment of discrete subaortic stenosis.

Tunnel-Like Subaortic Stenosis

Long segment or tunnel-like stenosis has been defined as a muscular or fibromuscular subaortic stenosis, the length of which was more than one third the aortic diameter.⁴⁴ While tunnel-like stenosis may be associated with other lesions, such as interrupted aortic arch and atrioventricular septal defect, this discussion will confine itself to diffuse, long segment, or tunnel-like stenosis in the setting of concordant atrioventricular and ventriculoarterial connections with an intact ventricular septum. The indications for operation for subaortic tunnel are similar to those described for membranous subaortic obstruction.

Surgical Treatment Options

Modified Konno Operation

Surgical Indications. The indications for the modified Konno operation in the relief of subaortic obstruction are evolving. Roughneen and others described their experience with the modified Konno operation in 16 children.^{45,46} Indications for operation were recurrent subaortic stenosis (3), hypertrophic subaortic stenosis (3), tunnel stenosis of the LVOT (2), and subaortic stenosis following atrioventricular septal defect (2), or ventricular septal defect (VSD) (5). Long-term follow-up will be important for these patients, as it is likely a large number of these patients will have recurrent sub AS.

Surgical Approach. The degree of hypoplasia encountered in tunnel-like subaortic stenosis does not lend itself to transaortic resection, as might be performed for membranous subaortic stenosis. The surgical treatment of tunnel-like stenosis requires a more extensive procedure. In the presence of a suitable aortic valve, the modified Konno operation has become a favored option when approaching tunnel-like subaortic stenosis. It has the great appeal of enlarging the LVOT while preserving the native aortic valve. Excellent technical reviews of this technique are available.^{45,47,48}

Briefly, under moderate hypothermia with bicaval cannulation, an aortotomy is performed, and the aortic valve and subaortic area is examined. Only if the aortic valve is satisfactory should the valve-sparing modified Konno operation be performed. If the valve is inadequate, a more extensive procedure designed to enlarge the LVOT and replace the aortic valve will be necessary, such as the Konno-Rastan (discussed later) or Ross-Konno operation.

After inspection of the aortic valve, the infundibulum of the right ventricle is incised in a transverse fashion. Visualization of the ventricular septum from these two

perspectives (through the aortic valve and through the infundibulum) allows an accurate incision through the ventricular septum (Fig. 123-5). Indentation of the safe area of ventricular septum (leftward of the nadir of the right coronary leaflet) with a right-angled clamp placed through the aortic valve allows an accurate incision through the septum via the infundibulotomy. Alternatively, a stitch can be placed from the LVOT to the right ventricular outflow tract (RVOT) to pull up and help guide this incision. It is important that the trajectory of this incision be directed toward the apex of the left ventricle, which from the surgeon's perspective is almost directly leftward, and carried as distally as necessary to relieve the obstruction. Proximally the incision can be carried up to, and if necessary into, the commissure between the right and left aortic leaflets. Septal tissue can be débrided from the left ventricle side of the septum, but this should be on the leftward portion of the incision, to spare the left-sided conduction apparatus as it courses down the ventricular septum. The resulting VSD is then closed with a generous patch (Dacron or polytetrafluoroethylene) augmenting the LVOT. The aortic valve is carefully débrided of any fibrous tissue, and the incision is closed.

Surgical Results. The modified Konno operation is highly effective in reducing the LVOT gradient, and it can be achieved without damage to the conduction tissue.

In the series by Jahangiri and colleagues,⁴⁵ 15 of 46 patients with tunnel-like sub AS underwent a modified Konno procedure with excellent relief of LVOT obstruction and minimal incidence of aortic regurgitation and heart block.⁴⁵ Caldarone and colleagues⁴⁹ reported similar results among 18 patients. Although the technique is highly effective in relieving subaortic stenosis resulting from a variety of lesions, complications can occur. In general, operative mortality among published reports has been negligible. However, right bundle branch block has been commonly noted following the modified Konno operation. This is significant in the setting of preexisting left bundle branch blocks, as may exist following trans-aortic resection of subaortic stenosis, and complete heart block has been noted in up to 12.5% of cases. Although the aortic valve is at risk and residual VSDs can occur, these complications are uncommon with careful technique. Given these results, some surgeons have advocated this operation for recurrent membranous subaortic stenosis. While the modified Konno certainly alters the geometry of the LVOT, thought to contribute to the genesis of membrane, its effect on additional recurrences is unknown.

Konno-Rastan Aortoventriculoplasty

Surgical Approach. The Konno-Rastan operation, described independently by Konno and Rastan in 1975

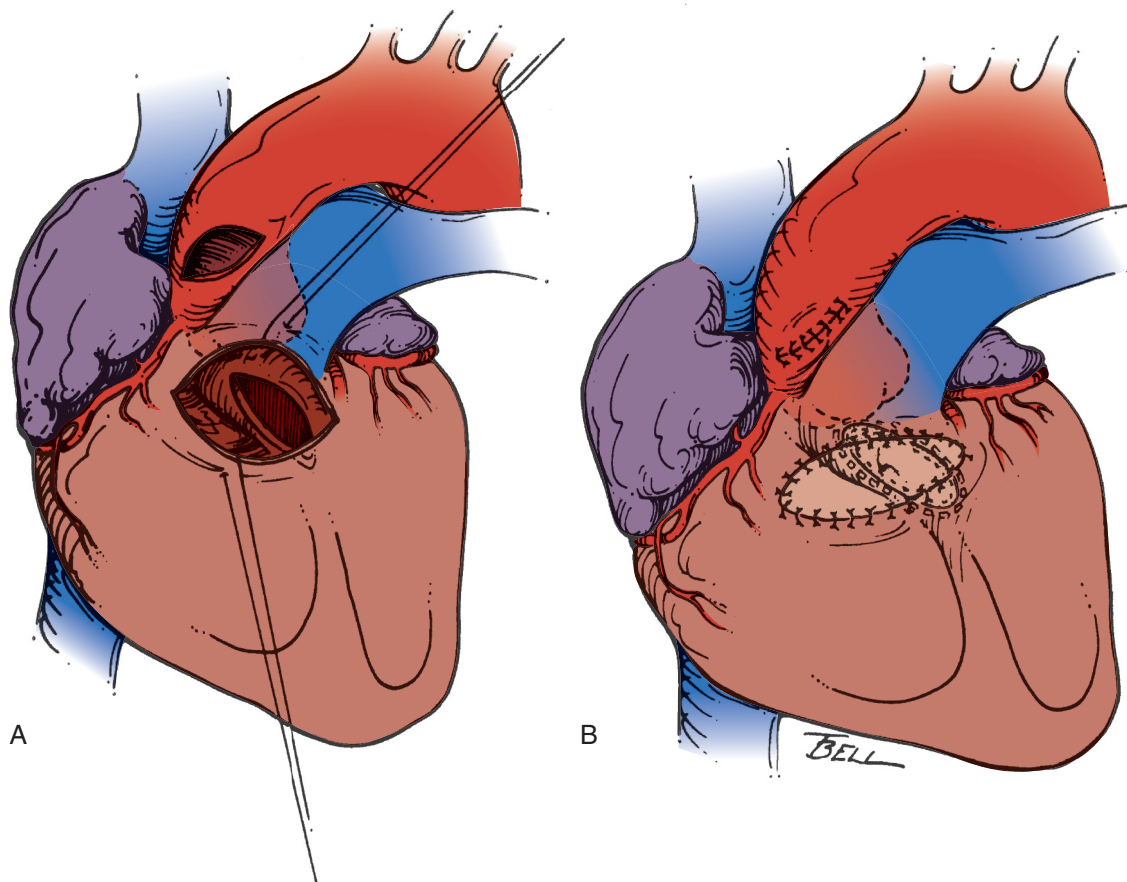


FIGURE 123-5 ■ Modified Konno operation. **A**, Transverse incision of the infundibulum showing the perspective of the ventricle septum through the aortic valve and the infundibulum. **B**, Superimposed patches of the ventricular septum and the infundibulum, respectively.

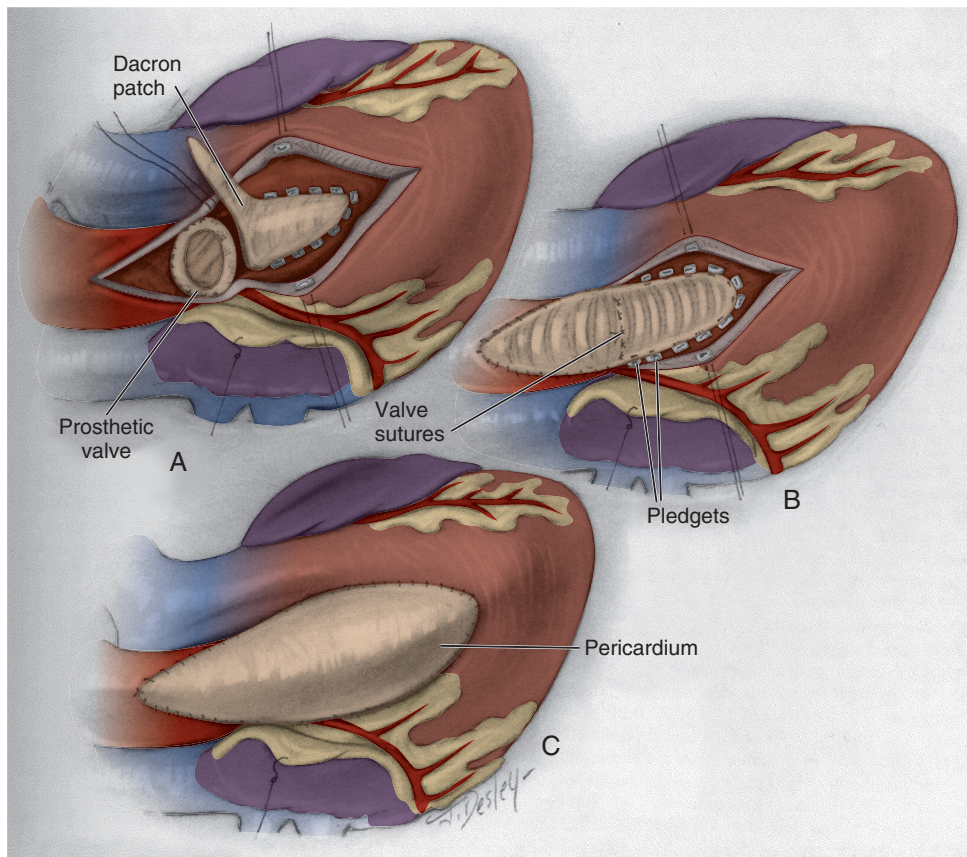


FIGURE 123-6 ■ Konno-Rastan aortoventriculoplasty. **A**, Atrioventriculoplasty with valve insertion. **B**, Closure of ventricular septal defect; aorta with Dacron patch. **C**, Closure of right ventricular outflow tract.

and 1976,^{50,51} is required when tunnel-like subaortic stenosis coexists with significant aortic valve pathology. Incision of the ventricular septum, as performed in the modified Konno operation through the aortic annulus, and the ascending aorta, provides effective relief of all levels of obstruction. This operation requires bicaval cannulation. A vertical aortotomy is made leftward of the right coronary artery. At this point, an incision in the infundibulum of the right ventricle is helpful in guiding the septal incision. The annulus of the aortic valve is incised leftward of the nadir of the right coronary leaflet, and extended into the interventricular septum, relieving the subaortic stenosis. The aortic annulus is débrided, and an appropriately sized mechanical (or biological) prosthesis is inserted and fixed into the posterior annulus. A patch of Dacron or polytetrafluoroethylene is fashioned such that it enlarges the LVOT, and it is sutured into place up to the aortic annulus enlarging the subaortic dimensions. Sutures are then passed through the valve sewing ring and patch, reestablishing annular continuity. The patch is then carried distally, enlarging and closing the ascending aorta (Fig. 123-6). The enlargement or width of the Dacron patch has to be considered carefully because the right coronary artery anatomy can be altered. Figure 123-7 is an example of a distorted right coronary artery following aortic root enlargement. If the aortic root is extremely hypoplastic, a Nicks-type incision in the contralateral sinus may allow a more uniform aortic root enlargement. The RVOT is repaired, allowing adequate

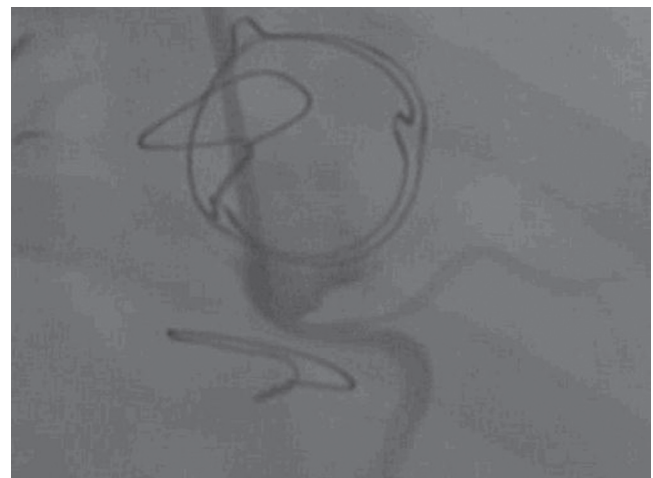


FIGURE 123-7 ■ Cardiac catheterization showing a distorted right coronary artery after Konno-Rastan aortoventriculoplasty.

clearance for the underlying augmented LVOT. Treated bovine pericardium works well for this application.

Surgical Results. The results of the Konno operation have improved since its introduction in 1975. Erez and colleagues⁵² reported their experience with the Konno operation in 60 pediatric patients between 1982 and 2000. Forty-two received mechanical valves, nine received homografts, six received xenografts, and fifteen received

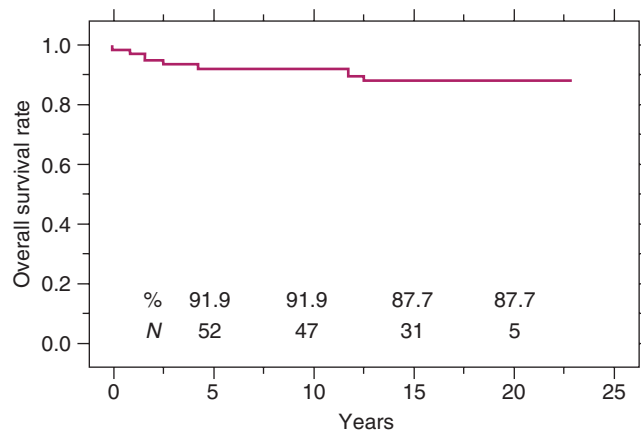


FIGURE 123-8 ■ Overall survival rate. The actuarial survival rates calculated with the Kaplan-Meier curves were 91.9% at 10 years and 87.7% at 15 years. (From Sakamoto T, Matsumura G, Kosaka Y, et al: Long-term results of Konno procedure for complex left ventricular outflow tract obstruction. *Eur J Cardiothorac Surg* 34:37–41, 2008.)

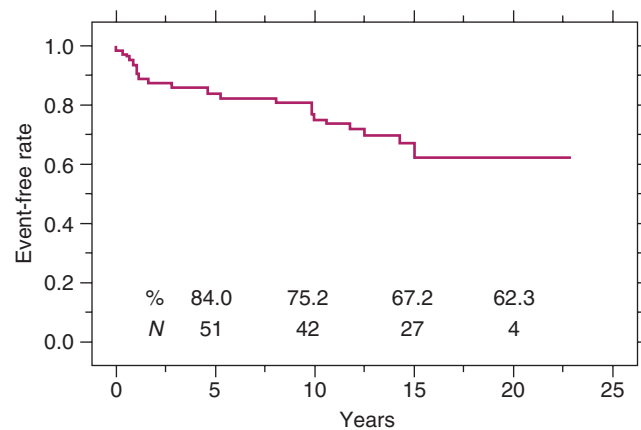


FIGURE 123-9 ■ Freedom from all events. Event-free rates including all mortality, reoperation, catheter intervention, and significant complications were 75.2% at 10 years and 67.2% at 15 years. (From Sakamoto T, Matsumura G, Kosaka Y, et al: Long-term results of Konno procedure for complex left ventricular outflow tract obstruction. *Eur J Cardiothorac Surg* 34:37–41, 2008.)

autografts. Operative mortality declined from 25% early in the experience to approximately 10%, which is comparable to other contemporary pediatric series.^{53–55} Similar recent results were reported in 63 patients by Sakamoto and colleagues⁵⁶ undergoing the Konno operation using a mechanical valve (Figs. 123-8 and 123-9). Although mortality has continued to decline, complications remain common. Sixteen percent of patients with a Konno operation or prosthetic valve required surgical reexploration for bleeding, whereas only 6.8% (1 of 15) of patients undergoing Ross-Konno operation required reoperation for bleeding. Heart block occurred in 8.8% of Konno or prosthetic valve operations and in 6.7% of Ross-Konno operations. Long-term survival for the Konno operation has been related to the underlying pathology and recurrent or residual LVOT obstruction that might require complex reoperations.

The freedom from reoperation following the Konno operation has not been satisfactory. Among patients

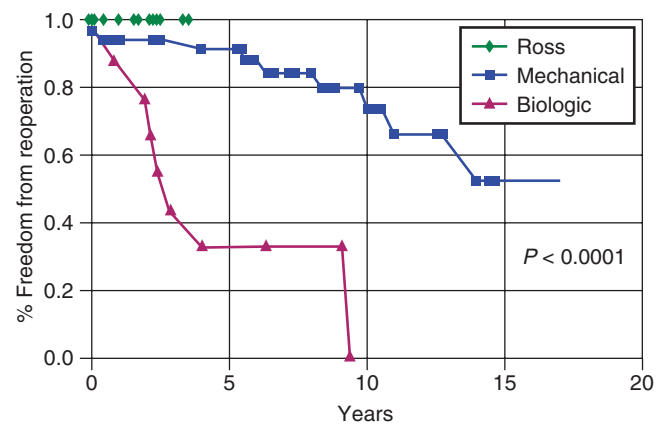


FIGURE 123-10 ■ Comparison of failure rate percentage of Ross, mechanical, and biological procedures and time to reoperation.

receiving biologic valves (homograft or xenografts), freedom from reoperation at 10 years was 0% (Fig. 123-10). Reoperation was primarily for valve failure. The patients with mechanical valves primarily required reoperation for valve outgrowth (6) and endocarditis (3).

Ross-Konno Operation. There is limited long-term follow-up on patients undergoing neonatal or infant Ross-Konno operation. Among the 15 patients undergoing the Ross-Konno operation between 1997 and 2000, there was one operative death (6.7%) and two late deaths in syndromic children. While the authors concluded that the Ross-Konno operation was less morbid, the durability of the autograft in the aortic position remains a concern, especially in the very young.⁴⁹ Ohye and colleagues⁵⁷ have reported their neonatal and infant experience in 10 patients with the Ross-Konno operation. At a median follow-up of 48 months, they reported no reoperations on the autograft, although two patients have developed significant autograft insufficiency, and there was no operative mortality. More recently, Brown and colleagues⁵⁸ reported their experience in 14 patients with a mean follow-up of 5.7 years and an actuarial survival at 10 years of 86%. Freedom from RVOT and autograft reoperation at 10 years was 77% and 92%, respectively. Oka and colleagues⁵⁹ reported their experience in patients undergoing Ross-Konno and associated mitral valve procedures. Patients undergoing concomitant mitral valve operation had significantly more morbidity and mortality; actuarial survival at 5 years was 44% versus 92%.⁵⁹ Despite concerns about the durability of the autograft, the Ross-Konno probably presents the best available option for relief of complex LVOT obstruction in small children (Fig. 123-11).

Aortoapical Conduit. The aortoapical conduit is largely of historic interest. Brown and colleagues reported their experience in 22 children with tunnel-like stenosis between 1978 and 1992.³⁴ They reported one early death and six late deaths, for an overall mortality of 32%. The ACC is associated with a high rate of reoperation and poor long-term durability.⁶⁰ This technique has largely been abandoned in favor of surgical alternatives, such as

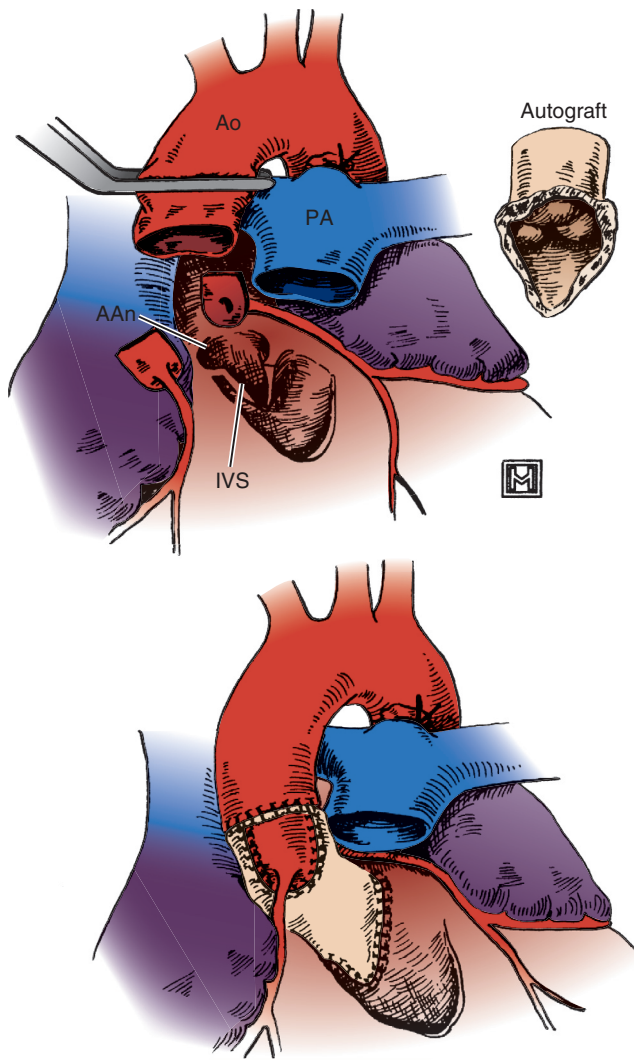


FIGURE 123-11 ■ Ross-Konno operation for complex left ventricular outflow tract obstruction in a small child. AAn, Aortic annulus; Ao, aorta; IVS, interventricular septum; PA, pulmonary artery.

the modified Konno, Konno-Rastan, and Ross-Konno procedures.

Hypertrophic Obstructive Cardiomyopathy

Hypertrophic obstructive cardiomyopathy (HOCM) is an autosomal dominant disease with limited information on children.⁶¹ Some of these patients develop a dynamic form of subaortic LVOT obstruction that results from myocardial hypertrophy prominently affecting the interventricular septum, but also can affect the mid-ventricle and LV apex. A variety of treatments, including calcium channel blockers, beta blockers, and dual-chamber pacing have met with mixed success.⁶²⁻⁶⁵

Surgical relief can be accomplished by transaortic septal myotomy designed to relieve the subaortic septal muscular obstruction. First described by Morrow and colleagues,⁶⁶ septal myotomy provides effective hemodynamic relief of the obstruction and can be expected to

provide both symptomatic relief and improvement in New York Heart Association class. Improvement in survival, however, has been more difficult to document. Despite an operative mortality of 1% to 2%, the subsequent annual mortality rate approaches 2%, comparable to that reported in patients treated nonsurgically.⁶⁷ Recently, the modified Konno operation has also been applied successfully to HOCM.

Surgical Indications

Surgical indications for this condition remain controversial.⁶⁸ In general, operation has been advocated for symptomatic patients (New York Heart Association class III-IV) with peak instantaneous gradients exceeding 50 mm Hg, or asymptomatic patients with gradients exceeding 100 mm Hg, despite medical management.^{69,70}

More recently, attenuation of the interventricular septum has been induced by the injection of absolute ethanol into the proximal septal coronary artery.⁷¹ This technique has been successful in lowering the outflow tract gradient by 60% to 80%, but 11% to 29% of these patients develop complete heart block.^{72,73} Although alcohol ablation holds promise, it represents a selective alternative to surgical therapy, and currently it has no place in the treatment of young children. Currently, septal myomectomy remains the gold standard for medically refractory symptomatic patients with high-grade LVOT obstruction.⁷⁴

Preoperative Assessment

In the preoperative assessment, it is important to establish the extent of the hypertrophy and the mechanism of any associated mitral regurgitation (MR). Most patients with HOCM have some MR, and it is generally related to systolic anterior motion (SAM) of the mitral valve. The typical posteriorly directed MR that occurs after the SAM of the mitral valve is generally alleviated with septal myectomy alone; however, if the MR precedes the SAM, the MR will likely persist after myectomy. Caution is warranted if placing a ring annuloplasty, because it increases the risk of SAM. In older patients, one must rule out coronary disease or any associated myocardial bridges.⁷⁵

Surgical Approach

Standard cardiopulmonary bypass with mild hypothermia is initiated. Because of the extreme hypertrophy, myocardial protection is critically important. Topical cooling and cold blood cardioplegia are used. Once the heart is arrested, vented, and cooled, an oblique hockey-stick incision is used to expose the aortic root. Looking into the subaortic area, the papillary muscles and chordae are obscured by the septum. An index finger in the LVOT and a thumb anterior to the RVOT confirms the septal thickness. The landmarks for the myectomy incisions are the area immediately below the middle of the right coronary cusp and the leftward muscle bar that extends to the mitral valve. The left bundle branch of the conduction system is under the commissure between the right and noncoronary cusp, and it extends leftward. After

resection, the Doppler gradient should remain less than 15 to 20 mm Hg. On occasion there will be inconsequential fistulous connections from the divided septal coronary arteries.^{76,77}

Surgical Results

Ommen and colleagues⁷⁸ reported a multi-institutional experience analyzing the effect of surgical myectomy on long-term survival in hypertrophic cardiomyopathy. Operative mortality was 0.8%, and 1-, 5-, and 10-year overall survival was 98%, 96%, and 83%, respectively. When comparing operated with nonoperated HOCM, operated myectomy patients experienced significantly improved survival ($P < 0.001$).⁷⁸ More recently, Swistel and colleagues⁷⁹ reported on 16 patients with complete follow-up at 2.5 years and no deaths, reoperations, or other adverse consequences. The mean preoperative, postoperative, and late LVOT gradients were 137 ± 45 , 10 ± 17 , and 6 ± 14 mm Hg.⁷⁹ Altarabsheh and colleagues⁸⁰ reported a large series of 127 children (12.9 ± 5.9 years) who underwent septal myectomy for HOCM. Preoperative mean gradient was 89 mm Hg and 95% had MR related to SAM. Mean follow-up was 8.3 years; there were no early deaths and four late deaths. Overall survival was 91%, 88%, 79%, and 73% at 1-, 5-, 10-, 15-, and 20 years, respectively. Six patients underwent repeated septal myectomy. The authors' data support improved late survival with myectomy compared with previous reports in patients with untreated HOCM.⁸⁰

Supravalvular Stenosis

Supravalvular aortic stenosis (SVAS) is the least common form of aortic stenosis, accounting for 6% to 7% of aortic outflow abnormalities. First described by Mencarelli in 1930,⁸¹ supravalvular aortic stenosis is the result of narrowing of the aorta beginning just above the aortic valve, usually at the level of the sinotubular junction. The gender incidence is more equitable than most forms of aortic stenosis with an approximately 1:1 male-to-female ratio. In 1961, Williams and colleagues⁸² described the common association of several other features, including characteristic facial features (elfin facies), mental retardation, and, infrequently, hypercalcemia.⁸² Soon afterwards, an association with Williams syndrome and peripheral pulmonary artery stenosis was identified.^{83,84}

In addition to its association with Williams syndrome, SVAS occurs in a familial form transmitted by autosomal dominant inheritance, and in a sporadic form. Microdeletion of chromosome 7q11.23 has been identified in patients suffering from all three forms of supravalvular stenosis.^{44,85} Affected individuals express only about 50% of the normal amount of tropoelastin, resulting in reduced elastin deposition and fiber disorganization within the arterial wall.

Clinical Presentation

Williams syndrome may be suggested on the basis of characteristic facies, and all patients with possible Williams syndrome should be evaluated for supravalvular aortic stenosis. Any asymptomatic patient with a familial

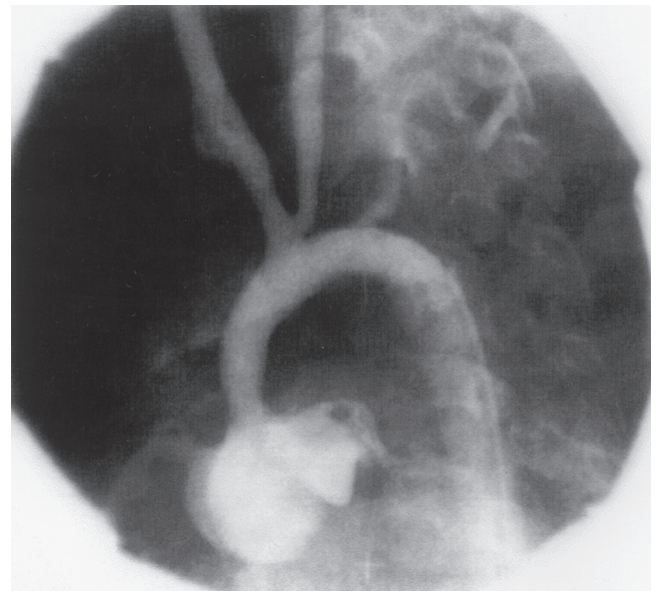


FIGURE 123-12 ■ Extent of supravalvular aortic stenosis determined by catheterization.

history should be evaluated, and the presence of a cardiac murmur or thrill should undergo echocardiography.

Other, nonaortic vascular lesions are commonly present and should be sought. These lesions include pulmonary artery stenosis (30%), renal artery stenosis (5%), and coarctation of the aorta (15%).⁸⁶ The degree of involvement in the aorta can vary from localized disease at the sinotubular junction with or without left main coronary ostial involvement, to diffuse involvement of the aortic arch and brachiocephalic vessels. Thus, patients with supravalvular aortic stenosis should undergo catheterization to fully delineate the extent of vascular involvement (Fig. 123-12).

Surgical Indications

Like the other forms of aortic obstruction, supravalvular aortic stenosis tends to be a progressive lesion. Indications for operation are generally consistent with those in other forms of aortic stenosis (symptoms, gradient >40 –50 mm Hg). Syncope or chest pain may represent cuspal adherence to the sinotubular junction and episodic coronary ischemia, and it is a clear indication for surgery.⁸⁷

Significant pulmonary artery stenosis is often present in patients requiring relief of supravalvular aortic stenosis. Surgery should not be delayed in these patients, as the natural history of associated pulmonary stenosis is generally indolent, with regression of these lesions over time. However, a few patients will have severe central or branch pulmonary artery stenosis, or both, and in the presence of markedly elevated right ventricular pressures, relief of the pulmonary artery stenosis should also be performed if the lesions are surgically accessible.

Surgical Approach

The surgical treatment of SVAS is determined by the extent of the stenosis. A variety of techniques have been used to relieve localized SVAS. In 1961 at the Mayo

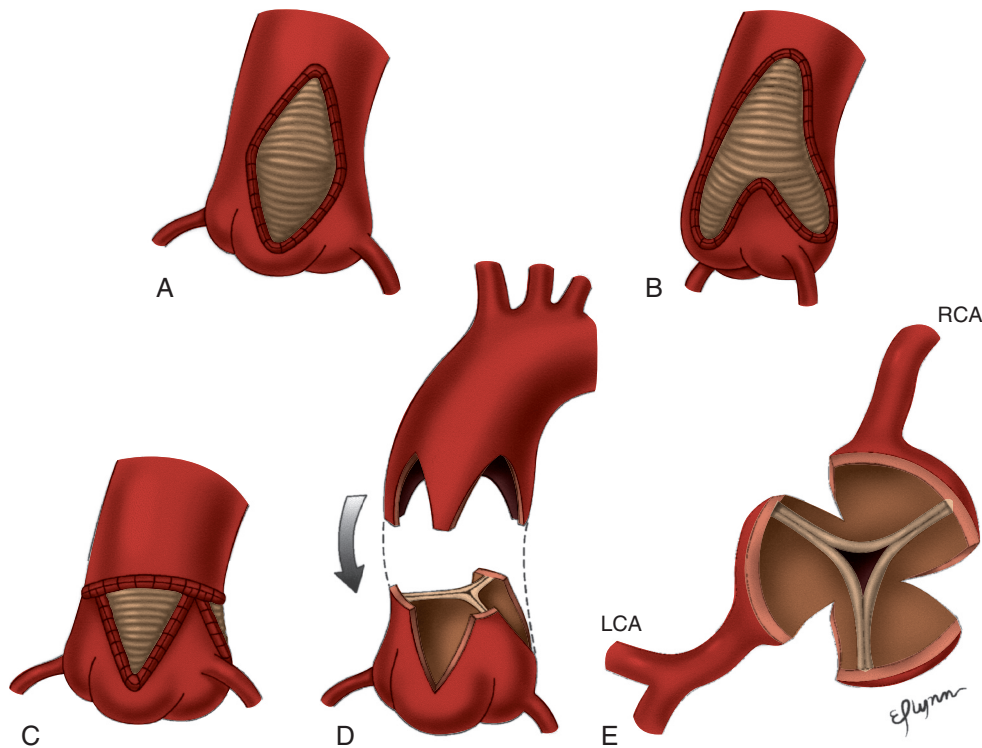


FIGURE 123-13 ■ Surgical treatment of supravulvar aortic stenosis. **A**, Single-patch technique into noncoronary sinus. **B**, Two-sinus augmentation technique (Doty). **C**, Three-patch (modified Brom). **D**, Autologous interdigitating technique. **E**, Cranial view of aortic sinus incisions. *LCA*, Left coronary artery; *RCA*, right coronary artery.

clinic, McGoon and colleagues⁸⁸ initially described a single-patch technique, with the placement of a teardrop or diamond-shaped patch across the sinotubular junction, extending between the bases of the noncoronary sinus into the ascending aorta. Doty and colleagues⁸⁹ extended the aortoplasty by fashioning a bifurcated, pantaloons shaped patch that straddled the commissure between the right-noncoronary leaflet, enlarging both the noncoronary and right coronary sinuses (Fig. 123-13). Concern about an untreated left coronary sinus, as well as the functional effect of an asymmetric augmentation on the aortic valve led Brom to propose a three-sinus repair.⁹⁰ A modification of this technique, proposed by Myers and colleagues⁹¹ accomplishes a three-sinus augmentation by placing counter incisions into the ascending aorta, enlarging the sinuses without prosthetic tissue.

Approximately 30% of patients will have diffuse stenosis involving the ascending aorta, sometimes with extension into the transverse arch.⁹² The diffuse form of supravulvar aortic stenosis has been shown to be an independent risk factor for death and reoperation.⁹³ When the lesion is limited to the ascending aorta, patch enlargement is usually possible using cardiopulmonary bypass. When the stenosis involves the transverse arch, deep hypothermic circulatory arrest is used to extend the patch across the entire transverse arch. Patients with lesions in the origins of the brachiocephalic vessels may require patch augmentation of these vessels as well.^{94,95}

Supravulvar aortic stenosis can also involve the coronary ostia, possibly in the form of restricted coronary inflow secondary to leaflet fusion along the narrowed and exaggerated sinotubular ridge, or less commonly because

of the encroachment on the ostial lumen by the disease. Although relief of the supravulvar stenosis treats the former, true ostial involvement may require specific attention. Modest encroachment on the coronary ostium by sinus tissue may be amenable to simple débridement, whereas severe cases may require patching of the ostium or bypass grafting.⁹⁶⁻⁹⁸

Surgical Results

There has been a gradual evolution from the single patch to the double patch, and ultimately to the three-sinus repair for the relief of discrete supravulvar aortic stenosis. In a review of 75 patients with supravulvar aortic stenosis, Stamm and colleagues⁹³ reviewed the effects of surgical technique on long-term outcomes. Comparison of the single versus multiple sinus augmentations (inverted bifurcated aortoplasty, $n = 35$; three sinus technique, $n = 6$) showed that patients undergoing single sinus augmentation had significantly higher mean gradients (20 vs. 10 mm Hg; $P = 0.008$) at a mean late follow-up of 12.8 years. Similar results have been reported by others.³⁴ Analysis has shown that single sinus augmentation is an independent risk factor for death and reoperation. These findings were independent from the year of operation (Fig. 123-14). The authors concluded that multiple sinus augmentation was superior to single sinus augmentation. It seems reasonable to expect that augmentation of all three sinuses, using techniques developed by Brom, Myers, and others may provide additional long-term advantages by allowing a more complete restoration of aortic root geometry.^{90,91}

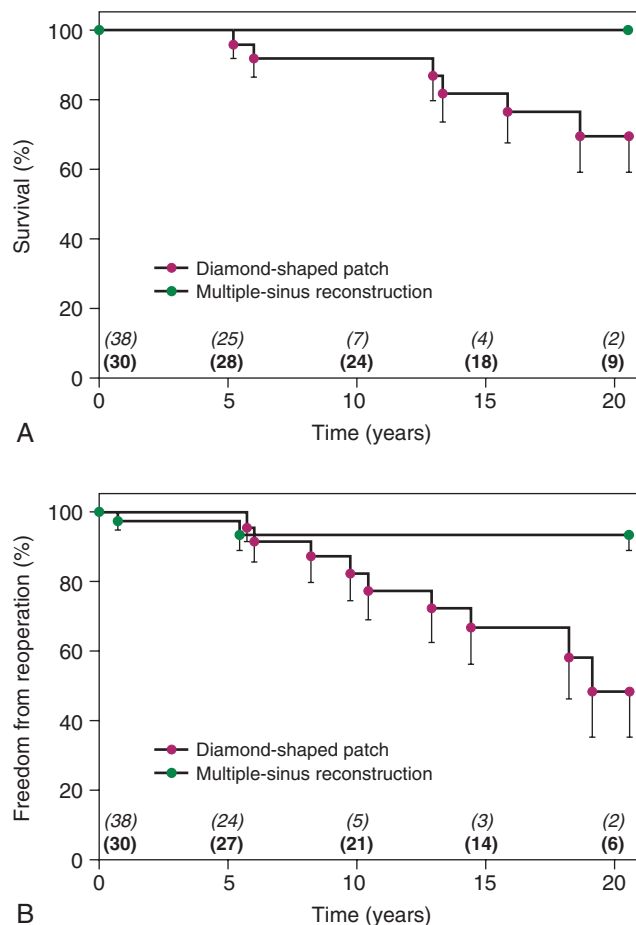


FIGURE 123-14 ■ **A**, Comparison of long-term survival in patients with single or multiple reconstructions. **B**, Freedom from reoperation percentage by type of operation and length of time to first reoperation.

The prognosis of diffuse supravulvar aortic stenosis appears to be worse than for the discrete variant, and it has been identified as an independent risk factor for reoperation and death (Fig. 123-15).

AORTIC REGURGITATION

Isolated congenital aortic regurgitation (AR) is a rare primary lesion, and it is usually secondary to another underlying congenital lesion.⁹⁹ Most commonly, AR is the consequence of efforts designed to relieve congenital aortic stenosis.¹⁰⁰

Primary Congenital Aortic Valve Regurgitation

Primary congenital AR is rare, but it most commonly occurs in patients with a congenitally bicuspid aortic valve.¹⁰¹ In this scenario, the anterior or right coronary leaflet is often deficient or incompletely fused to one of the adjacent leaflets. Over time, the progressive AR leads to increased thickening of the leaflet edges. Another rare but important association with primary AR is a quadricuspid aortic or truncal valve.¹⁰² Myers and

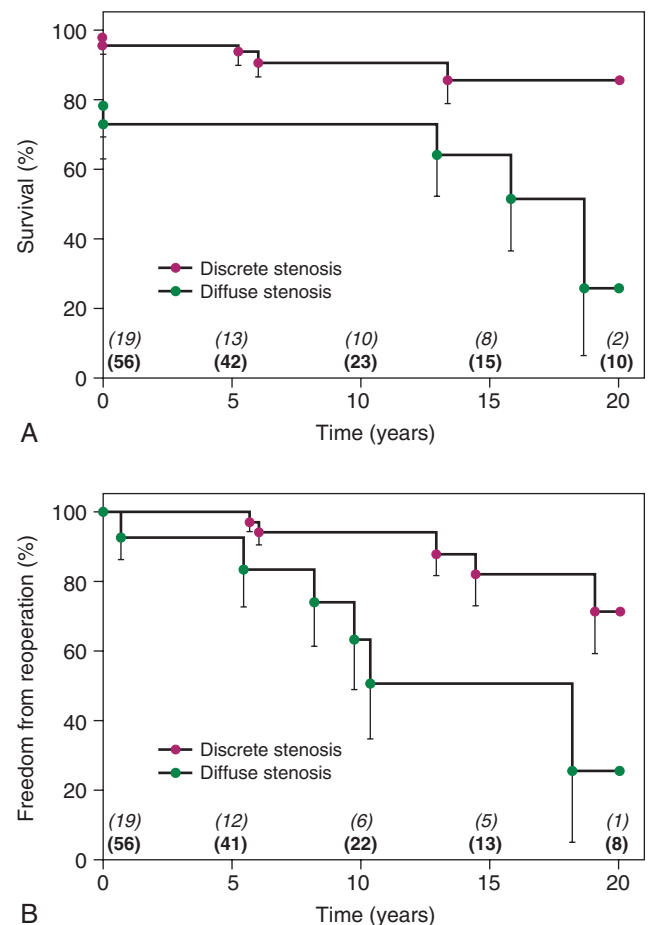


FIGURE 123-15 ■ **A**, Survival rate comparison of discrete and diffuse stenosis, in years. **B**, Freedom from reoperation of discrete and diffuse stenosis, in years.

colleagues¹⁰³ have reported on 36 patients who underwent valve repair for significant truncal valve regurgitation. A quadricuspid valve had worse freedom from reoperation and tricuspidization tended to improve freedom from reoperation. Neonatal repair and leaflet thinning were independent predictors of reoperation.¹⁰³

Aortic Regurgitation Associated with a Ventral Septal Defect

Aortic regurgitation can be associated with perimembranous or subarterial VSDs. It is less common that a perimembranous VSD has associated aortic regurgitation, because the defect is generally under the commissure between the right and noncoronary leaflets. In the case of subpulmonic VSD, right coronary leaflet prolapse is more common because it is not supported with a commissure.

In the setting of a perimembranous or subarterial VSD, associated aortic valve prolapse is an indication for surgery. Eroglu and colleagues¹⁰⁴ reported that 38% of these patients with prolapse developed aortic insufficiency within 1 year. Once present, the progression of aortic insufficiency was relatively rapid, with 31% of patients progressing from mild to moderate insufficiency

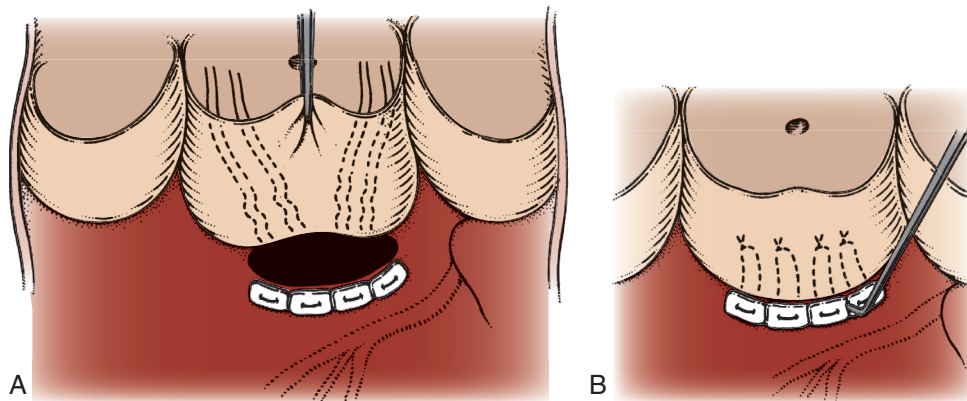


FIGURE 123-16 ■ Repair of the aortic valve including plication of the aortic sinus.

within 1.1 years. VSD closure in the setting of severe aortic insufficiency is less successful than with mild or moderate aortic insufficiency. Freedom from reoperation was 64% versus 77% at 10 years ($P < 0.05$).¹⁰⁵ Thus, repair of perimembranous or subarterial VSDs presenting with aortic valve prolapse is justified, even in the setting of hemodynamically small defects.

Simple VSD closure in the face of severe prolapse and aortic insufficiency may be inadequate. In these instances, repair of the aortic valve, including plication of the aortic sinus, may be effective (Fig. 123-16). Yacoub and colleagues¹⁰⁶ reported their results in 46 such patients, with an average follow-up of 8.4 years. Under these circumstances, VSD closure with aortic sinus plication is effective and durable.

Aortic Regurgitation following Balloon Dilation for Aortic Stenosis

Aortic regurgitation is most commonly associated with catheter-based balloon dilation in patients with congenital aortic stenosis. The most common lesion is tearing of the anterior leaflet at the anterior commissure (or raphe) in a patient with a bicuspid aortic valve. Bacha and colleagues¹⁰⁷ reported the Boston Children's Hospital experience in which 20 of 21 patients had right coronary cusp involvement.

Efforts to relieve aortic stenosis early in life come at the expense of introducing AR. These patients may present acutely with severe AR or years later with ventricular dysfunction in the setting of mixed aortic valve pathology. Determining the appropriate timing for operation in these often-asymptomatic patients can be difficult, and it should be noted that there might be different guidelines depending on the surgical approach. For example, expertise in aortic valve repair may persuade one toward earlier surgical intervention at a younger age.

Cheung and colleagues¹⁰⁸ have addressed the timing of operation for AR in children. They studied a group of 21 asymptomatic young patients (median age, 13 years) with AR undergoing the Ross operation. Eighteen of these patients had previously undergone aortic valvotomy (surgical or balloon) for aortic stenosis. In their

experience, the z-score of the preoperative left ventricular end-diastolic dimension was the most sensitive predictor of postoperative left ventricular performance. Postoperative left ventricular performance was significantly impaired in patients with a preoperative z-score of 4 or greater, and the authors recommended AVR in asymptomatic patients when the left ventricular end-diastolic z-score exceeded 3.¹⁰⁸ Accepted guidelines for aortic valve intervention in the adolescent and young adult include the appearance of symptoms, asymptomatic left ventricular systolic dysfunction, or asymptomatic progressive left ventricular enlargement with z-scores greater than 4.¹⁰⁹

Aortic Regurgitation Associated with a Dilated Aortic Root

Aortic root dilation can be seen in connective tissue disorders such as Marfan and Ehlers-Danlos syndromes, conotruncal abnormalities including tetralogy of Fallot and pulmonary atresia, and in patients having undergone a Damus-Kaye-Stansel procedure with a neo-aortic valve. The regurgitation in these patients often begins central as the commissural posts at the sinotubular junction dilate with resultant leaflet stretching and prolapse.

Marfan syndrome is a systemic collagen vascular disorder that can affect the aortic valve early in life. Van Karnebeck and colleagues reported the natural history of Marfan syndrome in 52 pediatric patients (25 male) with a mean age at presentation of 7.9 years (range, 1-16 years) with median follow-up of 7.7 years (range, 2-15 years).¹¹⁰ Sixty-three percent represented familial cases, and 33% were sporadic. Aortic dilation was present in 80% of patients, and aortic regurgitation developed in 13 (25%); 10 of 13 (77%) patients required aortic operation. The authors concluded that childhood and adolescence are crucial periods in the development of the cardiovascular manifestations associated with Marfan syndrome. When the syndrome is diagnosed in the newborn period, cardiac mortality is high (33% 1-year mortality) and is reported to result from multivalve disease.^{111,112}

With the potential for aortic dissection in older patients with Marfan syndrome, attempts have been made to identify patients that would benefit from pre-emptive surgery. Leggett and others reported that an

aortic ratio (normalized for age and body surface area) of 1.3 or greater, or a rate of progression exceeding 5% per year, indicates patients at increased risk for aortic root complications.¹¹³ Cameron and colleagues¹¹⁴ have suggested that indications for aortic root replacement in children with Marfan syndrome include aneurysm diameter measuring 5 cm or greater, aneurysm diameter increasing more than 1 cm/yr, and progressive aortic valve insufficiency.¹¹⁴ Indications for surgery in young children (<12 years) include a “giant” aneurysm that meets adult criteria for intervention, and rapid interval enlargement with progressive valvar insufficiency.¹¹⁵ Using these criteria, this group reported their experience with valve-sparing aortic root replacement in 51 patients (34 with Marfan syndrome) with aortic root aneurysm and competent aortic valves. There were no deaths, and valve function remained stable during follow-up.¹¹⁶

Myers and colleagues¹¹⁷ recently reported the Boston Children’s Hospital experience of a combined valve-sparing and valve reconstruction approach over a 12-year period. Thirty-four patients were included with seven having documented connective tissue disorders, with a mean age of 15.4 ± 8.7 years. The surgery consisted of reimplantation technique in 13 patients and remodeling in 21 patients. Valve repair consisted of leaflet procedures in 25 patients and subannular reduction in 15 patients. During a mean follow-up of 14.4 ± 2.8 months, there were five reoperations for AVR because of aortic regurgitation, and two patients exhibited moderate regurgitation. Freedom from structural valve deterioration (SVD) was $75.9\% \pm 9.4\%$ at 6 months, $70.1\% \pm 10.3\%$ at 1 year, and remained stable thereafter, although it was significantly worse in the reimplantation group ($P = 0.028$). A more severe degree of aortic regurgitation ($P = 0.001$) and smaller graft-to-aortic annulus ratio ($P = 0.003$) were the only predictors of SVD.

AORTIC VALVE RECONSTRUCTIVE TECHNIQUES

Aortic valve reconstruction is particularly attractive for children with limited valve replacement options. The effectiveness of reconstructive techniques for aortic insufficiency has been variable, and it is related to the etiology of the underlying aortic valve disease. In some specific instances, such as in association with a VSD, repair can be successful and durable as noted previously. However, there are other situations in which there is complex aortic valve disease, and results have been variable.

Aortic Valve Leaflet Prolapse

There have been several techniques described for aortic valve leaflet prolapse. In addition to the original leaflet resuspension techniques described by Trussler,^{117a} Cosgrove and colleagues¹¹⁸ described a central triangular shaped wedge resection of the prolapsed leaflet, and Boodhwani and colleagues¹¹⁹ recently reported on plication of the free edge of the prolapsing leaflet.

When there is associated leaflet prolapse with a VSD, the Yacoub technique is often used. The defect can be

approached through an aortotomy, and then interrupted nonabsorbable sutures are supported with pledgets and inserted through the rightward crest of the septum, through the annulus of the aortic valve, through the redundant portion of right coronary sinus of Valsalva to achieve plication, and then through the media of the aorta.¹⁰⁶

Aortic Valve Leaflet Extensions

When aortic insufficiency results from lack of central leaflet coaptation, reparative techniques often use some variant of leaflet extension. Fixed pericardium, either bovine or autologous, has been used to extend the diseased leaflets, thereby increasing the area of coaptation. Myers and colleagues¹⁰³ compared untreated autologous, glutaraldehyde-treated bovine and PhotoFix-bovine pericardium in 78 children with rheumatic aortic valve disease. During a median follow-up of 10.7 years, 15 patients required reoperation, and fresh autologous and PhotoFix pericardium trended toward better durability than glutaraldehyde-fixed bovine pericardium did.¹⁰³

The results of aortic valve repair using leaflet extensions has been used increasingly and reported by a number of centers with acceptable early results in patients with primary congenital aortic valve disease and rheumatic disease. Polimenakos and colleagues¹²⁰ recently reported a large experience with 142 pediatric patients with primary congenital aortic valve disease undergoing pericardial aortic cusp extension valvuloplasty with a median follow-up of 14.4 years. Sixty-four patients underwent aortic valve reintervention and freedom from reoperative aortic cusp extension valvuloplasty or AVR at 18 years was $82.1\% \pm 4.2\%$ and $60\% \pm 7.2\%$, respectively. A review by Bacha and colleagues¹⁰⁷ reported on 81 pediatric patients undergoing surgical aortic valvuloplasty, including 65 undergoing aortic leaflet augmentation with pericardium. While freedom from aortic valve reintervention was only 63% at 5 years, this technique can be valuable when valve replacement options are considered unsuitable.

Others have reported results in patients primarily with rheumatic aortic valve disease. Duran and Gometza¹²¹ reported their experience with leaflet extension in 72 patients. Over a limited follow-up (≤ 5 years) there were two late deaths (2.8%) and four (5.5%) reoperations between 4 and 38 months postoperatively. Similar results have been reported by Grinda and colleagues.¹²² Among 89 patients (mean age, 16 years) undergoing leaflet extension, the 5-year survival and freedom from reoperation was 96% and 92%, respectively.

AORTIC VALVE REPLACEMENT

Aortic valve substitutes include biologic, bioprosthetic, and mechanical valves. The available options for biologic valve replacement include xenografts, homografts, and autografts. The choice of valve substitute in the pediatric population must balance several competing factors including durability, size, growth potential, and the need for anticoagulation.

Aortic Valve Replacement with Bioprosthetic Aortic Valves

Bioprosthetic valves have been used for several decades in adult patients. Experience has been accumulating in pediatric patients, but currently there are limited reports. There are several contributing factors that are clearly important to the limited longevity of bioprosthetic valves in younger patients, including patient-prosthesis mismatch (PPM) and the propensity to calcify. Flameng and colleagues¹²³ reported that PPM predicts structural valve degeneration in bioprosthetic heart valves. Additional confounding valve related factors were also found to be important, such as valve design (stented or stentless), tissue type (porcine aortic valve or bovine pericardium), and anticalcification treatments to mitigate calcification. In a large follow-up study including 648 adult patients, the absence of antimicrobial treatment and PPM were independent predictors of SVD. Freedom from SVD at 10 years was significantly worse in patients receiving a nontreated ($70\% \pm 4.3\%$) versus treated ($90\% \pm 3.6\%$) valve ($P < 0.0001$), and in patients with PPM and nontreated valves ($59.8\% \pm 7.0\%$) versus those with PPM and treated valves ($88.7 \pm 3.6\%$; $P < 0.0001$).¹²⁴ Based on this series and others, longer-term outcomes on bioprosthetic heart valves in children are needed.

Aortic Valve Replacement: Comparing Mechanical and Biologic Valves

The surgeon is faced with several options for AVR in the pediatric patient. Each option presents a unique profile of advantages, disadvantages, and performance characteristics that will be reviewed.

A major decision point in valve selection for pediatric AVR is between mechanical versus biologic (xenograft, homograft, and autograft). The early mortality of mechanical AVR is 0% to 13%, and the late mortality is 0% to 11%. The incidence of reoperation on these valves

is 6% to 16%.¹²⁵⁻¹²⁷ Patients receiving xenografts appear to have a lower mortality (early and late mortality, 0%), but a higher risk of reoperation, as approximately 50% will require repeat AVR within 6 years. In general, homografts and autografts have superior resistance to postoperative endocarditis compared with mechanical valves. Mechanical valves demonstrated a higher risk of prosthesis endocarditis in the early postoperative period that declines within 1 year, approximating the low level hazard of biologic valves.¹²⁸ The risk of endocarditis in the autograft and homograft appear comparable, and they are preferred over other prostheses in the setting of active endocarditis.

Because of their tendency to degenerate, xenograft valves have generally been avoided among pediatric patients. Turrentine and colleagues¹²⁹ compared the results of mechanical versus biological valves (autograft, homograft, and xenograft) in the aortic position. They reported a lower incidence of valve-related complications in the autograft group as compared with all other valve options. The homograft and xenograft performed particularly poorly in terms of freedom from reoperation, with 70% (7/10) xenografts and 50% (1/2) homografts requiring replacement for deterioration within 9 years (Fig. 123-17). While efforts to develop xenografts suitable for the pediatric population continues, follow-up remains short.¹³⁰ Thus, in the absence of compelling indications for their use, homografts and xenografts in the aortic position in children should probably be avoided.

Comparisons between the autograft (Ross operation) and mechanical AVR have also been reported. Following the Ross operation, Elkins has reported an 89% freedom from reoperation or death at 6 years, as compared with only 49% among children receiving a mechanical AVR.¹³¹ However, these populations were from different time periods, with the mechanical AVR being performed before 1986. A more contemporary study reported by Alexiou and colleagues¹³² reported results more consistent with those obtained with the Ross operation. They performed mechanical AVR on 56 children between 1972

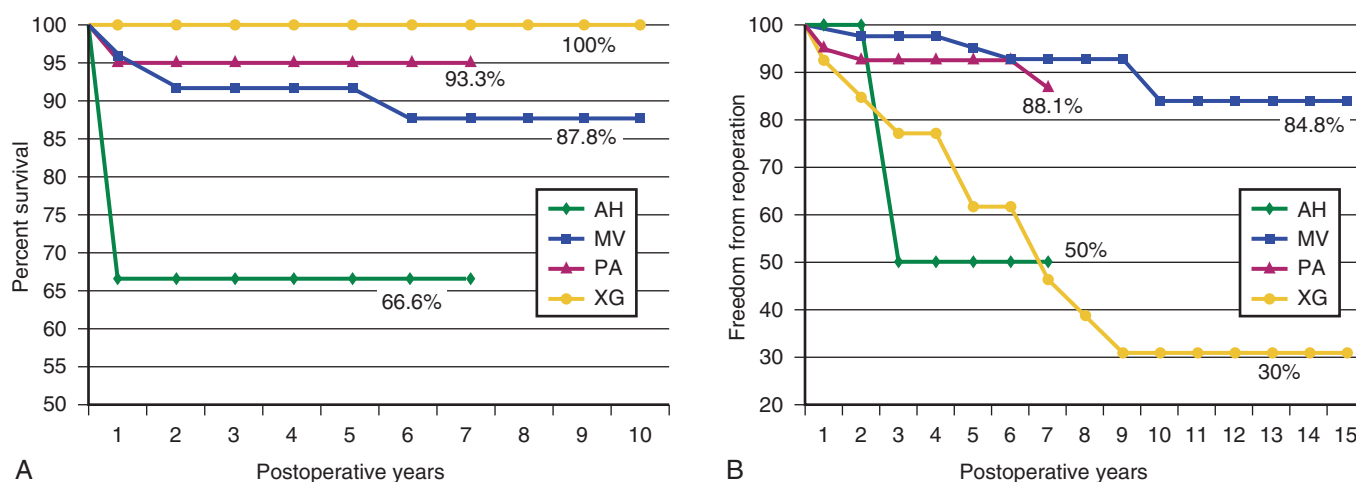


FIGURE 123-17 ■ Survival (A) and freedom from reoperation (B) rates comparing mechanical and biological valve replacements in postoperative years. AH, Aortic homograft; MV, mechanical valves; PA, pulmonary autograft; XG, xenograft tissue valves.

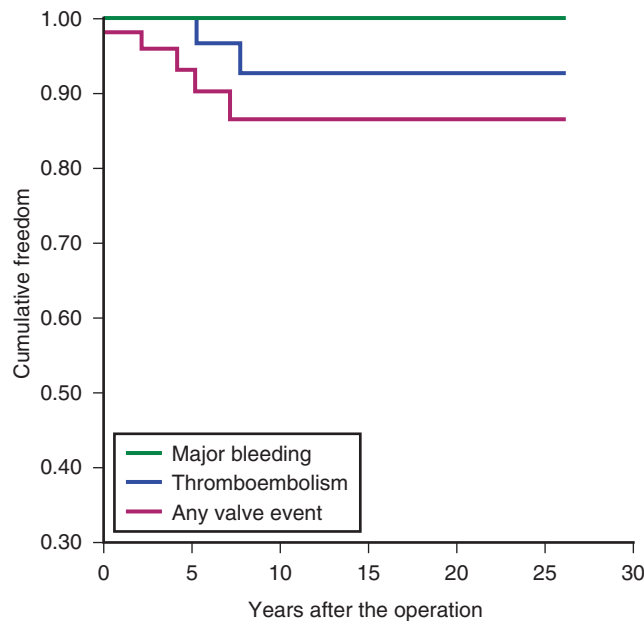


FIGURE 123-18 ■ Freedom from late events in mechanical aortic valve replacements.

and 1999. Freedom from late events, including thrombosis, hemorrhage, and reoperation, was approximately 90% at 6 years (Fig. 123-18). This group presented excellent results with pediatric AVR, but it should be noted that the majority of these patients were older than 10 years, and 50% underwent aortic root enlargement at the time of valve insertion. There were two major (valve thrombosis, stroke) and four minor (nose bleeds) complications related to anticoagulation. Interestingly, a recent review of 45 pediatric patients receiving bileaflet mechanical aortic valves reported a 6% incidence of repeat valve replacement at 10 years, similar to that reported in many Ross operation series.¹³³

The indications for valve replacement can also affect outcomes. Lubiszewska and colleagues¹³⁴ found mechanical valves in the aortic position to be satisfactory substitutes, especially for aortic insufficiency. These children often have a normal or enlarged aortic annulus, and adult sized valves are readily accepted.

In a review of 51 patients undergoing AVR (25 mechanical, 19 autografts, 6 homografts), Lupinetti and colleagues¹³⁵ reported a significantly higher incidence of late complications in those receiving a mechanical valve. The most common long-term complication reported in this group was the development of subaortic stenosis because of pannus ingrowth. Others have also reported significant numbers of anticoagulation related complications. Cabalka and colleagues¹³⁶ reported six serious complications among 36 patients undergoing isolated AVR between 1982 and 1994, with all occurring in the setting of supratherapeutic prothrombin times. Freedom from anticoagulation-related bleeding for isolated AVR was approximately 80% at 4 years.

We recently reviewed our experience at Boston Children's Hospital from 2004 to 2013, during which time 38 patients underwent AVR with the On-X prosthetic valve (On-X Life Technologies, Inc., Austin, TX). During a

median follow-up of 4.3 years, there was no evidence of structural valve failure or deterioration, no patients had greater than mild prosthetic valve regurgitation, and one patient had moderate stenosis. No patients had evidence of valve thrombosis, embolism, or other bleeding complications. Survival was $98\% \pm 1.9\%$ at 1 year and $91.3\% \pm 5\%$ at 5 and 8 years, and it was significantly better in patients with isolated AVR ($P < 0.001$).

Aortic Valve Replacement: Comparing Autografts and Homografts

Homografts share some of the advantages provided by the autograft, but they also present serious disadvantages. Besides a lack of growth potential, early degeneration requiring replacement has been documented, especially among young patients, and some authors have reported inferior hemodynamics as compared with autograft.^{137,138} This has led some investigators to compare outcomes of the Ross procedure with its most comparable alternative, the homograft.

In the earliest and largest series comparing the autograft to homografts in young patients, Gerosa and colleagues¹³⁹ compared the results of 103 young patients receiving a homograft in the aortic position to 43 receiving an autograft. The 15-year freedom from reoperation was $54\% \pm 8\%$ versus $68\% \pm 11\%$, freedom from endocarditis was $97\% \pm 2\%$ versus $75\% \pm 10\%$, and freedom from any complication was $41\% \pm 7\%$ versus $50\% \pm 10\%$. Primary tissue failure was identified in 19 homografts, but in none of the autografts.

Aklog and colleagues¹⁴⁰ examined the performance of these two options in a prospective randomized trial. A total of 182 patients were randomized, with a mean age of 37 years (range, 2-64 years). Ninety-seven patients received a pulmonary autograft, and 85 patients received a homograft. Thirty-day mortality was 1% for autografts and 4% for homografts, and actuarial survival was 97.8% and 95.3% at 48 months, respectively. There were no autograft-related reoperations. Freedom from reoperation was slightly higher in the autograft group (94.2% vs. 87.7%; $P = \text{NS}$). Regarding the pediatric age group, they reported that 2 of 6 (33%) children required reoperation on the homograft, compared with 0 of 10 in the autograft group. Furthermore, there was echocardiographic evidence of progressive, subclinical deterioration in the homograft group that was absent in the autograft group. The authors concluded that the autograft appeared to be superior in the pediatric population, and they suggested that longer follow-up will reveal a continued durability advantage.

Lupinetti and colleagues¹⁴¹ examined the comparative effects of autografts and homografts on left ventricular remodeling in the pediatric population. While the authors reported that initial LVOT gradients and left ventricular wall thickness (surrogates for hemodynamic efficiency) were comparable among 78 children undergoing the Ross operation and 25 receiving a homograft, a divergence was noted over time. Whereas peak LVOT velocities decreased over time after the Ross operation, they increased significantly over a similar time period in the homograft group. The decrease in left ventricular wall

thickness seen in those undergoing the Ross operation was absent in the homograft group. This effect may be most important in young patients in whom significant somatic growth can be expected.

Thus, while the homograft may provide acceptable palliation among older patients, its lack of durability appears to be a serious disadvantage, especially among younger children. Under these circumstances, its use should probably be relegated to an option for children deemed unsuitable for the autograft or a mechanical valve.

Aortic Valve Replacement with the Pulmonary Autograft (Ross Operation)

The transplantation of the pulmonary valve to the aortic position, introduced by Donald Ross in 1967, has several potential advantages over other valve replacement options in pediatric patients.¹⁴² Most notably among children, the growth potential of the autograft is a unique feature, especially in the infant population in which small caliber homografts are the only alternative. In addition, superior hemodynamics are obtainable, and there is no need for systemic anticoagulation.

The autograft may be inserted into the aortic position using a variety of techniques, including the subcoronary technique, the root inclusion technique, or the root replacement technique. Excellent reviews of each technique are available.^{143,144} The autograft root replacement is usually performed with bicaval cannulation. The aortic valve is inspected and if irreparable, the pulmonary artery is opened at the bifurcation. The pulmonary valve is inspected, and valves with important anatomic abnormalities (bicuspid valve, significant leaflet fenestrations) are not suitable for use in the aortic position, and an alternative valve replacement is chosen. Small leaflet fenestrations, particularly near the valve commissures, are probably acceptable.

The autograft is excised with a rim of infundibular muscle. Posteriorly, care must be taken to avoid the first septal perforator, because significant ventricular dysfunction may accompany its injury. After débridement of the aortic annulus, the autograft is oriented anatomically and sutured into the aortic position. The coronary arteries are inserted into the appropriate sinus, and the distal anastomosis between the autograft and the ascending aorta is performed. The RVOT is reconstructed with the aid of a cryopreserved homograft. Although some groups have advocated direct approximation of the pulmonary arteries to the right ventricle (similar to the REV technique), oversized homografts provide excellent durability and are probably a superior option.¹⁴⁵ Disadvantages of the Ross operation include increased technical complexity, homograft reconstruction of the RVOT, and potential autograft failure.

Elkins has reported his midterm and late results with the Ross operation between 1986 and 2001.¹⁴⁶ Operative mortality was 4.5%, with a 12-year actuarial survival of $92\% \pm 3\%$. Actuarial freedom from autograft replacement and from RV homograft replacement was $93\% \pm 3\%$ and $90\% \pm 4\%$ at 12 years, respectively. Most contemporary series place the operative mortality between

0% and 4%.¹⁴⁷⁻¹⁵⁰ Because of the low mortality and effectiveness of the Ross operation, it has become the procedure of choice at some institutions.

In a recent large series reported by Pessotto and colleagues,¹⁴⁸ 67 children underwent the Ross operation. Two neonates (2/67, 3%) undergoing a Ross-Konno procedure after a failed attempt at balloon dilation for critical aortic stenosis died of multisystem organ failure. Two patients (2/67, 3%) have required reoperation for progressive autograft insufficiency; in one patient, annular reduction was successful in salvaging the autograft.

The question of durability is a concern that continues to be examined. The longest follow-up to date has been reported by Chambers and Ross,¹⁵¹ who described the experience of the 131 hospital survivors undergoing the Ross operation between 1967 and 1984. Of the survivors, they reported that the freedom from autograft replacement was 88% at 10 years and 75% at 20 years. Interestingly, this was similar to freedom from reoperation on the RVOT (89% and 80%). Of the 30 autografts explanted, only three showed histologic signs of focal degenerative changes. All others showed evidence of transmural cellular viability.

In a recent pediatric series, conflicting information has been emerging. While Brown and colleagues¹⁵² have reported a low incidence of autograft failure requiring replacement at 10 years (4%), others have reported autograft failure rates as high as 31% at 13 years.¹⁵³ While the long-term fate and patient selection criteria remain an area of investigation, the Ross operation remains an important option for the pediatric patient with severe aortic valve disease.

Contraindications to the Pulmonary Autograft (Ross Operation)

The Ross operation requires careful patient selection. Systemic collagen vascular disorders and anatomic abnormalities of the pulmonary valve constitute a clear contraindication to the Ross operation. Others have also suggested that the Ross operation should be avoided in the setting of systemic inflammatory conditions, such as rheumatoid arthritis, lupus, and rheumatic heart disease.¹⁵⁴⁻¹⁵⁶ There have been mixed results in patients with bicuspid aortic valve disease.

Al-Halees and colleagues¹⁵⁷ reviewed their results with 78 patients undergoing the Ross operation in the Middle East. Eighty percent of these patients suffered from rheumatic disease of the aortic valve, and 28% had significant mitral regurgitation. Five (8%) of these patients have required reoperation between 20 and 26 months postoperatively—four for autograft failure and one for recurrent mitral regurgitation. One autograft demonstrated histologic evidence of valvulitis consistent with rheumatic disease. Choudhary and colleagues¹⁵⁸ performed the Ross operation in 75 patients suffering from rheumatic aortic valve disease. Two patients required reoperation for autograft failure, and 13 showed evidence of moderate or severe autograft insufficiency, with leaflet thickening, generally between 12 and 24 months after operation. Autograft function was significantly inferior in rheumatic patients.

Bicuspid aortic valve disease is considered to be contraindication for the Ross procedure by some; however, the data remain controversial. Examining the pulmonary trunk in patients with bicuspid aortic valve disease, de Sa and colleagues¹⁵⁹ reported histologic evidence of cystic medial necrosis, elastic fragmentation, and smooth muscle cell abnormalities. They suggested that these findings manifest themselves as subsequent autograft dilation; however, conflicting results have also been reported. Luciani and colleagues¹⁶⁰ have reported no histopathology of the pulmonary trunk in the setting of bicuspid aortic valve disease, and they noted no greater tendency for autografts in this setting to dilate. Likewise, in a large pediatric experience, Elkins and colleagues^{161,162} reported that preoperative aortic regurgitation, but not valve morphology, was associated with autograft degeneration.

PROSTHETIC MECHANICAL VALVES, ANTICOAGULATION, AND PREGNANCY

Prosthetic valves, systemic anticoagulation, and pregnancy are important issues for young women with aortic valve disease. Edmunds reported that women with mechanical valves were at risk for thrombotic complications if anticoagulation were interrupted.¹⁶³ However, it has been suggested that up to 30% of fetuses exposed to warfarin between the sixth and ninth weeks of gestation will develop warfarin embryopathy (nasal hypoplasia, stippled epiphyses).¹⁶⁴ Warfarin exposure during the second trimester has been implicated in central nervous system abnormalities in approximately 3% of fetuses.¹⁶⁵ In 1994, major European centers were queried about the clinical approach to anticoagulation, prosthetic valves, and pregnancy.¹⁶⁶ There were 214 pregnancies in 182 women, 151 pregnancies in 133 women with mechanical valves, and 63 pregnancies in 45 women with bioprosthetic valves. Including abortions (spontaneous and therapeutic), 83% of pregnancies among women with bioprosthetic valves, and 73% of pregnancies among women with mechanical prosthesis, resulted in healthy children, consistent with other reports.¹⁶⁷

Anticoagulation was administered in 150 of the 151 pregnancies among 133 women with mechanical valves. Thirty-four women received subcutaneous heparin throughout the pregnancy, 50 received warfarin for the duration of gestation, and 66 received subcutaneous heparin for the first trimester and warfarin thereafter. Warfarin was discontinued, and subcutaneous heparin was restarted 2 to 4 weeks before the estimated date of confinement. No cases of warfarin embryopathies were reported. There were 13 mechanical valve thromboses; 12 of these were in the mitral position, and 10 were taking heparin ($P < 0.05$). The single woman suffering aortic valve thrombosis refused all anticoagulation and died from valve thrombosis. Of the seven major bleeding complications, five occurred in women taking heparin and two were in women taking warfarin ($P < 0.05$). The incidence of spontaneous abortions did not differ between the two groups (10% and 12%). Among the 45 women with bioprosthetic valves, pregnancy tended to accelerate

deterioration of these valves. Thirty-one percent of these women required replacement during pregnancy or shortly thereafter.

More recent series reporting on large numbers of pregnancies in women receiving warfarin for prosthetic valves suggest that the risk of warfarin embryopathy may be overstated, and the incidence of spontaneous abortion, thromboembolic episodes, or bleeding have been shown to be similar to those among women treated with heparin during the first trimester.^{168,169} However, warfarin dosages, but not the international normalized ratio [INR], were found to influence fetal outcomes.¹⁷⁰

In conclusion, these authors suggested that mechanical valves were preferable in women of childbearing potential and that oral warfarin therapy for the duration (except the last 2 weeks) was appropriate.

Potential discrepancies between these two bodies of data may be related to techniques used for monitoring warfarin anticoagulation. In the early 1990s, the United States adopted the INR (patient's prothrombin time divided by the control time using the thromboplastin standard of the World Health Organization). Before the adoption of INR, the use of thromboplastins of low responsiveness may have contributed to over-anticoagulation, equivalent to INRs of up to 9 in some preparations.^{171,172} Warfarin embryopathy is thought to be a dose-related phenomenon, and may have been exacerbated by these discrepancies.

Finally, the Ross operation has been proposed as an excellent option for young women anticipating future motherhood. In a retrospective review of pregnancy in 8 women following the Ross operation, there were 14 uncomplicated pregnancies and no deterioration in autograft function during or after the pregnancies.¹⁷³

SUMMARY

Congenital aortic valve disease is a progressive, lifelong condition that can be palliated, but not cured. The surgical management of congenital disease of the aortic valve and root remains challenging. In general, there has been a movement away from indirect surgical therapies (e.g., apical-aortic conduits) toward more direct surgical procedures designed to address the pathology directly (e.g., valve repair, Konno-Rastan, modified Konno, Ross operation). Despite the development of techniques designed to relieve stenosis at all levels, the ultimate success of palliation will often depend on the suitability of associated left heart structures.

Areas such as patient selection (particularly in the neonatal population), evolving aortic valve repair techniques, and the long-term results of procedures such as the Ross operation remain areas of investigation. The development of catheter-based interventions designed to treat specific forms of aortic root and valve pathology will continue. Lifelong surveillance is mandatory to provide long-lasting preservation of left ventricular function.

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SURGERY FOR CONGENITAL ANOMALIES OF THE CORONARY ARTERIES

Julie A. Brothers • J. William Gaynor

CHAPTER OUTLINE

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CORONARY ARTERY FISTULA

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 Surgical Results

CONGENITAL OSTIAL ATRESIA OF THE LEFT MAIN CORONARY ARTERY

Anatomy
Pathophysiology
Clinical Presentation
Diagnostic Imaging
Surgical Management
Surgical Results

OUTCOMES

This chapter discusses the management of coronary artery anomalies in patients without other congenital heart defects. Most coronary artery anomalies in number, origin, and distribution are of intellectual interest only. However, a few are clinically significant because they may result in myocardial ischemia, left ventricular dysfunction, and sudden death. Anomalies discussed in this chapter include anomalous origin of a coronary artery from the pulmonary artery, anomalous coronary artery that courses between the aorta and pulmonary artery, coronary artery fistula, and congenital atresia of the left main coronary artery.

In normal coronary anatomy, two coronary arteries arise from separate ostia in the right and left aortic sinuses

of Valsalva. The left main coronary artery (LMCA) originates from the left aortic sinus and usually bifurcates into the left anterior descending coronary artery (LAD) and the left circumflex coronary artery. The LAD runs in the anterior interventricular groove, and the left circumflex coronary artery courses in the left atrioventricular groove. The right coronary artery (RCA) originates anteriorly from the right aortic sinus, runs along the right atrioventricular groove, and usually gives rise to the posterior descending artery at its terminus.

In most individuals, each coronary artery ostium is located centrally in the appropriate sinus of Valsalva. In some patients, the ostium may be eccentrically located, and in others a coronary artery may arise close to a valve

BOX 124-1 Origin of Both Coronary Arteries from One Sinus

1. Left main coronary artery originates from right sinus of Valsalva (either from right coronary artery or separate ostia).
Left main coronary artery courses anterior to pulmonary artery.
Left main coronary artery courses through interventricular septum.
Left main coronary artery courses between aorta and pulmonary artery.
Left main coronary artery courses posterior to aorta.
In rare cases, the left anterior descending coronary or left circumflex coronary artery alone may originate from the right sinus.
2. Single left main coronary artery arises from the left sinus and bifurcates into the left anterior descending coronary and left circumflex coronary arteries. The left circumflex coronary artery crosses the crux and continues as the right coronary artery.
3. Single right coronary artery from sinus, which crosses crux, continues as left anterior descending coronary and left circumflex coronary artery.
4. Right coronary artery originates from left sinus of Valsalva (either from left main coronary artery or as separate ostium).
Right coronary artery courses posterior to aorta.
Right coronary artery courses interior anterior to pulmonary artery.
Right coronary artery courses between aorta and pulmonary artery.

commissure. One or both coronary ostia may arise from the tubular aorta above the sinotubular junction, which is usually a benign finding. However, this high take-off of the coronary artery becomes significant if an aortotomy is necessary for aortic valve replacement or for another indication; if not recognized, the coronary artery could be transected. Another anomaly is when both coronary arteries arise from the same aortic sinus with either a single ostium or two separate ostia (Box 124-1). This is generally not clinically significant if the aberrant vessel courses posterior to the aorta or anterior to the pulmonary artery, but it becomes important if either the aberrant LMCA or RCA courses between the two great vessels, because this may lead to myocardial ischemia and sudden death.

ANOMALOUS ORIGIN OF A CORONARY ARTERY FROM THE PULMONARY ARTERY

Anomalous origin of a coronary artery from the pulmonary artery is a rare congenital anomaly that is almost always fatal if not diagnosed and treated.^{1,2} Although anomalous origin of the LMCA from the pulmonary artery (ALCAPA) is the most common, other coronary arteries may rarely also arise from the pulmonary artery. The RCA arises from the pulmonary artery approximately 10 times less frequently than ALCAPA but is also

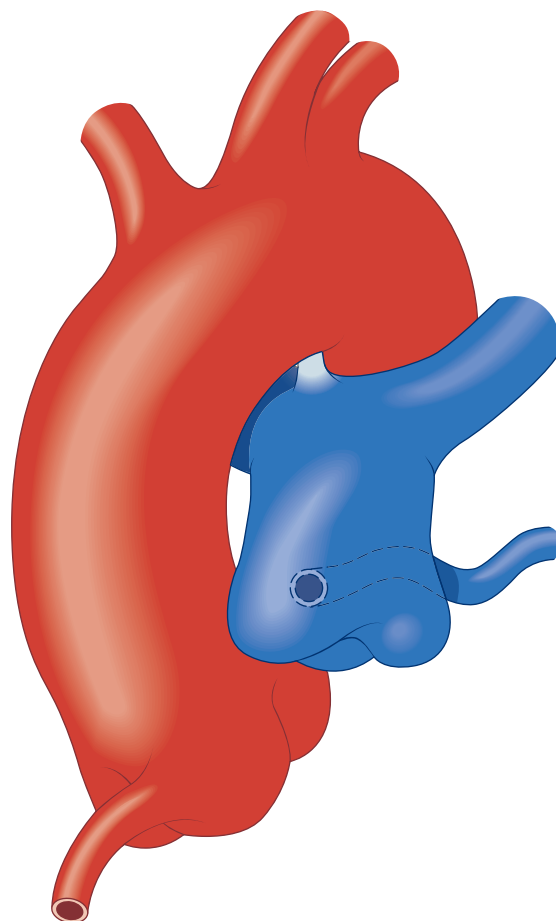


FIGURE 124-1 ■ The aorta and pulmonary artery showing anomalous origin of the left main coronary artery from the posterior-facing sinus of the pulmonary artery with the anomalous artery coursing behind the pulmonary artery. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 881.)

associated with ischemia and sudden cardiac death. The LAD, the circumflex, or both the left and right coronary arteries may arise from the pulmonary artery; these variants are extremely rare and are almost uniformly fatal.

ALCAPA is the most important congenital coronary artery anomaly in this class. The incidence of ALCAPA ranges from 1 in 30,000 to 1 in 300,000 people. It is the most common cause of myocardial infarction in childhood. If not diagnosed and treated, the mortality rate is 90% by age 1 year. ALCAPA is otherwise known as the Bland-White-Garland syndrome, after Bland and colleagues reported on both clinical and autopsy findings in an infant with this anomaly in 1933.³

Anatomy

In ALCAPA, the LMCA usually arises from the main pulmonary artery (MPA); occasionally, it arises from the right pulmonary artery. It usually originates from the rightward aspect of the posterior (facing) sinus of the MPA (Figs. 124-1 and 124-2), but it may also originate from the leftward aspect of the posterior (facing) and, in rare cases, from the anterior (nonfacing) sinus of

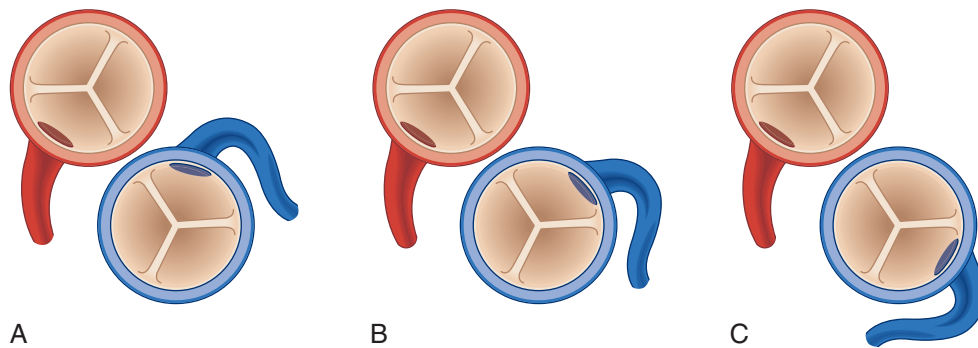


FIGURE 124-2 ■ **A**, Anomalous origin of the left main coronary artery from the rightward aspect of the posterior-facing sinus of the pulmonary artery. **B**, Anomalous origin of the left main coronary artery from the leftward aspect of the posterior-facing sinus. **C**, Anomalous origin of the left main coronary artery from the nonfacing sinus of the pulmonary artery. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 882.)

the MPA (see Fig. 124-2). An anomalous RCA most commonly originates from the anterior portion of the pulmonary artery.

Although ALCAPA usually occurs in isolation, other associated cardiac defects include patent ductus arteriosus (PDA), ventricular septal defect (VSD), coarctation of the aorta, and tetralogy of Fallot.

Pathophysiology

Children with ALCAPA usually develop symptoms after closure of the ductus arteriosus and the subsequent fall in pulmonary vascular resistance. During fetal life, the systemic and pulmonary circulation pressures are similar, and myocardial perfusion remains intact because the pulmonary arterial pressure is systemic. After birth but before ductal closure, the pulmonary artery pressure remains elevated, thereby maintaining perfusion of the anomalous coronary artery. This explains why children are rarely diagnosed with ALCAPA in the first few days of life. The clinical course after ductal closure is largely determined by the presence or absence of collaterals from the RCA to the left coronary system. If there is inadequate collateral circulation, myocardial ischemia and ventricular dysfunction result from insufficient myocardial perfusion.⁴ This occurs because of subsystemic pulmonary artery pressure, and the left ventricle is thus perfused with desaturated blood at a low pressure. However, if the pulmonary artery pressure remains elevated because of the presence of another cardiac defect, such as PDA or VSD, left ventricular perfusion pressure may be adequate to prevent ischemia. If this coronary anomaly is unknown before the catheter or surgical closure of these defects, it will become apparent shortly after closure because of the subsequent drop in pulmonary arterial pressure—usually with a fatal outcome.

Alternatively, if there is adequate collateralization, perfusion of the left coronary system is maintained. As the pulmonary vascular resistance falls, however, a left-to-right shunt develops from the RCA to the pulmonary artery. There is progressive dilation of the RCA and left coronary artery systems, with reversal of flow in the left coronary leading to a pulmonary-coronary steal. Although the shunt is relatively small compared with overall cardiac

output, it is significant with regard to coronary blood flow. Children with extensive collaterals may survive past infancy; however, there is usually progressive left ventricular dysfunction.⁵ In a small percentage of cases, the collateral vessels are enough to maintain adequate myocardial perfusion at rest and sometimes even during exertion, and these patients may not come to clinical attention until adulthood.⁶ In most children, however, severe mitral regurgitation is present secondary to papillary muscle dysfunction and ventricular dilation.

Clinical Presentation

Infants frequently present between 4 and 6 weeks of age after the pulmonary vascular resistance has dropped.⁷ However, infants may not be diagnosed until 2 to 3 months of age, when symptoms have increased in severity. Infants usually show signs and symptoms of congestive heart failure, including sweating and discomfort with feeding, tachypnea, poor weight gain, and pallor. The discomfort with feeding most likely represents myocardial ischemia. Children who do not present when they are infants may be diagnosed in later infancy as a result of the loud murmur of mitral regurgitation. Older children, adolescents, and adults may remain asymptomatic, whereas others may come to clinical attention because of exertional chest pain, pre-syncope, or syncope. There have been reports of sudden death with exercise in these older patients. The symptoms associated with anomalous origin of the RCA from the pulmonary artery are less severe, but myocardial ischemia and death can still occur.

Physical examination of the infant with ALCAPA may reveal signs of congestive heart failure, including tachypnea, tachycardia, and hepatomegaly. Left ventricular dysfunction caused by ALCAPA can be difficult to distinguish from a dilated cardiomyopathy. The left heart is usually enlarged, often with associated mitral regurgitation, and a gallop rhythm also may be present. If left heart failure has resulted in pulmonary hypertension, then there may also be evidence of right heart enlargement and an accentuated pulmonary component of the second heart sound on examination.

Infants with ALCAPA generally have an enlarged cardiac silhouette on chest radiograph, resulting mainly

from the enlarged left atrium and left ventricle. In infants with congestive heart failure, the electrocardiogram (ECG) can provide a useful diagnostic clue because there are classic findings of Q waves and ST-segment elevation in leads I, aVL, and V4-V6 as a result of lateral or anterolateral wall infarction. Although this pattern can be found in other causes of myocardial infarction or cardiomyopathy, if these electrocardiographic abnormalities are seen in an infant with congestive heart failure, the diagnosis of ALCAPA needs to be strongly considered. Certainly, any infant diagnosed with dilated cardiomyopathy must be extensively evaluated for ALCAPA. This diagnosis should also be considered in older children and adolescents with a dilated cardiomyopathy, because occasional patients survive past infancy.

Diagnostic Imaging

Echocardiography with color flow Doppler usually demonstrates a dilated left ventricle with severe mitral regurgitation. The mitral regurgitation commonly seen with ALCAPA is caused by infarction of the posterior leaflet of the mitral valve and subsequent poor movement of the leaflet; fibrosis and fibroelastosis of the papillary muscle also can be present. Imaging of the coronary arteries, including origin and course, has become possible as a result of improved echocardiographic techniques, but it can still be challenging. An enlarged RCA is almost always present and should raise suspicion of this diagnosis. Careful attention should be paid to the origins of both coronary arteries, including the abnormal origin of the LMCA to the pulmonary artery. If visualization of the anomalous vessel is unclear, color flow Doppler may reveal retrograde flow from the coronary artery to the pulmonary artery. However, underdiagnosis by echocardiography is relatively common; thus, if any question remains about visualization of both coronary ostia, then cardiac catheterization is mandatory to rule out ALCAPA.

Cardiac catheterization with angiography remains the gold standard in the diagnosis of ALCAPA. Cardiac catheterization demonstrates elevated filling and pulmonary arterial pressures and a low cardiac output. In older asymptomatic patients, it may show only mildly elevated pulmonary arterial pressures but normal filling pressures and cardiac output. A small left-to-right shunt may be present. An aortogram will demonstrate a single, dilated RCA arising normally from the aorta. If significant collaterals are present, aortic root angiography will show the collaterals providing late, retrograde filling of the left coronary artery with a blush of contrast subsequently filling the MPA. If there is a large left-to-right shunt from the collaterals, a step-up in oxygen saturation may be noted in the MPA. If doubt remains regarding the diagnosis, a main pulmonary arteriogram with distal balloon occlusion should demonstrate the anomalous left coronary artery.⁸

Magnetic resonance imaging (MRI) has emerged as a useful noninvasive diagnostic tool for delineating congenital coronary anomalies.^{9,10} Although there have been case reports of using this method in diagnosing ALCAPA, no case series with this anomaly have been reported. However, studies have shown that magnetic resonance

angiography has a similar sensitivity and specificity when compared with coronary angiography and may be especially helpful in delineating the proximal course of anomalous coronary arteries. Computed tomography (CT) has been used extensively for coronary artery delineation in adults. Advantages of this technique include rapid acquisition time and high resolution, but the disadvantages include radiation exposure and the need for a slower heart rate with ECG gating, precluding its use in infants.

Surgical Management

Indications for Surgery

Surgical repair is indicated in all patients with ALCAPA. In infants with congestive heart failure, surgery should occur within the first few days of diagnosis because risk of continuing myocardial ischemia and death is very high.¹¹ In older patients who present without symptoms, surgery is necessary but can be performed electively. In an infant who presents in severe heart failure secondary to myocardial infarction, surgery will probably need to be delayed for at least 24 hours to stabilize the patient using mechanical ventilation, inotropic support, and vasodilators, when necessary. Del Nido and colleagues reported that even in the sickest infants, a two-vessel surgical repair is possible if left ventricular assist devices (LVADs) are used postoperatively.¹² Others may need extracorporeal membrane oxygenation (ECMO). Because infants requiring surgery are often quite ill, it is important that centers performing ALCAPA surgery have these options available, or else the child should be transferred to a hospital with these capabilities.

The goal of surgery is restoration of a two-coronary system; therefore, simple ligation of the anomalous coronary should not be performed.¹³ Severe left ventricular dysfunction and mitral insufficiency are not contraindications to revascularization in infants, because significant recovery of function usually occurs. Because the severity of mitral regurgitation almost always decreases after revascularization, left ventricular aneurysmectomy and mitral valve repair or replacement are rarely indicated at the time of initial procedure, even if severe mitral regurgitation is present.

Surgical Techniques

The first successful operation for correction of ALCAPA was simple ligation of the anomalous artery at the pulmonary artery. Ligating the anomalous vessel prevents the left-to-right shunt, thereby allowing perfusion of the left ventricle through collaterals from the RCA. Because of the early mortality rates and increased risk of late sudden death with this procedure, a variety of techniques have been developed to create a dual coronary artery system, including coronary artery bypass grafting, aorto-pulmonary window, and direct reimplantation.

Bypass grafts were accomplished using the left subclavian artery, the internal mammary artery (IMA), and the saphenous vein. Meyer and colleagues reported the first successful left subclavian artery-to-left coronary artery bypass in 1968.¹⁴ The results of bypass grafting, especially

with saphenous vein grafts, have been disappointing. Takeuchi and associates were the first to describe the creation of an aortopulmonary window and intrapulmonary artery baffle using a pulmonary artery flap to direct blood flow from the aorta to the anomalous coronary artery.¹⁵ Finally, the procedure of choice in many institutions has become direct reimplantation of the anomalous coronary onto the aorta, as experience with the arterial switch operation for transposition of the great vessels has increased.^{16,17}

Coronary Artery Bypass Grafting. Coronary artery bypass grafting is rarely used in patients with ALCAPA. In the current era, it is usually used to create a dual coronary artery system after previous ligation or because of stenosis or occlusion after a previous attempt at repair. The IMA is the conduit of choice and can be used successfully, even in neonates and infants; in addition, there is some evidence for growth of the IMA after bypass grafting.¹⁸⁻²⁰ The saphenous vein should not be used unless it is the only conduit available, because of the risk of occlusion and poor long-term results.²¹ Similarly, left subclavian-to-left coronary artery anastomosis is infrequently used because of the risk of anastomotic stenosis or occlusion.^{22,23}

Direct Reimplantation. In most patients with ALCAPA, direct reimplantation of the anomalous coronary artery onto the aorta can be performed (Fig. 124-3).^{24,25} When the anomalous coronary ostium is in the posterior-facing sinus, the procedure is fairly straightforward. Direct implantation is possible even if the ostium is located in the nonfacing sinus by excising a large button of pulmonary artery to extend the coronary artery.

After induction of anesthesia and placement of monitoring lines, a median sternotomy is performed. The thymus is resected. The pericardium is opened and suspended in stay sutures. Because of the likelihood of myocardial ischemia and left ventricular dysfunction, there is a risk of ventricular fibrillation, so contact with the myocardium should be kept at a minimum until the patient is placed on cardiopulmonary bypass. This operation may be performed using either continuous low-flow bypass with moderate hypothermia (25° to 28° C) or deep hypothermic circulatory arrest (18° C) in very small infants. Before cannulation, an aortic purse-string suture is placed distally near the innominate artery, and another is placed in the right atrial appendage for a single venous cannula. Heparin is administered, the aortic and right atrial cannulas are inserted, and cardiopulmonary bypass is established. The left ventricle should be decompressed by placing a left ventricular vent via the right superior pulmonary vein. The pulmonary artery and epicardial course of the left coronary artery are visualized. If the anomalous left coronary artery originates far leftward in the posterior-facing sinus or on the anterior nonfacing sinus, direct reimplantation may not be possible.

The aorta and both pulmonary arteries are fully mobilized. To improve mobility of the pulmonary artery, the ductus (or ligamentum) arteriosus is ligated. Tourniquets are placed around both the right and the left branch pulmonary arteries to occlude the branch pulmonary

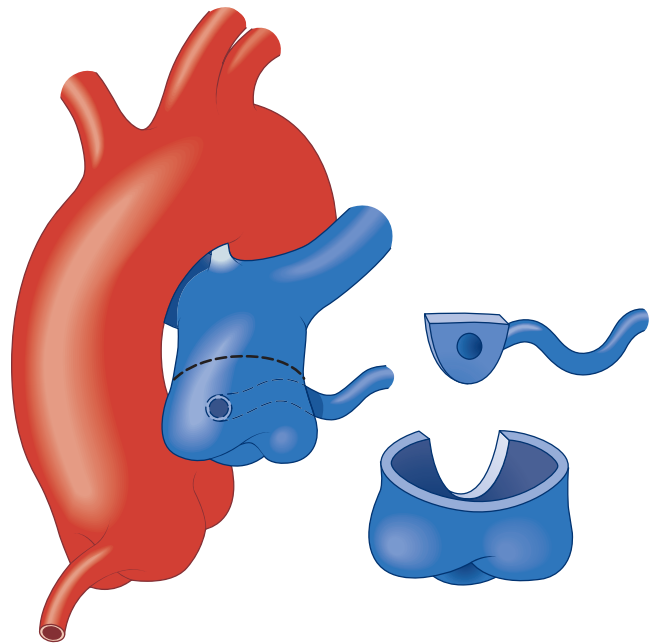


FIGURE 124-3 ■ After institution of cardiopulmonary bypass and induction of cardioplegia, the pulmonary artery is transected above the sinotubular junction, and the anomalous coronary ostium is excised with a generous button of pulmonary artery wall. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 883.)

arteries and prevent runoff of cardioplegia solution into the lungs. Another option to prevent runoff is to compress the origin of the coronary artery from the pulmonary artery during administration of cardioplegia solution. A cannula is inserted in the ascending aorta for administration of cardioplegia solution, the aorta is cross-clamped, and cold cardioplegia is administered via the aortic root. If circulatory arrest is used, the head vessels are then occluded with tourniquets after adequate cooling, the circulation is arrested, venous blood is drained into the reservoir, and the cannulas are removed. After adequate arrest, the pulmonary artery is transversely opened just above the sinotubular junction (see Fig. 124-3). The anomalous coronary orifice is identified. The pulmonary artery is divided and the coronary ostium is excised from the pulmonary artery with a generous button of arterial wall, as in the procedure used for the arterial switch operation. The segment of the pulmonary wall that is excised extends the proximal end of the coronary artery, thus allowing the aortic anastomosis to be accomplished without tension. To excise the coronary button, the pulmonary commissure may need to be taken down if the coronary ostium is located near a commissure. An alternative technique that can be used if the coronary arises anteriorly from the pulmonary artery or from a branch pulmonary artery involves extension of the coronary artery with a tube constructed from pulmonary artery wall to allow reimplantation (Fig. 124-4). The proximal portion of the coronary artery is mobilized with cautery, using caution to avoid any small branches. As in the arterial switch operation, the aorta is then opened transversely immediately above the sinotubular junction, and

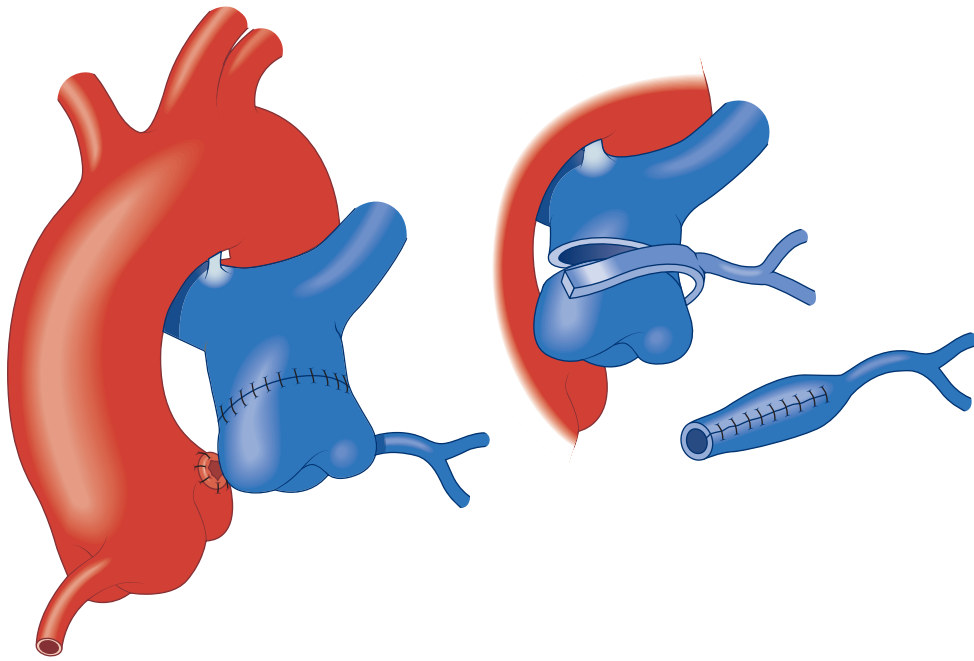


FIGURE 124-4 ■ Occasionally when the coronary artery arises from the leftward or anterior aspect of the pulmonary artery, direct reimplantation may not be possible. In these situations, a tube can be constructed from a segment of pulmonary artery to lengthen the coronary and allow reimplantation on the aorta. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 883.)

the incision is carried posteriorly above the left posterior sinus (Fig. 124-5). The sinus is then incised vertically to accept the coronary button. The coronary button is carefully aligned with the aortic incision to avoid twisting or kinking. A continuous suture of 7-0 polypropylene (Prolene) is used to start the anastomosis at the most inferior aspect of the coronary button, which is attached to the most inferior aspect of the incision in the sinus. The suture line is carried to the top of the incision anteriorly and posteriorly. The aorta is closed with a continuous suture of 7-0 Prolene, which is tied to the coronary button suture as the anastomosis is completed (see Fig. 124-5). Once the aorta has been closed, cardioplegia solution is administered and the anastomotic site is inspected for adequate filling of the coronary and for hemostasis. Occasionally, the anomalous artery may arise from the right pulmonary artery and run along or within the aortic wall to the sinus. If there is a common wall with the aorta, mobilization may not be possible. In this case, unroofing of the intra-mural segment should be performed.²⁶

In some cases, the pulmonary artery can be repaired primarily with a continuous suture of 7-0 Prolene (Fig. 124-6). The ductus should be divided to improve mobility of the pulmonary artery confluence, thus allowing reconstruction without tension. However, more often, the pulmonary artery is repaired with a patch of autologous pericardium (see Fig. 124-6). If a commissure was taken down during excision of the coronary button, the pulmonary artery should be reconstructed with pericardium and the commissure resuspended.

The patient is rewarmed and the aortic cross-clamp is removed. The cross-clamp may be removed before the pulmonary artery reconstruction to minimize ischemia

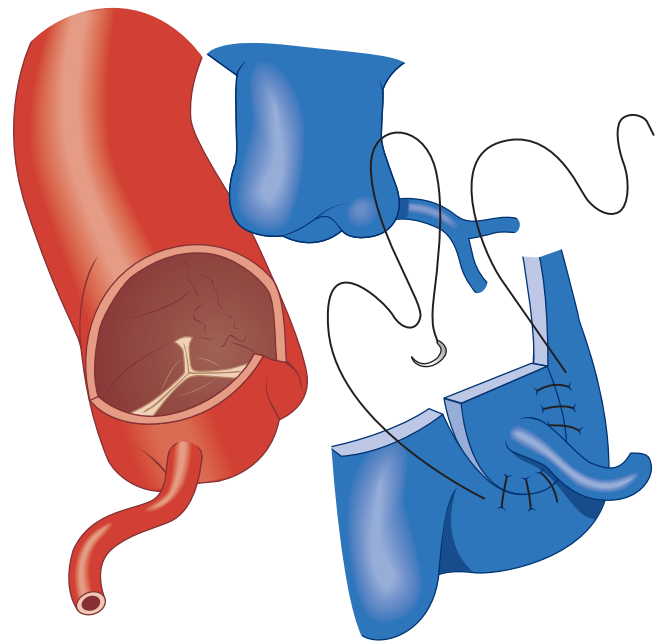


FIGURE 124-5 ■ After the anomalous coronary artery is mobilized, the aorta is opened transversely above the sinotubular junction and a vertical incision is made in the left posterior sinus to accept the reimplanted coronary. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 884.)

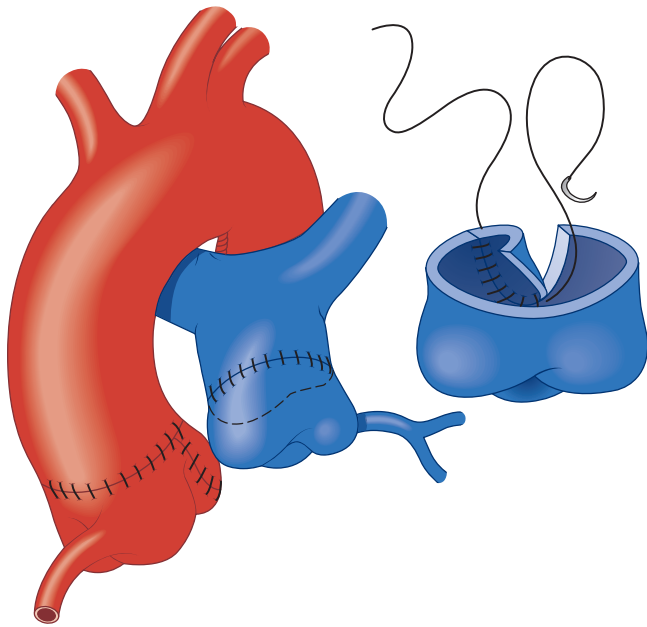


FIGURE 124-6 ■ After the coronary is reimplanted, the aorta is closed primarily. The pulmonary artery may often be closed primarily. Ligation and division of the ligamentum arteriosus improves mobility of pulmonary artery. Occasionally, patch repair of the defect in the pulmonary artery with autologous pericardium may be necessary (*inset*). (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 884.)

time. The left ventricle is inspected to assess for adequate perfusion and function, and suture lines are inspected for hemostasis. Right and left atrial lines are placed to adequately monitor pressure and for drug administration. Atrial and ventricular pacing wires are also placed. The patient is separated from cardiopulmonary bypass after complete rewarming. Attention should be paid to the ECG during reperfusion and after separation from bypass for evidence of ischemia. Inotropic support may be necessary temporarily if there was left ventricular dysfunction preoperatively.

Modified Takeuchi Operation. The Takeuchi operation, or intrapulmonary artery tunnel, is an alternative surgical strategy for repair of ALCAPA. Originally, Takeuchi and colleagues described the creation of an aortopulmonary window using a portion of anterior pulmonary artery wall to form a baffle that would direct blood from the aorta to the ostium of the anomalous coronary artery.¹⁵ In the modified repair, the baffle is constructed using a polytetrafluoroethylene (PTFE) (Gore-Tex) patch. Creating a baffle may not be possible if the ostium is located near a commissure or arises from a branch pulmonary artery. The procedure may be performed with either continuous low-flow cardiopulmonary bypass (25° C to 28° C) or deep hypothermic circulatory arrest (18° C). Cannulation is performed as for direct reimplantation.

After induction of cardioplegia, a longitudinal incision is made in the anterior portion of the pulmonary artery (Fig. 124-7), and the ostium of the anomalous coronary

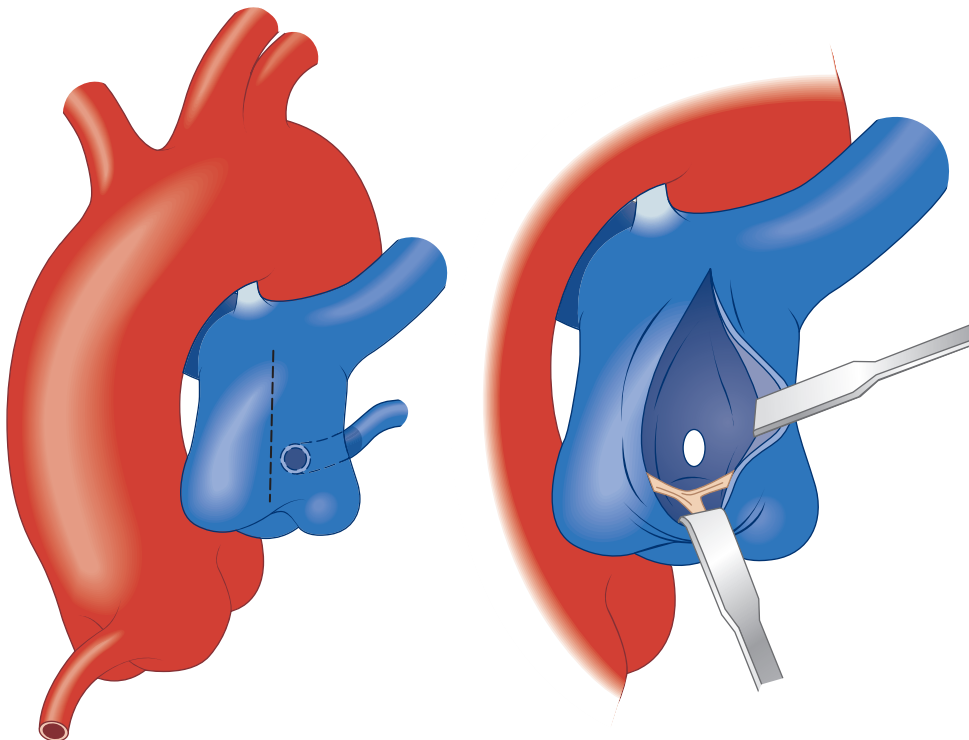


FIGURE 124-7 ■ After institution of cardiopulmonary bypass and induction of cardioplegia, a longitudinal incision is made in the main pulmonary artery, and the ostium of the abnormal coronary is identified. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 885.)

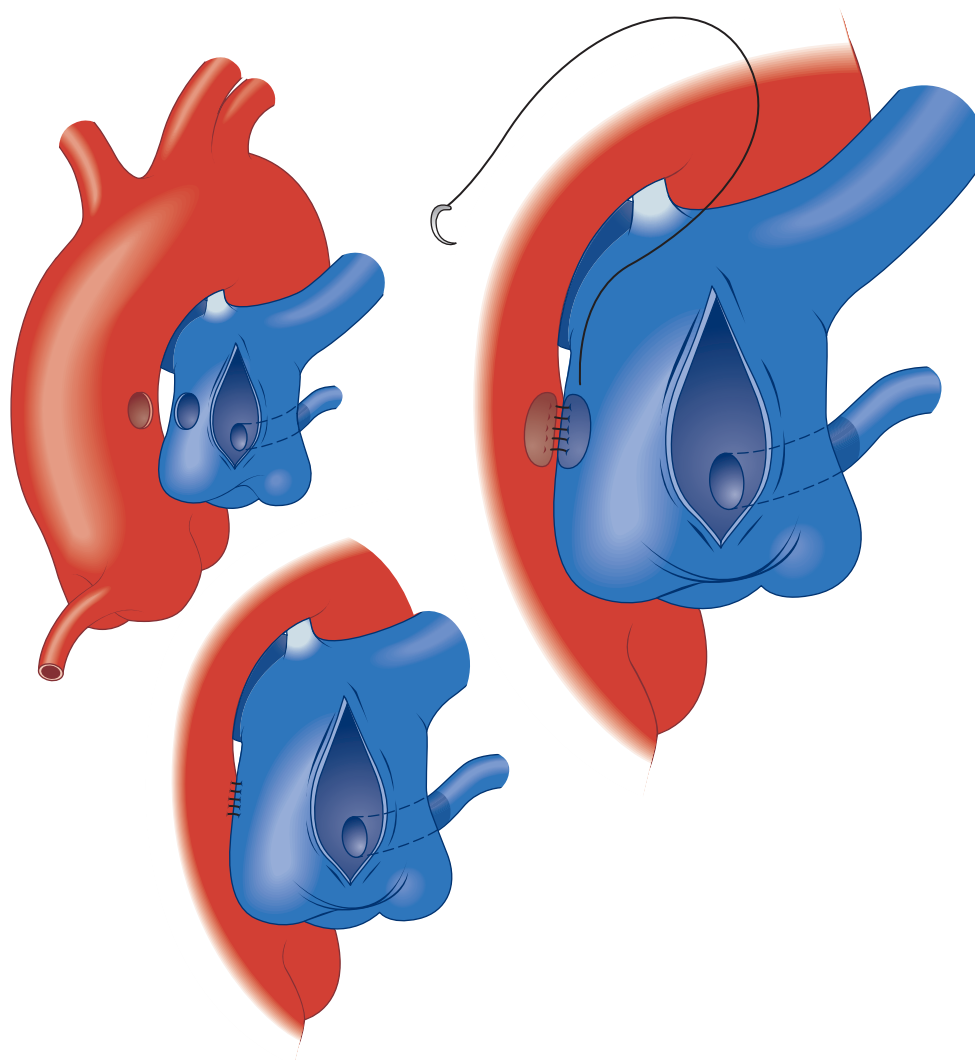


FIGURE 124-8 ■ Using a punch, a 5-mm opening is made in the aorta on the leftward aspect above the sinotubular junction. A similar opening is made in the pulmonary artery at the same level, and these are anastomosed to create an aortopulmonary window. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 885.)

is identified. Using a punch, a 5-mm diameter opening is made on the leftward aspect of the aorta above the sinotubular junction (Fig. 124-8). An anterior aortotomy should be performed if there is any question about placement of the aortic opening, and the incision should be directly visualized to avoid damage to the aortic valve. Creating the aortopulmonary window above the sinotubular junction allows a downward angle of the baffle into the sinus if the ostium is located deep in a sinus. After a similar incision is made in the pulmonary artery directly opposite the opening in the aorta, these are anastomosed using a continuous suture of 7-0 Prolene and creating an aortopulmonary window (see Fig. 124-8). A 4-mm PTFE tube graft is split longitudinally and customized to an appropriate length (Fig. 124-9). This graft acts as an intrapulmonary artery tunnel, baffling blood from the aortopulmonary window to the anomalous coronary ostium. The suture line starts at the anomalous coronary and is continued inferiorly along the pulmonary artery wall to the aortopulmonary window. The suture line is

completed by returning to the coronary artery and completing the superior aspect of the baffle. After the baffle is created, repair of the pulmonary artery can be accomplished using a prosthetic patch or autologous pericardium to avoid supra-valvar pulmonary artery obstruction (Fig. 124-10). The main complications of the modified Takeuchi operation include baffle leak, baffle occlusion, and supra-valvar pulmonary artery obstruction.

Postoperative Management

Regardless of the surgical technique used, the most common postoperative issues are those related to the infant's preoperative state: low cardiac output, left ventricular dysfunction, and hypotension. Optimizing the patient's hemoglobin, electrolytes, acid-base status, and fluid status and providing adequate inotropic support are extremely important. In infants and children with severe preoperative cardiac dysfunction, temporary support with an LVAD or ECMO may be necessary in

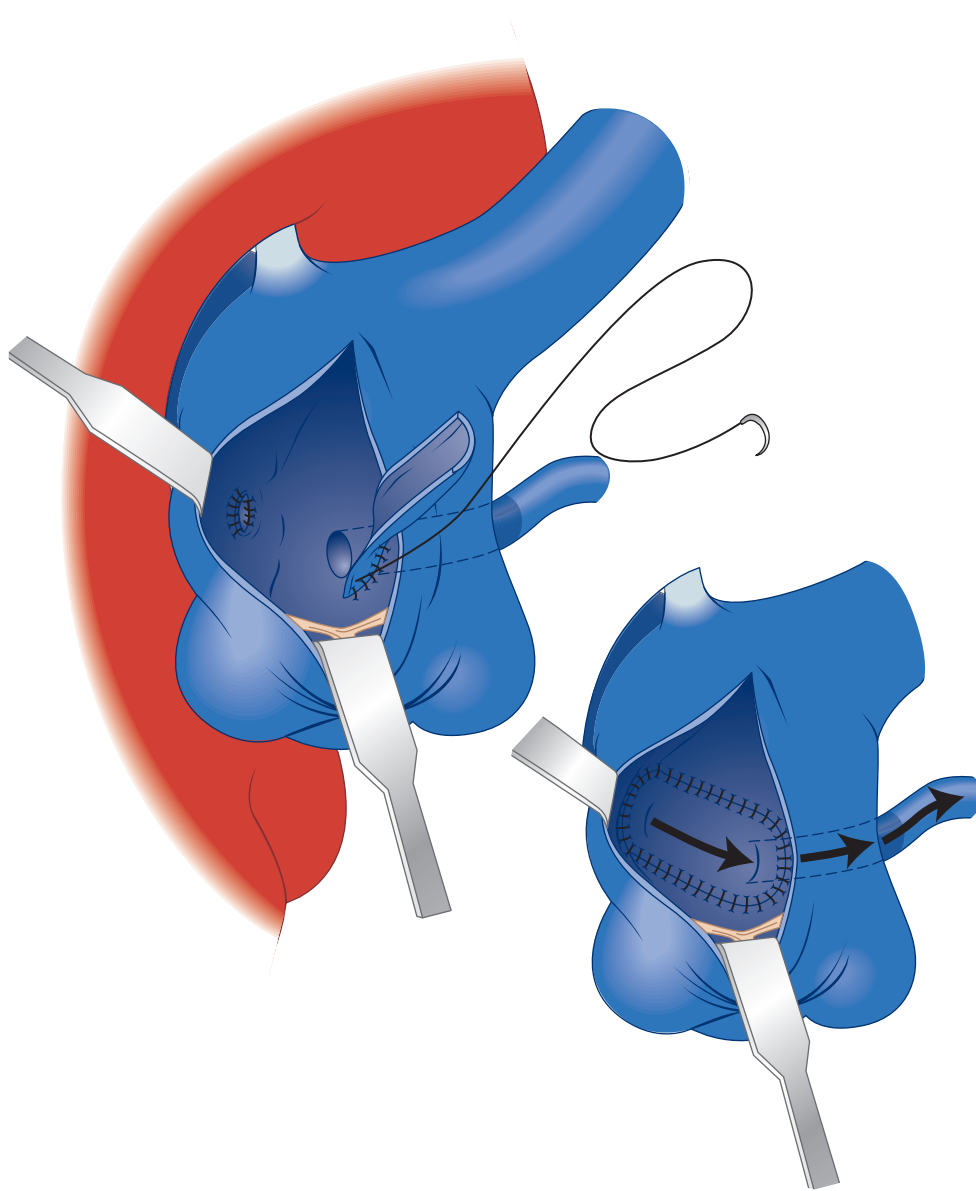


FIGURE 124-9 ■ A segment of 4-mm polytetrafluoroethylene (Gore-Tex) graft is opened longitudinally and used to fashion a baffle that directs blood flow from the aortopulmonary window to the anomalous coronary ostium. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 886.)

the postoperative period. Bleeding is also common postoperatively and is more frequently encountered in small infants and those who require mechanical support. Platelets and fresh-frozen plasma should be used aggressively to replace ongoing loss. Patients with low cardiac output or bleeding issues may require delayed sternal closure (2 to 3 days).

Results

Simple ligation of ALCAPA has been shown to have unacceptable early and late mortality rates. In general, survival after establishment of a dual coronary system is excellent.^{13,27} In 1987, Bunton and colleagues from Boston reported on 24 patients with ALCAPA.²⁸ From among these 24 patients, 11 received coronary ligation or ostial

closure, 11 had a Takeuchi repair, and 2 underwent other procedures. Of the patients who underwent coronary ligation or ostial closure, there was a 27% early mortality and a 25% late mortality over an average 10.5-year follow-up period. In those who underwent a Takeuchi procedure, there were no early or late deaths in over an 18.5-month follow-up period. After Takeuchi repair, two patients developed right ventricular outflow tract obstruction (one required a second operation), and one patient was found to have baffle occlusion.

Backer and colleagues reported the follow-up surgical results of 20 patients with ALCAPA who underwent different procedures.²⁹ There were two early deaths and one late death among nine patients who underwent ligation. In contrast, there were no deaths among the 10 patients who underwent creation of a dual coronary artery system

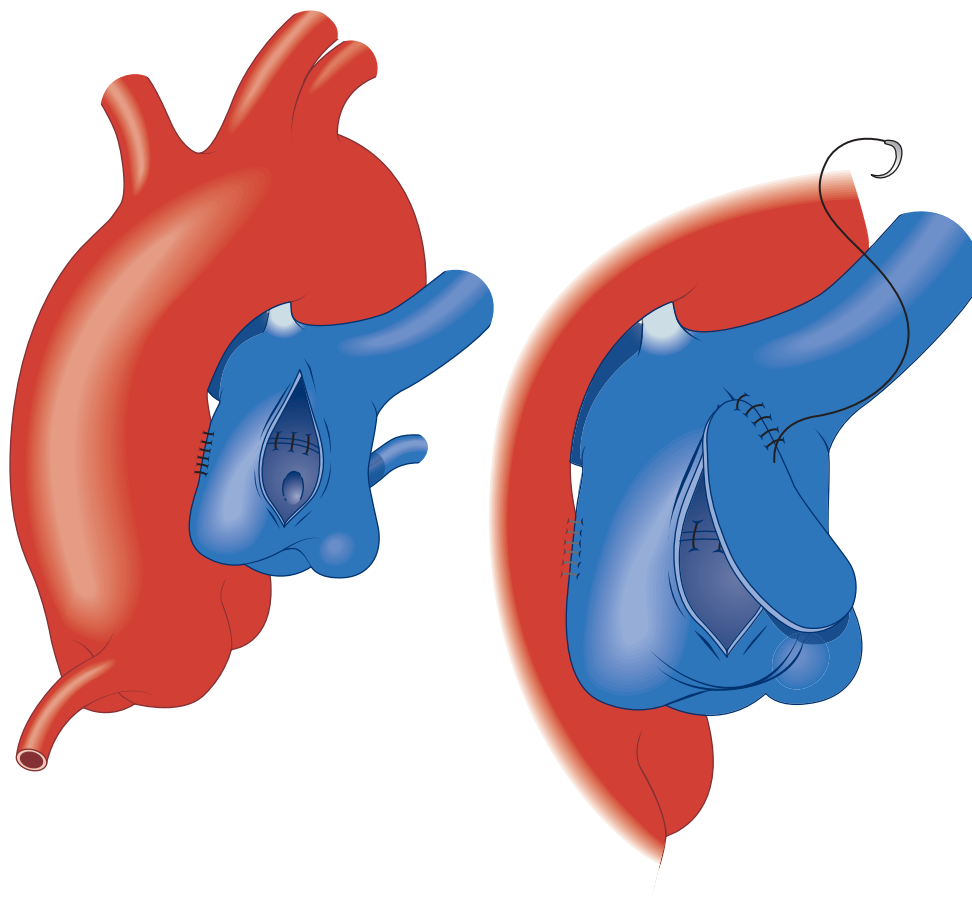


FIGURE 124-10 ■ After the baffle is completed, the pulmonary arteriotomy is repaired with a patch to avoid creation of supraventricular right ventricular outflow tract obstruction. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 887.)

and the one patient who had cardiac transplantation. Five patients had left subclavian-to-left coronary anastomosis, and two developed significant anastomotic stenosis.

Vouhe and associates from France reported on reimplantation of the anomalous coronary in 31 consecutive children.³⁰ Three hospital deaths and two additional deaths occurred within the first 3 months. No late deaths occurred. The only risk factor identified for early mortality was a shortening fraction of less than 20%. Twenty-three survivors were studied more than 1 year after repair. All patients had normal left ventricular function, and in five of seven patients who had severe mitral regurgitation preoperatively, the severity had decreased to mild or no regurgitation. The reimplanted coronary artery was patent in all patients.

A 2007 report by Lange and colleagues reviewed the long-term results of 56 patients with ALCAPA who underwent either subclavian artery anastomosis or coronary artery transfer.³¹ Patients who had had a Takeuchi procedure or a left mammary artery graft were excluded. There were similar early mortality rates (14%) for both surgical groups but no mortality in those undergoing repair in the last 13 years. Late mortality in each group was also similar, with one patient in each group. At final follow-up (mean 14.5 years for subclavian artery group and 8.7 years for coronary transfer group), 95% of patients had normal left ventricular function and 84%

had mitral regurgitation less than grade 2. However, if left ventricular function does not improve after revascularization, cardiac transplantation may be indicated.

Special Considerations

Mitral Regurgitation

There has been controversy regarding the management of mitral regurgitation during the initial surgery.³² In general, at least a moderate degree of mitral regurgitation is found at the initial presentation. Even in patients with severe mitral regurgitation, there have been several reports of significant improvement after coronary reperfusion alone, probably because of better left ventricular dysfunction and a decrease in left ventricular size postoperatively. Furthermore, valve repair at the time of initial surgery can result in longer ischemic times and can be technically more difficult to perform in an infant's heart than when the child is bigger. However, some authors recommend routine annuloplasty at the time of initial repair, whereas others propose annuloplasty or mitral valve replacement only with severe mitral regurgitation.³³ In summary, early surgical repair of the mitral valve is generally not necessary. If valve repair in the setting of severe mitral regurgitation is needed later, it is likely to be more successful and easier to do technically.

However, if severe mitral regurgitation persists late postoperatively, possible causes of ongoing myocardial ischemia should be investigated.

Late Presentation in the Adult

As discussed previously, ALCAPA in adults is rare, but it does occur. Surgery is indicated in all cases but is generally elective. In some adults, reimplantation can be performed. If this is not feasible, the surgical choice is coronary bypass grafting using the left internal thoracic artery in association with ligation of the proximal vessel; this is generally a low-risk procedure that all adult cardiothoracic surgeons can perform with a low mortality rate.

ANOMALOUS CORONARY ARTERY COURSE BETWEEN AORTA AND PULMONARY ARTERY

Anatomy

An anomalous course of a coronary artery between the two great vessels can result in myocardial ischemia and sudden death, notably in children and young adults. When there are two separate ostia, either the RCA or the LMCA may arise from the wrong sinus of Valsalva and subsequently course between the great vessels (Fig. 124-11). When the two ostia are in the same sinus, the ostium of the anomalous coronary artery is frequently small and slit-like with an acute-angle take-off.³⁴ A similar situation may be found if there is a single coronary artery arising from the right aortic sinus and the LMCA or LAD runs between the aorta and pulmonary artery, or if

the single coronary arises from the left aortic sinus and the RCA courses between the great vessels.³⁵⁻³⁸

Pathophysiology

When the anomalous coronary courses intramurally in the wall of the aorta between the aorta and pulmonary artery, it is associated with increased incidence of sudden death.³⁹⁻⁴⁵ The greatest danger of sudden death is during or just after maximal exertion. Both anomalous LMCA from the right sinus and RCA from the left sinus are associated with sudden death, but the former carries a higher risk. Based on autopsy studies of patients with an anomalous aortic origin of a coronary artery, sudden cardiac death is hypothesized to occur from decreased anomalous coronary blood flow resulting in myocardial ischemia or ventricular tachyarrhythmias (or both). This diminished blood flow is probably the result of an anatomic malformation of the anomalous vessel. The risk of ischemia is greatest with vigorous exercise, when there is a significantly greater cardiac output and oxygen demand placed on the heart.⁴⁶⁻⁴⁸

Clinical Presentation

The true prevalence of an anomalously coursing left or right coronary artery between the aorta and pulmonary artery is unknown, but estimates range from 0.1% to 0.3% of the general population.^{49,50} What makes this diagnosis especially challenging is that there are no characteristic physical findings in these patients, and the physical examination is almost always normal. In children, an innocent murmur may be auscultated, which prompts the referral to a cardiologist, who may perform an echocardiogram. Many patients with this anomaly are asymptomatic, and the initial presentation may be sudden death.⁴⁷⁻⁴⁹ When symptoms are present, they most commonly include chest pain, palpitations, dizziness, pre-syncope, or syncope during or just after exertion.^{42,51-54} The diagnosis must be considered in any young patient with exercise-induced complaints suggestive of myocardial ischemia or in those who experience aborted sudden death or sudden death.⁵⁵ Screening first-degree relatives with echocardiography has recently been suggested because of a potential genetic link with this anomaly.⁵²

Diagnostic Imaging

Anyone with pre-syncope, syncope, or chest pain during or just after exertion deserves attention and further evaluation. A resting ECG should be obtained to evaluate for ventricular hypertrophy, arrhythmias, and evidence of previous myocardial infarction.

Echocardiography with color Doppler should be performed to ensure normal intracardiac anatomy and to evaluate heart function, especially focusing on areas of abnormal wall motion signifying possible history of ischemia.^{52,53,56} The proximal coronary anatomy should be evaluated with close attention paid to the coronary artery origins. Improvements in two-dimensional echocardiography have made the identification of the origins of both coronary arteries possible in many patients, especially

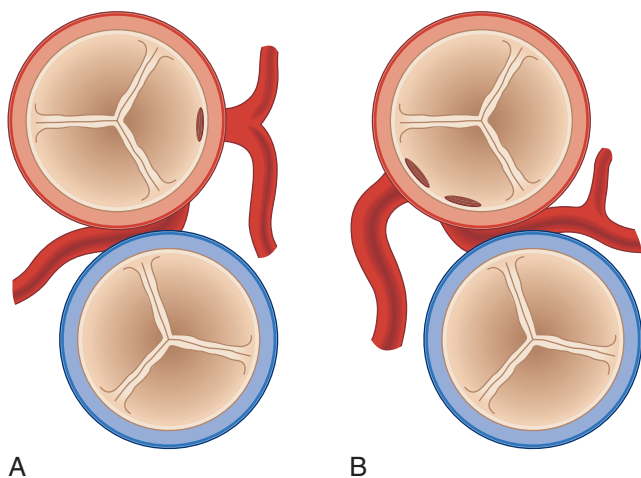


FIGURE 124-11 ■ **A**, Anomalous origin of the right coronary artery from the left aortic sinus with abnormal coursing of the right coronary artery between the aorta and pulmonary artery. **B**, Abnormal origin of the left main coronary artery from the right aortic sinus with abnormal coursing of the left main coronary artery between the aorta and pulmonary artery. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 890.)

when combined with color flow Doppler mapping to identify the anomalous origin. This technique may be necessary because in patients in whom the anomalous vessel courses intramurally within the aortic wall, when two-dimensional imaging is used alone, the anomalous vessel may appear to arise normally where it exits the aorta. Color Doppler imaging can demonstrate the abnormal direction of blood flow within the aortic wall, helping to delineate an anomalous vessel from one that arises normally.

Other noninvasive techniques, such as MRI or CT, may be used when the coronary artery origins cannot be adequately delineated, or to confirm the diagnosis.^{57,58} Occasionally, cardiac catheterization with angiography or transesophageal echocardiography is used to visualize the coronary anatomy; however, these more invasive options are not the first choice in children, although they may be used more often in adults. Indeed, although cardiac catheterization with coronary angiography still remains the gold standard for detecting anomalous coronary arteries, it is being replaced by noninvasive imaging. Coronary angiography may be necessary in adult patients to evaluate for other coronary disease before undergoing surgical intervention.⁵⁹

Most patients undergo further evaluation for myocardial ischemia at rest and stress. This usually includes an exercise stress test with some form of imaging study, such as a nuclear perfusion study or stress echocardiography. However, basing management decisions on a single exercise test may not be reliable, because ischemia is intermittent in patients with an anomalous aortic origin of a coronary artery, so a single test may be normal.⁶⁰ In a study performed at our institution evaluating children with anomalous aortic origin of a coronary artery, 9 of 16 who had a preoperative exercise test had presented with cardiovascular symptoms, but only 1 had an abnormal exercise test.⁵¹ Furthermore, normal exercise tests have been reported in patients who experienced sudden death after the test was performed.

Surgical Management

Indications for Surgery

Surgical intervention is indicated in any patient with anomalous aortic origin of a coronary artery with an interarterial course who has signs or symptoms of myocardial ischemia or ventricular arrhythmias. Furthermore, most would agree that surgery is indicated in asymptomatic patients with anomalous left coronary artery because of the high risk of sudden death. The management of asymptomatic patients with anomalous RCA has not been defined, and the controversy is even greater when treating children and young adults, who appear to have a higher risk of sudden death than those identified later in adulthood.

Surgical Techniques

Unroofing Procedure. The unroofing procedure has become the procedure of choice for patients with anomalous coronary artery with an interarterial and intramural

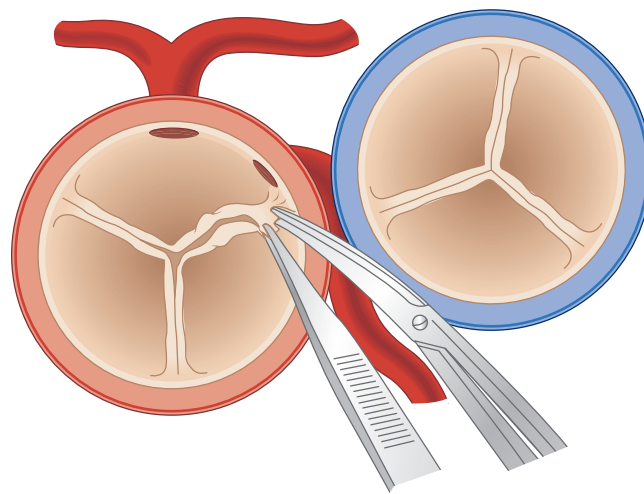


FIGURE 124-12 ■ When the coronary artery arises anomalously from the opposite sinus of Valsalva and courses between the pulmonary artery and the aorta, the ostium is frequently abnormal. Repair may be undertaken by remodeling the ostium. The abnormal ostium is usually located near a commissure, and this commissure must be initially taken down to allow remodeling of the ostium. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 891.)

course.^{51,53,61,62} After the median sternotomy is performed, the pericardium is opened and the anatomy is inspected. Cannulation of the aorta occurs close to the innominate artery, and a two-stage venous cannula is inserted via the right atrial appendage. After cardiopulmonary bypass is established with moderate hypothermia, a left ventricular vent is placed via the right superior pulmonary vein. A cannula is placed in the ascending aorta for administration of cardioplegia solution. The aorta is cross-clamped and cardioplegia solution is administered. A transverse aortotomy is performed after adequate arrest is achieved and the coronary ostia are identified. If the anomalous coronary ostium arises close to the aortic valve commissure, it may be necessary to take down the commissure (Fig. 124-12). To enlarge the often slit-like ostium, it is opened longitudinally starting at the anomalous coronary os and continuing into the correct sinus (Fig. 124-13). A segment of the common wall between the aorta and the coronary is excised, and the intimal surfaces are approximated with interrupted sutures using 8-0 Prolene. If necessary, the aortic valve commissure is resuspended with a pledgeted suture (Fig. 124-14). The aortotomy is then repaired, and the cross-clamp is removed after de-airing. As the patient is rewarmed, close attention should be paid to the ECG to evaluate for signs of myocardial ischemia. The patient is then separated from cardiopulmonary bypass in the usual fashion.

Creation of a Neo-Ostium. An alternative technique that may be used when the anomalous coronary passes intramurally below the aortic valve commissure is the creation of a neo-ostium in the correct sinus. A probe is passed through the intramural segment of the anomalous coronary into the correct sinus. The coronary artery is

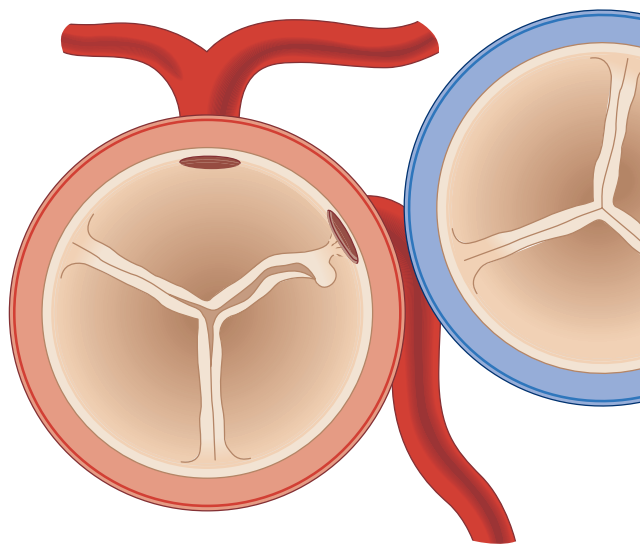


FIGURE 124-13 ■ After the commissure is detached, the abnormal coronary is incised longitudinally, beginning at the abnormal ostium, and this incision is carried into the right aortic sinus. A portion of the common wall between the aorta and coronary is excised. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 892.)

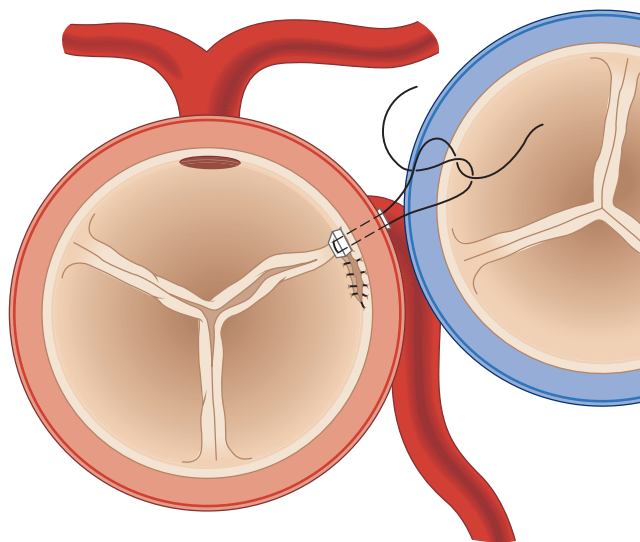


FIGURE 124-14 ■ The walls of the coronary artery and aorta are anastomosed with interrupted sutures of 8-0 polypropylene (Prolene), enlarging the ostium and preventing compression by the great vessels. The commissure of the aortic valve is resuspended with a pledgeted suture. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 892.)

opened at the location where it exits the aorta, and a neo-ostium is created. The intima is sewn to the aortic wall with interrupted sutures. This technique avoids the take-down and resuspension of the commissure.

Other Techniques. When there are two separate coronary ostia with an interarterial but not an intramural course, coronary artery translocation with reimplantation has been advocated.⁶² This is similar to reimplantation

done for the arterial switch procedure as described earlier for the ALCAPA repair. The coronary artery is excised with a button of aortic tissue and usually reimplanted above the commissure in the correct sinus. It has been suggested that compression of the coronary artery between the aorta and the pulmonary artery can be prevented by translocating the MPA to the left pulmonary artery, or by translocating the right pulmonary artery and bifurcation anterior to the aorta, thereby leaving the coronary circulation intact.⁶³ This technique may be used when the anomalous coronary course is not intramural but the ostia are close together. Combining coronary artery patch angioplasty using pericardium in addition to translocating the MPA to the left pulmonary artery has also recently been proposed.⁶⁴ Coronary artery bypass grafting using saphenous vein or IMA grafts may be appropriate in the older adult; however, concern about long-term graft patency in the young patient makes this a less desirable surgical option in children and young adults.

Surgical Results

No data exist regarding long-term neo-ostia patency rates after the unroofing procedure. Short- to mid-term results overall have been reassuring, with no reports of ostial stenosis by echocardiography. However, in a study by Romp and colleagues, one patient developed severe aortic insufficiency requiring aortic valve replacement 44 months after the initial operation.⁵⁴ At our institution in a study by Brothens and colleagues that evaluated children in the short to mid term after unroofing, subclinical evidence of postoperative myocardial ischemia was found in half of the patients with anomalous RCA and in one of eight patients with anomalous left coronary artery.⁵¹ This was despite patent neo-coronary ostia by echocardiography and with the patients remaining asymptomatic during testing. A follow-up study by Wittlieb-Weber and colleagues evaluating these same patients in the intermediate term after unroofing procedure found almost half (46%) of the 24 children experienced perioperative pericardial effusions and 4 (16%) developed mild aortic insufficiency.⁶⁵ The clinical implications of these findings in the long term are unknown, and further evaluations are needed over the next several years.

Although coronary artery reimplantation has been used by some, one study by Rinaldi and colleagues reported that two patients required emergency bypass grafting.⁶⁶ In an analogous procedure used for transposition of the great arteries, long-term follow-up studies demonstrated coronary obstruction in up to 8% of patients, with Pedra and associates noting proximal eccentric intimal thickening by intravascular ultrasound in most patients evaluated at least 5 years after the original surgery.⁶⁷ The long-term success of pulmonary artery translocation procedures is not known.

CORONARY ARTERY FISTULA

A coronary artery fistula is an abnormal communication between a coronary artery and a cardiac chamber or any of the great vessels (coronary sinus, venae cavae, pulmonary artery, or a pulmonary vein).^{68,69} Coronary

arteriovenous fistulas are those that end in right-sided structures, such as the right atrium, right ventricle, or pulmonary artery, whereas those that terminate in left-sided structures are called arterio-arterial fistulas.

Coronary artery fistulas are usually congenital, comprising 0.2% to 0.4% of congenital heart defects, but they make up almost half of all congenital coronary anomalies. They can be found in isolation or in association with other congenital heart disease. Acquired fistulas are the result of cardiac surgery, cardiac catheterization, or a complication from Kawasaki disease.⁷⁰

Anatomy

Coronary artery fistulas may arise from either the right or the left coronary artery; occasionally, both coronary arteries are affected.⁷¹ Most fistulas arise from a coronary artery with an otherwise normal distribution. The fistulous connection may occur in the midportion of the coronary artery with a normal vessel continuing beyond the fistula origin, or as an end artery at the termination of the vessel. The coronary is dilated and elongated in the portion of the vessel proximal to the fistula, usually in proportion to the size of the shunt across the fistulous connection. The portion of the vessel distal to the fistula usually returns to a small diameter.

The right ventricle and right atrium are the most common sites of termination. Fernandes and colleagues reported on 93 patients with coronary artery fistulas.⁷² A single fistula was present in 83 patients, and the other 10 had multiple fistulas. The RCA was the most common site of origin and the right ventricle was the most common drainage site. Fifty-six patients had isolated coronary fistulas, and the others had additional cardiac lesions. Lowe and colleagues reviewed 286 patients and found the RCA to be the site of origin in just over half of the patients, and the left coronary artery system the origin site in approximately one third.⁷³ The right ventricle was the most common site of drainage (39%), with the right atrium (including the coronary sinus and superior vena cava) and the pulmonary artery as the drainage sites in 33% and 20%, respectively. The site of drainage was the left atrium or left ventricle in the remaining 8%.

Pathophysiology

Coronary fistulas result in a left-to-right or left-to-left shunt. When a fistula drains to the right side of the circulation, there is usually a small- to moderate-sized shunt. However, when it drains into a left-sided chamber (i.e., left-to-left shunt), an aortic runoff develops, with physiology similar to that of aortic regurgitation. The effects of the shunt are related to the amount of blood flow from the fistula to the chamber and into which chamber the fistula drains. It can also be affected by myocardial ischemia resulting from coronary circulation steal.

Clinical Presentation

Patients with a coronary artery fistula are usually asymptomatic; they rarely present in infancy and are often diagnosed in adulthood. Many patients are diagnosed during a murmur evaluation. When symptomatic, the most

common complaints are shortness of breath with exercise and fatigue. Even though there may be coronary steal, angina is uncommon. Ventricular dysfunction and congestive heart failure are occasionally present and are much more common in the adult. Atrial fibrillation in an older patient may result from right atrial enlargement caused by a coronary artery fistula to the right atrium.

On examination of a patient with a coronary artery fistula, a continuous murmur is often auscultated. The murmur may be suggestive of a PDA, but it is heard lower on the sternal border, which is an atypical location for a PDA. As is the case with aortic regurgitation, large left-to-left shunts may cause a wide pulse pressure.

Natural History

In patients with congenital coronary arterial fistulas, most likely the fistula was present early in life and gradually increased in size over several years. Despite progressive enlargement of the coronary arteries, spontaneous rupture is rare and usually results from aneurysmal dilation and weakening of the vessel wall as a result of a congenital defect or atherosclerosis. Bacterial endocarditis can occur secondary to turbulent flow. Spontaneous closure of small fistulas has been reported.

Diagnostic Imaging

Depending on the size of the fistula, the ECG may be normal, or it may show evidence of ventricular volume overload. Atrial fibrillation may be noted in older adult patients who have a right atrial fistulous connection. If coronary steal is present, evidence of myocardial ischemia in the affected region may be noted. Chest films are usually normal but may show cardiomegaly or evidence of congestive heart failure. Giant aneurysms of the involved coronary artery can sometimes be noted. Two-dimensional echocardiography can demonstrate the enlarged coronary artery, the origin of the fistula, the chamber into which it drains, and any cardiac chamber enlargement or hypertrophy. The actual fistula may be demonstrated best by color Doppler. MRI is a promising additional noninvasive imaging technique used to diagnose and provide detailed anatomy of the coronary arterial fistula and may take the place of cardiac catheterization, but now it is used as an adjunctive imaging modality.

Coronary catheterization with selective coronary angiography remains the gold standard to accurately define the coronary anatomy and the hemodynamic significance of the fistula. Often, an experienced interventional cardiologist can successfully coil-embolize the coronary artery fistula without the morbidities associated with cardiopulmonary bypass and sternotomy.⁷⁴ However, the indications for coil embolization have not been defined; therefore, most patients undergo surgical closure as the preferred therapy.⁷⁵

Surgical Management

Indications for Surgery

All patients with symptomatic fistulas should undergo closure. Patients with very small fistulas may not require

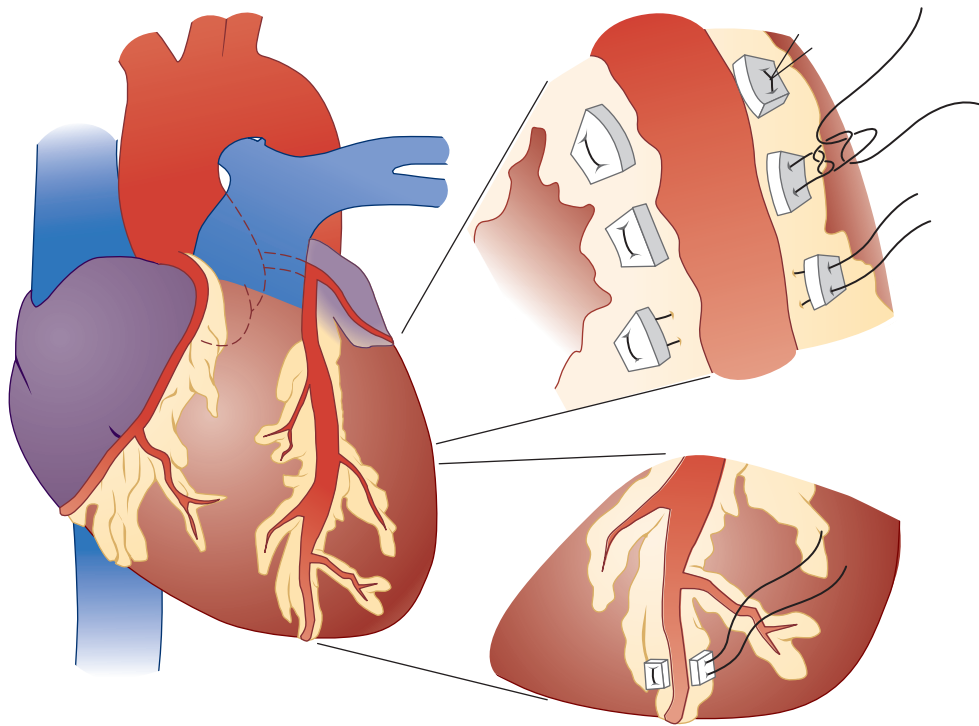


FIGURE 124-15 ■ If the termination site of the fistula is at the distal aspect of the coronary and no significant myocardium is in jeopardy, the coronary may be ligated proximal to the termination site. If the fistula terminates in the midportion of the left anterior descending coronary artery, the fistulous communication may be closed with multiple pledgeted sutures placed underneath the coronary artery so as not to impair distal perfusion. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 888.)

surgical closure; however, because the natural progression of a fistula is to enlarge, these patients should be closely followed.⁷⁶ Asymptomatic patients with moderate to large fistulas should undergo surgical closure electively.

Surgical Techniques

Coronary artery anatomy must be clearly defined by coronary angiography before surgical closure. Each operation should be individualized on the basis of anatomy. Often, the fistula can be ligated or oversewn at its origin or termination without the use of cardiopulmonary bypass; however, cardiopulmonary bypass should always be available.

Through a median sternotomy, the coronary anatomy is visualized and carefully inspected, and the site of the enlarged vessel is noted. The fistula can be ligated without the use of cardiopulmonary bypass when it is located at the distal end of the coronary artery and there is no viable myocardium distal to the fistula (Fig. 124-15). This is performed by placing a ligature around the coronary artery immediately proximal to the fistula, thereby temporarily occluding the fistula. The heart is observed for signs of ischemia, and the ECG is monitored closely. If there are no signs of ischemia and there is adequate myocardial perfusion, the ligature is tied. To ensure complete closure, a second suture ligature should also be placed. Intraoperative transesophageal echocardiography can be used to verify that the fistula is closed.

Cardiopulmonary bypass is indicated if the fistula arises from the middle of a coronary artery, if the fistula is inaccessible, if another cardiac lesion needs to be repaired simultaneously, or if the complete coronary course cannot be completely defined. The aorta and both cavae are cannulated and bypass is initiated. If cardioplegic arrest is necessary, the fistula should be temporarily compressed during administration of the cardioplegia to prevent runoff through the fistula into the heart. If adequate arrest is not possible because of flow through the fistula, retrograde administration of cardioplegia solution may be necessary.

A variety of techniques can be used to close the fistula. If it ends in the midportion of the LAD, the fistulous communication can be closed by placing multiple pledgeted sutures beneath the coronary artery, taking care to avoid compromising distal perfusion (see Fig. 124-15). However, if distal perfusion of the coronary bed is affected after closure of the fistula, coronary bypass grafting may be necessary. Another technique that can be used when the fistula arises from the midportion of the coronary is to open the coronary longitudinally on the epicardial surface and oversee the origin of the fistula from within the coronary artery (Fig. 124-16). The coronary artery can then be closed primarily.

If the fistula terminates in the right atrium or right ventricle, the fistula may be closed directly from within the cardiac chamber (Fig. 124-17). A right atriotomy is performed after cardiopulmonary bypass, and the termination site of the fistula is identified from within the

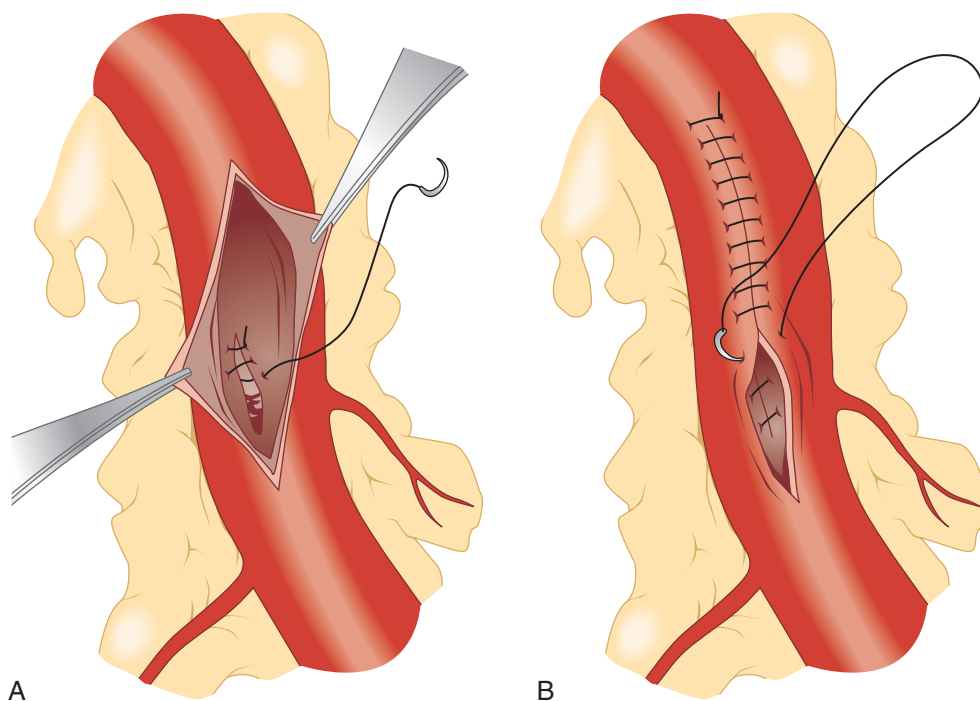


FIGURE 124-16 ■ **A**, When the fistulous communication arises from the midportion of the dilated coronary, the coronary may be opened longitudinally and the origin of the fistula oversewn from within the coronary. **B**, The coronary artery is closed primarily. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 889.)

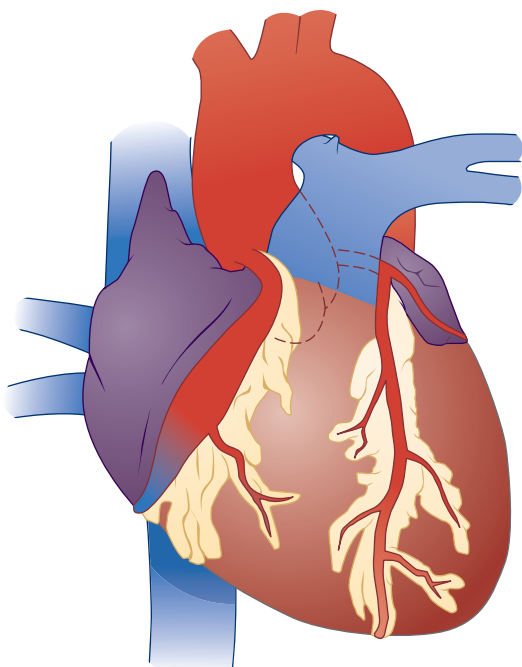


FIGURE 124-17 ■ A coronary arterial venous fistula arising from the midportion of the right coronary artery and terminating in the right atrium. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 890.)

chamber. Using cardioplegia may be helpful for localization. The termination site can be closed primarily or with a pericardial patch (Fig. 124-18).

Surgical Results

The operative mortality rate for coronary artery fistula repair is very low, and late results are outstanding with very few patients experiencing a recurrence of the fistula.^{71,77} Lowe and colleagues reported on 22 patients after surgical closure of coronary artery fistulas.⁷³ In 14 patients, the fistula was closed using sutures without cardiopulmonary bypass. The termination of a fistula within a cardiac chamber was closed using cardiopulmonary bypass in six patients. In the remaining two patients, saphenous vein bypass grafts were necessary to maintain distal perfusion after fistula closure. The operative mortality rate was zero, as was the long-term rate at an average follow-up of 10 years. Although a small residual fistula remained in one patient, there were no recurrences. Fernandes and colleagues reported on 56 patients who had coronary artery fistula closure.⁷² There was no early or late mortality, but two patients had perioperative myocardial infarctions. Finally, Mavroudis and colleagues reported on 17 pediatric patients with an average age of 5.5 years.⁷⁵ Eight underwent fistula closure using cardiopulmonary bypass, and one of these patients needed distal IMA bypass graft. There was complete closure in all patients, and there were no recurrences and no operative or late deaths.



FIGURE 124-18 ■ After institution of cardiopulmonary bypass and induction of cardioplegia, the right atrium is opened, and the termination site of the fistula is identified from within the right atrium. This may be done primarily or with a patch of pericardium. (Reprinted with permission from Gaynor JW: Coronary artery anomalies in children. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 890.)

CONGENITAL OSTIAL ATRESIA OF THE LEFT MAIN CORONARY ARTERY

Anatomy

Congenital atresia of the LMCA ostium is a congenital coronary anomaly that is quite rare, with fewer than 50 reported cases in the literature. In this coronary anomaly, there is no LMCA ostium; rather, the correctly positioned LAD and circumflex coronary arteries have a blind ending and they receive blood flow retrograde through the RCA via at least one collateral vessel.⁷⁸ On the inner aortic surface in the left sinus of Valsalva, there may be a dimple, a blind pouch, or no marking at all. This lesion should be differentiated from a single RCA where blood flow occurs in a centrifugal, or antegrade, manner. Most patients with a single RCA remain asymptomatic, except in the setting of atherosclerosis or other congenital heart defects. The congenital atresia of the LMCA ostium usually occurs in the absence of other structural heart disease; however, associations have been noted with supralvalvar aortic stenosis, VSD with pulmonic stenosis, right coronary ostial stenosis, and PDA and aortic regurgitation.^{78,79}

Pathophysiology

The main pathophysiology from congenital left main ostial atresia is inadequate collateral vessel flow from the RCA. Blood flows from the RCA to the left coronary artery system through collateral vessels, which are smaller in size than the left-sided coronary arteries; thus, there is inadequate blood flow through these smaller vessels to

perfuse the myocardium. This leads to myocardial ischemia and the potential for sudden death and causes these patients to be almost universally symptomatic.

Clinical Presentation

The timing of when these patients present with symptoms can occur at different ages, with some presenting during infancy and others in adolescence or adulthood. Despite age at presentation, almost every patient reported in the literature was symptomatic at diagnosis, although the signs and symptoms were different. The infants and toddlers generally present with heart failure symptoms, including feeding difficulty, failure to thrive, emesis, and dyspnea.^{78,80} Their clinical picture is similar to that of ALCAPA or dilated cardiomyopathy, both of which would need to be ruled out as well. The youngest patients also are more likely to have an associated cardiac defect, suggesting that there are earlier ischemic events from other congenital lesions that may increase the myocardial oxygen demand. School-age children and adolescents may be diagnosed after experiencing syncope, dyspnea, angina, and ventricular tachyarrhythmias, whereas adults are likely to have dyspnea and angina. Indeed, for any age, sudden death may be the first presentation.

Diagnostic Imaging

Accurate diagnostic imaging is essential in this diagnosis because symptoms are nonspecific and can be caused by other diseases. In young children, cardiomegaly with pulmonary congestion as a result of heart failure may be evident on chest radiograph, whereas in adults, the radiograph may be normal. The 12-lead ECG may be normal or may show a variety of abnormalities, including anterolateral Q waves, lateral T wave inversion, right bundle branch block, or ventricular tachycardia. The initial imaging procedure should be transthoracic echocardiography. This is likely to show a dilated left ventricle with poor function and mitral regurgitation, a finding also seen with ALCAPA and dilated cardiomyopathy. Delineation of the coronary artery ostia is essential. The use of Doppler color flow is helpful to demonstrate flow from the RCA retrograde to the left coronary artery system without evidence of blood flowing to the pulmonary artery. Although echocardiographic techniques have improved over the past several years, delineating coronary anatomy and blood flow can be difficult in some cases. Because of this, cardiac catheterization with coronary angiography remains the gold standard and should be performed on any patient who may have either ALCAPA or congenital atresia of the left main coronary ostium. The direction of flow from the RCA to the left coronary system and whether the PA is filled retrograde should be delineated. If any question remains regarding the diagnosis, selective RCA angiography should be performed.

Surgical Management

Once diagnosed, surgery should occur expeditiously because of the high risk of sudden death with this anomaly.

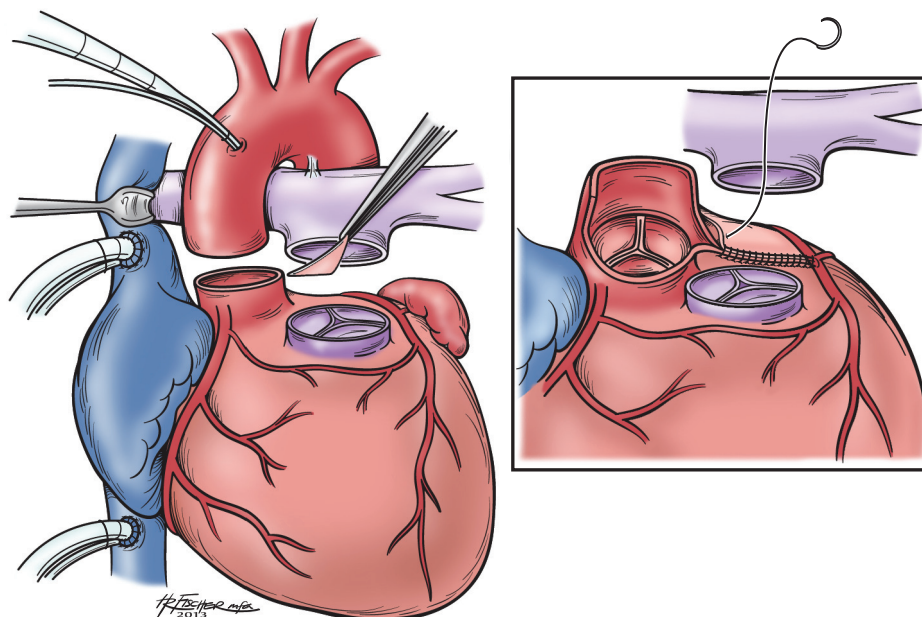


FIGURE 124-19 ■ Technique for ostioplasty of the left coronary ostium with homograft patch. Left coronary ostial atresia before intervention (*main illustration*) and with homograft patch augmentation of the ostium and left main coronary artery (*inset*). (Reprinted with permission from Kaczorowski DJ, Sathanandam S, Ravishankar C, et al: Coronary ostioplasty for congenital atresia of the left main coronary artery ostium. *Ann Thorac Surg* 94:1307–1310, 2012, Fig. 2.)

The literature mainly reports the use of coronary artery bypass grafting (CABG) for all ages.^{78,81,82} Some reports have described the creation of a dual coronary artery system for these patients, with the belief that, similar to ALCAPA, long-term outcomes may be improved.^{80,83,84} This type of surgical revascularization has important implications for children and young adults in whom the bypass graft longevity is of concern.

For the creation of a dual coronary artery system, there have been a few somewhat different surgical techniques described. Varghese and colleagues described the use of an autologous pericardial patch to attain surgical revascularization in a single case of left main coronary ostial atresia.⁸³ The aorta is transected under cardiopulmonary bypass to find the dimple from where the left coronary normally would be located. An incision is made vertically in the aorta to the location of the ostium and then extended down the LMCA; the incision should end prior to the LAD and circumflex coronary artery bifurcation. An atretic membrane, if present, should be removed. An autologous pericardial patch is then used to reconstruct the LMCA ostium that is atretic.

Bonnet and colleagues described surgical revascularization of the left main coronary arteries and included two of the patients with LMCA atresia.⁸⁴ To help attain myocardial preservation, after standard cardiopulmonary bypass, first hot-induction blood cardioplegia, followed by cold blood cardioplegia, and subsequent warm reperfusion are used. The MPA is then transected so that the aortic root and left coronary artery system can be visualized. The aortic incision starts on the anterior portion of the aortic root, continues toward the coronary orifice, and extends beyond the atretic portion. The aortic and coronary incisions are then connected together using an onlay patch, which is obtained from saphenous vein,

autologous pericardium, or PTFE. The creation of this patch enlarges not only the LMCA but also the section of the aorta that was incised, now creating a “funnel-shaped” neo-ostium.

A third revascularization procedure, as described by Kaczorowski and colleagues, is homograft patch ostioplasty in the treatment of LMCA ostial atresia (Fig. 124-19).⁸⁰ Bicaval cannulation is used and cardiopulmonary bypass established. Two of the three children in the report were initially diagnosed with ALCAPA; therefore, their pulmonary artery was opened to evaluate for a coronary ostium. When there was not one identified, an aortotomy was performed. No left main coronary ostium was identified in the aorta. After the blind-ending LMCA was located on the cardiac surface, in two patients, an incision was made in the aortic wall that was directed inferiorly to the aortic sinus. A second incision was made in the LMCA until its division into LAD and circumflex coronary arteries. Using a pulmonary homograft patch, the ostium was enlarged and also joined the aortic sinus to the proximal LMCA. In the third patient, the blind-ending LMCA was sewn onto the posterior aortic wall with anterior augmentation. To help confirm coronary patency, coronary probes should be used as well as noting evidence of back bleeding. The aortotomy is subsequently closed and the patient is removed from bypass.

Surgical Results

Postoperative morbidity and mortality, at least in the short-term, appear to be related to amount of myocardial damage at the time of diagnosis and operation. If LMCA ostial atresia is recognized early and the patient has enough collateral vessels, then short-term results are encouraging after surgical revascularization, notably with

those procedures that establish a dual coronary system. However, long-term outcome data are lacking in this population. Long-term results from CABG used for other coronary arterial abnormalities (e.g., ALCAPA) remain somewhat uncertain, although some reports using IMA grafts have shown good results.

OUTCOMES

Surgical outcomes after repair of anomalous coronary artery arising from the pulmonary arteries have significantly improved over the past several years, even in the high-risk patients who present with significant left ventricular dysfunction and mitral regurgitation. Overall survival is now greater than 90%. Mitral valve repair is rarely needed, even in patients with severe preoperative mitral regurgitation. Long-term outcome data are limited, particularly with regard to left ventricular function and late mortality. The data suggest that establishing a dual coronary system is associated with overall improved survival and left ventricular function when compared with simple ligation of the anomalous artery.⁸⁵

Similarly, there are limited data on long-term morbidity and mortality after surgical repair of anomalous aortic origin of a coronary artery coursing between the aorta and the pulmonary artery.^{13,60,65,86} Surgical mortality appears to be rare. It is unknown whether these surgical techniques truly reduce the incidence of myocardial ischemia and sudden cardiac death. After surgical closure of coronary artery fistulae, mortality is minimal with a low recurrence rate and excellent long-term outcome.^{72,75} No long-term data are currently available for operative mortality after LMCA ostial atresia repair. Short-term results are encouraging when there is early recognition of the anomaly, the patient has adequate collateral vessels, and surgical revascularization consists of establishing a dual coronary artery system.^{80,83,84}

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TRANSPOSITION OF THE GREAT ARTERIES: SIMPLE AND COMPLEX FORMS

Frank A. Pigula • Pedro J. del Nido

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SUMMARY

HISTORY

Transposition of the great arteries (TGA) was first recognized and described more than 2 centuries ago. Although reference was made to malposition of the aorta and pulmonary artery by Steno in 1672 and Morgagni in 1761, the anatomic description of TGA is credited to Baillie in 1797.¹ It was Farre in 1814 who introduced the term *transposition of aorta and pulmonary artery*, meaning that the aorta and pulmonary artery are displaced across

the ventricular septum.² An attempt to classify the various types of transposition was reported by von Rokitsansky, and the first clinical recognition of TGA in life was noted by Fanconi in 1932.^{3,4} In 1938, Taussig described the pathologic anatomy and hemodynamic and clinical characteristics of the cardiac defect.⁵

With the development of cardiac surgery in the 1950s, effective therapy for this disease is relatively new. Initial treatments were palliative and included atrial septectomy, first described by Blalock and Hanlon.⁶ The first successful attempts to reroute the circulations were at the atrial

level. These attempts were followed later by successful arterial level repair and correction of TGA and ventricular septal defect (VSD). These developments are further described in this chapter.

EPIDEMIOLOGY

Today TGA is known to be relatively common, accounting for 9.9% of infants with congenital heart disease, or 0.206 of 1000 live births, in one New England study.⁷ The 2:1 male-to-female ratio increases to 3.3:1 when the ventricular septum is intact.⁸ In complex forms of transposition, gender predominance has not been noted. If TGA is not treated, 90% of children with D-TGA (see [Classification and Embryology](#) section for explanation of D-TGA) and intact septum will die by 1 year of age.

CLASSIFICATION AND EMBRYOLOGY

TGA is generally classified as a type of conotruncal abnormality, a group of abnormalities that has a common theme of deranged development of the cardiac outflow tract. In this disease, there is ventriculoarterial discordance—the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. The more common form of the disease is associated with otherwise normal cardiac structural relationships, including normal ventricular (D) looping. There is atrioventricular concordance but ventriculoarterial discordance {S,D,D}. This set of relationships is commonly referred to as D-transposition (D-TGA). In this form of TGA, the aorta is, by definition, anterior and to the right of the pulmonary artery. This pattern results in the systemic and pulmonary circulations performing in parallel rather than in series. As a consequence, deoxygenated blood is continuously pumped to the body and never passes through the lungs, and oxygenated blood is recirculated through the lungs and does not supply the rest of the body. For the patient to survive, there must be an obligatory shunt elsewhere, usually at the level of the atrial septum, that allows mixing of oxygenated and deoxygenated blood.

Although some have used the term *transposition* to describe a discordant ventriculoarterial connection, other authors have used this term to describe any heart in which the aorta is anterior to the pulmonary artery. The term *TGA* has also been used to describe some patients with double-inlet ventricle or absent atrioventricular connection and patients with nonlateralized atrial arrangements (some heterotaxy syndromes). *D-TGA* has been used to describe a concordant atrioventricular and discordant ventriculoarterial arrangement, but this nomenclature does not adequately describe patients in whom the aorta is anterior and to the left of the pulmonary artery. Thus, in this chapter, complete TGA is defined as normal atrial situs, atrioventricular concordance, and ventriculoarterial discordance.

Several theories have been advanced regarding the morphogenesis of the abnormal relationship between the great arteries and the ventricles in patients with TGA. It has been suggested that the subaortic conus persists and

develops during normal looping of the ventricles while the subpulmonary conus undergoes absorption and thus establishes eventual fibrous continuity between the mitral and pulmonary valves, the reverse of the normal situation.⁹ In the normal heart, the subaortic conus does not grow, and dominant growth of the pulmonary conus forces the pulmonary valve anterior, superior, and to the left. In transposition, differential growth of the subaortic conus pushes the aorta anteriorly and disrupts aortic to mitral valve continuity. If the subpulmonary conus fails to develop, the pulmonary artery will maintain a posterior location and pulmonary to mitral valve continuity will occur. As a consequence of this relationship, the aortic valve becomes anterior to the pulmonary valve, permitting both semilunar valves to connect with the distal great vessels without the rotation that is hypothesized to occur in normal cardiac development. Because conal development determines rotation of the truncus arteriosus, the great arteries are similar in relationship at the semilunar valves as they are at the arch, resulting in no twist in the great arteries.

Some debate also exists about the relationship between the various conotruncal abnormalities, which include tetralogy of Fallot and double-outlet right ventricle. Recent evidence suggests that TGA may be unique in that it is not seen in the spectrum of conotruncal abnormalities generated from the most common experimental model of these disorders.¹⁰ A new animal model, which is the most reliable to date for producing isolated D-TGA, suggests that TGA may be the result of abnormal migration of neural crest cells during a critical phase of outflow tract development.¹¹

ANATOMY

Anatomic variations in TGA can increase the surgical complexity of repair, described later in this chapter. Normal atrial situs occurs in 95% of patients, whereas left-to-right juxtaposition of the atrial appendages signals the presence of other intracardiac anomalies. Although a true ostium secundum atrial septal defect (ASD) is present in 10% to 20% of cases, most atrial communications are through a patent foramen ovale. Right aortic arch is present in 4% of patients with intact ventricular septum and up to 16% of those with VSD.¹² Up to 50% of patients with TGA have an associated VSD, many of which spontaneously close.¹³ The VSDs are commonly perimembranous, although they may be found anywhere in the ventricular septum. Pulmonary stenosis or atresia, overriding or straddling atrioventricular valves, coarctation of the aorta, and interruption of the aortic arch have all been noted in association with transposition and VSD.

The spatial relationship of the great vessels is variable; however, the aorta is most frequently to the right and anterior to the pulmonary artery. In almost all cases, the sinuses of Valsalva and the coronary artery ostia face the corresponding pulmonary arterial sinuses. This situation is favorable for transfer of the coronary arteries with the arterial switch operation, although the origin of a coronary artery from a nonfacing sinus poses a problem for arterial switch in only a small number of patients. Many

	G.*	Q.	Y.
Usual coronary anatomy in TGA 68%	A I	1LCx-2R	A
Circumflex coronary from the right coronary artery 14%	AB I	1L-2CxR	D
Single right coronary artery 4.5%	B I	2LCxR	—
Single left coronary artery 1.5%	A II	1RLCx	—
Inverted origin of the coronary arteries 3%	B II	1R-2LCx	—
Inverted origin of the circumflex and right coronary artery 7%	AB II	1RL-2Cx	E

*G., Gittenberger-de-Groot; Q., Quaegebeur; Y., Yacoub

FIGURE 125-1 ■ The six most common types of coronary artery anatomy in transposition of the great arteries (TGA). Descriptive classification is on the left, and three simplified classification codes are on the right. CCA, Circumflex coronary artery; LAD, left anterior descending artery; RCA, right coronary artery.

classification systems have been used to describe the coronary anatomy in TGA. The most widely accepted scheme within the surgical community is the Leiden classification system, which is depicted with the other common systems of classification in Figure 125-1. The most common coronary pattern in D-TGA (68%) consists of the left main coronary arising from the leftward coronary sinus, giving rise to the left anterior descending and circumflex coronary arteries.¹⁴ The right coronary artery arises as a separate ostium from the rightward

posterior-facing sinus. Occasionally, there is no true circumflex coronary artery, but separate branches arise from the left coronary to supply the corresponding portion of the left ventricle. In up to 20% of cases, the circumflex coronary arises from the right coronary artery off the rightward posterior-facing sinus and passes behind the pulmonary artery. The left anterior descending artery then arises from a separate coronary ostium off the left coronary sinus. More rare coronary patterns involve a single right coronary artery from the rightward posterior sinus (4.5%) or a single left coronary artery from the leftward coronary sinus (1.5%).¹⁵ Intramural coronary arteries that proceed in the aortic wall for a distance before exiting to the epicardial surface have been described and commonly occur at the commissural attachment of the semilunar valve.¹⁶ A single coronary ostium or separate ostia close together arising from a single sinus have also been described. Abnormal coronary anatomy is more commonly seen in transposition with VSD than in the intact septum variety. Abnormal coronary patterns have also been found to be more common when the relationship of the great arterial trunks is not usual (aorta anterior and to the right).¹⁷

CLINICAL FEATURES

In complete TGA, the pulmonary and systemic circulations exist in parallel instead of in series. This results in nonoxygenated venous blood passing through the right ventricle to the aorta while the oxygenated pulmonary venous blood passes through the left ventricle back to the pulmonary arterial circulation. Mixing between the pulmonary and systemic circulations through a patent foramen ovale or ASD, a VSD, or a patent ductus arteriosus (PDA) is mandatory for survival. Patients with TGA and an intact ventricular septum survive initially because of aortopulmonary flow through a PDA. After birth, both ventricles are relatively noncompliant, and infants with TGA often have an increased pulmonary blood flow, which causes enlargement of the left atrium and functional incompetence of the foramen ovale, resulting in atrial-level mixing of oxygenated and nonoxygenated blood. Inadequacy of this mixing, however, may result in only marginal tissue oxygenation, which does not improve with oxygen administration.

Patients with TGA and significant VSD often have higher oxygen saturations by virtue of greater pulmonary blood flow and greater mixing at both atrial and ventricular levels. In children with high pulmonary blood flow, pulmonary resistance may progressively increase throughout infancy. Ferencz has observed significant histologic changes in children older than 2 years of age with TGA, and children as young as 1 month of age have had intimal fibrosis noted in the pulmonary arteries.¹⁸ This early development of severe pulmonary vascular disease in children with TGA is exacerbated in patients with associated VSD, but early important pulmonary vascular disease can occur in patients with TGA regardless of the presence of a VSD as demonstrated by Ferguson in 1960 and Ferencz in 1966.^{18,19} The rapidity of development of pulmonary obstructive disease may be related to

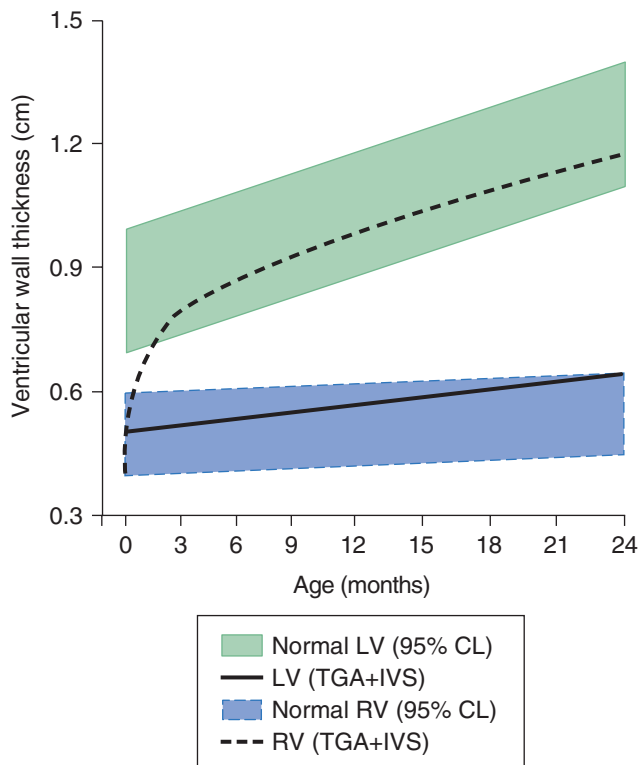


FIGURE 125-2 ■ The normal left ventricular (LV) wall thickness in transposition of the great arteries (TGA) after birth. The *solid line* shows the decreased development of LV mass in TGA that results from a rapid decrease in pulmonary vascular resistance and drop in LV pressure. The *upper bar* shows an increase in LV thickness with normally related great arteries. The *dashed line* shows the similar increase in right ventricular (RV) muscle mass over time in TGA. CL, Confidence limits; IVS, intact ventricular septum.

hypoxemia associated with increased sympathetic activity and in association with excessive pulmonary blood flow.²⁰

Although neonatal pulmonary vascular resistance is normal in infants with TGA, the resistance falls progressively during the neonatal period with associated changes in the pulmonary and systemic ventricular compliance. Shortly after birth in the normal infant, there is an increase in the left ventricular volume load and pressure load and a decrease in right ventricular volume and pressure load. These physiologic changes result in a rapid increase in the left ventricular myocardial mass.²¹ This normal development of the left ventricle is lost in infants with D-TGA where the left ventricle ejects to the lower resistance pulmonary vascular bed (Fig. 125-2). Thus, the left ventricle does not increase muscle mass relative to the right ventricle, and within a few weeks it loses the ability to maintain adequate cardiac output against significant afterload. This change occurs despite the fact that the left ventricle still maintains a volume load in patients with transposition and an intact ventricular septum. When, however, a VSD or large PDA is present, both volume and pressure overload of the left ventricle is maintained, and in D-TGA with left ventricular outflow tract (LVOT) obstruction without a VSD, a ventricular pressure load is imposed without a significant volume load. These physiologic changes in the neonatal heart are important for the consideration of surgical approaches

because after a few weeks to months of postuterine life, the left ventricle in D-TGA with intact ventricular septum takes on the characteristics and wall thickness of a pulmonary ventricle and may not be adequate to support the systemic circulation.

The most common clinical finding in the infant with TGA is cyanosis (arterial PO_2 of 25 to 40 mm Hg), which will vary in degree depending on associated anomalies. Typically, the cyanosis is more pronounced when the ventricular septum is intact and is often present at birth. The development of cyanosis later in infancy is usually associated with the presence of a significant VSD. Congestive heart failure may be the predominant clinical finding in patients with a large VSD or PDA, and the combination of cyanosis and increased pulmonary blood flow is almost pathognomonic of TGA in the infant. Symptoms of cardiac failure rarely present in the first week of life but commonly appear by 1 month of age as pulmonary vascular resistance decreases and pulmonary blood flow becomes excessive, even in the patient with an intact ventricular septum.

DIAGNOSIS

Physical Examination

Cardiac examination typically reveals a mildly overactive precordium, and 75% of patients with TGA and an intact ventricular septum have a soft systolic murmur. The second heart sound is typically single and loud because of the proximity of the aorta to the anterior chest wall, which may make assessment of pulmonary vascular resistance difficult.²⁰ End-diastolic gallop rhythms are often noted in patients with associated VSD. In the presence of a large PDA, the femoral pulses are often bounding. The liver may be enlarged in patients with a large systemic-to-pulmonary shunt and may be associated with tachypnea, intercostal retractions, and inability to successfully nurse. Children with significant valvular or subvalvular pulmonary stenosis often have a crescendo-decrescendo cardiac murmur along the left sternal border transmitted to the right clavicular area.

Diagnostic Studies

The electrocardiogram may be normal at birth but over time shows signs of increasing right ventricular or biventricular hypertrophy. Chest x-ray findings in D-TGA include an egg-shaped cardiac configuration, narrow superior mediastinum, and increased pulmonary markings with cardiomegaly.

The widespread use of fetal ultrasound techniques has resulted in the common antenatal diagnosis of TGA. This fact and the fact that most children with TGA are cyanotic in the first week of life have led to the initiation of treatment at a very early age. Whereas in the past, cardiac catheterization was generally necessary to confirm the diagnosis of TGA and to demonstrate the position of the cardiac chambers and the associated lesions, echocardiography is now usually all that is necessary in most cases. Echocardiographic views confirming a posterior

great vessel that divides into right and left pulmonary arteries and arises from the left ventricle in association with an anterior aorta arising from a right ventricle confirms the diagnosis of TGA.

The intracavitary shunts can be determined by Doppler echocardiography techniques, and several echocardiographic views can determine the size and location of VSDs with reference to the infundibular septum, the nature and size of atrial communications, the anatomy of the atrioventricular valves, and the presence and location of significant degrees of subpulmonary stenosis. In addition, in most cases the origins and anatomic distributions of the coronary arteries can be adequately visualized by echocardiography. Because most coronary arterial variations can be successfully addressed at operation, identification of the origins of the coronary arteries is usually sufficient by echocardiography to preclude angiography. Cardiac catheterization is now indicated only in infants in whom inadequate shunting is noted or in infants with associated intracardiac or extracardiac abnormalities that require clarification. It is usually reserved for the purpose of enlarging the interatrial septal communication in those patients with significant clinical instability characterized by acidemia or severe hypoxemia (see following).

PREOPERATIVE MEDICAL MANAGEMENT

Patients who are good anatomic candidates for an arterial switch procedure and have acceptable arterial oxygen saturation are generally referred for early operation if the clinical condition permits. Prostaglandin E1 is usually administered to maintain ductal patency, increase pulmonary blood flow, and improve stabilization of patients before early operative repair. Because relative dehydration can decrease the degree of interatrial shunting, volume infusions may improve hemodynamics in infants presenting with TGA and intact septum early in life. A major development in the treatment of TGA occurred in 1966 when Rashkind and Miller reported the use of a balloon catheter technique to enlarge the ASD in patients with TGA, causing improved early physiologic stability.²² If there is significant instability, as evidenced by persistent acidemia or hypoxemia despite conservative measures, the mainstay of management has become a Rashkind balloon atrial septostomy.

In the neonate with TGA, left atrial pressure is usually greater than the right atrial pressure. The pressure in the pulmonary (left) ventricle is dependent on the presence or absence of a VSD, valvar or subvalvar stenosis, the age of the patient, and the pulmonary vascular resistance. If inadequate interatrial shunting is noted, a Rashkind atrial septostomy is performed.²² A balloon-tipped catheter is passed through the systemic veins, through the right atrium and foramen ovale, and into the left atrium; the balloon is inflated and pulled vigorously across the atrial septum to tear the foramen ovale, improving the admixture of pulmonary and systemic venous blood and tissue oxygen delivery. Although this procedure is usually performed at cardiac catheterization, it can be performed in the intensive care unit with echocardiographic guidance

in children who are very unstable. Performance of a Rashkind atrial septostomy results in decompression of the left ventricle and therefore may result in poor left ventricular performance if a subsequent arterial switch procedure is delayed.

SURGICAL MANAGEMENT

Surgical Correction

Satisfactory correction of TGA results in rerouting of systemic venous blood to the pulmonary circulation and the pulmonary venous blood into the systemic arterial circulation. This may be accomplished at the atrial, the ventricular, or the great arterial level. The earliest repairs of TGA involve rerouting of the systemic and pulmonary venous returns at the atrial level, resulting in a physiologic but nonanatomic repair, as the morphologic right ventricle continues to function as the systemic ventricle. Both ventricular (Rastelli) and great arterial (arterial switch, aortic translocation) repairs are anatomic corrections, resulting in a morphologic left ventricle as the systemic ventricle.

Palliative Operations

Reported by Blalock and Hanlon in 1950, initial surgical therapy for TGA involved creation of an ASD using a closed technique to increase the mixing between systemic venous and pulmonary venous circulations.⁶

Although the early mortality rate was high with this operative approach, successful creation of an ASD resulted in significant palliation in many of these children. The introduction of the balloon atrial septostomy has essentially eliminated the need for operative atrial septectomy. Infants with associated cardiac abnormalities and a thick atrial septum who are considered for later atrial baffle repair may benefit from the Blalock-Hanlon technique, although the safety of cardiopulmonary bypass (CPB) has resulted in the common use of open atrial septectomy in these patients.

Pulmonary arterial banding has been used for palliation in patients with TGA and VSD in young infants who have intractable congestive heart failure until operative repair at 3 to 6 months of age. Because the results from use of the arterial switch procedure and VSD closure in infancy have improved, banding in most cases is unnecessary because complete repair can be accomplished in the neonatal period. Therefore, banding of the pulmonary artery has now been limited to very small neonates who might benefit from delay in corrective operation, patients with complex TGA for whom delayed repair is planned (i.e., LVOT obstruction), patients presenting late with TGA and intact ventricular septum who require preparation of the left ventricle prior to receiving an arterial switch operation, and patients who develop right ventricular dysfunction and failure after atrial baffle operations as a component of staged conversion to an arterial switch repair (see below). Pulmonary arterial banding in TGA is a delicate procedure, because limitation of pulmonary blood flow results in significant hypoxia and

metabolic acidosis, and loose banding results in inadequate protection of the pulmonary vascular bed and poor development of the left (pulmonary) ventricle. Thus, in many situations in which the left ventricle is prepared for conversion to an arterial switch procedure, banding must be associated with creation of an aortopulmonary shunt to maintain adequate pulmonary blood flow and prevent hypoxemia and ventricular dysfunction.

Atrial Repairs

Initial attempts to reverse the transposed vessels in patients with TGA by both Mustard and Bailey and their colleagues were frustrated by their inability to maintain coronary perfusion and by poor function of the anatomic left ventricle.^{1,23} Thus, initial surgical therapy was directed toward atrial transposition of pulmonary and systemic venous returns. In 1952, Lillehei and Varco transferred the right-sided pulmonary veins to the right atrium and connected the inferior vena cava to the left atrium.²⁴ A successful modification of this technique using an allograft to connect the inferior vena cava to the left atrium was described by Baffes in 1956.²⁵ In 1955, Albert suggested the concept of switching the atrial septum so that caval return was directed to the left ventricle and pulmonary venous return to the right ventricle at the atrial level.²⁶ This atrial switch concept was first successfully accomplished by Senning in 1959, using an ingenious technique for relocating the walls of the right atrium and the atrial septum.²⁷ In this operation, pulmonary and systemic venous return was rerouted by incising and realigning the atrial septum over the pulmonary veins and using the free right atrial wall to create a pulmonary venous baffle (Fig. 125-3). The Senning operation was not associated with a

high survival rate at first because of its complexity and because of the fact that the operation was performed in children between 1 and 2 years of age or children with a VSD, and significant pulmonary vascular obstructive disease had already developed in many of these children.

In 1964, Mustard described an alternate procedure for intra-atrial repair excising the atrial septum and creating a large interatrial baffle of pericardium to redirect pulmonary and systemic venous blood (Fig. 125-4).²⁸ This repair resulted in a larger atrial size than the Senning operation. In the Mustard operation, creation of a virtual common atrium is necessary with resection of the atrial septum and the ridge of tissue between the superior vena caval entrance and the superior aspect of the atrial septum. Inadequate resection of the atrial septum has resulted in the occurrence of baffle obstruction of the systemic venous return to the heart. Early results with the Mustard operation were markedly improved over the previously reported Senning repairs and reflected the significant number of patients in Toronto who had had successful Blalock-Hanlon atrial septectomies early in life. Because of its technical simplicity, the Mustard operation became the most commonly performed procedure for transposition during the 1960s, and it became clear that repair in the first few months of life could be accomplished with a low operative mortality rate and improved results compared with repair at a later age. In 1970, the Senning procedure reemerged as the persistent problems of baffle obstruction and arrhythmias following the Mustard operation became well defined, and the ability to use autologous tissue for the atrial reconstruction became a preferred approach. Performing the Senning operation in infancy after successful balloon atrial septostomy became the preferred technique in many centers.

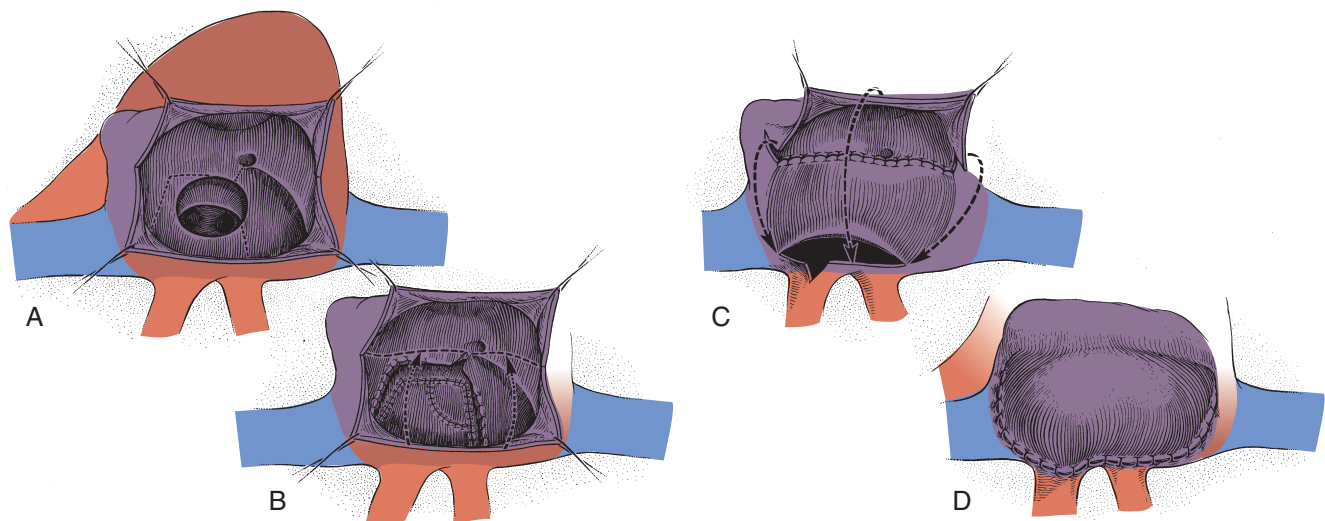


FIGURE 125-3 ■ The Senning operation. **A**, View from the right atrium showing incision lines (*dashed lines*) to create a flap of the posterior atrial septum and an incision into the base of the coronary sinus. **B**, The posterior flap of atrial septum is augmented with a piece of pericardium and sutured inferiorly over the origins of the pulmonary veins in the left atrium. The posterior wall of the right atrium is then sutured to the anterior portion of the atrial septum, baffling the vena caval return across the septum to the mitral valve. **C**, After completion of the venous baffle, the anterior wall of the right atrium is sutured to an opening made in the left atrium posterior to the interatrial septum at the entrance point of the right pulmonary veins, baffling the pulmonary venous blood over the systemic venous pathway into the right ventricle. **D**, Completed suture line showing repair with autologous tissue.

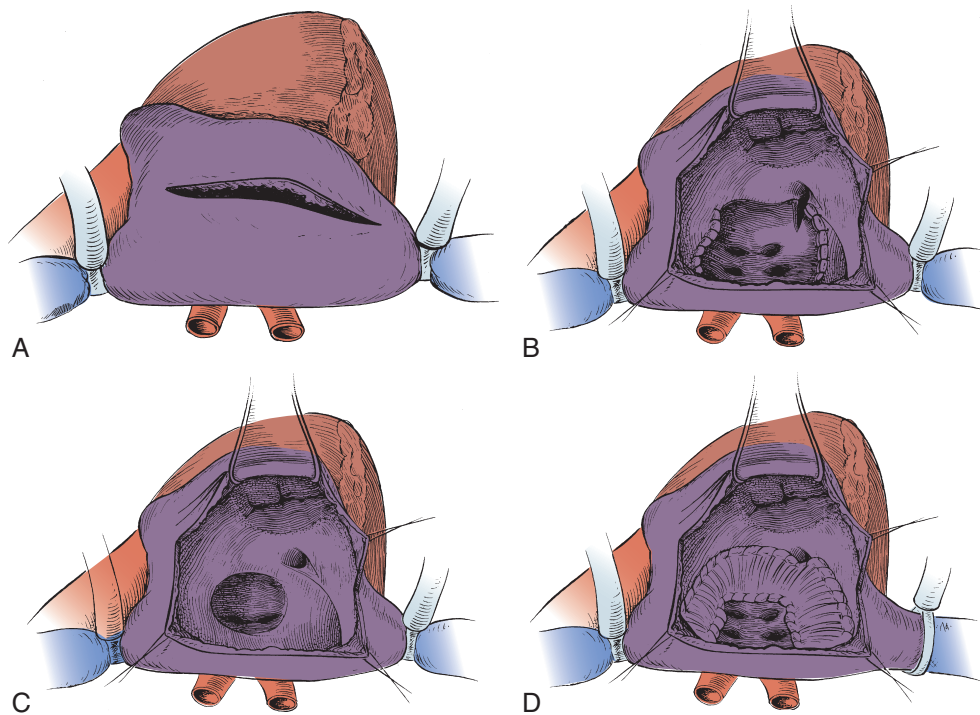


FIGURE 125-4 ■ The Mustard operation. **A**, Longitudinal incision is made in the right atrium away from the sinus node. **B**, The posterior aspect of the atrial septum is excised, creating a wide opening for baffling of the venous blood into the left atrium (*dotted lines*). **C**, The coronary sinus is cut back into the left atrium to avoid suturing near the atrioventricular node. Raw margins of atrial septum may be oversewn. The suture line for the placement of the baffle around the pulmonary veins is noted with the dotted line. **D**, Dacron or pericardium is used to baffle the vena caval blood flow to the left atrium across the mitral valve. Completion of this baffle allows venous blood to enter the right atrium and cross the tricuspid valve to the aorta.

Outcome after Senning and Mustard Operations

The Senning and Mustard operations share the feature of placing the right ventricle and the tricuspid valve in the systemic circulation. The children who undergo these operations are physiologically, but not anatomically, repaired. Both of these operations theoretically create the substrate for late complications. The first atrial switch type operation was described in the 1950s, and ample time has passed to observe and evaluate the results.

Overall outcomes of these two operations have been good. As techniques improved, the use of either Senning- or Mustard-type repairs in infancy was noted to be associated with a lower incidence of cerebral thrombosis and hypoxic injury as a result of cyanosis and peripheral emboli from right-to-left shunting. A standard approach developed using balloon atrial septostomy in infancy followed by the elective repair in infants between the ages of 3 and 8 months. Operative mortality rates in many larger series ranged between 2% and 10%, even for patients in early infancy.²⁹⁻³¹ Long-term actuarial survival rates for all patients with TGA undergoing atrial switch procedures is reported to be 88% at 10 years, 76% to 82% at 20 years, and 74% to 77% at 25 years.³² Results are slightly better in isolated TGA compared with TGA associated with VSD or other complicating conditions.

Late systemic (right) ventricular dysfunction occurs in 5% to 25% of patients. It is the most common cause of late mortality, being the cause of death in approximately

6% of patients in one large series.²⁹ Several challenges exist in following these patients. The reported incidence of late right ventricular dysfunction is variable. However, if right ventricular function is evaluated objectively, the systemic right ventricle virtually always functions abnormally compared with controls.

Echocardiographic analysis of right ventricular longitudinal shortening shows that right ventricular function could be judged abnormal in all 20 patients studied, depending on the parameter evaluated.³³ However, there has also been some difficulty in predicting which patients with measurable right ventricular dysfunction will progress and require further intervention. It has been suggested that late right ventricular dysfunction may be at least partially the result of perfusion defects, which are common in these patients, although the cause is unclear.³⁴ Another group suggests that marked increase of the right ventricular muscle mass (hypertrophy) in response to systemic afterload may be a contributor.³⁵

Late functional outcome has been reported to be good. One series with good long-term follow-up reported 66% of patients in New York Heart Association (NYHA) class I and 29% in class II.³² It should be noted that even in the asymptomatic patients, a significant percentage had suboptimal maximal oxygen uptake (MVO_2) when tested. A similar finding was noted by Ebenroth, who studied patients an average of 14 years after surgery and found that 75% had normal right ventricular ejection fractions and 84% perceived themselves to be in good health, but only 51% had normal exercise tolerance.⁴¹

Varied results from exercise testing in these patients have been reported. One study showed a decrease in the normal cardiovascular response to exercise over time.³⁶ Another showed no decrease in MVO_2 with aging, but maximal oxygen consumption in these patients was significantly less than that of individuals without congenital heart disease.³⁷ This finding was corroborated by a study using magnetic resonance imaging in a group of adult patients after atrial level repair.³⁸ Abnormal cardiac recovery after exercise was found despite the patients being in NYHA class I and on no medications. An echocardiographic study suggested that abnormalities in function during exercise might be caused by impaired atrioventricular transport leading to reduced stroke volumes with stress.³⁹

Late arrhythmias are common after atrial switch procedures. At a median follow-up of 23 years, only two thirds of patients are in sinus rhythm, and two thirds have experienced supraventricular tachycardia.³² Risk factors for supraventricular tachycardia include pulmonary hypertension and a history of junctional rhythm. A separate study found arrhythmias in 22% of patients an average of 23 years after the Mustard procedure and found that ventricular function was compromised in these patients compared to Mustard patients without arrhythmias, suggesting that late arrhythmias are a marker for systemic ventricular dysfunction.⁴⁰ By 14 years after surgery, pacemakers were required in 22% of patients for either sick sinus syndrome or bradycardia because of heart block.⁴¹

Treatment for right ventricular dysfunction in these patients is evolving. Because of the hypertrophy of the right ventricle, some have suggested angiotensin-converting enzyme (ACE) inhibition, which has been shown to be beneficial in left ventricular remodeling. Although there are some encouraging data for this patient population, results have not been consistent.⁴² There are several surgical options to deal with late right ventricular failure after atrial switch: tricuspid valve repair or replacement if the ventricular dysfunction is associated with severe tricuspid regurgitation, conversion to an arterial switch, or heart transplantation. Because severe right ventricular dysfunction is frequently, if not always, associated with severe tricuspid regurgitation in these patients, the first option seems an attractive one. The results have been disappointing, however, with no significant improvement in function after surgery.²⁹

In summary, overall functional results after atrial switch procedures have been good after mid- and long-term follow-up. However, assessment of the systemic right ventricle reveals that its function is not normal in the systemic circulation. There are significant risks for progressive late right ventricular dysfunction and late arrhythmias, and for heart failure. As patients age, they must be followed closely for these complications, and means of treatment must be refined.

Arterial Repairs

In spite of the excellent results with the Mustard and Senning procedures, both operations are associated with physiologic, and not anatomic, correction. The

morphologic right ventricle remains the systemic ventricle in these patients, and although most patients have had many years of successful function of the right ventricle as the systemic ventricle, concerns about its long-term function remain. Although it may not be inevitable that systemic morphologic right ventricles will fail with time, a considerable number of patients have now returned after an atrial baffle operation with complications of intractable atrial arrhythmias and right ventricular failure. Thus, there has been increasing interest in the more anatomic correction by the arterial switch operation in hopes of preventing late ventricular dysfunction and arrhythmias.

The success with the atrial switch operations for TGA with intact septum did not translate to repair of transposition with large VSD. Disappointing results with VSD closure and atrial repair in this group of patients continued to be a stimulus for development of an arterial switch procedure that was first successfully performed by Jatene and colleagues in 1975 and subsequently reported by Yacoub and coworkers.^{43,44} The success of the arterial switch procedure with reimplantation of the coronary arteries in some patients with TGA and VSD led to reintroduction of this technique for patients with intact ventricular septum. Yacoub's initial attempts in patients with TGA and an intact ventricular septum were unsuccessful in 1972; however, additional reports by 1976 suggested that such repair was possible in infancy.⁴⁵ Early mortality with the arterial switch in infancy was related to the development of pulmonary vascular obstructive disease and the complexity of the operation and to the fact that the left (pulmonary) ventricle was not prepared to sustain systemic pressure. Therefore, initial approaches included pulmonary arterial banding as a first stage, followed by arterial switch at a later time.⁴⁵ However, improvements in the techniques of coronary transfer, myocardial protection, and neonatal vessel reconstruction have resulted in improved survival statistics in the arterial switch. Brawn, Castañeda, Quaegebeur, and their associates subsequently demonstrated the feasibility of repair of simple transposition in the first few days of life by arterial switch operation while the pulmonary ventricle has a relatively high pressure producing results that rival or exceed those of atrial baffle operations.⁴⁶⁻⁴⁸

Technique

The principles of successful anatomic correction include dividing the aorta and pulmonary artery, excising the origins of the coronary arteries with a button of aortic wall, repositioning the coronary arteries to the posterior great vessel (pulmonary artery), and reconstructing each ventricular outflow to the appropriate distal vessel (Fig. 125-5). The details of the operative techniques, however, vary from one institution to another. The procedures are performed with a median sternotomy incision and the use of CPB and hypothermia, although hypothermic circulatory arrest is used for the procedure in varying degrees in many institutions. After the median sternotomy is performed, a portion of the anterior pericardium is excised for autologous patch reconstruction of the defects in the anterior great vessel. The pericardium may be used fresh

or fixed in glutaraldehyde to make it easier to manipulate during the operation. The ligamentum arteriosum or ductus arteriosus is dissected, and the pulmonary arteries are mobilized to the bifurcation of the vessels in the hilum of the lung bilaterally. It is important to mobilize the pulmonary arteries freely to permit anterior relocation of the pulmonary bifurcation without distortion of the pulmonary artery or aorta. The aorta is typically cannulated for bypass distally to allow room for manipulation of the proximal aorta during the reconstruction. After bypass is established, the ductus arteriosus is ligated and divided and the aortic end and pulmonary arterial end oversewn as necessary. The aorta is then clamped close to the aortic cannula and cardioplegia administered into the aortic root.

If a VSD is present, it is approached either through the right atrium across the tricuspid valve or, occasionally, through the anterior great vessel. The aorta is then transected above the level of the coronary ostia and the pulmonary artery is transected just below the bifurcation, with care not to carry the incision into the left pulmonary artery. The pulmonary artery bifurcation is brought anterior to the aorta (the Lecompte maneuver). The coronary ostia are examined and excised from the anterior great vessel with a button of aortic wall extending down into the base of the sinuses of Valsalva. The epicardial course of the coronaries is then mobilized adequately to allow turning the coronary ostia to the posterior great vessel without kinking of the epicardial course. In rare cases, the small conal branches of the coronaries may need to be sacrificed to permit adequate mobilization. An incision is then made in the posterior great vessel at the site for reattachment of the coronary ostia, and a medially based flap incision is created to allow takeoff of the coronary ostia without tension or kinking, and the coronary ostia are sewn to the incisions in the posterior great vessel.

Although transfer of the coronary arteries is one of the most technically challenging and important parts of the arterial switch procedure, experience and refinements in technique have made it possible to deal with most variations in coronary anatomy. When both coronaries come off a single sinus with the left coronary orifice near the commissural attachment of the aortic valve, it is possible to mobilize the commissure and excise the coronary arteries in the usual fashion. Alternatively, if the coronary ostia are close together or if there is a single coronary artery, a single button containing the adjacent ostia or common orifice can be excised and transferred to the posterior great vessel. This is done in a side-to-side fashion, and the distal aorta is fashioned to create an anterior flap that is sewn over the button to complete the anastomosis (see Fig. 125-5K-M). Another concept that is helpful in dealing with single coronary arteries is to translocate the button higher onto the posterior great vessel to alleviate any kinking that may occur with rotation of the flap.

After completion of the coronary anastomoses, the distal aorta is anastomosed to the posterior great vessel to which the coronary arteries have been transferred. Additional cardioplegia may be administered at this time to check for hemostasis of the suture lines and to confirm

good myocardial perfusion without kinking of the coronary anastomoses. The defects in the anterior great vessels from which the coronary arteries have been excised are then repaired with a generous portion of pericardium. The anterior great vessel is sutured to the pulmonary artery bifurcation, with care being taken to avoid tension on the pulmonary arteries that may interfere with symmetrical pulmonary blood flow. Finally, the ASD is closed either primarily or with a small patch of pericardium, and the atrium is closed. In the situation in which the great vessels are side to side rather than antero-posterior, it may be advisable to leave the pulmonary confluence posterior to the aorta and open the right pulmonary artery, closing the pulmonary bifurcation to transpose the opening in the pulmonary artery more to the right than usual. This may facilitate reconstruction to the right ventricle.

After completion of the repair, left atrial and right atrial lines are placed for postoperative monitoring and temporary pacemaker wires applied. The infant is weaned from bypass, maintaining a systemic pressure of approximately 60 mm Hg to prevent distention of the newly systemic left ventricle.

Postoperative Management

Continuous sedation with mechanical ventilation and moderate inotropic support are usually used in the first 12 to 18 hours after repair, as in other infants undergoing complex congenital heart repair. Neuromuscular blockade may be administered continuously during this period, or, in patients who are anticipated to have a more stable course and may be candidates for earlier extubation, it may be used intermittently on an as-needed basis. If the patient is stable after the initial postoperative period, sedation is reduced and the patient is weaned from the ventilator over the next 24 to 48 hours. After extubation, inotropic support is discontinued, umbilical lines are removed if they are present, and enteral feeding is commenced. Once enteral intake is satisfactory, the rest of the support equipment can be removed in preparation for discharge. The current usual hospital stay for correction of TGA is 10 to 12 days.⁴⁹⁻⁵¹

Outcome after Arterial Switch Operation

Early and Mid-term Follow-up. Initial results of the arterial switch operation would be considered poor by today's standards. Jatene's original series included a mortality of approximately 60%. This high early mortality rate was duplicated in other series, yet surgeons pressed on with this operation with the belief that it was physiologically superior to atrial level switch procedures.

Despite the early outcomes, results in the current era are excellent. The early mortality rate is less than 4%, even when complex forms of transposition are included in the analysis. Despite the excellent survival data, however, reoperations are required in 5% to 10% of patients. Reoperation for coronary lesion has been reported in approximately 2% of survivors, but frequency depends on screening protocols.⁵²

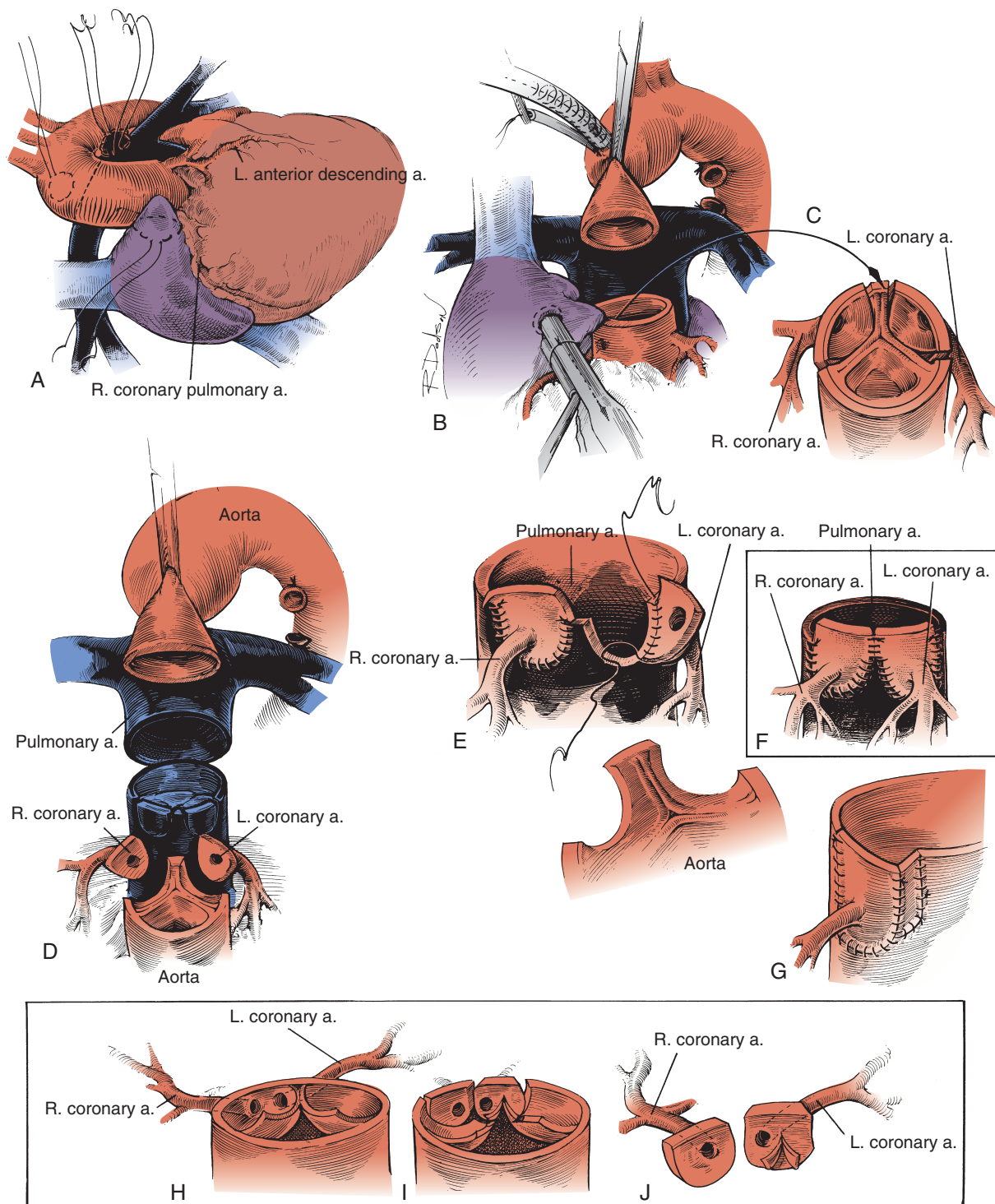


FIGURE 125-5 ■ The arterial switch operation. **A**, Cannulation site for cardiopulmonary bypass in the arterial switch operation. Single atrial or bicaval venous cannulation can be used. The ductus arteriosus is suture ligated and divided between sutures. **B**, Division of the ductus arteriosus and ascending aorta after initiation of cardioplegic arrest. **C**, Excision of the left and right coronary ostia with a button of aortic wall. **D**, Excision of corresponding segments of the posterior great vessel wall to which the coronary arteries will be reimplanted. Alternatively, medially based flap incisions can be used. **E**, Suturing of the coronary ostial buttons to the posterior great vessel. **F**, Completed anastomosis of the reimplanted coronary arteries. In some cases, the coronary buttons can be approximated together in the midline. **G**, Augmentation of the medial aspect of the anastomosis to prevent kinking is occasionally necessary although less common if medially based flap incisions are used for coronary reimplantation. **H**, If juxtacommissural origins of either coronary artery or both coronary arteries from the facing sinuses are present, excision of a portion of the native aortic valve may be necessary to allow mobilization. **I** and **J**, Separation of the coronary arteries is done, if possible, to prevent distortion and to provide easier implantation.

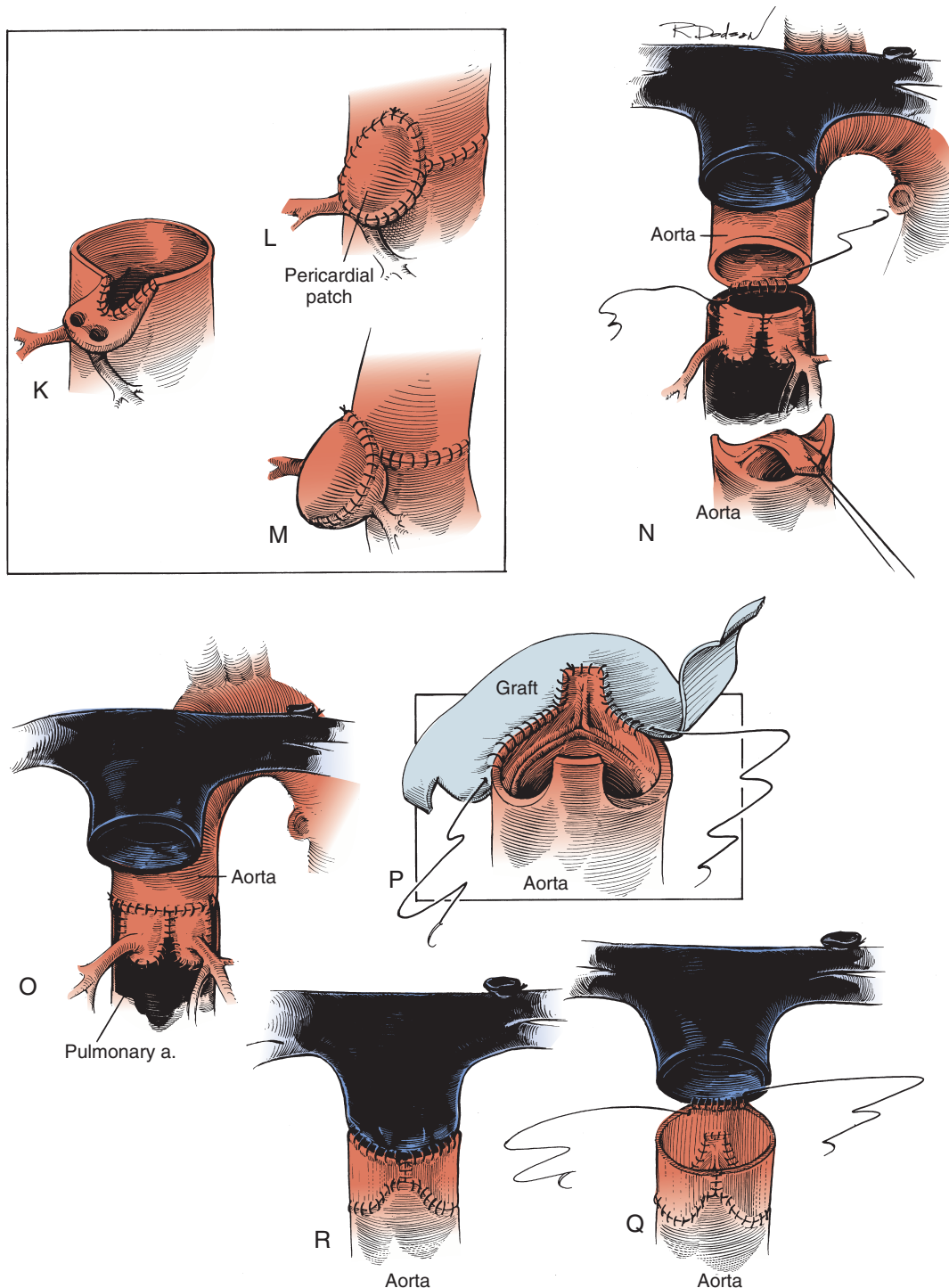


FIGURE 125-5, cont'd ■ **K**, If right and left intramural coronary arteries are present, the aortic coronary flap is left in place and sutured along the cephalic border to an incision in the anterior neo-aorta. **L** and **M**, A pericardial patch is then used to provide unrestricted entrance of blood into the coronary ostia. **N**, After completion of the coronary transfer, the distal aorta is anastomosed to the neo-aorta. **O**, The pulmonary bifurcation is brought anterior to the aorta in the Leconte maneuver. **P**, The defect in the aorta from which the coronary arteries have been excised is augmented with a pantaloon-shaped patch of pericardium. **Q**, The pulmonary bifurcation is then anastomosed to the augmented aorta. In most cases, pericardium is not sutured completely around the aorta to create a complete pericardial tube. **R**, Completed anastomosis of the pulmonary artery anterior to the new aorta.

In most series, reoperation is most commonly indicated for right ventricular outflow tract (RVOT) lesions, which may occur in up to approximately 10% of patients.^{53,54} However, technical modifications to the procedure are thought to be responsible for a reduction in reoperation for RVOT obstruction to less than 2% to 3%. More long-term follow-up data are now available on children undergoing neonatal arterial switch. Prifti and colleagues reported the results of a large series of patients with a mean follow-up of 3.5 years. The early mortality rate was 12.7% but significantly lower (5.7%) for those children with isolated TGA. Actuarial survival rates were 98%, 93%, and 91.5% at 1, 3, and 5 years, respectively, after surgery. Freedom from reoperation was 95%, 90.5%, and 83% at the same time points. The presence of a VSD adversely affected survival. Predictors of reintervention included VSD, coronary anomalies, aortic coarctation, and LVOT obstruction or moderate pulmonary stenosis.⁵⁵ Another series of 181 patients with a mean follow-up of 5.8 years revealed a 5.5% early mortality rate and 92% survival rate at 5 and 10 years. VSD was a risk factor for early and late death.⁵⁶ The largest series in the literature with long-term follow-up was reported in 2001 and included data on 1095 patients from a single institution. Mean follow-up was approximately 5 years. Early mortality was 8.6%. Survival was 89% at 1 year and 88% at 10 and 15 years (including those patients who died early). Simple TGA was found to be associated with improved survival (92% vs. 80% for complex TGA). Freedom from reintervention was 90%, 83%, and 82% at 5, 10, and 15 years, respectively, of follow-up.⁵⁷

Although the early mortality rate seems high in some of the larger series that include earlier results, the current operative mortality rate is approximately 2% to 3%.⁵⁸⁻⁶⁰ Analysis of large series found complex anatomy (large VSD, multiple VSDs, Taussig-Bing anomaly but not aortic coarctation), coronary anomalies, previous operation, and prolonged bypass time to be risk factors for early death.⁵⁸ Another study identified female gender and preoperative instability as risk factors for operative mortality and suggested that in the current era, abnormal coronary patterns were less of a factor. A recent review of contemporary data (1999-2005) reported that coronary anatomy was not a factor affecting survival and that factors affecting mortality included gestational age less than 36 weeks and bypass time less than 150 minutes.⁶¹

Although this seems to be true, a single coronary ostium and intramural coronary course are still risk factors for mortality in some studies.⁶² Coronary artery-related problems are the most common cause of early death, followed by right ventricular failure and pulmonary hypertension.⁶⁰ It has been suggested that risk factors for late death include an unusual relationship of the great vessels, single coronary ostium, prolonged bypass time, and coarctation of the aorta, although none of these proved to be significant in a multivariate analysis.⁵⁸

Cardiac rhythm abnormalities are unusual after arterial switch operation with over 90% of patients in normal sinus rhythm. Left ventricular function is generally normal. Most patients (>95%) are in NYHA functional class I at long-term follow-up.⁵⁹ Aortic stenosis is very

rare, and mild aortic insufficiency is seen in approximately 10% of patients. Although there was initial concern that the neo-aortic root dilated disproportionately, raising the concern of progressive aortic insufficiency, longitudinal analysis has shown that the neo-aorta undergoes dilation during the first year of life but then tends toward the normal size as further growth occurs.⁶³ Pulmonary stenosis is seen slightly more frequently.⁵⁶ Very few patients are taking cardiac medications at mid-term follow-up.^{60,64} Late coronary artery problems are rare.

Late Follow-up. A recent review of long-term outcomes compared those of the arterial switch operation to those of the Mustard and Senning atrial switch operations.⁶⁵ It was reported that the change from the atrial to the arterial switch in 1983 has led to improved long-term survival (Fig. 125-6) but that reoperation rates are similar. Interestingly, the reoperations performed following the arterial switch operation were predominately targeting RVOT lesions, but approximately 2% of patients required aortic valve replacement. Importantly, systemic ventricular dysfunction occurred in 9.1% of patients after atrial switch but only 0.4% of patients after the arterial switch.

Whereas early and long-term survival favors the arterial switch operation, the late neurologic outcome has been investigated. Despite evidence of neurologic impairment 3 to 4 years after arterial switch operation, these effects showed moderation at later follow-up.⁶⁶ More long-term longitudinal follow-up of patients entered into the Boston circulatory arrest study has shown a gradual moderation in developmental disabilities manifest in early childhood.^{67,68} Although this group shows that behavioral dysfunction (attention and executive functions) persists among these patients, few differences were found to be attributable to the method of operative treatment. This underscores the increasing awareness that children treated for congenital heart disease are at increased risk for behavioral and neuropsychiatric disabilities well into their childhood.⁶⁹

In summary, outcomes after arterial switch are generally very good. Follow-ups to date suggest that, as expected, the results are superior to atrial switch operations in terms of late ventricular function, freedom from arrhythmias, and functional status. The rapidly decreasing mortality for arterial switch operations has resulted in this surgical approach becoming the standard corrective surgical procedure at the present time and results in both an anatomic and a physiologic reconstruction of this cardiac defect.

Fate of the Neo-aortic Valve and Late Coronary Lesions. The arterial switch operation is generally considered a corrective operation because no future operations are planned. However, several longitudinal studies are reporting a significant rate of reoperation. Reoperation on the RVOT is generally the most common indication and is related to inadequate growth at the neopulmonary anastomotic site. However, progressive neo-aortic dilation and late coronary artery lesions are also being recognized as potential surgical problems.

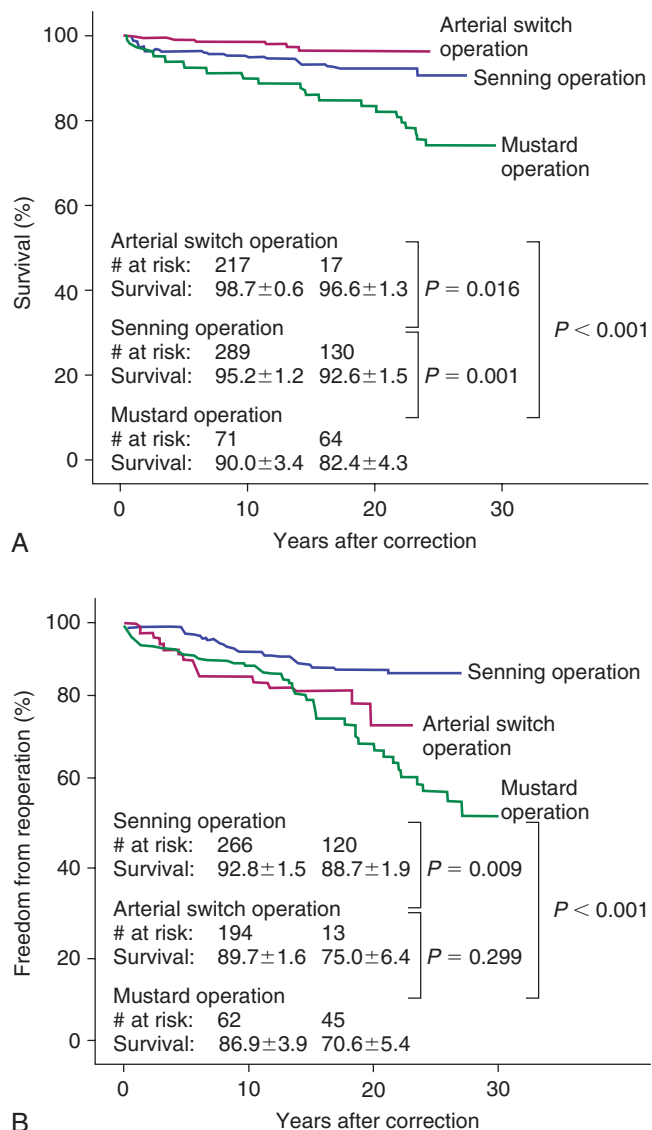


FIGURE 125-6 ■ **A**, Estimated survival among 929 hospital survivors after correction, stratified by type of operation: Senning versus Mustard versus arterial switch. **B**, Estimated freedom from reoperation among survivors, stratified by type of operation: Senning versus Mustard versus arterial switch. (From Horer, J, Schreiber C, Cleuziou J, et al: Improvement in long-term survival after hospital discharge but not in freedom from reoperation after the change from atrial to arterial switch for transposition of the great arteries. *Thorac Cardiovasc Surg* 137:347–354, 2009.)

In a recent review, Schwartz and coworkers reported that aortic root dilation (z-score > 3) is common after arterial switch operation, affecting approximately 50% of survivors at 10 years. Root dilation did not necessarily translate into aortic insufficiency—only approximately 7% of patients demonstrated significant aortic insufficiency (moderate or greater). However, approximately 5% of patients required neo-aortic valve or root surgery at 10 years. The authors reported that older age at the time of repair, VSD, and a previous pulmonary artery band were independent risk factors for aortic insufficiency in these patients.⁷⁰ Longer-term follow-up has

similarly shown that aortic root dilation is present in 66% of patients 20 years after arterial switch operation but that surgery on the neo-aortic root or valve remains uncommon. It is important to note that left ventricular function is preserved in these patients.⁷¹

A recent review of a European center's experience reported an incidence of aortic insufficiency that increased with time, with 2% of patients requiring aortic valve replacement an average of 11 years after the arterial switch operation. Independent risk factors identified for late aortic valve replacement were the presence of LVOT obstruction and aortic insufficiency at 1 year.⁷²

Although coronary issues are thought to be rare among hospital survivors after the arterial switch operation, Raisky and colleagues found that coronary lesions were detectable in 12% of survivors undergoing coronary angiography an average of 33 months after arterial switch. Forty-five percent of angiographically documented coronary lesions were observed in the absence of ischemia as assessed clinically and by myocardial perfusion imaging. Of the 55% of patients undergoing revascularization, 17 of 19 revascularized lesions resided within the left coronary system. Whereas 16 of 19 patients were treatable with angioplasty, 3 underwent surgical revascularization without any mortality.⁷³

Because of the excellent results obtained with the neonatal arterial switch operation, this has become the standard of care. However, there are occasions when the diagnosis of TGA with intact ventricular septum might be delayed, or when no surgery is immediately available, and late arterial switch operation is considered. In general, primary arterial switch operation within 3 weeks of life is noncontroversial. However, because of progressive deconditioning of the postnatal pulmonary left ventricle, primary arterial switch operation has been considered high risk, and rapid two-stage arterial switch operation has been advocated by some. However, several groups have reported that the rapid two-stage arterial switch operation results in impaired left ventricular contractility in up to 25% of patients, an increased incidence of neo-aortic insufficiency, and RVOT obstruction. Bisoi and associates reported the combined early mortality rate of the rapid two-stage arterial switch operation is higher than that for the late primary arterial switch operation (55% vs. 14%).^{74–77}

These results have prompted groups to perform primary arterial switch operation on children presenting later in infancy. When Kang and colleagues reported their outcomes for 105 patients undergoing late primary arterial switch operation (older than 3 weeks), they found no difference in hospital mortality (3.8% vs. 5.5%) or ECMO (5.7% vs. 3.6%) when compared to early primary arterial switch operation.⁷⁸

Similar results have been published by Edwin and coworkers, who reported no mortality (two ECMO) in six patients undergoing primary arterial switch operation between the ages of 31 and 66 days.⁷⁹

These experiences suggest that the rapid two-stage arterial switch operation may be unnecessary for most patients presenting well into infancy and that primary arterial switch operation, with ECMO backup, is justifiable.

COMPLEX TRANSPOSITION

Anatomic Variants of Transposition of the Great Arteries

Although discordant relationship between the ventricles and great vessels is an integral component of transposition, associated defects often dominate the clinical presentation and management of these infants. The term *complex transposition* refers to those defects in which there are conotruncal anomalies in addition to TGA. The associated conotruncal defects include malalignment or deviation of the conal septum into either the LVOT or RVOT or persistence of a conus over the left ventricle separating the mitral valve from the semilunar valve, also called the Taussig-Bing anomaly. Together these complex forms account for 10% to 15% of all transposition cases.⁸⁰

Conal Septum

The conal septum separates the two semilunar valves and forms part of the septation of the common arterial trunk, present early in fetal cardiac development, into the aorta and the pulmonary trunk. Although abnormal development of the conus with regression of the subpulmonary component rather than the subaortic component has been proposed as the cause of transposition, the position, orientation, and size of the conal septum may vary independent of ventriculoarterial connection.⁸¹ Thus, a prominent conal septum that deviates posteriorly can cause left ventricular outflow obstruction; similarly, anterior deviation of the conal septum can result in right ventricular outflow obstruction. In hearts with normally related great arteries, when the conal deviation is associated with a conoventricular septal defect, the downstream consequences of the ventricular outflow obstruction are hypoplasia or atresia of the affected great artery as seen in interrupted aortic arch (left ventricular outflow obstruction) and tetralogy of Fallot (right ventricular outflow obstruction). In transposition, however, the affected downstream circulation is the inverse with left ventricular outflow obstruction resulting in decreased pulmonary trunk blood flow and right ventricular outflow obstruction resulting in aortic arch hypoplasia, interruption, or both.^{82,83}

Transposition and Left Ventricular Outflow Tract Obstruction

LVOT obstruction in an infant with TGA can occur in the presence or absence of a VSD. In patients with an intact ventricular septum, most often the pressure gradient measured across the outflow tract is a result of dynamic displacement of the interventricular septum posteriorly as a result of the pressure difference between the right (systemic) and left (pulmonary) ventricles, with the latter functioning at lower pressures.

Once the left ventricle assumes the systemic circulation following an arterial switch, the septum usually bows toward the right ventricle and the pressure gradient disappears. A fixed obstruction from a prominent conal

septum deviated posteriorly or a fibrous ridge or muscle bundle is uncommon in the absence of a conoventricular septal defect and, in most cases, can be resected and does not preclude an arterial switch operation.

LVOT obstruction in the presence of a conoventricular septal defect most often results from posterior deviation of the conal septum. In long-standing obstruction, a fibrous ridge or even fibromuscular tunnel can develop, further increasing the degree of obstruction. The obstruction is usually subvalvar but can be associated with pulmonary valve hypoplasia or dysplasia (bicuspid valve and/or thickened leaflets) precluding the use of this valve for an arterial switch procedure. The degree of obstruction in LVOT obstruction with a VSD is often more severe than in TGA with intact septum, and the obstruction often progresses early in infancy during the first few months of life requiring surgical intervention because of progressive cyanosis.

Transposition and Right Ventricular Outflow Tract Obstruction

Similar to LVOT obstruction, deviation of the conal septum, in this case anteriorly into the RVOT, is the most common cause of obstruction to flow into the systemic circulation. In transposition, RVOT obstruction is almost always associated with a malalignment-type conoventricular septal defect and is also frequently associated with double-outlet right ventricle, also called Taussig-Bing anomaly. In this latter defect, there is persistence of a conus or infundibulum under the pulmonary trunk, resulting in muscular separation between the mitral and pulmonary valve annulus. This complex lesion accounts for 5% to 7% of transposition cases based on autopsy series.⁸⁴ Associated defects include downstream hypoplasia of the aortic valve and aortic arch with coarctation. In some infants, the degree of aortic valve and arch hypoplasia is severe, requiring maintenance of a patent arterial duct to achieve adequate systemic perfusion. Hypoplasia of the right ventricle and tricuspid valve has also been described in this complex to a degree that a two-ventricle repair was not possible.⁸⁵ Often enlargement of the RVOT is necessary in conjunction with an arterial switch operation to prevent the development of subpulmonary obstruction. Hypoplasia of the aortic valve annulus in transposition can vary in degree and in severe forms requires a transannular patch along with an arterial switch to relieve right ventricular outflow obstruction.

In most cases of RVOT obstruction and transposition, there is a significant mismatch in diameter between the pulmonary trunk and the ascending aorta. This fact complicates the arterial switch procedure because enlargement of the ascending aorta and, if aortic arch hypoplasia is present, enlargement of the entire transverse arch and isthmus are required to achieve a hemodynamically satisfactory result.

Double-Outlet Right Ventricle with Transposition

Double-outlet right ventricle with TGA is often termed *double-outlet right ventricle with subpulmonary VSD* to

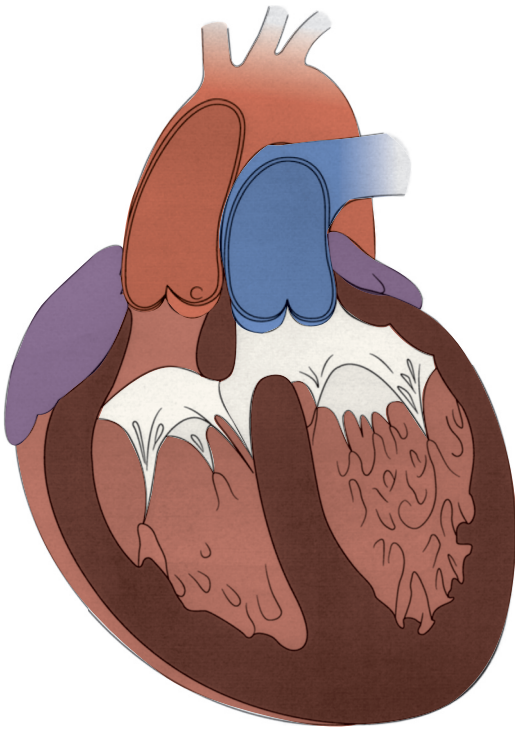


FIGURE 125-7 ■ Transposition with double-outlet right ventricle. The conal septum is positioned over the right ventricle. In cases in which there is deviation of the conal septum from this neutral position, the outflow semilunar valve and great artery often are hypoplastic.

describe the great vessel relationship to the right ventricle and to the VSD. Unlike double-outlet right ventricle with normally related great arteries, the vessel closest to the VSD in this case is the pulmonary trunk and determines the method of anatomic repair required for correction. Subpulmonary or subaortic obstruction can be associated with transposition and double-outlet right ventricle, usually resulting in hypoplasia of the downstream semilunar valve and great vessel. The relationship of the great vessels to each other often is that of a side-by-side arrangement with the aorta most commonly to the right of the pulmonary valve.

The VSD is described as a malalignment type because the conal septum does not meet the septomarginal trabecula, similar to double-outlet right ventricle with normally related great vessels (Fig. 125-7). The VSD can extend to the annulus of the tricuspid valve, and in these cases, the conduction tissue runs on the edge of the VSD in the posterocaudal margin of the defect starting at the junction with the tricuspid valve annulus.⁸⁶ In some cases, the VSD can extend to the inlet septum; this complicates the repair because the defect is partially covered by the septal leaflet of the tricuspid valve. In such cases, chordae from the tricuspid valve can attach to the crest of the septum and even straddle into the left ventricle. In most cases, however, the degree of straddling is limited and does not preclude a two-ventricle repair. Rarely, additional septal defects are present in the muscular septum or apical trabecular area, and these can be difficult to identify and close, particularly in the apical posterior septum.

Coronary Artery Anatomy

Coronary artery anatomy can also be variable with complex forms of transposition. Transposition and double-outlet right ventricle in particular is associated with unusual patterns of coronary artery anatomy, including a relatively high incidence of a single coronary artery giving rise to branches to both ventricles. The high association between side-by-side great vessels and unusual coronary artery pattern has been emphasized previously. In a detailed pathologic study, Uemura and associates found that a single coronary artery was present in 27% of hearts with a side-by-side great artery relationship.⁸⁷

Gordillo and colleagues have also described a higher incidence of unusual coronary artery pattern in double-outlet right ventricle with a subpulmonary VSD.⁸⁸ Coronary anatomy continues to be an important factor in anatomic repair of transposition, however, only when an arterial switch is contemplated as part of the repair. Although in most larger centers coronary artery pattern is no longer a significant risk factor for death, it can complicate the surgical procedure and may result in a higher rate of complications.

Aortic Arch Anatomy

Aortic arch anomalies occur in 7% to 10% of infants with transposition and VSD. This association is more common when the pulmonary valve overrides the ventricular septum, particularly in double-outlet right ventricle and transposition. A wide spectrum of arch obstruction exists from discrete coarctation at the level of the ductus to hypoplasia of the distal arch and even aortic arch interruption. The degree of severity of arch hypoplasia is thought to be associated with the degree of subaortic obstruction, usually from anterior deviation of the outlet or conal septum into the right ventricular outflow. Additionally, there can be relative hypoplasia of the tricuspid valve in comparison with the mitral valve, and in extreme cases, the degree of hypoplasia of the tricuspid valve can preclude a two-ventricle repair. It is important to recognize this association. Preoperative measurements of the atrioventricular valves normalized to body surface area can be most helpful in deciding surgical management.

Diagnosis and Preoperative Management

Echocardiography is usually the initial diagnostic study performed when complex congenital heart defects are detected because it provides not only the anatomic detail required to plan surgical repair but also physiologic information on valve function, presence, location, and severity of obstructions to flow, particularly in the outflow tracts of the ventricles as well as the pulmonary arteries and arch vessels. As with all echocardiographic studies, a systematic evaluation of chambers, connections, inflow and outflow valves, and ventricular size and function is imperative, particularly with difficult defects such as complex transposition. In addition, specific anatomic details—such as the relationship of the pulmonary root to the VSD, conal septal position, coronary artery pattern,

and chordal attachments of the atrioventricular valves with respect to the septum—are important for the development of a plan for surgical correction.

Cardiac catheterization is not required in most cases of complex transposition because echocardiography is usually sufficient to detail the anatomy and important physiologic features. Cardiac catheterization and angiography are therefore used to resolve specific questions where accurate pressure measurements are required, such as pulmonary artery pressures for calculation of pulmonary vascular resistance, or to measure the pressure gradient across a potentially restrictive VSD. Also, in cases in which a palliative procedure has been performed, catheterization and angiography are needed to identify potential anatomic distortion from the previous surgical interventions such as systemic-to-pulmonary shunts. Rarely is interventional catheterization required in infants unless there is a restrictive interatrial communication and inadequate mixing of blood from the pulmonary and systemic circuits, a situation more common in transposition with intact septum.

Transposition of the Great Arteries with Left Ventricular Outflow Tract Obstruction

Palliative Procedures. The pathophysiology of transposition results in cyanosis that often is unresponsive to oxygen therapy. When transposition is complicated by obstruction to the LVOT, cyanosis can be more severe, frequently worsening in the first few months of life. In the extreme, when there is atresia of the LVOT, pulmonary blood flow is entirely dependent on a patent arterial duct and/or systemic-to-pulmonary collaterals. In these cases, repair of this defect can be delayed by placing a systemic-to-pulmonary shunt and ligating collaterals or the arterial duct. The corrective procedure can then be deferred several months. In cases in which cyanosis is not severe, a systemic-to-pulmonary shunt is not indicated, and if delayed repair is contemplated, this can usually be deferred several weeks or months. The most common reason for delaying the corrective procedure is when resection of the left ventricular outflow is not feasible and a conduit will be required to establish right ventricle to pulmonary artery continuity (see [Rastelli Operation](#) section). The institutional philosophy at Children's Hospital Boston, however, is to achieve anatomic and physiologic correction of the cardiac defect as early in life as possible.

Surgical Technique. The preferred shunt procedure for TGA with LVOT obstruction is a modified Blalock shunt with an expanded polytetrafluoroethylene (PTFE) tube graft. In infants with a left aortic arch, the origin of the shunt is the base of the right subclavian artery, and the distal end connects to the right pulmonary artery. The surgical approach for a shunt is usually through a median sternotomy that provides access to the arch vessels and branch pulmonary arteries. The thymus gland is mobilized, and the innominate vein is freed from attachments to the pericardium and aorta. Because the course of the shunt will be parallel to the superior vena cava, tissue between the ascending aorta and superior

cava must be cleared. Once the innominate artery and right subclavian origin are dissected, the right pulmonary artery is mobilized from its origin to the bifurcation of the upper lobe. Heparin (50 U/kg) is administered to prevent thrombus formation in the vessels or the graft during insertion. The caudal side of the innominate-subclavian artery junction is identified for the anastomosis, and a curved vascular clamp is used for occlusion. The anastomosis is done with fine monofilament sutures (7-0 polypropylene), and care is taken not to damage the fragile intima of the innominate artery. The distal end is sewn to the cephalad side of the pulmonary artery, also with fine monofilament sutures. De-airing of the graft is performed, and brisk flow through the graft should be confirmed prior to completing the distal anastomosis. The graft is usually 3.5 mm in diameter for neonates and young infants and provides adequate pulmonary blood flow for several months until corrective surgery is performed. In some centers, a larger shunt (4.0 mm) is chosen in an effort to gain more time with palliation. This approach, although effective, runs the risk of producing pulmonary overcirculation in the early period after shunt insertion with complications such as inadequate renal perfusion and renal insufficiency or necrotizing enterocolitis. If a larger shunt is used, great care must be taken in the early postoperative period to maintain adequate systemic perfusion to avoid these complications.

Once the shunt is unclamped, the oxygen saturations should rise within seconds confirming adequate shunt flow. An additional indicator is a modest fall in diastolic pressure. The ductus arteriosus is typically ligated. Once stable, a single chest drain is left in the pericardial space and the sternum is closed. Low-dose heparin (10 to 20 U/kg/hr) can be continued in the postoperative period once mediastinal bleeding has subsided.

Corrective Procedures. Management of the LVOT obstruction in transposition depends on the severity and location of the obstruction. In cases in which the obstruction appears dynamic from leftward deviation of the interventricular septum because of systemic pressure in the right ventricle, an arterial switch procedure with closure of a VSD, when present, is the preferred method of correction. In these cases, the pulmonary valve annulus is within the normal range for the child's size, and instantaneous gradient across the left ventricular outflow, as estimated by echo Doppler, is less than 35 to 40 mm Hg in the presence of a small or closed arterial duct.

Transposition of the Great Arteries with Posterior Deviation of Conal Septum

In most cases in which the conal septum is the major source of left ventricular outflow obstruction and the pulmonary valve is adequate (z-score of -2.5 or better), the resection of the conal septum with closure of the VSD (when present) and an arterial switch procedure is the best option. This approach establishes anatomic repair and avoids the use of conduits, although there is a small but present risk of developing more severe LVOT obstruction later. Resection of the subpulmonary

obstruction is most often possible through the pulmonary trunk, by retracting the pulmonary valve leaflets. This approach also ensures adequate visualization of the hinge points of the leaflets because these can attach to the conal septum directly. The left ventricular outflow can also be seen through the mitral valve, although this approach is rarely better than through the pulmonary artery.

When the obstruction to the left ventricular outflow cannot be resected or is associated with pulmonary valve hypoplasia or severe dysplasia, the pulmonary root cannot be used to achieve a two-ventricle repair. In these cases, the aortic root arising from the right ventricular conus must be used for systemic flow and a conduit used to establish right ventricle to pulmonary artery continuity. There are two options to achieve this result: (1) the Rastelli operation, in which the aortic root is left attached to the right ventricle and left ventricular blood flow is diverted through the VSD to the aorta by means of a baffle, and (2) mobilization of the aortic root off the right ventricle, similar to a pulmonary autograft in normally related great vessels, and reimplantation of it into the opened left ventricular outflow, patch enlarging the left ventricular outflow and reimplanting the coronary arteries (autograft translocation and arterial switch operation). In both cases, a conduit is used to connect the right ventricle to the pulmonary artery bifurcation.

Rastelli Operation. For cases in which a large conoventricular VSD is present, Rastelli and colleagues described a procedure in which a synthetic semicircular patch is sewn to the edge of the VSD inferiorly and around the aortic annulus, diverting left ventricular flow through the VSD to the aorta.⁸⁹ The pulmonary root is closed, and a conduit is inserted between the right ventricle and the pulmonary artery. Frequently the VSD must be enlarged to prevent subaortic obstruction, and as described by Rastelli, the conal septum should be resected. The approach is via a sternotomy harvesting a patch of pericardium to be treated with glutaraldehyde (0.6% for 10 to 15 minutes), which may be required for pulmonary artery augmentation or for the gusset connecting the right ventricle to the conduit anteriorly. The main pulmonary artery and branches are dissected and mobilized to the level of the upper lobe bifurcation, similar to an arterial switch. Arterial cannulation at or near the level of innominate artery facilitates retraction of the ascending aorta, and bicaval cannulation permits continuous bypass without the need for circulatory arrest. Because the aorta is frequently anterior and the VSD is conoventricular, an infundibular incision in the right ventricle provides access to the VSD for baffling and then becomes the proximal site for connection of the right ventricle to pulmonary artery conduit. The ventriculotomy should be oblique, aiming toward the leftward and superior corner of the right ventricular infundibulum (Fig. 125-8). Care must be taken to avoid opening too close to the left coronary artery because this vessel usually arises from the left-facing sinus of the aorta. The advantage gained by placing the ventriculotomy as leftward as possible is that the right ventricle to pulmonary artery conduit can then be placed to the left of midline, avoiding compression by the sternum. The VSD and conal septum can be seen

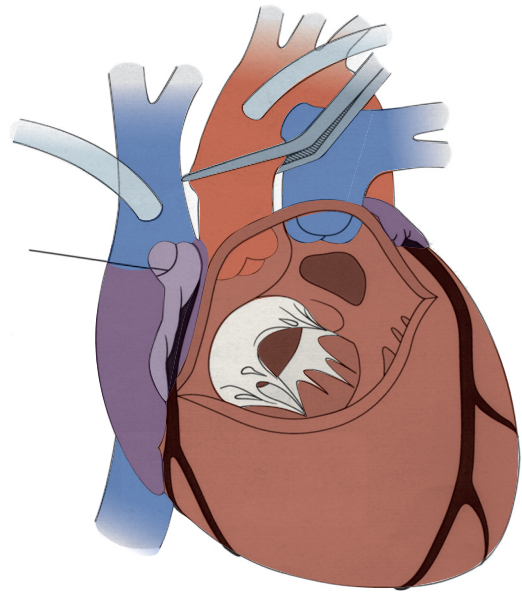


FIGURE 125-8 ■ Rastelli procedure. Right ventriculotomy to expose the ventricular septal defect and aortic valve.

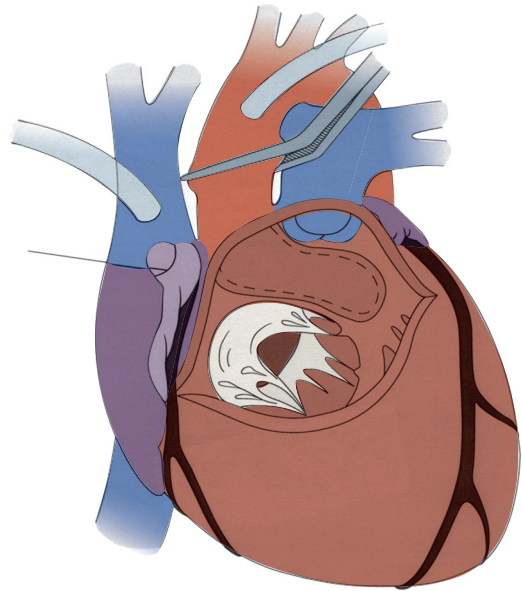


FIGURE 125-9 ■ Rastelli procedure. Baffle of left ventricular outflow through the ventricular septal defect to the rightward aorta.

easily through the ventriculotomy, and assessment is made regarding the need to enlarge the VSD. In conoventricular VSDs, conduction tissue runs on the inferior border of the VSD. Therefore, resection of the conal septum is safe, and the incision can be extended anteriorly to enlarge the VSD further if required. A tunnel-shaped synthetic patch (Dacron) is used to construct the baffle between the VSD and aortic annulus (Fig. 125-9). The pulmonary root can be closed through the ventriculotomy from the inside or from above once the pulmonary trunk is transected. The confluence of the pulmonary arteries should be mobilized to the left of the aorta as much as possible to facilitate connection with the right

ventricle to pulmonary artery conduit and avoid right pulmonary artery compression by the large aortic root. Once the distal anastomosis is created, the posterior portion of the conduit is sewn to the distal edge of the ventriculotomy. The anterior portion of the connection is created with homograft patch if the distal segment of the graft is available or the treated pericardium harvested at the beginning of the procedure can be used. Once the patient is off bypass, careful evaluation must be made of the adequacy of the left ventricular outflow by intraoperative echocardiography or by direct pressure measurement through needle puncture of the left ventricular cavity pressure and ascending aorta. A gradient higher than 10 to 15 mm Hg should be addressed surgically because this will likely progress over time. The most common place for residual obstruction is at the mid-portion of the VSD patch because this area requires the widest diameter of the semicircular patch. Placement of an additional patch can be done without removing the original baffle in cases in which the residual obstruction is at the level of the baffle.

Alternative techniques to avoid the use of conduits for right ventricle to pulmonary artery connection have been described by Lecompte and Vouhé in which the pulmonary arteries are mobilized and placed anterior to the aorta and a primary connection is made between the transected pulmonary trunk and the ventriculotomy. This connection is augmented with autologous pericardium, avoiding the use of a prosthetic conduit or homograft that will require replacement with growth.^{90,91}

Aortic Autograft Translocation and Arterial Switch. The potential long-term complications of the Rastelli operation are conduit obstruction, frequently caused by compression by the sternum because of the location of the conduit, or subaortic obstruction from a restrictive VSD or inadequate growth of the subaortic segment between the VSD and aortic annulus. To avoid these complications, an alternative procedure is to remove the aortic root from the infundibulum of the right ventricle, similar to a pulmonary autograft in normally related vessels (Fig. 125-10). Because this autograft is the

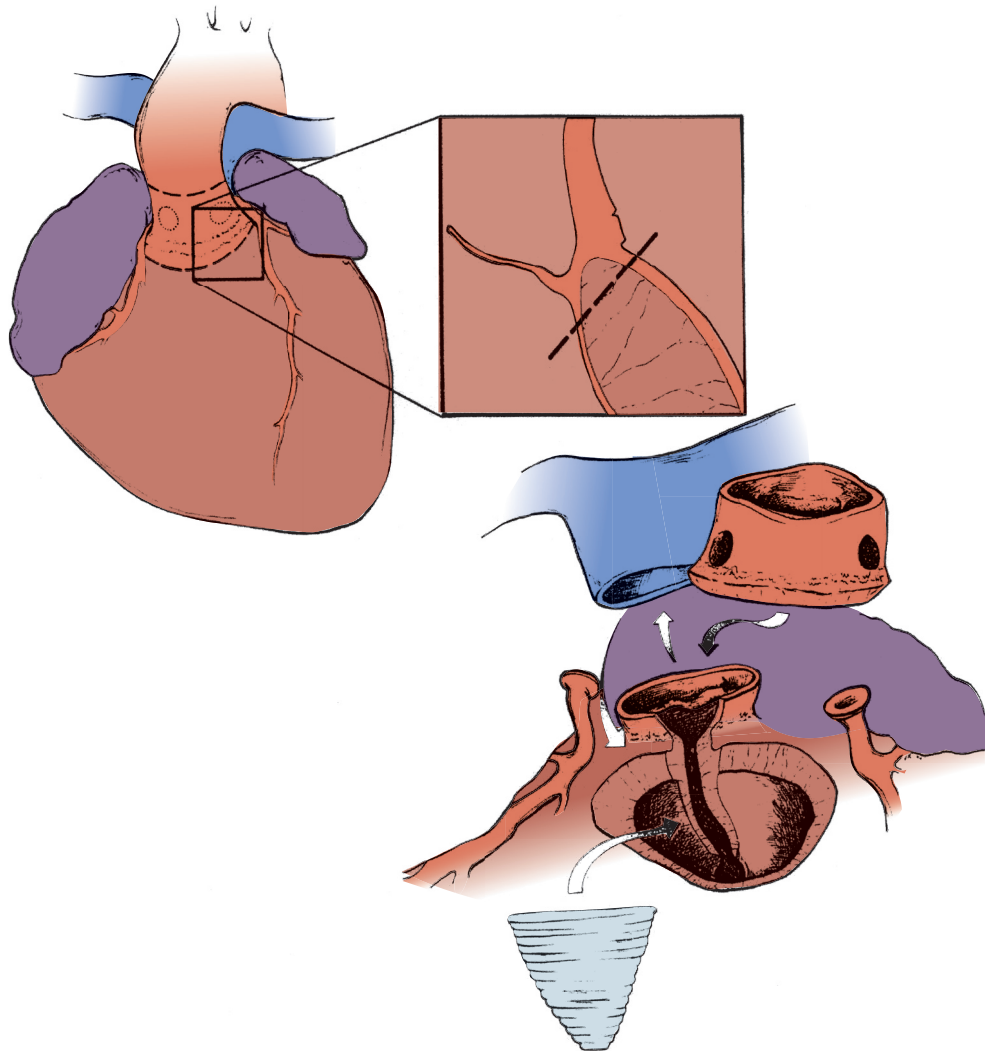


FIGURE 125-10 ■ Aortic root autograft. The aortic root is removed from the right ventricle in a manner similar to the method used for pulmonary root harvest for a pulmonary autograft procedure (*upper panel*). Enlargement of the left ventricular outflow tract and closure of ventricular septal defect (*lower panel*).

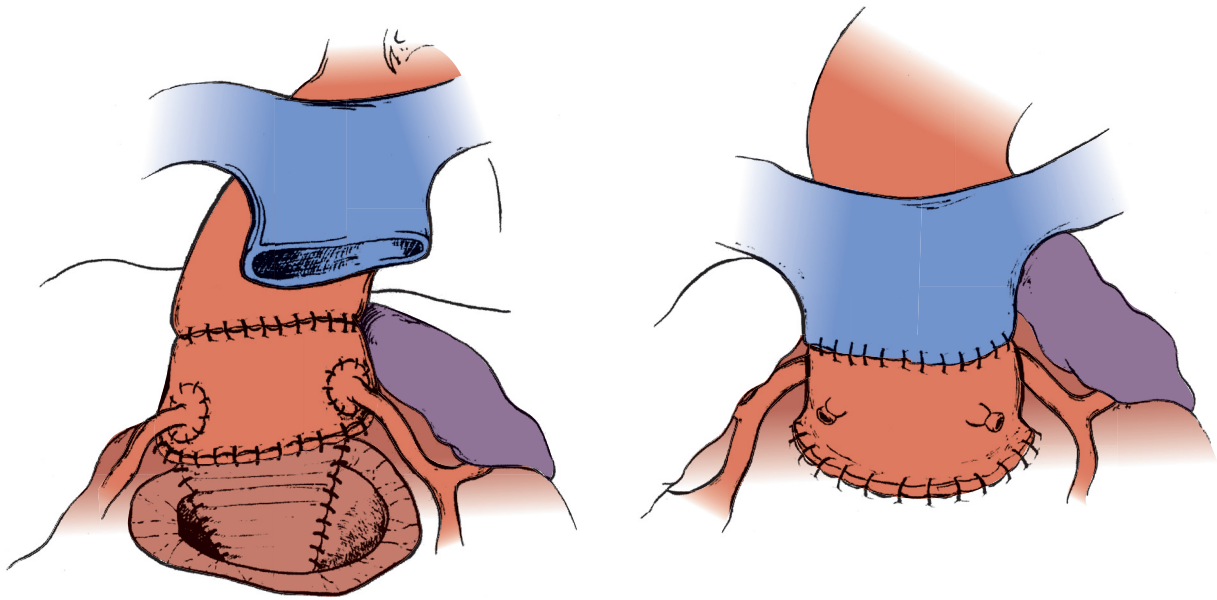


FIGURE 125-11 ■ Aortic root autograft. Right ventricle to pulmonary conduit, with the pulmonary arteries brought anterior to the aorta.

native aorta, the coronary arteries must be excised as circular buttons from the aortic root and mobilized away prior to resecting the aortic root. The left ventricular outflow can then be enlarged by incising across the conal septum into the existing VSD, or in cases in which there is no VSD or only a small restrictive defect, the incision is extended beyond the conal septum into the body of the left ventricle, similar to a Konno procedure.⁹² The aortic root autograft is then sewn to the native left ventricular outflow posteriorly, and a triangular-shaped synthetic patch is used to close the VSD up to the level of the aortic autograft. The coronary arteries are then reimplanted into the aortic root in their new location posteriorly, similar to an arterial switch procedure. A homograft conduit is then inserted between the right ventricular infundibulum and the central pulmonary arteries to establish right ventricle to pulmonary artery continuity. The pulmonary arteries can be mobilized and placed anterior to the aorta, as in the Lecompte operation, or in cases where the great vessel relationship is more side-by-side, the conduit can be placed to one side of the aorta (Fig. 125-11). The advantages of the aortic root translocation and arterial switch procedure are that the LVOT is by necessity enlarged to the size of the aortic root, the position of the aortic root with relation to the left ventricular outflow is more anatomic and therefore less tortuous, and the right ventricle to pulmonary artery conduit is in the anatomic position with respect to the right ventricle and therefore less susceptible to compression by the sternum.

Transposition of the Great Arteries with Double-Outlet Right Ventricle

Subpulmonary Ventricular Septal Defect. Double-outlet right ventricle with a subpulmonary VSD is an uncommon form of transposition that is frequently associated with unusual coronary artery anatomy or aortic

arch hypoplasia and coarctation. Subaortic stenosis from anterior deviation of the conal septum can also coexist with arch hypoplasia and at times requires a transannular patch to relieve the right ventricular outflow obstruction. When there is separation between the pulmonary valve and the mitral valve in double-outlet right ventricle and TGA, this combination is called the Taussig-Bing anomaly. In cases in which the VSD is conoventricular, two surgical options exist for anatomic repair. An intra-cardiac baffle technique has been described in which the left ventricular flow through the VSD is directed to the aorta that is usually rightward of the pulmonary valve, leaving room for right ventricular flow to go over the VSD patch to the pulmonary arteries.⁹³ The ability to baffle the VSD to the aorta without obstruction and while retaining the potential for growth is determined by the distance between the tricuspid valve annulus and the pulmonary root. In cases where the aorta is more posterior than the pulmonary valve, the pathway from VSD to aorta is more likely to be adequate. If this pathway is inadequate, there is a significant risk for late development of left ventricular outflow obstruction with growth of the child. The right ventricular outflow may also need to be enlarged with a patch in cases in which the left ventricle to aorta baffle occupies too much of the right ventricular outflow.

The more common method of achieving anatomic repair of TGA and double-outlet right ventricle is by a combination of closing the VSD to the pulmonary root, because it is closer, and then performing an arterial switch. This approach decreases the risk of late development of left ventricular outflow obstruction. However, because of the frequent association with single coronary artery and aortic arch hypoplasia, this operative approach is more technically demanding, and experience with complex coronary artery transfer is required. The surgical technique is similar to that of an arterial switch with mobilization of the pulmonary artery and branches, and

in cases with arch hypoplasia, dissection of the entire arch and branches is required. A single arterial cannula usually is sufficient except in severe arch obstruction or arch interruption in which a second arterial cannula through the arterial duct provides flow to the descending aorta. The VSD is best approached through an infundibular incision in the RVOT directly below the aortic root. A transatrial approach can be used, but because of the frequent extension of the VSD leftward and superior in the septum, adequate visualization of the most leftward extension of the VSD can be difficult with this approach. The frequent association of this form of TGA with a small or even hypoplastic tricuspid valve further complicates this approach. With the VSD closed, an arterial switch procedure is performed with similar techniques as described for simple transposition. In cases in which a coarctation or aortic arch hypoplasia is present, resection of the coarctation with patch augmentation of the aortic arch is required.

Noncommitted Ventricular Septal Defect. In rare cases, the VSD in double-outlet right ventricle is remote from the great vessels, either in the muscular septum or in the atrioventricular canal area. In these cases, enlargement of the VSD into the conoventricular area may be possible but likely requires extensive resection and may interfere with atrioventricular valve attachments or risk injury to conduction tissue. Although techniques have been described to achieve repair without VSD enlargement, the risk of late left ventricular outflow obstruction remains a significant concern.⁹⁴ For most of these children, management as single ventricle is likely to result in lower overall morbidity and mortality and is the preferred method in most centers.

Transposition of the Great Arteries with Aortic Arch Obstruction

TGA can be associated with coarctation of the aorta or aortic arch hypoplasia and can exist in the absence of a VSD although more commonly, a VSD is present along with other anomalies such as double-outlet right ventricle and "subaortic" obstruction.⁹⁵ An important aspect in the surgical management of neonates with the combination of TGA, VSD, and aortic arch hypoplasia is the recognition that other associated intracardiac anomalies, such as right ventricular outflow obstruction and right ventricular hypoplasia, often complicate repair.

The approach to repair of these lesions is similar to that for TGA with VSD with the additional need to mobilize the entire aortic arch and enough of the descending aorta to permit complete resection of ductal tissue and end-to-end anastomosis with or without patch augmentation. If the coarctation involves only the isthmus and junction with the arterial duct, then a simple resection with end-to-end anastomosis is sufficient. Frequently in infants with double-outlet right ventricle, the transverse arch is hypoplastic to varying degrees and requires patch augmentation.

Furthermore, there is almost always a significant size discrepancy between the ascending aorta and pulmonary trunk, with the latter being substantially larger. In these

cases, patch augmentation of the entire ascending aorta and arch, similar to the augmentation done for hypoplastic left heart syndrome, facilitates the arterial switch by eliminating the size discrepancy with the neo-aorta.

In cases in which the right ventricle is hypoplastic, careful evaluation of tricuspid valve annulus size and right ventricular volume should be done prior to surgery. In cases in which the tricuspid valve z-score is less than approximately 2.5 or the right ventricular volume is less than 15 mL/m², single ventricle management is probably a better option than an attempt at two-ventricle repair. If the right ventricle is borderline in size or there is concern that the combination of a mildly hypoplastic right ventricle and/or the infundibular incision will result in diminished right ventricular diastolic compliance, then leaving a small (≈ 3 to 4 mm) interatrial communication will permit right-to-left shunting, preserving systemic flow at the expense of mild cyanosis similar to repair of tetralogy of Fallot in infants.

Results

Transposition of the Great Arteries with Left Ventricular Outflow Tract Obstruction

Surgical repair of complex forms of transposition carries a significantly higher risk for morbidity and mortality than repair of simpler forms. Nevertheless, improvement in results with complex forms parallels those of simple transposition over the past 2 decades. In some respects, this improvement may be attributable to the recognition that the anatomic morphology of TGA with LVOT obstruction is heterogeneous, and the choice of operation becomes important. For example, the Rastelli operation, the aortic translocation, and arterial switch operation with resection of the obstructing LVOT tissue are three procedures that are designed to address the patient with TGA and LVOT obstruction. Thus, selection of the most appropriate operation that will meet the needs of the specific anatomy is important. Emani and colleagues reported their experience with 88 patients undergoing surgery for TGA with LVOT obstruction. Patients undergoing the Rastelli operation or aortic translocation were more likely to be older and to present with multilevel LVOT obstruction. Although all procedures can be performed with very low mortality, those undergoing the Rastelli operation were at highest risk for subsequent LVOT reintervention, whereas patients undergoing arterial switch operation with or without LVOT intervention or aortic translocation had a very low incidence of subsequent LVOT obstruction.⁹⁶ Long-term outcomes for the aortic translocation and primary arterial switch operation with LVOT resection are unavailable but will eventually be compared with results of the Rastelli experience. In a review of the 25-year experience with the Rastelli operation, Kreutzer and associates reported an overall mortality rate of 7% with no deaths in the most recent 7-year period.⁹⁷ On late follow-up, freedom from death or transplantation rates were 82%, 80%, 68%, and 52% at 5, 10, 15, and 20 years, respectively. Arrhythmias and sudden death accounted for almost one third of the late deaths and left ventricular dysfunction accounted for

another third. Freedom from death or reintervention rates were 53%, 24%, and 21% at 5, 10, and 15 years of follow-up, respectively. The most common indication for reintervention was conduit obstruction, but LVOT obstruction was also prevalent throughout the follow-up period.

Results with the Lecompte procedure (REV [réparation à l'étage ventriculaire] procedure) for TGA and LVOT obstruction are similar to those of the Rastelli procedure with respect to early mortality, with 3 of 42 patients dying early.⁹⁸ On late follow-up, however, there were no late deaths with a median follow-up of 5.4 years. Freedom from reoperation rates were $86\% \pm 8\%$ and $51\% \pm 22\%$ at 5 and 10 years, respectively, with the indication for reintervention being right ventricular outflow obstruction in all patients.

Transposition of the Great Arteries with Double-Outlet Right Ventricle

Transposition with double-outlet right ventricle, or the Taussig-Bing anomaly, still represents a significant surgical challenge with respect to early morbidity and mortality. In a 2001 review, Takeuchi and colleagues reported a 20% early mortality with side-by-side great vessel relationship and associated single coronary as a significant risk factor for death.⁹⁹ In the same report, infants that were managed as single ventricle with initial Glenn connection followed by Fontan had no operative deaths and no late deaths. Of the children undergoing an arterial switch, three required reoperation late—two for subaortic stenosis and one for supraaortic pulmonary stenosis. There were no late deaths in either group at an average follow-up of 24 months. Mavroudis and coworkers reported a series of 20 infants with Taussig-Bing anomaly comparing the arterial switch procedure with intracardiac tunneling technique described by Kawashima.¹⁰⁰ The operative mortality rate was 6% for the arterial switch group, and among the four children undergoing intracardiac baffle, there were no deaths. Of importance, however, was the fact that the average age at operation in these patients was 1.4 years, with most requiring at least one palliative procedure prior to repair. There was a high incidence of reoperation in the arterial switch group with aortic valve regurgitation a frequent complication late, likely reflecting the effects of pulmonary artery banding as a pre-switch palliation resulting in distortion of the neo-aortic root.

Transposition of the Great Arteries with Aortic Arch Obstruction

In recent reports, aortic arch hypoplasia or discrete coarctation have not been associated with increased mortality when the arterial switch and arch repair are undertaken together. Blume and associates reported a significant increase in overall mortality in children who had arch repair prior to arterial switch although the reasons for this were unclear.¹⁰¹ Tchervenkov and colleagues have reported no operative deaths in 12 patients undergoing arterial switch procedure for TGA with aortic arch obstruction and no late deaths after a mean follow-up

time of 42 months.⁹⁵ Other centers have reported a small but present incidence of aortic arch obstruction requiring reintervention with balloon dilation late.¹⁰²

Arterial Switch after Left Ventricular Retraining

There are two situations when left ventricular “retraining” might be necessary prior to arterial switch operation: (1) in patients with TGA and intact ventricular septum who present late, and (2) in patients that present with right ventricular dysfunction after atrial switch that is refractory to medical management. Surgical options to address the latter issue include tricuspid valve repair or replacement if there is significant tricuspid regurgitation, which has not had encouraging results, and heart transplantation, which is limited by donor availability and long-term complications. Perhaps the best option for these patients is conversion to an arterial switch. In this case, the left ventricle must be retrained to handle the systemic afterload in order for arterial switch to be successful. This is accomplished by “training” the left ventricle, imposing an afterload on the deconditioned left ventricle with the application of a pulmonary artery band. This can be performed via sternotomy without the use of CPB and is a long-term strategy, because one to three bandings over many months are typically required to adequately prepare the left ventricle.¹⁰³ The status of the left ventricle during banding must be closely assessed by echocardiography, magnetic resonance imaging, and cardiac catheterization, and various criteria have been developed to assess for adequate preparation of the ventricle. These include left ventricular mass index and left ventricle/right ventricle pressure ratio.

These procedures are significant undertakings, with substantial intensive care unit and hospital stays but when accomplished successfully can offer good long-term outcomes. Poirier and Mee reported a series of 84 patients who underwent arterial from atrial switch conversion with an 85% overall survival. Normal late left ventricular function and right ventricular function were seen in approximately 90% of these patients. The best results were obtained in patients undergoing conversion prior to adolescence, with less predictable results and higher mortality rates observed in older patients.¹⁰³

In unoperated infants who present after the early neonatal period, preliminary pulmonary artery banding followed closely by arterial switch operation (rapid two-stage switch) banding has been performed. However, the data from more recent experiences suggest that this approach is seldom required; pulmonary artery banding for left ventricular retraining following atrial switch often takes much longer, averaging 19 months in some reports.

SUMMARY

The treatment of TGA has evolved rapidly. Current results with the arterial switch operation are excellent and make this procedure the standard of care for neonates with this diagnosis. Experience is being gained with complex forms of transposition, allowing safe anatomic

repair for these patients as well. Continued surveillance of patients following repair is necessary to detect and deal with potential long-term complications in these patients.

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SURGERY FOR CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

William J. Brawn • David J. Barron

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SUMMARY

Congenitally corrected transposition of the great arteries (ccTGA) is a rare defect, seen in approximately 0.5% of patients with congenital heart defects.^{1,2} It entails discordance of the atrioventricular (AV) connections and discordance of the ventricular arterial connections, so there is double discordance. The morphology of the heart is distinctly abnormal, but the circulatory system is physiologically normal. Commonly, ccTGA is associated with ventricular septal defects (VSDs), pulmonary stenosis, dysplasia of the tricuspid valve, and conduction abnormalities (e.g., heart block usually develops).³⁻⁵ Although this condition can be compatible with a normal life span,^{6,7} the majority of patients require surgery to repair the associated cardiac anomalies, and many develop heart failure

because of systemic morphologic right ventricular (mRV) dysfunction, usually with tricuspid valve regurgitation.⁸⁻¹¹ Historically, surgery was directed toward managing the associated cardiac anomalies, closing the VSD, relieving pulmonary stenosis, repairing or replacing the tricuspid valve, and placing pacemakers to manage the conduction abnormalities. This so-called classical or conventional (physiologic) repair maintains the mRV as the systemic ventricle. More recently, the morphologic left ventricle (mLV) has been restored to the systemic circulation by an atrial switch (Senning or Mustard procedure) and an arterial switch or Rastelli procedure to connect the aorta to the mLV.¹²⁻¹⁵ This is referred to as *anatomic repair*, and it is the preferred technique for symptomatic patients.

GENERAL DESCRIPTION AND MORPHOLOGY

In the usual *situs solitus* arrangement with normal systemic and pulmonary venous drainage, the ventricular apex of the heart usually points to the left side of the patient, but *mesocardia* and *dextrocardia* are common, occurring in up to 20% of cases.^{4,16} Malposition of the ventricular mass so that it comes to lie in front of the atria and venous drainage to the heart can make surgical access to these structures difficult. In *situs inversus*, which occurs in approximately 5% of cases, *mesocardia* and *levocardia* can occur. It seems that extreme malposition of the ventricular mass is commonly associated with severe pulmonary stenosis or pulmonary atresia in association with a large VSD.¹⁶ Characteristically, the aorta is anterior and to the left side of the more deeply placed pulmonary artery—hence the older term for this condition, *L-transposition*. However, the aorta can be more anterior to the pulmonary artery and even on the right side. Likewise, the mLV is usually to the right and slightly inferior to the mRV; however, the position of the ventricles relative to each other can show great variability.³ The ascending aorta is often short and well over to the left side of the mediastinum in *situs solitus*, again making surgical access difficult. In the rarer form of *situs inversus*, the aorta lies anterior and to the right of the posterior pulmonary artery and is usually more accessible.

In ccTGA without associated cardiac anomalies (sometimes referred to as *isolated ccTGA*), the circulation is physiologically normal, with systemic venous return passing through the right atrium, through the mitral valve, and then into the mLV. Here, the mLV pumps blood through the pulmonary arteries into the lungs, from whence it returns to the pulmonary veins and to the left atrium. The blood flow continues through the tricuspid valve and into the mRV, where it is pumped around the systemic circulation via the aorta (Fig. 126-1). Without other cardiac anomalies, patients with congenitally corrected transposition can survive well into adult life without symptoms. It is the associated anomalies—VSD, pulmonary stenosis, abnormalities of the tricuspid valve, and development of arrhythmias or complete heart block—that predispose the patient to the development of cardiac failure early in life. However, even patients with isolated ccTGA can develop systemic ventricular (i.e., the mRV) dysfunction leading to congestive cardiac failure in childhood or early adult life, but predicting which patients will do so is one of the many challenges in managing the condition.

Ventricular Septal Defect

Ventricular septal defect occurs in approximately 70% of cases.⁴ It is usually isolated and in the perimembranous region. Isolated VSDs can also occur in the infundibular region, and they may be multiple. When associated with severe pulmonary stenosis or pulmonary atresia, the VSD is usually subaortic and large, extending from the perimembranous region to beneath the aortic valve. This is important, because it allows the VSD to be tunneled to

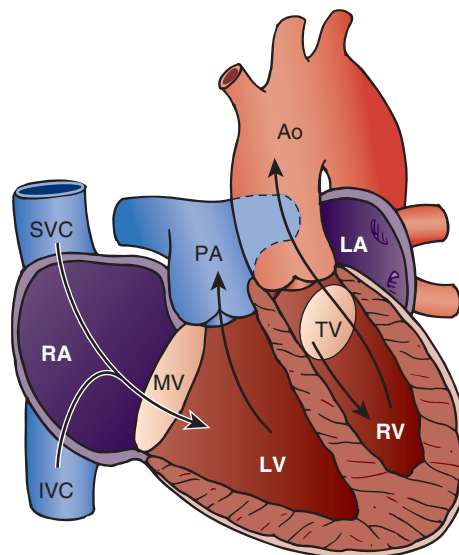


FIGURE 126-1 ■ Diagram of congenitally corrected transposition of the great arteries. Ao, Aorta; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve.

the aorta when the mLV is committed to the aorta as a systemic ventricle.

Pulmonary Outflow Tract Obstruction (Morphologic Left Ventricular Outflow Tract Obstruction)

Obstruction to the pulmonary artery from the LV is common in congenitally corrected transposition, occurring in probably up to 50% of cases.^{4,17} This is partly because the pulmonary artery is between the mitral and tricuspid valves, deep toward the crux of the heart. A potential exists for hypoplasia of the subpulmonary outflow tract. When hypoplasia occurs in association with a VSD, there may be accessory tissue around the VSD, which can balloon into the pulmonary valve. Accessory tissue tags can prolapse into the outflow tract from the mitral or the tricuspid valves, and over time fibrous tissue can be deposited in the subpulmonary area of the mLV outflow tract. Accessory attachments of the mitral or tricuspid mitral valve through the VSD can cause obstruction beneath the pulmonary valve. In the majority of these cases, the pulmonary valve and annulus are stenotic, and the morphology falls into the spectrum of requiring a Rastelli-type procedure to commit the mLV to the aorta. However, each case needs careful assessment because those with a normal-sized pulmonary valve and accessory tissue in the outflow tract may be more suitable for arterial switch and resection of tissue in the LVOT.

Mitral and Tricuspid Valves

The mitral valve is usually normal in congenitally corrected transposition. There are usually two well-formed papillary muscles on the lateral wall of the LV.

Occasionally, we have noted a cleft in the septal component of the mitral valve.¹⁸

The tricuspid valve, however, is a markedly different proposition. The valve itself may be intrinsically normal, but through dilation of the ventricle and the tricuspid valve annulus, it can become progressively regurgitant over time. However, more commonly the valve is dysplastic, and this predisposes to valvular regurgitation. There is a marked association with dysplasia and displacement of the septal components of the tricuspid valve well down into the body of the RV, sometimes for several centimeters, and this, in the setting of systemic pressures in the RV, can create severe tricuspid valve regurgitation. We have noted double orifices in the tricuspid valve, abnormal septal clefts, and marked annular dilation. Because of difficult access and the great variability in the pathology in this valve, repair can be difficult.¹⁸⁻²⁰

The Ebsteinoid displacement of the tricuspid valve into the body of the mRV is not associated with any atrialization of the RV free wall. Neither do these valves demonstrate any of the failed delamination or multiple leaflet fenestrations typical of Ebstein's anomaly. Thus, it is not strictly equivalent to an Ebstein tricuspid valve in a normal heart, and the term simply reflects the apical displacement of the tricuspid valve in this setting. In addition, when functioning at lower pulmonary pressures after a double-switch procedure, the regurgitation is markedly reduced; that is, it is not a low-pressure regurgitant valve, but tends to be a high-pressure regurgitant valve. The improved performance of the tricuspid valve after double-switch is also related to the more favorable septal alignment, which improves coaptation of the septal leaflet in the lower-pressure RV.

Rarely, straddling and override of the AV valves can occur, usually in association with a degree of hypoplasia of the LV or RV, many merging into the spectrum of double-inlet LV.²¹⁻²³ These hearts are managed according to the principles of any functionally univentricular circulation.

Other Associated Cardiac Anomalies

Abnormalities of the aortic arch, including interruption of the aorta and coarctation, can occur. We have seen a 20% incidence of coarctation or arch hypoplasia and 2% incidence of interruption. As might be expected, none were associated with pulmonary stenosis or atresia.²⁴

Coronary Arteries

Usually, the anterior sinus of the aortic valve gives rise to what would normally be the right coronary artery (Fig. 126-2). This divides to pass down the line of the interventricular septum as the anterior descending coronary artery. The other circumflex branch passes in the AV groove between the right atrium and the LV. The posterior sinus of the aortic valve gives rise to the morphologically right coronary artery passing in the AV groove between the left atrium and the RV. Almost universally, the coronary artery ostia face the corresponding sinuses of the pulmonary valve. This is an important consideration in the arterial switch procedure.

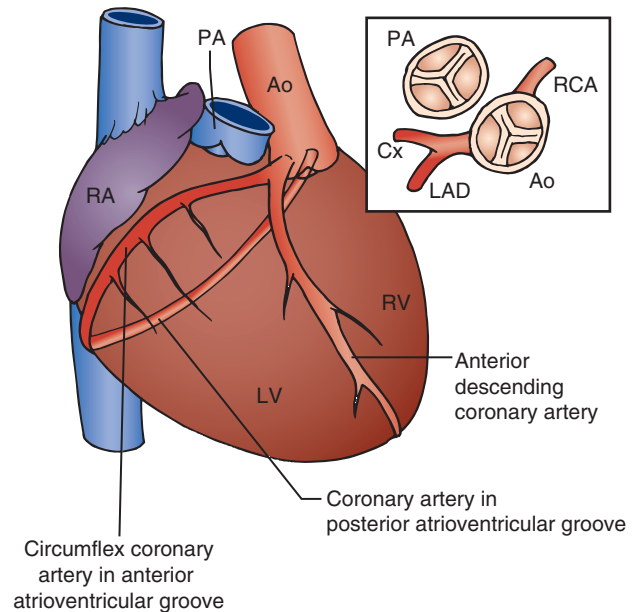


FIGURE 126-2 ■ Disposition of coronary arteries in congenitally corrected transposition of the great arteries. Ao, Aorta; Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RCA, right coronary artery; RV, right ventricle.

Conduction System

The abnormalities of the conduction system in congenitally corrected transposition have been well described.²⁵⁻²⁸ Because of malalignment of the AV septum, there is an anterior and a superior AV node in the atrial septum adjacent to the mitral and pulmonary valve. These nodes give rise to a penetrating bundle that passes around the free wall of the LV in a subendocardial position anterior to the pulmonary valve. The bundle then sweeps down onto the ventricular septum in the mLV, supplying a left bundle branch over the septal surface of the LV and a penetrating right branch into the mRV. The sinus node is in a normal position adjacent to the entrance of the superior vena cava into the right atrium (Fig. 126-3).

In the rarer form of situs inversus, the normally positioned AV node of that is in the triangle of Koch superior to the coronary sinus persists and gives a penetrating branch to the ventricular septum but inferior and posterior to the pulmonary valve. These pathways are important because in situs solitus, when there is a VSD in the perimembranous region, the bundle passes superior to the VSD around the pulmonary outflow tract and then down on the leftward or anterior margin of the VSD. In the rarer forms of situs inversus, the bundle passes on the inferior margin of the VSD on the mLV surface. Occasionally, both posterior and anterior AV nodes exist, and a loop of conduction tissue can encircle the VSD when it is present. Sutures to close the VSD are ideally placed from the mRV surface of the VSD to avoid damaging the conduction system.²⁹ The longer course of the conduction system to the ventricles associated with the malalignment of the atrioventricular septum has been given as a reason for the development of complete heart block.

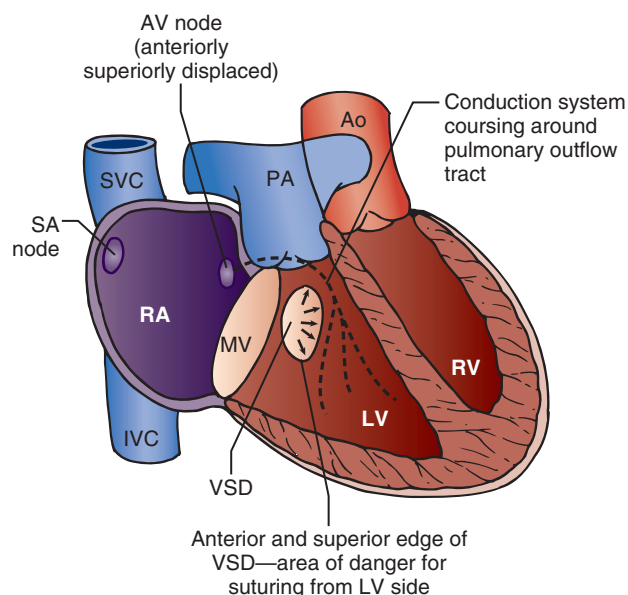


FIGURE 126-3 ■ Disposition of conduction system in congenitally corrected transposition of the great arteries and relationship to ventricular septal defect (VSD). Ao, Aorta; AV node, atrioventricular node; IVC, inferior vena cava; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SA node, sinus atrial node; SVC, superior vena cava.

CLINICAL PRESENTATION OF CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

A patient's clinical presentation depends on the presence or absence of associated cardiac anomalies. Without such anomalies, patients may be entirely free of symptoms well into late adult life; however, this is an unusual, if not rare, situation. More commonly, even in the absence of associated malformations, a degree of congestive cardiac failure develops over the lifetime of the patient, usually aggravated by the development of progressive tricuspid regurgitation.⁷

When associated with a VSD, presentation in early infancy is usually with congestive cardiac failure resulting from pulmonary overflow from the left-to-right shunt. In view of heart failure and the risks for pulmonary hypertension and progression to pulmonary vascular disease, medical management with diuretics and angiotensin-converting enzyme inhibitors is usually supplemented with pulmonary artery banding. VSD in this condition usually occurs with a degree of congenital pulmonary stenosis and can produce a nicely balanced circulation without heart failure or marked cyanosis. The patient may be well and in stable condition for many years without the need for medical or surgical intervention. When the pulmonary stenosis progresses or if it is severe initially, cyanosis may be the cause of clinical presentation, and early systemic-to-pulmonary shunting may be required. Pulmonary atresia with a large perimembranous VSD extending to the subaortic region is a well-recognized combination of associated cardiac anomalies,

and a neonate in this situation usually exhibits severe cyanosis and requires an early systemic shunt.

A small percentage of patients are seen in early infancy with severe congestive cardiac failure, sometimes associated with pulmonary hypertension. This is usually associated with marked tricuspid regurgitation secondary to dysplasia of the tricuspid valve, and it is often associated with a VSD that could aggravate the heart failure. Early surgical management is mandatory in these critically ill infants.¹⁸

Thus, there is a wide range of possible presentations that vary with the intracardiac anatomy, ranging from asymptomatic adults to infants in severe congestive cardiac failure. Depending on the degree of pulmonary stenosis or atresia, some patients may have well-balanced circulation with mild cyanosis, whereas others have severe cyanosis requiring systemic shunts in the neonatal period. Throughout the patient's life, the clinical course can be complicated by the development of complete heart block and other cardiac arrhythmias.

PROBLEM OF THE TRICUSPID VALVE AND THE MORPHOLOGIC RIGHT VENTRICLE IN THE SYSTEMIC CIRCULATION

The main concern highlighted in many papers^{8-11,19,30-32} has been the unpredictable way the mRV in association with tricuspid valve regurgitation can fail when it remains as the systemic ventricle. The development of RV failure can occur primarily without previous surgical intervention, and it is usually associated with dysplasia of the tricuspid valve, causing tricuspid regurgitation. RV failure can also occur secondarily after conventional repair of associated cardiac defects such as VSD closure or the relief of pulmonary stenosis or atresia when the RV remains in the systemic circulation.

The deterioration in the RV function associated with tricuspid regurgitation can also develop insidiously over many years without associated cardiac anomalies. There is then gradual deterioration of RV function with worsening of tricuspid regurgitation in association with the volume loading of the RV. These changes can commence in childhood or infancy and progress at a variable rate.^{19,30} When these changes are associated with dysplasia or Ebsteinoid displacement of the tricuspid valve, deterioration can be rapid. Secondary deterioration of ventricular function and development of tricuspid regurgitation are recognized to occur in an unpredictable way after conventional repair of associated cardiac anomalies. Thus, VSD closure with pulmonary artery debanding may be successful with the RV in the systemic circulation, although over time RV failure with tricuspid regurgitation can follow such a repair. In the situation of pulmonary atresia with VSD, closure of the VSD and placement of a valved conduit from the mLV to the pulmonary arteries may later be associated with the development of tricuspid regurgitation and RV failure.

It therefore seems that, either primarily or secondarily after conventional repair, the RV in the systemic

circulation is prone to failure and severe tricuspid regurgitation. Once the tricuspid regurgitation has developed, the volume loading of the RV accentuated by any systemic shunts or VSD can cause further dilation of the tricuspid valve and its annulus, creating more regurgitation, so that a vicious cycle of heart failure with increasing tricuspid regurgitation follows. The difficulty is recognizing which patients are likely to develop these complications after a conventional repair and then determining the best surgical procedure to repair their heart.

The development of mRV systemic failure without previous surgical intervention is almost always associated with dysplasia of the tricuspid valve. The suggested mechanism is that dilation of the RV, in association with its volume loading resulting from tricuspid regurgitation, displaces the ventricular septum into the mLV. The displacement of the septal components of the tricuspid valve prevents coaptation of leaflet tissue, thus accentuating the regurgitation. This vicious cycle of tricuspid valve dilation and ventricular volume overload with increasing regurgitation continues.¹⁹ In secondary mRV failure following conventional closure of VSD or relief of pulmonary valve stenosis, the fall in the mLV pressure and realignment of the ventricular septum to the pulmonary ventricle can have the same effect by creating tricuspid regurgitation. That can then be aggravated by volume overloading of the mRV. This is thought to be the mechanism of the development of tricuspid regurgitation and RV failure, which is supported by the observation that, in placing the pulmonary artery band to train the mLV, the tricuspid regurgitation can be acutely reduced by realignment of the ventricular septum.^{18,19} If this is the mechanism of mRV failure, then tricuspid regurgitation and RV failure can be expected to occur after conventional repair.

Anatomic repair of ccTGA restores the mLV to the systemic circulation by redirecting the systemic and pulmonary venous returns—via a Senning or Mustard procedure—and then performing an arterial switch if the pulmonary valve and LV outflow tract were unobstructed, or a Rastelli-type procedure with rerouting of the VSD to the aorta when the VSD was suitably placed beneath the aortic valve.²⁹ Several groups reported successful double-switch and Rastelli atrial switch procedures, showing that the mLV could be restored to the systemic circulation.^{12-15,33} The underlying theme in these reports was that the mLV restored to the systemic circulation could be a better long-term systemic ventricle and would have the added benefit of preventing the development of RV failure. In the double-switch procedure, besides restoring the mLV and mitral valve to the systemic circulation, the mRV becomes the pulmonary ventricle, works at lower pressures, and is decompressed. The amount of tricuspid regurgitation can be immediately reduced because of the lower working pressures of the RV with minimal need for any repair or replacement of the tricuspid valve. Maintenance of the alignment of the ventricular septum or its displacement into the RV cavity would aid in maintaining competency of the tricuspid valve by preventing displacement of the septal leaflet of the tricuspid valve. In essence, the mRV is now working as a pulmonary ventricle at low pulmonary artery pressures and can function satisfactorily in that setting.

Although accentuating the interrelationship between tricuspid valve regurgitation, RV volume overloading, and RV failure, several papers have highlighted the possible problem of RV myocardial ischemia as a cause of RV failure. The RV, working at systemic pressures with resultant hypertrophy of the myocardium, may not have sufficient coronary vascular supply. This results in ischemia of the RV myocardium, which, together with volume loading secondary to tricuspid valve regurgitation, may be the determining factor in RV failure in this condition.³⁴⁻³⁶

For two reasons, the double-switch type of operation has become popular over the past 20 years. First, at intermediate follow-up, it seems that restoration of mLV to the systemic circulation with the mRV working under lower pulmonary pressures prevents the development of RV failure and significant tricuspid regurgitation. The mLV seems to be holding up well as the systemic ventricle. In the second situation, when RV dysfunction exists with associated tricuspid regurgitation, the recruitment of the mLV to the systemic circulation and the delegation of the mRV to the pulmonary circulation is appealing, as it reduces the work that the RV has to do, and the literature supports markedly diminished tricuspid valve regurgitation.³⁷ A double-switch operation is possible when the mLV pressures have been maintained at systemic levels (e.g., in a VSD pulmonary artery banded situation or when there is pulmonary atresia and VSD). However, when the mLV has been working as a pulmonary ventricle at low pulmonary artery pressures, it is not possible to perform a primary double-switch procedure expecting that the LV will support the systemic circulation. The LV needs some preparation to cope with the systemic workload. To create a ventricle strong enough to support the systemic circulation, many centers first place a pulmonary artery band to retrain the LV, and later perform an arterial switch. This circumstance arises with patients who have ccTGA without associated anomalies in whom over the first few years of life tricuspid regurgitation and a degree of RV failure has occurred in the setting of low pulmonary artery pressures. Then it is possible to retrain the LV and perform a double-switch procedure once the ventricle has been retrained. It can take 6 months to 1 year, or longer, to accomplish this.

Training of the Left Ventricle

Training of the LV has become an important aspect in congenital heart management since Mee's group,³⁸ and others showed that it was possible to retrain the LV in infants with dextrotransposition after a failing atrial repair to restore the LV to the systemic circulation. This concept has been applied to patients with ccTGA. The method used for training is similar in the two groups. A pulmonary artery band is placed around the main pulmonary artery acutely, to raise the mLV pressure to approximately 75% to 80% of the systemic pressure. Inotropic support may be necessary, and band adjustment to loosen or tighten the band may be needed over the first few days or weeks after the initial procedure. It may take 6 to 18 months for the mLV to be adequately trained so that systolic pressures are at systemic levels and ventricular

function is good, with an adequate thickness of the LV free wall. Training of the mLV is generally more successful in younger patients, and the upper age limit at which success can be expected is believed to be a maximum of 15 or 16 years.³⁹ Recently reported late outcomes of anatomic repair have highlighted concerns over the late performance of “retrained” mLVs.^{24,40} Although by no means a universal finding, some studies have suggested that banding even at ages older than 2 years may be associated with poorer late performance of the mLV (see below).⁴¹ In view of this, Vouhe and colleagues⁴² have suggested a novel approach of banding symptomless infants with isolated ccTGA as a means of sustaining mLV pressures and restoring septal geometry early in life. Although an attractive idea, this remains a controversial approach due to the unpredictable natural history in isolated ccTGA, some of whom require no intervention for many years, even indefinitely.

INVESTIGATIONS AND EVALUATION

Echocardiography, both transthoracic and transesophageal, allows a diagnosis of ccTGA to be made and can show the important intracardiac morphology. It can be repeated on many occasions, with minimal effect on the patient, to fine-tune the diagnosis. Cardiac catheterization is usually performed in these patients before surgical intervention and is useful in confirming the morphology of the ventricular septum, as there may be multiple VSDs, and in clearly showing the pulmonary artery tree when previous surgery has been performed to place a pulmonary artery band or to create systemic-to-pulmonary artery shunt. It also can show clearly the coronary artery anatomy if an anatomic repair is to be considered. When a mLV has been retrained with a pulmonary artery band, it is necessary to measure ventricular pressures. When there is concern about pulmonary hypertension, cardiac catheterization with manipulation of pulmonary vascular resistance in the catheterization laboratory is mandatory.

As for other forms of congenital heart disease, computed tomography scan and magnetic resonance imaging have been increasingly used to delineate anatomy, with magnetic resonance imaging being particularly helpful in demonstrating the relationship of the VSD to the aorta in assessing for suitability for Rastelli in the setting of unusual cardiac position. Three-dimensional echocardiography will undoubtedly also become more widely used as it becomes more available, particularly in assessing tricuspid valve regurgitation.

SURGICAL OPTIONS

Historically, the decision to correct ccTGA surgically was fairly straightforward: the associated cardiac anomalies would be repaired (physiologic repair), the VSD could be closed, the pulmonary stenosis would be relieved, and the tricuspid valve would be repaired or replaced with or without a pacemaker system. However, since the inception of the double-switch procedures, it is necessary to

decide whether to allow the mRV to remain in the systemic circulation or to use a double-switch procedure to restore by the mLV to the systemic circulation. This decision is made despite knowledge that historically the RV in the systemic circulation will deteriorate unpredictably, and even though long-term follow-up results of the double-switch procedure are still limited. The algorithm in [Figure 126-4](#) illustrates the possible surgical management for patients with ccTGA and their associated cardiac abnormalities. When longer-term results become available, indications may well change.

Physiologic Repair (Conventional or Classic)

In a physiologic repair, the associated cardiac defects are repaired so that the mRV remains as the systemic ventricle. The VSD is closed with a patch, pulmonary outflow tract obstruction is relieved directly by resection of obstructing tissues, and, when this cannot be performed adequately, a valved conduit from the mLV to the pulmonary artery is placed to relieve the obstruction ([Fig. 126-5](#)). If there is associated tricuspid valve regurgitation, the tricuspid valve can be repaired; this can be difficult, however, because of the difficult dysplastic abnormalities associated with this valve. Clefts can be closed and annuloplasty can be performed.

Cardiopulmonary Bypass in Physiologic Repair

Normal cardiopulmonary bypass with ascending aortic and bicaval cannulation is instituted. Core cooling is taken to 28° or 25° C (by nasopharyngeal measurement), depending on the surgical complexity. Initial dissection of the heart may be limited to the cannulation sites only, if this is a reoperation with further pericardial adhesions taken down on bypass. Having mobilized the heart fully (which can be difficult because of the position of the ventricles), the aorta is cross-clamped, and the repair is performed using standard cardiopulmonary bypass techniques.

Closure of the Ventricular Septal Defect

In congenitally corrected transposition, the VSD is commonly in a perimembranous position. In this situation, the conduction system passes superiorly around the pulmonary outflow tract. Accordingly, to avoid damaging the conduction system, continuous or interrupted sutures are placed through the RV margin of the VSD.²⁹ Access to the VSD is usually via the mitral valve or the pulmonary artery. If a ventriculotomy has to be performed, access to the VSD can be gained via the ventriculotomy.

Placement of the Valved Conduit

The valved conduit from the LV to the pulmonary artery (Hancock, Medtronic, Inc., Minneapolis, MN) usually passes to the right side of the aorta and is behind the sternum. Sometimes, the course of the conduit can be curved away from the sternal incision, but once the

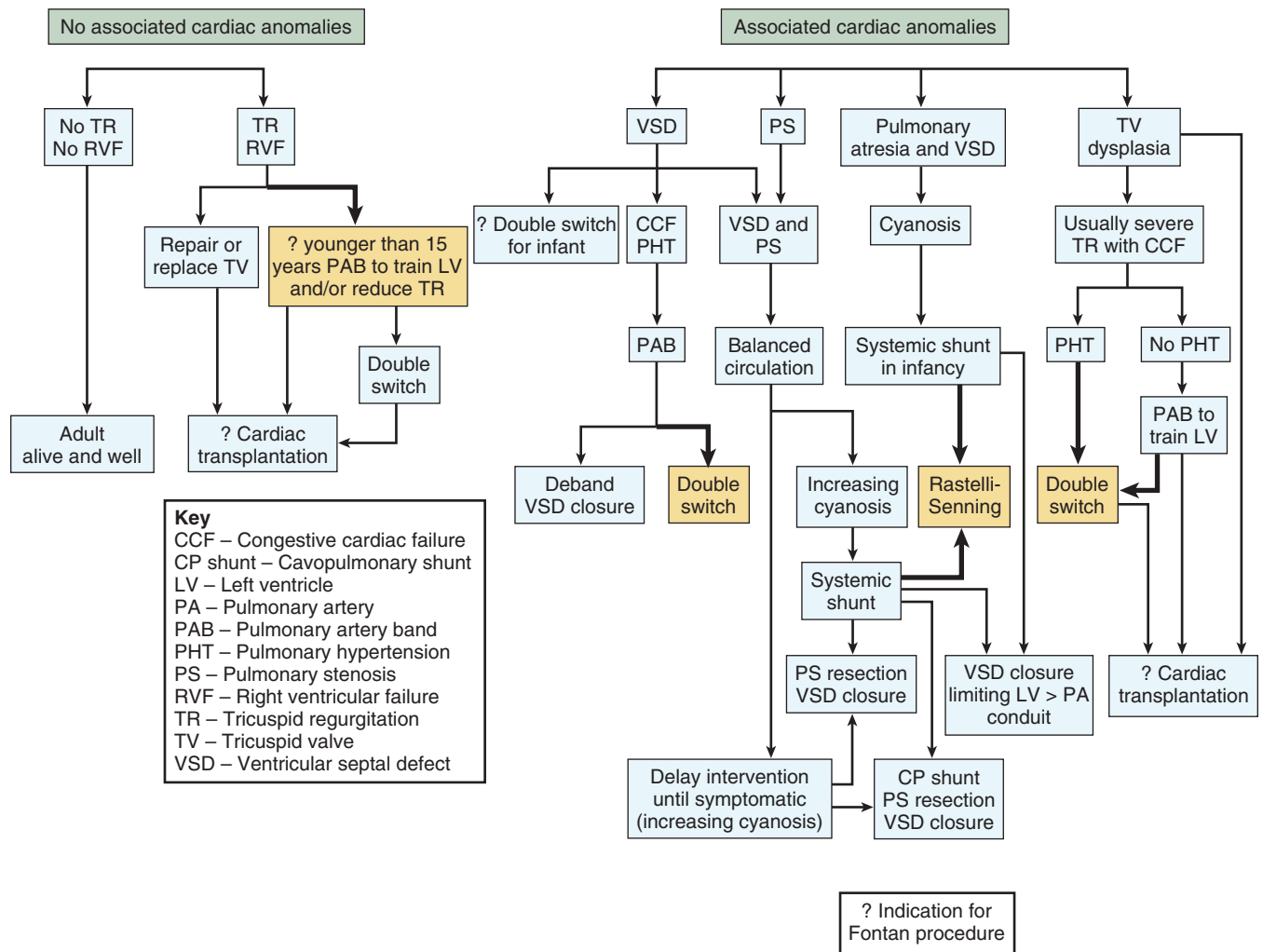


FIGURE 126-4 ■ Algorithm for management of congenitally corrected transposition. Preferred management pathways are highlighted with yellow boxes and bolded arrows.

conduit is placed, it is wise to either close the pericardium or place a protective membrane behind the sternum to allow future reentry when the valved conduit needs replacing. A left ventriculotomy should be more toward the apex of the ventricle, taking care to avoid the papillary muscles of the mitral valve on the inner aspect of the ventricle and superior to the conduction system as it passes around the LV outflow tract.

Tricuspid Valve Repair or Replacement

Our experience with repair or replacement of the tricuspid valve in ccTGA is limited, because we electively try to perform a double-switch procedure when there is tricuspid valve regurgitation. Access to the tricuspid valve can be difficult if it is deeply seated in the RV. Reparative procedures are limited unless one finds a cleft in the valve that can be directly sutured, or a secondary orifice that can be closed. Various annuloplasties and reinforcing surgical rings can be placed in an attempt to gain competence in these difficult valves. In general, however, we do not believe this is advisable and would prefer to replace the valve if a secure repair cannot be made. In general, we replace the valve with a bileaflet mechanical valve,

with reinforced inverting mattress sutures. To preserve ventricular function, we preserve as much valve apparatus as possible when suturing the new valve.

Palliative Surgical Procedures

Various palliative surgical procedures may be applicable to patients with ccTGA. If there is cyanosis, a systemic-to-pulmonary artery shunt, usually a modified Blalock-Taussig shunt, is our preference. When there is pulmonary overflow resulting from a large VSD in infancy, a pulmonary artery band is placed, usually through a midline sternotomy. It may be necessary to place, in an epicardial position, either temporary or permanent pacemaker systems at the time of this palliative surgery.

Anatomic Repair

Cardiopulmonary Bypass and General Considerations in Anatomic Repair

Routine cardiopulmonary bypass techniques are used with cold crystalloid cardioplegia and topical irrigation of the heart with iced slush solution. The

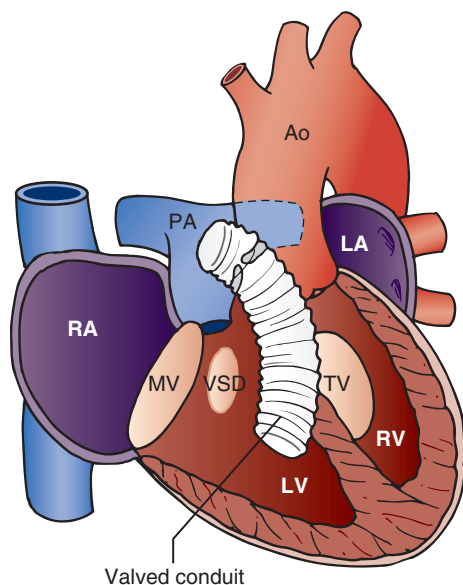


FIGURE 126-5 ■ Physiologic repair of congenitally corrected transposition of the great arteries with pulmonary stenosis and ventricular septal defects (VSDs). The procedure includes VSD closure and placement of a valved conduit from the left ventricle (LV) to the pulmonary artery (PA). Ao, Aorta; LA, left atrium; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

heart is completely mobilized by dividing all the previous adhesions. Cardiopulmonary bypass is begun routinely by cooling to 22° or 18° C (by nasopharyngeal measurement) if circulatory arrest is anticipated. Often, a considerable amount of open-heart return is present, and short periods of low flow or even circulatory arrest are necessary to provide a clear field for the reconstructive surgery, particularly for the Senning procedure. Certain aspects of the bypass and cannulation, however, are peculiar to the anatomic repair. The superior vena cava is cannulated high underneath the innominate vein to allow room at the superior vena caval–right atrial junction for placement of the superior pulmonary venous Senning suture line. The inferior vena cava is cannulated low to place the cannula below the site of the Eustachian valve. The Eustachian valve can then be incorporated into the suture line of the systemic venous pathway. Having cross-clamped the aorta and arrested the heart with St. Thomas's cardioplegia solution, the atrium is opened.

Our practice is to use aprotinin infusion during the operation and tissue fibrin glue to help with hemostasis. Because these are long operations, we invariably do not close the sternum at the end of the operation. In addition, when a valved conduit passes directly behind the sternum in front of the heart, we delay sternal closure until myocardial function has recovered, so that the heart is not compressed by the valved conduit.

Surgical Anatomic Repair of Congenitally Corrected Transposition of the Great Arteries

In an anatomic repair (as opposed to the conventional repair, when the mRV remains as the systemic ventricle),

the mLV is restored to the systemic circulation. This is done by recruiting the systemic veins to the RV and the pulmonary veins to the LV by the Senning or Mustard procedure. Our experience is with the Senning operation, but the Mustard procedure can also be used. An arterial switch is then performed when the pulmonary outflow tract is unobstructed, and the pulmonary valve can become the new aortic valve. If there is pulmonary stenosis or atresia with a suitably large subaortic VSD, the LV can be rerouted to the aorta by baffling the VSD to the aortic valve as a Rastelli procedure. A valved conduit then connects the mRV to the pulmonary artery. The conduit can pass either side of the aorta, but if possible we route it to the left side to avoid the conduit sitting immediately behind the sternum.

Atrial-Arterial Switch (Double Switch). After cardiopulmonary bypass is commenced, the interatrial groove is developed, the aorta is cross-clamped, and cardioplegia is instituted. Cardioplegia solution is refreshed every 25 to 30 minutes, either via the aortic root or directly into the coronary ostia. The Senning baffles are formed.^{18,43} The right atrium is opened just anterior to the crista terminalis; this incision is extended inferior, anterior, and parallel to the crista to reach the Eustachian valve. The interatrial septum is opened adjacent to the mitral valve annulus, extending the incision superiorly and inferiorly. The superior incision is then extended deeply into the limbus, back to the root of the superior vena cava, and it usually exits through the previously delineated interatrial groove. The atrial septum is then separated from the right pulmonary veins hinging on the wall of the right atrium, to create the posterior wall of the systemic venous chamber. The interatrial septum is checked for perforations, which might need additional sutures. When there is a VSD, it is closed through the mitral valve, passing sutures from the rightward side of the ventricle as in the conventional repair. However, excessive traction on the crux of the heart (as occurs particularly with mesocardia or dextrocardia) can create temporary or permanent heart block, even if the sutures are placed carefully on the rightward side of the ventricular septum. We usually use a bovine pericardial patch or a Gore-Tex patch held in position with multiple interrupted Teflon pledgeted or native pericardial pledgeted mattress sutures. The smooth patch is used so that if there is neo-aortic valve regurgitation, the likelihood of hemolysis is reduced.

We then turn our attention to the arterial switch. The aorta is transected 1 to 1.5 cm above the entrance of the coronary arteries. If these are not clearly visible because of adhesions, the anterior wall of the aorta is opened carefully for about one third of its circumference, and the coronary arteries are visualized before aortic transection is completed. After pulmonary banding, there may be marked fibrosis between the aorta and the pulmonary artery.

Careful dissection continues, incising the pulmonary artery at the site of the band. Next, dissection proceeds backward and forward between the aorta and the pulmonary artery to mobilize these vessels. The coronary arteries are then cut out of the aortic wall with large cuffs to provide good buttons of tissue around the coronary ostia.

It may be necessary to release some of the commissures of the aortic valve to provide plenty of room around the ostia. The ostia must be protected by a large amount of aortic wall around them. The coronary arteries are then mobilized carefully to avoid damaging the coronary arteries. In particular, the left anterior descending coronary artery may pass close anteriorly to the aortic wall. Having dissected out the coronary arteries and mobilized the pulmonary arteries, the ductus ligament is ligated and divided. The pulmonary artery is transected and completely mobilized. Next, incisions are made into the sinuses facing the coronary aortic sinuses, so that medially hinged flaps are created.⁴⁴

The coronary arteries are then swung back into the facing sinuses of the pulmonary artery and anastomosed with 6-0 or 5-0 Prolene. If the pulmonary artery is enlarged, particularly when there has been a band placed distally, it may be necessary to reduce its size by resecting tissue from the noncoronary sinus. In patients with a dilated pulmonary root, we place a subcommissural circumferential suture (4-0 polydioxanone) to tailor in the new aortic root in an attempt to prevent neo-aortic valve dilation and regurgitation in this group of patients.²⁴ A patch of pulmonary homograft or autologous pericardium is then sutured into the aortic defects. When the great vessels are side by side, the pulmonary arteries are generally left behind the aorta. When they are more or less in an anterior-posterior position, the pulmonary arteries are moved anterior to the aorta. The aorta is then reconstructed with a 5-0 or 4-0 Prolene suture. At this point, the heart receives more cardioplegia solution, and we turn our attention back to the Senning procedure.⁴⁵

The posterior wall of the systemic venous chamber is reconstructed with a continuous 5-0 Prolene suture, starting at the posterior lip of the left atrial appendage and passing superiorly, leaving plenty of space superiorly between the posterior margin of the superior vena cava and the suture line. The posterior suture line is then continued inferiorly in a direct line back to the inferior vena cava. Where there is dilation of the left atrium, it is important to gather tissue aggressively from the left atrial wall onto the posterior edge of the systemic venous baffle. The anterior wall of the systemic venous chamber is then reconstructed, starting inferiorly with suturing at the Eustachian valve. If that is not present, the suitable position on the internal aspect of the inferior vena cava is used, extending onto the cut edge of the atrial septum. The coronary sinus can be laid open into the floor of the left atrium to create more volume to the inferior limb if required. Because of the displacement of the AV node in ccTGA, this inferior suture line can be taken to either side of the coronary sinus according to preference. We generally include the coronary sinus into the systemic venous atrium (which is contrary to the classical Senning in which the coronary sinus is left in the pulmonary venous atrium to avoid the AV node). The suture line is then continued superiorly on the cut edge of the intra-atrial septum between the mitral and tricuspid valves onto the extension of the crista terminalis around the atrial appendage and back, so that the systemic venous chamber is completed. On occasion, we have found it helpful to supplement the upper third of the systemic

venous reconstruction with a small patch of bovine pericardium or native pericardium to enlarge the superior vena cava opening.

It is noticeable in this group of patients that the tricuspid valve is set more deeply in the ccTGA, and that the angulation of the superior vena cava back into the tricuspid valve opening is more acute. When the atrial septum is intact and no dilation of the atrial chambers exists, the venous pathway may be small. Supplementation with the patch helps to open out the superior vena cava pathway. The pulmonary venous pathways are then reconstructed, with a direct anastomosis of the free edge of the right atrium to the cut edge of the right pulmonary veins, commonly using an augmentation patch of pulmonary homograft to provide additional volume. At this point, bypass rewarming is commenced, the heart is de-aired, and, with aortic root suction applied, the aortic cross-clamp is removed. If heart block is a problem, temporary pacing wires are placed. The pulmonary arteries are then reconstructed, anastomosing the pulmonary artery to the distal left and right pulmonary arteries. When the patient is rewarmed, cardiac bypass is discontinued in a routine manner. Temporary pacing wires are placed, and if there was heart block preoperatively, permanent epicardial pacemaker wires may be placed. A left atrial line is routinely placed through the old right atrial appendage. The chest is usually left open for the first 24 to 48 hours (Fig. 126-6).

Rastelli-Senning Procedure. The Senning procedure is similar to the double-switch procedure. Having created the atrial incisions, an incision is made in the mRV between coronary arteries and well away from the aorta. Through the ventriculotomy, the VSD is visualized and baffled over to the aorta with a Dacron or Gore-Tex patch sutured with interrupted mattress, Teflon-pledgeted sutures. Sometimes, a continuous suture is used superiorly around the infundibulum and aorta. Depending on surgical access, the valved conduit (usually a Hancock, Medtronic, Inc.) is sutured directly to the pulmonary arteries and proximally to the ventriculotomy, or the Senning procedure is completed and then the conduit is placed. The ventriculotomy suture line is reinforced with Teflon-pledgeted mattress sutures, inside-out in the heel of the graft, and outside in the toe. Usually, the graft is placed to the left side of the aorta, but any route that allows the graft to be away from the sternum is chosen (Fig. 126-7). Usually, at least part of the graft is behind the sternum, and a Gore-Tex membrane is placed between the pericardial edges to allow safer sternal opening at conduit change.⁴⁶

Recently, it has been possible to move the aorta back to the LV by aortic translocation, and to combine this with a Senning procedure and placement of a valve conduit from the mRV to the pulmonary arteries. This technique and its modification have been described by several authors and open further possibilities for anatomic repair when intracardiac baffling could lead to tunnel stenosis.^{23,47,48}

Senning or Mustard Procedure (Special Note). We use the Senning procedure; however, the Mustard

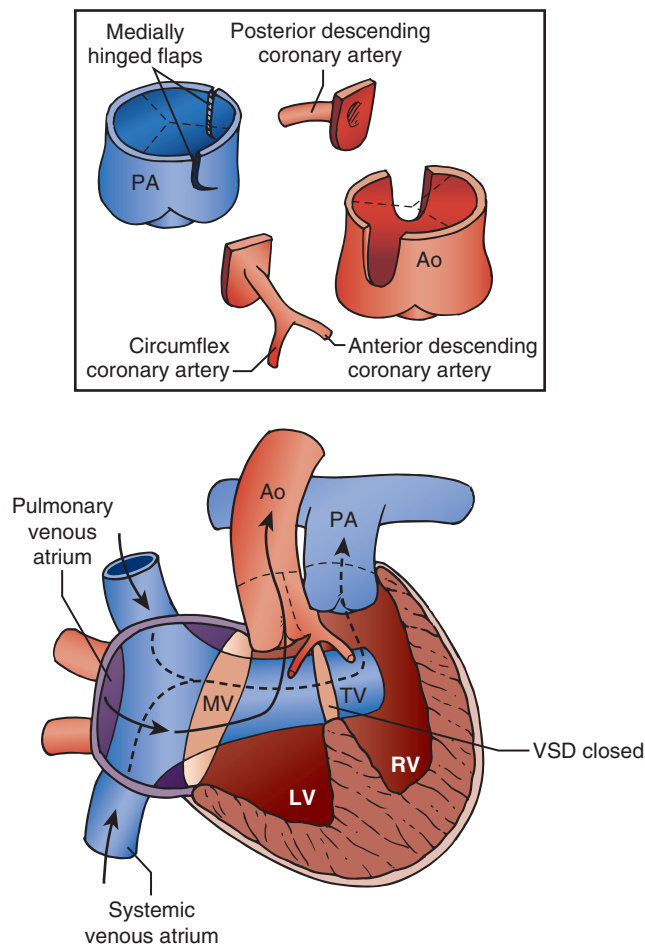


FIGURE 126-6 ■ Double-switch procedure. Ao, Aorta; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; RV, right ventricle; TV, tricuspid valve; VSD, ventricular septal defect.

procedure can be used with equal validity. Sometimes, because of the position of the heart in the Senning procedure, the pulmonary venous chamber is enlarged with a patch of pulmonary homograft, or we use the Shumacker modification, with in situ native pericardium.⁴⁹

Postoperative Management

A degree of low cardiac output is not unusual after operations with these long and complex procedures. Median times were 149 minutes for cardiac bypass and 131 minutes for aortic cross-clamp.¹⁸ Inotrope and ventilatory support are maintained until the cardiac output improves, and ventricular function is monitored by sequential echocardiographic evaluation. At the end of the operations, cardiac function and the pathways into and out of the heart are checked by epicardial or transesophageal echocardiography.

After chest closure, the patient is gradually weaned from all support in the intensive care unit. Recently, one patient who survived required postoperative extracorporeal membrane oxygenation support for 4 days at our institution.

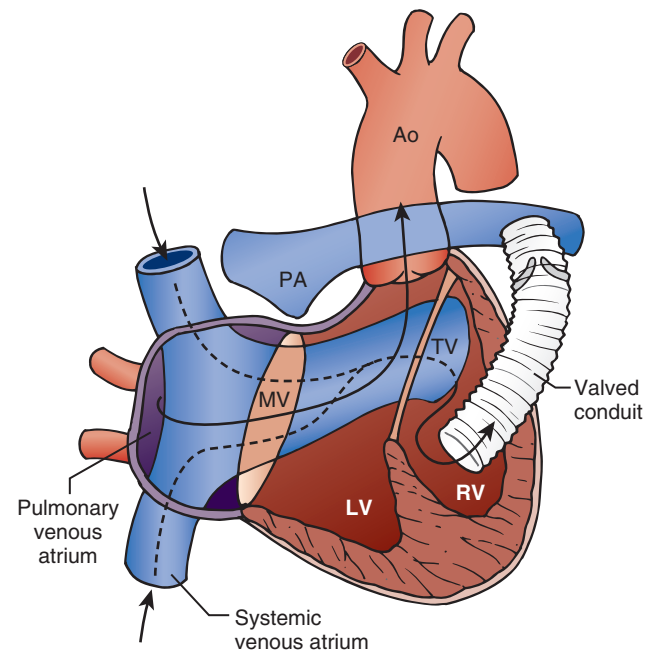


FIGURE 126-7 ■ Rastelli-Senning procedure for congenitally corrected transposition of the great arteries, with pulmonary atresia and ventricular septal defect. Ao, Aorta; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; RV, right ventricle; TV, tricuspid valve.

Alternative Procedures

The one-and-a-half technique can be used as an alternative to complete anatomic repair. This incorporates a bidirectional Glenn procedure with the arterial switch or Rastelli component. This has the advantage of simplifying the atrial switch component because only the IVC pathway has to be rerouted to the tricuspid valve. This can be achieved by excising the atrial septum and using a single circular patch of Gore-Tex to commit the IVC flow to the tricuspid valve (the so-called hemi-Mustard procedure).^{50,51}

This technique is particularly attractive if there is concern over the size of the RV after a Rastelli procedure, or in patients in whom a previous Glenn has already been performed for palliation of pulmonary atresia. However, the Glenn may be problematic if pulmonary vascular resistance is slightly raised, and it will deny access for transvenous pacing (or ablation) should rhythm disturbances occur in the future. In addition, there are concerns that the functional performance of the one-and-a-half circulation might not be as good as complete biventricular repair.

An additional option in the setting of ccTGA with VSD and pulmonary stenosis is to perform a one-and-a-half repair keeping the mRV as the systemic ventricle. The VSD is closed, and the subpulmonary stenosis is partially resected.⁵² This is done so that RV pressures and mLV pressures are maintained at a higher level, approximately 50% systemic, to maintain alignment of the ventricular septum and possibly to prevent development of the tricuspid valve regurgitation and systemic RV dysfunction in the longer term. This may be particularly

applicable to situations in which a Rastelli-Senning repair is not possible because of the position of the VSD.

Finally a Fontan-type procedure may have to be considered if it is not possible by virtue of position of the heart, location of the VSD, and hypoplasia of a ventricle to perform a septation; however, this is uncommon.

RESULTS

Physiologic Repair

Results from many centers throughout the world are now available.^{9-11,19,30,32} Although the early mortality is low (5% to 10%), all groups have highlighted the long-term failure of the mRV associated with tricuspid regurgitation. The Toronto group³⁵ in particular highlighted this long-term problem, and the Mavroudis group,³³ in their article comparing physiologic and anatomic repair, stated the problem clearly. Thus, survival in these patients is 75% at 5 years and 50% at 20 years. In addition, 56% require reoperation in the 20 years of follow-up.

Anatomic Repair

Anatomic repair has grown in popularity because of the poor long-term outcome of physiologic repair. Early results for anatomic repair are available from centers in North America, Japan, and Europe and have reported encouraging results with early mortality in the region of 0% to 5%.^{*}

Longer-term follow-up is now becoming available. In our series of 113 patients, the early mortality was 4.4%, and actuarial survival in the double-switch group was 84% at both 5 and 10 years versus 92% and 77% in the Rastelli-Senning group (log-rank, $P = 0.98$).²⁴ Within this group of patients, we have identified a subgroup of high-risk patients in the neonatal or infant age-group with severe congestive cardiac failure requiring ventilation and inotropic support. All these patients were in the double-switch group. As expected, the early mortality was high in this group (3/17, 17%) but the corollary is that the early mortality in the remaining "elective" cases was lower (2%). Freedom from reoperation for all patients was 94% at 1 year, 85% at 5 years, and 76% at 9 years. There were no reoperations for tricuspid valve regurgitation; in fact, preoperative tricuspid regurgitation was universally improved. The reoperations, as expected, were for conduit change in the Rastelli group, and this will be a continuing necessity.

As longer follow-up results are reported, there is a concern over the incidence of late mLV dysfunction occurring in 15% to 20% of patients at 20 years postoperatively. This has been reported by both ourselves and the Boston and Stanford groups with similar findings.^{15,24,37,40} The etiology appears to be multifactorial and related to the development of aortic regurgitation, later age at repair (>10 years), and the need for preoperative mLV retraining with a pulmonary artery band. Aortic

regurgitation is specific to the double-switch group, in which the old pulmonary valve becomes the new aortic valve. All our patients had some mild degree of aortic valve insufficiency. In four patients, it was moderately severe, and it required aortic valve replacement in two patients. Similar results have been reported in other series.^{33,53}

A few centers performing the atrial-arterial switch procedure have commented that the mLV retrained by application of the pulmonary artery band may have more problems with LV dysfunction in the postoperative period. We have noted this also, as have others, but the relationship is by no means consistent.^{54,55} The Boston group have shown a greater risk of late mLV dysfunction in patients who were initially banded at older than 2 years, whereas there was no incidence of late dysfunction in patients banded at younger than 2 years.⁴¹ This group of retrained mLVs will certainly require careful follow-up. These findings add to the interest in the controversial approach of early prophylactic pulmonary artery banding in symptomless infants discussed earlier,⁴² which might protect the mLV in these patients from late failure.

It has also been noted that LV dysfunction is associated with a high incidence of patients requiring pacing and of patients who have a prolonged QRS interval.⁵⁶ Resynchronization with biventricular pacing has improved mLV function in these patients, with some individual cases of dramatic improvement.^{24,40} This may be of value in patients requiring pacemaker insertion after a double-switch procedure.

Despite these concerns, the outcomes of anatomic repair remain substantially better than both the natural history and for traditional physiologic repair, with more than 75% of patients sustaining good mLV function at 20 years. It is also important to note that the group of high-risk patients with severe cardiac failure have done particularly well, with no incidence of late mLV failure. Thus, with new operations, new problems arise. Only longer-term follow-up will show whether the good early results are maintained.

SUMMARY

The algorithm in [Figure 126-4](#) summarizes our current management for these patients. We believe that the LV in the systemic circulation will be of benefit for the majority of patients with this condition; therefore, our preferred management pathways are highlighted with red arrows. Longer-term studies will show whether the problems of new aortic regurgitation, LV dysfunction, and the need for conduit change will increase over time. The problem of RV dysfunction and tricuspid regurgitation has been solved, however. An anatomic repair should be suitable for the majority of patients. Development of heart failure in the older patient may still require tricuspid valve surgery or cardiac transplantation. At this time, it is not possible to retrain the LV in older patients.³⁹ Debanding and closure of the VSD is *not* our preferred option.

When only physiologic repair is possible because of the position of the VSD, or because of the age of an older

*References 12, 13, 15, 18, 24, 37, 40, and 53.

patient, we would agree with Mavroudis and colleagues⁵² that the mLV pressure should be maintained at approximately 50% of systemic pressures to maintain ventricular septal alignment. This can prevent development of tricuspid regurgitation and deterioration of RV function. When there is hypoplasia of one of the ventricles, or complex AV valve morphology with straddling, the only option may be to use Fontan palliation; however, this applies to a minority of patients.

Longer-term follow-up of this rare group of patients is now being reported. Although we believe that the initial enthusiasm for anatomic repair is justified, some centers have reported that there is no statistical difference in long-term survival rates between some patients undergoing physiologic repair and others undergoing anatomic repair.⁵⁷ Certainly, there is no real cure for ccTGA. There are surgical options, each of which has complications that will require management in the future. Continued surveillance is most definitely necessary.

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CONGENITAL ANOMALIES OF THE MITRAL VALVE

Christian P. Brizard

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Recurrent Left Atrioventricular Valve Regurgitation

This chapter treats only the congenital anomalies of the mitral valve to the exclusion of the mitral valve in atrioventricular (AV) discordance, the mitral valve in univentricular hearts, and the mitral valve of the hypoplastic left heart syndrome. It also excludes all acquired mitral valve disease, including the mitral valve insufficiency secondary to myocardial infarction or stunning as seen in anomalous origin of the left coronary artery from the pulmonary artery. Because repair of secondary or recurrent left AV valve regurgitation is often found in studies of the congenital mitral valve, it is included here. Although the division between congenital valve stenosis and congenital mitral valve insufficiency is classical and seemingly practical, we shall try to avoid it. Congenital valve stenosis and congenital mitral valve insufficiency generate different pathophysiologies and mechanisms of adaptation from the cardiovascular system, but they do have similar pathologies and associated lesions, they are often combined, and they require similar surgical techniques for treatment. Mitral valve anomalies associated with congenital connective tissue disorders, in which the

embryology of the mitral valve itself is normal, are also covered in this chapter.

EMBRYOLOGY OF THE MITRAL VALVE

The embryology of the mitral valve is complex. The understanding of the formation of the leaflets and suspension apparatus has evolved,¹ and the current approach is based on immunohistochemistry, in vivo labeling of cushion tissue, and scanning electron micrograph of human and chick embryos.² In humans, the mitral valve develops between the 5th and the 15th weeks of embryonic life. The leaflet and chordal tissue derive from the endocardial cushion tissue lying on the inner surface of the AV junction. The separation between atrial and ventricular myocardium is dependent on the sulcus tissue located on the epicardial side of the junction. As the cushion tissue elongates and grows toward the ventricular cavity, it becomes progressively delaminated from the underlying myocardium, and the leaflet transitions into a

funnel-like structure completely attached to the myocardium. Then, perforations into the valve leaflet appear. The perforations grow and form the chordae tendineae. The atrial aspect of the cushion generates the spongy atrial layer, and the ventricular layer generates the fibrous part of the mitral valve and the chords. The development of the papillary muscle takes place at the same time and is originated from the myocardium. A horseshoe-shaped ridge lies in the left ventricle. Progressively, the anterior and posterior parts of the ridge lose contact with the ventricular wall. They will form the papillary muscles, and as they increase in size, they stay in contact with the cushion tissue at the tip of the papillary muscle. The midportion of the muscular ridge will be incorporated into the apical trabeculations of the left ventricle.³

Several AV cushions participate to form the final mitral valve. The most important are the superior and inferior cushions. However, there is no symmetry in the role of these two cushions. The superior cushion tissue generates most of the anterior leaflet of the mitral valve, whereas the inferior cushion generates most of the septal leaflet of the tricuspid valve. Smaller cushions are involved in the formation of the mural leaflet of the mitral valve. The wedging of the aortic root into the superior bridging leaflet, which originated primarily from the superior cushion, separates the developing mitral valve from its septal attachments.

PATHOLOGIC FEATURES

Supravalvar Mitral Ring

Often considered a congenital anomaly of the mitral valve, the supravalvar mitral ring is a fibrous construction attached to the posterior annulus of the mitral valve; it runs from both commissures to the mid height of the anterior leaflet. The lesion is stenotic, often to a greater extent than might be suggested by the extension of the ring. This is more a result of the limitation of the opening of the anterior leaflet than of the actual diaphragm effect of the ring (Fig. 127-1). Strictly attached to the mitral valve annulus, it is to be differentiated from the cor triatriatum. Like the subaortic membrane in the left ventricular outflow tract, the supravalvar mitral ring is an acquired lesion resulting from turbulent flow through the

mitral orifice. The primary lesion of the mitral valve responsible for the turbulent flow can be obvious, stenotic, and regurgitant, or it can be discrete or mild and difficult to identify. It can be related to a prominent coronary sinus, as found in the left superior vena cava draining into the coronary sinus.^{4,5} It is perhaps for these reasons that the supravalvar mitral ring is prone to reoccur after surgical resection, unless the underlying anatomic anomaly has been identified and corrected.

Cleft Mitral Valve

The cleft mitral valve is often isolated and can be easily differentiated from a left AV valve in a partial AV septal defect.^{6,7} It is an actual cleft with no suspension apparatus on the edges of the defect. The cleft is centered on the aortic commissure between the noncoronary and left coronary cusps.⁶ Each half of the anterior leaflet at the midportion bears the attachment of the strut chordae. With time, the cleft mitral valve regurgitation will generate secondary lesions at the edges of the cleft, such as thickening, rolling up, and retraction. The defect is never stenotic and may generate only little regurgitation for a long time.

Lesions Associated with Lack of Valvar Tissue

Three major anatomic types of lesions are almost always associated with a lack of valvar tissue to various degrees and are worth characterizing: parachute mitral valve, papillary muscle to commissure fusion, and hammock or arcade valve. There is, however, a continuum between these three types and with the normal anatomy. The functional lesion can be either predominantly regurgitant or predominantly stenotic, or it can be both stenotic and regurgitant. In rare cases, the valve functions normally.

Parachute Mitral Valve

The parachute mitral valve can be found in isolation. It is, however, almost always associated with another cardiac anomaly, such as atrial septal defect (ASD), ventricular septal defect (VSD), or coarctation,⁸ and it is often integrated in Shone syndrome.^{9,10} It can also be seen in hypoplasia of the left ventricle, resulting in the need for univentricular palliation. The gross pathology shows a

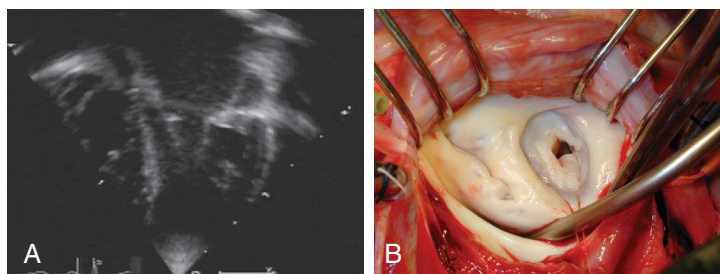


FIGURE 127-1 ■ **A**, Two-dimensional echocardiogram of supravalvar mitral ring, apical view. The membrane attached at mid height of the anterior leaflet is characteristic. The posterior part of the membrane is only suggested by the hyperechogenicity of the posterior annulus. **B**, Intraoperative photograph of a supravalvar mitral ring. Note the implantation of the supravalvar mitral ring high close to the annulus on the posterior leaflet side (*inferior side of the picture*) and at the mid level of the anterior leaflet (*left side of the picture*).



FIGURE 127-2 ■ Macroscopic view of a parachute mitral valve. A large predominant papillary muscle distributes anomalous chords to both commissures. A small diminutive papillary muscle is seen to the right of the valve.

predominant single papillary muscle, with the orifice of the mitral valve overriding the tip of the papillary muscle. The spectrum of lesions for the suspension apparatus starts with complete fusion of the tip of the papillary muscle to the free edge of the valve.⁹ At the other end of the spectrum are chords that are relatively normal appearing, with good mobility of the leaflet (Fig. 127-2). The accessory papillary muscle is usually small and devoted to a short segment of the free edge, or even to the under-surface of the leaflet tissue, as would be seen if it were a larger-than-normal secondary chord. The leaflet tissue can be intact or perforated.

The functional class depends on the interaction between the amount of tissue and the mobility of the leaflet; presence and size of the fenestrations; and presence, length, and quality of the chords.¹⁰ The parachute mitral valve almost always has a stenotic component, because the gradient is fixed but the valve grows. These patients may not require a valve operation.¹¹

Double-orifice mitral valve, in which the lesser papillary muscle supports a complete orifice, is an exceedingly rare variation of the parachute mitral valve. It should be differentiated from the left AV valve, where an accessory orifice is often found when there is a diminutive or absent left lateral leaflet (mural leaflet).

Papillary Muscle to Commissure Fusion

Fusion of papillary muscle to the commissure,¹² also called short chordae syndrome, is defined by the presence of short chordae and a papillary muscle tip that is attached or fused to the commissural area of the free edge (Fig. 127-3). In the most extreme form, the chords are completely absent. The papillary muscles can be of normal



FIGURE 127-3 ■ Macroscopic view of a mitral valve with papillary muscle to commissure fusion. Extremely short chords are distributed to the anterior commissure (*left*). The posterior papillary muscle is almost fused to the posterior commissure (*right*).

size and volume. The valve is then generally more regurgitant than restrictive, which is because of the lack of valvar tissue and the restriction of the leaflet motion. When the papillary muscles are hypertrophied, the bulk of their mass is generally responsible for a predominantly restrictive valve.

Hammock or Arcade Valve

In patients with hammock or arcade valve, the suspension apparatus may have lost all resemblance to the normal anatomy. The papillary muscles are not identifiable, or there are multiple small papillary muscles behind the posterior leaflet. The leaflets are suspended directly by a network of chords directly attached to the posterior wall of the ventricle. This attachment is generally displaced toward the base of the heart, with excess tension on the anterior leaflet and extreme limitation of posterior leaflet motion. The valve is most often predominantly regurgitant.

Isolated Mitral Leaflet Hypoplasia

This rare condition is almost restricted to the middle scallop of the posterior leaflet.^{12,13}

Isolated Dilation of the Mitral Valve Annulus and Isolated Elongation of the Chords and Papillary Muscle

When the anatomy of the mitral valve is otherwise normal, it is difficult to ascertain the congenital origin of dilation of the mitral valve annulus and elongation of the

suspension apparatus, but they are included in most studies of congenital anomalies of the mitral valve¹⁴ and account for 15% to 40% of the patients in published studies of congenital mitral valve regurgitation.^{10,15,16} However, there is no evidence of their congenital origin. Elongation of papillary muscles can be found at birth in the mitral or the tricuspid apparatus, but the muscles usually have an ischemic, beige aspect. Sometimes, the ischemic origin is demonstrated by acute rupture at or shortly after birth. Isolated dilation of the annulus is not found at birth.

Both dilation of the annulus and elongation of the suspension apparatus are usually associated with significant volume loading of the left ventricle (e.g., with a large VSD or large patent ductus arteriosus). The pathophysiology is of initial dilation of the posterior annulus under the effect of the volume loading, followed by elongation of the marginal chords and prolapse of the free edge of the anterior leaflet. In rare cases, minor anomalies of the valvar tissue or the papillary muscles indicate a true congenital origin. When a patient older than 4 years has an isolated mitral regurgitation combining anterior leaflet prolapse and various degrees of posterior leaflet retraction, especially if the latter is thickened, a rheumatic origin should be ruled out when the patient originates from a geographical area of high prevalence.

Functional mitral regurgitations secondary to cardiomyopathies are not discussed here.

Accessory Mitral Valve Tissue

The interchordal spaces are filled with a dense network of valve tissue. When there is continuity between the anterior and the posterior leaflet, the accessory valvar tissue may generate a gradient directly related to the size of the perforations in the accessory tissue (Fig. 127-4).¹⁷ When the accessory valve tissue is entrapped in the left

ventricular outflow tract, the mitral valve may become regurgitant because of the traction exerted by the accessory valvar tissue on the anterior leaflet, which results in the valve's opening at mid systole¹⁸; however, in that case, the left ventricular outflow tract obstruction is the predominant hemodynamic lesion and is usually responsible for the diagnosis.¹⁹ Often, the accessory mitral valve tissue does not generate significant gradient or insufficiency.

Mitral Valve Disease with Excess of Leaflet Tissue, and Mitral Valve Prolapse

It is debatable whether the mitral valve prolapse syndrome—in its most common form, limited to the middle scallop of the posterior defect—is congenital. In a large population of neonates,²⁰ and using strict criteria, the incidence of mild bulging of the anterior leaflet was negligible and no prolapses were detected. This tends to prove that mitral valve prolapse is an acquired disease. In its common form, it is the exception when encountered in neonates and infants. In adults, the histologic anomalies are limited to the middle scallop of the posterior leaflet, with predominant elastic fiber alteration and myxomatous tissue proliferation.²¹

The more extensive form of mitral valve prolapse is, however, seen in neonates and infants. In this form, an excess of tissue is distributed to both the anterior and posterior leaflets, and histologic examination reveals extensive infiltration of the spongiosa with myxomatous tissue. The histologic anomalies are identical to those found in patients with Marfan syndrome,^{21,22} Ehlers-Danlos syndrome, and osteogenesis imperfecta. Marfan syndrome is an autosomal dominant disorder with varying penetrance. The mutation is found on the fibrillin gene. Ehlers-Danlos syndrome is represented by a

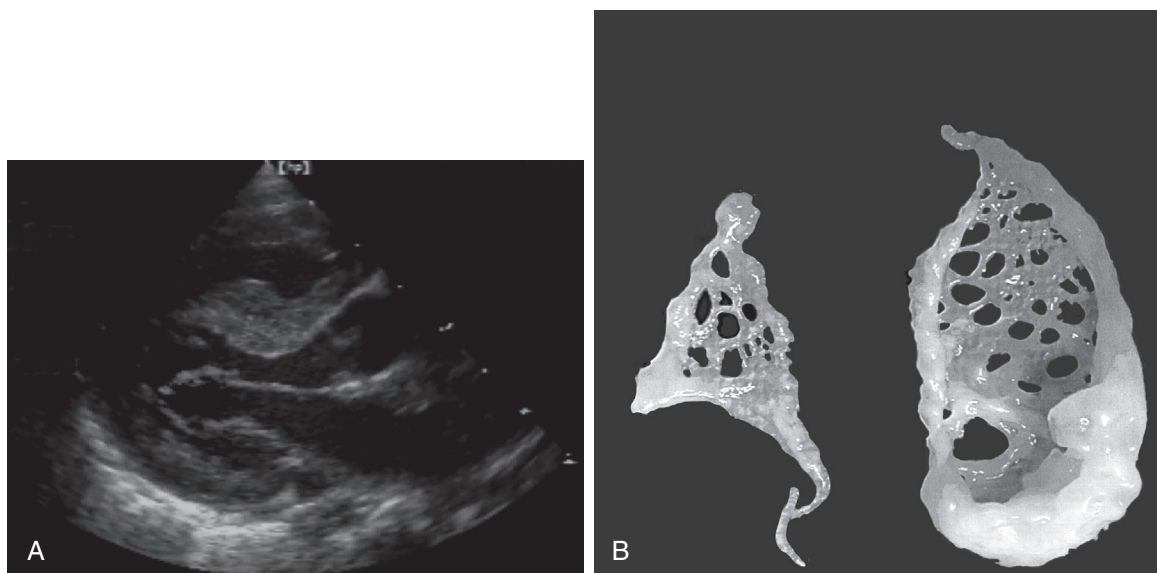


FIGURE 127-4 ■ Accessory mitral valve tissue. **A**, Long-axis view. The accessory mitral valve tissue is attached to the anterior and posterior leaflets of the mitral valve and blown like a windsock. **B**, Macroscopic view of the same tissue after surgical resection is characteristic of accessory mitral valve tissue attached to the suspension apparatus.

constellation of mutations linked to different subtypes.²³ The extensive form of the mitral valve prolapse syndrome is encountered in sporadic cases or in familial forms demonstrating autosomal dominant and X-linked inheritance. Three different loci, on chromosomes 16, 11, and 13, have been found to be linked to mitral valve prolapse, but no specific gene has been described.²⁴

Recurrent Left Atrioventricular Valve Regurgitation

After repair of complete or partial atrioventricular septal defect (AVSD), there are two main mechanisms for regurgitation in valves with a normally developed left lateral leaflet (LLL).²⁵ The cleft may be open because the cleft closure performed in the initial surgery has ruptured or because it was never done. In this case, the regurgitation occurs through the cleft directly. On color Doppler examination, the regurgitation jet is oriented vertically through the cleft.

Alternatively, when the cleft was completely closed and has remained so, the predominant mechanism for the regurgitation is the absence of a coaptation surface in front of the tip of the LLL. In the unrepaired AVSD, the small size of the zone of apposition is an inherent feature of these parts of the superior and inferior bridging leaflets. The direct closure of the cleft does not create a larger coaptation surface; in fact, the little coaptation surface that exists can be reduced and distorted by the cleft closure. This is even more so when the cleft closure has ruptured or is stretching the free edge of the valve. On color Doppler examination, the regurgitation jet oriented posteriorly hugging the posterior wall of the left atrium is characteristic of this mechanism (Fig. 127-5).

If the regurgitation is a long-standing condition, the secondary lesions or dysplastic lesions on the edges of the cleft are severe, with thickening and retraction of the leaflet tissue, and sometimes even calcification. On the other hand, the LLL is usually thin and pliable, with no secondary or dysplastic lesion. There is no restriction of the LLL motion and no prolapse.

In the presence of hypoplastic or absent LLL, the cleft cannot be closed at the time of the primary repair without generating inflow restriction. The residual or recurrent regurgitation occurs through the cleft. On an echocardiographic study, the anatomy is suspected when a strong asymmetry of the papillary muscles can be seen on the short-axis view of the left ventricle. The predominant papillary muscle, usually the anterior one, is connected to both superior and inferior bridging leaflets. The presence of a double orifice is also a strong indicator. It is usually directly suspended to a diminutive posterior papillary muscle and in the body of the inferior bridging leaflet. On Doppler examination, the regurgitation jet is oriented vertically through the cleft.

FUNCTIONAL CLASSIFICATION OF MITRAL VALVE ANOMALIES

Carpentier's functional classification of mitral valve anomalies describes leaflet motion, regardless of the

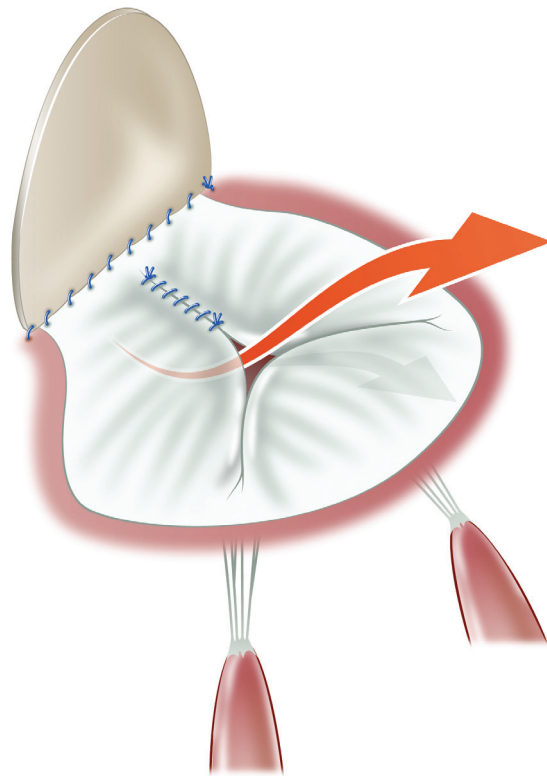


FIGURE 127-5 ■ Mechanism for the regurgitation in the absence of a zone of apposition facing the tip of the left lateral leaflet. The direction of the jet is posterior and hugging the posterior wall of the left atrium.

anatomy and the cause.²⁶ It is an essential tool for mitral valve repair and should be studied on echocardiography preoperatively.²⁷ It can also give significant clues to the lesions that will eventually be found during surgery.

Type I. Normal leaflet motion. The anomaly can be either a perforation or a defect of one or two leaflets, or an annular dilation. Annular dilation associated with a type II anomaly of the anterior leaflet is most likely functional.

Type II. Enhanced leaflet motion. Most pediatric mitral valve regurgitations with a predominant type II anomaly started as functional and progressively elongated the suspension apparatus of the anterior leaflet.

Type III. Restricted leaflet motion. The valve may be stenotic or regurgitant, or both. Most patients with congenital anomalies of the mitral valve belong to this type.

Table 127-1 shows the association between functional classification and the morphologic findings adapted from Carpentier and Brizard¹⁰ and Chauvaud and colleagues.²⁸

DIAGNOSIS

The diagnosis of a congenital mitral valve anomaly relies on the clinical findings, the chest radiograph, the electrocardiogram (ECG), and, most importantly, the echocardiographic study.²⁷ A positive diagnosis of an isolated mitral valve anomaly can often be made before the

TABLE 127-1 Functional Classification of Mitral Valve Anomalies

Functional Type	Anatomic Pathology	Surgical Technique
Type I	Posterior leaflet defect Cleft mitral valve	Posterior annulus plication Direct suture Patch enlargement
	Annular dilation	Adult-size annulus: remodeling annuloplasty with or without leaflet enlargement Less-than-adult-size annulus: posterior annuloplasty, leaflet enlargement
Type II	Elongated chords	PTFE chords, chordal shortening, chordal transfer
	Absent chords	Wedge resection, sliding plasty PTFE chords
	Elongated papillary muscle	Chordal transfer Sliding plasty
	Excess tissue	Papillary muscle shortening Chordal shortening
Type III	Lack of valvar tissue	Leaflet resection (techniques vary with patient age: triangular, quadrangular, central body of the leaflet) Posterior leaflet detachment and enlargement Anterior leaflet enlargement
	Papillary muscle to commissure fusion	Fenestration of papillary muscle Commissurotomy
	Parachute mitral valve	Fenestration of papillary muscle Splitting of papillary muscle Commissurotomy Posterior leaflet detachment and enlargement
	Hammock mitral valve	Mobilization of suspension apparatus, separation from posterior wall Anterior leaflet enlargement Posterior annuloplasty

PTFE, Polytetrafluoroethylene.

echocardiographic examination. However, when there are associated cardiac anomalies, the clinical investigation may only raise the index of suspicion of a mitral valve disease, or it may be missed completely. Echocardiography is part of the initial evaluation of all pediatric patients with cardiac signs, but when there are associated lesions, it is essential to the diagnosis of a congenital mitral valve anomaly. In most patients, the echocardiography shows the congenital nature of the anomaly by demonstrating the variance with the normal anatomy. The functional evaluation of the mitral valve and the impact of the lesion on the cardiovascular system are best made by echocardiographic study. Neither a catheter study nor a ventriculogram has any value in the diagnosis of or preoperative assessment for mitral valve disease, although the catheter study and angiography may be helpful for associated lesions (e.g., complex VSDs and some arch anomalies).

Clinical Examination

Patients rarely present with mitral stenosis during the neonatal period, but when they do, the associated lesions may predominate. Beyond the neonatal period, symptoms may include failure to thrive, dyspnea on exertion, pallor, hypotrophy, and a history of repeated chest infections. Signs of low cardiac output can be found, such as pallor and cold extremities, tachycardia, and dyspnea. Signs of pulmonary hypertension are present, with exacerbated second heart sound and palpation of the right ventricular impulse. A diminished first heart sound

suggests thick leaflets of limited excursion. A low-intensity mid-diastolic murmur is the only direct auscultation sign, and it can be absent in a low-output situation.

Patients presenting with mitral regurgitation in the neonatal period are rare. At all ages, patients with mitral regurgitation present with various degrees of failure to thrive and with dyspnea on feeding or exertion. An enlarged left ventricular impulse may be present, and a high-frequency, high-intensity holosystolic murmur is heard at the apex extending into the axillae.

Electrocardiography and Chest Radiography

The ECG shows left atrial and left ventricular enlargement in patients with mitral regurgitation. Right atrial and right ventricular enlargements are seen when pulmonary hypertension is present. In the pediatric population, there is almost always sinus rhythm.

Chest radiography demonstrates double density of the left atrial enlargement and various degrees of pulmonary plethora with an enlarged main pulmonary artery. Left ventricular enlargement in the presence of mitral valve regurgitation is evident.

Echocardiography

The echocardiographic study is essential. Systematically conducted, it provides all the information necessary for the diagnosis of the mitral anomaly, its severity, and its

impact on the physiology.²⁹ The anatomic lesion can usually be strongly suspected. Echocardiography provides indications for surgery and gives assistance to the surgeon in the repair.¹⁵

The four-chamber view obtained with the transthoracic echocardiographic study is best to provide an accurate transvalvar gradient and define the precise amplitude of any prolapse or restriction. The short-axis view of the mitral valve (en face view) gives a direct vision of the area of the mitral orifice and allows good localization of the origin of the regurgitant jet. It allows a precise analysis of the papillary muscles (presence, size, location, and symmetry). Transesophageal echocardiography is superior for anatomic details of the suspension apparatus and evaluation of the functional classification. The probe can be moved up and down in the esophagus, providing precise localization of the area of prolapse along the free edge of the anterior leaflet, using the anterior commissure (probe up) and the posterior commissure (probe down) as benchmarks.

For mitral stenosis, the peak instantaneous and mean gradients across the valve have to be interpreted according to the quality of the diastolic function of the heart and the associated lesions. The overall impact of the gradient on the indication for surgery has to be weighed with the pulmonary artery pressure, and even more with clinical tolerance.

Three-dimensional echocardiography is progressing rapidly with the exponential increase of computer power and miniaturization of the probes. However, the information generated is of little use in small patients because the spatial and temporal resolutions are still insufficient. Generally, in patients larger than 30 kg, the most obvious benefit of three-dimensional echocardiography is the ability to locate very precisely on the three-dimensional en face view image the site of a two-dimensional cut. It is then only on the two-dimensional cut that the degree of prolapse or restriction can be quantified precisely.

Other Investigation Techniques

Whatever imaging technique is used, there are limitations in small patients, in whom spatial and temporal resolutions are critical. Neither magnetic resonance imaging (MRI) nor computed tomography has enough spatial resolution for the valvar tissue or the suspension apparatus in small children.

MRI allows precise calculation of the ventricular volumes irrespective of the septal geometry; this may aid in making decisions about treating patients with small left ventricle in mitral valve stenosis.³¹ The regurgitation fraction is measured accurately. Gradients and flows are demonstrated with MRI. In small patients, MRI does not help with the analysis of the valve anatomy. On the other hand, MRI can provide useful functional and morphologic information preoperatively.³²

MEDICAL TREATMENT

Medical therapy should be vigorous when the annulus is too small to receive a mechanical prosthesis in the

anatomic position. When mitral regurgitation is predominant, the treatment should include an angiotensin-converting enzyme (ACE) inhibitor, diuretics, and, if necessary, red blood cell transfusion.³³ In patients with mitral stenosis, afterload reduction is contraindicated.

SURGICAL TREATMENT

Indications for surgical intervention in infants differ from those in adults, but the difference is related more to the size of the mitral valve annulus than to the age of the patient. When the annulus is close to an adult size, the timing of the surgical intervention is directly related to the probability of successful repair of the valve. One can now say that in patients older than 1 year of age, using a wide range of mitral valve repair techniques, repair of virtually all valves is an accessible goal. Valves with great probability of repair should be operated on as soon as the regurgitation is severe, regardless of symptom severity—especially valves that usually do not need annular stabilization. The timing is then related to the experience of the surgical team. Conversely, in patients with small annuli, an important multi-institutional retrospective study⁴ has demonstrated very strong risk association when there is a mismatch between the prosthetic size and the diameter of the recipient annulus.

In neonates and infants a repair can be technically challenging, and replacement is often possible only with mechanical prostheses in supra-annular position associated with significant mortality.³⁴ Therefore, surgery should be deferred as long as the patient can be managed medically. New techniques have been described recently to allow mitral valve replacement in annular position in small annuli, including in neonates.^{35,36} These techniques should allow for a slightly more acceptable rescue strategy and hence a more aggressive approach for severely symptomatic neonates or infants; they do not, however, represent a dramatic change in the treatment paradigm.

In pediatric patients, long-term ventricular function returns to normal in severely symptomatic patients when the operation is successful,^{37,38} which is different from the adult population and allows to wait longer for technical need. Recent retrospective series of mechanical valve replacements in patients younger than 24 months demonstrate favorable results. They describe patients who belong to the recent era with appropriate anticoagulation therapy and with prosthesis implanted in annular position.³⁹⁻⁴¹ An important multi-institutional retrospective study⁴² has demonstrated very strong risk association when there is a mismatch between the prosthetic size and the diameter of the recipient annulus (i.e., a ratio of prosthesis size to body weight of greater than 3).

On the other hand, repair of virtually all mitral valves for patients older than 1 year, using a wide range of techniques, is an accessible goal.^{15,28} In small mitral annuli, the repair is difficult, but replacement generates high mortality.^{34,43} The surgery should be delayed whenever possible, but it should be conducted without hesitation when it cannot be delayed,^{15,44} and associated cardiac lesions should be treated at the same time. For large

mitral annuli, repair is possible most of the time, and mitral valve replacement, when necessary, can now be done with very good long-term outcomes. Results of earlier series were less satisfactory.

Mitral Valve Replacement

Mitral valve replacement in the supra-annular position in infants should be avoided at all cost. This type of implantation is responsible for most or all of the perioperative and long-term deaths in units with experience of these patients.⁴⁵ Mitral valve repair in these cases is often a palliation, for the long or short term, but it allows annular growth and eventual replacement in patients who are in better condition technically.¹⁵

Mitral valve replacement in larger annuli is possible now, with excellent long-term results. Only mechanical valves should be implanted. Low-profile aortic valves have proved to be useful for pediatric mitral valve replacement. The valve must be removed from the valve holder and implanted with the opening toward the ventricular cavity. The bioprostheses have been associated with early degeneration and reoperation, and they should not be used in the pediatric age group.⁴⁶

Replacement of mechanical prostheses is not uncommon in pediatric units. The indication is usually the appearance of a gradient with pulmonary hypertension, at rest (on Doppler study or catheter study) or on exertion (on Doppler study).⁴⁷ A larger size can usually be implanted, and in exceptional cases, it may be more than two sizes greater than the prosthesis it replaces.⁴⁸ This is one of the most important motivations behind the policy of initial repair and postponement of the first replacement as much as possible. Technically, the replacement of a pediatric mechanical prosthesis differs significantly from replacement in the adult. Great care must be taken to remove all cuff tissue and pledgets. Everting mattress sutures, especially with pledgets, should be avoided, as they reduce the size of the annulus. Simple interrupted sutures or running polypropylene sutures are preferable. The mechanical valves implanted are designed for an adult flow at high velocity. When implanted in the mitral position in infants, they are submitted to approximately one fifth of the flow they are designed for and at low velocity. The target international normalized ratio (INR) has to be increased accordingly.

Two mitral valve replacement techniques^{35,36} in annular position have been recently described for neonates and infants. Both use the same glutaraldehyde bovine jugular valve available commercially either in a stented version (Melody, Medtronic, Minneapolis, MN) or an unstented version (Contegra, Medtronic) (Fig. 127-6).

Mitral Valve Repair

The techniques for mitral valve repair are described by Carpentier²⁶ for adult surgery, with modifications for pediatric patients and small congenital mitral valves.^{15,28} Cardiopulmonary bypass in Melbourne is conducted with moderate hypothermia 32° C, hemoglobin 10 g/dL, and a pump flow of 150 to 200 mL/min/kg or 1 liter/min/m². Warm-blood cardioplegia, administered every 20 to

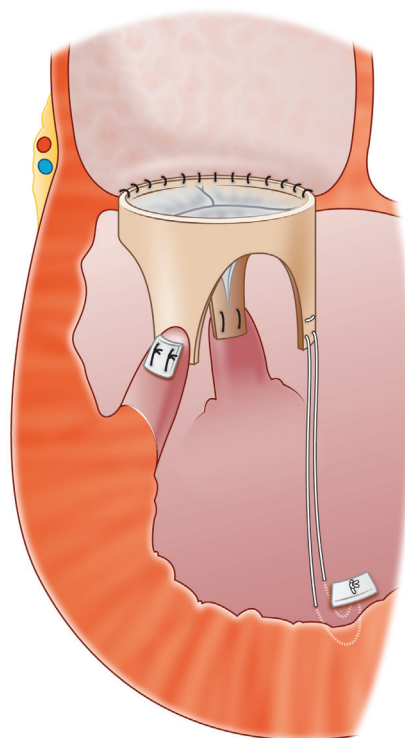


FIGURE 127-6 ■ Implantation of a Contegra valve in annular position. Note that the commissure suspended with the artificial chordae is toward the ventricular cavity (as opposed to facing the posterior wall).

30 minutes, provides myocardial protection. Venous cannulation should allow as much room into the AV groove. The superior vena cava is cannulated directly, at a distance from the cavoatrial junction and the inferior vena cava immediately at the origin. Limited dissection of the groove is performed. After cross-clamping, the left atrium is entered via the AV groove. The exposure is enhanced with mattress sutures, inserted into the posterior annulus, that pull the valve upward and toward the operator. The snigger on the inferior vena cava pulls upward and to the left. A self-retaining retractor for mitral surgery must be adapted to the size of the patient.

Alternative approaches are less satisfactory. The transatrial septal approach does not provide an edge for the retractor blades to anchor and it exposes the conduction tissue to more pressure. It also takes time to reconstruct.

During the preparation for bypass, the mandatory preoperative transesophageal echocardiographic study is performed. Once the mitral valve is satisfactorily exposed, it is systematically analyzed, integrating preoperative information. The functional class is confirmed, whereas the extension of mitral valve prolapse or restriction is based on echocardiographic studies only. The location (A1 to 3, P1 to 3) is eventually confirmed intraoperatively. Then, the morphologic and anatomic examination is performed, which includes the following elements: a supra-valvar ring is confirmed or eliminated, and determinations are made of (1) the annular diameter; (2) the texture, aspect, and size of the mitral valve leaflets; (3) the number,

aspect, and distribution of the chords; (4) the presence of commissural tissue and dedicated suspension apparatus; and (5) the presence, size, location, and morphology of the papillary muscles. The examination finishes with a careful check for accessory mitral valve tissue in the interchordal spaces. The measured diameters of the annulus and of the mitral valve opening are compared with that calculated for the patient's body surface area. In Melbourne, we use a modification of the sizes provided by Kirklin and Barratt-Boyes.⁴⁹

The treatment is adapted to the predominant functional class. A correlation between functional class, anatomic pathology, and surgical treatment is shown in Table 127-1. The techniques included in the table are identical to those used in adult mitral valve repair surgery.²⁶ Few modifications are dictated by the size of the pediatric patients.¹⁵

Correction of Type I: Remodeling Annuloplasty

The annuloplasty is mandatory in all operations for mitral valve insufficiency, except in some patients with an isolated type I mitral valve anomaly without annular dilation, mostly cleft mitral valves. The purpose of the annuloplasty is to adapt the area of the mitral valve orifice (in systole) to the leaflet tissue available. Attempts to perform mitral valve repair without annuloplasty have resulted in recurrence.²⁸ A remodeling annuloplasty involves inserting a rigid adult-size ring (or a size larger than would be indicated by the area of the anterior leaflet). To achieve an adult-size ring in children or teenagers, the leaflet tissue must be enlarged—usually the posterior leaflet, less often the anterior leaflet, or both.^{50,51} In patients with a type III mitral valve anomaly, the detachment of the posterior leaflet to gain access to the suspension apparatus is used for the leaflet enlargement.¹⁵ When no device is available for the size of the patient, or when the device is thought to be too small, the annuloplasty is limited to the posterior annulus. The annuloplasty must incorporate both trigones. Experience with our own patients¹⁵ suggests that the greater stability of the annuloplasty is achieved with either a continuous strip of polytetrafluoroethylene (PTFE) or a row of compression mattress sutures tied over themselves (Fig. 127-7; also see Figs. 127-1, 127-2, and 127-3). We use a sheet of expanded PTFE folded two or three times, to avoid corrugating. Mattress sutures should not be tied too tightly.

Correction of Type II

Correction of type II mitral valve anomalies is rarely necessary in patients with congenital mitral regurgitation. Type II is mostly a secondary lesion, or it is seen with associated lesions (mostly large volume loading of the left ventricle), but correction is always required in patients with a connective tissue disorder and mitral valve prolapse. Multiple techniques are available to correct the enhanced leaflet motion.¹⁵ Whether techniques should be used in isolation or in combination depends on the extension in width of the prolapsus (i.e., localized or extended to the whole width of the free

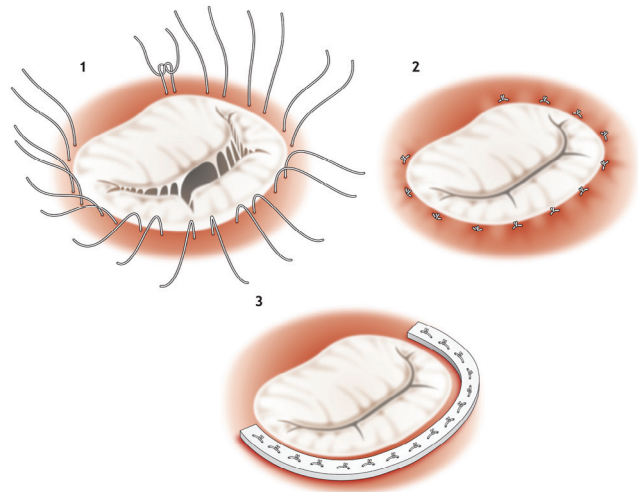


FIGURE 127-7 ■ Posterior annuloplasty made with a band of two or three layers of an expanded polytetrafluoroethylene sheet. Best results are obtained when the posterior annuloplasty is kept continuous. Alternately, the annuloplasty can be achieved by tying the mattress sutures over themselves (compression sutures).

edge). It is the height of the prolapsus (based on the preoperative echocardiographic study) that will dictate the choice of the technique.

All techniques are efficient and reliable, providing that the correction restores a large surface of apposition between anterior and posterior leaflets. Overcorrection, however, generates stress directly on the repaired area and negates the stress relief provided by the surface apposition. All overcorrections eventually fail.

Artificial chords are used when chords of appropriate strength and quality are not available in the area of the prolapse. The insertion requires rigorous technique to avoid overcorrection and large knots at the free edge (Fig. 127-8). Artificial chords are safe for pediatric patients and allow adequate growth of the repair from the papillary muscle and the leaflet tissue.⁵²

Chordal shortening requires thin and flexible chords. The correction generates significant shortening of the chords and is performed only when high and localized prolapse is considered (Fig. 127-9).

Chordal transfer between secondary chords and the free edge is preferred to chordal transfer from posterior leaflet to anterior leaflet, because the length is naturally adapted for the correction of localized prolapse (Fig. 127-10). The chord should be detached from the body of the anterior leaflet with a minimal amount of valvar tissue. It is then attached to the free edge directly at the required length with a small running suture.

Wedge resection and sliding plasty generate different degrees of correction of prolapsus to multiple chords. They are well adapted to prolapsus extended to a large segment of the anterior leaflet free edge (Figs. 127-11 and 127-12).

Papillary muscle shortening is essentially used in Marfan and mitral valve prolapse for the correction of combined anterior and posterior type II (Fig. 127-13).

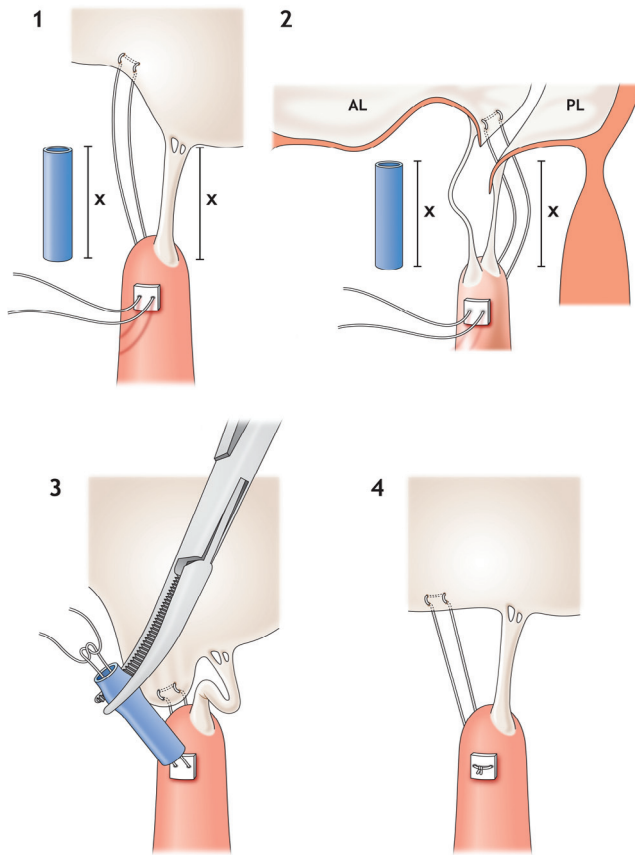


FIGURE 127-8 ■ Artificial chords of expanded polytetrafluoroethylene. Rigorous technique is necessary to avoid overcorrection and large knots at the free edge. 1, A template is made from a short plastic tube cut at the required length and slid over the distal part of the stitch. 2, This template can be taken from the facing posterior leaflet edge. 3, The free edge of the leaflet is lowered to the contact of the papillary muscle. The artificial chord is tied while the template is clamped. 4, The template is removed and the mattress suture is pulled to bring the knot in contact of the papillary muscle. AL, Anterior leaflet; PL, posterior leaflet.

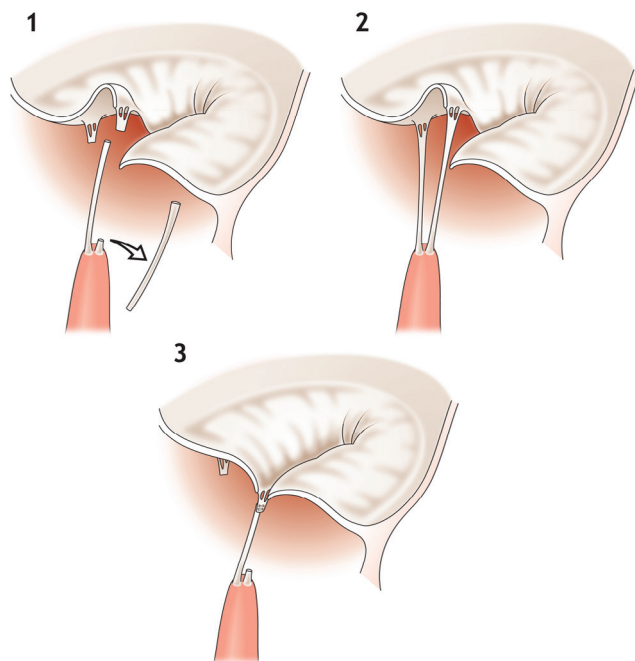


FIGURE 127-10 ■ Chordal transfer. Only secondary chordae should be used and NOT the basal chordae.

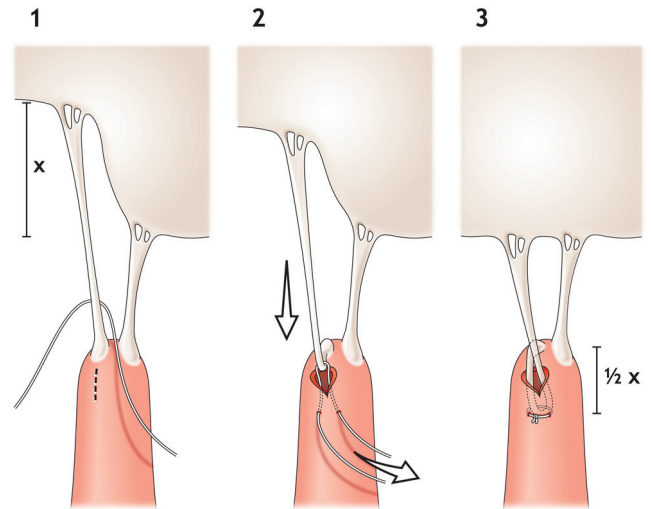


FIGURE 127-9 ■ Chordal shortening. Note the extent of the shortening achieved.

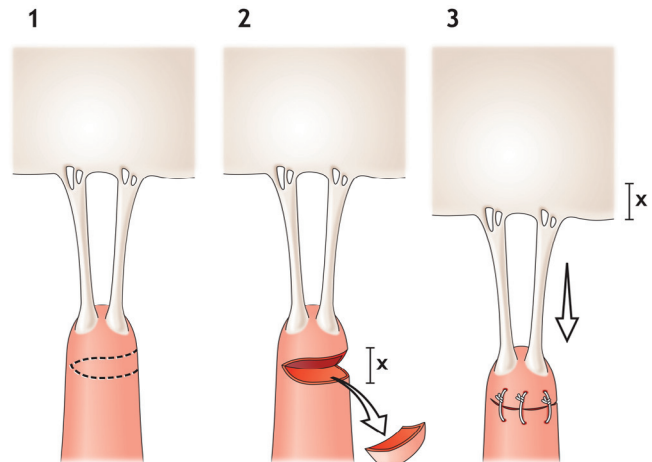


FIGURE 127-11 ■ Wedge resection. Achieves limited shortening distributed to several chordae.

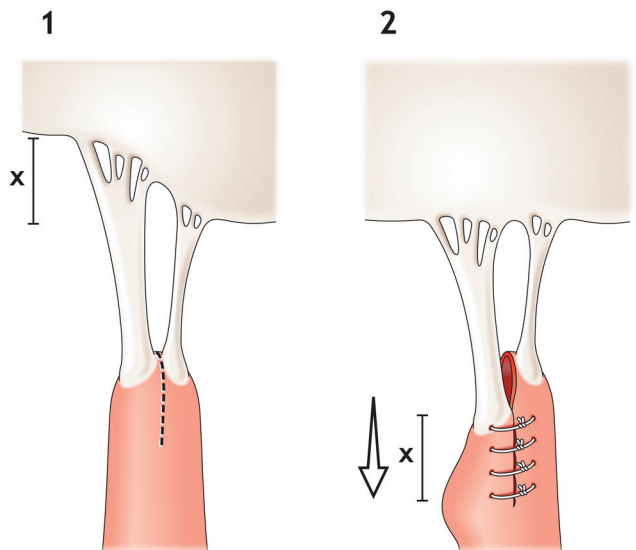


FIGURE 127-12 ■ Sliding plasty. Achieves controlled shortening for thickened chordae.

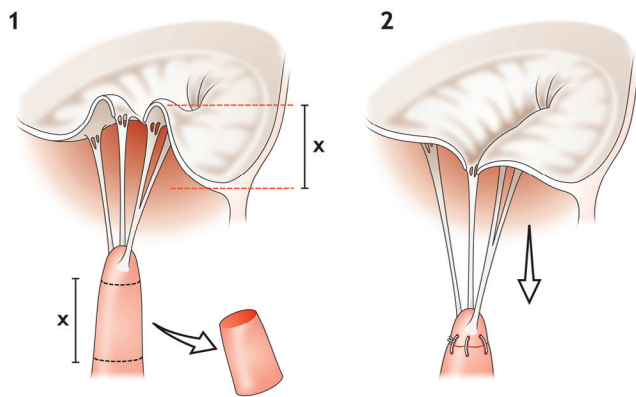


FIGURE 127-13 ■ Papillary muscle shortening.

Correction of Type III

Type III congenital mitral anomalies consist primarily of restricted leaflet motion and insufficient leaflet tissue, and their successful correction is essential, especially in the first year of life.

Mobilization of Papillary Muscles. Access to the suspension apparatus is necessary to adequately mobilize the papillary muscles. Access can be through the mitral valve orifice when it is sufficient, but often the mitral orifice is small and does not allow sufficient access to the suspension apparatus. In these situations, detachment of the posterior leaflet can provide good exposure to the papillary muscles. Adequate thinning, mobilization from the posterior wall, and splitting and fenestration of the papillary muscles can then be performed safely. The posterior leaflet is later reconstructed with enlargement of the leaflet tissue (Fig. 127-14).¹⁵

Enlargement of Valvar Leaflet with Pericardium Patch. Augmentation of the leaflet tissue is the only way to treat a lack of valvar tissue.¹⁵ The anterior leaflet, the posterior leaflet, or both can be extended. Extension of the posterior leaflet should be limited to less than half of the height of the leaflet; it can be limited to the area of the middle scallop. Alternatively, when the detachment is extended from one commissure to another, the extension should reproduce a shape with three scallops and two commissures to allow a large opening in diastole. Crescent-shaped patches with a short inner edge are stenotic and the stenosis worsens with time. The extension of the anterior leaflet should be done in the body of the leaflet, leaving a strip of valvar tissue close to the hinge point to avoid mechanical stress at this level. The height of the extension should not be greater than two fifths of the height of the leaflet, leaving the area close to the free edge intact to allow a supple and effective surface of coaptation. If possible, it should be symmetrical from trigone to trigone. Since the early 1980s, the best default material has been autologous pericardium treated intraoperatively with 0.625% glutaraldehyde. Long-term results have been somehow unpredictable. Animal studies have suggested that new treatment to bovine pericardium may provide a better alternative.⁵³ Long-term results in clinical valvar setting are not yet available.

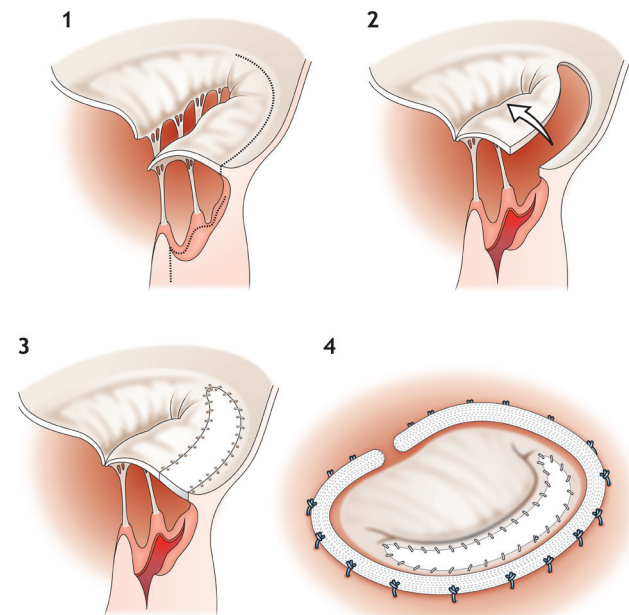


FIGURE 127-14 ■ Detachment of the posterior leaflet. 1, Hammock or papillary commissure fusion. Access to the suspension apparatus is limited through the natural mitral orifice. 2, After detachment of the posterior leaflet, mobilization and splitting of the suspension apparatus can be performed easily, even in the smallest valves. 3, After repair. 4, With annuloplasty.

Resection of Supravalvar Rings and Accessory Mitral Valve Tissue. Resection of supravalvar tissue requires an excellent exposure of the leaflet tissue. The supravalvar tissue can sometimes be peeled off the valvar tissue. More often, careful blunt dissection is needed. If perforation of the anterior leaflet occurs, it should be closed with simple figure-eight sutures (Fig. 127-15).

Resection of accessory mitral valve tissue requires similarly rigorous surgical technique. A good exposure of the subvalvar apparatus is needed to perfectly delineate the mitral valve chords from what can be resected without compromising the integrity of the suspension apparatus (Fig. 127-16). Various approaches to the suspension apparatus may have to be combined, such as through the mitral valve orifice and the aortic valve, and via detachment of the posterior leaflet.

Repair of Recurrent Left Atrioventricular Valve Regurgitation. Two separate anatomies leading to different surgical techniques have to be identified according to the size of the LLL.²⁵ The most common one is the normally developed LLL. The least common is the absent or diminutive LLL.

In the presence of a normal LLL, in some cases, the AV valve can be repaired by suturing or resuturing the cleft. To achieve a stable long-term result with simple suturing, the cleft should be thin and pliable and there should be redundant leaflet tissue to avoid putting suture under stress and to allow for a large zone of apposition facing the tip of the LLL. When the cleft has not ruptured or when there is significant retraction of the edges of the cleft, the valve should be repaired with adjunction of valvar tissue and pericardial patch should be used. The

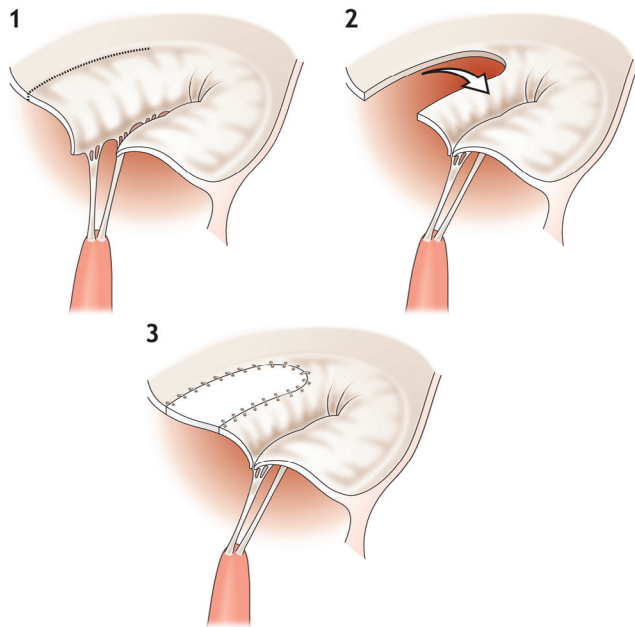


FIGURE 127-15 ■ Patch enlargement of the anterior leaflet to treat the lack of tissue in congenital valve or the retraction of the rheumatic leaflet.

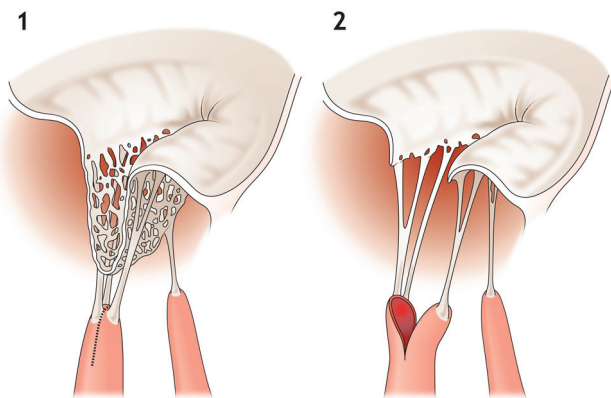


FIGURE 127-16 ■ Excision of extravalvar tissue within a parachute mitral valve. Great care must be taken to preserve the suspension apparatus.

area of the combined superior and inferior bridging leaflet can be augmented at the septal end of the leaflets.³⁴ At Royal Children's Hospital in Melbourne, we prefer creating a coaptation surface in front of the LLL using the cleft patch augmentation technique.²⁵

The area of the cleft closure is débrided of all secondary lesions around the regurgitation zone. Sufficient resection is performed to reach pliable leaflet tissue. The area of the cleft is then closed with a long and narrow patch. The patch extends into the ventricular cavity so as to create a coaptation surface to face the tip of the LLL (Fig. 127-17).

In the case of absent or hypoplastic LLL, the cleft is reopened where it had been partially closed, and a surface of coaptation is constructed on both edges of the cleft. In this anatomy, at Royal Children's Hospital, three different techniques are used, according to the difficulty and

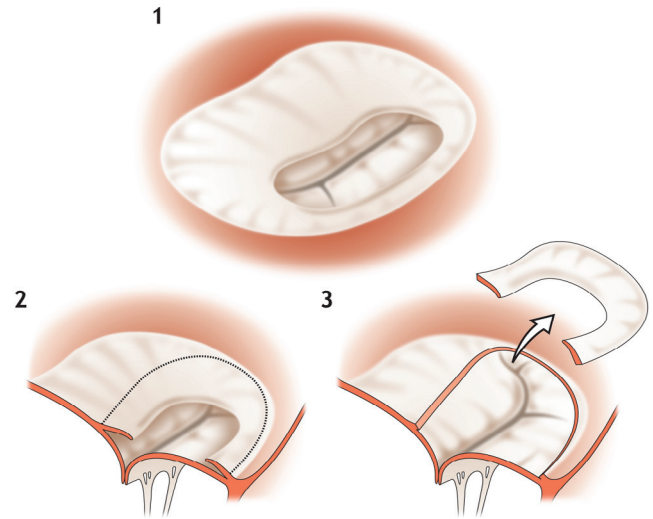


FIGURE 127-17 ■ Excision of supralvalvar mitral ring.

the anatomy; most commonly, the edges of the cleft can be directly suspended using expanded PTFE chords (Fig. 127-18). A patch may be necessary to increase the surface area of the superior bridging leaflet and favor the creation of a large coaptation surface between native valvar tissue. Alternatively, we have used a partial mitral valve homograft of adapted size to reproduce the zone of apposition. This technique has demonstrated very good immediate and intermediate results in our experience and should allow sufficient palliation time to wait until an adult-size prosthesis can be used.

The double orifice should not be closed, because it is never regurgitant and can produce a valuable area of valve opening.

RESULTS

Mitral Valve Stenosis and Predominant Stenotic Valves

Between 1996 and 2014, 42 patients, 21 of whom were younger than 1 year, were operated on for congenital mitral stenosis. The most common pathologies were supramitral mitral ring (as predominant mechanism) ($n = 15$), papillary muscle to commissure fusion ($n = 12$), and parachute mitral valve ($n = 6$). Fourteen patients had Shone syndrome. There were three deaths, all Shone syndrome patients and all eventually after secondary mitral valve replacement. There were 10 reoperations and 4 mitral valve replacements (2 mechanical and 2 Contegra).

Mitral Valve Insufficiency and Predominant Regurgitant Valves

Ninety-eight patients were operated on for predominant congenital mitral regurgitation. There were 33 patients with mitral cleft. All are alive; one needed a reoperation, and all but two have no or mild residual regurgitation.

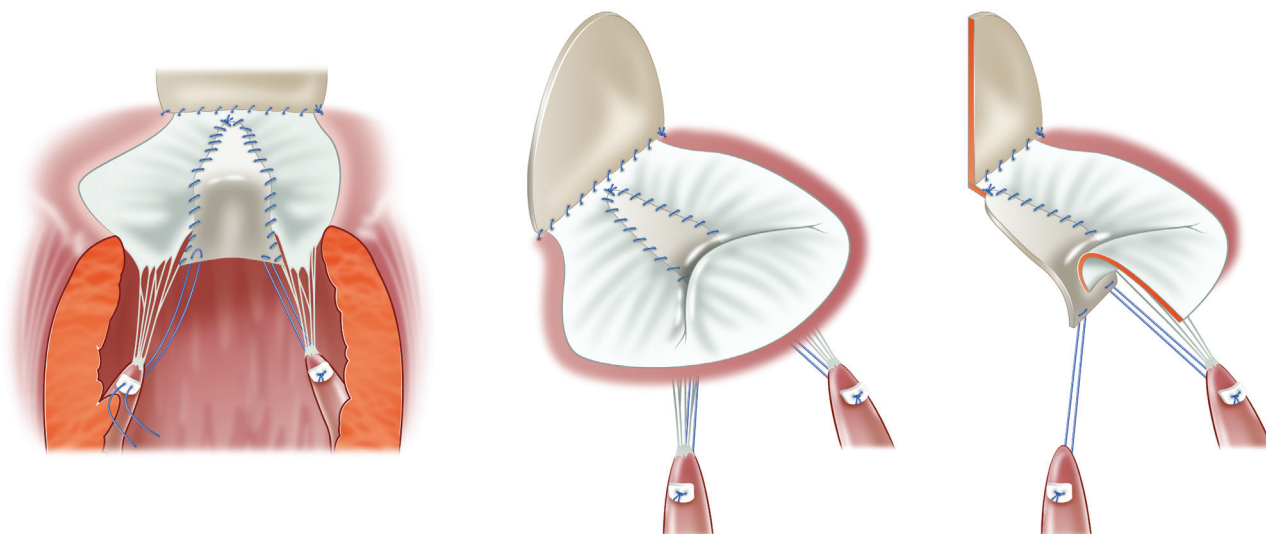


FIGURE 127-18 ■ Re-do left atrioventricular valve repair. Most common anatomy with large left lateral leaflet and two papillary muscles. A narrow pericardial patch is sutured to the edges of the cleft and extended into the inflow of the valve to enlarge the zone of apposition facing the tip of the left lateral leaflet. Suspension to the free edge of the patch is done with artificial chords.

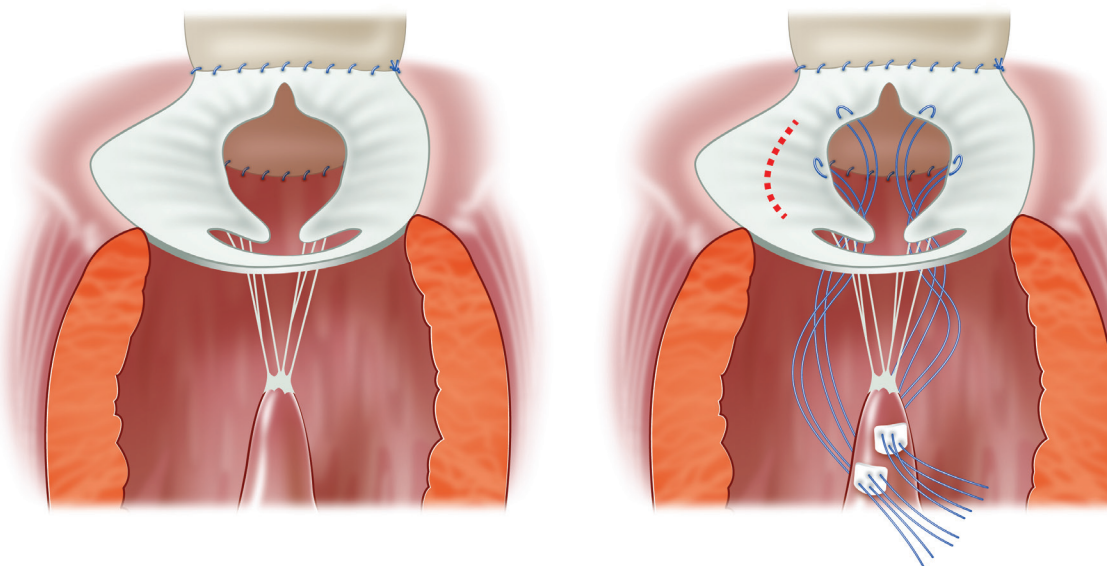


FIGURE 127-19 ■ Re-do left atrioventricular valve repair. Rare anatomy with absent left lateral leaflet. Suspension of the free edges of the superior and inferior bridging leaflet with artificial chords and posterior annuloplasty. Suitable when the edges of the cleft are flexible.

There were 65 patients with causes other than a mitral cleft, and in this group, 30 patients were younger than 1 year. This whole group had 13 reoperations and 5 deaths. The freedom from reoperation at 5 years for patients younger than 1 year of age compared with patients older than 1 year is significantly different: 59% versus 95.7% ($P = 0.007$). Two patients have had a mechanical replacement and one had a Contegra; all are alive.

Recurrent Left Atrioventricular Valve Regurgitation

Since 1978, more than 700 patients were operated on at Royal Children's Hospital in Melbourne for complete

or partial AVSD. From 1996 to 2008, 42 patients were reoperated on for recurrent severe mitral regurgitation with the technique described in this chapter.²⁵ Five patients had a diminutive or absent LLL, and 37 had a normally developed LLL. The 42 patients had one to four (2.36 ± 1.1) left AV valve repairs, not including valve replacement. The actuarial risk for needing a second reoperation in the normal LLL group was 41% (6% to 63%; 95% CI) in the direct cleft closure group as opposed to 8% (up to 82%) in the cleft patch augmentation group ($P = 0.04$). In the diminutive or absent LLL group (Fig. 127-19), three out of five patients eventually required valve replacement at 1, 10, and 12 years postoperatively.

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HYPOPLASTIC LEFT HEART SYNDROME

Bret A. Mettler • Frank A. Pigula

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Hypoplastic left heart syndrome (HLHS) is characterized by a generalized underdevelopment of the left ventricle and its dependent structures: the mitral valve, the aortic valve, and the preductal and ductal aorta. Because the anatomic severity of HLHS constitutes a spectrum of disease, the value of a consistent, defined nomenclature has been recognized. Such a nomenclature has been proposed by the Congenital Heart Surgery Nomenclature and Database Project.¹ The project has proposed an operative definition for hypoplastic left heart syndrome as “a spectrum of cardiac malformations, characterized by a severe underdevelopment of the left heart–aorta complex, consisting of aortic and/or mitral atresia, stenosis, or hypoplasia with marked hypoplasia or absence of the left ventricle, and hypoplasia of the ascending aorta and the aortic arch.”

The treatment of HLHS has dramatically changed over the past 2 decades. With little to offer prior to Norwood’s introduction of stage I palliation in 1983,

treatment has developed into a three-stage progression to the Fontan operation. Although the 1-month mortality rate for untreated patients is 95%, the current 1-month survival rate among specialized centers approaches 80% to 90%.

This chapter discusses the anatomic and physiologic challenges posed by these patients, as well as the management schemes devised to meet them.

DEMOGRAPHICS AND INCIDENCE

Two large epidemiologic reports have estimated the prevalence of HLHS to be 0.16 to 0.18 out of 1000 live births.^{2,3} Males account for 57% to 67% of new cases, and the risk of sibling recurrence has been reported to be 0.5%.^{4,5} No environmental risk factors associated with the diagnosis of HLHS have been identified.⁶

CLINICAL PRESENTATION

On physical examination, children with HLHS may appear entirely normal at birth. Within hours to days, however, tachypnea and pallor may become apparent with nonspecific chest radiographic and electrocardiographic findings.^{7,8} Depending on the adequacy of the ductal and atrial communications, there may be rapid progress to acidosis, cyanosis, and cardiopulmonary collapse. An exception to this usual sequence occurs in neonates presenting with a restrictive atrial septum; these children will present immediately after birth in severe respiratory distress, respiratory acidosis, and cyanosis that is unresponsive to medical management.

Other congenital lesions should be sought. Natowicz and colleagues⁹ reported that 28% of patients with HLHS suffered from a genetic disorder, a major noncardiac abnormality, or both. Looking specifically at the central nervous system among infants with HLHS, Glauser and colleagues¹⁰ documented anomalies in 29% and microcephaly in 27%. Blood flow pattern in the fetus with HLHS may have important implications for brain development. Shillingford and coworkers¹¹ reported a correlation between microcephaly and the size of the ascending aorta. Dent and colleagues,¹² using magnetic resonance imaging (MRI) postnatally, identified ischemic lesions in 23% of patients. Thus, the preoperative evaluation of these neonates should also include genetic and neurologic evaluations.

DIAGNOSIS

Echocardiography has become the diagnostic procedure of choice in patients with HLHS. Details such as aortic valve size and status (atretic versus patent), aortic dimensions, origin of the coronary arteries, brachiocephalic branching, status of the atrial septum, function of the tricuspid and pulmonary valves, and presence of systemic or pulmonary venous anomalies should be sought. Coronary anomalies, although rare, are more likely encountered in the setting of mitral stenosis and aortic atresia and can take the form of coronary-ventricular fistulas, hypoplasia, tortuosity, or single coronary arteries (e.g., anomalous left coronary from the pulmonary artery).¹²⁻¹⁸ Coronary abnormalities may be more frequent in mitral stenosis–aortic atresia (MS/AA) variants of HLHS, and these patients undergo additional scrutiny (discussed in further detail, later).

Cardiac Catheterization

Cardiac catheterization in patients with HLHS should be reserved for those with equivocal anatomy who may be candidates for biventricular repair, for those in whom coronary anomalies are suspected, or to delineate abnormal pulmonary venous return.

Fetal Diagnosis

Improvements in fetal echocardiography have led to an increasing frequency of antenatal diagnoses of HLHS.

Tworetzky and colleagues¹⁹ reported that prenatal diagnosis was associated with improved preoperative clinical condition as well as improved survival after the Norwood operation. Unfortunately, improved survival following Norwood palliation in children with a prenatal diagnosis has not been consistently demonstrated.²⁰ Mahle and others²¹ have reported that although antenatal diagnosis improves these patients' preoperative clinical condition and may reduce the incidence of neurologic injury, an impact on surgical survival has not been shown.

PATHOPHYSIOLOGY

In HLHS, the right ventricle must support both the systemic and the pulmonary circulation. Pulmonary venous return must have access to the right atrium, via an atrial septal defect, via a patent foramen ovale, or, in rare cases, via anomalous pulmonary venous connections to the systemic veins. Systemic output, delivered via the ductus arteriosus, is entirely dependent on ductal patency (Fig. 128-1). Ductal involution may be a rapid process, restricting right ventricle–dependent systemic blood flow and leading to progressive metabolic acidosis, tachypnea, and irritability before cardiopulmonary collapse.

The functional size of the interatrial communication is an important physiologic determinant in these patients. In the presence of an unrestrictive atrial communication,

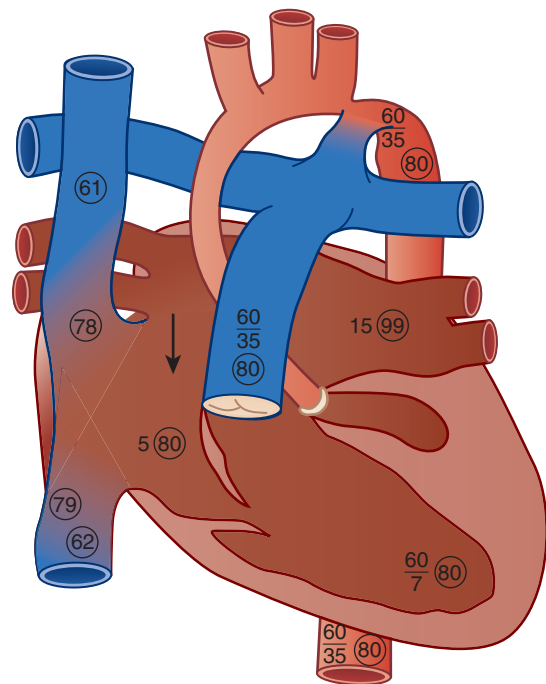


FIGURE 128-1 ■ Hemodynamics and oxygen saturations (*in circles*) of hypoplastic left heart syndrome in the unoperated state. Pulmonary venous return must cross the atrial septum (*arrow*), where there is mixing with systemic venous return in the right atrium. Systemic cardiac output is dependent on a patent ductus arteriosus. (Reprinted with permission from Jacobs ML: Hypoplastic left heart syndrome. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 859.)

pulmonary blood flow quickly becomes excessive and the signs and symptoms of congestive heart failure predominate.

A subset of neonates are born with a mildly restrictive interatrial septum (gradient of 2 to 5 mm Hg), such that pulmonary resistance is modestly elevated. This often serves to balance systemic and pulmonary blood flow, and these children may be physiologically stable, requiring little intervention before surgery. Whenever possible, allowing spontaneous respirations in an awake child often allows for the neonate to regulate the balance of pulmonary to systemic blood flows, attaining a stable circulation that greatly simplifies their preoperative management.

Finally, a few children present with severe restriction of the atrial communication. These neonates suffer from a prompt and profound hypoxemia at birth, leading rapidly to a metabolic acidosis. This variant, the functional equivalent of obstructed total anomalous pulmonary venous return (TAPVR), represents a true hemodynamic emergency requiring immediate relief. As with obstructed TAPVR, medical management of patients with this variant is uniformly unsuccessful. Interventions designed to enlarge and maintain the atrial communication have been successfully applied, such as balloon atrial septostomy and stenting.²²

CAUSES

HLHS can be experimentally created in the chick embryo by left atrial ligation.²³ These experimental findings were anticipated clinically by Remmell-Dow and colleagues,²⁴ who suggested that abnormal development of the atrial septum, including underdevelopment of the eustachian valve and limbus, reduced right-to-left shunting at the atrial level, resulting in hypoplasia of the left heart structures. Premature closure of the foramen ovale has similarly been implicated, as have primary abnormalities of the aortic valve.²⁵⁻²⁷

Although identifiable genetic sequences have been reported to be associated with HLHS, their relevance remains unclear.²⁸ An understanding of the developmental factors leading to HLHS assumes new relevance as intervention during the process of cardiac morphogenesis itself (i.e., fetal surgery) is pursued.

SURGICAL TRIAGE

Patients satisfying all facets of the definition of HLHS are clearly destined for single-ventricle palliation. However, there are patients for which the decision between the pursuit of single-ventricle palliation and biventricular repair is not so clear. Once pursued, the ability to cross over to the competing treatment is difficult, and efforts to stratify patients with equivocal anatomy have been made. Rhodes and colleagues²⁹ combined four factors (body surface area, indexed aortic root dimension, left ventricle length, and indexed mitral valve area) to predict death after biventricular repair for critical aortic stenosis in the neonate. However, application of these

criteria to hypoplastic, but nonstenotic, left heart structures using Rhodes's criteria has proven unsatisfying, as these criteria appear to be too stringent in this setting.³⁰ Recognizing this, the Congenital Heart Surgeons Society (CHSS) sponsored a multi-institutional study to delineate the outcomes and risk factors of critical aortic stenosis in the neonate.³¹

Presented by Lofland and colleagues,³¹ this study identified multiple morphologic and functional factors that can be used to predict which surgical approach, single-ventricle palliation or biventricular repair, is more likely to result in the survival of any particular patient. This study determined that solution of a multivariable equation using these factors can predict a patient's survival. This equation, which can be found on the CHSS website (www.chssdc.org) is as follows:

$$\begin{aligned} \text{Survival benefit} = & \text{intercept} + (\text{age at entry}) \\ & + (\text{z-score of aortic valve at the sinuses}) \\ & + (\text{grade of EFE [endocardial fibroelastosis]}) \\ & + (\text{ascending aortic diameter}) \\ & + (\text{presence of moderate or severe tricuspid regurgitation}) \\ & + (\text{z-score of the left ventricular length}) \end{aligned}$$

The prediction model was tested and refined by Hickey and the CHSS.³² They reported that the consequences of inappropriate pursuit of a repair strategy (biventricular versus single ventricle), as predicted by the model, was minimal for single-ventricle palliation but was very significant among patients undergoing biventricular repair. This report underscores the importance of the initial decisions made when assessing and triaging neonates with borderline left heart structures to a treatment strategy.

MANAGEMENT

The natural history of HLHS is dismal: 95% of untreated patients die within 1 month.³³ Medical treatment modifies the natural history, primarily by delaying the demise.³⁴

The surgical management of HLHS represents the paradigm from which a generalized approach to the shunted single ventricle has evolved. Simply stated, the cardiovascular system in HLHS consists of a single pumping chamber supporting two parallel circulations. These parallel circulations can be considered to be in competition with each other for blood flow. For any given cardiac output, the flow apportioned to each circulation is inversely proportional to the resistance of that circulation (i.e., high pulmonary vascular resistance, low pulmonary blood flow). Thus, efforts to control the circulation have focused on controlling the competing vascular resistances. These efforts have generally involved manipulation of the pulmonary vascular resistance using inspired gasses (oxygen, carbon dioxide [CO₂], and nitrous oxide) and pressures.³⁵⁻³⁸

More recently, an alternative approach that targets manipulation of the systemic vascular resistance to maintain the balance between the pulmonary and systemic circulations has been shown to be effective.

Manipulation of the Pulmonary Vascular Resistance

Carbon Dioxide

Inspired CO₂ has been suggested to improve the hemodynamic status after the Norwood operation.³⁵ Tabbutt and colleagues³⁹ compared the use of hypoxia (17% fraction of inspired oxygen [FiO₂]) to CO₂ in 10 neonates with HLHS prior to the Norwood operation under the conditions of fixed minute ventilation, anesthesia, and paralysis. Although both strategies reduced the ratio of pulmonary to systemic blood flow (Qp/Qs), CO₂ increased both superior vena cava co-oximetry and cerebral oximetry, whereas hypoxia reduced these indices of oxygen delivery. Bradley and coworkers⁴⁰ reported similar results among postoperative patients. It is important to note, however, that these benefits were only realized when the *minute ventilation* remained constant.

Although thought by some physicians to reflect a direct effect, there is evidence showing that the increase in pulmonary vascular resistance is reversed by alkalization, suggesting that the effect is mediated by [H⁺] and pH.⁴¹

Oxygen

Because the neonatal pulmonary vasculature is also sensitive to the concentration of inspired oxygen, hypoxic mixtures incorporating nitrogen have also been used to control the circulation in patients with HLHS. Animal models have shown that nitrogen-induced hypoxic mixtures increase the pulmonary vascular resistance and increase systemic blood flow. However, the prolonged use of hypoxic mixtures has been shown to quickly induce anatomic changes in the pulmonary vasculature. In animals, changes in arterial wall thickness and muscularity can be seen within 24 hours, and fewer intra-acinar arteries are recruited into the circulation.⁴²⁻⁴⁴

Day and colleagues⁴⁵ reported their clinical experience using hypoxia to manipulate the pulmonary vascular resistance in 20 neonates with single-ventricle, duct-dependent circulation awaiting heart transplant. Of these 20 patients, 8 survived; of the 10 patients who underwent lung biopsy or autopsy, 9 showed medial hypertrophy in distal arterioles, and 7 of these 9 patients died. Although the outcome cannot be completely ascribed to hypoxic management, this strategy suggests that prolonged supportive care of the neonatal single ventricle may expose these patients to significant risks.

Systemic Vascular Resistance

Manipulation of the systemic vascular resistance is a demonstrated means of controlling the shunted circulation. In fact, our ability to pharmacologically control the systemic vascular resistance probably exceeds our current ability to selectively manage the pulmonary vascular resistance. This clinical approach usually uses an irreversible α -adrenergic antagonist, phenoxybenzamine, to achieve systemic vasodilation. The desired systemic vascular resistance, defined as that which optimizes the Qp/

Qs and systemic oxygen delivery, is then obtained by titrating an α -adrenergic agonist, usually norepinephrine. Specifics of this approach have been reported in the literature.⁴³⁻⁴⁵

A review of this strategy identified the use of phenoxybenzamine, continuous systemic venous oxygen monitoring, and the reduction of deep hypothermic circulatory arrest (DHCA) time as factors favoring survival to the bidirectional Glenn operation.⁴⁶ To date, no studies directly comparing outcomes for these two fundamentally different management schemes have been performed.

OPERATIVE PROCEDURE STAGE I

The anatomic goals of the stage I or Norwood operation for HLHS is threefold: (1) to provide unobstructed blood flow from the systemic right ventricle to the systemic circulation, (2) to ensure an unobstructed connection between the pulmonary venous return and the systemic right ventricle, and (3) to establish a reliable source of pulmonary blood flow. Although these goals are unchanged from those originally articulated by Norwood and colleagues in 1980, the methods by which these goals are achieved continue to evolve.

Standard Norwood Operation

The “standard” Norwood operation is performed through a median sternotomy. The branch pulmonary arteries are dissected and controlled. We routinely anastomose a 3.5-mm stretch Gore-Tex graft to the underside of the innominate artery. The graft may later serve as the right modified Blalock-Taussig shunt and is left long while it is used as the primary arterial cannulation site. Venous cannulation is performed in the right atrial appendage, through a purse-string suture large enough to allow subsequent atrial septectomy. The patient is cooled to 18° C and put on bypass, the ductus is divided, and the brachiocephalic vessels are mobilized and loosely snared. The main pulmonary artery is divided and the branch bifurcation is closed, primarily or with a patch. After at least 20 minutes of cooling and at a rectal temperature of 18° C, the brachiocephalic vessels are snared and the descending aorta is clamped. For truly diminutive aortas (<2 mm), cardioplegia is administered via a side arm into the arterial cannula, and direct needle insufflation is used in the larger aorta. We perform the Norwood operation during continuous regional low-flow perfusion, as previously described.⁴⁷⁻⁴⁹

The atrial septectomy is performed through a right atrial purse-string suture during a period of low-flow sucker bypass. The ductal remnant is amputated from the aorta, and the aorta is filleted open distally beyond the site of coarctation and proximally to a point adjacent to the lip of the transected pulmonary valve. The ductal insertion site is circumferentially resected, and the back wall of the aorta is sewn together, either directly or using an interdigitating technique. Proximally, a side-to-side anastomosis between the aorta and pulmonary valve is performed, and the arch is augmented using a piece of

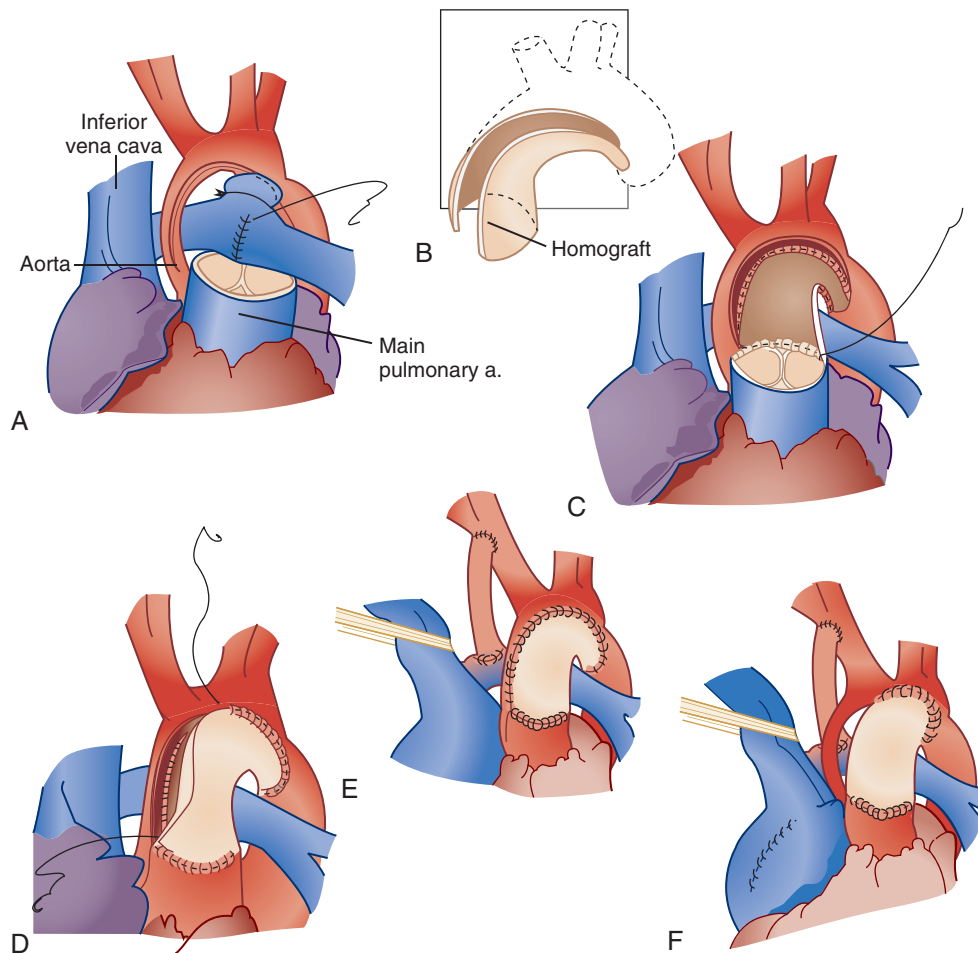


FIGURE 128-2 ■ Technique of the Norwood operation. **A**, The pulmonary artery is transected and the bifurcation closed. The hypoplastic aorta is incised and ductal tissue excised. **B** and **C**, Graft material, usually pulmonary homograft, is cut to the appropriate size and shape for arch reconstruction. **D**, Inclusion of the pulmonary valve into the systemic circulation, with completion of the arch augmentation. **E**, Pulmonary blood flow is provided by the right modified Blalock-Taussig shunt. **F**, Anastomosis of the pulmonary artery to the arch; bypassing the diminutive ascending aorta is not recommended. Proximity of the very small ascending aorta to the shunt allows potential coronary steal and myocardial ischemia. In these cases, arch reconstruction should proceed as illustrated in **A**, or alternatively implanted into the side of the neo-aorta. (Reprinted with permission from Castañeda AR: Hypoplastic left heart syndrome. In Castañeda AR, Jonas R, Mayer JE, et al, editors: *Cardiac surgery of the neonate and infant*, Philadelphia, 1994, WB Saunders, p 371.)

pulmonary homograft or fixed autologous pericardium (Fig. 128-2). Central bypass is resumed after cannulation of the reconstructed aorta, and the pulmonary anastomosis of the shunt is completed.

Results of Norwood Operation

With experience and with advances in surgical, anesthetic, and critical care management, current survival of the Norwood operation approaches 90% at specialized centers.^{50,51} In one of the largest single-center series ever reported, Mahle and colleagues⁵² reported their 15-year (1984-1999) experience with the Norwood operation for 840 patients with HLHS. Of these 840 patients, 65% were male and 35% female, a gender ratio similar to that reported elsewhere. The 1-, 2-, 5-, 10-, and 15-year survival rates for the group were 51%, 43%, 40%, 39%, and 39%, respectively. Risk factors identified for death were earlier era of operation, age older than 14 days, and

weight less than 2.5 kg. Neither anatomic subtype nor heterotaxy was associated with mortality.

Because of the continuing evolution occurring among surgical and medical management techniques applied to HLHS, contemporary experience is important. Tweddell and colleagues⁵¹ reported their experience with 115 consecutive patients with HLHS who underwent the Norwood operation between 1992 and 2001. They reported that, with the introduction of new management techniques in 1996, they were able to obtain a 93% hospital survival rate for neonates undergoing the Norwood operation for HLHS. These strategies included the use of phenoxybenzamine, continuous systemic venous oxygen monitoring, aprotinin, modified ultrafiltration, and, most recently, continuous cerebral perfusion. This report is also of interest because it attempts to quantify the influence of anatomic and operative variables on survival to stage II palliation rather than on operative survival. Only duration of DHCA was associated with

survival to stage II palliation; no other anatomic or physiologic variable, including weight, was predictive.

A more recent review of the surgical experience of 237 patients undergoing stage I palliation at Children's Hospital Boston between 2001 and 2006 reported a hospital survival rate of 88.6%.⁵⁰ An arteriopulmonary shunt was used in 157 patients, and a right ventricle to pulmonary artery (RV-PA) conduit in 80 patients. Although the source of pulmonary blood flow did not impact hospital survival, the RV-PA conduit imparted a significant survival advantage during the interstage period (Fig. 128-3).

Anatomic Subtypes

Whereas previous studies^{16,17} reported a trend toward higher mortality rates among patients with aortic valve atresia, the Children's Hospital Boston review identified patients with aortic atresia *and* mitral stenosis to be a group at higher risk than other anatomic subtypes

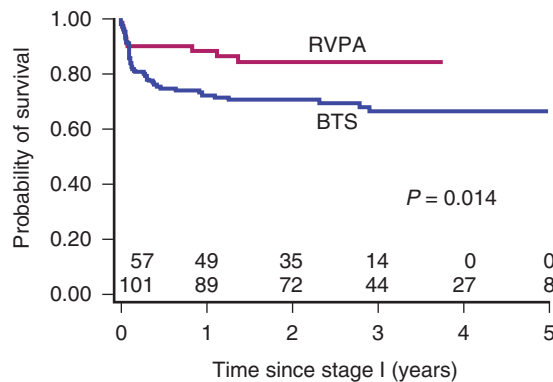


FIGURE 128-3 ■ Conditional survival based on the source of pulmonary blood flow after stage I palliation. There was no perioperative difference in survival between the arteriopulmonary (Blalock-Taussig) shunt (BTS) or the right ventricle to pulmonary artery conduit (RVPA). However, the RVPA showed a significant survival advantage during the interstage period (interstage mortality: BTS 15% vs. RVPA 0%; $P = 0.014$).

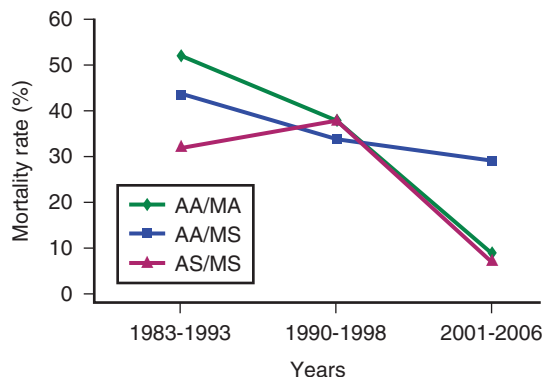


FIGURE 128-4 ■ Era effect for mortality among hypoplastic left heart syndrome anatomic subtypes aortic atresia with mitral atresia (AA/MA), aortic atresia with mitral stenosis (AA/MS), and aortic stenosis with mitral stenosis (AS/MS). Although anatomic subtypes AA/MA and AS/MS have shown improved survival, subtype AA/MS lags behind.

(Fig. 128-4). Thirty-eight of 165 (23%) patients with HLHS had MS/AA. Hospital mortality and need for transplant for patients with MS/AA was significantly higher than for other anatomic subgroups (29% vs. 7.8%, $P = 0.006$; Fig. 128-5). Recently, we identified the presence of significant left ventricle to epicardial coronary artery fistula in these patients and, in one case, autopsy-proven aortocoronary atresia. A retrospective review of these patients identified echocardiographic evidence of coronary artery fistulas in 20 patients (53%) with MS/AA. The presence of suggestive echocardiographic findings was associated with a greater hospital mortality (50% vs. 6%, $P = 0.04$; Fig. 128-6). It is among this cohort of patients that the increased risk seems to be isolated; patients with MS/AA without evidence of fistulas demonstrated survival similar (94%) to other anatomic subtypes (aortic atresia–mitral atresia [AA/MA], 8.6%, and aortic stenosis–mitral stenosis [AS/MS], 7.2%; $P = 0.9$). Although these findings were originally interpreted as small muscular ventricular septal defects, cardiac catheterization has

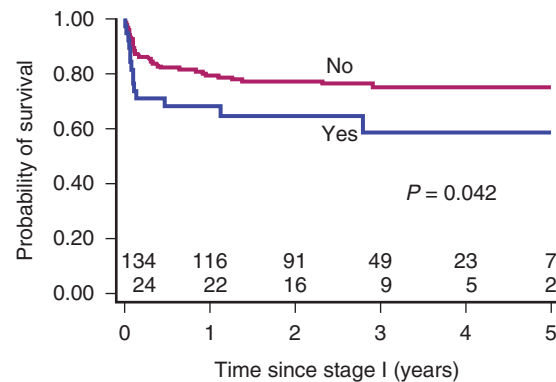


FIGURE 128-5 ■ Likelihood of survival for patients with aortic atresia with mitral stenosis (AA/MS) variant as compared with other subtypes of hypoplastic left heart syndrome. Overall survival is significantly worse for AA/MS ($P = 0.042$).

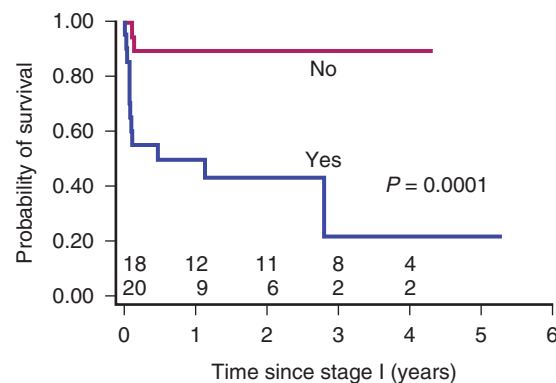


FIGURE 128-6 ■ Hypoplastic left heart syndrome (HLHS), anatomic subtype aortic atresia with mitral stenosis (AA/MS). Analysis (echocardiographic of angiographic) showed left ventricle to coronary artery fistulas to be a highly significant risk factor for death after stage I palliation for HLHS. Risk appears to reside in this subgroup (mortality, 50%) because mortality for patients with AA/MS without fistulas is similar to that for other anatomic subtypes (approximately 6%, $P = 0.0001$).

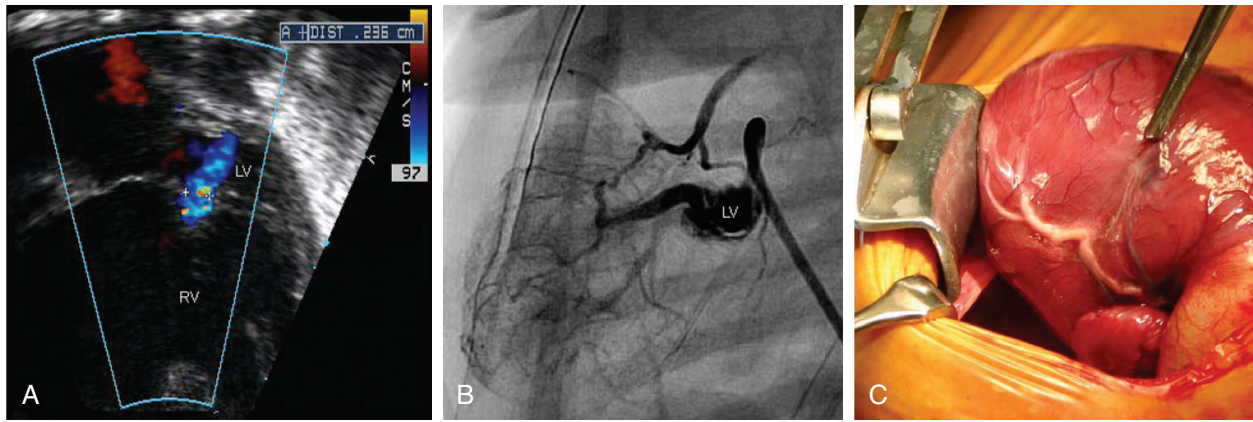


FIGURE 128-7 ■ Diagnosis of left ventricle to coronary artery fistulas. **A**, Echocardiographic examinations often reveal flow “across” the interventricular septum and have been considered to represent ventricular septal defects. **B**, Angiographic demonstration of left ventricle to coronary artery fistulas with retrograde filling of the ascending aorta in addition to the right coronary artery system. **C**, Intraoperative examination has consistently revealed a small “duvet” or “pucker” in the myocardium, presumably at the site of the fistulas, with a thickened and corkscrew appearance of the epicardial coronary artery.

clearly identified left ventricle to coronary artery fistulas in these patients (Fig. 128-7). No advantage to the arteriopulmonary shunt or the Sano modification has been identified for these patients. The exact mechanisms for the increased failure of stage I palliation in patients with AA/MS and fistulas is still unclear. We hypothesize that the presence of fistulas may contribute to dysfunction of the interventricular septum in these marginal patients. However, this remains to be proven.

Based on this experience, we have changed our institutional policy regarding the preoperative evaluation of these patients. Patients identified as being in the AA/MA subtype undergo preoperative angiography to confirm and define the incidence of left ventricle to coronary artery fistulas. In the past, many of these patients were diagnosed, by echocardiogram, with small ventricular septal defects, but in fact these echocardiographic findings most likely represent a left ventricle to coronary artery fistula. If these patients are confirmed as a high-risk group, alternative treatment pathways, such as the hybrid stage I palliation or primary transplantation, may be considered.

Source of Pulmonary Blood Flow

Surgeon experience and institutional preference have been cited as reasons for choosing the source of pulmonary blood flow after the Norwood procedure.⁵³⁻⁵⁵ A prospective, multi-institutional randomized study was performed with the primary outcome death or cardiac transplantation 12 months after randomization.⁵⁶ Transplant-free survival at 12 months was greater in the patients who underwent an RV-PA conduit; however, this group had more unintended interventions and complications. Right ventricular size and function were similar within both cohorts. At 12 months of age to study completion, there was no difference in survival or transplant-free survival between the groups. Mid-term analysis of these data is currently being performed to identify if these conclusions remain true.

Interstage and Mid-term Survival

Of the 188 survivors discharged from the hospital after stage I palliation, 20 (10.6%) died in the interstage period. The median age at interstage mortality was 75 days, and it occurred exclusively in patients with an arteriopulmonary shunt (see Fig. 128-3). The cumulative pre-Glenn mortality (hospital + interstage) rate was 19.8% (47 of 237).

Low Birth Weight, Older Age

Low birth weight (<2.5 kg), consistently identified as a risk factor, was the subject of a subanalysis performed by Weinstein and colleagues.⁵⁷ They reported a 47% survival rate among 67 patients weighing less than 2.5 kg who underwent the Norwood operation between 1990 and 1997. Although lower than the institution's overall survival rate of 74%, these results are very similar to those reported by Bove and Lloyd, Forbess and colleagues, and others.⁵⁸⁻⁶⁰ Although the patients were higher risk, there was no appreciable weight gain in neonates awaiting surgery, and the authors concluded that delaying surgery in the hope of somatic growth is unwarranted.

Whereas some reports have demonstrated poorer survival when Norwood palliation is performed after 2 to 4 weeks of life, recent reports suggest otherwise. Duncan and colleagues⁶¹ reported 100% survival among 9 patients, aged 36 to 108 days, who underwent palliation for single-ventricle variants. Reviewing their experience with the Norwood operation for HLHS, Rossi and others⁶² reported a 90% survival rate among patients older than 2 weeks of age; 100% (4 of 4) of those older than 4 weeks survived.

Norwood Operation for Hypoplastic Left Heart Syndrome Variants

Although the Norwood operation was devised specifically to treat HLHS, it has been widely applied to various

BOX 128-1 Anatomic Variants of the Great Vessels, for Which the Norwood Operation Is Performed

NORMALLY RELATED GREAT VESSELS

- Mitral atresia with ventricular septal defect (VSD)
- Mitral atresia and aortic stenosis with VSD and small left ventricle
- Interrupted aortic arch with severe subaortic obstructions
- Unbalanced atrioventricular septal defect

ABNORMALLY RELATED GREAT VESSELS

- Double-inlet left ventricle with D-transposition of the great arteries
- Tricuspid atresia, VSD, transposition
- Complex double-outlet right ventricle with arch hypoplasia

forms of congenital heart disease that show systemic outflow tract obstruction and a duct-dependent systemic circulation. Because of the impact of great vessel relationships on arch reconstruction, it is useful to define these variants as those that present with normal versus abnormal relationships between the great arteries (i.e. transposition complexes) (Box 128-1).

Surgical Results for Hypoplastic Left Heart Syndrome Variants

Whereas some groups have identified the presence of a well-developed morphologic left ventricle as being protective, others have not.^{63,64} A recent comparison of the Norwood operation performed for HLHS (102 patients, 70 with aortic atresia) and other diagnoses (56 patients) between 1998 and 2001 by Gaynor and colleagues⁶⁵ identified no difference in survival between the Norwood operation for HLHS versus other anatomic diagnoses (78% vs. 75%).

Although the presence of abnormally related great arteries has not been identified as a risk factor for mortality, they may render the constructed neoarch susceptible to twists or kinks, and modifications may be required (Figs. 128-8 and 128-9).⁶⁶

Extracorporeal Membrane Oxygenation for Hypoplastic Left Heart Syndrome

Once thought to be futile, perioperative support with extracorporeal membrane oxygenation (ECMO) may salvage a significant proportion of infants with post-cardiotomy failure following the Norwood operation. Pizarro and colleagues⁶⁷ reported that 50% (6 of 12) of patients requiring ECMO support following Norwood operation were discharged home in good condition. Prematurity, renal dysfunction, and the initiation of ECMO outside of the operating room were risk factors for death. In the setting of a shunt-dependent circulation, Jaggers and colleagues⁶⁸ have reported improved survival when the shunt is left open during ECMO support.

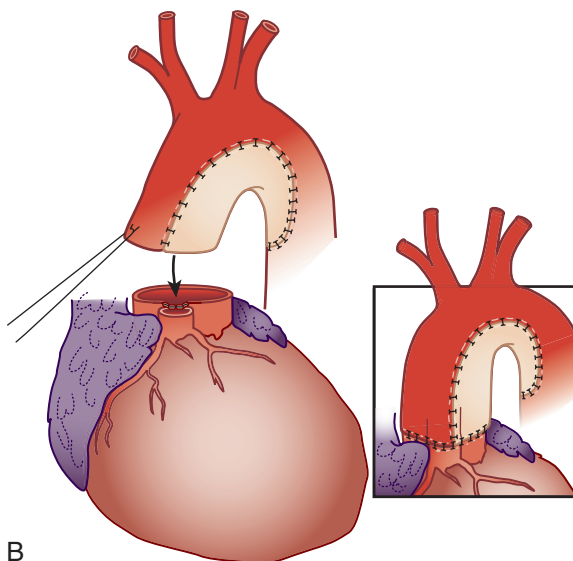
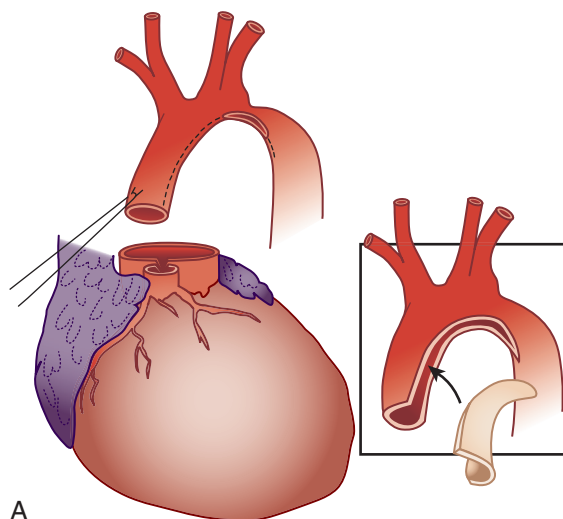


FIGURE 128-8 ■ **A**, Single left ventricle with ventriculoarterial discordance and a rightward and anterior aorta. The atrial septum is excised, and both great vessels are transected just about at the sinotubular junction. Augmentation of the arch is accomplished with pulmonary homograft. **B**, A side-to-side anastomosis between the aorta and pulmonary artery is fashioned. The reconstructed aorta is then anastomosed to both great vessels in an end-to-end fashion. (Reprinted with permission from Mosca RS, Hennein HA, Kulik TJ, et al: Modified Norwood operation for single left ventricle and ventriculoarterial discordance: an improved surgical technique. *Ann Thorac Surg* 64:1126–1132, 1997.)

Modifications

The gradual improvement in survival for the Norwood operation is the result of continuous reappraisal of our surgical and management techniques. Bartram and colleagues⁶⁹ performed a systematic review of the causes of surgical mortality of 122 patients undergoing the Norwood operation between 1980 and 1995. Although this review is historical in nature, it deserves attention because it identifies the weaknesses of this operation.

Bartram and colleagues⁶⁹ reported that inappropriate pulmonary blood flow (too much or too little) was responsible for 36% of the deaths. The second most

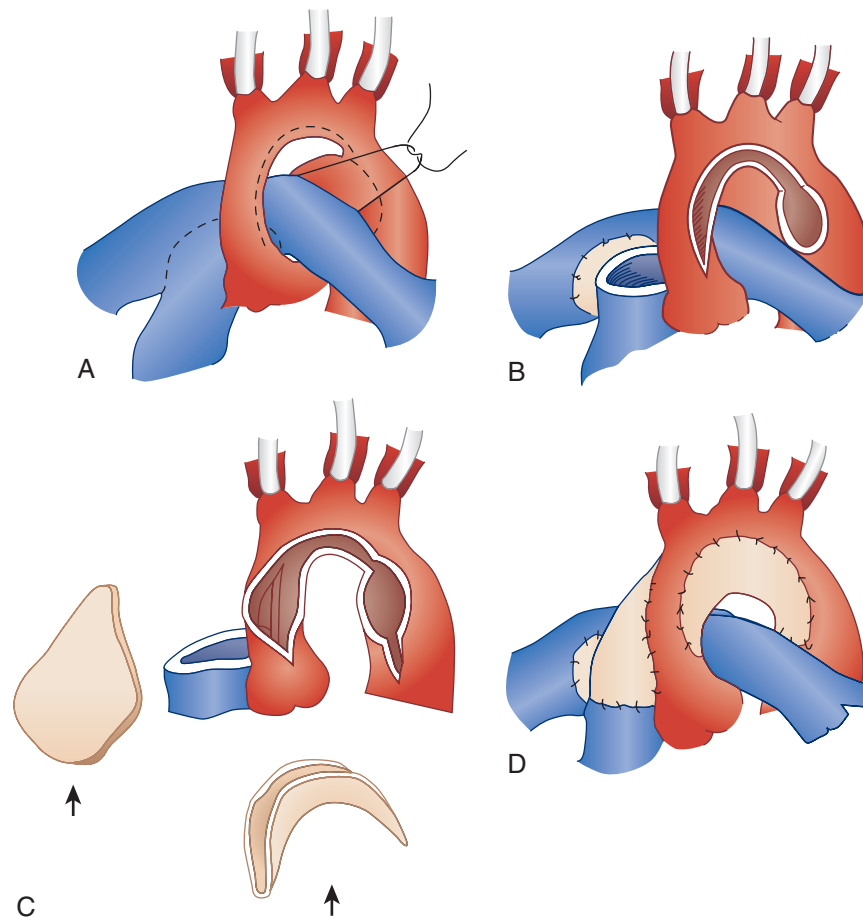


FIGURE 128-9 ■ Operative technique for abnormally related great arteries as might be seen with single left ventricle and transposed great arteries, with the aorta anterior and leftward. **A**, Ligation of ductus and lines of incision. **B**, Closure of the pulmonary artery bifurcation. **C**, Overlapping incisions in ascending aorta and the arch. Augmentation is accomplished with separate patches. **D**, Completed reconstruction. (Reprinted with permission from Jacobs ML, Rychik J, Murphy JD, et al: Results of Norwood's operation for lesions other than hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg* 110:1555–1562, 1995.)

common cause of death was impaired coronary perfusion, occurring in 27% of patients, followed by neo-aortic obstruction (14%), right ventricular failure (13%), and bleeding (7%). Other groups have identified an association between the duration of DHCA and both short and intermediate survival.⁵¹ Modifications have been introduced into the procedure that attempt to nullify these weaknesses.

Control of Pulmonary Blood Flow. Control of pulmonary blood flow by pharmacologic titration of the systemic vascular resistance represents a fundamental shift in the management of palliated single ventricles. This approach has been reported to assist in balancing the pulmonary and systemic circulations and improving systemic oxygen delivery.^{51,70} This approach appears to contribute to improved survival of neonates undergoing the Norwood operation for HLHS.

Coronary Circulation. Because of systemic runoff into the pulmonary circulation via the arteriopulmonary shunt, the myocardium is vulnerable to coronary steal and ischemia after the Norwood operation.⁷¹ A technical

modification of the Norwood operation designed to reduce the vulnerability of the myocardium to ischemia was proposed by Imoto and colleagues.⁷² They reasoned that with placement of shunt inflow proximal to the semilunar (pulmonary) valve, the coronary circulation would be protected from the low diastolic blood pressures that accompany continuous diastolic runoff.

In general, this technique uses a 5- or 6-mm Gore-Tex conduit anastomosed proximally to the infundibulum of the right ventricle, coursing leftward of the pulmonary valve. The conduit is then inserted into the patch (Gore-Tex or pericardium) used to repair the pulmonary bifurcation. One technical point to be stressed using this technique is excision of right ventricle muscle at the site of insertion, because muscular ingrowth with the anticipated right ventricle hypertrophy may obstruct the conduit. Variations of this technique, interposing a valved segment of human saphenous vein between the right ventricle and pulmonary artery, have also been reported.⁷³

Early clinical results have been encouraging. Malec and colleagues⁷⁴ documented higher mean diastolic blood pressures in patients receiving the RV-PA conduit. Although preliminary data based on hemodynamic data

obtained prior to stage II suggests that these patients will be excellent candidates for subsequent surgical staging; the long-term sequelae of a ventriculotomy in this setting remain unknown.⁷⁵

Arch Modifications. Neoaortic obstruction is an important complication of the Norwood operation, occurring in approximately 20% of patients.^{76,77} Azakie and colleagues⁷⁸ related this complication to the size of the ascending aorta (<3 mm). Machii and Becker⁷⁹ suggested that longitudinal and circumferential extension of ductal tissue into the aorta also contributes.

Despite the high incidence of recurrent coarctation, the diagnosis may remain elusive. The reliability of neonatal echocardiography is degraded as a result of thymic resection, as well as the variable position of the reconstructed aorta. Given the morbidity and mortality associated with postoperative arch obstruction, inconclusive or suggestive echocardiographic and clinical examinations are an indication for cardiac catheterization. Because arch gradients are influenced by multiple factors, including the presence of an arteriopulmonary shunt, vascular resistances, and cardiac output, we tend to aggressively treat even minor gradients. If imaging suggests a significant caliber discrepancy across the aortic arch, treatment (either catheter or surgical) of the arch is strongly considered, even in the presence of a minor gradient (5 to 10 mm Hg).

Both surgical and interventional techniques designed to reduce neoaortic arch obstruction have been introduced. Fraser and Mee⁸⁰ reported the technique of using a direct anastomosis of the pulmonary artery to the aortic arch (Fig. 128-10). The operative survival rate was 83% among 59 patients with a median follow-up of 37 months; the incidence of neoaortic arch obstruction was only 5%. These authors and others have suggested that patients with very small ascending aortas (≤ 2.5 mm) are at a higher risk undergoing this technique and have suggested several modifications to nullify the risk in these patients.^{81,82}

In a review by Bautista-Hernandez and colleagues,⁸³ circumferential coarctectomy was found to reduce the incidence of neoaortic arch obstruction after stage I palliation. In addition, patients undergoing arch reconstruction using only autologous tissue (fixed pericardium or direct pulmonary artery to aorta anastomosis) were found to be less likely to require intervention for arch obstruction than were patients reconstructed with homograft material. More aggressive techniques of arch reconstruction, such as the interdigitation technique, have been adopted by some groups (personal communication). One of these techniques uses a counter-incision along the greater curvature on the descending aorta, into which the opened transverse arch is inserted. The entire arch is then augmented using standard techniques.

Recoarctation: Catheter Intervention. Soongswang and colleagues⁸⁴ reported a multi-institutional experience with transcatheter balloon dilation of the neoaorta following the Norwood operation in 58 patients. Although the operation was successful in 89% of patients, there were 3 early and 10 late deaths, 9 patients required

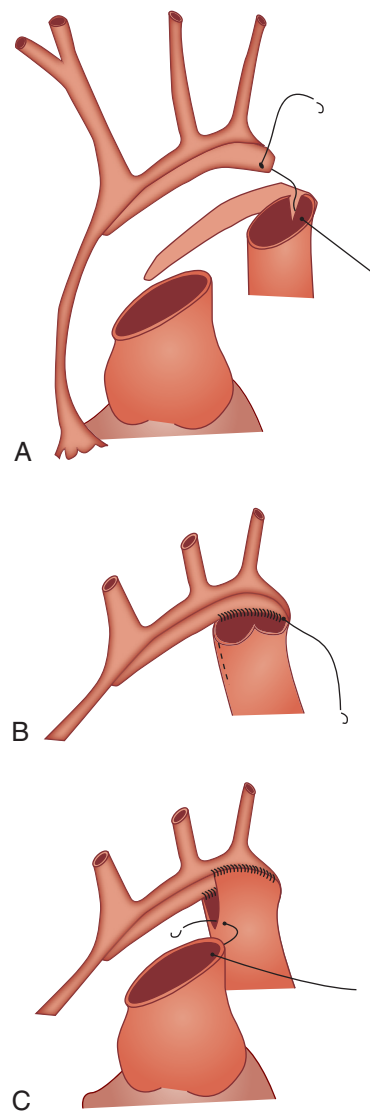


FIGURE 128-10 ■ Modifications to the Norwood procedure have resulted in a reduced incidence of arch obstruction. This technique is probably unsuitable for a very small ascending aorta (≤ 2.5 mm). (Reprinted with permission from Poirer NC, Drummond-Webb JJ, Hisamochi K, et al: Modified Norwood procedure with a high-flow cardiopulmonary bypass strategy results in low mortality without late arch obstruction. *J Thorac Cardiovasc Surg* 120:875-884, 2000.)

reintervention for arch obstruction (6 catheter, 3 surgical), and freedom from reintervention was 78% at 1 year.

Perfusion Management. Studying 350 neonates between 1992 and 1997, Clancy and colleagues⁸⁵ reported that the duration of DHCA was an independent risk factor for death. Among patients undergoing the Norwood operation, data reported by Tweddell and coworkers⁵¹ suggest that DHCA exposure was associated with interstage mortality. DHCA was once considered unavoidable for neonatal aortic arch reconstruction; however, newer techniques have allowed a dramatic reduction, even elimination of the need for DHCA (Fig. 128-11).⁴⁷⁻⁴⁹ The benefits of this approach remain unclear; two studies to date have not identified an advantage (as

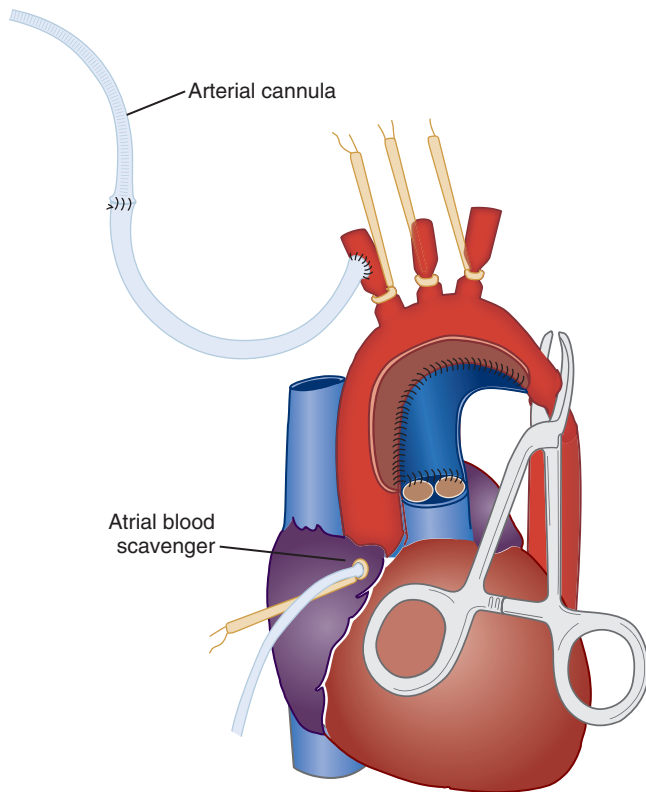


FIGURE 128-11 ■ Operative field during aortic arch reconstruction during regional low-flow perfusion. Arterial inflow is through the cannulated shunt after the anastomosis to the innominate artery is performed. Exposure is maintained by the brachiocephalic snares, a clamp on the descending aorta, and a right atrial scavenger. When using this technique for arch reconstruction in the setting of a two-ventricle repair, or when incorporating the right ventricle to pulmonary artery conduit into the Norwood procedure, the shunt is oversewn on completion of the procedure.

measured by survival and neurodevelopmental outcomes at 1 year of age) to using regional perfusion of the brain during stage I palliation.^{86,87}

Interstage Mortality

Although the efforts described in this chapter have translated into improved survival following the Norwood operation, the palliated state renders these patients physiologically fragile. This vulnerability is thought to be responsible for an interstage mortality rate ranging between 4% and 15%.^{51,78,88}

To date, the only operative variables associated with interstage mortality is longer duration of DHCA⁵¹ and the presence of an arteriopulmonary shunt.⁵⁰ Recent initiatives, such as the development of home monitoring programs and/or anticoagulation protocols, may also be helpful. Although earlier progression to stage II will reduce the period of vulnerability, this approach is limited by the rate of decline in pulmonary vascular resistance. Reporting their experience with early Glenn operations, Reddy and colleagues⁸⁹ reported a reoperation rate of 17%; reoperation was more likely among patients younger than 2 months of age. In general, postponement of the bidirectional Glenn until 3 months of age is preferable.

STAGE II

Originally, survivors of the Norwood operation were staged directly to the Fontan operation within the first year of life. It was soon recognized, however, that this approach resulted in significant morbidity and mortality.⁹⁰ Consequently, the insertion of an intermediate stage, the superior bidirectional cavopulmonary anastomosis (bidirectional Glenn or hemi-Fontan), was introduced by Jacobs and Norwood and resulted in improved survival.⁹¹

Stage I survivors are generally evaluated at 4 to 6 months for progression to stage II. Anatomically, the adequacy of the arch reconstruction, the branch pulmonary arteries, and intra-atrial communication should be assessed. Physiologically, catheterization is helpful to assess ventricular function and pulmonary vascular resistance.

Operative Technique

Bidirectional Glenn

The neck and the chest are prepared and draped. In the advent of cavitory entry, the right neck provides ready access for peripheral cannulation. Following cannulation of the ascending aorta and with venous cannulas in the high superior vena cava and right atrial appendage, the patient is cooled to between 30° C and 32° C. We prefer to perform a bidirectional Glenn operation with the heart beating. After division of the azygous vein, the superior vena cava is clamped at its insertion into the right atrium just above the sinoatrial node and transected, and the atrial orifice is oversewn. The pulmonary remnant of the Blalock-Taussig shunt is excised, and the pulmonary arteriotomy is enlarged to accommodate the superior vena cava. The anastomosis is performed with an absorbable 7-0 suture taking care not to purse-string the anastomosis. The patient is rewarmed, ventilated, and weaned from cardiopulmonary bypass. Saturations in the range of 70% to 85% with superior vena cava pressure of 10 to 12 mm Hg, with an atrial pressure of 5 to 6, are expected. Superior vena cava pressures exceeding 16 or a transpulmonary gradient exceeding 8 to 10 mm Hg should prompt critical appraisal of the anastomosis.

Hemi-Fontan

Introduced by Jacobs and Norwood⁹¹ in 1989, the hemi-Fontan operation is the preferred form of superior cavopulmonary anastomosis for some groups. Briefly, the central pulmonary arteries are opened anteriorly and anastomosed to a counter-incision along the base of the right atrial appendage. Separate patches are then used to augment the central pulmonary arteries, as well as to exclude the superior vena cava–pulmonary artery anastomosis from the heart. Although some surgeons have reported improved survival of the Fontan procedure following the hemi-Fontan as compared with the bidirectional Glenn, this is not uniform.^{92,93}

This modification differs from the bidirectional Glenn in several important ways. Because an intra-atrial patch

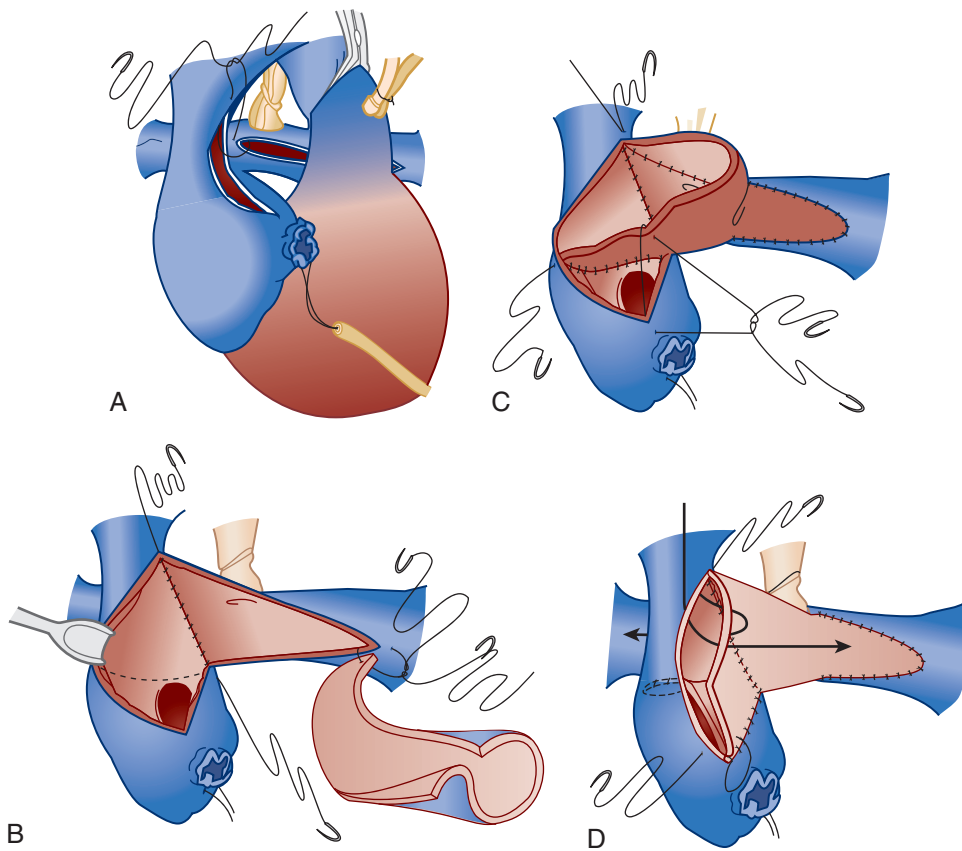


FIGURE 128-12 ■ Stage II, hemi-Fontan operation for hypoplastic left heart syndrome. **A**, The pulmonary arteries are opened anteriorly. **B**, The superior vena cava and the right pulmonary artery are anastomosed side to side. **C**, Flow from the superior vena cava is into the pulmonary arteries, as indicated by the arrows (**D**). (Reprinted with permission from Jacobs ML: Hypoplastic left heart syndrome. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 863.)

is required to exclude the superior cavopulmonary anastomosis from the heart, cross-clamping of the aorta is required; some surgeons use a period of DHCA (Fig. 128-12A, B).⁹⁴ Furthermore, intra-atrial suture lines, implicated in the genesis of atrial arrhythmias, are required.⁹⁵

Results of Stage II

Regardless of which technique is preferred, the results of the stage II procedure have been reproducibly excellent, exceeding 95% in large series.^{58,96} Assessments of longer-term complications (e.g., sinus node dysfunction and arrhythmias) are more difficult. Although Cohen and colleagues⁹⁶ reported a higher incidence of sinus node dysfunction on postoperative day 1 in patients undergoing hemi-Fontan as compared with bidirectional Glenn, there was no difference by the time of hospital discharge. Furthermore, at the time of subsequent Fontan, the authors reported no difference in early sinus node dysfunction.

FONTAN

The Fontan operation is destination therapy for HLHS (Fig. 128-13). By diverting all systemic venous return to

the pulmonary circuit, physiologic septation of the circulation is accomplished.⁹⁷ Although HLHS has been cited as a risk factor for early Fontan failure, other reports place early survival of Fontan for HLHS as high as 98%.^{93,98} Exercise performance among HLHS patients undergoing Fontan appears to be comparable to other single-ventricle variants.⁹⁹

Since its introduction in 1971, the Fontan operation has undergone a steady evolution. Progressive atrial dilation and atrial arrhythmias led to modifications of the original operation, first to the lateral tunnel technique and then to the extracardiac conduit. Experimental data suggest that the extracardiac conduit is superior to the lateral tunnel with respect to energy efficiency. Comparing the intra-atrial lateral tunnel, the extra-atrial lateral tunnel, and the extracardiac conduit, Lardo and coworkers¹⁰⁰ found the extracardiac conduit to be most hydrodynamically efficient.

Short-term clinical advantages, including postoperative arrhythmias, shorter intensive care unit (ICU) stays, and earlier extubations, have also been reported.¹⁰¹ Although few long-term data are available, there appears to be an important reduction in atrial arrhythmias over the intermediate term.^{100,102} Also, the extracardiac Fontan may provide important versatility when addressing certain anatomic subsets, notably the heterotaxy variants presenting with systemic venous abnormalities. In these

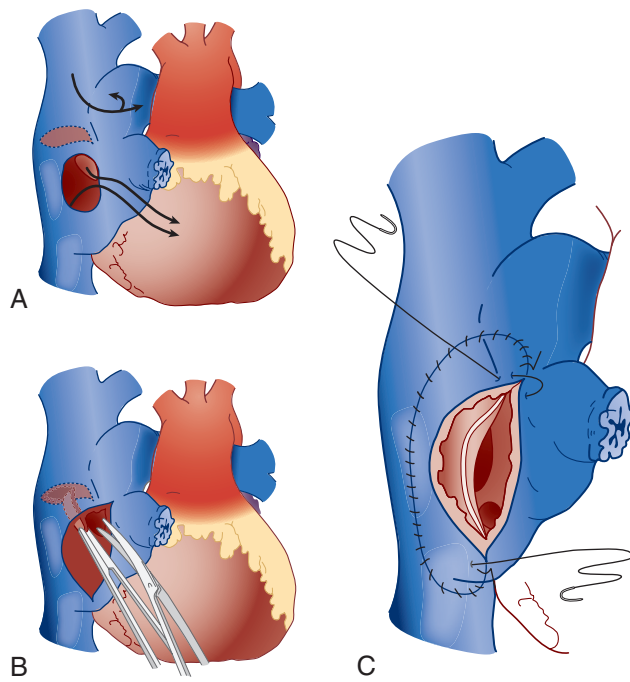


FIGURE 128-13 ■ Stage III, completion Fontan for hypoplastic left heart syndrome. **A**, The hemi-Fontan. **B**, The previously placed homograft separating the right atrium from the superior vena cava is excised. **C**, Total cavopulmonary connection is accomplished using the lateral tunnel technique. (Reprinted with permission from Jacobs ML: Hypoplastic left heart syndrome. In Kaiser LR, Kron IL, Spray TL, editors: *Mastery of cardiothoracic surgery*, Philadelphia, 1998, Lippincott-Raven, p 864.)

circumstances, unifocalization of the inferior systemic venous return to an extracardiac conduit may greatly simplify the completion Fontan. Potential disadvantages of the extracardiac conduit Fontan, including thrombogenicity and lack of growth potential, remain to be assessed over the long term.

TRANSPLANTATION

Whereas most centers have devoted their efforts to surgical palliation using the Norwood operation, a few groups have concentrated on neonatal transplantation as the primary treatment. The technical details of heart transplantation for HLHS have been well described.^{101,103}

The Loma Linda group reported their experience with heart transplantation as the primary treatment for HLHS.¹⁰⁴ Between 1985 and 1995, 190 infants with HLHS were listed for heart transplant. Actuarial survival rates at 1, 5, and 7 years were 84%, 76%, and 70%, respectively; 14 patients were delisted, and 34 of the remaining 176 (19%) patients died while awaiting transplant. Inclusion of these 34 patients listed with the intent to transplant lowers the survival of transplantation to 74% (129 of 176). Year of transplantation was not a risk factor for death. Outcomes for transplantation versus Norwood operation, on an intent-to-treat basis, were reported by Jenkins and colleagues.¹⁰⁵ Examining 231 patients born between 1989 and 1994, they reported that

transplantation resulted in greater survival through 7 years of follow-up. Multivariate analysis identified birth weight less than 3 kg, creatinine level of 2 mg/dL or higher, and atrial septostomy as significant risk factors for death in both groups.

A decision analysis performed on the same patients found that regional and local factors, such as organ availability and institutional dedication to a particular treatment, imparted a powerful influence on outcome.¹⁰⁴ Also, it is difficult to assess the rate at which improvement can be expected among the competing strategies. For example, Jenkins and colleagues¹⁰⁶ reported 1-year survival of the Norwood operation to be only 42% between 1989 and 1994, significantly lower than more contemporary results (66%, 1996 to 2001). In contrast, Razzouk and colleagues¹⁰⁷ did not correlate improved operative survival among patients transplanted between 1985 and 1995.

Finally, competing long-term complications of each strategy remains to be considered. For example, it does not appear that children are particularly privileged with respect to transplant complications; up to 35% of pediatric transplant recipients will develop diffuse graft arteriosclerosis, for which re-transplantation may be required.^{104,108,109}

In part because of the special needs of a neonatal heart transplant program, the ongoing risk of transplant-related complications, and continued improvements in staged outcomes, staged surgery for HLHS has become the primary treatment offered at most institutions. However, transplantation for specific indications, such as coronary abnormalities and valvular disease, remains an important treatment option.

NEURODEVELOPMENTAL OUTCOMES

With improving survival after the surgical treatment for HLHS, a broader, long-term assessment of neurologic outcomes has assumed a new prominence. Although studies are impaired by methodologic difficulties, most indicate that DHCA is detrimental to ultimate neurodevelopmental outcome.¹¹⁰ Kern reported a negative correlation between stage I circulatory arrest time and full scale IQ, an average of 4.4 years after the Norwood operation.¹¹¹

These deficits appear to persist. Mahle and colleagues¹¹² assessed the neurodevelopmental outcome of 115 survivors of the Norwood operation at an average age of 9 years. They reported a mean IQ of 86 (range, 50 to 118) with 18% meeting criteria for mental retardation (IQ < 70). Only 3 of 23 (13%) were thought to have completely normal neurodevelopment.

When compared with children undergoing a Fontan operation for other indications, patients with HLHS demonstrated significantly lower intelligence scores than did their counterparts; the use of circulatory arrest was identified as a predictor.¹¹³ As mentioned, use of regional perfusion techniques have failed to show improved neurodevelopmental outcomes, and emerging data suggest that these children have abnormal cerebral circulatory patterns and preexisting cerebral lesions at the time of birth. As such, modifications of intraoperative variables

may have little impact on a predestined neurologic outcome.

HYBRID PROCEDURES

Ductal stenting and bilateral pulmonary artery banding for HLHS ("hybrid" procedure) was introduced in 1993 by Gibbs and colleagues.¹¹⁴ This approach has been extended and modified by others and, in select centers, constitutes the preferred management scheme for patients with HLHS. A review by Galantowicz and Cheatham¹¹⁵ described their experience with 29 neonates with HLHS between 2001 and 2004. They describe a comprehensive hybrid strategy for the treatment of HLHS. Following ductal stenting and bilateral pulmonary artery banding, patients undergo a comprehensive stage II procedure, which consists of aortic arch repair, repair of the branch pulmonary arteries, surgical atrial septectomy, and a modified bidirectional Glenn operation. This procedure is considered comprehensive by virtue of the fact that it is anticipated to be the only open-heart procedure required for staging to the Fontan circulation. The bidirectional Glenn operation is modified by anastomosing the open-ended stump of the superior vena cava attached to the right atrium to the underside of the right pulmonary artery. A patch of pericardium is sewn over the superior vena cava and right atrium orifice inside the right atrium to separate the circulations.

At the time of stage III (Fontan operation), the pericardial patch is perforated and dilated using catheter techniques via the right internal jugular vein. A covered stent is placed between the inferior vena cava and superior vena cava orifice, completing septation of the circulation. Alternatively and more recently, an extracardiac Fontan is often used, avoiding myocardial arrest.

A surgeon and institutional learning curve was initially seen with adoption of the hybrid technique.¹¹⁵ Galantowicz and colleagues have prospectively reported on 40 patients who underwent a hybrid Norwood procedure. Overall survival through the second stage of palliation was 83%, comparable to the traditional Norwood strategy.¹¹⁶ More recently, centers with a well-established Norwood program adopting the hybrid procedure are able to achieve results comparable to those with the traditional Norwood pathway.^{117,118}

An important risk factor identified is the presence of a retrograde aortic arch obstruction; identified as a "3" sign on echocardiogram, it is most associated with aortic atresia.¹¹⁹ If a retrograde aortic arch obstruction is identified at birth or early interstage, a traditional Norwood operation is recommended over a hybrid approach. Banding of the pulmonary arteries in the neonatal period was shown to require an increased need for pulmonary artery interventions but did not show worse hemodynamics and did not decrease Fontan candidacy.^{120,121} Because of these results, some centers recommend angiograms on completion, and early intervention, sometimes at the time of surgical intervention, is recommended.¹²²

Initial enthusiasm of the hybrid procedure, avoiding cardiopulmonary bypass and myocardial arrest, has not

shown less interstage ventricular dysfunction or atrioventricular valve regurgitation.¹²³ Additionally, gastrointestinal complications after a traditional Norwood procedure were no greater than after a hybrid procedure.^{124,125}

The fragile nature of the palliated circulation in these children requires frequent interstage evaluations (every 1 to 2 weeks), with liberal use of screening echocardiograms to assess ventricular function and developing obstruction through the ductal stent, aortic arch, or pulmonary arteries. Based on echocardiographic findings and physical examination, cardiac catheterization to confirm and treat stenosis with redilation has been an important adjunct.

EMERGING THERAPIES

Fetal Intervention

Since March 2000, fetal intervention for evolving HLHS has been pursued in selected fetuses at Children's Hospital Boston. Qualification criteria have been previously published.¹²⁶ The lesions targeted in this disease are the stenotic aortic valve and the intact atrial septum.

Since 2000, 42 fetuses with HLHS in evolution underwent attempted aortic valvuloplasty,¹²⁷ the technical aspects of which have been described in detail previously.^{127,128} Among 26 fetuses that underwent technically successful in utero aortic valvuloplasty, 8 achieved a biventricular circulation postnatally. All of these fetuses had improved Doppler flow characteristics across the aortic valve on follow-up fetal echocardiography. The other 18 patients with a technically successful procedure were managed postnatally with a strategy of single-ventricle palliation, as were the 4 patients in whom fetal aortic valvuloplasty was technically unsuccessful and the 14 control patients who did not undergo fetal intervention.

The only factors that differed significantly between groups were postintervention left ventricular ejection fraction ($48\% \pm 18\%$ in fetuses that underwent biventricular repair and $34\% \pm 11\%$ in those that did not; $P = 0.03$) and presence of antegrade flow in the transverse arch, which was found in all 8 patients who had a biventricular repair and 9 of 18 that underwent single-ventricle palliation ($P = 0.02$) (Fig. 128-14).

As described earlier, although fetal intervention for HLHS with intact atrial septum has shown a trend toward improved hospital survival (3 of 14, 21%, versus 7 of 18, 39%; $P = 0.45$) and 6-month survival (69% vs. 38%; $P = 0.2$), the experience is too small to be conclusive.

Regardless of the lack of conclusive evidence, the early experience would seem to justify continued efforts at prenatal and postnatal efforts to rehabilitate the left ventricle as a contributor to the circulation. Although the ultimate goal of a septated biventricular circulation may not be attainable in all cases, any contribution to the combined ventricular output from the left ventricle would be a welcome contribution to the Fontan circulation in patients requiring single-ventricle palliation.

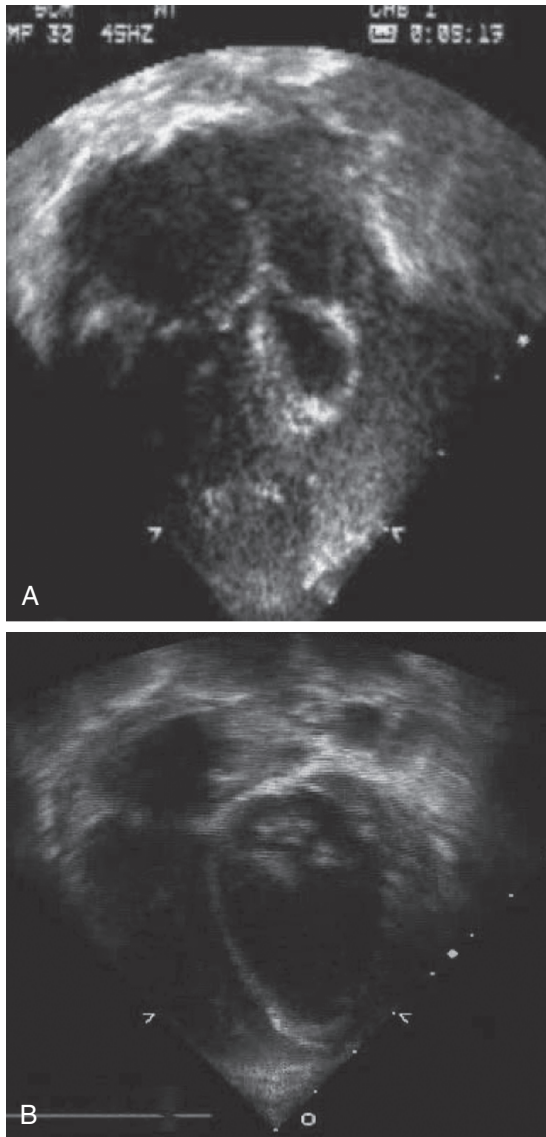


FIGURE 128-14 ■ Anatomic recruitment of the hypoplastic left ventricle into the systemic circulation. Staged intervention suggests that the postnatal left ventricle retains some capacity for growth. **A**, Echocardiogram of newborn with hypoplastic left heart syndrome, showing a hypoplastic left ventricle and thickened endocardium, consistent with endocardial fibroelastosis (EFE). **B**, Echocardiogram of the same child at age 22 months. The child was treated with stage I palliation, including EFE resection, followed by bidirectional Glenn operation with further EFE resection before subsequently undergoing successful biventricular repair at age 22 months.

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MANAGEMENT OF SINGLE VENTRICLE AND CAVOPULMONARY CONNECTIONS

Kirk R. Kanter

CHAPTER OUTLINE

TERMINOLOGY AND ANATOMY

NATURAL HISTORY

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Single-ventricle circulation is a generic term that covers a wide range of structural cardiac abnormalities. It is widely accepted that the definitive surgical palliation for these hearts is the Fontan circulation, whereby the pulmonary and systemic blood flows are in series with the single ventricle connected to the systemic circulation. To optimize clinical outcomes with the Fontan, many patients need prior interventions to adjust the pulmonary or systemic circulation. Because of the changing physiology in the early years of life, a series of operations is often necessary.

TERMINOLOGY AND ANATOMY

In this chapter, the term *single ventricle* refers to congenital cardiac malformations that lack two completely

well-developed ventricles in which functionally there is only a single ventricular chamber that supports both the pulmonary and systemic circulations. A truly morphologic univentricular heart is rare; more often there is an additional rudimentary chamber. Over the years, numerous classifications and terms for these hearts have emerged. The Congenital Heart Surgery Nomenclature and Database Project minimum data set categorized single ventricles into seven broad categories¹: hearts with common inlet atrioventricular connection (double-inlet right ventricle and double-inlet left ventricle), hearts with absence of one atrioventricular connection (tricuspid atresia and mitral atresia), hearts with common atrioventricular valve and only one well-developed ventricle (unbalanced common atrioventricular canal defect), hearts with only one fully developed ventricle and heterotaxia syndrome (single-ventricle heterotaxia

syndrome), and other rare forms of univentricular hearts that do not fit in one of these categories. A more comprehensive classification of the Congenital Heart Surgery Nomenclature and Database Project subclassifies these categories of single ventricle into four hierarchies spanning more than three printed pages.² Tricuspid atresia is the most common type of single ventricle, with an incidence of 1% to 3% of all congenital heart lesions.

In addition, there are some cardiac abnormalities in which, in the presence of two well-developed ventricles, the anatomy precludes biventricular repair. Examples include hearts with major straddling of the atrioventricular valve and double-outlet right ventricle with remote ventricular septal defect. Treatment strategies for these nonseptatable hearts are the same as those applied to univentricular hearts.

The management of hypoplastic left heart syndrome, a common form of univentricular heart with a dominant right ventricle and rudimentary left ventricle is not discussed in this chapter. [Chapter 128](#) is dedicated to this topic.

NATURAL HISTORY

Patients born with a single functional ventricle generally have a dismal long-term prognosis without eventual surgical intervention. Current results of the Fontan procedure as the final palliative surgical procedure for these patients are generally good, but it must be recognized that management of these patients begins at birth if they are to be satisfactory candidates for the Fontan procedure. The natural history of single-ventricle circulations is greatly influenced by the degree of pulmonary blood flow and associated lesions, such as coarctation of the aorta, systemic outflow tract obstruction, and anomalies of pulmonary or systemic venous return. In addition, noncardiac abnormalities may be present.

Severe obstruction to pulmonary blood flow at birth is an important determinant for early death. Patients with unobstructed pulmonary flow can develop congestive heart failure in infancy or later, and, if unoperated, can develop pulmonary vascular disease. The clinical course may be worsened by the presence of left-sided obstructive lesions such as coarctation of the aorta. In a small subset of patients, the pulmonary and systemic circulations are well balanced because of unrestricted systemic blood flow and sufficient pulmonary obstruction to control pulmonary blood flow. These patients have a more favorable life expectancy. The aim of surgical intervention is to improve the natural history by balancing blood flow between the pulmonary and systemic circulations and ultimately separating these circulations. In addition, other significant hemodynamic abnormalities should be corrected.

CLINICAL PRESENTATION AND PREOPERATIVE EVALUATION

Clinical presentation is determined by the amount of pulmonary blood flow and the associated cardiac lesions.

Patients with restricted pulmonary blood flow will exhibit cyanosis. Some may have a duct-dependent pulmonary circulation and will become rapidly cyanosed as the ductus arteriosus closes after birth. In the case of a large left-to-right shunt, the patient will present with congestive heart failure. Symptoms will deteriorate with falling pulmonary resistance in the first weeks after birth. Although in most single ventricles there is mixing of circulations, streaming may occur, particularly in complex hearts, resulting in differential saturations in the great arteries.

A precise anatomic diagnosis is essential to allow proper planning of the surgical procedures. In particular, information on the size and course of the pulmonary arteries, degree of pulmonary blood flow, and presence of accessory lesions is required, as well as an assessment of cardiac function. History, clinical presentation, chest x-ray, and electrocardiogram offer important but nonspecific information. Echocardiography provides detailed information on the structure and function of the heart and has the advantage that it is a noninvasive investigation that can be performed at the bedside. In particular, in infants who have excellent echocardiographic windows, enough information often can be gathered to proceed to operation. Cardiac catheterization is uncommonly needed to evaluate pulmonary vascular resistance or accessory sources of pulmonary blood flow. Interventional procedures, such as balloon atrial septostomy for restrictive atrial communication in hearts without two well-formed atrioventricular valves, can be carried out to supplement, or sometimes replace, surgical treatment.

SURGICAL PREPARATION FOR THE FONTAN CIRCULATION

Because the ultimate success of the Fontan operation depends on a suitably low pulmonary vascular resistance and adequate pulmonary artery architecture, it is critical to commence the preparation for a Fontan procedure in the newborn period by appropriately regulating pulmonary blood flow. There is a wide variation in the distribution of pulmonary and systemic blood flow in patients with single-ventricle circulation. Some patients have restricted pulmonary blood flow, others have unrestricted pulmonary flow, and a few have a naturally balanced circulation. Most patients, therefore, require palliative procedures leading up to the Fontan circulation, either to restrict or to augment pulmonary blood flow. The choice of procedure is guided by the underlying anatomy and pulmonary vascular resistance, both of which are subject to change over time. It should always be borne in mind that improper palliative procedures can result in the loss of Fontan candidacy. The ultimate goal of surgical procedures leading up to the Fontan circulation are to (1) improve clinical symptoms, (2) provide optimal pulmonary artery architecture and low pulmonary vascular resistance, (3) preserve systolic and diastolic ventricular function, (4) preserve atrioventricular valve function, (5) relieve systemic ventricular outflow tract obstruction, and (6) provide anatomic setup for a definitive Fontan repair.

Inadequate Pulmonary Blood Flow

In the neonatal and early infantile period, when pulmonary vascular resistance is still high, if the child is ductal dependent or has inadequate systemic oxygen saturations, a systemic to pulmonary artery shunt, usually a modified Blalock-Taussig shunt, is performed.³ Although this was classically performed through a thoracotomy approach, a sternotomy is now commonly used because it allows for concomitant ductal ligation and correction of stenosis of the proximal left pulmonary artery if present.^{4,5} Despite decades of experience with the modified Blalock-Taussig shunt, there remains a persistent early and intermediate morbidity and mortality with this procedure.⁶

Excessive Pulmonary Blood Flow

In the case of excessive pulmonary blood flow, it is imperative to limit the pulmonary blood flow to protect the patient from developing pulmonary vascular disease and ventricular dysfunction as a result of chronic volume overload.⁷ Adequate tightness of a pulmonary artery band can be difficult to achieve, and a band that is too loose initially can result in unprotected pulmonary arteries until the child grows into the band. The resultant pulmonary vascular disease may affect the ultimate suitability of the child for the Fontan procedure. Other complications of pulmonary artery banding include distortion of the pulmonary arteries, especially if the band migrates, and erosion of the band. Because of the fixed diameter of the pulmonary band, as the child grows, pulmonary blood flow will eventually be inadequate and cyanosis will result, necessitating further surgical intervention. Often in infants with unobstructed pulmonary blood flow and single-ventricle anatomy, a concomitant coarctation will need to be repaired at the time of pulmonary artery banding.

To avoid the complications of pulmonary artery banding in the neonate or infant with excessive pulmonary blood flow and single-ventricle physiology, Bradley and colleagues suggested the strategy of pulmonary artery division with placement of a systemic to pulmonary artery shunt; this strategy has yielded excellent clinical results.⁸

Systemic Outflow Obstruction (Subaortic Stenosis)

Some children with single ventricles can present in infancy with systemic ventricular outflow tract obstruction (subaortic stenosis), which may also develop later. The resultant myocardial hypertrophy can adversely affect the eventual suitability for a Fontan procedure. Patients at risk are those in whom the aorta arises above a small outlet chamber, such as in tricuspid atresia or double-inlet left ventricle with a rudimentary right ventricle and transposition of the great arteries, particularly if the ventricular septal defect (sometimes referred to as a bulboventricular foramen) is small or if there is coexisting aortic arch obstruction.⁹ A modified Damus-Kaye-Stansel procedure can be performed to establish unobstructed systemic arterial outflow. This involves transection of both great arteries, anastomosis of the

facing aortic and pulmonary walls, and connection of the distal aorta to the perimeter of the reconstructed proximal great artery. Depending on the pulmonary vascular status, blood flow to the central pulmonary arteries can be reestablished via a systemic to pulmonary shunt, a bidirectional cavopulmonary anastomosis, or the Fontan operation.¹⁰ The Damus-Kaye-Stansel can be performed as a primary procedure¹¹ or after a previous pulmonary artery band.^{7,12,13} Alternatively, a Norwood strategy can be followed in these patients^{14,15} (see [Chapter 128](#)). Some have advocated direct relief of the systemic outflow obstruction by surgical enlargement of the ventricular septal defect (bulboventricular foramen) or resection of subaortic stenosis.^{7,16,17}

Obstructed Pulmonary Venous Return

A particularly unfavorable subset of patients with single ventricles is those with total anomalous pulmonary venous connection.¹⁸⁻²⁰ Even with successful correction of the pulmonary venous return, these patients can have persistent pulmonary artery hypertension, probably related to fetal pulmonary vein and artery abnormalities,²⁰ which precludes the application of the Fontan procedure. To a lesser extent, children with a restrictive atrial communication and an abnormal left atrioventricular valve (as in mitral atresia) are at risk for the development of pulmonary artery hypertension.²¹ Opening of the atrial septum by percutaneous atrial septostomy or stent placement in the catheterization laboratory or surgical atrial septectomy should be performed once this condition has been recognized.

BIDIRECTIONAL CAVOPULMONARY ANASTOMOSIS

The original cavopulmonary shunt was the Glenn procedure (anastomosis of the divided right pulmonary artery to the superior vena cava with ligation of the proximal superior vena cava).²² The advantages of a venous over an arterial shunt in the palliation of cyanotic heart disease are twofold. First, the venous blood that enters the pulmonary artery is much more desaturated, and therefore a higher take-up of oxygen per milliliter of blood is possible. Second, systemic venous return is diverted to the lungs, thus reducing the volume load on the single ventricle. The original Glenn anastomosis fell into disfavor; it could not be used in neonates because of elevated pulmonary vascular resistance.²³ There were also reports of the development of ipsilateral pulmonary arteriovenous malformations.²⁴ However, it was noted that patients with a previous classical Glenn anastomosis fared better with a subsequent Fontan procedure.²⁵ For patients considered high risk for the Fontan procedure, a bidirectional cavopulmonary anastomosis (the divided superior vena cava anastomosed to the pulmonary arteries supplying both lungs) could be used successfully as an alternative to the Fontan or as a staging procedure for the Fontan^{26,27} ([Fig. 129-1](#)). The hemi-Fontan modification of the cavopulmonary shunt involves patch augmentation of the central pulmonary arteries and a connection between the

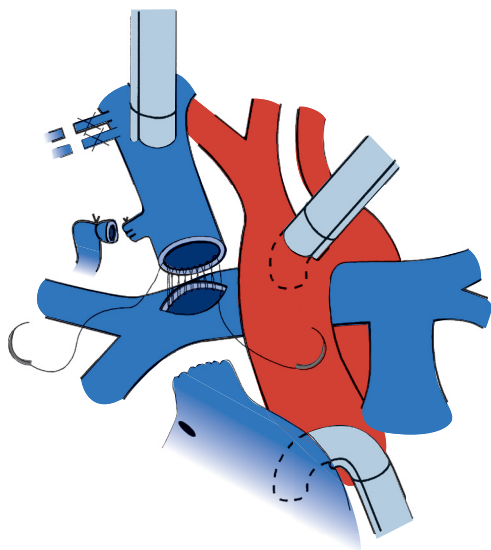


FIGURE 129-1 ■ Bidirectional cavopulmonary shunt. The superior vena cava is fully mobilized, including the junction with the innominate vein. The azygos vein and small venous branches near the innominate vein junction are ligated to prevent runoff into the inferior vena cava territory. The main and right pulmonary arteries and a right systemic to pulmonary artery shunt, if present, are mobilized. Cardiopulmonary bypass is instituted with venous drainage from a cannula in the right atrial appendage and a further cannula in the superior vena cava near the innominate junction with return via the ascending aorta. The operation is performed on a beating heart with moderate hypothermia (28°C to 32°C), but a period of aortic cross-clamping may be required for correction of other cardiac anomalies. Any right-sided systemic aortopulmonary shunt is occluded and subsequently taken down. The right and main pulmonary arteries are mobilized. The superior vena cava is snugged down. A vascular clamp is applied just above the cavoatrial junction, taking care not to damage the sinus node. The superior vena cava is divided immediately above the clamp, the cardiac end is oversewn, and the clamp is released. The upper margin of the right pulmonary artery is incised. The superior vena cava is anastomosed in an end-to-side manner with the upper margin of the right pulmonary artery. The suture is interrupted in several places to help avoid a purse-string effect and narrowing of the anastomosis. Additional sources of pulmonary blood supply, such as forward flow over a stenosed pulmonary outflow tract or left-sided arterial pulmonary shunt, are usually left in place.

right atrial–superior vena cava junction and pulmonary arteries. Norwood and Jacobs reported improved survival with the Fontan operation in children with hypoplastic left heart syndrome who had undergone an intermediate hemi-Fontan procedure.²⁸ Subsequent studies showed significantly improved outcomes in patients with a Fontan procedure who were staged with a bidirectional cavopulmonary anastomosis compared with those who were not staged.^{21,29} The bidirectional cavopulmonary anastomosis can be performed safely in children younger than 6 months³⁰ and is now routinely performed electively between 4 and 6 months of age, even in children without prior surgical palliation.

Additional Sources of Pulmonary Blood Flow

Whether an additional source of pulmonary blood flow (such as a patent ductus arteriosus, patent right

ventricular outflow tract or a tight pulmonary artery band, or systemic to pulmonary artery shunt) should be eliminated at the time of the cavopulmonary anastomosis remains open to discussion. Comparisons of patients with and without sources of additional pulmonary blood flow after a bidirectional cavopulmonary anastomosis have shown no deleterious effect at the time of the eventual Fontan procedure.³¹⁻³³ Evidence shows that leaving an additional source of pulmonary blood flow after the bidirectional cavopulmonary anastomosis can enhance pulmonary arterial growth.^{32,34} Some patients do not tolerate this increased pulmonary blood flow, which manifests as pleural effusions and superior vena cava syndrome. These patients can be managed by catheter-based techniques to occlude the sources of additional pulmonary blood flow.³⁵

Some have argued that a bidirectional Glenn anastomosis with an additional source of pulmonary blood flow can serve as definitive palliation without a subsequent Fontan procedure, especially in high-risk cases.^{36,37} A multi-institutional paper from Italy reviewed 246 patients with a mean age 4.7 ± 6.2 years (range, 12 months to 30 years) who underwent a bidirectional cavopulmonary anastomosis leaving intact antegrade accessory pulmonary blood flow.³¹ On intermediate follow-up of 4.2 ± 2.8 years, 173 patients (70.3%) did not require a completion Fontan procedure and had a mean resting arterial oxygen saturation of $87\% \pm 4\%$. The actuarial freedom from a Fontan procedure at 7 years was 70.2% for the entire cohort. These results suggest that this strategy provided sustained palliation for selected patients with a single-ventricle circulation and may indicate that the Fontan route is not necessarily the universal palliation for all single-ventricle circulations.

Bilateral Bidirectional Cavopulmonary Anastomoses

Approximately 15% of children with single ventricles undergoing a bidirectional cavopulmonary anastomosis will have a persistent left superior vena cava draining to the coronary sinus.^{38,39} Although an earlier report from the Hospital for Sick Children in Toronto suggested that the presence of a second superior vena cava was a risk factor for thrombosis and failure to progress to the Fontan procedure,³⁹ a report from our institution did not identify any adverse clinical outcomes in patients undergoing bilateral bidirectional cavopulmonary anastomoses compared with those undergoing a unilateral bidirectional cavopulmonary anastomosis.³⁸

Kawashima Operation and Pulmonary Arteriovenous Malformations

Some children with single-ventricle anatomy, particularly those with heterotaxy syndrome, have an interrupted inferior vena cava with azygos continuation to the right superior vena cava or hemiazygos continuation to a persistent left superior vena cava. After initial palliation in infancy, as necessary, with pulmonary artery banding or a systemic to pulmonary artery shunt determined by the status of the pulmonary blood flow, definitive palliation can be accomplished with a Kawashima operation.⁴⁰ This

consists of a bidirectional cavopulmonary anastomosis (bilateral in the case of a persistent left superior vena cava) without the division of the azygos (hemiazzygos) continuation. In effect, this routes all of the systemic venous return except hepatic and mesenteric flow to the pulmonary arteries. A significant percentage of these patients will develop pulmonary arteriovenous malformations (AVMs) in both lungs with resultant cyanosis. This is analogous to the ipsilateral pulmonary AVMs observed with the classical Glenn anastomosis.²⁴ There seems to be some factor in the hepatic venous effluent that, if not circulated to the lung, results in the development of these AVMs.⁴¹ Rerouting the hepatic and mesenteric venous blood flow to the pulmonary arteries by completing the Fontan procedure has been shown to resolve this problem in most patients.⁴²⁻⁴⁴

Glenn Anastomosis versus Hemi-Fontan Procedure

As an intermediate stage to the Fontan procedure, either a bidirectional Glenn anastomosis or a hemi-Fontan procedure can be performed. Although there are advocates for both operations, there are few studies comparing the two operations in similar groups of patients. The hemi-Fontan procedure, as described initially by Norwood and Jacobs,²⁸ involves patch augmentation of the central pulmonary arteries and a connection between the right atrial-superior vena cava junction and pulmonary arteries with elimination of alternative sources of pulmonary blood flow. Although it is a more extensive operation, it simplifies the eventual Fontan procedure, particularly if a lateral tunnel Fontan is planned.⁴⁵ It also has the potential advantage of allowing nonsurgical completion of the Fontan circulation in the cardiac catheterization laboratory,⁴⁶ although this nonoperative Fontan completion can also be used with the bidirectional Glenn anastomosis.⁴⁷ Sinus node dysfunction appears to be more common early after the hemi-Fontan procedure compared with the bidirectional Glenn anastomosis, but this was no longer significant at time of hospital discharge.⁴⁸ Based on magnetic resonance imaging (MRI) reconstructions and computational and experimental fluid dynamics methodologies, it appears that the bidirectional Glenn anastomosis is more energy efficient than the hemi-Fontan procedure.⁴⁹

ONE AND ONE-HALF VENTRICLE REPAIR

In children with a marginal pulmonary ventricle, the standard surgical options are a Fontan procedure or a high-risk biventricular repair, as is commonly seen in patients with pulmonary atresia and intact ventricular septum.⁵⁰ To reduce the risk of biventricular repair and to combat the long-term attrition related to the "Fontan state," Billingsley and colleagues proposed recruiting the hypoplastic pulmonary ventricle to manage part of the systemic venous return by closing the atrial communication, enlarging the right ventricular outflow tract, and adding a cavopulmonary anastomosis so that the small right ventricle is tasked with pumping only the venous

return from the inferior vena cava and not the entire cardiac output.⁵¹ The concept of a one and one-half ventricle repair has since been extended to other abnormalities,⁵²⁻⁵⁴ such as unbalanced atrioventricular septal defects and straddling atrioventricular valves, and as an adjunct to the repair of Ebstein anomaly.⁵⁵ Strict criteria to distinguish which patients would benefit from a one and one-half ventricle repair as opposed to a biventricular repair or a Fontan procedure are not well defined.⁵⁶ Similar physiology can be achieved by only partially closing the atrial communication without performing a cavopulmonary anastomosis. This allows decompression of the smaller right-sided ventricle through this atrial communication with the disadvantage of some systemic arterial desaturation. The advantage of this modification of the one and one-half ventricle repair is that, if the pulmonary ventricle grows sufficiently to handle the complete cardiac output, the atrial communication easily can be closed in the catheterization laboratory at a later date, thus allowing for complete separation of the pulmonary and systemic circulations.

SELECTION CRITERIA FOR THE FONTAN PROCEDURE

The initial selection criteria for the procedure described by Fontan and colleagues for patients with tricuspid atresia, known as the "ten commandments," were stringent (Box 129-1).⁵⁷ With increasing experience, these criteria have been relaxed; however, because of the unique physiology that accompanies the Fontan circulation, proper patient selection remains crucial.

The age of patients undergoing the Fontan operation has been progressively lowered as experience has been gained. Increased pressure and volume load of the single ventricle, such as occurs after systemic to pulmonary artery shunts, is a risk factor for subsequent failure of the Fontan operation; therefore, early ventricular unloading with a bidirectional Glenn anastomosis has been advocated. In short-term studies, regression of ventricular mass was observed in children younger than 3 years who underwent a bidirectional Glenn anastomosis but not in children 10 years or older who underwent the same procedure.⁵⁸ Similarly, younger age at the time of

BOX 129-1

The "Ten Commandments" for Selection of Patients with Tricuspid Atresia for the Fontan Procedure

1. Minimum age 4 years
2. Sinus rhythm
3. Normal caval drainage
4. Right atrium of normal volume
5. Mean pulmonary artery pressure ≤ 15 mm Hg
6. Pulmonary arterial resistance < 4 U/m²
7. Pulmonary artery to aorta diameter ratio ≥ 0.75
8. Normal ventricular functions (ejection fraction > 0.6)
9. Competent left atrioventricular valve
10. No impairing effects of previous shunts

bidirectional Glenn shunt or Fontan operation was also associated with superior exercise performance compared with those in whom surgery was delayed until a later age.⁵⁹ In contrast to Fontan's initial restriction of minimum age older than 4 years, recent data show that for patients with a dominant left ventricle (e.g., tricuspid atresia), with an average follow-up of more than 7.5 years, postoperative exercise capacity, cardiac index, and ventricular ejection fraction were significantly better in children who had their Fontan completion when they were younger than 3 years compared with a group who were older than 3 years.⁶⁰ A multivariable analysis of risk factors after the Fontan operation in 406 patients did not identify young age as a risk factor for unfavorable outcome.⁶¹ Pizarro and colleagues demonstrated in 107 children that Fontan completion can be performed safely in children at a median age of 13 months.⁶² It remains to be seen if a very early Fontan procedure has a better long-term outcome than one performed at a later age, particularly in patients with well-balanced circulations. It is certain that current strategies of early unloading of the single ventricle with an intermediate bidirectional cavopulmonary anastomosis or hemi-Fontan procedure has allowed for successful Fontan completion at a younger age.

Preoperative sinus rhythm is not an absolute requirement for a successful Fontan procedure,^{63,64} although patients without preoperative sinus rhythm are more likely to have heterotaxy syndrome, which is a predictor of post-Fontan rhythm disturbances.^{65,66} The requirement in Fontan's "ten commandments" for normal right atrial volume or normal caval drainage no longer seems to be of concern. On the other hand, unobstructed pulmonary venous drainage is an absolute necessity (see [Obstructed Pulmonary Venous Return](#) section).

The pulmonary vasculature and ventricular function remains the most important selection criteria for successful outcome after the Fontan operation.⁶¹ Pulmonary arteriolar resistance ($<4 \text{ U/m}^2$)⁶⁷ and mean pulmonary artery pressure ($<15 \text{ mm Hg}$) should be low.^{61,66} Assessment of the pulmonary vascular bed can be difficult, in particular in the presence of accessory sources of pulmonary blood flow such as aortopulmonary collateral vessels or surgical shunts.

Small size of the central pulmonary arteries has been considered a predictor of poor outcome after the Fontan procedure (death or takedown). Various attempts have been made to standardize these measurements. The McGoon ratio, originally used in patients with pulmonary atresia and ventricular septal defect,⁶⁸ is obtained from the sum of the diameters of the immediately prebranching portion of the left and right pulmonary arteries divided by the diameter of the descending aorta just above the diaphragm. In a retrospective study, Fontan and colleagues⁶⁹ found that the risk of early death or Fontan takedown rose sharply when the McGoon ratio was less than 1.8. The Nakata pulmonary artery index⁷⁰ is derived from the sum of the diameter of the left and right pulmonary arteries (measured just before the origin of the upper lobe branches) divided by the body surface area. Patients with unfavorable outcome after a modified Fontan for tricuspid atresia were shown to have a lower

pulmonary artery index than those with good results (185 ± 47 versus $276 \pm 83 \text{ mm}^2/\text{m}^2$),⁷¹ but this was not confirmed by others.^{72,73} The usefulness of these indices has been questioned because they do not take into account the compliance and maturity of the pulmonary vascular system, the peripheral and intraparenchymal pulmonary arteries, or any distortion of the central pulmonary arteries that may have occurred because of previous shunts or bands. Furthermore, many of these studies implicating small pulmonary artery size as a risk factor for poor Fontan outcomes were performed before current strategies of earlier staged Fontans using total cavopulmonary connections.⁷²

Adequate ventricular function remains a prime determinant for a successful Fontan circulation.⁶¹ The incidence of common causes of impaired systemic ventricular performance seen in the past can be reduced. For example, early elimination of volume overload by an intermediate bidirectional cavopulmonary connection or hemi-Fontan procedure can preserve ventricular function.^{45,74} Also, aggressive treatment of systemic ventricular outflow obstruction (see [Systemic Outflow Obstruction](#) section) can reduce deleterious ventricular hypertrophy in these patients with resultant improved ventricular function at the time of the Fontan procedure. Also, some feel that the presence of systemic to pulmonary collateral artery connections can increase the volume load of the single ventricle with resultant impaired ventricular function or increased workload on the heart.⁷⁵⁻⁷⁸ The impact of these collaterals can be reduced in the cardiac catheterization laboratory by coil occlusion, although some groups question its usefulness.⁷⁹⁻⁸²

Atrioventricular valve insufficiency remains a risk factor for the Fontan procedure,⁸³ particularly in children with heterotaxy syndrome.^{18,66} Because this can cause volume overload of the single ventricle with the potential for impaired ventricular function, it is important to address this surgically when possible. Repair of the incompetent systemic atrioventricular valve can be performed reliably at the time of the bidirectional cavopulmonary anastomosis or at the time of the Fontan.⁸⁴⁻⁸⁶ If necessary, atrioventricular valve replacement is an option.⁸⁷

SURGICAL EVOLUTION OF THE FONTAN PROCEDURE

The Fontan procedure was first applied in 1968 for tricuspid atresia based on the principle that the right atrium could be used as a pumping chamber for the pulmonary circulation.⁸⁸ The original description of the atriopulmonary connection included the insertion of an aortic or pulmonary homograft valve at both the inflow and the outflow of the right atrium as well as a classical Glenn anastomosis of the superior vena cava to the right pulmonary artery. Kreutzer and colleagues described the use of the patient's native pulmonary valve between the right atrium and pulmonary artery.⁸⁹ Bjork and coworkers were worried about the long-term durability of conduits and valve prostheses and devised a valveless atrioventricular anastomosis whereby the right atrial appendix is

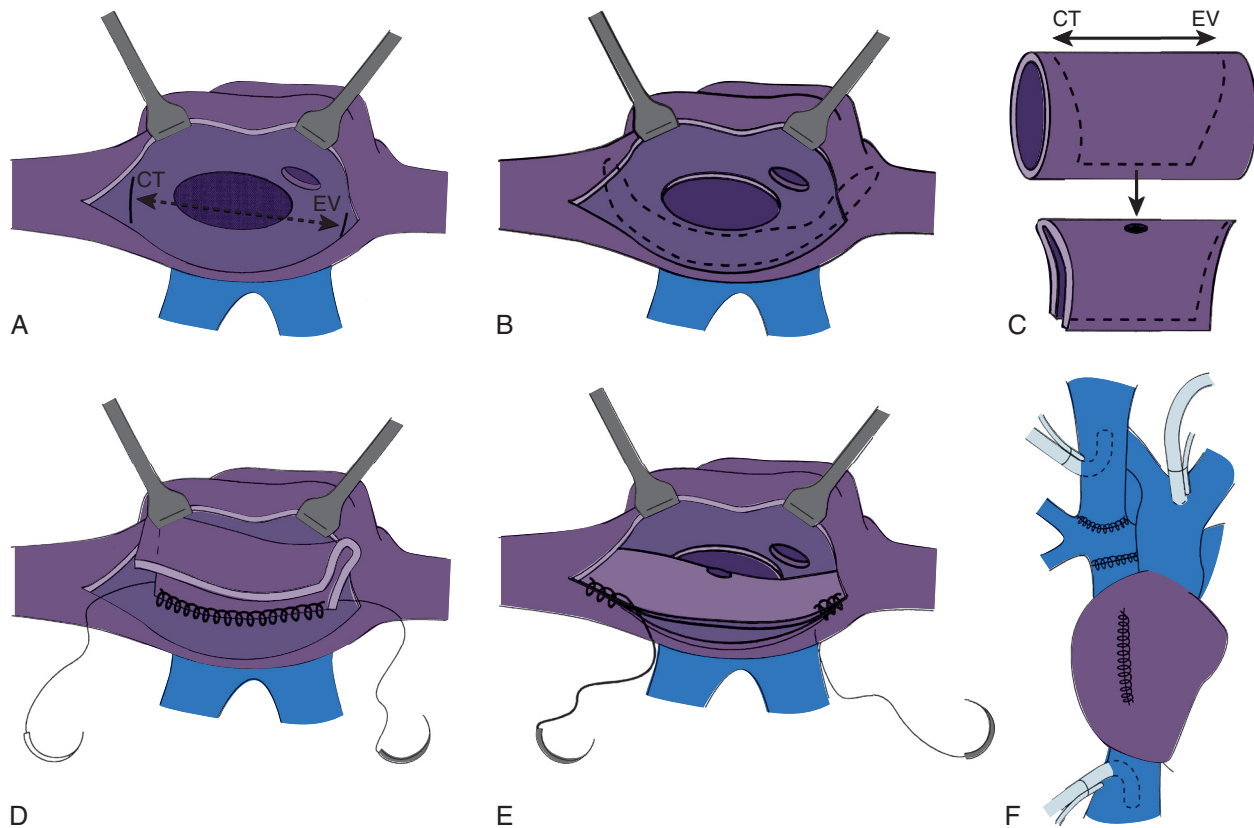


FIGURE 129-2 ■ Lateral tunnel Fontan. The beginning of the operation may involve performing a bidirectional cavopulmonary anastomosis (see Fig. 129-1), or this may already be in place. For cardiopulmonary bypass, a venous cannula is placed low down on the inferior vena cava and a further cannula high up in the superior vena cava near the junction with the innominate vein. The ascending aorta is cannulated. The operation is performed using moderate hypothermia. Any existing systemic to pulmonary artery shunts are taken down. The aorta is cross-clamped, and cold blood cardioplegia is infused. A needle vent is placed in the ascending aorta. The main pulmonary artery is transected. To prevent bleeding or aneurysm formation after closure of the proximal pulmonary artery stump, the suture line is reinforced with two small Teflon felt strips and the pulmonary valve leaflets are included in the suture line. The distal main pulmonary artery is closed, taking care not to distort or narrow the branch pulmonary arteries. **A**, The right atrium is opened along the crest of the septum. The atrial septal defect is enlarged if necessary, and the size of the intra-atrial baffle is measured between the eustachian valve (EV) and crista terminalis (CT). **B**, Future site of baffle between the superior vena cava and inferior vena cava. **C**, A Gore-Tex tube of at least 16-mm diameter is cut to size and opened longitudinally, and if required, a 4- to 5-mm fenestration is cut. **D** and **E**, The prosthetic baffle is sewn halfway around the junction of the inferior vena cava with the right atrium, along the posterior wall of the atrial septum, along the CT, and halfway around the junction with the superior vena cava. Care is taken to avoid injury to the sinus node. **F**, The cardiac end of the transected superior vena cava is anastomosed in an end-to-side manner with the undersurface of the right pulmonary artery.

anastomosed to the right ventricle with the aid of an autologous pericardial patch.⁹⁰ It soon became apparent that neither valves nor the rudimentary right ventricle needed to be incorporated into the Fontan connection, so the Fontan procedure evolved into a direct atriopulmonary connection with closure of the atrial communication for tricuspid atresia.

Lateral Tunnel Fontan (Total Cavopulmonary Connection)

Studies in hydrodynamic models by de Leval and colleagues revealed that the atriopulmonary connection performed poorly in terms of flow energetics because of turbulence that was further exaggerated by pulsation.⁹¹ In contrast, a cavopulmonary connection had mainly laminar flow patterns. In this design, the superior vena cava blood drains directly into the pulmonary artery, and inferior vena cava blood is baffled through a straight intra-atrial

conduit to the pulmonary artery (Fig. 129-2). Additional theoretical advantages are a reduced risk of thrombosis because of less blood stasis and exposure of only a limited portion of the right atrium to high venous pressures, thus reducing the risk of arrhythmias. In addition, because the coronary sinus remains in the lower pressure pulmonary venous atrium, myocardial venous drainage is unobstructed. This introduction of total cavopulmonary connection, coupled with an intermediate stage of a bidirectional Glenn anastomosis²⁶ or a hemi-Fontan procedure,²⁸ greatly improved clinical results with the Fontan procedure.⁷⁴

Fontan Fenestration

Another important clinical improvement was the creation of a fenestration in the Fontan baffle,⁹² which allows systemic venous blood to shunt to the pulmonary venous atrium, achieving better preload for the systemic

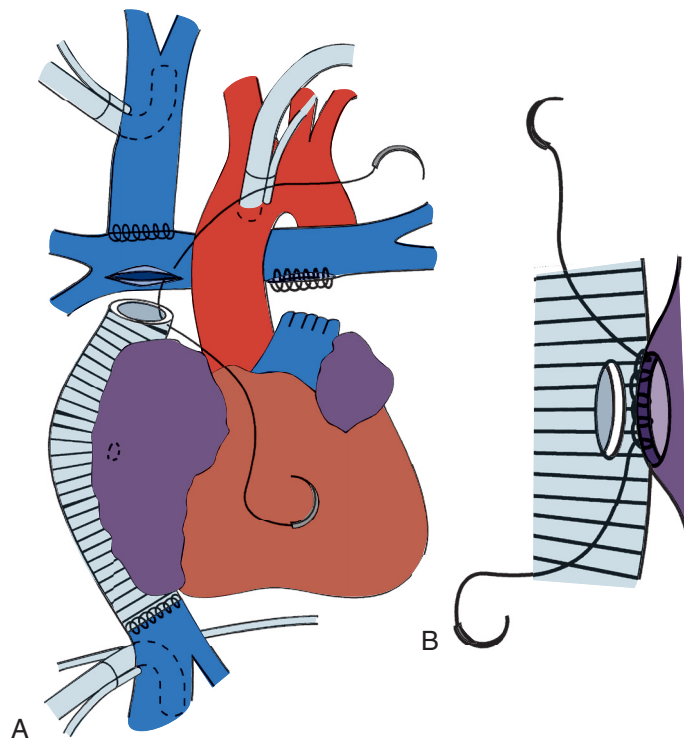


FIGURE 129-3 ■ Construction of extracardiac Fontan on cardiopulmonary bypass. Cannulation for cardiopulmonary bypass is as described for the lateral tunnel Fontan operation (see Fig. 129-2). It is particularly important that the inferior vena cava is cannulated low down. Any systemic to pulmonary artery shunts are taken down. Transection and closure of the main pulmonary artery can be facilitated by a short period of cardioplegic arrest. A needle vent is placed in the ascending aorta. The space between the right lower pulmonary vein and the inferior vena cava is dissected. The cannula in the inferior vena cava is snared, and a clamp is placed across the cavoatrial junction, taking care to avoid occluding the coronary sinus. **A**, The cavopulmonary junction is transected on the clamp, and the cardiac end is oversewn. A Gore-Tex tube of at least 16-mm diameter (22-mm diameter in adults) is anastomosed in an end-to-end manner to the transected inferior vena cava. The conduit is gently curved around the atrium toward the right pulmonary artery. The cavopulmonary shunt is temporarily occluded, and the inferior surface of the right pulmonary artery is incised. The top end of the prosthesis is anastomosed in an end-to-side manner to the pulmonary artery. If a fenestration is required, a side-biting clamp is placed on the free wall of the right atrium and a further clamp opposite on the prosthesis. A 5-mm fenestration is cut in the prosthesis, and a slightly larger hole is cut in the opposite right atrial wall. **B**, To avoid obstruction of the fenestration by atrial tissue, the anastomotic suture line is placed a few millimeters away from the hole in the prosthesis.

ventricle at the cost of some systemic arterial desaturation. Thus, cardiac output is maintained and systemic venous pressure is reduced. The fenestration can be closed later by a transcatheter approach. A retrospective study by Bridges and associates showed a significant decrease in pleural effusions and hospital stay compared with nonfenestrated patients.⁹³ Consequently, the fenestrated Fontan circuit has become the procedure of choice for the high-risk population.

Baffle fenestration remains controversial in standard-risk patients, with a number of retrospective studies showing no benefit from fenestration,^{61,94,95} whereas other studies showed a decreased rate of Fontan failure and lower incidence of significant pleural effusions.⁹⁶ A prospective randomized trial by Lemler and colleagues showed improved clinical outcome with less pleural drainage, shorter hospital stay, and less need for additional postoperative procedures in patients with a fenestration.⁹⁷ Fontan fenestration has also been shown to have a beneficial effect on late outcome.⁹⁸

Apart from those patients in whom low saturations are a clinical indication for closure of the fenestration, it is not known whether fenestrations should be closed and,

if so, when. A quarter or more of fenestrations will close spontaneously.⁹⁶ The remainder can be relatively easily occluded by catheter intervention. A follow-up of patients with a mean of 3.4 years following device closure showed improved oxygen saturation with an average increase of 9.4%, reduced need for anticongestive treatment, and improved somatic growth. However, 12% of patients developed new arrhythmias.⁹⁹

Lateral Tunnel versus Extracardiac Conduit

Another modification in the design of the Fontan pathway involves the use of an extracardiac interposition graft between the transected inferior vena cava and pulmonary artery (Fig. 129-3).¹⁰⁰ The extracardiac conduit initially was designed to avoid pulmonary and systemic venous obstruction in patients with a small atrium. Its use has the additional advantage that it avoids extensive atrial suture lines that are potentially arrhythmogenic. Thrombogenicity and lack of growth of the prosthetic conduit remain potential late problems.

The hemodynamic superiority of cavopulmonary connections with total right heart bypass over atriopulmonary connections is generally accepted, and most surgeons now create some form of cavopulmonary connection with complete exclusion of the right heart. The lateral tunnel Fontan optimizes flow dynamics in the pulmonary artery, leaves the coronary sinus in the low pressure atrium, and has a low risk of damage to the atrioventricular node. The same advantages can be attributed to the extracardiac Fontan procedure. Computational flow dynamics show no significant differences in energetics or geometry between the two types of cavopulmonary connections, with the cross-sectional area of the pulmonary arteries having a far more significant impact on hemodynamics than the type of Fontan connection.^{101,102} The extracardiac Fontan procedure has the additional advantage that no intra-atrial access is required and thus can be done without aortic cross-clamping and, in suitable cases, also without the use of cardiopulmonary bypass.¹⁰³⁻¹⁰⁶

A theoretical advantage of the extracardiac Fontan operation over the lateral tunnel Fontan is thought to be the absence of arrhythmogenic suture lines, but bradyarrhythmias have been observed with the extracardiac Fontan.¹⁰⁷ Although some reports have shown more postoperative arrhythmias with the lateral tunnel Fontan,^{108,109} other studies have shown no difference in postoperative arrhythmias comparing the two surgical techniques.^{48,110,111} One study from the Medical University of South Carolina found an increased incidence of sinus node dysfunction in a contemporaneous extracardiac group.¹¹²

Drawbacks of the extracardiac Fontan operation include the thrombogenicity of the prosthetic conduit and lack of conduit growth, in particular with the current tendency for surgery in small children. At the age of 2 to 4 years and body weight of 12 to 15 kg, the inferior vena cava diameter and inferior vena cava to pulmonary artery distance are approximately 60% to 80% of adult values. Oversizing the conduit may be tempting, but this has been shown to result in unfavorable Fontan hemodynamics and conduit thrombosis.¹¹³ Intermediate follow-up of about 3 years of children with an extracardiac Fontan has shown an average reduction in conduit cross-sectional area of 14%.¹¹⁴ Clearly, these extracardiac conduits need careful observation over time.

Nonoperative Fontan

The concept of completing the Fontan procedure in the cardiac catheterization laboratory was introduced with promising results from studies with laboratory animals¹¹⁵ and children.^{46,47} This technique requires modification of the operative technique for the bidirectional Glenn anastomosis or the hemi-Fontan procedure to allow for the percutaneous seating of a covered stent as an intra-atrial conduit. Although this procedure currently uses experimental stents and innovative techniques, it is promising and bears careful study and follow-up.

Fontan for Biventricular Hearts

Certain cardiac defects with two well-formed ventricles are better served with a Fontan procedure than with a

high-risk biventricular repair. A typical group of patients have double-outlet right ventricle with a remote ventricular septal defect or a straddling atrioventricular valve, which would make a biventricular repair problematic. Results with the Fontan procedure in these patients are good.^{67,116,117} Other anatomic substrates in which the Fontan procedure might be more desirable than a biventricular repair are congenitally corrected transposition of the great arteries (with difficult anatomy for a double-switch procedure) or unbalanced atrioventricular septal defects.

OUTCOME AFTER THE FONTAN PROCEDURE

Early Mortality and Morbidity

Approximately 40 years after the introduction of the Fontan operation, the early mortality after the Fontan procedure, which historically was in excess of 20%,¹¹⁸ has steadily come down to less than 5%.^{112,119-122} This is in spite of liberalizing the original patient selection criteria and extending the procedure to many forms of complex single ventricle. Multiple factors have contributed to this improved early outcome. Certainly, volume unloading of the single ventricle by an early bidirectional cavopulmonary anastomosis or a hemi-Fontan procedure has markedly improved the suitability for a subsequent Fontan operation,^{21,28,29,74} although some physicians argue that staging with an intermediate bidirectional cavopulmonary anastomosis is unnecessary.⁹⁵ The introduction of the total cavopulmonary connection with its more energy-efficient circulation, with the use of either a lateral tunnel⁹¹ or an extracardiac conduit,¹²³ has clearly been a huge advance in the improved outcome of the Fontan operation. Other factors potentially responsible for the improvement in the early results with the Fontan operation (identified by some but disputed by others) are the use of an atrial fenestration^{61,94,96,97} and preoperative occlusion of aortopulmonary collaterals.^{75,78,81}

Patients with a single ventricle and heterotaxy syndrome always have been a particularly high-risk population for the Fontan procedure because of multiple associated cardiovascular abnormalities, including variable anatomy of the sinus node and conduction system, potential for pulmonary venous obstruction, and atrioventricular valve regurgitation. Some reports have shown improved outcomes with these patients after the Fontan procedure, although early mortality and the incidence of postoperative rhythm disturbances and atrioventricular valve regurgitation are higher in the heterotaxy patients compared with the nonheterotaxy patients.^{18,63,65,66}

Pleural and pericardial effusions constitute the most common early morbidity after the Fontan operation. Prolonged chest tube drainage has been associated with longer cardiopulmonary bypass times.^{109,121} It is interesting to note that effusions are reduced in patients having Fontan completion without cardiopulmonary bypass¹⁰³ or nonoperative Fontan completion by catheter techniques.⁴⁷ The use of a baffle fenestration has been reported

to reduce the duration of postoperative chest tube drainage.^{96,97}

Sinus node dysfunction and atrial arrhythmias occur frequently after the Fontan procedure, particularly in patients with heterotaxy syndrome.¹⁸ It has been proposed that an extracardiac conduit will result in fewer atrial arrhythmias compared with a lateral tunnel Fontan procedure. Although some authors have found this to be true,^{108,109} others have found no difference in arrhythmias comparing the two techniques,^{110,111} and there is even one report of a higher incidence of sinus node dysfunction with the extracardiac Fontan.¹¹²

The incidence of early Fontan takedown is generally 1% to 3% in many series and is thought to be related to improper patient selection or to unrecognized or unrecognized anatomic problems, such as outflow tract obstruction or pulmonary or systemic venous pathway obstruction.^{61,98,119,122} Although Fontan takedown has a high mortality, some of these patients can be candidates for a subsequent successful Fontan after correction of underlying treatable abnormalities.¹²⁴

An uncommon but serious complication after the Fontan procedure is hemidiaphragmatic paralysis as a result of phrenic nerve injury. Patients with a paralyzed hemidiaphragm have longer hospital stays and a higher incidence of prolonged pleural effusions and ascites.^{125,126} There is evidence that subdiaphragmatic venous hemodynamics are abnormal, even after diaphragm plication.¹²⁷

Late Outcomes

With improving operative survival, late outcome after the Fontan operation is becoming increasingly important. In 1990, 2 decades after the introduction of the procedure, Fontan reported that the “Fontan state” was associated with a premature decline in functional status and survival.¹¹⁸ Even when atriopulmonary and atrioventricular Fontan procedures were performed under perfect conditions, there was a gradual attrition with a predicted survival of 86%, 81%, and 73% at 5, 10, and 15 years, respectively, after the operation. More current series with follow-up of patients undergoing total cavopulmonary connection show overall actuarial survival of 91% at 10 years with the lateral tunnel Fontan¹²² and 93.6% at 10 years¹²⁸ and 85% at 15 years¹²⁹ with the extracardiac Fontan. A study from Children’s Hospital Boston showed that for operative survivors, there was no difference in freedom from death or transplantation after 20 years between patients with an atriopulmonary connection and those with a total cavopulmonary connection.¹³⁰

In addition to ongoing late mortality with the Fontan operation, these survivors have impairment of exercise function. In a large multicenter study examining 546 patients, despite a normal ejection fraction in 73% of patients, only 28% had a normal diastolic grade.⁷⁴ Peak oxygen consumption on exercise was only 65% of normal for age; this finding has been corroborated by others.^{131,132} It is worrisome that age-adjusted exercise capacity tended to worsen with age.^{74,133}

The exact reasons for the late attrition after the Fontan operation are unknown but no doubt are complex and multifactorial. Serial angiographic measurement of

pulmonary artery size in Fontan patients shows that pulmonary artery growth lags behind somatic growth¹³⁴ or even fails to grow at all, resulting in a decreasing pulmonary artery index with time.¹³⁵ A correlation can be made between low pulmonary artery index and length of follow-up as well as with an unfavorable outcome.¹³⁵

Atrial Arrhythmias

With the widespread adoption of the total cavopulmonary connection (either lateral tunnel or extracardiac Fontan) rather than atriopulmonary connections, the incidence of late atrial arrhythmias and the need for pacemakers have greatly diminished.^{122,128} Patients with the older atriopulmonary connection are more prone to significant atrial arrhythmias (see [Fontan Conversion](#) section for a discussion on management of these patients). Children with heterotaxy syndrome remain at risk for late arrhythmias after the Fontan operation, even with the newer total cavopulmonary connection techniques.^{18,65,66}

Venovenous Collaterals

After the Fontan operation, significant venovenous collateral channels can develop, which result in significant right-to-left shunting with resultant hypoxemia and cyanosis. These abnormal venous channels can be between the systemic veins and the pulmonary veins or pulmonary venous atrium. Once recognized, they can usually be interrupted by interventional catheterization techniques and less commonly require surgical intervention.^{136,137} In patients with progressive cyanosis after the Fontan operation, an aggressive search for collateral vessels should be made using cardiac catheterization and angiography followed by interruption of significant collateral channels.

Thromboembolism and Prophylactic Anticoagulation

Thromboembolic complications occur both early and late after the Fontan procedure. The true incidence of thromboembolism is not known, but various studies have shown an incidence of “silent” intracardiac thrombus ranging from 9% to 33%,^{107,138-140} with a higher rate found when transesophageal echocardiography is used. Cerebrovascular events, including thromboembolic strokes, occur in 2% to 9% of Fontan patients.^{141,142} The presence of a fenestration may increase this risk,¹⁴² whereas the use of aspirin may ameliorate it.¹⁴¹ Many factors contribute to the risk for thrombus formation, including suboptimal flow patterns, arrhythmias, cyanosis, presence of foreign material in the circulation, pre-existent coagulopathies, and liver dysfunction.

Information on the prevention of thromboembolic complications after the Fontan procedure is inconsistent. Some centers recommend aspirin alone as prophylaxis,^{143,144} whereas others recommend anticoagulation with warfarin.^{140,145} It is well known that anticoagulant therapy is not without risk. Anticoagulant-related bleeding is a cause for concern, particularly in active children. In the presence of cyanosis or heart failure, anticoagulation control can be difficult. Reviews of the

need for and type of anticoagulation after the Fontan operation have emphasized the lack of a uniform consensus and have underscored the need for prospective clinical studies.¹⁴⁶⁻¹⁴⁸

Protein-Losing Enteropathy

Protein-losing enteropathy is a relatively rare but debilitating complication with a reported incidence of up to 15%. The condition involves the loss of protein within the gastrointestinal tract and can occur from weeks to years after the Fontan operation, with 50% mortality at 5 years following diagnosis.¹⁴⁹ The precise reasons for its occurrence are not known, but it has been suggested that it may be related to abnormal mesenteric blood flow.¹⁵⁰ Clinical manifestations are related to the degree of hypoproteinemia; the nonselective loss of proteins can result in peripheral edema, ascites and effusions, immunodeficiency, and coagulopathy. A detailed investigation of the cardiovascular system should take place and hemodynamics optimized if possible. Symptomatic treatment is with diuretics, diet supplements, and intermittent albumin infusions. Steroids¹⁵¹ and heparin therapy¹⁵² have been shown to improve symptoms and to reduce protein loss in some patients. It is postulated that they act through stabilizing the intestinal mucosal membrane, thus reducing the protein leak. Other treatment modalities that have shown some success are sildenafil use,¹⁵³ atrial pacing,¹⁵⁴ and creation of a surgical fenestration.¹⁵⁵ Ultimately, patients with protein-losing enteropathy may require cardiac transplantation with expected resolution of the enteropathy.¹⁵⁶

Plastic Bronchitis

Plastic bronchitis is another poorly understood and unusual complication after the Fontan procedure. Non-inflammatory mucin-containing casts are formed in the trachea and bronchus. Symptomatic treatment is by bronchoscopic clearance. Small series and case reports have advocated different treatment options, including Fontan baffle fenestration,¹⁵⁷ thoracic duct ligation,¹⁵⁸ and aerosolized tissue plasminogen activator.^{159,160}

MANAGEMENT OF THE FAILING FONTAN

Even with current improvements in surgical strategies for management of children with a single ventricle, there continues to be a seemingly irreducible incidence of late failure, defined as Fontan takedown, need for transplantation, or death.^{29,119,120} Preservation of ventricular function is of paramount importance for successful long-term outcome in patients with univentricular hearts.⁶¹ Methods to preserve ventricular function include volume unloading of the heart with a bidirectional cavopulmonary anastomosis at an early age,²⁹ aggressive relief of systemic ventricular outflow tract obstruction to prevent myocardial hypertrophy and diastolic noncompliance, and repair of atrioventricular valve regurgitation. Although not universally accepted, elimination of systemic to pulmonary

collateral blood flow can help preserve ventricular function as well.⁷⁵ Sometimes dysfunction of the Fontan circulation may be related to atrial arrhythmias or conduction abnormalities, which may respond to conventional pacing techniques^{161,162} or resynchronization pacing.¹⁶³

Fontan Conversion

Conversion of the failing classical atriopulmonary Fontan with refractory arrhythmias to a total cavopulmonary connection with concomitant arrhythmia surgery and correction of hemodynamically significant lesions was introduced by Mavroudis and colleagues in 1998.¹⁶⁴ The operation consists of defined cryoablation lesion sets in the atrium, repair of residual defects such as atrioventricular valve regurgitation, conversion to an extracardiac Fontan connection, and pacemaker placement. An update of their Fontan conversion series in 111 patients¹⁶⁵ reported 1 early death, 6 late deaths, and 6 subsequent transplants, with good rhythm control in over 85% of patients. Other centers have reported similarly good results with this challenging group of patients with low mortality rates and good rhythm control.^{100,166} Conversion to a total cavopulmonary connection with either a lateral tunnel approach or an extracardiac conduit appear equally efficacious.^{167,168}

Heart Transplantation

For patients with a failing Fontan in whom heart failure is the dominant feature or with protein-losing enteropathy refractory to more conventional therapies, cardiac transplantation offers the only solution. Although some series have reported early mortality with transplantation in patients with Fontan procedures in excess of 50%,^{169,170} others have reported 1-year survival rates ranging from 71% to 86%.^{15,156,171,172} Importantly, hospital survivors show uniform resolution of protein-losing enteropathy after transplantation.^{156,171} Of course, there is an incidence of death on the waiting list before heart transplantation¹⁵⁶ as well as the need for chronic immunosuppression and concerns for post-transplant infection, rejection, and late graft failure.

Mechanical Circulatory Support

Mechanical support of the failing Fontan is problematic because of the single functional ventricle. Case reports have described the use of the Berlin Heart as a successful bridge to transplant as a left ventricular assist device (systemic ventricular apical cannulation for pump inflow with ascending aortic cannulation for pump outflow)¹⁷³ and as a "right ventricular" assist device (Fontan systemic venous pathway cannulation for pump inflow with pulmonary artery cannulation for pump outflow).¹⁷⁴ Designs for indwelling axial flow pumps for support of the failing Fontan circulation as a bridge to recovery or as a bridge to transplant have also been tested.^{175,176} Because of the ongoing shortage of suitable donor hearts for transplantation and the seemingly inevitable incidence of Fontan failure with time, it is hoped that mechanical devices will be designed and tested in the future to successfully

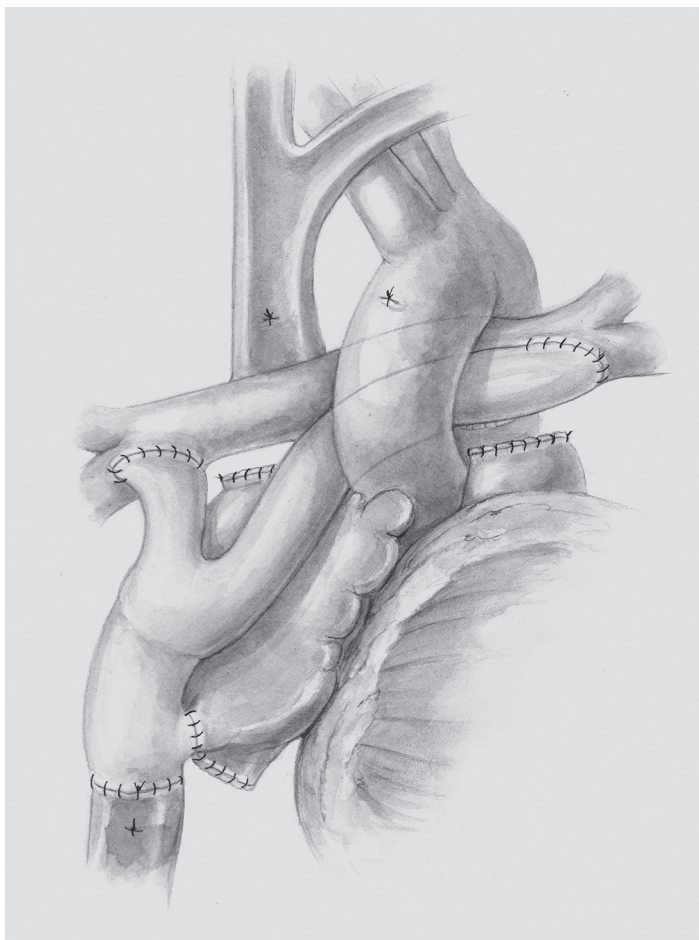


FIGURE 129-4 ■ A completed Y-graft Fontan is shown, emphasizing the importance of anastomosing the right and left limbs of the Y-graft away from the Glenn anastomosis. The fenestration to the right atrium is also depicted.

support the patient with a failing Fontan circulation indefinitely, without the need for transplantation.

COMPUTER MODELING TO OPTIMIZE FONTAN ENERGETICS

Computational fluid dynamics¹⁷⁷ have demonstrated designs of the total cavopulmonary connection that can cause flow disturbances and energy dissipation. Optimizing flow and diminishing power loss in the Fontan circuit presumably can improve hemodynamic efficiency and potentially improve long-term outcomes. In vitro and computational fluid dynamics studies have shown reduced energy losses with caval offset¹⁷⁸ and with flaring of the cavopulmonary anastomosis,¹⁷⁹ thus prompting modification of the total cavopulmonary connection surgical procedure.

Using computational fluid dynamics, an optimized total cavopulmonary connection using a bifurcated Y-graft for the superior vena cava to pulmonary artery connection and another bifurcated Y-graft for the inferior vena cava to pulmonary artery connection was proposed¹⁸⁰ (U.S. Patent No. 7811244). Although this “Optiflo” connection had superior flow characteristics predicted by

flow modeling, the optimized design from a surgical standpoint was cumbersome. Subsequent studies developing surgical designs to balance hepatic blood flow distribution to the right and left pulmonary arteries in children with acquired pulmonary AVMs showed favorable results with a bifurcated Y-graft connection from the inferior vena cava to the branch pulmonary arteries.¹⁸¹ Comparison of the Y-graft Fontan connection with more conventional Fontan connections using computational fluid dynamics have demonstrated improved flow characteristics, reduced energy losses, and balanced hepatic flow distribution to the pulmonary arteries.^{182,183} Based on these improvements in flow dynamics predicted by computerized modeling, the Y-graft Fontan concept has been used clinically¹⁸⁴⁻¹⁸⁷ (Fig. 129-4).

A novel computer-based surgical planning framework that enables one to virtually perform multiple surgical scenarios and determine the one that will yield the best hemodynamic performance before even entering the operating room has been proposed.¹⁸⁸ Such a surgical planning platform offers a unique solution for cases in which hemodynamics (and in particular hepatic flow distribution) are vital to the operation but in which the small patient population and large number of anatomic variations pose a severe obstacle to the establishment of surgical guidelines from clinical studies alone.

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EBSTEIN MALFORMATION

Sameh M. Said • Joseph A. Dearani

CHAPTER OUTLINE

HISTORICAL ASPECTS**PATHOLOGIC ANATOMY**

Tricuspid Valve

Right Ventricle

Associated Cardiac Defects

CLASSIFICATIONS OF EBSTEIN MALFORMATION**GENETIC FACTORS****PATHOPHYSIOLOGY****CLINICAL PRESENTATIONS**

Symptoms

Cyanosis and Heart Failure

Exertional Dyspnea, Fatigue, Cyanosis, and Palpitations

Palpitations

Paradoxical Embolization

Physical Examination

DIAGNOSTIC WORK-UP

Chest Radiography

Electrocardiography

Echocardiography

Cardiac Catheterization

Magnetic Resonance Imaging

NATURAL HISTORY**MANAGEMENT**

Neonates and Infants

Indications for Operation

Children and Adults

Indications for Operation

Operative Management

POSTOPERATIVE CARE**OUTCOMES****HISTORICAL ASPECTS**

In an 1866 report titled “Concerning a very rare case of insufficiency of the tricuspid valve caused by a congenital malformation,” Dr. Wilhelm Ebstein (1836-1912), a German physician, described the unusual cardiac findings of a 19-year-old laborer who died of cyanotic heart disease. He accurately described the characteristic anatomic and hemodynamic abnormalities of Ebstein malformation¹ (Fig. 130-1). By 1950, only three case reports of Ebstein malformation had been published.

PATHOLOGIC ANATOMY

Ebstein malformation of the tricuspid valve (TV) is characterized by² (Fig. 130-2):

1. Failure of delamination of the septal, inferior, and anterior leaflets of the TV with subsequent adherence of the leaflets to the underlying myocardium
2. Apical displacement of the functional TV annulus (septal>inferior>anterior)
3. Dilation of the atrialized portion of the right ventricle (RV)

4. Anterior leaflet fenestrations, redundancy or tethering
5. Dilation of the true anatomic TV annulus³

Tricuspid Valve

There is a highly variable TV morphology; the valve is almost always incompetent, and rarely stenotic. The anterior leaflet is usually large and is attached to the annulus; however, it may contain several fenestrations⁴ (Fig. 130-3) and have various points of incomplete delamination. The chordae tendineae may be short and poorly formed.

The inferior and septal leaflet development is variable and most often rudimentary and may even be absent due to failure of the delamination process. The leading edges may be freely mobile with chordal or papillary muscular support, or they may be tethered (adherent) to the endocardium (linear attachment). The point of maximal displacement is at the commissure between the inferior and septal leaflets. In normal hearts, the downward displacement of the septal and posterior leaflets in relation to the anterior mitral valve leaflet is less than 8 mm/m² body surface area. The spectrum of abnormality in Ebstein

malformation can range from only minimal displacement of the septal and inferior leaflets to an imperforate membrane or muscular shelf between the inlet and trabecular zones of the RV. The range of variability is infinite, and the most important pathologic finding is “failure of delamination” of the leaflets. There often is marked dilation of the true TV annulus, which is not displaced, and a large chamber separating the true annulus from the functional RV is the “atrialized” portion of the RV (aRV).

Right Ventricle

The RV is divided into two regions: the area involved with the malformation (i.e., the inlet portion or the aRV)

that is functionally integrated with the right atrium (RA), and the area that is not involved by the malformation and consists of the other two components of the RV—the trabecular and outlet portions, which constitute the functional RV. The “atrialized” portion of the RV can become disproportionately dilated and may account for more than half of the RV volume. The majority ($>2/3$) of hearts with Ebstein malformation have RV dilation. Dilation often involves not only the atrialized inlet portion of the RV but also the functional RV apex and outflow tract. In some cases, RV dilation is so marked that the ventricular septum is deviated leftward, compressing the left ventricular (LV) chamber. In such cases, the short-axis view demonstrates a circular RV and a D-shaped LV.

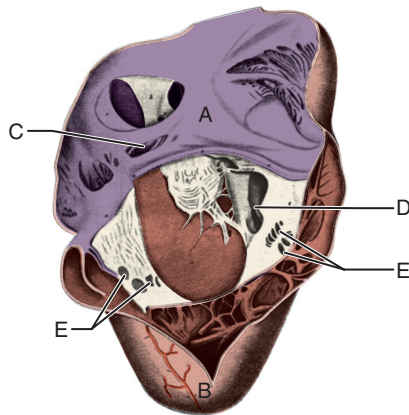


FIGURE 130-1 ■ Figure from the original Ebstein anomaly case report. The right atrium and right ventricle are shown opened along the right border beginning at the superior vena cava. A, Right atrium; B, right ventricle; C, rudimentary septal leaflet of tricuspid valve with its chordae tendineae, which insert on the endocardium of the ventricular septum; D, opening through which one can get into the right conus arteriosus, and in the opposite direction, one can get into the sac that is formed by membrane; E, fenestrations seen in the tricuspid leaflets. (From Said SM, Dearani JA: Ebstein anomaly, congenital tricuspid valve regurgitation and dysplasia. In Allen HD, Driscolle DJ, Shaddy RE, Feltes TF, editors: *Moss and Adams' heart disease in infants, children, and adolescents*, ed 8, Philadelphia, 2013, Lippincott Williams & Wilkins, Figure 39-1.)

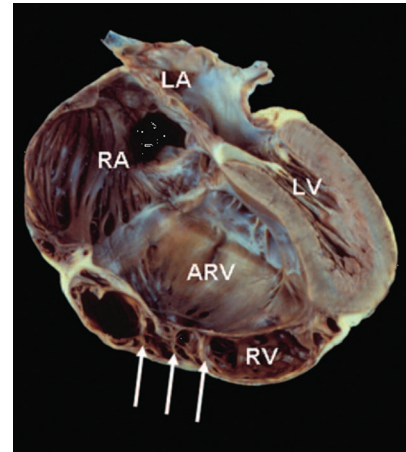


FIGURE 130-2 ■ Severe Ebstein malformation of tricuspid valve (four-chamber view) showing marked downward displacement of shelflike posterior leaflet with attachment to underlying free wall by numerous muscular stumps (arrows), markedly dilated atrialized portion of right ventricle (ARV), small functional portion of right ventricle (RV), leftward bowing of ventricular septum, and marked dilation of right atrium (RA). LA, Left atrium; LV, left ventricle. (From Said SM, Dearani JA: Ebstein anomaly, congenital tricuspid valve regurgitation and dysplasia. In Allen HD, Driscolle DJ, Shaddy RE, Feltes TF, editors: *Moss and Adams' heart disease in infants, children, and adolescents*, ed 8, Philadelphia, 2013, Lippincott Williams & Wilkins, Figure 39-5.)

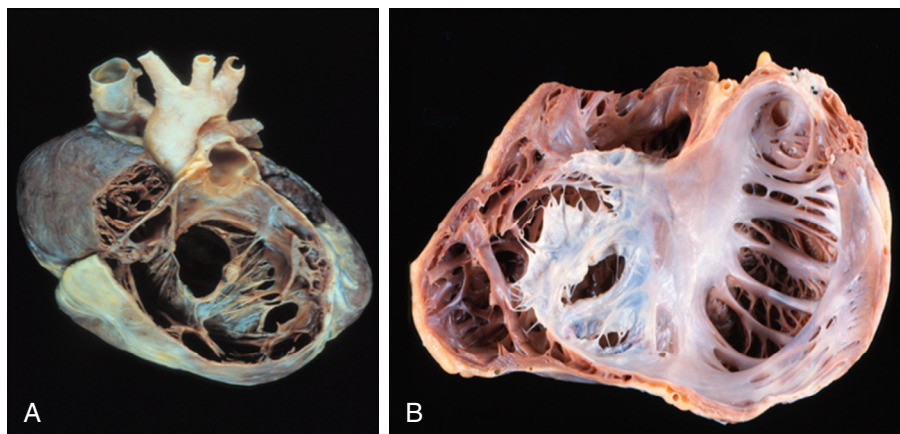


FIGURE 130-3 ■ A and B, Ebstein heart: marked fenestrations and tethering of the tricuspid valve anterior leaflet. (From Said SM, Dearani JA: Ebstein anomaly, congenital tricuspid valve regurgitation and dysplasia. In Allen HD, Driscolle DJ, Shaddy RE, Feltes TF, editors: *Moss and Adams' heart disease in infants, children, and adolescents*, ed 8, Philadelphia, 2013, Lippincott Williams & Wilkins, Figure 39-2.)

Associated Cardiac Defects

The most common associated cardiac defects include^{5,6}:

- Atrial septal defect (ASD): either patent foramen ovale or an ASD, mostly secundum, is present in 80% to 94% of the patients
- Ventricular septal defect with or without pulmonary atresia
- RV outflow tract obstruction: this can occur secondary to structural abnormalities (pulmonary valve stenosis or pulmonary atresia), branch pulmonary artery stenosis, and rarely the displaced TV
- Patent ductus arteriosus
- Coarctation of the aorta
- Accessory conduction pathways (Wolff-Parkinson-White [WPW] syndrome) are present in up to 15% to 20% of patients and may predispose patients to arrhythmias. The majority of these pathways are located around the orifice of the malformed TV.
- Left-sided lesions (uncommon)
 - Mitral valve prolapse
 - Accessory mitral valve tissue
 - Subaortic stenosis
 - Bicuspid or atretic aortic valve
 - Muscle bands in the LV cavity
 - Myocardial changes resembling LV non-compaction⁷
- Congenitally corrected transposition of the great arteries (cc-TGA): In patients with cc-TGA, an abnormal systemic atrioventricular valve (morphologic TV) that fulfills the criteria of Ebstein valve is present in 15% to 50% of cases. This Ebsteinoid displacement of the TV into the morphologic RV is different from the classic right-sided Ebstein malformation in that there is usually lack of atrialization of the RV free wall.⁸

CLASSIFICATIONS OF EBSTEIN MALFORMATION

Several classifications have been proposed for Ebstein malformation. In general, classification systems of Ebstein

malformation are difficult since there are infinite variations in the anatomy and no two hearts are alike.

Carpentier in 1988 proposed the following⁹:

Type A: the volume of the true RV is adequate

Type B: a large atrialized component of the RV exists, but the anterior leaflet of the TV moves freely

Type C: severe restriction of the anterior leaflet movement that can cause significant RV outflow tract obstruction

Type D: near complete atrialization of the ventricle except for a small infundibular component

Another classification proposed four types of Ebstein malformation based on valve analysis during surgery.¹⁰

This is our preferred approach, which is to describe the exact anatomy of each of the involved structures of the heart as visualized at the time of surgery (Table 130-1).

This includes comment about the extent of failure of delamination of each leaflet, status of the leading edges of the leaflets, degree of displacement of the septal leaflet, description of the aRV, and size of the RA and RV.

GENETIC FACTORS

Genetic factors in Ebstein malformation are heterogeneous. Most cases are sporadic and familial Ebstein is rare. Rare cases of cardiac transcription factor NKX2.5 mutations, 10p13-p14 deletion, and 1p34.3-p36.11 deletion have been described in association with Ebstein malformation.^{11,12} The results of a mutational analysis in a cohort of 141 unrelated probands with Ebstein malformation has been reported;¹³ eight were found to have a mutation in the gene *MYH7*, and six of the eight patients also had LV noncompaction. This result may warrant genetic testing and family evaluation in this subset of patients.

PATHOPHYSIOLOGY

The functional impairment of the RV and the incompetence of the deformed TV retard forward flow of blood through the right side of the heart into the lungs.

TABLE 130-1 Types of Ebstein Valve Based on the Anatomic Findings during Surgery

Type	Anterior Leaflet		Posterior Leaflet	Septal Leaflet	Atrialized RV Chamber Size
	Size	Mobility			
I	Larger	Mobile	Apically displaced, dysplastic, or absent		Varies from relatively small to large
II	Relatively small and displaced in a spiral fashion toward the apex		Displaced, dysplastic, and usually not reconstructible		Moderately large
III					
IV	Severely deformed; displaced into the RVOT; few or no chordae; direct insertion of the papillary muscles into the leading edge of the valve is common		Typically dysplastic or absent	Represented by a ridge of fibrous material descending apically from the membranous septum	Nearly the entire RV cavity is atrialized; TV tissue is displaced into the RVOT and may cause obstruction of blood flow (functional tricuspid stenosis)

RV, Right ventricle; RVOT, right ventricular outflow tract; TV, tricuspid valve.

Moreover, during contraction of the atrium, the atrialized portion of the RV (which is adjacent to and in continuity with the RA) balloons out (if very thin) or acts as a passive reservoir, thus decreasing the volume to be ejected. During ventricular systole, the atrialized RV contracts, creating a pressure wave that impedes venous filling of the RA, which is in the diastolic phase. In most cases, there is a communication between the left and right atria, resulting from either patency of the foramen ovale or a distinct secundum ASD. The shunt of blood through the septal opening is generally from right to left, but may be bidirectional in some patients. The overall effect of these structural abnormalities on the RA is to produce gross dilation, which may reach enormous proportions, even in infants. This dilation leads to further incompetence of the TV and further widening of the interatrial communication.¹⁴

As a consequence of atrial dilation, atrial tachyarrhythmias are common and become more likely as time goes on. In addition, approximately 15% of patients will have one or more accessory conduction pathways associated with WPW syndrome, and 1% to 2% of patients will have atrioventricular nodal reentrant tachycardia (AVNRT).^{15,16} In end-stage heart failure, ventricular arrhythmias can be present.

CLINICAL PRESENTATIONS

Clinical presentations vary widely, because they depend on the anatomic severity and can range from a severely symptomatic neonate to an asymptomatic octogenarian.¹⁷

The most common presentation varies with age at presentation¹⁸:

- Fetuses: an abnormal routine prenatal scan (86%)
- Neonates: cyanosis (74%)
- Infants: heart failure (43%)
- Children: an incidental murmur (63%)
- Adolescents and adults: arrhythmia (42%), decreased exercise tolerance, fatigue, or right-sided heart failure

Symptoms

Cyanosis and Heart Failure

- Secondary to significant tricuspid regurgitation
- Can appear soon after birth, because of high pulmonary vascular resistance
- Often improves as pulmonary vascular resistance decreases

Exertional Dyspnea, Fatigue, Cyanosis, and Palpitations

- Can occur at a later age
- Can recur and can be insidious in onset

Palpitations

- Secondary to atrial tachyarrhythmia (atrial flutter and fibrillation most common)

- May be present in 20% to 30% of cases
- Some of these arrhythmias are due to WPW syndrome

Paradoxical Embolization

- In the presence of an interatrial communication, patients with Ebstein malformation are at risk for paradoxical embolization, brain abscesses, and sudden death.

Physical Examination

Findings vary with the severity of pathology and the magnitude of right-to-left interatrial shunting.¹⁹

- Murmur and click; commonly mistaken for mitral valve prolapse
- Cyanosis
 - Can be severe in infants
 - Usually milder in older children
 - Digital clubbing will depend on the degree and duration of cyanosis
- Prominent “a” wave in the distended jugular veins
- Hepatomegaly
 - Represents passive hepatic congestion resulting from tricuspid regurgitation and elevated RA pressure
 - Becomes pulsatile because of systolic expansion of the liver
- Palpable, prominent diffuse apical impulse
- Systolic thrill at the left lower sternal border
- Widely split first and second heart sounds, resulting from right bundle branch block
- Prominent S3 or a loud S4 give the impression of multiple heart sounds (triple or quadruple gallop)
- Systolic murmur
 - Secondary to tricuspid regurgitation
 - Increases in intensity with inspiration and may be associated with a mid-diastolic murmur owing to high diastolic flow volume across the tricuspid annulus
 - Can be extremely soft or absent in adults because the low velocity of to-and-fro flow and rapid equalization of pressure across the TV does not result in blood flow turbulence
- Jugular venous pulse rarely showing a large V wave despite severe regurgitation of the TV because the large RA engulfs the increased volume

DIAGNOSTIC WORK-UP

Chest Radiography

The cardiac silhouette varies from almost normal to a markedly enlarged globe-shaped heart with a narrow waist similar to that seen with pericardial effusion (Fig. 130-4). The vascular pedicle is narrow because the pulmonary trunk is not border forming and the ascending aorta, with rare exception, is often small and inconspicuous or absent. Symptomatic neonates can have massive

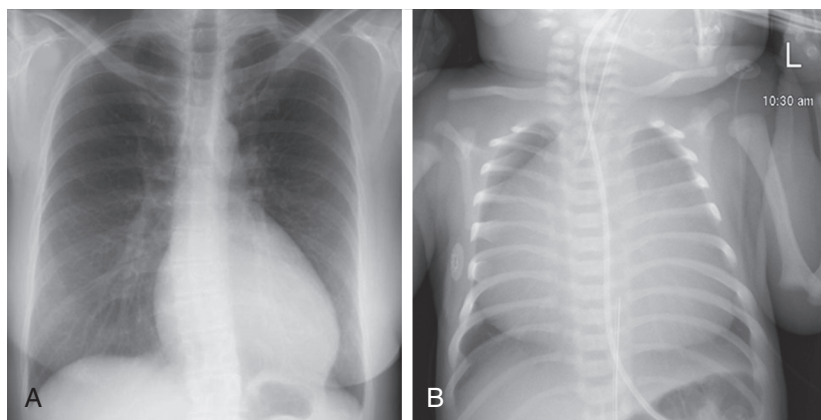


FIGURE 130-4 ■ **A**, Chest radiograph of a patient with Ebstein malformation with severe tricuspid regurgitation and a small atrial septal defect before tricuspid valve surgery. **B**, Cardiomegaly, a narrow waist, and a cardiothoracic ratio of 0.56 in a neonate with Ebstein malformation showing massive cardiomegaly (“wall-to-wall” heart). (From Said SM, Dearani JA: Ebstein anomaly, congenital tricuspid valve regurgitation and dysplasia. In Allen HD, Driscolle DJ, Shaddy RE, Feltes TF, editors: *Moss and Adams’ heart disease in infants, children, and adolescents*, ed 8, Philadelphia, 2013, Lippincott Williams & Wilkins, Figures 39-11 and 39-12.)

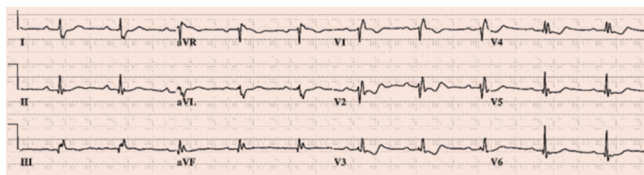


FIGURE 130-5 ■ Electrocardiogram of a patient with severe Ebstein malformation showing the typical changes, with prolongation of the PR interval (226 ms), right bundle-branch block, and somewhat bizarre configuration of the QRS complex. (From Said SM, Dearani JA: Ebstein anomaly, congenital tricuspid valve regurgitation and dysplasia. In Allen HD, Driscolle DJ, Shaddy RE, Feltes TF, editors: *Moss and Adams’ heart disease in infants, children, and adolescents*, ed 8, Philadelphia, 2013, Lippincott Williams & Wilkins, Figure 39-13.)

heart size and outcome is poor if the cardiothoracic ratio is greater than 0.65.

The most consistent and dramatic feature is the enlarged RA silhouette; this is seldom normal, even if the cardiac silhouette is otherwise normal. Lung fields may be normal or decreased because of hypoplasia from severe cardiomegaly (often seen in neonates).

Electrocardiography

Ebstein malformation can be diagnosed using the electrocardiogram, which is rarely normal even with a mild malformation (Fig. 130-5).

The major electrophysiologic changes include the following²⁰:

- Intra-atrial conduction disturbance including PR interval prolongation and tall P waves
- Right bundle branch block
- WPW preexcitation
- Supraventricular tachycardia
- Atrial flutter or fibrillation
- Arrhythmogenic atrialized RV
- Deep Q waves in leads V1–4 and in inferior leads

Complete heart block is rare, but first-degree heart block occurs in 42% of patients because of RA enlargement and the structural abnormalities of the atrioventricular (AV) conduction system.

The AV node may be compressed but is in the normal location. Apical displacement of the septal leaflet is associated with discontinuity of the central fibrous body and the septal AV ring with direct muscular connections,

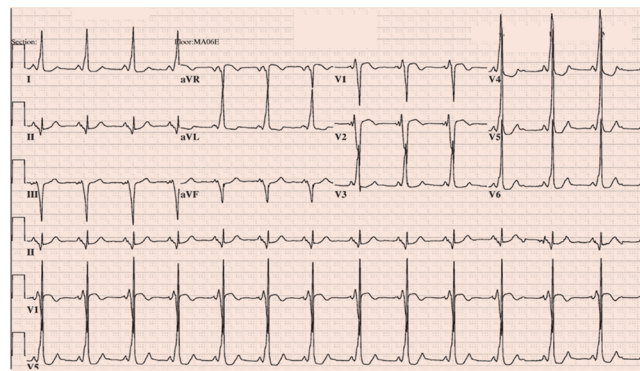


FIGURE 130-6 ■ Electrocardiogram of a patient with severe Ebstein malformation, showing sinus rhythm with preexcitation (Wolf-Parkinson-White syndrome). A delta wave is noted in the ascending limb of the QRS complex. (From Said SM, Dearani JA: Ebstein anomaly, congenital tricuspid valve regurgitation and dysplasia. In Allen HD, Driscolle DJ, Shaddy RE, Feltes TF, editors: *Moss and Adams’ heart disease in infants, children, and adolescents*, ed 8, Philadelphia, 2013, Lippincott Williams & Wilkins, Figure 39-14.)

creating a substrate for accessory pathways and preexcitation (Fig. 130-6).

More than one accessory pathway is present in 6% to 36% of cases; most of them are located around the orifice of the malformed TV. In addition, wide QRS tachycardia over a septal accessory AV pathway, ventricular tachycardia, as well as ectopic atrial tachycardia, atrial flutter, and atrial fibrillation, can occur.

Echocardiography

Two-dimensional echocardiography is the diagnostic test of choice (Fig. 130-7). More recently, three-dimensional echocardiography is also being used as an adjunct for additional details about TV anatomy. It accurately evaluates the TV and the size and function of different cardiac chambers.

Apical displacement of the septal leaflet by at least 8 mm/m² body surface area is considered a diagnostic feature of Ebstein malformation. The presence of at least three accessory attachments of the leaflet to the ventricular wall confirms leaflet tethering that causes restricted motion of the leaflet.²¹ Marked enlargement of the RA and atrialized RV is present. When the combined area of the RA and atrialized RV is larger than the combined area of the functional RV, left atrium (LA), and LV in the

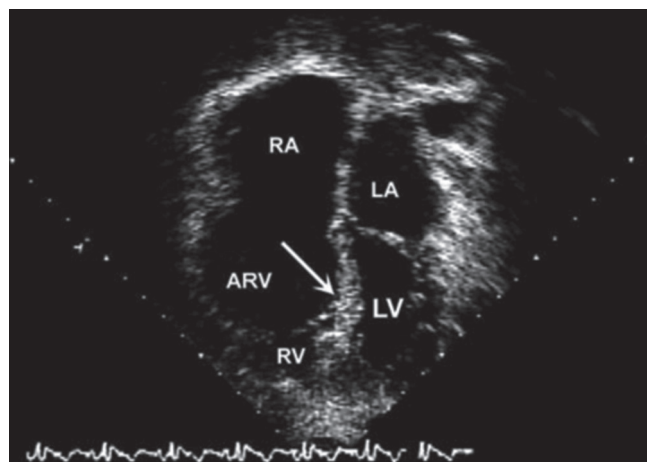


FIGURE 130-7 ■ Example of an echocardiogram (four-chamber view, apex down) of a patient with severe Ebstein malformation showing a grossly displaced septal leaflet (arrow). The anterior leaflet is severely tethered (“failure of delamination”) and nearly immobile. The atrialized right ventricle (ARV) is large and the functional right ventricle (RV) is small. LA, Left atrium; LV, left ventricle; RA, right atrium. (From Said SM, Dearani JA: Ebstein anomaly, congenital tricuspid valve regurgitation and dysplasia. In Allen HD, Driscoll DJ, Shaddy RE, Feltes TF, editors: *Moss and Adams’ heart disease in infants, children, and adolescents*, ed 8, Philadelphia, 2013, Lippincott Williams & Wilkins, Figure 39-15.)

apical four-chamber view at end diastole, the risk of mortality is increased.

Echocardiography allows assessment of the site and degree of TV regurgitation and the feasibility of valve repair. Ebstein malformation can be diagnosed in utero using fetal echocardiography in as early as the eighteenth week of pregnancy.²² Fetal echocardiography remains a challenge because of the small size of the heart, and it may be difficult to distinguish Ebstein malformation from pulmonary atresia or other causes of TR. Important features that can be determined echocardiographically and that can predict outcome in neonates with Ebstein malformation include the patency of the RV outflow tract and the Great Ormond Street echocardiography (GOSE) score.²³ The GOSE score, as described by Celermajer and colleagues,²³ is calculated in the four-chamber view to create a ratio of the combined areas of the RA and atrialized RV compared with the functional RV, LA, and the LV areas (Fig. 130-8). Patients with the most severe GOSE score (grades 3 and 4) have a poor prognosis (Table 130-2).

Cardiac Catheterization

Cardiac catheterization is rarely necessary, apart from preoperative coronary angiography in older patients. Pulmonary artery pressures are usually normal, although the RV end-diastolic pressure may be elevated. Despite severe TV regurgitation, the RA pressure may be normal, especially with marked RA dilation. Hemodynamic catheterization can also be performed in certain situations when there is LV dysfunction or when there is suspicion of elevated pulmonary artery pressure or elevated LV end-diastolic pressure. This is particularly important if a bidirectional cavopulmonary anastomosis is being considered.

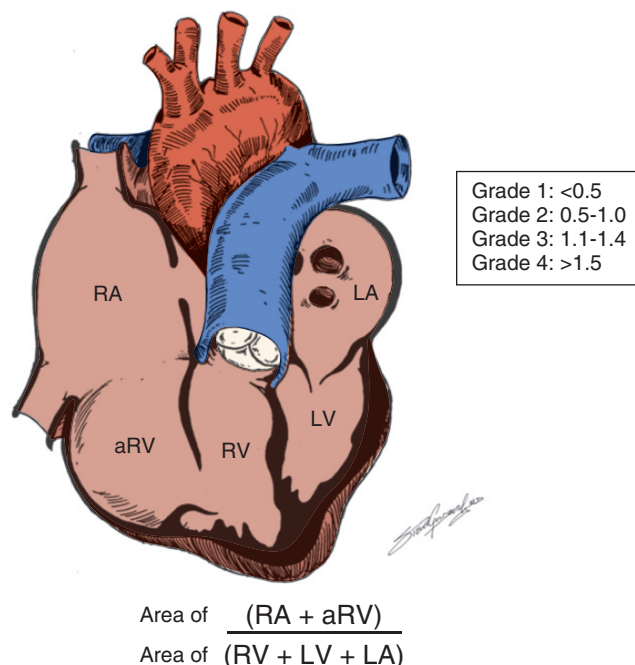


FIGURE 130-8 ■ Great Ormond Street echocardiography (GOSE) score. aRV, Atrialized RV; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Knott-Craig CJ, Goldberg SP: Management of neonatal Ebstein’s anomaly. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 112–116, 2007, Figure 1.)

TABLE 130-2 Mortality Risk by GOSE Score

GOSE score*	Ratio	Mortality
1-2	<1.0	8%
3 (acyanotic)	1.1-1.4	10% early, 45% late
3 (cyanotic)	1.1-1.4	100%
4	>1.5	100%

*GOSE 1, <0.5; GOSE 2, 0.5-1.0; GOSE 3, 1.1-1.4; GOSE 4, >1.5. GOSE, Great Ormond Street echocardiography.

Magnetic Resonance Imaging

Recently, cardiac magnetic resonance imaging has emerged as another tool for evaluation of patients with Ebstein malformation. It provides quantitative measurement of RA and RV size and systolic function, even in the presence of significant distortion of RV anatomy²⁴ (Fig. 130-9). It also provides additional imaging of TV anatomy.

Axial imaging provides a more reliable analysis of disease severity, such as the atrialized RV volume. The ability to create three-dimensional images may provide greater delineation of disease severity. In general, echocardiographic imaging provides detailed valve anatomy and cardiac magnetic resonance imaging provides detailed ventricular anatomy.

NATURAL HISTORY

The prognosis of Ebstein malformation when diagnosed prenatally is poor. In a study of fetuses with Ebstein

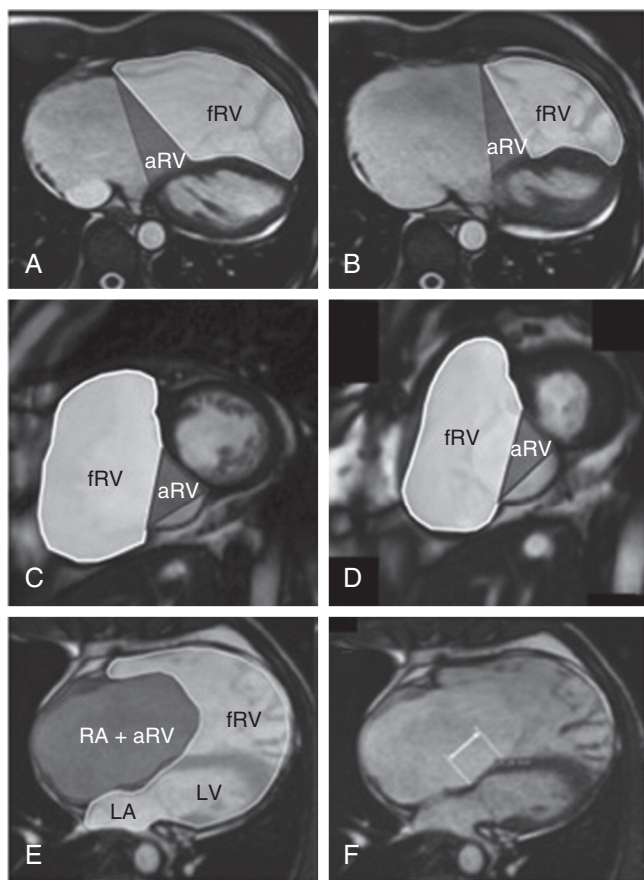


FIGURE 130-9 ■ Cardiac magnetic resonance imaging showing systolic and diastolic contours of functional right ventricle and atrialized portion of the right ventricle in (A and B) axial and (C and D) short-axis views. E, Severity index representing the ratio of areas of the right atrium and atrialized right ventricle in numerator and summation of functional right ventricle and left atrium and left ventricular areas in denominator (i.e., Severity index = [Right atrial area + Atrialized right ventricular area] / [Functional right ventricular area + Left atrial area + Left ventricular area]). F, Degree of apical displacement of septal leaflet of tricuspid valve (in millimeters) measured in ventricular diastole. aRV, Atrialized right ventricle; fRV, functional right ventricle; LA, left atrium; LV, left ventricle; RA, right atrium. (A-D from Yalonetsky S, Tobler D, Greutmann M, et al: Cardiac magnetic resonance imaging and the assessment of Ebstein anomaly in adults. *Am J Cardiol* 107:767-773, 2011, Figure 2.)

malformation or TV dysplasia from Children's Hospital Boston, eight (24% of 33) pregnancies were terminated, nine (27%) fetuses died in utero, and 16 (49%) fetuses survived to birth. Only seven (21% of 33) prenatally diagnosed patients survived beyond the neonatal period.²⁵ Survival was related to the severity of Ebstein malformation and the presence of RV or LV dysfunction. Elective early delivery may be needed in fetuses that exhibit signs of distress.

It is not uncommon for Ebstein malformation to be undiagnosed until adulthood. The oldest patient in the Mayo surgical series was 79 years old at time of diagnosis and subsequent surgery. However, late diagnosis is also associated with reduced survival. The mean age of diagnosis in a study of the natural history of 72 unoperated patients was 23.9 ± 10.4 years. In this group of patients,

arrhythmias were the most common clinical presentation (51%).²⁶ The estimated cumulative overall survival rates were 89%, 76%, 53%, and 41% at 1, 10, 15, and 20 years of follow-up, respectively. Predictors of cardiac-related death on univariate analysis included (1) cardiothoracic ratio of 0.65 or greater, (2) increasing severity of TV displacement on echocardiography, (3) New York Heart Association (NYHA) class III or IV, (4) cyanosis, (5) severe TR, and (6) younger age at diagnosis. However, in a multivariate model, younger age at diagnosis, male sex, cardiothoracic ratio of 0.65 or greater, and the severity of TV leaflet displacement on echocardiography were predictors of late cardiac mortality.

MANAGEMENT

Neonates and Infants

Indications for Operation

In neonates or infants who remain in congestive heart failure or are profoundly cyanotic, operative therapy is required. In the newborn period, three pathways can be considered: the biventricular repair (Knott-Craig approach),²⁷ single-ventricle repair (i.e., RV exclusion technique, or Starnes approach), and cardiac transplantation.

Biventricular Repair (Knott-Craig Approach). In this approach, the TV is repaired and the ASD is partially closed. This is a monocusp type of valve repair based on a satisfactory anterior leaflet.²⁸ The subtotal closure of the ASD allows right-to-left shunting, which may be necessary in the early postoperative period when there is a high risk of RV dysfunction or elevated pulmonary vascular resistance. RA reduction is performed routinely and is important to reduce the size of the markedly enlarged heart to allow room for the lungs (Fig. 130-10).

The postoperative care of a newborn after a biventricular repair can be challenging. Delayed sternal closure is used liberally. Tolerance of early low peripheral oxygenation is common, and inhaled nitric oxide may be necessary to decrease pulmonary vascular resistance. Prophylactic use of a peritoneal dialysis catheter can also be used to ensure complete decompression of the abdomen.

Although early mortality for this operation is high (25%-30%), the intermediate outcome with the biventricular approach appears to be promising. In 2007, Knott-Craig and colleagues²⁹ published their experience with 27 neonates and young infants. These patients had concomitant anatomic or functional pulmonary atresia ($n = 18$), ventricular septal defect ($n = 3$), small LV ($n = 3$), and hypoplastic branch pulmonary arteries ($n = 3$). Twenty-five patients received a biventricular repair, with TV repair in twenty-three and valve replacement in two. Survival to hospital dismissal was 74%; risk was greater when there was anatomic pulmonary atresia. There were no late deaths (median follow-up, 5.4 years; maximum, 12 years). All patients were in functional NYHA class I. Although these early results for repair of Ebstein malformation during the neonatal period are poor compared with many other neonatal anomalies corrected in the first

FIGURE 130-10 ■ Biventricular repair of neonatal Ebstein (Knott-Craig). **A**, Partition of the tricuspid valve orifice into two openings by approximation of the annuloplasty stitch. **B**, Once the valve is judged to be competent, the “caudal” orifice is closed, thereby plicating the atrialized portion of the right ventricle. **C**, Creation of a competent monocuspid valve by taking down the anterior leaflet from the annulus, fenestrating it, and augmenting it with a pericardial patch. **D**, The atrial septal defect (ASD) is closed with a fenestrated patch, and an annuloplasty stitch is placed with one pledgeted end in the coronary sinus and the other pledgeted end at the location of the commissure between anterior and posterior leaflets. (From Knott-Craig CJ, Goldberg SP: Management of neonatal Ebstein’s anomaly. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 112–116, 2007, Figures 4, 5, and 6.)

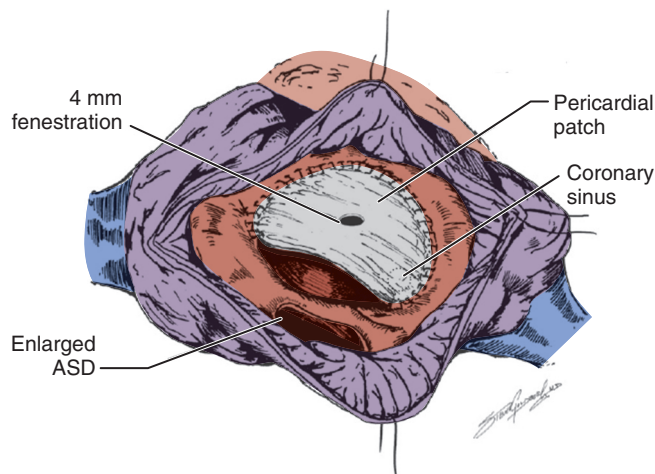
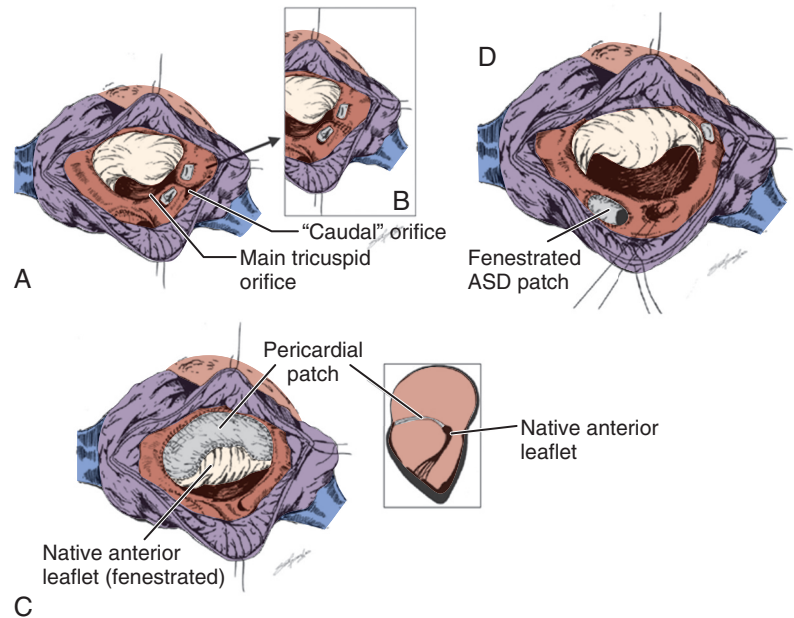


FIGURE 130-11 ■ Starnes repair of neonatal Ebstein malformation. ASD, Atrial septal defect. (From Knott-Craig CJ, Goldberg SP: Management of neonatal Ebstein’s anomaly. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 112–116, 2007, Figure 2.)

month of life (e.g., arterial switch procedure, Norwood stage I), they have become a benchmark for this difficult patient population.

Right Ventricular Exclusion (Starnes Approach).

Alternatively, the RV exclusion approach, pioneered by Starnes and colleagues,³⁰ involves fenestrated patch closure of the TV orifice, enlarging the interatrial connection, and placing a systemic-to-pulmonary artery shunt (Fig. 130-11). This approach is particularly appealing in patients who also have anatomic pulmonary atresia or other important RV outflow tract obstruction. A small fenestration (using a 4- to 5-mm punch) is placed in the TV patch to allow RV decompression as it passively fills with blood from the thebesian veins.³¹ This also allows progressive involution of the enlarged dysfunctional RV, which is helpful in the long term when preparing for the

eventual Fontan procedure.³² In patients who have a patent RV outflow tract, a competent pulmonary valve is required to prevent blood from entering the RV, resulting in RV distention. If patients have an incompetent pulmonary valve, the main pulmonary artery should be ligated or the incompetent pulmonary valve should be closed. These issues must be considered because significant dilation of a poorly functioning RV eventually results in compression and impairment of LV function. Similar to the biventricular approach, RA reduction is routinely performed to allow space for the lungs.

Modified Starnes Approach (Total Ventricular Exclusion). A modification to the Starnes single-ventricle approach, total RV exclusion, has been advocated by Sano and associates,³³ in which the free wall of the RV is resected and closed primarily or with a polytetrafluoroethylene patch. This procedure acts like a large RV plication and RV volume reduction procedure (Fig. 130-12). This adaptation of the Starnes method may improve LV filling and provide additional space for the lungs and decompression of the LV.

Postoperative care is similar to that of any shunt-palliated patient with a univentricular heart. Optimizing systemic perfusion and obtaining adequate oxygenation is the primary goal. Delayed sternal closure and peritoneal drainage are also beneficial. As with other patients with a shunt-dependent pulmonary circulation, careful surveillance is required between the first operation and the second-stage procedure (bidirectional cavopulmonary shunt), which is usually performed at 3 to 6 months of age.

Results of the single-ventricle pathway have been reported by Reemtsen and colleagues.³⁴ Of 16 neonates, two patients had TV repair, one patient had heart transplant, 10 patients had a RV exclusion procedure with a fenestrated TV patch, and three patients had a RV exclusion procedure with a nonfenestrated TV patch. The

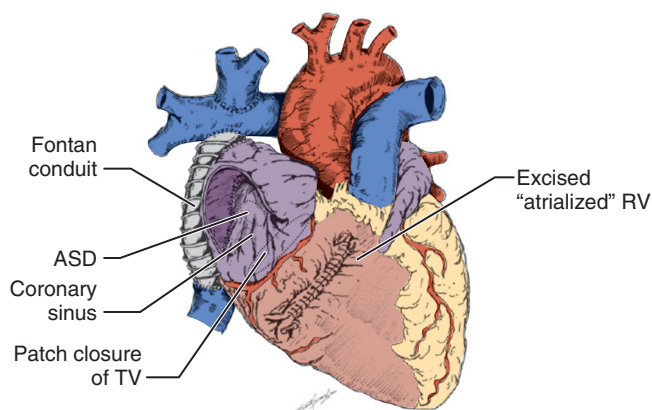


FIGURE 130-12 ■ Sano "RV exclusion" procedure. ASD, Atrial septal defect; RV, right ventricle; TV, tricuspid valve. (From Knott-Craig CJ, Goldberg SP: Management of neonatal Ebstein's anomaly. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 112–116, 2007, Figure 3.)

operative survival was 80% (8 of 10) in patients with a fenestration, and 33% in patients with no fenestration, leading the authors to recommend fenestration of the TV patch. Among the nine hospital survivors of RV exclusion, three underwent completion of the Fontan, and all nine have had a successful bidirectional cavopulmonary shunt (second stage).

Heart Transplantation. Heart transplantation remains an option in the most severe cases of Ebstein malformation, but it is rarely necessary in the current era because of the improved results with the Knott-Craig and Starnes approaches. Limitations of heart transplantation include the scarcity of donor organs in the neonatal age group and the side effects of long-term immunosuppression and its associated complications in the transplant recipient. Finally, the development of smaller ventricular assist devices and advances in extracorporeal membrane oxygenation has provided mechanical support options in the perioperative period for these infants.

Children and Adults

Indications for Operation

Although medical management, including diuretics and antiarrhythmic drugs, can be used to manage some of the symptoms of heart failure and arrhythmias, eventually most patients require operation. Observation alone is usually advised for asymptomatic patients with no right-to-left shunting, mild cardiomegaly, and normal exercise tolerance. Most patients in NYHA class I or II can be managed medically. Operation is offered when symptoms are present (fatigue most common), increasing cyanosis becomes evident, or if paradoxical embolism occurs. Operation is also advised if there is objective evidence of deterioration, such as decreasing exercise performance by exercise testing, progressive increase in heart size on chest radiography, progressive RV dilation or reduction of systolic RV function by echocardiography, or appearance of atrial or ventricular arrhythmias. In borderline situations, the echocardiographic determination of high

probability of TV repair makes the decision to proceed with operation easier. In our practice, we advise operation between 2 and 5 years of age because of our ability to successfully perform an anatomic (cone-type) repair in 95% to 98% of children. Once symptoms develop and patients progress to NYHA class III or IV, medical management has little to offer; operation then becomes the only chance for improvement.

A biventricular repair is possible for the vast majority of patients. In some circumstances, a 1.5-ventricle repair (adding a bidirectional cavopulmonary shunt) is advantageous when there is significant RV dilation or dysfunction, or if the resultant TV repair has a small effective orifice (uncommon). The bidirectional cavopulmonary shunt can also reduce hemodynamic stress on a more complex TV repair, because the volume of the RV is decreased by 35% to 45%, depending on the patient's age. Cardiac transplantation is rarely indicated and is reserved for patients with severe biventricular dysfunction.

Operative Management

Our operative management of patients with Ebstein malformation consists of (1) closure of any atrial septal communications (except during infancy); (2) correction of associated anomalies (e.g., closure of ventricular septal defect); (3) performance of any indicated antiarrhythmia procedures, such as the maze procedure (cryoablation or radiofrequency ablation), surgical division of accessory conduction pathways, or cryoablation of AVNRT; (4) internal plication (apex to base) of the atrialized portion of the RV; (5) repair of the TV; and (6) right reduction atrioplasty. In the current era, intraoperative electrophysiologic mapping for localization of accessory conduction pathways in patients with ventricular preexcitation is rarely required. When preexcitation is present, preoperative mapping and ablation is performed in the catheterization laboratory. Intraoperative transesophageal echocardiography is used routinely.

Anatomic Cone Repair. Anatomic variability of EM continues to be a challenge for the surgeon since the earliest repair techniques in 1958.^{35,36} Most repair techniques address the abnormal TV in a manner that focuses on the concept of monocusp repair.³⁷ Monocusp repair depends on an adequate anterior leaflet with a freely mobile leading edge that allows coaptation with the ventricular septum. Significant degrees of RV or annular dilation or significant tethering of the anterior leaflet can preclude a successful monocusp repair.

The early Mayo Clinic experience focused on the Danielson monocusp repair, and the use of the Sebens stitch (suture attachment of the anterior papillary muscle to the ventricular septum) was common. The French experience (Carpentier)³⁸ focused on mobilization (surgical delamination) of the anterior leaflet with annular reattachment, resulting in an anterior leaflet monocusp repair. The Brazilian experience (da Silva) was an extension of the French technique. The difference was surgical delamination of all available leaflet tissue, with approximated circumferential leaflets anchored at the true annulus resulting in a "cone" of leaflet tissue. The

Brazilian experience with cone repair in 52 patients has been reported.^{39,40} Mean age was 18.5 ± 13.8 years, and mean follow-up was 57 ± 45 months. There were two early deaths (3.8%) and two late deaths. The Brazilian group also reported an increase in the indexed RV functional area in the early preoperative period; however, that remained unchanged at intermediate follow-up. The reduction of TR was maintained at intermediate follow-up.

Operation for EM is performed through sternotomy using cardiopulmonary bypass, aortic and bicaval cannulation with cross-clamping, and cold blood

cardioplegia. The principle of cone repair (CR) is complete surgical delamination and recruitment of all undelaminated leaflet tissue, which is reanchored at the true right AV junction, creating a 360-degree "leaflet cone." Leaflet-to-leaflet approximation is generally done with interrupted monofilament sutures to avoid a pursestring effect that can decrease the height of the reconstructed leaflet (Fig. 130-13). The atrialized, inferior RV (i.e., smooth and not trabeculated) is plicated internally from "apex to annulus." The plication typically crosses the true annulus to partially reduce the size of the dilated annulus (Fig. 130-14). Care is taken to avoid distortion or

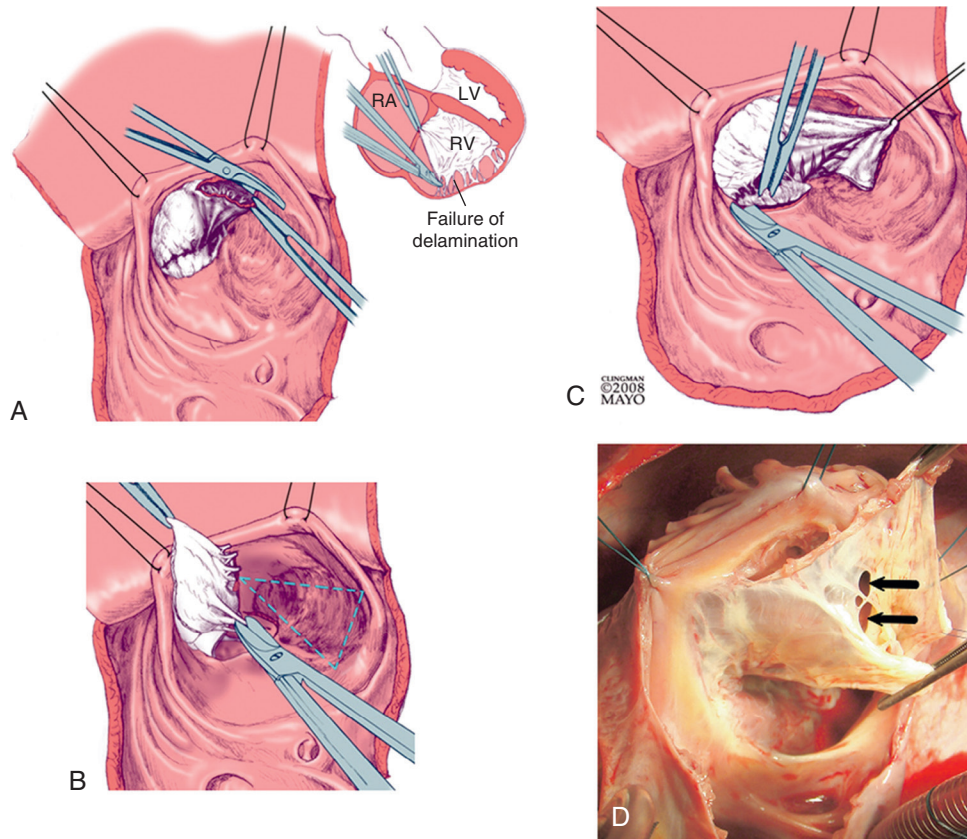


FIGURE 130-13 ■ Operative steps for the da Silva technique for Ebstein anomaly repair. **A**, The first incision is made with a no. 15 blade in the anterior leaflet at the twelve-o'clock position; the incision is a few millimeters away from the true annulus. The incision is then extended rightward in a clockwise fashion using a scissors. It is common for there to be a true space between the anterior leaflet and the right ventricle in this region (i.e., normally delaminated leaflet). However, when the transition is met between the anterior and inferior (posterior) leaflets, it is common for there to be failure of delamination (*inset*) resulting in fibrous and muscular attachments between the leaflet and myocardium. The diagram demonstrates the scissors approaching the area where there is some adherence of leaflet tissue to the underlying myocardium. Dissection continues such that a portion of distal anterior leaflet and some inferior leaflet tissue is surgically delaminated. The most important aspect of this surgical delamination is to incise all fibrous and muscular attachments between the body of the leaflet and the right ventricular myocardium, but to maintain intact all fibrous (and occasionally muscular) attachments of the leading edge of the leaflet to the underlying myocardium. Importantly, do not disrupt chordal attachments to the leading edge of any leaflet. **B**, As the anterior and surgically delaminated inferior leaflet is reflected away from the right ventricular myocardium, all fibrous and muscular attachments into the body of the underside of the leaflet are incised as shown with the scissors. It is important to keep all attachments of the leading edge of the leaflet intact. If the edge is linearly attached, then surgical fenestrations are created as depicted earlier. The *dotted triangle* represents the atrialized right ventricle. **C**, Dissection is continued with a scissors, with the goal of taking down all attachments between the septal leaflet and myocardium but preserving all attachments of the leading edge to the endocardium as described above. The dissection should proceed medially to the antero-septal commissure. The leaflet tissue is typically fragile and thin in this area. There can be marked variability in the status of the leading edge of the septal leaflet, as was described for the anterior and inferior leaflets. If there is a linear attachment, then surgically created fenestrations are also made in this leaflet (not shown). **D**, The mobilized anterior and inferior (posterior) leaflets. Natural fenestrations are shown at the junction of the anterior and inferior leaflets (*arrows*). LV, Left ventricle; RA, right atrium; RV, right ventricle. (From Said SM, Dearani JA: Ebstein anomaly, congenital tricuspid valve regurgitation and dysplasia. In Allen HD, Driscoll DJ, Shaddy RE, Feltes TF, editors: *Moss and Adams' heart disease in infants, children, and adolescents*, ed 8, Philadelphia, 2013, Lippincott Williams & Wilkins, Figure 39-22AD.)

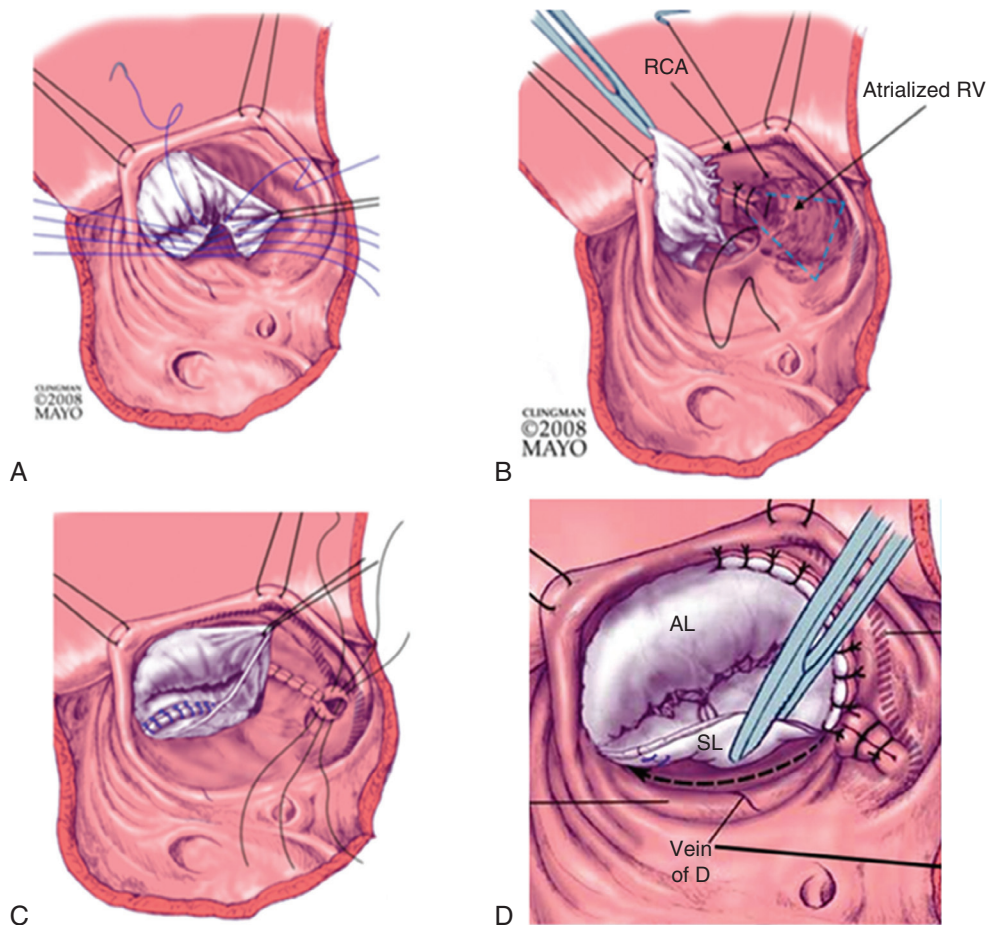


FIGURE 130-14 ■ **A**, After the anterior, inferior, and septal leaflets are completely mobilized, the cut edge of the inferior leaflet is rotated clockwise to meet the proximal edge that has been prepared on the mobilized septal leaflet. The two leaflets are approximated with interrupted fine monofilament sutures completing the cone reconstruction. This results in 360 degrees of leaflet tissue that will compose the new tricuspid valve orifice. **B**, After the cone reconstruction is completed, the atrialized right ventricle (RV) is examined to determine whether plication is necessary. Note the position of the right coronary artery (RCA) in the true tricuspid valve annulus and that the main RCA or the posterior descending coronary artery can be compromised. This figure demonstrates the technique for internal plication of the atrialized right ventricle from apex to base. Monofilament suture is used; the suture is begun distally toward the apex of the right ventricle. It is important to conduct frequent examinations of the outside of the inferior wall of the right ventricle to ensure that inadvertent compromise of the right coronary artery is avoided. **C**, The suture line is advanced toward the base of the heart (i.e., toward the atrioventricular groove). As the dotted lines of the triangle are effectively approximated, the atrialized RV is excluded. The suture line sometimes crosses the atrioventricular groove to reduce the size of the dilated annulus. After the sides of the triangle are approximated, the entrance into the excluded atrialized segment of the right ventricle is then closed to eliminate the “blind pouch.” **D**, After the plication is completed, the newly constructed tricuspid valve is then reattached at the level of the true tricuspid annulus. Because the neotricuspid valve will have an orifice that is smaller than the original dilated atrioventricular junction, a plication of the inferior annulus is usually necessary to meet the size of the smaller neotricuspid valve. Reattachment of the septal leaflet should be done to the ventricular septum and to the ventricular side of the conduction tissue, which is usually marked by a small vein (Vein of D). AL, Anterior leaflet; SL, septal leaflet. (**A**, **C**, and **D** from Said SM, Dearani JA: Ebstein anomaly, congenital tricuspid valve regurgitation and dysplasia. In Allen HD, Driscolle DJ, Shaddy RE, Feltes TF, editors: *Moss and Adams’ heart disease in infants, children, and adolescents*, ed 8, Philadelphia, 2013, Lippincott Williams & Wilkins, Figure 39-22. **B** from Dearani JA, Said SM, O’Leary PW, et al: Anatomic repair of Ebstein’s malformation: lessons learned with cone reconstruction. *Ann Thorac Surg* 95:220–226, discussion 226–228, 2013, Figure 3A.)

compromise of the right coronary artery that is located in the AV groove. Additional inferior annular plication is done as needed to reduce annular size to match the size of the neo-tricuspid valve (neoTV; Fig. 130-15A); this area also requires reinforcement with pledgeted mattress sutures. When there is a marked size discrepancy between the neoTV and true annulus, annular plication is performed at multiple sites around the anterior and inferior annuli to avoid an exaggerated plication in one location that could compromise the right coronary artery (see Fig. 130-15B). Reattachment of the neoTV to the true annulus

is done with interrupted or continuous suture; continuous suture does pursestring the annulus, causing further reduction in annular size, which may be desired when significant annular reduction is needed.

A flexible annuloplasty band—anteroseptal commissure clockwise to inferoseptal commissure with anchoring in the coronary sinus—is used to stabilize the repair as the tricuspid annulus is usually dilated (Fig. 130-16A). The normal adult TV annular size is 20 to 24 mm; the adult ring size is most often a 26- or 28-mm ring. The use of a 26- or 28-mm ring is usually possible in many

FIGURE 130-15 ■ Technique of tricuspid annular plication. This can be performed in a single inferior (**A**) or multiple (**B**) anterior and inferior sites of the annulus. Multiple plication sites help to avoid an exaggerated plication in one location that could compromise the right coronary artery (RCA). (From Dearani JA, Said SM, O'Leary PW, et al: Anatomic repair of Ebstein's malformation: lessons learned with cone reconstruction. *Ann Thorac Surg* 95:220–226, discussion 226–228, 2013, Figure 1AB.)

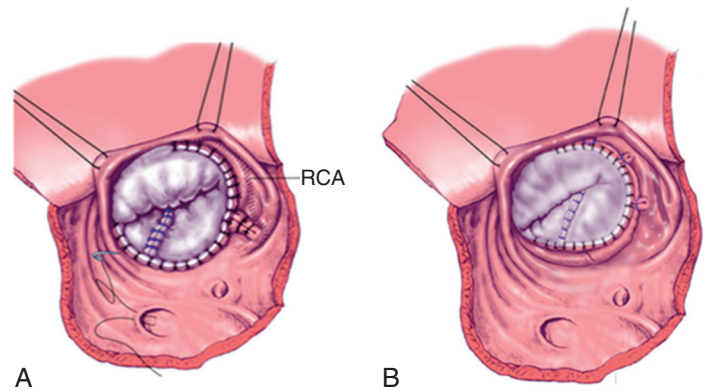


FIGURE 130-16 ■ **A**, The tricuspid annulus is usually dilated, and a flexible annuloplasty ring is typically used when somatic growth is complete. **B**, In younger patients when somatic growth is not complete, an eccentric ring confined to the inferior annulus (anteroinferior to inferoseptal commissures) can be used. RCA, Right coronary artery. (From Dearani JA, Said SM, O'Leary PW, et al: Anatomic repair of Ebstein's malformation: lessons learned with cone reconstruction. *Ann Thorac Surg* 95:220–226, discussion 226–228, 2013, Figure 2AB.)

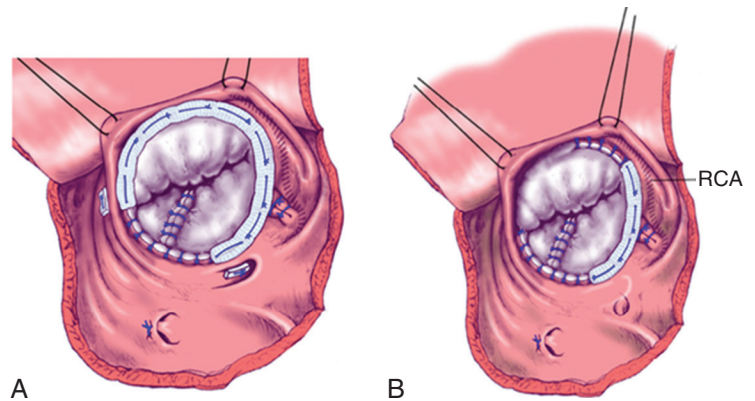
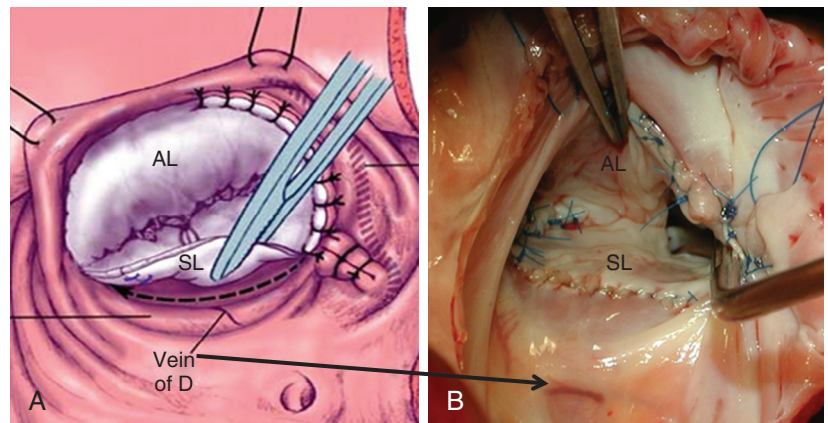


FIGURE 130-17 ■ **A**, Reattachment of the septal leaflet (SL) should be done to the ventricular side of the conduction tissue (dotted line arrow), which is usually marked by a small vein (Vein of D). **B**, Intraoperative photograph showing the reattachment of the completely mobilized tricuspid valve leaflets. AL, Anterior leaflet. (From Dearani JA, Said SM, O'Leary PW, et al: Anatomic repair of Ebstein's malformation: lessons learned with cone reconstruction. *Ann Thorac Surg* 95:220–226, discussion 226–228, 2013, Figure 3AB.)



younger patients (≈ 6 years old) because the starting size of the annulus is often much larger. When somatic growth is a concern, eccentric partial ring support from anteroinferior to inferoseptal commissure (down to coronary sinus) is used, because this is the area most vulnerable to annular dilation (see Fig. 130-16B). The septal leaflet reattachment is performed to the ventricular side of the conduction tissue. All suture lines are done twice for reinforcement. The reanchoring of the neoTV of circumferential leaflet tissue surrounding the tricuspid orifice with its hinge point at the AV groove mimics normal TV anatomy—namely, an anatomic repair (Fig. 130-17).

Adjuncts to Cone Repair. In addition to ring placement, other modifications that we applied selectively to CR to optimize a successful repair include:

1. Leaflet augmentation with Cor Matrix membrane (Cor Matrix Cardiovascular, Santa Cruz, CA) or autologous pericardium to increase leaflet height (Fig. 130-18)
2. Cone augmentation with a small triangular patch to avoid tricuspid stenosis (Fig. 130-19)
3. Leaflet plication to increase leaflet height
4. Surgical fenestrations to create autologous neo-chordae when a linear attachment is present (Fig. 130-20)

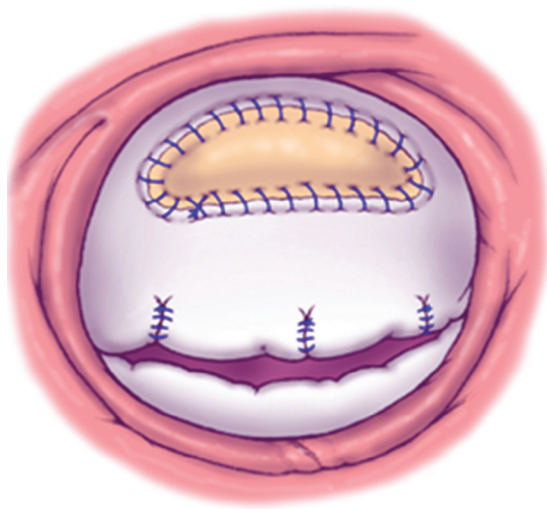


FIGURE 130-18 ■ Tricuspid valve anterior leaflet augmentation can be performed using Cor Matrix membrane or autologous pericardium to increase the leaflet height and to improve surface area coaptation. Several small plications along the annular free edge of the leaflet can also be performed to increase the leaflet height. (From Dearani JA, Said SM, O’Leary PW, et al: Anatomic repair of Ebstein’s malformation: lessons learned with cone reconstruction. *Ann Thorac Surg* 95:220–226, discussion 226–228, 2013, Figure 4.)

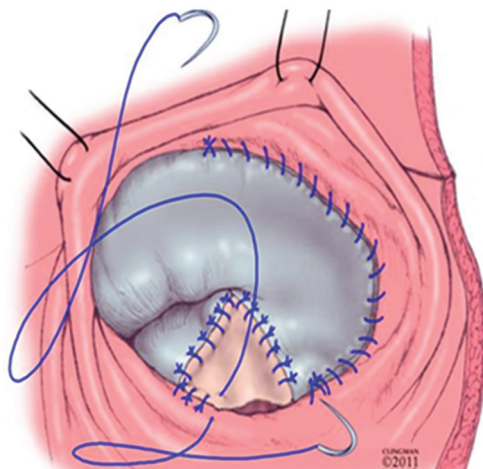


FIGURE 130-19 ■ A triangular patch is used to augment the reconstructed cone to avoid tricuspid valve stenosis when there is a paucity of septal leaflet tissue and absent inferior leaflet. (From Dearani JA, Said SM, O’Leary PW, et al: Anatomic repair of Ebstein’s malformation: lessons learned with cone reconstruction. *Ann Thorac Surg* 95:220–226, discussion 226–228, 2013, Figure 5.)

5. The Sebening stitch, which involves approximation of the mobilized “base-intact” anterior papillary muscle to the ventricular septum (Fig. 130-21B)
6. Modified Sebening stitch that involves approximation of the head of the mobilized “base-intact” RV free wall papillary muscle to a corresponding head of a papillary muscle arising from the ventricular septum supporting the septal leaflet (as opposed to anterior papillary muscle approximation to the ventricular septum; see Fig. 130-21A)
7. Artificial Gore-Tex (WL Gore, Flagstaff, AZ) chordae

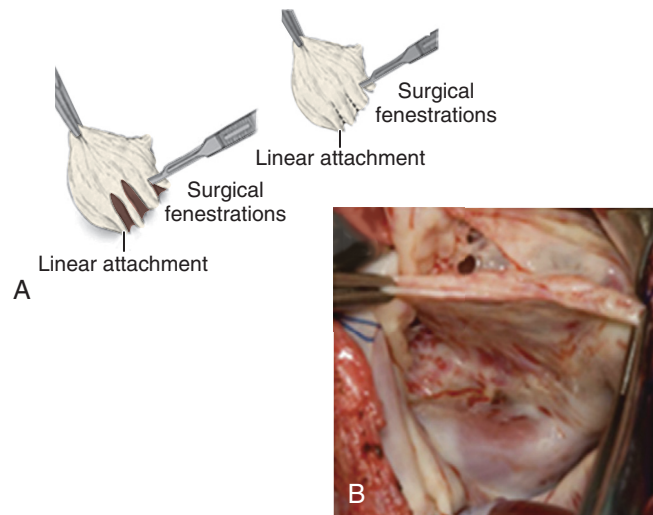


FIGURE 130-20 ■ A and B, In the presence of a linear attachment where the leading edge is completely adherent, surgical neo-chordae are created by making several fenestrations apically in the distal portion of the leaflet to allow unrestricted forward blood flow into the ventricle. (From Dearani JA, Said SM, O’Leary PW, et al: Anatomic repair of Ebstein’s malformation: lessons learned with cone reconstruction. *Ann Thorac Surg* 95:220–226, discussion 226–228, 2013, Figure 6AB.)

Leaflet augmentation is applied when the height of the anterior leaflet is shallow or when the rotated cone will result in a smaller than normal orifice. Importantly, when leaflet augmentation is used, the patch is placed between the mid leaflet and annulus and should never involve the leading edge. Importantly, the patch is kept as small as possible.

Relative contraindications to the cone reconstruction include older age (>60 years), moderate pulmonary hypertension, significant LV dysfunction (ejection fraction < 30%), absent septal leaflet, poor delamination or poor quality of the anterior leaflet (i.e., <50% delamination of the anterior leaflet), and severe muscularization of the anterior leaflet not amenable to sufficient debulking to obtain a pliable leaflet. Severe RV enlargement and severe dilation of the right AV junction (true tricuspid annulus) can also make successful CR challenging because there is significant stress on the many suture lines necessary to perform the CR.

In 2007, Dr. da Silva published his series of 40 patients who underwent the cone reconstruction.³⁹ In this series, the operative mortality was one patient (2.5%). After a mean follow-up of 4 years (range, 3 months to 12 years), only one patient died and two patients required late TV re-repair. The cone technique has the potential to cause TV stenosis, particularly when there is a paucity of leaflet tissue, although no patients in this initial cohort experienced this complication. Additional follow-up is required to determine whether this method of repair has long-term durability.

Tricuspid Valve Re-Repair. Although challenging, TV re-repair is still possible in Ebstein malformation. We have reported our experience with TV re-repair for Ebstein malformation previously.⁴¹ This has been

FIGURE 130-21 ■ **A**, The modified Sebening stitch in which the head of the mobilized right ventricular free wall papillary muscle is approximated to the corresponding smaller head of a septal papillary muscle (as opposed to approximation to the ventricular septum in the original Sebening stitch). **B**, It is important to avoid dimpling of the right ventricular free wall, as this indicates excessive tension. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Dearani JA, Said SM, Burkhart HM, et al: Strategies for tricuspid re-repair in Ebstein malformation using the cone technique. *Ann Thorac Surg* 96:202–208, discussion 208–210, 2013, Figure 5AB.)

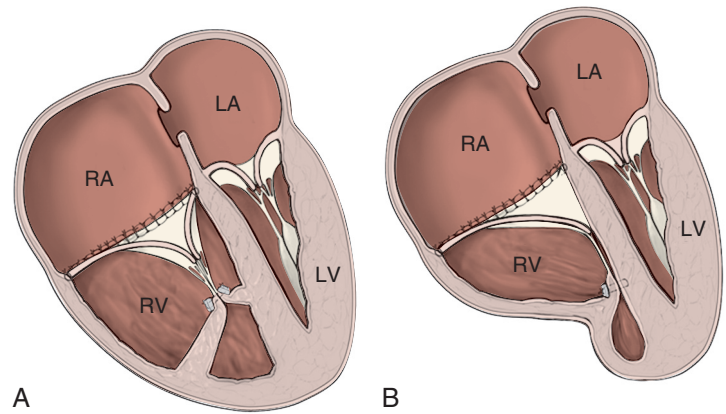
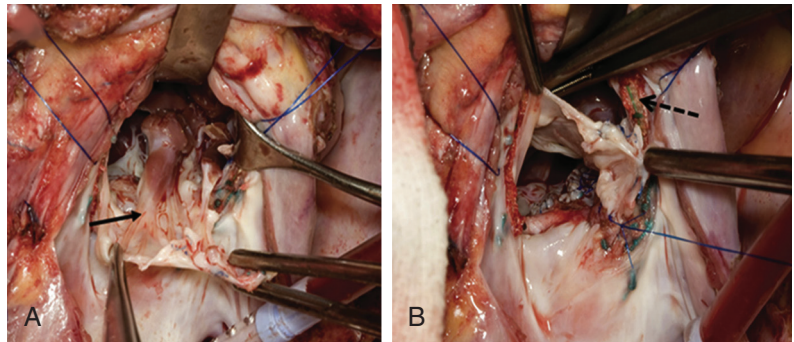


FIGURE 130-22 ■ A surgeon's view into the right atrium; the patient's head is to the left. **A**, The anterior leaflet has been detached from the annulus. There is a linear attachment of the leading edge of the anterior leaflet with a direct papillary muscle insertion (black arrow). **B**, The anterior leaflet was mobilized and is being prepared to be reattached to the anterior annulus. The dotted line arrow identifies the previous ring, which was the only repair maneuver at the initial operation. (From Dearani JA, Said SM, Burkhart HM, et al: Strategies for tricuspid re-repair in Ebstein malformation using the cone technique. *Ann Thorac Surg* 96:202–208, discussion 208–210, 2013, Figure 1AB.)



performed in 32 patients to date; our previous report of 20 patients demonstrated a median age of 15 years (range, 4 to 68 years). Four patients (20%) had prior bidirectional cavopulmonary anastomosis. Preoperative heart failure was present in eight patients (40%). Recurrent tricuspid regurgitation was due to incomplete leaflet coaptation with tethered anterior leaflet in all patients; and 10 patients (50%) had diminutive septal leaflet. This was possible because prior repair techniques focused on annuloplasty maneuvers in all patients with no or incomplete surgical delamination of leaflet tissue (Fig. 130-22). Re-repair strategies followed the previously mentioned cone reconstruction principles with complete 360 degree mobilization and recruitment of all available leaflet tissues.

There have been no early or late deaths in this group. Mean follow-up was 7.7 ± 10.7 months; during follow-up, 18 patients had no or mild TR and 2 patients had moderate TR.

Tricuspid Valve Replacement. Tricuspid valve replacement remains a reasonable option in those patients who cannot undergo valve repair. In our experience, the most common reason for the inability to obtain a satisfactory CR is significant muscularization of the anterior leaflet not amenable to debulking or resection, or absent septal leaflet; this is determined intraoperatively. Other indications to consider valve replacement include relative older age (>60 years) or massive RV or annular dilation; this is also ultimately determined intraoperatively. We have previously reported good durability with porcine bioprostheses in patients with EM. However, our preference is always to repair the TV whenever possible, and with our

larger experience we have learned that it is feasible for almost all patients.

Bioprosthetic (porcine) valve replacement, as opposed to mechanical valve replacement, is generally preferred because of relative good durability of the porcine bioprosthesis in the tricuspid position and the lack of need for warfarin anticoagulation.⁴² Bioprosthetic valves do not have the thromboembolic complications of mechanical valves, but they require warfarin anticoagulation for the first 3 to 6 months postoperatively. Mechanical valves in the tricuspid position are sometimes associated with a higher frequency of valve malfunction and thrombotic complications compared with mechanical valves in other cardiac positions, particularly when RV function is poor⁴³ and discs do not open and close properly.

When the TV cannot be reconstructed and replacement is necessary, the suture line is deviated to the atrial side of the AV node and membranous septum to avoid injury to the conduction mechanism. A small vein crossing the tricuspid annulus adjacent to the membranous septum typically marks the AV node. To avoid injury to the right coronary artery, the anterior suture line is deviated toward the atrial side of the TV annulus anteriorly (where the smooth and trabeculated portions of the RA meet each other) and posterolaterally where the tissues are frequently thin. The coronary sinus can be left to drain into the RA if there is sufficient room between it and the AV node; if the distance is short, the coronary sinus can be left to drain into the RV so that heart block can be avoided. The struts of the porcine bioprosthesis are oriented so that they straddle the area of the membranous septum and conduction tissue. The valve sutures are tied with the heart beating (after intracardiac

communications are closed) to detect any disturbances in AV conduction. Tricuspid replacement also has the advantage of a short cross-clamp time (after ASD closure), which may be preferred when mild or moderate LV dysfunction is present or when there is surgeon inexperience or low confidence with a difficult tricuspid repair that might result in a prolonged cardiac ischemic time.

The 1.5-Ventricle Repair. We use the bidirectional cavopulmonary shunt selectively; it is applied in approximately 20% of patients undergoing operation. The bidirectional cavopulmonary shunt is helpful when the RV is severely dilated and functioning poorly. Although uncommon, it can also be applied when a successful TV repair has resulted in an effective valve orifice that has mild to moderate stenosis (mean gradient > 6 mm Hg). Because concomitant LV dysfunction may be present in advanced stages, it is important to document by direct pressure measurements that the pulmonary arterial and LA pressures are low; otherwise, the bidirectional cavopulmonary shunt will not be feasible. If the LV end-diastolic pressure is less than 12 mm Hg, the transpulmonary gradient is less than 10 mm Hg, and the mean pulmonary arterial pressures are less than 18 mm Hg, a bidirectional cavopulmonary shunt is permissible. Even in the presence of moderate LV dysfunction (an ejection fraction of 35% to 40%), it is usually feasible to perform a bidirectional cavopulmonary shunt in the setting of Ebstein malformation.

Others have suggested that the construction of a bidirectional cavopulmonary shunt may allow for less than perfect TV repairs, because LV filling is not completely dependent on forward flow through the RV.⁴⁴ In addition, the shunt may allow patients to tolerate longer intervals between repeated TV operations for progressive tricuspid regurgitation or failing TV prostheses. This may be due to the smaller regurgitant volume and therefore a decreased volume load to the RV.

Chavaud and colleagues⁴⁵ and Quiñonez and coworkers⁴⁶ have proposed that the use of a bidirectional cavopulmonary shunt can decrease operative mortality and facilitate the postoperative management when there is severe RV dysfunction. The literature suggests that the frequency of bidirectional cavopulmonary shunt application in patients with Ebstein malformation is increasing: in a series of 150 patients in a European registry, almost 26% underwent a 1.5-ventricle repair. Although the early results appear to be improved, late results of a bidirectional cavopulmonary shunt in patients with Ebstein malformation are unknown.

Disadvantages of the bidirectional cavopulmonary shunt include pulsations of the head and neck veins, facial swelling, and the development of arteriovenous fistulae in the pulmonary vasculature. In addition, the placement of this shunt compromises access to the heart from the internal jugular approach for electrophysiologic studies and for pacemaker lead placement. The bidirectional cavopulmonary shunt has promising applications in the management of patients with Ebstein malformation, particularly those with RV failure, but it is our belief that it should be reserved for these selected patients until the late outcomes are well described.

Surgical Treatment of Arrhythmias. The most common atrial tachyarrhythmias in Ebstein malformation are atrial fibrillation and flutter. We have successfully used the right-sided cut-and-sew lesions of Cox-Maze III procedure in the early era of maze surgery and now use the modified RA maze lesions when arrhythmia surgery is applied. With the availability of newer devices, such as radiofrequency or cryoablation, the procedure time for maze procedure is shortened significantly. Consequently, our current preference is to perform a biatrial maze procedure when there is chronic atrial fibrillation, LA dilation, or concomitant mitral regurgitation. We follow the lesions in both atria that have been described previously.^{47,48} In the presence of atrial flutter, we prefer to add a "cavotricuspid isthmus" lesion, which is the posterolateral TV annulus to the coronary sinus to the inferior vena cava. We also make an effort to close the LA appendage.

In patients with AV nodal reentrant tachycardia who underwent unsuccessful ablation in the electrophysiologic laboratory preoperatively, we perform perinodal cryoablation on cardiopulmonary bypass after opening the RA and closure of the intracardiac shunt. This involves multiple applications of the cryoprobe around and in the os of the coronary sinus, which is then carried anteriorly toward the proximal AV node until temporary complete heart block is noted, at which time the rewarming is begun; normal AV conduction returns shortly thereafter. In case of accessory conduction pathway as in WPW syndrome, mapping and ablation is performed preoperatively. Intraoperative mapping and ablation is rarely performed in the current era.

Heart Transplantation. Transplantation is an option in patients with Ebstein malformation with severe biventricular dysfunction (i.e., LV ejection fraction < 25%). In our experience, patients with severe RV dysfunction and normal or mild to moderately depressed LV function can be managed with a conventional operation, which can include placement of a bidirectional cavopulmonary shunt at the time of tricuspid repair or replacement. Other patients with Ebstein malformation who should be considered for transplantation are those with significant LV dilation and dysfunction or those with severe nonstructural mitral regurgitation with significant LV dysfunction. Hemodynamic cardiac catheterization to ascertain left-sided filling pressures and pulmonary artery pressures is also helpful in this group of patients when trying to determine feasibility of conventional operation versus transplantation.

POSTOPERATIVE CARE

Early postoperative management begins in the operating room. Discontinuation of bypass is accomplished with epinephrine and milrinone. To minimize RV dilation, higher heart rates (100 to 120 beats/min) are preferred and are obtained with temporary atrial pacing if needed. Low-dose vasopressin can be helpful with right-sided heart failure because systemic vasoplegia is not uncommon in this group of patients. This may be due to the use

preoperative afterload reducing agents, liver congestion, or humoral factors from atrial natriuretic peptide secondary to atrial dilation.

Volume administration should be done cautiously to avoid RV distention; RA pressures less than 10 to 12 mm Hg are preferred. This strategy can result in mild metabolic acidosis in the early postoperative period but is tolerated as long as urine output is satisfactory and peripheral perfusion is normal. Extubation is performed after metabolic parameters have normalized (≈ 12 hours). Nitric oxide can be helpful to offset the pulmonary vasoconstrictive effects of inotropic support, thereby reducing afterload to the dysfunctional RV.

Medical therapy at hospital discharge includes beta blocker or angiotensin-converting enzyme inhibitor, or both, and selective use of sildenafil for 6 to 8 weeks for patients who have mildly elevated pulmonary artery pressures or for patients who live at high altitude. Importantly, amiodarone therapy is used for 2 to 3 months when there are documented arrhythmias and frequently when RV plication has been performed. Long-term arrhythmia surveillance with appropriate exercise testing is essential with this diagnosis.

OUTCOMES

Our experience with surgery for Ebstein malformation now approaches 1000 patients. Analysis of various groups of patients within this large cohort has been published previously.⁴⁹ We have performed 170 cone repairs to date; our initial experience was published recently.⁵⁰ Between June 2007 and December 2011, 89 patients (47 female; 53%) underwent cone reconstruction (median age, 19 years; range, 19 days to 68 years). The indications for operation were progressive cardiomegaly in 43 (48%), cyanosis in 29 (33%), and heart failure in 13 (15%). Prior TV repair was performed in 12 patients (13%). Severe tricuspid regurgitation (TR) was present in 75 patients (84%). All patients underwent cone reconstruction. Modifications included ringed annuloplasty in 57 patients (64%), leaflet augmentation in 28 patients (31%), and autologous chordae in 17 patients (19%). Bidirectional cavopulmonary anastomosis was performed in 21 patients (24%). Early mortality occurred in 1 patient (1%). Early reoperation for recurrent TR occurred in 12 patients (13%); re-repair was performed in 6 patients (50%), and 6 (50%) required replacement. Mean follow-up was 19.7 ± 24.7 months. There was no late mortality or reoperation. At follow-up, 72 patients (87%) had no or mild TR, 9 patients (11%) had moderate TR, and 2 patients (2%) had severe TR. Ringed annuloplasty was associated with less than moderate TR at dismissal ($P = 0.01$).

Most of the literature focuses on survival and reoperation, with little discussion about the functional outcome for patients with Ebstein malformation after surgery. We reported our experience of 539 patients with Ebstein malformation (pre-cone era) who underwent 604 cardiac operations.⁵¹ The mean age at the initial operation was 24 years (range, 8 days to 79 years) and 53% were female. Survival at 5, 10, 15, and 20 years was 94%, 90%, 86%, and 76%, respectively. Survival free of late reoperation

was 86%, 74%, 62%, and 46% at 5, 10, 15, and 20 years, respectively. Two hundred and thirty-seven (83%) patients were in NYHA functional class I or II, and 34% were taking no cardiac medication. The reported exercise tolerance was comparable to that of the patients' peers. In a small subset of these patients, formal exercise testing was conducted. There was improvement in exercise tolerance after operation, but this improvement was believed to be a result of the elimination of the right-to-left shunt at the atrial level rather than improvement in ventricular function. Late reoperation, rehospitalization, and atrial tachyarrhythmias continue to be a problem, with a rate of freedom from rehospitalization (for cardiac causes including reoperation) of 91%, 79%, 68%, 53%, and 35% at 1, 5, 10, 15, and 20 years, respectively. Thus, further improvement in the durability of TV repair and replacement, as well as improved control of atrial arrhythmias, could lead to improved quality of life in patients with Ebstein malformation.

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ADULT CONGENITAL CARDIAC SURGERY

Anne Marie Valente • Sitaram M. Emani • Michael J. Landzberg • Emile A. Bacha

CHAPTER OUTLINE

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Tetralogy of Fallot

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Single-Ventricle Physiology and Fontan
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SUMMARY

Patients with congenital heart disease require lifelong surveillance. The number of adults living with congenital heart disease continues to grow, in part because of advances in the diagnosis and treatment of congenital heart lesions.^{1,2} There are more than 1 million adults with congenital heart disease in the United States; this population grows by approximately 5% each year.^{3,4}

The challenges of caring for adults with congenital heart disease were underscored in the medical literature by Dr. Joseph Perloff beginning in the 1970s, when he described the pediatric congenital cardiac patient becoming a postoperative adult.⁵ However, it was not until 1990 at the 22nd Bethesda Conference of the American College of Cardiology (ACC) that the care of adults with congenital heart disease was formally recognized as a subspecialty of cardiology care.⁶ In 2001, the 32nd Bethesda Conference attempted to address the changing profile of adults living with congenital heart disease by developing guidelines for resource allocation.²

There is a paucity of literature related to the surgical care of adults with congenital heart disease. Many patients are considered for additional surgery after initial palliations earlier in life. Other patients present with previously undiscovered congenital heart disease requiring surgical intervention. This chapter discusses the expanding adults with congenital heart disease (ACHD) population and its unique challenges. Important aspects of preoperative evaluation and perioperative management are highlighted, and several of the most common lesions encountered by surgeons caring for adults with congenital heart disease are discussed.

EPIDEMIOLOGY

There are more adults than children living with congenital heart disease, and the population continues to grow. The prevalence of adults with congenital heart disease in Quebec, Canada, was 6.12 per 1000 for the year 2010, which was a 57% increase compared with 2000. This compares with an only 10% increase in the prevalence of children with congenital heart disease during the same time period.⁷ This presents several unique challenges to the health care providers that care for these patients.

In 2001, the 32nd Bethesda Conference developed guidelines for resource allocation and program development directed at adults with congenital heart disease. The model for delivery of care focuses on classification of congenital heart defects into different levels of anatomic complexity ([Box 131-1](#)), with referral to specialized adult congenital disease centers for increasing levels of such classification. More than half of the ACHD population is believed to be at increased risk for sudden cardiac death, need for reoperation, and other severe complications. This report estimated that 15% of the ACHD population have anatomically complex disease and require regular follow-up at a specialized center for adult congenital heart disease, and an additional 38% have moderate anatomic complexity of disease requiring periodic follow-up in a specialized center.² The British Cardiac Society Working Party published a similar document addressing the care for the GUCH (grown-up congenital heart) population.⁸ The consensus of both documents is

BOX 131-1 Adult Congenital Heart Disease Lesions by Severity**SIMPLE COMPLEXITY**

- Isolated congenital aortic valve disease
- Isolated congenital mitral valve disease (except parachute valve, cleft leaflet)
- Isolated patent foramen ovale or small atrial septal defect
- Isolated small ventricular septal defect (no associated lesions)
- Mild pulmonic stenosis
- Previously ligated or occluded ductus arteriosus
- Repaired secundum or sinus venosus defect without residua
- Repaired ventricular septal defect without residua

MODERATE COMPLEXITY

- Aortic to left ventricular fistula
- Anomalous pulmonary venous drainage, partial or total
- Atrioventricular canal defects (partial or complete)
- Coarctation of the aorta
- Ebstein anomaly
- Infundibular right ventricular outflow obstruction of significance
- Ostium primum atrial septal defect
- Patent ductus arteriosus (not closed)
- Pulmonary valve regurgitation (moderate to severe)
- Pulmonic valve stenosis (moderate to severe)
- Sinus of Valsalva fistula/aneurysm
- Sinus venosus defect
- Subvalvar or supravalvar aortic stenosis (except hypertrophic cardiomyopathy)
- Tetralogy of Fallot
- Ventricular septal defect with
 - Absent valve or valves
 - Aortic regurgitation
 - Coarctation of the aorta
 - Mitral disease
 - Right ventricular outflow tract obstruction
 - Straddling tricuspid/mitral valve
 - Subaortic stenosis

SEVERE COMPLEXITY

- Conduits, valved or nonvalved
- Cyanotic congenital heart (all forms)
- Double-outlet ventricle
- Eisenmenger syndrome
- Fontan procedure
- Mitral atresia
- Single ventricle (also called double inlet or outlet, common, or primitive)
- Pulmonary atresia (all forms)
- Pulmonary vascular obstructive diseases
- Transposition of the great arteries
- Tricuspid atresia
- Truncus arteriosus/hemitruncus
- Other abnormalities of atrioventricular or ventriculoarterial connection not included above (e.g., crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)

that all patients (with the exception of those with simple heart lesions) should receive lifelong specialized ACHD care.

STRUCTURED ACHD PROGRAMS

Over the past decade, there has been an increase in the number of centers with specialized multidisciplinary teams committed to the lifelong care of ACHD patients. Many challenges are involved in creating and maintaining a successful team of specialized ACHD providers. Health care providers who specialize in the care of these patients have various levels of experience in ACHD diagnosis and management. Although they are committed to the care of their patients, they may not have had the benefit of training in this subspecialty.⁹ Programs that specialize in ACHD care excel in multidisciplinary collaboration with specialists in not only congenital cardiac disease but also reproductive and obstetric care, nephrology, hepatology, hematology, pulmonary, rheumatology, psychiatric support, palliative care, and transition education. From a cardiac perspective, it is essential to have experienced clinicians with expertise in imaging, electrophysiology, interventional catheterization, congenital cardiac surgery, cardiac anesthesia, critical care, advanced heart failure management, and transplant medicine. The organizational structure should be regionally coordinated, so that regional centers caring for adults with congenital heart disease can easily consult and refer to the specialized programs.¹⁰

Lapse in medical care in adults with congenital heart disease results in adverse outcomes. In a study of 158 adult patients referred to one ACHD center, lapse of medical care, defined as an interval of more than 2 years, occurred for 99 patients (63%). The median duration of lapse of care was 10 years. Patients with lapse of care were 3.1 times more likely to require urgent cardiac interventions ($P = 0.003$).¹¹ In a multicenter study of 922 patients at 12 ACHD centers, 42% experienced a gap in cardiology care that lasted longer than 3 years, and 8% had a gap longer than a decade. The mean age at the first gap was 19.9 years. The most common reasons for gaps included feeling well, being unaware that follow-up was required, and complete absence from medical care. Disease complexity was predictive of a gap in care among 59% of mild, 42% of moderate, and 26% of severe disease patients reporting gaps ($P < 0.0001$).¹²

Emergencies in the ACHD patient are of particular concern. In one multicenter study of hospital admissions of adults with congenital heart disease, 63% of emergent admissions required cooperation with another specialized department.¹³ An additional challenge that faces the ACHD population is lack of insurance coverage. Congenital heart disease patients without private insurance and older than 17 years are at higher risk of being admitted via the emergency room.¹⁴

A critical volume of patients is needed to maintain expertise in the various disciplines required in the care of ACHD patients. Adult congenital heart surgery should be performed only by surgeons who are experienced in all aspects of congenital heart surgery.¹⁵ In an analysis of

Adapted from Warnes CA, Liberthson R, Danielson GK, et al: Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol* 37:1170–1175, 2001.

the Nationwide Inpatient Sample, early mortality and length of stay were lower for patients who underwent ACHD procedures performed by surgeons with expertise in congenital heart disease.¹⁶ The choice of location for surgery should depend on not only the surgeon but also the multidisciplinary team's support for management of adult comorbidities. The optimal surgical location may be center dependent. Certain factors place adults with congenital heart disease at higher risk of death when surgery is performed at freestanding pediatric hospitals. These risk factors include older age, male sex, government-sponsored insurance, and greater surgical complexity.¹⁷ Additionally, greater surgical complexity, government-sponsored insurance, DiGeorge syndrome, weekend admissions, and depression result in higher resource use in ACHD surgical admissions.¹⁸ Analysis of the Nationwide Inpatient Sample examining ACHD surgical admissions to adult hospitals identified nonelective admissions, government-sponsored insurance, surgical complexity, heart failure, renal failure, and complications as risk factors for higher resource utilization.¹⁹

SURGICAL INDICATIONS IN ACHD PATIENTS

The ACC and American Heart Association (AHA) have developed guidelines for management of adults with congenital heart disease, which include recommendations for surgical interventions.²⁰ It is important to recognize the decision to proceed with surgery in the ACHD patient is multifactorial. The goals of prolonging survival and improving quality of life are paramount. The use of previously established measures of physical functioning (such as New York Heart Association [NYHA] class) is difficult to assess in the ACHD patient. Many patients, having lived with the sequelae of cardiac disease since birth, do not perceive themselves as "limited" in the setting of markedly diminished objective exercise capacity.²¹ There is a common misconception that surgical palliation of a congenital heart defect in infancy or childhood is "curative." Therefore, by the time that patients are formally evaluated, ventricular dysfunction may be severe and irreversible.²² Despite this, NYHA class of III or higher has been associated with increased operative mortality, major adverse events, and greater length of stay in ACHD patients undergoing surgery.²³

Pediatric surgical risk scoring systems, such as Aristotle or STAT, may offer some prognostic value in ACHD patients but have limitations in their applicability. For example, high-risk surgeries often include procedures primarily done in infants (such as the Norwood operation or interrupted aortic arch repair), and the distribution of procedures in ACHD patients is skewed toward those classified as lower risk. Furthermore, patient comorbidities that may influence surgical outcome in the pediatric population (such as those in the Aristotle Comprehensive Scoring system, including low birth weight, prematurity, and noncardiac congenital anomalies) may not be as applicable in the adult population, whereas diabetes, hypertension, vascular disease, markers of hepatic disease, and NYHA class may be more meaningful.^{24, 25} In a

multicenter study of 2012 ACHD patients requiring surgery from 13 European countries, preoperative cyanosis, arrhythmias, and NYHA class of III or higher were risk factors for hospital mortality.²⁶

A subset of ACHD patients are referred for primary surgical correction. The principle reason for this is late diagnosis, for example, patients with atrial septal defects or aortic coarctation. Patients may also be referred as adults for a condition that was previously considered inoperable, or because they are from a geographic region without local surgical congenital heart expertise, or because they have anatomically complex lesions but balanced systemic and pulmonary blood flows. Patients with unrepaired tetralogy of Fallot and pulmonary atresia have a poor prognosis; survival beyond the fifth decade is rare.²⁷

PREOPERATIVE EVALUATION

The evaluation of an ACHD patient who is being considered for surgery is extensive. It begins with a thorough review of the underlying anatomy and physiology. This must include retrieval of any previous surgical reports, if possible, so that any unusual features or complications are known and can be anticipated. A further understanding of the current cardiac anatomy can be gained by the use of specific imaging modalities. Imaging should not only focus on cardiac function but also examine for any residua of previous surgery that should be addressed. The imager must be aware of the various potential residual sequelae to evaluate for, such as branch pulmonary artery stenosis at the insertion site of previously taken down systemic to pulmonary artery shunts. Three-dimensional echocardiography is particularly useful for understanding valvular morphology and mechanisms that contribute to valvular dysfunction.

Cardiovascular magnetic resonance imaging (CMR) is increasingly used to quantify ventricular volumes, function, and vascular anatomy.^{28,29} Gadolinium-enhanced contrast CMR can also evaluate myocardial viability. Cardiac computed tomography (CT) is an alternative for patients who have contraindications to CMR, and it provides excellent coronary imaging.³⁰

Imaging can also be helpful to determine the anatomic relationships of certain vascular structures, particularly the relationship of the aorta to the sternum (Fig. 131-1). This is particularly important for repeat sternotomy, which may be associated with inadvertent aortic entry. Preoperative duplex ultrasonography of the femoral and iliac arteries and veins shows the status of the patency of these vessels in ACHD patients who have undergone previous interventions. This is essential in the case of those patients who may need urgent peripheral cannulation for cardiopulmonary bypass.

Cardiac catheterization is often required to determine the cardiac hemodynamics and to determine if there are any associated lesions that should be addressed in the catheterization laboratory.³¹ Coronary angiography should be considered based on the presence of risk factors, presence of angina, noninvasive evidence of ischemia, reduced systemic ventricular function, history of myocardial infarction, or for those patients with prior

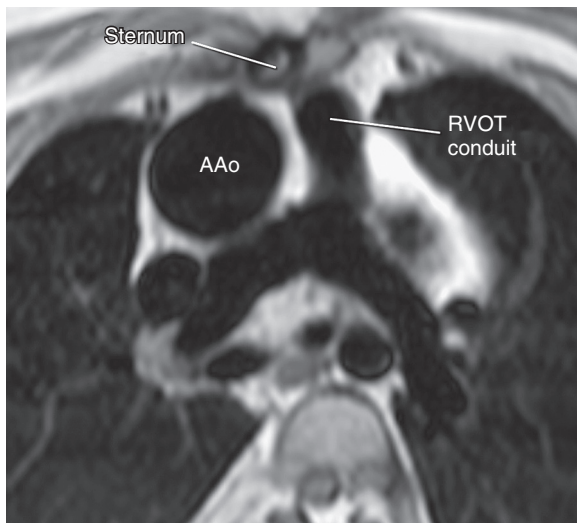


FIGURE 131-1 ■ Turbo-spin echocardiographic magnetic resonance image in the axial plane demonstrates the ascending aorta (AAo) and right ventricular outflow tract (RVOT) conduit closely adherent to the posterior table of the sternum.

coronary or great artery surgery. This includes adults with transposition of the great arteries who have undergone an arterial switch procedure with coronary translocation.³² There is a consensus that selective coronary angiography should be performed in men older than 40 years who have congenital heart disease and have been referred for surgery and in similar postmenopausal women.^{20,33} As many as 33% of selected ACHD patients may have an asymptomatic coronary artery anomaly that is discovered with coronary angiography; this is an important preoperative finding.³⁴ Exercise capacity should be examined with objective exercise testing.³⁵

An intensive electrophysiologic evaluation of the preoperative ACHD patient is essential. The incidence of arrhythmias is highest in those patients with moderate or severe ACHD complexity. For example, as many as one third of adults with repaired tetralogy of Fallot develop symptomatic atrial tachycardia,³⁶ approximately 10% develop high-grade ventricular arrhythmias,³⁷ and approximately 5% require permanent pacemaker placement for sinus node dysfunction or atrioventricular block. Additionally, an increasing number of adults with repaired tetralogy of Fallot are receiving implantable cardioverter defibrillators for treatment of ventricular tachyarrhythmia.³⁸

The importance of a multisystem approach to the ACHD patient during the preoperative evaluation cannot be overemphasized. In a retrospective analysis of more than 1100 ACHD patients, 9% had moderate or severe renal dysfunction with a reported threefold increase in mortality.³⁹ Lung function can be significantly diminished in the ACHD patient as a result of previous thoracotomy and resultant scoliosis and restrictive lung disease. ACHD patients with cyanosis are at risk for multisystem derangement, including abnormal hematologic indices, coagulopathy, nephropathy, and hepatic dysfunction.⁴⁰ Heart failure should be identified and medical therapies maximized to achieve critical predictors of improved outcomes.¹⁹

ACHD patients and their families should be educated on the potential benefits and possible risks of the surgical procedure. Some adults with congenital heart disease have emotional problems from previous childhood interventions, and their concerns must be addressed preoperatively. Additionally, patients may have a deleterious body image based on previous surgical scars.⁴¹ A dedicated discussion to the options regarding surgical entry, including possible techniques to minimize further scarring, is often helpful.

PERIOPERATIVE MANAGEMENT

The physiology of the ACHD patient is often complex, and an experienced cardiac anesthetist must be responsible for the care of the patient from the preinduction period through the postoperative management. The experienced anesthetist is essential in managing shifts in the vascular resistance of both the systemic and pulmonary circulations, dynamics of intracardiac shunting, and intravascular volume status. Possible harmful hemodynamic effects related to each anesthetic agent must be considered.⁴² For example, spinal anesthesia can result in a reduction in preload and decrease in pulmonary blood flow. It can also result in a drop in the systemic vascular resistance and an increase in pulmonary to systemic shunting, thus worsening hypoxemia. Narcotics may contribute to an acute reduction in systemic vascular resistance during induction.

Coordination of the operating room team in planning and completing successful sternal reentry is essential. Most surgeries performed on ACHD patients are reoperations. Reoperations are associated with a higher risk, particularly in those patients with cyanosis, transposed great arteries (anterior aorta), pulmonary atresia, or poor ventricular function.⁴³ In one report, early mortality for reoperation approached 10% for those ACHD patients who underwent five sternotomies.⁴⁴ The surgeon must recognize the relationships of cardiac structures in the ACHD patient, many of whom have greatly distorted anatomy, particularly when pericardial integrity has been lost as a result of prior surgical interventions. CMR or CT provides excellent visualization of the relationship of cardiac structures to the sternum (see Fig. 131-1).²⁴ In some patients, there is no discernible space between the posterior table of the sternum and a cardiac structure.

Dilated or hypertensive right heart structures are at particular risk during repeat sternotomy. For example, patients with a systemic right ventricle, such as those with complete transposition of the great arteries who have undergone atrial switch repair (Mustard, Senning), have an enlarged anterior right ventricle that may be adherent to the posterior shelf of the sternum. Aneurysmal, thin-walled right ventricular outflow tract patches and dilated ascending aortas may also be closely related to the sternum. The surgeon must be aware of the location of previously placed extracardiac conduits or shunts to avoid possible injury on sternal reentry. Another example includes a massively dilated and thinned-out right atrium in a classic Fontan. It typically crosses the midline and abuts the sternum, and injury to this structure can propagate because

the wall is typically very thin. Additionally, preoperative knowledge of the coronary anatomy is helpful to avoid inadvertent coronary injury. Certain congenital diagnoses have a higher incidence of anomalous coronary origins and courses, such as tetralogy of Fallot, where the left anterior descending coronary artery crosses the right ventricular outflow tract in at least 5% of cases.⁴⁵

Sternal Reentry Protocol

When there is a high possibility of risk to cardiac structures, femoral cannulation may be required. Femoral-to-femoral cardiopulmonary bypass can be established quickly; it allows blood salvage and control of systemic blood flow and pressure and lowers central venous pressure. Venous filling pressure must be controlled above zero to avoid entraining air into the circulation. Once this is established, retrosternal dissection can safely proceed. In some high-risk cases, it is important to dissect out the groin vessels prior to sternotomy.

Management of Bleeding during Resternotomy

Inadvertent injury to cardiac structures can result in life-threatening venous or arterial bleeding. Determining the source of bleeding is critical in the management of hemorrhage. Sources of venous bleeding include the right atrium, right ventricle, innominate vein, and/or pulmonary conduit. Venous bleeding not only causes blood loss but also allows air into the circulation, resulting in paradoxical air embolism. Therefore, positive venous pressure is needed when there is significant venous bleeding to prevent air embolism in those patients with intracardiac shunting. Additional efforts to minimize air entrainment into the circulation include placing the patient in the Trendelenburg position and rotating the table to the patient's left side.

Major arterial bleeding demands immediate control, even if temporary with a clamp, a suture, or direct compression of the bleeding site. Urgent peripheral femoral cannulation and initiation of cardiopulmonary bypass are typically needed. Once bypass is initiated, systemic cooling is performed so that flows can be lowered to control the bleeding site. Low-flow bypass is often sufficient to complete the dissection and repair any aortic injury. If the heart fibrillated, it is crucial to avoid distention, especially if aortic regurgitation is present. Manual compression of the heart may decrease distention until it begins ejecting, and left ventricular vent placement is crucial.

Unique factors that are important in the ACHD surgical patient include the systemic effects of chronic cyanosis, arrhythmia burden, presence of aortopulmonary collaterals, and ventricular dysfunction. Long-standing cyanosis results in intrinsic hemostatic abnormalities, and postoperative hemostasis may be difficult to achieve. ACHD patients with chronic cyanosis often have multiple collateral vessels that are friable and difficult to coagulate. The difficulty in achieving perioperative hemostasis is exacerbated by extensive suture lines and long cardiopulmonary bypass times, which lead to a decrease in

platelet number and activity through consumption coagulopathy and fibrinolysis.

Several strategies to minimize occurrence and effects of postoperative blood loss include the following:

- Preoperative phlebotomy with postoperative autologous blood transfusion
- Preoperative stimulation of bone marrow production with iron repletion in the iron-deficient patient or with erythropoietin
- Extensive and precise hemostasis during sternotomy and dissection
- Ultrafiltration during cardiopulmonary bypass to raise the hematocrit, and administration of a cell saver device
- Administration of antifibrinolytic agents
- Administration of platelets, fresh-frozen plasma, or cryoprecipitate
- Direct application of surgical glue to suture lines

ACHD patients who have depressed ventricular function or abnormal diastolic function and limited cardiac reserve do not tolerate large volume shifts well, and meticulous attempts must be made to achieve postoperative hemostasis. Patients with decreased ventricular function may need mechanical ventricular support (e.g., ventricular assist device, extracorporeal membrane oxygenation) for a limited time in the immediate postoperative period, and appropriate devices should be available during the surgical procedure so that they can be used if a patient fails to wean from cardiopulmonary bypass.

Efforts must be made to provide optimal myocardial protection during the surgery. Almost all ACHD patients are at risk for perioperative myocardial injury by several mechanisms, depending on the underlying physiology. These include washout of cardioplegia as a result of acquired collateral vessels that involve the coronary circulation, increased pulmonary venous return causing ventricular distention, and inadequate myocardial preservation as a result of extensive ventricular hypertrophy.

Strategies to improve myocardial protection include the following:

- More frequent administration of cardioplegia
- Venting of the heart to prevent overdistention
- In selected cases, the use of low-flow hypothermic cardiopulmonary bypass

A low cardiac output state can occur immediately postoperatively for a variety of reasons. Volume management is critical and depends on adequate hemostasis. Many ACHD patients have poorly compliant ventricles, because of either hypertrophy or restrictive ventricular physiology, and this may contribute to a low output state. Postoperative arrhythmias can cause an acute change in the cardiac output. Any arrhythmia must be recognized and treated immediately.

Low systemic perfusion with accompanying low systemic vascular resistance can occur postoperatively as well. It occurs most often in patients with preoperative heart failure and congestion of systemic venous pressure, those with known presurgical liver disease, or in patients with established risk factors for postoperative systemic inflammatory response syndrome (SIRS).

Additional surgical consideration for adult patients with history of long-standing congenital heart disease or

prior congenital heart surgery include propensity for calcification of cardiac structures and patch material, which can alter the surgical treatment. For example, patients with circumferential calcification of patent ductus arteriosus are at risk for fracture and bleeding with simple ligation using the traditional thoracotomy approach, and sternotomy with patch closure through the pulmonary artery may be the preferred approach. Similarly, treatment of a residual patch margin ventricular septal defect is complicated by the presence of calcification, which may prevent simple patch closure and necessitate excision of the calcified portion of the patch. Preoperative imaging must be carefully examined for evidence of calcification in the operative field.

POSTOPERATIVE MANAGEMENT

ACHD surgical care must be performed in a setting with a structured ACHD program that has a multidisciplinary team approach, and this is evident postoperatively. Intensivist and nursing staff should be skilled in working with ACHD patients. The physiology of the lesion often dictates postoperative care. Avoidance of acidosis and maintenance of adequate oxygenation and systemic perfusion are paramount. Postoperative bleeding should be anticipated and controlled. Patients should be reexplored if bleeding is excessive after the first several postoperative hours. Recognition and treatment of arrhythmias must be prompt and successful to avoid hemodynamic instability. Most ACHD patients return from the operating room with both atrial and ventricular temporary pacing wires, which may be used in determining the type of arrhythmia so as to direct therapy. Monitoring lines may be very useful: a transthoracic left atrial line, right atrial line, or pulmonary artery line may be left in the patient. The intensive care outcomes on adults operated on for congenital heart disease are favorable.⁴⁶ The early mortality for 2851 adult congenital patients operated on at the Mayo Clinic from 1993 to 2006 was 2.4%.⁴⁴

Most ACHD patients have residual cardiac issues after repeat surgery, and they must be educated regarding the need for lifelong follow-up. Several organizations are dedicated to improving the care of adults with congenital heart disease. The International Society for Adult Congenital Heart Disease (ISACHD) was founded in 1994 with a mission to promote, maintain, and pursue excellence in the care of adults with congenital heart disease (www.isachd.org). The Adult Congenital Heart Association (ACHA), a national nonprofit organization founded in 1988 by a group of ACHD survivors and their families, is dedicated to improving the quality of life and extending the lives of adults with congenital heart defects. More than 60 specialized clinics for adults with congenital heart disease are listed on the ACHA website (www.achaheart.org).

SPECIFIC LESIONS

To provide successful care to congenital heart patients in adulthood, adult congenital heart surgeons should be

experienced in all aspects of congenital heart disease that are encountered in childhood. Although a thorough review of specific lesions is beyond the scope of this chapter, the management of several more common lesions encountered in adulthood is discussed here. As mentioned earlier, the surgical indications for most congenital heart lesions encountered in adulthood are sparse. However, the ACC/AHA guidelines for the management of adults with congenital heart disease is an excellent summary of the current data.²⁰ Another set of guidelines was published by an international team of experts in 2001.^{33,47}

Atrial Septal Defect

Atrial septal defect (ASD) is one of the most common congenital heart defects. The clinical presentation of left-to-right shunting across an ASD is right ventricular volume overload and pulmonary overcirculation. ASDs that are large may develop during childhood; however, many are not discovered until adult life when patients develop exercise intolerance, atrial arrhythmias, or dyspnea.^{48,49} The indications for closure of an ASD include otherwise unexplained right atrial or right ventricular enlargement, regardless of symptoms. Additionally, patients with ASDs and evidence of established paradoxical embolism, the recurrence of which cannot be otherwise controlled, should be referred for closure, even in the absence of right heart overload. The long-term prognosis after closure for patients younger than 25 years is comparable to that of the general population. Patients corrected at an older age, particularly those older than 40 years, may have decreased long-term survival and experience higher rates of sequelae, including atrial arrhythmias, pulmonary hypertension, and right heart failure.⁴⁹ Therefore, some have questioned the benefit to repairing ASDs in later life, although general consensus and experience suggest improvement in symptomatic patients regardless of age at presentation, extending far into the older adult population.⁵⁰ Among the several types of ASDs, the most common is a secundum ASD—a defect in the region of the fossa ovalis. Surgical repair of secundum ASD has been performed since 1954. Secundum ASDs can often be closed with occluder devices placed percutaneously.⁵¹ However, certain anatomic determinants make percutaneous closure less favorable, including large defects, inadequate tissue rims, and anomalous draining pulmonary veins. Surgical closure is required for primum ASDs, sinus venosus defects (Fig. 131-2), and coronary sinus septal defects.

It is important to recognize the possibility of pulmonary arterial hypertension in the older patient with unrepaired ASD, although it is much more prevalent in patients with large unrepaired ventricular septal defects, complete atrioventricular canal, or patent ductus arteriosus. When pulmonary arterial hypertension is present, pulmonary vascular resistance can increase, compromising potential benefits of ASD closure. Greatest extreme and potential for pathology is noted with reversal of intracardiac shunting and systemic oxygen desaturation, resulting in Eisenmenger physiology. Patients with ASD and Eisenmenger syndrome have a reduced life

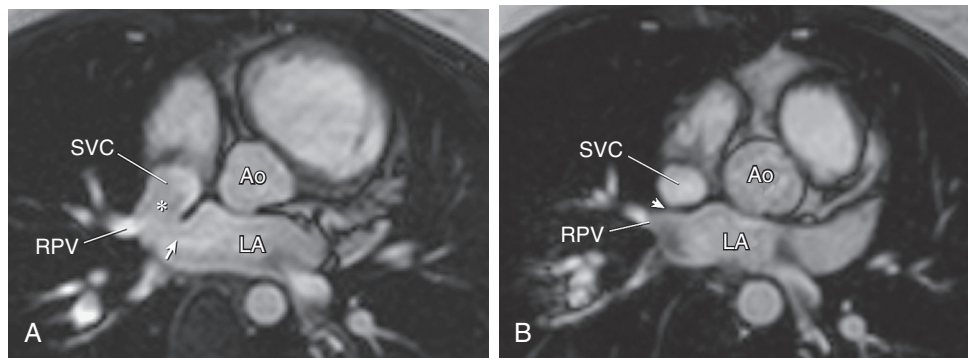


FIGURE 131-2 ■ Previously healthy 33-year-old woman with increasing shortness of breath with exertion. **A**, Cine magnetic resonance image in the axial plane demonstrates a sinus venosus defect (*) in the wall that separates the superior vena cava (SVC) and the right upper pulmonary vein (RPV). The arrow indicates the orifice of the RPV through which blood can flow between the left atrium (LA) and the SVC. **B**, Repeat imaging in the same patient performed 1 year after surgery confirms closure of the sinus venosus defect (arrow). Ao, Aorta.

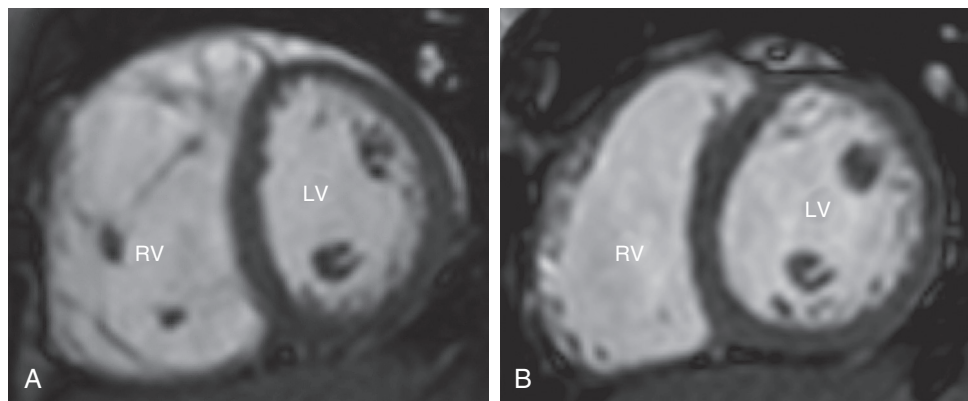


FIGURE 131-3 ■ **A**, Cine magnetic resonance image in the short-axis plane in the same patient as shown in Figure 131-2 demonstrates severe right ventricular (RV) dilation with a preoperative RV end-diastolic volume of 150 mL/m². **B**, Repeat imaging in the same patient performed 1 year after surgical closure demonstrates decreased RV end-diastolic volume to normal at 80 mL/m². LV, Left ventricle.

expectancy.⁵² For patients with ASD and pulmonary arterial hypertension, surgery is not recommended unless the pulmonary vascular resistance is demonstrated to be sufficiently low. In patients with evidence of elevated pulmonary vascular resistance, invasive testing with oxygen or vasodilators such as nitric oxide may be useful in determining appropriateness for surgical candidacy. Patients with ASDs with measured pulmonary vascular resistance greater than 8 Wood units are unlikely to improve with surgery (and repair may shorten survival); current recommendations suggest that when resistance is as high as 4 Wood units, decision regarding surgical repair should include consultation with clinicians with expertise in the assessment and care of pulmonary vascular disease.

The closure of ASDs can sometimes be performed via a transxiphoid or mini-sternotomy approach, conferring a satisfactory cosmetic result without compromising the safety or accuracy of the repair.⁵³ In some select cases, closure of an ASD can be performed safely and effectively via an endoscopic approach, which further minimizes the degree of invasiveness and hastens postoperative recovery.⁵⁴

The operative mortality for surgical closure of ASD should be less than 1%. Most symptomatic adults experience clinical improvement.⁵⁵ In one report,

cardiopulmonary performance in adult patients with surgically repaired ASD was improved at 4 months postoperatively compared with preoperative assessment, and complete restitution to normal was documented 10 years after shunt closure.⁵⁶ The right ventricular volumes begin to decrease immediately after ASD closure (Fig. 131-3) and are significantly reduced as early as 3 months after closure.⁵⁷

The long-term outcomes after ASD closure are generally excellent; however, the benefits are related to the timing of closure. Murphy and colleagues reported that patients repaired before the age of 25 years had 27-year survival rates similar to those of normal controls. However, the 27-year survival rate for patients between the ages of 25 and 40 years of age was 84%, and the survival rate was decreased to 40% for those patients older than 41 years.⁴⁹ The presence of arrhythmias preoperatively is a risk factor for postoperative rhythm disturbance, which occurs in approximately 60% of patients. Additional risk factors for recurrent arrhythmias after closure include age older than 40 years (some series have extended this to older than 60 years) and postoperative onset of atrial fibrillation, atrial flutter, or junctional rhythm.⁵⁸ Therefore, patients referred for ASD closure with existing arrhythmias and patients older than 40 (or

60) years should be considered for ablation at the time of repair.

Sinus Venosus Defect

In a retrospective review of 108 patients at the Mayo Clinic who had undergone sinus venosus defect repair over a 24-year period, symptomatic improvement was noted in 77%. Early mortality was less than 1%. Postoperative mortality was related to older age at repair and poor NYHA class preoperatively. Long-term complications from repair included sinus node dysfunction in 6% and atrial fibrillation in 14%. The presence of atrial fibrillation was related to older age at time of repair.⁵⁹

The choice of surgical technique for repair of sinus venosus defect depends on the patient's particular anatomy, such as size of defect and distance of the anomalous draining pulmonary veins from the superior vena cava (SVC) and right atrium. A single patch repair was used in most of the patients in the Mayo series. A double patch technique consisting of pericardial patch closure of the ASD with rerouting of the pulmonary veins to the left atrium and enlargement of the SVC with a second pericardial patch has been shown in select centers to be associated with less residual vessel stenosis and arrhythmia.⁶⁰ Sinus node injury is prevented by placement of the SVC incision just anterior to the entry of the pulmonary veins into the SVC. The Warden procedure is an alternative technique, which involves division of the SVC above the insertion of the anomalous pulmonary veins with placement of a pericardial patch on the cardiac end of the SVC. The right atrial appendage is opened and anastomosed to the cut end of the SVC.⁶¹

Tetralogy of Fallot

Most adults with tetralogy of Fallot (TOF) underwent repair in childhood. These patients, when referred for surgical consideration in adulthood, often have multiple residual lesions that may need to be surgically addressed, on average 2.9 procedures per patient per reoperation.⁶² TOF is the most common form of cyanotic congenital heart disease. The principal pathologic abnormality involves varying degrees of hypoplasia of the infundibulum, often with anterior, superior, and leftward deviation of the conal septum. As a result, TOF is characterized by right ventricular outflow tract obstruction, right ventricular hypertrophy, a large conoventricular septal defect, and an aorta that overrides the ventricular septum.

Lillehei is attributed with performing the first surgical repair of TOF in 1954; the 30-year survival rate from reoperations for the first 106 patients undergoing surgical repair was 91%.⁶³ The 20-year survival rate of patients treated from the late 1950s to 1972 was approximately 90%.^{64,65} Patients with TOF born prior to the early 1970s were often palliated with systemic artery to pulmonary artery shunts to increase pulmonary blood flow prior to the definitive repair. Most adult survivors with TOF underwent "definitive" repair much later in life than is currently the standard of care, which is younger than 1 year. Definitive surgical repair typically involves patch closure of the ventricular septal defect and an

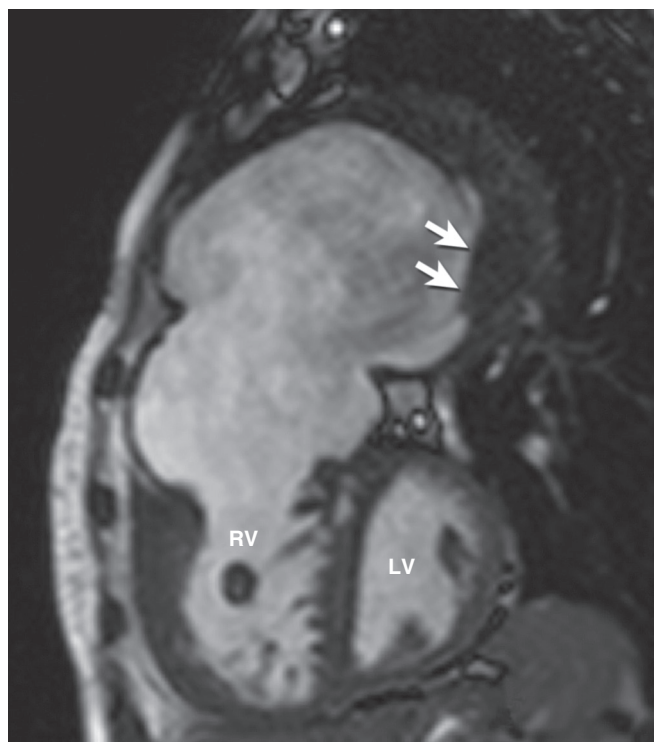


FIGURE 131-4 ■ Woman, 26 years old, with tetralogy of Fallot with pulmonary atresia who had undergone right ventricular conduit in infancy. Cine magnetic resonance image demonstrates a giant right ventricular (RV) outflow tract aneurysm measuring 13 cm × 8 cm × 8 cm. A large hemispherical thrombus (arrows) occupies the posterior aspect of the aneurysm. LV, Left ventricle. (From Valente A: Adult congenital heart disease. In Libby P, editor: *Essential atlas of cardiovascular disease*, Philadelphia, 2009, Springer/Current Medicine Group.)

infundibular or transannular right ventricular outflow tract patch to relieve the obstruction. However, adults who underwent definitive repair several decades ago were likely to have undergone a generous right ventricular incision and, compared with current technique, less attention to the preservation of the pulmonary valve. Right ventricular outflow tract aneurysms in the ACHD patient are common (Fig. 131-4), and they contribute to right ventricular dysfunction.⁶⁶ Surgical remodeling techniques can be used to reduce the size of the akinetic portion of the right ventricular outflow tract.

Surgical repair of TOF commonly results in anatomic and functional abnormalities in the ACHD population. Common sequelae include right ventricular dilation from pulmonary regurgitation, residual ventricular septal defects (often at the patch margin), tricuspid regurgitation, right ventricular outflow patch aneurysms, and branch pulmonary artery stenoses (commonly at the insertion site of previously taken down systemic to pulmonary artery shunts). The hemodynamic burden of these residua is often well tolerated in childhood. However, the prevalence of exercise intolerance, arrhythmias, heart failure, and death (Fig. 131-5) increase during adulthood.^{67,68} The factors that may contribute to worsening clinic status are demonstrated in Figure 131-6. Gatzoulis and colleagues reported risk factors for sudden death in 793 patients with repaired TOF from six centers

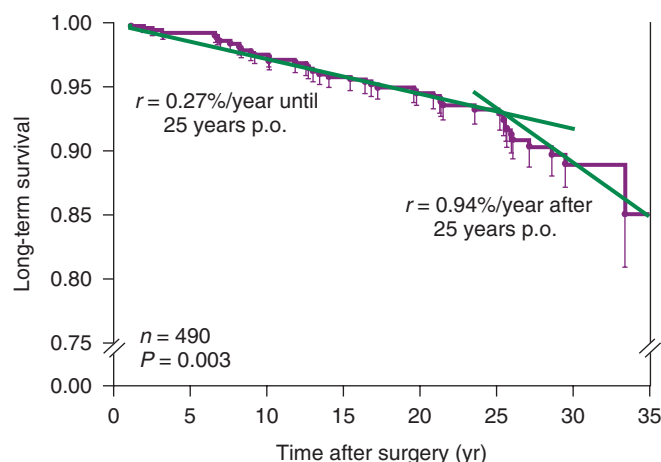


FIGURE 131-5 ■ Long-term survival curve after correction of tetralogy of Fallot. (Adapted from Nollert G, Fischlein T, Bouterwek S, et al: Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *J Am Coll Cardiol* 30[5]:1374–1383, 1997.)

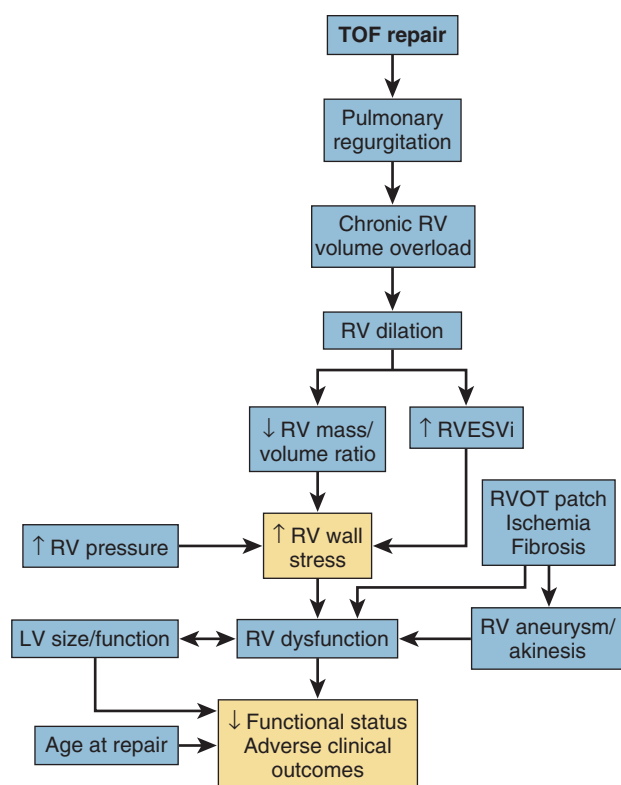


FIGURE 131-6 ■ Factors influencing right ventricular (RV) dysfunction and impaired clinical status after tetralogy of Fallot (TOF) repair. LV, Left ventricle; RVESVi, right ventricular end-systolic volume index; RVOT, right ventricular outflow tract. (Adapted from Geva T: Indications and timing of pulmonary valve replacement after tetralogy of Fallot repair. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 11–22, 2006.)

in the United Kingdom and found that older age of repair and QRS duration 180 ms were independent predictors of sudden death. The major hemodynamic abnormality in these patients was the presence of at least moderate pulmonary regurgitation.⁶⁹ Chronic right ventricular volume overload can also dilate the tricuspid valve annulus

with resultant tricuspid valve regurgitation. Progressive tricuspid valve regurgitation can accelerate right ventricular contractile failure and right atrial dilation, which is associated with increased prevalence of atrial arrhythmias.⁶⁹ Adults with repaired TOF commonly have cardiac issues that are not present in childhood, such as progressive aortic root dilation, which is present in at least 15% of adults with repaired TOF. This aortic root dilation may lead to aortic insufficiency.⁷⁰ Left ventricular dysfunction is associated with impaired clinical status and increased risk of sudden cardiac death.^{67,71} Additionally, multiple other organ systems may be affected, and it is not uncommon for ACHD patients with repaired TOF to have renal, hepatic, and pulmonary comorbidities.

In considering an ACHD TOF patient for further surgery, investigation into any heart rhythm disturbances is critical. Programmed ventricular stimulation provides reasonably good predictive information on the risk of future clinical ventricular tachycardia.⁷² A positive study may prompt either catheter ablation of the ventricular tachycardia circuit or implantable cardioverter defibrillator placement. Myocardial fibrosis, as demonstrated by gadolinium-enhanced CMR, has been significantly associated with clinical arrhythmia in adults with repaired TOF.⁷³ Rarely, adults with repaired TOF may have intra-atrial reentrant tachycardia (atrial flutter) or atrial fibrillation from chronic atrial dilation. Definitive elimination can often be achieved with a combined right and left atrial maze procedure, which can be performed during a surgery that is addressing residual hemodynamic issues.

An important question in the care of ACHD patients is the timing of pulmonary valve replacement (PVR) after TOF repair. Multiple factors can contribute to the progression of pulmonary regurgitation, including increasing capacitance of the pulmonary artery, right ventricular dilation, and increased right ventricular compliance.⁷⁴

The decision regarding timing of PVR after TOF repair should involve consideration of the benefit of right ventricular volume reduction prior to irreversible dysfunction and the risk of subsequent valve failure and need for repeat intervention. Although there are few controlled or randomized data suggesting optimal timing of PVR for residual pulmonary regurgitation after repair of TOF, Geva has proposed the following clinical criteria in combination with CMR criteria to use in the decision making of PVR in the asymptomatic patient with repaired TOF.⁷⁵

Repaired TOF with at least 25% pulmonary regurgitation fraction as measured by CMR and two or more of the following criteria:

1. Right ventricular (RV) end-diastolic volume index $> 150 \text{ mL/m}^2$ (z-score > 4); in patients whose body surface area falls outside published normal data, RV/left ventricular (LV) end-diastolic volume ratio > 2
2. RV end-systolic volume index $\geq 80 \text{ mL/m}^2$
3. LV ejection fraction $< 55\%$
4. RV ejection fraction $< 47\%$
5. Large RV outflow tract (RVOT) aneurysm
6. QRS duration $> 140 \text{ ms}$
7. Sustained tachyarrhythmia related to right heart volume load

8. Other hemodynamically significant lesions such as RVOT obstruction with RV systolic pressure $> 2/3$ systemic, severe branch PA stenosis, moderate to severe tricuspid regurgitation, residual atrial or ventricular septal defects with a Qp/Qs > 1.5 , and severe aortic dilation or regurgitation

The operative mortality for PVR after TOF repair is low (about 1%).⁷⁶ However, a continued low risk of death remains after PVR. Of 70 adults with TOF, Therrien reported a survival rate of 92% at 5 years and 86% at 10 years, after PVR.⁷⁷ The longevity of the valve must also be considered, because there is a wide variation in the rates of freedom from valve failure and reoperation, depending on type of valve and patient age.

Patients with TOF who undergo PVR generally have symptomatic improvement with a decrease in right ventricular end-diastolic and end-systolic volumes without significant change in the right ventricular ejection fraction.⁷⁸⁻⁸⁰ Additionally, there is evidence that exercise performance tends to improve after PVR.⁸¹

Ebstein Anomaly

Ebstein anomaly is a congenital malformation of the tricuspid valve and right ventricular sinus. It is a rare disorder, accounting for about 1% of all congenital heart defects.⁸² It was first described in 1866 in a 19-year-old laborer with severe tricuspid regurgitation caused by a severely malformed tricuspid valve. Ebstein anomaly is characterized by several morphologic features, which have varying degrees of severity. The pathogenesis involves failure of delamination of the septal and posterior leaflets of the tricuspid valve, resulting in adherence of the tricuspid valve leaflets to the ventricular myocardium. This results in apical displacement of the functional tricuspid valve annulus and dilation of the "atrialized" portion of the right ventricle. There are varying degrees of hypertrophy and thinning of the right ventricular wall, dilation of the true tricuspid valve annulus, and often fenestrations, redundancy, and tethering of the anterior leaflet. These abnormalities result in varying degrees of tricuspid regurgitation and ventricular dysfunction. Although patients with Ebstein anomaly share common features, no two cases are identical, and there is a great deal of variability in morphology.⁸³ This must be taken into consideration whenever surgical intervention is considered.

The tricuspid valve leaflets are often markedly dysplastic in severe cases. The incomplete fibrous transformation of leaflets results in a downward displacement of the hinge point of the posterior and septal leaflets in a spiral fashion below the true valve annulus. The valve leaflets may be tethered by short chordae and papillary muscles or attached to the myocardium directly or by muscular bands. Fenestrations of the leaflets are common, and chordae may be sparse or absent. In the most severe cases, the septal leaflet is a ridge of fibrous tissue that is directed toward the ventricular apex, the posterior leaflet consists of a few remnants of leaflet tissue near the apex, and the anterior leaflet may be displaced into the right ventricular outflow tract. The anterior leaflet leading edge is particularly important in determining the feasibility of tricuspid valve repair. The leading edge may be free and mobile,

have hyphenated attachments (focal, segmental direct attachments to the underlying myocardium), or have linear direct attachments (entire leading edge attached to the endocardium). Varying degrees of right atrial and ventricular dilation may be present. With severe right ventricular dilation, the ventricular septum is displaced and the left ventricle may be compressed with resultant left ventricular dysfunction.⁸⁴

Associated cardiac lesions include interatrial shunts, patent foramen ovale or ASDs, pulmonary valve stenosis or atresia, and, rarely, ventricular noncompaction. Interatrial shunts are often associated with right-to-left shunting and arterial desaturation. There is a risk of paradoxical embolism and stroke in this setting. Additionally, up to 20% of patients with Ebstein anomaly may have Wolff-Parkinson-White syndrome.⁸⁵ The accessory pathway is typically located along the posterior and septal aspect of the tricuspid ring. As many as half of these patients have more than one accessory pathway.

Ebstein anomaly of the left-sided atrioventricular valve is commonly seen in patients with physiologically corrected transposition of the great arteries. The systemic (morphologically tricuspid) atrioventricular valve is associated with the left-sided systemic morphologic right ventricle. The nature of the displacement of this valve is similar to right-sided Ebstein anomaly, but the anterior leaflet is often smaller. The functional right ventricle and tricuspid valve annulus are very rarely severely dilated.

The diagnosis of Ebstein anomaly is confirmed by two-dimensional echocardiography with the septal leaflet at the crux of the heart demonstrating apical displacement of 0.8 cm/m² or greater. Three-dimensional echocardiography can be particularly helpful in examining the morphology of the tricuspid valve leaflets (Fig. 131-7). CMR is useful for determining ventricular volumes and function, as well as visualization of the position of the tricuspid valve⁸⁶ (Fig. 131-8). The technique of delayed enhancement CMR can identify ventricular fibrosis⁸⁷ in these patients, which has been reported in both right and left ventricular myocardium of patients with Ebstein anomaly.

Patients with mild Ebstein anomaly may live normal life spans, and asymptomatic patients without right-to-left shunting or significant cardiomegaly may be managed medically and may not require surgical intervention. However, many adults living with congenital heart disease do not recognize their limited exercise capacity and may not report their limitations. In a study of 21 adults with Ebstein anomaly, exercise capacity was significantly reduced compared with controls (peak oxygen consumption 21.9 ± 5.4 versus 33.6 ± 8.3 mL/kg/min; $P = 0.000001$). All of these adults considered themselves to be in NYHA class I (71%) or class II (29%); however, objective cardiopulmonary stress testing indicated considerable reduction in the exercise performance of this group.⁸⁸

Several factors should promote consideration of surgery. These include increasing symptoms with decreasing exercise tolerance, cyanosis, documented paradoxical embolism, progressive cardiomegaly, right ventricular dilation or dysfunction, and progression of atrial or ventricular arrhythmias. A biventricular repair is usually possible; however, in cases of severe right ventricular

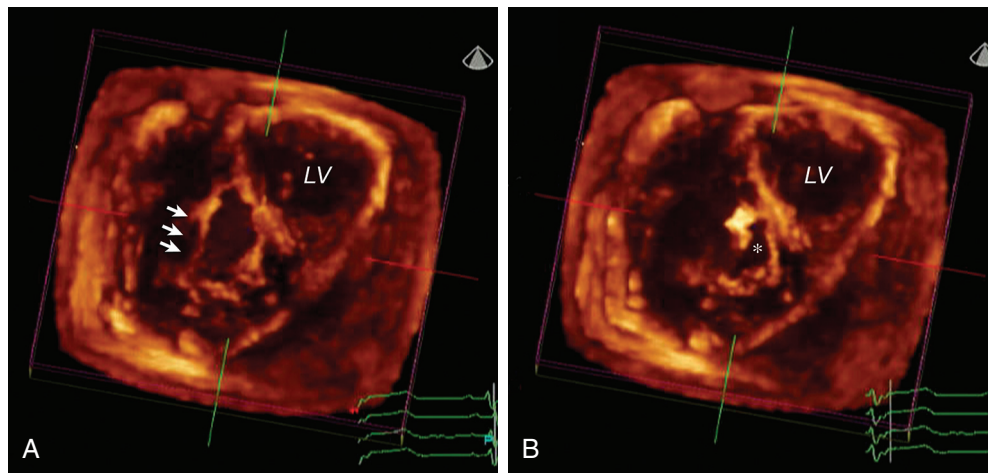


FIGURE 131-7 ■ **A**, Three-dimensional echocardiographic image of Ebstein anomaly in diastole demonstrates the redundant anterior leaflet of the tricuspid valve (arrows) with diminutive septal leaflet. **B**, Three-dimensional echocardiogram in systole illustrates failure of tricuspid valve coaptation (*). LV, Left ventricle. (From Valente A: Adult congenital heart disease. In Libby P, editor: *Essential atlas of cardiovascular disease*, Philadelphia, 2009, Springer/Current Medicine Group.)

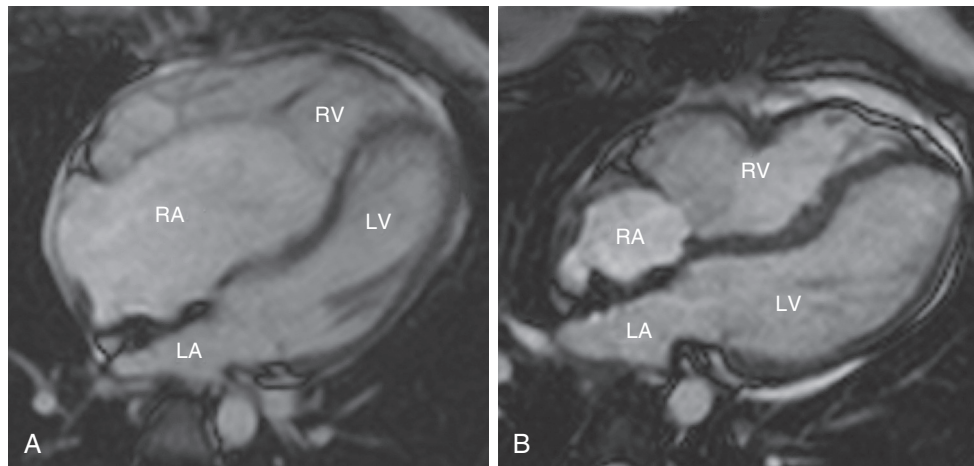


FIGURE 131-8 ■ Woman, 42 years old, with Ebstein anomaly and previous closure of an atrial septal defect with a CardioSEAL device. **A**, Cine magnetic resonance imaging (MRI) four-chamber view demonstrates how failure of delamination of the tricuspid valve septal leaflet results in apical displacement of its hinge point. **B**, Cine MRI in the four-chamber view in the same patient performed 1 year after tricuspid valvuloplasty. There is marked improvement in the right heart dilation. LA, Left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

dysfunction with preserved left ventricular function, a bidirectional cavopulmonary shunt may be considered.⁸⁹ Cardiac transplantation is a rare option usually reserved for cases with severe left ventricular dysfunction.

Surgical repair most often involves tricuspid valve repair or replacement. Factors that are favorable for a valve repair include a large, mobile anterior leaflet with a free leading edge. The presence of leaflet tethering, presence of tricuspid valve leaflet tissue in the right ventricular outflow tract or direct insertion of the papillary muscle head into the leading edge of the anterior leaflet makes repair more difficult. Leaflets that have extensive hyphenated attachments or linear attachment of the leading edge to the underlying endocardium are not appropriate for repair. The Mayo Clinic authors reported that if more than 50% of the anterior leaflet has failure of delamination, valve replacement is preferred.⁸³

Many modifications have been made to the original valvuloplasty described by Hunter and Lillehei.⁹⁰ The

original repairs created a monocuspid valve, and whereas subsequent adaptations focused on trying to create a two- or three leaflet valve, most recent technical modifications have focused on monocusp creation with “cone” repair. The principle underlying the cone repair is redistribution of redundant anterior and posterior leaflet to re-create a septal leaflet that is attached to the true annulus, along with annular reduction. Compared with conventional repair techniques, cone repair is associated with more significant reduction in tricuspid regurgitation.⁹¹ When the valve cannot be adequately repaired, a bioprosthetic valve is implanted. Care must be taken to avoid damage to the conduction system, and the suture line is deviated away from the atrioventricular node and membranous septum. The suture line may be deviated cephalad to the tricuspid valve annulus to avoid injury to the right coronary artery.

Considerations should also include closure of any interatrial communications, correction of other associated

anomalies (e.g., pulmonary stenosis), possible plication of the atrialized portion of the right ventricle, and right atrial reduction. A right-sided maze procedure is usually performed, with or without cryoablation of the right atrial isthmus. A left-sided maze is completed in the setting of left atrial enlargement or atrial fibrillation. Occasionally, surgical treatment of accessory conduction pathways is performed. Patients with Ebstein anomaly and arrhythmia show substantial improvement after surgical intervention; however, arrhythmias are not totally abolished. In a study of 45 adults with preoperative arrhythmias who had undergone Ebstein surgery, 39% of the surviving cohort continued to have arrhythmias.⁹²

The largest experience of surgical outcomes in patients with Ebstein anomaly has been reported from the Mayo Clinic. The mean age at the time of initial operation at the Mayo Clinic was 24 years, and 26.5% of the patients had undergone a prior cardiac procedure. Late survival was 84.7% at 10 years and 71.2% at 20 years. Risk factors for poor outcome included right and/or left ventricular systolic dysfunction, increased hemoglobin levels, male sex, hypoplastic pulmonary arteries, and right ventricular outflow tract obstruction.⁹³ Hospitalizations were common even after surgical intervention, with the arrhythmias being the most common admitting diagnosis ($\approx 39\%$). One third of patients continued to report fatigue and shortness of breath.⁹⁴

Single-Ventricle Physiology and Fontan Surgery

Univentricular hearts are rare congenital anomalies, comprising approximately 1% of all congenital heart defects at birth.⁹⁵ The prognosis without surgical intervention in childhood is poor, although, in rare cases, patients with well-balanced circulations survive with reasonable functional capacity into adulthood.⁹⁶

The physiology in infancy depends on several factors, including obstruction to ventricular inflow and outflow, flow across the interatrial septum, systemic and pulmonary venous return, and atrioventricular valve regurgitation. Surgical repair in childhood often involves several staged procedures. An initial palliation with a shunt may be performed, with the ultimate goal of a Fontan physiology.

The Fontan operation was developed in 1971 for palliation of tricuspid valve atresia.⁹⁷ Since that time, several modifications have been performed with the goal of directing systemic venous return directly to the pulmonary arteries without an interposing ventricle. The classic Fontan operation consisted of a valved conduit between the right atrium and main pulmonary artery.⁹⁷ Many of the current adults with single-ventricle physiology have a modified classic Fontan, which involves a direct anastomosis of the right atrium to the pulmonary artery. The next major modification, often referred to as a lateral tunnel, involved creation of an end-to-side anastomosis of the SVC to the undivided right pulmonary artery with an intra-atrial tunnel completed with a patch that tunnels the inferior vena caval blood through the tunnel to the transected SVC.⁹⁸ More recently, extracardiac conduits have been performed.⁹⁹

At the time of Fontan surgery, an ASD may be created in the baffle to “fenestrate” the baffle to allow some right-to-left shunting in the case of elevated systemic venous pressure.¹⁰⁰ This fenestration can often be closed percutaneously later in life to eliminate this residual cause for cyanosis.¹⁰¹ In an analysis of 261 patients with Fontan physiology with a mean age at follow-up of 25 years, actuarial event-free survival rates were 74.8% at 10 years, 68.3% at 20 years, and 53.6% at 25 years. The causes of death were determined to be thromboembolic, heart failure related, and sudden death.¹⁰²

The potential complications that arise in the adult patient with previous Fontan surgery are multiple. Patients with the “older style” Fontans are particularly at risk for right atrial dilation (Fig. 131-9) with thrombus formation and atrial arrhythmias.¹⁰³ These two problems may lead to diminished cardiac output, reduced exercise capacity, and diminished quality of life. The strategy of Fontan conversion was introduced in the early 1990s in an effort to improve outcomes of adult survivors of atrio-pulmonary Fontan procedures.¹⁰⁴ The addition of intra-operative ablation has decreased arrhythmia recurrence¹⁰⁵ with the knowledge that as many as 50% of Fontan patients experience atrial tachycardia by 20 years of follow-up.¹⁰³ The goals of Fontan conversion are to excise a portion of the massively dilated right atrium and eliminate underlying atrial arrhythmias. The Fontan anatomy is reconstructed with a lateral tunnel or extracardiac conduit.¹⁰⁶

Surgical considerations when evaluating a patient for possible Fontan conversion are multiple. These patients usually have undergone several previous sternotomies. They are often in a chronically low cardiac output state, and their output drops further with occurrence of atrial arrhythmias. Multisystem dysfunction involvement is common, including hepatic dysfunction,^{107,108} renal dysfunction, and coagulation abnormalities. High central venous pressure leads to increased bleeding during sternal reentry. The electrophysiologic issues may be multiple, and coordination with an experienced electrophysiologist is crucial to success.¹⁰⁶ Risk factors for death, transplant, or dialysis include ventricular dysfunction, ischemic time greater than 100 minutes, age older than 25 years, more than mild atrioventricular valve regurgitation, cardiopulmonary bypass time greater than 240 minutes, and dominant right or indeterminate ventricular morphology.¹⁰⁶

Deal and colleagues reported their experience with Fontan conversion surgery and 117 patients. Late mortality was 5.9% and attributed to intractable heart failure, coronary artery disease, discontinuation from renal dialysis, injury following motor vehicle accident, and sudden death after sedation administration. The overall arrhythmia recurrence was 12.8% during a mean follow-up of 56 months.¹⁰⁹

SUMMARY

Adult congenital heart surgery is a growing discipline with increasing clinical relevance. Many ACHD patients are at risk for poor outcomes because of the natural progression of uncorrected defects and/or

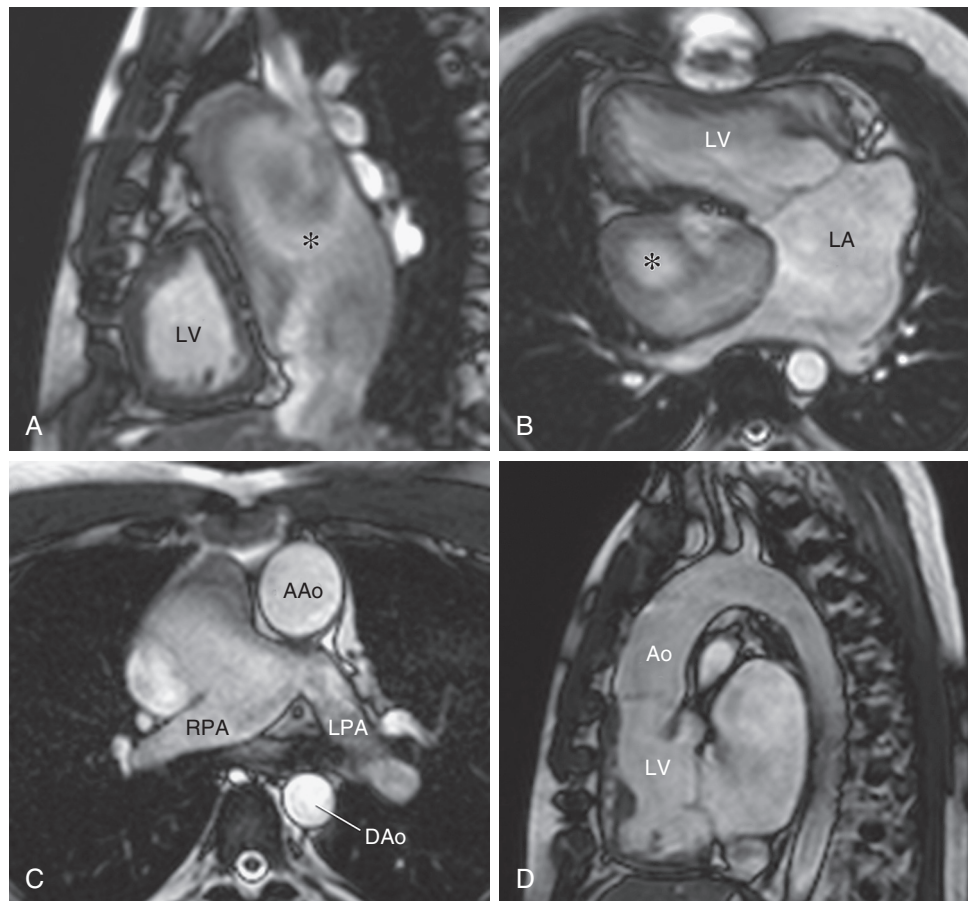


FIGURE 131-9 ■ A 39-year-old patient with dextrocardia and tricuspid atresia who had undergone a modified classic Fontan operation in his childhood who presented with exercise intolerance and atrial fibrillation. **A**, Cine magnetic resonance image (MRI) in an oblique sagittal plane demonstrates a severely dilated right atrial portion of the Fontan pathway (*). **B**, Cine MRI in an axial plane demonstrates dextrocardia and the dilated Fontan pathway (*) in cross-section. **C**, Cine MRI in the axial plane demonstrates the connection of the classic Fontan pathway to the unobstructed branch pulmonary arteries. **D**, Cine MRI in an oblique sagittal plane illustrates the single ventricular outflow. AAo, Ascending aorta; Ao, aorta; DAo, descending aorta; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; RPA, right pulmonary artery.

progression of hemodynamically significant residual lesions. Once the condition is recognized, surgical intervention in the ACHD population can decrease the risk for poor outcomes. This unique population is rapidly growing, and continued development of specialized programs for ACHD care must continue. Surgical subspecialty training and certification in ACHD cardiac surgery has come of age. The success of this field lies in the collaboration of a multidisciplinary team dedicated to life-long care and optimization of outcomes for this population.

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ARRHYTHMIA AND PACEMAKER SURGERY IN CONGENITAL HEART DISEASE

Francis Fynn-Thompson • Frank Cecchin

CHAPTER OUTLINE

INDICATIONS AND TECHNIQUES FOR ELECTROPHYSIOLOGIC DEVICE THERAPY IN PEDIATRIC AND CONGENITAL HEART DISEASE

Pacemakers
Cardiac Resynchronization Therapy
Implantable Cardioverter-Defibrillators
Cardiac Sympathetic Denervation

ARRHYTHMIA THERAPY IN ADULTS WITH CONGENITAL HEART DISEASE

Electrophysiologic Substrates in Congenital Heart Disease

Intra-atrial Reentrant Tachycardia (Atrial Flutter)
Atrial Fibrillation

Accessory Pathways

Ventricular Tachycardia
Sinoatrial Node Dysfunction in Patients with Congenital Heart Disease
Atrioventricular Block in Congenital Heart Disease

Pacemaker and Cardioverter-Defibrillator Implantation in Adults with Congenital Heart Disease

SUMMARY

The progress in the management of cardiac arrhythmias related to congenital heart disease (CHD) over the past 40 years mirrors the improvement in outcomes associated with heart disease in children. During the earliest era in the management of CHD, postoperative arrhythmias and heart block were a substantial cause of perioperative mortality. With the advent of direct myocardial pacing and cardiac defibrillation more than 50 years ago, mortality rates dropped substantially. In fact, the earliest history of pacing dates back to the repair of CHD. In 1958, Brockman and colleagues¹ were the first to report the use of a myocardial pacing electrode after repair of a ventricular septal defect. Subsequent advances in arrhythmia detection and therapy coupled with the remarkable progress in pacemaker and defibrillator technology have resulted in a significant evolution in the field of arrhythmia therapy. As a result of the miniaturization of technology and the advances in transvenous techniques, cardiac surgeons have been displaced by the cardiologist in most primary electrophysiologic interventions, both diagnostic and therapeutic. This is especially true in the domain of adult cardiac surgery, where most ablative and pacemaker procedures have been transformed into a transvenous approach performed in the laboratory by cardiologists. Although the same is largely true in treatment of pediatric arrhythmias and arrhythmias associated with CHD,

the inherent size and anatomic constraints in those patients often require more surgical participation in the arrhythmia therapy. There is also a growing population of adults with CHD who have an increasing need for reoperation and arrhythmia surgery as they age.²

INDICATIONS AND TECHNIQUES FOR ELECTROPHYSIOLOGIC DEVICE THERAPY IN PEDIATRIC AND CONGENITAL HEART DISEASE

When pacemakers were first developed in the early 1960s, the implants were all performed by cardiothoracic surgeons using an epicardial approach. Since then, the devices have been adapted to a transvenous approach, and in adults with normal cardiac anatomy, the implants are performed by a cardiologist more than 95% of the time. However, this is not the case for children and CHD patients, for whom congenital cardiac surgeons still perform nearly half of the device procedures. Indications and surgical techniques for the use of electrophysiologic devices in children and CHD patients present the surgeon with unique challenges. A child's chest cavity or vascular dimensions could be too small to host the generator and

leads required, and once implanted, leads could stretch as the child grows, increasing the risk that the leads will later dislodge or fracture. A review of indications and techniques for optimal surgical placement of electrophysiologic devices in the pediatric population is presented.

Pacemakers

The recommendations for permanent pacing in children and patients with CHD are updated regularly. The last update was a practice guideline published in 2012 jointly by the American Heart Association (AHA), the American College of Cardiology Foundation (ACCF), and the Heart Rhythm Society (HRS), and its recommendations are listed in [Box 132-1](#).² A class I indication for pacing exists for atrioventricular (AV) block that persists for more than 7 days after cardiac surgery. (The 7-day cutoff is the starting point, with longer waits for very small or unstable patients who have adequate backup temporary pacing.) The recommendations put special emphasis on age-appropriate heart rates and the presence of CHD or ventricular dysfunction to guide treatment decisions.

Additional indications for permanent pacing may not be as obvious as those listed in the AHA/ACCF/HRS guidelines. If a child with a congenital heart defect requires surgery, it may be prudent to preemptively implant a pulse generator or epicardial leads during the surgery. This can benefit children with preoperative rhythm abnormalities who do not meet the indications listed in [Box 132-1](#), but for whom pacing will be needed postoperatively based on the known natural history of a particular cardiac anomaly or type of surgery. For example, an infant with L-transposition of the great arteries (L-TGA) undergoing ventricular septal defect closure is at risk for complete AV block, even without cardiac surgery, and may benefit from prophylactic epicardial lead placement. Such placement can also assist children undergoing Fontan revision surgery in conjunction with an atrial maze procedure that is likely to result in sinus node dysfunction.³ Careful preoperative screening with 24-hour Holter monitors and electrocardiography (ECG) can help to select the patients who would benefit from prophylactic epicardial lead placement.

BOX 132-1 Recommendations for Permanent Pacing in Children, Adolescents, and Patients with Congenital Heart Disease

CLASS I

1. Advanced second- or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output. (Level of evidence: C)
2. Sinus node dysfunction with correlation of symptoms during age-inappropriate bradycardia. The definition of bradycardia varies with the patient's age and expected heart rate. (Level of evidence: B)
3. Postoperative advanced second- or third-degree AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery. (Level of evidence: B)
4. Congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction. (Level of evidence: B)
5. Congenital third-degree AV block in the infant with a ventricular rate less than 55 beats/min or with congenital heart disease and a ventricular rate less than 70 beats/min. (Level of evidence: C)

CLASS IIA

1. Congenital heart disease and sinus bradycardia for the prevention of recurrent episodes of intra-atrial reentrant tachycardia; sinus node dysfunction may be intrinsic or secondary to antiarrhythmic treatment. (Level of evidence: C)
2. Congenital third-degree AV block beyond the first year of life with an average heart rate less than 50 beats/min, abrupt pauses in ventricular rate that are two or three times the basic cycle length, or associated with symptoms resulting from chronotropic incompetence. (Level of evidence: B)
3. Sinus bradycardia with complex congenital heart disease with a resting heart rate less than 40 beats/min or pauses in ventricular rate longer than 3 seconds. (Level of evidence: C)

4. Congenital heart disease and impaired hemodynamics because of sinus bradycardia or loss of AV synchrony. (Level of evidence: C)
5. Unexplained syncope in the patient with prior congenital heart surgery complicated by transient complete heart block with residual fascicular block after a careful evaluation to exclude other causes of syncope. (Level of evidence: B)

CLASS IIB

1. Transient postoperative third-degree AV block that reverts to sinus rhythm with residual bifascicular block. (Level of evidence: C)
2. Congenital third-degree AV block in asymptomatic children or adolescents with an acceptable rate, a narrow QRS complex, and normal ventricular function. (Level of evidence: B)
3. Asymptomatic sinus bradycardia after biventricular repair of congenital heart disease with a resting heart rate less than 40 beats/min or pauses in ventricular rate longer than 3 seconds. (Level of evidence: C)

CLASS III

1. Transient postoperative AV block with return of normal AV conduction in the otherwise asymptomatic patient. (Level of evidence: B)
2. Asymptomatic bifascicular block with or without first-degree AV block after surgery for congenital heart disease in the absence of prior transient complete AV block. (Level of evidence: C)
3. Asymptomatic type I second-degree AV block. (Level of evidence: C)
4. Asymptomatic sinus bradycardia with the longest relative risk interval less than 3 seconds and a minimum heart rate greater than 40 beats/min. (Level of evidence: C)

Epicardial pacing, the predominant method of pediatric pacing until relatively recently, is now used mainly for patients in whom transvenous pacing is contraindicated or who are undergoing concomitant heart surgery. Some of the contraindications to transvenous pacing include prosthetic tricuspid valves, right-to-left intracardiac shunts, CHD or surgery precluding transvenous access to the cardiac chambers, and small patient size.⁴ Although there are no absolute technical limitations to a transvenous route except in premature infants, venous capacitance and lead failure resulting from growth are important considerations. Although each institution should make individual decisions on the basis of local procedural capabilities and experience, we generally consider transvenous pacemaker implants in children weighing more than 10 kg.

Epicardial leads are available with sutureless (screw-on) or suture-on methods of fixation. Alternatively, a standard transvenous lead can be used in postoperative CHD patients with epicardial scarring. The transvenous lead can be placed using a transmural technique, with the lead passed through the myocardial wall and attached to the endocardium.⁵ The steroid-eluting suture-on epicardial leads are our preferred lead, because the steroid can suppress the subacute threshold rise resulting from tissue inflammatory response. Several studies have shown that these steroid-eluting leads have good intermediate-term performance, with stable acute and chronic pacing and sensing thresholds and longevity similar to transvenous leads.⁶⁻⁹ However, screw-on leads may be preferable for patients who have undergone prior heart surgery, as the depth of scarring can hinder suture-on techniques.

Bipolar pacing is particularly advantageous in patients with abdominal muscle stimulation, those at risk for phrenic nerve stimulation, and those with oversensing problems. Bipolar steroid-eluting suture-on epicardial leads are available, or two unipolar sutureless leads can be joined together into a bipolar pulse generator.

The surgical access can be from a midline sternotomy, a left thoracotomy, or a subxiphoid approach or via video-assisted thoracoscopy.¹⁰ Each method has advantages, but the aim is to allow implantation of the proper number of leads in an individual patient. Finding an optimal site for maintenance of acceptable long-term pacing and sensing thresholds can be difficult because of bleeding, limited myocardial access, myocardial scarring, and pericardial adhesions. In patients with prior extensive right atrial (RA) surgery, left atrial pacing sites and the Bachmann bundle in general have better chronic pacing and sensing thresholds than do right lateral or anterior atrial sites.¹¹ A left thoracotomy can be used for implantation of left atrial epicardial leads in children with CHD.¹² In small infants, short leads (15-25 cm) should be used because long leads left in the pericardial space can ensnare the heart, as noted in several case reports of cardiac strangulation or constriction of a great vessel by pacing leads.^{13,14}

The site of pacing is being recognized as an important determinant of ventricular performance. The systemic ventricle is the chamber of choice to pace and best if it is performed in an apical location.¹⁵ Annular and high outflow tract locations produce worse dyssynchrony. The

effects of pacing site on ventricular performance depend on baseline ventricular function. If ventricular dysfunction is present, it is better to expand the surgical entry access than to pace at a site known to produce ventricular dysfunction.

Once the leads are placed and tested, the pacemaker is typically set in a subrectus pocket, but in very small infants (<3 kg), the generator and leads can be left in the pleural cavity. Although uncommon, the abdominal-positioned generators can migrate into the pericardium,¹⁶ peritoneum,¹⁷ or pelvic space—a complication most often seen in very small infants.

Cardiac Resynchronization Therapy

Biventricular pacing is a treatment used in patients with symptomatic drug-refractory heart failure secondary to dilated cardiomyopathy and associated interventricular conduction delay or dyssynchrony. The aim of cardiac resynchronization therapy (CRT) treatment is to correct AV asynchrony, nonuniformity of ventricular activation, contraction, and relaxation sequences, while providing sequences that are as homogeneous as possible. The data in children for this therapy consist of retrospective reviews rather than the randomized trials seen in adults.

Indications for CRT are well established for adults with normal cardiac anatomy, but not for children and patients with CHD.^{18,19} The standard adult indication for CRT is a QRS duration of greater than 120 msec, an ejection fraction less than 35%, and class II heart failure. Unfortunately, this combination rarely occurs in children. Although 90% of adults meeting these criteria have left bundle branch block, it is more common in patients with CHD such as tetralogy of Fallot to have right bundle branch block and right ventricular (RV) dysfunction. Thus standard criteria for CRT rarely are applicable in the CHD population. CRT in CHD is thus used mainly in cases of poor ventricular function and increased QRS duration (>120 msec) regardless of the QRS morphology.

Types of CRT available are biventricular, dual site, multisite, and temporary. In biventricular pacing, two distinct ventricles are present, with a pacing lead on each ventricle. If two sites on the same ventricle are paced, then it is called *dual-site pacing*. When the systemic ventricle is a single ventricle, then dyssynchrony can be decreased by pacing two widely separate sites on the same ventricle, a maneuver called *multisided pacing*. For children, temporary CRT has been used to improve cardiac output in the early postoperative setting.^{20,21}

Implantable Cardioverter-Defibrillators

Indications for implantable cardioverter-defibrillator (ICD) implantation are listed in [Box 132-2](#). The majority of ICDs are implanted via the transvenous route, but this might not be possible in small patients or those with anatomic constraints. Because ICD leads are larger and prone to fibrosis at the coils, patient size limitations for a transvenous system are different from those for a pacemaker. We try to limit transvenous ICD implantation to children who weigh more than 30 kg.

BOX 132-2 Recommendations for ICD Therapy in Children, Adolescents, and Patients with Congenital Heart Disease

CLASS I

1. ICD implantation is indicated in the survivor of cardiac arrest after evaluation to define the cause of the event and to exclude any reversible causes. (Level of evidence: B)
 2. ICD implantation is indicated for patients with symptomatic sustained VT in association with congenital heart disease who have undergone hemodynamic and electrophysiologic evaluation.
- Catheter ablation or surgical repair may offer possible alternatives in carefully selected patients. (Level of evidence: C)

CLASS IIA

1. ICD implantation is reasonable for patients with congenital heart disease with recurrent syncope of undetermined origin in the presence of either ventricular dysfunction or inducible ventricular arrhythmias at electrophysiologic study. (Level of evidence: B)

CLASS IIB

1. ICD implantation may be considered for patients with recurrent syncope associated with complex congenital heart disease and advanced systemic ventricular dysfunction when thorough invasive and noninvasive investigations have failed to define a cause. (Level of evidence: C)

CLASS III

1. ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an

acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the class I, IIA, and IIB recommendations above. (Level of evidence: C)

2. ICD therapy is not indicated for patients with incessant VT or VF. (Level of evidence: C)
3. ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up. (Level of evidence: C)
4. ICD therapy is not indicated for NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D. (Level of evidence: C)
5. ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease. (Level of evidence: C)
6. ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, right or left ventricular outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease). (Level of evidence: C)
7. ICD therapy is not indicated for patients with ventricular tachyarrhythmias because of a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma). (Level of evidence: B)

CRT-D, Cardiac resynchronization therapy with defibrillator; *ICD*, implantable cardioverter-defibrillator; *NYHA*, New York Heart Association; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

Epicardial patches were once used regularly, but they were prone to breakage, infection, and pericardial restriction. Newer techniques use coils placed in subcutaneous or pericardial positions.²² The implantation can be performed as a hybrid procedure using an epicardial or transvenous sensing lead or as a completely subcutaneous system using a far-field electrogram for sensing. The three coil types currently available for hybrid procedures are the subcutaneous coil, superior vena cava (SVC) coil, and standard transvenous lead. The completely subcutaneous system is best used in patients with large body habitus and normal cardiac situs or those without transvenous access to the heart.²³ In young children, there have been issues of both ventricular oversensing and undersensing in addition to pocket erosion.²⁴

Because of the smaller surface area of the coils and the thoracic structure interference, proper can and lead placement is essential to obtain adequate defibrillation thresholds. To achieve the lowest defibrillation energy requirements, it is best if the center of the ventricular mass is between the coil and the can. The coil should not enter the pacemaker pocket, because this can result in a short circuit and device failure.

The two basic approaches used for nontransvenous ICD implantation are a minimally invasive approach and a full exposure via sternotomy or thoracotomy. The minimally invasive approach is preferred for patients with no prior heart surgery.

In the basic implantation sequence, a bipolar epicardial pacing lead is first placed, followed by a coil in the pericardial or pleural cavity. When a minimally invasive procedure is used, an active fixation transvenous lead is placed blindly into the posterior pericardial space, followed by extension of the screw to hold the coil in a stable position. The pace or sense connector is then capped. Intraoperative fluoroscopy or portable chest radiography is used to confirm proper lead position. If full exposure of the heart is available, a 5-cm SVC coil can be sutured directly in position. In levocardia, the best configuration is a high left lateral lead and right subrectus pocket (Fig. 132-1). Finally, defibrillation testing is performed, and if the defibrillation threshold is inadequate, then a second coil (length, 25 or 5 cm) is placed in a subcutaneous or pericardial location on the opposite side.

Cardiac Sympathetic Denervation

Left cardiac sympathetic denervation (LCSD), also known as *left cervical stellate ganglionectomy*, was first described in 1971.^{24a} Although LCSD is considered a highly effective method of surgical antiadrenergic therapy, its clinical use has been limited to a narrow set of indications. The procedure has been used primarily at a few centers for patients affected by the long QT syndrome (LQTS), and who are suboptimally controlled with standard medical therapy, usually consisting of beta-adrenergic

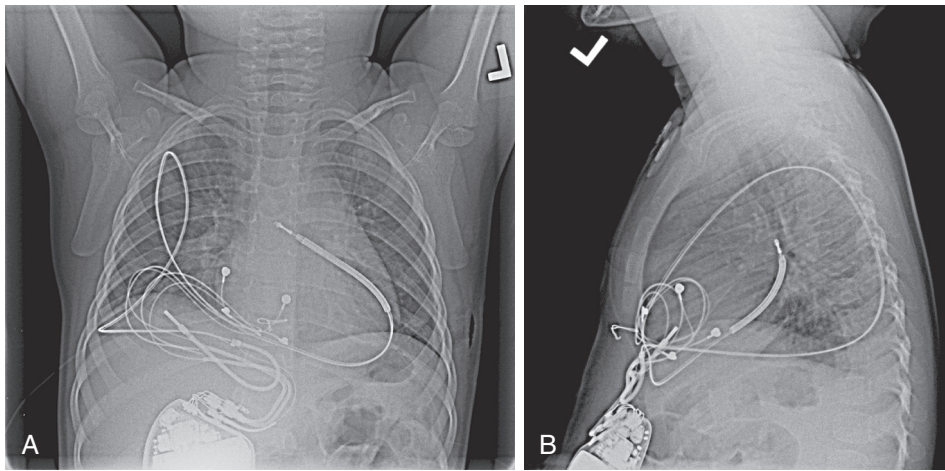


FIGURE 132-1 ■ Chest radiographs of an infant who underwent a minimally invasive nontransvenous cardioverter-defibrillator implantation. **A**, Anteroposterior view. **B**, Lateral view. Note the use of a standard transvenous lead in the pericardial cavity.

blocking medications. A recent multicenter report on a series of LQTS patients having undergone LCSD documented the efficacy of this intervention.^{24b} It reported on 147 patients having undergone LCSD, with 99% having been symptomatic and 48% having suffered an aborted cardiac arrest before the operation. On a mean follow-up of 7.8 years after LCSD, 46% were asymptomatic and ICD shocks decreased by 95%.

A more recent and emerging indication is in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT), a disorder of abnormal myocardial calcium homeostasis,²⁵ characterized by life-threatening ventricular arrhythmias triggered during states of high sympathetic output. Patients with CPVT typically have structurally and functionally normal hearts and a normal baseline electrocardiogram, including a normal QTc measurement.

The surgical technique used in performing the LCSD varies among centers.²⁴ Li and colleagues²⁶ reported the first small series of LQTS patients undergoing LCSD using the video-assisted thoracoscopic surgery (VATS) approach. We recently reported our experience^{27,28} with 24 young pediatric patients who underwent high left thoracic sympathectomy denervation using VATS, of whom 13 were diagnosed with LQTS, nine had CPVT, and two had idiopathic medically refractory ventricular tachycardia (VT). The LCSD procedure on all patients was performed by means of a left-sided VATS approach. After left lung isolation with a double-lumen endotracheal tube or the use of a bronchial blocker, the patient was positioned in a partial right lateral decubitus position. Three small stab incisions were made in the left side of the chest along the midaxillary line, with one incision at the level of the third intercostal space, one at the fourth, and one at the fifth. The first incision was used for the camera, the second for a grasper (or lung retractor if needed), and the third for the electrocautery hook dissector ([Fig. 132-2B](#)). After identifying the structures in the apex of the posterior chest wall and the heads of the ribs, the pleura was incised medial to the heads of the ribs, and the sympathetic chain was identified from the level of

about T1 to T5 (see [Fig. 132-2A](#)). Using electrocautery, the sympathectomy involved transection of the left sympathetic chain at the level of T1, sparing the superior aspect of the stellate ganglion, and then at T5, as well as transection of the associated lateral nerves of Kuntz between those levels.

No severe complications were related to the procedure. Minor and transient postoperative complications occurred in only three patients. Only one patient experienced recurrent but transient arrhythmia in the immediate postoperative period. Longer-term follow-up was available in 22 of 24 patients at a median follow-up of 28 months (range, 4-131 months). Sixteen (73%) of the 22 patients experienced a marked reduction in their arrhythmia burden, with 12 (55%) becoming completely arrhythmia free after sympathectomy. Six (27%) of the patients were nonresponsive to treatment; each had persistent symptoms at follow-up.

This emerging early experience supports the use of cardiac sympathectomy as an effective adjunctive therapy that may be particularly useful for patients who are refractory or intolerant to medical therapy, as well as for patients who receive excessive ICD shocks. LCSD using VATS provides a minimally invasive approach that appears effective and safe, although longer-term follow-up is still required.

ARRHYTHMIA THERAPY IN ADULTS WITH CONGENITAL HEART DISEASE

The number of adult patients with CHD continues to increase. It is estimated that there are currently 2 more than 1 million adults with CHD in the U.S., more than 100,000 in Canada, and 1.8 million in Europe.^{28a,29} Many of these patients bear the weight of many decades of long-standing alterations in the volume- and pressure-loading conditions that result from their heterogeneous and often palliated anatomic arrangements. Approximately 50% are classified as having moderate or severe disease (e.g., tetralogy of Fallot, Ebstein anomaly,

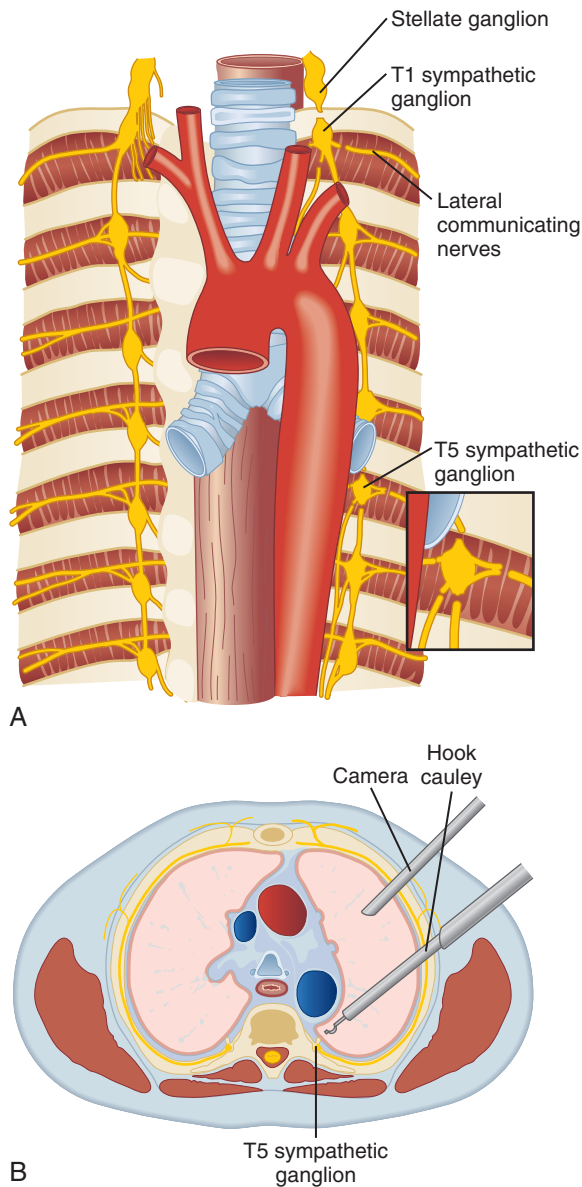


FIGURE 132-2 ■ High left thoracic sympathectomy. **A**, The parietal pleura is scored with electrocautery at the T5 level, revealing the underlying left sympathetic chain, which runs along the posterior chest wall just medial to the heads of the ribs. **B**, The parietal pleural incision is carried up to the T1 level with electrocautery, and the sympathetic chain is divided at the T1 and the T5 level and then isolated by division of all lateral branches.

single-ventricle palliations). Although arrhythmias can develop with even mild disease, the incidence is highest for patients in the moderate and severe categories. As a result of the substantial and cumulative disease burden, cardiac arrhythmias late in life are a substantial source of morbidity, hospital admissions, and mortality for adults with CHD.²⁹ They exhibit the full spectrum of arrhythmia issues, and their complex management presents challenges that are often considerable and shared equally by cardiologist and cardiac surgeon.

Electrophysiologic Substrates in Congenital Heart Disease

Intra-atrial Reentrant Tachycardia (Atrial Flutter)

The most common mechanism for symptomatic tachycardia in the adult CHD population is macroreentry in atrial muscle.³⁰ The terms *intra-atrial reentrant tachycardia* (IART) and *incisional tachycardia* have become common labels for this arrhythmia, to distinguish it from the typical variety of atrial flutter that occurs in structurally normal hearts.³¹⁻³³ Generally, IART tends to be slower than typical flutter, with atrial rates in the range of 150 to 250 beats per minute. In the setting of a healthy AV node, such rates frequently conduct in a rapid 1:1 atrial-to-ventricular pattern that can result in hypotension, syncope, or possibly cardiac arrest.^{34,35} Even if the ventricular response rate is safely titrated, sustained IART can cause debilitating symptoms in some patients from loss of AV synchrony, and it may contribute to thromboembolic complications³⁶ when the duration is protracted. Usually, IART appears many years after operations that involved an atriotomy or other surgical manipulation of RA tissue. It can follow simple procedures such as closure of an atrial septal defect on occasion, but the incidence is higher among patients with advanced dilation, thickening, and scarring of the right atrium.^{37,38} Other risk factors for IART include concomitant sinus node dysfunction ("tachy-brady" syndrome) and older age at time of heart surgery.³⁹

Thus, IART is a particular problem for older patients who have undergone the Mustard, Senning, or older-style Fontan operations, in which extensive suture lines and long-term hemodynamic stress result in markedly abnormal atrial myocardium. The route of propagation for an IART circuit varies according to the anatomic defect and type of surgical repair.⁴⁰ It is usually restricted to RA tissue (regardless of the surgical destination of this tissue) and is modulated by regions of fibrosis from suture lines or patches, which function in combination with natural conduction barriers (crista terminalis, valve orifices, and the superior and inferior caval orifices) to channel the wave front along a macro-reentrant loop.^{41,42} If a tricuspid valve is present, the isthmus between the valve ring and the inferior vena cava is a common component of such circuits, but when the tricuspid valve is absent or otherwise deformed, the circuits follow less predictable paths that can be deciphered only by formal electrophysiologic mapping. Frequently, multiple IART circuits are present in the same patient.⁴³ Once recognized, IART can be terminated with electrical cardioversion,⁴⁴ overdrive pacing maneuvers,⁴⁴ or administration of certain class I or III antiarrhythmic drugs.

The far more difficult task is prevention of recurrence. Multiple strategies have been developed for IART prevention, all of which can have value in certain patients, but none of which represents a universal solution. If the episodes are infrequent, well tolerated, and recognized promptly, it may be sufficient to rely on periodic cardioversion before embarking on more involved therapy. However, if IART episodes become frequent, cause

significant symptoms, or are associated with atrial thrombus formation, aggressive treatment is indicated. The therapeutic options for IART include (1) antiarrhythmic drugs, (2) pacemaker implantation to correct bradycardia or provide automatic atrial antitachycardia pacing, (3) catheter ablation, and (4) surgical intervention with a modified atrial maze operation. The choice must be tailored to the hemodynamic and electrophysiologic status of the individual patient. Chronic antiarrhythmic drugs are still prescribed in some cases, but the broad experience with pharmacologic therapy for this condition has been discouraging,^{34,45} even when potent agents such as amiodarone are used. Pacemaker implantation may be reasonable for patients with a picture of tachy-brady syndrome.³⁵ Pacemakers with advanced programming features that incorporate atrial tachycardia detection and automatic burst pacing to interrupt reentry may also be beneficial in select cases.^{35,46} Catheter ablation is now used at many centers as an early intervention for IART.⁴⁷ The technique has evolved rapidly since the introduction of three-dimensional mapping for improved circuit localization.^{31,48} When these technologies are combined with good anatomic definition and traditional electrophysiologic mapping maneuvers, short-term success rates of nearly 90% can be achieved.

Unfortunately, later tachycardia recurrence is still disappointingly common. The recurrence risk is particularly high (nearly 40%) among Fontan patients, who tend to have the largest number of IART circuits and the thickest or largest atrial dimensions. Although far from perfect, ablation outcomes for IART are likely to improve with continued experience and even now are far superior to the degree of control obtained with medications alone. Furthermore, even if IART episodes are not eliminated entirely by ablation, the procedure can often provide substantial improvement by reducing the frequency of episodes and eliminating the need for ongoing drug therapy.⁴⁸ If these measures fail to prevent IART, or if the patient is returning to the operating room for hemodynamic reasons, consideration should be given to surgical ablation during an RA maze operation. This procedure is used most often for the Fontan population with the most refractory variety of IART, and it is usually combined with revision of the Fontan connection from an older atriopulmonary anastomosis to a modern cavopulmonary connection in the same setting.⁴⁹

The Fontan operation for patients with a single ventricle results in extensive suture lines and abnormal hemodynamics that predispose patients to atrial tachycardias and sinus node dysfunction. Up to 50% of patients with a single ventricle who have undergone older-style Fontan operations develop atrial tachycardia within a decade of surgery. Fontan conversion has been proposed for patients suffering from a variety of late sequelae, including conduit and vascular obstruction, atrial arrhythmias, protein-losing enteropathy, and thrombotic complications. However, documented benefits have been limited to a small number of centers and over short follow-up periods, compared with the relatively extensive data available on initial Fontan procedures.^{50,51} Fontan conversion can provide symptomatic improvement in patients with late complications associated with this

circulation, including atrial tachycardias.⁵²⁻⁵⁴ Criteria for optimal patient selection and anticipated clinical outcomes remain controversial. Conversion alone does not appear to protect against recurrent atrial tachycardias,⁵⁵⁻⁵⁷ whereas concomitant maze surgery can suppress postoperative tachycardia.⁵⁸⁻⁶⁰ Several different surgical approaches have been reported in this heterogeneous patient population. The most recent series from eight centers that have reported outcomes on 10 or more patients have noted variable conversion failure rates, with an aggregate rate of death or transplantation of 8.4% in follow-up of a total of 203 patients.^{53,54,61-67} Significant long-term morbidities, such as renal failure, thrombotic events, and arrhythmia, have likewise been reported.

At Children's Hospital Boston, 40 patients underwent Fontan conversion between 1990 and 2006, 21 (53%) with and 19 (48%) without concomitant arrhythmia surgery.⁶⁸ Table 132-1 summarizes baseline characteristics and surgical considerations in all patients and according to whether they had arrhythmia surgery. Clinical indications for conversion included surgically correctable anatomic lesions ($n = 28$), thrombi ($n = 4$), intracardiac right-to-left shunting ($n = 4$), and medically refractory atrial tachyarrhythmia ($n = 29$), with 16 patients having more than one indication. Four patients had protein-losing enteropathy. In the 39 patients with preoperative catheterization, the ventricular end-diastolic pressure was 9.8 (1.0-22.0) mm Hg, with four having values greater than 12 mm Hg. Preexisting atrial arrhythmias were present in 29 (73%) patients; 10 had macro-reentrant atrial tachyarrhythmia, and 19 had atrial fibrillation (paroxysmal in 12; persistent in 7). Surgical characteristics are summarized in Table 132-1. Twenty-two patients (55%) had a 4-mm fenestration at the time of conversion. Resection of a large portion of the anterior RA wall was performed on 20 patients (50%). All patients with a biatrial maze procedure had a preoperative history of atrial fibrillation. Of 19 patients with a history of AF, 10 underwent a full maze and four had a limited RA maze procedure. Eighteen patients (45%) had concomitant pacemaker implantation (including six with previously implanted devices), and six additional patients required pacemaker placement postoperatively. Perioperative complications, including bleeding, thrombosis, seizures, and renal dysfunction requiring peritoneal dialysis, were observed (Table 132-2).

Six failed conversions (five perioperative deaths, one transplantation) were seen during follow-up, for an overall rate of 15%. Survival was 84% at 3 years postoperatively. Probability of survival did not differ between the two groups, between operative eras, or by whether an extracardiac conduit or a lateral tunnel revision was performed. Univariate predictors for late postoperative arrhythmia are shown in Table 132-3. Arrhythmia interventions including RA debulking, maze procedure, and pacemaker implantation were associated with reduced risk for late postoperative arrhythmias and lower postoperative atrial tachyarrhythmia severity scores. No independent predictors of improved arrhythmia outcomes were identified.

Our experience, concordant with other reports, suggests that survivors of Fontan conversion experience an

TABLE 132-1 Baseline Characteristics and Surgical Considerations

Characteristic	All Conversions (N = 40)	Concomitant Arrhythmia Surgery		P Value
		Yes: Group 1 (N = 21)	No: Group 2 (N = 19)	
Age at Fontan conversion (yr)*	19.0 (13.0, 25.0)	22.0 (16.6, 31.0)	16.6 (11.3, 23.3)	0.005
Anatomic diagnosis, N (%)				NS
Tricuspid atresia	24 (60)	15 (71)	9 (47)	
Single left ventricle	7 (18)	1 (5)	6 (32)	
Other	9 (23)	5 (24)	4 (21)	
Type of original Fontan, N (%)				0.01
APC	26 (65)	14 (67)	12 (63)	
RA-RV	11 (28)	7 (33)	4 (21)	
LT	2 (5)	0	2 (11)	
ECC	1 (3)	0	1 (5)	
NYHA class before conversion, N (%)				NS
Class I	3 (8)	2 (10)	1 (5)	
Class II	23 (58)	12 (57)	11 (58)	
Class III	14 (35)	7 (33)	7 (37)	
Time from Fontan to conversion (yr)*	14.8 (2.8, 27.6)	16.8 (15.1, 20.3)	10.1 (5.2, 12.3)	<0.0001
Type of Fontan conversion, N (%)				0.01
LT	22 (55)	7 (33)	15 (79)	
ECC	16 (40)	14 (67)	2 (11)	
RA-RV	2 (5)	0 (0)	2 (11)	
Prior atrial tachycardia, N (%)	29 (73)	20 (95)	9 (47)	<0.001
Prior atrial fibrillation, N (%)	19 (48)	14 (67)	5 (26)	0.01
Prior catheter ablation, N (%)	13 (33)	13 (32)	0	<0.0001
Preoperative AT severity score	5.3 ± 3.7	7.3 ± 2.6	3.2 ± 3.6	0.0002
Class III anti-arrhythmic drug, N (%)	14 (35)	14 (67)	0	<0.0001
Concomitant arrhythmia surgery, N (%)				—
Limited RA maze	10 (25)	10 (48)	0	
Full maze	10 (25)	10 (48)	0	
Isthmus cryoablation alone	1 (3)	1 (5)	0	
Pacemaker implantation, N (%)	24 (58)	20 (95)	4 (21)	<0.001
Total bypass time, min	189 ± 76	217 ± 64	159 ± 79	0.02
Aortic cross-clamp time, min	57 ± 36	59 ± 36	55 ± 42	NS

*Non-normally distributed continuous variables are expressed as median (25th and 75th percentiles).

APC, Atriopulmonary connection; AT, atrial tachycardia; ECC, extracardiac connection; LT, lateral tunnel; NS, nonsignificant; NYHA, New York Heart Association; RA, right atrium; RV, right ventricle.

TABLE 132-2 Perioperative Major Complications and Arrhythmia Status in 35 Early Operative Survivors

	All Early Survivors (N = 35)	Concomitant Arrhythmia Surgery		P Value
		Yes: Group 1 (N = 18)	No: Group 2 (N = 17)	
Major complication, N (%)	9 (26)	7 (39)	2 (12)	0.07
Intracranial hemorrhage	2 (6)	2 (11)	0	
Extensive bleeding	1 (3)	1 (6)	0	
Cerebrovascular event/seizure	3 (9)	3 (17)	0	
Thrombus	2 (6)	0	2 (12)	
Renal dysfunction	1 (3)	1 (6)	0	
Maximum serum creatinine (mg/dL)	1.2 ± 0.8	1.4 ± 1.0	1.0 ± 0.7	NS
Late atrial arrhythmia, N (%)	14 (40)	5 (28)	9 (53)	0.13
Atrial tachyarrhythmia severity score	3.5 ± 2.9	3.3 ± 3.0	3.7 ± 3.2	NS
Cardioversion, N (%)	8 (23)	4 (22)	4 (24)	NS
Subsequent catheter ablation, N (%)	3 (9)	1 (6)	2 (4)	NS
Antiarrhythmic drug (class III)	10 (29)	6 (33)	4 (24)	NS

improvement in functional status. However, it is our belief that this cannot be explained by overt hemodynamic improvement, because changes on postoperative catheterizations were often minimal and consistent with the effects of fenestration and, in some patients, simple

relief of conduit obstruction. In patients with preoperative arrhythmia who undergo the maze procedure, decrease in tachycardia occurrence and relief from symptoms is substantial, but it is not universal. In addition, significant morbidities and mortality occur primarily in

TABLE 132-3 Univariate Predictors for Late Postoperative Arrhythmia Status

	Late Atrial Arrhythmia			Improvement of AT Severity Score		
	OR	95% CI	P Value	OR	95% CI	P Value
Preoperative						
Atrial fibrillation	1.1	0.3, 4.4	0.88	0.6	0.1, 2.2	0.41
Interval AT onset to conversion (yr)	1.00	1.00, 1.00	0.20	1.00	1.00, 1.00	0.48
Age at conversion (yr)	0.98	0.90, 1.06	0.72	0.98	0.89, 1.07	0.64
Time to conversion (yr)	1.00	1.00, 1.00	0.34	1.00	1.00, 1.00	0.93
Operative						
Right atrial debulking	0.3	0.1, 1.2	0.09	4.2	1.0, 18.1	0.05
Fenestration	2.0	0.5, 8.3	0.34	1.1	0.3, 4.3	0.89
Maze procedure	0.3	0.1, 1.1	0.07	3.6	0.9, 14.9	0.03
Full maze procedure	0.1	0.0, 1.0	0.05	1.5	0.3, 7.2	0.64
Pacemaker placement	0.2	0.0, 0.7	0.02	5.8	1.3, 25.4	0.02
Follow-up (yr)	1.00	1.00, 1.00	0.02	1.00	1.00, 1.00	0.03

AT, Atrial tachycardia; CI, confidence interval; OR, odds ratio.

the perioperative period and are more frequent in our series than in most other reported series. Finally, other than the unfavorable effect of older age at conversion, strong preoperative and procedural predictors of morbidity and mortality were not identified. In particular, the performance of a maze procedure was not associated with a greater risk, and it provided significant benefit to those patients with preoperative arrhythmia. Overall, our findings suggest that, although electrophysiologic and symptomatic improvement can be obtained with Fontan conversion, it is still unclear whether overall survival is favored by Fontan conversion.

Atrial Fibrillation

The principal hemodynamic derangement and site of surgical scarring in CHD tends to involve right heart structures, so that IART arising from the right atrium is by far the most common form of atrial tachycardia. However, chronic hemodynamic stress is directed toward the left atrium in a subset of CHD patients, and atrial fibrillation can occur as a result. The CHD lesions commonly associated with atrial fibrillation include aortic stenosis, mitral valve deformities, and unrepaired single ventricle.⁶⁹ Management principles are similar to those for atrial fibrillation encountered in other forms of adult heart disease, beginning with medical therapy for anticoagulation and ventricular rate control, followed by electrical or medical cardioversion. As with IART, terminating an isolated atrial fibrillation episode in CHD is not difficult, but prevention of recurrence remains a challenge. Antiarrhythmic drugs can offer long-term protection against recurrence for some patients, but as with IART, pharmacologic therapy has been only marginally successful for this purpose. Pacemaker implantation can reduce atrial fibrillation recurrences in patients with sinus node dysfunction when fibrillation is part of the tachy-brady syndrome. Definitive elimination of atrial fibrillation can be achieved with a combined right and left atrial maze operation, which should be considered if a patient requires surgery to address other hemodynamic issues.⁷⁰

Accessory Pathways

The embryologic milieu responsible for congenital heart defects can have a direct effect on development of the conduction system. Sometimes this takes the form of simple displacement of the AV node and His bundle away from the usual septal position in the Koch triangle,³⁰ but occasionally the malformation results in accessory or duplicated AV connections with the potential for reentrant tachyarrhythmias. The most familiar example involves Ebstein anomaly of the tricuspid valve, which is complicated by Wolff-Parkinson-White syndrome in approximately 20% of cases.⁷¹ The accessory pathways in Ebstein anomaly are typically located along the posterior and septal aspect of the tricuspid ring where the valve leaflets are most abnormal,³² and nearly half of these patients are found to have multiple accessory pathways.^{33,72} The same observations hold true for patients with L-TGA, who not infrequently have Ebstein malformation in association with accessory pathways along their left-side tricuspid valve. Tachycardia events for patients with Ebstein anomaly become increasingly problematic in adolescent and adult years, when atrial dilation increases the likelihood of recurrent atrial flutter or atrial fibrillation with potentially rapid anterograde conduction over the accessory pathways. Definitive therapy with catheter ablation is currently viewed as the standard of care for patients with Ebstein anomaly and Wolff-Parkinson-White syndrome. However, compared with ablation for simple accessory pathways in a structurally normal heart, the short-term success rate appears lower, and the risk of recurrence higher, with Ebstein anomaly.^{37,38}

Ventricular Tachycardia

Serious ventricular arrhythmias are rare among CHD patients during their first decade or two of life, but once adulthood is reached, the potential for VT and sudden death becomes a looming concern in certain cases. Patients at greatest risk for developing VT appear to be

those who have undergone a ventriculotomy or patching for certain types of ventricular septal defects. In this scenario, the mechanism for VT is reminiscent of the macroreentrant circuits described earlier for IART, involving narrow conduction corridors defined by regions of surgical scar^{73,74} in conjunction with natural conduction barriers, such as the rim of a septal defect or the edge of a valve annulus. Less commonly, ventricular arrhythmias can develop independently of direct surgical scarring whenever a long-standing hemodynamic overload causes advanced degrees of ventricle dysfunction or hypertrophy. Examples of CHD lesions that can eventually lead to this myopathic variety of VT include (1) aortic valve disease,^{75,76} (2) L-TGA when the right ventricle has been recruited as the systemic ventricle,⁷⁷ (3) severe Ebstein anomaly, (4) certain forms of single ventricle, (5) Eisenmenger syndrome, and (6) unrepaired tetralogy of Fallot.⁷⁸

The bulk of literature and clinical experience regarding VT in CHD has centered on tetralogy of Fallot. The prevalence of VT after tetralogy repair has been estimated to be between 3% and 14% in several large clinical series.^{46,79-83} Some patients with slow VT may be hemodynamically stable at presentation, but VT tends to be rapid for the majority, causing syncope or cardiac arrest to be the presenting symptom. Although rare cases of abrupt AV block or rapidly conducted IART have been linked to catastrophic outcomes in patients with tetralogy,⁸⁴ sustained VT appears to be the single biggest contributor to the incidence (2% per decade) of sudden cardiac death.^{46,81,85-87}

Predicting VT events in patients with tetralogy has been a topic of intense investigation for nearly 30 years. To date, no perfect risk-stratification scheme has emerged, although several clinical variables with modest prognostic value have been identified, including (1) older age at time of definitive surgery, (2) history of palliative shunts, (3) high-grade ventricular ectopy, (4) inducible VT at electrophysiologic study, (5) abnormal RV hemodynamics, and (6) wide QRS width (180 msec). The correlation between QRS duration and VT^{46,82} is not surprising when one considers that the most dramatic degree of QRS prolongation tends to be seen among tetralogy patients with highly dysfunctional and dilated right ventricles. A recent cohort of 873 patients with tetralogy of Fallot from four large centers identified the following factors to be associated with death and sustained VT: RV mass-to-volume ratio ≥ 0.3 g/mL, left ventricle ejection fraction z-score < -2.0 , history of atrial tachyarrhythmia and elevated RV systolic pressure.^{87a}

When viewed in the aggregate, this long list of variables helps to define a clinical profile for the tetralogy patient at risk, but no single item can be viewed as completely independent, and none provides perfect predictive accuracy. To compensate for lack of specificity, the practical approach to VT risk stratification in older patients with tetralogy usually incorporates attention to symptom status. Certainly, any patient who has survived a cardiac arrest or sustained VT is treated aggressively, usually with an ICD.^{88,89} However, in the absence of a serious clinical event, a careful inquiry for more subtle symptoms

is often required to determine whether additional testing or treatment is needed.

At most centers, tetralogy patients who report concerning symptoms of palpitations, dizziness, or syncope usually undergo invasive evaluation with hemodynamic catheterization and an electrophysiology study. Programmed ventricular stimulation provides reasonably good predictive information on the risk of future clinical VT events.^{90,91} A positive study may prompt implantation of a primary-prevention ICD,⁸⁰ or, if monomorphic VT can be induced and is tolerated long enough to permit mapping, catheter ablation of the VT circuit might be considered.⁹²⁻⁹⁵ An electrophysiology study might also uncover IART as a contributing or confounding factor for a patient's symptoms, which could be addressed with ablation at the same time. Correctable hemodynamic issues could also be identified at catheterization and could shift therapy toward a surgical solution, such as relief of valve regurgitation combined with formal intraoperative VT mapping and ablation.⁹⁶

The proper approach to an entirely asymptomatic adult with repaired tetralogy remains unsettled. Most clinicians rely on a yearly evaluation with history and ECG, supplemented regularly with Holter monitoring or exercise testing to screen for high-grade ventricular ectopy, along with periodic echocardiography or magnetic resonance imaging to monitor the status of the right ventricle. Should nonsustained VT be detected on surveillance monitoring in an asymptomatic patient, or should RV function appear to be deteriorating, opinions still vary widely as to the appropriate response. Some clinicians advocate an electrophysiologic study to refine the arrhythmia risk, some recommend pulmonary valve replacement, some prescribe antiarrhythmic drugs, some implant a primary prevention ICD, and some might refrain from any treatment as long as the patient remains symptom free. Therapy continues to be individualized for asymptomatic patients depending largely on institutional experience and philosophy. With few exceptions,^{46,90} studies have been limited to single-center investigations with limited statistical power. Furthermore, because the event rate for sustained VT and sudden death in patients with CHD is low compared with conditions such as ischemic heart disease, the duration of prospective follow-up necessary to answer questions in the CHD field would probably have to extend beyond 10 years. Now that the population of adults with CHD at risk for VT has reached such a substantial size, the opportunity may finally have arrived for an organized assessment of VT management.

Sinoatrial Node Dysfunction in Patients with Congenital Heart Disease

Developmental defects involving the caval-atrial junction can be associated with atypical anatomy and function for the sinoatrial node. This issue is most relevant to complex forms of heterotaxy syndrome in patients with a single ventricle. In the asplenia variety of heterotaxy, bilateral superior caval veins often exist, each with its own sinoatrial node, which results in an interesting ECG pattern of fluctuation between two discrete P

waves at physiologic rates. Apart from the unusual ECG, the coexistence of two sinus nodes is of minimal clinical consequence. In contrast, patients with the polysplenia type of heterotaxy may lack a true sinus node altogether, which makes atrial depolarization dependent on slower atrial or junctional escape rhythms.⁵⁶ Most patients with this rare condition will ultimately require pacemaker implantation. A more common cause of sinus bradycardia in adults with CHD is surgical trauma to the sinoatrial node or its artery, as can occur during the Mustard, Senning, Glenn, and Fontan operations.^{30,39,97,98} Chronotropic incompetence is poorly tolerated in CHD patients with compromised hemodynamics, especially those with a single ventricle or AV valve regurgitation. The likelihood of a patient developing IART or atrial fibrillation is also increased significantly in this setting.³⁹ Implantation of a single- or dual-chamber pacing system is currently recommended⁹⁹ as a class I indication for any patient with CHD and sinoatrial node dysfunction who has symptoms directly attributable to slow heart rate. Pacemaker implantation is also advised as a class IIb indication for CHD patients with resting rates of 40 beats/min or sinus pauses in excess of 3 seconds, even in the absence of symptoms.

Atrioventricular Block in Congenital Heart Disease

The AV conduction tissues may be congenitally abnormal in terms of both location and function in specific forms of CHD, most notably L-TGA and endocardial cushion defects.¹⁰⁰⁻¹⁰² In the former condition, the AV node and His bundle are displaced in an anterior direction away from the usual position in the Koch triangle, whereas in the latter, the AV node and His bundle are displaced posterior to the Koch triangle. The functional properties of these displaced conduction systems are often abnormal. With L-TGA, it is estimated that 3% to 5% of patients will have complete AV block at birth, and an additional 20% will develop spontaneous complete block by adulthood.^{103,104} Even when intrinsic conduction appears normal, these patients appear to be more susceptible to traumatic AV block during surgical or catheter procedures. Surgical repair of certain forms of CHD can result in direct trauma to the AV conduction tissues. Although improved knowledge of the precise location for the AV node and His bundle in various forms of CHD^{30,61,101,105} has reduced the occurrence, closure of some ventricular septal defects, surgery for left-heart outflow obstruction, and replacement or repair of an AV valve may still be complicated by AV block. Fortunately, in more than half of cases, this injury is a transient affair related to myocardial stretch or edema rather than to the physical severing of the conduction tissues, and AV conduction recovers within 7 days of operation.¹⁰⁶ However, for any patient with postoperative AV block that is not expected to resolve or that persists at least 7 days after cardiac surgery, permanent pacemaker implantation is advised⁹⁹ as a class I indication. A pacemaker may be considered by some as a class IIb indication when surgical AV block recovers but the patient is left with permanent bifascicular block.⁸⁴

Pacemaker and Cardioverter-Defibrillator Implantation in Adults with Congenital Heart Disease

Standard transvenous systems are often contraindicated or difficult in CHD patients because of complexities of venous anatomy or because of the presence of significant intracardiac shunting that creates a thromboembolic risk from intravascular leads. Epicardial implantation is often indicated in these circumstances, although the surgery is more involved, and long-term lead performance may be inferior to transvenous systems. Epicardial lead placement in an older patient with CHD who has undergone multiple prior cardiac operations presents the surgeon with a highly scarred mediastinum; dissection down to the myocardial surface must be performed carefully and deliberately to uncover sites with good sensing and pacing function. Careful preoperative planning is often critical, and it is imperative for the surgeon to review all the imaging studies available including chest radiographs, angiograms, and echocardiograms. Many older patients also have chest computed tomography images or magnetic resonance images that are particularly helpful in providing a roadmap for the anatomic relationships and ventricular geometry. After reviewing these studies, a surgeon can often tailor the surgical approach to minimize the need for a large reoperative procedure by using a partial lower median sternotomy incision or a carefully placed limited thoracotomy incision.

If a patient with CHD is undergoing cardiac surgery for other hemodynamic reasons and it appears highly likely that epicardial pacing might be needed at some distant date, the surgeon may want to take advantage of wide intraoperative exposure to place leads for future use and tunnel them under either subcostal region for later easy access. Fortunately, 86% of leads placed at the time of cardiac surgery are found to function well when retrieved at a mean of 252 days after the operation.¹⁰⁷ The indications for ICD implantation in CHD patients are still evolving, but in general they follow guidelines that are similar to those for other varieties of adult heart disease. The most common type of CHD that requires ICD implantation is tetralogy of Fallot, followed by L-TGA and left-sided obstructive diseases.^{88,91} The experience with biventricular resynchronization pacing in CHD patients with depressed ventricular function is limited but promising.¹⁰⁸ Clinical studies are currently underway to refine selection criteria and to investigate the clinical merits of RV resynchronization to offset right bundle branch block after surgical closure of ventricular septal defects and tetralogy repair.

Whether a transvenous or an epicardial approach is being considered, careful preprocedural planning is essential for successful pacemaker or ICD implantation in adults with CHD. Some of these patients have anomalies of systemic venous return and the coronary veins. If pacing in the coronary sinus is needed for cardiac resynchronization or any other purpose, anomalies of the coronary sinus need to be considered, including ostial atresia,¹⁰⁹ unroofed coronary sinus, and extreme dilation caused by persistent left SVC. Venous occlusion is a recognized complication of permanent transvenous pacing

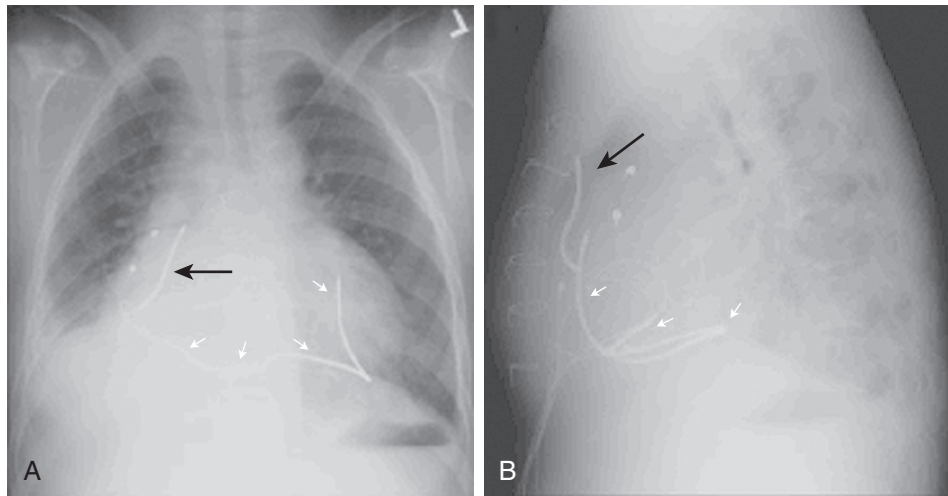


FIGURE 132-3 ■ Chest radiograph of an epicardial implantable cardioverter-defibrillator system in an adult in whom a Kawashima-type Fontan operation was performed for heterotaxy and double-outlet right ventricle. **A**, Posteroanterior projection. **B**, Lateral projection. Defibrillation was obtained via two coils placed in the pericardial space. A short (5-cm) coil is present (*large arrow*), typically used in the superior vena cava and now placed in the pericardial space along the right side of the spine. The second long (25-cm) coil (*small arrows*), normally implanted subcutaneously, lies under the heart and then ascends to the right of the spine.

leads.^{110,111} Venous occlusion is therefore common in adult patients with CHD and long-term pacing, who may have multiple leads in place for several decades. If venous access is needed in the setting of a complete venous occlusion, a variety of techniques for recanalization and venous dilation are now available.¹¹²

Transvenous chamber access can be an issue if complicated atrial baffling has been used to redirect venous return. One major challenge in this regard occurs when ventricular pacing is needed after a Fontan repair. An epicardial approach is used in most of these cases, but successful transvenous ventricular lead implantation after the Fontan operation has now been reported.¹¹³⁻¹¹⁵ Combined challenges of surgical obstacles, chamber access, and unusual ventricular geometry are present in patients with L-TGA after an atrial switch (Mustard or Senning) procedure.¹⁰ Extensive atrial baffling limits sites of atrial capture to small regions in the left atrial appendage (where phrenic nerve stimulation may be hard to avoid), anterior left atrial roof, or SVC to right atrium junction. Baffle obstruction is fairly common in these patients and may require endovascular stent placement before lead placement. In addition, the ventricular lead must be placed in a morphologic left ventricle that is thin and nontrabeculated, which requires close attention to lead-tip fixation and sensing parameters. Intracardiac shunts can lead to embolic stroke via right-to-left shunting or inadvertent lead placement in the systemic circulation.¹¹⁶ Trivial shunts that are predominately left to right are probably not absolute contraindications to transvenous leads, but larger shunts, particularly if right to left, need to be evaluated carefully by angiography or echocardiography before a final decision is made on the route for lead implantation. If transvenous leads are strongly preferred in such cases, shunt closure can be attempted beforehand with interventional techniques such as septal occluders, covered stents, or even surgery.^{117,118} If intracardiac shunting cannot be eliminated satisfactorily, epicardial lead

placement is probably the wisest alternative. Transvenous ICD lead implantation requires a thorough understanding of the ventricular anatomy and chamber positions to anchor the lead tip securely and ensure a suitable vector for defibrillation. When epicardial ICD leads are required, there has been a shift away from traditional patches to novel configurations involving coils (Fig. 132-3) placed in a subcutaneous or pericardial position.¹¹⁹ This can often be accomplished through a limited subxiphoid approach or a left mini-thoracotomy to provide access to the posterior pericardial space. The experience with this approach is limited, but it appears to offer increased flexibility that can accommodate a wide variety of ventricular geometries and heart sizes.

SUMMARY

Despite the evolution of the management of arrhythmias associated with CHD away from cardiac surgeons, definitive surgical arrhythmia therapy still plays an important role, but one that has been redefined in the current era. Given the success of transcatheter approaches to treat most forms of arrhythmias, only a small number of patients will require primary surgical ablation. However, with a growing population of adults with CHD, their specific arrhythmia challenges will necessitate the continued collaboration of cardiologist and cardiac surgeon to provide novel and often hybrid solutions. In the future, advances in device technology, implant techniques, and tissue engineering will further reshape arrhythmia therapy in children. Computer-enhanced telemanipulation and advances in lead technology will facilitate more minimally invasive surgical approaches to epicardial lead placement. In addition, resynchronization and multisite pacing will become more important tools in the management of heart failure associated with congenital heart disease.

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QUALITY IMPROVEMENT FOR THE TREATMENT OF PATIENTS WITH PEDIATRIC AND CONGENITAL CARDIAC DISEASE: THE ROLE OF THE CLINICAL DATABASE

Jeffrey P. Jacobs

CHAPTER OUTLINE

NOMENCLATURE

DATABASE

COMPLEXITY STRATIFICATION

DATA VERIFICATION

SUBSPECIALTY COLLABORATION

LONGITUDINAL FOLLOW-UP

QUALITY ASSESSMENT AND QUALITY IMPROVEMENT

SUMMARY: BRIDGING THE GAP FROM ANALYSIS OF OUTCOMES TO IMPROVEMENT OF QUALITY

Although significant progress has been made in the care of patients with pediatric and congenital cardiac disease, complications and death still occur. As a result, optimization of outcomes remains a constant goal. Substantial effort has been devoted to advancing the science of assessing the outcomes and improving the quality of care associated with the treatment of patients with pediatric and congenital cardiac disease.¹⁻²²⁷ The importance of these efforts is supported by the fact that congenital heart defects are the most common birth anomalies, with moderate to severe variants occurring in approximately 6 per 1000 live births.²²⁸

To perform meaningful, multi-institutional outcomes analyses and quality improvement, any database must incorporate the following seven essential elements:

1. A common language and nomenclature*
2. A database with an established uniform core dataset for collection of information[†]

3. A mechanism for evaluating case complexity[‡]
4. A mechanism to ensure and verify the completeness and accuracy of the data collected[§]
5. Collaboration between medical and surgical subspecialties^{||}
6. Standardized protocols for life-long follow-up[¶]
7. Strategies for quality assessment and quality improvement**

The foundation of these seven elements is the use of a common language and nomenclature. The remaining six elements are all dependent on this nomenclature; therefore, quality improvement in the domain of congenital cardiac disease depends on a solid understanding of cardiac morphology and nomenclature.

*References 1-55, 62-64, 66-71, 75, 77, 79, 81, 82, 87, 88, 93, 94, 96, 100, 103, 104, 110-112, 114-116, 128-140, 148, 152, 155, 162, 167-169, 171, 172, 178, 179, 188, 191, 200-202, 209, 210, 213, 216, 218, 221.

†References 1-23, 55, 58-60, 62-64, 71, 77, 79, 80-82, 87, 88, 90, 93, 95, 98, 100, 104-106, 110-113, 115, 117-123, 145, 146, 148, 152-155, 161, 163, 164, 171, 172, 174, 178, 179, 185, 188, 189, 204, 207, 210, 212, 214, 216, 220-227.

‡References 56, 57, 61, 65, 72-74, 76-79, 81-84, 88-91, 97-102, 104, 106, 107, 110-112, 124, 125, 141, 142, 147, 148-150, 152, 178, 179, 188, 204, 215-217, 221.

§References 77, 81, 85, 86, 88, 100, 104, 110-112, 126, 148, 152, 178, 179, 188, 216, 221.

||References 81, 100, 104, 110-140, 148, 152, 178, 179, 188, 216, 221.

¶References 104, 109-112, 127, 145, 146, 152, 164, 173, 178, 179, 184, 188, 189, 214, 216, 221.

**References 108, 110, 115, 143-148, 151, 152, 154, 156-160, 164-167, 170, 175, 176, 177-183, 186-188, 190, 192-199, 203, 205, 206, 208, 210, 211, 216, 219, 221, 222.

NOMENCLATURE

Substantial effort has been devoted to the standardization of nomenclature and definitions related to surgery for pediatric and congenital cardiac disease. During the 1990s, both the European Association for Cardio-Thoracic Surgery (EACTS) and the Society of Thoracic Surgeons (STS) created databases to assess the outcomes of congenital cardiac surgery. Beginning in 1998, these two organizations collaborated to create the International Congenital Heart Surgery Nomenclature and Database Project. By 2000, a common nomenclature and a common core minimal dataset were adopted by EACTS and STS and published in the *Annals of Thoracic Surgery*.^{21-54,114} In 2000, the International Nomenclature Committee for Pediatric and Congenital Heart Disease was established. This committee eventually evolved into the International Society for Nomenclature of Paediatric and Congenital Heart Disease (ISNPCHD). By 2005, members of the ISNPCHD cross-mapped the nomenclature of the International Congenital Heart Surgery Nomenclature and Database Project of the EACTS and STS with the European Paediatric Cardiac Code (EPCC) of the Association for European Paediatric Cardiology (AEPC), and therefore created the International Paediatric and Congenital Cardiac Code (IPCCC),¹¹² which is available for free download at <http://www.ipccc.net>.

Most international databases of patients with pediatric and congenital cardiac disease use the IPCCC as their foundation. Two versions of the IPCCC are used in the overwhelming majority of multi-institutional databases throughout the world:

1. The version of the IPCCC derived from the nomenclature of the International Congenital Heart Surgery Nomenclature and Database Project of the EACTS and the STS
2. The version of the IPCCC derived from the nomenclature of the EPCC of the AEPC

These two versions of the IPCCC are also often cited with the following abbreviated short names:

1. EACTS-STS-derived version of the IPCCC
2. AEPC-derived version of the IPCCC

The STS Congenital Heart Surgery Database, the EACTS Congenital Heart Surgery Database, and the Japan Congenital Cardiovascular Surgery Database (JCCVSD) all use the EACTS-STS-derived version of the IPCCC.

The ISNPCHD has published review articles that provide a unified and comprehensive classification, with definitions, for several complex congenital cardiac malformations: the functionally univentricular heart,⁹² hypoplastic left heart syndrome,⁹⁴ discordant atrioventricular connections,⁹⁶ and cardiac structures in the setting of heterotaxy.¹⁰³ These review articles include definitions and a complete listing of the relevant codes and terms in both versions of the IPCCC.

In collaboration with the World Health Organization (WHO), the ISNPCHD is developing the pediatric and congenital cardiac nomenclature that will be used in the eleventh version of the International Classification of Diseases (ICD-11). With a grant funded by the Children's Heart Foundation (www.childrensheartfoundation

.org), the ISNPCHD has also linked images and videos to the IPCCC. These images and videos are acquired from cardiac morphologic specimens and imaging modalities such as echocardiography, angiography, computerized axial tomography, and magnetic resonance imaging, as well as intraoperative images and videos.^{††} These images and videos are available for free download from the internet at (<http://www.IPCCC-awg.NET>). The IPCCC itself is available for free download from the internet at (<http://www.IPCCC.NET>).

The EACTS-STS-derived version of the IPCCC,^{110,112,114} and the common minimum database data set created by the International Congenital Heart Surgery Nomenclature and Database Project,²¹ are currently used by the STS Congenital Heart Surgery Database, the EACTS Congenital Heart Surgery Database, and the JCCVSD. Between 1998 and January 1, 2014 inclusive, this nomenclature and database was used by STS, EACTS, and JCCVSD to analyze the outcomes of 479,000 operations.

DATABASE

The STS Congenital Heart Surgery Database is the largest database in North America cataloging congenital cardiac malformations.^{117,152} It has grown annually since its inception, both in terms of the number of participating centers submitting data and the number of operations analyzed (Figs. 133-1, 133-2, and 133-3). As of January 1, 2014, the STS Congenital Heart Surgery Database currently had 111 participating centers, representing 120 hospitals performing pediatric and congenital cardiac surgery in North America: 117 of an estimated 125 centers from the United States of America that perform pediatric and congenital heart surgery and 3 of 8 centers from Canada that perform pediatric and congenital heart surgery.^{95,174} (The Report of the 2005 STS Congenital Heart Surgery Practice and Manpower Survey, undertaken by the STS Workforce on Congenital Heart Surgery, estimated that 122 centers in the United States of America perform pediatric and congenital heart surgery and 8 centers in Canada perform pediatric and congenital heart surgery.⁹⁵ The Report of the 2010 STS Congenital Heart Surgery Practice and Manpower Survey, undertaken by the STS Workforce on Congenital Heart Surgery, estimated that 125 centers in the United States of America perform pediatric and congenital heart surgery and 8 centers in Canada perform pediatric and congenital heart surgery.¹⁷⁴)

As of January 1, 2014, the STS Congenital Heart Surgery Database therefore contained data from an estimated 93.6% of hospitals (117 of 125) performing pediatric cardiac surgery in the United States. With penetrance of greater than 90%, the data in the STS Congenital Heart Surgery Database is representative of pediatric and congenital heart surgery in the United States. As of January 1, 2014, the number of cumulative total operations in the STS Congenital Heart Surgery Database was

^{††}References 162, 191, 200-202, 209, 213, 218.

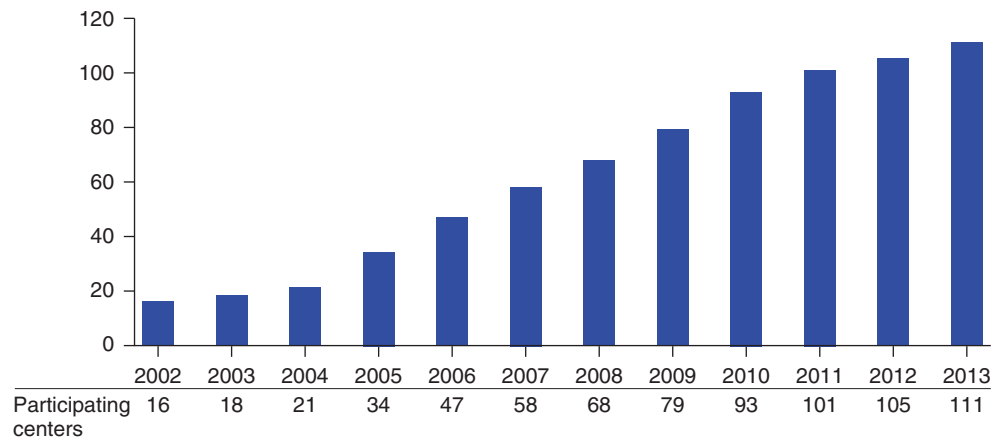


FIGURE 133-1 ■ The annual growth of the Society of Thoracic Surgeons Congenital Heart Surgery Database by number of participating centers submitting data. The aggregate report from the Fall 2013 Harvest of the Society of Thoracic Surgeons Congenital Heart Surgery Database¹⁹ includes data from 111 North American Congenital Database Participants representing 120 Congenital Heart Surgery hospitals in North America—117 in the United States and 3 in Canada.

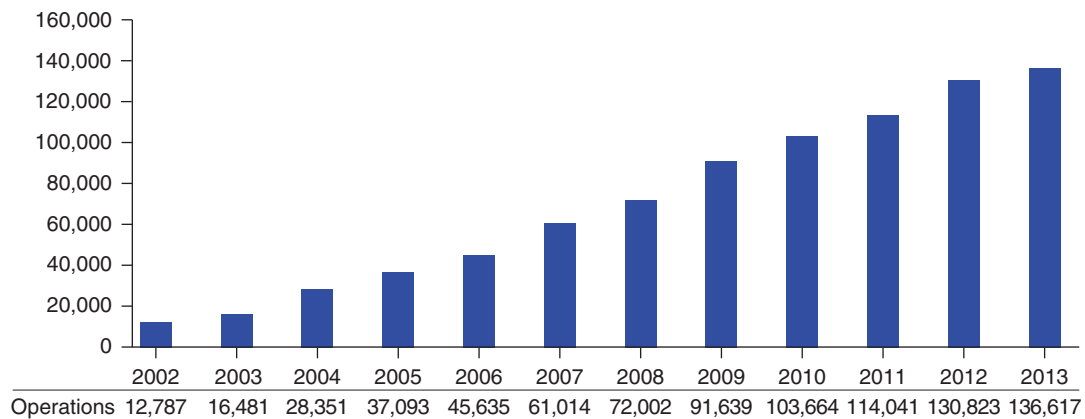


FIGURE 133-2 ■ The annual growth of the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database by the number of operations per averaged 4-year data collection cycle. The aggregate report from the Fall 2013 Harvest of the STS Congenital Heart Surgery Database¹⁹ includes 136,617 operations performed in the 4-year period of July 1, 2009, to June 30, 2013, inclusive, submitted from 120 hospitals in North America—117 in the United States and 3 in Canada.

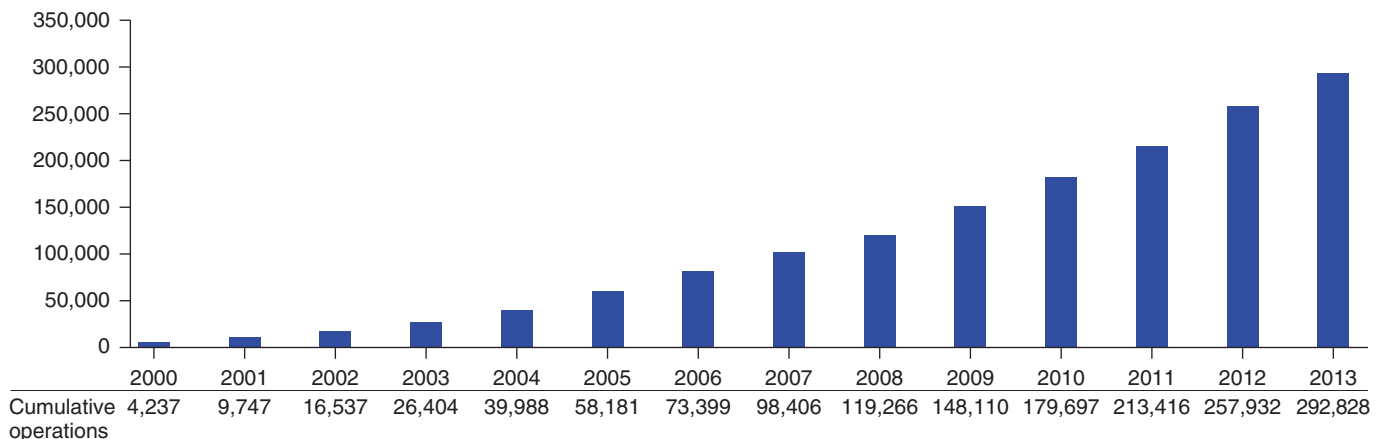


FIGURE 133-3 ■ The annual growth of the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database by the cumulative number of operations over time. As of January 1, 2014, the number of cumulative total operations in the STS Congenital Heart Surgery Database is 292,828. The aggregate report from the Fall 2013 Harvest of the STS Congenital Heart Surgery Database¹⁹ includes 136,617 operations performed in the 4-year period of July 1, 2009, to June 30, 2013, inclusive, submitted from 120 hospitals in North America—117 in the United States and 3 in Canada.

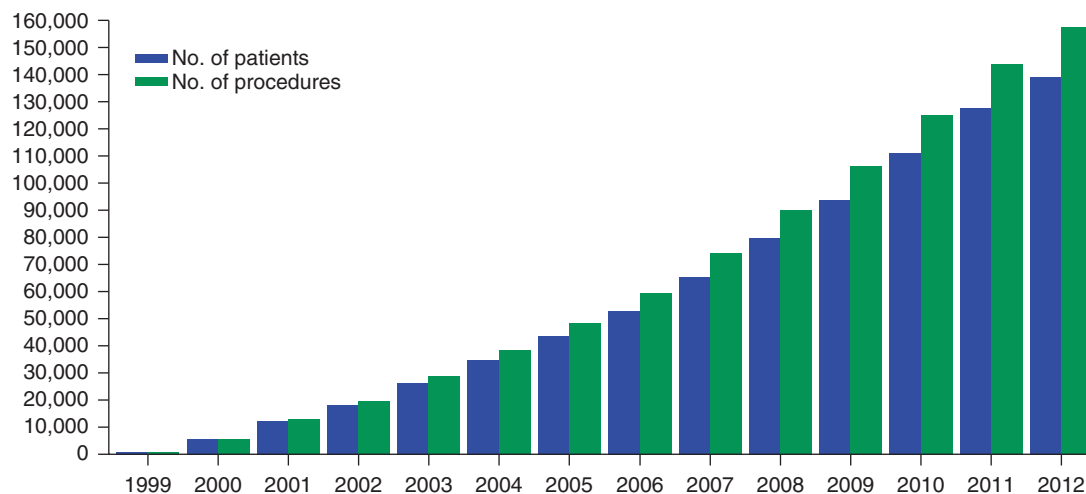


FIGURE 133-4 ■ The annual growth in the European Association for Cardio-Thoracic Surgery (EACTS) Congenital Database by both number of patients and number of operations. As of May 2013, the EACTS Congenital Heart Surgery Database contained 157,772 operations performed in 130,534 patients. As of May, 2013, the EACTS Congenital Heart Surgery Database had 348 centers from 76 countries registered, with 173 active centers from 46 countries submitting data. (Data courtesy Bohdan Maruszewski of the Children's Memorial Health Institute in Warsaw, Poland, Director of the European Association for Cardio-Thoracic Surgery Congenital Database, and Past-President of the European Congenital Heart Surgeons Association.)

292,828.¹⁹ The aggregate Participant Feedback Report from the Fall 2013 Harvest of the STS Congenital Heart Surgery Database includes 136,617 operations performed in the 4-year analytic window of July 1, 2009 to June 30, 2013, inclusive, submitted from 120 hospitals in North America—117 in the United States and 3 in Canada. In collaboration with EACTS, the STS has developed standardized methodology for tracking mortality and morbidity associated with the treatment of patients with congenital and pediatric cardiac disease.^{93,105,212}

The EACTS Congenital Heart Surgery Database is the largest database in Europe dealing with congenital cardiac malformations (Fig. 133-4).^{112,117} As of May 2013, the EACTS Congenital Heart Surgery Database contained 157,772 operations performed in 130,534 patients. As of May 2013, the EACTS Congenital Heart Surgery Database had 348 centers from 76 countries registered, with 173 active centers from 46 countries submitting data.

The JCCVSD has recently been operationalized based on nomenclature and database standards identical to those used by EACTS and STS.¹¹⁷ The JCCVSD began enrolling patients in 2008. By December 2011, more than 100 hospitals were submitting data, and by April 2013, more than 29,000 operations were entered into the JCCVSD, in just under 5 years of data collection (Fig. 133-5). In Japan, it is mandatory for specialists to enroll in this benchmarking project to examine their own performance objectively and to make efforts for continuous improvement. In the future, certification is to be performed solely on the basis of empirical data registered by the project. The developers of the JCCVSD hope to collaborate with their colleagues across Asia to create an Asian Congenital Heart Surgery Database.

In the United Kingdom, the United Kingdom Central Cardiac Audit Database (UKCCAD) uses the AEPC-derived version of the IPCCC as the basis for its national, comprehensive, validated, and benchmark-driven audit of

all pediatric surgical and transcatheter procedures undertaken since 2000.¹⁵² All 13 tertiary centers in the United Kingdom performing cardiac surgery or therapeutic cardiac catheterization in children with congenital cardiac disease submit data to the UKCCAD. Data about mortality are obtained from both results volunteered from the hospital databases, and by independently validated records of deaths obtained by the Office for National Statistics, using the patient's unique National Health Service number, or the general register offices of Scotland and Northern Ireland. Efforts are underway to link the UKCCAD to the EACTS Congenital Heart Surgery Database. Linkage of the UKCCAD to the EACTS Congenital Heart Surgery Database will require use of the cross-map of the AEPC-derived version of the IPCCC (used by the UKCCAD) to the EACTS-STS-derived version of the IPCCC (used by the EACTS, STS, and JCCVSD).

As of January 1, 2014, the STS Congenital Heart Surgery Database contains data from 292,828 operations, the EACTS Congenital Heart Surgery Database contains data from more than 157,772 operations, and the JCCVSD contains data from more than 29,000 operations. Therefore, the combined dataset of the STS Congenital Heart Surgery Database, the EACTS Congenital Heart Surgery Database, and JCCVSD contains data from more than 479,000 operations, all coded with the EACTS-STS-derived version of the IPCCC,^{100,110,112,114} and all coded with identical data specifications.²¹

COMPLEXITY STRATIFICATION

The importance of measuring complexity derives from the fact that analysis of outcomes using raw measurements of mortality, without adjustment for complexity, is inadequate. The mix of cases can vary greatly from

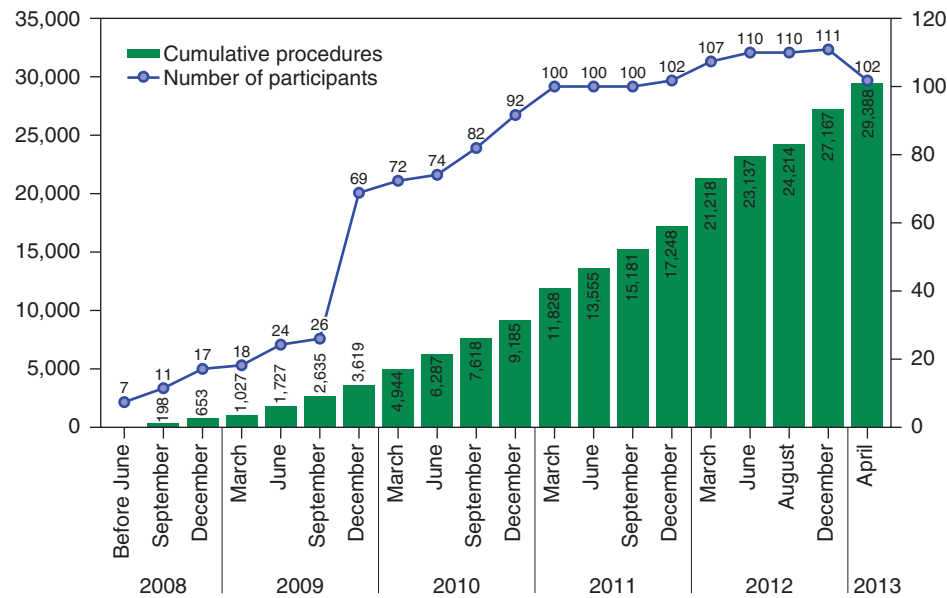


FIGURE 133-5 ■ The initial growth of the Japan Congenital Cardiovascular Surgery Database (JCCVSD). The JCCVSD has recently been operationalized based on identical nomenclature and database standards as that used by the European Association for Cardio-Thoracic Surgery and the Society of Thoracic Surgeons. The JCCVSD began enrolling patients in 2008. By December 2011, more than 100 hospitals were submitting data, and by April 2013, more than 29,000 operations were entered into the JCCVSD, in just under 5 years of data collection. The developers of the JCCVSD hope to collaborate with their colleagues across Asia to create an Asian Congenital Heart Surgery Database. (Data courtesy Arata Murakami, MD, The University of Tokyo, Tokyo, Japan.)

program to program. Without stratification of complexity, the analysis of outcomes will be flawed.^{††}

The analysis of outcomes after surgery requires a reliable method of estimating the risk of adverse events. However, formal risk modeling is challenging for rare operations. Complexity stratification provides an alternative methodology that can facilitate the analysis of outcomes of rare operations. Complexity stratification is a method of analysis in which the data are divided into relatively homogeneous groups (called *strata*). The data are analyzed within each stratum.

Three major multi-institutional efforts have attempted to measure the complexity of congenital cardiac surgical operations:

1. Risk Adjustment in Congenital Heart Surgery-1 methodology (RACHS-1 method)^{56,73,149}
2. Aristotle Basic Complexity Score (ABC Score)^{§§}
3. STS-EACTS Congenital Heart Surgery Mortality Categories (STS-EACTS Mortality Categories, or STAT Mortality Categories)¹⁵⁰

RACHS-1 and the ABC Score were developed at a time when limited multi-institutional clinical data were available and were therefore based largely on subjective probability (i.e., expert opinion). The STAT Mortality Categories are a tool for complexity stratification that was developed from an analysis of 77,294 operations entered into the EACTS Congenital Heart Surgery Database (33,360 operations) and the STS Congenital Heart Surgery Database (43,934 patients) between 2002 and 2007. Procedure-specific mortality rate estimates were calculated using a Bayesian model that adjusted for

small denominators. Operations were sorted by increasing risk and were grouped into five categories (the STS-EACTS Congenital Heart Surgery Mortality Categories) that were designed to be optimal with respect to minimizing within-category variation and maximizing between-category variation.

Table 133-1 compares RACHS-1, the ABC Score, and the STS-EACTS Mortality Categories. Table 133-2 shows the application in the STS Congenital Heart Surgery Database of the STAT Congenital Heart Surgery Mortality Categories.¹⁹⁸ STS has transitioned from the primary use of Aristotle and RACHS-1 to the primary use of the STAT Mortality Categories for three reasons:

1. STAT Score was developed primarily based on objective data, whereas RACHS-1 and Aristotle were developed primarily on subjective probability (i.e., expert opinion).
2. STAT Score allows for classification of more operations than RACHS-1 or Aristotle.
3. STAT Score has a higher c-statistic than RACHS-1 or Aristotle do.

Meaningful evaluation and comparison of outcomes require consideration of both mortality and morbidity, but the latter is much harder to measure. The STAT Mortality Categories provide an empirically based tool for analyzing mortality associated with operations for congenital heart disease.¹⁵⁰ STS has developed the STAT Morbidity Categories²¹⁵ on the basis of major postoperative complications and postoperative length of stay. Both major postoperative complications and postoperative length of stay were used, because models that assume a perfect one-to-one relationship between postoperative complications and postoperative length of stay are not likely to fit the data well. The incorporation of both

^{††}References 56, 61, 73, 74, 76, 82, 106, 149, 150.

^{§§}References 61, 74, 76, 82, 106, 149.

TABLE 133-1 **Results of Comparing the STS-EACTS Categories (2009) to the RACHS-1 Categories and the Aristotle Basic Complexity Score***

Method of Modeling Procedures	Model without Patient Covariates	Model with Patient Covariates	Percent of Operations That Can Be Classified
STS-EACTS Congenital Heart Surgery Mortality Categories (2009)	C = 0.778	C = 0.812	99%
RACHS-1 Categories	C = 0.745	C = 0.802	86%
Aristotle Basic Complexity Score	C = 0.687	C = 0.795	94%

*Using an independent validation sample of 27,700 operations performed in 2007 and 2008. In the subset of procedures for which STS-EACTS Category (STAT Mortality Category), RACHS-1 Category, and Aristotle Basic Complexity Score are defined, discrimination was highest for the STS-EACTS categories (C-index = 0.778), followed by RACHS-1 categories (C-index = 0.745), and Aristotle Basic Complexity scores (C-index = 0.687).
RACHS-1, Risk Adjustment in Congenital Heart Surgery-1; *STS-EACTS*, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery.

TABLE 133-2 **Discharge Mortality in Patients in the STS Congenital Heart Surgery Database***

STAT Mortality Category	Total Number of Operations	Discharge Mortality (%)
1	15,441	0.55
2	17,994	1.7
3	8,989	2.6
4	13,375	8.0
5	2,707	18.4

*Patients who underwent surgery between January 1, 2005, and December 31, 2009, inclusive,¹⁹⁸ stratified by STAT Mortality Categories (Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Categories).
STS, Society of Thoracic Surgeons.

major postoperative complications and postoperative length of stay allows for the creation of a much more informative model. The STAT Morbidity Categories provide an empirically based tool for analyzing morbidity associated with operations for congenital heart disease.²¹⁵

DATA VERIFICATION

Collaborative efforts involving EACTS and STS aim to enhance mechanisms to verify the completeness and accuracy of the data in the databases.^{21,126} A combination of three strategies may ultimately be required to allow for optimal verification of data:

- 1. Intrinsic data verification (designed to rectify inconsistencies of data and missing elements of data)
- 2. Site visits with “source data verification” (i.e., verification of the data at the primary source of the data)
- 3. External verification of the data from independent databases or registries (e.g., governmental death registries)

SUBSPECIALTY COLLABORATION

Under the leadership of the MultiSocietal Database Committee for Pediatric and Congenital Heart Disease,¹¹⁰⁻¹¹² further collaborative efforts are ongoing

between congenital and pediatric cardiac surgeons and other subspecialties, including:

- 1. Pediatric cardiac anesthesiologists, via the Congenital Cardiac Anesthesia Society^{105,119,139,207}
- 2. Pediatric cardiac intensivists, via the Pediatric Cardiac Intensive Care Society,¹⁹⁰ and
- 3. Pediatric cardiologists, via the Joint Council on Congenital Heart Disease, the American College of Cardiology (ACC), and the Association for European Paediatric Cardiology.¹¹⁸

Strategies have been developed to link databases together.¹¹¹ By linking different databases, it is possible to capitalize on the strengths and mitigate some of the weaknesses of these databases and therefore perform analyses not possible with either dataset alone. Linked databases have facilitated both comparative effectiveness research^{193,194,219} and longitudinal follow-up.^{145,146,173,214} Under the leadership of the MultiSocietal Database Committee for Pediatric and Congenital Heart Disease,¹¹⁰⁻¹⁴⁰ additional collaborative efforts are ongoing among congenital and pediatric cardiac surgeons and other subspecialties.

LONGITUDINAL FOLLOW-UP

The transformation of the STS Database to a platform for longitudinal follow-up will ultimately result in higher quality of care for all cardiothoracic surgical patients by facilitating longitudinal comparative effectiveness research on a national level.^{127,173,184,214} Several potential strategies will allow longitudinal follow-up with the STS Database, including the development of clinical longitudinal follow-up modules within the STS Database itself, and linking the STS Database to other clinical registries, administrative databases, and national death registries:

- 1. Using probabilistic matching with shared indirect identifiers, the STS Database can be linked to administrative claims databases (such as the CMS Medicare Database^{145,146} and the Pediatric Health Information System [PHIS] database¹¹¹) and become a valuable source of information about long-term

¹¹¹References 109, 164, 189, 193, 194, 210, 219.
¹¹¹References 109, 164, 189, 193, 194, 210, 219.

mortality, rates of rehospitalization, long-term morbidity, and cost.²⁰⁸

2. Using deterministic matching with shared unique direct identifiers, the STS Database can be linked to national death registries, such as the Social Security Death Master File (SSDMF) and the National Death Index (NDI), to verify life status over time.^{127,173,184,214}
3. Through either probabilistic matching or deterministic matching,¹⁸⁴ the STS Database can link to multiple other clinical registries, such as the National Cardiovascular Data Registry (NCDR) of the ACC, to provide enhanced clinical follow-up.
4. The STS Database can develop clinical longitudinal follow-up modules of its own to provide detailed clinical follow-up.^{109,127,173,184,214}

QUALITY ASSESSMENT AND QUALITY IMPROVEMENT

The STS Database is being used increasingly to document variation in outcomes^{182,198} and to measure quality.^{179,186} Funnel plots can be used to demonstrate this variation in outcome and to facilitate the identification of centers that are outliers in performance (Fig. 133-6). Quality improvement initiatives can be initiated in low-performing centers, and best practices can be obtained from high-performing centers.

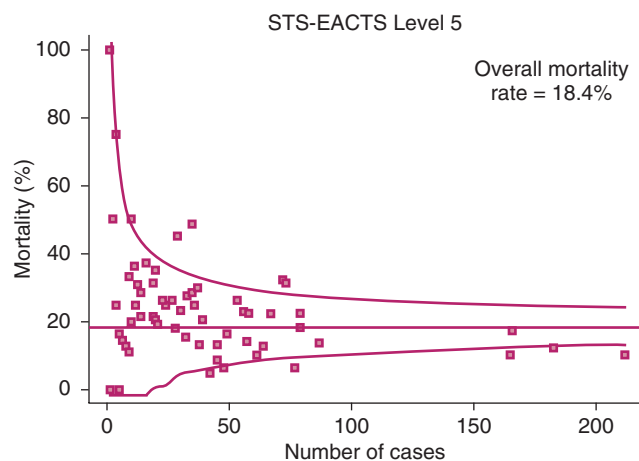


FIGURE 133-6 ■ Mortality data displayed as a funnel plot for STAT Category 5 operations.¹⁹⁸ The horizontal line depicts aggregate Society of Thoracic Surgeons (STS) mortality before discharge. Curved lines depicting exact 95% binomial prediction limits were overlaid to make a funnel plot. Squares represent the number of cases and mortality before discharge for individual STS Congenital Heart Surgery Database participants (centers). This analysis includes patients undergoing surgery during the 5-year analytic window of 2005 to 2009, inclusive, and includes 70 STS centers in the STS Congenital Heart Surgery Database and 2707 operations. Centers that were identified as outliers represented 18.6% of participating centers (13 of 70); 10% (7 of 70) were “high-performing outliers” and 8.6% (6 out of 70) were “low-performing outliers.” Quality improvement initiatives can be initiated in low-performing centers, and best practices can be obtained from high-performing centers. EACTS, European Association for Cardio-Thoracic Surgery.

STS has collaborated with the Congenital Heart Surgeons’ Society (CHSS) to develop and endorse metrics to assess the quality of care delivered to patients with pediatric and congenital cardiac disease.¹⁸⁶ Box 133-1 and Tables 133-3 and 133-4 present 21 “Quality Measures for Congenital and Pediatric Cardiac Surgery” that were developed and approved by the STS and endorsed by the CHSS. These quality measures are organized according to Donabedian’s Triad of Structure, Process, and Outcome.²²⁹ It is hoped that these quality measures can aid in congenital and pediatric cardiac surgical quality

Text continued on p. 2392

BOX 133-1

Quality Measures for Congenital and Pediatric Cardiac Surgery

1. Participation in a national database for pediatric and congenital heart surgery
2. Multidisciplinary rounds involving multiple members of the health care team
3. Availability of institutional pediatric extracorporeal life support program
4. Surgical volume for pediatric and congenital heart surgery: total programmatic volume and programmatic volume stratified by the five STS-EACTS mortality categories
5. Surgical volume for eight pediatric and congenital heart benchmark operations
6. Multidisciplinary preoperative planning conference to plan pediatric and congenital heart surgery operations
7. Regularly scheduled quality assurance and quality improvement cardiac care conference, to occur no less frequently than once every two months
8. Availability of intraoperative transesophageal echocardiography and epicardial echocardiography
9. Timing of antibiotic administration for pediatric and congenital cardiac surgery patients
10. Selection of appropriate prophylactic antibiotics and weight-appropriate dosage for pediatric and congenital cardiac surgery patients
11. Use of an expanded preprocedural and postprocedural “time-out”
12. Occurrence of new postoperative renal failure requiring dialysis
13. Occurrence of new postoperative neurologic deficit persisting at discharge
14. Occurrence of arrhythmia necessitating permanent pacemaker insertion
15. Occurrence of paralyzed diaphragm (possible phrenic nerve injury)
16. Occurrence of need for postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS)
17. Occurrence of unplanned reoperation and/or interventional cardiovascular catheterization procedure
18. Operative mortality stratified by the five STS-EACTS mortality levels
19. Operative mortality for eight benchmark operations
20. Index Cardiac Operations free of mortality and major complication
21. Operative survivors free of major complication

CPS, Mechanical CardioPulmonary Support; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; STS-EACTS, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery; VAD, ventricular assist device.

TABLE 133-3 Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery

Number	Type	Title of Indicator	Description
S-1	Structure	Participation in a national database for pediatric and congenital heart surgery	Participation in at least one multicenter, standardized data collection and feedback program that provides regularly scheduled reports of the individual center's data relative to national multicenter aggregates and that uses process and outcome measures.
S-2	Structure	Multidisciplinary rounds involving multiple members of the health care team	Occurrence of daily multidisciplinary rounds on pediatric and congenital cardiac surgery patients involving multiple members of the health care team, with recommended participation including but not limited to: cardiac surgery, cardiology, critical care, primary caregiver, family, nurses, pharmacist, and respiratory therapist; involvement of the family is encouraged.
S-3	Structure	Availability of institutional pediatric extracorporeal life support program	Availability of an institutional pediatric extracorporeal life support program for pediatric and congenital cardiac surgery patients; measure is satisfied by the availability of ECMO equipment and support staff, but also applies to ventricular assist devices (including extracorporeal, paracorporeal, and implantable).
S-4	Structure	Surgical volume for pediatric and congenital heart surgery: total programmatic volume and programmatic volume stratified by the five STS-EACTS mortality categories	Surgical volume for pediatric and congenital heart surgery: STS version 2.5: All Index Cardiac Operations* STS version 3.0: Same Surgical volume for pediatric and congenital heart surgery stratified by the five STS-EACTS mortality levels, a multi-institutional validated complexity stratification tool. See O'Brien and colleagues ¹⁵⁰ (Table 1, pp 1140-1146).
S-5	Structure	Surgical volume for eight pediatric and congenital heart benchmark operations	Surgical volume for eight benchmark pediatric and congenital heart operations: These eight benchmark pediatric and congenital heart operations are tracked when they are the primary procedure of an index cardiac operation.* Procedure type VSD repair Abbreviation VSD STS-CHSDB Diagnostic and Procedural Inclusionary and Exclusionary Criteria Procedural inclusionary criteria: 100 = VSD repair, Primary closure 110 = VSD repair, Patch 120 = VSD repair, Device† Diagnostic inclusionary criteria: 71 = VSD, Type 1 (Subarterial) (Supracristal) (Conal septal defect) (Infundibular) 73 = VSD, Type 2 (Perimembranous) (Paramembranous) (Conoventricular) 75 = VSD, Type 3 (Inlet) (AV canal type) 77 = VSD, Type 4 (Muscular) 79 = VSD, Type: Gerbode type (LV-RA communication) Diagnostic exclusionary criteria: 80 = VSD, Multiple Procedural inclusionary criteria: 350 = TOF repair, No ventriculotomy 360 = TOF repair, Ventriculotomy, Nontransanular patch 370 = TOF repair, Ventriculotomy, Transanular patch 380 = TOF repair, RV-PA conduit Diagnostic inclusionary criteria: 290 = TOF 2140 = TOF, Pulmonary stenosis Diagnostic exclusionary criteria: 300 = TOF, AVC (AVSD) 310 = TOF, Absent pulmonary valve 320 = Pulmonary atresia 330 = Pulmonary atresia, IVS 340 = Pulmonary atresia, VSD (Including TOF, PA) 350 = Pulmonary atresia, VSD-MAPCA (pseudotruncus) 360 = MAPCA(s) (major aortopulmonary collateral[s]) (without PA-VSD)

P-1	Process	Multidisciplinary preoperative planning conference to plan pediatric and congenital heart surgery operations *	Norwood	Norwood	Occurrence of a preoperative multidisciplinary planning conference to plan pediatric and congenital heart surgery cases. This conference will involve multiple members of the health care team, with recommended participation including but not limited to: cardiology, cardiac surgery, anesthesia, and critical care. This measure will be coded on a per operation basis. Reporting of compliance will be as a fraction of all cardiac operations.*	Procedural inclusion criteria: 170 = AVC (AVSD) repair, Complete (CAVSD) Diagnostic inclusion criteria: 100 = AVC (AVSD), Complete (CAVSD) Diagnostic exclusion criteria: 110 = AVC (AVSD), Intermediate (transitional) 120 = AVC (AVSD), Partial (incomplete) (PAVSD) (ASD, primum) 300 = TOF, AVC (AVSD) Procedural inclusion criteria: 1110 = Arterial switch operation (ASO) Procedural exclusion criteria: 1120 = Arterial switch operation (ASO) and VSD repair 1123 = Arterial switch procedure + Aortic arch repair 1125 = Arterial switch procedure and VSD repair + Aortic arch repair 1050 = Congenitally corrected TGA repair, Atrial switch and ASO (double switch) Procedural inclusion criteria: 1120 = Arterial switch operation (ASO) and VSD repair Procedural exclusion criteria: 1110 = Arterial switch operation (ASO) 1123 = Arterial switch procedure + Aortic arch repair 1125 = Arterial switch procedure and VSD repair + Aortic arch repair 1050 = Congenitally corrected TGA repair, Atrial switch and ASO (double switch) Procedural inclusion criteria: 950 = Fontan, Atrio-pulmonary connection 960 = Fontan, Atrio-ventricular connection 970 = Fontan, TCPC, Lateral tunnel, Fenestrated 980 = Fontan, TCPC, Lateral tunnel, Nonfenestrated 1000 = Fontan, TCPC, External conduit, Fenestrated 1010 = Fontan, TCPC, External conduit, Nonfenestrated 1030 = Fontan, Other 2340 = Fontan + Atrioventricular valvuloplasty Procedural exclusion criteria: Exclude patients age ≥ 7 years 1025 = Fontan revision or conversion (Re-do Fontan) Procedural inclusion criteria: Primary procedure must be: 230 = Truncus arteriosus repair Procedural exclusion criteria: Exclude any operation if any of the component procedures is: 240 = Valvuloplasty, Truncal valve 2290 = Valvuloplasty converted to valve replacement in the same operation, Truncal valve 250 = Valve replacement, Truncal valve 2220 = Truncus + Interrupted aortic arch repair (IAA) repair Procedural inclusion criteria: 870 = Norwood procedure
	Complete AV canal repair	AVC				
	Arterial switch	ASO				
	Arterial switch + VSD repair	ASO+VSD				
	Fontan	Fontan				
	Truncus repair	Truncus				
	Norwood	Norwood				

Continued

TABLE 133-3 Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery—cont'd

Number	Type	Title of Indicator	Description
P-2	Process	Regularly scheduled quality assurance and quality improvement cardiac care conference, to occur no less frequently than once every 2 months	Occurrence of a regularly scheduled quality assurance and quality improvement cardiac care conference to discuss care provided to patients who have undergone pediatric and congenital cardiac surgery operations, including reporting and discussion of all major complications and mortalities, and discussion of opportunities for improvement.
P-3	Process	Availability of intraoperative TEE and epicardial echocardiography	Reporting of compliance will be by reporting the date of occurrence. Annual compliance of 100% equals no fewer than six conferences per year. Availability of intraoperative TEE and appropriate physician and sonographer support for pediatric and congenital cardiac operations. Epicardial echocardiography and appropriate physician and sonographer support should be readily available for those patients in whom TEE is contraindicated or less informative. Availability means presence and availability of equipment and staff.
P-4	Process	Timing of antibiotic administration for pediatric and congenital cardiac surgery patients	This measure will be coded on a per operation basis. Reporting of compliance will be as the fraction of all cardiac operations with availability (as opposed to use) of TEE, epicardial echocardiography, or both.*
P-5	Process	Selection of appropriate prophylactic antibiotics and weight-appropriate dosage for pediatric and congenital cardiac surgery patients	Measure is satisfied for each cardiac operation when there is documentation that the patient has received prophylactic antibiotics within the hour immediately preceding surgical incision (2 hours if receiving vancomycin).*
P-6	Process	Use of an expanded pre-procedural and post-procedural "time-out"	Measure is satisfied for each cardiac operation when there is documentation that the patient received body weight appropriate prophylactic antibiotics as recommended for the operation.*
O-1	Outcome	Occurrence of new postoperative renal failure requiring dialysis	Measure is satisfied for each cardiac operation* when there is documentation of performance and completion of an expanded preprocedural and postprocedural "time-out" that includes the following four elements: 1. The conventional pre-procedural "time-out," which includes identification of patient, operative site, procedure, and history of any allergies. 2. A preprocedural briefing wherein the surgeon shares with all members of the operating room team the essential elements of the operative plan, including diagnosis, planned procedure, outline of essentials of anesthesia and bypass strategies, antibiotic prophylaxis, availability of blood products, anticipated or planned implants or device applications, and anticipated challenges. 3. A postprocedural debriefing wherein the surgeon succinctly reviews with all members of the operating room team the essential elements of the operative plan, identifying both the successful components and the opportunities for improvement. This debriefing should take place <i>before the patient leaves the operating room or its equivalent</i> and may be followed by a more in-depth dialogue involving team members at a later time. (The actual debriefing in the operating room is intentionally and importantly brief, in recognition of the fact that periods of transition may be times of instability or vulnerability for the patient.) 4. A briefing and execution of a hand-off protocol at the time of transfer (arrival) to the intensive care unit at the end of the operation, involving the anesthesiologist, surgeon, physician staff of the intensive care unit (including critical care and cardiology) and nursing. For each surgical admission (index cardiac operation*), code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days postoperatively or at the time of hospital discharge, whichever is longer. STS version 2.5: 220 = Acute renal failure requiring temporary dialysis 230 = Acute renal failure requiring permanent dialysis STS version 3.0: 230 = Renal failure—acute renal failure requiring dialysis at the time of hospital discharge 223 = Renal failure—acute renal failure requiring temporary dialysis with the need for dialysis not present at hospital discharge 224 = Renal failure—acute renal failure requiring temporary hemofiltration with the need for dialysis not present at hospital discharge

Unless a patient requires dialysis before surgery, renal failure that requires dialysis after surgery constitutes an operative complication, despite the fact that preoperative diminished renal perfusion may have contributed to the development of this complication.

This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the five STS-EACTS congenital heart surgery mortality categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)

O-2 Outcome Occurrence of new postoperative neurologic deficit persisting at discharge

For each surgical admission (index cardiac operation*), code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days postoperatively or at the time of hospital discharge, whichever is longer.

320 = Neurologic deficit, neurologic deficit persisting at discharge

This measure tracks "new postoperative neurologic deficits" that (1) occur during the time interval beginning at admission to operating room and ending at the time of hospital discharge and (2) persist at discharge.

Such new postoperative neurologic deficits may or may not be related to a stroke. If the new postoperative neurologic deficit is the result of a stroke (that occurs during the time interval beginning at admission to operating room and ending at the time of hospital discharge) and the neurologic deficit persists at discharge, then the following two complications should both be selected:

320 = Neurologic deficit, neurologic deficit persisting at discharge

420 = Stroke

Thus, this complication (320 = neurologic deficit, neurologic deficit persisting at discharge) should be coded when a patient has had a stroke (during the time interval beginning at admission to operating room and ending at the time of hospital discharge) and the neurologic deficit persists at discharge.

This measure does not include a neurologic deficit (which may or may not be related to a stroke) that does not persist at discharge.

NOTE: This complication (320 = Neurologic deficit, neurologic deficit persisting at discharge) should be coded even when the patient has a neurologic deficit that is present before admission to operating room and this neurologic deficit worsens (or a new neurologic deficit develops) during the time interval beginning at admission to operating room and ending at the time of hospital discharge.

This measure will be reported as a percentage of all Index Cardiac Operations. This measure will also be reported stratified by the five STS-EACTS congenital heart surgery mortality categories. (STS is developing congenital heart surgery morbidity categories. When these categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)

O-3 Outcome Occurrence of arrhythmia necessitating permanent pacemaker insertion

For each surgical admission (Index Cardiac Operation*), code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days postoperatively or at the time of hospital discharge, whichever is longer.

STS version 2.5:

60 = Postoperative AV block requiring permanent pacemaker

STS version 3.0:

74 = Arrhythmia necessitating pacemaker, permanent pacemaker

This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the five STS-EACTS congenital heart surgery mortality categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)

O-4 Outcome Occurrence of paralyzed diaphragm (possible phrenic nerve injury)

For each surgical admission (index cardiac operation*), code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days postoperatively or at the time of hospital discharge, whichever is longer.

STS version 2.5:

300 = Phrenic nerve injury/paralyzed diaphragm

STS version 3.0:

300 = Paralyzed diaphragm (possible phrenic nerve injury)

This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the five STS-EACTS Congenital Heart Surgery Mortality Categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)

TABLE 133-3 Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery—cont'd

Number	Type	Title of Indicator	Description
O-5	Outcome	Occurrence of need for postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS)	For each surgical admission (index cardiac operation*), code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days postoperatively or at the time of hospital discharge, whichever is longer. STS version 2.5: 40 = Postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS) STS version 3.0: 40 = Postoperative or Postprocedural mechanical circulatory support (IABP, VAD, ECMO, or CPS) This complication should be coded even when the patient had preoperative mechanical circulatory support if the patient has mechanical circulatory support postoperatively at any time until 30 days postoperatively or the time of hospital discharge, whichever is longer. This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the five STS-EACTS congenital heart surgery mortality categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)
O-6	Outcome	Occurrence of unplanned reoperation and/or interventional cardiovascular catheterization procedure	For each surgical admission (index cardiac operation*), code whether the complication occurred during the time interval beginning at admission to operating room and ending 30 days postoperatively or at the time of hospital discharge, whichever is longer. STS version 2.5: 20 = Reoperation during this admission (unplanned reoperation) 240 = Bleeding requiring reoperation STS version 3.0: 22 = Unplanned cardiac reoperation during the postoperative or postprocedural time period 24 = Unplanned interventional cardiovascular catheterization procedure during the postoperative or postprocedural time period 26 = Unplanned noncardiac reoperation during the postoperative or postprocedural time period 240 = Bleeding, requiring reoperation <i>n.b. does not include delayed sternal closure</i> This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the five STS-EACTS congenital heart surgery mortality categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.) This measure counts all patients who require any additional unplanned cardiac or noncardiac operation and/or interventional cardiovascular catheterization procedure occurring (1) within 30 days after surgery or intervention in or out of the hospital, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention.* The following operations will always be coded as "planned reoperation": (1) delayed sternal closure, (2) ECMO decannulation, (3) VAD decannulation, (4) removal of Broviac catheter. The following operations will always be coded as "Unplanned Reoperation": (1) reoperation for bleeding, (2) reoperation for infection, (3) reoperation for hemodynamic instability, (4) reoperation for initiation of ECMO or VAD, (5) reoperation for residual or recurrent lesion. Operative mortality stratified by the five STS-EACTS mortality levels, a multi-institutional validated complexity stratification tool. See O'Brien and colleagues¹⁵⁰ (Table 1, pp 1140-1146).
O-7	Outcome	Operative mortality stratified by the five STS-EACTS mortality levels	
O-8	Outcome	Operative mortality for eight benchmark operations	Operative mortality for eight benchmark pediatric and congenital heart operations: These eight benchmark pediatric and congenital heart operations are tracked when they are the primary procedure of an index cardiac operation,* and they are listed and described in this table in Measure Number S-5.

O-9 Outcome Index Cardiac Operations free of mortality and major complication

"Index Cardiac Operations free of mortality and major complication" is defined as the percent of pediatric and congenital heart surgery Index Cardiac Operations free of the following: (1) operative mortality, (2) any one or more of the following major complications occurring or diagnosed during the time interval beginning at admission to operating room and ending 30 days postoperatively or at the time of hospital discharge, whichever is longer:

(a) **Renal failure—acute renal failure requiring temporary or permanent dialysis (220, 230, 223, 224)**

- STS version 2.5:
- 220 = Acute renal failure requiring temporary dialysis
- 230 = Acute renal failure requiring permanent dialysis
- STS version 3.0:
- 230 = Renal failure—acute renal failure requiring dialysis at the time of hospital discharge
- 223 = Renal failure—acute renal failure requiring temporary dialysis with the need for dialysis not present at hospital discharge
- 224 = Renal failure—acute renal failure requiring temporary hemofiltration with the need for dialysis not present at hospital discharge

(b) **Neurologic deficit, neurologic deficit persisting at discharge**

- STS version 2.5:
- 320 = Postoperative neurologic deficit persisting at discharge
- STS version 3.0:
- 320 = Neurologic deficit, neurologic deficit persisting at discharge

(c) **Arrhythmia necessitating pacemaker, permanent pacemaker (60, 74)**

- STS version 2.5:
- 60 = Postoperative AV block requiring permanent pacemaker
- STS version 3.0:
- 74 = Arrhythmia necessitating pacemaker, permanent pacemaker

(d) **ECMO/VAD: postoperative mechanical circulatory support (IABP, VAD, ECMO or CPS) (40)**

- STS version 2.5:
- 40 = Postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS)
- STS version 3.0:
- 40 = Postoperative or postprocedural mechanical circulatory support (IABP, VAD, ECMO, or CPS)

(e) **Paralyzed diaphragm (possible phrenic nerve injury)**

- STS version 2.5:
- 300 = Phrenic nerve injury/paralyzed diaphragm
- STS version 3.0:
- 300 = Paralyzed diaphragm (possible phrenic nerve injury)

(f) **Unplanned reoperation (20, 22, 26 or 240)**

- STS version 2.5:
- 20 = Reoperation during this admission (unplanned reoperation)
- 240 = Bleeding requiring reoperation
- STS version 3.0:
- 22 = Unplanned cardiac reoperation during the postoperative or postprocedural time period, exclusive of reoperation for bleeding
- 24 = Unplanned interventional cardiovascular catheterization procedure during the postoperative or postprocedural time period
- 26 = Unplanned noncardiac reoperation during the postoperative or postprocedural time period
- 240 = Bleeding, requiring reoperation

This measure will be reported as percentage of all Index Cardiac Operations.* This measure will also be reported stratified by the five STS-EACTS congenital heart surgery mortality categories. (STS is developing congenital heart surgery morbidity categories. When these categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)

Continued

TABLE 133-3 Definitions of Quality Measures for Congenital and Pediatric Cardiac Surgery—cont'd

Number	Type	Title of Indicator	Description
O-10	Outcome	Operative survivors free of major complication	"Operative survivors free of major complication" is defined as the percent of all surviving (live at discharge and 30 days postoperatively) pediatric and congenital heart surgery index operations free of all the following itemized major complications: (a) Renal failure—acute renal failure requiring temporary or permanent dialysis (220, 230, 223, 224) STS version 2.5: 220 = Acute renal failure requiring temporary dialysis 230 = Acute renal failure requiring permanent dialysis STS version 3.0: 230 = Acute renal failure requiring dialysis at the time of hospital discharge 223 = Acute renal failure requiring temporary dialysis with the need for dialysis not present at hospital discharge 224 = Acute renal failure requiring temporary hemofiltration with the need for dialysis not present at hospital discharge (b) Neurologic deficit, neurologic deficit persisting at discharge STS version 2.5: 320 = Postoperative neurologic deficit persisting at discharge STS version 3.0: 320 = Neurologic deficit, neurologic deficit persisting at discharge (c) Arrhythmia necessitating pacemaker, permanent pacemaker (60, 74) STS version 2.5: 60 = Postoperative AV block requiring permanent pacemaker STS version 3.0: 74 = Arrhythmia necessitating pacemaker, permanent pacemaker (d) ECMO/VAD—postoperative mechanical circulatory support (IABP, VAD, ECMO or CPS) (40) STS version 2.5: 40 = Postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS) STS version 3.0: 40 = Postoperative mechanical circulatory support (IABP, VAD, ECMO, or CPS) (e) Paralyzed diaphragm (possible phrenic nerve injury) STS version 2.5: 300 = Phrenic nerve injury, paralyzed diaphragm STS version 3.0: 300 = Paralyzed diaphragm (possible phrenic nerve injury) (f) Unplanned reoperation (20, 22, 26, or 240) STS version 2.5: 20 = Reoperation during this admission (unplanned reoperation) 240 = Bleeding requiring reoperation STS version 3.0: 22 = Unplanned cardiac reoperation during the postoperative or postprocedural time period, exclusive of reoperation for bleeding 24 = Unplanned interventional cardiovascular catheterization procedure during the postoperative or postprocedural time period 26 = Unplanned non-cardiac reoperation during the postoperative or postprocedural time period 240 = Bleeding, Requiring reoperation This measure will be reported as percentage of all Index Cardiac Operations. This measure will also be reported stratified by the five STS-EACTS congenital heart surgery mortality categories. (STS is developing Congenital Heart Surgery Morbidity Categories. When these categories are published and available, this metric will be stratified by the STS Congenital Heart Surgery Morbidity Categories instead of the STS Congenital Heart Surgery Mortality Categories.)

*A *cardiac operation* is defined as an operation of operation type "CPB" or "No CPB Cardiovascular."

†This measure is applicable when one or more septal occluder devices are implanted in the course of a surgical operation for which the primary procedure of an index cardiac operation is VSD repair. A VSD device that is placed as a purely transcatheter technique, and not as a component of a cardiac operation, is classified as an *interventional cardiology procedure* and is not tracked as part of this measure.

ASD, Atrial septal defect; ASD, atrial switch operation; AV, atrioventricular; AVC, atrioventricular canal; AVSD, atrioventricular septal defect; CAVSD, complete atrioventricular septal defect; CHSDB, Congenital Heart Surgery Databases; CPB, cardiopulmonary bypass; CPS, mechanical CardioPulmonary Support; EACTS, European Association for Cardio-Thoracic Surgery; ECMO, extracorporeal membrane oxygenation; IAA, interrupted aortic arch; IABP, intra-aortic balloon pump; IAS, intact ventricular septum; LV, left ventricle; MAPCA, major aortopulmonary collateral; PA, pulmonary artery; PA-VSD, pulmonary atresia with ventricular septal defect; PA-VSD, partial ventricular septal defect; RA, right atrium; STS, Society of Thoracic Surgeons; TCPC, Total CavoPulmonary Connection; TGA, transposition of the great arteries; TEE, transesophageal echocardiography; TOF, tetralogy of Fallot; VAD, ventricular assist device; VSD, ventricular septal defect.

TABLE 133-4 Consensus Definitions of the Morbidities

Measure	Organ System	Complication	Definitions
12	Renal	Acute renal failure requiring dialysis at the time of hospital discharge	Acute renal failure* with a new postoperative or postprocedural requirement for dialysis, including peritoneal dialysis or hemodialysis. Code this complication if the patient requires dialysis at the time of hospital discharge or death in the hospital. (This complication should be chosen only if the dialysis was associated with acute renal failure.)
12	Renal	Acute renal failure requiring temporary dialysis with the need for dialysis not present at hospital discharge	Acute renal failure with a new postoperative or postprocedural requirement for temporary dialysis, including peritoneal dialysis and/or hemodialysis. Code this complication if the patient does not require dialysis at the time of hospital discharge or death in the hospital. (This complication should be chosen only if the dialysis was associated with acute renal failure.)
12	Renal	Acute renal failure requiring temporary hemofiltration with the need for dialysis not present at hospital discharge	Acute renal failure with a new postoperative or postprocedural requirement for temporary hemofiltration. Code this complication if the patient does not require dialysis at the time of hospital discharge or death in the hospital. (This complication should be chosen only if the hemofiltration was associated with acute renal failure.)
13	Neurologic	Neurologic deficit, neurologic deficit persisting at discharge	Newly recognized or newly acquired deficit of neurologic function leading to inpatient referral, therapy, or intervention not otherwise practiced for a similar unaffected inpatient, with a persisting neurologic deficit present at hospital discharge. In other words, new (onset intraoperatively, postoperatively, intraprocedurally, or postprocedurally) neurologic deficit persisting and present at discharge from hospital.
13	Neurologic	Stroke	Any confirmed neurologic deficit of abrupt onset caused by a disturbance in blood flow to the brain, when the neurologic deficit does not resolve within 24 hours.
13	Neurologic	Spinal cord injury, neurologic deficit persisting at discharge	Spinal cord injury with a persisting neurologic deficit present at hospital discharge; newly acquired or newly recognized deficit of spinal cord function indicated by physical examination findings, imaging studies, or both.
13	Neurologic	Peripheral nerve injury, neurologic deficit persisting at discharge	Peripheral nerve injury with a persisting neurologic deficit present at hospital discharge; newly acquired or newly recognized deficit of unilateral or bilateral peripheral nerve function indicated by physical examination findings, imaging studies, or both.
14	Arrhythmia necessitating pacemaker	Arrhythmia necessitating pacemaker, permanent pacemaker	Implantation and use of a permanent pacemaker for treatment of any arrhythmia including heart block (atrioventricular heart block).
15	Neurologic	Paralyzed diaphragm (possible phrenic nerve injury)	Presence of elevated hemidiaphragm on chest radiograph in conjunction with evidence of weak, immobile, or paradoxical movement assessed by ultrasound or fluoroscopy.
16	Mechanical support utilization	Postoperative or postprocedural mechanical circulatory support (IABP, VAD, ECMO, or CPS)	Use of postoperative or postprocedural mechanical support, of any type (IABP, VAD, ECMO, or CPS), for resuscitation or support during the postoperative or postprocedural time period. Code this complication if it occurs (1) within 30 days after surgery or intervention regardless of the date of hospital discharge, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention.
17	Operative, procedural	Unplanned cardiac reoperation during the postoperative or postprocedural time period, exclusive of reoperation for bleeding	Any additional unplanned cardiac operation occurring (1) within 30 days after surgery or intervention in or out of the hospital, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention. A <i>cardiac operation</i> is defined as any operation that is of the operation type of "CPB" or "No CPB Cardiovascular." The following operations will always be coded as "Planned Reoperation": (1) delayed sternal closure, (2) ECMO decannulation, (3) VAD decannulation, (4) removal of Broviac catheter. The following operations will always be coded as "Unplanned Reoperation": (1) reoperation for bleeding, (2) reoperation for infection, (3) reoperation for hemodynamic instability, (4) reoperation for initiation of ECMO or VAD, (5) reoperation for residual or recurrent lesion.
17	Operative, procedural	Unplanned interventional cardiovascular catheterization procedure during the postoperative or postprocedural period	Any unplanned interventional cardiovascular catheterization procedure occurring (1) within 30 days after surgery or intervention in or out of the hospital, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention.

Continued

TABLE 133-4 Consensus Definitions of the Morbidities—cont'd

Measure	Organ System	Complication	Definitions
17	Operative, procedural	Unplanned noncardiac reoperation during the postoperative or postprocedural time period	Any additional unplanned noncardiac operation occurring (1) within 30 days after surgery or intervention in or out of the hospital, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention.

**Acute renal failure* is defined as new onset oliguria with sustained urine output < 0.5 mL/kg/hr for 24 hours and/or a rise in creatinine > 1.5 times upper limits of normal for age (or twice the most recent preoperative/preprocedural values if these are available), with eventual need for dialysis (including peritoneal dialysis and/or hemodialysis) or hemofiltration. Acute renal failure that will be counted as an operative or procedural complication must occur prior to hospital discharge or after hospital discharge but within 30 days of the procedure. (An operative or procedural complication is any complication, regardless of cause, occurring (1) within 30 days after surgery or intervention in or out of the hospital, or (2) after 30 days during the same hospitalization subsequent to the operation or intervention. Operative and procedural complications include both intraoperative/intraprocedural complications and postoperative/postprocedural complications in this time interval.) The complication is to be coded even if the patient required dialysis, but the treatment was not instituted due to patient or family refusal.

CPB, Cardiopulmonary bypass; CPS, mechanical CardioPulmonary Support; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; VAD, ventricular assist device.

assessment and quality improvement initiatives. These initiatives will take on added importance as the public reporting of cardiac surgical performance becomes more common.^{143,176,177}

SUMMARY: BRIDGING THE GAP FROM ANALYSIS OF OUTCOMES TO IMPROVEMENT OF QUALITY

Clinical registries represent a foundational tool in the following interrelated process:

1. Measuring the outcomes of medical and surgical practices
2. Developing evidence for best medical and surgical practices,
3. Providing actionable feedback to clinicians, and
4. Improving quality of care and outcomes

Clinical registries are the best tool for measuring the outcomes of the processes of care.^{220,221} As described in this chapter, the ability to measure clinical outcomes properly requires using standardized clinical nomenclature, uniform standards for defining elements of data and collecting these data, strategies to adjust for the complexity of patients, techniques to verify the completeness and accuracy of data, and collaboration across medical and surgical subspecialties. All these elements exist in the ideal clinical registry.

Clinical registries can be used as a platform for developing evidence for best medical practices and performing comparative effectiveness research. The linkage of the STS Congenital Heart Surgery Database to the PHIS Database (funded by the National Institutes of Health [NIH]) exemplifies this approach.^{***} This linkage of clinical and administrative data facilitated comparative effectiveness research in the domains of perioperative methylprednisolone and outcome in neonates undergoing heart surgery¹⁹³ and antifibrinolytic medications in pediatric heart surgery.¹⁹⁴ Similarly, the NIH-funded ASCERT trial (American College of Cardiology

Foundation—Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies trial) also used linked clinical and administrative data to compare surgical and transcatheter strategies of coronary revascularization.^{230,231} Although randomized trials have been considered by many to be the gold standard of comparative effectiveness research, recent efforts have examined the possibility of using a clinical registry as a platform for randomized trials,^{232,233} potentially accomplishing the dual objectives of decreasing the cost of the trial and increasing the generalizability of the patients enrolled.

Clinical registries can provide actionable feedback to clinicians and therefore aid in initiatives to improve quality. Clinical registries can provide practitioners with accurate and timely feedback of their own outcomes and can benchmark these outcomes to regional, national, or even international aggregate data.^{182,198,234,235,236}

The ultimate goal of clinical registries is to improve quality of care and outcomes. Clinical registries have been used to create standardized measures of quality that have been endorsed by multiple professional medical societies and the National Quality Forum.^{186,237} Compliance with these measures and the public reporting of these measures should lead to improvements in the overall quality of care delivered to our patients.^{143,176,177}

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QUALITY IMPROVEMENT: SURGICAL PERFORMANCE

Meena Nathan • John M. Karamichalis

CHAPTER OUTLINE

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APPENDIX 134-1: BOSTON CHILDREN'S HOSPITAL TECHNICAL PERFORMANCE SCORE

BACKGROUND

According to the Centers for Disease Control and Prevention (CDC),¹ congenital heart disease (CHD) is the most common type of birth defect, affecting 1% of the population (40,000 births/year). CHD is the leading cause of illness and death associated with birth defects. Fifteen percent of all patients with CHD have associated genetic conditions, and 20% to 30% have physical, developmental, or cognitive problems.²⁻⁵ In 2004, the health care cost for hospitalization of individuals with CHD was approximately \$1.4 billion.¹ It is now feasible to offer surgical correction or palliation to most of these patients. In 2011, 33,733 congenital cardiac procedures were reported to the Society of Thoracic Surgeons (STS).⁶ Between 1999 and 2006, CHD was listed as the primary cause of death in 27,960 people. Among these, 48% were infants, often following complex interventions and prolonged ICU stay. Despite recent advances in surgical management, CHD has a significant societal impact in terms of morbidity, mortality, and health care resource utilization. Thus, this patient population presents an enormous challenge to the health care environment where optimal care can greatly influence not only short-term but also long-term physical, intellectual, and psychosocial outcomes.

Outcomes in congenital cardiac surgery are multifactorial and may be affected by (1) preoperative status, such as patient factors (e.g., birth weight, gestational age, complexity of CHD), hemodynamic stability, adequacy of diagnostic evaluation, and appropriateness of the surgical plan; (2) intraoperative factors, such as conduct of anesthesia and cardiopulmonary bypass, surgical technique, and early post-bypass hemodynamic management; and (3) postoperative course, such as serious adverse events

and complications. Among these many factors, technical adequacy of repair is likely a significant determinant of successful outcome. Indeed, the degree to which a congenital heart operation achieves its intended result may be the single most important factor determining long-term medical outcomes and costs.

Until recently, hospital mortality, often in the form of cumulative sum (CUSUM) analysis, had been used as a surrogate measure of technical performance in congenital heart surgery.⁷⁻⁹ Raw mortality data, however, do not correct for case complexity or other associated factors that can affect outcomes. One alternative, the hospital standardized mortality ratio (HSMR), is intended as an overall measure of in-hospital deaths, a proportion of which are preventable. High ratios may thus suggest potential problems with quality of care.¹⁰ The HSMR is a complex but inexpensive and relatively easy method to calculate, from national or other benchmark data, the patients' predicted risk of death. However, there are a number of methodological challenges in HSMR's construction and interpretation, largely because they are based on administrative databases.¹¹ Although risk-adjusted in-hospital death rates may be a reasonable measure of institutional performance, this measure is inadequate to assess the performance of individual physicians because many additional factors outside the control of an individual surgeon (e.g., the contribution and impact of other team members) must also be considered. This is especially problematic for high-risk operations, which require a complex multidisciplinary microsystem of dedicated teams composed of many individuals and specialties.

The technical performance score (TPS), developed to address the lack of systematic methods for evaluating operative technical adequacy across diagnoses and centers,

is a novel tool for assessing technical competency based on widely available clinical and echocardiographic characteristics.

DEVELOPMENT OF THE TECHNICAL PERFORMANCE SCORE

TPS was developed at Boston Children's Hospital to assess the adequacy of anatomic repair. The technical steps toward an adequate anatomic repair of a lesion are mostly under the control of the surgeon. Intraoperative technical excellence is one of the key factors in determining outcomes, especially in high-acuity operations.¹²⁻¹⁴ A deficit in tools available to measure technical adequacy of a surgical procedure was key to the development of the TPS. This tool was designed to be used for peer and self-assessment and was initially piloted in selected surgical procedures, including repairs of ventricular septal defect, tetralogy of Fallot, complete common atrioventricular canal, arterial switch, and, later, the stage I Norwood procedure.^{15,16} The use was then expanded to include more than 90% of congenital cardiac surgery operations.¹⁷

The score was created by dividing the surgical procedure into individual subcomponents or subprocedures, based on specific anatomic regions intervened on surgically. TPS is then assessed based on echocardiographic criteria that are designed to capture the individual components of specific operations, as well as unplanned surgical or catheter-based re-interventions prior to discharge in the anatomic areas relevant to the surgical procedure. The components of the score were defined and piloted by a modified consensus process of cardiologists and cardiac surgeons at our center. Based on these prespecified components (subprocedures) that were particular to each operation, each discharge echocardiogram could be classified into one of three categories (class 1 = optimal, class 2 = adequate, or class 3 = inadequate). If all subprocedures have a class 1 optimal score, the overall score for the entire procedure will be class 1 (optimal). If any individual subprocedure is scored as class 1 or 2, the overall TPS for the procedure will be class 2 (adequate). If any subprocedure is scored as class 3 (inadequate), or if the patient undergoes at least one surgical or catheter-based re-intervention in the anatomic area of interest prior to discharge, the TPS will be class 3. Certain specific procedures that result in an unexpected implantation of a permanent pacemaker will also result in the procedure being scored as inadequate (class 3).

PILOTING THE TECHNICAL PERFORMANCE SCORE

Initial validation was performed in four procedural groups—ventricular septal defect, tetralogy of Fallot, complete common atrioventricular canal, and arterial switch operation—using data from 2004.¹⁵ Despite significant diversity and complexity among procedures, technical adequacy of repair could be successfully determined in this group of congenital cardiac procedures using the TPS tool.

TABLE 134-1 Association between Technical Performance Score and Outcomes in the Norwood Population

	Optimal	Adequate	Inadequate	P Value
Hospital LOS median (range)	18 (2-96)	19 (4-141)	33 (1-125)	0.02
Hospital mortality	4 (5%)	2 (11%)	3 (27%)	0.02
ECMO	6 (8%)	2 (11%)	8 (53%)	<0.001

ECMO, Extracorporeal membrane oxygenation; LOS, length of stay.

The TPS tool was then validated for the stage I procedure by a retrospective analysis of 110 patients from January 2004 to December 2006. There were 77 (70%) in the optimal group, 18 (16%) in the adequate group, and 15 (14%) in the inadequate group. Inadequate technical performance was significantly associated with greater early mortality, occurrence of adverse events (such as need for extracorporeal membrane oxygenation), and length of stay (Table 134-1).¹⁶

A subgroup analysis of TPS in the Norwood population showed that optimal technical performance attenuated the effects of preoperative physiologic status and case complexity with reduced hospital mortality.¹²

STANDARDIZATION OF METHODOLOGY

As part of standardization of the tool for use among multiple institutions, we developed standardized echo protocols for echo acquisition and developed anatomic modules that could be used to standardize the images obtained by the echocardiographer performing the discharge echocardiogram. These anatomic modules (Appendix 134-1) also enable the clinician finalizing the TPS to be able to accurately score all components adequately.

VALIDATION OF TECHNICAL PERFORMANCE SCORE

In subsequent studies we were able to show that TPS was useful in predicting both short- and mid-term outcomes.^{13,18-21} Specifically, to define the relationship between TPS and major postoperative adverse events, we performed a prospective study¹³ that included intraoperative observations of operations in risk adjustment for congenital heart surgery (RACHS-1)^{22,23} categories 2 through 6 in 166 infants younger than 6 months. For the entire cohort, optimal TPS resulted in lower postoperative adverse events, lower postoperative pediatric risk of mortality (PRISM)²⁴ score, lower length of intensive care unit (ICU) stay and hospital stay, and shorter ventilation time ($P < 0.001$). Optimal TPS also resulted in low postoperative adverse events independent of RACHS-1 category, or preoperative PRISM (Fig. 134-1). In multivariable logistic regression, the strongest independent predictors of postoperative major adverse events were TPS, RACHS-1 category, and preoperative PRISM. In a

prospective follow-up study of our cohort of neonates and infants from index surgery for a minimum of 1 year, 7 of the 166 patients had early mortality.¹⁸ Among the remaining 159 patients, late death occurred in 13, and late unplanned interventions (in the anatomic area operated on at index surgery) were performed in 55. Using univariate analysis, inadequate TPS was associated with postdischarge mortality ($P < 0.0001$) and re-intervention ($P = 0.034$). However, on multivariable modeling, inadequate TPS was an independent predictor of only postdischarge mortality ($P = 0.017$) (Fig. 134-2). To expand the number of patients available for analysis and thereby to improve power, we performed a retrospective study of 725 patients who were followed for a minimum of 4 years²¹; TPS

was an independent predictor in multivariable analysis of both late postdischarge mortality and unplanned re-interventions (Fig. 134-3).

We also studied the association of TPS with neurodevelopmental outcomes using the Bayley Scale of Infant Development (BSID) III scores in a group of 140 children who underwent their initial cardiac operation in the first year of life.¹⁹ Inadequate TPS was an independent predictor of poor neurodevelopmental outcomes after adjusting for other significant patient-related factors (Table 134-2).

To enhance the simplicity and reproducibility of TPS assessment, we subsequently modified the TPS to exclude intraoperative revisions (the initial five modules included such revisions as a criterion by which TPS automatically fell to class 2 [adequate]). We created 30 procedural modules and then validated these modules by prospectively assigning TPS to all discharged patients undergoing operations for CHD at our center. All patients who were discharged between January 1, 2011, and April 30, 2013, were included in this study.²⁰ TPS was optimal in 956 (50%), adequate in 584 (30%), inadequate in 226 (12%), and indeterminate in 160 patients (8%). There were 51 (2.6%) early deaths and 111 (5.7%) major adverse events (Fig. 134-4). In univariate analyses, mortality and occurrence of adverse events were significantly associated with age, RACHS-1 categories, and TPS. In multivariable regression analyses, inadequate TPS was a strong independent predictor of mortality ($P < 0.001$; OR [odds ratio], 16.9; 95% confidence interval [CI], 6.7-42.9), adverse events ($P < 0.001$; OR, 6.9; 95% CI, 4.1-11.6), and ICU length of stay ($P < 0.001$; coefficient, 2.3; 95% CI, 2.0-2.6).

We subsequently analyzed hospital cost data in this group of patients and found that class 3 (inadequate) TPS was associated with a significantly higher hospital cost after adjusting for other significant variables such as RACHS-1 risk category, age, prematurity, genetic syndromes, presence of extracardiac nonchromosomal anomalies, weekend admissions, and the need for multiple procedures at index surgery (Table 134-3; Fig. 134-5).^{24a} TPS was an independent predictor of increased total hospital cost with the percentage of variance explained (R^2) increasing from 42% to 53% when TPS was added to the

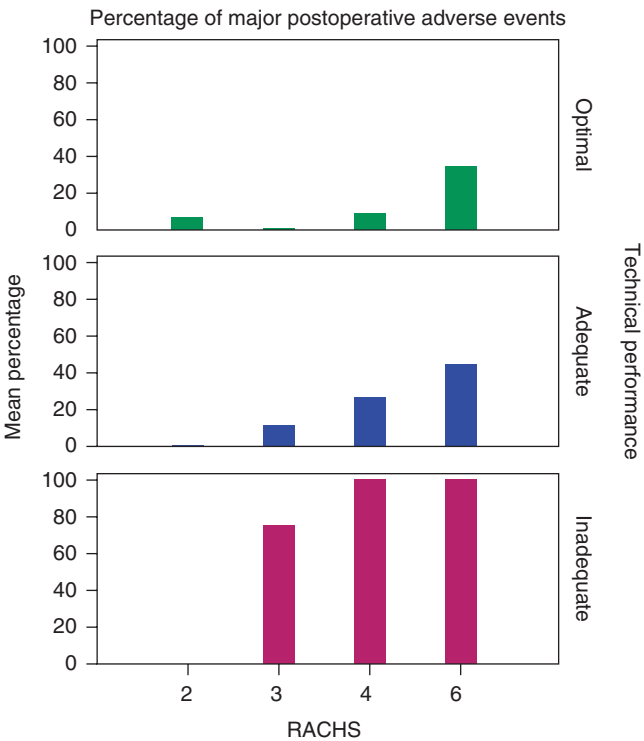


FIGURE 134-1 ■ Major postoperative adverse events as predicted by technical performance score and risk adjustment for congenital heart surgery (RACHS-1) risk categories in a prospective cohort of 166 infants younger than 6 months of age.

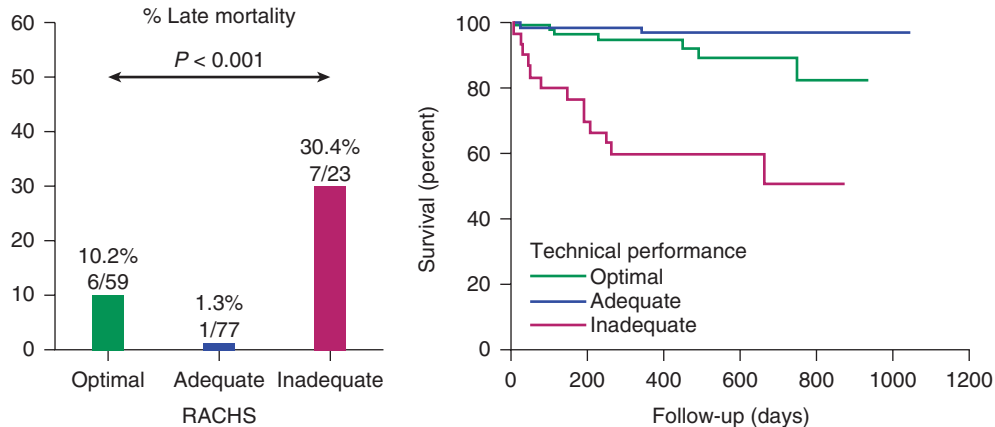


FIGURE 134-2 ■ Association between technical performance score and postdischarge mortality in a prospective cohort of 166 infants younger than 6 months of age. RACHS, Risk adjustment for congenital heart surgery.

TABLE 134-2 Multivariable Analysis of Bayley Scale of Infant Development (BSID) Cognitive Composite Score Adjusting for Preoperative Factors (Total R² = 14.6%)

	Regression Coefficient (SE)	P Value	Regression Coefficient (SE)	P Value	Partial R ²
Chromosomal anomalies	-15.1 (5.3)	0.005	-14.4 (5.2)	0.007	5.4%
Nonchromosomal anomalies	-10.4 (4.2)	0.02	-10.2 (4.2)	0.02	4.2%
RACHS-1 category 6	-11.4 (5.0)	0.03	-7.7 (5.3)	0.15	1.5%
TPS (vs. optimal)					
Adequate	—		-2.4 (3.1)	0.45	3.9%
Inadequate	—		-12.5 (5.1)	0.02	

The model on the left includes all presurgical and surgical risk factors significant at the 0.10 level. The model on the right adds in TPS. Inadequate TPS was significantly associated with a lower score after adjusting for chromosomal and nonchromosomal anomalies and RACHS-1 category.

RACHS-1, Risk adjustment for congenital heart surgery; TPS, technical performance score.

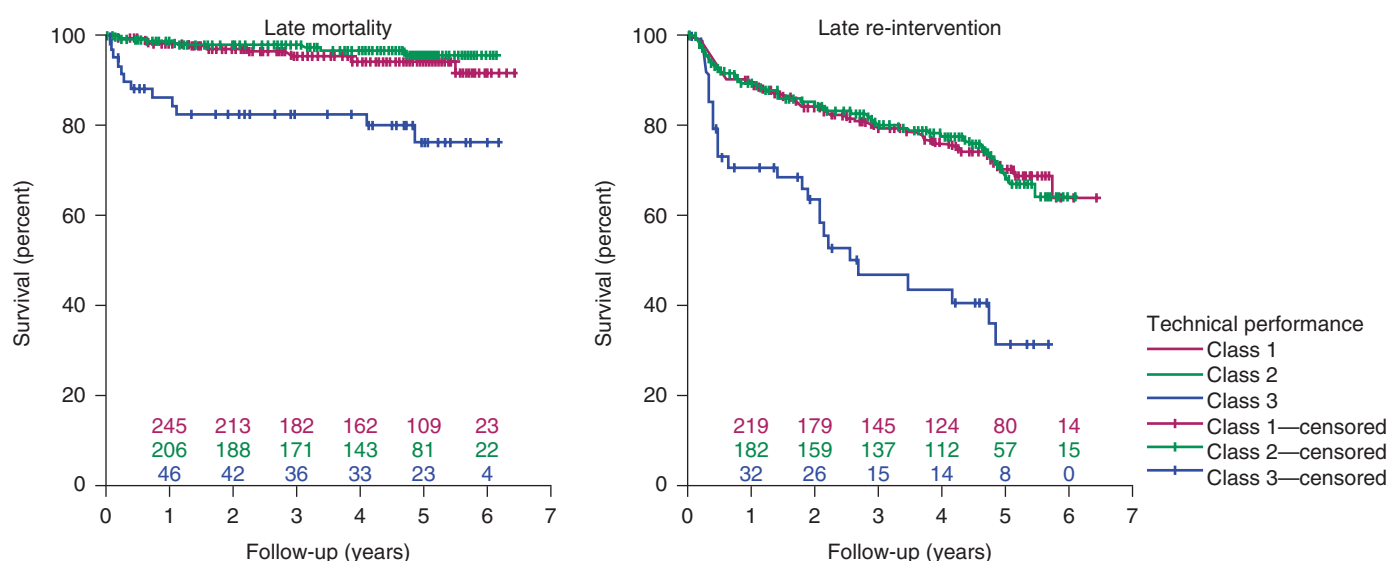


FIGURE 134-3 ■ Association between technical performance score and postdischarge mortality and postdischarge unplanned re-intervention in a cohort of 725 patients followed for 4 years.

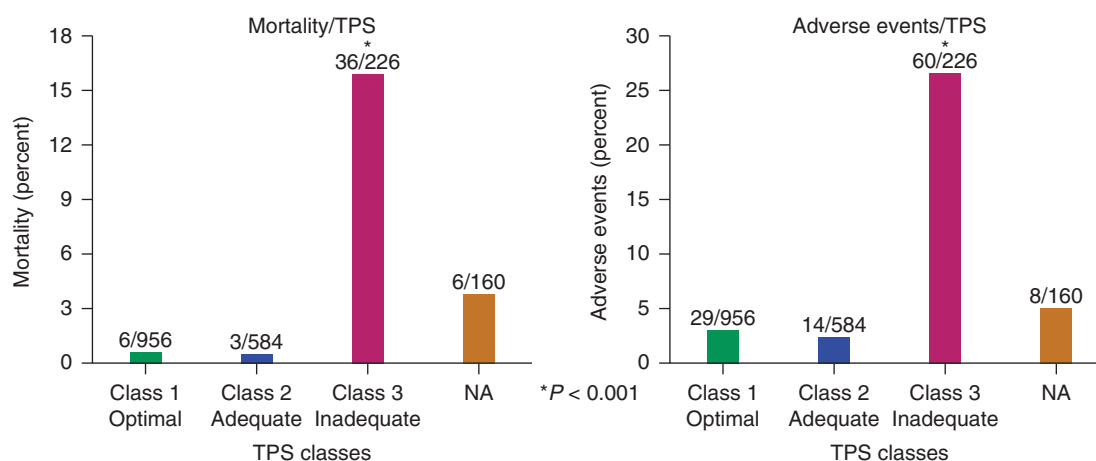


FIGURE 134-4 ■ Mortality and adverse events based on technical performance score in a prospective cohort of 1926 patients. NA, TPS could not be assigned; TPS, technical performance score.

model, indicating that TPS explained a large additional fraction of variability in total hospital cost.

To explore the predictive validity of TPS within the multicenter environment of the Pediatric Heart Network, we recently performed a secondary analysis using the

database of the Single Ventricle Reconstruction (SVR) trial. Specifically, in this 15-center study, we demonstrated that inadequate TPS was an independent predictor of longer time to extubation, higher early mortality, longer Norwood hospital length of stay (Fig. 134-6), greater

TABLE 134-3 Multivariable Analysis of Total Hospital Costs ($n = 1762$)*

Variable	<i>n</i>	Coefficient	Confidence Interval	<i>P</i> Value
RACHS-1 category				<0.001 all
1	179	Ref	—	
2	474	1.31	(1.18, 1.44)	
3	532	1.89	(1.71, 2.09)	
4	166	2.35	(2.07, 2.67)	
6	60	2.78	(2.32, 3.33)	
NA < 18 yr	143	2.64	(2.32, 3.00)	
Adults	208	1.87	(1.67, 2.09)	
Age				<0.001 all
Neonate	315	1.76	(1.62, 1.92)	
Infant	427	1.29	(1.21, 1.38)	
Children	779	Ref	—	
Prematurity				<0.001
Yes	63	1.47	(1.28, 1.69)	
Genetic syndromes				<0.001
Yes	93	1.24	(1.11, 1.39)	
Extracardiac anomalies				<0.001
Yes	116	1.36	(1.22, 1.50)	
Weekend admission				<0.001
Yes	98	1.34	(1.20, 1.51)	
Multiple procedures at index surgery				<0.001
Yes	250	1.31	(1.21, 1.41)	
Technical performance score				
Optimal	879	Ref	—	0.036
Adequate	544	1.07	(1.00, 1.13)	<0.001
Inadequate	198	2.01	(1.84, 2.20)	<0.001
Not scorable	141	0.61	(0.55, 0.67)	

*Inadequate TPS was associated with higher costs after adjusting for all variables known to be associated with higher hospital costs.

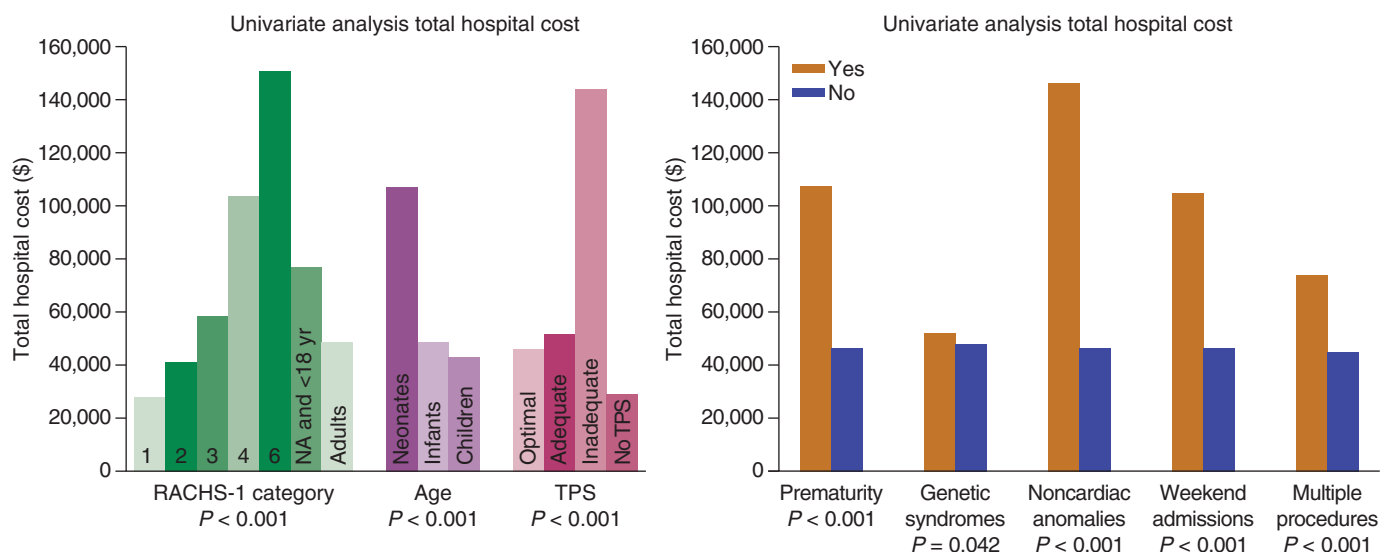


FIGURE 134-5 ■ Inadequate technical performance score (TPS) is associated with higher hospital costs. NA, Noncategorizable in RACHS-1 category; RACHS, risk adjustment for congenital heart surgery.

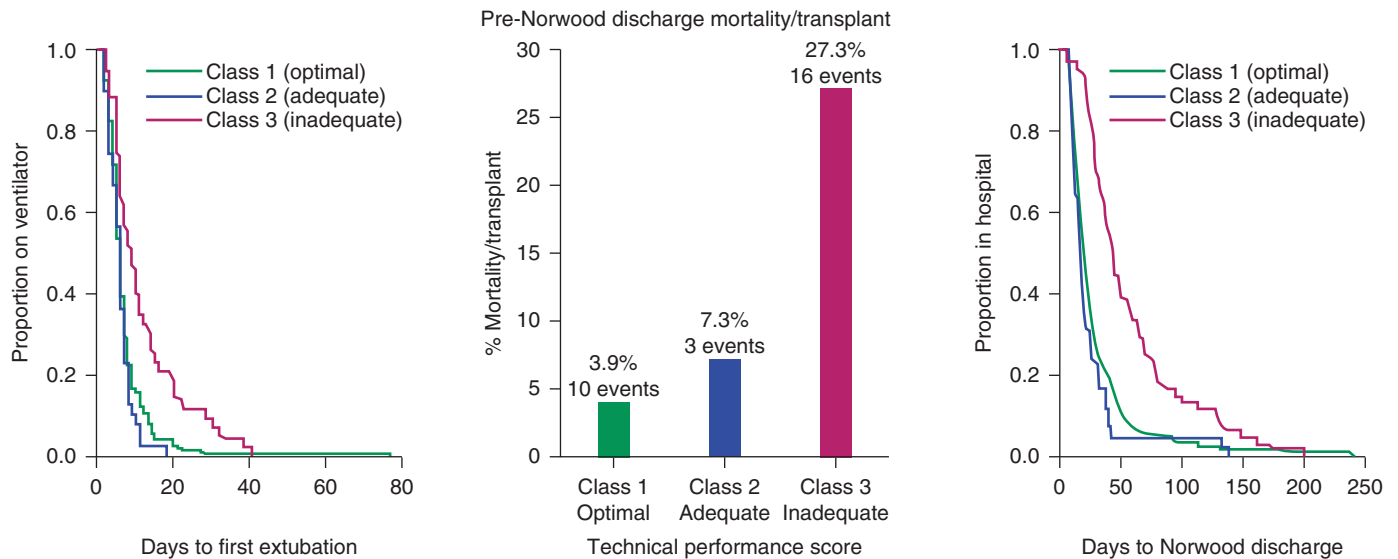


FIGURE 134-6 ■ Inadequate technical performance score is associated with longer time to extubation, higher mortality, and longer Norwood hospital length of stay in the Single Ventricle Reconstruction trial cohort.

proportion of pre-stage II re-interventions and lower Psychomotor Development Index scores at 14 months after adjusting for important preoperative factors.²⁵

FUTURE DIRECTION

Mortality and adverse events are no longer considered to be major outcome measures of quality of care. With current advances in surgical and other related technologies, attention is being turned to more subtle measures such as neurodevelopmental outcomes, resource utilization in the form of length of stay, readmissions, and unplanned postdischarge re-intervention. Although the role of human factors in outcomes after surgery has been well described,²⁶⁻²⁸ technical adequacy of the repair may still be the single most important factor in determining these more subtle outcomes; this has been demonstrated in other surgical fields.²⁹⁻³¹ Models of surgical skills assessment, including video recordings of skill tests and other methods, have been developed as part of surgical training programs.³²⁻³⁵ However, the use of a routine test (i.e., a test that is clinically indicated) as a tool for assessment of technical adequacy has not been described.

Our studies have shown that technical adequacy of the repair, as measured by TPS, has emerged as an important predictor of outcomes in congenital surgery. We describe a “technical imperative,” defined as an absolute rule whereby it is imperative to leave the operating room with a good or, better yet, an optimal technical result, even if this requires surgical revision and going back on bypass.^{12-14,16} Thus, a focus on the intraoperative assessment of the adequacy of the anatomic repair, primarily by echocardiography but also by pressure measurements and even intraoperative angiography, is paramount. Increasing intraoperative vigilance so as to detect and immediately repair significant residual lesions remains of prime importance. Our studies also indicate that residual defects repaired in a timely fashion, which usually means

immediately in the operating room or within 24 hours of surgery, result in no significant impact on patient outcome, even in highly complex cases.

The development and implementation of a system for measuring technical performance in congenital cardiac surgery operations can be used not only as an outcomes measurement tool but also as a tool for surgeons’ self and peer assessments. It can help determine how much of the interinstitutional variation can be attributed to adequacy of surgical repair versus other contributory factors, such as patient- and institution-related factors. The use of the TPS in conjunction with a risk adjustment method, such as RACHS-1, Aristotle, or STS-EACTS,^{22,23,36-38} allows for quality improvement for specific risk populations and enables a structured approach to management based on procedural complexity. TPS need not be limited to congenital cardiac procedures but may be applied to adult cardiac operations and, in fact, could potentially be expanded across all surgical specialties. This system may also be applicable to noncardiac procedures, such as interventional cardiac catheterization, electrophysiologic ablations, and radiologic interventions.

Prospective multicenter validation of this tool will allow for further refinement of the score, particularly for procedures such as valve repairs and prosthetic valve replacement. Accrual of data on sufficiently large numbers in each procedural group will allow us to determine the relative importance of the various components of each procedure and will lead to the development of a weighted scale for the components of each procedure. This will then enable us to determine which patient with a TPS of class 2 or class 3 would warrant closer follow-up and perhaps earlier intervention to optimize outcomes, thus improving quality of life while minimizing resource utilization and indirectly having a positive impact on health care costs. Development of TPS for intraoperative post-bypass transesophageal echocardiograms and epicardial echocardiograms would allow for timely correction of residual defects and lead to significant improvements in physical, psychosocial, and fiscal costs.

APPENDIX 134-1: BOSTON CHILDREN'S HOSPITAL TECHNICAL PERFORMANCE SCORE

Subprocedures	1	2	3	Other Modules
Aortic Arch, Descending Aorta				
Descending aorta	No or trivial gradient Peak gradient < 20 mm Hg	Mild gradient Peak gradient 20-40 mm Hg	Moderate to severe gradient Peak gradient > 40 mm Hg	
Aortic arch	No or trivial gradient Peak gradient < 20 mm Hg No apparent narrowing by imaging or color Doppler jet width	Mild gradient Peak gradient 20-40 mm Hg or < 30% narrowing by imaging or color Doppler jet width	Moderate to severe gradient Peak gradient > 40 mm Hg or > 30% narrowing by imaging or color Doppler jet width	
Aortic Valve/Truncal Valve (Repair)				
Aortic valve repair	No or trivial stenosis	Mild stenosis	Moderate to severe stenosis	LVOT
Truncal valve repair	Peak gradient < 20 mm Hg No or trivial regurgitation VC < 1 mm if < 10 kg VC < 2 mm if > 10 kg	Peak gradient 20-40 mm Hg Mild regurgitation VC 1-2 mm if < 10 kg VC 2-4 mm if > 10 kg	Peak gradient > 40 mm Hg Moderate to severe regurgitation VC > 2 mm if < 10 kg VC > 4 mm if > 10 kg	Supra-aortic anastomosis/ repair
Aortic Valve/Truncal Valve Replacement				
Prosthetic valve implantation	Trivial or no stenosis Peak velocity < 2.5 m/sec Trivial to no regurgitation	Mild stenosis Peak velocity < 3.5 m/sec Minor paravalvular leak (VC < 2 mm)	Moderate or severe stenosis Peak velocity > 3.5 m/sec Significant paravalvular leak (VC > 2 mm)	LVOT Supra-aortic anastomosis
Autograft implantation	No aortic valvar regurgitation or stenosis VC < 2 mm	Trivial to mild regurgitation or stenosis VC 2-4 mm Peak gradient < 30 mm	Moderate or severe stenosis Peak gradient > 30 mm Moderate or severe regurgitation VC > 4 mm	LVOT Supra-aortic anastomosis
Atrial Septum/Atrial Septectomy				
Atrial septectomy	No or trivial gradient Mean gradient < 2 mm Hg (Restrictive atrial septum left on purpose; higher gradient acceptable)	Mild residual obstruction Mean gradient 2-4 mm Hg (unless intended)	Moderate to severe residual obstruction Mean gradient > 4 mm Hg (unless intended)	
ASD Repair, Patch/Primary, Common Atrium/Sinus Venosus				
ASD repair	No or trivial residual shunt <2 mm if > 10 kg <1 mm if < 10 kg	Small residual shunt 2-3 mm if > 10 kg 1-2 mm if < 10 kg	Residual shunt >3 mm if > 10 kg >2 mm if > 10 kg	
SVC (for superior sinus venosus defect)	No SVC obstruction Mean gradient < 2 mm Hg	Trivial to mild SVC obstruction Mean gradient 2-4 mm Hg	Mild or greater SVC obstruction Mean gradient > 4 mm Hg	
IVC (for inferior sinus venosus defect)	No IVC obstruction Mean gradient < 2 mm Hg	Trivial to mild IVC obstruction Mean gradient 2-4 mm Hg	Mild or greater IVC obstruction Mean gradient > 4 mm Hg	

Subprocedures	1	2	3	Other Modules
AVV Plasty				
Left AV valve plasty (subaortic AV valve)	No or trivial stenosis Mean gradient < 3 mm Hg No or trivial regurgitation VC < 1 mm if < 10 kg VC < 2 mm if > 10 kg	Mild stenosis Mean gradient 3-6 mm Hg Mild regurgitation VC 1-2 mm if < 10 kg VC 2-4 mm if > 10 kg	Moderate or severe stenosis Mean gradient > 6 mm Hg Moderate or severe regurgitation VC > 2 mm if < 10 kg VC > 4 mm if > 10 kg	
Right AV valve plasty (subpulmonary AV valve)	No or trivial stenosis Mean gradient < 3 mm Hg No or trivial regurgitation VC < 3 mm if < 10 kg VC < 4 mm if > 10 kg	Mild stenosis Mean gradient 3-6 mm Hg) Mild regurgitation VC 3-5 mm if < 10 kg VC 4-6 mm if > 10 kg	Moderate or severe stenosis Mean gradient > 6 mm Hg Moderate or severe regurgitation VC > 5 mm if < 10 kg VC > 6 mm if > 10 kg	
Tricuspid valve annulus plication (cone)	No anatomic disruption of plication No coronary injury	No anatomic disruption of plication No coronary injury	Dehiscence of plication Coronary artery injury	
RV/RA plication/ excision (cone)	No anatomic disruption of plication No coronary injury	No anatomic disruption of plication No coronary injury	Dehiscence of plication Coronary artery injury	
AVV Replacement				
Mitral valve implantation	Trivial or no stenosis Mean velocity < 1.5 m/sec No paravalvar leak (follow manufacturer's guidelines for stenosis for prosthetic valve)	Mild stenosis Mean velocity 1.5-2.5 m/ sec Minor paravalvular leak (VC < 2 mm)	Moderate or severe stenosis Mean velocity > 2.5 m/sec Significant paravalvular leak (VC > 2 mm)	Coronary
Tricuspid valve implantation	Trivial or no stenosis Mean velocity < 1.5 m/sec No paravalvar leak (follow manufacturer's guidelines for stenosis if prosthetic valve)	Mild stenosis Mean velocity 1.5-2.5 m/ sec Minor paravalvular leak (VC < 2 mm)	Moderate or severe stenosis Mean velocity > 2.5 m/sec Significant paravalvular leak (VC > 2 mm)	Coronary
Branch Pulmonary Artery Reconstruction				
Branch pulmonary artery reconstruction	No residual stenosis Peak gradient < 20 mm Hg No discrete narrowing by imaging or color Doppler jet width	Mild residual stenosis Peak gradient 20-40 mm Hg or < 30% narrowing by imaging or color Doppler jet width	Moderate to severe residual stenosis Peak gradient > 40 mm Hg or > 30% narrowing by imaging or color Doppler jet width	
BT/Sano/Other Systemic to Pulmonary Artery Shunts, Including Unifocalization				
BT/Sano/other systemic to pulmonary artery shunts	Patent	Patent	Partial or complete occlusion, distortion of branch pulmonary arteries	
Cavopulmonary Anastomosis				
SVC-PA anastomosis	No obstruction	Mild distortion or obstruction	Moderate to severe obstruction	
Main pulmonary artery patch plasty	No pulmonary artery distortion Mean gradient < 2 mm	Mean gradient 2-4 mm Hg	Mean gradient > 4 mm Hg	
IVC inflow	No or trivial obstruction Mean gradient < 2 mm Hg	Mild obstruction Mean gradient 2-4 mm Hg	Moderate to severe obstruction Mean gradient > 4 mm Hg	
Tunnel/conduit- pulmonary artery anastomosis	No or trivial obstruction Mean gradient < 2 mm Hg	Mild distortion or obstruction Mean gradient 2-4 mm Hg	Moderate to severe obstruction Mean gradient > 4 mm Hg	
Fenestration (if present)	Patent	Patent	Fenestration not patent	
Coronary Reimplantation/Unroofing				
Coronaries reimplantation/ unroofing/baffle	No obstruction to coronary flow	No obstruction to coronary flow	Coronary flow compromise, ischemia/ infarction, with echo and/or ECG findings	Aortic valve Supra-aortic anastomosis

Continued

Subprocedures	1	2	3	Other Modules
LVOT/Sub-Aortic Stenosis Resection				
LVOT	Trivial LVOT obstruction (MIG < 20 mm Hg)	Mild LVOT obstruction (MIG 20-40 mm Hg)	Moderate or severe LVOT obstruction (MIG > 40 mm Hg)	Aortic valve Supra-aortic anastomosis
PDA Ligation/Division				
PDA closure	No residual PDA	Residual PDA ≤ 1 mm	Re-intervention or Residual PDA > 1 mm	Arch and descending aorta Branch pulmonary arteries
Pulmonary Valve Intervention				
Pulmonary valve reconstruction	No residual obstruction	Mild residual obstruction	Moderate to severe residual obstruction	Suprapulmonary anastomosis
Valve sparing	RVOT peak gradient < 20 mm Hg No or mild pulmonary valve regurgitation VC < 3 mm if < 10 kg VC < 5 mm if > 10 kg	RVOT peak gradient 20-40 mm Hg Mild PR VC 3-5 mm if < 10 kg VC 5-8 mm if > 10 kg	RVOT peak gradient > 40 mm Hg Moderate to severe PR VC > 5 mm if < 10 kg VC > 8 mm if > 10 kg	Main pulmonary artery Branch pulmonary arteries
Transannular patch	No residual obstruction RVOT peak gradient < 20 mm Hg PR—no consequence	Mild residual obstruction RVOT peak gradient 20-40 mm Hg PR—no consequence	Moderate to severe residual obstruction RVOT peak gradient > 40 mm Hg PR—no consequence	Suprapulmonary anastomosis Main pulmonary artery Branch pulmonary arteries
Pulmonary Valve Replacement				
Pulmonary valve replacement	Trivial or no stenosis Peak velocity < 2.5 m/sec No paravalvular leak (follow manufacturer's guidelines for stenosis if prosthetic valve)	Mild stenosis Peak velocity 2.5-3.5 m/sec Minor paravalvular leak (VC < 2 mm)	Moderate or severe stenosis Peak velocity > 3.5 m/sec Significant paravalvular leak (VC > 2 mm)	Suprapulmonary anastomosis Main pulmonary artery Branch pulmonary arteries Subpulmonary outflow
Pulmonary Veins				
Pulmonary vein confluence or baffle	No or trivial obstruction Mean gradient < 2 mm Hg	Mild obstruction Mean gradient 2-4 mm Hg	Moderate or severe obstruction Mean gradient > 4 mm Hg	
Scimitar vein baffle to left atrium	No or trivial obstruction Mean gradient < 2 mm Hg	Mild obstruction Mean gradient 2-4 mm Hg	Moderate or severe obstruction Mean gradient > 4 mm Hg	
Unroofing of coronary sinus	No obstruction Mean gradient < 2 mm Hg	Mild obstruction Mean gradient 2-4 mm Hg	Moderate or severe obstruction Mean gradient > 4 mm Hg	
RVOT Reconstruction/Sub-Pulmonary Stenosis Resection				
Relief of RVOT obstruction	No or trivial residual obstruction Peak gradient < 20 mm Hg	Mild residual obstruction Peak gradient 20-40 mm Hg	Moderate or severe residual obstruction Peak gradient > 40 mm Hg	Pulmonary valve Suprapulmonary Branch pulmonary arteries
RV-PA Conduit				
RV-PA conduit	Trivial to no valvar stenosis Peak gradient < 20 mm Hg Trivial to no valvar regurgitation VC < 3 mm	Mild stenosis Peak gradient 20-40 mm Hg Mild regurgitation VC 3-5 mm	Moderate or severe stenosis Peak gradient > 40 mm Hg Moderate or severe regurgitation VC > 5 mm	Subpulmonary Suprapulmonary Branch pulmonary arteries

Subprocedures	1	2	3	Other Modules
Supra-aortic Anastomosis/Repair				
Ascending aortic reconstruction	No residual gradient or narrowing	Mild narrowing or mild residual gradient	Moderate or severe residual stenosis	Aortic valve
Supra-aortic anastomosis	Peak gradient < 10 mm Hg	Peak gradient 10-20 mm Hg	Peak gradient > 20 mm Hg	Aortic arch
Suprapulmonary Anastomosis/Repair				
Main pulmonary artery reconstruction	No residual gradient or narrowing	Mild narrowing or mild residual	Moderate or severe residual stenosis	Pulmonary valve
Suprapulmonary anastomosis	Peak gradient < 10 mm Hg	Peak gradient 10-20 mm Hg	Peak gradient > 20 mm Hg	Branch pulmonary arteries
Systemic Venous Baffle				
Systemic venous baffle	No or trivial obstruction Mean gradient < 2 mm Hg	Mild obstruction Mean gradient 2-4 mm Hg	Moderate to severe obstruction Mean gradient > 4 mm Hg	
Transplant				
Left atrium anastomosis	No or trivial obstruction Mean gradient < 2 mm Hg	Mild obstruction Mean gradient 2-4 mm Hg	Moderate or severe obstruction Mean gradient > 4 mm Hg	
Aortic anastomosis	No obstruction Peak gradient < 10 mm	Mild obstruction Peak gradient 10-20 mm Hg	Moderate or severe obstruction Peak gradient > 20 mm Hg	
Pulmonary artery anastomosis	No obstruction Peak gradient < 10 mm Hg	Mild obstruction Peak gradient 10-20 mm Hg	Moderate or severe obstruction Peak gradient > 20 mm Hg	
SVC/IVC anastomosis	No or trivial obstruction Mean gradient < 2 mm Hg	Mild obstruction Mean gradient 2-4 mm Hg	Moderate or severe obstruction Mean gradient > 4 mm Hg	
PFO closure	No or trivial residual shunt <2 mm if > 10 kg <1 mm if < 10 kg	Small residual shunt 2-3 mm if > 10 kg 1-2 mm if < 10 kg	Residual shunt >3 mm if > 10 kg >2 mm if > 10 kg	
Ventricular Assist Devices				
Left ventricular/left atrial cannula	No obstruction to flow	Mild obstruction	Moderate or severe obstruction	
Ascending aortic cannula	No obstruction Peak gradient < 10 mm Hg	Mild obstruction Peak gradient 10-20 mm Hg	Moderate or severe obstruction Peak gradient > 20 mm Hg	
Pulmonary artery anastomosis	No obstruction Peak gradient < 10 mm Hg	Mild obstruction Peak gradient 10-20 mm Hg	Moderate or severe obstruction Peak gradient > 20 mm Hg	
Right atrial cannula	No obstruction	Mild obstruction	Moderate or severe obstruction	
VSD Repair				
VSD repair	No or trivial residual shunt <2 mm if > 10 kg <1 mm if < 10 kg	Residual defect 2-3 mm if > 10 kg 1-2 mm if < 10 kg	Residual defect >3 mm if > 10 kg >2 mm if < 10 kg	Aortic valve Tricuspid valve

If PFO was left open, fenestrated ASD closure was performed, or fenestrated VSD closure was performed, then ASD and VSD were not scored. Additional muscular VSDs not intervened on at time of surgery also were not scored.

ASD, Atrial septal defect; AV, atrioventricular; AVV, atrioventricular valve; BT, Blalock-Taussig; ECG, electrocardiogram; IVC, inferior vena cava; LVOT, left ventricular outflow tract; MIG, maximum instantaneous gradient; PFO, patent foramen ovale; PR, pulmonary regurgitation; RVOT, right ventricular outflow tract; RV-PA, right ventricle to pulmonary artery; SVC, superior vena cava; SVC-PA, superior vena cava to pulmonary artery; VC, vena contracta; VSD, ventricular septal defect.

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